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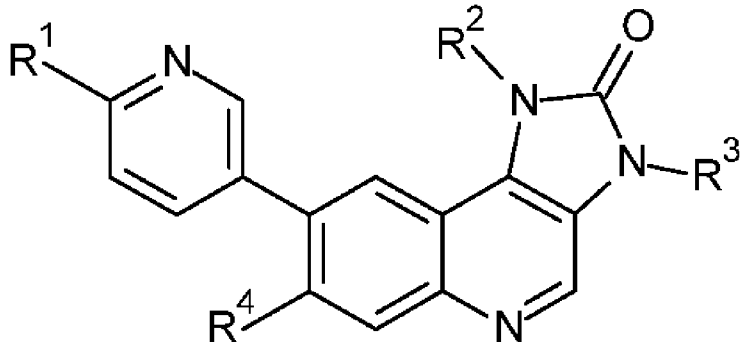

(I)

(57) Abstract: The specification generally relates to compounds of Formula (I): (I) and pharmaceutically acceptable salts thereof, where R^1, R^2, R^3 and R^4 have any of the meanings defined herein. The specification also relates to the use of compounds of Formula (I) and salts thereof to treat or prevent ATM mediated disease, including cancer. The specification further relates to pharmaceutical compositions comprising substituted imidazo[4,5-c]quinolin-2-one compounds and pharmaceutically acceptable salts thereof; kits comprising such compounds and salts; methods of manufacture of such compounds and salts; and intermediates useful in such manufacture.

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Imidazo[4,5-c]quinolin-2-one Compounds and Their Use in Treating Cancer

FIELD OF INVENTION

This specification relates to substituted imidazo[4,5-c]quinolin-2-one compounds and pharmaceutically acceptable salts thereof. These compounds and salts selectively modulate ataxia telangiectasia mutated ("ATM") kinase, and the specification therefore also relates to the use of substituted imidazo[4,5-c]quinolin-2-one compounds and salts thereof to treat or prevent ATM mediated disease, including cancer. The specification further relates to pharmaceutical compositions comprising substituted imidazo[4,5-c]quinolin-2-one compounds and pharmaceutically acceptable salts thereof; kits comprising such compounds and salts; methods of manufacture of such compounds and salts; and intermediates useful in such manufacture.

BACKGROUND

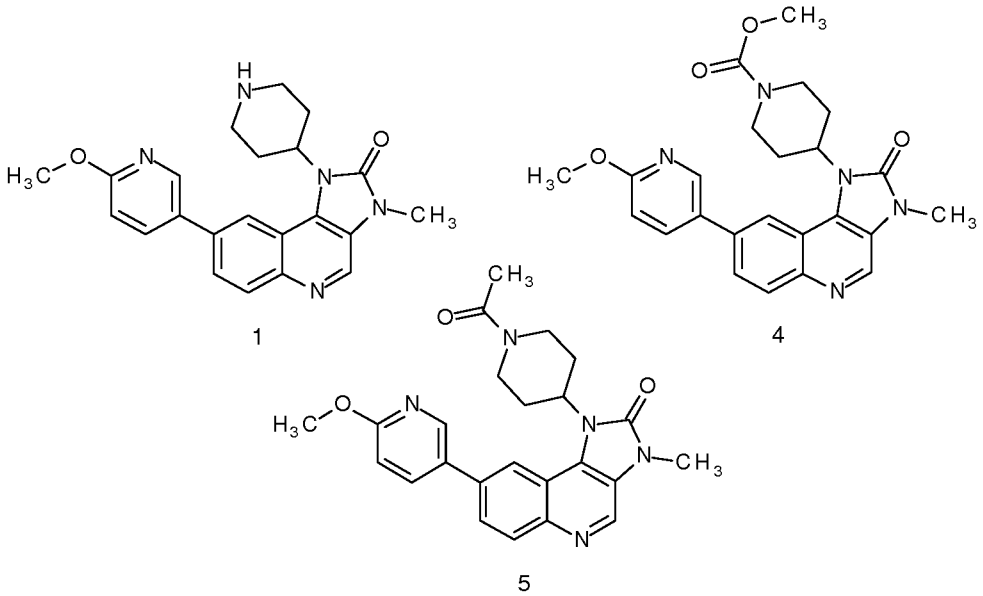
ATM kinase is a serine threonine kinase originally identified as the product of the gene mutated in ataxia telangiectasia. Ataxia telangiectasia is located on human chromosome 11q22-23 and codes for a large protein of about 350 kDa, which is characterized by the presence of a phosphatidylinositol ("PI") 3-kinase-like serine/threonine kinase domain flanked by FRAP-ATM-TRRAP and FATC domains which modulate ATM kinase activity and function. ATM kinase has been identified as a major player of the DNA damage response elicited by double strand breaks. It primarily functions in S/G2/M cell cycle transitions and at collapsed replication forks to initiate cell cycle checkpoints, chromatin modification, HR repair and pro-survival signalling cascades in order to maintain cell integrity after DNA damage (Lavin, M. F.; *Rev. Mol. Cell Biol.* **2008**, 759-769).

ATM kinase signalling can be broadly divided into two categories: a canonical pathway, which signals together with the Mre11-Rad50-NBS1 complex from double strand breaks and activates the DNA damage checkpoint, and several non-canonical modes of activation, which are activated by other forms of cellular stress (Cremona *et al.*, *Oncogene* **2013**, 3351-3360).

ATM kinase is rapidly and robustly activated in response to double strand breaks and is reportedly able to phosphorylate in excess of 800 substrates (Matsuoka *et al.*, *Science* **2007**, 1160-1166), coordinating multiple stress response pathways (Kurz and Lees Miller, *DNA Repair* **2004**, 889-900.). ATM kinase is present predominantly in the nucleus of the cell in an inactive homodimeric form but autophosphorylates itself on Ser1981 upon sensing a DNA double strand break (canonical pathway), leading to dissociation to a monomer with full kinase activity (Bakkenist *et al.*, *Nature* **2003**, 499-506). This is a critical activation event, and ATM phospho-Ser1981 is therefore both a direct pharmacodynamic and patient selection biomarker for tumour pathway dependency.

ATM kinase responds to direct double strand breaks caused by common anti-cancer treatments such as ionising radiation and topoisomerase-II inhibitors (doxorubicin, etoposide) but also to topoisomerase-I inhibitors (for example irinotecan and topotecan) *via* single strand break to double strand break conversion during replication. ATM kinase inhibition can potentiate the activity of any these agents, and as a result ATM kinase inhibitors are expected to be of use in the treatment of cancer.

CN102372711A reports certain imidazo[4,5-c]quinolin-2-one compounds which are mentioned to be dual inhibitors of PI 3-kinase α and mammalian target of rapamycin ("mTOR") kinase. Among the compounds reported in CN102372711A are the following:



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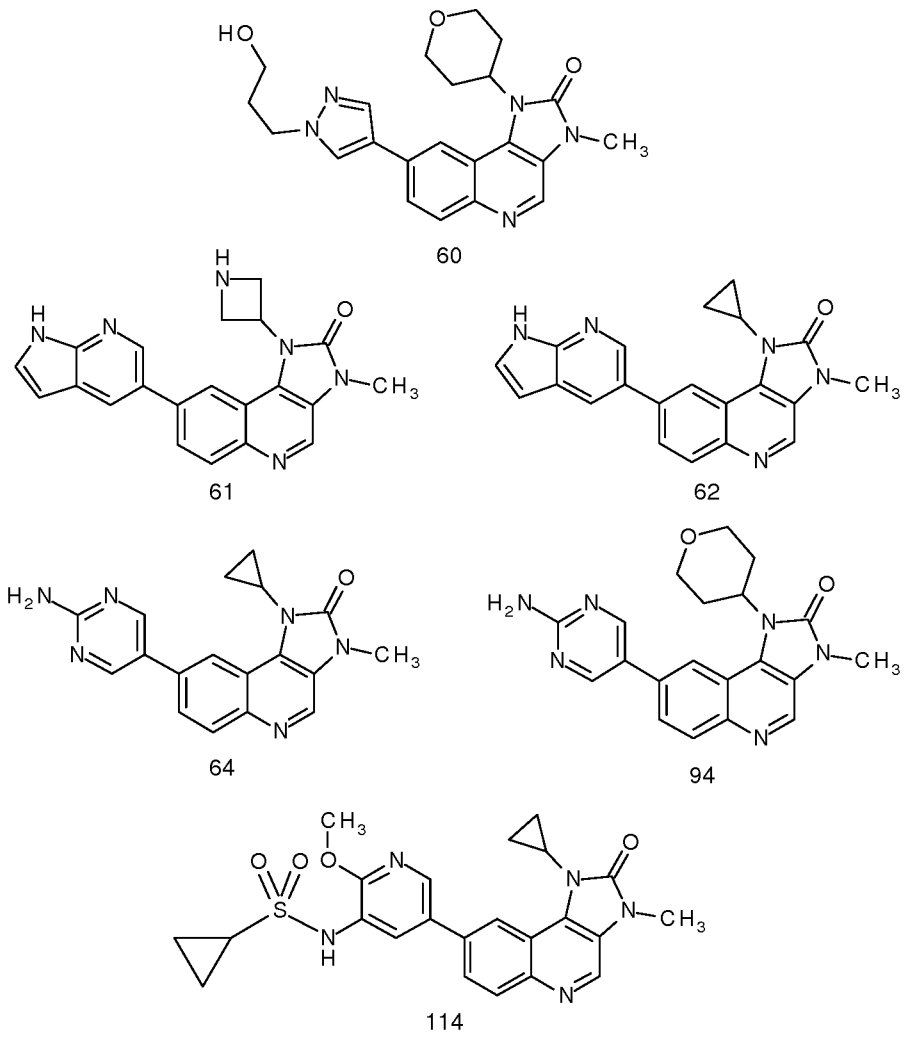
Certain compounds reported in CN102372711A

CN102399218A reports certain imidazo[4,5-c]quinolin-2-one compounds which are mentioned to be PI 3-kinase α inhibitors. Among the compounds reported in CN102399218A are the following:



Certain compounds reported in CN102399218A

While the compounds or CN102372711A and CN102399218A are reported to possess activity against PI 3-kinase α and in some cases mTOR kinase, there remains a need to develop new compounds that are more effective against different kinase enzymes, such as ATM kinase. There further exists a need for new compounds which act against certain kinase enzymes, like ATM kinase, in a highly selective fashion (*i.e.* by modulating ATM kinase more effectively than other biological targets).

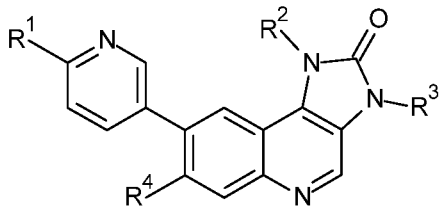
As demonstrated elsewhere in the specification (for example in the cell based assays described in the experimental section), the compounds of the present specification

generally possess very potent ATM kinase inhibitory activity, but much less potent activity against other tyrosine kinase enzymes, such as PI 3-kinase α, mTOR kinase and ataxia telangiectasia and Rad3-related protein ("ATR") kinase. As such, the compounds of the present specification not only inhibit ATM kinase, but can be considered to be highly selective inhibitors of ATM kinase.

As a result of their highly selective nature, the compounds of the present specification are expected to be particularly useful in the treatment of diseases in which ATM kinase is implicated (for example, in the treatment of cancer), but where it is desirable to minimise off-target effects or toxicity that might arise due to the inhibition of other tyrosine kinase enzymes, such as class PI 3-kinase α, mTOR kinase and ATR kinase.

SUMMARY OF INVENTION

Briefly, this specification describes, in part, a compound of Formula **(I)**:



(I)

or a pharmaceutically acceptable salt thereof, where:

R^1 is azetidinyl, pyrrolidinyl or piperidinyl, each of which is substituted by one methylamino group or one dimethylamino group;

R^2 is:

- isopropyl,
- C_4-C_6 cycloalkyl optionally substituted with one methoxy group,
- oxetanyl,
- tetrahydrofuranyl, or
- tetrahydropyranyl;

R^3 is hydro or methyl; and

R^4 is hydro or fluoro.

This specification also describes, in part, a pharmaceutical composition which comprises a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

This specification also describes, in part, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in therapy.

This specification also describes, in part, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

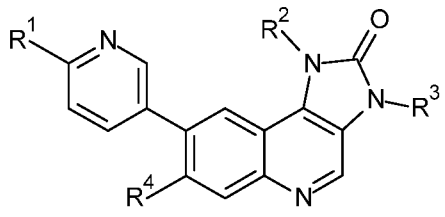
This specification also describes, in part, the use of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer.

This specification also describes, in part, a method for treating cancer in a warm blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof.

ILLUSTRATIVE EMBODIMENTS

Many embodiments of the invention are detailed throughout the specification and will be apparent to a reader skilled in the art. The invention is not to be interpreted as being limited to any particular embodiment(s) thereof.

In the first embodiment there is provided a compound of Formula **(I)**:



(I)

or a pharmaceutically acceptable salt thereof, where:

R^1 is azetidinyl, pyrrolidinyl or piperidinyl, each of which is substituted by one methylamino group or one dimethylamino group;

R^2 is:

- isopropyl,

- C_4-C_6 cycloalkyl optionally substituted with one methoxy group,
- oxetanyl,
- tetrahydrofuranyl, or
- tetrahydropyranyl;

$\mathbf{R^3}$ is hydro or methyl; and

$\mathbf{R^4}$ is hydro or fluoro.

A "hydro" group is equivalent to a hydrogen atom. Atoms with a hydro group attached to them can be regarded as unsubstituted.

"C_4-C_6 cycloalkyl" means a non-aromatic carbocyclic ring comprising 4 to 6 ring carbon atoms. C_4-C_6 cycloalkyl includes cyclobutyl, cyclopentyl, and cyclohexyl groups.

Where the term "optionally" is used, it is intended that the subsequent feature may or may not occur. As such, use of the term "optionally" includes instances where the feature is present, and also instances where the feature is not present. For example, a "C_4-C_6 cycloalkyl optionally substituted with one methoxy group" includes cyclobutyl, cyclopentyl and cyclohexyl groups with or without the specified substituent.

The term "pharmaceutically acceptable" is used to specify that an object (for example a salt, dosage form or excipient) is suitable for use in patients. An example list of pharmaceutically acceptable salts can be found in the *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, P. H. Stahl and C. G. Wermuth, editors, Weinhei*m/z*ürich:Wiley-VCH/VHCA, 2002. A suitable pharmaceutically acceptable salt of a compound of Formula **(I)** is, for example, an acid-addition salt. An acid addition salt of a compound of Formula **(I)** may be formed by bringing the compound into contact with a suitable inorganic or organic acid under conditions known to the skilled person. An acid addition salt may for example be formed using an inorganic acid selected from hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid. An acid addition salt may also be formed using an organic acid selected from trifluoroacetic acid, citric acid, maleic acid, oxalic acid, acetic acid, formic acid, benzoic acid, fumaric acid, succinic acid, tartaric acid, lactic acid, pyruvic acid, methanesulfonic acid, ethanesulfonic acid, ethanedisulfonic acid, benzenesulfonic acid, adipic acid, cinnamic acid, napadisylic acid, malic acid, malonic acid, saccharin and *para*-toluenesulfonic acid.

Therefore, in one embodiment there is provided a compound of Formula **(I)** or a pharmaceutically acceptable salt thereof, where the pharmaceutically acceptable salt is a

hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, trifluoroacetic acid, citric acid, maleic acid, oxalic acid, acetic acid, formic acid, benzoic acid, fumaric acid, succinic acid, tartaric acid, lactic acid, pyruvic acid, methanesulfonic acid, ethanesulfonic acid, ethanedisulfonic acid, benzenesulfonic acid, adipic acid, cinnamic acid, napadisylic acid, malic acid, malonic acid, saccharin or *para*-toluenesulfonic acid salt. In one embodiment there is provided a compound of Formula **(I)** or a pharmaceutically acceptable salt thereof, where the pharmaceutically acceptable salt is a methanesulfonic acid salt. In one embodiment there is provided a compound of Formula **(I)** or a pharmaceutically acceptable salt thereof, where the pharmaceutically acceptable salt is a *mono*-methanesulfonic acid salt, *i.e.* the stoichiometry of the compound of the compound of Formula **(I)** to methanesulfonic acid is 1:1. In one embodiment there is provided a compound of Formula **(I)** or a pharmaceutically acceptable salt thereof, where the pharmaceutically acceptable salt is a formic acid salt. In one embodiment there is provided a compound of Formula **(I)** or a pharmaceutically acceptable salt thereof, where the pharmaceutically acceptable salt is a *mono*-formic acid salt, *i.e.* the stoichiometry of the compound of the compound of Formula **(I)** to formic acid is 1:1.

A further embodiment provides any of the embodiments defined herein (for example the embodiment of claim 1) with the proviso that one or more specific Examples (for instance one, two or three specific Examples) selected from the group consisting of Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60 and 61 is individually disclaimed.

Some values of variable groups in Formula **(I)** are as follows. Such values may be used in combination with any of the definitions, claims (for example claim 1), or embodiments defined herein to provide further embodiments.

a) $\mathbf{R^1}$ is azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each of which is substituted by one dimethylamino group or one methylamino group.

b) $\mathbf{R^1}$ is 3-(dimethylamino)azetidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(dimethylamino)piperidin-1-yl, 4-(dimethylamino)piperidin-1-yl or 4-(methylamino)piperidin-1-yl.

c) **R¹** is 3-(dimethylamino)azetidin-1-yl, (3*R*)-3-(dimethylamino)pyrrolidin-1-yl, (3*S*)-3-(dimethylamino)pyrrolidin-1-yl, (3*R*)-3-(dimethylamino)piperidin-1-yl, 4-(dimethylamino)piperidin-1-yl or 4-(methylamino)piperidin-1-yl.

d) **R²** is isopropyl, cyclobutyl, 3-methoxycyclobut-1-yl, 3-methoxycyclopent-1-yl, 3-methoxycyclohex-1-yl, 4-methoxycyclohex-1-yl, oxetan-3-yl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl or tetrahydropyran-4-yl.

e) **R²** is isopropyl, cyclobutyl, *cis*-3-methoxycyclobut-1-yl, *trans*-3-methoxycyclobut-1-yl, *trans*-3-methoxycyclopent-1-yl, *cis*-3-methoxycyclohex-1-yl, *trans*-3-methoxycyclohex-1-yl, *trans*-4-methoxycyclohex-1-yl, oxetan-3-yl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl or tetrahydropyran-4-yl.

f) **R²** is isopropyl, cyclobutyl, *cis*-3-methoxycyclobut-1-yl, *trans*-3-methoxycyclobut-1-yl, (1*R*, 3*R*)-3-methoxycyclopent-1-yl, (1*S*, 3*R*)-3-methoxycyclohex-1-yl, (1*R*, 3*S*)-3-methoxycyclohex-1-yl, (1*S*, 3*S*)-3-methoxycyclohex-1-yl, (1*R*, 3*R*)-3-methoxycyclohex-1-yl, *trans*-4-methoxycyclohex-1-yl, oxetan-3-yl, (3*S*)-tetrahydrofuran-3-yl, (3*S*)-tetrahydropyran-3-yl, (3*R*)-tetrahydropyran-3-yl or tetrahydropyran-4-yl.

g) **R²** is isopropyl.

h) **R²** is C_4-C_6 cycloalkyl optionally substituted with one methoxy group.

i) **R²** is cyclobutyl, 3-methoxycyclobut-1-yl, 3-methoxycyclopent-1-yl, 3-methoxycyclohex-1-yl or 4-methoxycyclohex-1-yl.

j) **R²** is cyclobutyl, *cis*-3-methoxycyclobut-1-yl, *trans*-3-methoxycyclobut-1-yl, *trans*-3-methoxycyclopent-1-yl, *cis*-3-methoxycyclohex-1-yl, *trans*-3-methoxycyclohex-1-yl or *trans*-4-methoxycyclohex-1-yl.

k) **R²** is cyclobutyl, *cis*-3-methoxycyclobut-1-yl, *trans*-3-methoxycyclobut-1-yl, (1*R*, 3*R*)-3-methoxycyclopent-1-yl, (1*S*, 3*R*)-3-methoxycyclohex-1-yl, (1*R*, 3*S*)-3-methoxycyclohex-1-yl, (1*S*, 3*S*)-3-methoxycyclohex-1-yl, (1*R*, 3*R*)-3-methoxycyclohex-1-yl or *trans*-4-methoxycyclohex-1-yl.

l) **R²** is oxetanyl, tetrahydrofuranyl or tetrahydropyranyl.

m) **R²** is oxetan-3-yl, (3*S*)-tetrahydrofuran-3-yl, (3*S*)-tetrahydropyran-3-yl, (3*R*)-tetrahydropyran-3-yl or tetrahydropyran-4-yl.

n) **R²** is oxetan-3-yl.

o) **R²** is (3*S*)-tetrahydrofuran-3-yl.

p) $\mathbf{R^2}$ is (3*S*)-tetrahydropyran-3-yl or (3*R*)-tetrahydropyran-3-yl.

q) $\mathbf{R^2}$ is (3*S*)-tetrahydropyran-3-yl.

r) $\mathbf{R^2}$ is (3*R*)-tetrahydropyran-3-yl.

s) $\mathbf{R^2}$ is tetrahydropyran-4-yl.

t) $\mathbf{R^3}$ is hydro.

u) $\mathbf{R^3}$ is methyl.

v) $\mathbf{R^4}$ is hydro.

w) $\mathbf{R^4}$ is fluoro.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, where:

$\mathbf{R^1}$ is 3-(dimethylamino)azetidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(dimethylamino)piperidin-1-yl, 4-(dimethylamino)piperidin-1-yl or 4-(methylamino)piperidin-1-yl;

$\mathbf{R^2}$ is isopropyl, cyclobutyl, 3-methoxycyclobut-1-yl, 3-methoxycyclopent-1-yl, 3-methoxycyclohex-1-yl, 4-methoxycyclohex-1-yl, oxetan-3-yl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl or tetrahydropyran-4-yl;

$\mathbf{R^3}$ is methyl; and

$\mathbf{R^4}$ is hydro or fluoro.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, where:

$\mathbf{R^1}$ is 3-(dimethylamino)azetidin-1-yl, (3*R*)-3-(dimethylamino)pyrrolidin-1-yl, (3*S*)-3-(dimethylamino)pyrrolidin-1-yl, (3*R*)-3-(dimethylamino)piperidin-1-yl, 4-(dimethylamino)piperidin-1-yl or 4-(methylamino)piperidin-1-yl;

$\mathbf{R^2}$ is isopropyl, cyclobutyl, *cis*-3-methoxycyclobut-1-yl, *trans*-3-methoxycyclobut-1-yl, (1*R*, 3*R*)-3-methoxycyclopent-1-yl, (1*S*, 3*R*)-3-methoxycyclohex-1-yl, (1*R*, 3*S*)-3-methoxycyclohex-1-yl, (1*S*, 3*S*)-3-methoxycyclohex-1-yl, (1*R*, 3*R*)-3-methoxycyclohex-1-yl, *trans*-4-methoxycyclohex-1-yl, oxetan-3-yl, (3*S*)-tetrahydrofuran-3-yl, (3*S*)-tetrahydropyran-3-yl, (3*R*)-tetrahydropyran-3-yl or tetrahydropyran-4-yl;

$\mathbf{R^3}$ is methyl; and

$\mathbf{R^4}$ is hydro or fluoro.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, where:

R1 is 3-(dimethylamino)azetidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(dimethylamino)piperidin-1-yl, 4-(dimethylamino)piperidin-1-yl or 4-(methylamino)piperidin-1-yl;

R2 is cyclobutyl, 3-methoxycyclobut-1-yl, 3-methoxycyclopent-1-yl, 3-methoxycyclohex-1-yl or 4-methoxycyclohex-1-yl;

R3 is methyl; and

R4 is hydro or fluoro.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, where:

R1 is 3-(dimethylamino)azetidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(dimethylamino)piperidin-1-yl, 4-(dimethylamino)piperidin-1-yl or 4-(methylamino)piperidin-1-yl;

R2 is isopropyl;

R3 is methyl; and

R4 is hydro or fluoro.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, where:

R1 is 3-(dimethylamino)azetidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(dimethylamino)piperidin-1-yl, 4-(dimethylamino)piperidin-1-yl or 4-(methylamino)piperidin-1-yl;

R2 is oxetanyl, tetrahydrofuranyl or tetrahydropyranyl;

R3 is methyl; and

R4 is hydro or fluoro.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydrofuran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*trans*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*trans*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[*trans*-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-(*trans*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

1-cyclobutyl-8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-7-fluoro-1-[*trans*-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-[*trans*-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

1-cyclobutyl-8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-(oxetan-3-yl)imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*cis*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-[(*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[*trans*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-[*trans*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[*trans*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

7-Fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]imidazo[4,5-c]quinolin-2-one;

3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

1-(*cis*-3-methoxycyclobutyl)-3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]imidazo[4,5-c]quinolin-2-one; and

3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydrofuran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*trans*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*trans*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[(1*S*, 3*S*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[(1*R*, 3*R*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-(*trans*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

1-cyclobutyl-8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-7-fluoro-1-[(1*S*, 3*S*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-7-fluoro-1-[(1*R*, 3*R*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-[(1*S*, 3*S*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-[(1*R*, 3*R*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

1-cyclobutyl-8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-(oxetan-3-yl)imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*cis*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-[(1*S*, 3*R*)-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one ;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-[(1*R*, 3*S*)-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[(1*S*, 3*R*)-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[(1*R*, 3*S*)-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[(1*S*, 3*R*)-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one ;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[(1*R*, 3*S*)-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[(1*S*, 3*S*)-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[(1*R*, 3*R*)-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-[(1*S*, 3*S*)-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-[(1*R*, 3*R*)-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[(1*S*, 3*S*)-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[(1*S*, 3*S*)-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

7-Fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]imidazo[4,5-c]quinolin-2-one;

3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

1-(*cis*-3-methoxycyclobutyl)-3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]imidazo[4,5-c]quinolin-2-one; and

3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one.

In one embodiment there is provided 8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one, or a pharmaceutically acceptable salt thereof.

In one embodiment there is provided 8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one.

In one embodiment there is provided a pharmaceutically acceptable salt of 8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one.

In one embodiment there is provided 8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one, or a pharmaceutically acceptable salt thereof.

In one embodiment there is provided 8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one.

In one embodiment there is provided a pharmaceutically acceptable salt of 8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one.

In one embodiment there is provided 8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one, or a pharmaceutically acceptable salt thereof.

In one embodiment there is provided 8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one.

In one embodiment there is provided a pharmaceutically acceptable salt of 8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one.

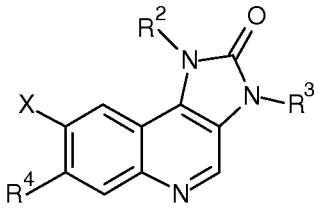
Compounds and salts described in this specification may exist in solvated forms and unsolvated forms. For example, a solvated form may be a hydrated form, such as a hemi-hydrate, a mono-hydrate, a di-hydrate, a tri-hydrate or an alternative quantity thereof. The invention encompasses all such solvated and unsolvated forms of compounds of Formula **(I)**, particularly to the extent that such forms possess ATM kinase inhibitory activity, as for example measured using the tests described herein.

Atoms of the compounds and salts described in this specification may exist as their isotopes. The invention encompasses all compounds of Formula **(I)** where an atom is

replaced by one or more of its isotopes (for example a compound of Formula **(I)** where one or more carbon atom is an ^{11}C or ^{12}C carbon isotope, or where one or more hydrogen atoms is a ^{2}H or ^{2}H isotope).

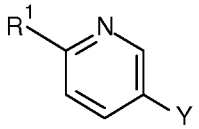
Compounds and salts described in this specification may exist as a mixture of tautomers. "Tautomers" are structural isomers that exist in equilibrium resulting from the migration of a hydrogen atom. The invention includes all tautomers of compounds of Formula **(I)** particularly to the extent that such tautomers possess ATM kinase inhibitory activity.

Compounds of Formula **(I)** may for example be prepared by the reaction of a compound of Formula **(II)**:



(II)

Or a salt thereof, where $\mathbf{R^2}$, $\mathbf{R^3}$ and $\mathbf{R^4}$ are as defined in any of the embodiments herein and **X** is a leaving group (for example a halogen atom, or alternatively a fluorine atom) with a compound of formula **(III)**:



(III)

or a salt thereof, where $\mathbf{R^1}$ is as defined in any of the embodiments herein and **Y** is a boronic acid, boronic ester or potassium trifluoroborate group (for example a boronic acid, boronic acid pinacol ester, or potassium trifluoroborate group). The reaction may be performed under standard conditions well known to those skilled in the art, for example in the presence of a palladium source (for example tetrakis triphenylphosphine palladium or palladium(II) acetate), optionally a phosphine ligand (for example Xantphos or S-phos), and a suitable base (for example cesium carbonate or triethylamine).

Compounds of Formula **(II)** are therefore useful as intermediates in the preparation of the compounds of Formula **(I)** and provide a further embodiment.

In one embodiment there is provided a compound of Formula **(II)**, or a salt thereof, where:

$\mathbf{R^2}$ is C_4-C_6 cycloalkyl optionally substituted with one methoxy group, isopropyl,oxetanyl, tetrahydrofuranyl or tetrahydropyranyl;

$\mathbf{R^3}$ is hydro or methyl;

$\mathbf{R^4}$ is hydro or fluoro; and

X is a leaving group. In one embodiment **X** is an iodine, bromine, or chlorine atom or a triflate group. In one embodiment **X** is a bromine atom.

In one embodiment there is provided a compound of Formula **(II)**, or a salt thereof, where:

$\mathbf{R^2}$ is isopropyl, cyclobutyl, 3-methoxycyclobut-1-yl, 3-methoxycyclopent-1-yl, 3-methoxycyclohex-1-yl, 4-methoxycyclohex-1-yl, oxetan-3-yl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl or tetrahydropyran-4-yl;

$\mathbf{R^3}$ is hydro or methyl;

$\mathbf{R^4}$ is hydro or fluoro; and

X is a leaving group. In one embodiment **X** is an iodine, bromine, or chlorine atom or a triflate group. In one embodiment **X** is a bromine atom.

In any of the embodiments where a compound of Formula **(II)** or a salt thereof is mentioned it is to be understood that such salts do not need to be pharmaceutically acceptable salts. A suitable salt of a compound of Formula **(II)** is, for example, an acid-addition salt. An acid addition salt of a compound of Formula **(II)** may be formed by bringing the compound into contact with a suitable inorganic or organic acid under conditions known to the skilled person. An acid addition salt may for example be formed using an inorganic acid selected from hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid. An acid addition salt may also be formed using an organic acid selected from trifluoroacetic acid, citric acid, maleic acid, oxalic acid, acetic acid, formic acid, benzoic acid, fumaric acid, succinic acid, tartaric acid, lactic acid, pyruvic acid, methanesulfonic acid, ethanesulfonic acid, ethanedisulfonic acid, benzenesulfonic acid, adipic acid, cinnamic acid, napadisylic acid, malic acid, malonic acid, saccharin and *para*-toluenesulfonic acid.

Therefore, in one embodiment there is provided a compound of Formula **(II)** or a salt thereof, where the salt is a hydrochloric acid, hydrobromic acid, sulphuric acid,

phosphoric acid, trifluoroacetic acid, citric acid, maleic acid, oxalic acid, acetic acid, formic acid, benzoic acid, fumaric acid, succinic acid, tartaric acid, lactic acid, pyruvic acid, methanesulfonic acid, ethanesulfonic acid, ethanedisulfonic acid, benzenesulfonic acid, adipic acid, cinnamic acid, napadisylic acid, malic acid, malonic acid, saccharin or *para*-toluenesulfonic acid salt.

In one embodiment there is provided a compound of Formula **(II)**, or a salt thereof, wherein the compound is selected from the group consisting of:

8-Bromo-7-fluoro-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-Bromo-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-Bromo-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-Bromo-3-methyl-1-(oxan-4-yl)imidazo[5,4-c]quinolin-2-one;

8-Bromo-1-(*cis*-3-methoxycyclobutyl)-3-methylimidazo[4,5-c]quinolin-2-one;

8-Bromo-1-(*cis*-3-methoxymethylcyclobutyl)-3-methylimidazo[4,5-c]quinolin-2-one;

8-Bromo-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methylimidazo[4,5-c]quinolin-2-one;

8-Bromo-3-methyl-1-[(3*S*)-oxan-3-yl]imidazo[5,4-c]quinolin-2-one;

8-Bromo-3-methyl-1-[(3*R*)-oxan-3-yl]imidazo[5,4-c]quinolin-2-one;

8-Bromo-7-fluoro-3-methyl-1-(oxan-4-yl)imidazo[5,4-c]quinolin-2-one;

8-Bromo-7-fluoro-3-methyl-1-[(3*S*)-oxan-3-yl]imidazo[5,4-c]quinolin-2-one;

8-Bromo-7-fluoro-3-methyl-1-[(3*R*)-oxan-3-yl]imidazo[5,4-c]quinolin-2-one;

8-Bromo-3-methyl-1-[(3*S*)-tetrahydrofuran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-Bromo-1-cyclobutyl-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-Bromo-1-(*trans*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-Bromo-1-(*trans*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-Bromo-1-(*cis*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-Bromo-1-[(3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-Bromo-1-[(*trans*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-Bromo-1-[(*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one; and

8-Bromo-1-[(*cis*-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one.

Compounds of formula **(III)** and **(IV)** can be prepared by methods similar to those shown in the Examples section.

In one embodiment there is provided any one of the novel intermediates described in the experimental section.

As a result of their ATM kinase inhibitory activity, the compounds of Formula **(I)**, and pharmaceutically acceptable salts thereof are expected to be useful in therapy, for example in the treatment of diseases or medical conditions mediated at least in part by ATM kinase, including cancer.

Where "cancer" is mentioned, this includes both non-metastatic cancer and also metastatic cancer, such that treating cancer involves treatment of both primary tumours and also tumour metastases.

"ATM kinase inhibitory activity" refers to a decrease in the activity of ATM kinase as a direct or indirect response to the presence of a compound of Formula **(I)**, or pharmaceutically acceptable salt thereof, relative to the activity of ATM kinase in the absence of compound of Formula **(I)**, or pharmaceutically acceptable salt thereof. Such a decrease in activity may be due to the direct interaction of the compound of Formula **(I)**, or pharmaceutically acceptable salt thereof with ATM kinase, or due to the interaction of the compound of Formula **(I)**, or pharmaceutically acceptable salt thereof with one or more other factors that in turn affect ATM kinase activity. For example, the compound of Formula **(I)**, or pharmaceutically acceptable salt thereof may decrease ATM kinase by directly binding to the ATM kinase, by causing (directly or indirectly) another factor to decrease ATM kinase activity, or by (directly or indirectly) decreasing the amount of ATM kinase present in the cell or organism.

The term "therapy" is intended to have its normal meaning of dealing with a disease in order to entirely or partially relieve one, some or all of its symptoms, or to correct or compensate for the underlying pathology. The term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be interpreted in a corresponding manner.

The term "prophylaxis" is intended to have its normal meaning and includes primary prophylaxis to prevent the development of the disease and secondary prophylaxis whereby the disease has already developed and the patient is temporarily or permanently

protected against exacerbation or worsening of the disease or the development of new symptoms associated with the disease.

The term "treatment" is used synonymously with "therapy". Similarly the term "treat" can be regarded as "applying therapy" where "therapy" is as defined herein.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in therapy.

In one embodiment there is provided the use of the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease mediated by ATM kinase.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease mediated by ATM kinase, where the disease mediated by ATM kinase is cancer.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease mediated by ATM kinase, where the disease mediated by ATM kinase is colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer or non-small cell lung cancer.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease mediated by ATM kinase, where the disease mediated by ATM kinase is colorectal cancer.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer or non-small cell lung cancer.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of colorectal cancer.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of Huntingdon's disease.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use as a neuroprotective agent.

A "neuroprotective agent" is an agent that preserves neuronal structure and/or function.

In one embodiment there is provided the use of the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by ATM kinase.

In one embodiment there is provided the use of the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by ATM kinase, where the disease mediated by ATM kinase is cancer.

In one embodiment there is provided the use of the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by ATM kinase, where the disease mediated by ATM kinase is colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer and non-small cell lung cancer.

In one embodiment there is provided the use of the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by ATM kinase, where the disease mediated by ATM kinase is colorectal cancer.

In one embodiment there is provided the use of the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer.

In one embodiment there is provided the use of the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large

B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer or non-small cell lung cancer.

In one embodiment there is provided the use of the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of colorectal cancer.

In one embodiment there is provided the use of the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of Huntingdon's disease.

In one embodiment there is provided the use of the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use as a neuroprotective agent.

In one embodiment there is provided a method for treating a disease in which inhibition of ATM kinase is beneficial in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof.

The term "therapeutically effective amount" refers to an amount of a compound of Formula **(I)** as described in any of the embodiments herein which is effective to provide "therapy" in a subject, or to "treat" a disease or disorder in a subject. In the case of cancer, the therapeutically effective amount may cause any of the changes observable or measurable in a subject as described in the definition of "therapy", "treatment" and "prophylaxis" above. For example, the effective amount can reduce the number of cancer or tumour cells; reduce the overall tumour size; inhibit or stop tumour cell infiltration into peripheral organs including, for example, the soft tissue and bone; inhibit and stop tumour metastasis; inhibit and stop tumour growth; relieve to some extent one or more of the symptoms associated with the cancer; reduce morbidity and mortality; improve quality of life; or a combination of such effects. An effective amount may be an amount sufficient to decrease the symptoms of a disease responsive to inhibition of ATM kinase activity. For cancer therapy, efficacy *in-vivo* can, for example, be measured by assessing the duration of survival, time to disease progression (TTP), the response rates (RR), duration of response, and/or quality of life. As recognized by those skilled in the art, effective amounts may vary

depending on route of administration, excipient usage, and co-usage with other agents. For example, where a combination therapy is used, the amount of the compound of formula **(I)** or pharmaceutcially acceptable salt described in this specification and the amount of the other pharmaceutically active agent(s) are, when combined, jointly effective to treat a targeted disorder in the animal patient. In this context, the combined amounts are in a "therapeutically effective amount" if they are, when combined, sufficient to decrease the symptoms of a disease responsive to inhibition of ATM activity as described above. Typically, such amounts may be determined by one skilled in the art by, for example, starting with the dosage range described in this specification for the compound of formula **(I)** or pharmaceutcially acceptable salt thereof and an approved or otherwise published dosage range(s) of the other pharmaceutically active compound(s).

"Warm-blooded animals" include, for example, humans.

In one embodiment there is provided a method for treating a disease in which inhibition of ATM kinase is beneficial in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and where the disease in which inhibition of ATM kinase is beneficial is cancer.

In one embodiment there is provided a method for treating a disease in which inhibition of ATM kinase is beneficial in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and where the disease in which inhibition of ATM kinase is beneficial is colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer or non-small cell lung cancer.

In one embodiment there is provided a method for treating a disease in which inhibition of ATM kinase is beneficial in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and where the disease in which inhibition of ATM kinase is beneficial is colorectal cancer.

In one embodiment there is provided a method for treating a disease in which inhibition of ATM kinase is beneficial in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and where the disease in which inhibition of ATM kinase is beneficial is Huntingdon's disease.

In one embodiment there is provided a method for treating cancer in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof.

In one embodiment there is provided a method for treating colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer or non-small cell lung cancer in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof.

In one embodiment there is provided a method for treating colorectal cancer in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof.

In one embodiment there is provided a method for treating Huntingdon's disease in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof.

In one embodiment there is provided a method for effecting neuroprotection in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof.

In one embodiment there is provided a method for treating cancer in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or

a pharmaceutically acceptable salt thereof. In one embodiment, said cancer is selected from colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer and non-small cell lung cancer. In one embodiment, said cancer is selected from colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, head and neck squamous cell carcinoma and lung cancer. In one embodiment, said cancer is colorectal cancer.

In any embodiment where cancer is mentioned in a general sense, said cancer may be selected from colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer and non-small cell lung cancer.

In any embodiment where cancer is mentioned in a general sense the following embodiments may apply:

In one embodiment the cancer is colorectal cancer.

In one embodiment the cancer is glioblastoma.

In one embodiment the cancer is gastric cancer.

In one embodiment the cancer is oesophageal cancer.

In one embodiment the cancer is ovarian cancer.

In one embodiment the cancer is endometrial cancer.

In one embodiment the cancer is cervical cancer.

In one embodiment the cancer is diffuse large B-cell lymphoma.

In one embodiment the cancer is chronic lymphocytic leukaemia.

In one embodiment the cancer is acute myeloid leukaemia.

In one embodiment the cancer is head and neck squamous cell carcinoma.

In one embodiment the cancer is breast cancer. In one embodiment the cancer is triple negative breast cancer.

"Triple negative breast cancer" is any breast cancer that does not express the genes for the oestrogen receptor, progesterone receptor and Her2/neu.

In one embodiment the cancer is hepatocellular carcinoma.

In one embodiment the cancer is lung cancer. In one embodiment the lung cancer is small cell lung cancer. In one embodiment the lung cancer is non-small cell lung cancer.

In one embodiment the cancer is non-metastatic cancer. In one embodiment the cancer is metastatic cancer. In one embodiment the metastatic cancer comprises metastases of the central nervous system. In one embodiment the metastases of the central nervous system comprise brain metastases. In one embodiment the metastases of the central nervous system comprise leptomeningeal metastases.

"Leptomeningeal metastases" occur when cancer spreads to the meninges, the layers of tissue that cover the brain and the spinal cord. Metastases can spread to the meninges through the blood or they can travel from brain metastases, carried by the cerebrospinal fluid (CSF) that flows through the meninges.

The anti-cancer treatment described in this specification may be useful as a sole therapy, or may involve, in addition to administration of the compound of Formula **(I)**, conventional surgery, radiotherapy or chemotherapy; or a combination of such additional therapies. Such conventional surgery, radiotherapy or chemotherapy may be administered simultaneously, sequentially or separately to treatment with the compound of Formula **(I)**.

Radiotherapy may include one or more of the following categories of therapy:

i. External radiation therapy using electromagnetic radiation, and intraoperative radiation therapy using electromagnetic radiation;

ii. Internal radiation therapy or brachytherapy; including interstitial radiation therapy or intraluminal radiation therapy; or

iii. Systemic radiation therapy, including but not limited to iodine 131 and strontium 89.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered in combination with radiotherapy. In one embodiment the radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iii) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of glioblastoma, lung cancer (for example small cell lung cancer or non-small cell lung cancer), breast cancer (for example triple negative breast cancer), head and neck squamous cell carcinoma,

oesophageal cancer, cervical cancer or endometrial cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered in combination with radiotherapy. In one embodiment the radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iii) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of glioblastoma, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered in combination with radiotherapy. In one embodiment the radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iii) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of metastatic cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered in combination with radiotherapy. In one embodiment the radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iii) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of metastases of the central nervous system, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered in combination with radiotherapy. In one embodiment the radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iii) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of leptomeningeal metastases, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered in combination with radiotherapy. In one embodiment the radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iii) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with radiotherapy. In one embodiment the

radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iii) above.

In one embodiment there is provided a method of treating cancer in a warm-blooded animal who is in need of such treatment, which comprises administering to said warm-blooded animal a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof and radiotherapy, wherein the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and radiotherapy are jointly effective in producing an anti-cancer effect. In one embodiment the cancer is selected from glioblastoma, lung cancer (for example small cell lung cancer or non-small cell lung cancer), breast cancer (for example triple negative breast cancer), head and neck squamous cell carcinoma, oesophageal cancer, cervical cancer and endometrial cancer. In one embodiment the cancer is glioblastoma. In one embodiment, the cancer is metastatic cancer. In one embodiment the metastatic cancer comprises metastases of the central nervous system. In one embodiment the metastases of the central nervous system comprise brain metastases. In one embodiment the metastases of the central nervous system comprise leptomeningeal metastases. In any embodiment the radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iii) above.

In one embodiment there is provided a method of treating cancer in a warm-blooded animal who is in need of such treatment, which comprises administering to said warm-blooded animal a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof and simultaneously, separately or sequentially administering radiotherapy, wherein the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and radiotherapy are jointly effective in producing an anti-cancer effect. In one embodiment the cancer is glioblastoma. In one embodiment, the cancer is metastatic cancer. In one embodiment the metastatic cancer comprises metastases of the central nervous system. In one embodiment the metastases of the central nervous system comprise brain metastases. In one embodiment the metastases of the central nervous system comprise leptomeningeal metastases. In any embodiment the radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iii) above.

Chemotherapy may include one or more of the following categories of anti-tumour substance:

iv. Antineoplastic agents and combinations thereof, such as DNA alkylating agents (for example cisplatin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustards like ifosfamide, bendamustine, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas like carmustine); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); anti-tumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, liposomal doxorubicin, pirarubicin, daunomycin, valrubicin, epirubicin, idarubicin, mitomycin-C, dactinomycin, amrubicin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, irinotecan, topotecan and camptothecin); inhibitors of DNA repair mechanisms such as CHK kinase; DNA-dependent protein kinase inhibitors; inhibitors of poly (ADP-ribose) polymerase (PARP inhibitors, including olaparib); and Hsp90 inhibitors such as tanespimycin and retaspimycin, inhibitors of ATR kinase (such as AZD6738); and inhibitors of WEE1 kinase (such as AZD1775/MK-1775);

v. Antiangiogenic agents such as those that inhibit the effects of vascular endothelial growth factor, for example the anti-vascular endothelial cell growth factor antibody bevacizumab and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib (ZD6474), sorafenib, vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW 786034) and cediranib (AZD2171); compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354; and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin), or inhibitors of angiopoietins and their receptors (Tie-1 and Tie-2), inhibitors of PLGF, inhibitors of delta-like ligand (DLL-4);

vi. Immunotherapy approaches, including for example *ex-vivo* and *in-vivo* approaches to increase the immunogenicity of patient tumour cells, such as *trans*fection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor; approaches to decrease T-cell anergy or regulatory T-cell

function; approaches that enhance T-cell responses to tumours, such as blocking antibodies to CTLA4 (for example ipilimumab and tremelimumab), B7H1, PD-1 (for example BMS-936558 or AMP-514), PD-L1 (for example durvalumab, also known as MEDI4736) and agonist antibodies to CD137; approaches using transfected immune cells such as cytokine-transfected dendritic cells; approaches using cytokine-transfected tumour cell lines, approaches using antibodies to tumour associated antigens, and antibodies that deplete target cell types (e.g., unconjugated anti-CD20 antibodies such as Rituximab, radiolabeled anti-CD20 antibodies Bexxar and Zevalin, and anti-CD54 antibody Campath); approaches using anti-idiotypic antibodies; approaches that enhance Natural Killer cell function; and approaches that utilize antibody-toxin conjugates (e.g. anti-CD33 antibody Mylotarg); immunotoxins such as moxetumumab pasudotox; agonists of toll-like receptor 7 or toll-like receptor 9;

vii. Efficacy enhancers, such as leucovorin.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered in combination with at least one additional anti-tumour substance. In one embodiment there is one additional anti-tumour substance. In one embodiment there are two additional anti-tumour substances. In one embodiment there are three or more additional anti-tumour substances. In any embodiment the additional anti-tumour substance is selected from one or more of the anti-tumour substances listed under points (i) - (iv) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance. In one embodiment there is one additional anti-tumour substance. In one embodiment there are two additional anti-tumour substances. In one embodiment there are three or more additional anti-tumour substances. In any embodiment the additional anti-tumour substance is selected from one or more of the anti-tumour substances listed under points (iv) - (vii) above.

In one embodiment there is provided a method of treating cancer in a warm-blooded animal who is in need of such treatment, which comprises administering to said warm-blooded animal a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof and at least one additional anti-tumour substance, wherein the amounts of the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and the additional anti-tumour substance are jointly effective in producing an anti-cancer effect. In any embodiment the additional anti-tumour substance is selected from one or more of the anti-tumour substances listed under points (iv) - (vii) above.

In one embodiment there is provided a method of treating cancer in a warm-blooded animal who is in need of such treatment, which comprises administering to said warm-blooded animal a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and simultaneously, separately or sequentially administering at least one additional anti-tumour substance to said warm-blooded animal, wherein the amounts of the compound of Formula **(I)**, or pharmaceutically acceptable salt thereof, and the additional anti-tumour substance are jointly effective in producing an anti-cancer effect. In any embodiment the additional anti-tumour substance is selected from one or more of the anti-tumour substances listed under points (iv) - (vii) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one anti-neoplastic agent for use in the treatment of cancer. In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered in combination with at least one anti-neoplastic agent. In one embodiment the anti-neoplastic agent is selected from the list of antineoplastic agents in point (iv) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one anti-neoplastic agent for use in the simultaneous, separate or sequential treatment of cancer. In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one anti-neoplastic agent. In one embodiment the antineoplastic agent is selected from the list of antineoplastic agents in point (iv) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from cisplatin, oxaliplatin, carboplatin, valrubicin, idarubicin, doxorubicin, pirarubicin, irinotecan, topotecan, amrubicin, epirubicin, etoposide, mitomycin, bendamustine, chlorambucil, cyclophosphamide, ifosfamide, carmustine, melphalan, bleomycin, olaparib, durvalumab, AZD1775 and AZD6738.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from cisplatin, oxaliplatin, carboplatin, doxorubicin, pirarubicin, irinotecan, topotecan, amrubicin, epirubicin, etoposide, mitomycin, bendamustine, chlorambucil, cyclophosphamide, ifosfamide, carmustine, melphalan, bleomycin, olaparib, AZD1775 and AZD6738.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from doxorubicin, irinotecan, topotecan, etoposide, mitomycin, bendamustine, chlorambucil, cyclophosphamide, ifosfamide, carmustine, melphalan, bleomycin and olaparib.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from doxorubicin, irinotecan, topotecan, etoposide, mitomycin, bendamustine, chlorambucil, cyclophosphamide, ifosfamide, carmustine, melphalan and bleomycin.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the

compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from doxorubicin, pirarubicin, amrubicin and epirubicin.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of acute myeloid leukaemia, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from doxorubicin, pirarubicin, amrubicin and epirubicin.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of breast cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from doxorubicin, pirarubicin, amrubicin and epirubicin.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of triple negative breast cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from doxorubicin, pirarubicin, amrubicin and epirubicin.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of hepatocellular carcinoma, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from doxorubicin, pirarubicin, amrubicin and epirubicin.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with irinotecan.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of colorectal cancer,

where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with irinotecan.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of colorectal cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with FOLFIRI.

FOLFIRI is a dosage regime involving a combination of leucovorin, 5-fluorouracil and irinotecan.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with olaparib.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of gastric cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with olaparib.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with topotecan.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of lung cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with topotecan.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of small cell lung cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with topotecan.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered

simultaneously, separately or sequentially with immunotherapy. In one embodiment the immunotherapy is one or more of the agents listed under point (iii) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with an anti-PD-L1 antibody (for example durvalumab).

According to a further embodiment there is provided a kit comprising:

a) A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

b) A further additional anti-tumour substance in a further unit dosage form;

c) Container means for containing said first and further unit dosage forms; and optionally

d) Instructions for use. In one embodiment the anti-tumour substance comprises an anti-neoplastic agent.

In any embodiment where an anti-neoplastic agent is mentioned, the anti-neoplastic agent is one or more of the agents listed under point (iv) above.

The compounds of Formula **(I)**, and pharmaceutically acceptable salts thereof, may be administered as pharmaceutical compositions, comprising one or more pharmaceutically acceptable excipients.

Therefore, in one embodiment there is provided a pharmaceutical composition comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

The pharmaceutically acceptable excipient(s) selected for inclusion in a particular composition will depend on factors such as the mode of administration and the form of the composition provided. Suitable pharmaceutically acceptable excipients are well known to persons skilled in the art and are described, for example, in the *Handbook of Pharmaceutical Excipients*, Sixth edition, Pharmaceutical Press, edited by Rowe, Ray C; Sheskey, Paul J; Quinn, Marian. Pharmaceutically acceptable excipients may function as, for example, adjuvants, diluents, carriers, stabilisers, flavourings, colorants, fillers, binders, disintegrants, lubricants, glidants, thickening agents and coating agents. As persons skilled in the art will appreciate, certain pharmaceutically acceptable excipients may serve more

than one function and may serve alternative functions depending on how much of the excipient is present in the composition and what other excipients are present in the composition.

The pharmaceutical compositions may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing), or as a suppository for rectal dosing. The compositions may be obtained by conventional procedures well known in the art. Compositions intended for oral use may contain additional components, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The compound of Formula **(I)** will normally be administered to a warm-blooded animal at a unit dose within the range 2.5-5000 mg/m^2 body area of the animal, or approximately 0.05-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 0.1-250 mg of active ingredient. The daily dose will necessarily be varied depending upon the host treated, the particular route of administration, any therapies being co-administered, and the severity of the illness being treated. Accordingly the practitioner who is treating any particular patient may determine the optimum dosage.

The pharmaceutical compositions described herein comprise compounds of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and are therefore expected to be useful in therapy.

As such, in one embodiment there is provided a pharmaceutical composition for use in therapy, comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

In one embodiment there is provided a pharmaceutical composition for use in the treatment of a disease in which inhibition of ATM kinase is beneficial, comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

In one embodiment there is provided a pharmaceutical composition for use in the treatment of cancer, comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

In one embodiment there is provided a pharmaceutical composition for use in the treatment of a cancer in which inhibition of ATM kinase is beneficial, comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

In one embodiment there is provided a pharmaceutical composition for use in the treatment of colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer or non-small cell lung cancer, comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

EXAMPLES

The various embodiments of the invention are illustrated by the following Examples. The invention is not to be interpreted as being limited to the Examples. During the preparation of the Examples, generally:

i. Operations were carried out at ambient temperature, *i.e.* in the range of about 17 to 30°C and under an atmosphere of an inert gas such as nitrogen unless otherwise stated;

ii. Evaporations were carried out by rotary evaporation or utilising Genevac equipment in vacuo and work-up procedures were carried out after removal of residual solids by filtration;

iii. Flash chromatography purifications were performed on an automated Armen Glider Flash : Spot II Ultimate (Armen Instrument, Saint-Ave, France) or automated Presearch combiflash companions using prepacked Merck normal phase Si60 silica cartridges (granulometry : 15-40 or 40-63μm) obtained from Merck, Darmstad, Germany, silicycle silica cartridges or graceresolv silica cartridges;

iv. Preparative chromatography was performed on a Waters instrument (600/2700 or 2525) fitted with a ZMD or ZQ ESCi mass spectrometers and a Waters X-Terra or a Waters X-Bridge or a Waters SunFire reverse-phase column (C-18, 5 microns silica, 19 mm or 50 mm diameter, 100 mm length, flow rate of 40 mL / minute) using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile or decreasingly polar mixtures of water (containing 0.1% formic acid) and acetonitrile as eluents;

v. Yields, where present, are not necessarily the maximum attainable;

vi. Structures of end-products of Formula **(I)** were confirmed by nuclear magnetic resonance (NMR) spectroscopy, with NMR chemical shift values measured on the delta scale. Proton magnetic resonance spectra were determined using a Bruker advance 700 (700MHz), Bruker Avance 500 (500 MHz), Bruker 400 (400 MHz) or Bruker 300 (300 MHz) instrument; ^{19}F NMR were determined at 282 MHz or 376 MHz; ^{13}C NMR were determined at 75 MHz or 100 MHz; measurements were taken at around 20 - 30°C unless otherwise specified; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublet of doublet; dt, doublet of triplets; bs, broad signal;

vii. End-products of Formula **(I)** were also characterised by mass spectroscopy following liquid chromatography (LCMS); LCMS was carried out using an Waters Alliance HT (2790 & 2795) fitted with a Waters ZQ ESCi or ZMD ESCi mass spectrometer and an X Bridge 5µm C-18 column (2.1 x 50 mm) at a flow rate of 2.4 mL/min, using a solvent system of 95% A + 5% C to 95% B + 5% C over 4 minutes, where A = water, B = methanol, C = 1:1 methanol:water (containing 0.2% ammonium carbonate); or by using a Shimadzu UFLC or UHPLC coupled with DAD detector, ELSD detector and 2020 EV mass spectrometer (or equivalent) fitted with a Phenomenex Gemini-NX C18 3.0x50 mm, 3.0 µM column or equivalent (basic conditions) or a Shim pack XR – ODS 3.0 x 50 mm, 2.2 µM column or Waters BEH C18 2.1 x 50 mm, 1.7 µM column or equivalent using a solvent system of 95% D + 5% E to 95% E + 5% D over 4 minutes, where D = water (containing 0.05% TFA), E = Acetonitrile (containing 0.05% TFA) (acidic conditions) or a solvent system of 90% F + 10% G to 95% G + 5% F over 4

minutes, where F = water (containing 6.5 mM ammonium hydrogen carbonate and adjusted to pH 10 by addition of ammonia), G = Acetonitrile (basic conditions);

viii. Intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, mass spectral, HPLC and/or NMR analysis;

ix. X-ray powder diffraction spectra were determined (using a Bruker D4 Analytical Instrument) by mounting a sample of the crystalline material on a Bruker single silicon crystal (SSC) wafer mount and spreading out the sample into a thin layer with the aid of a microscope slide. The sample was spun at 30 revolutions per minute (to improve counting statistics) and irradiated with X-rays generated by a copper long-fine focus tube operated at 40kV and 40mA with a wavelength of 1.5418 angstroms. The collimated X-ray source was passed through an automatic variable divergence slit set at V20 and the reflected radiation directed through a 5.89mm antiscatter slit and a 9.55mm detector slit. The sample was exposed for 0.03 seconds per 0.00570° 2-theta increment (continuous scan mode) over the range 2 degrees to 40 degrees 2-theta in theta-theta mode. The running time was 3 minutes and 36 seconds. The instrument was equipped with a Position sensitive detector (Lynxeye). Control and data capture was by means of a Dell Optiplex 686 NT 4.0 Workstation operating with Diffrac+ software;

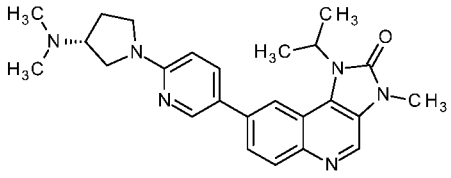
x. Differential Scanning Calorimetry was performed on a TA Instruments Q1000 DSC. Typically, less than 5mg of material contained in a standard aluminium pan fitted with a lid was heated over the temperature range 25°C to 300°C at a constant heating rate of 10°C per minute. A purge gas using nitrogen was used at a flow rate 50ml per minute

xi. The following abbreviations have been used: h = hour(s); r.t. = room temperature (~18-25°C); conc. = concentrated; FCC = flash column chromatography using silica; DCM = dichloromethane; DIPEA = diisopropylethylamine; DMA = *N*,*N*-dimethylacetamide; DMF = *N*,*N*-dimethylformamide; DMSO = dimethylsulfoxide; Et_2O = diethyl ether; EtOAc = ethyl acetate; EtOH = ethanol; K_2CO_3 = potassium carbonate; MeOH = methanol; MeCN = acetonitrile; MTBE = Methyltertbutylether; $MgSO_4$ = anhydrous magnesium sulphate; Na_2SO_4 = anhydrous sodium sulphate; THF = tetrahydrofuran; sat. = saturated aqueous solution; and

xii. IUPAC names were generated using either "Canvas" or "IBIS", AstraZeneca proprietary programs. As stated in the introduction, the compounds of the invention comprise an imidazo[4,5-c]quinolin-2-one core. However, in certain Examples the IUPAC name describes the core as an imidazo[5,4-c]quinolin-2-one. The imidazo[4,5-c]quinolin-2-one and imidazo[5,4-c]quinolin-2-one cores are nevertheless the same, with the naming convention different because of the peripheral groups.

Example 1

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one

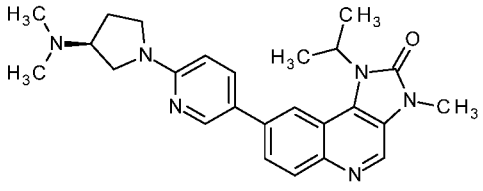
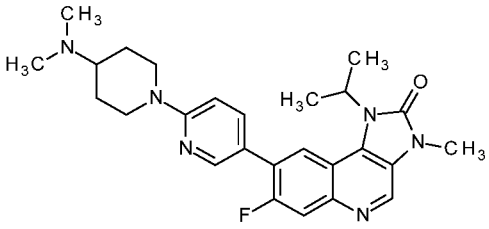
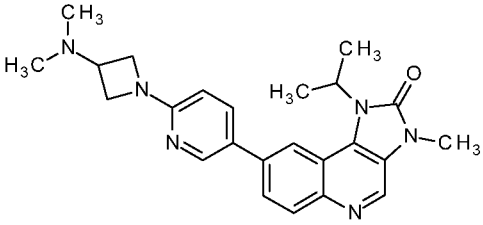


A suspension of 8-(6-fluoro-3-pyridyl)-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one (1 g, 2.97 mmol) and (R)-*N*,*N*-dimethylpyrrolidin-3-amine (1.4 g, 12.26 mmol) in MeCN (10 mL) was heated to 150 °C for 4 h in a microwave reactor then allowed to cool to ambient temperature. The reaction mixture was diluted with DCM (200 mL), washed twice with water (100 mL) and the organic layer dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by FCC, elution gradient 0 to 4% 2N methanolic ammonia in DCM, to afford the desired material as a white solid (1.210 g, 95 %).*NMR Spectrum:* ^{1}H NMR (500MHz, $CDCl_3$) δ 1.78 (6H, d), 1.89 - 2.1 (1H, m), 2.22 - 2.33 (1H, m), 2.35 (6H, s), 2.75 - 3.02 (1H, m), 3.25 - 3.42 (1H, m), 3.44 - 3.56 (1H, m), 3.58 (3H, s), 3.66 - 3.8 (1H, m), 3.78 - 3.97 (1H, m), 5.19 - 5.44 (1H, m), 6.52 (1H, dd), 7.78 (1H, dd), 7.82 (1H, dd), 8.18 (1H, d), 8.30 (1H, s), 8.58 (1H, dd), 8.66 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 431.

The material could also be isolated as a methanesulfonic acid salt using the following procedure:

The isolated material (632 mg, 1.47 mmol) was suspended in DCM (2 mL) and treated with methanesulfonic acid (161 mg, 1.68 mmol) in DCM (5 mL). The solution was evaporated to dryness then triturated with diethyl ether to afford the desired material as a methanesulfonic acid salt (770 mg, 100 %). *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.67 (6H, d), 2.13 - 2.3 (1H, m), 2.32 (3H, s), 2.43 - 2.48 (1H, m), 2.88 (6H, s), 3.4 - 3.56 (4H, m), 3.64 (1H, dd), 3.68 - 3.84 (1H, m), 3.94 (1H, dd), 4.03 (1H, p), 5.35 (1H, p), 6.73 (1H, d), 7.95 (1H, dd), 8.07 (1H, dd), 8.11 (1H, d), 8.35 (1H, d), 8.55 - 8.77 (1H, m), 8.89 (1H, s), 9.88 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 431

The following compounds could be prepared in an analogous fashion from the appropriate amine and either 8-(6-fluoro-3-pyridyl)-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one or 7-fluoro-8-(6-fluoro-3-pyridyl)-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one.

Example	Structure	Name
2*		8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one
3**		8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one
4***		8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one

* The reaction was heated in MeCN at 150°C for 4 h.

** The reaction was performed in MeCN with 4 equivalents of DIPEA present and heated at reflux for 16 h. Following purification and isolation the material was further purified by recrystalisation from hot MeCN.

*** The reaction was performed in MeCN with 7 equivalents of DIPEA present and heated at 150°C for 4 h

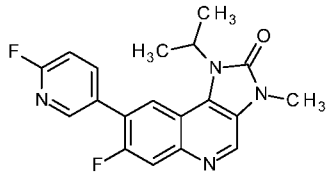
Example 2: (Free base) *NMR Spectrum:* ^{1}H NMR (500MHz, $CDCl_3$) δ 1.78 (6H, d), 1.92 - 2.04 (1H, m), 2.24 - 2.33 (1H, m), 2.35 (6H, s), 2.79 - 2.95 (1H, m), 3.29 - 3.4 (1H, m), 3.43 - 3.55 (1H, m), 3.58 (3H, s), 3.74 (1H, s), 3.87 (1H, dd), 5.22 - 5.42 (1H, m), 6.52 (1H, dd), 7.78 (1H, dd), 7.82 (1H, dd), 8.18 (1H, d), 8.30 (1H, s), 8.58 (1H, dd), 8.66 (1H, s). (Methane sulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.69 (6H, d), 2.2 - 2.31 (1H, m), 2.32 (3H, s), 2.43 - 2.58 (1H, m), 2.90 (6H, s), 3.43 - 3.57 (4H, m), 3.65 (1H, dd), 3.71 - 3.81 (1H, m), 3.96 (1H, dd), 3.99 - 4.11 (1H, m), 5.36 (1H, p), 6.74 (1H, d), 7.95 (1H, dd), 8.08 (1H, dd), 8.13 (1H, d), 8.36 (1H, d), 8.66 (1H, d), 8.88 (1H, s), 9.86 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 431.

Example 3: (Free base) *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.37 (2H, qd), 1.65 (6H, d), 1.85 (2H, d), 2.20 (6H, s), 2.31 - 2.4 (1H, m), 2.86 - 2.95 (2H, m), 3.50 (3H, s), 4.41 (2H, d), 5.28 (1H, p), 7.00 (1H, d), 7.83 - 7.91 (2H, m), 8.27 (1H, d), 8.43 - 8.48 (1H, m), 8.88 (1H, s). (Methane sulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.60 (2H, dd), 1.66 (6H, d), 2.10 (2H, d), 2.32 (4H, s), 2.80 (6H, d), 2.93 (1H, s), 3.52 (4H, s), 4.60 (2H, d), 5.32 (1H, dt), 7.11 (1H, d), 7.91 - 7.97 (2H, m), 8.33 (1H, d), 8.50 (1H, s), 8.99 (1H, s), 9.41 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 463.

Example 4: (Free base) *NMR Spectrum:* ^{1}H NMR (500MHz, $CDCl_3$) δ 1.79 (6H, d), 2.26 (6H, s), 3.31 (1H, tt), 3.59 (3H, s), 3.95 (2H, dd), 4.14 - 4.21 (2H, m), 5.28 - 5.35 (1H, m), 6.45 (1H, dd), 7.78 (1H, dd), 7.81 (1H, dd), 8.19 (1H, d), 8.30 (1H, s), 8.55 (1H, dd), 8.68 (1H, s). (Methane sulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.69 (6H, d), 2.32 (3H, s), 2.85 (6H, s), 3.52 (3H, s), 4.19 (2H, dd), 4.30 (3H, d), 5.39 (1H, p), 6.68 (1H, d), 8.03 (1H, d), 8.13 (1H, dd), 8.17 (1H, d), 8.40 (1H, d), 8.67 (1H, d), 8.99 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 417.

The preparation of 8-(6-fluoro-3-pyridyl)-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one and 7-fluoro-8-(6-fluoro-3-pyridyl)-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one are described below.

Intermediate A0: 7-Fluoro-8-(6-fluoro-3-pyridyl)-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one

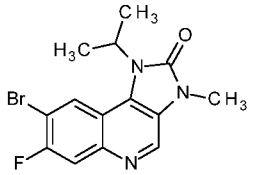


Dichlorobis(di-tert-butyl(3-sulfopropyl)phosphonio)palladate(II) (0.05M solution in water, 11.83 mL, 0.59 mmol) was added to a degassed mixture of 8-bromo-7-fluoro-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one (4.0 g, 11.83 mmol), (6-fluoropyridin-3-yl)boronic acid (2.0 g, 14.19 mmol) and 2M potassium carbonate solution (17.74 mL, 35.48 mmol) in 1,4-dioxane (50 mL) and water (12.5 mL). The mixture was purged with nitrogen and heated to 80°C for 1 h then allowed to cool and concentrated under reduced pressure to remove. The remaining solution was diluted with DCM (250 mL), washed with water (200 mL) and the organic layer dried with a phase separating cartridge and evaporated to afford crude product. The crude product was purified by FCC, elution gradient 0 to 10% MeOH in DCM, to afford the desired material as a white solid (3.70 g, 88 %). *NMR Spectrum*: ^{1}H NMR (500MHz, $CDCl_3$) δ 1.77 (6H, dd), 3.58 (3H, d), 5.20 (1H, s), 7.11 (1H, ddd), 7.93 (1H, d), 8.06 - 8.14 (1H, m), 8.22 (1H, d), 8.46 - 8.51 (1H, m), 8.72 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 355.3

Dichlorobis(di-tert-butyl(3-sulfopropyl)phosphonio)palladate(II) (0.05M solution in water) can be prepared as described below:

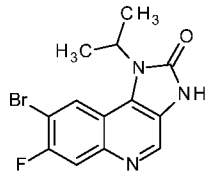
Degassed water (30 mL) was added to sodium tetrachloropalladate(II) (0.410 g, 1.39 mmol) and 3-(di-tert-butylphosphino)propane-1-sulfonic acid (0.748 g, 2.79 mmol) at ambient temperature under an inert atmosphere. The suspension was stirred for 5 minutes, then the solid removed by filtration and discarded to leave the desired reagent as a red-brown solution.

Intermediate A1: 8-Bromo-7-fluoro-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one



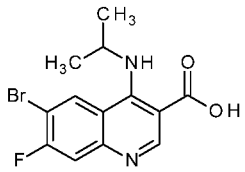
A solution of sodium hydroxide (11.29 g, 282.28 mmol) in water (600 mL) was added to a stirred mixture of 8-bromo-7-fluoro-1-isopropyl-3H-imidazo[4,5-c]quinolin-2-one (61 g, 188.19 mmol), tetrabutylammonium bromide (6.07 g, 18.82 mmol) and methyl iodide (23.53 mL, 376.37 mmol) in DCM (1300 mL) and the mixture stirred at ambient temperature for 17 h. The same process was repeated on an identical scale and the reaction mixtures combined, concentrated and diluted with MeOH (750 mL). The precipitate was collected by filtration, washed with MeOH (500 mL) and the solid dried under vacuum to afford the desired material as a white solid (108 g, 85%). NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.76 (6H, d), 3.57 (3H, s), 5.13 (1H, t), 7.83 (1H, d), 8.41 (1H, d), 8.69 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 380

Intermediate A2: 8-Bromo-7-fluoro-1-isopropyl-3H-imidazo[4,5-c]quinolin-2-one



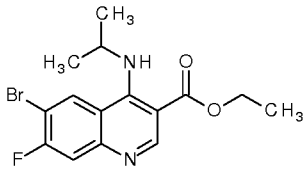
Triethylamine (164 mL, 1173.78 mmol) was added in one portion to 6-bromo-7-fluoro-4-(isopropylamino)quinoline-3-carboxylic acid (128 g, 391.26 mmol) in DMF (1500 mL) and the mixture stirred at ambient tempertaure under an inert atmosphere for 30 minutes. Diphenylphosphoryl azide (101 mL, 469.51 mmol) was added and the solution stirred for a further 30 minutes at ambient temperature then 3 h at 60°C. The reaction mixture was poured into ice water, the precipitate collected by filtration, washed with water (1 L) and dried under vacuum to afford the desired material as a yellow solid (122 g, 96 %). *NMR Spectrum:* ^{1}H NMR (400MHz, DMSO-d6) δ 1.62 (6H, d), 5.12-5.19 (1H, m), 7.92 (1H, d), 8.57 (1H, d), 8.68 (1H, s), 11.58 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 324

Intermediate A3: 6-Bromo-7-fluoro-4-(isopropylamino)quinoline-3-carboxylic acid



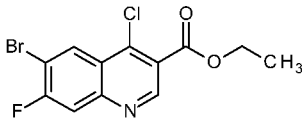
2N Sodium hydroxide solution (833 mL, 1666.66 mmol) was added portionwise to ethyl 6-bromo-7-fluoro-4-(isopropylamino)quinoline-3-carboxylate (148 g, 416.66 mmol) in THF (1500 mL) at 15°C and the resulting mixture stirred at 60°C for 5 h. The reaction mixture was concentrated, diluted with water (2 L) and the mixture acidified with 2M hydrochloric acid. The precipitate was collected by filtration, washed with water (1 L) and dried under vacuum to afford the desired material as a white solid (128 g, 94 %). *NMR Spectrum:* ^{1}H NMR (400MHz, DMSO-d6) δ 1.24-1.36(6H, m), 4.37(1H, s), 7.78(1H, t), 8.55(1H, s), 8.90(1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 327

Intermediate A4: Ethyl 6-bromo-7-fluoro-4-(isopropylamino)quinoline-3-carboxylate



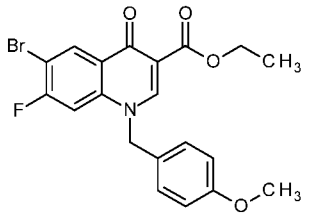
DIPEA (154 mL, 884.07 mmol) was added portionwise to propan-2-amine (39.2 g, 663.05 mmol) and ethyl 6-bromo-4-chloro-7-fluoroquinoline-3-carboxylate (147 g, 442.04 mmol) in DMA (600 mL) at ambient temperature and the resulting mixture stirred at 100°C for 4 h. The reaction mixture was poured into ice water, the precipitate collected by filtration, washed with water (1 L) and dried under vacuum to afford the desired material as a light brown solid (148 g, 94 %). *NMR Spectrum:* ^{1}H NMR (400MHz, DMSO-d6) δ 1.26-1.33 (9H, m), 4.17-4.25 (1H, m), 4.32-4.37 (2H, m), 7.28 (1H, d), 8.50 (1H, d), 8.59 (1H, d), 8.86 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 355

Intermediate A5: Ethyl 6-bromo-4-chloro-7-fluoroquinoline-3-carboxylate



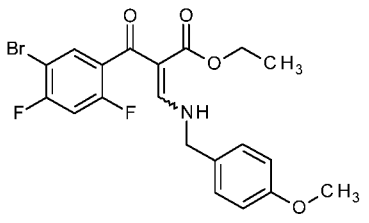
DMF (0.535 mL, 6.91 mmol) was added to ethyl 6-bromo-7-fluoro-1-[(4-methoxyphenyl)methyl]-4-oxo-quinoline-3-carboxylate (200 g, 460.56 mmol) in thionyl chloride (600 mL) at 10°C under an inert atmosphere and the resulting mixture stirred at 70°C for 3 h. The mixture was evaporated to dryness and the residue azeotroped with toluene (300 mL) to afford crude product. The crude product was purified by crystallisation from hexane to afford the desired material as a white solid (147 g, 96 %). *NMR Spectrum:* ^{1}H NMR (400MHz, $CDCl_3$) δ 1.49 (3H, t), 4.51-4.56 (2H, m), 7.91 (1H, d), 8.71 (1H, d), 9.26 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 334

Intermediate A6: Ethyl 6-bromo-7-fluoro-1-[(4-methoxyphenyl)methyl]-4-oxo-quinoline-3-carboxylate



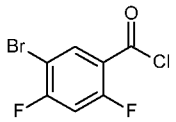
DBU (76 mL, 506.32 mmol) was added slowly to ethyl-2-(5-bromo-2,4-difluoro-benzoyl)-3-[(4-methoxyphenyl)methylamino]prop-2-enoate (230 g, 506.32 mmol) in acetone (800 mL) at 10°C over a period of 5 minutes under an inert atmosphere and the resulting mixture stirred at ambient temperature for 16 h. The precipitate was collected by filtration, washed with Et_2O (3 x 500 mL) and dried under vacuum to afford the desired material as a white solid (166 g, 75 %). *NMR Spectrum:* ^{1}H NMR (400MHz, DMSO-d6) δ 1.29 (3H, t), 3.72 (3H, s), 4.22-4.27 (21H, m), 5.57 (2H, s), 6.92-6.95 (2H, m), 7.24 (2H, d), 7.79 (1H, d), 8.40 (1H, d), 8.89 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 434.

Intermediate A7: Ethyl-2-(5-bromo-2,4-difluoro-benzoyl)-3-[(4-methoxyphenyl)methylamino]prop-2-enoate



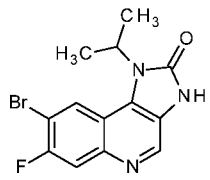
(E)-Ethyl 3-(dimethylamino)acrylate (80 mL, 555.50 mmol) was added dropwise to a mixture of DIPEA (132 mL, 757.50 mmol) and 5-bromo-2,4-difluoro-benzoyl chloride (129 g, 505.00 mmol) in toluene (600 mL) at ambient temperature under an inert atmosphere. The resulting solution was stirred at 70°C for 17 h then allowed to cool. (4-Methoxyphenyl)methanamine (66.0 mL, 505.29 mmol) was added portionwise to the mixture and the reaction stirred for 3 h at ambient temperature. The reaction mixture was diluted with DCM (2 L), washed sequentially with water (4 x 200 mL), saturated brine (300 mL), the organic layer dried over Na_2SO_4, filtered and evaporated to afford the desired material as a light brown solid (230 g, 100 %) which was used in the next step without further purification. *NMR Spectrum:* ^{1}H NMR (400MHz, $CDCl_3$) δ 1.09 (3H, t), 3.82 (3H, s), 4.00-4.10 (2H, m), 4.55 (2H, t), 6.84-6.96 (3H, m), 7.20-7.29 (2H, m), 7.55 (1H, d), 8.18 (1H, t) *Mass Spectrum:* m/z (ES+)[M+H]+ = 454

Intermediate A8: 5-Bromo-2,4-difluoro-benzoyl chloride



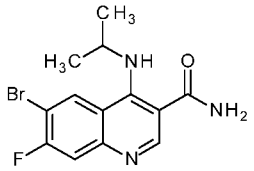
Thionyl chloride (55.4 mL, 759.50 mmol) was added portionwise to a mixture of DMF (7.84 mL, 101.27 mmol) and 5-bromo-2,4-difluorobenzoic acid (120 g, 506.33 mmol) in toluene (600 mL) at 15°C over a period of 5 minutes under an inert atmosphere. The resulting mixture was stirred at 70°C for 4 h then evaporated to dryness and the residue was azeotroped with toluene to afford the desired material as a brown oil (129 g, 100 %) which was used directly in the next step without purification. *NMR Spectrum:* ^{1}H NMR (400MHz, $CDCl_3$) δ 7.04-7.09 (1H, m), 8.34-8.42 (1H, m).

Intermediate A2 8-Bromo-7-fluoro-1-isopropyl-3H-imidazo[4,5-c]quinolin-2-one can also be prepared as described below:



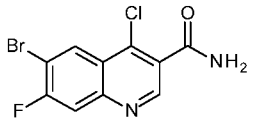
1,3,5-Trichloro-1,3,5-triazinane-2,4,6-trione (5.91 g, 25.45 mmol) was added portionwise to a stirred suspension of 6-bromo-7-fluoro-4-(isopropylamino)quinoline-3-carboxamide (16.6 g, 50.89 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (15.22 mL, 101.79 mmol) in methanol (200 mL) at 5°C.The resulting suspension was stirred at ambient temperature for 1 h. The reaction was filtered and the solid dried in a vacuum oven for 2 h to afford the desired material as a pale yellow solid (14.18 g, 86 %). Additional material was obtained after leaving the filtrate to stand for 2 days and then filtering. The additional solid isolated was heated in EtOH (50 mL) for 30 minutes then allowed to cool and filtered to provide additional desired material as a white solid (2.6 mg). Analytical data was consistent with that obtained from alternative preparations described earlier.

Intermediate A9: 6-Bromo-7-fluoro-4-(isopropylamino)quinoline-3-carboxamide



Propan-2-amine (2.80 ml, 32.62 mmol) was added to a suspenion of 6-bromo-4-chloro-7-fluoro-quinoline-3-carboxamide (10 g, 29.65 mmol) and potassium carbonate (8.20 g, 59.31 mmol) in acetonitrile (250 mL) and the mixture stirred at 95°C for 4 h. Further propan-2-amine (2 mL) was added and the mixture stirred at 95°C for another 4 h then at ambient temperature overnight. Water was added to the mixture and the solid collected by filtration and dried under vacuum to afford the desired material (8.25 g, 85 %). *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.25 (6H, d), 4.17 (1H, d), 7.51 (1H, s), 7.69 (1H, d), 8.11 (2H, s), 8.61 (1H, s), 8.67 (1H, d). *Mass Spectrum:* m/z (ES+)[M+H]+ = 236.

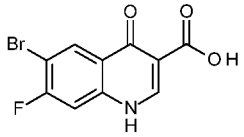
Intermediate A10: 6-Bromo-4-chloro-7-fluoro-quinoline-3-carboxamide



DMF (0.5 mL) was added to a stirred suspension of 6-bromo-7-fluoro-4-oxo-1H-quinoline-3-carboxylic acid (22.5 g, 78.66 mmol) in thionyl chloride (140 g, 1179.85 mmol) and the mixture heated to reflux for 2 h. The reaction was allowed to cool, concentrated *in vacuo* and the residue azeotroped twice with toluene to afford a yellow

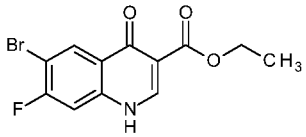
solid. This solid was added portionwise to a solution of ammonium hydroxide (147 mL, 1179.85 mmol) at 0°C. The white suspension was stirred for 15 minutes then the solid filtered, washed with water and dried under vacuum to afford the desired material (23.80 g, 100 %) as a white powder. *NMR Spectrum:* ^{1}H NMR (400MHz, DMSO-d6) δ 8.92 (1H, s), 8.59 (1H, d), 8.21 (1H, s), 8.09 (1H, d), 7.98 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 304.8.

Intermediate A11: 6-Bromo-7-fluoro-4-oxo-1H-quinoline-3-carboxylic acid



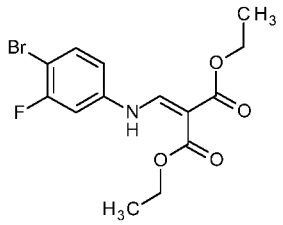
A solution of sodium hydroxide (18.34 g, 458.44 mmol) in water (100 mL) was added to a stirred suspension of ethyl 6-bromo-7-fluoro-4-oxo-1H-quinoline-3-carboxylate (28.8 g, 91.69 mmol) in EtOH (500 mL) at ambient temperature. The reaction mixture was then stirred at 75°C for 2 h, allowed to cool and the pH adjusted to 4 using 2N hydrochloric acid. The precipitate was collected by filtration, washed with water and dried under vacuum to afford the desired material (23.30 g, 89 %) as a white powder. *NMR Spectrum:* ^{1}H NMR (400MHz, DMSO-d6) δ 14.78 (1H, s), 13.45 (1H, s), 8.93 (1H, s), 8.46 (1H, d), 7.70 (1H, d). *Mass Spectrum:* m/z (ES+)[M+H]+ = 287.8.

Intermediate A12: Ethyl 6-bromo-7-fluoro-4-oxo-1H-quinoline-3-carboxylate



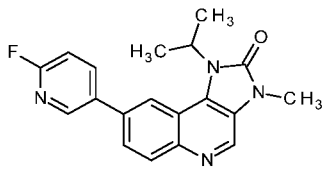
A solution of diethyl 2-[(4-bromo-3-fluoro-anilino)methylene]propanedioate (90 g, 249.88 mmol) in diphenyl ether (600 mL, 3.79 mol) was stirred at 240°C for 2.5 h. The mixture was allowed to cool to 70°C, the solids collected by filtration and dried in a vacuum oven to afford the desired material (50g, 64%) as a white solid which was used without further purification. *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6, (100°C)) δ 1.26 - 1.33 (3H, m), 4.25 (2H, q), 7.52 (1H, d), 8.37 (1H, d), 8.48 (1H, s), 12.05 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 314.

Intermediate A13: Diethyl 2-[(4-bromo-3-fluoro-anilino)methylene]propanedioate



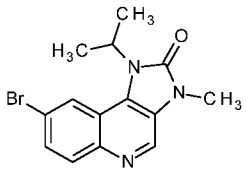
A solution of 4-bromo-3-fluoroaniline (56.6 g, 297.87 mmol) and 1,3-diethyl 2-(ethoxymethylidene)propanedioate (72.45 g, 335.06 mmol) in EtOH (560 mL) was stirred at 80°C for 4 h. The reaction mixture was allowed to cool, the solids collected by filtration and dried in an oven to afford the desired material (90g, 84%) as an off-white solid which was used without further purification. *NMR Spectrum:* ^{1}H NMR (400MHz, DMSO-d6) δ 1.26 (6H, q), 4.14 (2H, q), 4.22 (2H, q), 7.18 - 7.25 (1H, m), 7.57 (1H, dd), 7.64 - 7.7 (1H, m), 8.33 (1H, d), 10.62 (1H, d). *Mass Spectrum:* m/z (ES+)[M+H]+ = 360.

Intermediate B0: 8-(6-Fluoro-3-pyridyl)-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one



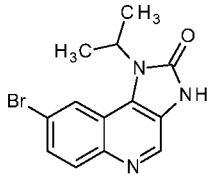
8-Bromo-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one (4.57 g, 14.27 mmol), (6-fluoropyridin-3-yl)boronic acid (2.61 g, 18.55 mmol) and 2M potassium carbonate (22 mL, 44.00 mmol) were suspended in 1,4-dioxane (90 mL). The mixture was degassed then dichloro [1,1'- bis(di-tertbutylphosphino)ferrocene]palladium(II) (0.465 g, 0.71 mmol) added and the reaction heated to 80 °C for 2 h under an inert atmosphere. The mixture was allowed to cool, diluted with EtOAc (200 mL) then washed with water (50 mL), brine, and the organic phase dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FCC, elution gradient 0 to 5% MeOH in DCM, to afford material which was subsequently triturated with diethyl ether to afford the desired material as an off-white solid (4.46 g, 93 %). *NMR Spectrum*: ^{1}H NMR (500MHz, DMSO-d6) δ 1.66 (6H, d), 3.50 (3H, s), 5.36 (1H, p), 7.36 (1H, dd), 7.95 (1H, dd), 8.15 (1H, d), 8.39 - 8.52 (2H, m), 8.72 (1H, d), 8.90 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 337.

Intermediate B1: 8-Bromo-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one



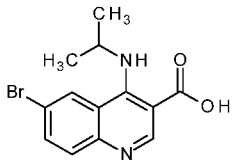
N,N-Dimethylformamide dimethyl acetal (54.2 mL, 408.29 mmol) was added to a solution of 8-bromo-1-isopropyl-3H-imidazo[4,5-c]quinolin-2-one (25.00 g, 81.66 mmol) in DMF (375 mL). The mixture was heated to 80°C for 3 h then allowed to cool to ambient temperature and stirred for 16 h. The precipitate was collected by filtration, washed with water (4 x 300 mL) and dried under vacuum at 50°C to afford the desired material as a white solid (23.82 g, 91 %). *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.63 (6H, d), 3.49 (3H, s), 5.15 - 5.23 (1H, m), 7.75 (1H, dd), 7.99 (1H, d), 8.44 (1H, d), 8.91 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 320.

Intermediate B2: 8-Bromo-1-isopropyl-3H-imidazo[4,5-c]quinolin-2-one



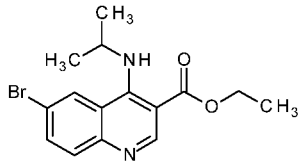
Triethylamine (45.3 mL, 332.06 mmol) was added to 6-bromo-4-(isopropylamino)quinoline-3-carboxylic acid (34.22 g, 110.69 mmol) in DMF (342 mL) at ambient temperature. After stirring at ambient temperature for 30 minutes, diphenyl phosphorazidate (26.2 mL, 121.76 mmol) was added and the resulting mixture stirred at 60 °C for 2 h. The reaction mixture was poured into water (1500 mL); the precipitate collected by filtration, washed with water (2 x 700 mL) and dried under vacuum at 50°C to afford the desired material as a beige solid (29.6 g, 87 %), which was used without further purification. *NMR Spectrum:* ^{1}H NMR (500MHz, $CDCl_3$) δ 1.64 (6H, d), 5.06 - 5.21 (1H, m), 7.75 (1H, d), 7.98 (1H, d), 8.43 (1H, s), 8.69 (1H, s), 11.57 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 306.

Intermediate B3: 6-Bromo-4-(isopropylamino)quinoline-3-carboxylic acid



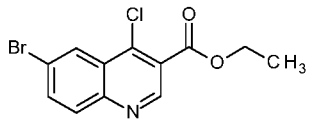
Ethyl 6-bromo-4-(isopropylamino)quinoline-3-carboxylate (38.0 g, 112.69 mmol) was suspended in methanol (800 mL) and water (200 mL). 10M sodium hydroxide solution (33.8 mL, 338.07 mmol) was added and the mixture stirred at ambient temperature for 1 h. THF (200 mL) was added and the resultant mixture stirred for 16 h. Water (400 mL) was added and the organics removed under reduced pressure. The resulting aqueous solution was acidified to pH 4-5 with 2M HCl and the precipitate collected by filtration, washed with water and dried under vacuum to afford the desired material as a white solid (34.7 g, 100 %). *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.33 (6H, d), 4.39 (1H, s), 7.78 (1H, d), 7.92 (1H, dd), 8.38 (1H, d), 8.88 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 309.

Intermediate B4: Ethyl 6-bromo-4-(isopropylamino)quinoline-3-carboxylate



Propan-2-amine (11.00 ml, 128.02 mmol) was added to a suspenion of ethyl 6-bromo-4-chloroquinoline-3-carboxylate (36.61 g, 116.38 mmol) and potassium carbonate (32.2 g, 232.77 mmol) in acetonitrile (250 mL) at 0°C. The mixture was stirred at 54 °C under reflux for 3 h. Further potassium carbonate (10.7 g, 77.6 mmol) and propan-2-amine (3.6 ml, 42.7 mmol) were added and stirring continued at 48°C for a further 16 h. The solvents were removed *in vacuo* and the resulting residue partitioned between DCM (400 mL) and water (500 mL). The aqueous layer was re-extracted with DCM (2 x 200 mL); the combined organic layers were passed through a phase separating paper and concentrated under reduced pressure to afford the desired material as a beige solid (38.6 g, 98 %). *NMR Spectrum:* ^{1}H NMR (500MHz, $CDCl_3$) δ 1.40 (6H, d), 1.43 (3H, t), 4.32 - 4.37 (1H, m), 4.40 (2H, q), 7.72 (1H, dd), 7.81 (1H, d), 8.29 (1H, d), 8.95 (1H, d), 9.10 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 337.

Intermediate B5: Ethyl 6-bromo-4-chloroquinoline-3-carboxylate

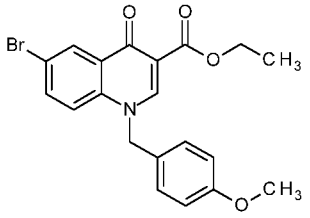


DMF (0.119mL, 1.54mmol) was added to ethyl 6-bromo-1-[(4-methoxyphenyl)methyl]-4-oxoquinoline-3-carboxylate (160g, 384.37mmol) in thionyl chloride (800mL) at ambient temperature under air. The resulting mixture was stirred at 75°C for 16 h then the solvent removed under reduced pressure. The resulting mixture was azeotroped twice with toluene then *n*-hexane (500mL) added. The precipitate was collected by filtration, washed with *n*-hexane (200mL) and dried under vacuum to afford the desired material (100g, 83%) as a brown solid. *NMR Spectrum*: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.47 (3H, t), 4.51 (2H, q), 7.95 (1H, dd), 8.11 (1H, d), 8.60 (1H, d), 9.24 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 314, 316.

On a larger scale, ethyl 6-bromo-1-[(4-methoxyphenyl)methyl]-4-oxoquinoline-3-carboxylate (5765 g, 13.85 mol) was charged to the vessel with thionyl chloride (28.8 L). An exotherm from 20-26°C was observed. DMF (4.4 mL) was added with no observed exotherm and the batch heated to 75°C and stirred for 17 h. HPLC showed 1.3% starting material remained with 98.0% product. The reaction was concentrated *in vacuo* and the residue azeotroped with toluene (25 L). The resulting solid was then slurried in heptane (18.5 L) for 2.5 h, filtered and washed with heptane (3 x 4 L). The solid was dried under vacuum at 35°C to give 4077 g of the desired material (93% crude yield) which contained ~5% of ethyl 6-bromo-1-[(4-methoxyphenyl)methyl]-4-oxoquinoline-3-carboxylate in addition to ~4% hydrolysis product by HPLC (90% pure). The crude material (4077 g) was returned to the vessel and reprocessed with thionyl chloride (14.5 L) and DMF (2.2 mL). The mixture was heated to 75°C for 40 h. The thionyl chloride was removed *in vacuo* and the residue azeotroped with toluene (10 L). The residue was slurried in heptane (18 L) for ~16 h at 20°C. The solid was collected by filtration, one portion being filtered under nitrogen and washed with heptane (3 L) to yield 2196 g of desired material (90% NMR assay, 99% by HPLC). The remainder of the batch was filtered under air and washed with heptane (3 L) to yield 1905 g of the desired material (88% NMR assay, 99% by HPLC).

The yellow solids were combined for further processing (4101 g, 3653 g active, 83% yield, 99% by HPLC).

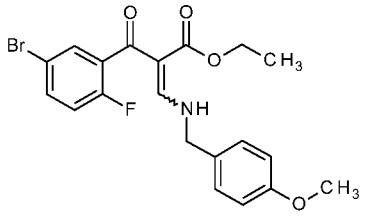
Intermediate B6: Ethyl 6-bromo-1-[(4-methoxyphenyl)methyl]-4-oxoquinoline-3-carboxylate



DBU (102mL, 679.62mmol) was added drop-wise to ethyl 2-(5-bromo-2-fluorobenzoyl)-3-[(4-methoxyphenyl)methylamino]prop-2-enoate (296.5g, 679.62mmol), in acetone (1.2 L) at ambient temperature over a period of 2 minutes. The resulting solution was stirred for 16 h then the solid removed by filtration and washed with MTBE to afford the desired material (180g, 64%) as light yellow solid. *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.30 (3H ,t), 3.71 (3H, s), 4.25 (2H ,q), 5.60 (2H, s), 6.90-6.95 (2H, m), 7.12-7.25 (2H, m), 7.67 (1H, d), 7.80-7.90 (1H, m), 8.30 (1H, d), 8.92 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 418.

On a larger scale, ethyl 2-(5-bromo-2-fluorobenzoyl)-3-[(4-methoxyphenyl)methylamino]prop-2-enoate (8434 g, (7730 g assumed active), 17.71 mol) was charged to the vessel with acetone (23.2 L) at 15°C. DBU (2.8 L, 18.72 mol) was added over 25 minutes with an observed exotherm from 18-23°C over the addition. A precipitate formed after ~25 minutes and the batch continued to exotherm reaching a maximum of 37°C after 1 h. The reaction was stirred at 20°C for 16.5 h at which point HPLC indicated consumption of starting material and 96.5% product. The resulting precipitate was collected by filtration washing with TBME (4x 3.4 L). The solid was then dried under vacuum at 40°C to give 6033 g of the desired material as a white solid (81.6% yield over 3 steps, 99.8% purity by HPLC). Analytical data was consistent with that obtained on previous batches.

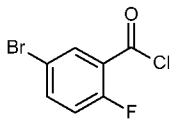
Intermediate B7: Ethyl 2-(5-bromo-2-fluorobenzoyl)-3-[(4-methoxyphenyl)methylamino]prop-2-enoate



(E)-Ethyl 3-(dimethylamino)acrylate (98g, 685.00mmol) was added portion-wise to 5-bromo-2-fluorobenzoyl chloride (163g, 685mmol) and DIPEA (120mL, 685.00mmol) in toluene (800mL) at 10°C over a period of 10 minutes. The resulting solution was stirred at 70°C for 16 h then allowed to cool. (4-Methoxyphenyl)methanamine (94g, 685mmol) was added to the mixture over a period of 20 minutes at ambient temperature. The resulting solution was stirred for 3 h then the reaction mixture diluted with DCM (4 L), and washed with water (3 x 1L). The organic phase was dried over Na_2SO_4, filtered and evaporated to give the desired material (300g, 100%) as brown oil, which was used immediately in the subsequent reaction without further purification. *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 436.

On a larger scale, 5-bromo-2-fluorobenzoyl chloride (4318 g, 4205 g active, 17.71 mol) was charged to the vessel as a solution in toluene (7.5 L). DIPEA (3150 mL, 18.08 mol) was added with no observed exotherm. Ethyl-3-(dimethylamino)acrylate (2532 g, 17.71 mol) was added portionwise over 30 minutes maintaining a batch temperature <40°C. An exotherm from 21-24°C was noted over the 30 minute addition with a further slow rise to 38°C over 1 h. The reaction was stirred at 20-30°C for 16.5 h. 4-Methoxybenzylamine (2439 g, 17.78 mol) was added portionwise over 30 mins maintaining a batch temperature <40°C. An exotherm of 25-30°C was observed over the addition with cooling provided by a reduced jacket temperature of 15°C. The reaction was stirred for 4 h at 20-30°C after which HPLC indicated 93.2% of desired material. The batch was split for workup with each half of the mixture diluted with DCM (28.6 L) and washed with water (3 x 7.8 L). The organics were dried over MgSO4 (~550 g) and filtered, washing with DCM (4 L). The combined organics were then concentrated to give 8444 g of the desired material as an oil (8434 g, 106% yield, 94.7% purity by HPLC). Analytical data was consistent with that obtained from previous batches.

Intermediate B8: 5-Bromo-2-fluorobenzoyl chloride

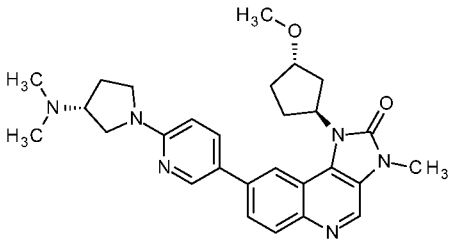


Thionyl chloride (75.0mL, 1027.36mmol) was added drop-wise to 5-bromo-2-fluorobenzoic acid (150g, 684.91mmol), in toluene (1.2 L) and DMF (12mL) at ambient temperature over a period of 1 h. The resulting mixture was stirred at 70°C for 16 h then the mixture allowed to cool and concentrated *in vacuo* to afford the desired material (160g, 98%) as light yellow oil, which was used without further purification. *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 7.26 – 7.31 (1H, m), 7.83 (1H, dd), 8.02 (1H, d).

On a larger scale, 3-bromo-6-fluorobenzoic acid (3888 g, 17.75 mol) was charged to the vessel at 20°C followed by toluene (29.2 L). Thionyl chloride (1950 ml, 26.88 mol) was added, followed by DMF (310 mL) with no observed exotherm. The mixture was heated to 65-75°C (solution obtained above ~45°C) with no observed exotherm and slight gas evolution. The reaction was stirred for 40 h at this temperature at which point HPLC analysis showed 87.6% product, 3.4% starting material. The reaction was concentrated *in vacuo* and azeotroped with toluene (18 L) to give 4328 g of the desired material (103% yield, 87.3% by HPLC).

Example 5

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one



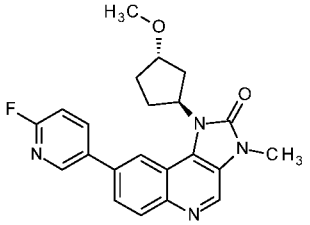
A suspension of 8-(6-fluoro-3-pyridyl)-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one (75 mg, 0.19 mmol) and (R)-*N*,*N*-dimethylpyrrolidin-3-amine (87 mg, 0.76 mmol) in MeCN (1 mL) was heated to 150 °C for 4 h in a microwave reactor then the mixture allowed to cool to rambient temperature. The reaction mixture was

diluted with DCM (40 mL), washed twice with water (2 x 20 mL) and the organic layer dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by FCC, elution gradient 0 to 6% 2N methanolic ammonia in DCM, to afford the desired material as a white solid (70.0 mg, 75 %). *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.82 (2H, s), 2.06 - 2.3 (10H, m), 2.36 - 2.45 (1H, m), 2.5 - 2.57 (1H, m), 2.72 - 2.86 (1H, m), 3.17 (1H, dd), 3.27 (3H, s), 3.33 - 3.44 (1H, m), 3.48 (3H, s), 3.63 (1H, d), 3.73 (1H, dd), 4.05 - 4.16 (1H, m), 5.55 (1H, q), 6.61 (1H, d), 7.88 (1H, dd), 7.93 (1H, dd), 8.07 (1H, d), 8.27 (1H, d), 8.57 (1H, d), 8.82 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 487.

The material could also be isolated as a methanesulfonic acid salt using the following procedure:

The isolated material (64 mg, 0.13 mmol) was suspended in DCM (2 mL) and treated with methanesulfonic acid (17 mg, 0.18 mmol) in DCM (2 mL). The solution was evaporated to dryness to afford the desired material as a methaesulfonic acid salt (80 mg, 104 %). *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.7 - 1.95 (1H, m), 2.1 - 2.27 (4H, m), 2.30 (3H, s), 2.37 - 2.47 (2H, m), 2.52 - 2.57 (1H, m), 2.88 (6H, s), 3.27 (3H, s), 3.42 - 3.49 (1H, m), 3.50 (3H, s), 3.63 (1H, dd), 3.69 - 3.8 (1H, m), 3.94 (1H, dd), 3.98 - 4.07 (1H, m), 4.06 - 4.17 (1H, m), 5.44 - 5.68 (1H, m), 6.73 (1H, d), 7.94 (1H, d), 8.03 (1H, dd), 8.11 (1H, d), 8.32 (1H, s), 8.62 (1H, d), 8.88 (1H, s), 9.83 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 487.

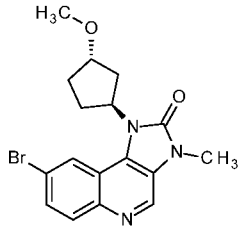
Intermediate C0: 8-(6-Fluoro-3-pyridyl)-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one



8-bromo-1-((1*S*,3*S*)-3-methoxycyclopentyl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-one (250 mg, 0.66 mmol), (6-fluoropyridin-3-yl)boronic acid (122 mg, 0.86 mmol) and 2M

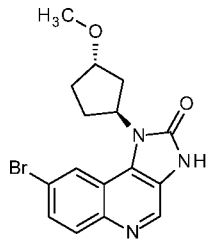
potassium carbonate (1 ml, 2.00 mmol) were suspended in 1,4-dioxane (4 ml),degassed, then [Pd-118] (22 mg, 0.03 mmol) was added. The reaction was heated to 80 °C for 1 h under nitrogen and cooled to RT. The reaction mixture was diluted with EtOAc (50 ml) then washed with water (2 x 25 ml) and then the organic phase was dried over MgSO4, filtered and concentrated in vacuo. The crude product was purified by FCC, elution gradient 0 to 3% 2N methanolic ammonia in DCM . Pure fractions were evaporated to dryness to afford 8-(6-fluoropyridin-3-yl)-1-((1*S*,3*S*)-3-methoxycyclopentyl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-one (185 mg, 70.9 %) as an off-white solid.

Intermediate C1: 8-Bromo-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one



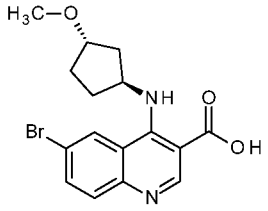
NaH (60% in mineral oil) (0.444 g, 11.11 mmol) was added to a mixture of 8-bromo-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3H-imidazo[4,5-c]quinolin-2-one (1.15 g, 3.17 mmol) in DMF (15 mL) under nitrogen at 0°C then the mixture stirred for 30 minutes. Methyl iodide (0.596 mL, 9.52 mmol) was added and the reaction mixture was stirred at ambient temperature for 16 h. Water was slowly added to the reaction and the solid filtered under vacuum and dried in a vacuum oven for 3 h to afford the desired material as a white solid (674 mg – slighly contaminated with residual DMF). *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.22 (1H, s), 1.74 - 1.92 (1H, m), 2.11 - 2.24 (3H, m), 2.25 - 2.33 (1H, m), 3.27 (3H, s), 3.49 (3H, s), 4.07 - 4.15 (1H, m), 5.27 - 5.53 (1H, m), 7.74 (1H, dd), 7.98 (1H, dd), 8.36 (1H, s), 8.91 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 376.

Intermediate C2: 8-Bromo-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3H-imidazo[4,5-c]quinolin-2-one



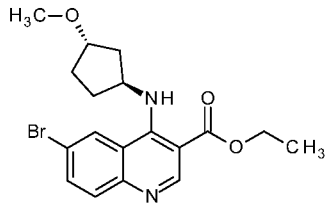
Diphenyl phosphoryl azide (1.075 ml, 4.99 mmol) was added to a mixture of 6-bromo-4-[[(1*S*,3*S*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylic acid (1.46 g, 4.16 mmol) and triethylamine (1.738 mL, 12.47 mmol) in DMF (9 mL) under nitrogen and the reaction heated at 60 °C for 4 h. The reaction was cooled to ambient temperature, the solid filtered under vacuum and washed with water. The solid was dried in a vacuum oven overnight to afford the desired material. An additional crop of material was isolated by repeating the filtration step and combined with the previous crop (1.15 g, 79 %). *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.56 - 1.82 (1H, m), 1.98 (1H, t), 2.08 - 2.31 (3H, m), 2.46 (1H, s), 4.43 (1H, s), 4.78 (1H, d), 5.26 - 5.64 (1H, m), 7.73 (1H, dd), 7.96 (1H, dd), 8.35 (1H, s), 8.67 (1H, s), 11.62 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 348.

Intermediate C3: 6-Bromo-4-[[(1*S*,3*S*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylic acid



NaOH (2M) (13.98 mL, 27.95 mmol) was added to a mixture of ethyl 6-bromo-4-[[(1*S*,3*S*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylate (2.65 g, 6.99 mmol) in THF (15 mL) and the reaction heated at 60°C for 5 h. The reaction was cooled to ambient temperature and the organic solvent removed under reduced pressure. The aqueous residue was adjusted to pH7 using hydrochloric acid (2M) and the solid was filtered under vacuum and dried in a vacuum oven for 24 h to afford, the desired material as a grey solid (1.46 g). *Mass Spectrum:* m/z (ES+)[M+H]+ = 351.

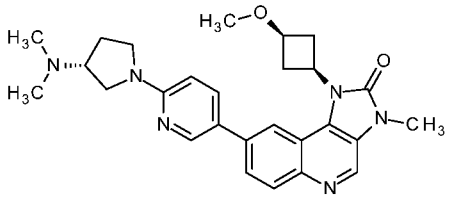
Intermediate C4: Ethyl 6-bromo-4-[[(1*S*,3*S*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylate



Triethylamine (3.90 mL, 27.98 mmol) was added to (1*S*,3*S*)-3-aminocyclopentanol hydrocloride salt (1g, 7.27 mmol) in acetonitrile (15.6 mL) and stirred for 5 minutes. ethyl 6-bromo-4-chloroquinoline-3-carboxylate (2.2 g, 6.99 mmol) was added and the reaction mixture was heated at 100 °C for 2 h. The solid was isolated by filtration, dissolved in DCM and washed with water. The filtrate was concentrated to dryness and the residue disolved in DCM (25 mL) and washed with water (25 mL). The organics were combined and dried over a phase separating cartridge and the solvent was removed under reduced pressure to afford the desired material as an orange solid (2.65 g) and used directly without further purification. *Mass Spectrum:* m/z (ES+)[M+H]+ = 379.

Example 6

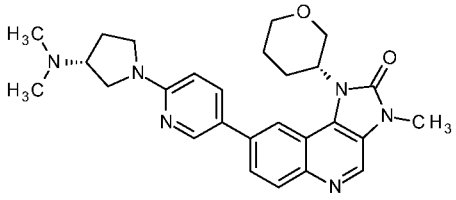
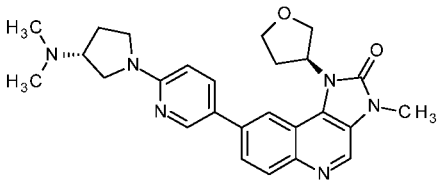
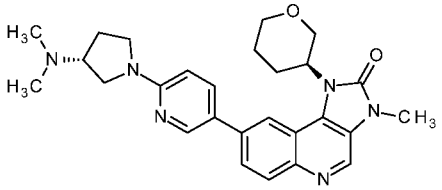
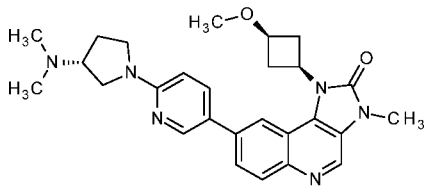
8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one

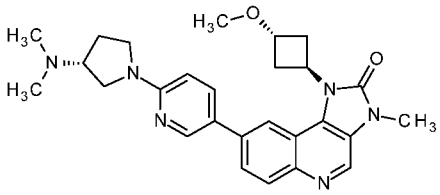
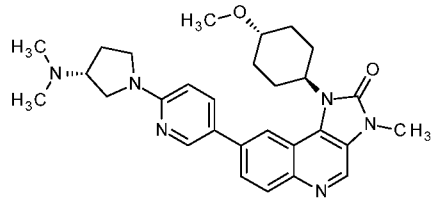
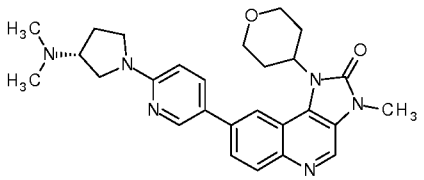
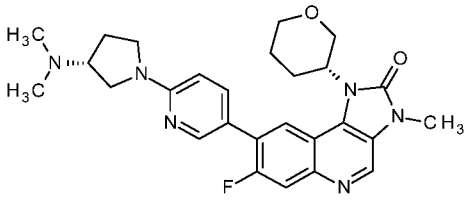
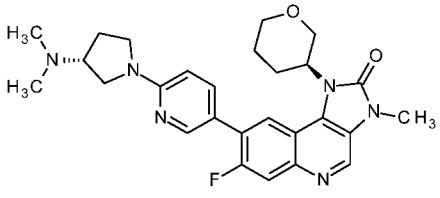


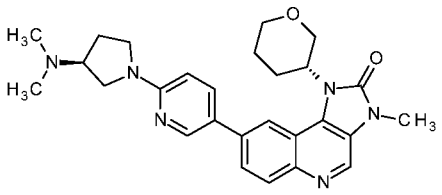
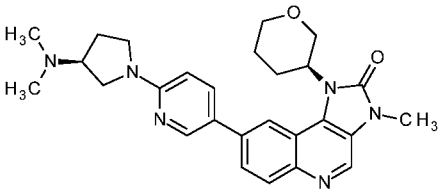
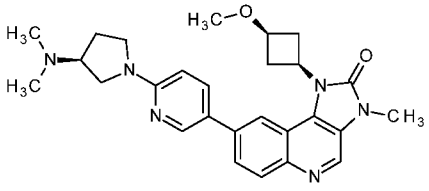
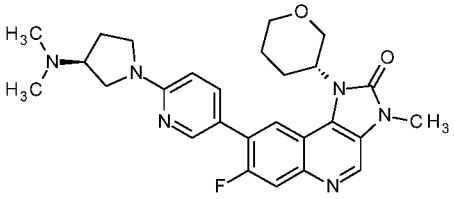
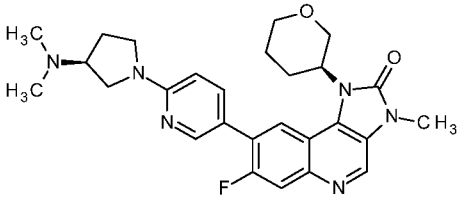
A mixture of DIPEA (0.159 mL, 0.91 mmol), 8-(6-fluoro-3-pyridyl)-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one (120 mg, 0.30 mmol) and (R)-*N*,*N*-dimethylpyrrolidin-3-amine hydrochloride (68.4 mg, 0.45 mmol) in DMSO (2 mL) was stirred at 150°C for 12 h then allowed to cool to ambient temperature. The reaction mixture was diluted with EtOAc (50 mL), washed with water (25 mL), brine (25 mL) and the organic layer dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% ammonia) and MeCN as eluents, to afford the desired material as a

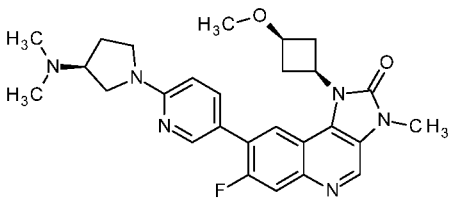
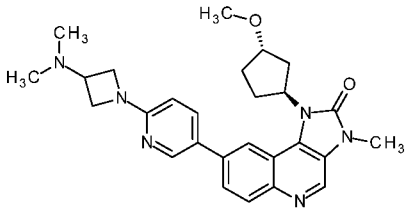
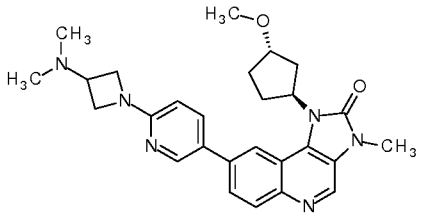
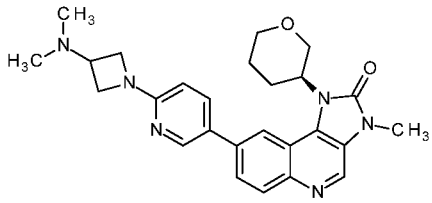
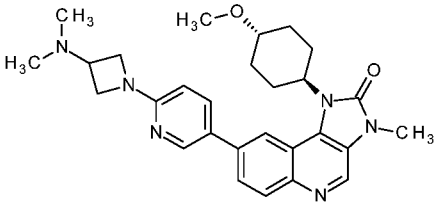
yellow solid (77 mg, 51.8 %). *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.87-1.93 (1H, m),2.19-2.26 (7H, m), 2.74-3.02(5H, m), 3.18-3.24 (4H, m),3.33-3.43 (1H,m), 3.47 (3H,s),3.63-3.86 (3H, m),4.99-5.05 (1H, t),6.60-6.93 (1H, d), 7.82-7.84 (2H, d), 8.23-8.26 (1H, d), 8.43 (1H, s), 8.85-8.86 (1H,d). *Mass Spectrum:* m/z (ES+)[M+H]+ = 491.

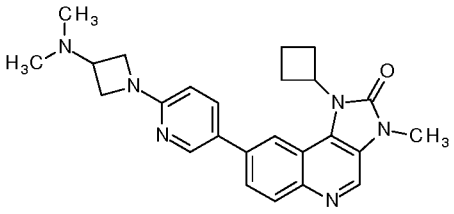
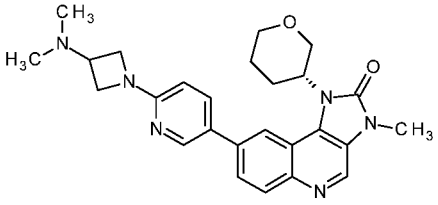
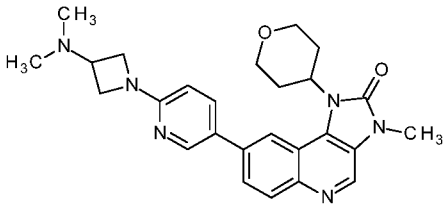
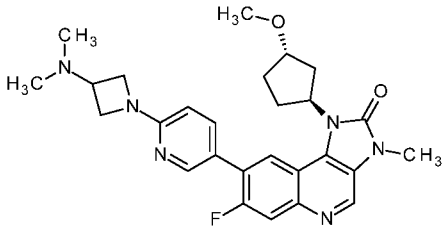
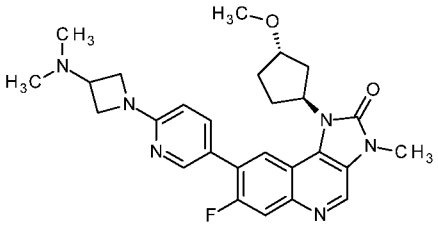
The following compounds were prepared in an analogous fashion from the appropriate amine and fluoropyridyl intermediate, purified by appropriate chromatographic techniques and isolated as either the free base, formic acid salt or methanesulfonic acid salt.

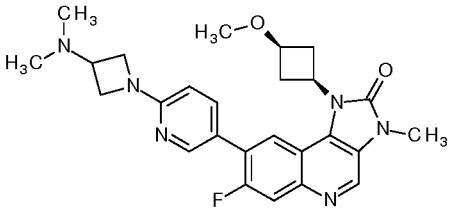
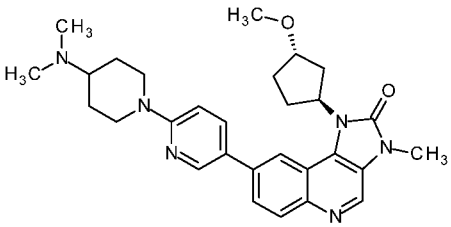
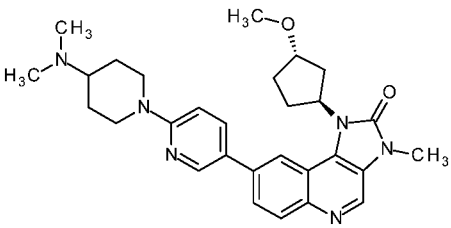
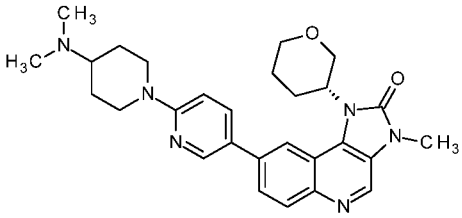
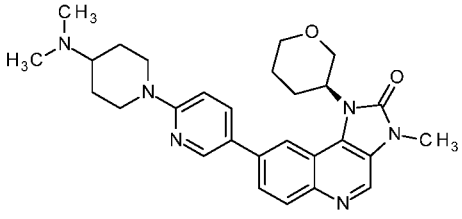
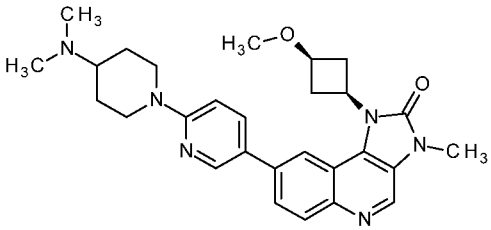
Example	Structure	Name
7*		8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
8**		8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydrofuran-3-yl]imidazo[4,5-c]quinolin-2-one
9*		8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
10*		8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one

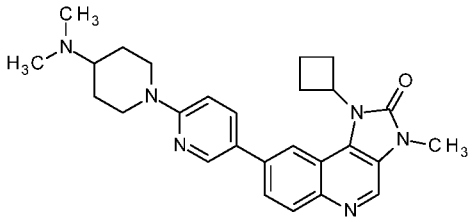
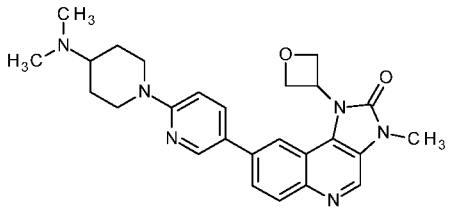
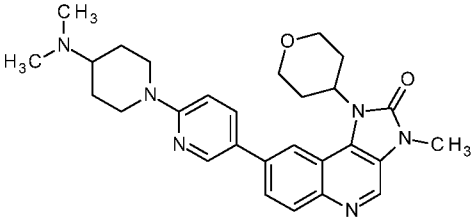
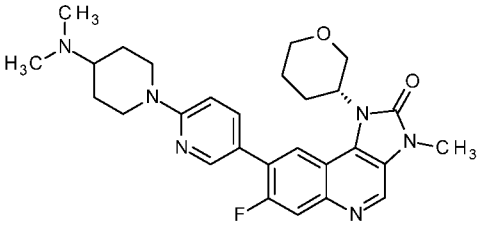
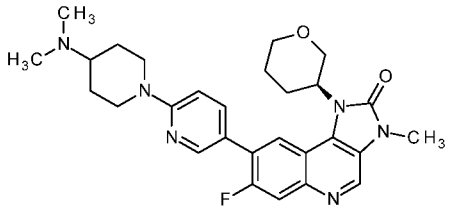
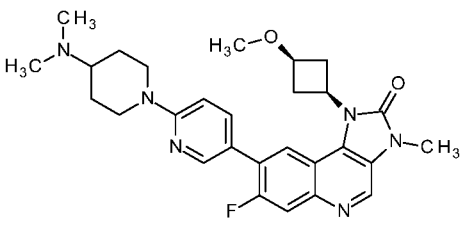
Example	Structure	Name
11* **		8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*trans*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one
12** **		8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*trans*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one
13*		8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one
14*		8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
15*		8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one

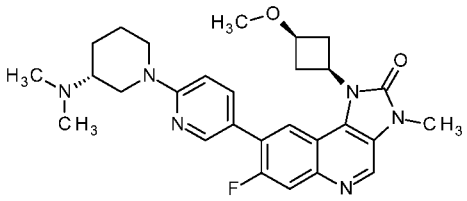
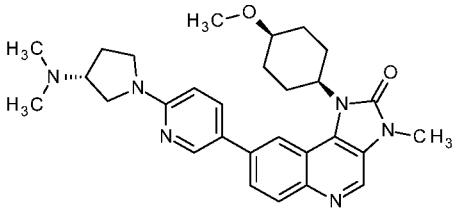
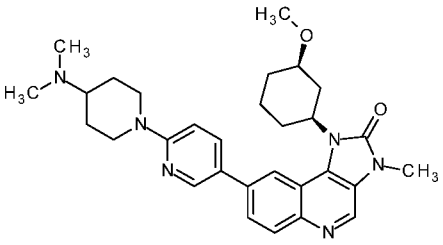
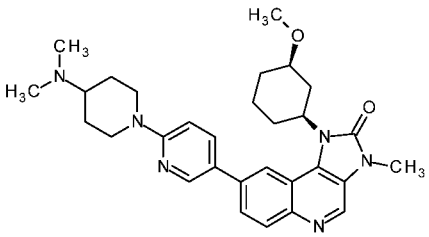
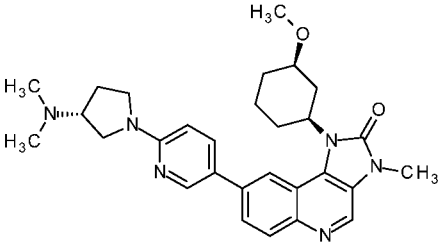
Example	Structure	Name
16*		8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
17*		8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
18*		8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one
19*		8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
20*		8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one

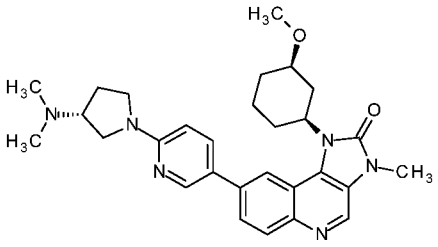
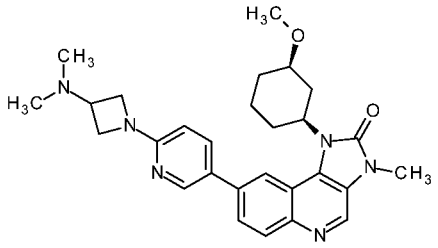
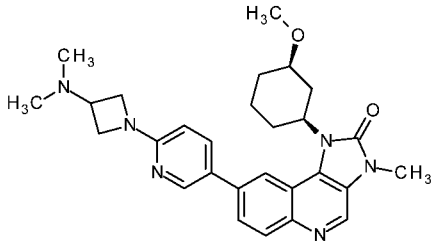
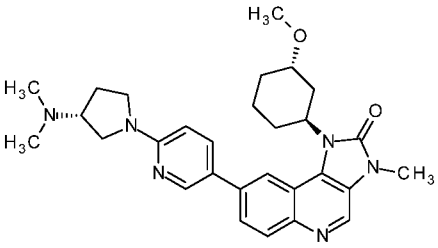
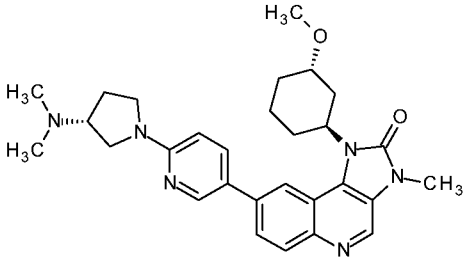
Example	Structure	Name
21*		8-[6-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one
22***		8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[*trans*-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 1
23***		8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[*trans*-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 2
24***		8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
25****		8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-(*trans*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one

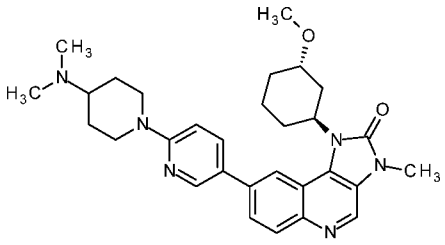
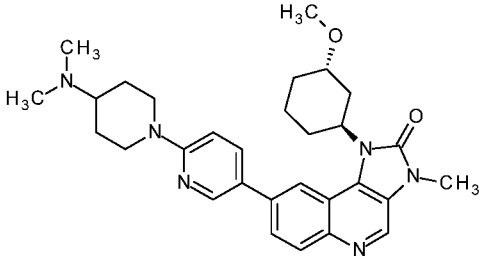
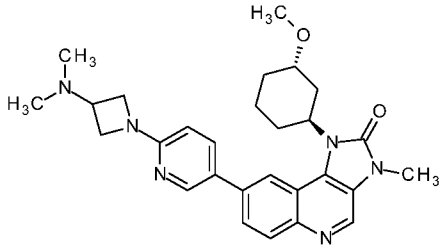
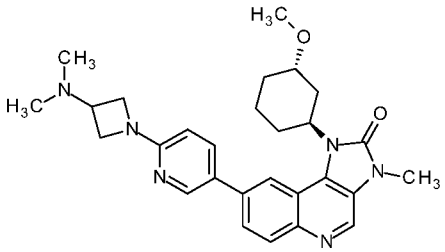
Example	Structure	Name
26* **		1-cyclobutyl-8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-imidazo[4,5-c]quinolin-2-one
27** **		8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
28*** **		8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one
29** **		8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-7-fluoro-1-[*trans*-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 2
30** **		8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-7-fluoro-1-[*trans*-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 1

Example	Structure	Name
31*		8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one
32*		8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-[*trans*-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 2
33*		8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-[*trans*-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 1
34*		8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
35*		8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
36*		8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one

Example	Structure	Name
37**		1-cyclobutyl-8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-imidazo[4,5-c]quinolin-2-one
38*		8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-(oxetan-3-yl)imidazo[4,5-c]quinolin-2-one
39*		8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one
40*		8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
41*		8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
42*		8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one

Example	Structure	Name
43*		8-[6-[(3*R*)-3-(dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one
44***		8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*cis*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one
45***		8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-[(*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 1
46***		8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-[*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 2
47***		8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 1

Example	Structure	Name
48***		8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 2
49***		8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 1
50***		8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 2
51****		8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[*trans*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 1
52****		8-[6-[(3*R*)-3-(dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[*trans*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 2

Example	Structure	Name
53****		8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-[*trans*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 1
54****		8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-1-[*trans*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 2
55****		8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[*trans*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 2
56****		8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[*trans*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 1

* The reaction was performed in DMSO with an excess (2 – 5 equivalents) of DIPEA present and heated between 130 – 150°C for 2 – 16 h.

** The reaction was performed in NMP and heated at 130°C for 0.5 – 3 h.

*** The reaction was performed in MeCN and heated at 150°C for 4 h.

**** The reaction was performed in DMF with an excess of K_2CO_3 present and heated between 80 – 100°C for 16 h.

***** The reaction was performed in MeCN with an excess (1 – 5 equivalents) of Et_3N present and heated at 80°C for 3 - 16 h.

Examples 22 & 23 were separated from a racemic mixture by preparative chiral HPLC, eluting isocratically with 30% isopropyl alcohol (modified with 0.1% diethylamine) in hexane as eluent, to afford **Example 22** as the first eluting product and **Example 23** as the second eluting product.

Examples 29 & 30 were separated from a racemic mixture by preparative chiral HPLC, eluting isocratically with 42% ethanol (modified with 0.1% diethylamine) in hexane as eluent, to afford **Example 30** as the first eluting product and **Example 29** as the second eluting product.

Examples 32 & 33 were separated from a racemic mixture by preparative chiral HPLC, eluting isocratically with 5% methanol (modified with 0.1% triethylamine) in acetonitrile as eluent, to afford **Example 33** as the first eluting product and **Example 32** as the second eluting product.

Examples 46, 48 and **50** were derived from **Intermediate S0**

Examples 45, 47 and **49** were derived from **Intermediate T0**

Examples 51 & 52 were separated from a racemic mixture by preparative chiral-HPLC, eluting isocratically with 95% methyl tert-butyl ether in MeOH (modified with diethylamine) as eluent, to afford **Example 51** as the first eluting product and **Example 52** as the second eluting product.

Examples 53 & 54 were separated from a racemic mixture by preparative chiral-HPLC, eluting isocratically with 85% hexane in EtOH (modified with diethylamine) as eluent, to afford **Example 54** as the first eluting product and **Example 53** as the second eluting product.

Examples 55 & 56 were separated from a racemic mixture by preparative chiral-HPLC, eluting isocratically with 90% methyl tert-butyl ether in MeOH (modified with diethylamine) as eluent, to afford **Example 56** as the first eluting product and **Example 55** as the second eluting product.

Example 7: (Formic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.81-1.87 (3H, m), 2.17-2.24 (8H, m), 2.63-2.71 (1H, m), 2.82-2.88 (1H, m), 3.16-3.22 (1H, m), 3.37-3.42 (2H, m), 3.48 (3H, s), 3.63-3.67 (1H, m), 3.73-3.79 (1H, m), 3.95 (1H, d), 4.12-4.26 (2H, m), 4.92-4.99 (1H, m), 6.65 (1H, d), 7.89-7.97 (2H, m), 8.09 (1H, d), 8.16 (1H, s), 8.27 (1H, d), 8.57 (1H, d), 8.83 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 473.

Example 8: *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 2.15 - 2.3 (1H, m), 2.32 (3H, s), 2.35 - 2.45 (1H, m), 2.44 - 2.49 (1H, m), 2.51 - 2.57 (1H, m), 2.89 (6H, s), 3.43 - 3.52 (1H, m), 3.54 (3H, s), 3.64 (1H, dd), 3.67 - 3.82 (1H, m), 3.85 - 3.99 (2H, m), 3.98 - 4.09 (1H, m), 4.1 - 4.22 (2H, m), 4.27 (1H, td), 5.78 - 5.89 (1H, m), 6.72 (1H, d), 7.95 (1H, dd), 8.04 - 8.22 (2H, m), 8.54 (1H, d), 8.68 (1H, d), 8.89 (1H, s), 9.86 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 459.

Example 9: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.79-1.86 (3H, m), 2.14-2.22 (8H, m), 2.65-2.81 (2H, m), 3.15-3.21 (1H, m), 3.37-3.44 (2H, m), 3.48 (3H, s), 3.65-3.76 (2H, m), 3.94 (1H, d), 4.15-4.21 (2H, m), 4.91-4.99 (1H, m), 6.65 (1H, d), 7.89-7.97 (2H, m), 8.09 (1H, d), 8.27 (1H, s), 8.57 (1H, d), 8.83 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 473.

Example 10: (Formic acid salt) *NMR Spectrum:* ^{1}H NMR (400MHz, D_2O) δ 2.33-2.60 (5H, m), 2.64-2.77 (1H, m), 2.94-3.09 (6H, m), 3.10-3.19 (6H, m), 3.36-3.42 (1H, m), 3.54-3.66 (3H, m), 3.83-4.05 (3H, m), 6.33-6.35 (1H, m), 6.81-6.82 (2H, m), 7.07-7.17 (2H, m), 7.52 (1H, s), 8.12 (1H, s), 8.35 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 473.

Example 11: (Free base) *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.82 (1H, dd), 2.09 - 2.3 (7H, m), 2.56 (2H, ddd), 2.71 - 2.88 (1H, m), 3.11 - 3.27 (6H, m), 3.33 - 3.45 (1H, m), 3.48 (3H, s), 3.63 (1H, d), 3.74 (1H, dd), 4.11 - 4.33 (1H, m), 5.54 (1H, s), 6.61

(1H, d), 7.87 (1H, dd), 7.95 (1H, dd), 8.04 (1H, d), 8.18 (1H, d), 8.49 - 8.64 (1H, m), 8.81 (1H, s). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 2.16 - 2.29 (1H, m), 2.31 (3H, s), 2.42 - 2.47 (1H, m), 2.56 (2H, ddd), 2.88 (6H, s), 3.18 - 3.26 (5H, m), 3.41 - 3.54 (4H, m), 3.63 (1H, dd), 3.7 - 3.82 (1H, m), 3.94 (1H, dd), 4.01 (1H, q), 4.22 (1H, tt), 5.48 - 5.64 (1H, m), 6.73 (1H, d), 7.91 (1H, dd), 8 - 8.15 (2H, m), 8.22 (1H, d), 8.64 (1H, d), 8.85 (1H, s), 9.85 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 473.

Example 12: (Free base) *NMR Spectrum:* ^{1}H NMR (400MHz, $CDCl_3$) δ 1.43 - 1.52 (2H, m), 2.13 (3H, d), 2.36 (3H, d), 2.47 (6H, s), 2.72 - 2.80 (2H, m), 3.03 - 3.08 (1H, m), 3.38 - 3.43 (1H, m), 3.45 (3H, s), 3.46 - 3.57 (2H, m), 3.59 (3H, s), 3.78 (1H, t), 3.94 (1H, t), 4.85 - 4.90 (1H, m), 6.55 (1H, d), 7.77 - 7.86 (2H, m), 8.17 - 8.26 (2H, m), 8.55 (1H, d), 8.68 (1H, s). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.36 - 1.58 (2H, m), 2.15 (2H, d), 2.25 - 2.39 (3H, m), 2.60 - 2.77 (6H, m), 2.99 (6H, s), 3.35 - 3.48 (4H, m), 3.55 - 3.68 (4H, m), 3.68 - 3.79 (1H, m), 3.79 - 3.91 (1H, m), 3.97 - 4.14 (2H, m), 4.93 - 5.04 (1H, m), 6.80 (1H, d), 7.94 (1H, dd), 8.06 (1H, dd), 8.16 (1H, d), 8.37 (1H, s), 8.56 (1H, d), 8.79 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 501.

Example 13: *NMR Spectrum:* ^{1}H NMR (300MHz, $CDCl_3$) δ 1.93-2.01 (2H, m), 2.45-3.11 (10H, m), 3.51-3.71 (7H, m), 3.72-3.83 (1H, m), 3.93-4.15(2H, m), 4.21-4.29 (2H, m), 5.01-5.18 (1H, m), 6.50-6.59(1H, m), 7.77-7.89 (2H, m), 8.10-8.21(1H, m), 8.35 (1H, s), 8.55-8.59 (1H, m), 8.70 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 473.

Example 14: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.7-1.9 (3H, m), 2.13 - 2.37 (8H, m), 2.62 - 2.72 (2H, m), 3.1-3.3 (1H, m), 3.35-3.55 (5H, m), 3.68 (1H, s), 3.91 (1H, s), 4.07 - 4.26 (3H, m), 4.90 (1H, s), 6.67 (1H, d), 7.73 - 8.04 (2H, m), 8.20 (1H, d), 8.44 (1H, s), 8.88 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 491.

Example 15: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.73-1.87 (3H, m), 2.11-2.23 (8H, m), 2.64-2.69 (1H, m), 2.79-2.83 (1H, m), 3.15-3.21 (1H, m), 3.37-3.44 (2H, m), 3.47 (3H, s), 3.63-3.79 (2H, m), 3.91 (1H, d), 4.09-4.22 (2H, m), 4.85-4.93 (1H, m), 6.65

(1H, d), 7.83-7.90 (2H, m), 8.19 (1H, d), 8.43 (1H, s), 8.89 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 491.

Example 16: (Formic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.79-1.88 (3H, m), 2.13-2.26 (8H, m), 2.62-2.76 (1H, m), 2.82-2.87 (1H, m), 3.17-3.23 (1H, m), 3.37-3.45 (2H, m), 3.48 (3H, s), 3.62-3.79 (2H, m), 3.95 (1H, d), 4.15-4.25 (2H, m), 4.91-4.99 (1H, m), 6.64 (1H, d), 7.88-7.97 (2H, m), 8.09 (1H, d), 8.17 (1H, s), 8.26 (1H, s), 8.56 (1H, d), 8.83 (1H, d). *Mass Spectrum:* m/z (ES+)[M+H]+ = 473.

Example 17: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.73-1.93 (3H, m), 2.10 – 2.30 (2H, m), 2.30 (6H, s), 2.60-2.80 (1H, m), 2.80-3.00 (1H, m), 3.20-3.50 (3H, m), 3.50 (3H, s), 3.60 – 3.80 (2H, m), 3.90-4.00 (1H, m), 4.10-4.40 (2H, m), 4.95 (1H, m), 6.64 (1H, d), 7.85-8.00 (2H, m), 8.10 (1H, d), 8.25 (1H, d), 8.57 (1H, d), 8.83 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 473.

Example 18: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.80-1.95 (1H, m), 2.22-2.50 (7H, m), 2.81-2.86 (2H, m), 2.96-3.02 (3H, m), 3.21 (3H, s), 3.32 (1H, s), 3.39-3.43 (1H, m), 3.49 (3H, s), 3.67-3.79 (1H, m), 3.82-3.89 (2H, m), 5.08-5.11 (1H, m), 6.63-6.65 (1H, m), 7.88-7.91 (1H, m), 8.02-8.09 (2H, m), 8.35-8.35 (1H, m), 8.64-8.65 (1H, m), 8.84 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 473.

Example 19: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.69-1.90 (3H, m), 2.09-2.23(8H, m), 2.58-2.85 (2H, m), 3.10-3.21 (1H, t), 3.35-3.45 (2H, m), 3.48 (3H, s), 3.60-3.80 (2H, m), 3.88-3.95 (1H, d), 4.07-4.21 (2H, m),4.80-4.95 (1H, m), 6.60-6.67 (1H, d), 7.8-7.91 (2H, m), 8.12-8.22 (1H, d), 8.42 (1H, s), 8.87 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 491.

Example 20: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.70-1.95 (3H, m), 2.05-2.25 (2H, m), 2.30 (6H, s), 2.55-2.75 (1H, m), 2.75-2.92 (1H, m), 3.15-3.25 (1H, m), 3.30-3.42 (2H, m), 3.50 (3H, s), 3.70-3.80 (1H, m), 3.80-3.90 (1H, m), 3.85-3.95 (1H, m), 4.05 - 4.25 (2H, m), 4.82-4.98 (1H, m), 6.64 (1H, d), 7.80-7.92 (2H, m), 8.18 (1H, d), 8.43 (1H, s), 8.88(1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 491.

Example 21: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.87-1.93 (1H, m), 2.19-2.28 (7H, m), 2.77-2.82 (2H, t), 2.90-3.02 (3H, m), 3.18-3.25 (4H, m), 3.32-3.48 (1H, m), 3.63-3.69 (3H, m), 3.74-3.86 (3H, m), 5.03 (1H, s), 6.61-6.64 (1H, d), 7.83-7.85 (2H, t), 8.25 (1H, s), 8.43 (1H, s), 8.86-8.87 (1H, d). *Mass Spectrum:* m/z (ES+)[M+H]+ = 491.

Example 22: (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.90 - 2.04 (1H, m), 2.19 - 2.41 (3H, m), 2.69 (1H, m), 2.69 - 3.65 (4H, m), 2.94 (6H, s), 3.38 (3H, s), 3.59 (3H, s), 4.11 - 4.30 (4H, m), 4.37 - 4.51 (2H, m), 5.65 (1H, bs), 6.71 (1H, d), 7.93 (1H, d), 8.01 - 8.18 (2H, m), 8.39 (1H, s), 8.52 (1H, s), 8.81 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 473.

Example 23: (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.87 - 2.03 (1H, m), 2.30 (3H, m), 2.45 - 2.62 (1H, m), 2.64- 2.82 (4H, m), 2.94 (6H, s), 3.38 (3H, s), 3.59 (3H, s), 4.11 - 4.31 (4H, m), 4.37 - 4.50 (2H, m), 5.50 - 5.78 (1H, bs), 6.71 (1H, d), 7.93 (1H, d), 8.01 - 8.21 (2H, m), 8.39 (1H, s), 8.52 (1H, s), 8.80 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 473.

Example 24: (Free base) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.84 - 2.01 (2H, m), 2.16 - 2.28 (4H, m), 2.28 - 2.43 (3H, s), 2.71 - 2.89 (1H, m), 3.36 -3.48 (1H, m), 3.48 -3.68 (4H, s), 3.89 - 4.07 (3H, m), 4.13 - 4.27 (3H, m), 4.30 - 4.48 (1H, t), 4.98 - 5.16 (1H, m), 6.61 (1H, d), 7.94 (2H, d), 8.12 (1H, d), 8.34 (1H, d), 8.46 (1H, s), 8.74 (1H, s). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.7 - 1.89 (2H, m), 2.08 - 2.2 (1H, m), 2.28 (3H, s), 2.61 - 2.75 (1H, m), 2.80 (6H, s), 3.40 (1H, td), 3.48 (3H, s), 3.93 (1H, d), 4.08 - 4.26 (5H, m), 4.24 - 4.33 (2H, m), 4.9 - 5.02 (1H, m), 6.68 (1H, d), 7.92 (1H, dd), 8.06 (1H, dd), 8.12 (1H, d), 8.29 (1H, d), 8.61 (1H, dd), 8.87 (1H, s), 10.22 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 459.

Example 25: (Free base) *NMR Spectrum:* ^{1}H NMR (400MHz, $CDCl_3$) δ 1.38 - 1.53 (2H, m), 2.12 (2H, d), 2.34 (6H, s), 2.37 (2H, s), 2.68 - 2.83 (2H, m), 3.35 - 3.43 (2H, m), 3.45 (3H, s), 3.59 (3H, s), 4.03 (2H, t), 4.21 (2H, t), 4.86 (1H, s), 6.48 (1H, d), 7.76 - 7.85 (2H, m), 8.18 - 8.25 (2H, m), 8.53 (1H, d), 8.69 (1H, s) (Methanesulfonic acid salt) *NMR*

Spectrum: ^{1}H NMR (300MHz, MeOH-d4) δ 1.36 - 1.55 (2H, m), 2.14 (2H, d), 2.34 (2H, d), 2.60 - 2.79 (5H, m), 2.90 (6H, s), 3.32 - 3.46 (4H, m), 3.58 (3H, s), 4.12 - 4.28 (3H, m), 4.36 - 4.49 (2H, m), 4.93 - 5.03 (1H, m), 6.74 (1H, d), 7.94 (1H, dd), 8.08 (1H, dd), 8.16 (1H, d), 8.36 (1H, s), 8.54 (1H, d), 8.81 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 487.

Example 26: (Free base) *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.79 – 2.00 (2H, m), 2.13 (6H, s), 2.40 - 2.48 (2H, m), 3.07 (2H, pd), 3.22 (1H, ddd), 3.48 (3H, s), 3.78 (2H, dd), 3.95 - 4.18 (2H, m), 5.47 (1H, q), 6.54 (1H, dd), 7.87 (1H, dd), 8.00 (1H, dd), 8.06 (1H, d), 8.33 (1H, d), 8.58 (1H, dd), 8.82 (1H, s). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.79 - 2.07 (2H, m), 2.29 (3H, s), 2.40 - 2.47 (2H, m), 2.78 (6H, s), 3.07 (2H, pd), 3.49 (3H, s), 4.14 (3H, d), 4.2 - 4.38 (2H, m), 5.49 (1H, s), 6.52 - 6.85 (1H, m), 7.90 (1H, dd), 8.03 - 8.19 (2H, m), 8.35 (1H, d), 8.65 (1H, dd), 8.85 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 429.

Example 27: (Formic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, D_2O) δ 1.31-1.60 (2H, m), 1.60-1.75 (1H, m), 1.75-2.11 (1H, m), 2.68 (6H, s), 3.15 (3H, s), 3.20-3.41 (1H, m), 3.45-3.68 (1H, m), 3.85-3.92 (2H, m), 3.92-4.01 (4H, m), 4.02-4.14 (2H, m), 6.12 (1H, d), 6.78-7.05 (3H, m), 7.16 (1H, d), 7.40 (1H, s), 8.11 (1H, s) 8.33 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 459.

Example 28: *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.90 - 2.10 (2 H, m), 2.28 (6H, s), 2.81 - 3.02 (2H, m), 3.32 - 3.43 (1H, m), 3.57 - 3.76 (5H, m), 3.85 - 4.06 (2H, m), 4.14 - 4.27 (4H, m), 5.12 - 5.30 (1H, m), 6.64 (1H, d), 7.94 (1H, d), 8.05 (1H, d), 8.15 (1H, d), 8.46 - 8.55 (2H, m), 8.80 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 459.

Example 29: *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.90 - 2.02 (1H, m), 2.25 - 2.40 (9H, m),2.49 - 2.60 (1H, m), 2.57 - 2.73 (1H, m), 3.33 - 3.35 (4H, m), 3.59 (3H, s), 3.94 (2H, dd), 4.15 - 4.24 (3H, m), 5.60 (1H, t), 6.62 (1H, d), 7.80 (1H, d), 7.90 (1H, d), 8.30 - 8.36 (2H, m), 8.81 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 491.

Example 30: *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.92 - 1.98 (1H, m), 2.24 - 2.33 (3H, m), 2.40 (6H, s), 2.48 - 2.60 (1H, m), 2.62 - 2.67 (1H, m), 3.35 (3H, s), 3.49 -

3.53 (1H, m), 3.59 (3H, s), 3.99 (2H, dd), 4.15 - 4.17 (1H, m), 4.24 (1H, t), 5.55 - 5.63 (1H, m), 6.62 (1H, dd), 7.83 (1H, d), 7.92 (1H, dt), 8.33(1H, d), 8.37 (1H, t), 8.81 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 491.

Example 31: *NMR Spectrum:* ^{1}H NMR (400MHz, $CDCl_3$) δ 2.33 (6H, s), 2.85-3.00 (2H, m), 3.04-3.22 (2H, m), 3.29 (3H, s), 3.33-3.50 (1H, m), 3.57 (3H, s), 3.75-4.00 (1H, m), 4.00-4.15 (2H, m), 4.15-4.30 (2H, m), 4.71-5.00 (1H, m), 6.35-6.50 (1H, d), 7.60-7.91 (2H, m), 8.12-8.30 (1H, m), 8.43 (1H, s), 8.68 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 477.

Example 32: *NMR Spectrum:* ^{1}H NMR (400MHz, $CDCl_3$) δ 1.59 (2H, td), 1.88 - 2.09 (4H, m), 2.17 - 2.31 (2H, m), 2.34 (6H, s), 2.48 - 2.63 (1H, m), 2.73 (1H, ddd), 2.93 (3H, td), 3.37 (3H, s), 3.58 (3H, s), 4.19 (1H, dd), 4.44 (2H, d), 5.49 - 5.66 (1H, m), 6.80 (1H, d), 7.81 (2H, td), 8.18 (1H, d), 8.30 (1H, d), 8.56 (1H, d), 8.66 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 501.

Example 33: *NMR Spectrum:* ^{1}H NMR (400MHz, $CDCl_3$) δ 1.58 (2H, qd), 1.89 - 2.04 (4H, m), 2.34 (8H, s), 2.51 (1H, dddd), 2.73 (1H, ddd), 2.93 (3H, td), 3.37 (3H, s), 3.58 (3H, s), 4.19 (1H, dd), 4.44 (2H, d), 5.5 - 5.68 (1H, m), 6.80 (1H, d), 7.81 (2H, td), 8.18 (1H, d), 8.30 (1H, d), 8.56 (1H, d), 8.66 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 501.

Example 34: (Formic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.35-1.55 (2H, m), 1.85-2.00 (4H, m), 2.10-2.20 (1H, m), 2.31 (6H, s), 2.50-2.60 (1H, m), 2.60-2.80 (1H, m), 2.89 (2H, t), 3.35-3.45 (1H, m), 3.45 (3H, s), 3.90-3.98 (1H, m), 4.10-4.30 (2H, m), 4.40-4.50 (2H, m), 4.88-5.2 (1H, m), 7.01 (1H, d), 7.85-8.00 (2H, m), 8.10 (1H, d), 8.21 (1H, s), 8.26 (1H, s), 8.60 (1H, s), 8.83 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 487.

Example 35: (Formic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.35-1.55 (2H, m), 1.85-2.00 (4H, m), 2.10-2.20 (1H, m), 2.31 (6H, s), 2.50-2.80 (2H, m), 2.89 (2H, t), 3.35-3.45 (1H, m), 3.45 (3H, s), 3.90-3.98 (1H, m), 4.10-4.30 (2H, m), 4.40-4.50

(2H, m), 4.88-5.2 (1H, m), 7.01 (1H, d), 7.85-8.00 (2H, m), 8.10 (1H, d), 8.24 (1H, s), 8.28 (1H, s), 8.60 (1H, s), 8.83 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 487.

Example 36: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.34-1.43 (2H, m), 1.82-1.86 (2H, m), 2.20 (6H, s), 2.33-2.37 (1H, m), 2.77-3.05 (6H, m), 3.23 (3H, s), 3.49 (3H, s), 3.84-3.89 (1H, m), 4.38-4.42 (2H, d), 5.08-5.14 (1H, t), 6.98-7.01 (1H, d), 7.87-8.08 (3H, m), 8.35-8.36 (1H, d), 8.64-8.65 (1H, d), 8.82 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 487

Example 37: (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (400MHz, $CDCl_3$) δ 1.46 - 1.63 (2H, m), 1.8 - 1.98 (2H, m), 2.01 (2H, s), 2.29 (3H, s), 2.34 - 2.39 (1H, m), 2.45 - 2.48 (1H, m), 2.52 - 2.54 (1H, m), 2.59 - 2.8 (6H, m), 2.90 (2H, t), 3.01 - 3.15 (2H, m), 3.50 (3H, s), 4.55 (2H, d), 5.50 (1H, p), 7.08 (1H, d), 7.91 (1H, dd), 8.06 (1H, dd), 8.09 (1H, d), 8.37 (1H, d), 8.66 (1H, d), 8.85 (1H, s), 9.36 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 457

Example 38: *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 1.38 (2H, qd), 1.84 (2H, d), 2.20 (6H, s), 2.36 (1H, ddd), 2.8 - 2.98 (2H, m), 3.54 (3H, s), 4.40 (2H, d), 5.01 - 5.13 (2H, m), 5.27 (2H, t), 6.19 (1H, p), 6.99 (1H, d), 7.96 (1H, dd), 8.04 (1H, dd), 8.11 (1H, d), 8.45 (1H, d), 8.67 (1H, d), 8.90 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 459

Example 39: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.29-1.45 (2H, m), 1.80-1.98 (4H, m), 2.15-2.25 (6H, m), 2.31-2.45 (1H, m), 2.67-2.78 (2H, m), 2.81-2.98 (2H, m), 3.51 (3H, s), 3.53-3.65 (2H, m), 3.98-4.15 (2H, m), 4.35-4.44 (2H, m), 5.04-5.21 (1H, m), 6.90-7.04 (1H, m), 7.89-7.98 (1H, m), 8.01-8.04 (1H, m), 8.04-8.15 (1H, m), 8.31-8.51 (1H, m), 8.61-8.70 (1H, m), 8.85 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 487.

Example 40: (Formic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.55-1.71 (2H, m), 1.88-1.96 (2H,m), 2.06-2.15 (2H, m), 2.19-2.30 (1H, m), 2.60 (6H,s), 2.72-3.06 (4H, m), 3.50-3.60 (4H, m), 3.98-4.05 (1H, d), 4.17-4.23 (1H,d), 4.32-4.42 (1H, t), 4.53-4.65 (2H, d), 4.95-5.17 (1H, m), 7.04-7.07 (1H, d), 7.81-7.85 (1H, d), 7.92-7.96 (1H,

d), 8.33 (1H, d), 8.46 (1H,s), 8.56 (1H, s), 8.81 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 505.

Example 41: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) 1.30-1.50 (2H, m), 1.70-1.90 (4H, m), 2.10-2.25 (1H, m), 2.19 (6H, s), 2.30-2.42 (1H, m), 2.60-2.75 (1H, m), 2.82-2.98 (2H, m), 3.30-3.40 (1H, m), 3.48 (3H, s), 3.85-3.95 (1H, m), 4.10-4.25 (2H, m), 4.35-4.50 (2H, m), 4.82-4.97 (1H, m), 7.00 (1H, d), 7.83-7.93 (2H, m), 8.20 (1H, d), 8.45 (1H, s), 8.86 (1H, s), *Mass Spectrum:* m/z (ES+)[M+H]+ = 505.

Example 42: *NMR Spectrum:* ^{1}H NMR (400MHz, DMSO-d6) δ 1.38 (2H, qd), 1.85 (2H, d), 2.20 (6H, s), 2.36 (1H, ddd), 2.73 - 2.84 (2H, m), 2.85 - 3.04 (4H, m), 3.19 (3H, s), 3.48 (3H, s), 3.83 (1H, p), 4.40 (2H, d), 5.03 (1H, p), 6.98 (1H, d), 7.78 - 7.89 (2H, m), 8.28 (1H, d), 8.45 (1H, s), 8.85 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 505.

Example 43: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.50-1.70 (1H, m), 1.70-2.00 (2H, m), 2.10-2.25 (1H, m), 2.70-3.05 (10H, m), 3.05-3.15 (1H, m), 3.18 (3H, s), 3.25-3.45 (2H, m), 3.48 (3H, s), 3.80-3.90 (1H, m), 4.00-4.15 (1H, m), 4.55 (1H, t), 4.90-5.10 (1H,m), 7.10 (1H, d), 7.78 (1H, d), 7.80-8.00 (1H, m), 8.35 (1H, d), 8.50 (1H, s), 8.85 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 505.

Example 44: (Free base) *NMR Spectrum:* ^{1}H NMR (300MHz, $CDCl_3$) δ 1.59 - 1.72 (2H, m), 1.78 (2H, d), 2.15 - 2.44 (3H, m), 2.45 - 2.51 (1H, m), 2.56 (6H, s), 2.84 (2H, bs), 3.17 – 3.40 (4H, m), 3.46 - 3.67 (6H, m), 3.71 - 3.85 (1H, m), 3.93 (1H, dd), 4.92 (1H, bs), 6.54 (1H, d), 7.78 (1H, dd), 7.85 - 7.95 (1H, m), 8.20 (1H, d), 8.53 (1H, s), 8.58 - 8.65 (1H, m), 8.70 (1H, s). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.57 - 1.82 (4H, m), 2.21 (2H, dd), 2.28 - 2.43 (1H, m), 2.62 - 2.93 (4H, m), 2.71 (3H, s), 3.00 (6H, s), 3.18 - 3.24 (2H, m), 3.49 - 3.65 (5H, m), 3.69 - 3.90 (2H, m), 3.96 - 4.13 (2H, m), 4.88-4.92 (1H, m), 6.76 (1H, d), 7.83 (1H, dd), 8.01 (1H, dd), 8.08 (1H, d),8.18-8.51 (1H, m), 8.52 (1H, d), 8.76 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 501.

Example 45: (Free base) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.25 - 1.40 (1H, m), 1.42 - 1.65 (3H, m), 1.97 - 2.07 (4H, m), 2.17 - 2.28 (1H, m), 2.37 (6H, s), 2.39 -

2.63 (4H, m), 2.85 - 3.01 (2H, m), 3.39 (3H, s),3.39-3.51 (1H, m), 3.56 (3H, s), 4.42 - 4.54 (2H, m), 4.86 - 4.93 (1H, m), 6.99 (1H, d), 7.87 (1H, dd), 7.93 (1H, dd), 8.10 (1H, d), 8.27 (1H, s), 8.49 (1H, d), 8.74 (1H, s). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) 1.22 - 1.37 (1H, m), 1.46 - 1.66 (1H, m), 1.67 - 1.87 (2H, m), 2.01 - 2.12 (2H, m), 2.17 - 2.29 (3H, m), 2.35 - 2.59 (3H, m), 2.71 (3H, s), 2.93 (6H, s), 2.94 - 3.12 (2H, m), 3.40 (3H, s), 3.42 - 3.58 (2H, m), 3.60 (3H, s), 4.66 (2H, d), 4.87 - 4.93 (1H, m), 7.10 (1H, d), 7.97 - 8.12 (2H, m), 8.17 (1H, d), 8.37 (1H, s), 8.56 (1H, d), 8.91 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 515.

Example 46: (Free base) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.30 (1H, m, 1.53 (3H, m), 2.04 (4H, dd), 2.22 (1H, d), 2.37 (6H, s), 2.38 - 2.35 (4H, m), 2.93 (2H, m), 3.39 (4H, m), 3.56 (3H, s), 4.43 - 4.54 (2H, d), 4.89 (1H, m), 6.99 (1H, d), 7.90 (2H, m), 8.10 (1H, d), 8.27 (1H, s), 8.49 (1H, s), 8.74 (1H, s). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) 1.25 - 1.40 (1H, m), 1.55 (1H, m), 1.76 (2H, m), 2.05 (2H, d), 2.16 - 2.26 (3H, m), 2.44 (3H, m), 2.71 (3H, s), 2.93 (6H, s),2.97 - 3.05 (2H, t), 3.49 (8H, m), 4.64 (2H, d), 4.90 (1H, m),7.06 (1H, d), 7.92 (1H, dd), 8.09 (1H, d),8.11 (1H, d), 8.28 (1H, s), 8.53 (1H, s), 8.77 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 515.

Example 47: (Free base) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.26 - 1.37 (1H, m), 1.47 - 1.67 (1H, m), 1.91 - 2.02 (2H, m), 2.02 - 2.12 (2H, m), 2.17 - 2.28 (1H, m), 2.29 - 2.39 (1H, m), 2.40 (6H, s), 2.44 - 2.51 (3H, m), 2.95 - 3.07 (1H, m), 3.44 (3H, s), 3.44-3.63 (2H, m), 3.63 (3H, s), 3.71 - 3.83 (1H, m), 3.83 - 3.93 (1H, m), 4.90 - 4.96 (1H, m), 6.71 (1H, d), 7.85 - 8.03 (2H, m), 8.13 (1H, dd), 8.31 (1H, s), 8.47 (1H, t), 8.72 - 8.80 (1H, m). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.27 - 1.38 (1H, m), 1.46 - 1.62 (1H, m), 2.01 - 2.12 (2H, m), 2.16 - 2.39 (2H, m), 2.36 - 2.53 (3H, m), 2.55 - 2.67 (1H, m), 2.71 (3H, s), 2.92 (6H, s), 3.39 (3H, s), 3.40 - 3.52 (1H, m), 3.54 - 3.59 (1H, m), 3.59 (3H, s), 3.62 - 3.75 (1H, m), 3.78 - 4.00 (2H, m), 3.99 - 4.11 (1H, m), 4.89 - 5.02 (1H, m), 6.79 (1H, d), 7.92 (1H, dd), 8.03 (1H, dd), 8.14 (1H, d), 8.33 (1H, s), 8.54 (1H, d), 8.79 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 501.

Example 48: (Free base) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.30 (1H, m), 1.44 - 1.65 (1H, m), 1.85 - 2.11 (3H, m), 2.33 (1H, m), 2.33 – 2.50 (9H, m), 22.95 (1H, m),

3.29 (1H, m), 3.33 (1H, d), 3.39 (3H, s), 3.40 - 3.52 (2H, m), 3.54 (3H, s), 3.66 - 3.77 (1H, m), 3.83 (1H, m), 4.85 (1H, s), 6.64 (1H, d), 7.86 (2H, m, 8.07 (1H, d), 8.22 (1H, s), 8.42 (1H, dd), 8.70 (1H, s). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) 1.31 (1H, m), 1.53 (1H, m), 1.99 - 2.11 (2H, m), 2.21 (1H, d), 2.26 - 2.53 (4H, m), 2.71 (4H, m), 3.03 (6H, s), 3.39 (4H, m), 3.59 (4H, m), 3.69 - 3.93 (2H, m), 4.02 - 4.18 (2H, m), 4.95 (1H, s), 6.80 (1H, d), 7.93 (1H, dd), 8.03 (1H, dd), 8.13 (1H, d), 8.32 (1H, s), 8.53 (1H, s), 8.80 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 501.

Example 49: (Free base) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.20 - 1.39 (1H, m), 1.44 - 1.64 (1H, m), 1.98 - 2.11 (2H, m), 2.15 - 2.27 (1H, m), 2.30 (6H, s), 2.35 - 2.51 (3H, m), 3.35-3.41 (1H, m), 3.38 (3H, s), 3.41 - 3.52 (1H, m), 3.56 (3H, bs), 3.94 (2H, dd), 4.20 (2H, t), 4.91 - 4.96 (1H, m), 6.60 (1H, d), 7.85 (1H, dd), 7.94 (1H, dd), 8.09 (1H, dd), 8.25 (1H, s), 8.43 (1H, s), 8.73 (1H, s). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) 1.26 - 1.40 (1H, m), 1.45 - 1.60 (1H, m), 1.99 - 2.11 (2H, m), 2.21 (1H, d), 2.45 - 2.53 (3H, m), 2.70 (3H, s), 2.94 (6H, s), 3.39 (3H, s), 3.41 - 3.53 (1H, m), 3.60 (3H, s), 4.21 - 4.28 (3H, m), 4.38 - 4.51 (2H, m), 4.93 - 4.99 (1H, m), 6.74 (1H, dd), 7.95 (1H, dd), 8.07 (1H, dd), 8.16 (1H, d), 8.35 (1H, s), 8.55 (1H, d), 8.83 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 487.

Example 50: (Free base) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.29 (1H, m), 1.43 - 1.60 (1H, m), 1.96 - 2.10 (2H, m), 2.21 (1H, d), 2.34 – 2.45 (9H, m), 3.31 – 3.50 (5H, m), 3.55 (3H, s), 3.97 (2H, m), 4.16 - 4.28 (2H, m), 4.89 (1H, m), 6.60 (1H, dd), 7.89 (2H, dd), 8.08 (1H, d), 8.20 - 8.27 (1H, d), 8.43 (1H, dd), 8.72 (1H, s). Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) 1.31 (1H, m), 1.44 - 1.60 (1H, m), 1.98 - 2.11 (2H, m), 2.21 (1H, d), 2.44 (3H, m), 2.69 (3H, s), 2.91 (6H, s), 3.39 (4H, m), 3.59 (3H, s), 4.12 - 4.29 (3H, m), 4.36 - 4.49 (2H, m), 4.96 (1H, m), 6.73 (1H, dd), 7.92 (1H, dd), 8.01 - 8.19 (2H, m), 8.33 (1H, s), 8.53 (1H, dd), 8.80 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 487.

Example 51: (Free base) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.49 (1H, s), 1.78 - 1.83 (1H, m), 1.89 (1H, d), 1.91 - 2.06 (2H, m), 2.15 (1H, d), 2.30 - 2.43 (9H, m), 2.50 - 2.61 (1H, m), 2.76 - 2.87 (1H, m), 2.94 - 3.07 (1H, m), 3.41 (3H, s), 3.46 - 3.56 (1H,

m), 3.58 (3H, s), 3.77 (1H, t), 3.81 - 3.92 (2H, m), 5.31 - 5.42 (1H, m), 6.70 (1H, d), 7.93 (1H, dd), 8.03 (1H, dd), 8.13 (1H, d), 8.56 (2H, dd), 8.75 (1H, s). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) 1.48 (1H, t), 1.76 - 1.91 (2H, m), 1.98 (1H, d), 2.13 (1H, d), 2.25 - 2.44 (2H, m), 2.46 - 2.58 (1H, m), 2.57 - 2.67 (1H, m), 2.71 (3H, s), 2.76 - 2.87 (1H, m), 3.02 (6H, s), 3.41 (3H, s), 3.57 (3H, s), 3.59 - 3.68 (1H, m), 3.69 - 3.93 (3H, m), 4.01 - 4.15 (2H, m), 5.27 - 5.42 (1H, m), 6.78 (1H, d), 7.95 (1H, dd), 8.07 (1H, dd), 8.13 (1H, d), 8.60 (2H, dd), 8.78 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 501.

Example 52: (Free base) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.50 (1H, t), 1.78 - 1.93 (2H, m), 1.91 - 2.08 (2H, m), 2.15 (1H, d), 2.31 – 2.40 (9H, m), 2.50 - 2.62 (1H, m), 2.81 – 2.85 (1H, m), 3.00 (1H, p), 3.41 (3H, s), 3.46 - 3.58 (1H, m), 3.58 (3H, s), 3.77 (1H, t), 3.81 - 3.93 (2H, m), 5.37 (1H, t), 6.70 (1H, d), 7.93 (1H, dd), 8.03 (1H, dd), 8.13 (1H, d), 8.56 (2H, dd), 8.75 (1H, s). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) 1.49 (1H, t), 1.76 - 1.91 (2H, m), 1.99 (1H, d), 2.13 (1H, d), 2.28 - 2.44 (2H, m), 2.47 - 2.60 (1H, m), 2.60 - 2.69 (1H, m), 2.71 (3H, s), 2.76 - 2.89 (1H, m), 3.02 (6H, s), 3.41 (3H, s), 3.58 (3H, s), 3.59 - 3.68 (1H, m), 3.69 - 3.94 (3H, m), 4.01 - 4.17 (2H, m), 5.28 - 5.43 (1H, m), 6.79 (1H, d), 7.97 (1H, dd), 8.08 (1H, dd), 8.14 (1H, d), 8.62 (2H, t), 8.80 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 501.

Example 53: (Free base) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.28 - 1.33 (1H, m), 1.47 - 1.61 (3H, m), 1.73 - 1.92 (2H, m), 2.02 (3H, t), 2.16 (1H, d), 2.30 - 2.42 (6H, m), 2.48 - 2.62 (2H, m), 2.81 - 2.86 (1H, m), 2.95 (2H, t), 3.44 (3H, s), 3.59 (3H, s), 3.84 (1H, s), 4.52 (2H, d), 5.36 (1H, t), 7.02 (1H, d), 7.94 (1H, dd), 8.03 (1H, dd), 8.13 (1H, d), 8.62 (2H, dd), 8.76 (1H, s). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) 1.41 - 1.56 (1H, m), 1.67 - 1.84 (4H, m), 1.99 (1H, d), 2.18 (3H, t), 2.36 (1H, d), 2.45 - 2.62 (1H, m), 2.71 (3H, s), 2.79 - 2.88 (1H, m), 2.92 (6H, s), 3.01 (2H, t), 3.44 (3H, s), 3.47 - 3.56 (1H, m), 3.59 (3H, s), 3.85 (1H, s), 4.67 (2H, d), 5.30 - 5.45 (1H, m), 7.07 (1H, d), 7.97 - 8.10 (2H, m), 8.15 (1H, d), 8.67 (2H, dd), 8.84 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 515.

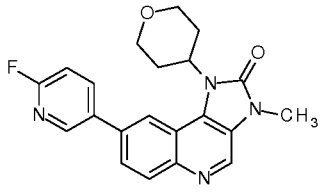
Example 54: (Free base) *NMR Spectrum:* ^{1}H NMR (400MHz, MeOH-d4) δ 1.46 - 1.61 (3H, m), 1.73 - 1.83 (1H, m), 1.87 (1H, d), 1.94 - 2.07 (3H, m), 2.16 (1H, d), 2.30 - 2.35 (1H, m), 2.38 (6H, s), 2.48 - 2.61 (2H, m), 2.82 - 2.87 (1H, m), 2.94 (2H, t), 3.43 (3H, s), 3.58 (3H, s), 3.84 (1H, s), 4.52 (2H, d), 5.35 (1H, t), 7.00 (1H, d), 7.93 (1H, dd), 8.01 (1H, dd), 8.12 (1H, d), 8.60 (2H, dd), 8.75 (1H, s). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) 1.41 - 1.57 (1H, m), 1.65 - 1.92 (4H, m), 1.98 (1H, d), 2.17 (3H, t), 2.35 (1H, d), 2.46 - 2.62 (1H, m), 2.71 (3H, s), 2.79 - 2.88 (1H, m), 2.92 (6H, s), 3.01 (2H, t), 3.43 (3H, s), 3.51 (1H, s), 3.58 (3H, s), 3.84 (1H, s), 4.67 (2H, d), 5.27 - 5.43 (1H, m), 7.06 (1H, d), 7.97 (1H, dd), 8.05 (1H, dd), 8.13 (1H, d), 8.64 (2H, dd), 8.80 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 515.

Example 55: (Free base) *NMR Spectrum:* ^{1}H NMR (400MHz, MeOH-d4) δ 1.51 (1H, t), 1.75 - 1.91 (2H, m), 2.00 (1H, d), 2.14 (1H, d), 2.29 (6H, s), 2.34 (1H, d), 2.49 - 2.61 (1H, m), 2.74 - 2.89 (1H, m), 3.33 - 3.39 (1H, m), 3.40 (3H, s), 3.59 (3H, s), 3.83 (1H, s), 3.94 (2H, dd), 4.22 (2H, dd), 5.30 - 5.41 (1H, m), 6.64 (1H, d), 7.92 (1H, dd), 8.05 (1H, dd), 8.14 (1H, d), 8.53 (1H, s), 8.58 (1H, s), 8.76 (1H, s). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) 1.47 (1H, t), 1.75 - 1.90 (2H, m), 1.98 (1H, d), 2.13 (1H, d), 2.32 (1H, d), 2.44 - 2.61 (1H, m), 2.70 (3H, s), 2.76 - 2.88 (1H, m), 2.92 (6H, s), 3.40 (3H, s), 3.57 (3H, s), 3.78 - 3.87 (1H, m), 4.13 - 4.29 (3H, m), 4.36 - 4.50 (2H, m), 5.24 - 5.40 (1H, m), 6.72 (1H, d), 7.94 (1H, dd), 8.09 (1H, dd), 8.13 (1H, d), 8.55 - 8.64 (2H, m), 8.79 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 487.

Example 56: (Free base) *NMR Spectrum:* ^{1}H NMR (400MHz, MeOH-d4) δ 1.44 - 1.55 (1H, m), 1.77 - 1.92 (2H, m), 2.00 (1H, d), 2.14 (1H, d), 2.30 (6H, s), 2.32 - 2.38 (1H, m), 2.56 (1H, t), 2.76 - 2.87 (1H, m), 3.34 - 3.39 (1H, m), 3.40 (3H, s), 3.59 (3H, s), 3.83 (1H, s), 3.94 (2H, dd), 4.22 (2H, t), 5.30 - 5.42 (1H, m), 6.64 (1H, d), 7.93 (1H, dd), 8.05 (1H, dd), 8.14 (1H, d), 8.53 (1H, d), 8.58 (1H, d), 8.77 (1H, s). (Methanesulfonic acid salt) *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) 1.40 - 1.56 (1H, m), 1.75 - 1.88 (2H, m), 1.99 (1H, d), 2.13 (1H, d), 2.34 (1H, d), 2.46 - 2.62 (1H, m), 2.70 (3H, s), 2.77 - 2.89 (1H, m), 2.95 (6H, s), 3.40 (3H, s), 3.58 (3H, s), 3.79 - 3.87 (1H, m), 4.18 - 4.31 (3H, m), 4.38 - 4.51 (2H, m), 5.27 - 5.42 (1H, m), 6.73 (1H, d), 7.98 (1H, dd), 8.11 (1H, dd), 8.15 (1H, d), 8.62 (2H, s), 8.82 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 487.

The preparation of the fluoropyridyl intermediates required for **Examples 6 – 56** are described below:

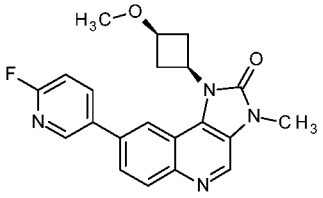
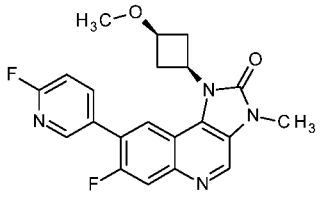
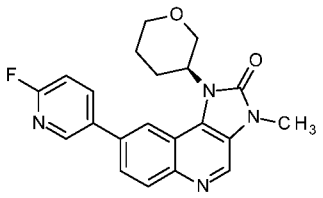
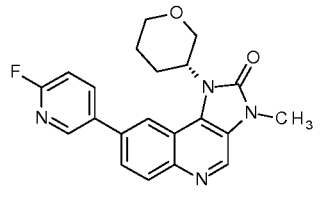
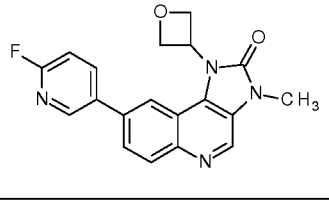
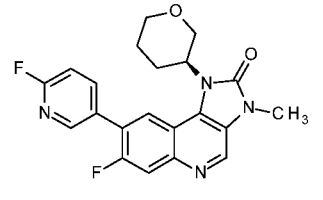
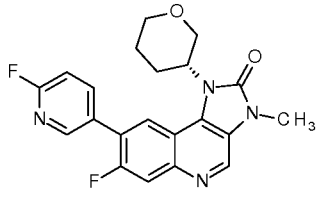
Intermediate D0: 8-(6-Fluoropyridin-3-yl)-3-methyl-1-(oxan-4-yl)imidazo[5,4-c]quinolin-2-one

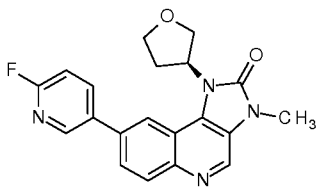
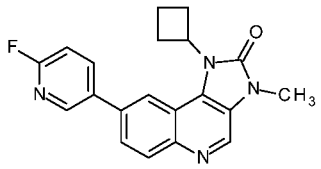
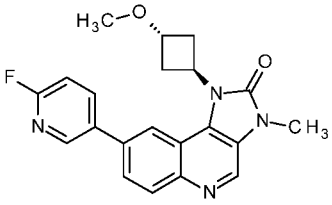
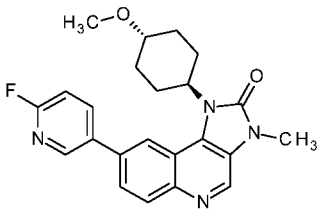
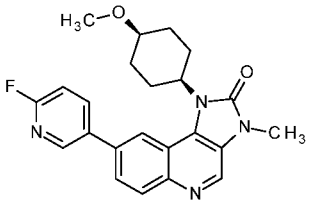
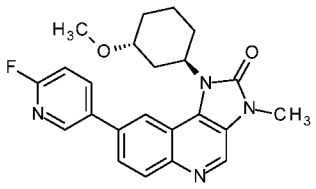
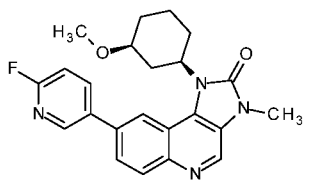


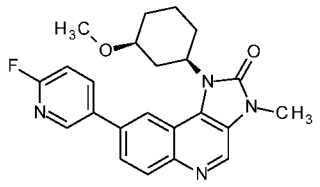
Monopalladium(IV) disodium tetrachloride (0.975 g, 3.31 mmol) was added to 8-bromo-3-methyl-1-(oxan-4-yl)imidazo[5,4-c]quinolin-2-one (60.0 g, 165.64 mmol), (6-fluoropyridin-3-yl)boronic acid (25.7 g, 182.21 mmol), K_2CO_3 (68.7 g, 496.93 mmol) and 3-(di-*tert*-butylphosphino)propane-1-sulfonic acid (0.445 g, 1.66 mmol) in 1,4-dioxane (400 mL) and water (100 mL) at ambient temperature under air. The resulting mixture was stirred at 80°C for 16 h. The reaction mixture was diluted with water and the precipitate collected by filtration, washed with water (200 mL) and dried under vacuum. The resulting solid was dissolved with DCM (18 L) and the mixture filtered through celite to remove Palladium residues. The solvent was removed under reduced pressure to afford the desired material (60.0 g, 96 %) as a white solid, which was used without further purification.
NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.85-2.01 (2H, m), 2.86-3.02 (2H, m), 3.57-3.68 (5H, m), 4.16-4.31 (2H, m), 5.11 (1H, t), 6.98-7.19 (1H, m), 7.83 (1H, dd), 8.16 (1H, td), 8.30 (1H, dd), 8.50 (1H, s), 8.60 (1H, s), 8.77 (1H, s).
Mass Spectrum: m/z (ES+)[M+H]+ = 379.2

The following intermediates were prepared in an analogous fashion from the appropriate bromo intermediate.

Intermediate	Structure	Name

Intermediate	Structure	Name
Intermediate E0 *		8-(6-fluoro-3-pyridyl)-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one
Intermediate F0 **		7-fluoro-8-(6-fluoro-3-pyridyl)-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one
Intermediate G0 **		8-(6-fluoro-3-pyridyl)-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
Intermediate H0 **		8-(6-fluoro-3-pyridyl)-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
Intermediate I0 ***		8-(6-fluoro-3-pyridyl)-3-methyl-1-(oxetan-3-yl)imidazo[4,5-c]quinolin-2-one
Intermediate J0 ****		7-fluoro-8-(6-fluoro-3-pyridyl)-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
Intermediate K0 **		7-fluoro-8-(6-fluoro-3-pyridyl)-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one

Intermediate	Structure	Name
Intermediate L0 ***		8-(6-fluoro-3-pyridyl)-3-methyl-1-[(3*S*)-tetrahydrofuran-3-yl]imidazo[4,5-c]quinolin-2-one
Intermediate M1 ***		1-cyclobutyl-8-(6-fluoro-3-pyridyl)-3-methyl-imidazo[4,5-c]quinolin-2-one
Intermediate N0 ****		8-(6-fluoro-3-pyridyl)-1-(*trans*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one
Intermediate O0 **		8-(6-fluoro-3-pyridyl)-1-(*trans*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one
Intermediate P0 **		8-(6-fluoro-3-pyridyl)-1-(*cis*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one
Intermediate R0 **		8-(6-fluoro-3-pyridyl)-1-[*trans*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one (1:1 mixture of enantiomers)
Intermediate S0 **		8-(6-fluoro-3-pyridyl)-1-[*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 1

Intermediate	Structure	Name
Intermediate T0 **		8-(6-fluoro-3-pyridyl)-1-[*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 2

* The reaction was performed using chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) as the catalyst and was stirred at 90°C for 2 h.

** The reaction was performed using $Pd(Ph3P)_4$ as the catalyst and either Cs_2CO_3 or Na_2CO_3 as the base in a mixture of 1,4-dioxane and water as the solvent. The reaction was heated between 80 - 100°C for 2 - 16 h.

*** The reaction was performed using dichloro[1,1'-bis(di-tert-butylphosphino)ferrocene]palladium(II) as the catalyst and K_2CO_3 as the base in a mixture of 1,4-dioxane and water as the solvent. The reaction was heated between 80°C for 1 h.

**** The reaction was performed using dichloro [1,1'- bis(di-tertbutylphosphino)ferrocene]palladium(II) as the catalyst and K_2CO_3 as the base in a mixture of 1,4-dioxane and water as the solvent. The reaction was heated between 80°C for 1 h.

Intermediate E0: *NMR Spectrum:* ^{1}H NMR (400MHz, DMSO-d6) δ 2.83 (2H, s), 3.01 (2H, d), 3.20 (3H, s), 3.51 (3H, s), 3.86 (1H, s), 5.07 - 5.18 (1H, m), 7.37 (1H, d), 7.96 (1H, d), 8.16 (1H, d), 8.49 (2H, d), 8.75 (1H, s), 8.92 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 379

Intermediate F0: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 2.76 – 2.81 (2H, m), 2.91 – 3.05 (2H, m), 3.13 (3H, s), 3.49 (3H, s), 3.78-3.82 (1H, qu), 5.07-5.10 (1H, qu),7.40 (1H, dd), 7.94 (1H, d),8.32 (1H, td), 8.45 (d) 8.59 (1H, s),8.95 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 397

Intermediate G0: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.83-1.86 (2H, m), 2.15-2.19 (1H, m), 2.49-2.64 (1H, m), 3.38-3.41 (1H, m), 3.49 (3H, s), 3.93 (1H, d), 4.15-

4.26 (2H,m), 4.91-5.10 (1H,m), 7.42 (1H, dd), 7.96 (1H,dd), 8.13 (1H, d), 8.38 (1H,s), 8.44 (1H, td), 8.72 (1H,d), 8.96 (1H,s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 379.1

Intermediate H0: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.80-1.83 (2H, m), 2.15-2.18 (1H, m), 2.49-2.73 (1H, m), 3.37-3.41 (1H, m), 3.49 (3H, s), 3.93 (1H, d), 4.16-4.26 (2H,m), 4.90-5.10 (1H,m), 7.42 (1H, dd), 7.97 (1H,dd), 8.14 (1H, d), 8.38 (1H,s), 8.45 (1H, td), 8.71 (1H,d), 8.95 (1H,s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 379

Intermediate I0: *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d_6) δ 3.55 (3H, s), 5.07 (2H, dd), 5.28 (2H, t), 6.09 - 6.31 (1H, m), 7.29 - 7.43 (1H, m), 8.02 (1H, dd), 8.18 (1H, d), 8.49 (1H, ddd), 8.56 (1H, d), 8.77 (1H, d), 8.97 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 351

Intermediate J0: *NMR Spectrum*: ^{1}H NMR (500MHz, DMSO-d6) δ 1.71 - 1.87 (2H, m), 2.14 (1H, d), 2.57 - 2.76 (1H, m), 3.32 - 3.42 (1H, m), 3.49 (3H, s), 3.90 (1H, d), 4.06 - 4.16 (1H, m), 4.21 (1H, t), 4.79 - 5.1 (1H, m), 7.36 - 7.54 (1H, m), 7.97 (1H, d), 8.32 (1H, d), 8.37 (1H, tt), 8.62 (1H, s), 8.95 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 397

Intermediate K0: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.75-1.91(2H, m), 2.10-2.20(1H, m), 2.59-2.78(1H, m), 3.30-3.41 (1H, m), 3.50(3H,s), 3.89-3.95(1H,d) 4.04-4.15 (1H, d), 4.20-4.32(1H,t), 4.80-5.00(1H,t),7.34-7.39(1H,d), 7.89-7.95(1H, d), 8.30-8.40(2H, m), 8.59(1H,s),8.95 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 397

Intermediate L0: *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d_6) δ 2.33 - 2.44 (1H, m), 2.53 - 2.67 (1H, m), 3.55 (3H, s), 3.91 (1H, td), 4.13 - 4.22 (2H, m), 4.27 (1H, td), 5.79 - 5.9 (1H, m), 7.3 - 7.41 (1H, m), 8.02 (1H, dd), 8.18 (1H, d), 8.49 (1H, ddd), 8.68 (1H, d), 8.77 (1H, d), 8.96 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 365

Intermediate M0: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d_6) δ 1.77 - 2.01 (2H, m), 2.46 (2H, ddt), 3.09 (2H, pd), 3.51 (3H, s), 5.53 (1H, p), 7.32 - 7.44 (1H, m), 7.96 (1H, dd), 8.15 (1H, d), 8.43 - 8.54 (2H, m), 8.75 (1H, d), 8.91 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 349

Intermediate N0: *NMR Spectrum:* ^{1}H NMR (500MHz, DMSO-d6) δ 2.52 - 2.63 (2H, m), 3.15 - 3.2 (2H, m), 3.21 (3H, s), 3.50 (3H, s), 4.14 - 4.37 (1H, m), 5.58 (1H, tt), 7.37 (1H, ddd), 7.94 (1H, dd), 8.08 - 8.22 (1H, m), 8.32 (1H, d), 8.44 (1H, ddd), 8.72 (1H, dd), 8.89 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 379

Intermediate O0: *NMR Spectrum:* ^{1}H NMR (400MHz, MeOH-d4) δ 1.45 - 1.53 (2H, m), 2.16 (2H, d), 2.34 (2H, d), 2.60 - 2.80 (2H, m), 3.37 - 3.41 (1H, m), 3.43 (3H, s), 3.61 (3H, s), 4.94 - 5.06 (1H, m), 7.29 (1H, dd), 8.00 (1H, d), 8.24 (1H, d), 8.35 - 8.45 (1H, m), 8.47 (1H, s), 8.66 (1H, s), 8.86 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 407

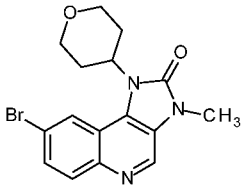
Intermediate P0: *NMR Spectrum:* ^{1}H NMR (300MHz, $CDCl_3$) δ 1.64 (2H, t), 1.77 (2H, d), 2.14 - 2.28 (2H, m),2.64 - 2.78 (2H, m), 3.07 (3H, br), 3.56 (1H, s), 3.64 (3H, s), 4.98 (1H, br), 7.10 (1H, dd), 7.77 (1H, dd), 8.11 - 8.23 (1H, m), 8.26 (1H, d), 8.56 (1H, s), 8.64 (1H, s), 8.76 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 407

Intermediate R0: *NMR Spectrum:* ^{1}H NMR (300MHz, $CDCl_3$) δ 1.40 - 1.54 (1H, m), 1.74 - 1.86 (2H, m), 1.98 (1H, d), 2.13 (1H, d), 2.35 (1H, d), 2.54 (1H, t), 2.89 - 2.96 (1H, m), 3.39 (3H, s), 3.59 (3H, s), 3.83 (1H, s), 5.28 (1H, t), 7.11 (1H, dd), 7.85 (1H, dd), 8.14 - 8.24 (1H, m), 8.31 (1H, d), 8.68 (2H, d), 8.72 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 407

Intermediate S0: *NMR Spectrum:* ^{1}H NMR (300MHz, $CDCl_3$) δ 1.92 (1H, dd), 2.02 - 2.12 (1H, m), 2.50 (1H, m), 3.16 (4H, d), 3.35 (3H, s), 3.48 (3H, s), 4.11 (1H, m), 4.88 (1H, m), 7.38 (1H, dd), 7.91 - 7.98 (1H, d), 8.14 (1H, d), 8.30 (1H, s), 8.42 (1H, d), 8.68 (1H, d), 8.88 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 407

Intermediate T0: *NMR Spectrum:* ^{1}H NMR (300MHz, $CDCl_3$) δ 1.14 - 1.59 (2H, m), 1.96 - 2.12 (2H, m), 2.21 (1H, d), 2.48-2.59 (3H, m), 3.34 - 3.35 (1H, m), 3.38 (3H, s), 3.61 (3H, s), 4.79 - 4.83 (1H, m), 7.13 (1H, ddd), 7.47 - 7.50 (1H, m), 7.65 (1H, dd), 7.79 (1H, dd), 8.27 (1H, d), 8.56 (1H, d), 8.75 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 407

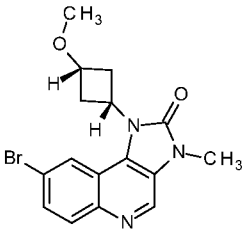
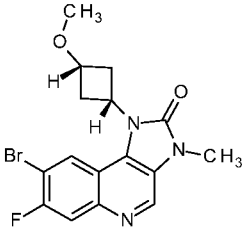
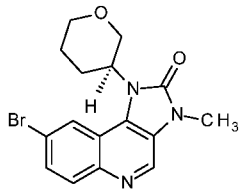
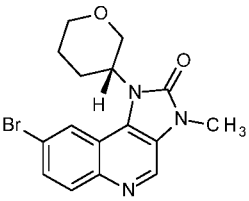
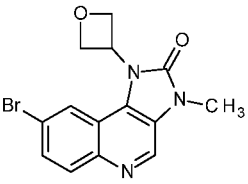
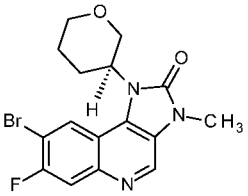
Intermediate D1: 8-Bromo-3-methyl-1-(oxan-4-yl)imidazo[5,4-c]quinolin-2-one

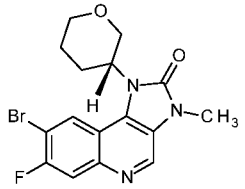
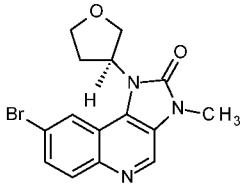
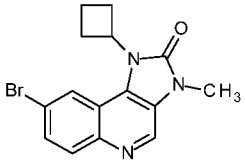


A solution of sodium hydroxide (10.34g, 258.48mmol) in water (900mL) was added to a stirred mixture of 8-bromo-1-(oxan-4-yl)-3H-imidazo[4,5-c]quinolin-2-one (60.0g, 172.32mmol), iodomethane (48.9g, 344.63mmol) and tetrabutylammonium bromide (5.55g, 17.23mmol) in DCM (1500mL) at ambient temperature under air. The resulting mixture was stirred for 16 h then the DCM removed under reduced pressure. The precipitate was collected by filtration, washed with water (200mL) and dried under vacuum to afford the desired material (58.0g, 93%) as a brown solid, which was used without further purification. *NMR Spectrum*: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.81-1.98 (2H, m), 2.82-3.00 (2H, m), 3.60 (3H, s), 3.63 (2H, td), 4.05-4.35 (2H, m), 4.93 (1H, t), 7.69 (1H, dd), 8.03 (1H, d), 8.36 (1H, s), 8.71 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 364.

On a larger scale, 8-bromo-1-(oxan-4-yl)-3H-imidazo[4,5-c]quinolin-2-one (1300 g, 3.73 mol) was charged to the vessel along with tetrabutylammonium bromide (130 g, 0.40 mol) and 2-MeTHF (20.8 L). A solution of NaOH (240 g, 6.00 mol) in water (20.8 L) was then added over 5 minutes with an observed exotherm from 18-24°C. The biphasic mixture was heated to 42-48°C before the addition of methyl iodide (465 mL, 7.47 mol) as a solution in 2-MeTHF (930 mL). The reaction was stirred at 45°C for 17 h at which point HPLC analysis showed 2.9% starting material and 97.1% product. The reaction mixture was combined with that of the other large scale batches for concentration *in vacuo*. The resulting aqueous suspension was then returned to the vessel and slurried for 1 h with the product material obtained from the development batches combined at this point. The product was then isolated by filtration, washing with water (2 x 12 L) before oven drying under vacuum at 40°C. In total 3479 g of 8-bromo-3-methyl-1-(oxan-4-yl)imidazo[5,4-c]quinolin-2-one was isolated. Analytical data was consistent with that obtained from previous batches.

The following intermediates were prepared in an analogous fashion from the appropriate 3H-imidazo[4,5-c]quinolin-2-one intermediate:

Intermediate	Structure	Name
Intermediate E1		8-Bromo-1-(*cis*-3-methoxycyclobutyl)-3-methylimidazo[4,5-c]quinolin-2-one
Intermediate F1		8-Bromo-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methylimidazo[4,5-c]quinolin-2-one
Intermediate G1		8-bromo-3-methyl-1-[(3*S*)-oxan-3-yl]imidazo[5,4-c]quinolin-2-one
Intermediate H1 *		8-bromo-3-methyl-1-[(3*R*)-oxan-3-yl]imidazo[5,4-c]quinolin-2-one
Intermediate I1 *		8-bromo-3-methyl-1-(oxetan-3-yl)imidazo[5,4-c]quinolin-2-one
Intermediate J1 **		8-bromo-7-fluoro-3-methyl-1-[(3*S*)-oxan-3-yl]imidazo[5,4-c]quinolin-2-one

Intermediate	Structure	Name
Intermediate K1		8-bromo-7-fluoro-3-methyl-1-[(3*R*)-oxan-3-yl]imidazo[5,4-c]quinolin-2-one
Intermediate L1		8-bromo-3-methyl-1-[(3*S*)-tetrahydrofuran-3-yl]imidazo[4,5-c]quinolin-2-one
Intermediate M1		8-bromo-1-cyclobutyl-3-methyl-imidazo[4,5-c]quinolin-2-one

* The reaction had not proceeded to completion so additional methyl iodide, sodium hydroxide and tetrabutylammonium bromide were added and the reaction stirred a further 16 – 18 h.

** The reaction was stirred for 72 h at ambient temperature.

Intermediate E1: *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 2.72 - 2.86 (2H, m), 2.9 - 3.08 (2H, m), 3.22 (3H, s), 3.49 (3H, s), 3.85 - 3.89 (1H, m), 4.88 - 5.06 (1H, m), 7.74 (1H, dd), 7.98 (1H, d), 8.50 (1H, d), 8.92 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 362, 364.

Intermediate F1: *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 2.70-2.85(2H, m), 2.93-3.07(2H, m), 3.22(3H, s), 3.48(3H, s), 3.73-4.00(1H, m), 4.86-5.15(1H, m), 7.75-8.07(1H, d), 8.52-8.73(1H, d), 8.93(1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 380.

Intermediate G1: *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.82 – 1.88 (2H, m), 2.09 – 2.15 (1H, m), 2.55 -2.78 (1H, m), 3.30 - 3.47 (1H, m) 3.48 (3H, s), 3.92 (1H,d), 4.02 - 4.22 (2H, m), 4.68-4.88 (1H, m), 7.75 (1H, d), 7.99 (1H, d), 8.35 (1H, s), 8.92 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 362.2.

Intermediate H1: *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.80-1.86 (2H, m), 2.07-2.12 (1H, m), 2.61-2.75 (1H, m), 3.32-3.46 (1H, m), 3.47 (3H, s), 3.92-3.98 (1H, m), 4.01-4.20 (2H,m), 4.72-4.83 (1H,m),7.76 (1H,dd), 8.00 (1H,d), 8.34 (1H,d), 8.92 (1H,s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 362, 364.

Intermediate I1: *NMR Spectrum:* ^{1}H NMR (400MHz, DMSO-d6) δ 3.53 (3H, s), 5.01 (2H, dd), 5.22 (2H, t), 6 - 6.18 (1H, m), 7.77 (1H, dd), 8.00 (1H, d), 8.51 (1H, d), 8.97 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 334, 336

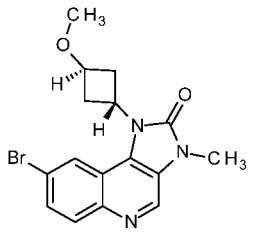
Intermediate J1: *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.88-190 (2H, m), 2.09 (1H, d), 2.70 (1H, ddd), 3.36 - 3.44 (1H, m), 3.47 (3H, s), 3.94 (1H, d), 4.07 (1H, dd), 4.15 (1H, t), 4.79 (1H, ddd), 7.97 (1H, d), 8.48 (1H, d), 8.93 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 380, 382.

Intermediate K1: *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.86 (2H, dd), 2.11 (1H, d), 2.69 (1H, ddd), 3.37 - 3.45 (1H, m), 3.48 (3H, s), 3.95 (1H, d), 4.08 (1H, dd), 4.18 (1H, t), 4.80 (1H, ddd), 7.98 (1H, d), 8.50 (1H, d), 8.94 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 380, 382.

Intermediate L1: *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d_6) δ 2.40 - 2.48 (1H, m), 2.58 - 2.67 (1H, m), 3.63 (3H, s), 3.98 - 4.05 (1H, m), 4.19 - 4.28 (2H, m), 4.46 - 4.51 (1H, td), 5.68 - 5.76 (1H, m), 7.72 (1H, d), 8.07 (1H, d), 8.67 (1H, d), 8.76 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 348.

Intermediate M1: *NMR Spectrum*: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.95 - 2.12 (2H, m), 2.52 - 2.59 (2H, m), 3.17 - 3.28 (2H, m), 3.59 (3H, s), 5.18 - 5.27 (1H, m), 7.8 (1H, d), 8.02 (1H, d), 8.37 (1H, d), 8.70 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 332.

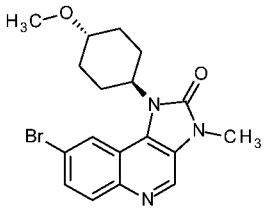
Intermediate N1: 8-Bromo-1-(*trans*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one

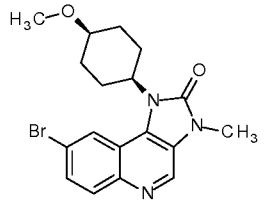
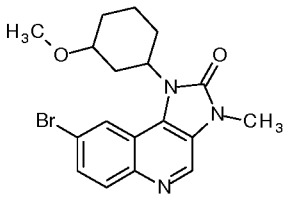
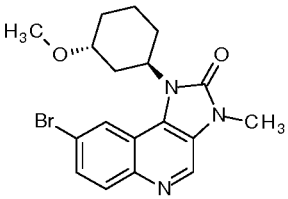
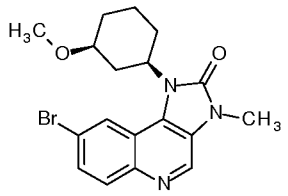
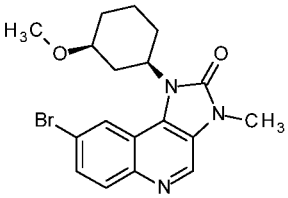


To a suspension of 8-bromo-1-(*trans*-3-hydroxycyclobutyl)-3H-imidazo[4,5-c]quinolin-2-one (1.8 g, 5.39 mmol) in DMF (20 mL) under nitrogen at RT was added NaH (60% in mineral oil) (0.75 g, 18.75 mmol) and the solution was stirred for 30 minutes. Methyl iodide (1 mL, 15.99 mmol) was added and the reaction mixture stirred at ambient temperature for one h. A second identical reaction was perfomed using 8-bromo-1-((*trans*)-3-hydroxycyclobutyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one (0.5 g, 1.50 mmol), DMF (5 mL), NaH (60% in mineral oil) (0.22 g, 5.50 mmol) and methyl iodide (0.3 mL, 4.80 mmol) and the reactions combined. The combined reaction mixture was carefully quenched with water and then stirred in water for thirty minutes. The solid was filtered off, washed thoroughly with water then dried to afford the desired material as an off white solid (1.965 g, 79 %).

NMR Spectrum: ^{1}H NMR (500MHz, DMSO-d6) δ 2.5 - 2.56 (2H, m), 3.11 - 3.21 (2H, m), 3.23 (3H, s), 3.48 (3H, s), 4.20 (1H, dt), 5.34 - 5.54 (1H, m), 7.72 (1H, dd), 7.95 (1H, d), 8.28 (1H, d), 8.90 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 362, 364.

The following intermediates were prepared in an analogous fashion from the appropriate 3H-imidazo[4,5-c]quinolin-2-one intermediate:

Intermediate	Structure	Name
Intermediate O1*		8-bromo-1-(*trans*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one

Intermediate	Structure	Name
Intermediate P1*		8-bromo-1-(*cis*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one
Intermediate Q1*		8-bromo-1-[(3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one (1:1:1: mixture of isomers)
Intermediate R1**		8-bromo-1-[(*trans*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one (1:1 mixture of enantiomers)
Intermediate S1**		8-bromo-1-[(*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 1
Intermediate T1**		8-bromo-1-[(*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one – Isomer 2

* The reaction was stirred at 0°C for 1 h then at ambient temperature overnight

** **Intermediates R1, S1** and **T1** were separated from a racemic mixture, **Intermediate Q1**, by Supercritical Fluid Chromatography using an SFC prep 350 machine and a CHIRALPAK AD-H SFC (5*25cm, 5um) column (Flow rate 150 mL/min, Pressure 100 bar, Temperature 34°C, Mobile Phase A: CO2: 50, Mobile Phase B: MeOH: 50). **Intermediate R1** was eluted first followed by **Intermediate S1** and finally **Intermediate T1**. **Intermediate T1** was subsequently purified again using the SFC prep 350 machine and a CHIRALPAK AD-H SFC (5*25cm, 5um) column (Flow rate 150 mL/min, Pressure 100 bar, Temperature 34°C, Mobile Phase A: CO2: 60, Mobile Phase B: MeOH: 40).

Intermediate O1: *NMR Spectrum*: ^{1}H NMR (300MHz, $CDCl_3$) δ 1.40 - 1.60 (2H, m), 2.08 (2H, d), 2.35 (2H, d), 2.63-2.77 (2H, m), 3.33 - 3.44 (1H, m), 3.45 (3H, s), 3.57 (3H, s), 4.68 (1H, s), 7.70 (1H, dd), 8.05 (1H, d), 8.30 (1H, s), 8.70 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 390.

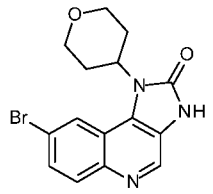
Intermediate P1: *NMR Spectrum*: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.64-1.77 (4H, m), 2.21 - 2.32 (2H, m), 2.65 (2H, s), 3.56 (3H, s), 3.65 (4H, d), 4.98 (1H, s), 7.71 (1H, dd), 8.03 (1H, d), 8.74 (1H, s), 8.83 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 390.

Intermediate R1: *NMR Spectrum*: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.40 - 1.63 (1H, m), 1.75 - 1.94 (2H, m), 2.01 (1H, d), 2.09 (1H, d), 2.32 (1H, d), 2.45-2.52 (1H, m), 2.84 (1H, d), 3.50 (3H, s), 3.57 (3H, s), 3.81-3.84 (1H, m), 5.10 (1H, t), 7.70 (1H, dd), 8.03 (1H, d), 8.66 (1H, d), 8.70 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 390.

Intermediate S1: *NMR Spectrum*: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.40-1.53 (2H, m), 1.96 - 2.13 (2H, m), 2.22 (1H, d), 2.44-2.54 (3H, m), 3.37-3.42 (1H, m), 3.42 (3H, s), 3.60 (3H, s), 4.66 (1H, s), 7.70 (1H, dd), 8.06 (1H, d), 8.29 (1H, s), 8.73 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 390.

Intermediate T1: *NMR Spectrum*: ^{1}H NMR (300MHz, $CDCl_3$) δ 1.40-1.53 (2H, m), 1.96 - 2.13 (2H, m), 2.22 (1H, d), 2.44-2.54 (3H, m), 3.37-3.42 (1H, m), 3.42 (3H, s), 3.60 (3H, s), 4.66 (1H, s), 7.70 (1H, dd), 8.06 (1H, d), 8.29 (1H, s), 8.73 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 390.

Intermediate D2: 8-Bromo-1-(oxan-4-yl)-3H-imidazo[4,5-c]quinolin-2-one



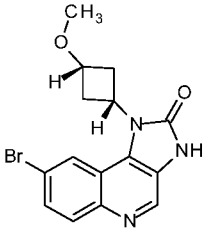
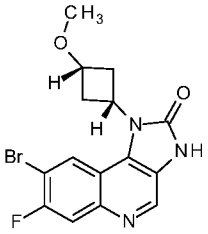
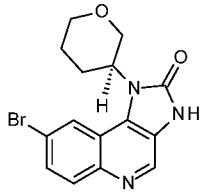
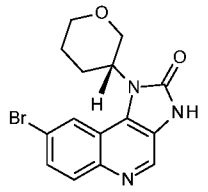
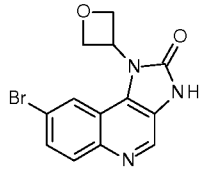
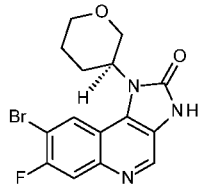
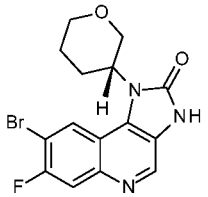
Triethylamine (143mL, 1025.07mmol) was added to 6-bromo-4-(oxan-4-ylamino)quinoline-3-carboxylic acid (120g, 341,69mmol) in DMF (600mL) at ambient

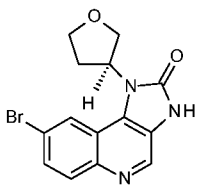
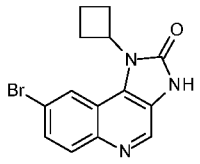
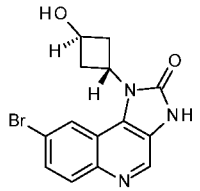
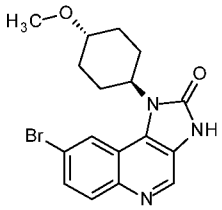
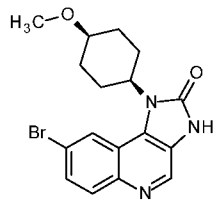
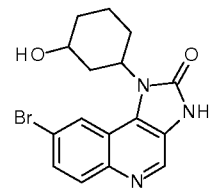
temperature under air. The resulting mixture was stirred for 30 minutes then diphenyl phosphorazidate (113g, 410,03mmol) was added. The resulting mixture was stirred for 30 minutes at ambient temperature then at 60°C for 2 h. The solvent was removed under reduced pressure and the reaction mixture diluted with water. The precipitate was collected by filtration, washed with water (250mL) and dried under vacuum to afford the desired material (120g, 101%) as a brown solid, which was used without further purification. *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.72-1.95 (2H, m), 2.59-2.80 (2H, m), 3.58 (2H, td), 3.98-4.11 (2H, m), 4.75-5.04 (1H, m), 7.75 (1H, dd), 7.97 (1H, d), 8.43 (1H, s), 8.71 (1H, s), 11.71 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 348.

On a larger scale, 6-bromo-4-(oxan-4-ylamino)quinoline-3-carboxylic acid (2011 g, (2005 g active), 5.71 mol) was added to the vessel with DMF (18.2 L). Triethylamine (4.7 L, 33.72 mol) was added with an endotherm observed from 21-18°C. Diphenyl phosphorazidate (1600 mL, 7.42 mol) was added over 10 minutes with an observed exotherm from 21°C to 23°C over the addition. The exotherm continued with the batch reaching 55°C after 1 h (jacket held at 30°C) with gas evolution. The reaction initially went into solution with a precipitate then forming after ~30 minutes. Once the temperature had stabilised the batch was analysed by HPLC showing consumption of starting material and 99% product. The batch was heated to 60°C for h with HPLC again indicating consumption of starting material and 98% product. The batch was concentrated *in vacuo* to a minimum volume (~3 volumes) and the residue added to water (17 L) rinsing in with a further portion of water (10 L). The mixture was slurried for 1 h and filtered, washing with water (2x 17 L). The solid was then returned to the vessel and slurried in sat. $NaHCO_3$ solution (10 L) and MeOH (495 mL) for 1 h. The solid was collected by filtration, washing with water (2x 3.5 L) and then oven dried *in vacuo* at 40°C for 116 h to obtain 2023 g of desired material. Analytical data was consistent with that obtained from previous batches.

The following 3H-imidazo[4,5-c]quinolin-2-one intermediates were prepared in a similar fashion from the appropriate carboxylic acid intermediates:

Intermediate	Structure	Name

Intermediate	Structure	Name
Intermediate E2		8-Bromo-1-(*cis*-3-methoxycyclobutyl)-3H-imidazo[4,5-c]quinolin-2-one
Intermediate F2		8-Bromo-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3H-imidazo[4,5-c]quinolin-2-one
Intermediate G2 *		8-bromo-1-[(3*S*)-oxan-3-yl]-3H-imidazo[4,5-c]quinolin-2-one
Intermediate H2 *		8-bromo-1-[(3*R*)-oxan-3-yl]-3H-imidazo[4,5-c]quinolin-2-one
Intermediate I2*		8-bromo-1-(oxetan-3-yl)-3H-imidazo[4,5-c]quinolin-2-one
Intermediate J2*		8-bromo-7-fluoro-1-[(3*S*)-oxan-3-yl]-3H-imidazo[4,5-c]quinolin-2-one
Intermediate K2*		8-bromo-7-fluoro-1-[(3*R*)-oxan-3-yl]-3H-imidazo[4,5-c]quinolin-2-one

Intermediate	Structure	Name
Intermediate L2**		8-bromo-1-[(3*S*)-tetrahydrofuran-3-yl]-3H-imidazo[4,5-c]quinolin-2-one
Intermediate M2**		8-bromo-1-cyclobutyl-3H-imidazo[4,5-c]quinolin-2-one
Intermediate N2*		8-bromo-1-(*trans*-3-hydroxycyclobutyl)-3H-imidazo[4,5-c]quinolin-2-one
Intermediate O2*		8-bromo-1-(*trans*-4-methoxycyclohexyl)-3H-imidazo[4,5-c]quinolin-2-one
Intermediate P2*		8-bromo-1-(*cis*-4-methoxycyclohexyl)-3H-imidazo[4,5-c]quinolin-2-one
Intermediate Q2**		8-bromo-1-(3-hydroxycyclohexyl)-3H-imidazo[4,5-c]quinolin-2-one (mixture of isomers)

* The reaction was stirred at 60°C for 60 – 90 mins.

** The reaction was stirred at 60°C overnight.

Intermediate E2: *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 2.75 - 2.82 (2H, m), 2.9 - 3.05 (2H, m), 3.22 (3H, s), 3.80 - 3.90 (1H, m), 4.85 - 4.99 (1H, m), 7.71 (1H, dd),

7.94 (1H, d), 8.48 (1H, d), 8.69 (1H, s), 10.42 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 348, 350.

Intermediate F2: *NMR Spectrum*: ^{1}H NMR (300MHz, $CDCl_3$) δ 2.75 (2H, m), 2.95 (2H, m), 3.25 (3H, s), 3.85 (1H, m), 4.75 (1H, m), 8.00 (1H, d), 8.62-8.58 (2H, t). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 366.

Intermediate G2: *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.84-2.11 (3H, m), 2.62-2.76 (1H, m), 3.35-3.44 (1H, m), 3.92-4.22 (3H, m), 4.71-4.80 (1H,m), 7.76 (1H, dd), 7.98 (2H,d), 8.32 (1H, dd), 8.71 (1H, s),11.85 (1H, bs). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 350.

Intermediate H2: *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.82-2.11 (3H, m), 2.61-2.75 (1H, m), 3.34-3.43 (1H, m), 3.91-4.21 (3H, m), 4.69-4.78 (1H,m), 7.75 (1H, dd), 7.99 (2H,d), 8.33 (1H, dd), 8.69 (1H, s),11.70 (1H, bs). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 350.

Intermediate I2: *NMR Spectrum*: ^{1}H NMR (500MHz, DMSO-d6, 100°C) δ 4.98 (2H, dd), 5.19 (2H, t), 5.97 - 6.06 (1H, m), 7.74 (1H, dd), 7.96 (1H, d), 8.50 (1H, d), 8.71 (1H, s), 11.75 (1H, s).. *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 321.

Intermediate J2: *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.77 - 1.93 (2H, m), 2.10 (1H, d), 2.68 (1H, qd), 3.34 - 3.44 (1H, m), 3.94 (1H, d), 4.08 (1H, dd), 4.18 (1H, t), 4.75 (1H, ddd), 7.94 (1H, d), 8.48 (1H, d), 8.69 (1H, s), 11.63 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 366, 368.

Intermediate K2: *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.7 - 1.93 (2H, m), 2.10 (1H, d), 2.63 - 2.75 (1H, m), 3.49 - 3.61 (1H, m), 3.84 - 4.03 (1H, m), 4.08 (1H, dd), 4.19 (1H, t), 4.76 (1H, t), 7.95 (1H, d), 8.49 (1H, d), 8.70 (1H, s), 11.66 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 366, 368.

Intermediate L2: *Mass Spectrum: m/z* (ES+)[M+H]+ = 334.

Intermediate M2: *Mass Spectrum: m/z* (ES+)[M+H]+ = 318.

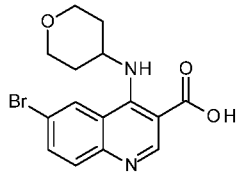
Intermediate N2: *NMR Spectrum*: ^{1}H NMR (500MHz, DMSO-d6) δ 2.32 - 2.44 (2H, m), 3.18 - 3.28 (2H, m), 4.45 (1H, d), 5.26 (1H, d), 5.42 (1H, ddd), 7.71 (1H, dd), 7.93 (1H, d), 8.29 (1H, d), 8.65 (1H, s), 11.56 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 334, 336.

Intermediate O2: *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.41 (2H, q), 1.96 (2H, d), 2.17 (2H, d), 2.49 (2H, d), 3.23 (1H, d), 3.32 (2H, s), 4.65 (1H, t), 7.73 (1H, dd), 7.95 (1H, d), 8.32 (1H, d), 8.66 (1H, s), 11.58 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 376.

Intermediate P2: *NMR Spectrum*: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.73 (4H, dd), 2.30 (2H, d), 2.69 (2H, s), 3.59 (3H, s), 3.69 (1H, s), 4.99 (1H, s), 7.74 (1H, dd), 8.05 (1H, d), 8.88 (1H, s), 10.39 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 376.

Intermediate Q2: Mixture of *cis* and *trans* isomers (ratio 1:2, unassigned) *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.09 – 1.34 (2H, m), 1.35 – 1.58 (2H, m), 1.58 – 1.79 (1H, m), 1.78 – 2.07 (6H, m), 2.07 – 2.47 (4H, m), 3.01 – 3.15 (1H, m), 3.51 – 3.73 (1H, m), 4.19 (1H, s), 4.53 – 4.77 (1H, m), 4.8 – 4.96 (2H, m), 5.03 (1H, s), 7.74 (2H, 2 x d), 7.97 (2H, 2 x d), 8.31 (1H, s), 8.55 (1H, s), 8.66 (1H, s), 8.68 (1H, s), 11.56 (1H, s), 11.62 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 362.

Intermediate D3: 6-Bromo-4-(oxan-4-ylamino)quinoline-3-carboxylic acid

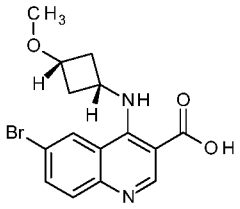
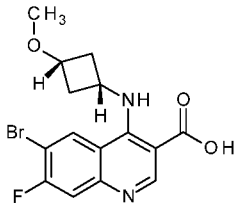


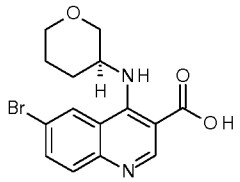
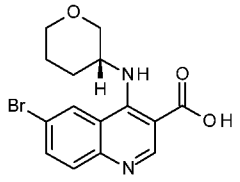
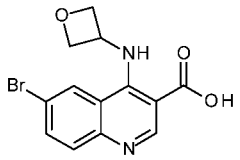
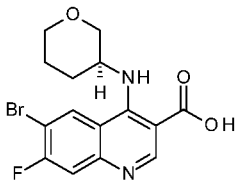
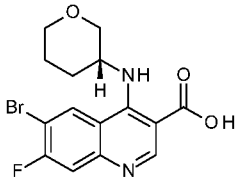
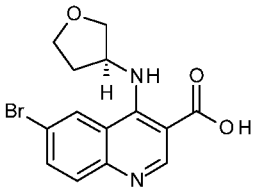
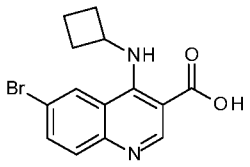
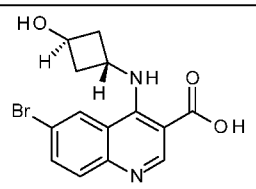
A solution of sodium hydroxide (79g, 1977.60mmol) in water (1500mL) was added to a stirred mixture of ethyl 6-bromo-4-(oxan-4-ylamino)quinoline-3-carboxylate (150g, 395.52mmol) in MeOH (1500mL) at ambient temperature under air. The resulting mixture was stirred at 70°C for 2 h then the solvent removed under reduced pressure. The reaction

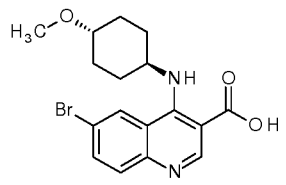
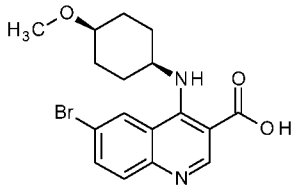
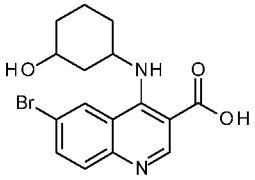
mixture was adjusted to pH=3 with 2M hydrochloric acid. The precipitate was collected by filtration, washed with water (500mL) and dried under vacuum to afford the desired material (120g, 86%) as a white solid, which was used without further purification. *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.75-1.82 (2H, m), 2.05-2.09 (2H, m), 3.85-3.94 (5H, m), 7.95 (1H, d), 8.18 (1H, d), 8.65 (1H, s), 9.01 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 351.1.

On a larger scale, ethyl 6-bromo-4-(oxan-4-ylamino)quinoline-3-carboxylate (1925 g, 5.08 mol) was charged to the vessel with EtOH (12.5 L). 2M NaOH (12.5 L, 25.03 mol) was then added with an exotherm from 22-35°C over the 20 minute addition. The batch was heated to 70-80°C for 17 h at which point HPLC indicated 98.3% product and <1% starting material. The batch was concentrated *in vacuo* to remove EtOH and returned to the vessel. A 2M HCl solution (13 L) was then added until pH 5-6 was obtained maintaining a batch temperature below 50°C. An exotherm from 20-32°C was observed over the 40 minute addition. A precipitate formed which was slurried at 20-25°C for 1.5 h before filtration, washing with water until pH neutral (3x 7 L). The collected solid was dried under vacuum at 70°C to give 1794 g of desired material. Analytical data was consistent with that obtained from previous batches.

The following carboxylic acid intermediates were prepared in a similar fashion from the appropriate ester precursor:

Intermediate	Structure	Name
Intermediate E3*		6-Bromo-4-[(*cis*-3-methoxycyclobutyl)amino]quinoline-3-carboxylic acid
Intermediate F3		6-Bromo-7-fluoro-4-[(*cis*-3-methoxycyclobutyl)amino]quinoline-3-carboxylic acid

Intermediate	Structure	Name
Intermediate G3 **		6-bromo-4-[[(3*S*)-oxan-3-yl]amino]quinoline-3-carboxylic acid
Intermediate H3 **		6-bromo-4-[[(3*R*)-oxan-3-yl]amino]quinoline-3-carboxylic acid
Intermediate I3 ***		6-bromo-4-(oxetan-3-ylamino)quinoline-3-carboxylic acid
Intermediate J3***		6-bromo-7-fluoro-4-[[(3*S*)-tetrahydropyran-3-yl]amino]quinoline-3-carboxylic acid
Intermediate K3***		6-bromo-7-fluoro-4-[[(3*R*)-tetrahydropyran-3-yl]amino]quinoline-3-carboxylic acid
Intermediate L3***		6-bromo-4-[[(3*S*)-tetrahydrofuran-3-yl]amino]quinoline-3-carboxylic acid
Intermediate M3***		6-bromo-4-(cyclobutylamino)quinoline-3-carboxylic acid
Intermediate N3***		6-bromo-4-[(*trans*-3-hydroxycyclobutyl)amino]quinoline-3-carboxylic acid

Intermediate	Structure	Name
Intermediate O3* **		6-bromo-4-[(*trans*-4-methoxycyclohexyl)amino]quinoline-3-carboxylic acid
Intermediate P3* **		6-bromo-4-[(*cis*-4-methoxycyclohexyl)amino]quinoline-3-carboxylic acid
Intermediate Q3* **		6-bromo-4-[(3-hydroxycyclohexyl)amino]quinoline-3-carboxylic acid (mixture of isomers)

* The reaction was performed using a mixture of THF, MeOH and water as the solvent.

** The reaction was stirred between 60 – 70°C for 1 - 3 h.

*** The reaction was performed using a mixture of THF and water as the solvent and heated at 60°C for 3 – 16 h.

Intermediate E3: *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 351

Intermediate F3: *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.98-1.91 (2H, m), 2.88-2.84 (2H, m), 3.17 (1H, s), 3.77-3.70 (1H, t), 4.22-4.19 (1H, t), 7.73 (1H, d), 8.44 (1H, d), 8.88 (1H, s), 13.27 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 369.

Intermediate G3: *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.50-1.57 (1H, m), 1.61 - 1.82 (2H, m), 1.98- 2.13 (1H, m), 3.48-3.72 (3H, m), 3.89 (1H, d), 4.15 -4.26 (1H, m), 7.77 (1H, dd), 7.95 (1H, d), 8.31(1H, d), 8.90 (1H,s), 13.38 (1H, bs). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 351.

Intermediate H3: *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.50-1.56 (1H, m), 1.62 - 1.83 (2H, m), 1.99- 2.12 (1H, m), 3.50-3.71 (3H, m), 3.89 (1H, d), 4.16 -4.28 (1H,

m), 7.78 (1H, dd), 7.94 (1H, d), 8.30(1H, d), 8.94 (1H,s), 13.50 (1H, bs). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 351.

Intermediate I3: *NMR Spectrum*: ^{1}H NMR (500MHz, DMSO-d_6) δ 4.62 (2H, t), 4.91 (2H, t), 5.02 – 5.13 (1H, m), 7.78 (1H, d), 7.90 (1H, dd), 8.15 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 321.

Intermediate J3: *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.51 (1H, m), 1.74 (2H, m), 2.04 (1H, m), 3.60 (3H, m), 3.82 (1H, d), 4.15 (1H, m), 7.73 (1H, m), 8.44 (1H, m), 8.92 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 369.

Intermediate K3: *Mass Spectrum: m/z* (ES+)[M+H]+ = 369.

Intermediate L3: *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.95 - 2.05 (1H, m), 2.31 - 2.41 (1H, m), 3.79 - 3.87 (2H, m), 3.89 - 3.95 (2H, m), 4.82 - 4.92 (1H, m), 7.78 (1H, d), 7.92 - 7.94 (1H, m), 8.44 (1H, d), 8.90 (1H, s), 13.3 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 337.

Intermediate M3: *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.81 - 1.95 (3H, m), 2.01 - 2.15 (3H, m), 4.53 - 4.55 (1H, m), 7.74 (1H, d), 7.88 (1H, d), 8.25 (1H, s), 8.89 (1H, s), 13.27 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 321.

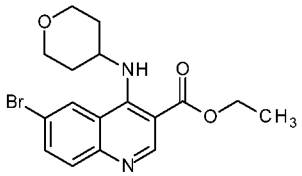
Intermediate N3: *NMR Spectrum*: ^{1}H NMR (500MHz, DMSO-d_6) δ 2.27 - 2.46 (4H, m), 4.36 (1H, s), 4.71 (1H, d), 5.28 (1H, s), 7.75 (1H, d), 7.92 (1H, dd), 8.22 (1H, dd), 8.85 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 337.

Intermediate O3: *Mass Spectrum: m/z* (ES+)[M+H]+ = 379.

Intermediate P3: *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.66 (2H, s), 1.84 (6H, s), 3.27 (3H, s), 3.41 (1H, s), 7.96 (1H, d), 8.19 (1H, d), 9.02 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 379.

Intermediate Q3: Mixture of *cis* and *trans* isomers (ratio 1:2, unassigned) *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.09 – 1.25 (2H, m), 1.26 – 1.46 (4H, m), 1.48 – 1.66 (2H, m), 1.68 – 1.92 (4H, m), 1.92 - 2.10 (3H, m), 2.27 (1H, d), 3.49 – 3.64 (2H, m), 3.99 (1H, s), 4.10 (2H, s), 4.51 (1H, s), 4.72 (1H, s), 4.83 (1H, s), 7.84 (2H, 2 x d), 8.01 (2H, 2 x d), 8.42 (1H, s), 8.48 (1H, s), 8.91 (2H, 2 x s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 365.

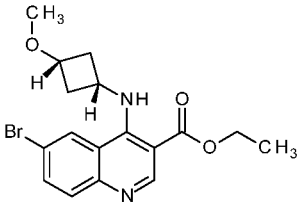
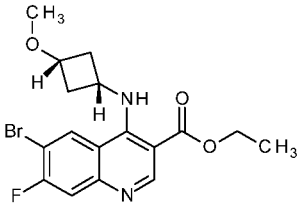
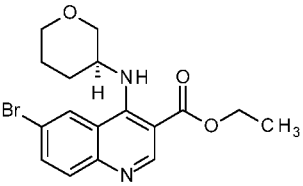
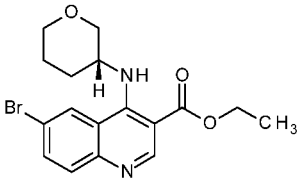
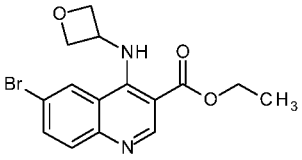
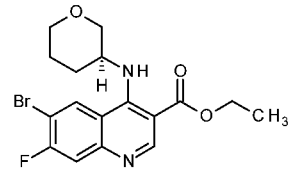
Intermediate D4: Ethyl 6-bromo-4-(oxan-4-ylamino)quinoline-3-carboxylate

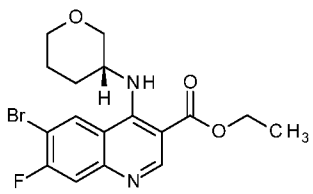
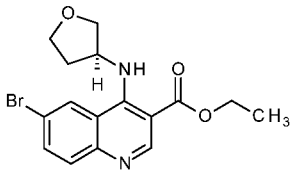
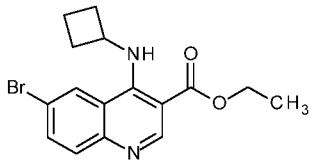
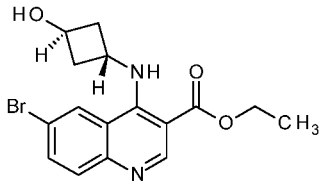
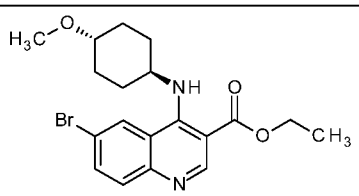
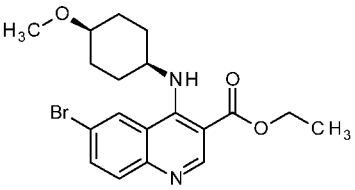
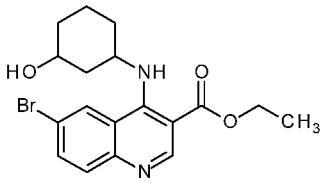


DIPEA (139mL, 794.75mmol) was added to ethyl 6-bromo-4-chloroquinoline-3-carboxylate (100g, 317.90mmol) and tetrahydro-2H-pyran-4-amine (35.4g, 349.69mmol) in DMA (1000mL) at ambient temperature under air. The resulting mixture was stirred at 60°C for 16 h then the solvent removed under reduced pressure. The mixture was azeotroped twice with toluene to afford the desired material (150g, 124%) as a brown solid, which was used without further purification. *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.36 (3H, t), 1.58-1.75 (2H, m), 1.90-2.02 (2H, m), 3.40 (2H, t), 3.81-3.98 (2H, m), 3.98-4.19 (1H, m), 4.37 (2H, q), 7.82 (1H, d), 7.92 (1H, dd), 8.56 (1H, s), 8.86 (1H, s). *Mass Spectrum*: *m/z* (ES-)[M-H]- = 378, 380.

On a larger scale, ethyl 6-bromo-4-chloroquinoline-3-carboxylate (2196 g, (1976 g active), 6.28 mol) was charged to the vessel with DMA (16 L). Tetrahydro-2H-pyran-4-amine (1224 g, 12.10 mol) was added over 10 minutes with an observed exotherm of 21-27°C. DIPEA (3.5 L, 20.09 mol) was added with no observed exotherm. The mixture was heated to 75-85°C and the resulting solution stirred for 18.5 h at 80°C. HPLC indicated consumption of starting material and 99.2% product. The reaction was cooled to 50°C and then poured into water (50 L). The resulting suspension was stirred for 2 h at ambient temperature and the solids isolated by filtration, washing with water (8 L then 2 x 4L). The solid was dried under vacuum at 40°C for 55 h to give 2307 g of desired material. Analytical data was consistent with that obtained from previous batches.

The following ester intermediates were prepared in an analogous fashion from the appropriate amine and either ethyl 6-bromo-4-chloro-7-fluoroquinoline-3-carboxylate or ethyl 6-bromo-4-chloroquinoline-3-carboxylate:

Intermediate	Structure	Name
Intermediate E4*		Ethyl 6-bromo-4-[(*cis*-3-methoxycyclobutyl)amino]quinoline-3-carboxylate
Intermediate F4**		Ethyl 6-bromo-7-fluoro-4-[(*cis*-3-methoxycyclobutyl)amino]quinoline-3-carboxylate
Intermediate G4 ***		ethyl 6-bromo-4-[[(3*S*)-oxan-3-yl]amino]quinoline-3-carboxylate
Intermediate H4 ***		ethyl 6-bromo-4-[[(3*R*)-oxan-3-yl]amino]quinoline-3-carboxylate
Intermediate I4 ****		ethyl 6-bromo-4-(oxetan-3-ylamino)quinoline-3-carboxylate
Intermediate J4***		ethyl 6-bromo-7-fluoro-4-[[(3*S*)-tetrahydropyran-3-yl]amino]quinoline-3-carboxylate

Intermediate	Structure	Name
Intermediate K4* **		ethyl 6-bromo-7-fluoro-4-[[(3*R*)-tetrahydropyran-3-yl]amino]quinoline-3-carboxylate
Intermediate L4***		ethyl 6-bromo-4-[[(3*S*)-tetrahydrofuran-3-yl]amino]quinoline-3-carboxylate
Intermediate M4		ethyl 6-bromo-4-(cyclobutylamino)quinoline-3-carboxylate
Intermediate N4* **		ethyl 6-bromo-4-[(*trans*-3-hydroxycyclobutyl)amino]quinoline-3-carboxylate
Intermediate O4* **		ethyl 6-bromo-4-[(*trans*-4-methoxycyclohexyl)amino]quinoline-3-carboxylate
Intermediate P4* **		ethyl 6-bromo-4-[(*cis*-4-methoxycyclohexyl)amino]quinoline-3-carboxylate
Intermediate Q4* **		ethyl 6-bromo-4-[(3-hydroxycyclohexyl)amino]quinoline-3-carboxylate (mixture of isomers)

* The reaction was stirred at 75°C for 5 h.

** The reaction was stirred at 85°C for 3 h.

*** The reaction was stirred at 80°C for 2 - 16 h.

**** The reaction was stirred at 90°C for 1 - 3 h.

***** The reaction was stirred at 100°C for 16 h optionally using Et_3N as the base.

Intermediate E4: *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.38 (3H, t), 1.85-1.98(2H, m), 2.75-7.89 (2H, m), 3.17 (3H, s), 3.65-3.78 (1H, m), 3.98-4.05 (1H, m), 4.35 (2H, q), 7.60 (1H, d), 7.70 (1H, dd), 8.40 (1H,d), 8.84-8.85 (1H, m). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 379.

Intermediate F4: *NMR Spectrum*: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.44-1.41 (3H, t), 2.21-2.14 (2H, m), 3.05-2.98 (2H, m), 3.30 (3H, s), 3.94-3.75 (1H, m), 4.11-4.06 (1H, m), 4.43-4.37 (2H, d), 7.70 (1H, d), 8.29 (1H, d), 9.07 (1H, d), 9.69 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 397.

Intermediate G4: *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.36 (3H, t), 1.70-1.74 (1H, m), 1.75-1.77 (2H, m), 2.03-2.05 (1H, m), 3.58-3.61 (3H, m), 3.80-3.85 (1H, m), 4.01-4.03 (1H, m), 4.35 (2H, q), 7.80 (1H, d), 7.89 (1H, dd), 8.58 (1H, s), 8.67 (1H, d), 8.93 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 380.8.

Intermediate H4: *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.50 - 1.56(1H, m), 1.62 – 1.84 (2H, m), 1.99 – 2.13 (1H, m), 3.51 – 3.73 (3H, m), 3.89 (1H, d), 4.12 -4.22 (1H, m), 7.77 (1H, d), 7.90 (1H, d), 8.31 (1H, s), 8.94 (1H, s), 13.41 (1H, bs). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 379.

Intermediate I4: *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.34 (3H, t), 4.34 (2H, q), 4.62 - 4.68 (2H, m), 4.77 (1H, q), 4.86 (2H, t), 7.78 (1H, d), 7.85 (1H, ddd), 8.42 (1H, d), 8.73 (1H, d), 8.79 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 353.

Intermediate J4: *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.33 (3H, m), 1.51 (1H, m), 1.74 (2H, m), 2.04 (1H, m), 3.60 (3H, m), 3.82 (1H, d), 4.02 (1H, m), 4.35 (2H, m), 7.73 (1H, m), 8.49 (1H, m), 8.79 (1H, m), 8.88 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 397.

Intermediate K4: *Mass Spectrum: m/z* (ES+)[M+H]+ = 397.

Intermediate L4: *NMR Spectrum*: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.45 (3H, t), 2.12 - 2.19 (1H,m), 2.48 - 2.55 (1H, m), 3.87 - 4.04 (2H, m), 4.12 (2H, td), 4.43 (2H, q), 4.76 - 4.86 (1H, m), 7.80 (1H, dd), 7.95 (1H, d), 8.34 (1H, d), 9.14 (1H, s), 9.64 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 365.

Intermediate M4: *NMR Spectrum*: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.45 (3H, t), 1.77 - 2.01 (2H, m), 2.16 - 2.31 (2H, m), 2.58 - 2.71 (2H, m), 4.45 (3H, m), 7.74 (1H, dd), 7.82 (1H, d), 8.23 (1H, d), 9.09 (1H, s), 9.57 (1H, d) *Mass Spectrum: m/z* (ES+)[M+H]+ = 349.

Intermediate N4: *NMR Spectrum*: ^{1}H NMR (500MHz, DMSO-d6) δ 1.34 (3H, t), 2.34 (4H, t), 4.33 (3H, q), 4.56 (1H, q), 5.21 (1H, d), 7.75 (1H, d), 7.85 (1H, dd), 8.31 (1H, d), 8.85 (1H, s), 9.13 (1H, d). *Mass Spectrum: m/z* (ES+)[M+H]+ = 366.

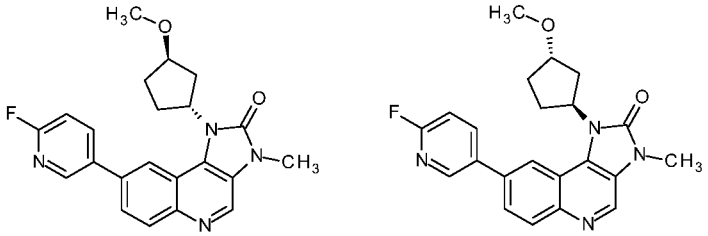
Intermediate O4: *NMR Spectrum*: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.40-1.59 (1H, 4H), 1.45 (3H, t), 2.08 - 2.18 (2H, m), 2.18 - 2.27 (2H, m), 3.23 - 3.34 (1H, m), 3.39 (3H, s), 3.99-4.05 (1H, m), 4.41 (2H, q), 7.75 (1H, dd), 7.83 (1H, d), 8.27 (1H, d), 9.08 (1H, d), 9.12 (1H, s) *Mass Spectrum: m/z* (ES+)[M+H]+ = 407.

Intermediate P4: *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.35 (3H, t), 1.54-1.61 (2H, m), 1.63 - 1.83 (6H, m), 3.24 (3H, s), 3.96 (1H, d), 4.35 (2H, q), 7.78 (1H, d), 7.87 (1H, dd), 8.44 (1H, d), 8.61 (1H, d), 8.87 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 407.

Intermediate Q4: Mixture of *cis* and *trans* isomers (ratio 1:2, unassigned) *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.06 – 1.2 (2H, m), 1.21 – 1.42 (10H, m), 1.42 – 1.61 (2H, m), 1.63 – 1.86 (4H, m), 1.87 – 2.01 (2H, m), 2.20 (1H, d), 3.39 – 3.57 (2H, m), 3.71 – 3.87 (1H, m), 3.95 (1H, s), 4.22 – 4.48 (5H, m), 4.61 (1H, s), 4.79 (1H, s), 7.77 (1H, s), 7.80 (1H, s), 7.84 – 7.90 (2H, m), 8.35 (1H, d), 8.42 (2H, 2 x d), 8.69 (1H, d), 8.84 (1H, s), 8.88 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 393.

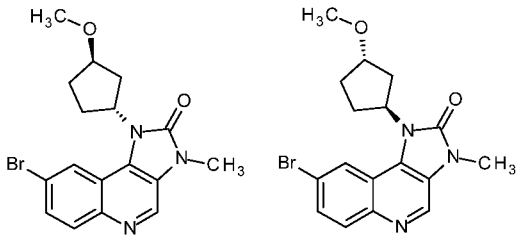
The preparation of 8-(6-Fluoro-3-pyridyl)-1-[(1R,3R)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one: 8-(6-fluoro-3-pyridyl)-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one (1:1 mixture) is described below:

Intermediate U0: 8-(6-Fluoro-3-pyridyl)-1-[(1R,3R)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one: 8-(6-fluoro-3-pyridyl)-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one (1:1 mixture)



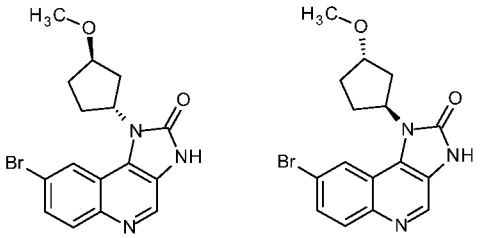
A mixture of 8-bromo-1-[(1R,3R)-3-methoxycyclopentyl]-3-methylimidazo[4,5-c]quinolin-2-one: 8-bromo-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3-methylimidazo[4,5-c]quinolin-2-one (1:1 mixture) (1.5 g, 3.99 mmol), (6-fluoropyridin-3-yl)boronic acid (0.674 g, 4.78 mmol) and chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.314 g, 0.40 mmol) in dioxane:water (10:1 mixture) (16.5 mL) was heated to 120 °C for 45 mins in the microwave reactor then allowed to cool and concentrated *in vacuo*. The crude product was purified by FCC, elution gradient 0 to 10% MeOH in DCM, to afford the desired material as a yellow solid (1.20 g, 77 %). *NMR Spectrum*: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.91 - 1.99 (1H, m), 2.21- 2.36 (3H, m), 2.58 - 2.78 (2H, m), 3.38 (3H, s), 3.62 (3H, s), 4.15 - 4.17 (1H, m), 5.52 - 5.65 (1H, m), 7.12 (1H, dd), 7.83 (1H, dd), 8.13 (1H, td), 8.31 (1H, d), 8.40 (1H, d), 8.59 (1H, d), 8.76 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 393.

Intermediate U1: 8-bromo-1-[(1*R*,3*R*)-3-methoxycyclopentyl]-3-methylimidazo[4,5-c]quinolin-2-one: 8-bromo-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3-methylimidazo[4,5-c]quinolin-2-one (1:1 mixture)



A mixture of 6-bromo-4-[[(1*R*,3*R*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylic acid: 6-bromo-4-[[(1*S*,3*S*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylic acid (1:1 mixture) (13g, 35.8mmol), tetrabutylammonium bromide (1.16g, 3.60mmol), iodomethane (7.645g, 53.86mmol) and sodium hydroxide (2.15g, 53.75mmol) in DCM (600mL) and water (380mL) was stirred at ambient temperature overnight. The resulting solution was concentrated under vacuum to remove the organics and the solids collected by filtration, washed with water (5x10mL) and dried in a vacuum oven to afford the desired material (racemic mixture) (9.8g, 73%) as a off-white solid. *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.81-1.87 (1H, m), 2.33-2.51 (4H, m), 2.45-2.51 (1H, m), 3.28 (3H, s), 3.49 (3H, s), 4.02-4.21 (1H, m), 5.40 (1H, p), 7.73 (1H, dd), 7.98 (1H, d), 8.35 (1H, d), 8.91 (1H, s). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 375.9.

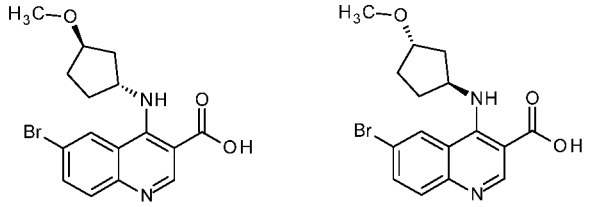
Intermediate U2: 8-bromo-1-[(1*R*,3*R*)-3-methoxycyclopentyl]-3H-imidazo[4,5-c]quinolin-2-one: 8-bromo-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3H-imidazo[4,5-c]quinolin-2-one (1:1 mixture)



A mixture of 6-bromo-4-[[(1*R*,3*R*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylic acid: 6-bromo-4-[[(1*S*,3*S*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylic acid (1:1 mixture) (17g, 46.54mmol), triethylamine (14.1g, 139.34mmol) in DMF (270mL) was stirred at ambient temperature for 1 h. Diphenyl phosphorazidate (25.6g, 93.02mmol) was added dropwise with stirring and the solution stirred at ambient temperature for a further 20 minutes before being heated to 60°C for 1 h. The reaction was allowed to cool and concentrated under vacuum. The residue was diluted with water (300mL), the solids

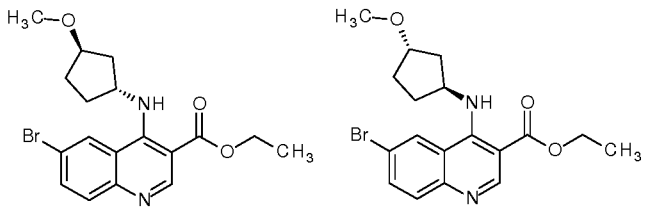
collected by filtration and dried in an oven under reduced pressure to afford the desired material (as a racemic mixture) (13g, 77%) as a off-white solid. *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 362.2.

Intermediate U3: 6-bromo-4-[[(1*R*,3*R*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylic acid: 6-bromo-4-[[(1*S*,3*S*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylic acid (1:1 mixture)



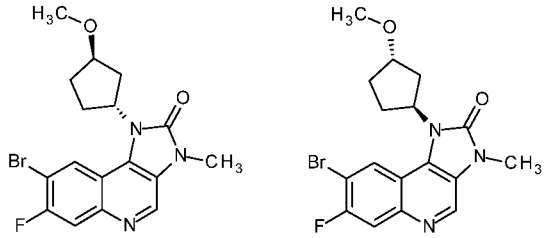
2N Sodium hydroxide (150mL) was added to a mixture of ethyl 6-bromo-4-[[(1*R*,3*R*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylate: ethyl 6-bromo-4-[[(1*S*,3*S*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylate (1:1 mixture) (18.6g, 47.2mmol) in MeOH (500mL) and water (100mL) and the resulting solution stirred for 15 h at ambient temperature. The mixture was concentrated under vacuum and the residue diluted with water (300mL). The pH value of the solution was adjusted to 5 with 2N hydrochloric acid, the solids collected by filtration and dried in an oven under reduced pressure to afford the desired material (as a racemic mixture) (17.1g) as a off-white solid. *NMR Spectrum*: ^{1}H NMR (400MHz, DMSO-d6) δ 1.60-1.71 (2H, m), 1.81-1.88 (1H, m), 1.96-2.02 (1H, m), 2.03- 2.10 (2H, m), 3.21 (3H, s), 3.91-3.96 (1H, m), 4.51-4.72 (1H, m), 7.77 (1H, d), 7.93 (1H, d), 8.45 (1H, d), 8.85 (1H, s), 13.30 (1H, bs). *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 365.2.

Intermediate U4: Ethyl 6-bromo-4-[[(1*R*,3*R*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylate: ethyl 6-bromo-4-[[(1*S*,3*S*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylate (1:1 mixture)



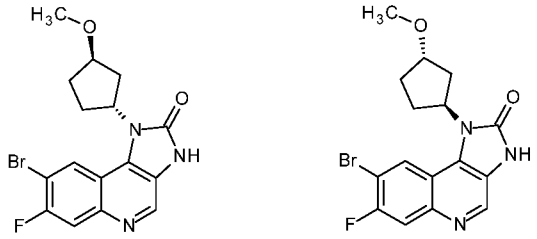
A mixture of ethyl 6-bromo-4-chloroquinoline-3-carboxylate (15g, 47.69mmol), (*trans*)-3-methoxycyclopentan-1-amine (racemic mixture) (8.09g, 26.68mmol) and DIPEA (19.68g, 152.27mmol) in DMA (100mL) was stirred at 80°C for 4 h under an inert atmosphere. The reaction was quenched by the addition of water (500mL), the solids collected by filtration and dried in an oven under reduced pressure to afford the desired material (as a racemic mixture) (18.6 g) as a light brown solid. *Mass Spectrum*: *m/z* (ES+)[M+H]+ = 393, 395.

Intermediate V1: 8-bromo-7-fluoro-1-[(1*R*,3*R*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one and 8-bromo-7-fluoro-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one (1:1 mixture)



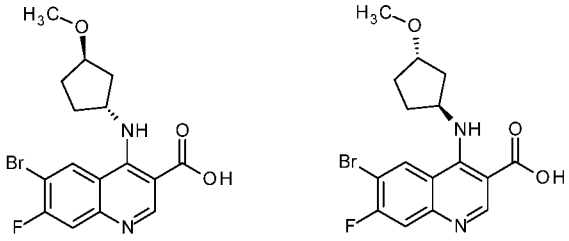
A mixture of 8-bromo-7-fluoro-1-[(1*R*,3*R*)-3-methoxycyclopentyl]-3H-imidazo[4,5-c]quinolin-2-one: 8-bromo-7-fluoro-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3H-imidazo[4,5-c]quinolin-2-one (1:1 mixture) (2.8 g, 7.33 mmol), sodium hydroxide (440 mg, 11.00 mmol,), tetrabutylammonium bromide (240 mg, 0.75 mmol) and methyl iodide (1.6 g, 11.27 mmol) in DCM (150 mL) and water (100 mL) was stirred for 12 h at ambient temperature. The resulting mixture was concentrated *in vacuo* and the residue triturated with water. The solids were collected by filtration and dried to afford the desired material as a white solid (2.5 g, 86%). *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.76 - 1.86 (1H, m), 2.11 – 2.32 (4H, m), 2.41 - 2.44 (1H, m), 3.27 (3H, s), 3.30 (3H, s), 4.12 – 4.15 (1H, m), 5.38 – 5.45 (1H, m), 7.96 (1H, d), 8.53 (1H, d), 8.94 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 394.

Intermediate V2: 8-bromo-7-fluoro-1-[(1*R*,3*R*)-3-methoxycyclopentyl]-3H-imidazo[4,5-c]quinolin-2-one and 8-bromo-7-fluoro-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3H-imidazo[4,5-c]quinolin-2-one (1:1 mixture)



A mixture of 6-bromo-7-fluoro-4-[[(1*R*,3*R*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylic acid: 6-bromo-7-fluoro-4-[[(1*S*,3*S*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylic acid (1:1 mixture) (2.9 g, 7.53 mmol) and triethylamine (2.3 g, 22.73 mmol) in DMA (20 mL) was stirred at ambient temperature for 30 mins. Diphenyl phosphorazidate (2.5 g, 9.09 mmol) was added and the resulting solution stirred for 2 h at 60°C. The reaction mixture was allowed to cool and the solids collected by filtration. The solid was dried in an oven under reduced pressure to afford the desired material as a white solid (2.8 g, 97%). *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.78 - 1.88 (1H, m), 2.11 – 2.31 (4H, m), 2.41 - 2.45 (1H, m), 3.27 (3H, s), 4.08 – 4.15 (1H, m), 5.34 – 5.39 (1H, m), 7.92 (1H, d), 8.51 (1H, d), 8.68 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 380.

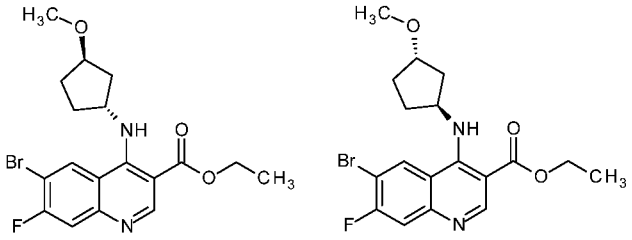
Intermediate V3: 6-bromo-7-fluoro-4-[[(1*R*,3*R*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylic acid and 6-bromo-7-fluoro-4-[[(1*S*,3*S*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylic acid (1:1 mixture)



A mixture of ethyl 6-bromo-7-fluoro-4-[[(1*R*,3*R*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylate: ethyl 6-bromo-7-fluoro-4-[[(1*S*,3*S*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylate (1:1 mixture) (3.4 g, 8.23 mmol) and 2N sodium hydroxide (12 mL) in MeOH (15 mL) and THF (15 mL) was stirred for 12 h at ambient temperature. The pH of the solution was adjusted to 3 with 1M HCl and the resultant solid collected by filtration and dried to afford the desired material as a white solid (2.9 g, 91%). *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.61 - 1.71 (2H, m), 1.76 - 1.86 (1H, m), 1.92 - 2.03 (1H, m), 2.11 - 2.26 (2H, m), 3.21 (3H, s), 3.86 – 3.96 (1H,

m), 4.56 – 4.64 (1H, m), 7.70 (1H, d), 8.56 (1H, d), 8.88 (1H, s), 13.31 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 383.

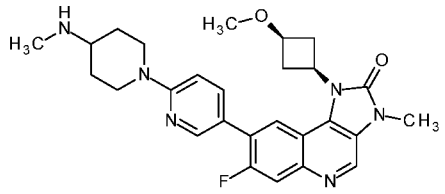
Intermediate V4: Ethyl 6-bromo-7-fluoro-4-[[(1*R*,3*R*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylate and Ethyl 6-bromo-7-fluoro-4-[[(1*S*,3*S*)-3-methoxycyclopentyl]amino]quinoline-3-carboxylate (1:1 mixture)



A mixture of ethyl 6-bromo-4-chloro-7-fluoroquinoline-3-carboxylate (2 g, 6.01 mmol), (1*R*,3*R*)-3-methoxycyclopentanamine hydrochloride and (1*S*,3*S*)-3-methoxycyclopentanamine hydrochloride (1:1 mixture) (1.4 g, 9.21 mmol) and DIPEA (1.6 g, 12.38 mmol) in DMA (10 mL) was stirred for 2 h at 80°C. The reaction mixture was allowed to cool and the residue triturated with water. The solids were collected by filtration and dried to afford the desired material as a white solid (2.4 g, 97%). *Mass Spectrum: m/z* (ES+)[M+H]+ = 411.

Example 57

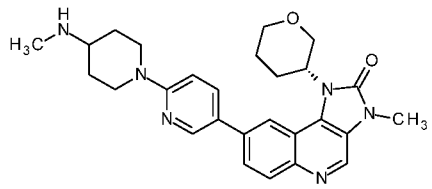
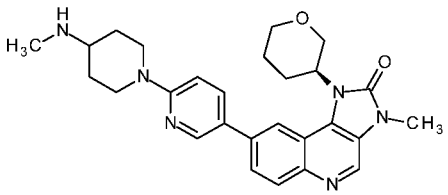
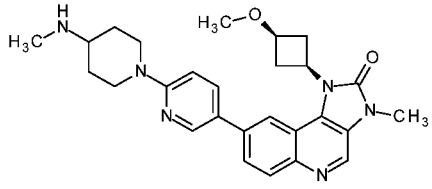
7-Fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]imidazo[4,5-c]quinolin-2-one

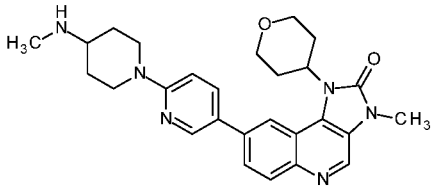


A mixture of 7-fluoro-8-(6-fluoro-3-pyridyl)-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one (120mg, 0.30 mmol), tert-butyl methyl(piperidin-4-yl)carbamate dihydrochloride (130 mg, 0.45 mmol) and DIPEA (0.106 mL, 0.61 mmol) in DMSO (2 mL) was stirred at 130°C for 5 h. The crude product, 3-tert-butyl-1-[1-[5-[7-fluoro-1-(3-methoxycyclobutyl)-3-methyl-2-oxo-imidazo[4,5-c]quinolin-8-yl]-2-pyridyl]-

4-piperidyl]-1-methyl-urea, was purified by flash C18 chromatography, elution gradient 5 to 45% MeCN in (0.1% FA) water, and the appropriate fractions combined and concentrated *in vacuo*. The residue was treated with TFA (2 mL, 25.96 mmol) in DCM (3.0 mL) and the mixture stirred at ambient temperature for 12 h. The solvent was removed under reduced pressure and the crude product purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µm silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% AMMONIA) and MeCN as eluents, to afford the desired material as a yellow solid (40.0 mg, 26.9 %). *NMR Spectrum*: ^{1}H NMR (300MHz, DMSO-d6) δ 1.30-1.50 (2H, m), 1.90-2.10 (2H, m), 2.45 (3H, s), 2.72-2.88 (2H, m), 2.88-3.05 (5H, m), 3.15 (3H, s), 3.45 (3H, s), 3.75-3.90 (1H,m), 4.32-4.45 (2H, m), 4.95-5.15 (1H,m), 7.02 (1H, s), 7.80-7.92(2H, m), 8.25-8.30(1H, d), 8.35 (1H, s), 8.25-8.40 (1H, m), 8.85 (1H, s). *Mass Spectrum: m/z* (ES+)[M+H]+ = 491.

The following examples were prepared in an analogous fashion from the appropriate intermediates.

Example	Structure	Name
58*		3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
59*		3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one
60**		1-(*cis*-3-methoxycyclobutyl)-3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]imidazo[4,5-c]quinolin-2-one

Example	Structure	Name
61**		3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one

* The displacement reaction was performed at 130°C for 16 h and the deprotection carried out at ambient temperature for 30 minutes.

** The displacement reaction was performed at 130°C for 3 - 5 h and the deprotection carried out at ambient temperature for 1 h.

Example 58: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.42 (2H, m), 1.82 (2H, m), 2.01 (2H, d), 2.15 (1H, d), 2.50 (3H, s), 2.70 (1H, m), 2.95 (2H, t), 3.10 (1H, m), 3.40 (1H, m), 3.48 (3H, s), 3.92 (1H, d), 4.18 (2H, m), 4.45 (2H, d), 4.93 (1H, bs), 7.06 (1H, d), 7.90 - 8.89 (7H, m). *Mass Spectrum:* m/z (ES+)[M+H]+ = 473.

Example 59: *NMR Spectrum:* ^{1}H NMR (300MHz, MeOH-d4) δ 1.65 (2H, q), 1.95 (2H, m), 2.25 (3H, m), 2.76 (3H, s), 2.85 (1H, m), 3.12 (2H, t), 3.40 (1H, m), 3.60 (4H, m), 4.05 (1H, d), 4.22 (1H, d), 4.40 (1H, t), 4.60 (2H, d), 5.19 (1H, bs), 7.20 (1H, d), 8.15 (1H, d), 8.27 (2H, s), 8.60 (2H, d), 9.10 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 473.

Example 60: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.10-1.30 (2H, m), 1.87-1.91 (2H, m), 2.32 (3H, s), 2.49-2.63 (1H, m), 2.77-2.85 (2H, m), 2.95-3.05 (4H, m), 3.20 (3H, s), 3.49 (3H, s), 3.84-3.89 (1H, m), 4.25-4.29 (2H, m), 5.08-5.14 (1H, m), 6.98 (1H, d), 7.87-7.91 (1H, m), 8.01-8.08 (2H, m), 8.36 (1H, d), 8.64 (1H, d), 8.83 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 473.

Example 61: *NMR Spectrum:* ^{1}H NMR (300MHz, DMSO-d6) δ 1.20-1.24 (2H, m), 1.85-1.93 (4H, m), 2.30 (3H, s), 2.49-2.54 (1H, m), 2.69-2.74 (2H, m), 2.97-3.06 (2H, m), 3.32 (3H, s), 3.54-3.62 (2H, m), 4.05-4.10 (2H, m), 4.23-4.27 (2H, m), 5.00-5.13 (1H, m), 6.99 (1H, d), 7.91-7.94 (1H, m), 7.98-8.02 (1H, m), 8.08-8.11 (1H, m), 8.37 (1H, s), 8.62 (1H, d), 8.85 (1H, s). *Mass Spectrum:* m/z (ES+)[M+H]+ = 473.

BIOLOGICAL ASSAYS

The following assays were used to measure the effects of the compounds of the present invention: a) ATM cellular potency assay; b) PI3K cellular potency assay; c) mTOR cellular potency assay; d) ATR cellular potency assay. During the description of the assays, generally:

i. The following abbreviations have been used: 4NQO = 4-Nitroquinoline *N*-oxide; Ab = Antibody; BSA = Bovine Serum Albumin; CO_2 = Carbon Dioxide; DMEM = Dulbecco's Modified Eagle Medium; DMSO =Dimethyl Sulphoxide; EDTA = Ethylenediaminetetraacetic Acid; EGTA = Ethylene Glycol Tetraacetic Acid; ELISA = Enzyme-linked Immunosorbent Assay; EMEM = Eagle's Minimal Essential Medium; FBS = Foetal Bovine Serum; h = H(s); HRP = Horseradish Peroxidase; i.p. = intraperitoneal; PBS = Phosphate buffered saline; PBST = Phosphate buffered saline / Tween; TRIS = Tris(Hydroxymethyl)aminomethane; MTS reagent: [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt, and an electron coupling reagent (phenazine methosulfate) PMS; s.c. sub-cutaneously.

ii. IC_{50} values were calculated using a smart fitting model in Genedata. The IC_{50} value was the concentration of test compound that inhibited 50% of biological activity.

Assay a): ATM Cellular Potency

Rationale:

Cellular irradiation induces DNA double strand breaks and rapid intermolecular autophosphorylation of serine 1981 that causes dimer dissociation and initiates cellular ATM kinase activity. Most ATM molecules in the cell are rapidly phosphorylated on this site after doses of radiation as low as 0.5 Gy, and binding of a phosphospecific antibody is detectable after the introduction of only a few DNA double-strand breaks in the cell.

The rationale of the pATM assay is to identify inhibitors of ATM in cells. HT29 cells are incubated with test compounds for 1h prior to X-ray-irradiation. 1h later the cells

are fixed and stained for pATM (Ser1981). The fluorescence is read on the arrayscan imaging platform.

Method details:

HT29 cells (ECACC #85061109) were seeded into 384 well assay plates (Costar #3712) at a density of 3500 cells / well in 40µl EMEM medium containing 1% L glutamine and 10% FBS and allowed to adhere overnight. The following morning compounds of Formula **(I)** in 100% DMSO were added to assay plates by acoustic dispensing. After 1h incubation at 37°C and 5% CO_2, plates (up to 6 at a time) were irradiated using the X-RAD 320 instrument (PXi) with equivalent to ~600cGy. Plates were returned to the incubator for a further 1h. Then cells were fixed by adding 20µl of 3.7% formaldehyde in PBS solution and incubating for 20 minutes at r.t. before being washed with 50µl / well PBS, using a Biotek EL405 plate washer. Then 20µl of 0.1% Triton X100 in PBS was added and incubated for 20 minutes at r.t., to permeabalise cells. Then the plates were washed once with 50µl / well PBS, using a Biotek EL405 plate washer.

Phospho-ATM Ser1981 antibody (Millipore #MAB3806) was diluted 10000 fold in PBS containing 0.05% polysorbate/Tween and 3% BSA and 20µl was added to each well and incubated over night at r.t. The next morning plates were washed three times with 50µl / well PBS, using a Biotek EL405 plate washer, and then 20µl of secondary Ab solution, containing 500 fold diluted Alexa Fluor® 488 Goat anti-rabbit IgG (Life Technologies, A11001) and 0.002mg/ml Hoeschst dye (Life technologies #H-3570), in PBS containing 0.05% polysorbate/Tween and 3% BSA, was added. After 1h incubation at r.t., the plates were washed three times with 50µl / well PBS, using a Biotek EL405 plate washer, and plates were sealed and kept in PBS at 4°C until read. Plates were read using an ArrayScan VTI instrument, using an XF53 filter with 10X objective. A two laser set up was used to analyse nuclear staining with Hoeschst (405nm) and secondary antibody staining of pSer1981 (488nm).

Assay b): ATR Cellular Potency

Rationale:

ATR is a PI 3-kinase-related kinase which phosphorylates multiple substrates on serine or threonine residues in response to DNA damage during or replication blocks. Chk1, a downstream protein kinase of ATR, plays a key role in DNA damage checkpoint control. Activation of Chk1 involves phosphorylation of Ser317 and Ser345 (the latter regarded as the preferential target for phosphorylation/activation by ATR). This was a cell based assay to measure inhibition of ATR kinase, by measuring a decrease in phosphorylation of Chk1 (Ser 345) in HT29 cells, following treatment with compound of Formula **(I)** and the UV mimetic 4NQO (Sigma #N8141).

Method details:

HT29 cells (ECACC #85061109) were seeded into 384 well assay plates (Costar #3712) at a density of 6000 cells / well in 40µl EMEM medium containing 1% L glutamine and 10% FBS and allowed to adhere overnight. The following morning compound of Formula **(I)** in 100% DMSO were added to assay plates by acoustic dispensing. After 1h incubation at 37°C and 5% CO_2, 40nl of 3mM 4NQO in 100% DMSO was added to all wells by acoustic dispensing, except minimum control wells which were left untreated with 4NQO to generate a null response control. Plates were returned to the incubator for a further 1h. Then cells were fixed by adding 20µl of 3.7% formaldehyde in PBS solution and incubating for 20 mins at r.t. Then 20µl of 0.1% Triton X100 in PBS was added and incubated for 10 minutes at r.t., to permeabalise cells. Then the plates were washed once with 50µl / well PBS, using a Biotek EL405 plate washer.

Phospho-Chk1 Ser 345 antibody (Cell Signalling Technology #2348) was diluted 150 fold in PBS containing 0.05% polysorbate/Tween and 15µl was added to each well and incubated over night at r.t. The next morning plates were washed three times with 50µl / well PBS, using a Biotek EL405 plate washer, and then 20µl of secondary Ab solution, containing 500 fold diluted Alexa Fluor 488 Goat anti-rabbit IgG (Molecular Probes #A-11008) and 0.002mg/ml Hoeschst dye (Molecular Probes #H-3570), in PBST, was added. After 2h incubation at r.t., the plates were washed three times with 50µl / well PBS, using a Biotek EL405 plate washer, and plates were then sealed with black plate seals until read. Plates were read using an ArrayScan VTI instrument, using an XF53 filter with 10X

objective. A two laser set up was used to analyse nuclear staining with Hoeschst (405nm) and secondary antibody staining of pChk1 (488nm).

Assay c): PI3K Cellular Potency

Rationale:

This assay was used to measure PI3K-α inhibition in cells. PDK1 was identified as the upstream activation loop kinase of protein kinase B (Akt1), which is essential for the activation of PKB. Activation of the lipid kinase phosphoinositide 3 kinase (PI3K) is critical for the activation of PKB by PDK1.

Following ligand stimulation of receptor tyrosine kinases, PI3K is activated, which converts PIP2 to PIP3, which is bound by the PH domain of PDK1 resulting in recruitment of PDK1 to the plasma membrane where it phosphorylates AKT at Thr308 in the activation loop.

The aim of this cell-based mode of action assay is to identify compounds that inhibit PDK activity or recruitment of PDK1 to membrane by inhibiting PI3K activity. Phosphorylation of phospho-Akt (T308) in BT474c cells following treatment with compounds for 2h is a direct measure of PDK1 and indirect measure of PI3K activity.

Method details:

BT474 cells (human breast ductal carcinoma, ATCC HTB-20) were seeded into black 384 well plates (Costar, #3712) at a density of 5600 cells / well in DMEM containing 10% FBS and 1% glutamine and allowed to adhere overnight.

The following morning compounds in 100% DMSO were added to assay plates by acoustic dispensing. After a 2h incubation at 37°C and 5% CO_2, the medium was aspirated and the cells were lysed with a buffer containing 25mM Tris, 3mM EDTA, 3mM EGTA, 50mM sodium fluoride, 2mM Sodium orthovanadate, 0.27M sucrose, 10mM β-glycerophosphate, 5mM sodium pyrophosphate, 0.5% Triton X-100 and complete protease inhibitor cocktail tablets (Roche #04 693 116 001, used 1 tab per 50ml lysis buffer).

After 20 minutes, the cell lysates were *trans*ferred into ELISA plates (Greiner # 781077) which had been pre-coated with an anti total-AKT antibody in PBS buffer and non-specific binding was blocked with 1% BSA in PBS containing 0.05% Tween 20.

Plates were incubated over night at 4°C. The next day the plates were washed with PBS buffer containing 0.05% Tween 20 and further incubated with a mouse monoclonal anti-phospho AKT T308 for 2h. Plates were washed again as above before addition of a horse anti-mouse-HRP conjugated secondary antibody. Following a 2h incubation at r.t., plates were washed and QuantaBlu substrate working solution (Thermo Scientific #15169, prepared according to provider's instructions) was added to each well. The developed fluorescent product was stopped after 60 minutes by addition of Stop solution to the wells. Plates were read using a Tecan Safire plate reader using 325nm excitation and 420nm emission wavelengths respectively. Except where specified, reagents contained in the Path Scan Phospho AKT (Thr308) sandwich ELISA kit from Cell Signalling (#7144) were used in this ELISA assay.

Assay d): mTOR Cellular Potency

Rationale:

This assay was used to measure mTOR inhibition in cells. The aim of the phospho-AKT cell based mechanism of action assay using the Acumen Explorer is to identify inhibitors of either PI3Kα or mTOR-Rictor (Rapamycin insensitive companion of mTOR). This is measured by any decrease in the phosphorylation of the Akt protein at Ser473 (AKT lies downstream of PI3Kα in the signal *trans*duction pathway) in the MDA-MB-468 cells following treatment with compound.

Method details:

MDA-MB-468 cells (human breast adenocarcinoma #ATCC HTB 132) were seeded at 1500 cells / well in 40µl of DMEM containing 10% FBS and 1% glutamine into Greiner 384 well black flat-bottomed plates. Cell plates were incubated for 18h in a 37°C incubator before dosing with compounds of Formula **(I)** in 100% DMSO using acoustic dispensing. Compounds were dosed in a 12 point concentration range into a randomised plate map. Control wells were generated either by dosing of 100% DMSO (max signal) or addition of a reference compound (a PI3K-β inhibitor) that completely eliminated the pAKT signal (min control). Plates were incubated at 37°C for 2h; cells were then fixed by the addition of 10µl of a 3.7% formaldehyde solution. After 30 minutes the plates were

washed with PBS using a Tecan PW384 plate washer. Wells were blocked and cells permeabilised with the addition of 40µl of PBS containing 0.5% Tween20 and 1% Marvel™ (dried milk powder) and incubated for 60 minutes at r.t. The plates were washed with PBS containing 0.5% (v/v) Tween20 and 20µl rabbit anti-phospho AKT Ser473 (Cell Signalling Technologies, #3787) in same PBS-Tween + 1% Marvel™ was added and incubated overnight at 4°C.

Plates were washed 3 times with PBS + 0.05% Tween 20 using a Tecan PW384. 20µl of secondary antibody Alexa Fluor 488 anti-Rabbit (Molecular Probes, #A11008) diluted in PBS + 0.05% Tween20 containing 1% Marvel™ was added to each well and incubated for 1h at r.t. Plates were washed three times as before then 20µl PBS added to each well and plates sealed with a black plate sealer.

The plates were read on an Acumen plate reader as soon as possible, measuring green fluorescence after excitation with 488nm laser. Using this system IC_{50} values were generated and quality of plates was determined by control wells. Reference compounds were run each time to monitor assay performance.

Table 2: Potency Data for Examples 1 - 61 in Assays a) - d)

Example	Assay a) ATM Cell IC_{50} (µM)	Assay b) ATR Cell IC_{50} (µM)	Assay c) PI3Kα Cell IC_{50} (µM)	Assay d) mTOR Cell IC_{50} (µM)
1	0.00111	1.51	0.47	
2	0.0127	6.76		
3	0.0021	>30	19.3	
4	0.00761	18	0.243	
5	0.000312	0.284		
6	0.0017	>30		
7	0.000626	1.42	1.22	0.616
8	0.00104	0.261		
9	0.000842	2.48		
10	0.000752	3.21		
11	0.00077	1.08		

Example	Assay a) ATM Cell IC_{50} (µM)	Assay b) ATR Cell IC_{50} (µM)	Assay c) PI3Kα Cell IC_{50} (µM)	Assay d) mTOR Cell IC_{50} (µM)
12	0.000434	0.223		
13	>0.0239			
14	0.00151			
15	0.00146	>30		
16	0.0186	>22.3		
17	0.0137	>30		
18	0.0127	17.5		
19	0.0634	>30		
20	0.0365	>30	>10	>30
21	0.0258	>30		
22	0.0134	6.71		
23	0.0228	>24		
24	0.0166	9.23		
25	0.00661	2.52		
26	0.00929	>20.1		
27	0.0059	5.95		
28	0.0195	18.8		
29	0.00968	>30		
30	0.0249	>30		
31	0.0338	>30	>30	12.8
32	0.000307	>30	0.663	1.5
33	0.000332	>25.7	1.09	NV
34	0.000395	>30		2
35	0.0014	>30		16.5
36	0.000357	>30	0.987	3.9
37	0.000911	>30		
38	0.00391	>30		
39	0.00269	>30		

Example	Assay a) ATM Cell IC_{50} (µM)	Assay b) ATR Cell IC_{50} (µM)	Assay c) PI3Kα Cell IC_{50} (µM)	Assay d) mTOR Cell IC_{50} (µM)
40	0.00324	>30		22.1
41	0.00202	>30		
42	0.00154	>30	>30	>15.3
43	0.072	>30		
44	0.000889	1.12		
45	0.000618	>30		
46	0.0077	>10		
47	0.0027	1.8		
48	0.00234	0.201		
49	0.0153	1.91		
50	0.0167	1.97		
51	0.000589	0.0906		
52	0.000112	0.0616		
53	0.000269	>21.4		
54	0.000061	>25.6		
55	0.00338	0.804		
56	0.0157	1.19		
57	0.00116	>30	>30	7.72
58	0.00225	>21.8		
59	0.00138	>30		
60	0.000502	>30	0.292	0.989
61	0.000753	>25.5		

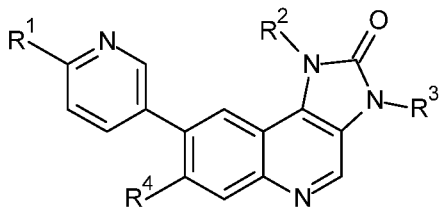
Table 3 shows comparative data for certain Compounds of CN102399218A and CN102372711A in tests a) b) c) and d).

Table 3: Potency Data for Certain Compounds of CN102399218A and CN102372711A in Assays a) - d)

Reference Compound	**Assay a) ATM Cell IC_{50} (μM)**	**Assay b) ATR Cell IC_{50} (μM)**	**Assay c) PI3Ka Cell IC_{50} (μM)**	**Assay d) mTOR Cell IC_{50} (μM)**
CN102372711A Compound 1	0.125	0.281	0.188	0.237
CN102372711A Compound 4	0.0112	0.0686	0.102	0.0729
CN102372711A Compound 5	0.0265	0.0644	0.153	0.113
CN102399218A Compound 60	1.76	>0.0771	4.67	2.31
CN102399218A Compound 61	3.46	1.48	1.73	0.177
CN102399218A Compound 62	0.08	0.0563	0.149	0.0155
CN102399218A Compound 64	0.216	0.162	0.247	0.287
CN102399218A Compound 94	0.494	0.0129	0.0804	0.0414
CN102399218A Compound 114	0.0741	0.0686	0.0131	0.0469

Claims

1. A compound of Formula **(I)**:



(I)

or a pharmaceutically acceptable salt thereof, where:

$\mathbf{R^1}$ is azetidinyl, pyrrolidinyl or piperidinyl, each of which is substituted by one methylamino group or one dimethylamino group;

$\mathbf{R^2}$ is:

- isopropyl,
- C_4-C_6 cycloalkyl optionally substituted with one methoxy group,
- oxetanyl,
- tetrahydrofuranyl, or
- tetrahydropyranyl;

$\mathbf{R^3}$ is hydro or methyl; and

$\mathbf{R^4}$ is hydro or fluoro.

2. The compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in claim 1, where $\mathbf{R^1}$ is azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each of which is substituted by one dimethylamino group or one methylamino group.

3. The compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in claim 1 or claim 2, where $\mathbf{R^1}$ is 3-(dimethylamino)azetidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(dimethylamino)piperidin-1-yl, 4-(dimethylamino)piperidin-1-yl or 4-(methylamino)piperidin-1-yl.

4. The compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of the preceding claims, where $\mathbf{R^2}$ is cyclobutyl, 3-

methoxycyclobut-1-yl, 3-methoxycyclopent-1-yl, 3-methoxycyclohex-1-yl, 4-methoxycyclohex-1-yl, isopropyl, oxetan-3-yl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl or tetrahydropyran-4-yl.

5. The compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of the preceding claims, where $\mathbf{R^3}$ is methyl.

6. The compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof as claimed in any one of the preceding claims, where $\mathbf{R^4}$ is hydro.

7. The compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in claim 1, where:

$\mathbf{R^1}$ is 3-(dimethylamino)azetidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(dimethylamino)piperidin-1-yl, 4-(dimethylamino)piperidin-1-yl or 4-(methylamino)piperidin-1-yl;

$\mathbf{R^2}$ is cyclobutyl, 3-methoxycyclobut-1-yl, 3-methoxycyclopent-1-yl, 3-methoxycyclohex-1-yl, 4-methoxycyclohex-1-yl, isopropyl, oxetan-3-yl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl or tetrahydropyran-4-yl;

$\mathbf{R^3}$ is methyl; and

$\mathbf{R^4}$ is hydro or fluoro.

8. The compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in claim 1, where the compound is selected from the group consisting of:

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(Dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(Dimethylamino)azetidin-1-yl]-3-pyridyl]-1-isopropyl-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[(1*S*,3*S*)-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydrofuran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*trans*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*trans*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(Dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[*trans*-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(Dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(Dimethylamino)azetidin-1-yl]-3-pyridyl]-1-(*trans*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

1-Cyclobutyl-8-[6-[3-(dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(Dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(Dimethylamino)azetidin-1-yl]-3-pyridyl]-3-methyl-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(Dimethylamino)azetidin-1-yl]-3-pyridyl]-7-fluoro-1-[*trans*-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(Dimethylamino)azetidin-1-yl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(Dimethylamino)-1-piperidyl]-3-pyridyl]-1-[*trans*-3-methoxycyclopentyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(Dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(Dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(Dimethylamino)-1-piperidyl]-3-pyridyl]-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

1-Cyclobutyl-8-[6-[4-(dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(Dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-(oxetan-3-yl)imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(Dimethylamino)-1-piperidyl]-3-pyridyl]-3-methyl-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(Dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(Dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-3-methyl-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(Dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)-1-piperidyl]-3-pyridyl]-7-fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-(*cis*-4-methoxycyclohexyl)-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(Dimethylamino)-1-piperidyl]-3-pyridyl]-1-[(*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(Dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[*cis*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]-3-pyridyl]-1-[*trans*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[4-(Dimethylamino)-1-piperidyl]-3-pyridyl]-1-[*trans*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

8-[6-[3-(Dimethylamino)azetidin-1-yl]-3-pyridyl]-1-[*trans*-3-methoxycyclohexyl]-3-methyl-imidazo[4,5-c]quinolin-2-one;

7-Fluoro-1-(*cis*-3-methoxycyclobutyl)-3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]imidazo[4,5-c]quinolin-2-one;

3-Methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]-1-[(3*R*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

3-Methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]-1-[(3*S*)-tetrahydropyran-3-yl]imidazo[4,5-c]quinolin-2-one;

1-(*cis*-3-Methoxycyclobutyl)-3-methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]imidazo[4,5-c]quinolin-2-one; and

3-Methyl-8-[6-[4-(methylamino)-1-piperidyl]-3-pyridyl]-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-2-one.

9. A pharmaceutical composition which comprises a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, and at least one pharmaceutically acceptable excipient.

10. A compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, for use in therapy.

11. A compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, for use in the treatment of cancer.

12. A compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to claim 11, where the compound of Formula **(I)** is administered simultaneously, separately or sequentially with radiotherapy.

13. A compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to claim 11, where the compound of Formula **(I)** is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from cisplatin, oxaliplatin, carboplatin, valrubicin, idarubicin, doxorubicin, pirarubicin, irinotecan, topotecan, amrubicin, epirubicin, etoposide, mitomycin, bendamustine, chlorambucil, cyclophosphamide, ifosfamide, carmustine, melphalan, bleomycin, olaparib, durvalumab, AZD1775 and AZD6738.

14. Use of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, in the manufacture of a medicament for the treatment of cancer.

15. A method for treating cancer in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/076416

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/444 A61K31/4545 A61P35/00 C07D471/04
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/139731 A1 (NOVARTIS AG) 9 December 2010 (2010-12-09) claims; examples 5, 97, 140, 179, 212, 247	1-15
A	WO 2008/103636 A1 (NOVARTIS AG) 28 August 2008 (2008-08-28) page 4, line 21 - line 24; claims	1-15
A	CN 102 372 711 B (SHANDONG XUANZHU PHARM. CO. LTD.) 17 September 2014 (2014-09-17) cited in the application paragraph [[0395]]; claims	1-15
A,P	WO 2015/170081 A1 (ASTRAZENECA AB) 12 November 2015 (2015-11-12) page 1, line 19 - page 2, line 15; claims; examples	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 December 2016	20/12/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Helps, Ian

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/EP2016/076416

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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A61P 35/00(2006.01)
C07D 471/04(2006.01)

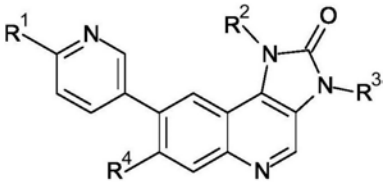
权利要求书5页 说明书84页

(54)发明名称

咪唑并[4,5-c]喹啉-2-酮化合物以及它们在治疗癌症中的用途

(57)摘要

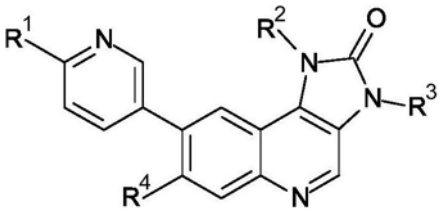
本说明书总体上涉及具有式(I):(I)的化合物及其药学上可接受的盐,其中R^1、R^2、R^3和R^4具有本文所定义的含义中的任一种。本说明书还涉及具有式(I)的化合物及其盐治疗或预防ATM介导的疾病,包括癌症的用途。本说明书进一步涉及包含经取代的咪唑并[4,5-c]喹啉-2-酮化合物及其药学上可接受的盐的药物组合物;包含此类化合物和盐的试剂盒;生产此类化合物和盐的方法;以及在此类生产中有用的中间体。



(I)

CN 108348515 A

1.一种具有式(I)的化合物：



(I)

或其药学上可接受的盐，其中：

R^1是氮杂环丁烷基、吡咯烷基、或哌啶基，其各自被一个甲基氨基基团或被一个二甲基氨基基团取代；

R^2是：

-异丙基、

任选地被一个甲氧基基团取代的-C_4-C_6环烷基、

-氧杂环丁烷基、

-四氢呋喃基、或

-四氢吡喃基；

R^3是氢或甲基；并且

R^4是氢或氟。

2.如权利要求1所述的具有式(I)的化合物或其药学上可接受的盐，其中R^1是氮杂环丁烷-1-基、吡咯烷-1-基、或哌啶-1-基，其各自被一个二甲基氨基基团或被一个甲基氨基基团取代。

3.如权利要求1或权利要求2所述的具有式(I)的化合物或其药学上可接受的盐，其中R^1是3-(二甲基氨基)氮杂环丁烷-1-基、3-(二甲基氨基)吡咯烷-1-基、3-(二甲基氨基)哌啶-1-基、4-(二甲基氨基)哌啶-1-基或4-(甲基氨基)哌啶-1-基。

4.如前述权利要求中任一项所述的具有式(I)的化合物或其药学上可接受的盐，其中R^2是环丁基、3-甲氧基环丁-1-基、3-甲氧基环戊-1-基、3-甲氧基环己-1-基、4-甲氧基环己-1-基、异丙基、氧杂环丁烷-3-基、四氢呋喃-3-基、四氢吡喃-3-基或四氢吡喃-4-基。

5.如前述权利要求中任一项所述的具有式(I)的化合物或其药学上可接受的盐，其中R^3是甲基。

6.如前述权利要求中任一项所述的具有式(I)的化合物或其药学上可接受的盐，其中R^4是氢。

7.如权利要求1所述的具有式(I)的化合物或其药学上可接受的盐，其中：

R^1是3-(二甲基氨基)氮杂环丁烷-1-基、3-(二甲基氨基)吡咯烷-1-基、3-(二甲基氨基)哌啶-1-基、4-(二甲基氨基)哌啶-1-基、或4-(甲基氨基)哌啶-1-基；

R^2是环丁基、3-甲氧基环丁-1-基、3-甲氧基环戊-1-基、3-甲氧基环己-1-基、4-甲氧基环己-1-基、异丙基、氧杂环丁烷-3-基、四氢呋喃-3-基、四氢吡喃-3-基、或四氢吡喃-4-基；

R^3是甲基；并且

R^4是氢或氟。

8.如权利要求1所述的具有式(I)的化合物或其药学上可接受的盐，其中该化合物选自

下组，该组由以下组成：

8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[(1S,3S)-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3S)-四氢呋喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(反式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(反式-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[反式-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-(反式-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

1-环丁基-8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-7-氟-1-[反式-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[反式-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

1-环丁基-8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-(氧杂环丁烷-3-基)咪唑并[4,5-c]喹啉-2-酮；

8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-

甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3R)-3-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(顺式-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(顺式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[顺式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[顺式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[反式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[反式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[反式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]咪唑并[4,5-c]喹啉-2-酮；

3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

1-(顺式-3-甲氧基环丁基)-3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]咪唑并[4,5-c]喹啉-2-酮；和

3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮。

9.一种药物组合物，其包含如权利要求1至8中任一项所述的具有式(I)的化合物或其药学上可接受的盐，以及至少一种药学上可接受的赋形剂。

10.如权利要求1至8中任一项所述的具有式(I)的化合物或其药学上可接受的盐，用于在疗法中使用。

11.如权利要求1至8中任一项所述的具有式(I)的化合物或其药学上可接受的盐，用于在癌症的治疗中使用。

12.根据权利要求11所述的、用于在癌症的治疗中使用的具有式(I)的化合物或其药学上可接受的盐，其中该具有式(I)的化合物与放射疗法被同时地、分别地或顺序地给予。

13.根据权利要求11所述的、用于在癌症的治疗中使用的具有式(I)的化合物或其药学上可接受的盐，其中该具有式(I)的化合物与至少一种另外的抗肿瘤物质被同时地、分别地或顺序地给予，该另外的抗肿瘤物质选自：顺铂、奥沙利铂、卡铂、戊柔比星、伊达比星、多柔比星、吡柔比星、伊立替康、拓扑替康、氨柔比星、表柔比星、依托泊苷、丝裂霉素、苯达莫司

汀、苯丁酸氮芥、环磷酰胺、异环磷酰胺、卡莫司汀、美法仑、博莱霉素、奥拉帕尼、度伐鲁单抗、AZD1775以及AZD6738。

14.如权利要求1至8中任一项所述的具有式(I)的化合物或其药学上可接受的盐在生产用于治疗癌症的药物中的用途。

15.一种用于在需要这种治疗的温-血动物中治疗癌症的方法，该方法包括向所述温血动物给予治疗有效量的如权利要求1至8中任一项所述的具有式(I)的化合物或其药学上可接受的盐。

咪唑并[4,5-c]喹啉-2-酮化合物以及它们在治疗癌症中的用途

技术领域

[0001] 本说明书涉及经取代的咪唑并[4,5-c]喹啉-2-酮化合物及其药学上可接受的盐。这些化合物和盐选择性地调节共济失调毛细血管扩张症突变的(“ATM”)激酶,并且因此本说明书还涉及经取代的咪唑并[4,5-c]喹啉-2-酮化合物及其盐治疗或预防ATM介导的疾病(包括癌症)的用途。本说明书进一步涉及包含经取代的咪唑并[4,5-c]喹啉-2-酮化合物及其药学上可接受的盐的药物组合物;包含此类化合物和盐的试剂盒;生产此类化合物和盐的方法;以及在此类生产中有用的中间体。

背景技术

[0002] ATM激酶是丝氨酸苏氨酸激酶,最初鉴定为在共济失调毛细血管扩张症中的突变基因的产物。共济失调毛细血管扩张症位于人染色体11q22-23上并且编码约350kDa的一个大蛋白质,其由磷脂酰肌醇(“PI”)3-激酶样丝氨酸/苏氨酸激酶结构域的存在来表征,该结构域由调节ATM激酶活性和功能的FRAP-ATM-TRRAP结构域和FATC结构域侧翼。ATM激酶已被鉴定为通过双链断裂引起的DNA损伤应答的主要参与者。它主要在S/G2/M细胞周期过渡中并在坍塌复制叉处起作用以引发细胞周期检查点、染色质修饰、HR修复以及促存活信号级联放大,以便在DNA损伤后保持细胞完整性(拉文(Lavin),M.F.;分子细胞生物学综述(Rev.Mol.CellBiol.)2008,759-769)。

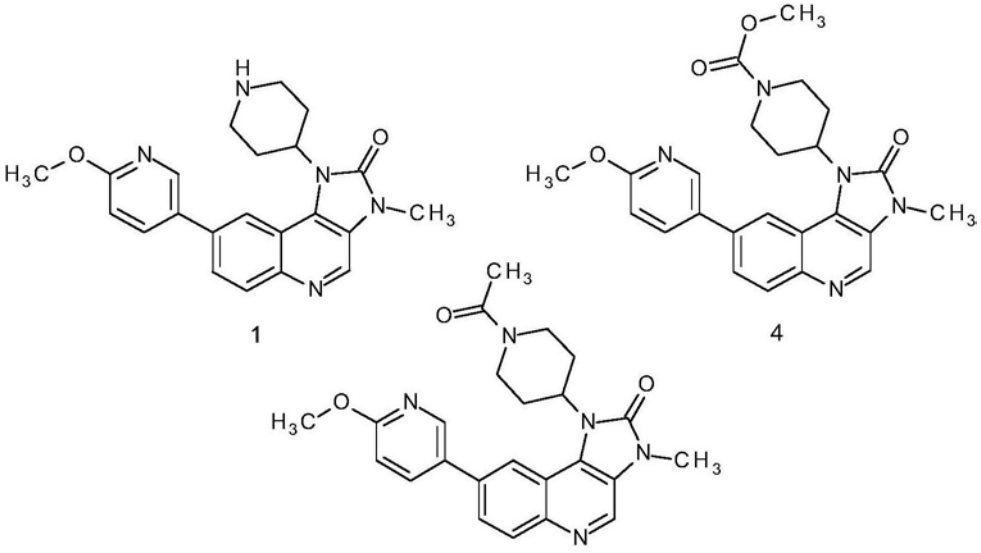
[0003] ATM激酶信号大致可分为两类:典型途径,该途径与来自双链断裂的Mre11-Rad50-NBS1复合物在一起发信号并激活DNA损伤检查点;和活化的若干非典型模式,这些模式通过其他形式的细胞应激被激活(克雷莫纳(Cremona)等人,癌基因(Oncogene)2013,3351-3360)。

[0004] ATM激酶迅速地、强劲地被激活以响应于双链断裂,且据说能够在过量的800种底物中磷酸化(Matsuoka等人,Science[科学]2007,1160-1166),协调多个应激反应途径(Kurz和Lees Miller,DNA Repair[DNA修复]2004,889-900.)。ATM激酶以无活性同型二聚体形式主要存在于细胞的细胞核中,但在感测到DNA双链断裂(典型途径)时在Ser1981上自磷酸化,导致具有全激酶活性的单体的解离(贝克汉尼斯特(Bakkenist)等人,自然(Nature)2003,499-506)。这是一个关键的激活事件,并且因此针对肿瘤途径依赖性,ATM磷酸-Ser1981是直接药效学的和患者的选择生物标志物两者。

[0005] ATM激酶响应于由常见抗癌治疗如电离辐射和拓扑异构酶-II抑制剂(多柔比星,依托泊苷)所造成的直接的双链断裂,而且通过复制过程中的单链断裂至双链断裂转换还响应于拓扑异构酶-I抑制剂(例如伊立替康和托泊替康)。ATM激酶抑制可以增强任何这些试剂的活性,并且结果是ATM激酶抑制剂预期在癌症的治疗中是有用的。

[0006] CN102372711A报道了某些咪唑并[4,5-c]喹啉-2-酮化合物,这些化合物被称为PI3-激酶α和哺乳动物雷帕霉素靶蛋白(“mTOR”)激酶的双重抑制剂。在CN102372711A中报道的这些化合物如下:

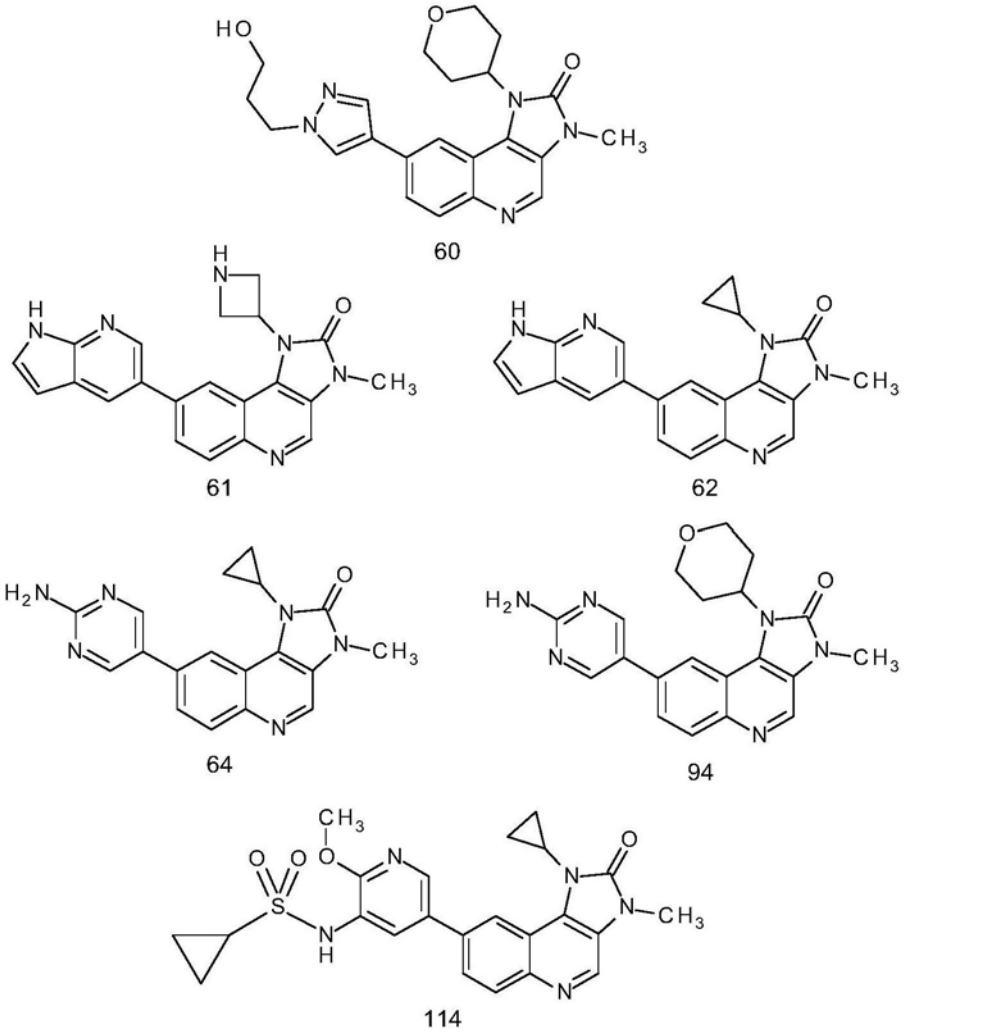
[0007]



[0008] 在CN102372711A中报道的某些化合物

[0009] CN102399218A报道了某些咪唑并[4,5-c]喹啉-2-酮化合物,这些化合物被称为PI3-激酶α抑制剂。在CN 102399218A中报道的这些化合物如下：

[0010]



[0011] 在CN 102399218A中报道的某些化合物

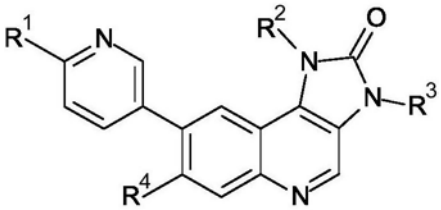
[0012] 虽然这些化合物或CN 102372711A以及CN 102399218A被报道具有对抗PI 3-激酶α并且在某些情况下对抗mTOR激酶的活性，但对研发更有效对抗不同激酶(如ATM激酶)的新化合物仍存在需求。对以高选择性方式(即，通过比其他生物靶标更有效地调节ATM激酶)作用于某些激酶(像ATM激酶)的新化合物进一步存在需求。

[0013] 如在本说明书中别处(例如在实验部分中描述的基于细胞的测定中)证明的，本说明书的这些化合物通常具有非常强的ATM激酶抑制活性，但对其他酪氨酸激酶，如PI 3-激酶α、mTOR激酶以及共济失调毛细血管扩张症和Rad3-相关蛋白(“ATR”)激酶具有小得多的活性。因此，本说明书的这些化合物不仅抑制ATM激酶，还可以被认为是ATM激酶的高选择性抑制剂。

[0014] 作为其高选择性性质的结果，本说明书的这些化合物预期在ATM激酶牵连于其中的疾病的治疗中(例如，在癌症的治疗中)特别有用，但其中希望的是最小化由于其他酪氨酸激酶，如PI 3-激酶α类、mTOR激酶以及ATR激酶的抑制可能产生的脱靶作用或毒性。

[0015] 发明概述

[0016] 简言之，本说明书部分地描述了具有式(I)化合物：

[0017] 

(I)

[0018] 或其药学上可接受的盐，其中：

[0019] R^1是氮杂环丁烷基、吡咯烷基、或哌啶基，其各自被一个甲基氨基基团或被一个二甲基氨基基团取代；

[0020] R^2是：

[0021] -异丙基、

[0022] 任选地被一个甲氧基基团取代的-C_4-C_6环烷基、

[0023] -氧杂环丁烷基、

[0024] -四氢呋喃基、或

[0025] -四氢吡喃基；

[0026] R^3是氢或甲基；并且

[0027] R^4是氢或氟。

[0028] 本说明书还部分地描述了包含具有式(I)的化合物或其药学上可接受的盐，以及至少一种药学上可接受的赋形剂的药物组合物。

[0029] 本说明书还部分地描述了具有式(I)的化合物或其药学上可接受的盐，用于在疗法中使用。

[0030] 本说明书还部分地描述了具有式(I)的化合物或其药学上可接受的盐，用于在癌症的治疗中使用。

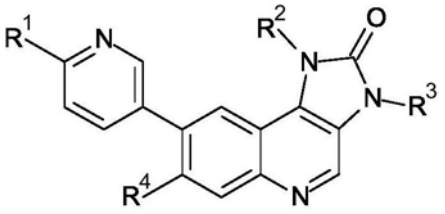
[0031] 本说明书还部分地描述了具有式(I)的化合物或其药学上可接受的盐在生产用于治疗癌症的药物中的用途。

[0032] 本说明书还部分地描述了用于在需要这种治疗的温血动物中治疗癌症的方法，该方法包括向所述温血动物给予治疗有效量的具有式(I)的化合物或其药学上可接受的盐。

[0033] 说明性实施例

[0034] 本发明的许多实施例在整个说明书中详细描述，并且对于本领域有技术的读者而言将是明显的。本发明不被解释为受限于其任何具体的一个或多个实施例。

[0035] 在第一个实施例中，提供了具有式(I)的化合物：

[0036] 

(I)

[0037] 或其药学上可接受的盐，其中：

[0038] R^1是氮杂环丁烷基、吡咯烷基、或哌啶基，其各自被一个甲基氨基基团或被一个二甲基氨基基团取代；

[0039] R^2是：

[0040] -异丙基、

[0041] 任选地被一个甲氧基基团取代的-C_4-C_6环烷基、

[0042] -氧杂环丁烷基、

[0043] -四氢呋喃基、或

[0044] -四氢吡喃基；

[0045] R^3是氢或甲基；并且

[0046] R^4是氢或氟。

[0047] “氢”基团相当于氢原子。其上附接氢基团的原子可被认定为是未经取代的。

[0048] “C_4-C_6环烷基”表示含有4至6个环碳原子的非芳香族碳环。C_4-C_6环烷基包括环丁基、环戊基、和环己基基团。

[0049] 在使用术语“任选地”的情况下，意指随后的特征可以存在或可以不存在。因此，使用术语“任选地”包括特征存在的情况、以及还有特征不存在的情况。例如，“任选地被一个甲氧基基团取代的C_4-C_6环烷基”包括具有或不具有具体取代基的环丁基、环戊基和环己基基团。

[0050] 术语“药学上可接受的”通常是指对象(例如盐、剂型或赋形剂)是适合在患者中使用的。药学上可接受的盐的实例列表可以发现于：Handbook of Pharmaceutical Salts: Properties, Selection and Use[药用盐手册：性质、选择和使用]，P.H.Stahl和C.G.Wermuth编辑，Weinheim/zürich:Wiley-VCH/VHCA(魏因海姆/苏黎世：威利(Wiley)-VCH出版社/VHCA)，2002。具有式(I)的化合物的适合的药学上可接受的盐例如是酸-加成盐。在技术人员已知的条件下，具有式(I)的化合物的酸加成盐可以通过使该化合物与适合的无机酸或有机酸接触来形成。酸加成盐例如可以使用选自盐酸、氢溴酸、硫酸和磷酸的无机酸来形成。酸加成盐还可以使用有机酸来形成，该有机酸选自：三氟乙酸、柠檬酸、马来酸、草酸、乙酸、甲酸、苯甲酸、富马酸、琥珀酸、酒石酸、乳酸、丙酮酸、甲磺酸、乙磺酸、乙二

磺酸、苯磺酸、己二酸、肉桂酸、萘二磺酸、苹果酸、丙二酸、邻磺酰苯甲酰亚胺以及对甲苯磺酸。

[0051] 因此，在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，其中该药学上可接受的盐是盐酸盐、氢溴酸盐、硫酸盐、磷酸盐、三氟乙酸盐、柠檬酸盐、马来酸盐、草酸盐、乙酸盐、甲酸盐、苯甲酸盐、富马酸盐、琥珀酸盐、酒石酸盐、乳酸盐、丙酮酸盐、甲磺酸盐、乙磺酸盐、乙二磺酸盐、苯磺酸盐、己二酸盐、肉桂酸盐、萘二磺酸盐、苹果酸盐、丙二酸盐、邻磺酰苯甲酰亚胺盐、或对甲苯磺酸盐。在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，其中该药学上可接受的盐是甲磺酸盐。在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，其中该药学上可接受的盐是单-甲磺酸盐，即具有式(I)的化合物与甲磺酸的化学计量是1:1。在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，其中该药学上可接受的盐是甲酸盐。在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，其中该药学上可接受的盐是单-甲酸盐，即具有式(I)的化合物与甲酸的化学计量是1:1。

[0052] 另外的实施例提供了本文所定义的任何实施例(例如如权利要求1所述的实施例)，其条件是一个或多个具体的实例(例如一个、两个或三个具体实例)单独地被放弃，该实例选自下组，该组由以下实例组成：1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29、30、31、32、33、34、35、36、37、38、39、40、41、42、43、44、45、46、47、48、49、50、51、52、53、54、55、56、57、58、59、60以及61。

[0053] 式(I)中的可变基团的一些值如下。这些值可以与任何定义、权利要求(例如权利要求1)、或本文所定义的实施例组合使用以提供另外的实施例。

[0054] a)R^1是氮杂环丁烷-1-基、吡咯烷-1-基、或哌啶-1-基，其各自被一个二甲基氨基基团或一个甲基氨基基团取代。

[0055] b)R^1是3-(二甲基氨基)氮杂环丁烷-1-基、3-(二甲基氨基)吡咯烷-1-基、3-(二甲基氨基)哌啶-1-基、4-(二甲基氨基)哌啶-1-基、或4-(甲基氨基)哌啶-1-基。

[0056] c)R^1是3-(二甲基氨基)氮杂环丁烷-1-基、(3R)-3-(二甲基氨基)吡咯烷-1-基、(3S)-3-(二甲基氨基)吡咯烷-1-基、(3R)-3-(二甲基氨基)哌啶-1-基、4-(二甲基氨基)哌啶-1-基、或4-(甲基氨基)哌啶-1-基。

[0057] d)R^2是异丙基、环丁基、3-甲氧基环丁-1-基、3-甲氧基环戊-1-基、3-甲氧基环己-1-基、4-甲氧基环己-1-基、氧杂环丁烷-3-基、四氢呋喃-3-基、四氢吡喃-3-基、或四氢吡喃-4-基。

[0058] e)R^2是异丙基、环丁基、顺式-3-甲氧基环丁-1-基、反式-3-甲氧基环丁-1-基、反式-3-甲氧基环戊-1-基、顺式-3-甲氧基环己-1-基、反式-3-甲氧基环己-1-基、反式-4-甲氧基环己-1-基、氧杂环丁烷-3-基、四氢呋喃-3-基、四氢吡喃-3-基、或四氢吡喃-4-基。

[0059] f)R^2是异丙基、环丁基、顺式-3-甲氧基环丁-1-基、反式-3-甲氧基环丁-1-基、(1R,3R)-3-甲氧基环戊-1-基、(1S,3R)-3-甲氧基环己-1-基、(1R,3S)-3-甲氧基环己-1-基、(1S,3S)-3-甲氧基环己-1-基、(1R,3R)-3-甲氧基环己-1-基、反式-4-甲氧基环己-1-基、氧杂环丁烷-3-基、(3S)-四氢呋喃-3-基、(3S)-四氢吡喃-3-基、(3R)-四氢吡喃-3-基、或四氢吡喃-4-基。

[0060] g)R^2是异丙基。

[0061] h)R^2是任选地被一个甲氧基基团取代的C_4-C_6环烷基。

[0062] i)R^2是环丁基、3-甲氧基环丁-1-基、3-甲氧基环戊-1-基、3-甲氧基环己-1-基、或4-甲氧基环己-1-基。

[0063] j)R^2是环丁基、顺式-3-甲氧基环丁-1-基、反式-3-甲氧基环丁-1-基、反式-3-甲氧基环戊-1-基、顺式-3-甲氧基环己-1-基、反式-3-甲氧基环己-1-基、或反式-4-甲氧基环己-1-基。

[0064] k)R^2是环丁基、顺式-3-甲氧基环丁-1-基、反式-3-甲氧基环丁-1-基、(1R,3R)-3-甲氧基环戊-1-基、(1S,3R)-3-甲氧基环己-1-基、(1R,3S)-3-甲氧基环己-1-基、(1S,3S)-3-甲氧基环己-1-基、(1R,3R)-3-甲氧基环己-1-基、或反式-4-甲氧基环己-1-基。

[0065] l)R^2是氧杂环丁烷基、四氢呋喃基、或四氢吡喃基。

[0066] m)R^2是氧杂环丁烷-3-基、(3S)-四氢呋喃-3-基、(3S)-四氢吡喃-3-基、(3R)-四氢吡喃-3-基、或四氢吡喃-4-基。

[0067] n)R^2是氧杂环丁烷-3-基。

[0068] o)R^2是(3S)-四氢呋喃-3-基。

[0069] p)R^2是(3S)-四氢吡喃-3-基或(3R)-四氢吡喃-3-基。

[0070] q)R^2是(3S)-四氢吡喃-3-基。

[0071] r)R^2是(3R)-四氢吡喃-3-基。

[0072] s)R^2是四氢吡喃-4-基。

[0073] t)R^3是氢。

[0074] u)R^3是甲基。

[0075] v)R^4是氢。

[0076] w)R^4是氟。

[0077] 在一个实施例中,提供了具有式(I)的化合物或其药学上可接受的盐,其中:

[0078] R^1是3-(二甲基氨基)氮杂环丁烷-1-基、3-(二甲基氨基)吡咯烷-1-基、3-(二甲基氨基)哌啶-1-基、4-(二甲基氨基)哌啶-1-基、或4-(甲基氨基)哌啶-1-基;

[0079] R^2是异丙基、环丁基、3-甲氧基环丁-1-基、3-甲氧基环戊-1-基、3-甲氧基环己-1-基、4-甲氧基环己-1-基、氧杂环丁烷-3-基、四氢呋喃-3-基、四氢吡喃-3-基、或四氢吡喃-4-基;

[0080] R^3是甲基;并且

[0081] R^4是氢或氟。

[0082] 在一个实施例中,提供了具有式(I)的化合物或其药学上可接受的盐,其中:

[0083] R^1是3-(二甲基氨基)氮杂环丁烷-1-基、(3R)-3-(二甲基氨基)吡咯烷-1-基、(3S)-3-(二甲基氨基)吡咯烷-1-基、(3R)-3-(二甲基氨基)哌啶-1-基、4-(二甲基氨基)哌啶-1-基、或4-(甲基氨基)哌啶-1-基;

[0084] R^2是异丙基、环丁基、顺式-3-甲氧基环丁-1-基、反式-3-甲氧基环丁-1-基、(1R,3R)-3-甲氧基环戊-1-基、(1S,3R)-3-甲氧基环己-1-基、(1R,3S)-3-甲氧基环己-1-基、(1S,3S)-3-甲氧基环己-1-基、(1R,3R)-3-甲氧基环己-1-基、反式-4-甲氧基环己-1-基、氧杂环丁烷-3-基、(3S)-四氢呋喃-3-基、(3S)-四氢吡喃-3-基、(3R)-四氢吡喃-3-基、或四氢吡喃-4-基;

[0085] R^3是甲基;并且

[0086] R^4是氢或氟。

[0087] 在一个实施例中,提供了具有式(I)的化合物或其药学上可接受的盐,其中:

[0088] R^1是3-(二甲基氨基)氮杂环丁烷-1-基、3-(二甲基氨基)吡咯烷-1-基、3-(二甲基氨基)哌啶-1-基、4-(二甲基氨基)哌啶-1-基、或4-(甲基氨基)哌啶-1-基;

[0089] R^2是环丁基、3-甲氧基环丁-1-基、3-甲氧基环戊-1-基、3-甲氧基环己-1-基、或4-甲氧基环己-1-基;

[0090] R^3是甲基;并且

[0091] R^4是氢或氟。

[0092] 在一个实施例中,提供了具有式(I)的化合物或其药学上可接受的盐,其中:

[0093] R^1是3-(二甲基氨基)氮杂环丁烷-1-基、3-(二甲基氨基)吡咯烷-1-基、3-(二甲基氨基)哌啶-1-基、4-(二甲基氨基)哌啶-1-基、或4-(甲基氨基)哌啶-1-基;

[0094] R^2是异丙基;

[0095] R^3是甲基;并且

[0096] R^4是氢或氟。

[0097] 在一个实施例中,提供了具有式(I)的化合物或其药学上可接受的盐,其中:

[0098] R^1是3-(二甲基氨基)氮杂环丁烷-1-基、3-(二甲基氨基)吡咯烷-1-基、3-(二甲基氨基)哌啶-1-基、4-(二甲基氨基)哌啶-1-基、或4-(甲基氨基)哌啶-1-基;

[0099] R^2是氧杂环丁烷基、四氢呋喃基、或四氢吡喃基;

[0100] R^3是甲基;并且

[0101] R^4是氢或氟。

[0102] 在一个实施例中,提供了具有式(I)的化合物或其药学上可接受的盐,其中该化合物选自下组,该组由以下组成:

[0103] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮;

[0104] 8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮;

[0105] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮;

[0106] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮;

[0107] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[(1S,3S)-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮;

[0108] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮;

[0109] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮;

[0110] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3S)-四氢呋喃-3-基]咪唑并[4,5-c]喹啉-2-酮;

[0111] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0112] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0113] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(反式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0114] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(反式-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0115] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮；

[0116] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0117] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0118] 8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0119] 8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0120] 8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0121] 8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0122] 8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0123] 8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0124] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[反式-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0125] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0126] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-(反式-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0127] 1-环丁基-8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0128] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0129] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮；

[0130] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-7-氟-1-[反式-3-甲氧基

环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0131] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0132] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[反式-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0133] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0134] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0135] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0136] 1-环丁基-8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0137] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-(氧杂环丁烷-3-基)咪唑并[4,5-c]喹啉-2-酮；

[0138] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮；

[0139] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0140] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0141] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0142] 8-[6-[(3R)-3-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0143] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(顺式-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0144] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(顺式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0145] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[顺式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0146] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[顺式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0147] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[反式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0148] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[反式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0149] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[反式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0150] 7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]咪唑并[4,5-c]喹啉-2-酮；

[0151] 3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0152] 3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0153] 1-(顺式-3-甲氧基环丁基)-3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]咪唑并[4,5-c]喹啉-2-酮；以及

[0154] 3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮。

[0155] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，其中该化合物选自下组，该组由以下组成：

[0156] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0157] 8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0158] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0159] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0160] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[(1S,3S)-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0161] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0162] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0163] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3S)-四氢呋喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0164] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0165] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0166] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(反式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0167] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(反式-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0168] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮；

[0169] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3R)-

四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0170] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0171] 8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0172] 8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0173] 8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0174] 8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0175] 8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0176] 8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0177] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[(1S,3S)-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0178] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[(1R,3R)-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0179] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0180] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-(反式-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0181] 1-环丁基-8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0182] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0183] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮；

[0184] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-7-氟-1-[(1S,3S)-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0185] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-7-氟-1-[(1R,3R)-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0186] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0187] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(1S,3S)-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0188] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(1R,3R)-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0189] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0190] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0191] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0192] 1-环丁基-8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0193] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-(氧杂环丁烷-3-基)咪唑并[4,5-c]喹啉-2-酮；

[0194] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮；

[0195] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0196] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-3-甲基-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0197] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0198] 8-[6-[(3R)-3-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0199] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(顺式-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0200] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(1S,3R)-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0201] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(1R,3S)-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0202] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[(1S,3R)-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0203] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[(1R,3S)-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0204] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[(1S,3R)-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0205] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[(1R,3S)-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0206] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[(1S,3S)-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0207] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[(1R,3R)-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0208] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(1S,3S)-3-甲氧基环己基]-

3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0209] 8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(1R,3R)-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0210] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[(1S,3S)-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0211] 8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[(1S,3S)-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮；

[0212] 7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]咪唑并[4,5-c]喹啉-2-酮；

[0213] 3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0214] 3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(3S)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮；

[0215] 1-(顺式-3-甲氧基环丁基)-3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]咪唑并[4,5-c]喹啉-2-酮；以及

[0216] 3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮。

[0217] 在一个实施例中，提供了8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮，或其药学上可接受的盐。

[0218] 在一个实施例中，提供了8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮。

[0219] 在一个实施例中，提供了8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮的药学上可接受的盐。

[0220] 在一个实施例中，提供了8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮，或其药学上可接受的盐。

[0221] 在一个实施例中，提供了8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮。

[0222] 在一个实施例中，提供了8-[6-[(3S)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3R)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮的药学上可接受的盐。

[0223] 在一个实施例中，提供了8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮，或其药学上可接受的盐。

[0224] 在一个实施例中，提供了8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮。

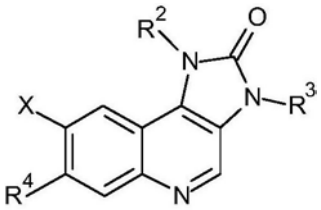
[0225] 在一个实施例中，提供了8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮的药学上可接受的盐。

[0226] 本说明书中描述的化合物和盐能以溶剂化形式和非溶剂化形式存在。例如，溶剂化形式可以是水合形式，如半-水合物、一-水合物、二-水合物、三-水合物或其可替代的数量。本发明涵盖具有式(I)的化合物的所有这些溶剂化和非溶剂化形式，特别是在这些形式具有ATM激酶抑制活性的程度上，如例如使用本文所描述的测试测量的。

[0227] 本说明书所描述的这些化合物和盐的原子能以它们的同位素存在。本发明涵盖了具有式(I)的所有化合物,其中原子被其同位素中的一个或多个替换(例如具有式(I)的化合物,其中一个或多个碳原子是^{11}C或^{12}C碳同位素,或其中一个或多个氢原子是^{2}H或^{2}H同位素)。

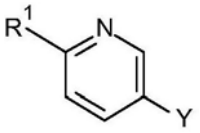
[0228] 本说明书中所描述的化合物和盐可以按互变异构体的混合物存在。“互变异构体”是结构异构体,其存在于由氢原子的迁移产生的平衡中。本发明包括具有式(I)的化合物的所有互变异构体,特别是在这些互变异构体具有ATM激酶抑制活性的程度上。

[0229] 具有式(I)的化合物例如可以通过具有式(II)的化合物:

[0230] 

(II)

[0231] 或其盐(其中R^2、R^3和R^4是如本文任何实施例中所定义的,并且X是离去基团(例如卤素原子,或可替代地是氟原子))与具有式(III)的化合物:

[0232] 

(III)

[0233] 或其盐(其中R^1是如本文任何实施例中所定义的,并且Y是硼酸、硼酸酯或三氟硼酸钾基团(例如硼酸、硼酸频哪醇酯、或三氟硼酸钾基团)进行反应来制备。该反应可以在本领域普通技术人员熟知的标准条件下进行,例如在钯来源(例如四合三苯基膦钯或乙酸钯(II))、任选地膦配体(例如Xantphos或S-phos)、以及适合的碱(例如碳酸铯或三乙胺)存在下进行。

[0234] 因此具有式(II)的化合物在具有式(I)的化合物的制备中作为中间体是有用的,并且提供了另一个实施例。

[0235] 在一个实施例中,提供了具有式(II)的化合物或其盐,其中:

[0236] R^2是任选地被一个甲氧基基团取代的C_4-C_6环烷基、异丙基、氧杂环丁烷基、四氢呋喃基、或四氢吡喃基;

[0237] R^3是氢或甲基;

[0238] R^4是氢或氟;并且

[0239] X是离去基团。在一个实施例中,X是碘、溴、或氯原子或三氟甲磺酸盐基团。在一个实施例中,X是溴原子。

[0240] 在一个实施例中,提供了具有式(II)的化合物或其盐,其中:

[0241] R^2是异丙基、环丁基、3-甲氧基环丁-1-基、3-甲氧基环戊-1-基、3-甲氧基环己-1-基、4-甲氧基环己-1-基、氧杂环丁烷-3-基、四氢呋喃-3-基、四氢吡喃-3-基、或四氢吡喃-4-基;

[0242] R^3是氢或甲基;

[0243] R^4是氢或氟;并且

[0244] X是离去基团。在一个实施例中,X是碘、溴、或氯原子或三氟甲磺酸盐基团。在一个实施例中,X是溴原子。

[0245] 在具有式(II)的化合物或其盐被提及的任何实施例中,要理解的是此类盐不必是药学上可接受的盐。具有式(II)的化合物的适合的盐例如是酸-加成盐。具有式(II)的化合物的酸加成盐可以通过在技术人员已知的条件下使该化合物与适合的无机酸或有机酸接触来形成。酸加成盐例如可以使用选自盐酸、氢溴酸、硫酸和磷酸的无机酸来形成。酸加成盐还可以使用有机酸来形成,该有机酸选自:三氟乙酸、柠檬酸、马来酸、草酸、乙酸、甲酸、苯甲酸、富马酸、琥珀酸、酒石酸、乳酸、丙酮酸、甲磺酸、乙磺酸、乙二磺酸、苯磺酸、己二酸、肉桂酸、萘二磺酸、苹果酸、丙二酸、邻磺酰苯甲酰亚胺以及对甲苯磺酸。

[0246] 因此,在一个实施例中,提供了具有式(II)的化合物或其盐,其中该盐是盐酸盐、氢溴酸盐、硫酸盐、磷酸盐、三氟乙酸盐、柠檬酸盐、马来酸盐、草酸盐、乙酸盐、甲酸盐、苯甲酸盐、富马酸盐、琥珀酸盐、酒石酸盐、乳酸盐、丙酮酸盐、甲磺酸盐、乙磺酸盐、乙二磺酸盐、苯磺酸盐、己二酸盐、肉桂酸盐、萘二磺酸盐、苹果酸、丙二酸、邻磺酰苯甲酰亚胺、或对甲苯磺酸盐。

[0247] 在一个实施例中,提供了具有式(II)的化合物或其盐,其中该化合物选自下组,该组由以下组成:

[0248] 8-溴-7-氟-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮;

[0249] 8-溴-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮;

[0250] 8-溴-1-[(1S,3S)-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮;

[0251] 8-溴-3-甲基-1-(氧杂环己烷-4-基)咪唑并[5,4-c]喹啉-2-酮;

[0252] 8-溴-1-(顺式-3-甲氧基环丁基)-3-甲基咪唑并[4,5-c]喹啉-2-酮;

[0253] 8-溴-1-(顺式-3-甲氧基甲基环丁基)-3-甲基咪唑并[4,5-c]喹啉-2-酮;

[0254] 8-溴-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基咪唑并[4,5-c]喹啉-2-酮;

[0255] 8-溴-3-甲基-1-[(3S)-氧杂环己烷-3-基]咪唑并[5,4-c]喹啉-2-酮;

[0256] 8-溴-3-甲基-1-[(3R)-氧杂环己烷-3-基]咪唑并[5,4-c]喹啉-2-酮;

[0257] 8-溴-7-氟-3-甲基-1-(氧杂环己烷-4-基)咪唑并[5,4-c]喹啉-2-酮;

[0258] 8-溴-7-氟-3-甲基-1-[(3S)-氧杂环己烷-3-基]咪唑并[5,4-c]喹啉-2-酮;

[0259] 8-溴-7-氟-3-甲基-1-[(3R)-氧杂环己烷-3-基]咪唑并[5,4-c]喹啉-2-酮;

[0260] 8-溴-3-甲基-1-[(3S)-四氢呋喃-3-基]咪唑并[4,5-c]喹啉-2-酮;

[0261] 8-溴-1-环丁基-3-甲基-咪唑并[4,5-c]喹啉-2-酮;

[0262] 8-溴-1-(反式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮;

[0263] 8-溴-1-(反式-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮;

[0264] 8-溴-1-(顺式-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮;

[0265] 8-溴-1-[(3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮;

[0266] 8-溴-1-[(反式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮;

[0267] 8-溴-1-[(顺式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮;以及

[0268] 8-溴-1-[(顺式-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮。

[0269] 具有式(III)和(IV)的化合物可以通过与实例部分中所示的那些类似的方法制

备。

[0270] 在一个实施例中，提供了在实验部分中所描述的新颖的中间体中的任何一种。

[0271] 作为其ATM激酶抑制活性的结果，预期具有式(I)的化合物、及其药学上可接受的盐在疗法中(例如在至少部分由ATM激酶介导的疾病或医学病状，包括癌症的治疗中)是有用的。

[0272] 在提及“癌症”的情况下，这包括非转移性癌症和转移性癌症两者，使得治疗癌症涉及治疗原发性肿瘤和肿瘤转移两者。

[0273] “ATM激酶抑制活性”是指作为对具有式(I)的化合物或其药学上可接受的盐的存在的直接或间接响应，ATM激酶的活性相对于在不存在具有式(I)的化合物或其药学上可接受的盐下ATM激酶的活性降低。此类活性的降低可以归因于具有式(I)的化合物或其药学上可接受的盐与ATM激酶的直接相互作用，或归因于具有式(I)的化合物或其药学上可接受的盐与一种或多种反过来影响ATM激酶活性的其他因素相互作用。例如，具有式(I)的化合物或其药学上可接受的盐可以通过直接与ATM激酶结合、通过(直接或间接)引起另一因素以降低ATM激酶活性、或通过(直接或间接)降低存在于细胞或有机体中的ATM激酶的量来降低ATM激酶。

[0274] 术语“疗法”旨在具有其正常的含义：处理疾病，以便完全或部分缓解其症状的一种、一些或全部，或以便针对潜在病理进行纠正或补偿。术语“疗法”还包括“预防”，除非有相反的具体指示。术语“治疗的”和“治疗地”应以相应的方式被解释。

[0275] 术语“预防”旨在具有其正常的含义，并包括防止疾病发展的初级预防和继发性预防，其中该疾病已经发展并且患者被暂时或永久保护对抗疾病的加重或恶化或者对抗与疾病相关的新症状的发展。

[0276] 术语“治疗”(treatment)与“疗法”(therapy)同义地使用。类似地，术语“治疗”(treat)可视为“施加疗法”(applying therapy)，其中“疗法”(therapy)是如本文所定义的。

[0277] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在疗法中使用。

[0278] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐在药物生产中的用途。

[0279] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在由ATM激酶介导的疾病的治疗中使用。

[0280] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在由ATM激酶介导的疾病的治疗中使用，其中该由ATM激酶介导的疾病是癌症。

[0281] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在由ATM激酶介导的疾病的治疗中使用，其中该由ATM激酶介导的疾病是结肠直肠癌、胶质母细胞瘤、胃癌、卵巢癌、弥漫性大B细胞淋巴瘤、慢性淋巴细胞性白血病、急性髓性白血病、头颈部鳞状细胞癌、乳腺癌、肝细胞癌、小细胞肺癌或非小细胞肺癌。

[0282] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在由ATM激酶介导的疾病的治疗中使用，其中该由ATM激酶介导的疾病是结肠直肠癌。

[0283] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在癌症

的治疗中使用。

[0284] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在以下疾病的治疗中使用：结肠直肠癌、胶质母细胞瘤、胃癌、卵巢癌、弥漫性大B细胞淋巴瘤、慢性淋巴细胞性白血病、急性髓性白血病、头颈部鳞状细胞癌、乳腺癌、肝细胞癌、小细胞肺癌或非小细胞肺癌。

[0285] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在结肠直肠癌的治疗中使用。

[0286] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在亨廷顿病的治疗中使用。

[0287] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于用作神经保护剂。

[0288] “神经保护剂”是保持神经元结构和/或功能的试剂。

[0289] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐在生产用于治疗由ATM激酶介导的疾病的药物中的用途。

[0290] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐在生产用于治疗由ATM激酶介导的疾病的药物中的用途，其中该由ATM激酶介导的疾病是癌症。

[0291] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐在生产用于治疗由ATM激酶介导的疾病的药物中的用途，其中该由ATM激酶介导的疾病是结肠直肠癌、胶质母细胞瘤、胃癌、卵巢癌、弥漫性大B细胞淋巴瘤、慢性淋巴细胞性白血病、急性髓性白血病、头颈部鳞状细胞癌、乳腺癌、肝细胞癌、小细胞肺癌和非小细胞肺癌。

[0292] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐在生产用于治疗由ATM激酶介导的疾病的药物中的用途，其中该由ATM激酶介导的疾病是结肠直肠癌。

[0293] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐在生产用于治疗癌症的药物中的用途。

[0294] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐在生产用于治疗以下疾病的药物中的用途：结肠直肠癌、胶质母细胞瘤、胃癌、卵巢癌、弥漫性大B细胞淋巴瘤、慢性淋巴细胞性白血病、急性髓性白血病、头颈部鳞状细胞癌、乳腺癌、肝细胞癌、小细胞肺癌或非小细胞肺癌。

[0295] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐在生产用于治疗结肠直肠癌的药物中的用途。

[0296] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐在生产用于治疗亨廷顿病的药物中的用途。

[0297] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐在生产用于用作神经保护剂的药物中的用途。

[0298] 在一个实施例中，提供了在需要这种治疗的温-血动物中用于治疗其中ATM激酶的抑制是有益的疾病的方法，该方法包括向所述温血动物给予治疗有效量的具有式(I)的化合物或其药学上可接受的盐。

[0299] 术语“治疗有效量”是指如在本文任何实施例中所描述的具有式(I)的化合物的量，该量在受试者中有效地提供“疗法”，或在受试者中有效地“治疗”疾病或病症。在癌症的

情况下，如在以上“疗法”、“治疗”和“预防”的定义中所述的，治疗有效量可以在受试者中引起任何可观察的或可测量的变化。例如，该有效量可以降低癌或肿瘤细胞的数量；降低总体肿瘤大小；抑制或停止肿瘤细胞浸润至外周器官，例如包括软组织和骨；抑制并停止肿瘤转移；抑制和停止肿瘤生长；在某种程度上缓解与癌症相关的症状中的一种或多种；降低发病率和死亡率；提高生命质量；或这些作用的组合。有效量可以是足以减少响应于ATM激酶活性的抑制的疾病的症状的量。对于癌症疗法，例如可以通过评估存活期、疾病进展时间(TTP)、应答率(RR)、响应期、和/或生命质量来测定体内疗效。如由本领域技术人员所认可的，有效量可以取决于给予途径、赋形剂的使用、以及与其他药剂共同使用而改变。例如，在使用联合疗法的情况下，在动物患者中，对于治疗靶向的失调，当组合时，本说明书中所描述的具有式(I)的化合物或药学上可接受的盐的量和其他一种或多种药学上有活性的药剂的量是共同有效的。在该背景下，如果它们在组合时足以降低如以上所述的响应于ATM活性抑制的疾病的症状，组合的量是“治疗有效量”的。典型地，本领域普通技术人员可以通过例如从针对具有式(I)的化合物或其药学上可接受的盐的、本说明书中所描述的剂量范围开始，以及从其他一种或多种药学上有活性的化合物的一个或多个批准的或另外公开的剂量范围开始，来确定此类量。

[0300] “温血动物”包括例如人类。

[0301] 在一个实施例中，提供了用于在需要这种治疗的温-血动物中治疗其中ATM激酶的抑制是有益的疾病的方法，该方法包括向所述温血动物给予治疗有效量的具有式(I)的化合物或其药学上可接受的盐，并且其中ATM激酶的抑制是有益的疾病是癌症。

[0302] 在一个实施例中，提供了用于在需要这种治疗的温-血动物中治疗其中ATM激酶的抑制是有益的疾病的方法，该方法包括向所述温血动物给予治疗有效量的具有式(I)的化合物或其药学上可接受的盐，并且其中ATM激酶的抑制是有益的疾病是结肠直肠癌、胶质母细胞瘤、胃癌、卵巢癌、弥漫性大B细胞淋巴瘤、慢性淋巴细胞性白血病、急性髓性白血病、头颈部鳞状细胞癌、乳腺癌、肝细胞癌、小细胞肺癌或非小细胞肺癌。

[0303] 在一个实施例中，提供了用于在需要这种治疗的温-血动物中治疗其中ATM激酶的抑制是有益的疾病的方法，该方法包括向所述温血动物给予治疗有效量的具有式(I)的化合物或其药学上可接受的盐，并且其中ATM激酶的抑制是有益的疾病是结肠直肠癌。

[0304] 在一个实施例中，提供了用于在需要这种治疗的温-血动物中治疗其中ATM激酶的抑制是有益的疾病的方法，该方法包括向所述温血动物给予治疗有效量的具有式(I)的化合物或其药学上可接受的盐，并且其中ATM激酶的抑制是有益的疾病是亨廷顿病。

[0305] 在一个实施例中，提供了用于在需要这种治疗的温-血动物中治疗癌症的方法，该方法包括向所述温血动物给予治疗有效量的具有式(I)的化合物或其药学上可接受的盐。

[0306] 在一个实施例中，提供了用于在需要这种治疗的温-血动物中治疗结肠直肠癌、胶质母细胞瘤、胃癌、卵巢癌、弥漫性大B细胞淋巴瘤、慢性淋巴细胞性白血病、急性髓性白血病、头颈部鳞状细胞癌、乳腺癌、肝细胞癌、小细胞肺癌或非小细胞肺癌的方法，该方法包括向所述温血动物给予治疗有效量的具有式(I)的化合物或其药学上可接受的盐。

[0307] 在一个实施例中，提供了用于在需要这种治疗的温-血动物中治疗结肠直肠癌的方法，该方法包括向所述温血动物给予治疗有效量的具有式(I)的化合物或其药学上可接受的盐。

[0308] 在一个实施例中，提供了用于在需要这种治疗的温-血动物中治疗亨廷顿病的方法，该方法包括向所述温血动物给予治疗有效量的具有式(I)的化合物或其药学上可接受的盐。

[0309] 在一个实施例中，提供了用于在需要这种治疗的温-血动物中实现神经保护的方法，该方法包括向所述温血动物给予治疗有效量的具有式(I)的化合物或其药学上可接受的盐。

[0310] 在一个实施例中，提供了用于在需要这种治疗的温-血动物中治疗癌症的方法，该方法包括向所述温血动物给予治疗有效量的具有式(I)的化合物或其药学上可接受的盐。在一个实施例中，所述癌症选自以下：结肠直肠癌、胶质母细胞瘤、胃癌、卵巢癌、弥漫性大B细胞淋巴瘤、慢性淋巴细胞性白血病、急性髓性白血病、头颈部鳞状细胞癌、乳腺癌、肝细胞癌、小细胞肺癌以及非小细胞肺癌。在一个实施例中，所述癌症选自以下：结肠直肠癌、胶质母细胞瘤、胃癌、卵巢癌、弥漫性大B细胞淋巴瘤、慢性淋巴细胞性白血病、头颈部鳞状细胞癌以及肺癌。在一个实施例中，所述癌症是结肠直肠癌。

[0311] 在癌症以一般意义被提及的任何实施例中，所述癌症可以选自：结肠直肠癌、胶质母细胞瘤、胃癌、卵巢癌、弥漫性大B细胞淋巴瘤、慢性淋巴细胞性白血病、急性髓性白血病、头颈部鳞状细胞癌、乳腺癌、肝细胞癌、小细胞肺癌以及非小细胞肺癌。

[0312] 在癌症以一般意义被提及的任何实施例中，可以采用以下实施例：

[0313] 在一个实施例中，该癌症是结肠直肠癌。

[0314] 在一个实施例中，该癌症是胶质母细胞瘤。

[0315] 在一个实施例中，该癌症是胃癌。

[0316] 在一个实施例中，该癌症是食道癌。

[0317] 在一个实施例中，该癌症是卵巢癌。

[0318] 在一个实施例中，该癌症是子宫内膜癌。

[0319] 在一个实施例中，该癌症是宫颈癌。

[0320] 在一个实施例中，该癌症是弥漫性大B细胞淋巴瘤。

[0321] 在一个实施例中，该癌症是慢性淋巴细胞性白血病。

[0322] 在一个实施例中，该癌症是急性髓性白血病。

[0323] 在一个实施例中，该癌症是头颈部鳞状细胞癌。

[0324] 在一个实施例中，该癌症是乳腺癌。在一个实施例中，该癌症是三阴性乳腺癌。

[0325] “三阴性乳腺癌”是不表达雌激素受体、孕酮受体和Her2/neu的基因的任何乳腺癌。

[0326] 在一个实施例中，该癌症是肝细胞癌。

[0327] 在一个实施例中，该癌症是肺癌。在一个实施例中，该肺癌是小细胞肺癌。在一个实施例中，该肺癌是非小细胞肺癌。

[0328] 在一个实施例中，该癌症是非转移性癌症。在一个实施例中，该癌症是转移性癌症。在一个实施例中，该转移性癌症包括中枢神经系统的转移。在一个实施例中，该中枢神经系统的转移包括脑转移。在一个实施例中，该中枢神经系统的转移包括柔脑膜转移。

[0329] 当癌症扩散到脑膜(覆盖脑和脊髓的组织层)时，“柔脑膜转移”发生。转移可以通过血液扩散至脑膜，或它们可以从脑转移开始行进，由流经脑膜的脑脊髓液(CSF)运载。

[0330] 在本说明书中所描述的抗-癌治疗可以作为单一疗法是有用的，或者除了给予具有式(I)的化合物以外，还可以包括常规手术、放射疗法或化学疗法；或此类另外的疗法的组合。这种常规手术、放射疗法或化学疗法可以与具有式(I)的化合物同时地、顺序地或分别地施用，以进行治疗。

[0331] 放射疗法可以包括以下类别的疗法中的一种或多种：

[0332] i.使用电磁辐射的外部放射疗法，和使用电磁辐射的术中放射疗法；

[0333] ii.内部放射疗法或近距离放射疗法；包括间质性放射疗法或腔内放射疗法；或

[0334] iii.全身放射疗法，包括但不限于碘131和锶89。

[0335] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在癌症的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与放射疗法被组合给予。在一个实施例中，该放射疗法选自列于以上点(i)-(iii)下的一种或多种类别的放射疗法。

[0336] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在胶质母细胞瘤、肺癌(例如小细胞肺癌或非小细胞肺癌)、乳腺癌(例如三阴性乳腺癌)、头颈部鳞状细胞癌、食道癌、宫颈癌或子宫内膜癌的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与放射疗法被组合给予。在一个实施例中，该放射疗法选自列于以上点(i)-(iii)下的一种或多种类别的放射疗法。

[0337] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在胶质母细胞瘤的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与放射疗法被组合给予。在一个实施例中，该放射疗法选自列于以上点(i)-(iii)下的一种或多种类别的放射疗法。

[0338] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在转移性癌症的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与放射疗法被组合给予。在一个实施例中，该放射疗法选自列于以上点(i)-(iii)下的一种或多种类别的放射疗法。

[0339] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在中枢神经系统转移的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与放射疗法被组合给予。在一个实施例中，该放射疗法选自列于以上点(i)-(iii)下的一种或多种类别的放射疗法。

[0340] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在柔脑膜转移的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与放射疗法被组合给予。在一个实施例中，该放射疗法选自列于以上点(i)-(iii)下的一种或多种类别的放射疗法。

[0341] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在癌症的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与放射疗法被同时地、分别地或顺序地给予。在一个实施例中，该放射疗法选自列于以上点(i)-(iii)下的一种或多种类别的放射疗法。

[0342] 在一个实施例中，提供了在需要这种治疗的温血动物中治疗癌症的方法，该方法包括向所述温血动物给予具有式(I)的化合物或其药学上可接受的盐和放射疗法，其中该具有式(I)的化合物或其药学上可接受的盐，和放射疗法在产生抗癌作用方面是共同有效

的。在一个实施例中，该癌症选自胶质母细胞瘤、肺癌(例如小细胞肺癌或非小细胞肺癌)、乳腺癌(例如三阴性乳腺癌)、头颈部鳞状细胞癌、食道癌、宫颈癌以及子宫内膜癌。在一个实施例中，该癌症是胶质母细胞瘤。在一个实施例中，该癌症是转移性癌症。在一个实施例中，该转移性癌症包括中枢神经系统的转移。在一个实施例中，该中枢神经系统的转移包括脑转移。在一个实施例中，该中枢神经系统的转移包括柔脑膜转移。在任何实施例中，该放射疗法选自列于以上点(i)-(iii)下的一种或多种类别的放射疗法。

[0343] 在一个实施例中，提供了在需要这种治疗的温血动物中治疗癌症的方法，该方法包括向所述温血动物给予具有式(I)的化合物或其药学上可接受的盐，并且同时地、分别地或顺序地给予放射疗法，其中该具有式(I)的化合物或其药学上可接受的盐，和放射疗法在产生抗癌作用方面是共同有效的。在一个实施例中，该癌症是胶质母细胞瘤。在一个实施例中，该癌症是转移性癌症。在一个实施例中，该转移性癌症包括中枢神经系统的转移。在一个实施例中，该中枢神经系统的转移包括脑转移。在一个实施例中，该中枢神经系统的转移包括柔脑膜转移。在任何实施例中，该放射疗法选自列于以上点(i)-(iii)下的一种或多种类别的放射疗法。

[0344] 化学疗法可以包括以下类别的抗肿瘤物质中的一种或多种：

[0345] iv.抗肿瘤剂及其组合，如DNA烷基化剂(例如顺铂、奥沙利铂、卡铂、环磷酰胺、氮芥(像异环磷酰胺)、苯达莫司汀、美法仑、苯丁酸氮芥、白消安、替莫唑胺(temozolamide)以及亚硝基脲(像卡莫司汀))；抗代谢物(例如吉西他滨和抗叶酸剂，如氟嘧啶类，像5-氟尿嘧啶和替加氟、雷替曲塞、甲氨蝶呤、阿糖胞苷、以及羟基脲)；抗肿瘤抗生素(例如蒽环类，像阿霉素、博莱霉素、多柔比星、脂质体多柔比星、吡柔比星、道诺霉素、戊柔比星、表柔比星、伊达比星、丝裂霉素-C、更生霉素、氨柔比星以及光辉霉素)；抗有丝分裂剂(例如长春花生物碱类，像长春新碱、长春碱、去乙酰长春酰胺和长春瑞滨，以及紫杉烷类，像泰素和多西他赛和保罗激酶(polokinase)抑制剂)；和拓扑异构酶抑制剂(例如表鬼臼毒素类，像依托泊苷和替尼泊苷、安吖啶、伊立替康、拓扑替康以及喜树碱)；DNA修复机制的抑制剂，如CHK激酶；DNA依赖性蛋白激酶抑制剂；聚(ADP-核糖)聚合酶的抑制剂(PARP抑制剂，包括奥拉帕尼(olaparib))；和Hsp90抑制剂，如坦螺旋霉素(tanespimycin)和瑞他霉素(retaspimycin)、ATR激酶的抑制剂(例如AZD6738)；和WEE1激酶的抑制剂(如AZD1775/MK-1775)；

[0346] v.抗血管生成剂，如抑制血管内皮生长因子的那些，例如抗-血管内皮细胞生长因子抗体贝伐单抗和例如VEGF受体酪氨酸激酶抑制剂如凡德他尼(ZD6474)、索拉非尼、瓦他拉尼(PTK787)、舒尼替尼(SU11248)、阿西替尼(AG-013736)、帕唑帕尼(GW 786034)以及西地尼布(AZD2171)；如在国际专利申请WO97/22596、WO 97/30035、WO 97/32856以及WO 98/13354中披露的那些化合物；和通过其他机理起作用的化合物(例如利诺胺、整合素αvβ3功能的抑制剂和血管抑素)、或血管生成素及其受体(Tie-1和Tie-2)的抑制剂、PLGF的抑制剂、δ-样配体的抑制剂(DLL-4)；

[0347] vi.免疫治疗方法，包括例如体外-和体内-方法以提高患者肿瘤细胞的免疫原性，如用细胞因子如白细胞介素2、白细胞介素4或粒性白细胞-巨噬细胞集落刺激因子转染；减少T-细胞无反应性或调节性T细胞功能的方法；增强对肿瘤的T细胞应答的方法，如用于CTLA4(例如易普利姆玛和曲美木单抗)、B7H1、PD-1(例如BMS-936558或AMP-514)、PD-L1(例如度伐鲁单抗(durvalumab)，还被称为MEDI4736)的阻断抗体和用于CD137的激动剂抗体；

使用转染的免疫细胞如细胞因子转染的树突状细胞的方法;使用细胞因子转染的肿瘤细胞系的方法,使用肿瘤相关抗原的抗体,和耗尽靶细胞类型的抗体(例如未缀合的抗CD20抗体,如利妥昔单抗、放射性标记的抗CD20抗体托西莫(Bexxar)和泽娃灵(Zevalin)、以及抗CD54抗体坎帕斯(Campath))的方法;使用抗-独特型抗体的方法;增强自然杀伤细胞功能的方法;和利用抗体-毒素偶联物(例如,抗CD33抗体麦罗塔(Mylotarg))的方法;免疫毒素,如moxetumomab pasudotox;Toll样受体7或toll样受体9的激动剂;

[0348] vii.功效增强剂,如亚叶酸。

[0349] 在一个实施例中,提供了具有式(I)的化合物或其药学上可接受的盐,用于在癌症的治疗中使用,其中该具有式(I)的化合物或其药学上可接受的盐与至少一种另外的抗肿瘤物质被组合给予。在一个实施例中,有一种另外的抗肿瘤物质。在一个实施例中,有两种另外的抗肿瘤物质。在一个实施例中,有三种或更多种另外的抗肿瘤物质。在任何实施例中,该另外的抗肿瘤物质选自列于以上点(i)-(iv)下的一种或多种类别的抗肿瘤物质。

[0350] 在一个实施例中,提供了具有式(I)的化合物或其药学上可接受的盐,用于在癌症的治疗中使用,其中该具有式(I)的化合物或其药学上可接受的盐与至少一种另外的抗肿瘤物质被同时地、分别地或顺序地给予。在一个实施例中,有一种另外的抗肿瘤物质。在一个实施例中,有两种另外的抗肿瘤物质。在一个实施例中,有三种或更多种另外的抗肿瘤物质。在任何实施例中,该另外的抗肿瘤物质选自列于以上点(iv)-(vii)下的一种或多种类别的抗肿瘤物质。

[0351] 在一个实施例中,提供了在需要这种治疗的温血动物中治疗癌症的方法,该方法包括向所述温血动物给予具有式(I)的化合物或其药学上可接受的盐和至少一种另外的抗肿瘤物质,其中该具有式(I)的化合物或其药学上可接受的盐以及另外的抗肿瘤物质的量在产生抗癌作用方面是共同有效的。在任何实施例中,该另外的抗肿瘤物质选自列于以上点(iv)-(vii)下的一种或多种类别的抗肿瘤物质。

[0352] 在一个实施例中,提供了在需要这种治疗的温血动物中治疗癌症的方法,该方法包括向所述温血动物给予具有式(I)的化合物或其药学上可接受的盐,并且同时地、分别地或顺序地向所述温血动物给予至少一种另外的抗肿瘤物质,其中该具有式(I)的化合物或其药学上可接受的盐以及另外的抗肿瘤物质的量在产生抗癌作用方面是共同有效的。在任何实施例中,该另外的抗肿瘤物质选自列于以上点(iv)-(vii)下的一种或多种类别的抗肿瘤物质。

[0353] 在一个实施例中,提供了具有式(I)的化合物或其药学上可接受的盐、以及至少一种抗肿瘤剂,用于在癌症的治疗中使用。在一个实施例中,提供了具有式(I)的化合物或其药学上可接受的盐,用于在癌症的治疗中使用,其中该具有式(I)的化合物或其药学上可接受的盐与至少一种抗肿瘤剂被组合给予。在一个实施例中,该抗肿瘤剂选自在以上点(iv)中的抗肿瘤剂的列表。

[0354] 在一个实施例中,提供了具有式(I)的化合物或其药学上可接受的盐、以及至少一种抗肿瘤剂,用于在癌症的治疗中同时、分别或顺序使用。在一个实施例中,提供了具有式(I)的化合物或其药学上可接受的盐,用于在癌症的治疗中使用,其中该具有式(I)的化合物或其药学上可接受的盐与至少一种抗肿瘤剂被同时地、分别地或顺序地给予。在一个实施例中,该抗肿瘤剂选自在以上点(iv)中的抗肿瘤剂的列表。

[0355] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在癌症的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与至少一种另外的抗肿瘤物质被同时地、分别地或顺序地给予，该抗肿瘤物质选自：顺铂、奥沙利铂、卡铂、戊柔比星、伊达比星、多柔比星、吡柔比星、伊立替康、拓扑替康、氨柔比星、表柔比星、依托泊苷、丝裂霉素、苯达莫司汀、苯丁酸氮芥、环磷酰胺、异环磷酰胺、卡莫司汀、美法仑、博莱霉素、奥拉帕尼、度伐鲁单抗、AZD1775以及AZD6738。

[0356] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在癌症的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与至少一种另外的抗肿瘤物质被同时地、分别地或顺序地给予，该抗肿瘤物质选自：顺铂、奥沙利铂、卡铂、多柔比星、吡柔比星、伊立替康、拓扑替康、氨柔比星、表柔比星、依托泊苷、丝裂霉素、苯达莫司汀、苯丁酸氮芥、环磷酰胺、异环磷酰胺、卡莫司汀、美法仑、博莱霉素、奥拉帕尼、AZD1775以及AZD6738。

[0357] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在癌症的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与至少一种另外的抗肿瘤物质被同时地、分别地或顺序地给予，该抗肿瘤物质选自：多柔比星、伊立替康、拓扑替康、依托泊苷、丝裂霉素、苯达莫司汀、苯丁酸氮芥、环磷酰胺、异环磷酰胺、卡莫司汀、美法仑、博莱霉素以及奥拉帕尼。

[0358] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在癌症的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与至少一种另外的抗肿瘤物质被同时地、分别地或顺序地给予，该抗肿瘤物质选自：多柔比星、伊立替康、拓扑替康、依托泊苷、丝裂霉素、苯达莫司汀、苯丁酸氮芥、环磷酰胺、异环磷酰胺、卡莫司汀、美法仑以及博莱霉素。

[0359] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在癌症的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与至少一种另外的抗肿瘤物质被同时地、分别地或顺序地给予，该抗肿瘤物质选自：多柔比星、吡柔比星、氨柔比星以及表柔比星。

[0360] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在急性髓性白血病的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与至少一种另外的抗肿瘤物质被同时地、分别地或顺序地给予，该抗肿瘤物质选自：多柔比星、吡柔比星、氨柔比星以及表柔比星。

[0361] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在乳腺癌的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与至少一种另外的抗肿瘤物质被同时地、分别地或顺序地给予，该抗肿瘤物质选自：多柔比星、吡柔比星、氨柔比星以及表柔比星。

[0362] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在三阴性乳腺癌的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与至少一种另外的抗肿瘤物质被同时地、分别地或顺序地给予，该抗肿瘤物质选自：多柔比星、吡柔比星、氨柔比星以及表柔比星。

[0363] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在肝细

胞癌的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与至少一种另外的抗肿瘤物质被同时地、分别地或顺序地给予，该抗肿瘤物质选自：多柔比星、吡柔比星、氨柔比星以及表柔比星。

[0364] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在癌症的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与伊立替康被同时地、分别地或顺序地给予。

[0365] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在结肠直肠癌的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与伊立替康被同时地、分别地或顺序地给予。

[0366] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在结肠直肠癌的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的与FOLFIRI被同时地、分别地或顺序地给予。

[0367] FOLFIRI是包含亚叶酸、5-氟尿嘧啶以及伊立替康的组合的给药方案。

[0368] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在癌症的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与奥拉帕尼被同时地、分别地或顺序地给予。

[0369] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在胃癌的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与奥拉帕尼被同时地、分别地或顺序地给予。

[0370] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在癌症的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与拓扑替康被同时地、分别地或顺序地给予。

[0371] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在肺癌的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与拓扑替康被同时地、分别地或顺序地给予。

[0372] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在小细胞肺癌的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与拓扑替康被同时地、分别地或顺序地给予。

[0373] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在癌症的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与免疫疗法被同时地、分别地或顺序地给予。在一个实施例中，该免疫疗法是列于以上点(iii)下的这些药剂中的一种或多种。

[0374] 在一个实施例中，提供了具有式(I)的化合物或其药学上可接受的盐，用于在癌症的治疗中使用，其中该具有式(I)的化合物或其药学上可接受的盐与抗-PD-L1抗体(例如度伐鲁单抗)被同时地、分别地或顺序地给予。

[0375] 根据另一个实施例，提供了试剂盒，该试剂盒包含：

[0376] a)处于第一单位剂型的、具有式(I)的化合物或其药学上可接受的盐；

[0377] b)处于另外的单位剂型的又另外的抗肿瘤物质；

[0378] c)包含所述第一单位剂型和另外的单位剂型的容器装置；以及任选地

[0379] d)使用说明书。在一个实施例中,该抗肿瘤物质包括抗肿瘤剂。

[0380] 在抗肿瘤剂被提及的任何实施例中,该抗肿瘤剂是列于以上点(iv)下的这些药剂中的一种或多种。

[0381] 具有式(I)的化合物及其药学上可接受的盐可以作为药物组合物被给予,该药物组合物包含一种或多种药学上可接受的赋形剂。

[0382] 因此,在一个实施例中,提供了包含具有式(I)的化合物或其药学上可接受的盐、以及至少一种药学上可接受的赋形剂的药物组合物。

[0383] 针对包含于具体组合物中而选择的一种或多种药学上可接受的赋形剂将取决于如以下因素,如给予方式和提供的组合物的形式。适合的药学上可接受的赋形剂是本领域技术人员所熟知的并且例如,描述于HandbookofPharmaceuticalExcipients[药用赋形剂手册]中,第六版,英国医药出版社(Pharmaceutical Press),由Rowe,Ray C;Sheskey,Paul J;Quinn,Marian编写。药学上可接受的赋形剂可以用作例如,佐剂、稀释剂、载体、稳定剂、调味剂、着色剂、填料、粘合剂、崩解剂、润滑剂、助流剂、增稠剂以及包衣剂。如本领域技术人员将理解的是,某些药学上可接受的赋形剂可用于多于一种功能,并且可用于可替代性作用,这取决于组合物中存在多少赋形剂并且该组合物中存在哪些其他赋形剂。

[0384] 该药物组合物可处于适合于以下的形式:口服使用(例如作为片剂、锭剂、硬或软胶囊、水性或油性悬浮液、乳剂、可分散粉剂或颗粒剂、糖浆剂或酏剂),局部使用(例如作为乳膏、软膏剂、凝胶剂、或者水性或油性溶液或悬浮液),通过吸入给予(例如作为细碎粉末或液体气雾剂),通过吹入给予(例如作为细碎粉末),或肠胃外给予(例如作为用于静脉内、皮下、肌内或肌内给药的无菌水性或油性溶液),或作为用于直肠给药给予的栓剂。这些组合物可以通过本领域熟知的常规程序来获得。旨在用于口服使用的组合物可含有另外的组分,例如,一种或多种着色剂、甜味剂、调味剂和/或防腐剂。

[0385] 具有式(I)的化合物通常以范围为2.5-5000mg/m^2动物体表面积内的一个单位剂量或大约0.05-100mg/kg给予至温-血动物,并且这通常提供治疗-有效剂量。单位剂型如片剂或胶囊剂通常含有例如0.1-250mg的活性成分。每日剂量将必然取决于所治疗的宿主、具体的给予途径、共给予的任何疗法、以及正在治疗的疾病的严重性而变化。因此,治疗任何具体患者的执业医生可以确定最佳剂量。

[0386] 本文所描述的这些药物组合物包含具有式(I)的化合物或其药学上可接受的盐,并且因此预期在疗法中是有用的。

[0387] 同样地,在一个实施例中,提供了用于在疗法中使用的药物组合物,该药物组合物包含具有式(I)的化合物或其药学上可接受的盐、以及至少一种药学上可接受的赋形剂。

[0388] 在一个实施例中,提供了用于在其中ATM激酶的抑制是有益的疾病的治疗中使用的药物组合物,该药物组合物包含具有式(I)的化合物或其药学上可接受的盐,以及至少一种药学上可接受的赋形剂。

[0389] 在一个实施例中,提供了用于在癌症的治疗中使用的药物组合物,该药物组合物包含具有式(I)的化合物或其药学上可接受的盐,以及至少一种药学上可接受的赋形剂。

[0390] 在一个实施例中,提供了用于在其中ATM激酶的抑制是有益的癌症的治疗中使用的药物组合物,该药物组合物包含具有式(I)的化合物或其药学上可接受的盐、以及至少一种药学上可接受的赋形剂。

[0391] 在一个实施例中，提供了用于在治疗以下疾病中使用的药物组合物：结肠直肠癌、胶质母细胞瘤、胃癌、卵巢癌、弥漫性大B细胞淋巴瘤、慢性淋巴细胞性白血病、急性髓性白血病、头颈部鳞状细胞癌、乳腺癌、肝细胞癌、小细胞肺癌或非小细胞肺癌，该药物组合物包含具有式(I)的化合物或其药学上可接受的盐，以及至少一种药学上可接受的赋形剂。

[0392] 实例

[0393] 通过以下实例阐明本发明的多个实施例。本发明不被解释为受限于这些实例。在实例的制备期间，通常：

[0394] i.操作在环境温度下进行，即在约17至30℃的范围内和在惰性气体如氮气的气氛下进行，除非另有说明；

[0395] ii.通过旋转蒸发或使用Genevac真空设备进行蒸发，并且在通过过滤去除残余固体之后进行后处理程序；

[0396] iii.在自动Armen GliderFlash:SpotII Ultimate(阿芒仪器(Armen Instrument)，圣阿韦(Saint-Ave)，法国)上或自动Presearch combiflash上伴随使用从德国达姆施塔特的默克公司(Merck,Darmstad,Germany)获得的预包装Merck正相Si60二氧化硅柱体(粒度计：15-40μm或40-63μm)、silicycle二氧化硅柱体或graceresolv二氧化硅柱体进行快速色谱纯化；

[0397] iv.在装有ZMD或ZQ ESCi质谱仪和沃特斯X-Terra反相柱或沃特斯X-Bridge反相柱或沃特斯SunFire反相柱(C-18，5微米二氧化硅，19mm或50mm直径，100mm长度，40mL/分钟的流速)的沃特斯仪器(600/2700或2525)上，使用水(含有1％氨)和乙腈的极性递减混合物或者水(含有0.1％甲酸)和乙腈的极性递减混合物作为洗脱液进行制备型色谱法；

[0398] v.产率，在存在的情况下，不必是可达到的最大值；

[0399] vi.具有式(I)的终-产物的结构通过核磁共振(NMR)光谱法证实，其中以δ角测量NMR化学位移值。使用Bruker advance 700(700MHz)、Bruker Avance 500(500MHz)、Bruker400(400MHz)或Bruker 300(300MHz)仪器测定质子核磁共振谱；在282MHz或376MHz处测定^{19}F NMR；在75MHz或100MHz处测定^{13}C NMR；除非另外指明，在大约20℃-30℃下进行测量；使用以下缩写：s，单峰；d，二重峰；t，三重峰；q，四重峰；m，多重峰；dd，双二重峰；ddd，双二重峰的双重峰；dt，双三重峰；bs，宽峰信号；

[0400] vii.具有式(I)的终-产物在液相色谱法之后还通过质谱法(LCMS)来表征；使用装有沃特斯ZQ ESCi或ZMD ESCi质谱仪和XBridge 5μm C-18柱(2.1x 50mm)的沃特斯Alliance HT(2790&2795)在2.4mL/min的流速下，使用95％A+5％C至95％B+5％C的溶剂系统(其中A＝水，B＝甲醇，C＝1:1甲醇:水(含有0.2％碳酸铵))经4分钟；或通过使用装有Phenomenex Gemini-NX C183.0x50mm、3.0μM柱或等效物(碱性条件)的Shimadzu UFLC或UHPLC外加DAD检测器、ELSD检测器和2020EV质谱仪(或等效物)，或ShimpackXR-ODS 3.0x50mm、2.2μM柱，或沃特斯BEH C182.1x 50mm、1.7μM柱或等效物；使用95％D+5％E至95％E+5％D的溶剂系统(其中D＝水(含有0.05％TFA)，E＝乙腈(含有0.05％TFA)(酸性条件))经4分钟或90％F+10％G至95％G+5％F的溶剂系统(其中F＝水(含有6.5mM碳酸氢铵并且通过添加氨调至pH 10)，G＝乙腈(碱性条件))经4分钟进行LCMS；

[0401] viii.中间体总体上未经完全表征且纯度通过薄层色谱、质谱、HPLC和/或NMR分析来评估；

[0402] ix.通过将结晶物质样品安装在Bruker单硅晶体(SSC)晶片支架上且借助于显微镜载片将样品展布成薄层来测定(使用BrukerD4分析仪器)X射线粉末衍射谱。使样品以每分钟30转离心(以改良计数统计)且用由在40kV和40mA下操作的铜制长细聚焦管产生的具有1.5418埃的波长的X射线来辐照。使准直X射线源穿过设定在V20下的自动可变发散狭缝且引导反射的辐射穿过5.89mm防散射狭缝和9.55mm检测器狭缝。在θ-θ模式中从2°至40°2-θ的范围内,使样品每0.00570°2-θ增量暴露0.03秒(连续扫描模式)。运行时间是3分36秒。该仪器装备有位置敏感性检测器(联凯(Lynxeye))。对照和数据采集是通过用Diffrac+软件操作的Dell Optiplex686NT 4.0工作站进行的;

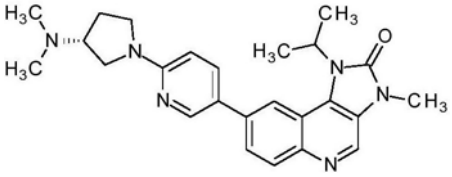
[0403] x.在TA仪Q1000DSC上进行差示扫描量热法。典型地,将包含在装有盖子的标准铝盘中的小于5mg的物质以每分钟10℃的恒定加热速率在温度范围为25℃至300℃加热。以每分钟50mL流速使用经氮气净化的气体。

[0404] xi.使用以下缩写:h=小时;r.t.=室温(约18-25℃);conc.=浓缩的;FCC=使用二氧化硅的快速柱色谱法;DCM=二氯甲烷;DIPEA=二异丙基乙胺;DMA=N,N-二甲基乙酰胺;DMF=N,N-二甲基甲酰胺;DMSO=二甲基亚砜;Et_2O=二乙醚;EtOAc=乙酸乙酯;EtOH=乙醇;K_2CO_3=碳酸钾;MeOH=甲醇;MeCN=乙腈;MTBE=甲基叔丁基醚;$MgSO_4$=无水硫酸镁;Na_2SO_4=无水硫酸钠;THF=四氢呋喃;sat.=饱和水性溶液;并且

[0405] xii.使用"Canvas"或"IBIS",阿斯利康(AstraZeneca)专有程序生成IUPAC名称。如引言中所述的,本发明的这些化合物包括咪唑并[4,5-c]喹啉-2-酮核心。然而,在某些实例中,IUPAC名称将该核心描述为咪唑并[5,4-c]喹啉-2-酮。尽管该咪唑并[4,5-c]喹啉-2-酮和咪唑并[5,4-c]喹啉-2-酮核心是相同的,但是由于周边基团,命名约定不同。

[0406] 实例1

[0407] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮

[0408] 

[0409] 将8-(6-氟-3-吡啶基)-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮(1g,2.97mmol)和(R)-N,N-二甲基吡咯烷-3-胺(1.4g,12.26mmol)在MeCN(10mL)中的悬浮液在微波反应器中加热至150℃持续4h,然后允许冷却至环境温度。将反应混合物用DCM(200mL)稀释,用水(100mL)洗涤两次,并将有机层经$MgSO_4$干燥,过滤并蒸发以提供粗产物。将该粗产物通过FCC进行纯化,洗脱梯度为在DCM中0至4%2N甲醇氨,以提供呈白色固体的所希望的物质(1.210g,95%)。NMR谱:^1H NMR(500MHz,$CDCl_3$)δ1.78(6H,d),1.89-2.1(1H,m),2.22-2.33(1H,m),2.35(6H,s),2.75-3.02(1H,m),3.25-3.42(1H,m),3.44-3.56(1H,m),3.58(3H,s),3.66-3.8(1H,m),3.78-3.97(1H,m),5.19-5.44(1H,m),6.52(1H,dd),7.78(1H,dd),7.82(1H,dd),8.18(1H,d),8.30(1H,s),8.58(1H,dd),8.66(1H,s)。质谱:m/z(ES+)[M+H]+=431。

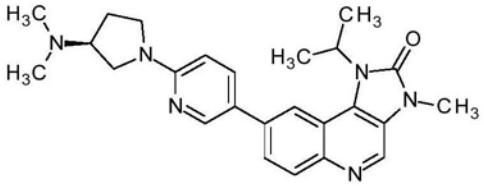
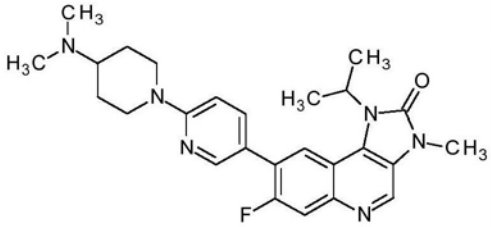
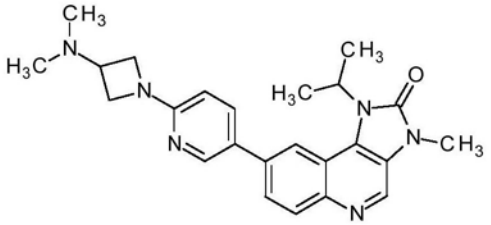
[0410] 使用以下程序还可以将该物质分离为甲磺酸盐:

[0411] 将分离的物质(632mg,1.47mmol)悬浮于DCM(2mL)中,并用在DCM(5mL)中的甲磺酸

(161mg,1.68mmol)处理。将该溶液蒸发至干燥,然后用二乙醚研磨以提供呈甲磺酸盐的所希望的物质(770mg,100%)。NMR谱:^{1}H NMR(500MHz,DMSO-d6)δ1.67(6H,d),2.13-2.3(1H,m),2.32(3H,s),2.43-2.48(1H,m),2.88(6H,s),3.4-3.56(4H,m),3.64(1H,dd),3.68-3.84(1H,m),3.94(1H,dd),4.03(1H,p),5.35(1H,p),6.73(1H,d),7.95(1H,dd),8.07(1H,dd),8.11(1H,d),8.35(1H,d),8.55-8.77(1H,m),8.89(1H,s),9.88(1H,s)。质谱:m/z(ES+)[M+H]+=431

[0412] 以类似的方式从适合的胺以及8-(6-氟-3-吡啶基)-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮或7-氟-8-(6-氟-3-吡啶基)-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮制备以下化合物。

[0413]

实例	结构	名称
2*		8-[6-[(3*S*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮
3**		8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮
4***		8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮

[0414] *将该反应在MeCN中在150℃下加热4h。

[0415] **该反应在MeCN中与存在的4当量的DIPEA进行反应,并且在回流下加热16h。纯化和分离之后,通过从热的MeCN中重结晶,将该物质进一步进行纯化。

[0416] ***将该反应在MeCN中与存在的7当量的DIPEA进行反应,并在150℃下加热4h。

[0417] 实例2:(游离碱)NMR谱:^{1}H NMR(500MHz,$CDCl_3$)δ1.78(6H,d),1.92-2.04(1H,m),2.24-2.33(1H,m),2.35(6H,s),2.79-2.95(1H,m),3.29-3.4(1H,m),3.43-3.55(1H,m),3.58(3H,s),3.74(1H,s),3.87(1H,dd),5.22-5.42(1H,m),6.52(1H,dd),7.78(1H,dd),7.82(1H,dd),8.18(1H,d),8.30(1H,s),8.58(1H,dd),8.66(1H,s)。(甲磺酸盐)NMR谱:^{1}H NMR(500MHz,DMSO-d6)δ1.69(6H,d),2.2-2.31(1H,m),2.32(3H,s),2.43-2.58(1H,m),2.90(6H,s),3.43-3.57(4H,m),3.65(1H,dd),3.71-3.81(1H,m),3.96(1H,dd),3.99-4.11(1H,m),5.36(1H,p),6.74(1H,d),7.95(1H,dd),8.08(1H,dd),8.13(1H,d),8.36(1H,d),8.66(1H,d),8.88(1H,s),9.86(1H,s)。质谱:m/z(ES+)[M+H]+=431。

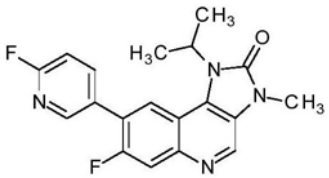
[0418] 实例3:(游离碱)NMR谱:^{1}H NMR(500MHz,DMSO-d6)δ1.37(2H,qd),1.65(6H,d),1.85(2H,d),2.20(6H,s),2.31-2.4(1H,m),2.86-2.95(2H,m),3.50(3H,s),4.41(2H,d),

5.28(1H,p),7.00(1H,d),7.83-7.91(2H,m),8.27(1H,d),8.43-8.48(1H,m),8.88(1H,s)。(甲磺酸盐)NMR谱:^{1}H NMR(500MHz,DMSO-d6)δ1.60(2H,dd),1.66(6H,d),2.10(2H,d),2.32(4H,s),2.80(6H,d),2.93(1H,s),3.52(4H,s),4.60(2H,d),5.32(1H,dt),7.11(1H,d),7.91-7.97(2H,m),8.33(1H,d),8.50(1H,s),8.99(1H,s),9.41(1H,s)。质谱:m/z(ES+)[M+H]+=463。

[0419] 实例4:(游离碱)NMR谱:^{1}HNMR(500MHz,$CDCl_3$)δ1.79(6H,d),2.26(6H,s),3.31(1H,tt),3.59(3H,s),3.95(2H,dd),4.14-4.21(2H,m),5.28-5.35(1H,m),6.45(1H,dd),7.78(1H,dd),7.81(1H,dd),8.19(1H,d),8.30(1H,s),8.55(1H,dd),8.68(1H,s)。(甲磺酸盐)NMR谱:^{1}H NMR(500MHz,DMSO-d6)δ1.69(6H,d),2.32(3H,s),2.85(6H,s),3.52(3H,s),4.19(2H,dd),4.30(3H,d),5.39(1H,p),6.68(1H,d),8.03(1H,d),8.13(1H,dd),8.17(1H,d),8.40(1H,d),8.67(1H,d),8.99(1H,s)。质谱:m/z(ES+)[M+H]+=417。

[0420] 8-(6-氟-3-吡啶基)-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮和7-氟-8-(6-氟-3-吡啶基)-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮的制备描述如下。

[0421] 中间体A0:7-氟-8-(6-氟-3-吡啶基)-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮

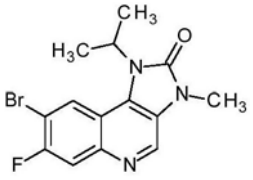
[0422] 

[0423] 将二氯双(二-叔-丁基(3-磺丙基)磷鎓基)钯酸盐(II)(在水中的0.05M溶液,11.83mL,0.59mmol)添加至8-溴-7-氟-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮(4.0g,11.83mmol)、(6-氟吡啶-3-基)硼酸(2.0g,14.19mmol)以及在1,4-二噁烷(50mL)和水(12.5mL)中的2M碳酸钾溶液(17.74mL,35.48mmol)的脱气混合物中。将该混合物用氮净化并加热至80℃持续1h,然后允许冷却并在减压下浓缩以去除。将剩余的溶液用DCM(250mL)稀释,用水(200mL)洗涤并且将有机层用相分离柱干燥并且蒸发以得到粗产物。将该粗产物通过FCC进行纯化,洗脱梯度为DCM中0至10%MeOH,以提供呈白色固体的所希望的物质(3.70g,88%)。NMR谱:^{1}H NMR(500MHz,$CDCl_3$)δ1.77(6H,dd),3.58(3H,d),5.20(1H,s),7.11(1H,ddd),7.93(1H,d),8.06-8.14(1H,m),8.22(1H,d),8.46-8.51(1H,m),8.72(1H,s)。质谱:m/z(ES+)[M+H]+=355.3

[0424] 二氯双(二-叔-丁基(3-磺丙基)磷鎓基)钯酸盐(II)(在水中的0.05M溶液)可以按下面所描述的进行制备:

[0425] 在环境温度下,在惰性气氛下,将脱气水(30mL)添加至四氯钯酸钠(II)(0.410g,1.39mmol)和3-(二-叔-丁基膦基)丙烷-1-磺酸(0.748g,2.79mmol)中。将该悬浮液搅拌5分钟,然后将固体通过过滤去除并丢弃,以留下呈红棕色溶液的所希望的溶剂。

[0426] 中间体A1:8-溴-7-氟-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮

[0427] 

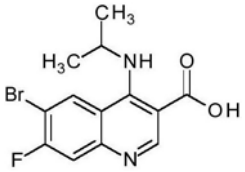
[0428] 将在水(600mL)中的氢氧化钠(11.29g,282.28mmol)溶液添加至8-溴-7-氟-1-异丙基-3H-咪唑并[4,5-c]喹啉-2-酮(61g,188.19mmol)、四丁基溴化铵(6.07g,18.82mmol)和碘甲烷(23.53mL,376.37mmol)在DCM(1300mL)中的搅拌混合物里,并且将该混合物在环境温度下搅拌17h。以相同的规模重复同一程序并且将该反应混合物合并,浓缩并用MeOH(750mL)稀释。将沉淀通过过滤收集,用MeOH(500mL)洗涤并且将固体在真空下干燥以得到呈白色固体的所希望的物质(108g,85%)。NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.76(6H,d),3.57(3H,s),5.13(1H,t),7.83(1H,d),8.41(1H,d),8.69(1H,s)。质谱:m/z(ES+)[M+H]+=380

[0429] 中间体A2:8-溴-7-氟-1-异丙基-3H-咪唑并[4,5-c]喹啉-2-酮

[0430] 

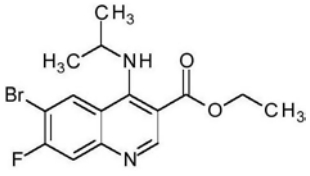
[0431] 将三乙胺(164mL,1173.78mmol)一次性添加至在DMF(1500mL)中的6-溴-7-氟-4-(异丙基氨基)喹啉-3-甲酸(128g,391.26mmol)中,并且将该混合物在环境温度下在惰性气氛下搅拌30分钟。添加二苯基磷酰基叠氮化物(101mL,469.51mmol)并且将溶液在环境温度下再次搅拌30分钟然后在60℃下搅拌3h。将该反应混合物倾倒入冰水中,将沉淀通过过滤收集,用水(1L)洗涤并且在真空下干燥,以得到呈黄色固体的所希望的物质(122g,96%)。NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ1.62(6H,d),5.12-5.19(1H,m),7.92(1H,d),8.57(1H,d),8.68(1H,s),11.58(1H,s)。质谱:m/z(ES+)[M+H]+=324

[0432] 中间体A3:6-溴-7-氟-4-(异丙基氨基)喹啉-3-甲酸

[0433] 

[0434] 在15℃下,将2N氢氧化钠溶液(833mL,1666.66mmol)分批添加至在THF(1500mL)中的6-溴-7-氟-4-(异丙基氨基)喹啉-3-甲酸乙酯(148g,416.66mmol)里,并且将所得混合物在60℃下搅拌5h。将该反应混合物浓缩,用水(2L)稀释,并且将该混合物用2M盐酸进行酸化。将沉淀通过过滤收集,用水(1L)洗涤并在真空下干燥,以得到呈白色固体的所希望的物质(128g,94%)。NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ1.24-1.36(6H,m),4.37(1H,s),7.78(1H,t),8.55(1H,s),8.90(1H,s)。质谱:m/z(ES+)[M+H]+=327

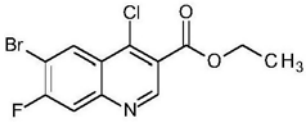
[0435] 中间体A4:6-溴-7-氟-4-(异丙基氨基)喹啉-3-甲酸乙酯

[0436] 

[0437] 在环境温度下,将DIPEA(154mL,884.07mmol)分批添加至在DMA(600mL)中的丙-2-胺(39.2g,663.05mmol)和6-溴-4-氯-7-氟喹啉-3-甲酸乙酯(147g,442.04mmol)里,并且将所得混合物在100℃下搅拌4h。将该反应混合物倒入冰水中,通过过滤将沉淀物收集,用水(1L)洗涤,并且在真空下干燥以提供呈浅棕色固体的所希望的物质(148g,94%)。NMR谱:^{1}H

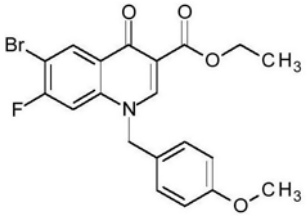
NMR(400MHz,DMSO-d6)δ1.26-1.33(9H,m),4.17-4.25(1H,m),4.32-4.37(2H,m),7.28(1H,d),8.50(1H,d),8.59(1H,d),8.86(1H,s)。质谱:m/z(ES+)[M+H]+=355

[0438] 中间体A5:6-溴-4-氯-7-氟喹啉-3-甲酸乙酯

[0439] 

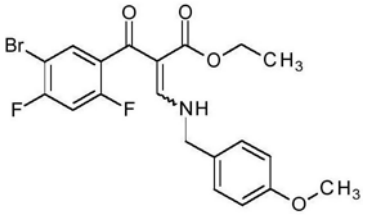
[0440] 在10℃且在惰性气氛下,将DMF(0.535mL,6.91mmol)添加至在亚硫酰氯(600mL)中的6-溴-7-氟-1-[(4-甲氧基苯基)甲基]-4-氧代-喹啉-3-甲酸乙酯(200g,460.56mmol)里,并且将所得混合物在70℃下搅拌3h。将该混合物蒸发至干燥,并且将残余物与甲苯(300mL)共沸以提供粗产物。将该粗产物通过从己烷结晶进行纯化,以得到呈白色固体的所希望的物质(147g,96%)。NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.49(3H,t),4.51-4.56(2H,m),7.91(1H,d),8.71(1H,d),9.26(1H,s)。质谱:m/z(ES+)[M+H]+=334

[0441] 中间体A6:6-溴-7-氟-1-[(4-甲氧基苯基)甲基]-4-氧代-喹啉-3-甲酸乙酯

[0442] 

[0443] 在10℃下,经5分钟的时间段,在惰性气氛下将DBU(76mL,506.32mmol)缓慢添加至在丙酮(800mL)中的乙基-2-(5-溴-2,4-二氟-苯甲酰基)-3-[(4-甲氧基苯基)甲基氨基]丙-2-烯酸酯(230g,506.32mmol)里,并且将所得混合物在环境温度下搅拌16h。通过过滤将沉淀物收集,用Et_2O(3x 500mL)洗涤,并且在真空下干燥以提供呈白色固体的所希望的物质(166g,75%)。NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ1.29(3H,t),3.72(3H,s),4.22-4.27(21H,m),5.57(2H,s),6.92-6.95(2H,m),7.24(2H,d),7.79(1H,d),8.40(1H,d),8.89(1H,s)。质谱:m/z(ES+)[M+H]+=434。

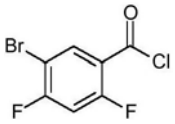
[0444] 中间体A7:乙基-2-(5-溴-2,4-二氟-苯甲酰基)-3-[(4-甲氧基苯基)甲基氨基]丙-2-烯酸酯

[0445] 

[0446] 在环境温度下,在惰性气氛下,将(E)-乙基3-(二甲基氨基)丙烯酸酯(80mL,555.50mmol)滴加至DIPEA(132mL,757.50mmol)和5-溴-2,4-二氟-苯甲酰基氯化物(129g,505.00mmol)在甲苯(600mL)中的混合物中。将所得的溶液在70℃下搅拌17h然后允许冷却。将(4-甲氧基苯基)甲胺(66.0mL,505.29mmol)分批添加至该混合物中并将该反应在环境温度下搅拌3h。将该反应混合物用DCM(2L)稀释,顺序地用水(4x 200mL)、饱和盐水(300mL)洗涤,将有机层经Na_2SO_4干燥,过滤并且蒸发以得到呈浅棕色固体的所希望的物质(230g,100%),将其不进行进一步纯化而用于下一步。NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.09(3H,t),

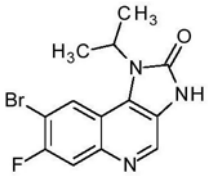
3.82(3H,s),4.00-4.10(2H,m),4.55(2H,t),6.84-6.96(3H,m),7.20-7.29(2H,m),7.55(1H,d),8.18(1H,t)质谱:m/z(ES+)[M+H]+=454

[0447] 中间体A8:5-溴-2,4-二氟-苯甲酰氯

[0448] 

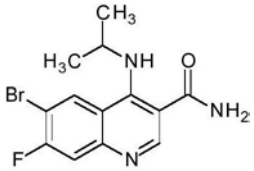
[0449] 在15℃下,经5分钟的时间段,在惰性气氛下,将亚硫酰氯(55.4mL,759.50mmol)分批添加至DMF(7.84mL,101.27mmol)和5-溴-2,4-二氟苯甲酸(120g,506.33mmol)在甲苯(600mL)中的混合物中。将所得的混合物在70℃下搅拌4h然后蒸发至干燥并将残余物与甲苯共沸,以得到呈棕色油状的所希望的物质(129g,100%),将其不进行纯化直接用于下一步。NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ7.04-7.09(1H,m),8.34-8.42(1H,m)。

[0450] 中间体A2:8-溴-7-氟-1-异丙基-3H-咪唑并[4,5-c]喹啉-2-酮还可以按下面所描述的进行制备:

[0451] 

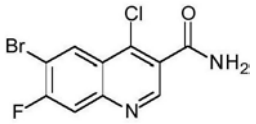
[0452] 在5℃下,将1,3,5-三氯-1,3,5-三嗪-2,4,6-三酮(5.91g,25.45mmol)分批添加至6-溴-7-氟-4-(异丙基氨基)喹啉-3-甲酰胺(16.6g,50.89mmol)和1,8-二氮杂二环[5.4.0]十一碳-7-烯(15.22mL,101.79mmol)在甲醇(200mL)中的搅拌悬浮液里。将所得悬浮液在环境温度下搅拌1h。将该反应过滤,并且将固体在真空烘箱中干燥2h,以提供呈浅黄色固体的所希望的物质(14.18g,86%)。在留下滤液静置2天并且然后过滤之后,获得另外的材料。将分离的另外的固体在EtOH(50mL)中加热30分钟,然后允许冷却并过滤以提供呈白色固体的另外的所希望的物质(2.6mg)。分析数据与从先前所描述的替代性制剂获得的是一致的。

[0453] 中间体A9:6-溴-7-氟-4-(异丙基氨基)喹啉-3-甲酰胺

[0454] 

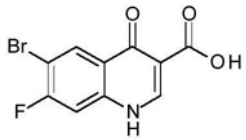
[0455] 将丙-2-胺(2.80mL,32.62mmol)添加至6-溴-4-氯-7-氟-喹啉-3-甲酰胺(10g,29.65mmol)和碳酸钾(8.20g,59.31mmol)在乙腈(250mL)中的悬浮液里,并且将该混合物在95℃下搅拌4h。添加另外的丙-2-胺(2mL),并且将该混合物在95℃下再搅拌4h,然后在环境温度下搅拌过夜。将水添加至该混合物中并将固体通过过滤收集,并且在真空下干燥以得到所希望的物质(8.25g,85%)。NMR谱:^{1}H NMR(500MHz,DMSO-d6)δ1.25(6H,d),4.17(1H,d),7.51(1H,s),7.69(1H,d),8.11(2H,s),8.61(1H,s),8.67(1H,d)。质谱:m/z(ES+)[M+H]+=236。

[0456] 中间体A10:6-溴-4-氯-7-氟-喹啉-3-甲酰胺

[0457] 

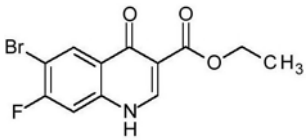
[0458] 将DMF(0.5mL)添加至6-溴-7-氟-4-氧代-1H-喹啉-3-甲酸(22.5g,78.66mmol)在亚硫酰氯(140g,1179.85mmol)中的搅拌悬浮液里,并且将该混合物加热至回流2h。允许该反应冷却,在真空中浓缩,并且将残余物用甲苯共沸两次以提供黄色固体。在0℃下,将该固体分批添加至氢氧化铵的溶液(147mL,1179.85mmol)中。将白色悬浮液搅拌15分钟然后将固体过滤,用水洗涤并在真空下干燥以得到呈白色粉末状的所希望的物质(23.80g,100%)。NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ8.92(1H,s),8.59(1H,d),8.21(1H,s),8.09(1H,d),7.98(1H,s)。质谱:m/z(ES+)[M+H]+=304.8。

[0459] 中间体A11:6-溴-7-氟-4-氧代-1H-喹啉-3-甲酸

[0460] 

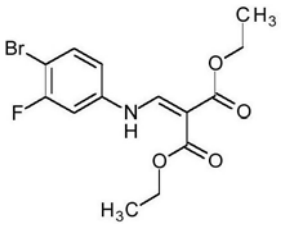
[0461] 在环境温度下,将氢氧化钠(18.34g,458.44mmol)在水(100mL)中的溶液添加至6-溴-7-氟-4-氧代-1H-喹啉-3-甲酸乙酯(28.8g,91.69mmol)在EtOH(500mL)中的搅拌悬浮液中。然后将该反应混合物在75℃下搅拌2h,允许冷却并使用2N盐酸将pH调节至4。将沉淀通过过滤收集,用水洗涤并在真空下干燥,以得到呈白色粉末状的所希望的物质(23.30g,89%)。NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ14.78(1H,s),13.45(1H,s),8.93(1H,s),8.46(1H,d),7.70(1H,d)。质谱:m/z(ES+)[M+H]+=287.8。

[0462] 中间体A12:6-溴-7-氟-4-氧代-1H-喹啉-3-甲酸乙酯

[0463] 

[0464] 在240℃下,将2-[(4-溴-3-氟-苯胺基)亚甲基]丙二酸二乙酯(90g,249.88mmol)在二苯醚(600mL,3.79mol)中的溶液搅拌2.5h。允许混合物冷却至70℃,通过过滤收集固体并且在真空烘箱中干燥以提供呈白色固体的所希望的物质(50g,64%),将该物质无需进一步纯化而使用。NMR谱:^{1}H NMR(500MHz,DMSO-d6,(100℃))δ1.26-1.33(3H,m),4.25(2H,q),7.52(1H,d),8.37(1H,d),8.48(1H,s),12.05(1H,s)。质谱:m/z(ES+)[M+H]+=314。

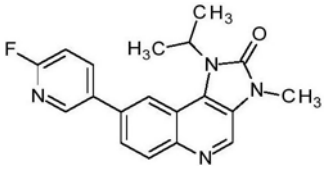
[0465] 中间体A13:2-[(4-溴-3-氟-苯胺基)亚甲基]丙二酸二乙酯

[0466] 

[0467] 将4-溴-3-氟苯胺(56.6g,297.87mmol)和1,3-二乙基2-(乙氧基亚甲基)丙二酸酯(72.45g,335.06mmol)在EtOH(560mL)中的溶液在80℃下搅拌4h。允许反应混合物冷却,通过过滤将这些固体收集,并且在烘箱中干燥以提供呈灰白色固体的所希望的物质(90g,84%),将该物质无需进一步纯化而使用。NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ1.26(6H,q),

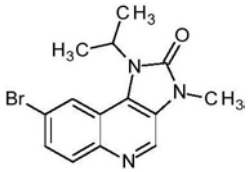
4.14(2H,q),4.22(2H,q),7.18-7.25(1H,m),7.57(1H,dd),7.64-7.7(1H,m),8.33(1H,d),10.62(1H,d)。质谱:m/z(ES+)[M+H]+=360。

[0468] 中间体B0:8-(6-氟-3-吡啶基)-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮

[0469] 

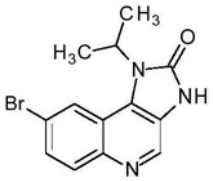
[0470] 将8-溴-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮(4.57g,14.27mmol)、(6-氟吡啶-3-基)硼酸(2.61g,18.55mmol)以及2M碳酸钾(22mL,44.00mmol)悬浮于1,4-二噁烷(90mL)中。在惰性气氛下,将该混合物脱气然后添加二氯[1,1'-双(二-叔丁基膦基)二茂铁]钯(II)(0.465g,0.71mmol),并且将该反应加热至80℃持续2h。允许将该混合物冷却,用EtOAc(200mL)稀释然后用水(50mL)、盐水洗涤,并将有机相经$MgSO_4$干燥,过滤并在真空中浓缩。将该粗产物通过FCC进行纯化,洗脱梯度为在DCM中0至5%MeOH,以提供物质,随后将该物质用二乙醚研磨以提供呈灰白色固体的所希望的物质(4.46g,93%)。NMR谱:^{1}HNMR(500MHz,DMSO-d6)δ1.66(6H,d),3.50(3H,s),5.36(1H,p),7.36(1H,dd),7.95(1H,dd),8.15(1H,d),8.39-8.52(2H,m),8.72(1H,d),8.90(1H,s)。质谱:m/z(ES+)[M+H]+=337。

[0471] 中间体B1:8-溴-1-异丙基-3-甲基-咪唑并[4,5-c]喹啉-2-酮

[0472] 

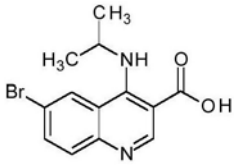
[0473] 将N,N-二甲基甲酰胺二甲缩醛(54.2mL,408.29mmol)添加至8-溴-1-异丙基-3H-咪唑并[4,5-c]喹啉-2-酮(25.00g,81.66mmol)在DMF(375mL)中的溶液中。将该混合物加热至80℃持续3h,然后允许冷却至环境温度并搅拌16h。将沉淀通过过滤收集,用水(4x 300mL)洗涤并在真空下在50℃下干燥以得到呈白色固体的所希望的物质(23.82g,91%)。NMR谱:^{1}H NMR(500MHz,DMSO-d6)δ1.63(6H,d),3.49(3H,s),5.15-5.23(1H,m),7.75(1H,dd),7.99(1H,d),8.44(1H,d),8.91(1H,s)。质谱:m/z(ES+)[M+H]+=320。

[0474] 中间体B2:8-溴-1-异丙基-3H-咪唑并[4,5-c]喹啉-2-酮

[0475] 

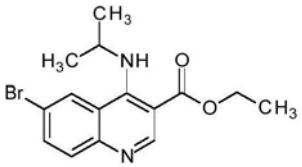
[0476] 在环境温度下,将三乙胺(45.3mL,332.06mmol)添加至在DMF(342mL)中的6-溴-4-(异丙基氨基)喹啉-3-甲酸(34.22g,110.69mmol)中。在环境温度下搅拌30分钟后,添加叠氮磷酸二苯酯(26.2mL,121.76mmol),并且将所得混合物在60℃下搅拌2h。将反应混合物倾倒入水(1500mL)中;通过过滤收集沉淀,用水(2x 700mL)洗涤并在真空下在50℃下干燥,以得到呈米黄色固体的所希望的物质(29.6g,87%),将其不进行进一步纯化而使用。NMR谱:^{1}HNMR(500MHz,$CDCl_3$)δ1.64(6H,d),5.06-5.21(1H,m),7.75(1H,d),7.98(1H,d),8.43(1H,s),8.69(1H,s),11.57(1H,s)。质谱:m/z(ES+)[M+H]+=306。

[0477] 中间体B3:6-溴-4-(异丙基氨基)喹啉-3-甲酸

[0478] 

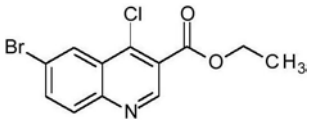
[0479] 将6-溴-4-(异丙基氨基)喹啉-3-甲酸乙酯(38.0g,112.69mmol)悬浮于甲醇(800mL)和水(200mL)中。添加10M氢氧化钠溶液(33.8mL,338.07mmol)并将该混合物在环境温度下搅拌1h。添加THF(200mL)并将所得的混合物搅拌16h。添加水(400mL)并将有机物在减压下去除。将所得的水性溶液用2M HCl酸化至pH 4-5并通过过滤收集沉淀,用水洗涤并在真空下干燥以得到呈白色固体的所希望的物质(34.7g,100%)。NMR谱:^{1}H NMR(500MHz,DMSO-d6)δ1.33(6H,d),4.39(1H,s),7.78(1H,d),7.92(1H,dd),8.38(1H,d),8.88(1H,s)。质谱:m/z(ES+)[M+H]+=309。

[0480] 中间体B4:6-溴-4-(异丙基氨基)喹啉-3-甲酸乙酯

[0481] 

[0482] 在0℃下,将丙-2-胺(11.00mL,128.02mmol)添加至6-溴-4-氯喹啉-3-甲酸乙酯(36.61g,116.38mmol)和碳酸钾(32.2g,232.77mmol)在乙腈(250mL)中的悬浮液里。将该混合物在54℃下在回流下搅拌3h。添加另外的碳酸钾(10.7g,77.6mmol)和丙-2-胺(3.6mL,42.7mmol),并且在48℃下再持续搅拌16h。将溶剂在真空中去除,并且将所得的残余物在DCM(400mL)和水(500mL)之间分配。将水层用DCM(2x 200mL)重新提取;将合并的有机层穿过相分离纸并在减压下浓缩,以得到呈米黄色固体的所希望的物质(38.6g,98%)。NMR谱:^{1}HNMR(500MHz,$CDCl_3$)δ1.40(6H,d),1.43(3H,t),4.32-4.37(1H,m),4.40(2H,q),7.72(1H,dd),7.81(1H,d),8.29(1H,d),8.95(1H,d),9.10(1H,s)。质谱:m/z(ES+)[M+H]+=337。

[0483] 中间体B5:6-溴-4-氯喹啉-3-甲酸乙酯

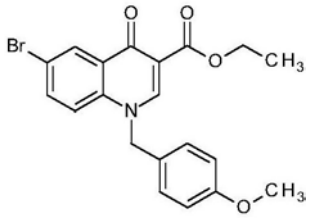
[0484] 

[0485] 在环境温度下,在空气下,将DMF(0.119mL,1.54mmol)添加至在亚硫酰氯(800mL)中的6-溴-1-[(4-甲氧基苯基)甲基]-4-氧代喹啉-3-甲酸乙酯(160g,384.37mmol)中。将所得的混合物在75℃下搅拌16h然后将溶剂在减压下去除。将所得的混合物与甲苯共沸两次然后添加正己烷(500mL)。将沉淀通过过滤收集,用正己烷(200mL)洗涤并在真空下干燥,以得到呈棕色固体的所希望的物质(100g,83%)。NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.47(3H,t),4.51(2H,q),7.95(1H,dd),8.11(1H,d),8.60(1H,d),9.24(1H,s)。质谱:m/z(ES+)[M+H]+=314,316。

[0486] 以更大的规模,将6-溴-1-[(4-甲氧基苯基)甲基]-4-氧代喹啉-3-甲酸乙酯(5765g,13.85mol)填装至具有亚硫酰氯(28.8L)的容器中。观察到从20-26℃的放热。添加DMF(4.4mL)没有观察到放热,并将该批次加热至75℃,并搅拌17h。HPLC显示1.3%起始物质剩余和98.0%产物。将该反应在真空中浓缩并将残余物与甲苯(25L)共沸。然后将所得固体

在庚烷(18.5L)中浆化2.5h,过滤并用庚烷(3x 4L)洗涤。将固体在真空下在35℃下干燥以给出4077g所希望的物质(93%粗产量),通过HPLC,该物质除了约4%水解产物之外,还含有约5%的6-溴-1-[(4-甲氧基苯基)甲基]-4-氧代喹啉-3-甲酸乙酯(90%纯)。将该粗物质(4077g)返回至容器中并用亚硫酰氯(14.5L)和DMF(2.2mL)重新处理。将该混合物加热至75℃持续40h。将亚硫酰氯在真空中去除并且将残余物与甲苯(10L)共沸。在20℃下,将该残余物在庚烷(18L)中浆化约16h。将固体通过过滤收集,在氮下一次性过滤并用庚烷(3L)洗涤以产出2196g所希望的物质(NMR测定纯度为90%,HPLC纯度为99%)。将该批次的剩余物在空气下过滤并用庚烷(3L)洗涤以产出1905g所希望的物质(NMR测定纯度为88%,HPLC纯度为99%)。将这些黄色固体合并用于进一步加工(4101g,3653g有活性,83%产率,HPLC纯度为99%)。

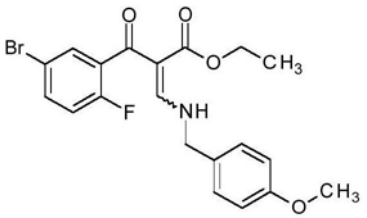
[0487] 中间体B6:6-溴-1-[(4-甲氧基苯基)甲基]-4-氧代喹啉-3-甲酸乙酯

[0488] 

[0489] 在环境温度下,经2分钟的时间段将DBU(102mL,679.62mmol)滴加至在丙酮(1.2L)中的2-(5-溴-2-氟苯甲酰基)-3-[(4-甲氧基苯基)甲基氨基]丙-2-烯酸乙酯(296.5g,679.62mmol)中。将所得的溶液搅拌16h然后将固体通过过滤去除并用MTBE洗涤,以得到呈浅黄色的所希望的物质(180g,64%)。NMR谱:^{1}HNMR(400MHz,DMSO-d6)δ1.30(3H,t),3.71(3H,s),4.25(2H,q),5.60(2H,s),6.90-6.95(2H,m),7.12-7.25(2H,m),7.67(1H,d),7.80-7.90(1H,m),8.30(1H,d),8.92(1H,s)。质谱:m/z(ES+)[M+H]+=418。

[0490] 以更大的规模,在15℃下,将2-(5-溴-2-氟苯甲酰基)-3-[(4-甲氧基苯基)甲基氨基]丙-2-烯酸乙酯(8434g,(7730g假定有活性),17.71mol)填装至具有丙酮(23.2L)的容器中。经25分钟添加DBU(2.8L,18.72mol),在添加中观察到放热从18-23℃。约25分钟后沉淀形成并且该批次持续放热,1h后达到37℃的最高值。将该反应在20℃下搅拌16.5h,在此时HPLC显示起始物质的消耗和96.5%产物。将所得沉淀物通过过滤收集,用TBME(4x 3.4L)洗涤。然后将固体在真空下在40℃下干燥,以给出6033g呈白色固体的所希望的物质(经3个步骤81.6%产率,HPLC纯度为99.8%)。分析数据与针对先前批次获得的是一致的。

[0491] 中间体B7:2-(5-溴-2-氟苯甲酰基)-3-[(4-甲氧基苯基)甲基氨基]丙-2-烯酸乙酯

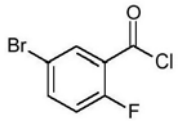
[0492] 

[0493] 在10℃下,经10分钟的时间将(E)-乙基3-(二甲基氨基)丙烯酸酯(98g,685.00mmol)分批添加至在甲苯(800mL)中的5-溴-2-氟苯甲酰氯(163g,685mmol)和DIPEA(120mL,685.00mmol)里。将所得溶液在70℃下搅拌16h然后允许冷却。经一个20分钟的时间

段，在环境温度下，将(4-甲氧基苯基)甲胺(94g，685mmol)添加至该混合物中。将所得的溶液搅拌3h然后将该反应混合物用DCM(4L)稀释，并用水(3x 1L)洗涤。将有机相经Na_2SO_4干燥，过滤并且蒸发以给出呈棕色油状的所希望的物质(300g，100％)，将其不进行进一步纯化立刻使用于随后的反应中。质谱:m/z(ES+)[M+H]+＝436。

[0494] 以更大的规模，将5-溴-2-氟苯甲酰氯(4318g，4205g有活性，17.71mol)填装至容器中，作为在甲苯(7.5L)中的溶液。添加DIPEA(3150mL，18.08mol)，没有观察到放热。经30分钟分批添加乙基-3-(二甲基氨基)丙烯酸酯(2532g，17.71mol)，维持批次温度<40℃。注意到经30分钟添加、从21-24℃放热，经1h中进一步缓慢升高至38℃。将该反应在20-30℃下搅拌16.5h。经30min分批添加4-甲氧基苄胺(2439g，17.78mol)，维持批次温度<40℃。在添加中观察到25-30℃的放热，通过降低夹套温度15℃提供冷却。将该反应在20-30℃下搅拌4h，这之后HPLC显示93.2％的所希望的物质。将批次分离用于后处理，将该混合物的每一半用DCM(28.6L)稀释并用水(3x 7.8L)洗涤。将有机物经MgSO4(约550g)干燥并过滤，用DCM(4L)洗涤。然后将合并的有机物浓缩以给出8444g呈油状的所希望的物质(8434g，106％产率，HPLC纯度为94.7％)。分析数据与针对先前批次获得的是一致的。

[0495] 中间体B8:5-溴-2-氟苯甲酰氯

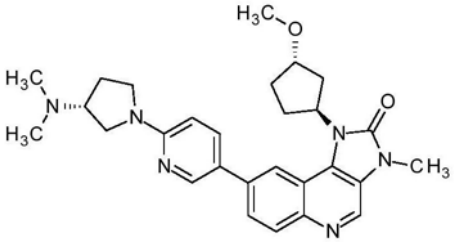
[0496] 

[0497] 在环境温度下，经1h的时间段将亚硫酰氯(75.0mL，1027.36mmol)滴加至在甲苯(1.2L)和DMF(12mL)中的5-溴-2-氟苯甲酸(150g，684.91mmol)中。将所得的混合物在70℃下搅拌16h然后允许将该混合物冷却并在真空中浓缩，以得到呈浅黄色油状的所希望的物质(160g，98％)，将其不进行进一步纯化而使用。NMR谱:^{1}H NMR(400MHz，DMSO-d6)δ7.26-7.31(1H，m)，7.83(1H，dd)，8.02(1H，d)。

[0498] 以更大的规模，在20℃下，将3-溴-6-氟苯甲酸(3888g，17.75mol)填装至容器中随后填装甲苯(29.2L)。添加亚硫酰氯(1950mL，26.88mol)，随后添加DMF(310mL)，没有观察到放热。将该混合物加热至65-75℃(约45℃之上获得溶液)，没有观察到放热和轻微气体逸出。将该反应在此温度下搅拌40h，此时HPLC分析显示87.6％产物，3.4％起始物质。将该反应在真空中浓缩并与甲苯(18L)共沸，以给出4328g所希望的物质(103％产率，HPLC纯度为87.3％)。

[0499] 实例5

[0500] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[(1S，3S)-3-甲氧基环戊基]-3-甲基-咪唑并[4，5-c]喹啉-2-酮

[0501] 

[0502] 将8-(6-氟-3-吡啶基)-1-[(1S，3S)-3-甲氧基环戊基]-3-甲基-咪唑并[4，5-c]喹啉-2-酮(75mg，0.19mmol)和(R)-N，N-二甲基吡咯烷-3-胺(87mg，0.76mmol)在MeCN(1mL)中

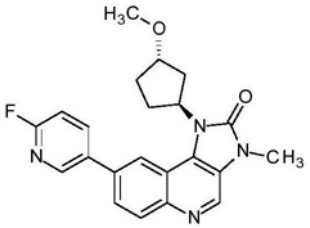
的悬浮液在微波反应器中加热至150℃持续4h，然后允许该混合物冷却至环境温度。将该反应混合物用DCM(40mL)稀释，用水(2x 20mL)洗涤两次，并将有机层经$MgSO_4$干燥，过滤并蒸发以提供粗产物。将该粗产物通过FCC进行纯化，洗脱梯度为在DCM中0至6％2N甲醇氨，以提供呈白色固体的所希望的物质(70.0mg，75％)。NMR谱：^{1}H NMR(500MHz，DMSO-d6)δ1.82(2H，s)，2.06-2.3(10H，m)，2.36-2.45(1H，m)，2.5-2.57(1H，m)，2.72-2.86(1H，m)，3.17(1H，dd)，3.27(3H，s)，3.33-3.44(1H，m)，3.48(3H，s)，3.63(1H，d)，3.73(1H，dd)，4.05-4.16(1H，m)，5.55(1H，q)，6.61(1H，d)，7.88(1H，dd)，7.93(1H，dd)，8.07(1H，d)，8.27(1H，d)，8.57(1H，d)，8.82(1H，s)。质谱：m/z(ES+)[M+H]+＝487。

[0503] 使用以下程序还可以将该物质分离为甲磺酸盐：

[0504] 将分离的物质(64mg，0.13mmol)悬浮于DCM(2mL)中，并用在DCM(2mL)中的甲磺酸(17mg，0.18mmol)进行处理。将该溶液蒸发至干燥以提供呈甲磺酸盐的所希望的物质(80mg，104％)。

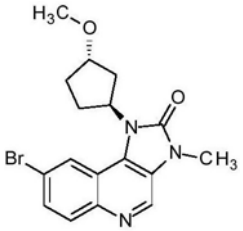
[0505] NMR谱：^{1}H NMR(500MHz，DMSO-d6)δ1.7-1.95(1H，m)，2.1-2.27(4H，m)，2.30(3H，s)，2.37-2.47(2H，m)，2.52-2.57(1H，m)，2.88(6H，s)，3.27(3H，s)，3.42-3.49(1H，m)，3.50(3H，s)，3.63(1H，dd)，3.69-3.8(1H，m)，3.94(1H，dd)，3.98-4.07(1H，m)，4.06-4.17(1H，m)，5.44-5.68(1H，m)，6.73(1H，d)，7.94(1H，d)，8.03(1H，dd)，8.11(1H，d)，8.32(1H，s)，8.62(1H，d)，8.88(1H，s)，9.83(1H，s)。质谱：m/z(ES+)[M+H]+＝487。

[0506] 中间体C0：8-(6-氟-3-吡啶基)-1-[(1S，3S)-3-甲氧基环戊基]-3-甲基-咪唑并[4，5-c]喹啉-2-酮

[0507] 

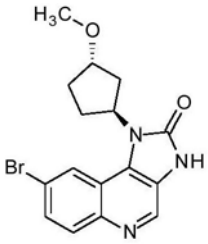
[0508] 将8-溴-1-((1S，3S)-3-甲氧基环戊基)-3-甲基-1H-咪唑并[4，5-c]喹啉-2(3H)-酮(250mg，0.66mmol)、(6-氟吡啶-3-基)硼酸(122mg，0.86mmol)和2M碳酸钾(1mL，2.00mmol)悬浮于1，4-二噁烷(4mL)中，进行脱气，然后添加[Pd-118](22mg，0.03mmol)。在氮气下将该反应加热至80℃持续1h，并且冷却至室温。将该反应混合物用EtOAc(50mL)稀释，然后用水(2x 25mL)洗涤，并然后将有机相经MgSO4干燥，过滤并在真空中进行浓缩。将该粗产物通过FCC进行纯化，洗脱梯度为在DCM中0至3％2N甲醇氨。将纯的级分蒸发至干燥以提供呈灰白色固体的8-(6-氟吡啶-3-基)-1-((1S，3S)-3-甲氧基环戊基)-3-甲基-1H-咪唑并[4，5-c]喹啉-2(3H)-酮(185mg，70.9％)。

[0509] 中间体C1：8-溴-1-[(1S，3S)-3-甲氧基环戊基]-3-甲基-咪唑并[4，5-c]喹啉-2-酮

[0510] 

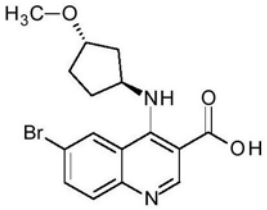
[0511] 在氮气且在0℃下，将NaH(在矿物油中60％)(0.444g，11.11mmol)添加至8-溴-1-[(1S,3S)-3-甲氧基环戊基]-3H-咪唑并[4,5-c]喹啉-2-酮(1.15g，3.17mmol)在DMF(15mL)中的混合物里，然后将该混合物搅拌30分钟。添加碘甲烷(0.596mL，9.52mmol)，并且将该反应混合物在环境温度下搅拌16h。将水缓慢添加至反应中，并且将固体在真空下过滤，并且在真空烘箱中干燥3h，以提供呈白色固体的所希望的物质(674mg-被残余DMF轻微污染)。NMR谱：^{1}HNMR(500MHz，DMSO-d6)δ1.22(1H,s)，1.74-1.92(1H,m)，2.11-2.24(3H,m)，2.25-2.33(1H,m)，3.27(3H,s)，3.49(3H,s)，4.07-4.15(1H,m)，5.27-5.53(1H,m)，7.74(1H,dd)，7.98(1H,dd)，8.36(1H,s)，8.91(1H,s)。质谱：m/z(ES+)[M+H]+＝376。

[0512] 中间体C2：8-溴-1-[(1S,3S)-3-甲氧基环戊基]-3H-咪唑并[4,5-c]喹啉-2-酮

[0513] 

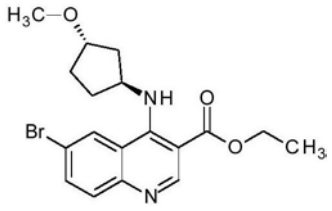
[0514] 在氮气下，将二苯基膦酰基叠氮化物(1.075mL，4.99mmol)添加至6-溴-4-[[(1S,3S)-3-甲氧基环戊基]氨基]喹啉-3-甲酸(1.46g，4.16mmol)和三乙胺(1.738mL，12.47mmol)在DMF(9mL)中的混合物里，并且将该反应在60℃下加热4h。将该反应冷却至环境温度，将固体在真空下过滤并用水洗涤。将该固体在真空烘箱中干燥过夜以提供所希望的物质。通过重复过滤步骤将另外的物质分离，并且与先前的产物(1.15g，79％)合并。NMR谱：^{1}HNMR(500MHz，DMSO-d6)δ1.56-1.82(1H,m)，1.98(1H,t)，2.08-2.31(3H,m)，2.46(1H,s)，4.43(1H,s)，4.78(1H,d)，5.26-5.64(1H,m)，7.73(1H,dd)，7.96(1H,dd)，8.35(1H,s)，8.67(1H,s)，11.62(1H,s)。质谱：m/z(ES+)[M+H]+＝348。

[0515] 中间体C3：6-溴-4-[[(1S,3S)-3-甲氧基环戊基]氨基]喹啉-3-甲酸

[0516] 

[0517] 将NaOH(2M)(13.98mL，27.95mmol)添加至6-溴-4-[[(1S,3S)-3-甲氧基环戊基]氨基]喹啉-3-甲酸乙酯(2.65g，6.99mmol)在THF(15mL)中的混合物里，并且将该反应在60℃下加热5h。将该反应冷却至环境温度，并在减压下去除有机溶剂。使用盐酸(2M)将水性残余物调节至pH 7，并将固体在真空下过滤，并在真空烘箱中干燥24h以提供呈灰色固体的所希望的物质(1.46g)。质谱：m/z(ES+)[M+H]+＝351。

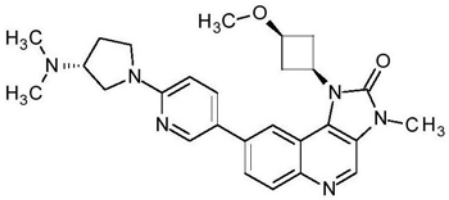
[0518] 中间体C4：6-溴-4-[[(1S,3S)-3-甲氧基环戊基]氨基]喹啉-3-甲酸乙酯

[0519] 

[0520] 将三乙胺(3.90mL,27.98mmol)添加至在乙腈(15.6mL)中的(1S,3S)-3-氨基环戊醇盐酸盐(1g,7.27mmol)里,并搅拌5分钟。添加6-溴-4-氯喹啉-3-甲酸乙酯(2.2g,6.99mmol)并将该反应混合物在100℃下加热2h。通过过滤将该固体分离,溶解于DCM中并用水洗涤。将滤液浓缩至干燥,并将残余物溶解于DCM(25mL)中,并用水(25mL)洗涤。将有机物合并,并经相分离柱干燥,并且将溶剂在减压下去除以提供呈橙色固体的所希望的物质(2.65g),并且无需进一步纯化而直接使用。质谱:m/z(ES+)[M+H]+=379。

[0521] 实例6

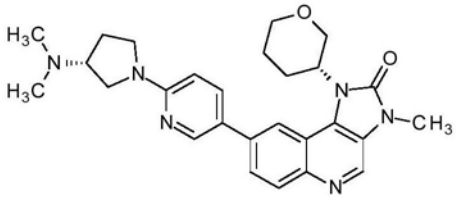
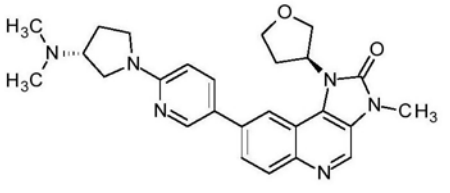
[0522] 8-[6-[(3R)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮

[0523] 

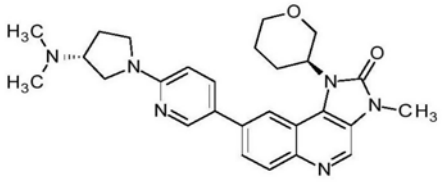
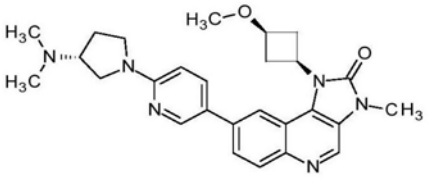
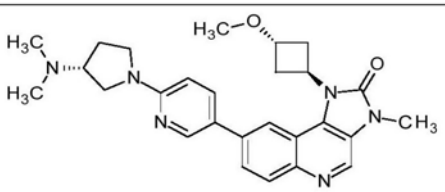
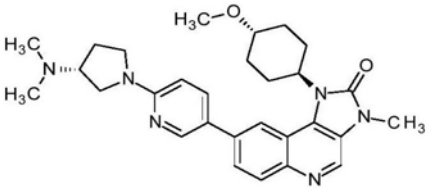
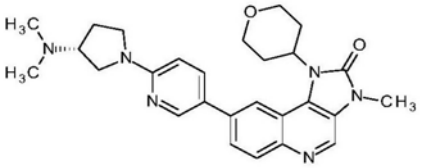
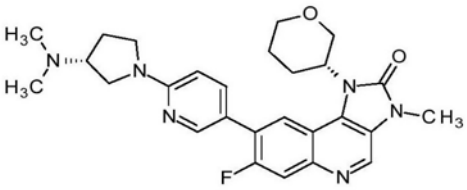
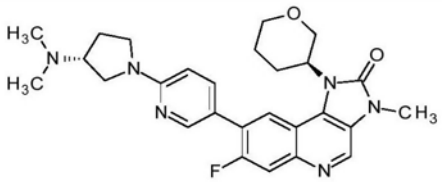
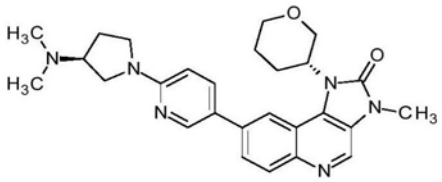
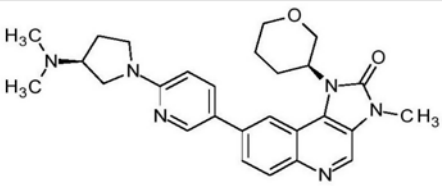
[0524] 在150℃下,将DIPEA(0.159mL,0.91mmol)、8-(6-氟-3-吡啶基)-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮(120mg,0.30mmol)和(R)-N,N-二甲基吡咯烷-3-胺盐酸盐(68.4mg,0.45mmol)在DMSO(2mL)中的混合物搅拌12h,然后允许冷却至环境温度。将该反应混合物用EtOAc(50mL)稀释,用水(25mL)、盐水(25mL)洗涤,并且将有机层经Na_2SO_4干燥,过滤并蒸发以提供粗产物。将该粗产物通过制备型HPLC(Waters XBridge Prep C18OBD柱,5μ二氧化硅,19mm直径,100mm长度)进行纯化,使用水(含有0.1%氨)和MeCN的极性递减混合物作为洗脱液,以提供呈黄色固体的所希望的物质(77mg,51.8%)。NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ1.87-1.93(1H,m),2.19-2.26(7H,m),2.74-3.02(5H,m),3.18-3.24(4H,m),3.33-3.43(1H,m),3.47(3H,s),3.63-3.86(3H,m),4.99-5.05(1H,t),6.60-6.93(1H,d),7.82-7.84(2H,d),8.23-8.26(1H,d),8.43(1H,s),8.85-8.86(1H,d)。质谱:m/z(ES+)[M+H]+=491。

[0525] 以类似的方式从适当的胺和氟吡啶基中间体制备以下化合物,将其通过适当的色谱技术进行纯化,并且将其分离为游离碱、甲酸盐或甲磺酸盐。

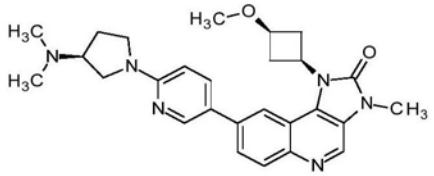
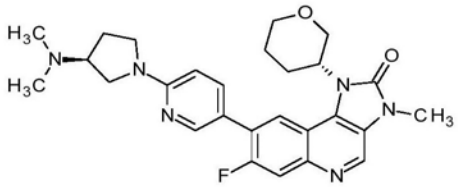
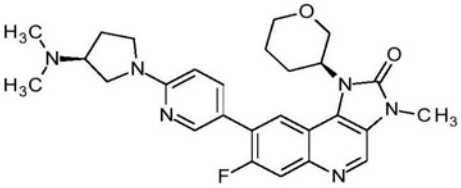
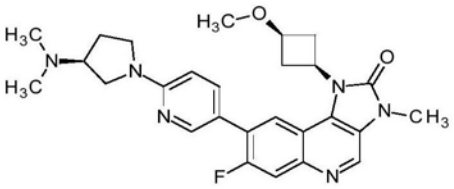
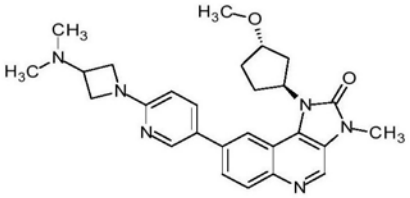
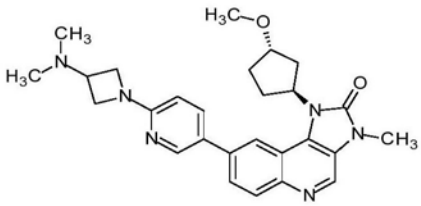
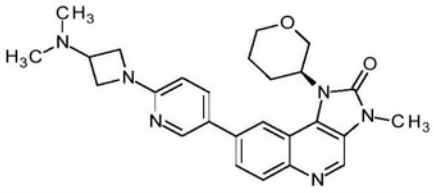
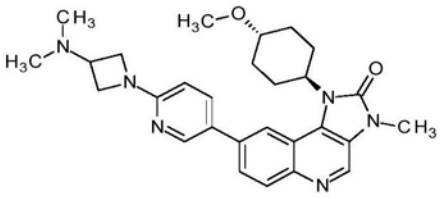
[0526]

实例	结构	名称
7*		8-[6-[(3*R*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3*R*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
8**		8-[6-[(3*R*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3*S*)-四氢呋喃-3-基]咪唑并[4,5-c]喹啉-2-酮

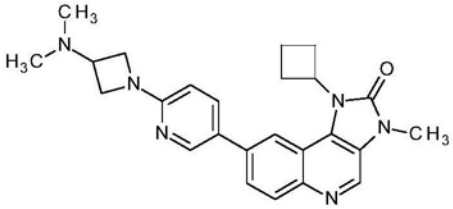
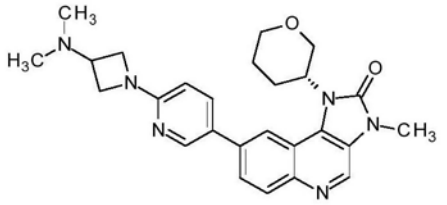
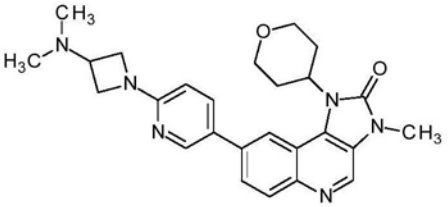
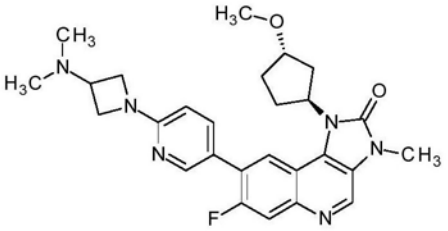
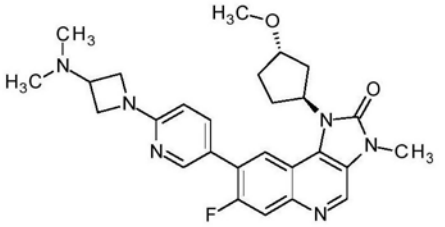
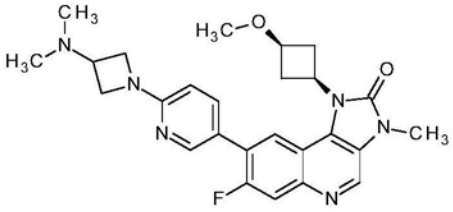
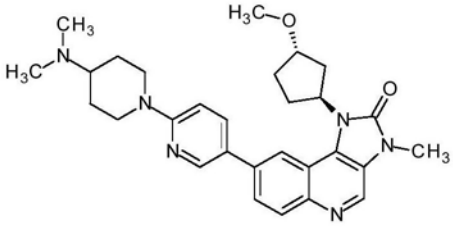
[0527]

实例	结构	名称
9*		8-[6-[(3*R*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3*S*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
10*		8-[6-[(3*R*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(*顺式*-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
11***		8-[6-[(3*R*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(*反式*-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
12****		8-[6-[(3*R*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(*反式*-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
13*		8-[6-[(3*R*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮
14*		8-[6-[(3*R*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3*R*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
15*		8-[6-[(3*R*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3*S*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
16*		8-[6-[(3*S*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3*R*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
17*		8-[6-[(3*S*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-3-甲基-1-[(3*S*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮

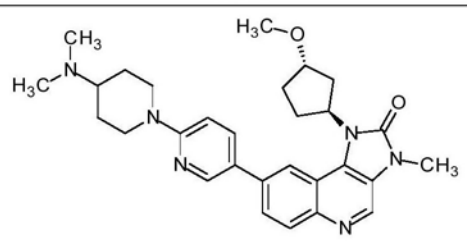
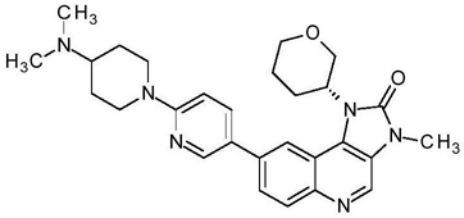
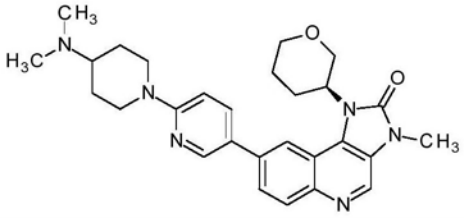
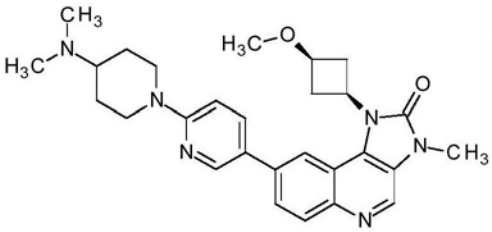
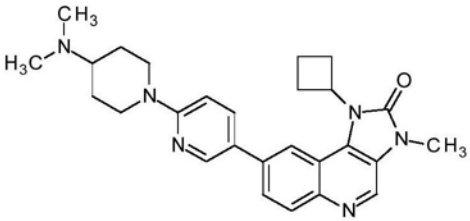
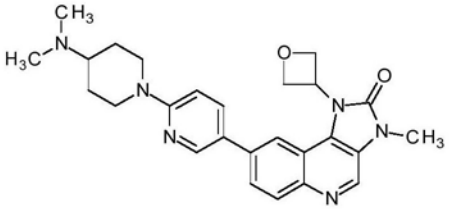
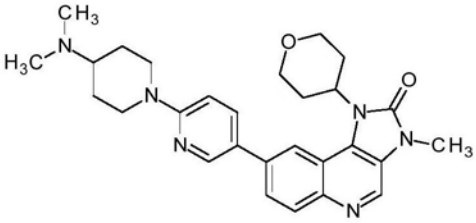
[0528]

实例	结构	名称
18*		8-[6-[(3*S*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(*顺式*-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
19*		8-[6-[(3*S*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3*R*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
20*		8-[6-[(3*S*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-3-甲基-1-[(3*S*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
21*		8-[6-[(3*S*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-7-氟-1-(*顺式*-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
22*****		8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[*反式*-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 1
23*****		8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[*反式*-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 2
24*****		8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-1-[(3*S*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
25****		8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-(*反式*-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮

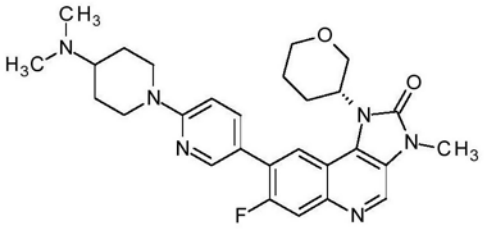
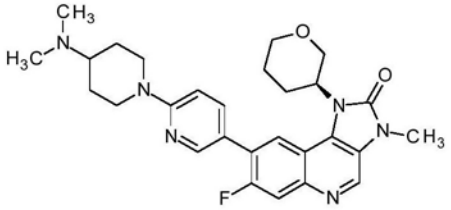
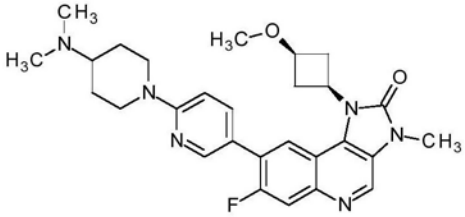
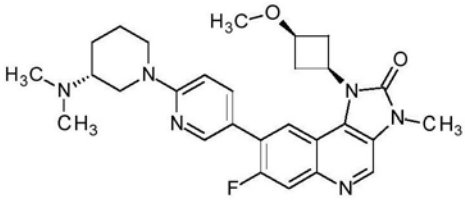
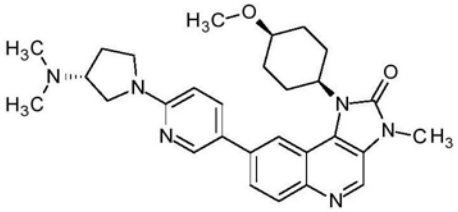
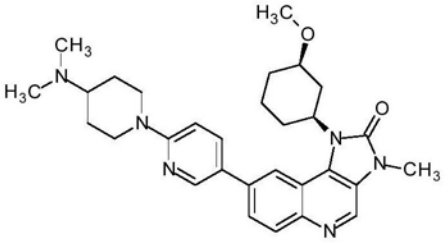
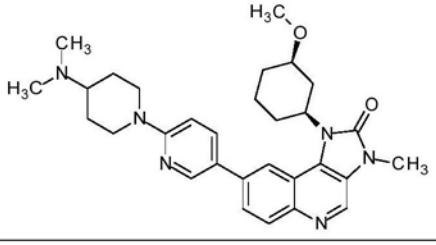
[0529]

实例	结构	名称
26***		1-环丁基-8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮
27****		8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-1-[(3*R*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
28*****		8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-3-甲基-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮
29****		8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-7-氟-1-[反式-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 2
30****		8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-7-氟-1-[反式-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 1
31*		8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
32*		8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[反式-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 2

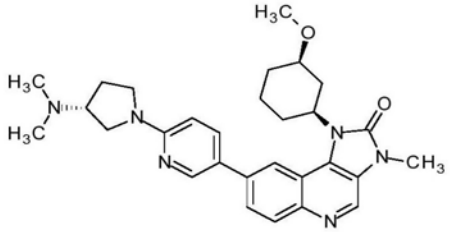
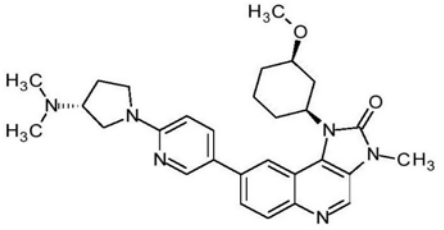
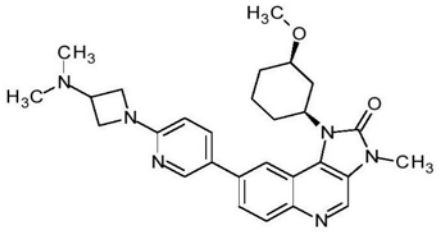
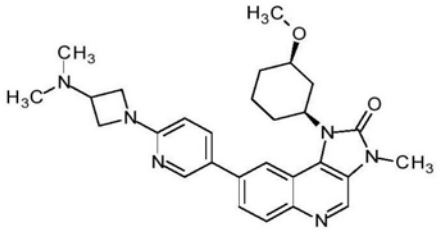
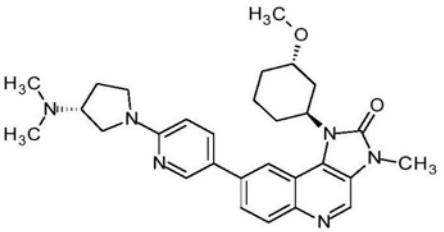
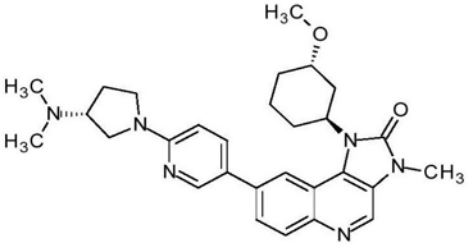
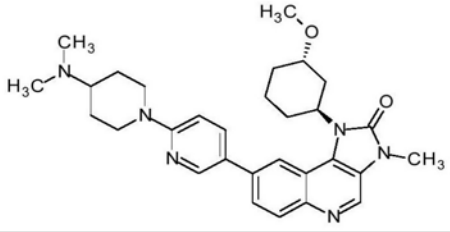
[0530]

实例	结构	名称
33*		8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[反式-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体1
34*		8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-[(3*R*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
35*		8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-[(3*S*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
36*		8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-(*顺式*-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
37**		1-环丁基-8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮
38*		8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-(氧杂环丁烷-3-基)咪唑并[4,5-c]喹啉-2-酮
39*		8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-3-甲基-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮

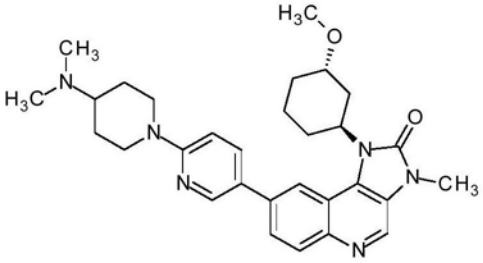
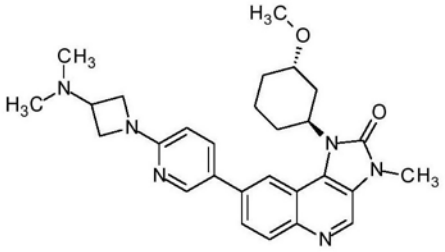
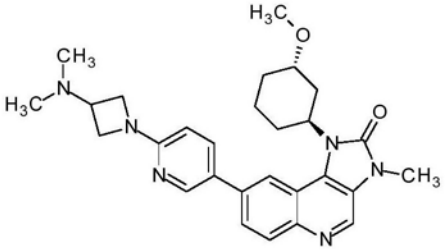
[0531]

实例	结构	名称
40*		8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-3-甲基-1-[(3*R*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
41*		8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-3-甲基-1-[(3*S*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
42*		8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-1-(*顺式*-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
43*		8-[6-[(3*R*)-3-(二甲基氨基)-1-哌啶基]-3-吡啶基]-7-氟-1-(*顺式*-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
44*****		8-[6-[(3*R*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-(*顺式*-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
45*****		8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(*顺式*-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体1
46*****		8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[*顺式*-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体2

[0532]

实例	结构	名称
47*****		8-[6-[(3*R*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[*顺式*-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 1
48*****		8-[6-[(3*R*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[*顺式*-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 2
49*****		8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[*顺式*-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 1
50*****		8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[*顺式*-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 2
51****		8-[6-[(3*R*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[*反式*-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 1
52****		8-[6-[(3*R*)-3-(二甲基氨基)吡咯烷-1-基]-3-吡啶基]-1-[*反式*-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 2
53****		8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[*反式*-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 1

[0533]

实例	结构	名称
54****		8-[6-[4-(二甲基氨基)-1-哌啶基]-3-吡啶基]-1-[反式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体2
55****		8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[反式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 2
56****		8-[6-[3-(二甲基氨基)氮杂环丁烷-1-基]-3-吡啶基]-1-[反式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 1

[0534] *将该反应在DMSO中与存在的过量的(2-5当量)的DIPEA进行反应,并在130℃-150℃之间的温度下加热2h-16h。

[0535] **将该反应在NMP中进行,并在130℃下加热0.5h-3h。

[0536] ***将该反应在MeCN中进行,并在150℃下加热4h。

[0537] ****将该反应在DMF中与存在的过量的K_2CO_3进行反应,并在80℃-100℃之间的温度下加热16h。

[0538] *****将该反应在MeCN中与存在的过量(1-5当量)的Et_3N进行反应,并在80℃下加热3h-16h。

[0539] 将实例22&23通过制备型手性HPLC,用在己烷中的30%异丙醇(用0.1%二乙胺改性)作为洗脱液进行等度洗脱从外消旋混合物中进行分离,以提供作为第一洗脱产物的实例22和作为第二洗脱产物的实例23。

[0540] 将实例29&30通过制备型手性HPLC,用在己烷中的42%乙醇(用0.1%二乙胺改性)作为洗脱液进行等度洗脱从外消旋混合物中进行分离,以提供作为第一洗脱产物的实例30和作为第二洗脱产物的实例29。

[0541] 将实例32&33通过制备型手性HPLC,用在乙腈中的5%甲醇(用0.1%三乙胺改性)作为洗脱液进行等度洗脱从外消旋混合物中进行分离,以提供作为第一洗脱产物的实例33和作为第二洗脱产物的实例32)。

[0542] 实例46、48和50衍生自中间体S0

[0543] 实例45、47和49衍生自中间体T0

[0544] 将实例51&52通过制备型手性-HPLC,用在MeOH(用二乙胺改性)中的95%甲基叔丁醚作为洗脱液进行等度洗脱从外消旋混合物中进行分离,以提供作为第一洗脱产物的实例

51和作为第二洗脱产物的实例52。

[0545] 将实例53&54通过制备型手性-HPLC，用在EtOH(用二乙胺改性)中的85％己烷作为洗脱液进行等度洗脱从外消旋混合物中进行分离，以提供作为第一洗脱产物的实例54和作为第二洗脱产物的实例53。

[0546] 将实例55&56通过制备型手性-HPLC，用在MeOH(用二乙胺改性)中的90％甲基叔丁醚作为洗脱液进行等度洗脱从外消旋混合物中进行分离，以提供作为第一洗脱产物的实例56和作为第二洗脱产物的实例55。

[0547] 实例7：(甲酸盐)NMR谱：^{1}H NMR(300MHz,DMSO-d6)δ1.81-1.87(3H,m),2.17-2.24(8H,m),2.63-2.71(1H,m),2.82-2.88(1H,m),3.16-3.22(1H,m),3.37-3.42(2H,m),3.48(3H,s),3.63-3.67(1H,m),3.73-3.79(1H,m),3.95(1H,d),4.12-4.26(2H,m),4.92-4.99(1H,m),6.65(1H,d),7.89-7.97(2H,m),8.09(1H,d),8.16(1H,s),8.27(1H,d),8.57(1H,d),8.83(1H,s)。质谱：m/z(ES+)[M+H]+＝473。

[0548] 实例8：NMR谱：^{1}H NMR(500MHz,DMSO-d6)δ2.15-2.3(1H,m),2.32(3H,s),2.35-2.45(1H,m),2.44-2.49(1H,m),2.51-2.57(1H,m),2.89(6H,s),3.43-3.52(1H,m),3.54(3H,s),3.64(1H,dd),3.67-3.82(1H,m),3.85-3.99(2H,m),3.98-4.09(1H,m),4.1-4.22(2H,m),4.27(1H,td),5.78-5.89(1H,m),6.72(1H,d),7.95(1H,dd),8.04-8.22(2H,m),8.54(1H,d),8.68(1H,d),8.89(1H,s),9.86(1H,s)。质谱：m/z(ES+)[M+H]+＝459。

[0549] 实例9：NMR谱：^{1}HNMR(300MHz,DMSO-d6)δ1.79-1.86(3H,m),2.14-2.22(8H,m),2.65-2.81(2H,m),3.15-3.21(1H,m),3.37-3.44(2H,m),3.48(3H,s),3.65-3.76(2H,m),3.94(1H,d),4.15-4.21(2H,m),4.91-4.99(1H,m),6.65(1H,d),7.89-7.97(2H,m),8.09(1H,d),8.27(1H,s),8.57(1H,d),8.83(1H,s)。质谱：m/z(ES+)[M+H]+＝473。

[0550] 实例10：(甲酸盐)NMR谱：^{1}HNMR(400MHz,D_2O)δ2.33-2.60(5H,m),2.64-2.77(1H,m),2.94-3.09(6H,m),3.10-3.19(6H,m),3.36-3.42(1H,m),3.54-3.66(3H,m),3.83-4.05(3H,m),6.33-6.35(1H,m),6.81-6.82(2H,m),7.07-7.17(2H,m),7.52(1H,s),8.12(1H,s),8.35(1H,s)。质谱：m/z(ES+)[M+H]+＝473。

[0551] 实例11：(游离碱)NMR谱：^{1}H NMR(500MHz,DMSO-d6)δ1.82(1H,dd),2.09-2.3(7H,m),2.56(2H,ddd),2.71-2.88(1H,m),3.11-3.27(6H,m),3.33-3.45(1H,m),3.48(3H,s),3.63(1H,d),3.74(1H,dd),4.11-4.33(1H,m),5.54(1H,s),6.61(1H,d),7.87(1H,dd),7.95(1H,dd),8.04(1H,d),8.18(1H,d),8.49-8.64(1H,m),8.81(1H,s)。(甲磺酸盐)NMR谱：^{1}H NMR(500MHz,DMSO-d6)δ2.16-2.29(1H,m),2.31(3H,s),2.42-2.47(1H,m),2.56(2H,ddd),2.88(6H,s),3.18-3.26(5H,m),3.41-3.54(4H,m),3.63(1H,dd),3.7-3.82(1H,m),3.94(1H,dd),4.01(1H,q),4.22(1H,tt),5.48-5.64(1H,m),6.73(1H,d),7.91(1H,dd),8-8.15(2H,m),8.22(1H,d),8.64(1H,d),8.85(1H,s),9.85(1H,s)。质谱：m/z(ES+)[M+H]+＝473。

[0552] 实例12：(游离碱)NMR谱：^{1}H NMR(400MHz,$CDCl_3$)δ1.43-1.52(2H,m),2.13(3H,d),2.36(3H,d),2.47(6H,s),2.72-2.80(2H,m),3.03-3.08(1H,m),3.38-3.43(1H,m),3.45(3H,s),3.46-3.57(2H,m),3.59(3H,s),3.78(1H,t),3.94(1H,t),4.85-4.90(1H,m),6.55(1H,d),7.77-7.86(2H,m),8.17-8.26(2H,m),8.55(1H,d),8.68(1H,s)。(甲磺酸盐)NMR谱：^{1}H NMR(300MHz,MeOH-d4)δ1.36-1.58(2H,m),2.15(2H,d),2.25-2.39(3H,m),2.60-2.77(6H,m),2.99(6H,s),3.35-3.48(4H,m),3.55-3.68(4H,m),3.68-3.79(1H,m),3.79-3.91

(1H,m),3.97-4.14(2H,m),4.93-5.04(1H,m),6.80(1H,d),7.94(1H,dd),8.06(1H,dd),8.16(1H,d),8.37(1H,s),8.56(1H,d),8.79(1H,s)。质谱:m/z(ES+)[M+H]+=501。

[0553] 实例13:NMR谱:^{1}H NMR(300MHz,$CDCl_3$)δ1.93-2.01(2H,m),2.45-3.11(10H,m),3.51-3.71(7H,m),3.72-3.83(1H,m),3.93-4.15(2H,m),4.21-4.29(2H,m),5.01-5.18(1H,m),6.50-6.59(1H,m),7.77-7.89(2H,m),8.10-8.21(1H,m),8.35(1H,s),8.55-8.59(1H,m),8.70(1H,s)。质谱:m/z(ES+)[M+H]+=473。

[0554] 实例14:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.7-1.9(3H,m),2.13-2.37(8H,m),2.62-2.72(2H,m),3.1-3.3(1H,m),3.35-3.55(5H,m),3.68(1H,s),3.91(1H,s),4.07-4.26(3H,m),4.90(1H,s),6.67(1H,d),7.73-8.04(2H,m),8.20(1H,d),8.44(1H,s),8.88(1H,s)。质谱:m/z(ES+)[M+H]+=491。

[0555] 实例15:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.73-1.87(3H,m),2.11-2.23(8H,m),2.64-2.69(1H,m),2.79-2.83(1H,m),3.15-3.21(1H,m),3.37-3.44(2H,m),3.47(3H,s),3.63-3.79(2H,m),3.91(1H,d),4.09-4.22(2H,m),4.85-4.93(1H,m),6.65(1H,d),7.83-7.90(2H,m),8.19(1H,d),8.43(1H,s),8.89(1H,s)。质谱:m/z(ES+)[M+H]+=491。

[0556] 实例16:(甲酸盐)NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ1.79-1.88(3H,m),2.13-2.26(8H,m),2.62-2.76(1H,m),2.82-2.87(1H,m),3.17-3.23(1H,m),3.37-3.45(2H,m),3.48(3H,s),3.62-3.79(2H,m),3.95(1H,d),4.15-4.25(2H,m),4.91-4.99(1H,m),6.64(1H,d),7.88-7.97(2H,m),8.09(1H,d),8.17(1H,s),8.26(1H,s),8.56(1H,d),8.83(1H,d)。质谱:m/z(ES+)[M+H]+=473。

[0557] 实例17:NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ1.73-1.93(3H,m),2.10-2.30(2H,m),2.30(6H,s),2.60-2.80(1H,m),2.80-3.00(1H,m),3.20-3.50(3H,m),3.50(3H,s),3.60-3.80(2H,m),3.90-4.00(1H,m),4.10-4.40(2H,m),4.95(1H,m),6.64(1H,d),7.85-8.00(2H,m),8.10(1H,d),8.25(1H,d),8.57(1H,d),8.83(1H,s)。质谱:m/z(ES+)[M+H]+=473。

[0558] 实例18:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.80-1.95(1H,m),2.22-2.50(7H,m),2.81-2.86(2H,m),2.96-3.02(3H,m),3.21(3H,s),3.32(1H,s),3.39-3.43(1H,m),3.49(3H,s),3.67-3.79(1H,m),3.82-3.89(2H,m),5.08-5.11(1H,m),6.63-6.65(1H,m),7.88-7.91(1H,m),8.02-8.09(2H,m),8.35-8.35(1H,m),8.64-8.65(1H,m),8.84(1H,s)。质谱:m/z(ES+)[M+H]+=473。

[0559] 实例19:NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ1.69-1.90(3H,m),2.09-2.23(8H,m),2.58-2.85(2H,m),3.10-3.21(1H,t),3.35-3.45(2H,m),3.48(3H,s),3.60-3.80(2H,m),3.88-3.95(1H,d),4.07-4.21(2H,m),4.80-4.95(1H,m),6.60-6.67(1H,d),7.8-7.91(2H,m),8.12-8.22(1H,d),8.42(1H,s),8.87(1H,s)。质谱:m/z(ES+)[M+H]+=491。

[0560] 实例20:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.70-1.95(3H,m),2.05-2.25(2H,m),2.30(6H,s),2.55-2.75(1H,m),2.75-2.92(1H,m),3.15-3.25(1H,m),3.30-3.42(2H,m),3.50(3H,s),3.70-3.80(1H,m),3.80-3.90(1H,m),3.85-3.95(1H,m),4.05-4.25(2H,m),4.82-4.98(1H,m),6.64(1H,d),7.80-7.92(2H,m),8.18(1H,d),8.43(1H,s),8.88(1H,s)。质谱:m/z(ES+)[M+H]+=491。

[0561] 实例21:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.87-1.93(1H,m),2.19-2.28(7H,m),2.77-2.82(2H,t),2.90-3.02(3H,m),3.18-3.25(4H,m),3.32-3.48(1H,m),3.63-3.69(3H,

m),3.74-3.86(3H,m),5.03(1H,s),6.61-6.64(1H,d),7.83-7.85(2H,t),8.25(1H,s),8.43(1H,s),8.86-8.87(1H,d)。质谱:m/z(ES+)[M+H]+=491。

[0562] 实例22:(甲磺酸盐)NMR谱:^{1}H NMR(300MHz,MeOH-d4)δ1.90-2.04(1H,m),2.19-2.41(3H,m),2.69(1H,m),2.69-3.65(4H,m),2.94(6H,s),3.38(3H,s),3.59(3H,s),4.11-4.30(4H,m),4.37-4.51(2H,m),5.65(1H,bs),6.71(1H,d),7.93(1H,d),8.01-8.18(2H,m),8.39(1H,s),8.52(1H,s),8.81(1H,s)。质谱:m/z(ES+)[M+H]+=473。

[0563] 实例23:(甲磺酸盐)NMR谱:^{1}H NMR(300MHz,MeOH-d4)δ1.87-2.03(1H,m),2.30(3H,m),2.45-2.62(1H,m),2.64-2.82(4H,m),2.94(6H,s),3.38(3H,s),3.59(3H,s),4.11-4.31(4H,m),4.37-4.50(2H,m),5.50-5.78(1H,bs),6.71(1H,d),7.93(1H,d),8.01-8.21(2H,m),8.39(1H,s),8.52(1H,s),8.80(1H,s)。质谱:m/z(ES+)[M+H]+=473。

[0564] 实例24:(游离碱)NMR谱:^{1}H NMR(300MHz,MeOH-d4)δ1.84-2.01(2H,m),2.16-2.28(4H,m),2.28-2.43(3H,s),2.71-2.89(1H,m),3.36-3.48(1H,m),3.48-3.68(4H,s),3.89-4.07(3H,m),4.13-4.27(3H,m),4.30-4.48(1H,t),4.98-5.16(1H,m),6.61(1H,d),7.94(2H,d),8.12(1H,d),8.34(1H,d),8.46(1H,s),8.74(1H,s)。(甲磺酸盐)NMR谱:^{1}HNMR(500MHz,DMSO-d6)δ1.7-1.89(2H,m),2.08-2.2(1H,m),2.28(3H,s),2.61-2.75(1H,m),2.80(6H,s),3.40(1H,td),3.48(3H,s),3.93(1H,d),4.08-4.26(5H,m),4.24-4.33(2H,m),4.9-5.02(1H,m),6.68(1H,d),7.92(1H,dd),8.06(1H,dd),8.12(1H,d),8.29(1H,d),8.61(1H,dd),8.87(1H,s),10.22(1H,s)。质谱:m/z(ES+)[M+H]+=459。

[0565] 实例25:(游离碱)NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.38-1.53(2H,m),2.12(2H,d),2.34(6H,s),2.37(2H,s),2.68-2.83(2H,m),3.35-3.43(2H,m),3.45(3H,s),3.59(3H,s),4.03(2H,t),4.21(2H,t),4.86(1H,s),6.48(1H,d),7.76-7.85(2H,m),8.18-8.25(2H,m),8.53(1H,d),8.69(1H,s)。(甲磺酸盐)NMR谱:^{1}H NMR(300MHz,MeOH-d4)δ1.36-1.55(2H,m),2.14(2H,d),2.34(2H,d),2.60-2.79(5H,m),2.90(6H,s),3.32-3.46(4H,m),3.58(3H,s),4.12-4.28(3H,m),4.36-4.49(2H,m),4.93-5.03(1H,m),6.74(1H,d),7.94(1H,dd),8.08(1H,dd),8.16(1H,d),8.36(1H,s),8.54(1H,d),8.81(1H,s)。质谱:m/z(ES+)[M+H]+=487。

[0566] 实例26:(游离碱)NMR谱:^{1}H NMR(500MHz,DMSO-d6)δ1.79-2.00(2H,m),2.13(6H,s),2.40-2.48(2H,m),3.07(2H,pd),3.22(1H,ddd),3.48(3H,s),3.78(2H,dd),3.95-4.18(2H,m),5.47(1H,q),6.54(1H,dd),7.87(1H,dd),8.00(1H,dd),8.06(1H,d),8.33(1H,d),8.58(1H,dd),8.82(1H,s)。(甲磺酸盐)NMR谱:^{1}H NMR(500MHz,DMSO-d6)δ1.79-2.07(2H,m),2.29(3H,s),2.40-2.47(2H,m),2.78(6H,s),3.07(2H,pd),3.49(3H,s),4.14(3H,d),4.2-4.38(2H,m),5.49(1H,s),6.52-6.85(1H,m),7.90(1H,dd),8.03-8.19(2H,m),8.35(1H,d),8.65(1H,dd),8.85(1H,s)。质谱:m/z(ES+)[M+H]+=429。

[0567] 实例27:(甲酸盐)NMR谱:^{1}HNMR(300MHz,D_2O)δ1.31-1.60(2H,m),1.60-1.75(1H,m),1.75-2.11(1H,m),2.68(6H,s),3.15(3H,s),3.20-3.41(1H,m),3.45-3.68(1H,m),3.85-3.92(2H,m),3.92-4.01(4H,m),4.02-4.14(2H,m),6.12(1H,d),6.78-7.05(3H,m),7.16(1H,d),7.40(1H,s),8.11(1H,s)8.33(1H,s)。质谱:m/z(ES+)[M+H]+=459。

[0568] 实例28:NMR谱:^{1}HNMR(300MHz,MeOH-d4)δ1.90-2.10(2H,m),2.28(6H,s),2.81-3.02(2H,m),3.32-3.43(1H,m),3.57-3.76(5H,m),3.85-4.06(2H,m),4.14-4.27(4H,m),5.12-5.30(1H,m),6.64(1H,d),7.94(1H,d),8.05(1H,d),8.15(1H,d),8.46-8.55(2H,m),

8.80(1H,s)。质谱:m/z(ES+)[M+H]+=459。

[0569] 实例29:NMR谱:^{1}H NMR(300MHz,MeOH-d4)δ1.90-2.02(1H,m),2.25-2.40(9H,m),2.49-2.60(1H,m),2.57-2.73(1H,m),3.33-3.35(4H,m),3.59(3H,s),3.94(2H,dd),4.15-4.24(3H,m),5.60(1H,t),6.62(1H,d),7.80(1H,d),7.90(1H,d),8.30-8.36(2H,m),8.81(1H,s)。质谱:m/z(ES+)[M+H]+=491。

[0570] 实例30:NMR谱:^{1}H NMR(300MHz,MeOH-d4)δ1.92-1.98(1H,m),2.24-2.33(3H,m),2.40(6H,s),2.48-2.60(1H,m),2.62-2.67(1H,m),3.35(3H,s),3.49-3.53(1H,m),3.59(3H,s),3.99(2H,dd),4.15-4.17(1H,m),4.24(1H,t),5.55-5.63(1H,m),6.62(1H,dd),7.83(1H,d),7.92(1H,dt),8.33(1H,d),8.37(1H,t),8.81(1H,s)。质谱:m/z(ES+)[M+H]+=491。

[0571] 实例31:NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ2.33(6H,s),2.85-3.00(2H,m),3.04-3.22(2H,m),3.29(3H,s),3.33-3.50(1H,m),3.57(3H,s),3.75-4.00(1H,m),4.00-4.15(2H,m),4.15-4.30(2H,m),4.71-5.00(1H,m),6.35-6.50(1H,d),7.60-7.91(2H,m),8.12-8.30(1H,m),8.43(1H,s),8.68(1H,s)。质谱:m/z(ES+)[M+H]+=477。

[0572] 实例32:NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.59(2H,td),1.88-2.09(4H,m),2.17-2.31(2H,m),2.34(6H,s),2.48-2.63(1H,m),2.73(1H,ddd),2.93(3H,td),3.37(3H,s),3.58(3H,s),4.19(1H,dd),4.44(2H,d),5.49-5.66(1H,m),6.80(1H,d),7.81(2H,td),8.18(1H,d),8.30(1H,d),8.56(1H,d),8.66(1H,s)。质谱:m/z(ES+)[M+H]+=501。

[0573] 实例33:NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.58(2H,qd),1.89-2.04(4H,m),2.34(8H,s),2.51(1H,dddd),2.73(1H,ddd),2.93(3H,td),3.37(3H,s),3.58(3H,s),4.19(1H,dd),4.44(2H,d),5.5-5.68(1H,m),6.80(1H,d),7.81(2H,td),8.18(1H,d),8.30(1H,d),8.56(1H,d),8.66(1H,s)。质谱:m/z(ES+)[M+H]+=501。

[0574] 实例34:(甲酸盐)NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ1.35-1.55(2H,m),1.85-2.00(4H,m),2.10-2.20(1H,m),2.31(6H,s),2.50-2.60(1H,m),2.60-2.80(1H,m),2.89(2H,t),3.35-3.45(1H,m),3.45(3H,s),3.90-3.98(1H,m),4.10-4.30(2H,m),4.40-4.50(2H,m),4.88-5.2(1H,m),7.01(1H,d),7.85-8.00(2H,m),8.10(1H,d),8.21(1H,s),8.26(1H,s),8.60(1H,s),8.83(1H,s)。质谱:m/z(ES+)[M+H]+=487。

[0575] 实例35:(甲酸盐)NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ1.35-1.55(2H,m),1.85-2.00(4H,m),2.10-2.20(1H,m),2.31(6H,s),2.50-2.80(2H,m),2.89(2H,t),3.35-3.45(1H,m),3.45(3H,s),3.90-3.98(1H,m),4.10-4.30(2H,m),4.40-4.50(2H,m),4.88-5.2(1H,m),7.01(1H,d),7.85-8.00(2H,m),8.10(1H,d),8.24(1H,s),8.28(1H,s),8.60(1H,s),8.83(1H,s)。质谱:m/z(ES+)[M+H]+=487。

[0576] 实例36:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.34-1.43(2H,m),1.82-1.86(2H,m),2.20(6H,s),2.33-2.37(1H,m),2.77-3.05(6H,m),3.23(3H,s),3.49(3H,s),3.84-3.89(1H,m),4.38-4.42(2H,d),5.08-5.14(1H,t),6.98-7.01(1H,d),7.87-8.08(3H,m),8.35-8.36(1H,d),8.64-8.65(1H,d),8.82(1H,s)。质谱:m/z(ES+)[M+H]+=487

[0577] 实例37:(甲磺酸盐)NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.46-1.63(2H,m),1.8-1.98(2H,m),2.01(2H,s),2.29(3H,s),2.34-2.39(1H,m),2.45-2.48(1H,m),2.52-2.54(1H,m),2.59-2.8(6H,m),2.90(2H,t),3.01-3.15(2H,m),3.50(3H,s),4.55(2H,d),5.50(1H,p),

7.08(1H,d),7.91(1H,dd),8.06(1H,dd),8.09(1H,d),8.37(1H,d),8.66(1H,d),8.85(1H,s),9.36(1H,s)。质谱:m/z(ES+)[M+H]+=457

[0578] 实例38:NMR谱:^{1}HNMR(500MHz,DMSO-d6)δ1.38(2H,qd),1.84(2H,d),2.20(6H,s),2.36(1H,ddd),2.8-2.98(2H,m),3.54(3H,s),4.40(2H,d),5.01-5.13(2H,m),5.27(2H,t),6.19(1H,p),6.99(1H,d),7.96(1H,dd),8.04(1H,dd),8.11(1H,d),8.45(1H,d),8.67(1H,d),8.90(1H,s)。质谱:m/z(ES+)[M+H]+=459

[0579] 实例39:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.29-1.45(2H,m),1.80-1.98(4H,m),2.15-2.25(6H,m),2.31-2.45(1H,m),2.67-2.78(2H,m),2.81-2.98(2H,m),3.51(3H,s),3.53-3.65(2H,m),3.98-4.15(2H,m),4.35-4.44(2H,m),5.04-5.21(1H,m),6.90-7.04(1H,m),7.89-7.98(1H,m),8.01-8.04(1H,m),8.04-8.15(1H,m),8.31-8.51(1H,m),8.61-8.70(1H,m),8.85(1H,s)。质谱:m/z(ES+)[M+H]+=487。

[0580] 实例40:(甲酸盐)NMR谱:^{1}H NMR(300MHz,MeOH-d4)δ1.55-1.71(2H,m),1.88-1.96(2H,m),2.06-2.15(2H,m),2.19-2.30(1H,m),2.60(6H,s),2.72-3.06(4H,m),3.50-3.60(4H,m),3.98-4.05(1H,d),4.17-4.23(1H,d),4.32-4.42(1H,t),4.53-4.65(2H,d),4.95-5.17(1H,m),7.04-7.07(1H,d),7.81-7.85(1H,d),7.92-7.96(1H,d),8.33(1H,d),8.46(1H,s),8.56(1H,s),8.81(1H,s)。质谱:m/z(ES+)[M+H]+=505。

[0581] 实例41:NMR谱:^{1}H NMR(300MHz,DMSO-d6)1.30-1.50(2H,m),1.70-1.90(4H,m),2.10-2.25(1H,m),2.19(6H,s),2.30-2.42(1H,m),2.60-2.75(1H,m),2.82-2.98(2H,m),3.30-3.40(1H,m),3.48(3H,s),3.85-3.95(1H,m),4.10-4.25(2H,m),4.35-4.50(2H,m),4.82-4.97(1H,m),7.00(1H,d),7.83-7.93(2H,m),8.20(1H,d),8.45(1H,s),8.86(1H,s),质谱:m/z(ES+)[M+H]+=505。

[0582] 实例42:NMR谱:^{1}HNMR(400MHz,DMSO-d6)δ1.38(2H,qd),1.85(2H,d),2.20(6H,s),2.36(1H,ddd),2.73-2.84(2H,m),2.85-3.04(4H,m),3.19(3H,s),3.48(3H,s),3.83(1H,p),4.40(2H,d),5.03(1H,p),6.98(1H,d),7.78-7.89(2H,m),8.28(1H,d),8.45(1H,s),8.85(1H,s)。质谱:m/z(ES+)[M+H]+=505。

[0583] 实例43:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.50-1.70(1H,m),1.70-2.00(2H,m),2.10-2.25(1H,m),2.70-3.05(10H,m),3.05-3.15(1H,m),3.18(3H,s),3.25-3.45(2H,m),3.48(3H,s),3.80-3.90(1H,m),4.00-4.15(1H,m),4.55(1H,t),4.90-5.10(1H,m),7.10(1H,d),7.78(1H,d),7.80-8.00(1H,m),8.35(1H,d),8.50(1H,s),8.85(1H,s)。质谱:m/z(ES+)[M+H]+=505。

[0584] 实例44:(游离碱)NMR谱:^{1}H NMR(300MHz,$CDCl_3$)δ1.59-1.72(2H,m),1.78(2H,d),2.15-2.44(3H,m),2.45-2.51(1H,m),2.56(6H,s),2.84(2H,bs),3.17-3.40(4H,m),3.46-3.67(6H,m),3.71-3.85(1H,m),3.93(1H,dd),4.92(1H,bs),6.54(1H,d),7.78(1H,dd),7.85-7.95(1H,m),8.20(1H,d),8.53(1H,s),8.58-8.65(1H,m),8.70(1H,s)。(甲磺酸盐)NMR谱:^{1}H NMR(300MHz,MeOH-d4)δ1.57-1.82(4H,m),2.21(2H,dd),2.28-2.43(1H,m),2.62-2.93(4H,m),2.71(3H,s),3.00(6H,s),3.18-3.24(2H,m),3.49-3.65(5H,m),3.69-3.90(2H,m),3.96-4.13(2H,m),4.88-4.92(1H,m),6.76(1H,d),7.83(1H,dd),8.01(1H,dd),8.08(1H,d),8.18-8.51(1H,m),8.52(1H,d),8.76(1H,s)。质谱:m/z(ES+)[M+H]+=501。

[0585] 实例45：(游离碱)NMR谱：^{1}H NMR(300MHz,MeOH-d4)δ1.25-1.40(1H,m),1.42-1.65(3H,m),1.97-2.07(4H,m),2.17-2.28(1H,m),2.37(6H,s),2.39-2.63(4H,m),2.85-3.01(2H,m),3.39(3H,s),3.39-3.51(1H,m),3.56(3H,s),4.42-4.54(2H,m),4.86-4.93(1H,m),6.99(1H,d),7.87(1H,dd),7.93(1H,dd),8.10(1H,d),8.27(1H,s),8.49(1H,d),8.74(1H,s)。(甲磺酸盐)NMR谱：^{1}H NMR(300MHz,MeOH-d4)1.22-1.37(1H,m),1.46-1.66(1H,m),1.67-1.87(2H,m),2.01-2.12(2H,m),2.17-2.29(3H,m),2.35-2.59(3H,m),2.71(3H,s),2.93(6H,s),2.94-3.12(2H,m),3.40(3H,s),3.42-3.58(2H,m),3.60(3H,s),4.66(2H,d),4.87-4.93(1H,m),7.10(1H,d),7.97-8.12(2H,m),8.17(1H,d),8.37(1H,s),8.56(1H,d),8.91(1H,s)。质谱：m/z(ES+)[M+H]+＝515。

[0586] 实例46：(游离碱)NMR谱：^{1}H NMR(300MHz,MeOH-d4)δ1.30(1H,m,1.53(3H,m),2.04(4H,dd),2.22(1H,d),2.37(6H,s),2.38-2.35(4H,m),2.93(2H,m),3.39(4H,m),3.56(3H,s),4.43-4.54(2H,d),4.89(1H,m),6.99(1H,d),7.90(2H,m),8.10(1H,d),8.27(1H,s),8.49(1H,s),8.74(1H,s)。(甲磺酸盐)NMR谱：^{1}H NMR(300MHz,MeOH-d4)1.25-1.40(1H,m),1.55(1H,m),1.76(2H,m),2.05(2H,d),2.16-2.26(3H,m),2.44(3H,m),2.71(3H,s),2.93(6H,s),2.97-3.05(2H,t),3.49(8H,m),4.64(2H,d),4.90(1H,m),7.06(1H,d),7.92(1H,dd),8.09(1H,d),8.11(1H,d),8.28(1H,s),8.53(1H,s),8.77(1H,s)。质谱：m/z(ES+)[M+H]+＝515。

[0587] 实例47：(游离碱)NMR谱：^{1}H NMR(300MHz,MeOH-d4)δ1.26-1.37(1H,m),1.47-1.67(1H,m),1.91-2.02(2H,m),2.02-2.12(2H,m),2.17-2.28(1H,m),2.29-2.39(1H,m),2.40(6H,s),2.44-2.51(3H,m),2.95-3.07(1H,m),3.44(3H,s),3.44-3.63(2H,m),3.63(3H,s),3.71-3.83(1H,m),3.83-3.93(1H,m),4.90-4.96(1H,m),6.71(1H,d),7.85-8.03(2H,m),8.13(1H,dd),8.31(1H,s),8.47(1H,t),8.72-8.80(1H,m)。(甲磺酸盐)NMR谱：^{1}H NMR(300MHz,MeOH-d4)δ1.27-1.38(1H,m),1.46-1.62(1H,m),2.01-2.12(2H,m),2.16-2.39(2H,m),2.36-2.53(3H,m),2.55-2.67(1H,m),2.71(3H,s),2.92(6H,s),3.39(3H,s),3.40-3.52(1H,m),3.54-3.59(1H,m),3.59(3H,s),3.62-3.75(1H,m),3.78-4.00(2H,m),3.99-4.11(1H,m),4.89-5.02(1H,m),6.79(1H,d),7.92(1H,dd),8.03(1H,dd),8.14(1H,d),8.33(1H,s),8.54(1H,d),8.79(1H,s)。质谱：m/z(ES+)[M+H]+＝501。

[0588] 实例48：(游离碱)NMR谱：^{1}H NMR(300MHz,MeOH-d4)δ1.30(1H,m),1.44-1.65(1H,m),1.85-2.11(3H,m),2.33(1H,m),2.33-2.50(9H,m),22.95(1H,m),3.29(1H,m),3.33(1H,d),3.39(3H,s),3.40-3.52(2H,m),3.54(3H,s),3.66-3.77(1H,m),3.83(1H,m),4.85(1H,s),6.64(1H,d),7.86(2H,m,8.07(1H,d),8.22(1H,s),8.42(1H,dd),8.70(1H,s)。(甲磺酸盐)NMR谱：^{1}HNMR(300MHz,MeOH-d4)1.31(1H,m),1.53(1H,m),1.99-2.11(2H,m),2.21(1H,d),2.26-2.53(4H,m),2.71(4H,m),3.03(6H,s),3.39(4H,m),3.59(4H,m),3.69-3.93(2H,m),4.02-4.18(2H,m),4.95(1H,s),6.80(1H,d),7.93(1H,dd),8.03(1H,dd),8.13(1H,d),8.32(1H,s),8.53(1H,s),8.80(1H,s)。质谱：m/z(ES+)[M+H]+＝501。

[0589] 实例49：(游离碱)NMR谱：^{1}H NMR(300MHz,MeOH-d4)δ1.20-1.39(1H,m),1.44-1.64(1H,m),1.98-2.11(2H,m),2.15-2.27(1H,m),2.30(6H,s),2.35-2.51(3H,m),3.35-3.41(1H,m),3.38(3H,s),3.41-3.52(1H,m),3.56(3H,bs),3.94(2H,dd),4.20(2H,t),4.91-4.96(1H,m),6.60(1H,d),7.85(1H,dd),7.94(1H,dd),8.09(1H,dd),8.25(1H,s),8.43(1H,

s),8.73(1H,s)。(甲磺酸盐)NMR谱:^{1}H NMR(300MHz,MeOH-d4)1.26-1.40(1H,m),1.45-1.60(1H,m),1.99-2.11(2H,m),2.21(1H,d),2.45-2.53(3H,m),2.70(3H,s),2.94(6H,s),3.39(3H,s),3.41-3.53(1H,m),3.60(3H,s),4.21-4.28(3H,m),4.38-4.51(2H,m),4.93-4.99(1H,m),6.74(1H,dd),7.95(1H,dd),8.07(1H,dd),8.16(1H,d),8.35(1H,s),8.55(1H,d),8.83(1H,s)。质谱:m/z(ES+)[M+H]+=487。

[0590] 实例50:(游离碱)NMR谱:^{1}H NMR(300MHz,MeOH-d4)δ1.29(1H,m),1.43-1.60(1H,m),1.96-2.10(2H,m),2.21(1H,d),2.34-2.45(9H,m),3.31-3.50(5H,m),3.55(3H,s),3.97(2H,m),4.16-4.28(2H,m),4.89(1H,m),6.60(1H,dd),7.89(2H,dd),8.08(1H,d),8.20-8.27(1H,d),8.43(1H,dd),8.72(1H,s)。(甲磺酸盐)NMR谱:^{1}H NMR(300MHz,MeOH-d4)1.31(1H,m),1.44-1.60(1H,m),1.98-2.11(2H,m),2.21(1H,d),2.44(3H,m),2.69(3H,s),2.91(6H,s),3.39(4H,m),3.59(3H,s),4.12-4.29(3H,m),4.36-4.49(2H,m),4.96(1H,m),6.73(1H,dd),7.92(1H,dd),8.01-8.19(2H,m),8.33(1H,s),8.53(1H,dd),8.80(1H,s)。质谱:m/z(ES+)[M+H]+=487。

[0591] 实例51:(游离碱)NMR谱:^{1}HNMR(300MHz,MeOH-d4)δ1.49(1H,s),1.78-1.83(1H,m),1.89(1H,d),1.91-2.06(2H,m),2.15(1H,d),2.30-2.43(9H,m),2.50-2.61(1H,m),2.76-2.87(1H,m),2.94-3.07(1H,m),3.41(3H,s),3.46-3.56(1H,m),3.58(3H,s),3.77(1H,t),3.81-3.92(2H,m),5.31-5.42(1H,m),6.70(1H,d),7.93(1H,dd),8.03(1H,dd),8.13(1H,d),8.56(2H,dd),8.75(1H,s)。(甲磺酸盐)NMR谱:^{1}H NMR(300MHz,MeOH-d4)1.48(1H,t),1.76-1.91(2H,m),1.98(1H,d),2.13(1H,d),2.25-2.44(2H,m),2.46-2.58(1H,m),2.57-2.67(1H,m),2.71(3H,s),2.76-2.87(1H,m),3.02(6H,s),3.41(3H,s),3.57(3H,s),3.59-3.68(1H,m),3.69-3.93(3H,m),4.01-4.15(2H,m),5.27-5.42(1H,m),6.78(1H,d),7.95(1H,dd),8.07(1H,dd),8.13(1H,d),8.60(2H,dd),8.78(1H,s)。质谱:m/z(ES+)[M+H]+=501。

[0592] 实例52:(游离碱)NMR谱:^{1}HNMR(300MHz,MeOH-d4)δ1.50(1H,t),1.78-1.93(2H,m),1.91-2.08(2H,m),2.15(1H,d),2.31-2.40(9H,m),2.50-2.62(1H,m),2.81-2.85(1H,m),3.00(1H,p),3.41(3H,s),3.46-3.58(1H,m),3.58(3H,s),3.77(1H,t),3.81-3.93(2H,m),5.37(1H,t),6.70(1H,d),7.93(1H,dd),8.03(1H,dd),8.13(1H,d),8.56(2H,dd),8.75(1H,s)。(甲磺酸盐)NMR谱:^{1}H NMR(300MHz,MeOH-d4)1.49(1H,t),1.76-1.91(2H,m),1.99(1H,d),2.13(1H,d),2.28-2.44(2H,m),2.47-2.60(1H,m),2.60-2.69(1H,m),2.71(3H,s),2.76-2.89(1H,m),3.02(6H,s),3.41(3H,s),3.58(3H,s),3.59-3.68(1H,m),3.69-3.94(3H,m),4.01-4.17(2H,m),5.28-5.43(1H,m),6.79(1H,d),7.97(1H,dd),8.08(1H,dd),8.14(1H,d),8.62(2H,t),8.80(1H,s)。质谱:m/z(ES+)[M+H]+=501。

[0593] 实例53:(游离碱)NMR谱:^{1}H NMR(300MHz,MeOH-d4)δ1.28-1.33(1H,m),1.47-1.61(3H,m),1.73-1.92(2H,m),2.02(3H,t),2.16(1H,d),2.30-2.42(6H,m),2.48-2.62(2H,m),2.81-2.86(1H,m),2.95(2H,t),3.44(3H,s),3.59(3H,s),3.84(1H,s),4.52(2H,d),5.36(1H,t),7.02(1H,d),7.94(1H,dd),8.03(1H,dd),8.13(1H,d),8.62(2H,dd),8.76(1H,s)。(甲磺酸盐)NMR谱:^{1}H NMR(300MHz,MeOH-d4)1.41-1.56(1H,m),1.67-1.84(4H,m),1.99(1H,d),2.18(3H,t),2.36(1H,d),2.45-2.62(1H,m),2.71(3H,s),2.79-2.88(1H,m),2.92(6H,s),3.01(2H,t),3.44(3H,s),3.47-3.56(1H,m),3.59(3H,s),3.85(1H,s),4.67(2H,

d),5.30-5.45(1H,m),7.07(1H,d),7.97-8.10(2H,m),8.15(1H,d),8.67(2H,dd),8.84(1H,s)。质谱:m/z(ES+)[M+H]+=515。

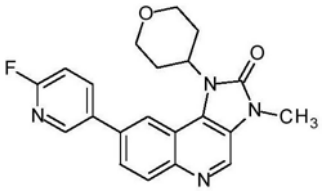
[0594] 实例54:(游离碱)NMR谱:^{1}H NMR(400MHz,MeOH-d4)δ1.46-1.61(3H,m),1.73-1.83(1H,m),1.87(1H,d),1.94-2.07(3H,m),2.16(1H,d),2.30-2.35(1H,m),2.38(6H,s),2.48-2.61(2H,m),2.82-2.87(1H,m),2.94(2H,t),3.43(3H,s),3.58(3H,s),3.84(1H,s),4.52(2H,d),5.35(1H,t),7.00(1H,d),7.93(1H,dd),8.01(1H,dd),8.12(1H,d),8.60(2H,dd),8.75(1H,s)。(甲磺酸盐)NMR谱:^{1}H NMR(300MHz,MeOH-d4)1.41-1.57(1H,m),1.65-1.92(4H,m),1.98(1H,d),2.17(3H,t),2.35(1H,d),2.46-2.62(1H,m),2.71(3H,s),2.79-2.88(1H,m),2.92(6H,s),3.01(2H,t),3.43(3H,s),3.51(1H,s),3.58(3H,s),3.84(1H,s),4.67(2H,d),5.27-5.43(1H,m),7.06(1H,d),7.97(1H,dd),8.05(1H,dd),8.13(1H,d),8.64(2H,dd),8.80(1H,s)。质谱:m/z(ES+)[M+H]+=515。

[0595] 实例55:(游离碱)NMR谱:^{1}HNMR(400MHz,MeOH-d4)δ1.51(1H,t),1.75-1.91(2H,m),2.00(1H,d),2.14(1H,d),2.29(6H,s),2.34(1H,d),2.49-2.61(1H,m),2.74-2.89(1H,m),3.33-3.39(1H,m),3.40(3H,s),3.59(3H,s),3.83(1H,s),3.94(2H,dd),4.22(2H,dd),5.30-5.41(1H,m),6.64(1H,d),7.92(1H,dd),8.05(1H,dd),8.14(1H,d),8.53(1H,s),8.58(1H,s),8.76(1H,s)。(甲磺酸盐)NMR谱:^{1}H NMR(300MHz,MeOH-d4)1.47(1H,t),1.75-1.90(2H,m),1.98(1H,d),2.13(1H,d),2.32(1H,d),2.44-2.61(1H,m),2.70(3H,s),2.76-2.88(1H,m),2.92(6H,s),3.40(3H,s),3.57(3H,s),3.78-3.87(1H,m),4.13-4.29(3H,m),4.36-4.50(2H,m),5.24-5.40(1H,m),6.72(1H,d),7.94(1H,dd),8.09(1H,dd),8.13(1H,d),8.55-8.64(2H,m),8.79(1H,s)。质谱:m/z(ES+)[M+H]+=487。

[0596] 实例56:(游离碱)NMR谱:^{1}H NMR(400MHz,MeOH-d4)δ1.44-1.55(1H,m),1.77-1.92(2H,m),2.00(1H,d),2.14(1H,d),2.30(6H,s),2.32-2.38(1H,m),2.56(1H,t),2.76-2.87(1H,m),3.34-3.39(1H,m),3.40(3H,s),3.59(3H,s),3.83(1H,s),3.94(2H,dd),4.22(2H,t),5.30-5.42(1H,m),6.64(1H,d),7.93(1H,dd),8.05(1H,dd),8.14(1H,d),8.53(1H,d),8.58(1H,d),8.77(1H,s)。(甲磺酸盐)NMR谱:^{1}H NMR(300MHz,MeOH-d4)1.40-1.56(1H,m),1.75-1.88(2H,m),1.99(1H,d),2.13(1H,d),2.34(1H,d),2.46-2.62(1H,m),2.70(3H,s),2.77-2.89(1H,m),2.95(6H,s),3.40(3H,s),3.58(3H,s),3.79-3.87(1H,m),4.18-4.31(3H,m),4.38-4.51(2H,m),5.27-5.42(1H,m),6.73(1H,d),7.98(1H,dd),8.11(1H,dd),8.15(1H,d),8.62(2H,s),8.82(1H,s)。质谱:m/z(ES+)[M+H]+=487。

[0597] 实例6-56需要的氟吡啶基中间体的制备描述如下:

[0598] 中间体D0:8-(6-氟吡啶-3-基)-3-甲基-1-(氧杂环己烷-4-基)咪唑并[5,4-c]喹啉-2-酮

[0599] 

[0600] 在环境温度且在空气下,将四氯化二钠单钯(IV)(0.975g,3.31mmol)添加至在1,4-二噁烷(400mL)和水(100mL)中的8-溴-3-甲基-1-(氧杂环己烷-4-基)咪唑并[5,4-c]喹啉-2-酮(60.0g,165.64mmol)、(6-氟吡啶-3-基)硼酸(25.7g,182.21mmol)、K_2CO_3(68.7g,

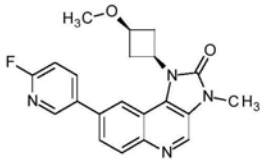
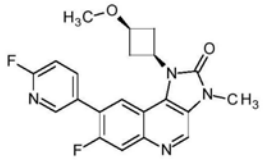
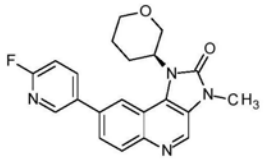
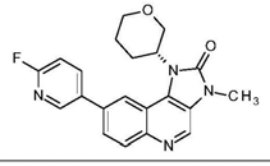
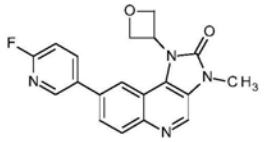
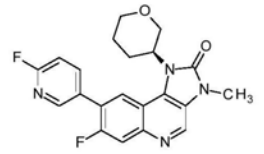
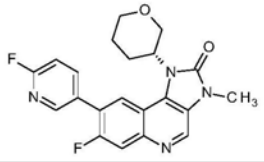
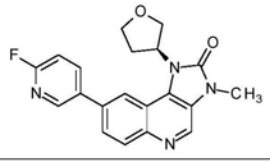
496.93mmol)、和3-(二-叔丁基膦基)丙烷-1-磺酸(0.445g,1.66mmol)里。将所得混合物在80℃下搅拌16h。将该反应混合物用水稀释,并将沉淀物通过过滤收集,用水(200mL)洗涤,并且在真空下进行干燥。将所得固体用DCM(18L)溶解,并且将混合物通过硅藻土过滤以去除钯残余物。将溶剂在减压下去除以提供呈白色固体的所希望的物质(60.0g,96%),将其不进行进一步纯化而使用。

[0601] NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.85-2.01(2H,m),2.86-3.02(2H,m),3.57-3.68(5H,m),4.16-4.31(2H,m),5.11(1H,t),6.98-7.19(1H,m),7.83(1H,dd),8.16(1H,td),8.30(1H,dd),8.50(1H,s),8.60(1H,s),8.77(1H,s)。

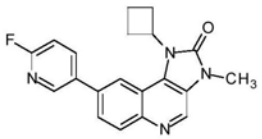
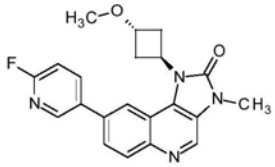
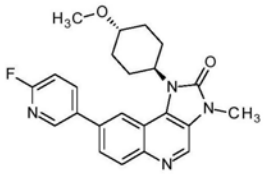
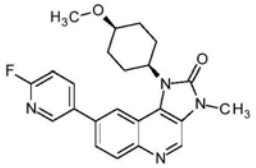
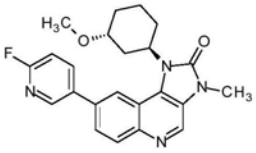
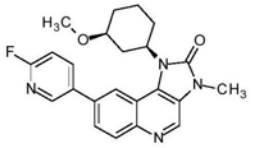
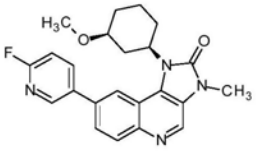
[0602] 质谱:m/z(ES+)[M+H]+=379.2

[0603] 以类似方式从适当的溴代中间体制备以下中间体。

[0604]

中间体	结构	名称
中间体 E0 *		8-(6-氟-3-吡啶基)-1-(*顺式*-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
中间体 F0 **		7-氟-8-(6-氟-3-吡啶基)-1-(*顺式*-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
中间体 G0 **		8-(6-氟-3-吡啶基)-3-甲基-1-[(3*S*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
中间体 H0 **		8-(6-氟-3-吡啶基)-3-甲基-1-[(3*R*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
中间体 I0 ***		8-(6-氟-3-吡啶基)-3-甲基-1-(氧杂环丁烷-3-基)咪唑并[4,5-c]喹啉-2-酮
中间体 J0 ****		7-氟-8-(6-氟-3-吡啶基)-3-甲基-1-[(3*S*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
中间体 K0 **		7-氟-8-(6-氟-3-吡啶基)-3-甲基-1-[(3*R*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
中间体 L0 ***		8-(6-氟-3-吡啶基)-3-甲基-1-[(3*S*)-四氢呋喃-3-基]咪唑并[4,5-c]喹啉-2-酮

[0605]

中间体	结构	名称
中间体 M1 ***		1-环丁基-8-(6-氟-3-吡啶基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
中间体 N0 ****		8-(6-氟-3-吡啶基)-1-(反式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
中间体 O0 **		8-(6-氟-3-吡啶基)-1-(反式-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
中间体 P0 **		8-(6-氟-3-吡啶基)-1-(*顺式*-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
中间体 R0 **		8-(6-氟-3-吡啶基)-1-[反式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮（对映异构体的 1 : 1 混合物）
中间体 S0 **		8-(6-氟-3-吡啶基)-1-[*顺式*-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 1
中间体 T0 **		8-(6-氟-3-吡啶基)-1-[*顺式*-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 2

[0606] *使用氯(2-二环己基膦基-2',4',6'-三异丙基-1,1'-联苯)[2-(2'-氨基-1,1'-联苯)]钯(II)作为催化剂进行反应,并且在90℃下搅拌2h。

[0607] **使用Pd(Ph3P)$_4$作为催化剂,并且使用Cs_2CO_3或Na_2CO_3作为碱,在1,4-二噁烷与水的作为溶剂的混合物中进行反应。将反应在80℃-100℃之间的温度下加热2h-16h。

[0608] ***使用二氯[1,1'-双(二-叔丁基膦基)二茂铁]钯(II)作为催化剂,并且使用K_2CO_3作为碱,在1,4-二噁烷与水的作为溶剂的混合物中进行反应。将反应在80℃下加热1h。

[0609] ****使用二氯[1,1'-双(二-叔丁基膦基)二茂铁]钯(II)作为催化剂,并且使用K_2CO_3作为碱,在1,4-二噁烷与水的作为溶剂的混合物中进行反应。将反应在80℃下加热1h。

[0610] 中间体E0:NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ2.83(2H,s),3.01(2H,d),3.20(3H,s),3.51(3H,s),3.86(1H,s),5.07-5.18(1H,m),7.37(1H,d),7.96(1H,d),8.16(1H,d),8.49(2H,d),8.75(1H,s),8.92(1H,s)。质谱:m/z(ES+)[M+H]+=379

[0611] 中间体F0:NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ2.76-2.81(2H,m),2.91-3.05(2H,m),3.13(3H,s),3.49(3H,s),3.78-3.82(1H,qu),5.07-5.10(1H,qu),7.40(1H,dd),7.94

(1H,d),8.32(1H,td),8.45(d)8.59(1H,s),8.95(1H,s)。质谱:m/z(ES+)[M+H]+=397

[0612] 中间体G0:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.83-1.86(2H,m),2.15-2.19(1H,m),2.49-2.64(1H,m),3.38-3.41(1H,m),3.49(3H,s),3.93(1H,d),4.15-4.26(2H,m),4.91-5.10(1H,m),7.42(1H,dd),7.96(1H,dd),8.13(1H,d),8.38(1H,s),8.44(1H,td),8.72(1H,d),8.96(1H,s)。质谱:m/z(ES+)[M+H]+=379.1

[0613] 中间体H0:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.80-1.83(2H,m),2.15-2.18(1H,m),2.49-2.73(1H,m),3.37-3.41(1H,m),3.49(3H,s),3.93(1H,d),4.16-4.26(2H,m),4.90-5.10(1H,m),7.42(1H,dd),7.97(1H,dd),8.14(1H,d),8.38(1H,s),8.45(1H,td),8.71(1H,d),8.95(1H,s)。质谱:m/z(ES+)[M+H]+=379

[0614] 中间体I0:NMR谱:^{1}H NMR(500MHz,DMSO-d_6)δ3.55(3H,s),5.07(2H,dd),5.28(2H,t),6.09-6.31(1H,m),7.29-7.43(1H,m),8.02(1H,dd),8.18(1H,d),8.49(1H,ddd),8.56(1H,d),8.77(1H,d),8.97(1H,s)。质谱:m/z(ES+)[M+H]+=351

[0615] 中间体J0:NMR谱:^{1}H NMR(500MHz,DMSO-d6)δ1.71-1.87(2H,m),2.14(1H,d),2.57-2.76(1H,m),3.32-3.42(1H,m),3.49(3H,s),3.90(1H,d),4.06-4.16(1H,m),4.21(1H,t),4.79-5.1(1H,m),7.36-7.54(1H,m),7.97(1H,d),8.32(1H,d),8.37(1H,tt),8.62(1H,s),8.95(1H,s)。质谱:m/z(ES+)[M+H]+=397

[0616] 中间体K0:NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ1.75-1.91(2H,m),2.10-2.20(1H,m),2.59-2.78(1H,m),3.30-3.41(1H,m),3.50(3H,s),3.89-3.95(1H,d)4.04-4.15(1H,d),4.20-4.32(1H,t),4.80-5.00(1H,t),7.34-7.39(1H,d),7.89-7.95(1H,d),8.30-8.40(2H,m),8.59(1H,s),8.95(1H,s)。质谱:m/z(ES+)[M+H]+=397

[0617] 中间体L0:NMR谱:^{1}H NMR(500MHz,DMSO-d_6)δ2.33-2.44(1H,m),2.53-2.67(1H,m),3.55(3H,s),3.91(1H,td),4.13-4.22(2H,m),4.27(1H,td),5.79-5.9(1H,m),7.3-7.41(1H,m),8.02(1H,dd),8.18(1H,d),8.49(1H,ddd),8.68(1H,d),8.77(1H,d),8.96(1H,s)。质谱:m/z(ES+)[M+H]+=365

[0618] 中间体M0:NMR谱:^{1}HNMR(300MHz,DMSO-d_6)δ1.77-2.01(2H,m),2.46(2H,ddt),3.09(2H,pd),3.51(3H,s),5.53(1H,p),7.32-7.44(1H,m),7.96(1H,dd),8.15(1H,d),8.43-8.54(2H,m),8.75(1H,d),8.91(1H,s)。质谱:m/z(ES+)[M+H]+=349

[0619] 中间体N0:NMR谱:^{1}HNMR(500MHz,DMSO-d6)δ2.52-2.63(2H,m),3.15-3.2(2H,m),3.21(3H,s),3.50(3H,s),4.14-4.37(1H,m),5.58(1H,tt),7.37(1H,ddd),7.94(1H,dd),8.08-8.22(1H,m),8.32(1H,d),8.44(1H,ddd),8.72(1H,dd),8.89(1H,s)。质谱:m/z(ES+)[M+H]+=379

[0620] 中间体O0:NMR谱:^{1}H NMR(400MHz,MeOH-d4)δ1.45-1.53(2H,m),2.16(2H,d),2.34(2H,d),2.60-2.80(2H,m),3.37-3.41(1H,m),3.43(3H,s),3.61(3H,s),4.94-5.06(1H,m),7.29(1H,dd),8.00(1H,d),8.24(1H,d),8.35-8.45(1H,m),8.47(1H,s),8.66(1H,s),8.86(1H,s)。质谱:m/z(ES+)[M+H]+=407

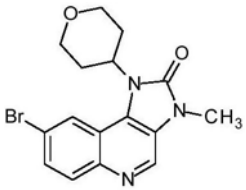
[0621] 中间体P0:NMR谱:^{1}H NMR(300MHz,$CDCl_3$)δ1.64(2H,t),1.77(2H,d),2.14-2.28(2H,m),2.64-2.78(2H,m),3.07(3H,br),3.56(1H,s),3.64(3H,s),4.98(1H,br),7.10(1H,dd),7.77(1H,dd),8.11-8.23(1H,m),8.26(1H,d),8.56(1H,s),8.64(1H,s),8.76(1H,s)。质谱:m/z(ES+)[M+H]+=407

[0622] 中间体R0:NMR谱:^{1}H NMR(300MHz,$CDCl_3$)δ1.40-1.54(1H,m),1.74-1.86(2H,m),1.98(1H,d),2.13(1H,d),2.35(1H,d),2.54(1H,t),2.89-2.96(1H,m),3.39(3H,s),3.59(3H,s),3.83(1H,s),5.28(1H,t),7.11(1H,dd),7.85(1H,dd),8.14-8.24(1H,m),8.31(1H,d),8.68(2H,d),8.72(1H,s)。质谱:m/z(ES+)[M+H]+=407

[0623] 中间体S0:NMR谱:^{1}H NMR(300MHz,$CDCl_3$)δ1.92(1H,dd),2.02-2.12(1H,m),2.50(1H,m),3.16(4H,d),3.35(3H,s),3.48(3H,s),4.11(1H,m),4.88(1H,m),7.38(1H,dd),7.91-7.98(1H,d),8.14(1H,d),8.30(1H,s),8.42(1H,d),8.68(1H,d),8.88(1H,s)。质谱:m/z(ES+)[M+H]+=407

[0624] 中间体T0:NMR谱:^{1}H NMR(300MHz,$CDCl_3$)δ1.14-1.59(2H,m),1.96-2.12(2H,m),2.21(1H,d),2.48-2.59(3H,m),3.34-3.35(1H,m),3.38(3H,s),3.61(3H,s),4.79-4.83(1H,m),7.13(1H,ddd),7.47-7.50(1H,m),7.65(1H,dd),7.79(1H,dd),8.27(1H,d),8.56(1H,d),8.75(1H,s)。质谱:m/z(ES+)[M+H]+=407

[0625] 中间体D1:8-溴-3-甲基-1-(氧杂环己烷-4-基)咪唑并[5,4-c]喹啉-2-酮

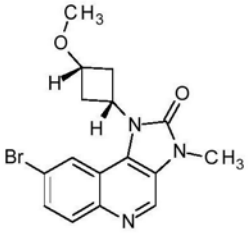
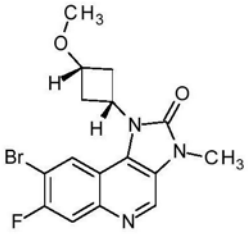
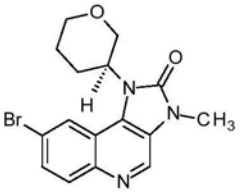
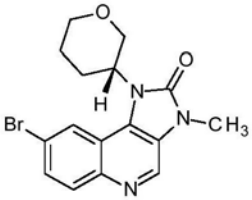
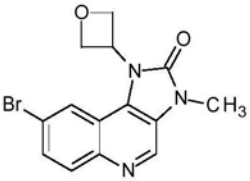
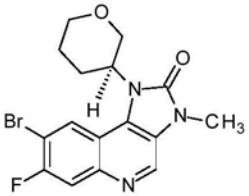
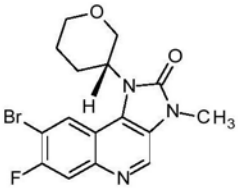
[0626] 

[0627] 在环境温度且在空气下,将在水(900mL)中的氢氧化钠(10.34g,258.48mmol)溶液添加至8-溴-1-(氧杂环己烷-4-基)-3H-咪唑并[4,5-c]喹啉-2-酮(60.0g,172.32mmol)、碘甲烷(48.9g,344.63mmol)和四丁基溴化铵(5.55g,17.23mmol)在DCM(1500mL)中的搅拌混合物里。将所得混合物搅拌16h然后将DCM在减压下去除。将沉淀物通过过滤收集,用水(200mL)洗涤并且在真空下进行干燥,以提供呈褐色固体的所希望的物质(58.0g,93%),将其不进行进一步纯化而使用。NMR谱:^{1}HNMR(400MHz,$CDCl_3$)δ1.81-1.98(2H,m),2.82-3.00(2H,m),3.60(3H,s),3.63(2H,td),4.05-4.35(2H,m),4.93(1H,t),7.69(1H,dd),8.03(1H,d),8.36(1H,s),8.71(1H,s)。质谱:m/z(ES+)[M+H]+=364。

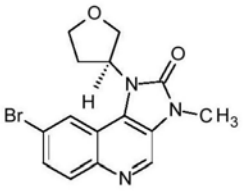
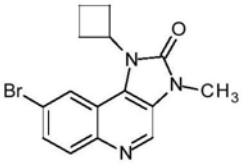
[0628] 以更大的规模,将8-溴-1-(氧杂环己烷-4-基)-3H-咪唑并[4,5-c]喹啉-2-酮(1300g,3.73mol)连同四丁基溴化铵(130g,0.40mol)和2-MeTHF(20.8L)填装到容器中。然后经5分钟添加NaOH(240g,6.00mol)于水(20.8L)中的溶液,观察到从18℃-24℃的放热。在添加碘甲烷(465mL,7.47mol)于2-MeTHF(930mL)中的溶液之前,将双相混合物加热至42℃-48℃。将反应在45℃搅拌17h,在此时HPLC分析示出2.9%起始物质和97.1%产物。将反应混合物与其他大规模批次的反应混合物合并,以用于在真空中浓缩。然后将所得水性悬浮液返回至容器中,并且与从在此时合并的发展批次获得的产物物质一起浆化1h。然后通过过滤分离产物,用水(2x 12L)洗涤,之后在真空下在40℃下烘箱干燥。分离到总计3479g的8-溴-3-甲基-1-(氧杂环己烷-4-基)咪唑并[5,4-c]喹啉-2-酮。分析数据与针对先前批次获得的是一致的。

[0629] 以类似方式从适当的3H-咪唑并[4,5-c]喹啉-2-酮中间体制备以下中间体:

[0630]

中间体	结构	名称
中间体 E1		8-溴-1-(*顺式*-3-甲氧基环丁基)-3-甲基咪唑并[4,5-c]喹啉-2-酮
中间体 F1		8-溴-7-氟-1-(*顺式*-3-甲氧基环丁基)-3-甲基咪唑并[4,5-c]喹啉-2-酮
中间体 G1		8-溴-3-甲基-1-[(3*S*)-氧杂环己烷-3-基]咪唑并[5,4-c]喹啉-2-酮
中间体 H1 *		8-溴-3-甲基-1-[(3*R*)-氧杂环己烷-3-基]咪唑并[5,4-c]喹啉-2-酮
中间体 I1 *		8-溴-3-甲基-1-(氧杂环丁烷-3-基)咪唑并[5,4-c]喹啉-2-酮
中间体 J1 **		8-溴-7-氟-3-甲基-1-[(3*S*)-氧杂环己烷-3-基]咪唑并[5,4-c]喹啉-2-酮
中间体 K1		8-溴-7-氟-3-甲基-1-[(3*R*)-氧杂环己烷-3-基]咪唑并[5,4-c]喹啉-2-酮

[0631]

中间体	结构	名称
中间体 L1		8-溴-3-甲基-1-[(3*S*)-四氢呋喃-3-基]咪唑并[4,5-c]喹啉-2-酮
中间体 M1		8-溴-1-环丁基-3-甲基-咪唑并[4,5-c]喹啉-2-酮

[0632] *反应尚未进行至完成,所以添加另外的碘甲烷、氢氧化钠和四丁基溴化铵,并且将反应再搅拌16-18h。

[0633] **将反应在环境温度下搅拌72h。

[0634] 中间体E1:NMR谱:^{1}HNMR(400MHz,DMSO-d6)δ2.72-2.86(2H,m),2.9-3.08(2H,m),3.22(3H,s),3.49(3H,s),3.85-3.89(1H,m),4.88-5.06(1H,m),7.74(1H,dd),7.98(1H,d),8.50(1H,d),8.92(1H,s)。质谱:m/z(ES+)[M+H]+=362,364。

[0635] 中间体F1:NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ2.70-2.85(2H,m),2.93-3.07(2H,m),3.22(3H,s),3.48(3H,s),3.73-4.00(1H,m),4.86-5.15(1H,m),7.75-8.07(1H,d),8.52-8.73(1H,d),8.93(1H,s)。质谱:m/z(ES+)[M+H]+=380。

[0636] 中间体G1:NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ1.82-1.88(2H,m),2.09-2.15(1H,m),2.55-2.78(1H,m),3.30-3.47(1H,m)3.48(3H,s),3.92(1H,d),4.02-4.22(2H,m),4.68-4.88(1H,m),7.75(1H,d),7.99(1H,d),8.35(1H,s),8.92(1H,s)。质谱:m/z(ES+)[M+H]+=362.2。

[0637] 中间体H1:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.80-1.86(2H,m),2.07-2.12(1H,m),2.61-2.75(1H,m),3.32-3.46(1H,m),3.47(3H,s),3.92-3.98(1H,m),4.01-4.20(2H,m),4.72-4.83(1H,m),7.76(1H,dd),8.00(1H,d),8.34(1H,d),8.92(1H,s)。质谱:m/z(ES+)[M+H]+=362,364。

[0638] 中间体I1:NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ3.53(3H,s),5.01(2H,dd),5.22(2H,t),6-6.18(1H,m),7.77(1H,dd),8.00(1H,d),8.51(1H,d),8.97(1H,s)。质谱:m/z(ES+)[M+H]+=334,336

[0639] 中间体J1:NMR谱:^{1}HNMR(400MHz,DMSO-d6)δ1.88-190(2H,m),2.09(1H,d),2.70(1H,ddd),3.36-3.44(1H,m),3.47(3H,s),3.94(1H,d),4.07(1H,dd),4.15(1H,t),4.79(1H,ddd),7.97(1H,d),8.48(1H,d),8.93(1H,s)。质谱:m/z(ES+)[M+H]+=380,382。

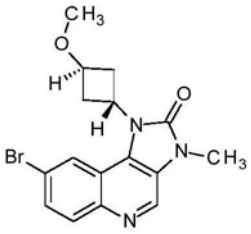
[0640] 中间体K1:NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ1.86(2H,dd),2.11(1H,d),2.69(1H,ddd),3.37-3.45(1H,m),3.48(3H,s),3.95(1H,d),4.08(1H,dd),4.18(1H,t),4.80(1H,ddd),7.98(1H,d),8.50(1H,d),8.94(1H,s)。质谱:m/z(ES+)[M+H]+=380,382。

[0641] 中间体L1:NMR谱:^{1}H NMR(400MHz,DMSO-d_6)δ2.40-2.48(1H,m),2.58-2.67(1H,m),3.63(3H,s),3.98-4.05(1H,m),4.19-4.28(2H,m),4.46-4.51(1H,td),5.68-5.76(1H,m),

7.72(1H,d),8.07(1H,d),8.67(1H,d),8.76(1H,s)。质谱:m/z(ES+)[M+H]+=348。

[0642] 中间体M1:NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.95-2.12(2H,m),2.52-2.59(2H,m),3.17-3.28(2H,m),3.59(3H,s),5.18-5.27(1H,m),7.8(1H,d),8.02(1H,d),8.37(1H,d),8.70(1H,s)。质谱:m/z(ES+)[M+H]+=332。

[0643] 中间体N1:8-溴-1-(反式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮

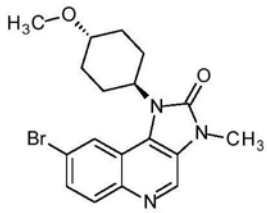
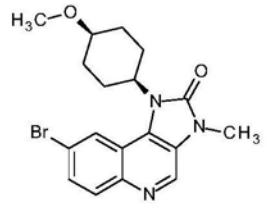
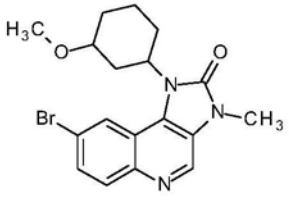
[0644] 

[0645] 在氮气且在室温下,向8-溴-1-(反式-3-羟基环丁基)-3H-咪唑并[4,5-c]喹啉-2-酮(1.8g,5.39mmol)在DMF(20mL)中的悬浮液里添加NaH(在矿物油中60%)(0.75g,18.75mmol),并且将该溶液搅拌30分钟。添加碘甲烷(1mL,15.99mmol)并将该反应混合物在环境温度下搅拌一小时。使用8-溴-1-((反式)-3-羟基环丁基)-1H-咪唑并[4,5-c]喹啉-2(3H)-酮(0.5g,1.50mmol)、DMF(5mL)、NaH(在矿物油中60%)(0.22g,5.50mmol)和碘甲烷(0.3mL,4.80mmol)进行第二次相同的反应,并将这些反应物合并。将合并的反应混合物用水小心淬灭,并且然后在水中搅拌三十分钟。将固体过滤出,用水充分洗涤,然后干燥以提供呈灰白色固体的所希望的物质(1.965g,79%)。

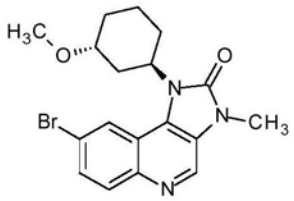
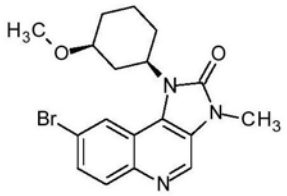
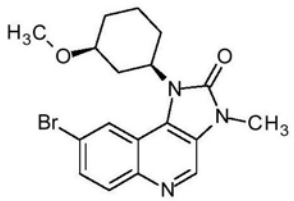
[0646] NMR谱:^{1}H NMR(500MHz,DMSO-d6)δ2.5-2.56(2H,m),3.11-3.21(2H,m),3.23(3H,s),3.48(3H,s),4.20(1H,dt),5.34-5.54(1H,m),7.72(1H,dd),7.95(1H,d),8.28(1H,d),8.90(1H,s)。质谱:m/z(ES+)[M+H]+=362,364。

[0647] 以类似方式从适当的3H-咪唑并[4,5-c]喹啉-2-酮中间体制备以下中间体:

[0648]

中间体	结构	名称
中间体O1*		8-溴-1-(反式-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
中间体P1*		8-溴-1-(顺式-4-甲氧基环己基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮
中间体Q1*		8-溴-1-[(3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮(异构体的1:1:1混合物)

[0649]

中间体	结构	名称
中间体 R1**		8-溴-1-[(反式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮(对映异构体的 1:1 混合物)
中间体 S1**		8-溴-1-[(顺式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 1
中间体 T1**		8-溴-1-[(顺式-3-甲氧基环己基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮 – 异构体 2

[0650] *将该反应在0℃下搅拌1h,然后在环境温度下搅拌过夜。

[0651] **通过超临界流体色谱法使用SFC制备型350机和CHIRALPAK AD-H SFC(5*25cm,5um)柱(流速150mL/min,压力100巴,温度34℃,流动相A:CO2:50,流动相B:MeOH:50)将中间体R1、S1和T1与外消旋混合物中间体Q1分离。首先洗脱中间体R1,随后洗脱中间体S1,并且最终洗脱中间体T1。随后使用SFC制备型350机和CHIRALPAK AD-H SFC(5*25cm,5um)柱(流速150mL/min,压力100巴,温度34℃,流动相A:CO2:60,流动相B:MeOH:40)将中间体T1再次进行纯化。

[0652] 中间体O1:NMR谱:^{1}HNMR(300MHz,$CDCl_3$)δ1.40-1.60(2H,m),2.08(2H,d),2.35(2H,d),2.63-2.77(2H,m),3.33-3.44(1H,m),3.45(3H,s),3.57(3H,s),4.68(1H,s),7.70(1H,dd),8.05(1H,d),8.30(1H,s),8.70(1H,s)。质谱:m/z(ES+)[M+H]+=390。

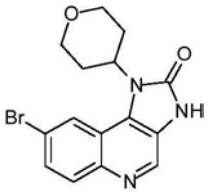
[0653] 中间体P1:NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.64-1.77(4H,m),2.21-2.32(2H,m),2.65(2H,s),3.56(3H,s),3.65(4H,d),4.98(1H,s),7.71(1H,dd),8.03(1H,d),8.74(1H,s),8.83(1H,s)。质谱:m/z(ES+)[M+H]+=390。

[0654] 中间体R1:NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.40-1.63(1H,m),1.75-1.94(2H,m),2.01(1H,d),2.09(1H,d),2.32(1H,d),2.45-2.52(1H,m),2.84(1H,d),3.50(3H,s),3.57(3H,s),3.81-3.84(1H,m),5.10(1H,t),7.70(1H,dd),8.03(1H,d),8.66(1H,d),8.70(1H,s)。质谱:m/z(ES+)[M+H]+=390。

[0655] 中间体S1:NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.40-1.53(2H,m),1.96-2.13(2H,m),2.22(1H,d),2.44-2.54(3H,m),3.37-3.42(1H,m),3.42(3H,s),3.60(3H,s),4.66(1H,s),7.70(1H,dd),8.06(1H,d),8.29(1H,s),8.73(1H,s)。质谱:m/z(ES+)[M+H]+=390。

[0656] 中间体T1:NMR谱:^{1}H NMR(300MHz,$CDCl_3$)δ1.40-1.53(2H,m),1.96-2.13(2H,m),2.22(1H,d),2.44-2.54(3H,m),3.37-3.42(1H,m),3.42(3H,s),3.60(3H,s),4.66(1H,s),7.70(1H,dd),8.06(1H,d),8.29(1H,s),8.73(1H,s)。质谱:m/z(ES+)[M+H]+=390。

[0657] 中间体D2:8-溴-1-(氧杂环己烷-4-基)-3H-咪唑并[4,5-c]喹啉-2-酮

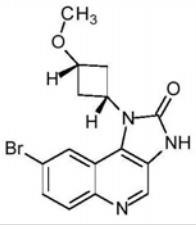
[0658] 

[0659] 在环境温度且在空气下,将三乙胺(143mL,1025.07mmol)添加至在DMF(600mL)中的6-溴-4-(氧杂环己烷-4-基氨基)喹啉-3-甲酸(120g,341,69mmol)里。将所得混合物搅拌30分钟,然后添加叠氮磷酸二苯酯(113g,410,03mmol)。将所得混合物在环境温度下搅拌30分钟,然后在60℃下搅拌2h。将溶剂在减压下去除,并将该反应混合物用水稀释。将沉淀物通过过滤收集,用水(250mL)洗涤并且在真空下进行干燥,以提供呈褐色固体的所希望的物质(120g,101%),将其不进行进一步纯化而使用。NMR谱:^{1}HNMR(400MHz,DMSO-d6)δ1.72-1.95(2H,m),2.59-2.80(2H,m),3.58(2H,td),3.98-4.11(2H,m),4.75-5.04(1H,m),7.75(1H,dd),7.97(1H,d),8.43(1H,s),8.71(1H,s),11.71(1H,s)。质谱:m/z(ES+)[M+H]+=348。

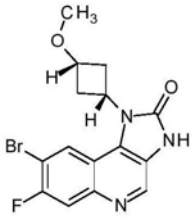
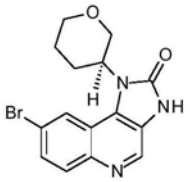
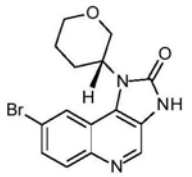
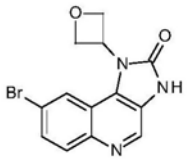
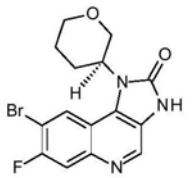
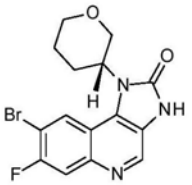
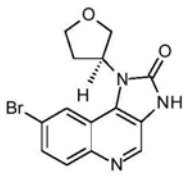
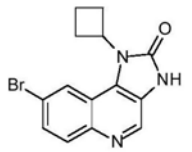
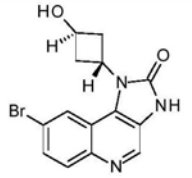
[0660] 以更大的规模,将6-溴-4-(氧杂环己烷-4-基氨基)喹啉-3-甲酸(2011g(2005g有活性),5.71mol)添加至具有DMF(18.2L)的容器中。添加三乙胺(4.7L,33.72mol),观察到从21℃-18℃的吸热。经10分钟添加叠氮磷酸二苯酯(1600mL,7.42mol),随着添加观察到从21℃至23℃的放热。放热继续,其中该批次在1h后达到55℃(夹套保持在30℃),伴随气体逸出。反应起初变为溶液,其中沉淀物然后在约30分钟后形成。一旦温度已经稳定,则通过HPLC分析该批次,示出起始物质的消耗和99%产物。将该批次加热至60℃持续h,HPLC再次指示起始物质的消耗和98%产物。在真空中浓缩该批次至最小体积(约3个体积),并且将残余物添加至水(17L)中,用再一部分的水(10L)冲洗。将混合物浆化1h,并且过滤,用水(2x 17L)洗涤。然后将固体返回至容器中,并且在饱和$NaHCO_3$溶液(10L)和MeOH(495mL)中浆化1h。通过过滤将该固体收集,用水(2x 3.5L)洗涤,并然后在真空中在40℃下烘箱干燥116h以获得2023g所希望的物质。分析数据与针对先前批次获得的是一致的。

[0661] 以类似方式从适当的羧酸中间体制备以下3H-咪唑并[4,5-c]喹啉-2-酮中间体:

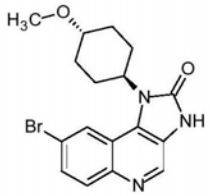
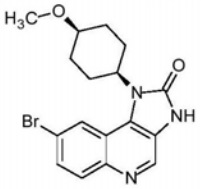
[0662]

中间体	结构	名称
中间体 E2		8-溴-1-(*顺式*-3-甲氧基环丁基)-3H-咪唑并[4,5-c]喹啉-2-酮

[0663]

中间体	结构	名称
中间体 F2		8-溴-7-氟-1-(顺式-3-甲氧基环丁基)-3H-咪唑并[4,5-c]喹啉-2-酮
中间体 G2*		8-溴-1-[(3*S*)-氧杂环己烷-3-基]-3H-咪唑并[4,5-c]喹啉-2-酮
中间体 H2*		8-溴-1-[(3*R*)-氧杂环己烷-3-基]-3H-咪唑并[4,5-c]喹啉-2-酮
中间体 I2*		8-溴-1-(氧杂环丁烷-3-基)-3H-咪唑并[4,5-c]喹啉-2-酮
中间体 J2*		8-溴-7-氟-1-[(3*S*)-氧杂环己烷-3-基]-3H-咪唑并[4,5-c]喹啉-2-酮
中间体 K2*		8-溴-7-氟-1-[(3*R*)-氧杂环己烷-3-基]-3H-咪唑并[4,5-c]喹啉-2-酮
中间体 L2**		8-溴-1-[(3*S*)-四氢呋喃-3-基]-3H-咪唑并[4,5-c]喹啉-2-酮
中间体 M2**		8-溴-1-环丁基-3H-咪唑并[4,5-c]喹啉-2-酮
中间体 N2*		8-溴-1-(反式-3-羟基环丁基)-3H-咪唑并[4,5-c]喹啉-2-酮

[0664]

中间体	结构	名称
中间体 O2*		8-溴-1-(反式-4-甲氧基环己基)-3H-咪唑并[4,5-c]喹啉-2-酮
中间体 P2*		8-溴-1-(顺式-4-甲氧基环己基)-3H-咪唑并[4,5-c]喹啉-2-酮
中间体 Q2**		8-溴-1-(3-羟基环己基)-3H-咪唑并[4,5-c]喹啉-2-酮(异构体的混合物)

[0665] *将该反应在60℃下搅拌60min-90min。

[0666] **将该反应在60℃下搅拌过夜。

[0667] 中间体E2:NMR谱:^{1}HNMR(400MHz,DMSO-d6)δ2.75-2.82(2H,m),2.9-3.05(2H,m),3.22(3H,s),3.80-3.90(1H,m),4.85-4.99(1H,m),7.71(1H,dd),7.94(1H,d),8.48(1H,d),8.69(1H,s),10.42(1H,s)。质谱:m/z(ES+)[M+H]+=348,350。

[0668] 中间体F2:NMR谱:^{1}H NMR(300MHz,$CDCl_3$)δ2.75(2H,m),2.95(2H,m),3.25(3H,s),3.85(1H,m),4.75(1H,m),8.00(1H,d),8.62-8.58(2H,t)。质谱:m/z(ES+)[M+H]+=366。

[0669] 中间体G2:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.84-2.11(3H,m),2.62-2.76(1H,m),3.35-3.44(1H,m),3.92-4.22(3H,m),4.71-4.80(1H,m),7.76(1H,dd),7.98(2H,d),8.32(1H,dd),8.71(1H,s),11.85(1H,bs)。质谱:m/z(ES+)[M+H]+=350。

[0670] 中间体H2:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.82-2.11(3H,m),2.61-2.75(1H,m),3.34-3.43(1H,m),3.91-4.21(3H,m),4.69-4.78(1H,m),7.75(1H,dd),7.99(2H,d),8.33(1H,dd),8.69(1H,s),11.70(1H,bs)。质谱:m/z(ES+)[M+H]+=350。

[0671] 中间体I2:NMR谱:^{1}H NMR(500MHz,DMSO-d6,100℃)δ4.98(2H,dd),5.19(2H,t),5.97-6.06(1H,m),7.74(1H,dd),7.96(1H,d),8.50(1H,d),8.71(1H,s),11.75(1H,s)。质谱:m/z(ES+)[M+H]+=321。

[0672] 中间体J2:NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ1.77-1.93(2H,m),2.10(1H,d),2.68(1H,qd),3.34-3.44(1H,m),3.94(1H,d),4.08(1H,dd),4.18(1H,t),4.75(1H,ddd),7.94(1H,d),8.48(1H,d),8.69(1H,s),11.63(1H,s)。质谱:m/z(ES+)[M+H]+=366,368。

[0673] 中间体K2:NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ1.7-1.93(2H,m),2.10(1H,d),2.63-2.75(1H,m),3.49-3.61(1H,m),3.84-4.03(1H,m),4.08(1H,dd),4.19(1H,t),4.76(1H,t),7.95(1H,d),8.49(1H,d),8.70(1H,s),11.66(1H,s)。质谱:m/z(ES+)[M+H]+=366,368。

[0674] 中间体L2:质谱:m/z(ES+)[M+H]+=334。

[0675] 中间体M2:质谱:m/z(ES+)[M+H]+=318。

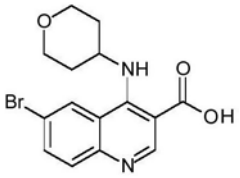
[0676] 中间体N2:NMR谱:^{1}H NMR(500MHz,DMSO-d6)δ2.32-2.44(2H,m),3.18-3.28(2H,m),4.45(1H,d),5.26(1H,d),5.42(1H,ddd),7.71(1H,dd),7.93(1H,d),8.29(1H,d),8.65(1H,s),11.56(1H,s)。质谱:m/z(ES+)[M+H]+=334,336。

[0677] 中间体O2:NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ1.41(2H,q),1.96(2H,d),2.17(2H,d),2.49(2H,d),3.23(1H,d),3.32(2H,s),4.65(1H,t),7.73(1H,dd),7.95(1H,d),8.32(1H,d),8.66(1H,s),11.58(1H,s)。质谱:m/z(ES+)[M+H]+=376。

[0678] 中间体P2:NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.73(4H,dd),2.30(2H,d),2.69(2H,s),3.59(3H,s),3.69(1H,s),4.99(1H,s),7.74(1H,dd),8.05(1H,d),8.88(1H,s),10.39(1H,s)。质谱:m/z(ES+)[M+H]+=376。

[0679] 中间体Q2:顺式和反式异构体(比率1:2,未指定的)的混合物NMR谱:^{1}HNMR(400MHz,DMSO-d6)δ1.09-1.34(2H,m),1.35-1.58(2H,m),1.58-1.79(1H,m),1.78-2.07(6H,m),2.07-2.47(4H,m),3.01-3.15(1H,m),3.51-3.73(1H,m),4.19(1H,s),4.53-4.77(1H,m),4.8-4.96(2H,m),5.03(1H,s),7.74(2H,2x d),7.97(2H,2x d),8.31(1H,s),8.55(1H,s),8.66(1H,s),8.68(1H,s),11.56(1H,s),11.62(1H,s)。质谱:m/z(ES+)[M+H]+=362。

[0680] 中间体D3:6-溴-4-(氧杂环己烷-4-基氨基)喹啉-3-甲酸

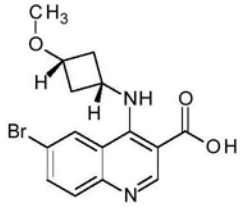
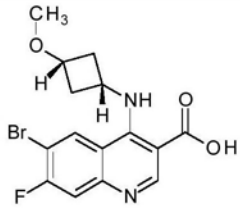
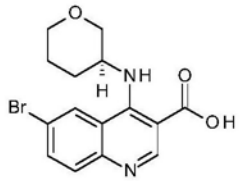
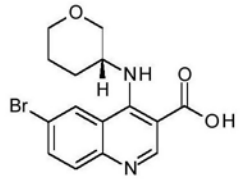
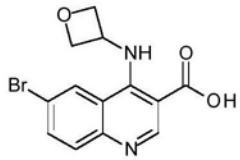
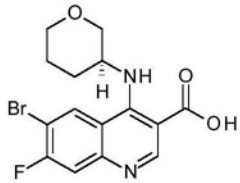
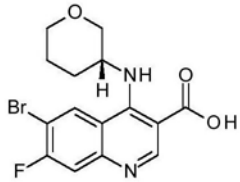
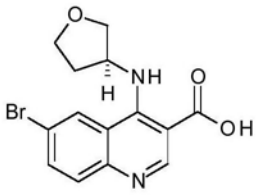
[0681] 

[0682] 在环境温度且在空气下,将氢氧化钠(79g,1977.60mmol)在水(1500mL)中的溶液添加至6-溴-4-(氧杂环己烷-4-基氨基)喹啉-3-甲酸乙酯(150g,395.52mmol)在MeOH(1500mL)中的搅拌混合物里。将所得混合物在70℃下搅拌2h,然后将溶剂在减压下去除。将反应混合物用2M盐酸调节至pH=3。将沉淀物通过过滤收集,用水(500mL)洗涤并且在真空下进行干燥,以提供呈白色固体的所希望的物质(120g,86%),将其不进行进一步纯化而使用。NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ1.75-1.82(2H,m),2.05-2.09(2H,m),3.85-3.94(5H,m),7.95(1H,d),8.18(1H,d),8.65(1H,s),9.01(1H,s)。质谱:m/z(ES+)[M+H]+=351.1。

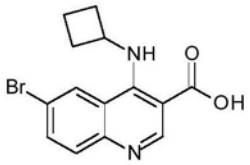
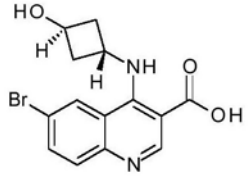
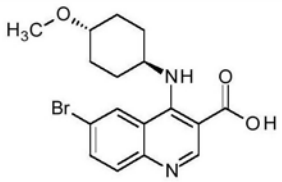
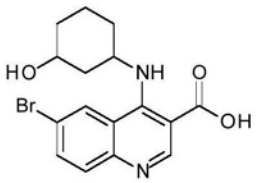
[0683] 以更大的规模,将6-溴-4-(氧杂环己烷-4-基氨基)喹啉-3-甲酸乙酯(1925g,5.08mol)填装到具有EtOH(12.5L)的容器中。然后添加2M NaOH(12.5L,25.03mol),随着20分钟添加伴随从22℃-35℃的放热。将该批次加热至70℃-80℃持续17h,在此时HPLC指示98.3%产物以及<1%的起始物质。将该批次在真空中浓缩以去除EtOH,并且返回至容器。然后添加2M HCl溶液(13L),直到获得pH 5-6,将批次温度保持在低于50℃。随着40分钟添加观察到从20℃-32℃的放热。在20℃-25℃将形成的沉淀物浆化1.5h,之后过滤,用水(3x 7L)洗涤直到pH呈中性。将收集的固体在真空下在70℃干燥,以给出1794g的所希望的物质。分析数据与针对先前批次获得的是一致的。

[0684] 以类似方式从适当的酯前体制备以下羧酸中间体:

[0685]

中间体	结构	名称
中间体 E3*		6-溴-4-[(*顺式*-3-甲氧基环丁基)氨基]喹啉-3-甲酸
中间体 F3		6-溴-7-氟-4-[(*顺式*-3-甲氧基环丁基)氨基]喹啉-3-甲酸
中间体 G3 **		6-溴-4-[[(3*S*)-氧杂环己烷-3-基]氨基]喹啉-3-甲酸
中间体 H3 **		6-溴-4-[[(3*R*)-氧杂环己烷-3-基]氨基]喹啉-3-甲酸
中间体 I3 ***		6-溴-4-(氧杂环丁烷-3-基氨基)喹啉-3-甲酸
中间体 J3***		6-溴-7-氟-4-[[(3*S*)-四氢吡喃-3-基]氨基]喹啉-3-甲酸
中间体 K3***		6-溴-7-氟-4-[[(3*R*)-四氢吡喃-3-基]氨基]喹啉-3-甲酸
中间体 L3***		6-溴-4-[[(3*S*)-四氢呋喃-3-基]氨基]喹啉-3-甲酸

[0686]

中间体	结构	名称
中间体 M3***		6-溴-4-(环丁基氨基)喹啉-3-甲酸
中间体 N3***		6-溴-4-[(反式-3-羟基环丁基)氨基]喹啉-3-甲酸
中间体 O3***		6-溴-4-[(反式-4-甲氧基环己基)氨基]喹啉-3-甲酸
中间体 P3***		6-溴-4-[(顺式-4-甲氧基环己基)氨基]喹啉-3-甲酸
中间体 Q3***		6-溴-4-[(3-羟基环己基)氨基]喹啉-3-甲酸（异构体的混合物）

[0687] *使用THF、MeOH和水的混合物作为溶剂进行该反应。

[0688] **将该反应在60℃-70℃之间搅拌1h-3h。

[0689] ***使用THF和水的混合物作为溶剂进行该反应，并且在60℃下加热3h-16h。

[0690] 中间体E3：质谱：m/z(ES+)[M+H]+＝351。

[0691] 中间体F3：NMR谱：^{1}H NMR(400MHz,DMSO-d6)δ1.98-1.91(2H,m),2.88-2.84(2H,m),3.17(1H,s),3.77-3.70(1H,t),4.22-4.19(1H,t),7.73(1H,d),8.44(1H,d),8.88(1H,s),13.27(1H,s)。质谱：m/z(ES+)[M+H]+＝369。

[0692] 中间体G3：NMR谱：^{1}HNMR(300MHz,DMSO-d6)δ1.50-1.57(1H,m),1.61-1.82(2H,m),1.98-2.13(1H,m),3.48-3.72(3H,m),3.89(1H,d),4.15-4.26(1H,m),7.77(1H,dd),7.95(1H,d),8.31(1H,d),8.90(1H,s),13.38(1H,bs)。质谱：m/z(ES+)[M+H]+＝351。

[0693] 中间体H3：NMR谱：^{1}HNMR(300MHz,DMSO-d6)δ1.50-1.56(1H,m),1.62-1.83(2H,m),1.99-2.12(1H,m),3.50-3.71(3H,m),3.89(1H,d),4.16-4.28(1H,m),7.78(1H,dd),7.94(1H,d),8.30(1H,d),8.94(1H,s),13.50(1H,bs)。质谱：m/z(ES+)[M+H]+＝351。

[0694] 中间体I3：NMR谱：^{1}H NMR(500MHz,DMSO-d_6)δ4.62(2H,t),4.91(2H,t),5.02-5.13(1H,m),7.78(1H,d),7.90(1H,dd),8.15(1H,s)。质谱：m/z(ES+)[M+H]+＝321。

[0695] 中间体J3：NMR谱：^{1}H NMR(300MHz,DMSO-d6)δ1.51(1H,m),1.74(2H,m),2.04(1H,

m),3.60(3H,m),3.82(1H,d),4.15(1H,m),7.73(1H,m),8.44(1H,m),8.92(1H,s)。质谱:m/z(ES+)[M+H]+=369。

[0696] 中间体K3:质谱:m/z(ES+)[M+H]+=369。

[0697] 中间体L3:NMR谱:^{1}H NMR(400MHz,DMSO-d_6)δ1.95-2.05(1H,m),2.31-2.41(1H,m),3.79-3.87(2H,m),3.89-3.95(2H,m),4.82-4.92(1H,m),7.78(1H,d),7.92-7.94(1H,m),8.44(1H,d),8.90(1H,s),13.3(1H,s)。质谱:m/z(ES+)[M+H]+=337。

[0698] 中间体M3:NMR谱:^{1}H NMR(400MHz,DMSO-d_6)δ1.81-1.95(3H,m),2.01-2.15(3H,m),4.53-4.55(1H,m),7.74(1H,d),7.88(1H,d),8.25(1H,s),8.89(1H,s),13.27(1H,s)。质谱:m/z(ES+)[M+H]+=321。

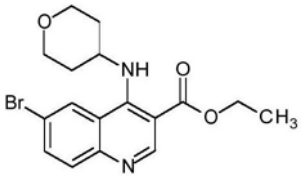
[0699] 中间体N3:NMR谱:^{1}HNMR(500MHz,DMSO-d_6)δ2.27-2.46(4H,m),4.36(1H,s),4.71(1H,d),5.28(1H,s),7.75(1H,d),7.92(1H,dd),8.22(1H,dd),8.85(1H,s)。质谱:m/z(ES+)[M+H]+=337。

[0700] 中间体O3:质谱:m/z(ES+)[M+H]+=379。

[0701] 中间体P3:NMR谱:^{1}HNMR(400MHz,DMSO-d6)δ1.66(2H,s),1.84(6H,s),3.27(3H,s),3.41(1H,s),7.96(1H,d),8.19(1H,d),9.02(1H,s)。质谱:m/z(ES+)[M+H]+=379。

[0702] 中间体Q3:顺式和反式异构体(比率1:2,未指定)的混合物NMR谱:^{1}HNMR(400MHz,DMSO-d6)δ1.09-1.25(2H,m),1.26-1.46(4H,m),1.48-1.66(2H,m),1.68-1.92(4H,m),1.92-2.10(3H,m),2.27(1H,d),3.49-3.64(2H,m),3.99(1H,s),4.10(2H,s),4.51(1H,s),4.72(1H,s),4.83(1H,s),7.84(2H,2x d),8.01(2H,2x d),8.42(1H,s),8.48(1H,s),8.91(2H,2x s)。质谱:m/z(ES+)[M+H]+=365。

[0703] 中间体D4:6-溴-4-(氧杂环己烷-4-基氨基)喹啉-3-甲酸乙酯

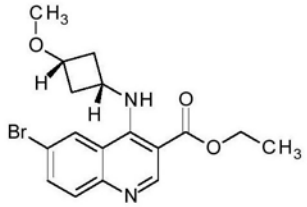
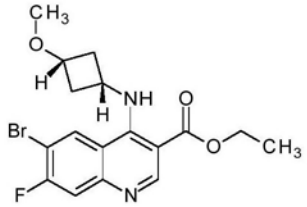
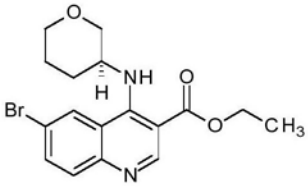
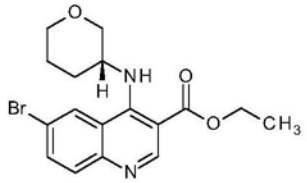
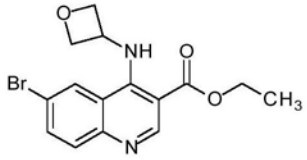
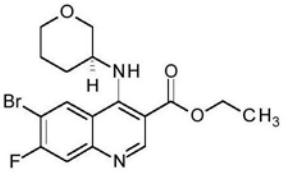
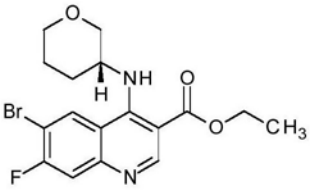
[0704] 

[0705] 在环境温度且在空气下,将DIPEA(139mL,794.75mmol)添加至在DMA(1000mL)中的6-溴-4-氯喹啉-3-甲酸乙酯(100g,317.90mmol)和四氢-2H-吡喃-4-胺(35.4g,349.69mmol)里。将所得的混合物在60℃下搅拌16h然后将溶剂在减压下去除。将混合物与甲苯共沸两次,以提供呈褐色固体的所希望的物质(150g,124%),将其不进行进一步纯化而使用。NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ1.36(3H,t),1.58-1.75(2H,m),1.90-2.02(2H,m),3.40(2H,t),3.81-3.98(2H,m),3.98-4.19(1H,m),4.37(2H,q),7.82(1H,d),7.92(1H,dd),8.56(1H,s),8.86(1H,s)。质谱:m/z(ES-)[M-H]-=378,380。

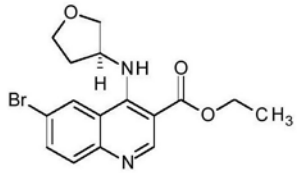
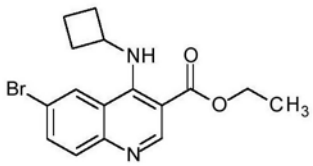
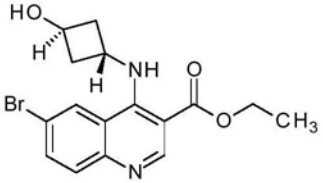
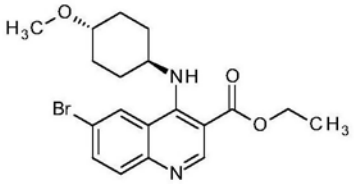
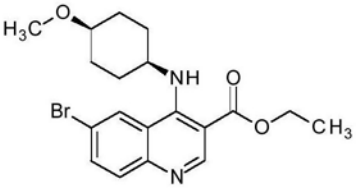
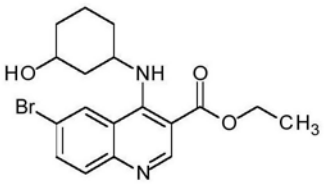
[0706] 以更大的规模,将6-溴-4-氯喹啉-3-甲酸乙酯(2196g(1976g有活性),6.28mol)填装到具有DMA(16L)的容器中。将四氢-2H-吡喃-4-胺(1224g,12.10mol)经10分钟添加,观察到21℃-27℃的放热。添加DIPEA(3.5L,20.09mol),没有观察到放热。将混合物加热至75℃-85℃,并且将所得溶液在80℃搅拌18.5h。HPLC指示起始物质的消耗和99.2%产物。将反应冷却至50℃,并且然后倾倒入水(50L)中。将所得悬浮液在环境温度下搅拌2h,并且通过过滤分离固体,用水洗涤(8L然后2x 4L)。将固体在真空下在40℃干燥55h,以给出2307g的所希望的物质。分析数据与针对先前批次获得的是一致的。

[0707] 以类似的方式从适当的胺以及6-溴-4-氯-7-氟喹啉-3-甲酸乙酯或6-溴-4-氯喹啉-3-甲酸乙酯制备以下酯中间体：

[0708]

中间体	结构	名称
中间体 E4*		6-溴-4-[(*顺式*-3-甲氧基环丁基)氨基]喹啉-3-甲酸乙酯
中间体 F4**		6-溴-7-氟-4-[(*顺式*-3-甲氧基环丁基)氨基]喹啉-3-甲酸乙酯
中间体 G4 ***		6-溴-4-[[(3*S*)-氧杂环己烷-3-基]氨基]喹啉-3-甲酸乙酯
中间体 H4 ***		6-溴-4-[[(3*R*)-氧杂环己烷-3-基]氨基]喹啉-3-甲酸乙酯
中间体 I4 ****		6-溴-4-(氧杂环丁烷-3-基氨基)喹啉-3-甲酸乙酯
中间体 J4***		6-溴-7-氟-4-[[(3*S*)-四氢吡喃-3-基]氨基]喹啉-3-甲酸乙酯
中间体 K4***		6-溴-7-氟-4-[[(3*R*)-四氢吡喃-3-基]氨基]喹啉-3-甲酸乙酯

[0709]

中间体	结构	名称
中间体 L4*****		6-溴-4-[[(3*S*)-四氢呋喃-3-基]氨基]喹啉-3-甲酸乙酯
中间体 M4		6-溴-4-(环丁基氨基)喹啉-3-甲酸乙酯
中间体 N4***		6-溴-4-[(反式-3-羟基环丁基)氨基]喹啉-3-甲酸乙酯
中间体 O4***		6-溴-4-[(反式-4-甲氧基环己基)氨基]喹啉-3-甲酸乙酯
中间体 P4***		6-溴-4-[(顺式-4-甲氧基环己基)氨基]喹啉-3-甲酸乙酯
中间体 Q4***		6-溴-4-[(3-羟基环己基)氨基]喹啉-3-甲酸乙酯（异构体的混合物）

[0710] *将该反应在75℃下搅拌5h。

[0711] **将反应在85℃下搅拌3h。

[0712] ***将反应在80℃下搅拌2h-16h。

[0713] ****将反应在90℃下搅拌1h-3h。

[0714] *****将该反应在100℃下搅拌16h,任选地使用Et_3N作为碱。

[0715] 中间体E4:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.38(3H,t),1.85-1.98(2H,m),2.75-7.89(2H,m),3.17(3H,s),3.65-3.78(1H,m),3.98-4.05(1H,m),4.35(2H,q),7.60(1H,d),7.70(1H,dd),8.40(1H,d),8.84-8.85(1H,m)。质谱:m/z(ES+)[M+H]+=379。

[0716] 中间体F4:NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.44-1.41(3H,t),2.21-2.14(2H,m),3.05-2.98(2H,m),3.30(3H,s),3.94-3.75(1H,m),4.11-4.06(1H,m),4.43-4.37(2H,d),7.70(1H,d),8.29(1H,d),9.07(1H,d),9.69(1H,s)。质谱:m/z(ES+)[M+H]+=397。

[0717] 中间体G4:NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ1.36(3H,t),1.70-1.74(1H,m),

1.75-1.77(2H,m),2.03-2.05(1H,m),3.58-3.61(3H,m),3.80-3.85(1H,m),4.01-4.03(1H,m),4.35(2H,q),7.80(1H,d),7.89(1H,dd),8.58(1H,s),8.67(1H,d),8.93(1H,s)。质谱:m/z(ES+)[M+H]+=380.8。

[0718] 中间体H4:NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ1.50-1.56(1H,m),1.62-1.84(2H,m),1.99-2.13(1H,m),3.51-3.73(3H,m),3.89(1H,d),4.12-4.22(1H,m),7.77(1H,d),7.90(1H,d),8.31(1H,s),8.94(1H,s),13.41(1H,bs)。质谱:m/z(ES+)[M+H]+=379。

[0719] 中间体I4:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.34(3H,t),4.34(2H,q),4.62-4.68(2H,m),4.77(1H,q),4.86(2H,t),7.78(1H,d),7.85(1H,ddd),8.42(1H,d),8.73(1H,d),8.79(1H,s)。质谱:m/z(ES+)[M+H]+=353。

[0720] 中间体J4:NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ1.33(3H,m),1.51(1H,m),1.74(2H,m),2.04(1H,m),3.60(3H,m),3.82(1H,d),4.02(1H,m),4.35(2H,m),7.73(1H,m),8.49(1H,m),8.79(1H,m),8.88(1H,s)。质谱:m/z(ES+)[M+H]+=397。

[0721] 中间体K4:质谱:m/z(ES+)[M+H]+=397。

[0722] 中间体L4:NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.45(3H,t),2.12-2.19(1H,m),2.48-2.55(1H,m),3.87-4.04(2H,m),4.12(2H,td),4.43(2H,q),4.76-4.86(1H,m),7.80(1H,dd),7.95(1H,d),8.34(1H,d),9.14(1H,s),9.64(1H,s)。质谱:m/z(ES+)[M+H]+=365。

[0723] 中间体M4:NMR谱:^{1}HNMR(400MHz,$CDCl_3$)δ1.45(3H,t),1.77-2.01(2H,m),2.16-2.31(2H,m),2.58-2.71(2H,m),4.45(3H,m),7.74(1H,dd),7.82(1H,d),8.23(1H,d),9.09(1H,s),9.57(1H,d)质谱:m/z(ES+)[M+H]+=349。

[0724] 中间体N4:NMR谱:^{1}HNMR(500MHz,DMSO-d6)δ1.34(3H,t),2.34(4H,t),4.33(3H,q),4.56(1H,q),5.21(1H,d),7.75(1H,d),7.85(1H,dd),8.31(1H,d),8.85(1H,s),9.13(1H,d)。质谱:m/z(ES+)[M+H]+=366。

[0725] 中间体O4:NMR谱:^{1}HNMR(400MHz,$CDCl_3$)δ1.40-1.59(1H,4H),1.45(3H,t),2.08-2.18(2H,m),2.18-2.27(2H,m),3.23-3.34(1H,m),3.39(3H,s),3.99-4.05(1H,m),4.41(2H,q),7.75(1H,dd),7.83(1H,d),8.27(1H,d),9.08(1H,d),9.12(1H,s)质谱:m/z(ES+)[M+H]+=407。

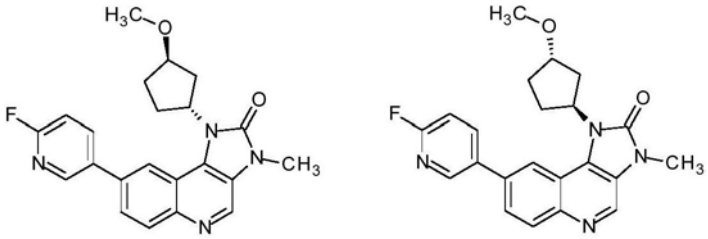
[0726] 中间体P4:NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ1.35(3H,t),1.54-1.61(2H,m),1.63-1.83(6H,m),3.24(3H,s),3.96(1H,d),4.35(2H,q),7.78(1H,d),7.87(1H,dd),8.44(1H,d),8.61(1H,d),8.87(1H,s)。质谱:m/z(ES+)[M+H]+=407。

[0727] 中间体Q4:顺式和反式异构体(比率1:2,未指定的)的混合物NMR谱:^{1}HNMR(400MHz,DMSO-d6)δ1.06-1.2(2H,m),1.21-1.42(10H,m),1.42-1.61(2H,m),1.63-1.86(4H,m),1.87-2.01(2H,m),2.20(1H,d),3.39-3.57(2H,m),3.71-3.87(1H,m),3.95(1H,s),4.22-4.48(5H,m),4.61(1H,s),4.79(1H,s),7.77(1H,s),7.80(1H,s),7.84-7.90(2H,m),8.35(1H,d),8.42(2H,2x d),8.69(1H,d),8.84(1H,s),8.88(1H,s)。质谱:m/z(ES+)[M+H]+=393。

[0728] 8-(6-氟-3-吡啶基)-1-[(1R,3R)-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮:8-(6-氟-3-吡啶基)-1-[(1S,3S)-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮(1:1混合物)的制备描述如下:

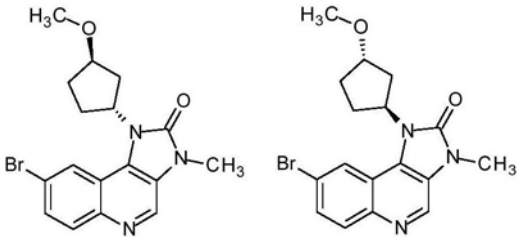
[0729] 中间体U0:8-(6-氟-3-吡啶基)-1-[(1R,3R)-3-甲氧基环戊基]-3-甲基-咪唑并

[4,5-c]喹啉-2-酮:8-(6-氟-3-吡啶基)-1-[(1S,3S)-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮(1:1混合物)

[0730] 

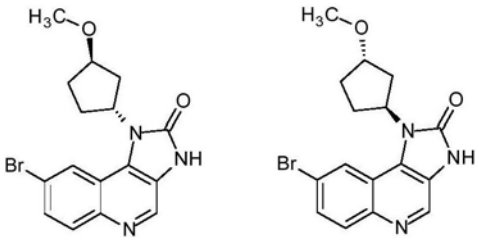
[0731] 将8-溴-1-[(1R,3R)-3-甲氧基环戊基]-3-甲基咪唑并[4,5-c]喹啉-2-酮:8-溴-1-[(1S,3S)-3-甲氧基环戊基]-3-甲基咪唑并[4,5-c]喹啉-2-酮(1:1混合物)(1.5g,3.99mmol)、(6-氟吡啶-3-基)硼酸(0.674g,4.78mmol)和氯(2-二环己基膦基-2',4',6'-三异丙基-1,1'-联苯)[2-(2'-氨基-1,1'-联苯)]钯(II)(0.314g,0.40mmol)在二噁烷:水(10:1混合物)(16.5mL)中的混合物在微波反应器中加热至120℃保持45min,然后允许冷却并且在真空中浓缩。将粗产物通过FCC纯化,洗脱梯度为在DCM中的0至10%MeOH,以提供呈黄色固体的所希望的物质(1.20g,77%)。NMR谱:^{1}H NMR(400MHz,$CDCl_3$)δ1.91-1.99(1H,m),2.21-2.36(3H,m),2.58-2.78(2H,m),3.38(3H,s),3.62(3H,s),4.15-4.17(1H,m),5.52-5.65(1H,m),7.12(1H,dd),7.83(1H,dd),8.13(1H,td),8.31(1H,d),8.40(1H,d),8.59(1H,d),8.76(1H,s)。质谱:m/z(ES+)[M+H]+=393。

[0732] 中间体U1:8-溴-1-[(1R,3R)-3-甲氧基环戊基]-3-甲基咪唑并[4,5-c]喹啉-2-酮:8-溴-1-[(1S,3S)-3-甲氧基环戊基]-3-甲基咪唑并[4,5-c]喹啉-2-酮(1:1混合物)

[0733] 

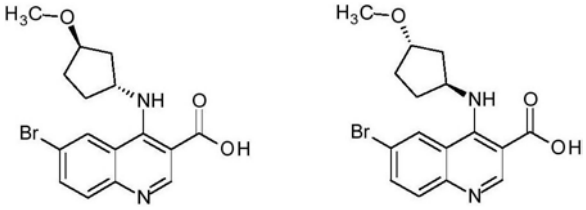
[0734] 在环境温度下,将6-溴-4-[[(1R,3R)-3-甲氧基环戊基]氨基]喹啉-3-甲酸:6-溴-4-[[(1S,3S)-3-甲氧基环戊基]氨基]喹啉-3-甲酸(1:1混合物)(13g,35.8mmol)、四丁基溴化铵(1.16g,3.60mmol)、碘甲烷(7.645g,53.86mmol)和氢氧化钠(2.15g,53.75mmol)于DCM(600mL)和水(380mL)中的混合物搅拌过夜。将所得溶液在真空下浓缩,以去除有机物,并且将固体通过过滤收集,用水(5x 10mL)洗涤,并且在真空烘箱中干燥,以提供呈灰白色固体的所希望的物质(外消旋混合物)(9.8g,73%)。NMR谱:^{1}H NMR(400MHz,DMSO-d6)δ1.81-1.87(1H,m),2.33-2.51(4H,m),2.45-2.51(1H,m),3.28(3H,s),3.49(3H,s),4.02-4.21(1H,m),5.40(1H,p),7.73(1H,dd),7.98(1H,d),8.35(1H,d),8.91(1H,s)。质谱:m/z(ES+)[M+H]+=375.9。

[0735] 中间体U2:8-溴-1-[(1R,3R)-3-甲氧基环戊基]-3H-咪唑并[4,5-c]喹啉-2-酮:8-溴-1-[(1S,3S)-3-甲氧基环戊基]-3H-咪唑并[4,5-c]喹啉-2-酮(1:1混合物)

[0736] 

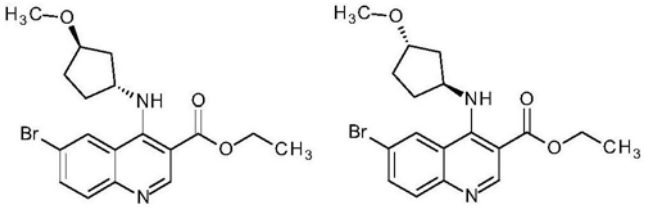
[0737] 在环境温度下，将6-溴-4-[[(1R,3R)-3-甲氧基环戊基]氨基]喹啉-3-甲酸:6-溴-4-[[(1S,3S)-3-甲氧基环戊基]氨基]喹啉-3-甲酸(1:1混合物)(17g,46.54mmol)，三乙胺(14.1g,139.34mmol)在DMF(270mL)中的混合物搅拌1h。将叠氮磷酸二苯酯(25.6g,93.02mmol)逐滴添加伴随搅拌，并且将该溶液在环境温度下再搅拌20分钟，然后加热至60℃保持1h。允许该反应冷却并在真空下浓缩。将残余物用水(300mL)稀释，将固体通过过滤收集，并且在烘箱中在减压下进行干燥，以提供呈灰白色固体的所希望的物质(作为外消旋混合物)(13g,77％)。质谱:m/z(ES+)[M+H]+＝362.2。

[0738] 中间体U3:6-溴-4-[[(1R,3R)-3-甲氧基环戊基]氨基]喹啉-3-甲酸:6-溴-4-[[(1S,3S)-3-甲氧基环戊基]氨基]喹啉-3-甲酸(1:1混合物)

[0739] 

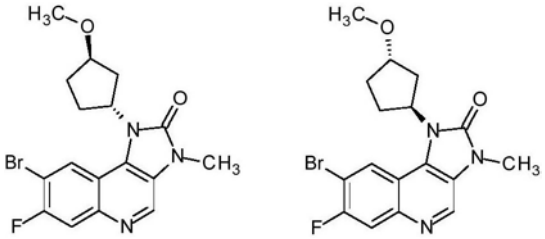
[0740] 将2N氢氧化钠(150mL)添加至6-溴-4-[[(1R,3R)-3-甲氧基环戊基]氨基]喹啉-3-甲酸乙酯:6-溴-4-[[(1S,3S)-3-甲氧基环戊基]氨基]喹啉-3-甲酸乙酯(1:1混合物)(18.6g,47.2mmol)于MeOH(500mL)和水(100mL)中的混合物中，并且将所得溶液在环境温度搅拌15h。将该混合物在真空下浓缩，并且将残余物用水(300mL)稀释。用2N盐酸将溶液的pH值调节至5，将固体通过过滤收集并且在烘箱中在减压下干燥，以提供呈灰白色固体的所希望的物质(作为外消旋混合物)(17.1g)。NMR谱:^{1}HNMR(400MHz,DMSO-d6)δ1.60-1.71(2H,m),1.81-1.88(1H,m),1.96-2.02(1H,m),2.03-2.10(2H,m),3.21(3H,s),3.91-3.96(1H,m),4.51-4.72(1H,m),7.77(1H,d),7.93(1H,d),8.45(1H,d),8.85(1H,s),13.30(1H,bs)。质谱:m/z(ES+)[M+H]+＝365.2。

[0741] 中间体U4:6-溴-4-[[(1R,3R)-3-甲氧基环戊基]氨基]喹啉-3-甲酸乙酯:6-溴-4-[[(1S,3S)-3-甲氧基环戊基]氨基]喹啉-3-甲酸乙酯(1:1混合物)

[0742] 

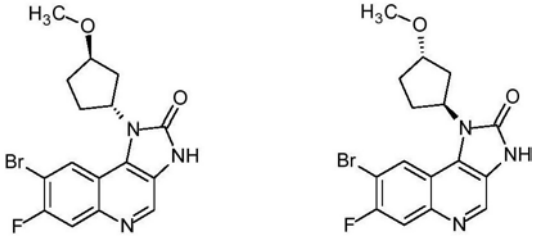
[0743] 在惰性气氛下，将6-溴-4-氯喹啉-3-甲酸乙酯(15g,47.69mmol)、(反式)-3-甲氧基环戊-1-胺(外消旋混合物)(8.09g,26.68mmol)和DIPEA(19.68g,152.27mmol)在DMA(100mL)中的混合物在80℃下搅拌4h。将反应通过添加水(500mL)淬灭，将固体通过过滤收集，并且在烘箱中在减压下进行干燥，以提供呈浅褐色固体的所希望的物质(作为外消旋混合物)(18.6g)。质谱:m/z(ES+)[M+H]+＝393,395。

[0744] 中间体V1:8-溴-7-氟-1-[(1R,3R)-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮和8-溴-7-氟-1-[(1S,3S)-3-甲氧基环戊基]-3-甲基-咪唑并[4,5-c]喹啉-2-酮(1:1混合物)

[0745] 

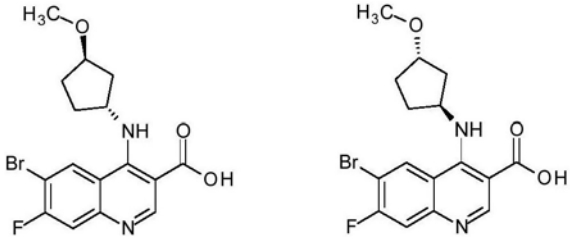
[0746] 在环境温度下,将8-溴-7-氟-1-[(1R,3R)-3-甲氧基环戊基]-3H-咪唑并[4,5-c]喹啉-2-酮:8-溴-7-氟-1-[(1S,3S)-3-甲氧基环戊基]-3H-咪唑并[4,5-c]喹啉-2-酮(1:1混合物)(2.8g,7.33mmol)、氢氧化钠(440mg,11.00mmol)、四丁基溴化铵(240mg,0.75mmol)和碘甲烷(1.6g,11.27mmol)在DCM(150mL)和水(100mL)中的混合物搅拌12h。将所得混合物在真空中浓缩,并且将残余物用水研磨。将固体通过过滤收集,并且进行干燥,以提供呈白色固体的所希望的物质(2.5g,86%)。NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ1.76-1.86(1H,m),2.11-2.32(4H,m),2.41-2.44(1H,m),3.27(3H,s),3.30(3H,s),4.12-4.15(1H,m),5.38-5.45(1H,m),7.96(1H,d),8.53(1H,d),8.94(1H,s)。质谱:m/z(ES+)[M+H]+=394。

[0747] 中间体V2:8-溴-7-氟-1-[(1R,3R)-3-甲氧基环戊基]-3H-咪唑并[4,5-c]喹啉-2-酮和8-溴-7-氟-1-[(1S,3S)-3-甲氧基环戊基]-3H-咪唑并[4,5-c]喹啉-2-酮(1:1混合物)

[0748] 

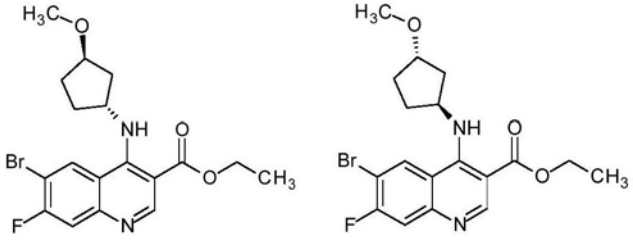
[0749] 在环境温度下,将6-溴-7-氟-4-[[(1R,3R)-3-甲氧基环戊基]氨基]喹啉-3-甲酸:6-溴-7-氟-4-[[(1S,3S)-3-甲氧基环戊基]氨基]喹啉-3-甲酸(1:1混合物)(2.9g,7.53mmol)和三乙胺(2.3g,22.73mmol)在DMA(20mL)中的混合物搅拌30min。添加叠氮磷酸二苯酯(2.5g,9.09mmol),并且将所得溶液在60℃搅拌2h。允许反应混合物冷却,并且将固体通过过滤收集。将固体在烘箱中在减压下干燥,以提供呈白色固体的所希望的物质(2.8g,97%)。NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.78-1.88(1H,m),2.11-2.31(4H,m),2.41-2.45(1H,m),3.27(3H,s),4.08-4.15(1H,m),5.34-5.39(1H,m),7.92(1H,d),8.51(1H,d),8.68(1H,s)。质谱:m/z(ES+)[M+H]+=380。

[0750] 中间体V3:6-溴-7-氟-4-[[(1R,3R)-3-甲氧基环戊基]氨基]喹啉-3-甲酸和6-溴-7-氟-4-[[(1S,3S)-3-甲氧基环戊基]氨基]喹啉-3-甲酸(1:1混合物)

[0751] 

[0752] 在环境温度下，将6-溴-7-氟-4-[[(1R,3R)-3-甲氧基环戊基]氨基]喹啉-3-甲酸乙酯:6-溴-7-氟-4-[[(1S,3S)-3-甲氧基环戊基]氨基]喹啉-3-甲酸乙酯(1:1混合物)(3.4g,8.23mmol)和2N氢氧化钠(12mL)在MeOH(15mL)和THF(15mL)中的混合物搅拌12h。将溶液的pH用1M HCl调节至3，并且将所得固体通过过滤收集，并且干燥，以提供呈白色固体的所希望的物质(2.9g,91％)。NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ1.61-1.71(2H,m),1.76-1.86(1H,m),1.92-2.03(1H,m),2.11-2.26(2H,m),3.21(3H,s),3.86-3.96(1H,m),4.56-4.64(1H,m),7.70(1H,d),8.56(1H,d),8.88(1H,s),13.31(1H,s)。质谱:m/z(ES+)[M+H]+＝383。

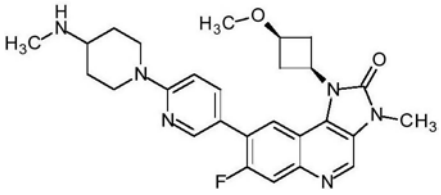
[0753] 中间体V4:6-溴-7-氟-4-[[(1R,3R)-3-甲氧基环戊基]氨基]喹啉-3-甲酸乙酯和6-溴-7-氟-4-[[(1S,3S)-3-甲氧基环戊基]氨基]喹啉-3-甲酸乙酯(1:1混合物)

[0754] 

[0755] 将6-溴-4-氯-7-氟喹啉-3-甲酸乙酯(2g,6.01mmol)、(1R,3R)-3-甲氧基环戊胺盐酸盐和(1S,3S)-3-甲氧基环戊胺盐酸盐(1:1混合物)(1.4g,9.21mmol)和DIPEA(1.6g,12.38mmol)于DMA(10mL)中的混合物在80℃搅拌2h。允许反应混合物冷却，并且将残余物用水研磨。将固体通过过滤收集，并且进行干燥，以提供呈白色固体的所希望的物质(2.4g,97％)。质谱:m/z(ES+)[M+H]+＝411。

[0756] 实例57

[0757] 7-氟-1-(顺式-3-甲氧基环丁基)-3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]咪唑并[4,5-c]喹啉-2-酮

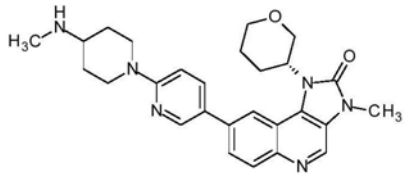
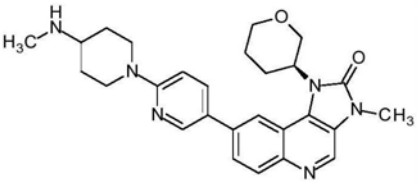
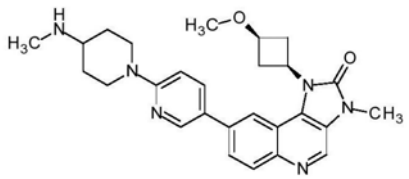
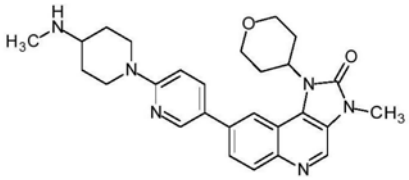
[0758] 

[0759] 在130℃下，将7-氟-8-(6-氟-3-吡啶基)-1-(顺式-3-甲氧基环丁基)-3-甲基-咪唑并[4,5-c]喹啉-2-酮(120mg,0.30mmol)、叔-丁基甲基(哌啶-4-基)氨基甲酸酯二盐酸化物(130mg,0.45mmol)和DIPEA(0.106mL,0.61mmol)在DMSO(2mL)中的混合物搅拌5h。将粗产物3-叔-丁基-1-[1-[5-[7-氟-1-(3-甲氧基环丁基)-3-甲基-2-氧代-咪唑并[4,5-c]喹啉-8-基]-2-吡啶基]-4-哌啶基]-1-甲基-脲通过快速C18色谱法进行纯化，洗脱梯度为在(0.1％FA)水中5％至45％MeCN，并且将适合的级分合并，并且在真空中浓缩。将残余物用在DCM(3.0mL)中的TFA(2mL,25.96mmol)处理，并且将该混合物在环境温度下搅拌12h。将溶剂在减压下去除，并且将该粗产物通过制备型HPLC(Waters XBridge Prep C18OBD柱,5μm二氧化硅,19mm直径,100mm长度)进行纯化，使用水(含有0.1％氨)和MeCN的极性递减混合物作为洗脱液，以提供呈黄色固体的所希望的物质(40.0mg,26.9％)。NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ1.30-1.50(2H,m),1.90-2.10(2H,m),2.45(3H,s),2.72-2.88(2H,m),2.88-3.05

(5H,m),3.15(3H,s),3.45(3H,s),3.75-3.90(1H,m),4.32-4.45(2H,m),4.95-5.15(1H,m),7.02(1H,s),7.80-7.92(2H,m),8.25-8.30(1H,d),8.35(1H,s),8.25-8.40(1H,m),8.85(1H,s)。质谱:m/z(ES+)[M+H]+=491。

[0760] 以类似方式从适当的中间体制备以下实例。

[0761]

实例	结构	名称
58*		3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(3*R*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
59*		3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]-1-[(3*S*)-四氢吡喃-3-基]咪唑并[4,5-c]喹啉-2-酮
60**		1-(*顺式*-3-甲氧基环丁基)-3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]咪唑并[4,5-c]喹啉-2-酮
61**		3-甲基-8-[6-[4-(甲基氨基)-1-哌啶基]-3-吡啶基]-1-四氢吡喃-4-基-咪唑并[4,5-c]喹啉-2-酮

[0762] *将置换反应在130℃下进行16h,并且将脱保护反应在环境温度下进行30分钟。

[0763] **将置换反应在130℃下进行3h-5h,并且将脱保护反应在环境温度下进行1h。

[0764] 实例58:NMR谱:^{1}H NMR(300MHz,DMSO-d6)δ1.42(2H,m),1.82(2H,m),2.01(2H,d),2.15(1H,d),2.50(3H,s),2.70(1H,m),2.95(2H,t),3.10(1H,m),3.40(1H,m),3.48(3H,s),3.92(1H,d),4.18(2H,m),4.45(2H,d),4.93(1H,bs),7.06(1H,d),7.90-8.89(7H,m)。质谱:m/z(ES+)[M+H]+=473。

[0765] 实例59:NMR谱:^{1}H NMR(300MHz,MeOH-d4)δ1.65(2H,q),1.95(2H,m),2.25(3H,m),2.76(3H,s),2.85(1H,m),3.12(2H,t),3.40(1H,m),3.60(4H,m),4.05(1H,d),4.22(1H,d),4.40(1H,t),4.60(2H,d),5.19(1H,bs),7.20(1H,d),8.15(1H,d),8.27(2H,s),8.60(2H,d),9.10(1H,s)。质谱:m/z(ES+)[M+H]+=473。

[0766] 实例60:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.10-1.30(2H,m),1.87-1.91(2H,m),2.32(3H,s),2.49-2.63(1H,m),2.77-2.85(2H,m),2.95-3.05(4H,m),3.20(3H,s),3.49(3H,s),3.84-3.89(1H,m),4.25-4.29(2H,m),5.08-5.14(1H,m),6.98(1H,d),7.87-7.91(1H,m),8.01-8.08(2H,m),8.36(1H,d),8.64(1H,d),8.83(1H,s)。质谱:m/z(ES+)[M+H]+=473。

[0767] 实例61:NMR谱:^{1}HNMR(300MHz,DMSO-d6)δ1.20-1.24(2H,m),1.85-1.93(4H,m),2.30(3H,s),2.49-2.54(1H,m),2.69-2.74(2H,m),2.97-3.06(2H,m),3.32(3H,s),3.54-3.62(2H,m),4.05-4.10(2H,m),4.23-4.27(2H,m),5.00-5.13(1H,m),6.99(1H,d),7.91-

7.94(1H,m),7.98-8.02(1H,m),8.08-8.11(1H,m),8.37(1H,s),8.62(1H,d),8.85(1H,s)。质谱:m/z(ES+)[M+H]+=473。

[0768] 生物学测定

[0769] 以下测定用于测量本发明的这些化合物的效果:a)ATM细胞效价测定;b)PI3K细胞效价测定;c)mTOR细胞效价测定;d)ATR细胞效价测定。在测定的描述中,通常:

[0770] i.使用以下缩写:4NQO=4-硝基喹啉N-氧化物;Ab=抗体;BSA=牛血清白蛋白;CO_2=二氧化碳;DMEM=杜氏改良的伊格尔氏培养基;DMSO=二甲基亚砜;EDTA=乙二胺四乙酸;EGTA=乙二醇四乙酸;ELISA=酶联免疫吸附测定;EMEM=伊格尔氏最小必需培养基;FBS=胎牛血清;h=H(s);HRP=辣根过氧化物酶;i.p.=腹膜内;PBS=磷酸盐缓冲盐水;PBST=磷酸盐缓冲盐水/吐温;TRIS=三(羟基甲基)氨基甲烷;MTS试剂:[3-(4,5-二甲基噻唑-2-基)-5-(3-羧基甲氧基苯基)-2-(4-磺基苯基)-2H-四氮唑,内盐,以及电子偶联剂(吩嗪硫酸甲酯)PMS;s.c.皮下。

[0771] ii.使用Genedata智能拟合模型计算IC_{50}值。IC_{50}值是抑制50%生物活性的测试化合物的浓度。

[0772] 测定a):ATM细胞效价

[0773] 基本原理:

[0774] 细胞辐照诱导DNA双链断裂和丝氨酸1981的快速分子间自磷酸化,这导致二聚体解离并引发细胞ATM激酶活性。在辐照剂量低至0.5Gy后,细胞中的大多数ATM分子在此位点上快速磷酸化,并且磷酸特异性抗体的结合是在细胞中引入只有少数DNA双链断裂后可检测的。

[0775] pATM测定的基本原理是识别细胞中ATM的抑制剂。先于X射线辐照,将HT29细胞用测试化合物孵育1h。1h后,将这些细胞固定并用pATM(Ser1981)染色。在测定扫描成像平台上读取荧光。

[0776] 方法细节:

[0777] 将HT29细胞(ECACC#85061109)以3500个细胞/孔的密度接种于384孔测定板(科斯塔(Costar)#3712)中包含1%L谷氨酰胺和10%FBS的40μl EMEM培养基中且允许其粘附过夜。次日早晨通过声学分配将在100%DMSO中的具有式(I)的化合物添加至测定板中。在37℃下和5%CO_2下孵育1h后,使用相当于约600cGy的X-RAD 320仪器(PXi)对这些板(多至一次6个)进行辐照。将板返回孵育箱中再孵育1h。然后将这些细胞通过添加在PBS溶液中的20μl的3.7%甲醛,并在室温下孵育20分钟来进行固定,之后使用Biotek EL405洗板机用50μl/孔PBS进行洗涤。然后添加在PBS中的20μl的0.1%Triton X100,并在室温下孵育20分钟以渗透细胞。然后使用Biotek EL405洗板机用50μl/孔PBS将这些板洗涤一次。

[0778] 将磷酸-ATM Ser1981抗体(密理博(Millipore)#MAB3806)10000倍稀释于包含0.05%聚山梨醇酯/吐温和3%BSA的PBS中,并且将20μl添加至每个孔,并且在室温下孵育过夜。次日早晨使用Biotek EL405洗板机,用50μl/孔PBS洗涤板三次,并且然后添加20μl在PBS中的二级抗体溶液,该二级抗体溶液包含500倍稀释的Alexa Fluor®488山羊抗兔IgG(生命技术公司(Life Technologies),A11001)以及0.002mg/mLHoeschst染料(生命技术公司#H-3570),该PBS包含0.05%聚山梨醇酯/吐温和3%BSA。在室温下孵育1h之后,使用Biotek EL405洗板机,用50μl/孔PBS将这些板洗涤三次,并且将这些板密封并在4℃下保持在PBS中直至读取。使用ArrayScan VTI仪,使用XF53滤光器以10×物镜来读取板。使用双激

光设置来分析细胞核的Hoeschst(405nm)染色和二级抗体的pSer1981(488nm)染色。

[0779] 测定b):ATR细胞效价

[0780] 基本原理：

[0781] ATR是PI 3-激酶-相关的激酶，其响应于DNA损伤或复制阻滞磷酸化丝氨酸或苏氨酸残基上的多个底物。Chk1(ATR的下游蛋白激酶)在DNA损伤检查点控制中起重要作用。Chk1的激活涉及Ser317和Ser345的磷酸化(后者视为通过ATR磷酸化/激活的优先目标)。这是基于细胞的测定，用以通过在用具有式(I)的化合物和UV模拟剂4NQO(西格玛(Sigma)#N8141)处理之后测量HT29细胞中Chk1(Ser345)的磷酸化减少，来测量ATR激酶的抑制。

[0782] 方法细节：

[0783] 将HT29细胞(ECACC#85061109)以6000个细胞/孔的密度接种于384孔测定板(科斯塔(Costar)#3712)中包含1％L谷氨酰胺和10％FBS的40μl EMEM培养基中且允许其粘附过夜。次日早晨通过声学分配将在100％DMSO中的具有式(I)的化合物添加至测定板中。在37℃下和5％CO_2下孵育1h后，通过声学分配将在100％DMSO中的40nl的3mM 4NQO添加至全部孔中，未用4NQO处理以产生空反应对照的最小对照孔除外。将板返回孵育箱中再孵育1h。然后通过添加在PBS溶液中的20μl 3.7％甲醛并在室温下孵育20min将细胞固定。然后添加在PBS中的20μl的0.1％Triton X100，并在室温下孵育10分钟以渗透细胞。然后使用Biotek EL405洗板机用50μl/孔PBS将这些板洗涤一次。

[0784] 将磷酸-Chk1Ser 345抗体(细胞信号传导技术公司(Cell Signalling Technology)#2348)150倍稀释于包含0.05％聚山梨醇酯/吐温的PBS中，并且将15μl添加至每个孔并且在室温下孵育过夜。次日早晨使用Biotek EL405洗板机，用50μl/孔PBS将板洗涤三次，并然后添加20μl于PBST中的二级抗体溶液(包含500倍稀释的Alexa Fluor488山羊抗兔IgG(分子探针(MolecularProbes)#A-11008)和0.002mg/mL Hoeschst染料(分子探针#H-3570))。在室温下孵育2h之后，使用Biotek EL405洗板机，用50μl/孔PBS将板洗涤三次，并且然后将板用黑色板密封物密封直至读取。使用ArrayScan VTI仪，使用XF53滤光器以10×物镜来读取板。使用双激光设置来分析细胞核的Hoeschst(405nm)染色和二级抗体的pChk1(488nm)染色。

[0785] 测定c):PI3K细胞效价

[0786] 基本原理：

[0787] 这一测定用于测量细胞中的PI3K-α抑制。PDK1被鉴定为蛋白激酶B(Akt1)的上游激活环激酶，其对PKB的激活是必需的。脂质激酶磷酸肌醇3激酶(PI3K)的激活对于通过PDK1激活PKB是至关重要的。

[0788] 受体酪氨酸激酶配体刺激后，PI3K被激活，它将PIP2转换为PIP3，PIP3由PDK1的PH结构域结合，这导致PDK1向细胞膜募集，在此处在激活环中的Thr308处磷酸化AKT。

[0789] 这种基于细胞的作用方式测定的目的是识别抑制PDK活性或通过抑制PI3K活性而导致PDK1向细胞膜募集的化合物。用化合物处理2h后BT474c细胞中磷酸-Akt(T308)的磷酸化是PDK1的直接度量并且是PI3K活性的间接度量。

[0790] 方法细节：

[0791] 将BT474细胞(人类乳腺管癌，ATCC HTB-20)以每孔5600个细胞的密度接种于黑色384孔板(科斯塔，#3712)中包含10％FBS和1％谷氨酰胺的DMEM中并且允许其粘附过夜。

[0792] 次日早晨通过声学分配将于100％DMSO中的化合物的添加到测定板中。在37℃和5％CO_2下孵育2h之后，抽吸培养基并且用包含25mM Tris、3mM EDTA、3mM EGTA、50mM氟化钠、2mM原钒酸钠、0.27M蔗糖、10mMβ-甘油磷酸盐、5mM焦磷酸钠、0.5％Triton X-100以及康普利特(complete)蛋白酶抑制剂混合片剂(罗氏(Roche)#04693116001，每50mL溶解缓冲液使用1片)的缓冲液溶解这些细胞。

[0793] 20分钟后，将细胞溶解物转移到已预涂布有PBS缓冲液中的抗全AKT抗体的ELISA板(葛莱娜(Greiner)#781077)中，并且用包含0.05％吐温20的PBS中的1％BSA来阻断非特异性结合。在4℃下将板孵育过夜。次日用包含0.05％吐温20的PBS缓冲液洗涤这些板并且再与小鼠单克隆抗磷酸AKT T308一起孵育2h。再次如上洗涤板，随后添加马抗小鼠HRP结合的二级抗体。在室温下孵育2h后，洗涤板并且向每一孔中添加QuantaBlu底物工作溶液(赛默科技公司(Thermo Scientific)#15169，根据供应商说明书制备)。60分钟后通过向孔中添加停止溶液以停止荧光产物的形成。使用帝肯(Tecan)Safire读板仪分别使用325nm激发波长和420nm发射波长读取板。除非有所说明，否则在这一ELISA测定中使用来自细胞信号传导公司(Cell Signalling)(#7144)的Path Scan磷酸AKT(Thr308)夹心ELISA试剂盒中所含的试剂。

[0794] 测定d)：mTOR细胞效价

[0795] 基本原理：

[0796] 该测定用于测量细胞中的mTOR抑制。使用Acumen Explorer，磷酸-AKT的基于细胞的作用机制测定的目的是识别PI3Kα或mTOR-Rictor(mTOR的雷帕霉素不敏感伴侣)的抑制剂。这是通过化合物处理后MDA-MB-468细胞中Ser473处的Akt蛋白(AKT位于信号转导通路中PI3Kα的下游)的磷酸化的任何降低测量的。

[0797] 方法细节：

[0798] 将MDA-MB-468细胞(人类乳腺癌#ATCC HTB 132)以每孔1500个细胞接种于葛莱娜384孔黑色平底板中的包含10％FBS和1％谷氨酰胺的40μl DMEM中。将细胞板在37℃孵育箱中孵育18h，之后使用声学分配给予在100％DMSO中的具有式(I)的化合物。在12点浓度范围中将化合物给予到随机板图中。或者通过给予100％DMSO(最大信号)或添加完全消除pAKT信号的参考化合物(PI3K-β抑制剂)(最小对照)来产生对照孔。将板在37℃下孵育2h；然后通过添加10μl 3.7％甲醛溶液将细胞固定。30分钟后，使用帝肯PW384洗板机用PBS洗涤这些板。将孔封闭，并且将细胞通过添加40μl包含0.5％吐温20和1％Marvel™(干乳粉)的PBS进行透化，并且在室温下孵育60分钟。将板用包含0.5％(v/v)吐温20的PBS进行洗涤，并且添加在相同PBS-吐温+1％Marvel™中的20μl兔抗磷酸AKT Ser473(细胞信号传导技术公司，#3787)，并且在4℃孵育过夜。

[0799] 使用帝肯PW384，用PBS+0.05％吐温20将板洗涤3次。向每一孔中添加于PBS+0.05％包含1％Marvel™的吐温20中稀释的20μl二级抗体Alexa Fluor 488抗兔(分子探针，#A11008)且在室温下孵育1h。如之前般将板洗涤三次，接着向每一孔中添加20μl PBS且用黑色板密封物对板进行密封。

[0800] 在用488nm激光激发之后，尽可能快地在Acumen读板仪上读取这些板，测量绿色荧光。使用该系统，产生IC_{50}值，并且通过对照孔确定板的质量。每次均设置参比化合物以监测测定性能。

[0801] 表2：实例1-61在测定a)-d)中的效价数据

[0802]

实例	测定 a) ATM 细胞 IC_{50} (μM)	测定 b) ATR 细胞 IC_{50} (μM)	测定 c) PI3Kα 细胞 IC_{50} (μM)	测定 d) mTOR 细胞 IC_{50} (μM)
1	0.00111	1.51	0.47	
2	0.0127	6.76		
3	0.0021	> 30	19.3	

[0803]

实例	测定 a) ATM 细胞 IC_{50} (μM)	测定 b) ATR 细胞 IC_{50} (μM)	测定 c) PI3Kα 细胞 IC_{50} (μM)	测定 d) mTOR 细胞 IC_{50} (μM)
4	0.00761	18	0.243	
5	0.000312	0.284		
6	0.0017	> 30		
7	0.000626	1.42	1.22	0.616
8	0.00104	0.261		
9	0.000842	2.48		
10	0.000752	3.21		
11	0.00077	1.08		
12	0.000434	0.223		
13	> 0.0239			
14	0.00151			
15	0.00146	> 30		
16	0.0186	> 22.3		
17	0.0137	> 30		
18	0.0127	17.5		
19	0.0634	> 30		
20	0.0365	> 30	> 10	> 30
21	0.0258	> 30		
22	0.0134	6.71		
23	0.0228	> 24		
24	0.0166	9.23		
25	0.00661	2.52		
26	0.00929	> 20.1		
27	0.0059	5.95		
28	0.0195	18.8		
29	0.00968	> 30		
30	0.0249	> 30		
31	0.0338	> 30	> 30	12.8
32	0.000307	> 30	0.663	1.5
33	0.000332	> 25.7	1.09	NV
34	0.000395	> 30		2
35	0.0014	> 30		16.5
36	0.000357	> 30	0.987	3.9
37	0.000911	> 30		
38	0.00391	> 30		
39	0.00269	> 30		
40	0.00324	> 30		22.1
41	0.00202	> 30		
42	0.00154	> 30	> 30	> 15.3
43	0.072	> 30		
44	0.000889	1.12		
45	0.000618	> 30		

[0804]

实例	测定a) ATM 细胞 IC_{50} (μM)	测定b) ATR 细胞 IC_{50} (μM)	测定c) PI3Kα 细胞 IC_{50} (μM)	测定 d) mTOR 细胞 IC_{50} (μM)
46	0.0077	> 10		
47	0.0027	1.8		
48	0.00234	0.201		
49	0.0153	1.91		
50	0.0167	1.97		
51	0.000589	0.0906		
52	0.000112	0.0616		
53	0.000269	> 21.4		
54	0.000061	> 25.6		
55	0.00338	0.804		
56	0.0157	1.19		
57	0.00116	> 30	> 30	7.72
58	0.00225	> 21.8		
59	0.00138	> 30		
60	0.000502	> 30	0.292	0.989
61	0.000753	> 25.5		

[0805] 表3示出在测试a)、b)、c)和d)中,CN 102399218A和CN 102372711A的某些化合物的比较性数据。

[0806] 表3:在测定a)-d)中针对CN102399218A和CN102372711A的某些化合物的效价数据

[0807]

参比化合物	测定a) ATM 细胞 IC_{50} (μM)	测定b) ATR 细胞 IC_{50} (μM)	测定c)PI3Ka 细胞 IC_{50} (μM)	测定 d) mTOR 细胞 IC_{50} (μM)
CN102372711A 化合物 1	0.125	0.281	0.188	0.237
CN102372711A 化合物 4	0.0112	0.0686	0.102	0.0729
CN102372711A 化合物 5	0.0265	0.0644	0.153	0.113
CN102399218A 化合物 60	1.76	> 0.0771	4.67	2.31
CN102399218A 化合物 61	3.46	1.48	1.73	0.177
CN102399218A 化合物 62	0.08	0.0563	0.149	0.0155
CN102399218A 化合物 64	0.216	0.162	0.247	0.287
CN102399218A	0.494	0.0129	0.0804	0.0414

[0808]

参比化合物	测定 a) ATM 细胞 IC_{50} (μM)	测定 b) ATR 细胞 IC_{50} (μM)	测定 c)PI3Ka 细胞 IC_{50} (μM)	测定 d) mTOR 细胞 IC_{50} (μM)
化合物 94				
CN102399218A 化合物 114	0.0741	0.0686	0.0131	0.0469