Title: IMIDAZO[4,5-C]QUINOLINE DERIVATIVES AND USES THEREOF

Abstract: The present invention relates to substituted imidazo[4,5-c]quinoline derivatives represented by the compounds formula (I), processes for their preparation, pharmaceutical compositions comprising said compounds and their use in the treatment of diseases or disorders mediated by one or more kinases (such as P3 kinase, mTOR and ALK-1), particularly proliferative diseases or disorders such as cancer. The compounds of formula (I) can also be used in the treatment of inflammation, angiogenesis related disorders and bacterial infections.

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IMIDAZO[4,5-C]QUINOLINE DERIVATIVES AND USES THEREOF

RELATED APPLICATION
The present application claims the benefit of U.S. Provisional Application No. 61/782,824, filed on March 14, 2013. The content of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION
The present invention relates to substituted imidazo[4,5-c]quinoline derivatives (referred to herein as compounds of formula (I)), processes for their preparation, pharmaceutical compositions comprising the compounds of formula (I) and their use in the treatment of diseases or disorders mediated by one or more kinases, for instance proliferative diseases or disorders. These compounds can also be used in the treatment of inflammatory disorders, angiogenesis related disorders and bacterial infections.

BACKGROUND OF THE INVENTION
Phosphatidylinositol-3-kinase or phosphoinositol-3-kinase (PI3-kinase or PI3K), are a family of lipid kinases. The PI3K family is composed of three classes, viz., Class I, II and III. Class III PI3K enzymes phosphorylate PI (phosphatidylinositol) alone, while, Class II PI3K enzymes phosphorylate both PI and PI 4-phosphate [PI(4)P]. Class I PI3K enzymes phosphorylate both PI, PI(4)P and PI 4,5-bisphosphate [PI(4, 5)P$_2$]. Class I PBKs are further divided into two groups, class IA and class IB, in terms of their activation mechanism. Class IA PBKs is composed of $\pi_{10a}$, $\pi_{10\theta} \beta$ and $\pi_{10\theta} \delta$ subtypes and are generally activated in response to growth factor-stimulation of receptor tyrosine kinases. Class IB is composed of $\pi_{10y}$ alone.

Activation of the PI3K (phosphoinositide 3-kinase) pathway is a recurrent feature observed in human tumors. Somatic aberrations of PBK-Akt-mTOR (phosphoinositide 3-kinase-Protein Kinase B-mammalian target of rapamycin) pathway genes have been commonly observed in a variety of malignancies, therefore this pathway has been extensively investigated as a mechanism in tumorigenesis and as a target for cancer therapy. Phosphatase and tensin homolog (PTEN), a tumor suppressor gene is homozygously mutated in a variety of human cancers. The lipid phosphatase activity of PTEN/MMAC antagonizes PI3K.
signaling and can therefore be seen as a counterpart of the PI3K oncogene. PTEN is second only to p53 as the most frequently deleted tumor suppressor gene in human cancers.

According to Schabbauer et al., (Arteriosclerosis, Thrombosis, and Vascular Biology 2004, 24, 1963), inhibition of PI3K-Akt pathway suppresses coagulation and inflammation. Hence the compounds that are PI3K and/or mTOR inhibitors, find use in the treatment of cancers, autoimmune and inflammatory diseases and disorders.

Protein kinases play important roles in regulating most cellular functions such as proliferation, cell cycle, cell metabolism, survival, apoptosis, DNA damage repair, cell motility and response to the microenvironment. Protein kinases can be divided into broad groups based upon the identity of the amino acid(s) (serine/threonine, tyrosine, lysine, and histidine) that they target.

The family of serine/threonine kinases includes, but is not limited to, DNA-PK (DNA-dependent protein kinase), ALK1 (activin receptor-like kinase 1) also known as ACVRL1, ALK2 (activin A receptor, type I) also known as ACVR1, CLK1 (CDC-like kinase 1), CLK4 (CDC-like kinase 4) and RIPK2 (receptor-interacting serine/threonine-protein kinase 2). DNA-PK has been shown to be a crucial component of both the DNA double-strand break (DSB) repair machinery and the V(D)J recombination apparatus. DNA-PK is required for the non-homologous end joining (NHEJ) pathway of DNA repair, which rejoins double-strand breaks. Hence, DNA-PK finds use in the treatment of cancers.

Aberrant activity of ALK (Activin Like Kinase) is involved in the development of brain tumors and overexpression of ALK has been reported in neuroblastomas and several cell lines derived from neural tissue. ALK mediated signaling could play a role in the development and/or progression of a number of common solid tumors (J. Cell. Physiol., 2004, 199(3), 330-58). ALK-1 is a type I cell surface receptor for transforming growth factor beta receptor type I (TGF-β1). Mutations in ALK-1 are associated with heredity hemorrhagic telangiectesia (HHT), suggesting a critical role for ALK-1 in the control of blood vessel development or repair (J. Med. Genet., 2003, 40, 494-502). Also, in vivo experiments on ALK-1 knockout mice provide the evidence of ALK-1 involvement in angiogenesis (Proc. Natl. Acad. Sci. USA, 2000, 97, 2626-2631).

Further, PI3K isoforms control inflammation at many levels, from the generation of inflammatory cells to the migration and function of these cells. More specifically, the gamma and delta isoforms of PI3K underpin the inflammatory responses. Genetic targeting of PI3Kγ
(πιτθγ) and ΡΒΚδ (πιτθδ) in mice has underlined a central role of these PI3K isoforms in inflammation and allergy, as they modulate chemotaxis of leukocytes and degranulation in mast cells. Proof-of-concept molecules such as CZC24832 selective for ΡΒΚγ have already successfully alleviated disease progress in models of inflammation.

Thus, inhibition of one or more kinases such as PI3K, mTOR, ALK and DNA-PK can be considered as a promising targeted therapies for the treatment of cancer, angiogenic disorders, inflammatory disorders or any disorders mediated by any one or more of the said kinases.

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. About 12.7 million cancer cases and 7.6 million cancer deaths (around 13% of all deaths) are estimated to have occurred in 2008 worldwide. About 5% to 10% of cancers are strongly hereditary. However, most cancers do not result from inherited genes but from damage to genes as a result from internal factors or external factors.

Angiogenesis is the process of forming new blood vessels and is critical in many normal and abnormal physiological states. Angiogenesis is normally observed in wound healing, fetal and embryonic development and formation of corpus luteum, endometrium and placenta. However, angiogenesis is also the fundamental step in the transition of tumors from a dormant state to a malignant state. In diseases like cancer, the body loses the ability to maintain balanced angiogenesis. New blood vessels feed diseased tissues, destroying normal tissues and sometimes are involved in tumor metastasis. Hence, anti-angiogenic agents are a very promising class of drugs to block or slow the cancer growth.

Currently there are several PI3K inhibitors at different stages of clinical trial, including GDC-0941 (Piramed Ltd. and Genentech Inc.), BEZ-235 and BGT-226 (Novartis AG), XL 147 and XL-765 (Exelixis Inc.), PX-866 (ProlX Pharmaceuticals), SF-1126 (Semaphore Pharmaceuticals), D-87503 (AEterna Zentaris Inc.), GSK-615 (GlaxoSmithkline Ltd.) and CAL-101 (Calistoga Pharmaceuticals). However, there is still a continuing need for an effective anti-proliferative agent considering the increasing mortality rate due to proliferative diseases including cancer.

WO2006/122806 describes imidazoquinolines as lipid kinase inhibitors that are used alone or in combination with one or more other pharmaceutically active compounds for the treatment of an inflammatory or obstructive airway disease such as asthma or a proliferative
disease such as a tumor disease.


TNF-α has been implicated as a mediator in several diseases such as inflammatory bowel disease, inflammation, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, osteoarthritis, refractory rheumatoid arthritis, chronic non-rheumatoid arthritis, osteoporosis/bone resorption, Crohn's disease, allergic asthma, septic shock, endotoxic shock, ischemia-reperfusion injury, multiple sclerosis, sepsis, chronic recurrent uveitis, ulcerative colitis and the like. Much research has been conducted to study the effect of TNF-α and anti-TNF-oc therapies. Studies in the area of cancer have shown that with TNF-oc therapy it is important to balance the cytotoxicity and systemic toxicity of the potential drug candidates.

Monoclonal antibody drugs such as Infliximab, Etanercept and Adalimumab are useful as anti-inflammatory agents, but have drawbacks such as route of administration (only parenteral), high cost and activation of latent tuberculosis (Rheumatology, 2007, 46(5), 887-888; Clin. Infect. Dis., 2004, 39, 295-299 and Ann. Rheum. Dis., 2005, 64, iv2-iv-14). Thus, despite the available treatment options for the treatment of inflammatory disorders, there still exists a need for improved anti-inflammatory agents.

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to a compound of formula (I) (as described herein) in all its isotopic forms, stereoisomeric and tautomeric forms and mixtures thereof in all ratios, or a pharmaceutically acceptable salt, a pharmaceutically acceptable solvate, a prodrug, a polymorph, an N-oxide or a carboxylic acid isostere thereof.

In another aspect, the present invention relates to processes for the preparation of the compound of formula (I) or a pharmaceutically acceptable salt thereof.

In yet another aspect, the present invention relates to a method of inhibiting activity of one or more kinases selected from PI3 kinase, mTOR or ALK-1 comprising contacting the said kinase with an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In yet another further aspect, the present invention relates to a method for the
treatment of a disease mediated by a kinase selected from PI3 kinase (PI3K), mTOR or ALK-1, comprising administering to a subject in need thereof; a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In yet another aspect, the present invention relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof; for use in the treatment of a disease mediated by a kinase selected from PI3 kinase (PI3K), mTOR or ALK-1.

In yet another aspect, the present invention relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof; for use in the treatment of a proliferative disease or disorder, mediated by a kinase selected from PI3 kinase (PI3K), mTOR and ALKI or combinations thereof.

In yet another aspect, the present invention relates to use of the compound of formula (I), for the manufacture of a medicament for the treatment of diseases mediated by PI3 kinase (PI3K), mTOR or ALK-1.

In another further aspect, the present invention relates to a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier, adjuvant or a vehicle.

These and other objectives and advantages of the present invention will be apparent to those skilled in the art from the following description.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a compound of formula (I),

\[ \text{formula (I)} \]

in all its isotopic forms, stereoisomeric and tautomeric forms and mixtures thereof in all ratios, or a pharmaceutically acceptable salt, a pharmaceutically acceptable solvate, a
prodrug, a polymorph, an N-oxide or a carboxylic acid isostere thereof;

wherein,

\[
\text{Ring A is } (C_6-C_{14}) \text{aryl or heteroaryl;} \\
X_1 \text{ is } \text{O or } \text{NR}_a; \\
5 \quad X_2 \text{ is } \text{O or } \text{NR}_a; \\
\text{R}_1 \text{ is hydrogen, CN, } -\text{NR}_a\text{R}_b, -\text{OR}_a \text{ or } (d-C_6) \text{ alkyl, wherein } (C_s-C_9) \text{ alkyl is } \\
\text{unsubstituted or substituted with one or more groups independently selected from the group } \\
\text{consisting of CN, } -\text{NR}_a\text{R}_b, \text{ nitro, halogen, } -\text{OR}_a, -\text{COOH, } -\text{C}(0)\text{O}-(C_1-C_6) \text{ alkyl and } - \\
P(0)(\text{OR}_3)(\text{OR}_4); \\
10 \quad \text{R}_2 \text{ at each occurrence is independently selected from the group consisting of halogen, } \\
\text{CN, nitro, } -\text{OR}_a, -\text{NR}_a\text{R}_b, (C_1-C_9) \text{ alkyl, halo-(C}_1\text{-C}_9) \text{ alkyl and } -\text{O}-(\text{halo-(C}_1\text{-C}_9) \text{ alkyl), } \\
\text{wherein } (C_1-C_9) \text{ alkyl is unsubstituted or substituted with halogen or CN; } \\
\text{R}_3 \text{ is hydrogen or } (C_1-C_9) \text{ alkyl; } \\
\text{R}_4 \text{ is halogen, } (C_6-C_{14}) \text{ aryl or heteroaryl; wherein each of the aryl and heteroaryl is } \\
\text{unsubstituted or substituted with one or more groups selected from } R_{11}; \\
\text{R}_4 \text{ is nitro, CN, } -\text{C}(0)\text{O}-(C_1-C_9) \text{ alkyl or } (Q-C_9)\text{alkyl, wherein } (C_1-C_9) \text{ alkyl is } \\
\text{unsubstituted or substituted with CN or } -\text{NR}_a\text{R}_b; \\
\text{R}_5 \text{ is hydrogen, } (C_1-C_9) \text{ alkyl, } -\text{C}(0)\text{O}-(C_1-C_9) \text{ alkyl or } -\text{S}(0)\text{S}-(C_1-C_9) \text{ alkyl; } \\
\text{R}_a \text{ at each occurrence is independently selected from the group consisting of } \\
\text{hydrogen, halogen, } -\text{OR}_a, \text{ CN, } -\text{NR}_a\text{R}_b, -\text{NR}_a\text{COR}_b, -\text{COOR}_a, -\text{CONR}_a\text{R}_b, \text{ halo-(C}_1\text{-C}_9) \text{ alkyl and } (C_1-C_9) \text{ alkyl; } \\
\text{R}_a \text{ and } \text{R}_b \text{ at each occurrence are independently selected from hydrogen and } (C_1-C_9)\text{ alkyl; and } \\
p \text{ is an integer from } 0 \text{ to } 4. \\
25 \quad \text{DEFINITIONS} \\
\text{Listed below are definitions, which apply to the terms as they are used throughout the } \\
\text{specification and the appended claims (unless they are otherwise limited in specific } \\
\text{instances), either individually or as part of a larger group. } \\
30 \quad \text{It will be understood that "substitution" or "substituted by" or "substituted with" } \\
\text{includes the implicit proviso that such substitution is in accordance with the permitted } \\
\text{valence of the substituted atom and the substituent, as well as represents a stable compound,}
which does not readily undergo transformation such as by rearrangement, cyclization, elimination, etc.

The term "halo" or "halogen" as used herein refers to an atom selected from fluorine (F), chlorine (Cl), bromine (Br) or iodine (I).

The term "alkyl" whether used alone or as part of a substituent group, refers to the radical of saturated aliphatic groups, including straight or branched-chain containing from 1 to 10 carbon atoms i.e. (Ci-Cio)alkyl group, for example, 1 to 6 carbons atoms ((Ci-Ce)alkyl group). Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, 1-methylbutyl, sec-butyl, teri-butyl, pentyl, neo-pentyl, «-hexyl, and n-decyl. Furthermore, unless stated otherwise, the alkyl groups may be unsubstituted or substituted with one or more substituents, for instance, from one to five identical or different substituents, for example, (Ci-Ce)alkyl, (C2-Cs)alkenyl, (C2-Cs)alkynyl, halogen, halo(Ci-Ce)alkyl, hydroxy, (Ce-Cio)aryl, heteroaryl, CN, nitro, -NR_Rb, -OR_c, -C(0)OR_c or -P(0)(OR_c)(OR_d); wherein R_a and R_b are as defined above. Examples of substituted alkyl include but not limited to hydroxymethyl, trifluoromethyl or benzyl.

The term "halo(Ci-Ce)alkyl", as used herein refers to, alkyl radical which is substituted by one or more halogen atoms (F, Cl, Br or I). Examples of halo(Ci-Ce)alkyl include, but not limited to, fluoromethyl, chloromethyl, bromomethyl, iodomethyl, difluoromethyl, trifluoromethyl and trichloromethyl. Unless stated otherwise, the halo(Ci-Ce)alkyl group may be unsubstituted or substituted with one or more substituents, for instance, halogen, CN, hydroxy, amino or nitro. Examples of substituted halo(Ci-Ce)alkyl include but not limited to 1,1-difluoropropan-2-ol, 3-amino-1,1-difluoro-2-propanol and 3-chloro-2-methylpropanenitrile.

The term "aryl" or "(Ci-C4) aryl" as used herein refers to a monocyclic or polycyclic hydrocarbon group having up to 14 ring carbon atoms, preferably up to 10 ring carbon atoms, more preferably up to 6 ring carbon atoms in which at least one carbocyclic ring is present that has a conjugated \( \pi \) electron system. Examples of aryl include, but are not limited to, phenyl, naphthyl, tetrahydroanaphtyl and the like. Aryl residues can be bonded via any desired position, and in substituted aryl residues, the substituents can be located in any desired position. Unless indicated otherwise, aryl group may be unsubstituted or substituted with one or more substituents independently selected from (Ci-Ce)alkyl, (C2-Cs)alkenyl, (C2-Cs)alkynyl, halogen, halo(d-C_e) alkyl, hydroxy, -0(C1-Cio) alkyl, -0-(halo(Ci-C_e)alkyl), (Ce-Ce)-...
Cio)aryl, -0(C₆-Cio)aryl, heteroaryl, CN, nitro, -C(0)Rₐ, -NRₐRₐ, and -ORₐ; wherein Rₐ and Rₐ are as defined above.

The term "heteroaryl" as used herein refers to an aromatic heterocyclic ring system containing 5 to 20 ring atoms, suitably 5 to 10 ring atoms, which may be a monocyclic or polycyclic, fused together or linked covalently. The rings may contain from 1 to 4 heteroatoms independently selected from N, O and S. An example of heteroaryl includes "nitrogen containing heteroaryl", which refers to an aromatic heterocyclic ring system, wherein at least one of the ring atom is nitrogen. The ring system may contain additional 1 to 4 heteroatoms independently selected from N, O and S. In the context of the present invention, the heteroaryl can be 6 to 10 membered nitrogen containing heteroaryl or 5 or 6-membered nitrogen containing heteroaryl. The nitrogen atom or sulfur atom of the heteroaryl ring may be oxidized or the nitrogen atom of the heteroaryl ring may be quaternized. Any suitable ring position of the heteroaryl moiety may be covalently linked to the any suitable position in the imidazo[4,5-c]quinoline core. Examples of heteroaryl include, but are not limited to, furanyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzoazolyl, benzothiazolyl, benzofuranyl, benzothienyl, phthalazinyl, benzimidazolyl, indolyl, isoindolyl, indazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, purinyl, indoliziny, benzoisothiazolyl, benzoxazolyl, pyrrolypyridyl, furopyridinyl, benzothiazolyl, benzoazolyl, benzotriazolyl and benzodiazolyl. The aforementioned heteroaryl groups may be C-attached or N-attached (where such is possible). For example, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). The oxidized form of the ring nitrogen and sulfur atom contained in the heteroaryl to provide the corresponding N-oxide, S-oxide or S,S-dioxide is also encompassed in the scope of the present invention.

Unless stated otherwise, the heteroaryl group may be unsubstituted or substituted with one or more substituents independently selected from (Ci-Ce)alkyl, (C₂-C₅)alkenyl, (C₂-C₅)alkynyl, halogen, halo(C₁-C₆) alkyl, hydroxy, -0(d-C₆)alkyl, -0(halo(C₁-C₆)alkyl), (C₆-Cio)aryl, heteroaryl, CN, nitro, -C(0)Rₐ, -ORₐ and -NRₐRₐ wherein Rₐ and Rₐ are as defined above.

The terms "compound of the present invention", "compound of the invention" and "compounds of formula (I)" includes compounds of formula (I) and stereoisomers, tautomers,
solvates, polymorphs, N-oxides and pharmaceutically acceptable salts thereof; unless indicated otherwise.

The term "stereoisomer" or "stereoisomeric" as used herein refers to all isomers of individual compounds that differ only in the orientation of their atoms in space. The term stereoisomer includes mirror image isomers (enantiomers), mixtures of mirror image isomers (racemates, racemic mixtures), geometric (cis/trans or syn/anti or E/Z) isomers, and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereoisomers). The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, individual diastereoisomers, or enantiomers, or may exist as geometric isomers, with all isomeric forms of said compounds being included in the present invention.

The term "tautomer" or "tautomeric" as used herein refers to the coexistence of two (or more) compounds that differ from each other only in the position of one (or more) mobile atoms and in electron distribution, for example, keto-enol and imine-enamine tautomers.

The term "pharmaceutically acceptable salts" as used herein includes salts of the compounds of formula (I) which are prepared by treating said compounds with a suitable acid or a base, depending on the particular substituents found on the compounds described herein.

The term "N-oxide" as used herein, refers to the oxide of the nitrogen atom of nitrogen-containing heteroaryl. N-oxide can be formed in presence of an oxidizing agent for example peroxide such as m-chloro-perbenzoic acid or hydrogen peroxide.

Within the context of the present invention and as used herein the term "polymorph" or "polymorphic form" refers to crystals of the same compound that differs only in the arrangement and/or conformation of the molecule (in the present invention, a compound of formula I) in the crystal lattice.

The present invention also includes within its scope all isotopically labeled forms of compounds of formula (I), wherein one or more atoms of compounds of formula (I) are replaced by their respective isotopes. All isotopes of any particular atom or element as specified are contemplated within the scope of the compounds of the invention. Examples of isotopes that may be incorporated into the compounds disclosed herein include, but are not limited to, isotopes of hydrogen such as $^2$H and $^3$H, carbon such as $^{11}$C, $^{13}$C and $^{14}$C, nitrogen such as $^{13}$N and $^{15}$N, oxygen such as $^{15}$O, $^{16}$O and $^{18}$O, chlorine such as $^{36}$Cl, fluorine such as $^{18}$F and sulphur such as $^{35}$S. Substitution with heavier isotopes, for example, replacing one or
more key carbon-hydrogen bonds with carbon-deuterium bond may show certain therapeutic advantages, resulting from longer metabolism cycles, (e.g., increased in-vivo half life or reduced dosage requirements), improved safety or greater effectiveness and hence may be preferred in certain circumstances.

The term "diseases or disorders mediated by a kinase selected from the group consisting of PI3 kinase, mTOR and ALK-1 or combination of said kinases" used herein refer to the diseases or disorders which is characterized by abnormal PI3 kinase or mTOR kinase or ALK 1 activity or a combination of abnormal activity of all the three kinases.

As used herein, the term "therapeutically effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to treat the target disorder.

The term "treat", "treating" or "treatment" means decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein), lessen the severity of the disease or improve the symptoms associated with the disease.

"Disease" means any condition or disorder that damage or interferes with the normal function of a cell, tissue, or organ.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "mammal" used herein refers to warm-blooded vertebrate animals of the class Mammalia, including humans, characterized by a covering of hair on the skin and, in the female, milk-producing mammary glands for nourishing the young. The term mammal includes animals such as cat, dog, rabbit, bear, fox, wolf, monkey, deer, mouse, pig as well as human.

The term "mediate" or "mediated by" as used herein means caused by or affected by.

The term "and/or" as used herein refers to the single element of the list or any combination of two or more elements of the list. For instance, PI3K and/or mTOR inhibitors as used herein refer to the compounds which inhibit PI3K or mTOR or both PI3K and mTOR.

The term "tumor" as used herein refers to an abnormal growth of tissue resulting from uncontrolled, progressive multiplication of cells. A tumor can be benign or malignant.
EMBODIMENTS

In one embodiment, the present invention provides a compound of formula (I), wherein ring A is phenyl or 5 or 6-membered nitrogen containing heteroaryl.

Another embodiment of the present invention is a compound of formula (I), wherein ring A is phenyl.

Another embodiment is a compound of formula (I), wherein ring A is phenyl; R2 is halogen and p is an integer from 0 to 4.

Another embodiment is a compound of formula (I), wherein ring A is 5 or 6-membered nitrogen containing heteroaryl.

Another embodiment is a compound of formula (I), wherein ring A is 5 or 6-membered nitrogen containing heteroaryl selected from pyrrolyl, thiazolyl, isoxazolyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl or pyridazinyl.

Another embodiment is a compound of formula (I), wherein ring A is pyridyl.

Another embodiment is a compound of formula (I), wherein ring A is 3-pyridyl.

Another embodiment of the present invention is a compound of formula (I), wherein ring A is phenyl or pyridyl.

Another embodiment is a compound of formula (I), wherein X1 is O or N(CN).

Another embodiment is a compound of formula (I), wherein X1 is O.

Another embodiment is a compound of formula (I), wherein X1 is N(CN).

Another embodiment is a compound of formula (I), wherein X2 is O.

Another embodiment is a compound of formula (I), wherein X2 is NR2, wherein R2 is hydrogen, (C1-C6)alkyl, -C(0)0-(C1-C6)alkyl or -S(0)2-(C1-C6)alkyl.

Another embodiment is a compound of formula (I), wherein X2 is NR2, wherein R2 is hydrogen, -C(0)0-C(CH3)3 or -S(0)2-CH3.

Another embodiment is a compound of formula (I), wherein X2 is -O- or -NR2, wherein R2 is hydrogen, -C(0)0OC(CH3)3 or -S(0)2CH3.

Another embodiment is a compound of formula (I), wherein R1 is hydrogen, -OR2 or (C1-C6) alkyl, wherein (C1-C6)alkyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of -OR2, -C(0)0-(Ci-Ce)alkyl and -COOH, wherein R2 is hydrogen or (Ci-C6)alkyl.

Another embodiment is a compound of formula (I), wherein R1 is selected from hydrogen, -OCH3 or (Ci-Ce) alkyl, wherein (C1-C6) alkyl is unsubstituted or substituted with
one or more groups independently selected from the group consisting of hydroxy, -C(0)0-CH2CH3 and -COOH.

Another embodiment is a compound of formula (I), wherein R3 is halogen or (Ci-C6)alkyl, wherein (Ci-Ce)alkyl is unsubstituted or substituted with halogen or CN.

Another embodiment is a compound of formula (I), wherein R3 is hydrogen or methyl.

Another embodiment is a compound of formula (I), wherein R3 is hydrogen.

Another embodiment is a compound of formula (I), wherein R3 is methyl.

Another embodiment is a compound of formula (I), wherein R4 is halogen.

Another embodiment is a compound of formula (I), wherein R4 is hydrogen or 6 to 10 membered nitrogen containing heteroaryl, wherein phenyl and the heteroaryl is unsubstituted or substituted with one or more groups selected from R4i.

Another embodiment is a compound of formula (I), wherein R4 is phenyl, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -ORa, CN, -NRaRb, -NRaCORb, -COORa, -CONRaNRA, halo-(Ci-Ce)alkyl and (Ci-Ce)alkyl, wherein Ra and Rb at each occurrence are independently selected from hydrogen and (Ci-C6)alkyl.

Another embodiment is a compound of formula (I), wherein R4 is phenyl, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -ORa, -NRaRb, COORa, halo-(Ci-C6)alkyl and (Ci-C6)alkyl, wherein Ra and Rb at each occurrence are independently selected from hydrogen and (Ci-C6)alkyl.

Another embodiment is a compound of formula (I), wherein R4 is phenyl, which is unsubstituted or substituted with one or more groups independently selected from -ORa, and -COORa; wherein Ra at each occurrence is independently selected from hydrogen and (Ci-C6)alkyl.

Another embodiment is a compound of formula (I), wherein R4 is 6 to 10 membered heteroaryl, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -ORa, CN, -NRaRb, -NRaCORb, -COORa, -CONRaNRA, halo-(Ci-C6)alkyl and (Ci-C6)alkyl.

Another embodiment is a compound of formula (I), wherein R4 is 6 to 10 membered nitrogen containing heteroaryl, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -ORa, CN, -NRaRb, -NRaCORb,
Another embodiment is a compound of formula (I), wherein \( R_4 \) is 6 to 10 membered nitrogen containing heteroaryl, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -OR\(_a\), -NR\(_b\), halo-(C\(_1\)-C\(_6\))alkyl and (C\(_1\)-C\(_6\))alkyl.

Another embodiment is a compound of formula (I), wherein \( R_4 \) is pyridyl, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -OR\(_a\), -NR\(_b\), halo-(C\(_1\)-C\(_6\))alkyl and (C\(_1\)-C\(_6\))alkyl.

Another embodiment is a compound of formula (I), wherein \( R_4 \) is 3-pyridyl, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -OR\(_a\), -NR\(_b\), halo-(C\(_1\)-C\(_6\))alkyl and (C\(_1\)-C\(_6\))alkyl.

Another embodiment is a compound of formula (I), wherein \( R_4 \) is pyridyl, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -OR\(_a\), -NR\(_b\), halo-(C\(_1\)-C\(_6\))alkyl and (C\(_1\)-C\(_6\))alkyl.

Another embodiment is a compound of formula (I), wherein \( R_4 \) is pyridyl, which is unsubstituted or substituted, represented by structural formula, wherein each of \( R_{411}, R_{412} \) and \( R_{413} \) is independently selected from the group consisting of hydrogen, halogen, -OR\(_a\), -NR\(_b\), halo-(C\(_1\)-C\(_6\))alkyl and (C\(_1\)-C\(_6\))alkyl.

Another embodiment is a compound of formula (I), wherein \( R_4 \) is pyridyl, which is unsubstituted or substituted, represented by structural formula, wherein each of \( R_{411}, R_{412} \) and \( R_{413} \) is independently selected from the group consisting of hydrogen, halogen, -OR\(_a\), -NR\(_b\), halo-(C\(_1\)-C\(_6\))alkyl and (C\(_1\)-C\(_6\))alkyl.

Another embodiment is a compound of formula (I), wherein \( R_4 \) is pyridyl, which is unsubstituted or substituted, represented by structural formula, wherein each of \( R_{411}, R_{412} \) and \( R_{413} \) is independently selected from the group consisting of hydrogen, halogen, -OR\(_a\), -NR\(_b\), halo-(C\(_1\)-C\(_6\))alkyl and (C\(_1\)-C\(_6\))alkyl.

Another embodiment is a compound of formula (I), wherein \( R_4 \) is pyridyl, which is unsubstituted or substituted, represented by structural formula, wherein each of \( R_{411}, R_{412} \) and \( R_{413} \) is independently selected from the group consisting of hydrogen, halogen, -OR\(_a\), -NR\(_b\), halo-(C\(_1\)-C\(_6\))alkyl and (C\(_1\)-C\(_6\))alkyl.
unsubstituted or substituted, represented by structural formula

wherein each of R411, R412 and R413 is independently selected from the group consisting of hydrogen, halogen, -0-(d-C6)alkyl, (C1-C6)alkyl, -NH2, -NH-(d-C6)alkyl, -N[(C1-C6)alkyl]2 and halo-(C1-C6)alkyl.

Another embodiment is a compound of formula (I), wherein R4 is pyridyl, which is

unsubstituted or substituted, represented by structural formula

wherein each of R411, R412 and R413 is independently selected from the group consisting of hydrogen, F, -OCH3, -CH3, -NH2, -NH-CH3, -N(CH3)2 and -CF3.

Another embodiment is a compound of formula (I), wherein R4 is substituted pyridyl, represented by the structural formula

wherein R411 is -NH2; R412 and R413 are independently selected from the group consisting of hydrogen, halogen, -0-(Ci-C6)alkyl, (C1-C6)alkyl, -NH2, -NH-(Ci-C6)alkyl, -N[(C1-C6)alkyl]2 and halo-(C1-C6)alkyl.

Another embodiment is a compound of formula (I), wherein R4 is substituted pyridyl, represented by the structural formula

wherein R411 is -NH2; R412 and R413 are independently selected from the group consisting of hydrogen, halogen, -0-(Cr C6)alkyl, (C1-C6)alkyl, -NH2, -NH-(C1-C6)alkyl, -N[(C1-C6)alkyl]2 and halo-(C1-C6)alkyl.

Another embodiment is a compound of formula (I), wherein R4 is substituted pyridyl, represented by the structural formula

wherein R411 is -NH2; R412 and R413 are independently selected from the group consisting of hydrogen, halogen, -0-(Cr C6)alkyl, (C1-C6)alkyl, -NH2, -NH-(C1-C6)alkyl, -N[(C1-C6)alkyl]2 and halo-(C1-C6)alkyl.

Another embodiment is a compound of formula (I), wherein R4 is substituted pyridyl, represented by the structural formula

wherein R411 is -NH2; R412 and R413 are independently selected from the group consisting of hydrogen, halogen, -0-(Cr C6)alkyl, (C1-C6)alkyl, -NH2, -NH-(C1-C6)alkyl, -N[(C1-C6)alkyl]2 and halo-(C1-C6)alkyl.

Another embodiment is a compound of formula (I), wherein R4 is substituted pyridyl, represented by the structural formula

wherein R411 is -NH2; R412 and R413 are independently selected from the group consisting of hydrogen, halogen, -0-(Cr C6)alkyl, (C1-C6)alkyl, -NH2, -NH-(C1-C6)alkyl, -N[(C1-C6)alkyl]2 and halo-(C1-C6)alkyl.
and \(R_4\) is hydrogen.

Another embodiment is a compound of formula (I), wherein \(R_4\) is unsubstituted pyridyl represented by structural formula

\[
\begin{array}{c}
\text{N} \\
\text{R}_{11} \quad \text{R}_{12} \\
\end{array}
\]

wherein \(R_{11}, R_{12}\) and \(R_{13}\) are hydrogen.

In each of the afore-discussed embodiments, the point of attachment.

Another embodiment is a compound of formula (I), wherein \(R_4\) is quinolinyl, which is unsubstituted or substituted with one or more groups selected from \(R_{14}\).

Another embodiment is a compound of formula (I), wherein \(R_4\) is indolyl, which is unsubstituted or substituted with one or more groups selected from \(R_{14}\).

Another embodiment is a compound of formula (I), wherein \(R_4\) is phenyl or 5- or 6-membered nitrogen containing heteroaryl; \(X_1\) is \(O\); \(x\) is \(O\); \(R_1\) is hydrogen, \(\text{CN}, \text{-NR}_a\text{R}_b, \text{-OR}_a\) or \((\text{C}_6\text{alkyl})\)alkyl, wherein \((\text{C}_1\text{-C}_6)\)alkyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of \(\text{CN}, \text{-NR}_a\text{R}_b, \text{nitro, halogen, -OR}_a, \text{-COOH, -C(0)(OR)_b or } (-\text{C}_1\text{-C}_6)\text{alkyl and } \text{-P(0)(OR}_a\text{)(OR}_b\text{)}; \) \(R_2\) is halogen, \(\text{CN}, \text{-NR}_a\text{R}_b\) or \((\text{C}_1\text{-C}_6)\)alkyl, wherein \((\text{C}_1\text{-C}_6)\)alkyl is unsubstituted or substituted by halogen or \(CN; \) \(R_3\) is hydrogen or \((\text{C}_1\text{-C}_6)\)alkyl; \(R_4\) is phenyl or 6 to 10 membered nitrogen containing heteroaryl, wherein phenyl or the heteroaryl is substituted or unsubstituted with one or more groups selected from \(R_{14}\); wherein \(R_{14}\) at each occurrence is independently selected from the group consisting of halogen, \(-\text{OR}_a, \text{CN, -NR}_a\text{R}_b, \text{-NR}_a\text{COR}_b, \text{-COOR}_a, \text{-CONR}_a\text{R}_b, \text{halo-(Q-C}_6\text{)alkyl and } \text{(C}_1\text{-C}_6)\)alkyl and \(\text{(C}_1\text{-C}_6)\)alkyl; \(R_a\) and \(R_b\) at each occurrence are independently selected from hydrogen and \((\text{C}_1\text{-C}_6)\)alkyl; and \(p\) is an integer from 0 to 4.

Another embodiment is a compound of formula (I), wherein \(R_4\) is phenyl or 5- or 6-membered nitrogen containing heteroaryl; \(X_1\) is \(O\); \(x\) is \(NR_y\), wherein \(R_y\) is hydrogen, \((Q-C)_6\)alkyl, \(-\text{C}(0)(\text{Q-C}_6)\)alkyl or \(-\text{R}_a(\text{Q-C}_6)\)alkyl; \(R_1\) is hydrogen, \(\text{CN, -NR}_a\text{R}_b, \text{-OR}_a\) or \((\text{C}_1\text{-C}_6)\)alkyl, wherein \((\text{C}_1\text{-C}_6)\)alkyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of \(\text{CN, -NR}_a\text{R}_b, \text{nitro, halogen, -OR}_a, \text{-COOH, -C(0)(Q-C}_6\text{)alkyl and } \text{-P(0)(OR}_a\text{)(OR}_b\text{)}; \) \(R_2\) is halogen, \(\text{CN, -NR}_a\text{R}_b\) or \((\text{C}_1\text{-C}_6)\)alkyl, wherein \((\text{C}_1\text{-C}_6)\)alkyl is unsubstituted or substituted by halogen or \(CN; \) \(R_3\) is hydrogen or \((\text{C}_1\text{-C}_6)\)alkyl; \(R_4\) is phenyl or 6- to 10- membered nitrogen containing heteroaryl,
selected from R₄₁; wherein R₄₁ at each occurrence is independently selected from the group consisting of halogen, -OR₄, CN, -NR₂R₄, -NR₄COR₄, -COOR₄, -CONR₂R₄, halo-(C₁-C₆)alkyl and (Ci-Ce)alkyl; R₄ and R₅ at each occurrence are independently selected from hydrogen and (Ci-Ce)alkyl; and p is an integer from 0 to 4.

Another embodiment is a compound of formula (I), wherein Ring A is selected from phenyl or 5- or 6-membered nitrogen containing heteroaryl; X₁ is =N(CN); X₂ is NR₃, wherein R₃ is hydrogen, (Q-Ce)alkyl, -C(0)O-(C₁-C₆)alkyl or -S(0)₂(C₁-C₆)alkyl; R₁ is hydrogen, CN, -NR₄R₅, -OR₄ or (Ci-C₆)alkyl, wherein (Ci-Ce)alkyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of CN, -NR₂R₅, nitro, halogen, -OR₄, -COOH, -C(0)O-(d-C₆)alkyl or -P(0)(OR₄)(OR₅); R₂ is halogen, CN, -NR₄R₅, or (Ci-C₆)alkyl, wherein (Ci-Ce)alkyl is unsubstituted or substituted by halogen or CN; R₃ is hydrogen or (Ci-Ce)alkyl; R₄ is phenyl or 6 to 10 membered nitrogen containing heteroaryl, wherein phenyl or the heteroaryl is substituted or unsubstituted with one or more groups selected from R₄₁; wherein R₄₁ at each occurrence is independently selected from the group consisting of halogen, -OR₄, CN, -NR₂R₄, -NR₄COR₄, -COOR₄, -CONR₂R₄, halo-(Ci-C₆)alkyl and (Ci-Ce)alkyl; R₄ and R₅ at each occurrence are independently selected from hydrogen and (Ci-Ce)alkyl; and p is an integer from 0 to 4.

Another embodiment is a compound of formula (I), wherein Ring A is selected from phenyl or 5 or 6-membered nitrogen containing heteroaryl, Xᵢ is =N(CN); X₂ is O; R₁ is hydrogen, CN, -NR₄R₅, -OR₄ or (Ci-C₆)alkyl, wherein (Ci-Ce)alkyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of CN, -NR₂R₅, nitro, halogen, -OR₄, -COOH, -C(0)O-(Ci-Ce)alkyl and -P(0)(OR₄)(OR₅); R₂ is halogen, CN, -NR₄R₅, or (Ci-C₆)alkyl, wherein (Ci-Ce)alkyl is unsubstituted or substituted by halogen or CN; R₃ is hydrogen or (Ci-C₆)alkyl; R₄ is phenyl or 6 to 10 membered nitrogen containing heteroaryl, wherein phenyl or the heteroaryl is substituted or unsubstituted with one or more groups selected from R₄₁; wherein R₄₁ at each occurrence is independently selected from the group consisting of halogen, -OR₄, CN, -NR₂R₄, -NR₄COR₄, -COOR₄, -CONR₂R₄, halo-(Ci-C₆)alkyl and (Ci-Ce)alkyl; R₄ and R₅ at each occurrence are independently selected from hydrogen and (Ci-Ce)alkyl; and p is an integer from 0 to 4.

Another embodiment is a compound of formula (I), wherein Ring A is phenyl; Xᵢ is O; X₂ is O; R₁ is hydrogen, -O(Ci-Ce)alkyl or (Ci-C₆)alkyl, wherein (Ci-C₆)alkyl is unsubstituted or substituted with one or more groups independently selected from the group
consisting of hydroxy, -COOH and -C(0)O-(Ci-Ce)alkyl; R2 is halogen or (Ci-C6)alkyl, wherein (Ci-Ce)alkyl is unsubstituted or substituted by halogen or CN; R3 is hydrogen or (Ci-C6)alkyl; R4 is phenyl, pyridyl, indolyl or quinolinyl, wherein each of phenyl, pyridyl, indolyl and quinolinyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -OR, -NR2Rb, -COOR, halo-(Ci-C6)alkyl and (Ci-Ce)alkyl, wherein R2 and Rb at each occurrence are independently selected from hydrogen and (Ci-C6)alkyl; and p is an integer from 0 to 4.

Another embodiment is a compound of formula (I), wherein Ring A is phenyl; X1 is O; X2 is O; R1 is hydrogen, -O(Ci-Ce)alkyl or (Ci-C6)alkyl, wherein (Ci-C6)alkyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of hydroxy, -COOH and -C(0)O-(Ci-Ce)alkyl; R2 is halogen or (Ci-C6)alkyl, wherein (Ci-Ce)alkyl is unsubstituted or substituted by halogen or CN; R3 is hydrogen or (Ci-C6)alkyl and R4 is pyridyl, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -NR2Rb, halo-(Ci-C6)alkyl, -OR and (Ci-Ce)alkyl, wherein R2 and Rb at each occurrence are independently selected from hydrogen and (Ci-Ce)alkyl; and p is an integer from 0 to 4.

Another embodiment is a compound of formula (I), wherein Ring A is phenyl; X1 is O; X2 is O; R1 is hydrogen, -O(Ci-Ce)alkyl or (Ci-C6)alkyl, wherein (Ci-C6)alkyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of hydroxy, -COOH and -C(0)O-(Ci-Ce)alkyl; R2 is halogen or (Ci-C6)alkyl, wherein (Ci-Ce)alkyl is unsubstituted or substituted by halogen or CN; R3 is hydrogen or methyl and R4 is pyridyl, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -NR2Rb, halo-(Ci-C6)alkyl, -OR and (Ci-C6)alkyl, wherein R2 and Rb at each occurrence are independently selected from hydrogen and (Ci-Ce)alkyl; and p is an integer from 0 to 4.

Another embodiment is a compound of formula (I), wherein Ring A is phenyl; X1 is O; X2 is O; R1 is hydrogen, -O(Ci-Ce)alkyl or (Ci-C6)alkyl, wherein (Ci-C6)alkyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of hydroxy, -COOH and -C(0)O-(Ci-Ce)alkyl; R3 is hydrogen or (Ci-C6)alkyl; R4 is pyridyl, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -O(Ci-Ce)alkyl, -N34, -NH-(Ci-C6)alkyl, -N[(Ci-C6)alkyl]2, halo-(Ci-C6)alkyl and (Ci-C6)alkyl; and p is 0.
Another embodiment is a compound of formula (I), wherein Ring A is phenyl; X₁ is O; X₂ is O; R₁ is hydrogen, -O-(Ci-Ce)alkyl or (Ci-Ce)alkyl; wherein (Ci-Ce)alkyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of hydroxy, -COOH and -C(0)0-(Ci-Ce)alkyl; R₂ is hydrogen or (Ci-Ce)alkyl; R₃ is hydrogen or (Ci-Ce)alkyl; R₄ is pyridyl, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of F, -OCH₃, -N₃, -NH-CH₃, -N(C(=)O)₂ and -CF₃; and p is 0.

Another embodiment is a compound of formula (I), wherein Ring A is phenyl; X₁ is O; X₂ is O; R₁ is hydrogen, -O-(Ci-Ce)alkyl or (Ci-Ce)alkyl, wherein (Ci-Ce)alkyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of hydroxy, -COOH and -C(0)0-(Ci-Ce)alkyl; R₂ is halogen or (Ci-Ce)alkyl, wherein (Ci-Ce)alkyl is unsubstituted or substituted by halogen or CN; R₃ is hydrogen or (Ci-Ce)alkyl; R₄ is selected from indolyl and quinolinyl, which are unsubstituted or substituted with one or more groups selected from R₄₁, wherein R₄₁ at each occurrence is independently selected from the group consisting of hydrogen, halogen, -ORₐ, CN, -NRₐRₐ, -NRₐCORₐ, -COORₐ, -CONRₐRₐ, halo-(Ci-C₆)alkyl and (Ci-C₆)alkyl and Rₐ and Rₐ, at each occurrence are independently selected from hydrogen and (Ci-Ce)alkyl; and p is an integer from 0 to 4.

Another embodiment is a compound of formula (I), wherein Ring A is phenyl; X₁ is O; X₂ is NRₐ; wherein Rₐ is hydrogen, (Ci-C₆)alkyl, -C(0)0-(Ci-C₆)alkyl or -SO₂C₆H₄- (Ci-C₆)alkyl; R₁ is hydrogen or (Ci-Ce)alkyl, wherein (Ci-Ce)alkyl is unsubstituted or substituted with one or more groups selected from -COOH and -C(0)0-(Ci-Ce)alkyl; R₂ is halogen, CN, -NRₐRₐ, or (Ci-Ce)alkyl, wherein (Ci-Ce)alkyl is unsubstituted or substituted by halogen or CN; R₃ is hydrogen or (Ci-Ce)alkyl; R₄ is 6 to 10 membered nitrogen containing heteroaryl, wherein the heteroaryl is unsubstituted or substituted with one or more groups selected from R₄₁; and wherein R₄₁ at each occurrence is independently selected from the group consisting of halogen, -ORₐ, CN, -NRₐRₐ, -NRₐCORₐ, -COORₐ, -CONRₐRₐ, halo-(Ci-C₆)alkyl and (Ci-C₆)alkyl; Rₐ and Rₐ, at each occurrence are independently selected from hydrogen and (Q-C₆)alkyl and p is an integer from 0 to 4.

Another embodiment is a compound of formula (I), wherein Ring A is phenyl; X₁ is NRₐ; X₂ is -NRₐ; wherein Rₐ is hydrogen, (Ci-C₆)alkyl, -C(0)0-(Ci-C₆)alkyl or -SO₂(Ci-Ce alkyl); R₁ is hydrogen or (Ci-Ce)alkyl which is unsubstituted or substituted with -COOH or -C(0)0-(Ci-C₆)alkyl; R₂ is halogen, CN, -NRₐRₐ, or (Ci-C₆)alkyl, wherein (Q-
alkyl is unsubstituted or substituted by halogen or CN; R₃ is hydrogen or methyl; R₄ is pyridyl, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -NRₐRₐ, halo-(Ci-Cₑ)alkyl, -ORₐ and (Ci-C₆)alkyl, wherein Rₐ and Rₐ at each occurrence are independently selected from hydrogen and (Q-

Another embodiment of the present invention is a compound of formula (I),

![Chemical Structure](image)

formula (I)

in all its isotopic forms, stereoisomeric and tautomeric forms and mixtures thereof in all ratios, or a pharmaceutically acceptable salt, a pharmaceutically acceptable solvate, a prodrug, a polymorph, an N-oxide, or a carboxylic acid isostere thereof;

wherein,

- Ring A is phenyl or 5 or 6-membered nitrogen containing heteroaryl;
- X₁ is O or NRₙ;
- X₂ is O or NRₙ;
- Rₜ is hydrogen, CN, -NRₐRₐ, -ORₐ or (C₁-Cₐ)alkyl, wherein (C₁-Cₐ)alkyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of CN, -NRₐRₐ, nitro, halogen, -ORₐ, -COOH, -C(0)O-(Ci-C₆)alkyl and -P(0)(ORₐ)(ORₐ);
- R₂ is halogen, CN, -NRₐRₐ, or (Ci-Cₑ)alkyl wherein (Ci-C₆)alkyl is unsubstituted or substituted by halogen or CN;
- Rₜ is hydrogen or (Ci-Cₑ)alkyl;
- R₄ is halogen, (C₆-C₄)aryl or heteroaryl; wherein aryl or the heteroaryl is unsubstituted or substituted with one or more groups selected from R₄;
- Rₜ is CN;
- Rₙ is selected from hydrogen, (Ci-Cₐ)alkyl, -C(0)O-(Ci-C₆)alkyl or -S(0)₂-(Ci-
alkyl;

\( R_{41} \) at each occurrence is independently selected from the group consisting of halogen, -OR\(_a\), CN, -NR\(_a\)R\(_b\), -NR\(_a\)COR\(_b\), -COOR\(_a\), -CONR\(_a\)R\(_b\), halo-(C-C\(_6\))alkyl and (C-C\(_6\)alkyl);

\( R_a \) and \( R_b \) at each occurrence are independently selected from hydrogen and (C-C\(_6\)alkyl); and

\( p \) is an integer from 0 to 4.

In one embodiment, \( p \) is 0.

Representative compounds, encompassed in accordance with the present invention include:

- Ethyl 2-(3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate,
- 8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-1-(4-(3-methyloxetan-3-yl)phenyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one,
- Ethyl 2-(3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidin-3-yl)acetate,
- 2-(3-(4-(8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-l-(tert-butoxycarbonyl)azetidin-3-yl)acetic acid,
- Ethyl 2-(3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-l-(methylsulfonyl)azetidin-3-yl)acetate,
- Ethyl 2-(3-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate,
- Ethyl 2-(3-(4-(3-methyl-2-oxo-8-(pyridin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate,
- 2-(3-(4-(3-Memyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetic acid,
- 8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-l-(4-(3-(2-hydroxyethyl)oxetan-3-yl)phenyl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-one,
- 8-(6-Amino-5-methylpyridin-3-yl)-l-(4-(3-(2-hydroxyethyl)oxetan-3-yl)phenyl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-one,
- Ethyl 2-(3-(4-(8-(2,6-difluoropyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-
c[quinolin-1-yl]phenyl)oxetan-3-yl)acetate,
Ethyl 2-(3-(4-(8-(lH-indol-6-yl)-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-c]quinolin-1-
yl)phenyl)oxetan-3-yl)acetate,
2-(3-(4-(8-(2-Fluoro-6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-
c]quinolin-1-yl)phenyl)oxetan-3-yl)acetic acid,
Ethyl 2-(3-(4-(3-methyl-2-oxo-8-(5-(trifluoromethyl)pyridin-3-yl)-2,3-dihydro-lH-imidazo[4,5-
c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate,
Ethyl 2-(3-(4-(8-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-
c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate,
Ethyl 2-(3-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-lH-imidazo[4,5-c]quinolin-
1-yl)phenyl)oxetan-3-yl)acetate,
Ethyl 2-(3-(4-(8-(4-hydroxyphenyl)-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-c]quinolin-
1-yl)phenyl)oxetan-3-yl)acetate,
Ethyl 2-(3-(4-(8-(isoquinolin-1-yl)-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-c]quinolin-
1-yl)phenyl)oxetan-3-yl)acetate,
Methyl 4-(l-(4-(3-(2-ethoxy-2-oxoethyl)oxetan-3-yl)phenyl)-3-methyl-2-oxo-2,3-dihydro-
IH-imidazo[4,5-c]quinolin-8-yl)benzoate,
teri-Butyl 3-(2-ethoxy-2-oxoethyl)-3-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-lH-
imidazo[4,5-c]quinolin-1-yl)phenyl)azetidine-1-carboxylate,
teri-Butyl 3-(2-ethoxy-2-oxoethyl)-3-(4-(3-methyl-2-oxo-8-(pyridin-3-yl)-2,3-dihydro-lH-
imidazo[4,5-c]quinolin-1-yl)phenyl)azetidine-1-carboxylate,
teri-Butyl 3-(2-ethoxy-2-oxoethyl)-3-(4-(8-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-
dihydro- IH-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidine-1-carboxylate,
2-(l-(teri-Butoxycarbonyl)-3-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-lH-
imidazo[4,5-c]quinolin-1-yl)phenyl)azetidin-3-yl)acetic acid,
2-(l-(teri-Butoxycarbonyl)-3-(4-(8-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-
IH-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidin-3-yl)acetic acid,
2-(l-(teri-Butoxycarbonyl)-3-(4-(3-methyl-2-oxo-8-(pyridin-3-yl)-2,3-dihydro-lH-
imidazo[4,5-c]quinolin-1-yl)phenyl)azetidin-3-yl)acetic acid,
8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-l-(4-(3-methoxyoxetan-3-yl)phenyl)-3-methyl-
IH-imidazo[4,5-c]quinolin-2(3H)-one,
Ethyl 2-(3-(4-(8-(6-anmino-5-(trifluoromethyl)pyridin-3-yl)-2-(cyanomino)-3-methyl-2,3-
dihydro-IH-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate,
Ethyl 2-(3-(4-(8-(6-anmino-5-(trifluoromethyl)pyridin-3-yl)-2-(cyanomino)-2,3-dihydro-IH-
imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate,
teri-Butyl 3-(4-(8-(6-anmino-5-(trifluoromethyl)pyridin-3-yl)-2-(cyanomino)-3-methyl-2,3-
dihydro-IH-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl) azetidine-1-
carboxylate,
teri-Butyl 3-(4-(8-(6-anmino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-
IH-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl) azetidine-1-carboxylate,
8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-1-(6-(3-methyloxetan-3-yl)pyridin-3-
yl)-IH-imidazo[4,5-c]quinolin-2(3H)-one and
N-(8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-1-(6-(3-methyloxetan-3-
yl)pyridin-3-yl)-IH-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide, or
an isotopic form, a stereoisomer, a tautomer, a polymorph, a prodrug, or a pharmaceutically
acceptable salt, solvate, an N-oxide or carboxylic acid isosteres thereof.

METHODS OF PREPARATION

The compounds of formula (I) can be prepared using various procedures; one such
procedure is depicted in the Scheme I below. Those with skill in the art will appreciate that
the specific starting compounds; reagents, such as bases, solvents and coupling agents; and
temperature conditions etc. identified in the Schemes can be altered to prepare compounds
encompassed by the present invention. Further, the procedures for the preparation of the
intermediates used in the synthesis of the compounds of formula (I) are illustrated in the
following Schemes A and B. In Scheme A, a process for the preparation of the compounds of
formula (le) which constitute key intermediates of the compounds of formula (I) is
illustrated. For ease of reference, the compounds referred to in the following scheme A are
designated as compound(s) (la), (lb), (lc), (Id) and (le) respectively.
In the compounds referred to in the above Scheme A; X₂ is O or NR₂, wherein R₂ is -C(0)0-(Ci-C₆)alkyl; and R₂, p and ring A are as defined in any one of the above embodiments.

As illustrated in Scheme A, the compound of formula (lb) (wherein X₂ is -O- or NR₂, wherein R₂ is -C(0)0-(Ci-Ce) alkyl) can be prepared by reacting the compound of formula (la) (wherein X₂ is O or NR₂, wherein R₂ is -C(0)0-(Ci-C6)alkyl) with carboxalkoxymethylene triphenylphosphorane such as carbethoxymethylene triphenylphosphorane in the presence of a solvent such as dichloromethane or toluene, at a temperature ranging from about 25 °C to about 110 °C.

The resulting compound of formula (lb) can be treated with boronic acid derivative of formula (lc) (wherein R₂, p and ring A are as defined in any one of the above embodiments), at a temperature ranging from about 20 °C to about 100 °C, in the presence of a catalyst such as cyclooctadiene rhodium chloride dimer and a base such as potassium hydroxide or potassium carbonate to obtain a compound of formula (ld). The resulting compound of formula (ld) can be subjected to reduction in the presence of a reducing agent such as ammonium formate/palladium on carbon (10%) or stannous chloride and an alcoholic solvent such as oHanoi to obtain a compound of formula (le) (wherein X₂ is O or NR₂, wherein R₂ is -C(0)0-(Ci-Ce)alkyl and R₂, p and ring A are as defined in any one of the above embodiments).

In certain embodiments, the compound of formula (le), wherein X₂ is -N-C(0)0-OC(CH₃)₃, can be subjected to deprotection.
In Scheme B a process for the preparation of the compounds of formula (2e) which constitute key intermediates of the compounds of formula (I) is illustrated. For ease of reference, the compounds referred to in the following scheme B are designated as compound(s) (2a), (2b), (2c), (2d) and (2e) respectively.

Scheme B

In the compounds referred to in the above Scheme B; X2 is O; hal is halogen such as bromine or fluorine; and Rj, R2, p and ring A are as defined in any one of the above embodiments.

As illustrated in Scheme B, the compound of formula (2b), can be prepared by reacting the compound of formula (2a) with a compound of formula: [EtOC(0)]2CHRi (wherein R1 is as defined in any one of the above embodiments), which encompasses the specific compounds such as diethylmalonate diethylmethylmalonate, diethylcyanomalonate, diethylaminomalonate and diethylmethoxymalonate; in the presence of a base such as sodium hydride and a solvent such as dimethylformamide at a temperature range from 0 °C to 25 °C. The resulting compound of formula (2b) can be subjected to reduction in the presence of a reducing agent such as lithium aluminum hydride and a solvent such as tetrahydrofuran to form a compound of formula (2c). The resulting compound of formula (2c) can be subjected to cyclization in the presence of a reagent such as tosyl chloride, a reducing agent such as butyl lithium and a solvent such as tetrahydrofuran to form a compound of formula (2d). The resulting compound of formula (2d) can be subjected to reduction in the presence of a reducing agent such as ammonium formate in palladium on carbon to obtain a compound.
of formula (2e) (wherein X2 is O; and Rj, R2, p and ring A are as defined in any one of the above embodiments).

In the following Scheme I, the reaction steps involved in the process for the preparation of the compounds of formula (I) are depicted. For ease of reference, the compounds referred to in the following scheme I are designated as compound(s) (1), (2), (3), (4), (5) and (6) respectively.

Scheme I

In the compounds as depicted in the Scheme I, the variables have the following meanings:

(i) X1 is O or N(CN); X2 is O; Ri, R2, R3, R4, p and ring A are as defined above in any one of the above embodiments; or

(ii) X1 is O or N(CN); X2 is -N(Rj), wherein Rj is -C(0)O-(C1-C6)alkyl, R1 is -CH2C(0)O-(C1-C6)alkyl; R2, R3, R4, p and ring A are as defined above in any one of the
above embodiments.

As illustrated in Scheme I, the compound of formula 1 can be treated with phosphorus oxychloride at a temperature of about 120 °C to obtain the compound of formula (2).

The resulting compound of formula (2) can be reacted with the compound of formula (le) or (2e) (as obtained by following processes depicted in Scheme A or B) in the presence of an acid such as acetic acid or a base such as sodium carbonate in a solvent such as dry dimethylformamide to obtain a compound of formula (3), wherein

(i) X2 is O; R1, R2, p and ring A are as defined above in any one of the above embodiments;

or

(ii) X2 is -N(R4), wherein R4 is -C(0)O-C₆ alkyl, R1 is -CH₂C(0)O-C₆ alkyl, R2, p and ring A are as defined above in any one of the above embodiments. The resulting compound of formula (3) (a nitro-quinolinol) is subjected to catalytic reduction to obtain a compound of formula (4) (quinoline-diamine compound). The resulting compound of formula (4) can be reacted with a reagent such as trichloromethylchloroformate or triphosgene in the presence of a base such as triethylamine or trimethylamine in a solvent such as dichloromethane or chloroform at a temperature of about 0°C to 25 °C to obtain a compound of formula (5) (wherein X₁ is O). Alternatively, the compound of formula (4) can be treated with a reagent such as dimethyl cyanocarbonimidodithioate or diphenyl-n-cyanocarbonimidate in presence of a base such as cesium carbonate and a solvent such as dimethylformamide to obtain a compound of formula (5), wherein X₁ is N(CN).

The resulting compound of formula (5) can be treated with a compound of formula: R₃-halogen (wherein R₃ is as defined for the compounds of formula (I)), in the presence of a base such as sodium hydride and a solvent such as dimethylformamide at a temperature of 25 °C to obtain a compound of formula (6).

The resulting compound of formula (6) can be treated with a compound of formula: R₄-B(OH)₂ in the presence of a coupling agent such as palladium dichlorobistrifluorophosphine and a base such as sodium carbonate or potassium carbonate at a temperature of about 100 °C to 120 °C to obtain a compound of formula (I) (wherein (i) X₁ is O or N(CN); X₂ is O; R₁, R₂, R₃, R₄, p and ring A are as defined in any one of the above embodiments; or (ii) X₁ is O or N(CN); X₂ is -N(R₄), wherein R₄ is -C(0)O-Ci-C₆ alkyl, R₁ is -CH₂C(0)O-Ci-C₆ alkyl, R₂-R₃, R₄, p and ring A are as defined above in any one
of the above embodiments).

The compound of formula (I), wherein X₁ is O or N(CN); X₂ is -N(Rₚ), wherein Rₚ is -C(0)0-(Ci-Cₖ)alkyl, ½ is -CH₂C(0)0-(Ci-Cₖ)alkyl, R₂, R₃, R₄, p and ring A are as defined in any one of the above embodiments, can be treated with an acid such as trifluoroacetic acid in a solvent such as dichloromethane to obtain a compound of formula (I), wherein X₁ is O or N(CN); X₂ is -N(Rₚ), wherein Rₚ is hydrogen, R₁ is -CH₂C(0)0-(Ci-Cₖ)alkyl, R₂, R₃, R₄, p and ring A are as defined above in any one of the above embodiments.

The compound of formula (I), wherein X₁ is O or N(CN); X₂ is -N(Rₚ), wherein Rₚ is hydrogen, Rᵢ is -CH₂C(0)0-(Ci-Cₖ)alkyl, R₂, R₃, R₄, p and ring A are as defined in any one of the above embodiments, can be treated with a sulfonating agent such as (Ci-Cₖ)alkyl-S(0)₂C₆ in the presence of a base such as triethylamine and a solvent such as dichloromethane to obtain a compound of formula (I), wherein X₁ is O or N(CN); X₂ is -N(Rₚ), wherein Rₚ is -S(0)₂(Ci-Cₖ)alkyl, Rᵢ is -CH₂C(0)0-(Ci-Cₖ)alkyl, R₂, R₃, R₄, p and ring A are as defined above in any one of the above embodiments. The compounds of formula (I), wherein Rᵢ is -CH₂C(0)0-(Ci-Cₖ)alkyl, can be treated with a base such as lithium hydroxide in a solvent such as tetrahydrofuran, methanol or a mixture thereof, to obtain a compound of formula (I), wherein R₁ is -CH₂C(0)OH.

According to a further aspect of the present invention, there is provided a process for the preparation of a compound of formula (I) and its pharmaceutically acceptable salt.

The present invention also encompasses certain intermediates formed in the process of preparation of a compound of formula (I) and its pharmaceutically acceptable salt.

According to a further aspect of the present invention, there is provided a process for the preparation of a compound of formula (I),

Wherein,
(i) X₁ is O or N(CN); X₂ is O; Rᵢ, R₂, R₃, R₄, P and ring A are as defined for formula (I); or
(ii) X₁ is O or N(CN); X₂ is -N(Rₚ), wherein Rₚ is -C(0)0-(Ci-Cₖ)alkyl, R₁ is
-CH₂C(0)-(C₆-H₆)alkyl, R₂, R₃, R₄, p and ring A are as defined for formula (I),

comprising the steps:

(a) reacting a compound of formula (2),

(b) subjecting the compound of formula (3) to catalytic reduction, to obtain a compound of formula (4);

wherein, either

(i) X₂ is O; Rᵢ, R₂, p and ring A are as defined in any one of the above embodiments; or

(ii) X₂ is -N(Rᵧ); wherein Rᵧ is -C(0)-(C₆-H₆)alkyl, R₁ is -CH₂C(0)-(C₆-H₆)alkyl, R₂, p and ring A are as defined for formula (I);

(i) with a compound of formula (1e), wherein X₂ is O or NRᵧ, Rᵧ is -C(0)-(C₆-H₆)alkyl, R₂, p and ring A are as defined in any one of the above embodiments, or

(ii) with a compound of formula (2e), wherein X₂ is O and Rj, R₂, p and ring A are as defined in any one of the above embodiments;

in the presence of an acid such as acetic acid or a base such as sodium carbonate in a solvent such as dry dimethylformamide to obtain a compound of formula (3),
wherein (i) $X_2$ is O; $R_i$, $R_2$, $p$ and ring A are as defined for formula (I); or (ii) $X_2$ is $-N(R_y)$, wherein $R_y$ is $-C(0)\_0-C\_1-C\_6$ alkyl, $R_1$ is $-CH_2C(0)\_0-C\_1-C\_6$ alkyl, $R_2$, $p$ and ring A are as defined for formula (I);

(c) treating the compound of formula (4) with a reagent such as trichloromethylchloroformate or trichlorosine in the presence of a base selected from triethylamine or trimethylamine and a solvent such as dichloromethane or chloroform to obtain a compound of formula (5) (wherein $X_1$ is O); or treating the compound of formula (4) with a reagent such as dimethyl cyanocarbonimidodithioate or diphenyl N-cyanocarbonimidate in the presence of a base such as cesium carbonate and a solvent such as dimethylformamide to obtain a compound of formula (5), wherein $X_1$ is N(CN);

(d) treating the compound of formula (5) with a compound of formula, $R_3$-halogen, (wherein $R_3$ is as defined for formula (I)), in the presence of a base such as sodium hydride and solvent such as dimethylformamide to obtain a compound of formula (6).
(6)

wherein (i) $X_i$ is O or N(CN); $X_2$ is O; $R_i$, $R_2$, $R_3$, $p$ and ring A are as defined for formula (I); or (ii) $X_i$ is O or N(CN); $X_2$ is -N($R_y$), wherein $R_y$ is -C(0)-C$_{6}$alkyl; $R_i$ is -CH$_2$C(0)-C$_{6}$alkyl; $R_2$, $R_3$, $p$ and ring A are as defined for formula (I);

(e) treating the compound of formula (6) with a compound of formula: R$_4$-B(OH)$_2$ in the presence of palladium dichlorobistriphenylphosphine as a coupling agent and a base selected from sodium carbonate or potassium carbonate to obtain a compound of formula (I), wherein (i) $X_i$ is O or N(CN); $X_2$ is O; $R_i$, $R_2$, $R_3$, $R_4$, $p$ and ring A are as defined above in any one of the above embodiments; or (ii) $X_i$ is O or N(CN); $X_2$ is -N($R_y$), wherein $R_y$ is -C(0)-C$_{6}$alkyl, $R_i$ is -CH$_2$C(0)-Ci-C$_{6}$alkyl, $R_2$, $R_3$, $R_4$, $p$ and ring A are as defined above.

According to another embodiment of the present invention, there is provided a process for the preparation of a compound of formula (I), wherein $X_i$ is O or N(CN); $X_2$ is -N($R_y$), wherein $R_y$ is hydrogen, $R_i$ is -CH$_2$C(0)-Ci-C$_{6}$alkyl, $R_2$, $R_3$, $R_4$, $p$ and ring A are as defined for formula (I);

(1)

(wherein $X_2$ is NR$_y$ and $R_y$ is hydrogen)

comprising,

treating the compound of formula (1) (wherein $X_i$ is O or N(CN); $X_2$ is -N($R_y$), wherein $R_y$ is -C(0)-d-C$_6$alkyl, $R_i$ is -CH$_2$C(0)-C$_{6}$alkyl, $R_2$, $R_3$, $R_4$, $p$ and ring A are as defined above), with an acid such as trifluoroacetic acid in a solvent such as dichloromethane to obtain a compound of formula (1) (wherein $X_i$ is O or N(CN); $X_2$ is -N($R_y$), wherein $R_y$ is hydrogen, $R_i$ is -CH$_2$C(0)-Ci-Cealkyl, $R_2$, $R_3$, $R_4$, $p$ and ring A are as defined above).
According to another embodiment of the present invention, there is provided a process for the preparation of a compound of formula (I), wherein $X_1$ is O or N(CN); $X_2$ is -N(Ry), wherein $R_2$ is -S(0)₂-C₆ alkyl, $R_i$ is -CH₂C(0)0-C₆ alkyl, $R_2$, $R_3$, $R_4$, $p$ and ring A are as defined for formula (I).

![Diagram](le)

(5)

(wherein $X_2$ is NRy and $R_5$ is -S(0)₂-(C₆)alkyl)

comprising,
treating the compound of formula (I) wherein $X_1$ is O or N(CN); $X_2$ is -N(Ry), wherein $R_y$ is hydrogen, $R_1$ is -CH₂C(0)0-(C₆)alkyl, $R_2$, $R_3$, $R_4$, $p$ and ring A are as defined for formula (I), with a sulfonating agent such as (C₆)alkyl-S(0)₂Cl in presence of a base such as triethylamine and a solvent such as dichloromethane to form a compound of formula (I), wherein $X_1$ is O or N(CN); $X_2$ is -N(Ry), wherein $R_2$ is -S(0)₂-(C₆)alkyl, $R_1$ is -CH₂C(0)0-(C₆)alkyl, $R_2$, $R_3$, $R_4$, $p$ and ring A are as defined for formula (I).

According to another embodiment of the present invention, the compounds of formula (I), wherein $R_1$ is -CH₂C(0)0-(C₆)alkyl is subjected to hydrolysis to obtain a compound of formula (I), wherein $R_1$ is -CH₂C(0)OH.

According to another embodiment, the process for the preparation of the compounds of formula (I), described herein may involve a further step of converting the compound of formula (I) to a pharmaceutically acceptable salt and/or a solvate and/or a prodrug.

According to another embodiment of the present invention, there is provided an intermediate compound represented by the structural formula (le),

![Diagram](le)

(wherein $X_2$ is O or NRy, $R_y$ is -C(0)0(C₆)alkyl, $R_2$, $p$ and ring A are as defined for formula (I).
According to another embodiment of the present invention, there is provided an intermediate compound represented by the structural formula (2e).

\[
\begin{array}{c}
\text{(2e)} \\
\text{X} \\
\text{A} \\
\text{NH}_2 \\
\text{R}_1 \\
\text{R}_2 \\
\end{array}
\]

wherein X2 is O and Rj, R2, p and ring A are as defined for formula (I).

Isotopically labeled forms of the compounds of formula (I) can be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described above and in the subsequent experimental section by using an appropriate isotopically labeled reagent in place of the corresponding non-labeled reagent.

In an embodiment, the compounds of formula (I) in their free base form are converted to their corresponding pharmaceutically acceptable salts. The compounds of the present invention represented by formula (I), which contain acidic groups, may be converted into salts with pharmaceutically acceptable bases. Such salts include, but are not limited to, alkali metal salts, like lithium, sodium and potassium salts; alkaline earth metal salts like calcium and magnesium salts; ammonium salts; [tris(hydroxymethyl)aminomethane], trimethylamine salts and diethylamine salts; salts with amino acids such as lysine, arginine and guanidine and salts with N,N-Dimethylimidodicarbonimidic diamide (metformin).

The compounds of the present invention represented by formula (I), which contain one or more basic groups, i.e. groups which can be protonated, can form an addition salt with an inorganic or organic acid. Examples of suitable acid addition salts include but are not limited to, hydrochlorides, hydrobromides, hydrofluorides, nitrates, acetates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, cinnamates, citrates, ethanesulfonates, fumarates, glucuronates, glutamates, glycolates, ketoglutarates, lactates, maleates, malonates, mesylates, oxalates, palmoates, perchlorates, phosphates, picrates, salicylates, succinates, sulfamates, sulfates, tartrates, tosylates and other acids known to the person skilled in the art.

Another embodiment is a compound of formula (I), wherein the pharmaceutically acceptable salt is selected from (a) an inorganic acid addition salt selected from hydrochloride, sulphate, phosphate and nitrate, and (b) an organic acid addition salt selected from acetate, maleate, tartarate, citrate, mesylate, besylate, tosylate and cinnamate.
The pharmaceutically acceptable salts of the present invention can be synthesized from the subject compound i.e. the compound of formula (I), which contains a basic or an acidic moiety, by conventional chemical methods. Generally, the salts can be prepared by treating the compound of formula (I) in its free base or acid form with an appropriate amount of the desired salt-forming inorganic or organic acid or a base in a suitable solvent or dispersant, or by cation or anion exchange. Suitable solvents used for preparing pharmaceutically acceptable salts of the compounds of Formula (I) include, for example, ethyl acetate, ether, alcohols, acetone, tetrahydrofuran, dioxane or mixtures of these solvents. These salts can also be used for purification of the compounds obtained.

It is further intended to encompass various polymorphs of compounds of formula (I) within the scope of the present invention. Various polymorphs of the compounds of formula (I), forming part of this invention can be prepared by crystallization of the compounds of formula (I) under different conditions. The different conditions are, for example, using different solvents that are commonly used or their mixtures for crystallization; crystallization at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs can also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs can be determined by infrared spectroscopy (IR), solid probe nuclear magnetic resonance (NMR) spectroscopy, differential scanning calorimetry (DSC), powder x-ray diffraction or such other techniques.

METHODS OF TREATMENT

The compounds of the present invention can be used for the treatment of proliferative diseases or disorders in a subject, comprising the step of administering to said subject a therapeutically effective amount of a compound of this invention or a pharmaceutically acceptable salt of the said compound or a composition of this invention.

As such, compounds of the present invention can be used to treat tumor cells, and thereby assist in reducing the size of a tumor.

The compounds of the present invention can be used for the treatment of inflammatory diseases in a subject, comprising the step of administering to said subject a therapeutically effective amount of a compound of this invention or a pharmaceutically acceptable salt of the said compound or a composition of this invention.
Compounds of the present invention can be used for the treatment of angiogenesis related disorders.

Compounds of the present invention inhibit one or more kinases including, PI3K, mTOR and ALK1, thus having utility in the treatment of diseases or disorders, which reciprocates to the inhibition of the activity of the said kinases.

According to another aspect of the present invention, there is provided compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of proliferative diseases, inflammation and angiogenesis related disorders.

According to another aspect of the present invention, there is provided compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of a proliferative disease or disorder mediated by a kinase selected from the group consisting of phosphatidylinositol 3 kinase (PI3 K), mammalian target of rapamycin (mTOR) and activin receptor-like kinase 1(ALK1) or combinations thereof.

According to another aspect of the present invention, there is provided compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of a diseases or disorders mediated by a PI3 kinase.

According to another aspect of the present invention, there is provided a method for the treatment of diseases or disorders mediated by a kinase selected from the group consisting of PI3 kinase, mTOR and ALK-1 or combinations thereof, comprising administering to a subject in need thereof; a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to another aspect of the present invention, there is provided a method for the treatment of diseases or disorders mediated by PI3 kinase, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to another aspect of the present invention, there is provided a method for the treatment of proliferative diseases, inflammatory diseases or angiogenesis related disorders mediated by a kinase selected from the group consisting of PI3 kinase, mTOR and ALK-1 or combination of said kinases, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to another aspect of the present invention, there is provided a method for
the treatment of proliferative diseases, inflammatory diseases or angiogenesis related
disorders mediated by PI3 kinase, comprising administering to a subject in need thereof; a
therapeutically effective amount of a compound of formula (I) or a pharmaceutically
acceptable salt thereof.

According to another aspect of the present invention, there is provided a method for
the treatment of proliferative diseases or disorders mediated by a kinase selected from the
group consisting of phosphatidylinositol 3 kinase (PI3K), mammalian target of rapamycin
(mTOR) and activin receptor-like kinase 1 (ALK-1) or a combination of said kinases,
comprising administering to a subject in need thereof; a therapeutically effective amount of a
compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to another aspect of the present invention, there is provided a method for
the treatment of proliferative diseases or disorders mediated by PI3 kinase, comprising
administering to a subject in need thereof; a therapeutically effective amount of a compound
of formula (I) or a pharmaceutically acceptable salt thereof.

According to another aspect of the present invention, there is provided a method of
inhibiting the activity of one or more kinases selected from a group consisting of PI3 kinase,
mTOR and ALK-1, comprising contacting the said kinase with an effective amount of a
compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to another aspect of the present invention, the proliferative disease mediated
by a kinase selected from the group consisting of phosphatidylinositol 3 kinase (PI3K),
mammalian target of rapamycin (mTOR) and activin receptor-like kinase 1 (ALK-1) or a
combination of said kinases is cancer.

According to another aspect of the present invention, the cancer is solid cancer or
hematological cancer.

According to another embodiment of the present invention, the cancer is selected
from the group consisting of leukemia such as acute lymphocytic leukemia; acute myeloid
leukemia; adult acute myeloid leukemia; acute lymphoblastic leukemia; chronic lymphocytic
leukemia; chronic myeloid leukemia; hairy cell leukemia, lung cancer including non-small-
cell lung cancer and small-cell lung cancer, brain tumors such as brain stem glioma;
glioblastoma; astrocytoma including cerebellar astrocytoma and cerebral astrocytoma, visual
pathway and hypothalamic glioma; supratentorial primitive neuroectodermal and pineal
tumors; medulloblastoma, lymphoma such as primary central nervous system lymphoma;
non-Hodgkin's lymphoma particularly mantle cell lymphoma, Hodgkin's disease, liver cancer such as hepatocellular carcinoma, kidney cancer such as renal cell carcinoma and Wilms' tumor, sarcoma such as Ewing's sarcoma family of tumors; osteosarcoma; rhabdomyosarcoma; soft tissue sarcomas, mesothelioma, bladder cancer, breast cancer, endometrial cancer, head and neck cancer, melanoma, cervical cancer, thyroid cancer, gastric cancer, germ cell tumor, cholangiocarcinoma, extracranial cancer, malignant fibrous histiocytoma of bone, retinoblastoma, esophageal cancer, multiple myeloma, oral cancer, pancreatic cancer, ependymoma, neuroblastoma, skin cancer, ovarian cancer, recurrent ovarian cancer, prostate cancer, testicular cancer, colorectal cancer, lymphoproliferative disease, refractory multiple myeloma, resistant multiple myeloma and myeloproliferative disorder, or a combination of one or more of the preceding cancers.

According to another embodiment of the present invention, the cancer is selected from the group consisting of leukemia, lung cancer, brain tumors, Hodgkin's disease, liver cancer, kidney cancer, bladder cancer, breast cancer, endometrial cancer, head and neck cancer, lymphoma, melanoma, cervical cancer, thyroid cancer, gastric cancer, germ cell tumor, cholangiocarcinoma, extracranial cancer, sarcoma, mesothelioma, malignant fibrous histiocytoma of bone, retinoblastoma, esophageal cancer, multiple myeloma, oral cancer, pancreatic cancer, neuroblastoma, skin cancer, ovarian cancer, recurrent ovarian cancer, prostate cancer, testicular cancer, colorectal cancer, lymphoproliferative disease, refractory multiple myeloma, cancer of urinary tract, resistant multiple myeloma and myeloproliferative disorder.

According to another embodiment of the present invention, the cancer is selected from the group consisting of breast cancer, prostate cancer, pancreatic cancer, lung cancer (non-small-cell lung cancer and small-cell lung cancer), head and neck cancer, ovarian cancer, colon cancer, rectal cancer, kidney cancer, gastric cancer, non-Hodgkin's lymphoma, primary central nervous system lymphoma, glioblastoma and astrocytoma.

According to another aspect of the present invention, there is provided a method for the treatment of inflammatory diseases or disorders, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to further aspect of the present invention, there is provided a method for the treatment of diseases mediated by TNF-a or IL-6, comprising administering to a subject
in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to another aspect of the present invention, there is provided a method for the treatment of inflammatory diseases or disorders mediated by PI3 kinase and/or mTOR, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to another aspect of the present invention, the inflammatory diseases or disorders are selected from the group consisting of rheumatoid arthritis, Crohn's disease, ulcerative colitis, inflammatory bowel disease, chronic non-rheumatoid arthritis, osteoporosis, septic shock, psoriasis and atherosclerosis or a combination of said inflammatory diseases or disorders.

According to another aspect of the present invention, there is provided a method for the treatment of angiogenesis related disorders mediated by one or more kinases, including but not limited to, PI3 kinase, mTOR and ALK-1 or a combination of said kinases comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to another aspect of the present invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof; for use in the treatment of angiogenesis related disorders mediated by vascular endothelial growth factor (VEGF).

According to another aspect of the present invention, the angiogenesis related disorder is an inflammatory disorder.

According to another aspect of the present invention, the inflammatory disorder which is an angiogenesis related disorder is selected from the group consisting of immune and non-immune inflammation, chronic articular rheumatism, disorders associated with inappropriate or inopportune invasion of vessels such as diabetic retinopathy, neovascular glaucoma, capillary proliferation in atherosclerotic plaques and osteoporosis.

According to another aspect of the present invention, the angiogenesis related disorder is selected from the group consisting of solid tumor, solid tumor metastasis, angiofibroma, retrolental fibroplasia, hemangioma or Kaposi's sarcoma.

According to another aspect of the present invention, there are provided methods for the manufacture of medicaments, comprising compounds of formula (I) or pharmaceutically acceptable salts thereof, for the treatment of one or more cancers as described herein above.
According to another aspect of the present invention, there are provided compounds of formula (I) or pharmaceutically acceptable salts thereof, for use in the treatment of one or more cancers as described herein above.

According to another aspect of the present invention, there is provided use of compounds of formula (I) or pharmaceutically acceptable salts thereof, for the manufacture of medicaments for the treatment of one or more cancers as described herein above.

According to another aspect of the present invention, there are provided methods for the manufacture of medicaments, comprising compounds of formula (I) or pharmaceutically acceptable salts thereof, for the treatment of angiogenesis related disorders.

According to another aspect of the present invention, there is provided use of compounds of formula (I) or pharmaceutically acceptable salts thereof, for the manufacture of medicaments for the treatment of angiogenesis related disorders.

According to another aspect of the present invention, there are provided methods for the manufacture of medicaments, comprising compounds of formula (I) or pharmaceutically acceptable salts thereof; for the treatment of inflammatory diseases or disorders.

According to another aspect of the present invention, there is provided use of compounds of formula (I) or pharmaceutically acceptable salts thereof; for the manufacture of medicaments for the treatment of inflammatory diseases or disorders.

According to another aspect of the present invention, a compound of formula (I) can be employed as a sole therapy or in combination with one or more further therapeutic agents for the treatment of indications described herein, such as cancer.

A compound of formula (I) can be administered either simultaneously or before or after the other therapeutic agent, either separately by the same or different route of administration, or together in the same pharmaceutical formulation.

PHARMACEUTICAL COMPOSITIONS

The pharmaceutical preparations according to the invention are prepared in a manner known per se and familiar to one skilled in the art. Pharmaceutically acceptable inert inorganic and/or organic carriers and/or additives can be used in addition to the compounds of formula (I), and/or their physiologically tolerable salts. For the production of pills, tablets, coated tablets and hard gelatin capsules it is possible to use, for example, lactose, corn starch or derivatives thereof, gum arabica, magnesia or glucose, etc. Carriers for soft gelatin
capsules and suppositories are, for example, fats, waxes, natural or hardened oils, etc. Suitable carriers for the production of solutions, for example injection solutions, or for emulsions or syrups are, for example, water, physiological sodium chloride solution or alcohols, for example, ethanol, propanol or glycerol, sugar solutions, such as glucose solutions or mannitol solutions, or a mixture of the various solvents which have been mentioned.

The pharmaceutical preparations or compositions normally contain about 1 to 99%, for example, about 5 to 70%, or from about 5 to about 30% by weight of the compound of the formula (I) or pharmaceutically acceptable salt thereof. The amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, as the active ingredient in the pharmaceutical preparations normally ranges from about 1 to 1000 mg.

The dose of the compounds of this invention, which is to be administered, can cover a wide range. The dose to be administered daily is to be selected so as to produce the desired therapeutic effect. A suitable dose is about 0.1 mg/kg to 50 mg/kg of the compound of formula (I) or pharmaceutically acceptable salt thereof, for example, about 1 mg/kg to 25 mg/kg of a compound of formula (I) or a pharmaceutically acceptable salt thereof, with the typical dose being about 1 mg/kg to 10 mg/kg of a compound of formula (I) or a pharmaceutically acceptable salt thereof. If required, higher or lower daily doses can also be administered. Actual dosage levels of the compounds of formula (I) which are the active ingredients contained in the pharmaceutical compositions of this invention can be varied so as to obtain an amount of the active ingredient, which is effective to achieve the desired therapeutic response for a particular subject (patient).

The pharmaceutical composition can be administered orally, for example in the form of pills, tablets, coated tablets, lozenges, capsules, dispersible powders or granules, suspensions, emulsions, syrups or elixirs. Administration, however, can also be carried out rectally, for example in the form of suppositories, or parenterally, for example intravenously, intramuscularly or subcutaneously, in the form of injectable sterile solutions or suspensions, or topically, for example in the form of solutions or ointments or transdermally, for example in the form of transdermal patches, or in other ways, for example in the form of aerosols, nasal sprays or nasal drops.

The selected dosage level will depend upon a variety of factors including the therapeutic activity of the specific compound of the present invention employed, the route of
administration, the time of administration, the rate of excretion of the particular compound
being employed, the duration of the treatment, other drugs, compounds and/or materials used
in combination with the particular compounds employed, the age, sex, weight, condition,
general health and prior medical history of the patient being treated, and like factors well
known in the medical arts.

In addition to the active ingredient i.e. the compound of formula (I) and/or its
pharmaceutically acceptable salts and carrier substances, the pharmaceutical preparations or
compositions can contain additives such as, for example, fillers, antioxidants, dispersants,
emulsifiers, defoamers, flavors, preservatives, solubilizers or colorants. They can also contain
one or more compounds of formula (I) and/or their pharmaceutically acceptable salts.
Furthermore, in addition to at least one compound of formula (I) and/or its pharmaceutically
acceptable salt, the pharmaceutical preparations can also contain one or more other
therapeutically or prophylactically active ingredients.

By "pharmaceutically acceptable" it is meant the carrier, diluent, excipients, and/or
salt must be compatible with the other ingredients of the formulation, and not deleterious to
the recipient thereof.

According to another aspect of the present invention there is provided a
pharmaceutical composition comprising a therapeutically effective amount of a compound of
formula (i) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically
acceptable excipient or carrier.

According to another aspect of the present invention there is provided a
pharmaceutical composition, comprising a therapeutically effective amount of a compound of
formula (I) or a pharmaceutically acceptable salt or a pharmaceutically acceptable solvate
thereof and at least one further pharmaceutically active compound, together with a
pharmaceutically acceptable excipient or carrier. A therapeutically or prophylactically active
compound in combination with one or more compounds of formula (I) for treatment of cancer
can be selected from, but not limited to, one or more of the following groups: (i) Kinase
inhibitors such as gefitinib, erlotinib, lapatinib, bevacizumab, avastin, sorafenib, Bcr-Abl
kinase inhibitors, such as imitinib and nilotinib or LY-317615 (Eli Lilly and Co.) (ii)
Alkylating agents such as mitomycin C, busulfan, oxaliplatin, cisplatin, carboplatin,
procarbazine or dacarbazine (iii) Antimetabolites such as methotrexate, mercaptopurine,
thioguanine, fludarabine phosphate, fluorouracil, vinblastine, vincristine, gemcitabine or
paclitaxel (iii) Antibiotics such as anthracyclines, dactinomycin or bleomycin (iv) Hormonal agents such as tamoxifen, flutamide, GnRH (Gonadotropin-Releasing Hormone) agonists or aromatase inhibitors or (v) Cancer vaccines such as avicine, oregovomab or theratope.

It is understood that modifications that do not substantially affect the activity of the various embodiments of this invention are included within the invention disclosed herein. Accordingly, the following examples are intended to illustrate but not to limit the present invention.

EXEMPLIFICATION

10 Synthetic Methods

The invention is further understood by reference to the following examples, which are intended to be purely exemplary of the invention. The present invention is not limited in scope by the exemplified embodiments, which are intended as illustrations of single aspects of the invention only. Any methods that are functionally equivalent are within the scope of the invention. Various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications fall within the scope of the appended claims. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art.

Nomenclature of the compounds exemplified in the present invention was derived from Chemdraw Ultra version 9.0.1 CambridgeSoft Corporation, Cambridge.

Reagents were purchased from commercial suppliers such as Labex Corporation, India; Spectrochem Ltd., India; Combi-Blocks Inc., CA, Clairvoyant Chemicals, India Avra Synthesis, India and Sigma Aldrich Chemical company and were are used as such.

Unless otherwise stated all temperatures are in degree Celsius. Also, in these examples and elsewhere, abbreviations have the following meanings:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>BSA</td>
<td>Bovine Serum Albumin</td>
</tr>
<tr>
<td>CHCl₃</td>
<td>Chloroform</td>
</tr>
<tr>
<td>CDCl₃</td>
<td>Deuterated Chloroform</td>
</tr>
<tr>
<td>HCl</td>
<td>hydrochloric acid</td>
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Preparation of Intermediates
Intermediate 1: Ethyl 2-(oxetan-3-ylidene)acetate
Carbethoxymethylene triphenyl phosphorane (74.5 mmol) was added to a solution of oxetane-3-one (67.7 mmol) in dichloromethane at RT. The reaction mixture was stirred for 0.5 hour at RT. The reaction mixture was concentrated under vacuum and purified (silica gel column, EtOAc/petroleum ether as eluent) to obtain the title compound. Yield: 93%; 1H NMR (300 MHz, CDCl3): δ 5.65 (s, 1H), 5.53 (s, 2H), 5.31 (s, 2H), 4.22-4.45 (q, 2H), 1.31-1.26 (t, 3H).

Intermediate 2: Ethyl 2-(3-(4-nitrophenyl)oxetan-3-yl)acetate
Potassium hydroxide solution (1.5 M, 38.9 mL) was added to a solution of cyclooctadiene rhodium chloride dimer (2.33 mmol) in dry dioxane and stirred for 1 minute, followed by the addition of 4-nitrophenyl boronic acid (117 mmol) and ethyl 2-(oxetan-3-ylidene)acetate
(Intermediate 1, 58.5 mmol). The entire reaction mixture was stirred for 18 hours. Reaction mixture was partitioned between ether and brine. The organic layer was concentrated and purified (silica gel column, EtOAc/ petroleum ether as eluent) to obtain the title compound. Yield: 90%; \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 8.25-8.22 (d, J=8.7 Hz, 2H), 7.41-7.38 (d, J=8.7Hz, 2H), 5.03-5.01 (d, J=6.0 Hz, 2H), 4.92-4.90 (d, J=6.0 Hz, 2H), 4.05-4.00 (q, 2H), 3.21 (s, 2H), 1.18- 1.13 (t, 3H).

Intermediate 3: Ethyl 2-(3-(4-aminophenyl)oxetan-3-yl)acetate

Ammonium formate (141 mmol) was added to a solution of ethyl 2-(3-(4-nitrophenyl)oxetan-3-yl)acetate ((Intermediate 2, 28.3 mmol) in dry EtOH and stirred. Palladium carbon (7 mmol) was added to the reaction mixture in an inert atmosphere. The reaction mixture was refluxed for 2 hours, cooled and filtered. The filtrate was concentrated and purified (silica gel column, EtOAc/ petroleum ether as eluent) to obtain the title compound. Yield: 97%; \(^1\)H NMR (300 MHz, DMSO-d\(_6\)): δ 6.88-6.85 (d, J=7.8Hz, 2H), 6.52-6.49 (d, J=7.8Hz, 2H), 4.97 (s, 2H), 4.70 (s, 4H), 3.94 (q, 2H), 2.99 (s, 2H), 1.07 (t, 3H).

Intermediate 4: Diethyl 2-(2-bromo-4-nitrophenyl)-2-methylmalonate

Sodium hydride was added to a solution of diethyl-2-methylmalonate (125 mmol) in anhydrous DMF at 0 °C under an inert atmosphere. The reaction mixture stirred for 10 minutes followed by addition of 2-bromo-l-fluoro-4-nitrobenzene (113 mmol). The reaction mixture was further stirred at RT and the solvent was evaporated. The residue was dissolved in DCM and partitioned with brine. The DCM layer was separated and dried over sodium sulfate. The solvent was evaporated and the crude solid was used for next step.

Intermediate 5: 2-(2-Bromo-4-nitrophenyl)-2-methylpropane-1,3-diol

Lithium aluminium hydride (22 mmol, 1 mL in THF) was slowly added to a solution of diethyl 2-(2-bromo-4-nitrophenyl)-2-methylmalonate (Intermediate 4, 20 mmol) in anhydrous THF at 0 °C under an inert atmosphere. The reaction was quenched with MeOH at 0 °C after about 10 minutes. The reaction mixture was diluted with DCM and washed with 1N HCl. The organic layer was separated, dried over sodium sulfate and concentrated. The crude product was purified (silica gel column, EtOAc/ petroleum ether as eluent) to obtain the title compound. Yield: 18%; \(^1\)H NMR (300 MHz, DMSO-d\(_6\)): δ 8.33 (bs, 1H), 8.17-8.14 (bd, J=8.7 Hz, 1H), 7.77-7.47 (d, J=8.7 Hz, 1H), 4.79-4.76 (t, 2H, 2-OH exchanged in D\(_2\)O), 3.98-
3.93 (m, 2H), 3.83-3.78 (m, 2H), 1.41 (s, 3H).

Intermediate 6: 3-(2-Bromo-4-nitrophenyl)-3-methyloxetane

2-(2-Bromo-4-nitrophenyl)-2-methylpropane-1,3-diol (Intermediate 5, 3.45 mmol) was stirred in THF at 0 °C. Butyl lithium (4.14 mmol) was added to the reaction mixture followed by the addition of tosyl chloride. The reaction mixture was stirred at RT for 1 hour, cooled to 0 °C. Butyl lithium was again added and the reaction mixture was heated at 65 °C for 2 hours. After completion of the reaction, ether was added to the reaction mixture and washed with saturated solution of NaHCO₃. The organic layer was separated, washed with water, dried over sodium sulfate and concentrated. The crude product was purified (silica gel column, EtOAc/petroleum ether as eluent) to obtain the title compound. Yield: 29%; ¹H NMR (300 MHz, DMSO-de): δ 8.38 (bs, 1H), 8.23-8.21 (bd, J = 6.6 Hz, 1H), 7.42-7.39 (d, J = 8.7 Hz, 1H), 4.96-4.94 (d, 2H), 4.54-4.52 (d, 2H), 1.74 (s, 3H).

Intermediate 7: 4-(3-Methyloxetan-3-yl)aniline

Ammonium formate (9.19 mmol) was added to 3-(2-bromo-4-nitrophenyl)-3-methyloxetane (Intermediate 6, 1.83 mmol) in dry EtOH and the reaction mixture was stirred, followed by the addition of palladium carbon in an inert atmosphere. The reaction mixture was refluxed for 2 hours. Reaction mixture was cooled and filtered. The filtrate was concentrated and purified (silica gel column, EtOAc/petroleum ether as eluent) to obtain the title compound. Yield: 46%; ¹H NMR (300 MHz, DMSO-de): δ 6.91-6.89 (d, J = 8.1 Hz, 2H), 6.55-6.52 (d, J = 8.1 Hz, 2H), 4.94 (s, 2H), 4.71-4.69 (d, 2H), 4.45-4.43 (d, 2H), 1.55 (s, 3H); MS: 164.2 (M+1).

Intermediate 8: teri-Butyl 3-(2-ethoxy-2-oxoethylidene)azetidine-1-carboxylate

teri-Butyl 3-oxoazetidine-1-carboxylate (29.2 mmol) and ethyl 2-(triphenylphosphoranylidene)acetate (35 mmol) were suspended in toluene (25 mL) and the reaction mixture was heated at 110 °C for 2 hours. The solvent was evaporated and the residue was purified (silica gel column, EtOAc/petroleum ether as eluent). Yield: 94%; ¹H NMR (300 MHz, CDCl₃): δ 5.64 (bs, 1H), 5.53-5.51 (m, 2H), 5.32-5.31 (m, 2H), 4.18 (q, J = 6.89, 2H), 1.47 (s, 9H), 1.27 (s, J = 6.89 Hz, 3H); MS: 243 (M+1).

Intermediate 9: teri-Butyl 3-(2-ethoxy-2-oxoethyl)-3-(4-nitrophenyl)azetidine-1-carboxylate
Aqueous K₂CO₃ solution (1.5 M, 62.2 mmol) was added to a solution of cyclooctadiene rhodium chloride dimer (1.03 mmol) in 1,4-dioxane (20 mL) and stirred for 5 minutes, followed by the addition of (4-nitrophenyl)boronic acid (20.72 mmol) and teri-butyl 3-(2-ethoxy-2-oxoethylidened)azetidine-1-carboxylate (Intermediate 8, 62.2 mmol) in THF (10 mL) successively. The reaction mixture was irradiated with microwave (300 W) at 100 °C for 5 minutes, then diluted with water and extracted using EtOAc. The organic layer was dried over sodium sulfate, filtered, concentrated and purified (silica gel column, EtOAc/petroleum ether) to obtain the title compound. Yield: 26%; ¹H NMR (300 MHz, CDCl₃): δ 7.42-7.32 (m, 4H), 4.29-4.22 (m, 4H), 4.05-4.01 (q, J=8.7 Hz, 2H), 3.05 (s, 2H), 1.59 (s, 9H), 1.17-1.14 (t, J=9 Hz, 3H); MS: 387 (M+Na).

Intermediate 10: teri-Butyl 3-(4-aminophenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate

Stannous chloride (5.38 mmol) was added to an ethanolic solution of teri-butyl 3-(2-ethoxy-2-oxoethyl)-3-(4-nitrophenyl)azetidine-1-carboxylate (Intermediate 9, 1.345 mmol) and the reaction mixture was heated at 70 °C for 1 hour. After completion of the reaction, the solvent was evaporated and the residue was dissolved in EtOAc and quenched with 10 M NaOH aqueous solution. The organic layer was separated, dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl₃) to obtain the title compound.

Yield: 33%; ¹H NMR (300 MHz, DMSO-d₆): δ 6.90-6.87 (d, J=9Hz, 2H), 6.51-6.48 (d, J=9Hz, 2H), 4.99 (s, 2H), 4.04-3.88 (m, 5H), 2.86 (s, 2H), 1.23 (s, 9H), 1.08-1.03(t, J=6Hz, 3H); MS: 357 (M+Na).

Intermediate 11: 6-bromo-4-chloro-3-nitroquinoline

A solution of 6-bromo-3-nitroquinolin-4-ol (37.2 mmol) in POCl₃ (50 mL) was stirred for 3 hours at 120 °C. After the completion of the reaction, the reaction mixture was cooled to RT and poured slowly into ice-water and extracted with DCM. The organic layer was washed with ice cooled water, dried over Na₂SO₄ and concentrated. The crude product was used in the further steps.

Intermediate 12: 6-bromo-N-(4-(3-methoxyoxetan-3-yl)phenyl)-3-nitroquinolin-4-amine

Step 1: N,N-Dibenzyl-4-bromoaniline

Sodium carbonate (305 mmol) was added to a solution of 4-bromoaniline (102 mmol) in
DMF (150 mL) and the reaction mixture was stirred, followed by the drop wise addition of benzyl bromide (224 mmol). The reaction mixture was heated at 80 °C for 5 hours. After completion of the reaction, the reaction mixture was filtered and the residue was washed with EtOAc. The filtrate was evaporated to obtain the title compound. Yield: 98%; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 7.37-7.32 (m, 4H), 7.29-7.22 (m, 8H), 6.62 (d, \(J=9\)Hz, 2H), 4.64 (s, 4H); MS: 352.

Step 2: 3-(4-(Dibenzylamino)phenyl) oxetan-3-ol
Butyl Lithium (248 mmol, 1.6M) was added drop wise to a cold solution (-78 °C) of N,N-dibenzyl-4-bromoaniline (compound of step 1, 99 mmol) in dry THF under nitrogen atmosphere. The temperature was maintained for 1 hour. Oxetan-3-one (109 mmol) was added and the reaction mixture was stirred at RT for 2 hours. After completion of the reaction, the reaction mixture was quenched with saturated solution of ammonium chloride, stirred for 15 minutes. The organic layer was separated, dried over sodium sulfate and evaporated. The title compound obtained as residue was purified (silica gel column, 25% EtOAc: 75% petroleum ether as eluent). Yield: (51%); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 7.50-7.32 (m, 4H), 7.30-7.24 (m, 8H), 6.68 (d, \(J=8.7\)Hz, 2H), 5.98 (s, 1H), 4.70 (s, 4H), 4.63-4.60 (m, 4H); MS: 346(M+1)+.

Step 3: N,N-dibenzyl-4-(3-methoxyoxetan-3-yl)aniline
Sodium hydride (39.1 mmol) was added to an ice-cold solution of 3-(4-(dibenzylamino)phenyl)oxetan-3-ol (compound of step 2, 26.1 mmol) in DMF (50 mL) and the reaction mixture was stirred for 30 minutes. Methyl iodide (39.1 mmol) was added and the reaction mixture was further stirred for 1 hour. After completion of the reaction, the reaction mixture was quenched reaction mixture with water and stirred for 10 minutes. The aqueous layer was extracted with EtOAc. The organic layer was dried over sodium sulfate and evaporated to obtain the title product. Yield: 96%; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 7.35-7.31 (m, 4H), 7.21-7.23 (m, 6H), 7.12 (d, \(J=8.4\)Hz, 2H), 6.70 (d, \(J=8.7\)Hz, 2H), 4.71 (s, 4H), 4.66 (m, 4H), 2.90 (s, 3H); MS: 360 (M+1)+.

Step 4: 4-(3-methoxyoxetan-3-yl)aniline
N, N-dibenzyl-4-(3-methoxyoxetan-3-yl)aniline (22.26 mmol) was dissolved in MeOH and CHCl\(_3\) and subjected to hydrogenation at hydrogen pressure of 300 psi and temperature of 50 °C for 5 hours in hydrogenation apparatus in presence of Pearlman’s catalyst (2.226 mmol). After completion of the reaction, the reaction mixture was filtered and the residue was
washed with methanol. The filtrate was evaporated and the crude mass was purified (silica gel column, 3% MeOH: 97% CHCl₃ as eluent). Yield: 36%; ¹H NMR (300 MHz, DMSO-d₆): δ 7.05-7.00 (m, 2H), 6.59 (d, J=8.7Hz, 2H), 5.15 (s, 2H), 4.70-4.65 (m, 4H), 2.91 (s, 3H); MS: 180 (M+1)⁺.

EXAMPLES

Example 1: Ethyl 2-(3-(4-(6-amino-3-nitro-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-4-yl)amino)phenyl)oxetan-3-yl)acetate (compound of step 2, 1.53 mmol) in EtOAc was stirred for 18 hours. After completion of the reaction, water was added and the reaction mixture was filtered. The residue was washed with water to obtain the title compound acid free. The title compound was recovered from the filtrate by partitioning the aqueous phase with EtOAc. The organic layer was separated, dried over sodium sulfate and concentrated, to obtain the title compound. Yield: 85%; ¹H NMR (300 MHz, DMSO-d₆): δ 10.07 (s, 1H), 9.07 (s, 1H), 8.69 (s, 1H), 8.02-7.99 (d, J = 8.7Hz, 1H), 7.94-7.91 (d, J =8.7Hz, 1H), 7.24-7.21 (d, J = 8.4Hz, 2H), 7.09-7.06 (d, J = 8.4Hz, 2H), 4.78 (m, 4H), 3.95 (q, 2H), 3.12 (s, 2H), 1.10 (t, 3H).

Step 2: Ethyl 2-(3-(4-(3-amino-6-bromoquinolin-4-yl)amino)phenyl)oxetan-3-yl)acetate

Stannous chloride (9.69 mmol) was added to a suspension of ethyl 2-(3-(4-(6-bromo-3-nitroquinolin-4-yl)amino)phenyl)oxetan-3-yl)acetate (compound of step 1, 3.23 mmol) in EtOAc and the reaction mixture was stirred at RT for 2 hours. After completion of the reaction, EtOAc was added and quenched with 10 M NaOH. Organic layer was separated, concentrated and purified (silica gel column MeOH/CHCl₃ eluent) to obtain the title compound. Yield: 43%; ¹H NMR (300 MHz, DMSO-d₆): δ 8.61 (s, 1H), 7.84-7.75 (m, 3H), 7.47-7.44 (d, J=8.4 Hz, 1H), 7.03-7.00 (d, J=8.1 Hz, 2H), 6.51-6.48 (d, J=7.8 Hz, 2H), 5.42 (s, 2H), 4.73 (m, 4H), 3.94-3.87 (q, 2H), 3.03 (s, 2H), 1.06-1.01 (t, 3H); MS: 457.3(M+1).

Step 3: Ethyl 2-(3-(4-(8-bromo-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-4-yl)amino)phenyl)oxetan-3-yl)acetate

Triethylamine (12.27 mmol) was added to a solution of ethyl 2-(3-(4-(3-amino-6-bromoquinolin-4-yl)amino)phenyl) oxetan-3-yl)acetate (compound of step 2, 1.53 mmol) in
dry DCM. The reaction mixture was cooled to 0 °C, triphosgene (1.53 mmol) dissolved in DCM was added slowly and stirred for 2 hours. After completion of the reaction, DCM was added and washed with water. Aqueous layer was extracted with DCM. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 62%; ¹H NMR (300 MHz, DMSO-d₆): δ 11.82 (s, 1H), 8.79 (s, 1H), 7.95-7.92 (d, J = 9.0 Hz, 1H), 7.66 (s, 1H), 7.63 (s, 4H), 7.06 (s, 1H), 4.92-4.85 (m, 4H), 4.03-3.96 (q, 2H), 3.29 (s, 2H), 1.12-1.08 (t, 3H); MS: 578.2 (M+1).

Step 4: Ethyl 2-(3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl) phenyl)oxetan-3-yl)acetate

Sodium hydride (1.12 mmol) was added to a solution of ethyl 2-(3-(4-(8-bromo-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (compound of step 3, 0.933 mmol) in dry DMF and stirred at RT. Methyl iodide (1.866 mmol) was added to it after 15 minutes and the reaction mixture was stirred for 3 hours. After completion of the reaction, water was added and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 62%; ¹H NMR (300 MHz, DMSO-d₆): δ 9.04 (s, 1H), 7.98-7.95 (d, J = 9.0 Hz, 1H), 7.67-7.64 (d, J = 8.7 Hz, 1H), 7.60 (s, 4H), 7.06 (s, 1H), 4.93-4.85 (m, 4H), 4.03-3.96 (q, 2H), 3.59 (s, 3H), 3.29 (s, 2H), 1.12-1.079 (t, 3H); MS: 496.9 (M+1).

Step 5: Ethyl 2-(3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate

Ethyl 2-(3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (compound of step 4, 0.201 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine (0.403 mmol) was suspended in dry DMF. Dichlorobis(triphenylphosphine)-Palladium (II) catalyst (0.016 mmol) and saturated solution of sodium carbonate (0.504 mmol) were added and reaction mixture was heated at 111 °C for 6 minutes in microwave (CEM Corp.). Reaction mixture was cooled, diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 44%; ¹H NMR (300 MHz, DMSO-d₆): δ 8.99 (s, 1H), 8.27 (s, 1H), 8.09-8.06 (d, J = 8.7 Hz, 1H), 7.89-7.69 (d, J = 8.7 Hz, 1H), 7.68-7.65 (m, 3H), 7.57-7.54 (m, 2H), 7.22 (s, 1H), 6.67 (s, 2H), 4.89-4.83 (m, 4H), 3.89-3.82 (q, 2H), 3.60 (s, 3H), 3.23 (s, 2H), 0.98-0.93 (t, 3H); MS: 578.2 (M+1).
Example 2: 8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-l-(4-(3-methyloxetan-3-yl)phenyl)-IH-imidazo[4,5-c]quinolin-2(3H)-one

Step 1: 6-Bromo-N-(4-(3-methyloxetan-3-yl)phenyl)-3-nitroquinolin-4-amine

4-(3-Methyloxetan-3-yl)aniline (Intermediate 7, 0.613 mmol) was stirred in dry DMF. Sodium bicarbonate (0.674 mmol) was added to it and stirred. 6-Bromo-4-chloro-3-nitroquinoline (Intermediate 11, 0.613 mmol) was added to it and stirred for 2 hours. Reaction mixture was poured in water and the yellow solid obtained was filtered and dried to obtain the title compound. Yield: 85%; ¹H NMR (300 MHz, DMSO-d₆): δ 10.10 (s, 1H), 9.07 (s, 1H), 8.67 (s, 1H), 8.02-7.91 (m, 2H), 7.25-7.22 (d, J=9.0 Hz, 2H), 7.11-7.08 (d, J=8.1Hz, 2H), 4.79-4.77 (d, 2H), 4.55-4.53 (d, 2H), 1.63 (s, 3H); MS: 493.9(M+1).

Step 2: 6-Bromo-N⁴-(4-(3-methyloxetan-3-yl)phenyl)quinoline-3,4-diamine

Stannous chloride (6.76 mmol) was added to the suspension of 6-bromo-N-(4-(3-methyloxetan-3-yl)phenyl)-3-nitroquinolin-4-amine (compound of step 1, 1.69 mmol) in EtOAc and stirred at RT for 2 hours. Reaction mixture was diluted with EtOAc and quenched with 10 M NaOH solution. Organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 54%; ¹H NMR (300 MHz, DMSO-d₆): δ 8.61 (s, 1H), 7.87 (s, 1H), 7.78-7.75 (d, J=9.0 Hz, 2H), 7.47-7.44 (d, J=8.7Hz, 1H), 7.05-7.02 (d, J=8.4Hz, 2H), 6.53-6.50 (d, J=8.4Hz, 2H), 5.41 (s, 2H), 4.74-4.72 (d, 2H), 4.48-4.46 (d, 2H), 1.57 (s, 3H); MS: 385.3 (M+1).

Step 3: 8-Bromo-l-(4-(3-methyloxetan-3-yl)phenyl)-IH-imidazo[4,5-c]quinolin-2(3H)-one

Triethylamine (5.46 mmol) was added to a solution of 6-bromo-N⁴-(4-(3-methyloxetan-3-yl)phenyl)quinoline-3,4-diamine (compound of step 2, 0.781 mmol) in dry DCM. Reaction mixture was cooled to 0 °C. Triphosgene (0.781 mmol) solution in DCM was added to the reaction mixture slowly and stirred for 2 hours. After completion of the reaction, DCM was added and washed with water. The aqueous layer was partitioned with DCM. The organic layers were combined, dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl₃ eluent) to obtain the title compound. Yield: 43.7%; ¹H NMR (300 MHz, DMSO-d₆): δ 11.81 (s, 1H), 8.79 (s, 1H), 7.95-7.92 (d, J=9.0 Hz, 1H), 7.65-7.53 (m, 5H), 7.00 (s, 1H), 4.93-4.91 (d, 2H), 4.65-4.64 (d, 2H), 1.74 (s, 3H).

Step 4: 8-Bromo-3-methyl-l-(4-(3-methyloxetan-3-yl)phenyl)-IH-imidazo[4,5-c]quinolin-2(3H)-one
c]quinolin-2(3H)-one
Sodium hydride (0.380 mmol) was added to a solution of 8-bromo-1-(4-(3-methyloxetan-3-yl)phenyl)-IH-imidazo[4,5-c]quinolin-2(3H)-one (compound of step 3, 0.317 mmol) in dry DMF and stirred at RT. Methyl iodide (0.634 mmol) was added to it after 15 minutes and stirred for 3 hours. After completion of the reaction, water was added and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 78 %; ¹H NMR (300 MHz, DMSO-d₆): δ 9.04 (s, 1H), 7.95-7.92 (d, J=9.0 Hz, 1H), 7.65-7.53 (m, 5H), 6.99 (s, 1H), 4.93-4.91 (d, 2H), 4.66-4.64 (d, 2H), 3.60 (s, 3H), 1.74 (s, 3H); MS: 424.4 (M+).

Step 5: 8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-1-(4-(3-methyloxetan-3-yl)phenyl)-IH-imidazo[4,5-c]quinolin-2(3H)-one
A solution of 8-bromo-3-methyl-1-(4-(3-methyloxetan-3-yl)phenyl)-IH-imidazo[4,5-c]quinolin-2(3H)-one (compound of step 4, 0.236 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine (0.354 mmol) was stirred in dry DMF. To this was added dichlorobis(triphenylphosphine)-palladium (II) catalyst (0.014 mmol) and saturated solution of sodium carbonate (0.589 mmol) and the reaction mixture was heated at 110 °C for 1 hour. After completion of the reaction, the reaction mixture was cooled, diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 40.3 %; ¹H NMR (300 MHz, DMSO-d₆): δ 8.98 (s, 1H), 8.25 (s, 1H), 8.09-8.06 (d, J=9.0 Hz, 1H), 7.90-7.87 (d, J=8.7Hz, 1H), 7.67-7.55 (m, 5H), 7.16 (s, 1H), 6.68 (s, 2H), 4.90- 4.88 (d, 2H), 4.62-4.60 (d, 2H), 3.60 (s, 3H), 1.74 (s, 3H); MS: 506.4 (M+).

Example 3: Ethyl 2-(3-(4-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-IH-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidin-3-yl)acetate
Step 1: teri-Butyl 3-(4-((6-bromo-3-nitroquinolin-4-yl)amino)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate
6-bromo-4-chloro-3-nitroquinoline (Intermediate 11, 2.087 mmol) and teri-butyl 3-(4-aminophenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate (Intermediate 10, 2.087 mmol) are dissolved in acetic acid (2 mL) and stirred over night. After completion of the reaction, water was added and yellow precipitate so obtained was filtered. The residue was washed
with water and dried to obtain the title compound. Yield: 40%; \( ^1H \) NMR (300 MHz, DMSO-\( d_6 \)): \( \delta \) 10.09 (s, 1H), 9.07 (s, 1H), 8.69 (s, 1H), 8.02-7.99 (d, J=9Hz, 1H), 7.94-7.91 (d, J=9Hz, 1H), 7.26-7.23 (d, J=9Hz, 2H), 7.08-7.05 (d, J=9Hz, 2H), 4.11-4.07 (m, 4H), 3.94-3.91 (m, 2H), 2.99 (s, 2H), 1.38 (s, 9H), 1.10-1.06 (t, J=6Hz, 3H); MS: 587 (M+2).

Step 2: teri-Butyl 3-(4-(3-amino-6-bromoquinolin-4-yl)amino)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate

Stannous chloride (0.683 mmol) was added to a solution of teri-butyl 3-(4-((3-amino-6-bromoquinolin-4-yl)amino)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate (compound of step 1, 0.171 mmol) in EtOAc (5 mL) and stirred at RT for 1 hour. After completion of the reaction, EtOAc was added and quenched with 10 M NaOH aqueous solution. The organic layer was separated and aqueous layer was extracted with EtOAc. The organic layers were combined, dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl\(_3\) as eluent). Yield: 78%; \( ^1H \) NMR (300 MHz, DMSO-\( d_6 \)): \( \delta \) 8.61 (s, 1H), 7.83-7.75 (m, 3H), 7.47-7.44 (d, J=9Hz, 1H), 7.04-7.01 (d, J=9Hz, 2H), 6.50-6.47 (d, J=9Hz, 2H), 5.42 (s, 2H), 4.06-4.01 (m, 4H), 3.95-3.90 (m, 2H), 2.89 (s, 2H), 1.23-1.15 (m, 9H), 1.07-1.02 (t, J=6Hz, 3H); MS: 557(M+2).

Step 3: teri-Butyl 3-(4-(8-bromo-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate

A solution of teri-butyl 3-(4-((3-amino-6-bromoquinolin-4-yl)amino)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate (compound of step 2, 1.561 mmol) and triethylamine (1.873 mmol) in DCM (5 mL) was added slowly to a solution of triphosgene (1.873 mmol) in DCM (2 mL) at 0 °C. The reaction mixture was stirred for 20 minutes at this temperature. After completion of the reaction, the reaction mixture was quenched with saturated aqueous NaHCO\(_3\), stirred for 5 minutes and extracted with DCM. The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated to obtain the title compound. Yield: 80%; \( ^1H \) NMR (300 MHz, DMSO-\( d_6 \)): \( \delta \) 8.79 (s, 1H), 7.95-7.92 (d, J=9Hz, 1H), 7.65-7.60 (m, 5H), 7.01 (s, 1H), 4.20 (s, 4H), 4.03-3.96 (q, J=6Hz, J=6 Hz, 2H), 3.17 (s, 2H), 1.40 (s, 9H), 1.13-1.08 (t, J=6Hz, 3H); MS: 583.2 (M+2).

Step 4: teri-Butyl 3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate

NaH (1.857 mmol, 60%) was added slowly to the pre-cooled solution of teri-butyl 3-(4-(8-bromo-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethy...
oxoethyl)azetidine-1-carboxylate (compound of step 3, 1.238 mmol) in DMF (6 mL) at a temperature below 0 °C. The reaction mixture was stirred at same temperature for 30 minutes, followed by the addition of methyl iodide (1.857 mmol). The reaction mixture was stirred at RT for 1 hour. After completion of the reaction DMF was evaporated and the product was extracted with EtOAc, and then dried over sodium sulfate. The solvent was evaporated and the residue was purified (silica gel column, MeOH/CHCl\(_3\) as eluent). Yield: 95%; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 9.04 (s, 1H), 7.98-7.95 (d, J=9Hz, 1H), 7.67-7.60 (m, 5H), 7.01 (s, 1H), 4.20 (s, 4H), 4.01-3.99 (q, J=6Hz, J=12 Hz, 2H), 3.59 (s, 3H), 3.17 (s, 2H), 1.40 (s, 9H), 1.13-1.08 (t, J=6Hz, 3H); MS: 597(M+2).

Step 5: teri-Butyl 3-(4-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate

Potassium carbonate was added to a solution of teri-Butyl 3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate (compound of step 4, 1.176 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine (1.763 mmol) in dioxane. Palladium(II)bis(triphenylphosphine) dichloride (0.059 mmol) was added to the reaction mixture in an inert atmosphere. The reaction mixture was heated at about 110 °C for about 8 minutes in microwave. After the completion of the reaction, dioxane was evaporated and EtOAc was added to the residue. The reaction was quenched with water and the aqueous layer was partitioned with EtOAc. The organic layer was separated, dried over Na\(_2\)SO\(_4\) and purified (silica gel column, MeOH/CHCl\(_3\) as eluent). Yield: 48.9 %; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 8.98 (s, 1H), 8.26 (s, 1H), 8.09-8.06 (d, J=9Hz, 1H), 7.91-7.87 (d, J=9Hz, 1H), 7.64-7.55 (m, 5H), 7.21 (s, 1H), 6.68 (s, 2H), 5.83-5.76 (m, 1H), 5.01-4.91 (m, 2H), 4.19 (s, 4H), 3.87-3.82 (m, 2H), 3.60 (s, 3H), 1.41 (s, 9H), 1.16 (m, 3H); MS: 677(M+1).

Step 6: Ethyl 2-(3-(4-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidin-3-yl)acetate

Trifluoroacetic acid (1.182 mmol) was added to a solution of teri-butyl 3-(4-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate (compound of step 5, 0.118 mmol) in DCM (5 mL) and stirred over night at RT. After completion of the reaction, trifluoroacetic acid was removed and the reaction was quenched with sodium bicarbonate.
solution and extracted with EtOAc. The organic layer was dried over sodium sulfate and purified (silica gel column, MeOH/CHCl₃ eluent). Yield: 44%; ¹H NMR (300 MHz, DMSO-d₆): δ 8.99 (s, 1H), 8.09-8.06 (d, J=9Hz, 2H), 7.91-7.86 (d, J=9Hz, 2H), 7.75-7.72 (d, J=9Hz, 1H), 7.65-7.62 (d, J=9Hz, 2H), 7.71 (s, 1H), 6.72 (s, 1H), 4.42-4.38 (m, 4H), 3.86-3.83 (m, 2H), 3.60 (s, 3H), 3.23 (s, 2H), 1.33 (m, 3H); MS: 577 (M+).

Example 4: 2-(3-(4-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-IH-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate

(Compound of step 5 of Example 3, 0.222 mmol) was dissolved in a mixture of THF and MeOH and the solution was stirred. Aqueous solution of lithium hydroxide (1.5 M, 1.108 mmol) was added, and the reaction mixture was stirred overnight at RT. After completion of the reaction, the solvent was evaporated and the reaction mixture was quenched with saturated ammonium chloride solution. The product was extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl₃). Yield: 10%; ¹H NMR (300 MHz, DMSO-d₆): δ 12.33 (s, 1H), 8.95 (s, 1H), 8.21 (s, 1H), 8.09-8.06 (d, J=9Hz, 1H), 7.91 (m, 1H), 7.67-7.62 (m, 4H), 7.20 (s, 1H), 4.16 (s, 4H), 3.58 (s, 3H), 3.05 (s, 2H), 1.40 (s, 9H); MS: 649 (M+).

Example 5: Ethyl 2-(3-(4-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-IH-imidazo[4,5-c]quinolin-1-yl)phenyl)-1-(methylsulfonyl)azetidin-3-yl)acetate

Triethylamine (0.078 mmol) was added to a solution of ethyl 2-(3-(4-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-IH-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidin-3-yl)acetate (compound of Example 3, 0.052 mmol) in THF (2 mL), followed by the addition of methylsulfonyl chloride (0.052 mmol). The reaction mixture was stirred at RT for 30 minutes. After completion of the reaction, DCM (5 mL) was added and the reaction mixture was quenched with water. The organic layer was separated and aqueous layer was partitioned with DCM. The organic layers were combined, dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl₃ as eluent). Yield: 88%; ¹H NMR (300 MHz, DMSO-d₆): δ 8.99 (s, 1H), 8.19 (s, 1H), 8.09-8.06 (d, J=9Hz, 1H), 7.89-7.86 (d, J=9Hz, 1H), 7.77 (s, 1H), 7.70-7.67 (d, J=9Hz, 2H), 7.62-7.59 (d, J=9Hz, 2H), 7.24
Example 6: Ethyl 2-[(3-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate
Ethyl 2-[(3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (compound of step 4 of Example 1, 0.151 mmol) and quinoline-3-boronic acid (0.302 mmol) was suspended in dry DMF. Dichlorobis(triphenylphosphine)-Palladium (II) catalyst (0.016 mmol) and saturated solution of sodium carbonate (0.504 mmol) were added and reaction mixture was heated at 111 °C for 6 minutes in microwave (CEM Corp.). Reaction mixture was cooled, diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 44%; ¹H NMR (300 MHz, DMSO-d₆): δ 9.05 (s, 1H), 8.89 (s, 1H), 8.38 (s, 1H), 8.21-8.18 (d, J= 9.0Hz, 1H), 8.10 (s, 1H), 8.04-7.99 (m, 2H), 7.78-7.65 (m, 6H), 7.44 (s, 1H), 4.93-4.83 (m, 4H), 3.77-3.74 (q, 2H), 3.63 (s, 3H), 3.25 (s, 2H), 0.90-0.85 (t, 3H); MS: 545.2 (M+1).

Example 7: Ethyl 2-[(3-(4-(3-methyl-2-oxo-8-(pyridin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate
Ethyl 2-[(3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (compound of step 4 of Example 1, 0.151 mmol) and pyridine-3-boronic acid (0.302 mmol) were suspended in dry DMF. Dichlorobis(triphenylphosphine)-Palladium (II) catalyst (0.016 mmol) and saturated solution of sodium carbonate (0.504 mmol) was added and reaction mixture was heated at 111 °C for 6 minutes in microwave (CEM Corp.). Reaction mixture was cooled, diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 44%; ¹H NMR (300 MHz, DMSO-d₆): δ 9.03 (s, 1H), 8.67 (s, 1H), 8.56-8.54 (d, J=3.9Hz, 1H), 8.16-8.13 (d, J=8.7 Hz, 1H), 7.99-7.96 (d, J=8.7Hz, 1H), 7.71-7.60 (m, 5H), 7.18 (s, 2H), 7.44-7.40 (m, 1H), 7.26 (s, 1H), 4.93-4.87 (m, 4H), 3.93-3.86 (q, 2H), 3.62 (s, 3H), 3.25 (s, 2H), 1.02-0.98 (t, 3H); MS: 418.1 (M+1)
Example 8: 2-(3-(4-(3-Methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]-quinolin-1-yl)phenyl)oxetan-3-yl)acetic acid

Ethyl 2-(3-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (compound of Example 6, 0.083 mmol) was stirred in THF:MeOH (4:1) at RT. Lithium hydroxide (1.5 M, 0.521 mmol) was added to it and stirred for 5 hours. Reaction mixture was concentrated and triturated with saturated solution of ammonium chloride. The compound was extracted with EtOAc. The EtOAc layer was dried over sodium sulfate and concentrated to obtain the title compound. 

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\text{H NMR (300 MHz, DMSO-de)}: \delta 9.05 \text{ (s, IH), 8.86 \text{ (s, IH), 8.38 \text{ (s, IH), 8.42 \text{ (s, IH), 8.22-8.19 \text{ (d, J=8.7 Hz), 8.13-8.11 \text{ (d, J=8.4 Hz, IH), 8.01-8.00 \text{ (m, 2H), 7.78-7.64 \text{ (m, 5H), 7.47 \text{ (s, IH), 7.12 (bs, 2H), 4.90-4.84 \text{ (m, 4H), 3.63 \text{ (s, 3H), 3.23 \text{ (s, 2H); MS: 517.2 (M+1).}}}
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Example 9: 8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(4-(3-(2-hydroxyethyl)oxetan-3-yl)phenyl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-one

Ethyl 2-(3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (Compound of Example 1, 0.172 mmol) was stirred in dry THF under argon atmosphere at 0°C. Lithium aluminium hydride (0.172 mL, 1 M solution) was added to it and stirred for 5 minutes at same temperature. Reaction mixture was diluted with EtOAc and washed with ammonium chloride solution. The organic layer was washed with brine dried over sodium sulfate and purified (silicagel column, MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 44%; 

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\text{H NMR (300 MHz, DMSO-d₆): } \delta 8.98 \text{ (s, IH), 8.15 \text{ (s, IH), 8.09-8.06 \text{ (d, J=8.7 Hz, IH), 7.87-7.85 \text{ (d, J=8.1 Hz, IH), 7.32 \text{ (s, IH), 7.66-7.645 \text{ (d, J=7.8 Hz, 2H), 7.48-7.45 \text{ (d, J=8.1 Hz, 2H), 7.20 \text{ (s, IH), 6.67 (s, 2H), 4.89-4.87 \text{ (d, 2H), 4.80-4.78 \text{ (d, 2H), 4.46 (t, IH), 3.60 (s, 3H), 3.23 (t, 2H), 2.25 (t, 2H); MS: 536.2 (M+1).}}}
\]

Example 10: 8-(6-Amino-5-methylpyridin-3-yl)-1-(4-(3-(2-hydroxyethyl)oxetan-3-yl)phenyl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-one

Step 1: Ethyl 2-(3-(4-(6-amino-5-methylpyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate

Ethyl 2-(3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (compound of step 4 of Example 1, 0.201 mmol) and 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (0.403 mmol) was suspended
in dry DMF. Dichlorobis(triphenylphosphine)-Palladium (II) catalyst (0.016 mmol) and saturated solution of sodium carbonate (0.504 mmol) were added and reaction mixture was heated at 111 °C for 6 minutes in microwave (CEM Corp.). The reaction mixture was cooled, diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 58 %; ¹H NMR (300 MHz, DMSO-d₆): δ 8.94 (s, 1H), 8.05-8.02 (d, J=9.0Hz, 1H), 7.92 (s, 1H), 7.83-7.80 (d, J=8.7Hz, 1H), 7.64-7.58 (m, 4H), 7.18 (s, 2H), 5.93 (s, 2H), 4.93-4.85 (m, 4H), 3.93-3.86 (q, 2H), 3.59 (s, 3H), 3.26 (s, 2H), 2.05 (s, 3H), 1.02-0.98 (t, 3H); MS: 524.5(M+1).

Step 2: 8-(6-amino-5-methylpyridin-3-yl)-l-(4-(3-(2-hydroxyethyl)oxetan-3-yl)phenyl)-3-methyl-lH-imidazo[4,5-c]quinolin-2(3H)-one

Ethyl 2-(3-(4-(6-amino-5-methylpyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-c]quinolin-l-yl)phenyl)oxetan-3-yl)acetate (compound of step 1, 0.172 mmol) was stirred in dry THF under argon atmosphere at 0°C. Lithium aluminium hydride (0.172 mL, 1 M solution) was added to it and stirred for 5 minutes at same temperature. Reaction mixture was diluted with EtOAc and washed with ammonium chloride solution. Organic layer was washed with brine dried over sodium sulfate and purified (silica gel column, MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 44%; ¹H NMR (300 MHz, DMSO-d₆): δ 8.93 (s, 1H), 8.05-8.02 (d, J = 8.7 Hz, 1H), 7.82-7.79 (m, 2H), 7.64-7.62 (d, J=8.1 Hz, 2H), 7.50 - 7.47 (d, J=7.8 Hz, 2H), 7.28 (s, 1H), 7.18 (s, 1H), 5.94 (s, 2H), 4.92-4.90 (d, 2H), 4.81-4.79 (d, 2H), 4.12 (t, 1H), 3.59 (s, 3H), 3.17 (t, 2H), 2.28 (t, 2H), 2.05 (s, 3H); MS: 482.0(M+1).

Example 11: Ethyl 2-(3-(4-(2,6-difluoropyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-c]quinolin-l-yl)phenyl)oxetan-3-yl)acetate

Ethyl 2-(3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-c]quinolin-l-yl)phenyl)oxetan-3-yl)acetate (compound of step 4 of Example 1, 0.121 mmol) and 2,6-difluoropyridine-3-boronic acid (0.181 mmol) were suspended in dry DMF. Dichlorobis(triphenylphosphine)-Palladium (II) catalyst (0.016 mmol) and saturated solution of sodium carbonate (0.504 mmol) was added and reaction mixture was heated at 111 °C for 6 minutes in microwave (CEM Corp.). The reaction mixture was cooled, diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and
purified (silica gel column, MeOH/CHCl₃ as eluent) to obtain the title compound. Yield 53%;

\[ ^1H \text{NMR (300 MHz, DMSO-d}_6): \delta 9.06 (s, 1H), 8.16-8.13 (d, J=9.0 Hz, 1H), 8.09-8.06 (d, J=8.4 Hz, 1H), 7.81-7.78 (d, J=8.7Hz, 1H), 7.63-7.60 (d, J=8.4Hz, 2H), 7.55-7.53 (d, J=8.4Hz, 2H), 7.25-7.20 (m, 2H), 4.95-4.86 (m, 4H), 3.89-3.82 (q, 2H), 3.62 (s, 3H), 3.23 (s, 2H). \]

Example 12: Ethyl 2-(3-(4-(8-(2-fluoro-6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (compound of step 4 of Example 1, 0.101 mmol) and indole-6-boronic acid (0.151 mmol) were suspended in dry DMF. Dichlorobis(triphenylphosphine)-Palladium (II) catalyst (0.016 mmol) and saturated solution of sodium carbonate (0.504 mmol) was added and the reaction mixture was heated at 111 °C for 6 minutes in microwave (CEM Corp.). The reaction mixture was cooled, diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 53%; \[ ^1H \text{NMR (300 MHz, DMSO-d}_6): \delta 11.13 (s, 1H), 8.96 (s, 1H), 8.11-8.08 (d, J=9.0Hz, 1H), 7.95-7.92 (m, 1H), 7.69-7.62 (m, 4H), 7.53 (m, 2H), 7.39 (bs, 1H), 7.31 (s, 1H), 6.92-6.89 (d, J=8.4Hz, 1H), 6.42 (s, 1H), 4.95-4.89 (m, 4H), 3.90-3.83 (q, 2H), 3.61 (s, 3H), 3.29 (s, 2H), 1.04-0.96 (t, 3H); MS: 533.5 (M+1). \]

Example 13: 2-(3-(4-(8-(2-fluoro-6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (Compound of Example 11, 0.113 mmol) in THF: MeOH (4:1) at RT and stirred for 5 hours. The reaction mixture was concentrated and triturated with saturated solution of ammonium chloride. The compound was extracted with EtOAc. The EtOAc layer was dried over sodium sulfate and concentrated to obtain the title compound. Yield: 65%; \[ ^1H \text{NMR (300 MHz, DMSO-d}_6): \delta 12.28 (s, 1H), 9.02 (s, 1H), 8.11-8.08 (d, J=9.0Hz, 1H), 7.79-7.67 (m, 2H), 7.60 (bs, 4H), 7.10 (s, 1H), 6.83-6.80 (d, J=8.1 Hz, 1H), 4.87 (bs, 4H), 3.84 (s, 3H), 3.61 (s, 3H), 3.18 (s, 2H). \]
Example 14: Ethyl 2-(3-(4-(3-methyl-2-oxo-8-(5-(trifluoromethyl)pyridin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate

Ethyl 2-(3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (compound of step 4 of Example 1, 0.100 mmol) and 5-methoxy-pyridin-3-ylboronic acid (0.15 mmol) were suspended in dry DMF.

Dichlorobis(triphenylphosphine)-Palladium (II) catalyst (0.016 mmol) and saturated solution of Na2CO3 (0.504 mmol) was added and reaction mixture was heated at 111 °C for 6 minutes in microwave (CEM Corp.). Reaction mixture was cooled, diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl3 as eluent) to obtain the title compound. Yield 49%; 1H NMR (300 MHz, DMSO-d6): δ 9.07 (s, 1 H), 8.86 (s, 1 H), 8.20-8.17 (d, J=9.0 Hz, 1 H), 8.05-8.02 (d, J=9.0 Hz, 1 H), 7.92 (bs, 2 H), 7.69-7.61 (m, 4 H), 7.28 (s, 1 H), 4.90-4.89 (m, 4 H), 3.88-3.81 (q, 2 H), 3.62 (s, 3 H), 3.26 (s, 2 H), 0.97-0.92 (t, 3 H); MS: 563.3 (M+1).

Example 15: Ethyl 2-(3-(4-(6-methoxy-pyridin-3-yl)-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate

Ethyl 2-(3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (compound of step 4 of Example 1, 0.1 mmol) and 6-methoxy-pyridin-3-ylboronic acid (0.15 mmol) were suspended in dry DMF. Dichlorobis(triphenylphosphine)-Palladium (II) catalyst (0.016 mmol) and saturated solution of sodium carbonate (0.504 mmol) was added and reaction mixture was heated at 111 °C for 6 minutes in microwave (CEM Corp.). Reaction mixture was cooled, diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column MeOH/CHCl3 as eluent) to obtain the title compound. Yield 46%; 1H NMR (300 MHz, DMSO-d6): δ 8.99 (s, 1 H), 8.24 (s, 1 H), 8.11-8.08 (d, J=8.7 Hz, 1 H), 7.92-7.89 (d, J=8.7 Hz, 1 H), 7.67-7.60 (m, 5 H), 7.11 (s, 1 H), 6.86-6.83 (d, J=8.4 Hz, 1 H), 4.96-4.88 (m, 4 H), 3.94-3.86 (q, 2 H), 3.86 (s, 3 H), 3.61(s, 3 H), 3.28 (s, 2 H), 1.03-0.98 (t, 3 H); MS: 525.3 (M+1).

Example 16: Ethyl 2-(3-(4-(5-methoxy-pyridin-3-yl)-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate

Ethyl 2-(3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (compound of step 4 of Example 1, 0.100 mmol) and 5-methoxy-pyridin-3-ylboronic acid (0.15 mmol) were suspended in dry DMF.
Dichlorobis(triphenylphosphine)-palladium (II) catalyst (0.016 mmol) and saturated solution of Na$_2$C$_2$O$_4$ (0.504 mmol) was added and reaction mixture was heated at 111 °C for 6 minutes in microwave (CEM Corp.). Reaction mixture was cooled, diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column MeOH/CHCl$_3$ as eluent) to obtain the title compound. Yield 51%; $^1$H NMR (300 MHz, DMSO-d$_6$): δ 8.84 (s, 1H), 8.28 (s, 2H), 8.24-8.21 (d, J=9.0 Hz, 1H), 7.83-7.80 (d, J=8.7 Hz, 1H), 7.59-7.49 (m, 4H), 7.39 (s, 1H), 7.15 (s, 1H), 5.12-4.94 (m, 4H), 4.03-3.95 (q, 2H), 3.92 (s, 3H), 3.72 (s, 3H), 3.24 (s, 2H), 1.13-1.08 (t, 3H); MS: 525.2 (M+1).

Example 17: Ethyl 2-(3-(4-(isooquinolin-1-yl)-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate

Ethyl 2-(3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (compound of step 4 of Example 1, 0.151 mmol) and isoquinoline-4-ylboronic acid (0.227 mmol) were suspended in dry DMF. Dichlorobis(triphenylphosphine)-Palladium (II) catalyst (0.016 mmol) and saturated solution of sodium carbonate (0.504 mmol) was added and reaction mixture was heated at 111 °C for 6 minutes in microwave (CEM Corp.). The reaction mixture was cooled, diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column MeOH/CHCl$_3$ as eluent) to obtain the title compound. Yield 46%; $^1$H NMR (300 MHz, DMSO-d$_6$): δ 9.24 (s, 1H), 8.98 (s, 1H), 8.36 (s, 1H), 8.31-8.28 (m, 4H), 8.07-8.05 (d, J=7.3 Hz, 1H), 7.86-7.84 (d, J=7.8 Hz, 1H), 7.78-7.75 (d, J=9.0 Hz, 1H), 7.69 (m, 2H), 7.54-7.51 (d, J=8.7 Hz, 2H), 7.33-7.30 (m, 3H), 4.78-4.70 (m, 4H), 3.83-3.78 (q, 2H), 3.74 (s, 3H), 2.98 (s, 2H), 0.99-0.94 (t, 3H); MS: 545.0 (M+1).

Example 18: Ethyl 2-(3-(4-(8-(4-hydroxyphenyl)-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate

Ethyl 2-(3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (compound of step 4 of Example 1, 0.100 mmol) and 4-hydroxyphenylboronic acid (0.151 mmol) were suspended in dry DMF. Dichlorobis(triphenylphosphine)-Palladium (II) catalyst (0.016 mmol) and saturated solution of sodium carbonate (0.504 mmol) was added and reaction mixture was heated at 111 °C for 6 minutes in microwave (CEM Corp.). Reaction mixture was cooled, diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified...
(silica gel column MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 45 %; ¹H NMR (300 MHz, CDC₁₃): δ 8.75 (s, 1H), 8.15-8.12 (d, J=8.7Hz, 1H), 7.84-7.81 (d, J=8.7Hz, 1H), 7.57-7.54 (m, 2H), 7.47 (s, 1H), 7.46 (s, 1H), 7.22-7.09 (d, J=8.4Hz, 2H), 7.11 (s, 1H), 6.89-6.81 (m, 3H), 5.12-5.02 (m, 4H), 4.10-4.03 (q, 2H), 3.69 (s, 3H), 3.25 (s, 2H), 1.20 (t, 3H); MS: 510.2 (M+1).

Example 19: Ethyl 2-(3-(4-(3-hydroxyphenyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-l-yl)phenyl)oxetan-3-yl)acetate

Ethyl 2-(3-(4-(8-bromo-3-methyl-2-oxo-2,3-dimhydro-1H-imidazo[4,5-c]quinolin-l-yl)phenyl)oxetan-3-yl)acetate (compound of step 4 of Example 1, 0.151 mmol) and 3-hydroxyphenylboronic acid (0.302 mmol) were suspended in dry DMF. Dichlorobis(triphenylphosphate)-Palladium (II) catalyst (0.016 mmol) and saturated solution of sodium carbonate (0.504 mmol) was added and reaction mixture was heated at 111 °C for 6 minutes in microwave (CEM Corp.). Reaction mixture was cooled, diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 39 %; ¹H NMR (300 MHz, DMSO-d₆): δ 9.55 (s, 1H), 8.99 (s, 1H), 8.10- 8.07 (d, J=8.7 Hz, 1H), 7.83-7.80 (d, J=8.7 Hz, 1H), 7.67-7.59 (m, 4H), 7.25 (s, 1H), 7.17-7.15 (m, 1H), 6.85 (s, 1H), 6.75-6.69 (m, 2H), 4.95-4.86 (m, 4H), 3.93-3.88 (q, 2H), 3.61 (s, 3H), 3.28 (s, 2H), 1.04-1.02 (t, 3H); MS: 510.0 (M+1).

Example 20: Methyl 4-[(4-(3-(2-ethoxy-2-oxoethyl)oxetan-3-yl)phenyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-8-yl)benzoate

Ethyl 2-(3-(4-(8-bromo-3-methyl-2-oxo-2,3-dimhydro-1H-imidazo[4,5-c]quinolin-l-yl)phenyl)oxetan-3-yl)acetate (compound of step 4 of Example 1, 0.151 mmol) and methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (0.302 mmol) were suspended in dry DMF. Dichlorobis(triphenylphosphine)-palladium (II) catalyst (0.016 mmol) and saturated solution of sodium carbonate (0.504 mmol) was added and reaction mixture was heated at 111 °C for 6 minutes in microwave (CEM Corp.). Reaction mixture was cooled, diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 43%; ¹H NMR (300 MHz, DMSO-d₆): δ 9.02 (s, 1H), 8.15- 8.12 (d, J=8.7Hz, 1H), 7.99-7.92 (m, 3H), 7.69-7.67 (d, J=8.1Hz, 2H), 7.60-7.57 (m, 4H), 7.31 (s, 1H), 5.02-4.95 (m, 4H),
3.90 (s, 3H), 3.83-3.80 (q, 2H), 3.61 (s, 3H), 3.23 (s, 2H), 0.95-0.91 (t, 3H); MS: 552.2 (M+l).

Example 21: teri-Butyl 3-(2-ethoxy-2-oxoethyl)-3-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-IH-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidine-1-carboxylate

eri-Butyl 3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-IH-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate (compound of step 4 of Example 3, 0.336 mmol) and quinolin-3-ylboronic acid (0.504 mmol) were dissolved in dioxane : water (4 : 1 mL) and K2CO3 (0.404 mmol) was added. The reaction mixture was degassed using argon, followed by addition of tetrakis(triphenylphosphine)-palladium (0) (0.013 mmol). The reaction mixture was heated at 110 °C for 8 minutes in microwave. After completion of the reaction, the solvent was evaporated and EtOAC was added to the residue. The reaction was quenched with water and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over anhydrous Na2SO4, and purified (silica gel column, 5% methanol in chloroform as eluent) to obtain the title compound Yield: 50%; 1H NMR (300 MHz, DMSO-d6): δ 9.05 (s, 1H), 8.84 (s, 1H), 8.40 (s, 1H), 8.21-8.18 (d, J=3Hz, 1H), 8.10-8.07 (d, J=3Hz, 1H), 8.04 (s, 2H), 7.76-7.63 (m, 6H), 7.44 (s, 1H), 4.22 (s, 4H), 3.84-3.78 (m, 2H), 3.62 (s, 3H), 3.10 (s, 2H), 1.40 (s, 9H), 0.92-0.87(m, 3H); MS: 644(M+1).

Example 22: teri-Butyl 3-(2-ethoxy-2-oxoethyl)-3-(4-(3-methyl-2-oxo-8-(pyridin-3-yl)-2,3-dihydro-IH-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidine-1-carboxylate

eri-Butyl 3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-IH-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate (compound of step 4 of Example 3, 0.168 mmol) and 3-pyridine boronic acid (0.252 mmol) was dissolved in dioxane : water (2 :1 mL) and K2CO3 (0.504 mmol) was added. The reaction mixture was degassed using argon, followed by addition of tetrakis(triphenylphosphine)- palladium (0) (0.04 mmol). The reaction mixture was heated at 110 °C for 8 minutes in microwave. After completion of the reaction, the solvent was evaporated and EtOAC was added to the residue. The reaction was quenched with water and the aqueous layer was extracted with EtOAc. The organic layer was dried over anhydrous Na2SO4 and purified (silica gel column, 5% methanol in chloroform as eluent) to obtain the title compound. Yield: 90%; 1H NMR (300 MHz, DMSO-d6): δ 9.03 (s, 1H), 8.69 (s, 1H), 8.51-8.50 (d, J=3Hz, 1H), 8.15-8.12 (d, J=9Hz, 1H), 7.99-7.96 (d, J=9Hz, 1H), 7.64 (s, 5H), 7.39-7.38 (d, J=3Hz, 1H), 7.22 (s, 1H), 4.21 (s, 4H), 3.93-3.86 (q, J=9Hz,
J=15Hz, 2H), 3.61 (s, 3H), 3.14 (s, 2H), 1.43 (s, 9H), 1.02-0.98 (t, J=9Hz, J=15Hz, 3H); MS: 594 (M+1).

Example 23: teri-butyl 3-(2-ethoxy-2-oxoethyl)-3-(4-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidine-1-carboxylate

teri-Butyl 3-(4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate (compound of step 4 of Example 3, 0.168 mmol), 2-methoxy-5-pyridineboronic acid (0.252 mmol) was dissolved in dioxane : water (2:1 mL) and K2CO3 (0.504 mmol) was added. The reaction mixture was degassed using argon, followed by addition of tetrakis(triphenylphosphine)palladium (0) (0.04 mmol).

The reaction mixture was heated at 110 °C for 8 minutes in microwave and the reaction was monitored by TLC. After completion of reaction, dioxane was removed under high vacuum and the residue was diluted with ethyl acetate (25 mL). The reaction was quenched with water and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over anhydrous Na2SO4 and purified (silica gel column, 5% methanol in chloroform as eluent) to obtain the title compound. Yield: 89%; 1H NMR (300 MHz, DMSO-d6): δ 8.99 (s, 1H), 8.32-8.26 (m, 2H), 8.11-8.08 (d, J=9Hz, 1H), 7.93-7.90 (d, J=9Hz, 1H), 7.64 (s, 4H), 7.58-7.55 (d, J=3Hz, 1H), 7.14 (s, 1H), 4.22 (s, 4H), 3.95-3.90 (m, 2H), 3.86 (s, 3H), 3.61 (s, 3H), 3.14 (s, 2H), 1.42 (s, 9H), 1.04-0.99 (t, J=9Hz, J=15Hz, 3H).

Example 24: 2-(l-(teri-butoxycarbonyl)-3-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidin-3-yl)acetic acid

teri-Butyl 3-(2-ethoxy-2-oxoethyl)-3-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidin-1-carboxylate (compound of Example 21, 0.153 mmol) was dissolved in THF : MeOH (2:0.5 mL) and stirred, 1.5 M aqueous solution of lithium hydroxide (0.917 mmol) was added and the reaction mixture was stirred at RT for 24 hours. The progress of the reaction was monitored by thin layer chromatography (10% MeOH:CHCl3). After completion of reaction, the solvent was evaporated; residue was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, 10% MeOH: CHCl3 as eluent) to obtain the title compound. Yield: 83%; ¾ NMR (300 MHz, DMSO-d6): δ 9.05 (s, 1H), 8.82 (s, 1H), 8.44 (s, 1H), 8.32-8.26 (m, 2H), 8.22-8.19 (d, J=9Hz,
Example 25: 2-(1-(terti-Butoxycarbonyl)-3-(4-(8-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidin-3-yl)acetic acid

terti-Butyl 3-(2-ethoxy-2-oxoethyl)-3-(4-(8-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidine-1-carboxylate (Compound of Example 23, 0.128 mmol) was dissolved in THF: MeOH (2:0.5 mL) and stirred. Lithium hydroxide (0.770 mmol, 1.5 M) was added and the reaction mixture was stirred at RT for 24 hours. After completion of the reaction, the solvent was evaporated and the reaction mass was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, 10% MeOH: CHCl₃ as eluent) to obtain the title compound. Yield: 64%; ¹H NMR (300 MHz, DMSO-d₆): δ 12.37 (s, 1H), 8.99 (s, 1H), 8.28 (s, 1H), 8.11-8.08 (d, J = 9Hz, 1H), 7.94-7.91 (d, J=9Hz, 1H), 7.66 (m, 4H), 7.54-7.51 (d, J=9Hz, 1H), 7.14 (s, 1H), 6.82-6.79 (d, J=9Hz, 1H), 4.23 (s, 4H), 3.86 (s, 3H), 3.61 (s, 3H), 3.10 (s, 2H), 1.42 (s, 9H); MS: 596 (M+1).

Example 26: 2-(1-(terti-Butoxycarbonyl)-3-(4-(3-methyl-2-oxo-8-(pyridin-3-yl)-2,3-dihydro-lH-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidin-3-yl)acetic acid

terti-Butyl 3-(2-ethoxy-2-oxoethyl)-3-(4-(3-methyl-2-oxo-8-(pyridin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidine-1-carboxylate (Compound of Example 22, 0.135 mmol) was dissolved in THF: MeOH (2:0.5 mL) and stirred. Lithium hydroxide (0.80 mmol, 1.5M) was added and the reaction mixture was stirred at RT for 24 hours. The solvent was evaporated and the reaction mass was quenched with saturated solution of ammonium chloride and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, 10% MeOH: CHCl₃ as eluent) to obtain the title compound. Yield: 58%; ¹H NMR (300 MHz, DMSO-d₆): δ 12.37 (s, 1H), 9.03 (s, 1H), 8.68 (s, 1H), 8.51-8.49 (d, J=6Hz, 1H), 8.16-8.13 (d, J=9Hz, 1H), 8.01-7.98 (d, J=9Hz, 1H), 7.65 (m, 5H), 7.41-7.39 (d, J=6Hz, 1H), 7.24 (s, 1H), 4.21 (s, 4H), 3.62 (s, 3H), 3.10 (s, 2H), 1.43 (s, 9H); MS: 566 (M+1).

Example 27: 8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-1-(4-(3-methoxyoxetan-3-yl)phenyl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-one
Step 1: 6-Bromo-N-(4-(3-methoxyoxetan-3-yl)phenyl)-3-nitroquinolin-4-amine

4-(3-methoxyoxetan-3-yl)aniline (Intermediate 12, 7.23 mmol) was added to a solution of 6-bromo-4-chloro-3-nitroquinoline (Intermediate 11, 7.23 mmol) and Na2CC>3 (14.46 mmol) in dry DMF and the resulting reaction mixture was stirred for 3 hours. After completion of the reaction, water was added and the reaction mixture was filtered. The residue was washed with water to obtain the title compound. The title compound was recovered from the filtrate by partitioning the aqueous phase with EtOAc. The organic layer was separated, dried over sodium sulfate and concentrated to obtain the title compound. Yield: 83 %; 1H NMR (300 MHz, DMSO-d$_6$): δ 10.14 (s, 1H), 8.08 (s, 1H), 8.65 (s, 1H), 8.02 (d, J=8.7Hz, 1H), 7.95 (d, J=9.0 Hz, 1H), 7.40 (d, J=8.4 Hz, 2H), 7.17 (d, J=8.1 Hz, 2H), 4.76 (s, 4H), 3.00 (s, 3H); MS: 430(M) +.

Step 2: 8-bromo-l-(4-(3-methoxyoxetan-3-yl)phenyl)-3-methyl-lH-imidazo[4,5-c]quinoline-3,4-diamine

Stannous Chloride (32.5 mmol) was added to a suspension of 6-bromo-N-(4-(3-methoxyoxetan-3-yl)phenyl)-3-nitroquinolin-4-amine (3.62 mmol) in EtOAc and the reaction mixture was stirred at RT for 2 hours. After completion of the reaction, EtOAc was added and quenched with 10 M NaOH. The organic layer was separated, concentrated and purified (silica gel column, MeOH/CHCl$_3$ as eluent) to obtain the title compound. Yield: (56 %); 1H NMR (300 MHz, DMSO-d$_6$): δ 8.60 (s,1H), 7.93 (s,1H), 7.85 (s,1H), 7.78 (d, J=8.7 Hz, 1H), 7.47 (d, J=7.8 Hz, 1H), 7.18 (d, J=8.1 Hz, 2H), 6.57 (d, J=8.4Hz, 2H), 5.46 (s, 2H), 4.70 (s, 4H), 2.95 (s, 3H); MS: 400(M) +.

Step 3: 8-Bromo-l-(4-(3-methoxyoxetan-3-yl)phenyl)-lH-imidazo[4,5-c]quinolin-2(3H)-one

Triethylamine (35.5 mmol) was added to a solution of 6-bromo-N^4-(4-(3-methoxyoxetan-3-yl)phenyl)quinoline-3,4-diamine (compound of step 2, 3.55 mmol) in dry dichloromethane. The reaction mixture was cooled to 0 °C, triphosgene (3.90 mmol) dissolved in DCM was added slowly and stirred for 2 hours. After completion of the reaction, DCM was added and washed with water. Aqueous layer was extracted with DCM. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl$_3$ as eluent) to obtain the title compound. Yield: 66 %; 1H NMR (300 MHz, DMSO-d$_6$): δ 8.80 (s, 1H), 7.94 (d, J=9 Hz, 1H), 7.76-7.73 (m, 6H), 6.95 (s, 1H), 4.90-4.84 (m, 4H), 3.16 (s, 3H); MS: 426 (M) +.

Step 4: 8-bromo-l-(4-(3-methoxyoxetan-3-yl)phenyl)-3-methyl-lH-imidazo[4,5-
Sodium hydride (4.5 mmol) was added to a solution of 8-bromo-1-(4-(3-methoxoyxetan-3-yl)phenyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one (Compound of step 3, 3 mmol) in dry DMF and stirred at RT. Methyl iodide (3 mmol) was added to it after 15 minutes and the reaction mixture was stirred for 3 hours. After completion of the reaction, water was added and extracted with EtOAc. The organic layer was dried over sodium sulfate, concentrated and purified by column chromatography (silica gel, MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 64%; 

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{^1}H\text{ NMR (300 MHz, DMSO-d}_6): \delta 9.04 (s, 1H), 7.98 (d, J=9 Hz, 1H), 7.78-7.63 (m, 5H), 6.95 (s, 1H), 4.91-4.84 (m, 4H), 3.60 (s, 3H), 3.33 (s, 3H); \text{MS: 441(M+1)}^+.
\]

Step 5: 
8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-1-(4-(3-methoxoyxetan-3-yl)phenyl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-one

8-Bromo-1-(4-(3-methoxoyxetan-3-yl)phenyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one (0.227 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine (0.341 mmol), dichlorobis(triphenylphosphine)palladium (II) (0.04 mmol) and 2 M aqueous Na₂C₃ (0.454 mmol) were added to DMF (5 mL) and refluxed for 1 hour. The reaction mixture was diluted with EtOAc and washed with water and brine. The solvent was evaporated to obtain solid residue, which was purified by column chromatography (silica gel, 1.5% MeOH in 99.5% CHCl₃) to obtain the title compound. Yield: 21%; 

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{^1}H\text{ NMR (DMSO-d}_6; 300MHz): \delta 9.10 (s, 1H), 8.13 (s, 1H), 8.10 (s, 1H), 7.99 (d, 1H, J= 8.7Hz), 7.77 (bs, 4H), 7.70 (s, 1H), 7.15 (s, 1H), 6.72 (s, 2H), 4.87 (q, 4H, J=6.6Hz), 3.62 (s, 3H), 3.10 (s, 3H); \text{MS: 522(M+1)}^+.
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Example 28: Ethyl 2-(3-(4-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-2-(cyanoimino)-3-methyl-2,3-dihydro-1H-imidazo [4,5-c]quinolin-1-yl)phenyl)oxetan-3 -yl)acetate

Step 1: Ethyl 2-(3-(4-(8-bromo-2-(cyanoimino)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3 -yl)acetate

Ethyl 2-(3-(4-(3-amino-6-bromoquinolin-4-ylamino)phenyl)oxetan-3-yl)acetate (compound of Example 1, step 2, 1.096 mmol) was stirred in dry DMF. Dimethyl cyanocarbonimidodithioate (2.192 mmol) and cesium carbonate (3.29 mmol) was added to it and stirred at 85 °C for 24 hours. Reaction mixture was cooled, diluted with water and extracted with ethyl acetate. Ethyl acetate layer was dried over sodium sulphate, concentrated.
and purified using column chromatography (silica gel column, MeOH/CHCl₃ (0 to 3 %) as eluent) to obtain the title compound. Yield: 48.5 %; ¹H NMR (300 MHz, DMSO-d₆): δ 13.72 (s, IH), 8.96 (s, IH), 8.04-8.07 (d, J= 9.0 Hz, IH), 7.77 - 7.74 (d, J=9.0 Hz ,IH), 7.68-7.61 (m, 4H), 6.95 (s, IH), 4.93-4.85 (m, 4H), 4.03-3.96 (q, 2H), 3.30 (s, 2H), 1.12-1.10 (t, 3H); MS: 602.2. 1(M+1).

Step 2: Ethyl 2-(3-(4-(8-bromo-2-(cyanoimino)-3-methyl-2,3-dihydro-lH-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate

Sodium hydride (0.592 mmol) was added to a solution of ethyl 2-(3-(4-(8-bromo-2-(cyanoimino)-2,3-dihydro- lH-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (compound of step 1, 0.592 mmol) in dry DMF and the reaction mixture was stirred at RT. Methyl iodide (0.889 mmol) was added to it about 15 minutes and was stirred for 3 hours. The reaction mixture was then diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate, concentrated and purified using column chromatography (silicagel, MeOH/CHCl₃ as eluent) to obtain the title product.

Yield: 41.2 %; ¹H NMR (300 MHz, DMSO-d₆): δ 9.25 (s,IH), 8.05-8.02 (d, J=9.0 Hz, IH), 7.75-7.71 (m, 3H), 7.62-7.63 (d, J =8.1 Hz, 2H), 6.83 (s, IH), 4.93-4.86 (m, 4H), 4.02 (q, 2H), 3.91 (s, 3H), 3.32 (s, 2H), 1.12-1.07 (t, 3H); MS: 522.1(M+1).

Step 3: Ethyl 2-(3-(4-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-2-(cyanoimino)-3-methyl-2,3-dihydro- lH-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate

Ethyl 2-(3-(4-(8-bromo-2-(cyanoimino)-3-methyl-2,3-dihydro-lH-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (Compound of step 2, 0.279 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine (0.418 mmol) was suspended in dry DMF. Dichlorobis(triphenylphosphine)-palladium (II) catalyst (0.017 mmol) and saturated solution of sodium carbonate (0.697 mmol) was added and reaction mixture was heated upto about 111 °C for 6 minutes in CEM microwave. The reaction mixture was cooled, diluted with water and extracted with ethyl acetate. Organic layer was dried over sodium sulphate, concentrated and purified using column chromatography (silicagel column, MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 41%; ¹H NMR (300 MHz, DMSO-d₆): δ 9.19 (s, IH), 8.20 (s, IH), 8.16-8.13 (d, J=9.0 Hz, IH), 7.96-7.93 (d, J=8.7Hz, IH), 7.79-7.77 (d, J=8.1Hz, 2H), 7.68 (s, IH), 7.60-7.58 (d, J=8.1Hz, 2H), 7.04 (s, IH), 6.84 (s, 2H), 4.87-4.85 (m, 4H), 3.94 (s, 3H), 3.83-3.81(q, 2H), 3.22(s, 2H), 0.96-0.92 (t, 3H); MS: 602.2. 1(M+1).
Example 29: Ethyl 2-(3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-2-(cyanoimino)-2,3-dihydro-IH-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate

Ethyl 2-(3-(4-(8-bromo-2-(cyanoimino)-3-methyl-2,3-dihydro-IH-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate (Compound of step 1 of Example 29, 0.148 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine (0.228 mmol) was suspended in dry DMF. Dichlorobis(triphenylphosphine)-palladium (II) catalyst (0.088 mmol) and saturated solution of sodium carbonate (0.370 mmol) was added and the reaction mixture was heated at about 111 °C for 6 minutes in CEM microwave. The reaction mixture was then cooled, diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate, concentrated and purified using column chromatography (silicagel column, MeOH/CHCl₃ as eluent) to obtain the title compound. Yield: 29 %.

1H NMR (300 MHz, DMSO-d₆): δ 13.69 (s, 1H), 8.92 (s, 1H), 8.23 (s, 1H), 8.15-8.12 (d, J=8.7Hz, 1H), 7.97-7.94 (d, J=8.7Hz, 1H), 7.73-7.71 (d, J=8.4Hz, 2H), 7.67 (s, 1H), 7.59-7.56 (d, J=9.0Hz, 2H), 7.13 (s, 1H), 6.70 (s, 2H), 4.95-4.83 (m, 4H), 3.88-3.81 (q, 2H), 3.23 (s, 2H), 0.97-0.92 (t, 3H); MS: 588.1(M+1).

Example 30: teri-Butyl 3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-2-(cyanoimino)-3-methyl-2,3-dihydro-IH-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate

Step 1: teri-Butyl 3-(4-(8-bromo-2-(cyanoimino)-2,3-dihydro-IH-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate

Dimethyl cyanocarbonimidodithioate (1.080 mmol) was added to the stirred solution of teri-butyl 3-(4-((3-amino-6-bromoquinolin-4-yl)amino)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate (Compound of step 2 of Example 3, 0.720 mmol) in DMF (3 mL) followed by the addition of cesium carbonate (2.160 mmol) and the resulting reaction mixture was heated at 80 °C overnight. The solvent was evaporated and the reaction mass was quenched with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄ and the crude product was further purified using column chromatography (silica gel column, MeOH/CHCl₃ (8 %) as eluent) to obtain the title compound. Yield: 19%;

1H NMR (300 MHz, DMSO-d₆): δ 13.77(s, 1H), 8.95 (s, 1H), 8.04-8.01 (d, J=9Hz, 1H), 7.76-7.73 (d, J=9Hz, 1H), 7.65 (s, 4H), 6.88 (s, 1H), 4.21 (s, 4H), 4.04-3.97 (q, J=9Hz, J=15Hz, 2H), 3.17 (s, 2H), 1.23 (s, 9H), 1.13-1.08 (t, J=9Hz, J= 15Hz, 3H); MS: 605 (M+1).
Step 2: teri-Butyl 3-(4-(8-bromo-2-(cyanoimino)-3-methyl-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate

NaH (0.691 mmol, 60%) was added slowly to the cool solution of teri-butyl 3-(4-(8-bromo-2-(cyanoimino)-23-dmydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)-azetidine-1-carboxylate (compound of step 1, 0.413 mmol) in DMF (3 mL). The temperature of the reaction mixture was maintained at 0 °C until the complete addition of NaH. The reaction mixture was stirred for 30 minutes, followed by the addition of methyl iodide (0.691 mmol). The reaction mixture was further stirred at RT for 1 hour. The solvent was evaporated and the reaction mass was extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, concentrated and purified using column chromatography (silica gel column, 5% MeOH: CHCl₃ as eluent). Yield: 43%; ¹H NMR (300 MHz, DMSO-de): δ 9.25 (s, 1H), 8.05-8.02 (d, J=9Hz, 1H), 7.71-7.66 (m, 5H), 6.75 (s, 1H), 4.21 (s, 4H), 4.00-3.95 (m, 2H), 3.90 (s, 3H), 3.18 (s, 2H), 1.23 (s, 9H), 1.13-1.08 (t, J=9Hz, J=15Hz, 3H); MS: 619 (M+1).

Step 3: teri-Butyl 3-(4-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-2-(cyanoimino)-3-methyl-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)-azetidine-1-carboxylate (Compound of step 2, 0.161 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine (0.242 mmol) was dissolved in dioxane : water (4mL : 1mL) and K₂CO₃ (0.404 mmol) was added. Tetrakis(triphenylphosphine)palladium (0) (0.08 mmol) was added to the reaction mixture degassed in an inert atmosphere. The reaction mixture was heated at 110 °C for 8 minutes in microwave. After the completion of the reaction, dioxane was evaporated and EtOAc was added to the residue. The reaction was quenched with water and the aqueous layer was partitioned with EtOAc. The organic layer was separated, dried over anhydrous Na₂SO₄, concentrated and purified using column chromatography (silicagel column, 5% MeOH: Chloroform as eluent). Yield: 46%; ¹H NMR (300 MHz, DMSO-d₆): δ 9.18 (s, 1H), 8.17-8.13 (m, 2H), 7.98-7.95 (d, J=9Hz, 1H), 7.79-7.76 (d, J=9Hz, 2H), 7.68 (s, 1H), 7.62-7.59 (d, J=9Hz, 2H), 7.03 (s, 1H), 6.61 (s, 2H), 4.20 (s, 4H), 3.93 (s, 3H), 3.84-3.82 (m, 2H), 3.06 (s, 2H), 1.41 (s, 9H), 0.983-0.936 (t, J=9Hz, J=15Hz, 3H); MS: 700.9 (M+1).
Example 31: teri-Butyl 3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-23-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate

   teri-Butyl 3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-23-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)azetidine-1-carboxylate (compound of step 4 of Example 3, 0.269 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine (0.403 mmol) was dissolved in DMF (2 mL) and saturated solution of sodium carbonate (0.672 mg in 0.5 mL water) was added, followed by addition of bis(triphenylphosphine)palladium(II) dichloride [(PPh₃)PdCl₂] (0.054 mmol). The reaction mixture was heated at 110 °C for 8 minutes in microwave and reaction was monitored by thin layer chromatography. After completion of reaction, DMF was removed and the residue was dissolved in ethyl acetate (25 mL). Water was added and the aqueous layer was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous Na₂SO₄, concentrated and purified by column chromatography (silica gel column, 5% MeOH and CHCl₃ as eluent). ¹H NMR (DMSO-d₆, 300 MHz): 8.98 (s, 1H), 8.26 (s, 1H), 8.09-8.06 (d, J=9Hz, 1H), 7.91-7.87 (d, J=9Hz, 1H), 7.64-7.55 (m, 5H), 7.21 (s, 1H), 6.68 (s, 2H), 4.91 (s, 2H), 4.19 (s, 4H), 3.87-3.82 (m, 2H), 3.60 (s, 3H), 1.41 (s, 9H), 1.16 (m, 3H). Yield: 10%, MS: 677(m+1).

Example 32: 8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-1-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-1H-imidazo[4,5-c]quinolin-2(3H)-one

   Step 1: Diethyl 2-methyl-2-(5-nitropyridin-2-yl)malonate

Sodium hydride was slowly added to a solution of diethyl-2-methylmalonate (125 mmol) in anhydrous DMF at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 10 minutes at same temperature, followed by the addition of 2-Bromo-5-nitropyridine (20 g, 99 mmol). The reaction mixture was further stirred for 2 hours at RT. After completion of reaction, the solvent was evaporated and the residue was dissolved in DCM. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain the title compound. Yield: 81%

   Step 2: 2-Ethyl-5-nitropyridine

Diethyl 2-methyl-2-(5-nitropyridin-2-yl)malonate (compound of step 1, 79 mmol) was stirred in concentrated HCl (200 mL) at 100 °C for 3 hours. After completion of reaction, the reaction mixture was quenched with water and the compound was extracted with chloroform,
dried over sodium sulfate and concentrated to obtain the title compound. Yield: 79%.

Step 3: 2-Methyl-2-(5-nitropyridin-2-yl)propane-1,3-diol
A reaction mixture of 2-ethyl-5-nitropyridine (compound of step 2, 32.9 mmol) and potassium teri-butoxide (8.2 mmol) was stirred in DMF at 0 °C. Formaldehyde (65.7 mmol) solution was added drop-wise to the reaction mixture while stirring. The reaction mixture was stirred for 1 hour at RT. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, ethyl acetate and petroleum ether as eluent) to obtain the title compound. Yield: 50%.

Step 4: 2-(3-Methyloxetan-3-yl)-5-nitropyridine
A solution of 2-Methyl-2-(5-nitropyridin-2-yl)propane-1,3-diol (compound of step 3, 16.5 mmol) in THF was stirred at 0 °C. Butyl lithium (2 M solution 16.5 mmol) was added and the reaction mixture was stirred for 15 minutes. After 15 minutes, tosyl chloride (16.5 mmol) was added to the reaction mixture. The reaction mixture was stirred at RT for 1 hour. Reaction mixture was cooled to 0 °C and butyl lithium (2 M solution 16.5 mmol) was further added and the reaction mixture was heated at 65 °C for 2 hours. After completion of reaction, the reaction mixture was diluted with ether and washed with saturated solution of sodium bicarbonate. The organic layer was separated, washed with water, dried over sodium sulfate, concentrated and purified (silica gel column, ethyl acetate and petroleum ether as eluent) to obtain the title compound. Yield: 62.4%.

Step 5: 6-(3-methyloxetan-3-yl)pyridin-3-amine
A solution of 2-(3-methyloxetan-3-yl)-5-nitropyridine (Compound of step 4, 15.45 mmol) in dry ethanol was stirred at RT, followed by the addition of ammonium formate (77 mmol). The reaction mixture was further stirred for 5 minutes at RT. Palladium carbon (3 mmol) was added carefully under nitrogen atmosphere. The reaction mixture was refluxed for 2 hours. After completion of reaction, the reaction mixture was cooled and filtered. The filtrate was concentrated and the residue was purified (silicagel column, ethyl acetate and petroleum ether as eluent) to obtain the title compound. Yield: 24%.

Step 6: 6-Bromo-N-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-3-nitroquinolin-4-amine
A solution of 6-(3-methyloxetan-3-yl)pyridin-3-amine (compound of step 5, 1.705 mmol) in dry DMF was stirred followed by the addition of sodium bicarbonate (2.04 mmol). The reaction mixture was further stirred for 5 minutes at RT. 6-Bromo-4-chloro-3-nitroquinoline
(Intermediate 11, 1.705 mmol) was added to the reaction mixture and the reaction mixture was further stirred for 2 hours. After completion of reaction, the reaction mixture was poured in water and the yellow solid obtained was filtered and dried to obtain the title compound. 

$^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 10.13 (s, 1H), 9.08 (s, 1H), 8.72-8.71 (d, J = 1.5 Hz, 1H), 8.40 (s, 1H), 8.04-8.01 (d, J = 9.0 Hz, 1H), 7.96-7.93 (d, J = 9.0 Hz, 1H), 7.48-7.45 (d, J = 8.7 Hz, 1H), 7.33-7.31 (d, J = 8.4 Hz, 1H), 4.90-4.88 (d, 2H), 4.51-4.49 (d, 2H), 1.65 (s, 3H); MS: 417 (M+1).

Step 7: 6-Bromo-N$^4$-(6-(3-methyloxetan-3-yl)pyridin-3-yl)quinoline-3,4-diamine

Stannous chloride dihydrate (9.6 mmol) was added to the suspension of 6-bromo-N-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-3-nitroquinolin-4-amine (Compound of step 6, 2.4 mmol) in ethyl acetate. The reaction mixture was stirred at RT for 2 hours. After completion of reaction, the reaction mixture was diluted with ethyl acetate and quenched with NaOH solution (10 M). The organic layer was separated and aqueous layer was extracted with ethyl acetate. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, methanol and chloroform as eluent) to obtain the title compound. Yield: 80%.

Step 8: 8-Bromo-1-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-1H-imidazo[4,5-c]quinolin-2(3H)-one

Triethylamine (7.9 mmol) was added to a solution of 6-bromo-N$^4$-(6-(3-methyloxetan-3-yl)pyridin-3-yl)quinoline-3,4-diamine (compound of step 7, 1.29 mmol) in dry dichloromethane. The reaction mixture was cooled to 0 °C followed by addition of triphosgene (1.29 mmol) solution in dichloromethane. The reaction mixture was stirred for 2 hours. After completion of reaction, the mixture was diluted with dichloromethane and washed with water. The aqueous layer was extracted with dichloromethane and the organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, methanol/chloroform as eluent) to obtain the title compound. Yield: 43.7 %; $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 11.94 (s, 1H), 8.83-8.82 (s, 2H), 8.16-8.12 (dd, J = 2.4 & 8.4 Hz, 1H), 7.97-7.94 (d, J = 9.0 Hz, 1H), 7.73-7.71 (d, J = 8.4 Hz, 1H), 7.66-7.65 (d, J = 2.1 Hz, 1H), 7.01 (d, J = 2.1 Hz, 1H), 5.03-5.01 (d, 2H), 4.63-4.61 (d, 2H), 1.76 (s, 3H); MS: 413 (M+1).

Step 9: 8-Bromo-3-methyl-1-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-1H-imidazo[4,5-c]quinolin-2(3H)-one

Sodium hydride (0.38 mmol) was added to a solution of 8-bromo-1-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-1H-imidazo[4,5-c]quinolin-2(3H)-one (compound of step 8, 0.317 mmol) in
dry DMF and stirred at RT. Methyl iodide was added to it after 15 minutes (0.634 mmol) and the reaction mixture was stirred for 3 hours. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/chloroform as eluent) to obtain the title compound. Yield: 78 %; \(^1^H\) NMR (300 MHz, DMSO-d\(_6\)): δ 9.08 (s, 1H), 8.83-8.82 (d, J = 2.1 Hz, 1H), 8.16-8.12 (dd, J=2.4 & 8.1 Hz, 1H), 8.01-7.98 (d, J=9.0Hz, 1H), 7.75-7.72 (d, J=8.4 Hz, 1H), 7.71-7.67 (dd, J=2.1 & 9.0 Hz, 1H), 7.01 (d, J=2.4Hz, 1H), 5.04-5.02 (d, 2H), 4.63-4.61 (d, 2H), 3.61 (s, 3H), 1.77 (s, 3H); MS: 427 (M+1).

Step 10: N-(8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-1-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-1H-imidazo[4,5-c]quinolin-2(3H)-one)

A reaction mixture of 8-bromo-3-methyl-1-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-1H-imidazo[4,5-c]quinolin-2(3H)-one (0.236 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine (0.354 mmol) in dry DMF was stirred for 5 minutes. Dichlorobis(triphenylphosphine)-palladium (II) catalyst (0.014 mmol)) and saturated solution of sodium carbonate (0.589 mmol)) were added and reaction mixture was cooled, diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/chloroform as eluent) to obtain the title compound. Yield (40.3%); \(^1^H\) NMR (300 MHz, DMSO-d\(_6\)): δ 9.01 (s, 1H), 8.88 (d, J=2.4 Hz, 1H), 8.27 (s, 1H), 8.20-8.17 (dd, J=2.4 & 8.4 Hz, 1H), 8.11-8.08 (d, J=8.7 Hz, 1H), 7.93-7.90 (dd, J=1.8 & 9.0 Hz, 1H), 7.73-7.70 (d, J=8.4 Hz, 1H), 7.63 (s, 1H), 7.12 (s, 1H), 6.71 (s, 2H), 5.01 (d, 2H), 4.59-4.57 (d, 2H), 3.62 (s, 3H), 1.76 (s, 3H); MS: 507 (M+1).

Example 33: N-(8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-1-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene) cyanamide

Step 1: N-(8-Bromo-1-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanoamide

Cesium Carbonate (1.55 mmol) and dimethyl cyanocarboximidodithioate (1.03 mmol) were added to a solution of 6-bromo-N\(^4\)-(6-(3-methyloxetan-3-yl)pyridin-3-yl)quinoline-3,4-diamine (compound of step 7 of Example 31, 0.51 mmol) in dry DMF. The reaction mixture was stirred at 80 °C for 16 hours. After completion of the reaction, the reaction mixture was
cooled, diluted with ethyl acetate and filtered through celite®. The filtrate was washed with water and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, methanol/chloroform as eluent) to obtain the title compound. Yield 48.2 %; 1H NMR (300 MHz, DMSO-d6): δ 13.90 (s, 1H), 8.98 (s, 1H), 8.88-8.87 (d, J=2.1 Hz, 1H), 8.22-8.18 (dd, J=2.4 & 8.4 Hz, 1H), 8.06-8.03 (d, J=9.0Hz, 1H), 7.78-7.76 (d, J=7.5Hz, 1H), 6.89 (d, J=2.1 Hz, 1H), 5.04-5.02 (d, 2H), 4.63-4.61 (d, 2H), 1.78 (s, 3H); MS: 435.1 (M+l).

Step 2: N-(8-Bromo-3-methyl-1-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-IH-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide

Sodium hydride (0.345 mmol) was added to a solution of N-(8-bromo-1-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-IH-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (compound of step 1, 0.230mmol) in dry DMF and the reaction mixture was stirred at RT. After 15 minutes of stirring, methyl iodide (0.345 mmol) was added and the reaction mixture was further stirred for 3 hours. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/CHCl3 as eluent) to obtain the title compound. Yield: 34 %; 1H NMR (DMSO-d6,300 MHz): δ 9.29 (s, 1H), 8.97-8.96 (d, J=2.1 Hz, 1H), 8.30-8.27 (dd, J=2.4 and 8.4 Hz, 1H), 8.08-8.05 (d, J=9.0Hz, 1H), 7.80-7.75 (m, 2H), 6.75 (d, J=2.4Hz, 1H), 5.04-5.02 (d, 2H), 4.64-4.62 (d, 2H), 3.89 (s, 3H), 1.78 (s, 3H); MS: 451.1 (M+l).

Step 3: N-(8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-1-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-IH-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide

A reaction mixture of N-(8-bromo-3-methyl-1-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-IH-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (compound of step 2, 0.062 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine (0.093 mmol) was stirred in dry DMF for 5 minutes. Dichlorobis(triphenylphosphine)-Palladium (II) catalyst (0.014 mmol)) and saturated solution of sodium carbonate (0.156 mmol)) were added and reaction mixture was heated at 110 °C for 1 hour. After the completion of reaction, the reaction mixture was cooled, diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, concentrated and purified (silica gel column, MeOH/chloroform as eluent) to obtain the title compound. Yield: 45.4 %; 1H NMR (300 MHz, DMSO-de): δ 9.22 (s, 1H), 9.01-9.00 (d, J=2.1Hz, 1H), 8.34-8.27 (m, 1H), 8.19-8.15 (m, 2H), 8.00-8.97 (dd, J=1.8, 9.0Hz, 1H), 7.78-7.75 (d, J=8.4Hz, 1H), 7.62 (s, 1H), 6.93 (d,
J=1.8Hz, 1H), 6.74 (s, 2H), 5.01-4.97 (m, 2H), 4.60-4.56 (m, 2H), 3.91 (s, 3H), 1.76 (s, 3H);
MS: 531.1 (M+l).

TESTING OF THE COMPOUNDS

The efficacy of the present compounds can be determined by a number of pharmacological assays well known in the art, such as those described below. The exemplified pharmacological assays, which follow herein, have been carried out with the compounds of the present invention.

Example 34: Protocol for kinase assay (PI3Kα)

pi 10a radioactive lipid kinase assay

The assay was designed as in the reference, Journal of Biomolecular Screening, 2002, 7, 5, 441-450, the disclosure of which is incorporated by reference for the teaching of the assay.

The pi 10a biochemical assay was performed using a radioactive assay measuring the incorporation of $^{32}$P into the pi 10a substrate, phosphatidylinositol (PI). For the generation of IC$_{50}$ curves, the reaction was performed in a 96-well MaxiSorp plates. Plates were pre-coated with 4 µg/well of a 1:1 ratio of phosphatidylinositol (PI: Avanti #840042C) and phosphatidylserine (PS: Avanti #840032C) diluted in CHCl$_3$. Equal amount of pi 10a (Upstate Millipore) protein was added to each well, containing 25 µL reaction buffer (50 mM MOPS, pH 7.0, 100 mM NaCl, 4 mM MgCl$_2$, 0.1% (w/v) BSA) whereas, for negative control, only reaction buffer was added. Compounds of the present invention dissolved in DMSO were treated at nine-point dose responses (0.3, 1, 3, 6, 10, 30, 60, 100 and 300 nM). Reactions were initiated by the addition of 25 µM ATP solution (Sigma, USA) containing 50 µCi/mL [$\gamma$-$^{32}$P]-ATP and incubated at RT for 2 hours with gentle shaking. Reactions were finally terminated by the addition of 100 µL of 50 mM EDTA stock solution. Plates were washed 3 times with TBS buffer. The plates were air dried, Microscint 0 (Perkin Elmer) was added to each well and the plates were sealed. The radioactivity incorporated into the immobilized PI substrate was determined with Top Count (Perkin Elmer). Inhibition was calculated using the following equation:
\[
\% \text{ Inhibition} = \frac{D_{\text{cpm}} - T_{\text{cpm}}}{D_{\text{cpm}}} \times 100
\]

\[T_{\text{cpm}} = ^{32}\text{P-} \text{cpm in presence of compounds of the present invention}\]
\[D_{\text{cpm}} = ^{32}\text{P-} \text{cpm in DMSO control (enzyme control deducted)}\]

Results: IC\(_{50}\) values of test compounds for PI3 kinase activity is indicated in Table 1.

Table 1:

<table>
<thead>
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<th>Example No.</th>
<th>IC(_{50}) in nM</th>
<th>Example No.</th>
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<th>Example No.</th>
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<td>18</td>
<td>++</td>
<td>36</td>
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</tbody>
</table>

Symbol | IC\(_{50}\) range | Class  
++ | \(\leq 100\) nM |  
+ | > 100 nM upto 1 \(\mu\)M

Example 35: Cytotoxicity assay

Propidium Iodide Assay

The assay was designed as in the reference, Anticancer Drugs, 2002, 13, 1-8, the disclosure of which is incorporated by reference for the teaching of the assay.

Cells from cell lines A2780 (ovarian cell line) and PC3 (prostate cell line) (both from ATCC) were seeded at a density of 3000 cells/well in a white opaque 96-well plate. Following incubation at 37 \(^\circ\)C/ 5 % CO\(_2\) for a period of 18-24 hours, the cells were treated with various concentrations (stock solution was prepared in DMSO and subsequent dilutions were made in media as per ATCC guidelines) of the test compounds for a period of 48 hours.

At the end of treatment, the culture medium was discarded, the cells were washed with 1 x PBS and 200 \(\mu\)l of 7 \(\mu\)g/mL propidium iodide was added to each well. The plates were frozen at -70 \(^\circ\)C overnight. For analysis, the plates were warmed to RT, allowed to thaw and were read in PoleStar fluorimeter with the fluorescence setting. The percentage of viable cells in

75
the non-treated set of wells was considered to be 100 and the percentage viability following
treatment was calculated accordingly. IC50 values were calculated from graphs plotted using
these percentages. Results for test compounds in individual cell lines are shown in Table 2.

Results: IC50 values for test compounds (referred to by the example numbers) are indicated in

Table 2.

<table>
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<td>22</td>
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</tr>
<tr>
<td>9</td>
<td>++          ++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Symbol | IC50 range | class
++     | ≤ 100 nM  |
+      | > 100 nM upt 3 µM

It should be noted that, as used in this specification and the appended claims, the
singular forms "a", "an", and "the" include plural referents unless the content clearly dictates
otherwise. Thus, for example, reference to a composition containing "a compound" includes
a mixture of two or more compounds. It should also be noted that the term "or" is generally
employed in its sense including "and/or" unless the content clearly dictates otherwise.

All publications and patent applications in this specification are indicative of the level
of ordinary skill in the art to which this invention pertains.

The invention has been described with reference to various specific and preferred
embodiments and techniques. However, it should be understood that many variations and
modifications may be made while remaining within the spirit and scope of the invention.
CLAIMS

1. A compound of formula (I)

wherein,

- Ring A is (C6-C4)aryl or heteroaryl;
- X1 is O or NR;
- X2 is O or NR;
- R1 is hydrogen, CN, -NR, -OR, (Q-C6)alkyl, wherein (C1-C6)alkyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of CN, -NR, -OR, -COOH, -C(0)0-(C1-C6)alkyl, and -P(0)(OR)(OR);
- R2 is halogen, CN, nitro, halogen, -OR, -NR-COR, -COOR, halo-(Ci-Qi)alkyl, wherein (C1-C6)alkyl is unsubstituted or substituted with halogen or CN;
- R3 is hydrogen or (Ci-Ce)alkyl;
- R4 is halogen, (C6-C4)aryl or heteroaryl; wherein each of the aryl and heteroaryl is unsubstituted or substituted with one or more groups selected from R4;
- R41 is nitro, CN, -C(0)0-(C1-C6)alkyl or (Q-C6)alkyl, wherein (C1-C6)alkyl is unsubstituted or substituted with CN or -NR-R;
- R1 is hydrogen, (C1-C6)alkyl, -C(0)0-(C1-C6)alkyl or -S(0)2-(C1-C6)alkyl;
- R41 at each occurrence is independently selected from the group consisting of hydrogen, halogen, -OR, CN, -NR-R, -NR-COR, -COOR, -CONR-R, halo-(Ci-Qi)alkyl, and (C1-C6)alkyl;

and (C1-C6)alkyl;

R and R, at each occurrence are independently selected from hydrogen and (C1-
c6)alkyl; and

p is an integer from 0 to 4; or

in all its isotopic forms, stereoisomeric and tautomeric forms and mixtures thereof in all ratios, or a pharmaceutically acceptable salt, a pharmaceutically acceptable solvate, a prodrug, a polymorph, an N-oxide or a carboxylic acid isostere thereof.

2. The compound according to claim 1, wherein Ring A is phenyl or 5 or 6-membered nitrogen containing heteroaryl.

3. The compound according to claim 1 or claim 2, wherein Ring A is phenyl or pyridyl.

4. The compound according to any one of the preceding claims 1 to 3, wherein X1 is O or N(CN).

5. The compound according to any one of the preceding claims 1 to 4, wherein X2 is -O- or NRy, wherein Ry is hydrogen, -C(0)OC(CH3)3 or -S(0)2CH3.

6. The compound according to any one of the preceding claims 1 to 5, wherein R1 is hydrogen, -ORa or (Ci-Ce)alkyl, wherein (Ci-Ce)alkyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of -ORa, -C(0)(Cr c6)alkyl and -COOH, wherein Ra is hydrogen or (Ci-C6)alkyl.

7. The compound according to any one of the preceding claims 1 to 6, wherein R3 is hydrogen or methyl.

8. The compound according to any one of the preceding claims 1 to 7, wherein R4 is halogen.

9. The compound according to any one of the preceding claims 1 to 7, wherein R4 is phenyl, wherein said phenyl is unsubstituted or substituted with one or more groups independently selected from group consisting of halogen, -ORa, CN, -NRbRa, -NRaCORb, -COORa, -CONRaRb, halo-(C1-C6)alkyl and (C1-C6)alkyl, wherein Ra and Rb at each occurrence are independently selected from hydrogen and (Ci-C6)alkyl.
10. The compound according to claim 9, wherein R4 is phenyl, wherein said phenyl is unsubstituted or substituted with one or more groups independently selected from -OR, and -COOR, wherein R at each occurrence is independently selected from hydrogen and (Ci-C6)alkyl.

11. The compound according to any one of the preceding claims 1 to 7, wherein R4 is 6 to 10 membered heteroaryl, wherein said heteroaryl is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -OR, CN, -NR, -NR, -CONR, halo-(Ci-C6)alkyl and (Ci-C6)alkyl.

12. The compound according to claim 11, wherein R4 is pyridyl, indolyl or quinolinyl, wherein each of pyridyl, indolyl or quinolinyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, -NR, halo-(Ci-C6)alkyl, -OR and (Ci-C6)alkyl; wherein R and R at each occurrence are independently selected from hydrogen and (Ci-C6)alkyl.

13. The compound according to claim 12, wherein R4 is unsubstituted or substituted pyridyl, represented by structural formula , wherein each of R, R, and R is independently selected from the group consisting of halogen, hydroxyl, -OR, CN, -NR, -CONR, halo-(Ci-C6)alkyl and (Ci-C6)alkyl, wherein R and R at each occurrence are independently selected from hydrogen and (Ci-C6)alkyl.

14. The compound according to claim 13, wherein each of R, R and R is independently selected from the group consisting of hydrogen, halogen, -0-(Ci-C6)alkyl, -NH, -NH-(Ci-C6)alkyl, -N[(Ci-C6)alkyl], halo-(Ci-C6)alkyl and (Ci-C6)alkyl.

15. The compound according to claim 14, wherein each of R, R and R is independently selected from the group consisting of hydrogen, halogen, -0-(Ci-C6)alkyl, -N(CH), -CF and -CH.

16. The compound according to claim 13, wherein R is -NH2, R and R are independently selected from the group consisting of hydrogen, halogen, -0-(Ci-C6)alkyl, -
NH₂, -NH-(C₁-C₆)alkyl, -N[(C₁-C₆)alkyl]₂, halo-(C₁-C₆)alkyl and (C₁-C₆)alkyl.

17. The compound according to claim 13, wherein R₄₁,₃ is -CF₃; and R₄₁₁ and R₄₁₂ are independently selected from the group consisting of hydrogen, halogen, -0-(C₁-C₆)alkyl, -NH₂, -NH-(C₁-C₆)alkyl, -N[(C₁-C₆)alkyl]₂, halo-(C₁-C₆)alkyl and (C₁-C₆)alkyl.

18. The compound according to claim 13, wherein R₄₁₁ is -NH₂ and R₄₁,₃ is -CF₃ and R₄₁₂ is selected from the group consisting of hydrogen, halogen, -0-(C₁-C₆)alkyl, -NH₂, -NH-(C₁-C₆)alkyl, -N[(C₁-C₆)alkyl]₂, halo-(C₁-C₆)alkyl and (C₁-C₆)alkyl.

19. The compound according to claim 13, wherein R₄₁₁ is -NH₂, R₄₁,₃ is -CF₃ and R₄₁₂ is hydrogen.

20. The compound according to any one of the preceding claims 1 to 19, selected from the group consisting of:

Ethyl 2-(3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate,

Ethyl 2-(3-(4-(8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-l-(4-(3-methyloxetan-3-yl)phenyl)-lH-imidazo[4,5-c]quinolin-2(3H)-one,

Ethyl 2-(3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-c]quinolin-l-yl)phenyl)azetidin-3-yl)acetate,

2-(3-(4-(8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-c]quinolin-l-yl)phenyl)-l-(teri-butoxycarbonyl)azetidin-3-yl)acetic acid,

Ethyl 2-(3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-lH-imidazo[4,5-c]quinolin-l-yl)phenyl)-(methylsulfonyl)azetidin-3-yl)acetate,

Ethyl 2-(3-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-lH-imidazo[4,5-c]quinolin-l-yl)phenyl)oxetan-3-yl)acetate,

Ethyl 2-(3-(4-(3-methyl-2-oxo-8-(pyridin-3-yl)-2,3-dihydro-lH-imidazo[4,5-c]quinolin-l-yl)phenyl)oxetan-3-yl)acetate,

2-(3-(4-(3-Methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-lH-imidazo[4,5-c]quinolin-l-yl)phenyl)oxetan-3-yl)acetic acid,

8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-l-(4-(3-(2-hydroxyethyl)oxetan-3-yl)phenyl)-3-methyl-lH-imidazo[4,5-c]quinolin-2(3H)-one,
8-(6-Amino-5-methylpyridin-3-yl)-1-(4-(3-(2-hydroxyethyl)oxetan-3-yl)phenyl)-3-methyl-
1H-imidazo[4,5-c]quinolin-2(3H)-one,
Ethyl 2-(3-(4-(8-(2,6-difluoropyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-
c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate,
5 Ethyl 2-(3-(4-(8-(1H-indol-6-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-
yl)phenyl)oxetan-3-yl)acetate,
2-(3-(4-(8-(2-Fluoro-6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-
c]quinolin-1-yl)phenyl)oxetan-3-yl)acetic acid,
Ethyl 2-(3-(4-(3-methyl-2-oxo-8-(5-(trifluoromethyl)pyridin-3-yl)-2,3-dihydro-1H-
imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate,
Ethyl 2-(3-(4-(8-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-
1-yl)phenyl)oxetan-3-yl)acetate,
Ethyl 2-(3-(4-(8-(5-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-
c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate,
Ethyl 2-(3-(4-(8-(isoquinolin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-
1-yl)phenyl)oxetan-3-yl)acetate,
Ethyl 2-(3-(4-(8-(4-hydroxyphenyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-
1-yl)phenyl)oxetan-3-yl)acetate,
2-(l-(tert-Butoxycarbonyl)-3-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1H-imidazo[4,5-
c]quinolin-1-yl)phenyl)azetidin-3-yl)acetic acid,
2-(l-(tert-Butoxycarbonyl)-3-(4-(8-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-
1H-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidin-3-yl)acetic acid,
2-(1-(tert-Butoxycarbonyl)-3-(4-(3-methyl-2-oxo-8-(pyridin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)azetidin-3-yl)acetic acid, 8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-l-(4-(3-methoxyoxetan-3-yl)phenyl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-one, Ethyl 2-(3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-2-(cyanoimino)-3-methyl-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate, Ethyl 2-(3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-2-(cyanoimino)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)oxetan-3-yl)acetate, teri-Butyl 3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-2-(cyanoimino)-3-methyl-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl) azetidine-1-carboxylate, teri-Butyl 3-(4-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl)-3-(2-ethoxy-2-oxoethyl) azetidine-1-carboxylate, 8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-l-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-IH-imidazo[4,5-c]quinolin-2(3H)-one, and N-(8-(6-Amino-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-l-(6-(3-methyloxetan-3-yl)pyridin-3-yl)-IH-imidazo[4,5-c]quinolin-2(3H)-ylidene) cyanamide, or a pharmaceutically acceptable salt, a stereoisomer, a tautomer or an N-oxide thereof.

21. A pharmaceutical composition comprising a therapeutically effective amount of a compound formula (I) as defined in any one of the claims 1 to 20, or a pharmaceutically acceptable salt, a stereoisomer, a tautomer or an N-oxide thereof; and a pharmaceutically acceptable excipient or a carrier.

22. A compound of formula (I) according to any one of the preceding claims 1 to 20 for use in the treatment of a proliferative disease or disorder, wherein the proliferative disease or disorder is mediated by a kinase selected from the group consisting of phosphatidylinositol 3 kinase (PI3K), mammalian target of rapamycin (mTOR) and activin receptor-like kinase 1 (ALK1) or combinations thereof.

23. The compound of formula (I) for the use according to claim 22, wherein the proliferative disease or disorder is cancer.
24. The compound of formula (I) for the use according to claim 23, wherein the cancer is selected from the group consisting of leukemia, lung cancer, brain tumors, Hodgkin's disease, liver cancer, kidney cancer, bladder cancer, breast cancer, endometrial cancer, head and neck cancer, lymphoma, melanoma, cervical cancer, thyroid cancer, gastric cancer, germ cell tumor, cholangiocarcinoma, extracranial cancer, sarcoma, mesothelioma, malignant fibrous histiocytoma of bone, retinoblastoma, esophageal cancer, multiple myeloma, oral cancer, pancreatic cancer, neuroblastoma, skin cancer, ovarian cancer, recurrent ovarian cancer, prostate cancer, testicular cancer, colorectal cancer, lymphoproliferative disease, refractory multiple myeloma, cancer of urinary tract, resistant multiple myeloma and myeloproliferative disorder.

25. The compound of formula (I) for the use according to claim 24, wherein the cancer is selected from the group consisting of breast cancer, prostate cancer, pancreatic cancer, lung cancer (non-small-cell lung cancer and small-cell lung cancer), head and neck cancer, ovarian cancer, colon cancer, rectal cancer, kidney cancer, gastric cancer, non-Hodgkin's lymphoma, primary central nervous system lymphoma, glioblastoma and astrocytoma.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/04 A61K31/437 A61P35/00

According to International Patent Classification (IPC) onto both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal , CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>CN 102 399 218 A (HUTCHISON MEDI PHARMA LTD) 4 April l 2012 (2012-04-04) claim 1; compounds 11,14-16,61</td>
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Date of the actual completion of the international search 13 May 2014

Date of mailing of the international search report 20/05/2014

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer Schuemacher, Anne

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