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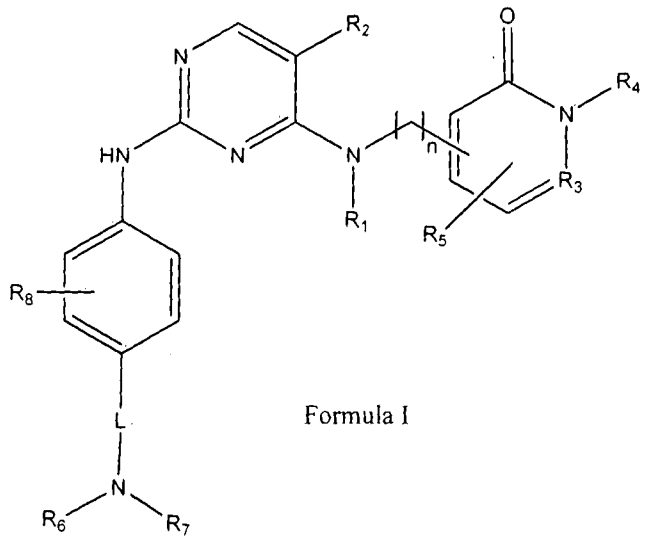
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(54) Title: PYRIMIDINE-2,4-DIAMINE DERIVATIVES AS KINASE INHIBITORS



Formula I

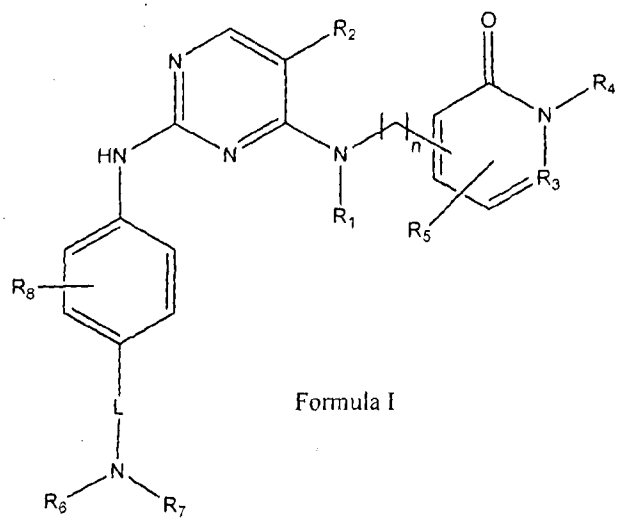
(57) Abstract: The present application relates to novel Pyrimidine-2,4-diamine derivatives as kinase inhibitors derivatives of formula (I), as protein kinase inhibitors. Formula (I). The invention particularly relates to compounds of formula (I), preparation of compounds and pharmaceutical compositions thereof. The invention further relates to prodrugs, derivatives, polymorphs, pharmaceutically acceptable salts and compositions comprising the said novel Pyrimidine-2,4-diamine derivatives as kinase inhibitors and their derivatives and their use in the treatment of various disorders.

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PYRIMIDINE-2,4-DIAMINE DERIVATIVES AS KINASE INHIBITORS

Field of the invention

The present application relates to novel Pyrimidine-2,4-diamine derivatives as kinase inhibitors derivatives of formula (I), as protein kinase inhibitors.



Formula I

The invention particularly relates to compounds of formula (I), preparation of compounds and pharmaceutical compositions thereof.

The invention further relates to prodrugs, derivatives, polymorphs, pharmaceutically acceptable salts and compositions comprising the said novel Pyrimidine-2,4-diamine derivatives as kinase inhibitors and their derivatives and their use in the treatment of various disorders.

Background of the Invention:

Protein Kinases are key regulators of cell function that constitute one of the largest and most functionally diverse gene families. Protein kinases participate in the signalling events that control the activation, growth and differentiation of cells in response to extracellular mediators and to changes in the environment. In general, these protein kinases fall into several groups; those which preferentially phosphorylate serine and/ or threonine residues and those which preferentially phosphorylate tyrosine residues.

Protein kinases play crucial role in regulating the different cell processes which include, but are not limited to, proliferation, differentiation, apoptosis, motility, transcription, translation, signaling process and various regulatory mechanisms, by adding phosphate groups to the target

protein residues. This phosphorylation event acts as molecular on/off switches that can modulate or regulate the target position biological function. Phosphorylation of targeted proteins occurs in response to a variety of extracellular signals. The appropriate protein kinase functions in signaling pathways to activate or deactivate. Uncontrolled signaling due to defective control of protein phosphorylation is known to contribute to various diseases. In the case of cancer, kinases are known to regulate many aspects of the cell growth, invasion that intrudes upon and destroys adjacent tissues and sometimes metastasis, or spreading to other locations in the body via lymph or blood.

The protein kinase family members include enzymes that control cell growth, migration, activation, proliferation, differentiation, signalling, survival and regulation of the cell cycle. Many diseases and/or disorders are associated with aberrant, abnormal or deregulated activity of one or more kinases. These diseases and/or disorders include, but are not limited to cancers, allergic diseases and/or disorders, autoimmune diseases and/or disorders, inflammatory diseases and/or disorder and/or conditions associated with inflammation and pain, proliferative diseases, hematopoietic disorders, haematological malignancies, bone disorders, fibrosis diseases and/or disorders, metabolic disorders, muscle diseases and/or disorders respiratory diseases and/or disorders, pulmonary disorders, genetic developmental diseases, neurological and neurodegenerative diseases/or disorders, chronic inflammatory demyelinating neuropathies, cardiovascular, vascular or heart diseases and/or disorders, ophthalmic/ocular diseases and/or disorders, wound repair, infection and viral diseases. Therefore, inhibition of one or more of kinases would have multiple therapeutic indications.

JAK kinases (Janus Kinases) are a family of cytoplasmic protein tyrosine kinases including JAKl, JAK2, JAK3 and TYK2. The protein tyrosine kinases JAK1, JAK2, JAK3 and TYK2 have essential roles in cytokine-dependent regulation of proliferation and function of cells involved in immune response. They are critical in signal transduction in response to their activation via tyrosine phosphorylation by stimulation of interleukin receptors. Each of the JAK kinases is selective for the receptors of certain cytokines, though multiple JAK kinases can be affected by particular cytokine or signalling pathways. JAKl interacts with, among others, the receptors for cytokines IL-2, IL-4, IL-7, IL-9 and IL-21, while JAK2 interacts with, among others, the receptors for IL-9 and TNF-a. Upon the binding of certain cytokines to their receptors (e.g., IL-2, IL-4, IL-7, IL-9, IL- 15 and IL-21), receptor oligomerization occurs, resulting in the

cytoplasmic tails of associated JAK kinases being brought into proximity and facilitating the trans-phosphorylation of tyrosine residues on the JAK kinase. This trans-phosphorylation results in the activation of the JAK kinase. Phosphorylated JAK kinases bind various STAT (Signal Transducer and Activator of Transcription) proteins. STAT proteins, which are DNA binding proteins activated by phosphorylation of tyrosine residues, function both as signaling molecules and transcription factors and ultimately bind to specific DNA sequences present in the promoters of cytokine-responsive genes. JAK/STAT signaling has been implicated in the mediation of many abnormal immune responses such as allergies, asthma, autoimmune diseases such as transplant (allograft) rejection, rheumatoid arthritis, amyotrophic lateral sclerosis and multiple sclerosis, as well as in solid and hematologic malignancies such as leukemia and lymphomas. For a review of the pharmaceutical intervention of the JAK/STAT pathway see Frank, (1999), Mol. Med. 5:432:456 and Seidel et al., (2000), Oncogene 19:2645-2656. The JAK kinases and JAK2 mutations are implicated in myeloproliferative disorders, cancers, including blood borne and solid tumors. Exemplary disorders include chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic eosinophilic leukemia (CEL), chronic myelomonocytic leukemia (CMML) and systemic mastocytosis (SM).

FAK (Focal Adhesion Kinase) is a non-receptor tyrosine kinase which transduces signaling from a group of stimuli (e.g. , integrins, cytokines, chemokines, and growth factors) to control a variety of cellular pathways and processes, including cell proliferation, migration, morphology, and cell survival. FAK is activated by FAC (focal adhesion complex)-associated growth factors and integrins. The binding to integrins of EMC (extracellular matrix) leads to the activation of FAK. The activation of FAK can be further enhanced by co-stimulation of the growth factors by ECM associated growth factors, such as bFGF, EGF or PDGF. Focal adhesion complex assembly and disassembly are essential for ceil attachment and movement. FAK doesn't phosphorylate other proteins. However, activated FAK auto phosphorylates and binds Src kinase which in turn phosphorylate other sites of FAK and other FAK binding proteins such as Cas and paxillin. Phosphorylated FAK provides the docking site for mediators of multiple signalling events and consequently involves in the regulation of ceil growth and survival through activation of Pi3K/Akt/mTOR and Grb2/SOS/RAS/Raf/MEK ERK pathways. Overexpression of FAK has been associated with malignancy in a variety of cancers. Inhibition of FAK has been shown the inhibition of tumour growth in different cancer cells (Oncogene 25: 4429-4440). However,

inhibition of FAK in normal human fibroblasts or immortalized mammary ceils didn't cause loss of attachment or apoptosis. Furthermore, loss of FAK activity (reconstitution of FAK-/-cells with kinase-dead FAK) reduced growth of v-Src tumors in mice and decreased angiogenesis. Therefore, Inhibition of FAK is a potential therapy for the treatment of hyper-proliferative diseases such as cancers.

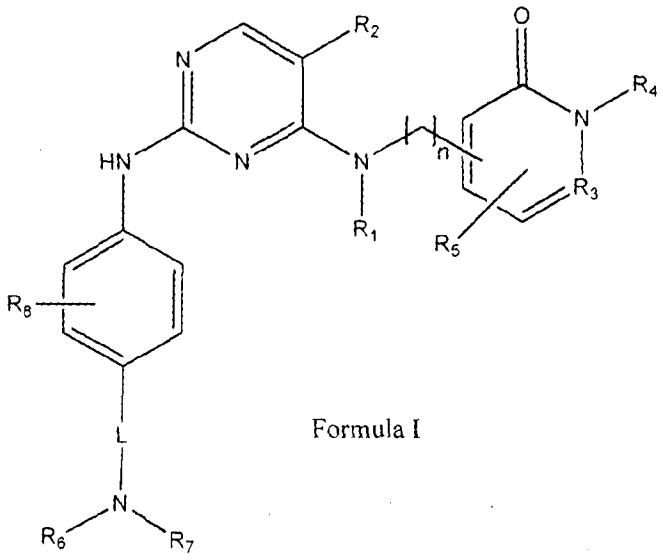
Axl is a receptor protein tyrosine kinase (RTK) that comprises a C-terminal extracellular ligand-binding domain and N-terminal cytoplasmic region containing the catalytic domain. The extracellular domain of Axl has a unique structure that juxtaposes immunoglobulin and fibronectin Type III repeats and is reminiscent of the structure of neural cell adhesion molecules. Axl and its two close relatives, Mer/Nyk and Sky (Tyro3/Rse/Dtk), collectively known as the Tyro3 family of RTK's, all bind and are stimulated to varying degrees by the same ligand, Gas6 (growth arrest specific-6), a ~76 kDa secreted protein with significant homology to the coagulation cascade regulator, Protein S. In addition to binding to ligands, the Axl extracellular domain has been shown to undergo hemophilic interactions that mediate cell aggregation, suggesting that one important function of Axl may be to mediate cell-cell adhesion. Axl is predominantly expressed in the vasculature in both endothelial cells (EC's) and vascular smooth muscle cells (VSMC's) and in cells of the myeloid lineage and is also detected in breast epithelial cells, chondrocytes, Sertoli cells and neurons. Several functions including protection from apoptosis induced by serum starvation, TNF-a or the viral protein E1A, as well as migration and cell differentiation have been ascribed to Axl signaling in cell culture.

Accordingly, a need exists for the identification of small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of kinases, particularly JAK, FAK or AXL as a means to treat or prevent associated diseases.

Summary of the invention

Provide herein are compounds and pharmaceutical compositions thereof, which are useful as protein kinase inhibitors, particularly receptor tyrosine kinase and non-receptor tyrosine kinase inhibitors, more particularly JAK (Janus Kinase), FAK (Focal Adhesion Kinase) or AXL.

In one aspect the present invention relates to pyrimidine-2,4-diamine derivatives of formula (I)



Formula I

wherein

L is direct bond or group selected from -$(CH_2)_p$-, –CO- or -SO_2-;

R_1 is hydrogen or alkyl;

R_2 is hydrogen, halogen, optionally substituted alkyl, haloalkyl, cyano, -$CONHR_1$;

R_3 is CR_9 or N;

R_4 is independently selected from optionally substituted alkyl, cyanoalkyl , -$(CH_2)_q CONR_{10}R_{11}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted cycloalkylalkyl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl; wherein optionally substituent, in each occurrence is independently selected from –OR_{12}, -SR_{12}, -$S(O)_2R_{12}$ or -$NR_{13}R_{14}$;

R_5 is independently selected from hydrogen, halogen, optionally substituted alkyl or -$NR_{13}R_{14}$;

R_6 and R_7 are

i) independently selected from hydrogen, alkyl or acyl;

ii) taken together with the nitrogen to which they are attached may optionally form 3 to 7 membered saturated, partially saturated or unsaturated ring having 0-2 additional heteroatoms

selected from N, O, S; wherein the said ring is optionally substituted with halo, alkyl, acyl, alkyloxy, hydroxyl, hydroxyalkyl, oxo, cycloalkyl, heterocycloalkyl or $-NR_{13}R_{14}$;

alternatively, when L is direct bond then R_6 or R_7 together with the nitrogen to which it is attached and adjacent carbon atom of the phenyl group may optionally form 3 to 7 membered saturated, partially unsaturated or fully unsaturated ring having 0-2 additional heteroatoms selected from N, O, S; wherein the said ring is optionally substituted with oxo;

R_8 is independently selected from hydrogen, halo or alkyloxy;

R_9 at each occurrence is independently selected from hydrogen, alkyl or $-NR_{13}R_{14}$;

R_{10} and R_{11} at each occurrence are independently selected from hydrogen, alkyl or alkyloxy;

R_{12} in each occurrence are independently selected from hydrogen or alkyl;

R_{13} and R_{14} in each occurrence are independently selected from hydrogen, alkyl, acyl or $-S(O)_2R_{12}$;

n is 0 or 1;

p is selected from 1 to 5; and

q is selected from 0 to 5;

or a pharmaceutically acceptable salts, stereoisomers, polymorphs or prodrugs thereof.

In another aspect the present invention provides a pharmaceutical composition comprising the compound of formula (I), and atleast one pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent).

In yet another aspect the present invention relates to the preparation of the compounds of formula (I).

In further yet another aspect the present invention, it provides pyrimidine-2,4-diamine derivatives of formula (I), which are used for the treatment and prevention in diseases or disorder, in particular their use in diseases or disorder where there is an advantage in inhibiting protein kinases enzymes, particularly receptor tyrosine kinase and non-receptor tyrosine kinase inhibitors, more particularly JAK (Janus Kinase), FAK (Focal Adhesion Kinase) or AXL.

In further yet another aspect of the present invention, it provides compounds of pyrimidine-2,4-diamine derivatives of formula (I), as protein kinases enzyme inhibitors are used as dual kinase inhibitors or multiple kinase inhibitors.

Detailed Description of the invention:

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in art to which the subject matter herein belongs. As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated in order to facilitate the understanding of the present invention.

As used herein, the term 'compound(s)' comprises the compounds disclosed in the present invention.

As used herein, the term "comprise" or "comprising" is generally used in the sense of include, that is to say permitting the presence of one or more features or components.

As used herein, the term "or" means "and/or" unless stated otherwise.

As used herein, the term "including" as well as other forms, such as "include", "includes" and "included" is not limiting.

As used herein the term "substituted" refers to a non-hydrogen radical is in the place of hydrogen radical on a carbon or nitrogen of the substituent. Thus, for example, a substituted alkyl substituent is an alkyl substituent in which at least one non-hydrogen radical is in the place of a hydrogen radical on the alkyl substituent. It should be recognized that if there are more than one substitution on a substituent, each non-hydrogen radical may be identical or different, unless otherwise stated.

As used herein, the term "optionally substituted" refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent including, but not limited to: halo, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, thiol, alkylthio, arylthio, alkylthioalkyl, arylthioalkyl, alkylsulfonyl, alkylsulfonylalkyl, arylsulfonylalkyl, alkoxy, aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkyl, amino, trifluoromethyl, cyano, nitro, alkylamino, arylamino, alkylaminoalkyl, arylaminoalkyl, aminoalkylamino, hydroxy, alkoxyalkyl, carboxyalkyl,

alkoxycarbonylalkyl, aminocarbonylalkyl, acyl, aralkoxycarbonyl, cyanoalkylyoxy, hydroxyalkyloxy, carboxylic acid, sulfonic acid, sulfonyl, phosphonic acid, aryl, heteroaryl, heterocyclic, and aliphatic. It is understood that the substituent may be further substituted.

As used herein, unless otherwise defined the term "alkyl" alone or in combination with other term(s) means saturated aliphatic groups, including C_1-C_{10} straight or C_1-C_{10} branched alkyl groups. In one embodiment the term "branched alkyl" means secondary or tertiary alkyl groups.

As used herein, unless otherwise defined the term "acyl" alone or in combination with other term(s) means RC(O)-, wherein R is alkyl as defined above. For example, acetyl, -$C(O)(CH_2)_4CH_3$, -$C(O)(CH_2)_6CH_3$ and the like.

As used herein, unless otherwise defined the term "halo" or "halogen" alone or in combination with other term(s) means fluorine, chlorine, bromine and Iodine.

As used herein, unless otherwise defined the term "haloalkyl" means alkyl substituted with one or more halogen atoms, where alkyl groups are as defined above. The term "halo" is used herein interchangeably with the term "halogen" means F, Cl, Br or I. Examples of "haloalkyl" include but are not limited to trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl and the like.

As used herein, unless otherwise defined the term "cyanoalkyl" means alkyl substituted with cyano group, where alkyl groups are as defined above. Examples of "cyanoalkyl" include but are not limited to cyanomethyl, cyanoethyl and the like.

As used herein, unless otherwise defined the term "cycloalkyl" alone or in combination with other term(s) means -C_3-C_{10} saturated cyclic hydrocarbyl ring. A cycloalkyl may be a single ring, which typically contains from 3 to 7 carbon ring atoms and more typically from 3 to 6 ring atoms. Examples of single-ring cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. A cycloalkyl may alternatively be polycyclic or contain more than one ring. Examples of polycyclic cycloalkyls include bridged, fused, and spirocyclic carbocyclyls.

As used herein, the term "heterocycloalkyl" alone or in combination with other term(s) means a saturated {i.e., "heterocycloalkyl") or partially saturated {i.e., "heterocycloalkenyl") ring structure containing a total of 3 to 12 ring atoms. At least one of the ring atoms is a heteroatom

{i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heterocycloalkyl may be a single-ring (monocyclic), bicyclic or polycyclic ring structure.

As used herein, the term "heteroaryl" alone or in combination with other term(s) means a 5-15 membered mono-, bi-, or other multi-cyclic, aromatic ring system containing one or more heteroatoms; wherein heteroatoms are selected from nitrogen, oxygen, and sulfur. Heteroaryls can also be fused to nonromantic rings. The term "fused" means that the second ring is attached or formed by having two adjacent atoms in common with the first ring. The term "fused" is equivalent to the term "condensed".

As used herein, the term "aryl" alone or in combination with other term(s) means a carbocyclic aromatic system containing one or two rings wherein such rings may be fused. The term "fused" means that the second ring is attached or formed by having two adjacent atoms in common with the first ring. The term "fused" is equivalent to the term "condensed". Examples of aryl groups include but are not limited to phenyl, naphthyl, 3,4-dihydroquinolin-2(1H)-one, benzo[d][1,3]dioxole, 2,3-dihydrobenzo [b][1,4]dioxine and the like. Unless otherwise specified, all aryl groups described herein may be substituted or unsubstituted.

As used herein, the term "cycloalkylalkyl" alone or in combination with other term(s) means alkyl substituted with cycloalkyl group, wherein the terms "alkyl" and "cycloalkyl" are as defined above.

As used herein, the term "arylalkyl" alone or in combination with other term(s) means alkyl substituted with aryl group, wherein the terms "alkyl" and "aryl" are as defined above.

As used herein, the term "heteroarylalkyl" alone or in combination with other term(s) means alkyl substituted with heteroaryl group, wherein the terms "alkyl" and "heteroaryl" are as defined above

As used herein, the term "alkyloxy" refers to alkyl (groups as defined above) hydrocarbon radical bonded to an oxygen atom that is attached to a core structure. Examples of alkyloxy groups include methoxy, ethoxy, propoxy and the like.

As used herein, the term "hydroxyl" means an -OH group.

As used herein, the term "hydroxyalkyl" means at least one hydroxy group, as defined herein, appended to the parent molecular moiety through an alkyl group as defined herein. Representative examples of hydroxyalkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-methyl-2-hydroxyethyl, 3-hydroxypropyl, 2,3-dihydroxypentyl, and 2-ethyl-4-hydroxyheptyl.

As used herein, the term "oxo" means a radical of the formula =0.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

As used herein, the term "treat", "treating" and "treatment" refer to a method of alleviating or abrogating a disease and/or its attendant symptoms.

As used herein, the term "prevent", "preventing" and "prevention" refer to a method of preventing the onset of a disease and/or its attendant symptoms or barring a subject from acquiring a disease. As used herein, "prevent", "preventing" and "prevention" also include delaying the onset of a disease and/or its attendant symptoms and reducing a subject's risk of acquiring a disease.

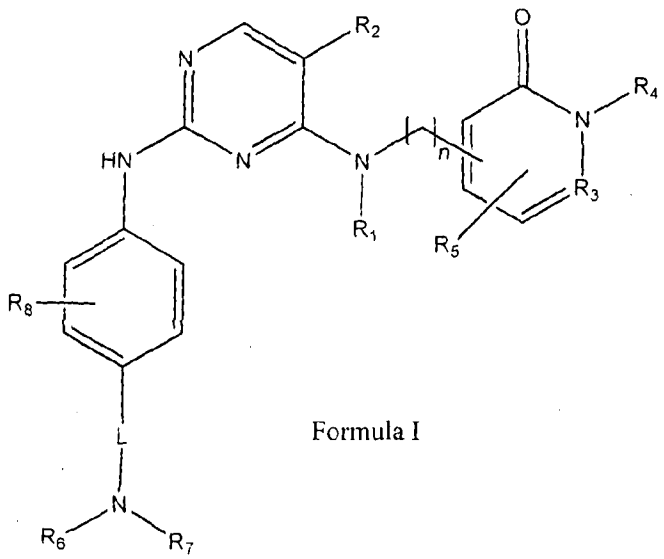
As used herein, the term "therapeutically effective amount" refers to that amount of the compound being administered sufficient to prevent development of or alleviate to some extent one or more of the symptoms of the condition or disorder being treated.

As used herein the term "modulate" refers to the ability of a compound to increase or decrease the function, or activity, of a kinase. "Modulation", as used herein in its various forms, is intended to encompass antagonism, agonism, partial antagonism and/or partial agonism of the activity associated with kinase. Kinase inhibitors are compounds that, e.g., bind to, partially or totally block stimulation, decrease, prevent, delay activation, inactivate, desensitize, or down regulate signal transduction. Kinase activators are compounds that, e.g., bind to, stimulate, increase, open, activate, facilitate, enhance activation, sensitize or up regulate signal transduction.

The present invention provides novel pyrimidine-2,4-diamine derivatives of formula (I), which are used for the treatment and prevention in diseases or disorder, in particular their use in diseases or disorder where there is an advantage in inhibiting protein kinases enzymes, particularly receptor tyrosine kinase and non-receptor tyrosine kinase inhibitors, more particularly JAK (Janus Kinase), FAK (Focal Adhesion Kinase) or AXL.

The present invention further provides to pharmaceutical compositions comprising the said novel pyrimidine-2,4-diamine compounds and their derivatives as therapeutic agents.

In our endeavor to provide novel pyrimidine-2,4-diamine compounds and their derivatives, the first embodiment of the present invention provides the structure of compounds as set forth in formula (I).



Formula I

wherein

L is direct bond or group selected from $-(CH_2)_p-$, –CO- or $-SO_2-$;

R_1 is hydrogen or alkyl;

R_2 is hydrogen, halogen, optionally substituted alkyl, haloalkyl, cyano, $-CONHR_1$;

R_3 is CR_9 or N;

R_4 is independently selected from optionally substituted alkyl, cyanoalkyl , $-(CH_2)_qCONR_{10}R_{11}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted cycloalkylalkyl, optionally substituted

arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl; wherein optionally substituent, in each occurrence is independently selected from $-OR_{12}$, $-SR_{12}$, $-S(O)_2R_{12}$ or $-NR_{13}R_{14}$;

R_5 is independently selected from hydrogen, halogen, optionally substituted alkyl or $-NR_{13}R_{14}$;

R_6 and R_7 are

i) independently selected from hydrogen, alkyl or acyl;

ii) taken together with the nitrogen to which they are attached may optionally form 3 to 7 membered saturated, partially saturated or unsaturated ring having 0-2 additional heteroatoms selected from N, O, S; wherein the said ring is optionally substituted with halo, alkyl, acyl, alkyloxy, hydroxyl, hydroxyalkyl, oxo, cycloalkyl, heterocycloalkyl or $-NR_{13}R_{14}$;

alternatively, when L is direct bond then R_6 or R_7 together with the nitrogen to which it is attached and adjacent carbon atom of the phenyl group may optionally form 3 to 7 membered saturated, partially unsaturated or fully unsaturated ring having 0-2 additional heteroatoms selected from N, O, S; wherein the said ring is optionally substituted with oxo;

R_8 is independently selected from hydrogen, halo or alkyloxy;

R_9 at each occurrence is independently selected from hydrogen, alkyl or $-NR_{13}R_{14}$;

R_{10} and R_{11} at each occurrence are independently selected from hydrogen, alkyl or alkyloxy;

R_{12} in each occurrence are independently selected from hydrogen or alkyl;

R_{13} and R_{14} in each occurrence are independently selected from hydrogen, alkyl, acyl or $-S(O)_2R_{12}$;

n is 0 or 1;

p is selected from 1 to 5; and

q is selected from 0 to 5;

or a pharmaceutically acceptable salts, stereoisomers, polymorphs or prodrugs thereof.

The embodiment below are illustrative of the present invention and are not intended to limit the claims to the specific embodiments exemplified.

According to one embodiment, specifically provided are compounds of formula (I), wherein n is 0 or 1,

According to another embodiment, specifically provided are compounds of formula (I), in which R_1 is hydrogen.

According to yet other embodiment, specifically provided are compounds of formula (I), in which R_2 is halogen (for example bromo, chloro or fluoro), alkyl (for example methyl) or haloalkyl (for example trifluoromethyl).

According to yet another embodiment, specifically provided are compounds of formula (I), in which R_2 is -$CONHR_1$; wherein R_1 is hydrogen.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R_3 is $-CR_9$ or N; wherein R_9 is hydrogen, methyl or $-N(CH_3)SO_2CH_3$.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R_4 is selected from optionally substituted alkyl, cyanoalkyl, -$(CH_2)_qCONR_{10}R_{11}$, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted cycloalkylalkyl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl.

According to yet another embodiment, specifically provided are compounds of formula (I), in which optionally substituted alkyl of R_4 is straight or branched C_1-C_5 alkyl, wherein straight or branched C_1-C_5 alkyl are methyl, ethyl, isopropyl, isobutyl or 3-pentane.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R_4 is optionally substituted alkyl; and optional substituent is selected from $-OCH_3$, -SCH_3, -$S(O)_2CH_3$ or $-N(CH_3)SO_2CH_3$.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R_4 is cyanoalkyl, wherein cyanoalkyl is 2-propanenitrile or -CH_2CN.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R_4 is -$(CH_2)_qCONR_{10}R_{11}$; wherein q is 1 or 2 and, R_{10} and R_{11} are independently hydrogen, alkyl (for example methyl or isopropyl) or alkoxy (for example methoxy).

According to yet another embodiment, specifically provided are compounds of formula (I), in which R_4 is cycloalkyl; wherein cycloalkyl is cyclopentane.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R_4 is aryl; wherein aryl is phenyl.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R_4 is cycloalkylalkyl; wherein cycloalkylalkyl is cyclopropylmethyl.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R_4 is arylalkyl; wherein arylalkyl is benzyl optionally substituted with methoxy.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R_4 is heteroarylalkyl (for example 5-methyl-1H-tetrazole).

According to yet another embodiment, specifically provided are compounds of formula (I), in which R_5 is hydrogen.

According to yet another embodiment, specifically provided are compounds of formula (I), in which L is direct bond or selected from -CO- or $-SO_2$.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R_6 and R_7 are independently selected from hydrogen, alkyl or acyl; wherein alkyl is methyl and acyl is $-C(O)CH_3$.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R_6 and R_7 are taken together with the nitrogen to which they are attached may optionally form 3 to 7 membered saturated ring (for example piperazine, piperidine, morpholine or 1,4-diazepane) or unsaturated ring (for example pyridinone); wherein the said ring may be optionally substituted with halo (for example fluoro), alkyl (for example methyl, and ethyl), acyl (for example $-COCH_3$), alkyloxy (for example methoxy), hydroxyl, hydroxyalkyl (for example $-CH_2OH$, $-CH_2CH_2OH$), oxo, cycloalkyl (cyclopropyl) or $-NR_{13}R_{14}$ (for example R_{13} and R_{14} are selected from hydrogen, methyl, $-COCH_3$, or $-SO_2CH_3$).

According to yet another embodiment, specifically provided are compounds of formula (I), wherein R_6 or R_7 (when L is direct bond) together with the nitrogen to which it is attached and adjacent carbon atom of the phenyl group may form 3 to 7 membered ring having 0-2

additional heteroatoms selected from N, O, S; wherein the said ring is optionally substituted with oxo.

According to yet another embodiment, specifically provided are compounds of formula (I), wherein R_8 is selected from hydrogen, halogen (for example fluorine) or alkoxy (for example methoxy).

Another embodiment of the present invention provided a pharmaceutical composition comprising the compound as disclosed, and a pharmaceutically acceptable carrier or diluent.

The compounds as disclosed in the present invention are formulated for pharmaceutical administration.

Yet another embodiment of the present invention provides use of the compounds as disclosed in the present invention for the preparation of a medicament for the treatment of cancer.

Yet another embodiment of the present invention provides a method of treatment of cancer, wherein the method comprises administration of an effective amount of the compound of the present invention to the subject in need thereof.

Yet another embodiment of the present invention provides a method for inhibiting growth of tumour cells and/or metastasis by administering an effective amount of the compound of the present invention to the subject in need thereof.

In yet another embodiment provides the compounds and pharmaceutically compositions of the present invention are used for the treatment and prevention in diseases or disorder, in particular their use in diseases or disorder where there is an advantage in inhibiting protein kinases enzymes, particularly receptor tyrosine kinase and non-receptor tyrosine kinase inhibitors, more particularly JAK (Janus Kinase), FAK (Focal Adhesion Kinase) or AXL.

In yet another embodiment provides the compounds and pharmaceutically compositions of the present invention are used in the treatment and/or prevention of diseases and/or disorders in which aberrant, abnormal or deregulated activity of JAK (Janus Kinase), FAK (Focal Adhesion Kinase) or AXL kinase contribute to the pathology and/or symptomology of such diseases and/or disorders. Such diseases and/or disorders mediated by one or more of these kinases are provided herein.

In yet another embodiment, the compounds of the invention are used in the treatment and/or prevention of diseases and/or disorders mediated by JAK (Janus Kinase), FAK (Focal Adhesion Kinase) or AXL kinase. Wherein JAK to which the compounds of the present invention bind and/or modulate includes any member of the JAK family. In some embodiments, the JAK is JAK1, JAK2, JAK3 or TYK2. In some embodiments, the JAK is JAK1 or JAK2. In some embodiments the JAK is JAK2.

In yet another embodiment, the compounds of the present invention are used as JAK (Janus Kinase), FAK (Focal Adhesion Kinase) or AXL kinase inhibitors. In some embodiments the compounds are used as multiple kinase inhibitors, particularly inhibiting JAK, FAK and AXL kinases. In some embodiments the compounds are used as dual kinase inhibitors, particularly inhibiting JAK and FAK, JAK and AXL or FAK and AXL; more particularly JAK and FAK; still more particularly JAK2 and FAK.

The said tumour cells include cancer such as but not limited to melanoma, renal cancer, prostate cancer, breast cancer, colon cancer and lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumours of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumour angiogenesis, spinal axis tumour, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations of said cancers.

The compounds of the present invention may be used as single drugs or as a pharmaceutical composition in which the compound is mixed with various pharmacologically acceptable materials.

The pharmaceutical composition is usually administered by a parenteral administration route, but can be administered by oral or inhalation routes. Examples of the parenteral administration include administration by injection, and percutaneous, transmucosal, transnasal and trans pulmonary administrations.

The injectable materials include a solution, a suspension, and a solid injection that is dissolved or suspended in a solvent before use.

The injection is used after one or more active ingredients are dissolved, suspended or emulsified in a solvent. Examples of the solvent include water-soluble solvents (e.g., distilled water, physiological saline and Ringer's solution), oil solvents (e.g., vegetable oils such as olive oil, sesame oil, cotton oil and corn oil, and alcohols such as propylene glycol, polyethylene glycol and ethanol), and combinations thereof.

The dosage of the compounds of the present invention varies depending on age, weight, symptom, therapeutic efficacy, dosing regimen and/or treatment time. Generally, they may be administered by a parenteral route (preferably intravenous administration) in an amount of 1 mg to 100 mg per time, from once a couple of days, once 3 days, once 2 days, once a day to a couple of times a day, in the case of an adult, or continuously administered by intravenous administration from 1 to 24 hours a day. Since the dosage is affected by various conditions, an amount less than the above dosage may sometimes work well enough, or higher dosage may be required in some cases.

Parenteral administration by injection includes all forms of injections, and also includes intravenous fluids. For example, it includes intramuscular injections, subcutaneous injections, intradermal injections, intra-arterial injections, intravenous injections, intraperitoneal injections, injections to spinal cavity, and intravenous drops.

The compounds of the present invention may be administered in combination with other drugs for (1) complementation and/or enhancement of prevention and/or therapeutic efficacy of the preventive and/or therapeutic drug of the present invention, (2) dynamics, absorption

improvement, dosage reduction of the preventive and/or therapeutic drug of the present invention, and/or (3) reduction of the side effects of the preventive and/or therapeutic drug of the present invention.

A concomitant medicine comprising the compounds of the present invention and other drug may be administered as a combination preparation in which both components are contained in a single formulation, or administered as separate formulations. The administration by separate formulations includes simultaneous administration and administration with some time intervals. In the case of the administration with some time intervals, the compound of the present invention can be administered first, followed by another drug or another drug can be administered first, followed by the compound of the present invention. The administration method of the respective drugs may be the same or different.

The dosage of the other drug can be properly selected, based on a dosage that has been clinically used. The compounding ratio of the compound of the present invention and the other drug can be properly selected according to age and weight of a subject to be administered, administration method, administration time, disorder to be treated, symptom and combination thereof. For example, the other drug may be used in an amount of 0.01 to 100 parts by mass, based on 1 part by mass of the compound of the present invention. The other drug may be a combination of two or more kind of arbitrary drugs in a proper proportion. The other drug that complements and/or enhances the preventive and/or therapeutic efficacy of the compound of the present invention includes not only those that have already been discovered, but those that will be discovered in future, based on the above mechanism.

General modes of preparation:

The general synthetic methods used in each General Procedure follow and include an illustration of a compound that was synthesized using the designated General Procedure. None of the specific conditions and reagents noted herein are to be construed as limiting the scope of the invention and are provided for illustrative purposes only. All starting materials are commercially available from Sigma-Aldrich (including Fluka and Discovery CPR) unless otherwise noted after the chemical name. Reagent/reactant names given are as named on the commercial bottle or as generated by IUPAC conventions, CambridgeSoft® ChemDraw Ultra

11.0. Names of final products are given as generated by IUPAC conventions or CambridgeSoft® ChemDraw Ultra 11.0.

Unless otherwise stated, work-up includes distribution of the reaction mixture between the organic and aqueous phase indicated within parentheses, separation of layers and drying the organic layer over sodium sulphate, filtration and evaporation of the solvent. Purification, unless otherwise mentioned, includes purification by silica gel chromatographic techniques, generally using ethyl acetate/petroleum ether mixture of a suitable polarity as the mobile phase. Use of a different eluent system is indicated within parentheses. The following abbreviations are used in the text: ACN (Acetonitrile), BuLi (n-Butyl lithium), CO (Carbon monoxide), d (doublet), DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene), dd (doublet of doublet), DCM (Dichloromethane) or (methylene chloride), DIEA (N,N-diisopropylethylamine), DMF (N,N-dimethylformamide), DMSO (Dimethyl sulphoxide), DMAP (Dimethylamino pyridine), DMA (Dimethylacetamide), EDCI.HCl (1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide HCl), equiv (Equivalent(s)), EtOAc (Ethyl acetate), EtOH (Ethanol), g (Gram(s)), h (Hour(s)), HATU (2-(1H-7-Azabenzo triazol-1-yl)--1,1,3,3-tetramethyl uronium hexafluorophosphate Methanaminium), HOBT (Hydroxybenzotriazole), IPA (Isopropyl alcohol), KOAc (Potassium Acetate), KOBt (Potassium t-butoxide), m (multiplet), MeOH (Methyl alcohol), MeMgBr (Methyl magnesium bromide), m-CPBA (meta chloro perbenzoic acid), min (Minute(s)), M (Molarity), Mmol (millimol), N (Normality), NaH (Sodium hydride), $NaIO_4$ (Sodium periodate), OsO4 (Osmium tetraoxide), Pd(OAC)2 (Palladium (II)acetate), PyBOP (Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate), Rac (Racemic), Rt (Retention time), RT (Room temperature), s (singlet), t (triplet), TBAF (Tetrabutyl ammonium fluoride), TBDMS-Cl (Tert-butyl dimethyl silyl chloride), TEA (Triethyl amine), TFA (Trifluoroacetic acid), THF (Tetra hydrofuran), TLC (Thin layer chromatography), Temp (Temperature), TFAA (Trifluoroacetic anhydride).

Compounds of this invention may be made by synthetic chemical processes, examples of which are shown herein. It is meant to be understood that the order of the steps in the processes may be varied, that reagents, solvents and reaction conditions may be substituted for those specifically mentioned, and that vulnerable moieties may be protected and deprotected, as necessary.

Analysis for the compounds of the present invention unless mentioned, was conducted in the general methods well known to the person skilled in the art. Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples, describing in detail the analysis of the compounds of the invention.

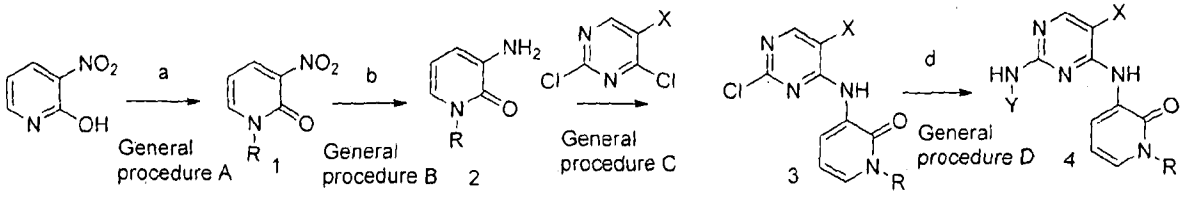
It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

The commercially available starting materials used in the following experimental description were prepared according to the procedure well known to the person skilled in art or purchased from Aldrich or Fluka unless otherwise reported.

GENERAL SYNTHETIC SCHEMES

Compounds of the invention may be prepared using the synthetic transformations illustrated in Scheme I

Scheme I



Compounds of the present invention may be prepared using the synthetic transformations illustrated in Scheme I. Starting materials are commercially available, may be prepared by the procedures described herein, by literature procedures, or by procedures that would be well known to one skilled in the art of organic chemistry. In step **a** commercially available 3-nitropyridin-2-ol is reacted with alkyl halide using conditions such as those described in General procedure #**A** to afford compound **1** which is further reduced using conditions such as those described in General procedure #**B** to afford compound **2.** Further compound **2** is reacted with appropriate 5-substitutued 2,4-dichloro pyrimidine using conditions such as those described in

General procedure #C to afford compound 3 which is again reacted with appropriate substituted aryl amines using conditions such as those described in General procedure #D to afford the compounds of present invention.

LIST OF GENERAL PROCEDURES

1. **General procedure A: N-alkylation of pyrridones**
2. **General procedure B: Reduction of nitro derivatives to Amine derivatives**
3. **General procedure C: Amination of pyrmidines at 4^{th} position**
4. **General procedure D: Amination of pyrmidines at 2^{nd} position**
5. **General procedure E: Formation of Boc protected amine from nitrile derivatives**
6. **General procedure F: Acidic cleavage of Boc protected amine**
7. **General procedure G: Preparation of sulfones**

PREPARATIONS AND EXAMPLES

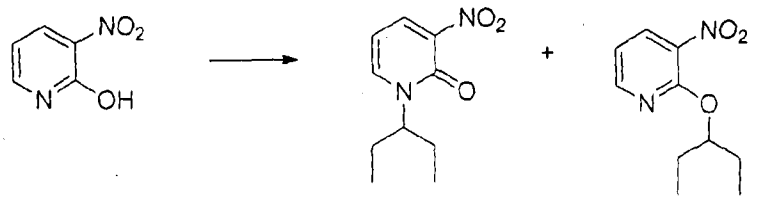
General procedure A: N-alkylation of pyridones:

Method #1

To a solution of substituted pyridin-2(1H)-one derivative (1 equiv) in an organic solvents (such as DMF, THF, Dioxane preferably DMF) is added a suitable base (such as K_2CO_3, CS_2CO_3, NaH etc. preferably K_2CO_3 2 to 5 equivalents preferably 2.5 equiv) followed by alkyl halide (2 to 5 eq, preferably 2 equiv). The reaction mixture is heated to about 50°C to 120°C (preferably 100°C) for about 1 to 12 h (preferably 3h). The reaction mixture is cooled to RT, poured into ice cold water and the product is extracted with ethyl acetate. The combined organic layers is washed successively with water and brine, dried over sodium sulphate and evaporated to dryness. The crude material is optionally purified by precipitation, crystallization or trituration from an appropriate solvent or solvents or by column chromatography to get the target compound.

Illustration of General Procedure #A: Method #1

Preparation#A.1: Synthesis of 3-nitro-1-(pentan-3-yl)pyridin-2(1H)-one:



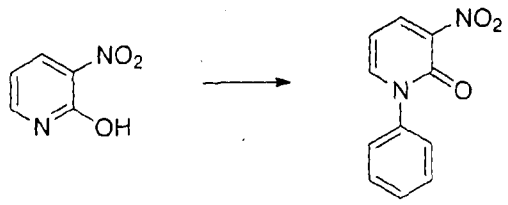
To a solution of 3-nitropyridin-2-ol (4g, 0.028mols, combi blocks) in DMF (15ml) was added K2CO3 (11.2g, 0.084 mol) followed by 3-bromo pentane (6.4g, 0.042mol, Aldrich). The reaction was heated to 100°C for 3h. The reaction mixture was cooled to room temperature and diluted with Ice cold water. The product was extracted with EtOAc (5 x 50 mL). The combined organic layers was successively washed with water (2x25ml), brine (2x25ml) and dried over sodium sulphate. The organic layer was concentrated under reduced pressure. The crude material was purified by silica gel (60-120) column chromatography by eluting with 05-10% EtOAc in hexane. First eluting compound was identified as *3-nitro-2-(pentan-3-yloxy)pyridine* 0.7g,(11.6%) ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (dd, *J*=2.4Hz, 1H) 8.38 (dd, *J* =6.4Hz, 1H) 7.19 (d, *J* = 4.8Hz,1H), 5.25 (m,1H), 1.7 (m,4H), 0.89 (t, *J*=8Hz, 6Hz) MS : m/z = 211 (M+H+), The second eluting compound containing the product was collected and evaporated to dryness to afford *3-nitro-1-(pentan-3-yl)pyridin-2(1H)-one* 1.5g, (25%) as yellowish liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29(dd, *J*=2Hz, 1H), 7.57 (dd, *J*=2.4Hz, 1H), 6.36 (t, *J*=7.6Hz, 1H), 5.06 (bs, 1H) , 1.92(m, 2H), 1.88 (m, 2H) 0.89 (t ,*J*=7.6Hz, 6H), Ms m/z : 211 $(M+H)^+$.

Method #2

To a solution of pyridin-2(1H)-one derivative in an organic solvents (such as DMF, THF, Dioxane preferably Dioxane) is added a suitable boronic acid (2 to 5 equiv preferably 2.5 equiv), copper(II)acetate (1 to 3 equiv preferably 1 equiv) and pyridine(5 to 12 equiv, preferably 8 equiv). The reaction mixture is heated to reflux a for about 4 to 24 h (preferably 12h). Cooled the reaction mixture to room temperature and quenched with 2N HCl. The product is extracted with ethyl acetate. The combined organic layers are washed with brine, dried over sodium sulphate and evaporated to dryness. The crude material is optionally purified by precipitation, crystallization or trituration from an appropriate solvent or solvents or by column chromatography to get the target compound.

Illustration of General Procedure #A: Method #2

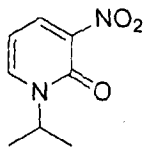
Preparation#A.1.1 of 3-nitro-1-phenylpyridin-2(1H)-one

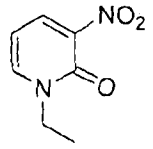
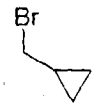
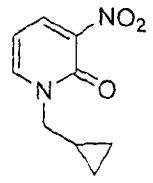
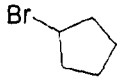
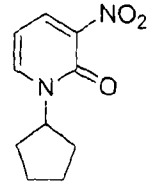


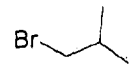
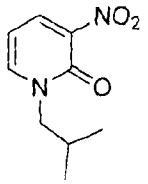
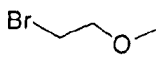
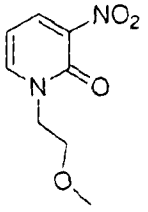
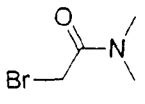
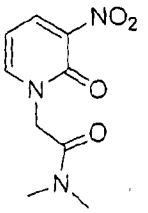
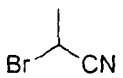
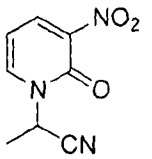
To a solution of pyridin-2(1H)-one (2g, 0.014mol, combi blocks) in 1,4-dioxane (20ml) was added phenyl bornic acid (3.4g, 0.0285mol, Spectrochem), copper(II)acetate (3.87g, 0.0214mol, Spectrochem) and added pyridine (8ml). The reaction mixture was refluxed for about 12h. Cooled the reaction mixture to room temperature and quenched with 2N HCl. The product is extracted with EtOAc (3 x 100mL). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure. The residue obtained was purified by silica gel (60-120) column chromatography by eluting with 5-10% EtOAc in Hexane. The relevant fractions containing the product were collected and evaporated to dryness to afforded *3-nitro-1-phenylpyridin-2(1H)-one* 1.3g, (42%) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 (dd, *J*=2.4Hz 1H,), 8.16 (dd, *J*=1.6Hz, 1H), 7.58-7.46(m,5H), 6.52(t, „*J*=7.2Hz 1H), Ms m/z: 217.1 $(M+H)^+$.

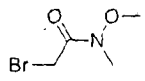
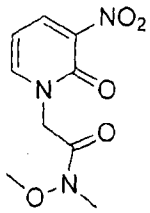
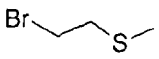
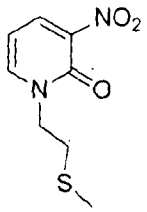
Other compounds synthesized using General procedure A are described in Table A.1

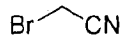
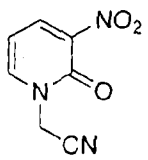
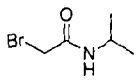
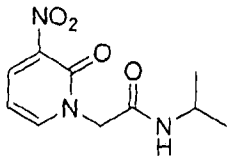
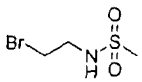
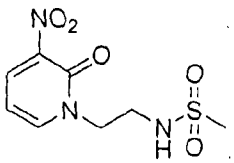
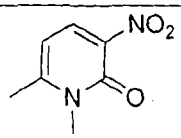
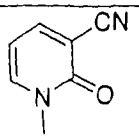
Table A.1: Other compounds synthesized using General procedure A

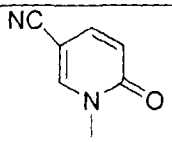
Compound no	Reagent/Source	Product	Method	Analytical Data
A.1.2			1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.34 (dd, *J* = 5.6 Hz, 1H), 8.25 (dd, *J* = 4.4 Hz, 1H), 6.47 (t, *J* = 7.2 Hz, 1H), 5.14 - 5.10 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 6H). MS m/z

				: 183.18 $(M+H)^+$.
A.1.3			1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.37 (dd, *J* = 4.8 Hz, 1H). 8.23 (dd, *J* = 3.6 Hz, 1H), 6.43 (t, *J* = 6 Hz, 1H), 4.05 (q, *J* = 5.6 Hz, 2H), 1.26 (t, *J* = 5.2 Hz, 3H). MS m/z: 169.15 $(M+H)^+$.
A.1.4			1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.41 - 8.40 (d, *J* = 2.8 Hz, 1H), 8.28 - 8.27 (d, *J* = 2 Hz, 1H), 6.46 - 6.43 (t, *J* = 6.8 Hz, 1H), 3.88 - 3.87 (d, *J* = 7.2 Hz, 2H), 1.27 - 1.23 (m, 1H), 0.53 - 0.50 (m, 2H), 0.49 - 0.40 (m, 2H).
A.1.5			1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.34 (dd, *J* = 6 Hz, 1H), 8.20 (dd, *J* = 5.6 Hz, 1H), 6.44 (t, *J* = 6.8 Hz, 1H), 5.15 - 5.12 (m, 1H), 2.09 - 2.07 (m, 2H), 1.85 -1.82 (m, 2H), 1.73 - 1.64 (m, 4H). MS m/z : 209.1, $(M+H)^+$.

A.1.6			1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.38 (dd, *J* = 2.8 Hz, 1H), 8.16 (dd, *J* = 4.8 Hz, 1H), 6.43 (dd, *J* = 6.8 Hz, 1H), 3.85 (d, *J* = 7.2 Hz, 2H), 2.51-2.49 (m, 1H), 0.86 (d, *J* = 6.8 Hz, 6H). MS m/z:167.2 $(M+H)^+$.
A.1.7			1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.42 - 8.41 (d, *J* = 1.6 Hz, 1H), 8.13 - 8.12 (d, *J* = 2 Hz, 1H), 6.44 - 6.40 (t, *J* = 7.6 Hz, 1H), 4.21 - 4.19 (t, *J* = 5.2 Hz, , 2H), 3.62 - 3.59 (t, *J* = 5.6 Hz, 2H), 3.30 (s,3H).
A.1.8			1	^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.41- 8.39 (dd, *J* = 5.2 Hz, 1H), 7.74 - 7.72 (dd, *J* = 4.4 Hz, 1H), 6.35 (t, *J* = 7.2 Hz, 1H), 4.85 (s, 2H), 3.21 (s, 3H), 3.01 (s, 3H).
A.1.9			1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.50 - 8.49 (d, *J* = 1.6 Hz, 1H), 8.30

				- 8.29 (d, J = 2 Hz, 1H), 6.59 - 6.56 (t, J = 7.6 Hz, 1H), 5.90 - 5.85 (m, 1H), 1.75 - 1.73 (d, J = 7.2 Hz, 3H).
A.1.10			1	^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.43 - 8.40 (dd, J = 5.6 Hz, 1H), 7.676 - 7.65 (dd, J = 4.4 Hz, 1H), 6.36 (t, J = 7.6 Hz, 1H), 4.94 (s, 2H), 3.90 (s, 3H), 3.25 (s, 3H).
A.1.11			1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.42 (dd, J = 5.6 Hz, 1H), 8.22 (dd, J = 4.4 Hz, 1H), 6.46 (dd, J = 7.0 Hz, 1H), 4.21 (t, J = 7.2 Hz, 2H), 2.83 (t, J = 6.4 Hz, 2H), 2.09 (s, 1H). MS m/z: 215.1$(M+H)^+$.

A.1.12			1	^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.52 (dd, *J* = 5.6 Hz, 1H), 8.26 (dd, *J* = 5.2 Hz, 1H), 6.56 (t, *J* = 6.8 Hz, 1H), 5.15 (s, 2H). MS m/z : 180 $(M+H)^+$.
A.1.13			1	^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.45-8.44 (dd, *J* = 9.6 Hz, 1H), 8.22-8.20 (d, *J* = 7.2 Hz,1H), 8.31-8.11(dd, *J* = 8.4 Hz,1H), 6.47-6.44 (t, *J* = 6.8 Hz,1H), 4.66 (s, 2H), 3.86-3.80 (m,1H), 1.09-1.07 (m, 6H); MS m/z : 240 $(M+H)^+$.
A.1.14			1	^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.41 (d, *J* = 2 Hz, 1H), 8.07 (d, *J* = 2.4 Hz, 1H), 7.21 (bs, 1H), 6.46 (dd, *J* = 6.8 Hz, 1H), 4.09 (t, *J* = 5.6Hz, 2H), 2.88 (s, 3H). MS m/z : 262 $(M+H)^+$.
A.1.15	MeI		1	^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.3 (d, *J* = 7.6Hz, 1H), 6.38(d, *J* = 7.6Hz, 1H), 3.5 (s, 3H), 2.51(s, 3H).
A.1.16	MeI		1	^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.416-8.104 (m, *J*=2,2H), 6.409-6.374 (t, *J*=7.2, 1H), 3.502 (s, 3H), MS m/z: 135.1

				$(M+H)^+$.
A.1.17.	MeI		1	^1H NMR (400 MHz, DMSO-d_6) : δ 8.601 (s, 1H), 7.686-7.656 (dd, J=9.2 Hz, 1H), 6.490-6.467 (d, *J*=9.2 Hz,1H), 3.454 (s,3H), MS m/z:135($(M+H)^+$.

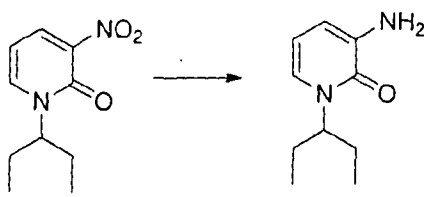
General procedure B: Reduction of nitro derivatives to Amine derivatives :

Method #1

A solution of appropriate Nitro derivative (1 equiv) in an protic solvent (such as EtOH, MeOH preferably EtOH) is treated with slurry of 10% palladium carbon in ethanol. The reaction is hydrogenated under balloon pressure for 3 to 7h (preferably 4hrs). The reaction mixture is filtered through a Celite® pad and washed with MeOH. The filtrate is evaporated to dryness under reduced pressure. The crude material is optionally purified by precipitation, crystallization or trituration from an appropriate solvent or solvents or by column chromatography to get the target compound.

Illustration of General Procedure B: Method 1

Preparation #B.1: 3-amino-1-(pentan-3-yl)pyridin-2(1H)-one



To a solution of 3-nitro-1-(pentan-3-yl)pyridin-2(1H)-one (1.5g,0.007mol, Preparation #A.1) in Ethanol (15ml) was added a slurry of 10% Pd/C(0.5 g, Hindustan platiniums) in ethanol (5 ml) and hydrogenated under balloon pressure for 3h. The reaction mixture was filtered through

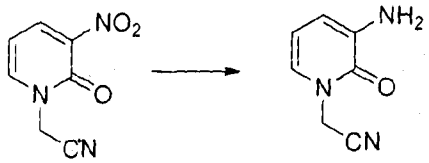
Celite® pad washed with ethanol (20ml) , the filtrate was evaporated under reduced pressure to afford *3-amino-1-(pentan-3-yl)pyridin-2(1H)-one* 0.85g,(70%) as light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.64 (m,1H), 6.51(m, 1H), 6.129 (t, *J*=7.2Hz, 1H) 4.9 (bs, 1H), 4.21(bs, 2H), 1.89-1.80 (m, 2H), 1.79 (m, 2H), 0.84 (t, *J*=7.2Hz, 6H), MS m/z : 180 $(M+H)^+$.

General Procedure #B. : Method# 2

To a solution of an appropriate Nitro derivative (1 equiv) in an organic solvent (such as THF, MeOH preferably MeOH:THF) is added ammonium chloride (1 to 3 equiv, preferably 1 equiv) in water. To this mixture Zinc powder (5 to 10 equiv preferably 10 equiv) is added portion wise and stirred at room temperature for about 15-45 min (preferably 30 min). The reaction mixture is filtered through a Celite® pad and washed with MeOH . The filtrate is evaporated to dryness under reduced pressure. The residue obtained is re-dissolved in EtOAc, washed successively with water and brine solution. The organic solvent is dried over sodium sulphate and concentrated under reduced pressure to obtain the target product.

Illustration of General Procedure #B: Method# 2

Preparation #B.1.1 : 2-(3-amino-2-oxopyridin-1(2H)-yl) acetonitrile

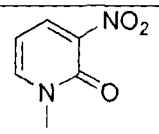
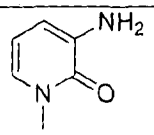
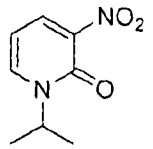
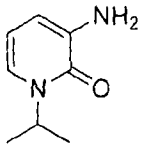
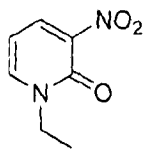
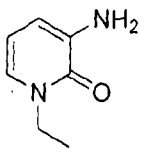


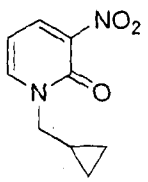
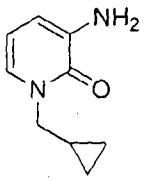
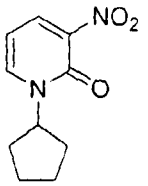
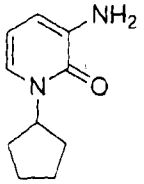
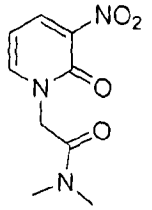
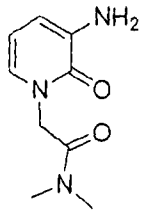
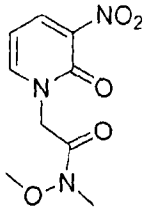
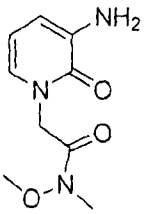
To a solution of 2-(3-nitro-2-oxopyridin-1(2H)-yl)acetonitrile (0.4g, 0.002mol, A.1.13) in THF (5ml), MeOH (10ml) was added ammonium chloride (1.2g, 0.02mol, rankem) in water (5ml). To this mixture Zinc power (1.16g, 0.017mol, finar) was added in portion wise for about 10 min and stirred at room temperature for 30 min. The reaction mixture was filtered through Celite® pad and washed with MeOH. The filtrate was evaporated to dryness under reduced pressure to obtain the residue. This residue was re-dissolved in ethyl acetate (25ml), washed successively with water (2x10ml) and brine (2x10ml) solution. The organic layer was dried over sodium sulphate and concentrated under reduced pressure to obtain the *2-(3-amino-2-oxopyridin-1(2H)-yl)acetonitrile* 0.25g (75%) as brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.96 (dd,

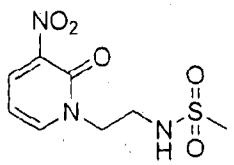
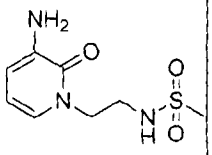
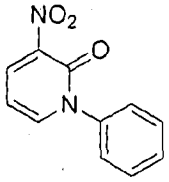
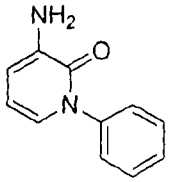
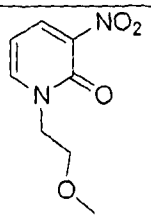
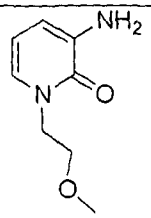
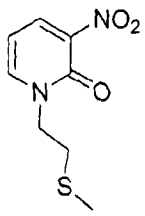
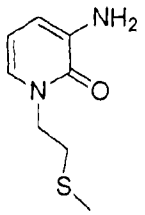
„*J*=4.8Hz,1H), 6.47 (dd, , *J*=5.6Hz, 1H), 6.13 (t, *J*=7.6Hz, 1H), 5.27 (bs,2H), 5.01 (s,2H). MS m/z : 150 $(M+H)^+$.

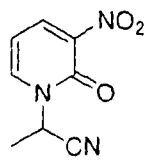
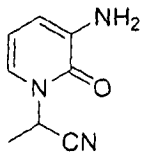
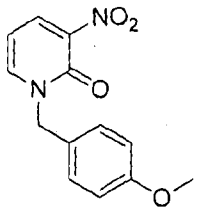
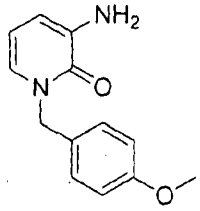
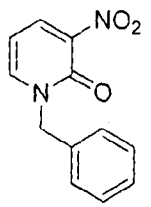
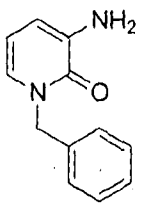
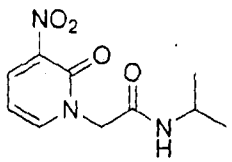
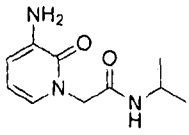
Other compounds synthesized using General procedure **B** are described in Table: B

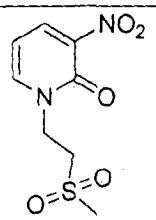
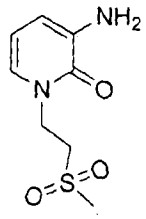
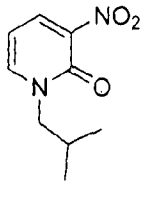
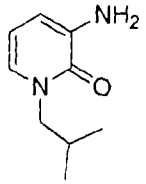
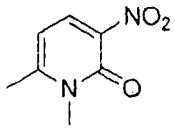
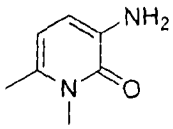
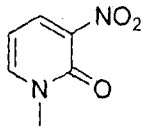
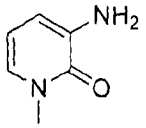
Table B.1: Other compounds synthesized using General procedure B

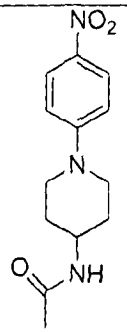
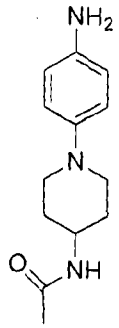
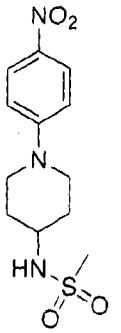
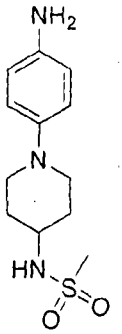
Compound no	Reagent/Source	Product	Method	Analytical Data
B.1.2			1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.88 - 6.86 (dd, *J* = 4.8 Hz, 1H), 6.43 (dd, *J* = 6.4Hz, 1H), 6.02 - 5.98 (t, *J* = 6.8 Hz), 5.05 (bs, 2H), 3.42 (s, 3H). MS m/z: 124.19 $(M+H)^+$.
B.1.3	 A.1.2		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.90 (dd, *J* = 5.2 Hz, 1H), 6.40 (dd, *J* = 5.6 Hz, 1H), 6.07 (t, *J* = 6.8 Hz, 1H), 5.14 - 5.11 (m, 1H), 5.04 (bs, 2H), 1.24 (d, *J* = 6.8 Hz, 6H). MS m/z: 153.19 $(M+H)^+$.
B.1.4	 A.1.3		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.87 (dd, *J* = 4.8 Hz, 1H), 6.40 (dd, *J* = 5.6 Hz, 1H), 6.02 (t, *J* = 6.8 Hz, 1H), 5.04 (bs, 2H), 3.88 (q, *J* = 6.8 Hz, 2H), 1.19 (t, *J* = 7.6 Hz, 3H). MS m/z : 139.17 $(M+H)^+$.

B.1.5	 A.1.4		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.92-6.9 (d , J = 2 Hz, 1H), 6.41 -6.41 (d, J = 2 Hz, 1H), 6.03 - 6.00 (t, J = 7.6 Hz, 1H), 5.05 (bs, 2H), 3.73 - 3.72 (d, J = 6.8 Hz, 2H), 1.21-1.18 (m,1H), 0.47-0.42 (m, 4H), MS m/z :166 $(M+H)^+$.
B.1.6	 A.1.5		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.86 (dd, J = 10.4 Hz, 1H), 6.39 (dd, J = 5.6 Hz, 1H), 6.06 (t, J = 7.2 Hz, 1H), 5.17 - 5.14 (m, 1H), 5.05 (bs, 2H), 1.98 - 1.95 (m, 2H), 1.81 - 1.78 (m, 2H), 1.67 - 1.61 (m, 4H).
B.1.7	 A.1.8		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.76-6.74 (dd, J = 6.4 Hz, 1H), 6.45 - 6.42 (dd, J = 5.2 Hz, 1H), 6.00 (t, J = 6.8 Hz, 1H), 5.00 (bs, H), 4.75 (s, 2H), 3.04 (s, 3H), 2.83 (s, 3H).
B.1.8	 A.1.10		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.85 - 6.82 (dd, J = 4.8 Hz, 1H), 6.46 - 6.43 (dd, J = 5.2 Hz, 1H), 6.43 (t, J = 5.2 Hz, 1H), 5.02 (bs, 2H), 4.82 (s, 2H), 3.78 (s, 3H), 3.12 (s, 3H).

B.1.9	 A.1.14		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.17 (t, *J* = 6Hz, 1H), 6.83(dd, *J* = 5.2 Hz, 1H), 6.44 (dd, *J* = 5.6 Hz, 1H), 6.045 (t, *J* = 6.8 Hz, 1H), 5.08 (bs, 1H),3.95 (t, *J* = 6 Hz, 2H), 3.26 (t, *J* = 8 Hz, 2H), 2.84 (s, 3H). MS m/z: 232 $(M+H)^+$.
B.1.10	 A.1.1		1	^{1}H NMR (400 MHz, DMSO-d_6) δ : 7.52-7.37(m,5H), 6.83 (dd, ,*J*=2Hz, 1H,), 6.52 (dd, ,J $_2$= 5.2Hz, 1H), 6.14(t,1H,J=6.8Hz), 5.2(bs,2H), MS m/z : 187.1 $(M+H)^+$.
B.1.11	 A.1.7		1	^{1}H NMR (400 MHz, DMSO d_6): δ 6.843-6.838 (d, *J*=2Hz, 1H), 6.439-6.435 (d, *J*=1.6Hz, 1H), 6.017-5.983 (t, *J*=6.8Hz, 1H), 5.050 (bs, 2H), 4.046-4.019 (t, *J*=5.6Hz, , 2H), 3.58-3.552 (t, *J*=5.6Hz, 2H), 3.228 (s,3H) , MS m/z:170 $(M+H)^+$.
B.1.12	 A.1.11		2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.89 (dd, *J* = 5.6 Hz, 1H), 6.42 (dd, *J* = 5.6 Hz, 1H), 6.02 (t, *J* = 8.0 Hz, 1H), 5.06 (bs, 2H), 4.04 (t, *J* = 7.6 Hz, 2H), 2.76 (t, *J* = 6.8 Hz, 2H), 2.07 (s, 1H). MS m/z: 185 $(M+H)^+$.

B.1.13	 A.1.9		2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.01-7.00 (d, J = 1.6 Hz, 1H), 6.45 - 6.44 (d, J = 1.2 Hz, 1H), 6.19 - 6.16 (t, J = 7.6 Hz, 1H), 5.88 - 5.83 (m, 1H), 5.28 (bs,2H), 1.70 - 1.68 (d, J = 7.2 Hz, 3H), MS m/z: 165 $(M+H)^+$.
B.1.14			2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.26 - 7.24 (m, 2H), 6.95 (d, J = 1.4, 1H), 6.88 (dd, J = 6.6 Hz, 2H), 6.40 (dd, J = 7.1 Hz, 1H), 6.02 (t, J = 6.8 Hz, 1H), 5.10 (s, 2H), 5.01(s, 2H), 3.71 (s, 3H).
B.1.15			2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.34-7.24 (m, 3H), 6.97 (dd, J = 6.8 Hz, 1H), 6.43 (dd, J = 7.1 Hz, 1H), 6.05 (t, J = 7.1Hz, 1H), 5.11 (s, 2H), 5.09 (s, 2H). MS m/z: 201 $(M+H)^+$.
B.1.16	 A.1.13		2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.99-7.97 (d, J = 7.6 Hz, 1H), 6.80-6.78 (dd, J = 7.2 Hz,1H), 6.44-6.42 (dd, J = 7.2 Hz, 1H), 6.01-5.97 (t, J = 7.6 Hz,1H), 5.01 (s, 2H), 4.44 (s,2H), 3.84-3.79 (m, 1H), 1.07-1.05 (m, 6H). MS m/z: 211 $(M+H)^+$.

B.1.17	 A.1.11		2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.91 (dd, J = 5.6 Hz, 1H), 6.43 (dd, J = 5.6 Hz, 1H), 6.06 (t, J = 6.8 Hz, 1H), 5.12 (bs, 2H), 4.25 (t, J = 7.6 Hz, 3H), 3.53 (t, J = 7.2 Hz, 2H), 3.06 (s, 3H). MS m/z : 217.1 $(M+H)^+$.
B.1.18	 A.1.6		2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.8 (dd, J = 5.6 Hz, 1H), 6.41 (dd, J = 5.6 Hz, 1H), 6.0 (t, J = 6.8 Hz, 1H), 5.04 (bs, 1H), 3.68 (d, J = 8.0 Hz, 2H), 2.08 - 2.04 (m, 1H), 0.83 (d, J = 6.8 Hz, 6H). MS m/z : 167 $(M+H)^+$.
B.1.19	 A.1.17		1	^{1}H NMR (400 MHz, DMSO-d_6): δ 6.37 (d, J = 7.6Hz, 1H), 5.9 (d, J = 7.2 Hz, 1H), 4.8 (bs, 2H), 3.5 (s,3H), 2.21 (s, 3H). MS m/z: 138.19 $(M+H)^+$.
B.1.20			1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.88 - 6.86 (dd, J = 4.8 Hz, 1H), 6.43 (dd, J = 6.4Hz, 1H), 6.02 - 5.98 (t, J = 6.8 Hz), 5.05 (bs, 2H), 3.42 (s, 3H). MS m/z: 124.19 $(M+H)^+$.

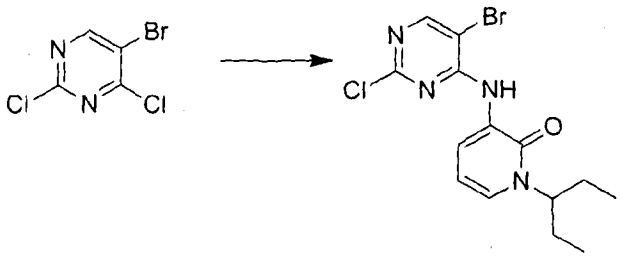
B.1.21	 **Preparation #6**		1	^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80 - 7.78 (d, J = 7.6 Hz, 1H), 6.69 - 6.67 (d, J = 8.8 Hz, 2H), 6.49 - 6.48 (d, J = 2.8 Hz, 2H), 4.55 (bs, 2H), 3.60 (m, 1H), 3.32 (s, 2H), 2.59 (s, 3H), 1.78 (s, 4H), 1.51 (s, 2H); MS m/z: 234 $(M+H)^+$.
B.1.22	 **Preparation #7**		1	^{1}HNMR (400MHz, DMSO-d_6): δ 7.09 - 7.07 (d, J = 7.2 Hz, 1H), 6.68 - 6.66 (d, J = 8.8 Hz, 1H), 6.48 - 6.46 (d, J = 8.8 Hz, 2H), 4.55 (bs, 2H), 3.31 - 3.20 (m, 3H), 2.93 (s, 3H), 2.59 - 2.56 (m, 2H), 1.89 - 1.87 (d, J = 10.0 Hz, 2H), 1.59 - 1.56 (m, 2H); MS m/z: 270 $(M+H)^+$.

General procedure C: Amination of pyrmidines at 4th position

A sealed tube is charged with an substituted pyrimidine derivative (1 equiv), DIPEA (2 to 5 equivalents preferably 2.5 equivalents), appropriate amine derivative (1 to 3 equivalents preferably 1 equivalents) and IPA. The reaction mixture is heated to 100 °C to 110°C (preferably 100°C) for about 4-12h (preferably 6hrs). The reaction mixture is cooled to 0°C, obtained solid is filtered, washed with cold IPA and dried under vacuum. Obtained crude material is optionally purified by precipitation, crystallization or trituration from an appropriate solvent or solvents or by column chromatography to get the target compound.

Illustration of General procedure C: Method #1

Preparation#C.1 : 3-((5-bromo-2-chloropyrimidin-4-yl)amino)-1-(pentan-3-yl)pyridin-2(1H)-one



A 50 mL sealed tube was charged with 5-bromo-2,4-dichloropyrimidine (1g,0.004mol, combi blocks), DIPEA (1.7g,0.013 mol, Spectrochem), 3-amino-1-(pentan-3-yl)pyridin-2(1H)-one (0.79g, 0.004mol, B.1.1) and IPA(10 mL). The reaction mixture was heated to 100 °C about 12h. The reaction mixture was cooled to 0°C, obtained solid was filtered washed with cold IPA and dried under vacuum. The crude material washed with hexane and dried to afford *3-((5-bromo-2-chloropyrimidin-4-yl)amino)-1-(pentan-3-yl)pyridin-2(1H)-one* 0.6g (37%) as off white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 (S, 1H), 8.53 (dd, *J*=2Hz, 1H), 8.32 (S,1H), 6.9 (dd, *J*=2Hz, 1H), 6.41 (t, *J*=7.6Hz, 1H), 4.9 (bs, 1H), 1.8 (m, 2H), 1.79 (m,2H), .87(t, *J*=7.6Hz, 6H), MS m/z : 370 $(M+H)^+$.

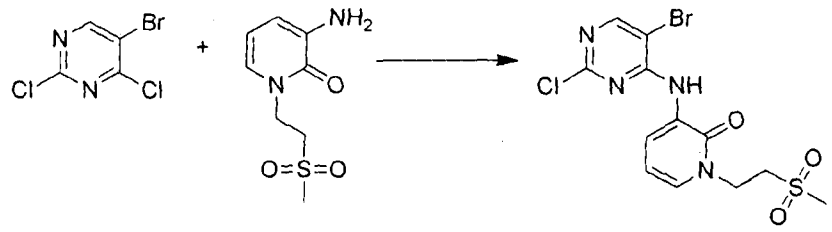
General procedure C: Method #2

Illustration of General procedure C: Method #2

To flask containing appropriate Amine Derivate (1 equiv) in organic solvents (Such as Toluene ,Xylene, Dioxane preferably toluene) a degassed for 10 -15min is added $Pd_2(dba)_3$ (0.05-0.1equiv. preferably 0.05 equiv.), Xantphos (0.05-0.1equiv. preferably 0.05 equiv) followed by base (such as Na_2CO_3,Cs_2CO_3,K_2CO_3 3 to 5 equiv. preferably Cs_2CO_3, 3equiv) and again degassed for 20 min. The 5-bromo-2,4-dichloropyrimidine (1 to 5 equiv, preferably 1.1 equiv) is added and heated to 80 to 100 °C (preferably 80 °C) for 10 to18h (preferably 16h). The reaction mixture is cooled to 0°C, The reaction mixture is filtered through a Celite® pad and washed with MeOH . The filtrate is evaporated to dryness under reduced pressure. The residue obtained is re-dissolved in EtOAc, washed successively with water and brine solution. The organic solvent is dried over sodium sulphate and concentrated under reduced pressure. The crude material is

optionally purified by precipitation, crystallization or trituration from an appropriate solvent or solvents or by column chromatography to get the target compound.

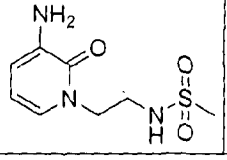
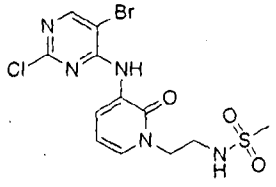
Preparation#C.1.1: 3-((5-bromo-2-chloropyrimidin-4-yl)amino)-1-(2-(methylsulfonyl)ethyl)pyridin-2(1H)-one:

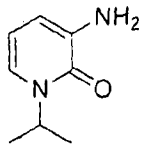
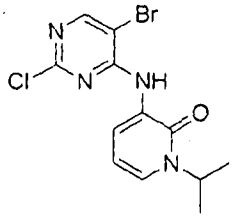
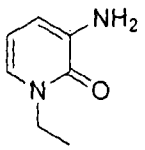
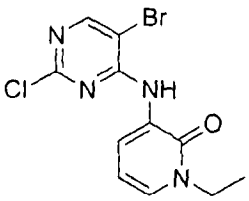
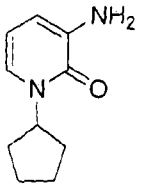
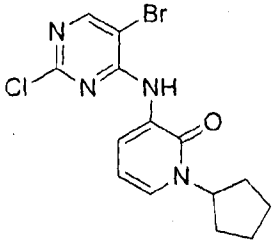


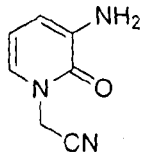
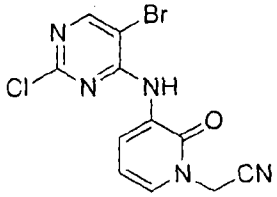
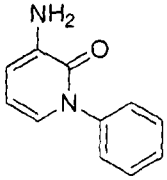
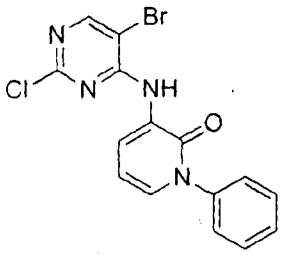
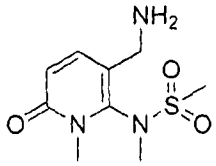
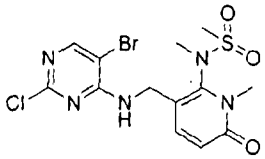
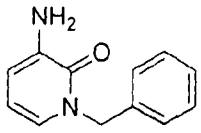
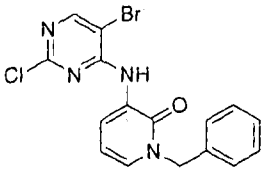
To a degassed solution of 3-amino-1-(2-(methylsulfonyl)ethyl)pyridin-2(1H)-one (0.28 g, 0.0013 mol) in toluene (20 mL), was added $Pd_2(dba)_3$ (60 mg, 0.06 mmol, 5 mol%), Xantphos (38 mg, 0.06 mmol, 5 mol%) followed by cesium carbonate (0.86 g, 0.002 mol) and degassed again for 20 min. Then 5-bromo-2,4-dichloropyrimidine (0.3 g, 0.0013 mol) was added and heated at 80 °C for 16h. The reaction mass was filtered through celite, evaporated under vacuum and subjected to column chromatography using silica gel (100-200 mesh). Compound was eluted in 1% methanol in dichloromethane. Concentration of the fractions under vacuum afforded the desired *3-((5-bromo-2-chloropyrimidin-4-yl)amino)-1-(2-(methylsulfonyl)ethyl)pyridin-2(1H)-one* (0.18 g, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.86 (s, 1H), 8.75 (s, 1H), 8.31 (dd, J_1 = 1.6 Hz, J_2 = 5.2 Hz, 1H), 6.48 - 6.47 (m, 1H), 4.40 - 4.43 (m, 2H), 3.59 - 3.65 (m, 2H), 6.06 (s, 3H). MS m/z : 365.0 $(M+H)^+$.

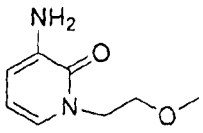
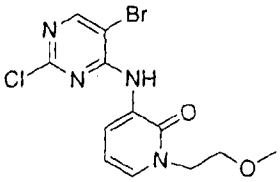
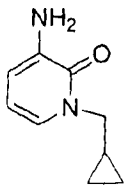
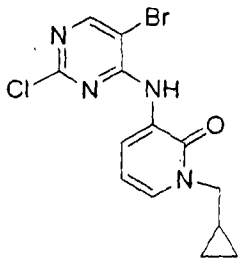
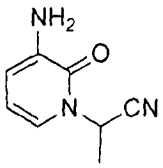
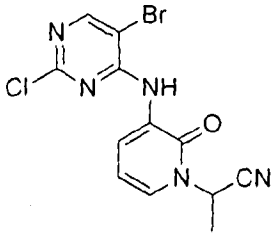
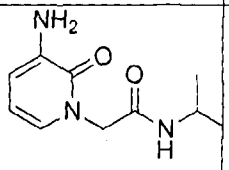
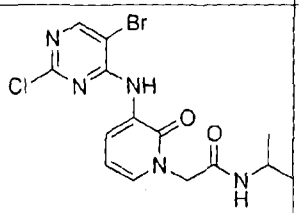
Other compounds synthesized using appropriate halo pyrimidines by following General procedure **C** are described in Table C

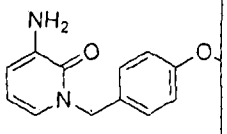
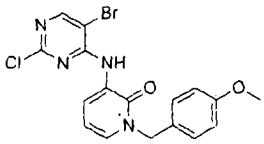
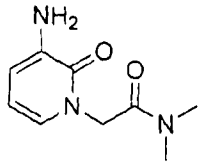
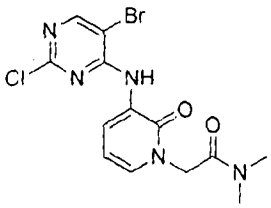
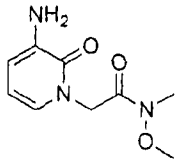
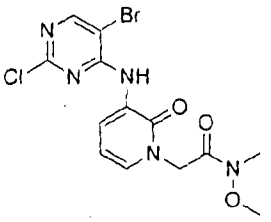
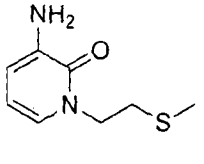
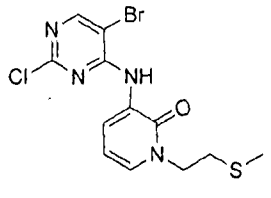
Table C.1: Other compounds synthesized using General procedure C

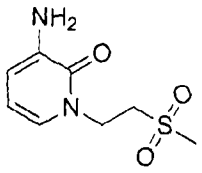
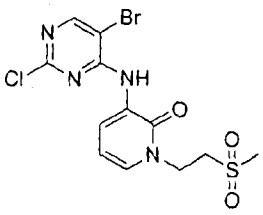
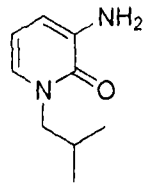
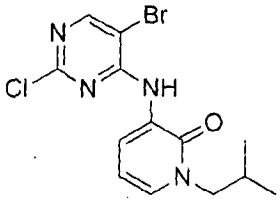
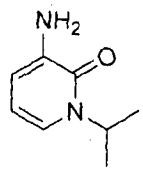
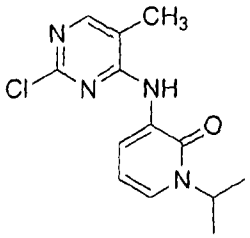
S. No	Amine	Product	Method	^{1}H NMR & MS : m/z
C.1.2			1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.90 (s, 1H), 8.59 (s, 1H), 8.32 (dd, J_1 = 1.6 Hz, J_2 = 5.6 Hz, 1H), 7.42 (dd, J_1 = 1.6

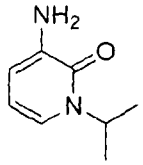
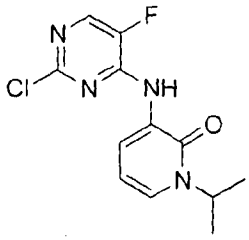
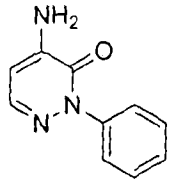
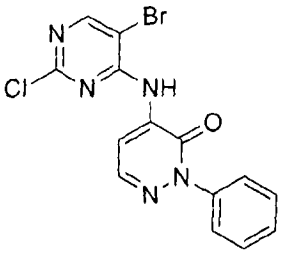
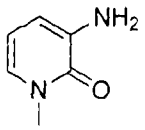
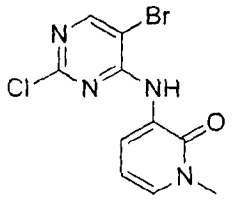
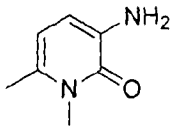
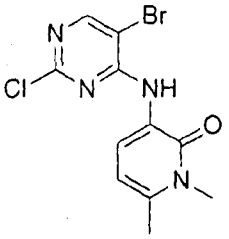
	B.1.9			Hz, J_2 = 5.2 Hz, 1H), 7.22 (t, J = 6.4 Hz, 1H), 6.45 (t, J = 8.0 Hz, 1H), 4.09 (t, J = 6.0 Hz, 2H), 3.33 (t, J = 7.2 Hz, 2H), 2.87 (s, 3H). MS m/z: 422.0 $(M+H)^+$.
C.1.3	 B.1.3		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.97 (s, 1H), 8.58 (s, 1H), 8.29 (dd, J_1 = 1.6 Hz, J_2 = 6 Hz, 1H), 7.57 (dd, J_1 = 1.6 Hz, J_2 = 6.4 Hz, 1H), 6.49 (t, J = 7.2 Hz, 1H), 5.12 (m, 1H), 1.35 (d, J = 6.8 Hz, 6H). MS m/z: 343.61 $(M+H)^+$.
C.1.4	 B.1.4		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.93 (s, 1H), 8.58 (s, 1H), 8.30 (dd, J_1 = 1.2 Hz, J_2 = 6.0 Hz, 1H), 7.53 (dd, J_1 = 1.2 Hz, J_2 = 5.6 Hz, 1H), 6.44 (t, J = 6.8 Hz, 1H), 4.04 (q, J = 7.6 Hz, 2H), 1.27 (t, J = 6.8 Hz, 3H). MS m/z: 329.0 $(M+H)^+$.
C.1.5	 B.1.6		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.96 (s, 1H), 8.58 (s, 1H), 8.30 (dd, J_1 = 1.2 Hz, J_2 = 6.0 Hz, 1H), 7.52 (dd, J_1 = 1.6 Hz, J_2 = 6.0 Hz, 1H), 6.47 (t, J = 7.6 Hz, 1H), 5.15 (m, 1H), 2.07 -2.03 (m, 2H), 1.86 - 1.65 (m, 6H). MS m/z: 369.0 $(M+H)^+$.

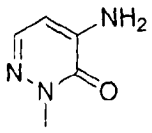
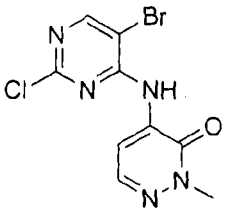
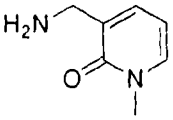
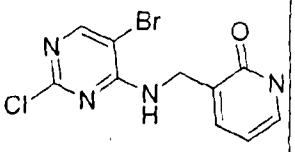
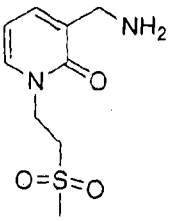
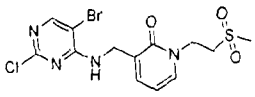
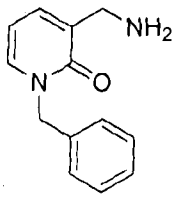
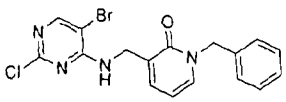
C.1.6	 B.1.1		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.79 (s, 1H), 8.61 (s, 1H), 8.31 (dd, J_1 = 1.2 Hz, J_2 = 6 Hz, 1H), 7.58 (dd, J_1 = 2.0 Hz, J_2 = 5.2 Hz, 1H), 6.54 (t, J = 7.2 Hz, 1H), 5.15 (s, 2H). MS m/z: 340.56 $(M+H)^+$.
C.1.7	 B.1.10		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.92 (s, 1H), 8.60 (s, 1H), 8.40 (dd, J_1 = 2.0 Hz, J_2 = 5.2 Hz, 1H), 7.58 - 7.48 (m, 6H), 6.55 (t, J = 6.8 Hz, 1H). MS m/z: 377 $(M+H)^+$.
C.1.8	 Preparation#3, Step-5		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.31 (s, 1H), 8.25 (t, J = 10.0 Hz, 1H), 7.40 (d, J = 9.2 Hz, 1H), 6.51 (d, J = 9.2 Hz, 1H), 4.52 - 4.47 (m, 1H), 4.28 - 4.22 (m, 1H), 3.40 (s, 3H), 3.37 (s, 3H), 3.34 (s, 3H). MS m/z: 436.1 $(M+H)^+$.
C.1.9	 B.1.15		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.91 (s, 1H), 8.58 (s, 1H), 8.30 (dd, J_1 = 7.5 Hz, J_2 = 1.6 Hz, 1H),7.65 (dd, J_1 = 6.8 Hz, J_2 = 1.4 Hz, 1H), 7.40 - 7.29 (m, 5H), 6.47 (t, J = 7.0 Hz, 1H), 5.23 (s, 2H). MS m/z: 391.0 $(M+H)^+$.

C.1.10	 B.1.11		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.90 (s, 1H), 8.59 (s, 1H), 8.30 -8.29 (d, J = 1.2 Hz, 1H), 7.46 - 7.45 (d, J = 1.2 Hz, 1H), 6.44 - 6.40 (t, J = 6.8 Hz, 1H), 4.20 - 4.17 (t, J = 5.6 Hz, 1H), 3.65 - 3.62 (t, J = 5.2 Hz, 1H), 3.25 - 3.62 (t, J = 5.2 Hz, 2H). MS m/z: 360 $(M+H)^+$.
C.1.11	 B.1.5		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.94 (s, 1H), 8.59 (s, 1H), 8.33 - 8.33 (d, J = 1.2 Hz, 1H), 7.57 - 7.57 (d, J = 1.2 Hz, 1H), 6.46 - 6.43 (t, J = 7.2 Hz, 1H), 3.89 - 3.87 (t, J = 7.2Hz, 1H), 1.29-1.23 (m, 1H), 0.49 - 0.40 (m, 4H). MS m/z: 360 $(M+H)^+$
C.1.12	 B.1.13		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.82 (s, 1H), 8.62 (s, 1H), 8.33 (d, J = 2.0 Hz, 1H), 7.62 - 7.62 (d, J = 1.2 Hz, 1H), 6.60 - 6.57 (t, J = 7.2 Hz, 1H), 5.93 - 5.88 (m, 1H), 1.76 - 1.74 (d, J = 6.8 Hz, 3H). MS m/z: 356 $(M+H)^+$
C.1.13			1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.82 (s, 1H), 8.58 (s, 1H), 8.32 (dd, J = 7.2 Hz, 1H), 8.15 - 8.13 (s, 1H), 7.43 - 7.41 (dd, J = 6.8 Hz, 1H), 6.44 -

	B.1.16			6.40 (t, J = 7.2 Hz, 1H), 4.62 (s, 2H), 3.88 - 3.79 (m, 1H), 1.09 -1.08 (m, 2H),
C.1.14	 B.1.14		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.91 (s, 1H), 8.58 (s, 1H), 8.28 (dd, J_1 = 7.6 Hz, J_2 = 1.7 Hz, 1H), 7.63 (dd, J_1 = 6.8 Hz, J_2 = 1.3 Hz, 1H), 7.32 (d, J = 8.8 Hz, 2H), 6.91 - 6.89 (m, 2H), 6.45 (t, J = 7.3 Hz, 1H), 5.14 (s, 2H), 3.72 (s, 3H). MS m/z: 422.0 $(M+H)^+$.
C.1.15	 B.1.9		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.83 (s, 1H), 8.58 (s, 1H), 8.32 (dd, J_1 = 2Hz, J_2 = 6.0 Hz, 1H), 7.37 (dd, J_1 = 1.6 Hz, J_2 = 5.2 Hz, 1H), 4.92 (s, 2H), 3.07 (s, 3H), 2.86 (s, 3H).
C.1.16	 B.1.8		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.81 (s, 1H), 8.59 (s, 1H), 8.34 (dd, J_1 = 2.4 Hz, J_2 = 5.6 Hz, 1H), 7.45 (dd, J_1 = 1.6 Hz, J_2 = 5.2 Hz, 1H), 6.46 (t, J = 6.8 Hz, 1H), 5.00 (s, 2H), 3.81 (s, 3H), 3.15 (s, 3H). MS m/z: 402.0 $(M+H)^+$.
C.1.17	 B.1.12		2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.89 (s, 1H), 8.58 (s, 1H), 8.31 (dd, J_1 = 1.6 Hz, J_2 = 6.4 Hz, 1H), 7.53 (dd, J_1 = 2.0 Hz, J_2 = 5.6 Hz, 1H), 6.44 (t, J

				= 7.2 Hz, 1H), 4.19 (t, J = 6.8 Hz, 2H), 2.84 (t, J = 6.8 Hz, 2H), 2.10 (s, 3H). MS m/z: 384.10 $(M+H)^+$.
C.1.18	 B.1.17		2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.86 (s, 1H), 8.75 (s, 1H), 8.31 (dd, J_1 = 1.6 Hz, J_2 = 5.2 Hz, 1H), 6.48 -6.47 (m, 1H), 4.40 - 4.43 (m, 2H), 3.59 - 3.65 (m, 2H), 6.06 (s, 3H). MS m/z: 365.0 $(M+H)^+$.
C.1.19	 B.1.18		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.93 (s, 1H), 8.58 (s, 1H), 8.30 (t, J = 4.0 Hz, 1H), 7.46 (dd, J_1 = 1.6 Hz, J_2 = 5.6 Hz, 1H), 6.42 (t, J = 7.6 Hz, 1H), 3.84 (d, J = 7.2 Hz, 2H), 2.10 - 2.12 (m, 1H), 0.81 - 088 (m, 10H). MS m/z: 357.0 $(M+H)^+$.
C.1.20	 B.1.3		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.58 (dd, J_1 = 1.2 Hz, J_2 = 6.0 Hz, 1H), 8.33 (s, 1H), 8.02 (s, 1H), 7.08 (dd, J_1 = 1.6 Hz, J_2 = 5.2 Hz, 1H), 6.41 (t, J = 7.6 Hz, 1H), 5.30 (m, 1H), 2.23 (s, 3H), 1.41 (d, J = 6.8 Hz, 6H).

C.1.21	 B.1.3		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.75 (s, 1H), 8.41 (d, J = 2.9 Hz, 1H), 8.15 (dd, J_1 = 7.3 Hz, J_2 = 1.4 Hz, 1H), 7.58 (dd, J_1 = 6.8 Hz, J_2 = 1.4 Hz, 1H), 6.46 (t, J = 7.1 Hz, 1H), 5.13 - 5.08 (m, 1H), 1.24 (m, 6H). MS m/z: 283.1 $(M+H)^+$.
C.1.22			1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.92 (s, 1H), 8.60 (s, 1H), 8.40 (dd, J= 5.2 Hz, 1H), 7.58 - 7.48 (m, 6H), 6.55 (t, J = 6.8 Hz, 1H). MS m/z: 377 $(M+H)^+$.
C.1.23	 B.1.20		1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.90 (s, 1H), 8.58 (s, 1H), 8.32-8.23 (dd, J = 6.0 Hz, 1H), 7.52 - 7.50 (dd, J = 5.6 Hz, 1H), 6.43 – 6.40 (t, J = 6.8Hz, 1H), 3.57 (s, 3H). MS m/z: 315.5 $(M+H)^+$.
C.1.24	 B.1.19		1	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91(s, 1H), δ 8.45(d, J = 7.2Hz, 1H), 8.29(s, 1H), 6.2(d, J = 8Hz), 3.65(s, 3H), 2.39 (s, 3H). MS m/z: 329.19 $(M+H)^+$.

C.1.25			1	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 (s, 1H), 8.45 (s, 1H), 8.26 (d, *J* = 4.8Hz, 1H), 7.85 (d, *J* = 4.4Hz, 1H), 3.89 (s, 3H). MS m/z: 316 $(M+H)^+$.
C.1.26	 Preparation#2. step#3		1	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.295 (s, 1H), 8.033-8.019 (m, *J*=5.6,1H), 7.653-7.631 (dd, *J*=2,1H), 7.172-7.168 (d, *J*=1.6,1H), 6.220-6.187 (t, *J*=6.8,1H), 4.378-4.364 (d, *J*=5.6,2H), 3.468 (s, 3H), MS m/z: 329.0 $(M+H)^+$.
C.1.27	 Preparation#2. step#3		1	^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.300 (s,1H), 8.050-8.021 (t, *J* = 5.6 Hz,1H), 7.674-7.669 (d, *J* = 2 Hz,1H), 7.188-7.175 (d, *J*=5.2 Hz,1H), 6.267-6.233 (t, *J* = 6.8 Hz,1H), 4.389-4.375 (d, *J* = 5.6 Hz,2H), 4.353-4.323 (t, *J* =5.2 Hz,2H), 3.601-3.566 (t, *J* = 7.2 Hz,2H), 3.06 (s,3 H), MS m/z: 423.0 $(M+H)^+$.
	 Preparation # 1		1	^{1}H NMR (400 MHz, DMSO) : δ 8.295 (s,1H), 8.028-8.011(bs,1H), 7.767-7.746 (dd, *J* = 1.6Hz, 1H), 7.346-7.302 (m, 5H), 7.282-7.166 (m, 1H), 6.270-6.236 (m,1H), 5.147

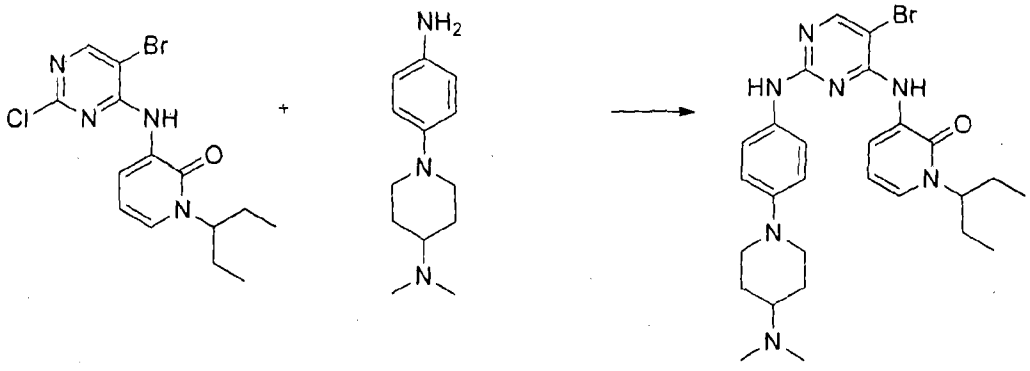
	Step#3			(s,2H), 4.384 (s,2H), MS m/z: 405 $(M+H)^+$.

General procedure D: Amination of pyrmidines at 2nd position Method #1

A sealed tube is charged with a substituted pyrimidine derivative (1 equiv), appropriate amine derivative (1 to 3 equiv preferably 1 equiv) , n-BuOH and Conc. HCl. The reaction mixture is heated to 100 °C to 140°C (preferably 120°C) for about 8 to 12hrs (preferably 10hrs). The reaction mixture is cooled to RT diluted with Ice cold water and basified with saturated sodium bicarbonate solution. The product is extracted with ethyl acetate. Combined organic layers washed successively with water, brine, dried over sodium sulphate and concentrated under reduced pressure. The crude material obtained is optionally purified by precipitation, crystallization or trituration from an appropriate solvent or solvents or by column chromatography, preparative HPLC to get the target compound.

Illustration of General D:

Method #D.1 : 3-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-(pentan-3-yl)pyridin-2(1H)-one:



A 50 mL sealed tube was charged with 3-((5-bromo-2-chloropyrimidin-4-yl)amino)-1-(pentan-3-yl)pyridin-2(1H)-one (0.15g, 0.4mmol ,Preparation# C.1), 1-(4-aminophenyl)-N,N-dimethylpiperidin-4-amine (0.09g, 0.4mmol, WO20087123A2), n-BUOH (2 ml) and Conc. HCl (0.05ml). The reaction mixture was heated to 120 °C for about 12hrs. The reaction mixture was cooled to RT. Diluted the reaction mixture with Ice cold water and basified with saturated

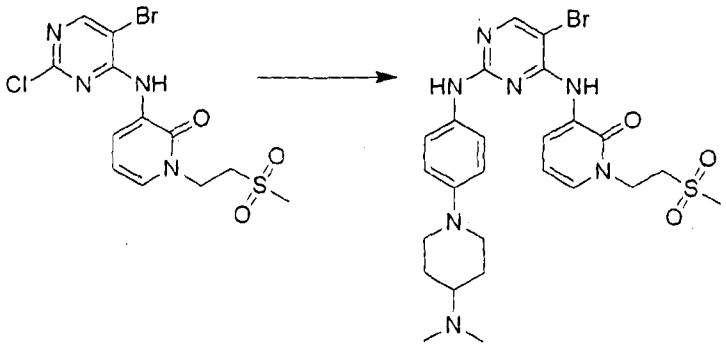
sodium bicarbonate solution. The product was extracted with ethyl acetate (3x20ml), washed successively with water (2x15ml) and brine (2x20ml). The organic layer was dried over sodium sulphate and concentrated under reduced pressure. Crude material was purified by column chromatography eluting with 5% methanol in DCM. The relevant fractions containing the product were collected and evaporated to dryness to afford *3-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-(pentan-3-yl)pyridin-2(1H)-one (0.05g, 22%)* as white solids. ^{1}H NMR (400 MHz, DMSO-d_6) : δ 9.25(S, 1H), 8.51 (S, 2H), 8.22 (S, 1H), 7.43 (d, *J*=9Hz, 2H), 7.32 (dd, *J*= 3Hz, 4Hz,1H), 6.93 (d, *J*=8Hz, 2H), 6.31(t, *J*=6.8Hz, 1H), 4.9 (m, 1H), 3.65(d, *J*=9Hz, 2H), 2.67 (m, 2H), 2.19 (S, 6H), 1.85 (m, 6H), 1.53 (dd, *J*=6Hz,8Hz, 2H), 0.73 (t, *J*=6.4Hz,7Hz, 6H). MS m/z : 554 $(M+H)^+$.

General D: Amination of pyrimidines at 2nd position Method #2

A sealed tube is charged with a substituted pyrimidine derivative (1 equiv), appropriate amine derivative (1 to 3 equiv preferably 1 equiv) , n-BuOH and TFA. The reaction mixture is heated to 100 °C to 140°C (preferably 120°C) for about 8 to 12hrs (preferably 10hrs). The reaction mixture is cooled to RT diluted with Ice cold water and basified with saturated sodium bicarbonate solution. The product is extracted with ethyl acetate. Combined organic layers washed successively with water, brine, dried over sodium sulphate and concentrated under reduced pressure. The crude material obtained is optionally purified by precipitation, crystallization or trituration from an appropriate solvent or solvents or by column chromatography, preparative HPLC to get the target compound

Illustration of General procedure D: Method #2:

Preparation#D1.1: 3-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-(2-(methylsulfonyl)ethyl)pyridin-2(1H)-one:

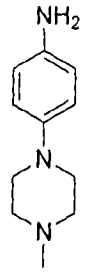
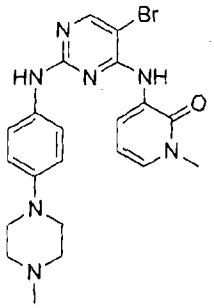
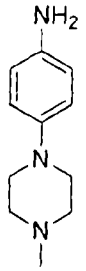
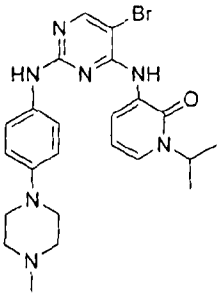
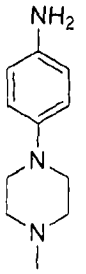
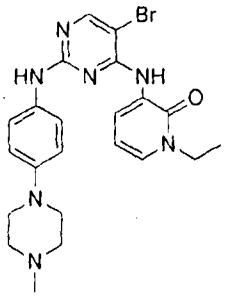


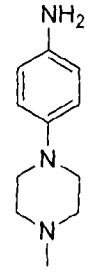
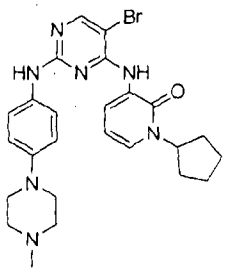
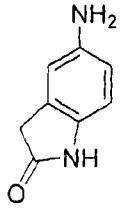
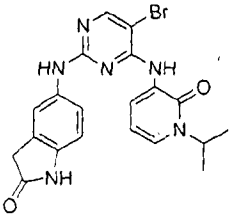
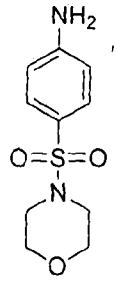
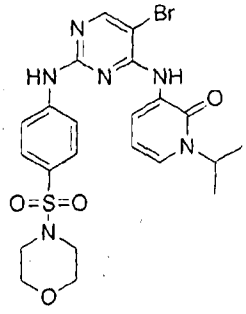
A 50 mL sealed tube was charged with 3-((5-bromo-2-chloropyrimidin-4-yl)amino)-1-(2-(methylsulfonyl)ethyl)pyridin-2(1H)-one (0.20 g, 0.49 mmol,Preparation#C1.2), 1-(4-aminophenyl)-N,N-dimethylpiperidin-4-amine (0.11 g, 0.49 mmol, WO20087123A2), n-BuOH (2 ml) and trifluoroacetic acid (0.05 mL,Spectrochem). The reaction mixture was heated at 100 °C for about 16h. The reaction mixture was cooled in ice. The solid precipitate was filtered, washed with saturated sodium bicarbonate solution and dried under vacuum to afford *3-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)amino)-1-(2-(methylsulfonyl)ethyl)pyridin-2(1H)-one* - 0.095g (33%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.28 (s, 1H), 8.49 (bs, 2H), 8.23 (s, 1H), 7.44 - 7.41 (m, 3H), 6.91 (d, J = 8.0 Hz, 2H), 6.28 (m, 1H), 4.40 (t, J = 6.8 Hz, 2H), 3.66 - 3.61 (m, 4H), 3.05 (s, 3H), 2.62 (t, J = 2.0 Hz, 2H), 2.23 (s, 6H), 1.86 - 1.83 (m, 2H), 1.51 - 1.48 (m, 2H). MS m/z : 591.2 $(M+H)^+$.

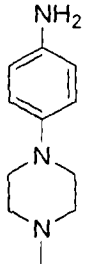
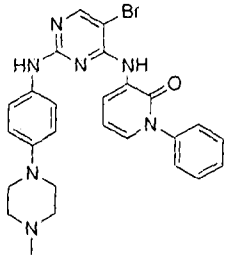
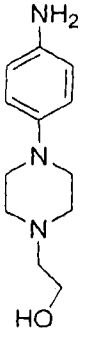
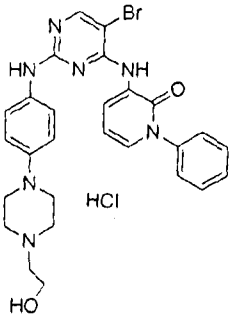
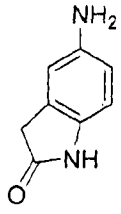
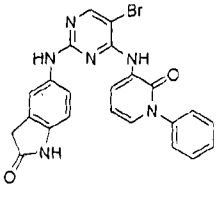
Other compounds synthesized using appropriate halo pyrimidines (synthesized using General Procedure **C** from Table C.1) by following General procedure **D** are described in Table **D.1**

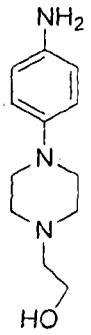
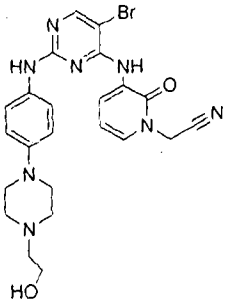
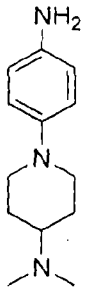
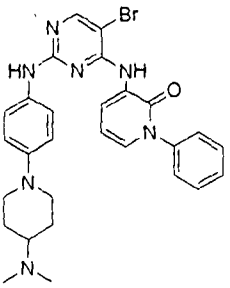
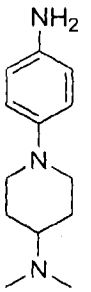
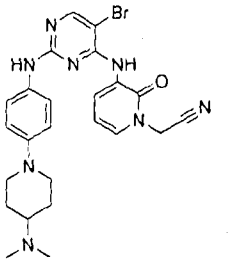
Table D.1: Other compounds synthesized using General procedure D

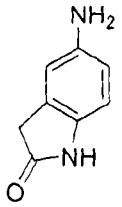
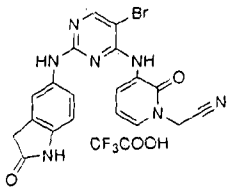
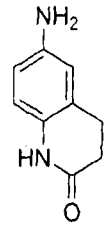
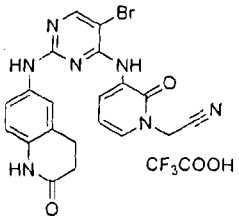
S. No	Side chain LHS/ source	Product	AU	Met hod	Analytical data

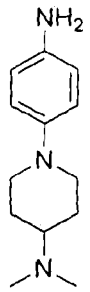
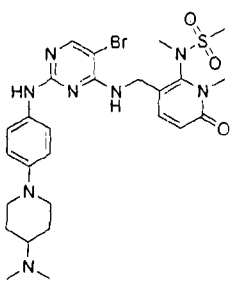
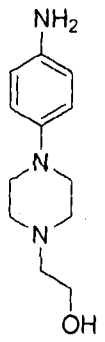
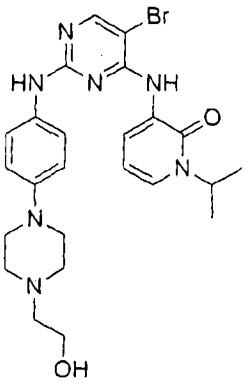
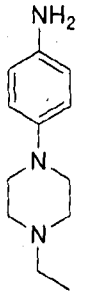
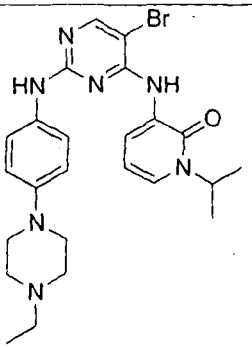
D.1.2			130	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.27 (s, 1H), 8.53 (bs, 2H), 8.23 (s, 1H), 7.44 - 7.38 (m, 3H), 6.91 (d, J = 8.8 Hz, 2H), 6.24 (t, 1H), 3.56 (s, 3H), 3.09 (t, J = 4.4 Hz, 4H), 2.52 - 2.51 (m, 4H), 2.22 (s, 3H). MS m/z: 472.1 (M+2).
D.1.3			150	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.27 (s, 1H), 8.58 (s, 1H), 8.50 (bs, 1H), 8.23 (s, 1H), 7.45 - 7.42 (m, 3H), 6.91 (d, J = 8.8 Hz, 2H), 6.29 (t, J = 6.8 Hz, 1H), 5.15 - 5.11 (m, 1H), 3.09 (bs,4H), 2.50(bs, 4H), 2.24 (s, 3H), 1.35 (d, J = 6.8 Hz, 6H). MS m/z: 498.2 $(M+H)^+$.
D.1.4			151	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.27 (s, 1H), 8.55 (bs, 2H), 8.23 (s, 1H), 7.44 - 7.40 (m, 3H), 6.91 (d, J = 8.8 Hz, 2H), 6.27 (t, J = 7.2 Hz, 1H), 4.02 (q, J_1 = 7.2 Hz, J_2 = 6.8 Hz, 2H), 3.09 (bs, 4H), 2.50 (bs, 4H), 2.24 (s, 3H), 1.26 (t, 3H). MS m/z: 484 $(M+H)^+$.

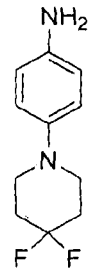
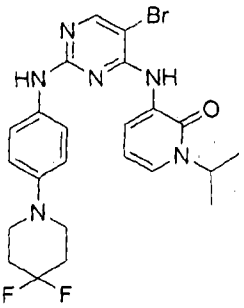
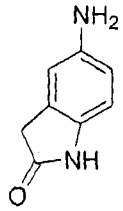
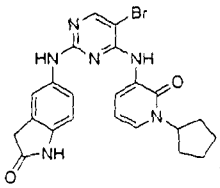
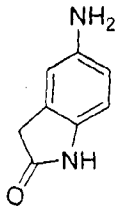
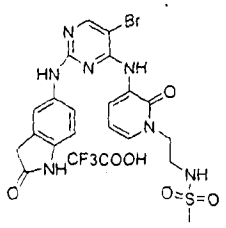
D.1.5			185	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.26 (s, 1H), 8.57 (s, 1H), 8.49 (s, 1H), 8.22 (s, 1H), 7.44 - 7.39 (m, 3H), 6.91 (d, J = 8.8 Hz, 2H), 6.28 (t, J = 6.8 Hz, 1H), 5.16 (m, 1H), 3.08 (t, J = 4.8 Hz, 4H), 2.45 (t, J = 4.8 Hz, 4H), 2.2 (s, 3H), 2.05 (bs, 2H), 1.84 - 1.64 (m, 6H). MS m/z: 524.2 $(M+H)^+$.
D.1.6			186	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.27 (s, 1H), 9.37 (s, 1H), 8.06 (s, 1H), 8.48 (bs, 1H), 8.25 (s, 1H), 7.56 (s, 1H), 7.46 (d, J = 6.8 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.32 (t, J = 7.2 Hz, 1H), 5.13 (m, 1H), 3.47 (s, 2H), 1.35 (d, J = 6.4 Hz, 6H). MS m/z: 455.4 $(M+H)^+$.
D.1.7			199	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.06 (s, 1H), 8.73 (s, 1H), 8.57 (d, J = 6.4 Hz, 1H), 8.40 (s, 1H), 7.96 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 9.2 Hz, 2H), 7.50 (d, J = 5.2 Hz, 1H), 6.39 (t, J = 7.2 Hz, 1H), 5.16 (m, 1H), 3.63 (t, J = 3.6 Hz, 4H), 2.85 (t, J = 4.4 Hz, 3H), 1.34 (d, J = 6.4 Hz, 6H). MS

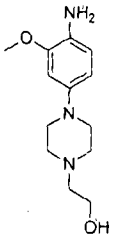
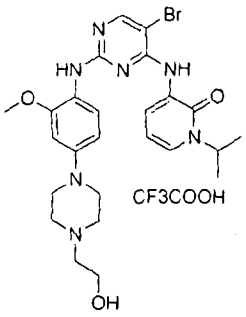
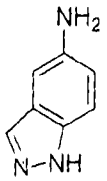
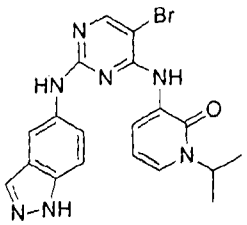
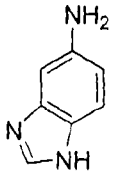
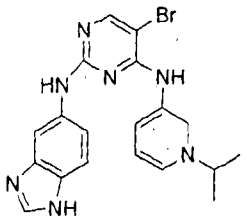
					m/z: 549.1 $(M+H)^+$.
D.1.8			207	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.32 (s, 1H), 8.62 (bs, 1H), 8.54 (s, 1H), 8.25 (s, 1H), 7.57 - 7.45 (m, 7H), 7.38 (dd, J_1 = 2 Hz, J_2 = 4.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.37 (t, J = 6.8 Hz, 1H), 3.09 (t, J = 4.8 Hz, 4H), 2.46 (t, J = 5.2 Hz, 4H), 2.22 (s, 3H). MS m/z : 532.2 $(M+H)^+$.
D.1.9			225	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.32 (bs, 1H), 9.62 (s, 1H), 8.68 (s, 1H), 8.59 (s, 1H), 8.29 (s, 1H), 7.57 -7.47 (m, 1H), 7.40 (d, J = 1.6 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 6.38 (t, J = 7.6 Hz, 1H), 3.83 - 3.74 (m, 4H), 3.61 (d, J = 11.2 Hz, 2H), 3.25 - 3.12 (m, 6H). MS m/z : 562.1 $(M+H)^+$.
D.1.10			230	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.28 (s, 1H), 9.42 (s, 1H), 8.61 (bs, 1H), 8.55 (s, 1H), 8.27 (s, 1H), 7.59 - 7.33 (m, 8H), 6.78 (d, J = 8.4 Hz, 1H), 6.38 (t, J = 6.8 Hz, 1H), 3.48 (s, 2H). MS m/z : 487.3 (M-H).

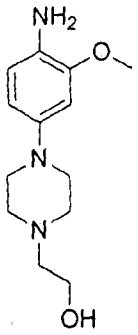
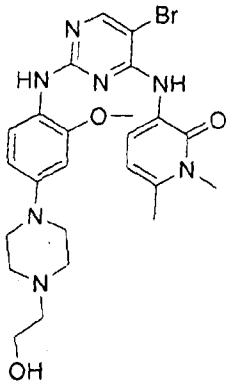
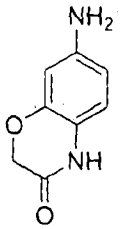
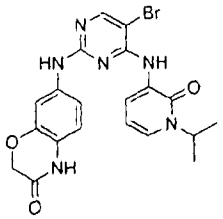
D.1.11			240	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.31 (s, 1H), 8.60 (bs, 1H), 8.39 (s, 1H), 8.25 (s, 1H), 7.49 -7.42 (m, 3H), 6.90 (d, J = 9.2 Hz, 2H), 6.38 (t, J = 6.8 Hz, 1H), 5.15 (s, 2H), 4.42 (t, J = 4.8 Hz, 1H), 3.53 (dd, J_1 = 6 Hz, J_2 = 5.6 Hz, 2H), 3.08 (bs, 4H), 2.56 (bs, 4H), 2.44 (t, J = 6.4 Hz, 2H). MS m/z: 525.2 $(M+H)^+$.
D.1.12			244	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.31 (s, 1H), 8.64 (bs, 1H), 8.54 (s, 1H), 8.24 (s, 1H), 7.57 - 7.43 (m, 6H), 7.37 (dd, J_1 = 2 Hz, J_2 = 5.6 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.36 (t, J = 7.2 Hz, 1H), 3.64 (d, J = 12 Hz, 2H), 2.62 (t, J = 10.4 Hz, 2H), 2.20 (bs, 7H), 1.83 (d, J = 12 Hz, 2H), 1.47 (t, J = 2.8 Hz, 2H). MS m/z : 560.2 $(M+H)^+$.
D.1.13			253	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.31 (s, 1H), 8.60 (bs, 1H), 8.39 (s, 1H), 8.25 (s, 1H), 7.49 (d, J = 1.6 Hz, 1H), 7.47 - 7.41 (m, 2H), 6.91 (d, J = 9.6 Hz, 2H), 6.37 (t, J = 7.6 Hz, 1H), 5.15 (s, 2H), 3.64 (d, J =

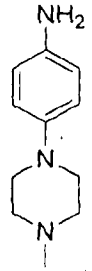
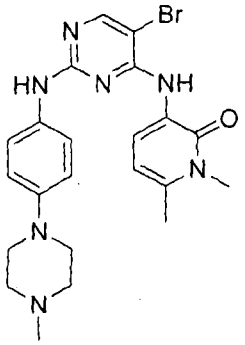
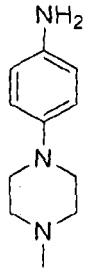
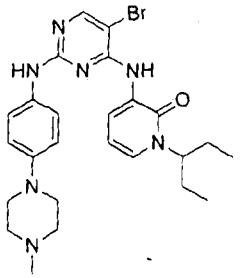
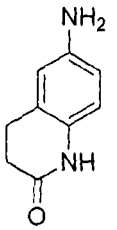
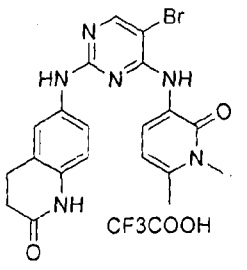
					9.2 Hz, 2H), 2.67 (t, J = 1.6 Hz, 2H), 2.25 (bs, 7H), 1.86 (d, J = 11.6 Hz, 2H), 1.51 (m, 2H). MS m/z : 523.2 $(M+H)^+$.
D.1.14			254	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.30 (s, 1H), 9.51 (s, 1H), 8.52 (bs, 1H), 8.48 (s, 1H), 8.29 (s, 1H), 7.54 -7.50 (m, 2H), 7.30 (d, J = 10.4 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.40 (t, J = 7.6 Hz, 1H), 5.15 (s, 2H), 3.47 (s, 2H). MS m/z : 452.3 $(M+H)^+$.
D.1.15			278	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.99 (s,1H), 9.46 (s,1H), 8.56 (bs,1H), 8.44 (s,1H), 8.29 (s,1H),7.50-7.47 (m, 2H),7.29 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.38 (t, J = 7.6 Hz,1H), 5.15 (s,2H), 2.85 (t, J = 7.2 Hz, 2H), 2.44 (t, J = 8.0Hz, 2H), MS m/z : 464.3 M-H).

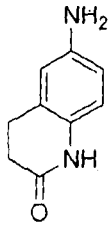
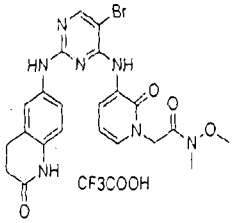
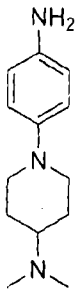
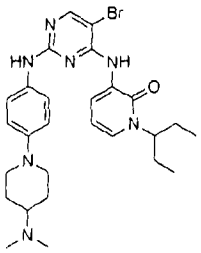
D.1.16			311	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.84 (s,1H), 8.01 (s,1H),7.35-7.32 (m, 3H), 7.20(t, J = 5.6 Hz, 1H), 6.76 (d, J = 9.2 Hz, 2H), 6.49 (d, J = 10 Hz, 1H), 4.46-4.38 (m,2H), 3.55 (bs,2H), 3.40 (s, 3H), 3.35 (s, 3H), 3.14 (s,3H), 2.67 (t, J = 2 Hz, 2H), 2.19 (bs, 7H), 1.81 (d, J = 12.4 Hz, 2H), 1.47 (t, J = 3.2 Hz, 2H). MS m/z : 619.2 $(M+H)^+$.
D.1.17			188	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.26 (s, 1H), 8.58 (s, 1H), 8.49 (bs, 1H), 8.22 (bs, 1H) ,7.45 - 7.42 (m, 3H), 7.38 (m, 3H), 6.90 (d, J = 8.0 Hz, 2H), 6.29 (bs, 1H), 5.13 (m, 1H), 4.42 (bs, 1H), 3.54 (m, 2H), 3.08 (m, 4H), 2.56 - 2.45 (m, 8H), 1.33 (d, J = 8 Hz, 6H). MS m/z: 528.2 $(M+H)^+$.
D.1.18			204	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.26 (s, 1H), 8.58 (s, 1H), 8.49 (bs, 1H), 8.22 (s, 1H) , 7.46 - 7.42 (m, 3H), 6.91 (d, J = 8.0 Hz, 2H) (d, J = 8.0 Hz, 1H), 5.13 (p, J = 8.0 Hz, 1H), 3.08 (t, J = 4.0 Hz, 4H), 2.36 -

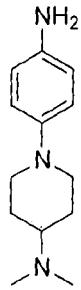
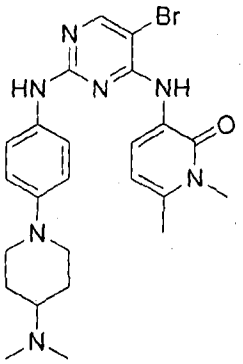
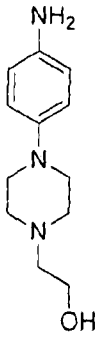
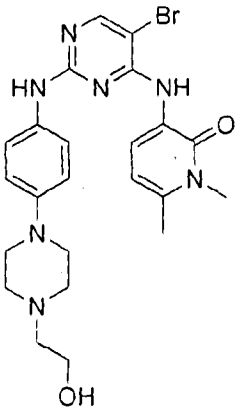
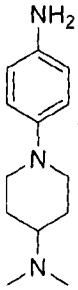
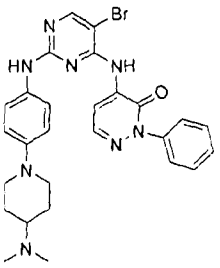
					2.32 (m, 2H), 1.34 (d, J = 8 Hz, 6H), 1.03 (t, J = 8.0 Hz, 3H). MS m/z :512.2 $(M+H)^+$.
D.1.19			219	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.30 (s, 1H), 8.59 (s, 1H), 8.51 (s, 1H), 8.24 (s, 1H), 7.47-7.44 (m, 3H), 6.98 (d, J = 8.0 Hz, 2H), 6.31 (t, J = 8.0 Hz, 1H), 5.13 (p, J = 6.4 Hz, 1H), 3.31 - 3.25 (m, 4H), 2.12 - 2.02 (m, 4H), 1.34 (d, J = 8.0 Hz, 6H). MS m/z: 519.2 $(M+H)^+$.
D.1.20			224	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.27 (s, 1H), 9.37 (s,1H), 8.59 (s, 1H), 8.49 (bs, 1H), 8.24 (s, 1H), 7.56 (s, 1H), 7.41 (dd, J_1 = 2 Hz, J_2 = 5.2 Hz, 1H), 7.34 (d, J = 8.0 Hz,1H), 6.76 (d, J = 8.0 Hz, 1H), 6.30 (t, J = 8.0 Hz, 1H), 5.18 - 5.14 (m, 1H), 3.46 (s, 2H), 2.08 - 2.04 (m), 1.84 - 1.65 (m, 7H). MS m/z: 481.1 $(M+H)^+$.
D.1.21			263	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.34 (s, 1H), 9.71 (s, 1H), 8.72 (bs, 1H), 8.59 (s, 1H), 8.47 (s, 1H), 8.29 (s, 1H), 7.51 (bs, 1H), 7.38 - 7.21 (m, 3H), 6.80 (d, J = 8.0 Hz, 1H),

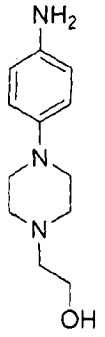
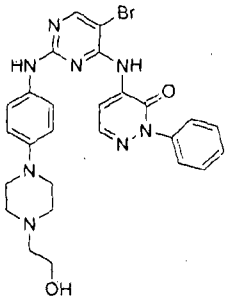
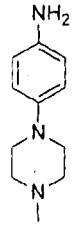
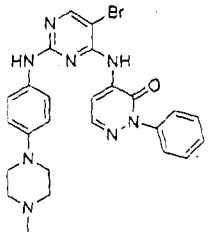
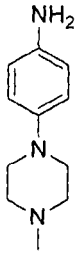
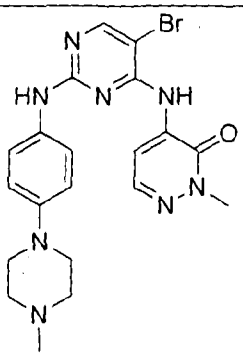
					6.28 (t, J = 6.8 Hz, 1H), 4.08 (t, J = 6.0 Hz, 3H), 3.48 (s, 2H), 3.30 -3.38 (m, 2H), 2.90 (s, 3H). MS m/z : 536.2 (M+2).
D.1.22			283	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.83 (bs, 1H), 8.60 (s, 1H), 8.26 (bs, 1H), 8.18 (s, 2H), 7.39 (s, 2H), 6.72 (m, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.19 (s, 1H), 3.96 - 3.84 (m, 7H), 3.63 - 3.60 (m, 3H), 3.50 - 3.09 (m, 7H), 1.34 (d, J = 4.0 Hz, 6H). MS m/z : 558.3 $(M+H)^+$.
D.1.23			286	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.96 (s, 1H), 9.49 (s, 1H), 8.61 (s, 1H), 8.50 (bs, 1H), 8.29 (s, 1H), 8.07-8.00 (s, 1H) , 8.00 (s, 1H), 7.51-7.43 (m, 3H), 6.21 (bs, 1H), 5.13 (t, J = 4.0 Hz, 1H), 1.34 (d, J = 8.0 Hz, 6H). MS m/z : 440.1 $(M+H)^+$.
D.1.24			298	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.33 (s, 1H), 9.50 (s, 1H), 8.63 (s, 1H), 8.57 (bs, 1H), 8.29 (s, 1H), 8.24 (s, 1H), 8.14 (s, 2H), 7.98 (s, 1H), 7.33 -7.54 (m, 3H), 6.25 (s, 1H), 5.15 (p, J = 8.0 Hz, 1H), 1.34

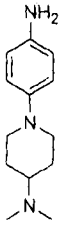
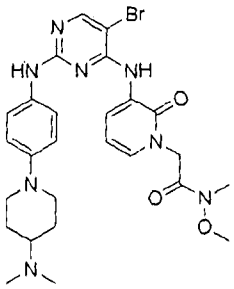
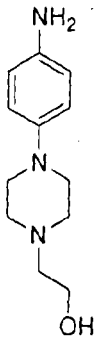
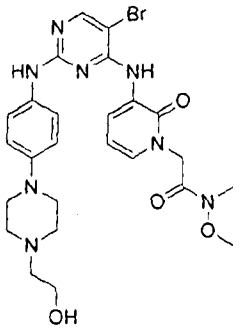
					(d, J = 8.0 Hz, 6H). MS m/z : 440.1 $(M+H)^+$.
D.1.25			289	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.38 (s, 1H), 8.31 (s, 1H), 8.17 (s, 1H), 8.12 (s, 1H), 7.32 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 2.5 Hz, 1H), 6.5 (d, J = 2.4 Hz, 1H), 6.01 (d, J = 6.5 Hz 1H), 4.4 (s, 1H), 3.7 (s, 1H), 3.57 (dd, J = 4.4 Hz, 6.0 Hz, 5H), 3.31 (s, 4H), 2.5 (m, 4H), 2.34 (s, 6H). MS m/z : 546.2 (M+2).
D.1.26			297	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.6 (s, 1H), 9.47 (s, 1H), 8.63 (s, 2H), 8.56 (d, J = 6.0 Hz, 1H), 8.28 (s, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.41 (s, 1H), 7.16 (dd, J = 2.5 Hz, 7.0 Hz, 1H), 6.36 (t, J = 7.3 Hz, 1H), 5.1 (m,1H), 4.55 (s, 2H), 1.36 (d, J = 6.8 Hz, 6H). MS m/z : 471.1 $(M+H)^+$.

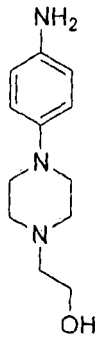
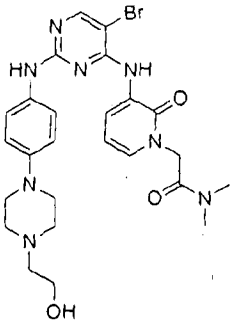
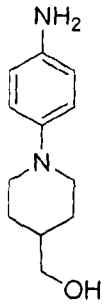
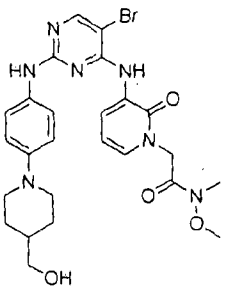
D.1.27			213	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.25 (s,1H), 8.46 (bs, 2H), 8.20 (s, 1H), 7.45 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 9.2 Hz, 2H), 6.1 (d, J = 8.0 Hz, 2H), 3.56 (s, 3H), 3.09 (bs, 4H), 2.49 (s, 3H), 2.29 (s, 3H). MS m/z: 486.2 (M+2).
D.1.28			211	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.26 (s, 1H), 8.59 (s, 1H), 8.51 (bs, 1H), 8.23 (s,1H), 7.44 (d, J = 2.0 Hz, 2H), 7.33 (d, J = 5.2 Hz, 1H), 6.93 (d, J = 9.2 Hz, 2H), 6 .31 (t, J = 7.6Hz, 6.8Hz, 1H), 4.8 (bs, 1H), 3.1(t, J = 5.2Hz, 4.6Hz, 4H), 2.22 (s, 3H), 1.90-1.70 (m, 4H), 0.73 (t, J = 7.2 Hz, 6H). MS m/z: 526.2 $(M+H)^+$.
D.1.29			277	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.01 (s, 1H), 9.44 (s, 1H), 8.54 (s, 1H), 8.39 (s, 1H), 8.24 (s, 1H), 7.46 (s, 1H), 7.29 (d, J = 8.2 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.18 (d, J = 7.4 Hz, 1H), 3.57 (s, 3H), 2.86 (t, J = 8.0 Hz, 7.0 Hz, 2H), 2.67 (t, J = 2.0 Hz,

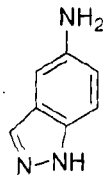
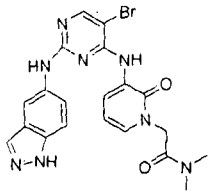
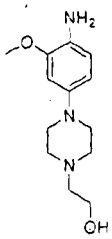
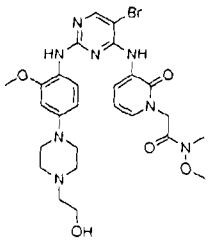
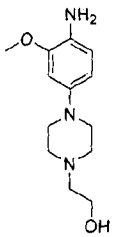
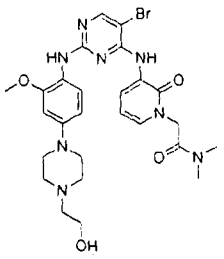
					2H), 2.51 (s, 3H). MS m/z : 455.2 $(M+H)^+$.
D.1.30			276	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.03 (s, 1H), 9.67 (s, 1H), 8.61 (s, 1H), 8.48 (s, 1H), 8.30 (s, 1H), 7.45 (s, 1H), 7.4 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 2.7 Hz 1H), 7.29 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.30 (t, J = 7.2 Hz, 8.0 Hz, 1H), 4.98 (s, 2H), 3.81 (s, 3H), 3.15 (s, 3H), 2.88 (t, J = 7.3 Hz,8.0 Hz, 2H). MS m/z : 528.1 $(M+H)^+$.
D.1.31			248	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.25 (s, 1H), 8.51 (s, 2H), 8.22 (s, 1H), 7.43 (d, J = 9.0 Hz, 2H), 7.32 (dd, J = 3.0 Hz, 4.0 Hz,1H), 6.93 (d, J = 8.0 Hz, 2H), 6.31 (t, J = 6.8 Hz, 1H), 4.9 (m, 1H), 3.65 (d, J = 9.0 Hz, 2H), δ 2.67 (m, 2H), 2.19 (s, 6H), 1.85 (m, 6H), 1.53 (dd, J = 6.0 Hz, 8.0 Hz, 2H), 0.73 (t, J = 6.4 Hz, 7.0 Hz, 6H). MS m/z : 554.3 $(M+H)^+$.

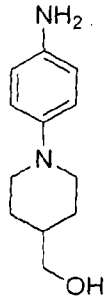
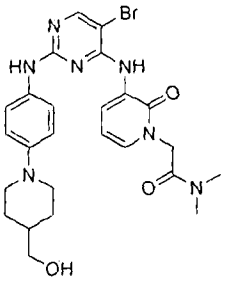
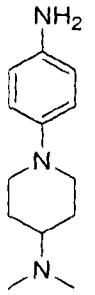
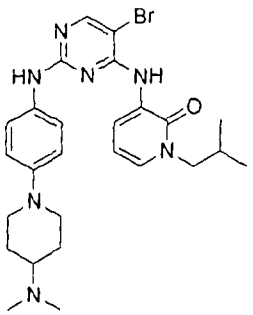
D.1.32			247	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.23 (s,1H), 8.46 (s, 1H), 8.20 (s, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.17 (d, *J* = 7.0 Hz, 1H) , 3.6 (d, *J* = 9.0 Hz, 2H), 3.56 (s, 3H), 2.67 (m, 3H), 2.51 (s, 3H), 2.20 (s, 6H), 1.85 (d, *J* = 9.0 Hz, 2H), 1.53 (dd, *J* = 6.0 Hz, 8.1Hz, 2H), MS m/z : 512.2 $(M+H)^+$.
D.1.33			246	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.24 (s, 1H), 8.46 (s, 2H), 8.20 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.1 (d, *J* = 8.0 Hz, 1H), 4.42 (s, 1H), 3.50 (s, 3H), 3.50 (t, *J* = 5.2 Hz, 5.6 Hz, 2H), δ 3.17 (bs, 4H), 2.67 (t, *J* = 5.0 Hz, 4.0 Hz, 4H), 2.56 (t, *J* = 5.2 Hz, 5.0 Hz, 2H), 2.49 (s, 3H). MS m/z : 514.2 $(M+H)^+$.
D.1.34			241	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.5 (s, 1H), 8.81 (s, 1H), 8.30 (s, 1H), 8.02 (s, 1H), 7.63 (d, *J* = 8.0 Hz ,2H), 7.53 (m, 5H), 6.97 (d, *J* = 8.8 Hz, 2H), 3.69 (d, *J* = 6.0 Hz, 2H), 2.67 (t, *J* = 1.6 Hz, 1.2 Hz, 2H), 2.25 (s, 6H), 1.87 (d, *J* = 1.2 Hz,

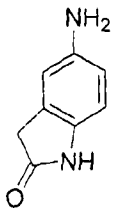
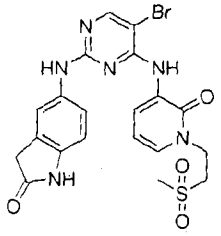
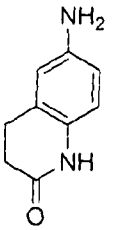
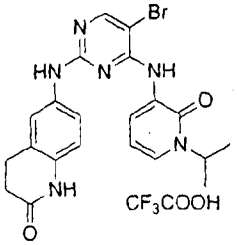
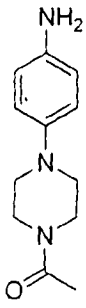
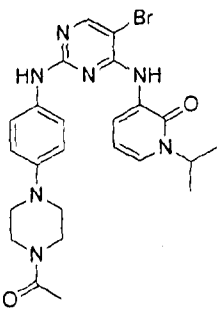
					2H), 1.55 (t, J = 8.0 Hz, 2H), MS m/z: 561.2 $(M+H)^+$.
D.1.35			231	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.51 (s, 1H), 8.80 (s, 1H), 8.37 (s, 1H), 8.01 (s, 1H), 7.63 (d, J = 8.0 Hz , 2H), 7.55-7.44 (m, 5H), 6.96 (d, J = 6.0 Hz, 2H), 4.43 (t, J = 4.8 Hz, 5.2 Hz, 1H), 3.56 (t, J = 6.0 Hz, 5.6 Hz, 2H), 3.1 (bs, 4H), 2.61 (bs, 4H), 2.45 (t, J = 6.4 Hz, 2H), MS m/z : 563.2 $(M+H)^+$.
D.1.36			178	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.52 (s, 1H), 8.80 (s, 1H), 8.38 (bs, 2H), 8.02 (d, J = 1.8 Hz,1H), 7.63 (d, J = 8.0 Hz, 2H), 7.55-7.44 (m, 5H), 6.96 (d, J = 8.8 Hz, 2H), 3.11 (bs, 4H), 2.41 (bs, 4H), 2.24 (s, 3H). MS m/z : 535.2 (M+2).
D.1.37			162	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.47 (s, 1H), 8.72 (s, 1H), 8.35 (bs, 2H), 7.85 (bs, 1H), 7.44 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz , 2H), 3.75 (s, 3H), 3.09 (bs, 4H), 2.50 (bs, 4H), 2.22 (s, 3H). MS m/z :

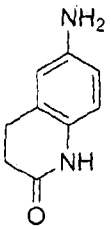
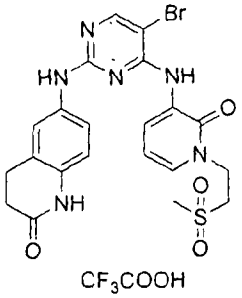
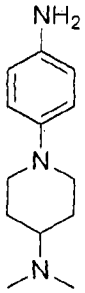
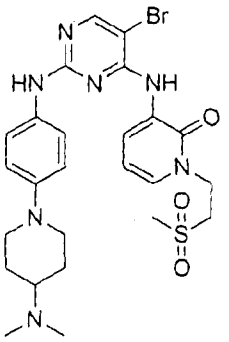
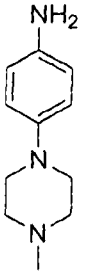
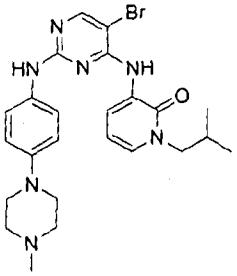
					473.1 (M+2).
D.1.38			242	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.28 (s, 1H), 8.55 (bs, 1H), 8.43 (s, 1H), 8.23 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.34 (dd, *J* = 6.8 Hz, 1.2 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.28 (t, *J* = 6.8 Hz, 1H), 4.98 (s, 2H), 3.81 (s, 3H), 3.64 (d, *J* = 8.4 Hz, 2H), 3.15 (s, 3H), 2.55 (m, 3H), 2.20 (s, 6H), 1.84 (d, *J* = 11.6 Hz, 2H), 1.50 (m, 2H). MS m/z: 585.3(M+H)$^+$.
D.1.39			214	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.29 (s, 1H), 8.56 (bs, 1H), 8.43 (s, 1H), 8.23 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.34 (dd, *J* = 6.8 Hz, 1.2 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.29 (t, *J* = 6.8 Hz, 1H), 4.95 (s, 2H), 4.42 (bs, 1H), 3.81 (s, 3H), 3.53 (m, 2H), 3.15 (s, 3H), 3.09 (m, 4H), 2.56 (m, 4H), 2.44 (t, *J* = 5.6 Hz, 2H). MS m/z: 587.2 (M+H)$^+$.

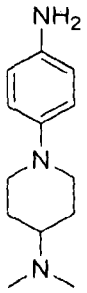
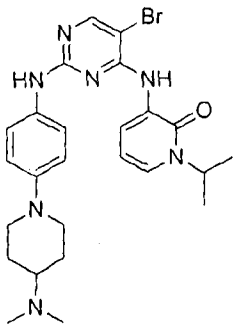
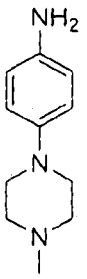
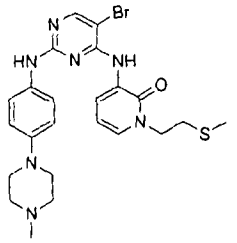
D.1.40			218	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.29 (s, 1H), 8.54 (bs, 1H), 8.45 (s, 1H), 8.23 (s, 1H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.26 (dd, *J* = 8.6 Hz, 1.2 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.26 (t, *J* = 7.6 Hz, 1H), 4.90 (s, 2H), 4.42 (bs, 1H), 3.54 (m, 2H), 3.07 (s, 7H), 2.86 (s, 3H), 2.56 (m, 4H), 2.44 (t, *J* = 8.4 Hz, 2H). MS m/z : 571.2 $(M+H)^+$.
D.1.41			261	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.27 (s, 1H), 8.56 (bs, 1H), 8.43 (s, 1H), 8.23 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.35 (dd, *J* = 6.8 Hz, 1.2 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.28 (t, *J* = 7.2 Hz, 1H), 4.98 (s, 2H), 4.47 (t, *J* = 5.6 Hz, 1H), 3.81 (s, 3H), 3.63 (d, *J* = 12.4 Hz, 2H), 3.29 (d, *J* = 6.0 Hz, 2H), 3.15 (s, 3H), 2.59 (m, 2H), 1.75 (d, *J* = 12 Hz, 2H), 1.49 (m, 1H), 1.24 (m, 2H). MS m/z : 572.2 $(M+H)^+$.

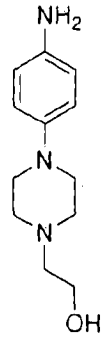
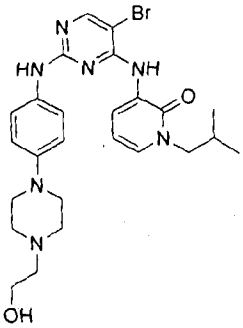
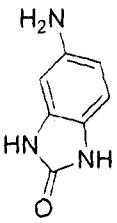
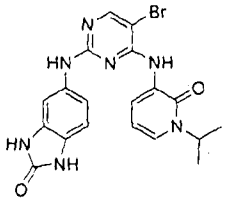
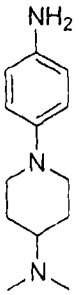
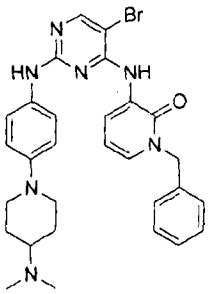
D.1.42			272	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.96 (s, 1H), 9.51 (s, 1H), 8.48 (s, 1H), 8.42 (s, 1H), 8.29 (s, 1H), 8.08 (s, 1H), 8.01 (s, 1H), 7.50 (s, 2H), 7.26 (dd, *J* = 7.2 Hz, 1.2 Hz, 1H), 6.17 (bs, 1H), 4.90 (s, 2H), 3.07 (s, 3H), 2.86 (s, 3H). MS m/z : 483.1 $(M+H)^+$.
D.1.43			282	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.39 (s, 1H), 8.35 (s, 1H), 8.31 (s, 1H), 8.15 (s, 1H), 7.30 (d, *J* = 7.6 Hz, 2H), 6.64 (s, 1H), 6.51 (d, *J* = 6.8 Hz, 1H), 4.95 (s, 2H), 4.43 (s, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.55 (d, *J* = 6.0 Hz, 2H), 3.14 (s, 7H), 2.42 (m, 2H), 2.58 (m, 5H). MS m/z : 617.2 $(M+H)^+$.
D.1.44			291	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.38 (s, 1H), 8.37 (s, 1H), 8.31 (bs, 1H), 8.15 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.22 (dd, *J* = 6.8 Hz, 0.8 Hz, 1H), 6.64 (s, 1H), 6.51 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 6.09 (bs, 1H), 4.87 (s, 2H), 4.43 (t, *J* = 5.2 Hz, 1H), 3.75 (s, 3H), 3.54 (m, 2H), 3.17 (m, 4H), 3.06 (s, 3H), 2.85 (s, 3H), 2.59 (m, 3H), 2.45 (m,

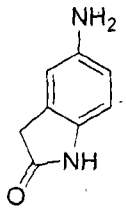
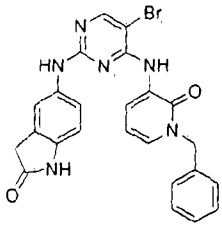
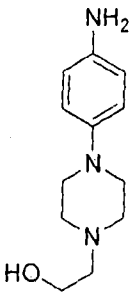
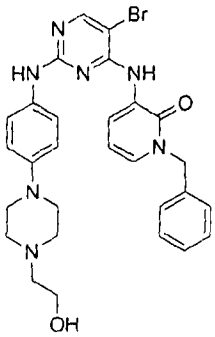
					3H). MS m/z : 601.3 $(M+H)^+$.
D.1.45			307	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.27 (s, 2H), 8.55 (bs, 1H), 8.45 (s, 1H), 8.23 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.26 (dd, *J* = 6.8 Hz, 1.2 Hz, 1H), 4.90 (s, 2H), 4.47 (t, *J* = 5.6 Hz, 1H), 3.62 (d, *J* = 12.4 Hz, 2H), 3.28 (m, 2H), 3.07 (s, 3H), 2.86 (s, 3H), 2.66 (s, 2H), 1.75 (d, *J* = 10.2 Hz, 2H), 1.46 (m, 1H), 1.26 (m, 2H). MS m/z : 558.2 (M+2).
D.1.46			249	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.28 (s, 1H), 8.55 (bs, 1H), 8.23 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 4.0 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.25 (t, *J* = 8.0 Hz, 1H), 3.82 (d, *J* = 8.0 Hz, 2H), 3.70 - 3.67 (m, 2H), 2.73 - 2.41 (m, 8H), 2.14 - 2.09 (m, 1H), 1.92 (d, *J* = 8.0 Hz, 2H), 1.57 (d, *J* = 8.0 Hz, 2H), 0.88 - 0.83 (m, 6H). MS m/z : 540.2 $(M+H)^+$.

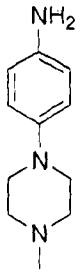
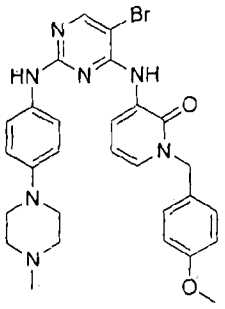
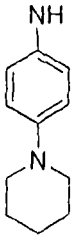
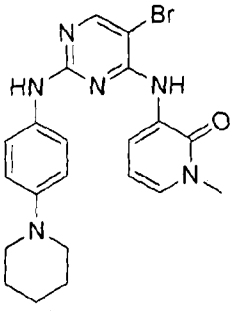
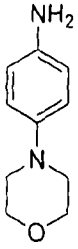
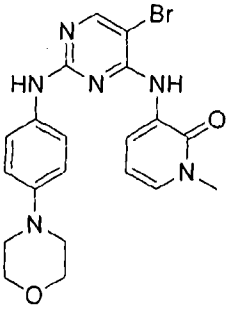
D.1.47			262	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.27 (s, 1H), 9.30 (s, 1H), 8.50 (s, 2H), 8.26 (s, 1H), 7.56 (s, 1H), 7.45 (d, *J* = 1.6 Hz, 1H), 7.32 (d, *J* = 4.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.31 (t, *J* = 7.6 Hz, 1H), 4.40 (t, *J* = 8.0 Hz, 2H), 3.63 (t, *J* = 8.0 Hz, 2H), 3.46 (s, 2H), 3.05 (s, 3H). MS m/z: 519.1 $(M+H)^+$.
D.1.48			279	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.08 (s, 1H), 9.91 (bs, 1H), 8.90 (s, 1H), 8.30 (bs, 2H), 7.52 (dd, *J* = 1.2, 6.0 Hz, 2H), 7.41 (bs, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 3H), 6.30 (d, *J* = 6.8 Hz, 1H), 5.13 - 5.10 (m, 1H), 2.86 (t, *J* = 8.0 Hz, 2H), 2.52 - 2.49 (m, 2H), 1.34 (d, *J* = 6.8 Hz, 6H). MS m/z: 469.1 $(M+H)^+$.
D.1.49			296	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.30 (s, 1H), 8.59 (s, 1H), 8.51 (bs, 1H), 8.23 (s, 1H), 7.45 (dd, *J* = 1.6 Hz, 6.8 Hz, 3H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.31 (t, *J* = 5.2 Hz, 1H), 5.17 - 5.10 (m, 1H), 3.60 - 3.56 (m, 4H), 3.11 - 3.02 (m, 4H), 3.03 (s, 1H), 1.34 (d, *J* = 6.8

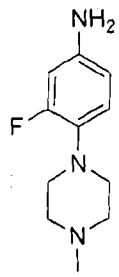
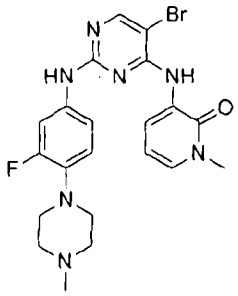
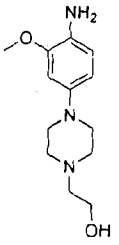
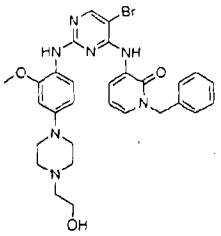
					Hz, 6H). MS m/z : 526.2 $(M+H)^+$.
D.1.50			304	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.01 (s, 1H), 9.53 (bs, 1H), 8.59 (s, 1H), 8.50 (bs, 1H), 8.28 (s, 1H), 7.47 (d, *J* = 2.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.30 (t, *J* = 8.0 Hz, 1H), 4.42 - 4.39 (m, 2H), 3.63 (t, *J* = 6.8 Hz, 2H), 2.85 (t, *J* = 8.0 Hz, 2H), 2.51 - 2.43 (m, 2H). MS m/z : 533.2 $(M+H)^+$.
D.1.51			305	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.28 (s, 1H), 8.49 (bs, 2H), 8.23 (s, 1H), 7.44 - 7.41 (m, 3H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.28 (m, 1H), 4.40 (t, *J* = 6.8 Hz, 2H), 3.66 - 3.61 (m, 4H), 3.05 (s, 3H), 2.62 (t, *J* = 2.0 Hz, 2H), 2.23 (s, 6H), 1.86 - 1.83 (m, 2H), 1.51 - 1.48 (m, 2H). MS m/z : 592.2 (M+2).
D.1.52			205	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.27 (s, 1H), 8.55 (s, 2H), 8.23 (s, 1H), 7.44 - 7.35 (m, 3H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.25 (t, *J* = 8.0 Hz, 1H), 3.82 (d, J = 7.2 Hz, 2H), 3.08 (t, *J* =

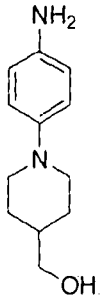
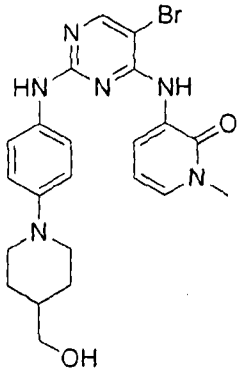
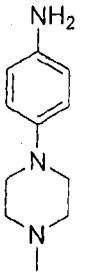
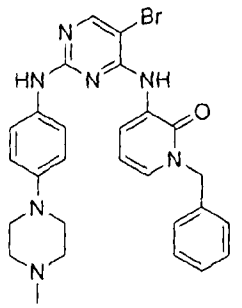
					4.0 Hz, 4H), 2.50 - 2.44 (m, 4H), 2.22 - 2.10 (m, 5H), 1.87 (s, 2H), 0.87 (d, *J* = 6.4 Hz, 6H). MS m/z: 512.2 $(M+H)^+$.
D.1.53			217	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.29 (s, 1H), 8.59 (bs, 2H), 8.23 (s, 1H), 7.46 - 7.44 (m, 3H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.31 (t, *J* = 7.6 Hz, 1H,), 5.17 - 5.10 (m, 1H), 3.73 - 3.70 (m, 2H), 2.90 (bs, 1H), 2.66 - 2.49 (m, 8H), 2.02 - 1.99 (m, 2H), 1.70 - 1.62 (m, 2H), 1.28 - 1.23 (m, 6H). MS m/z : 526.2 $(M+H)^+$.
D.1.54			222	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.28 (s, 1H), 8.51 (bs, 2H), 8.23 (s, 1H), 7.44 - 7.41 (m, 3H), 6.91 (d, *J* = 8.0 Hz, 2H,), 6.27 (t, *J* = 6.8 Hz, 1H), 4.18 (t, *J* = 8.0 Hz, 2H), 3.08 (t, *J* = 4.0 Hz, 4H), 2.84 (t, *J* = 6.8 Hz, 2H), 2.50 - 2.44 (m, 4H), 2.22 (s, 3H), 2.10 (s, 3H). MS m/z : 530.2 $(M+H)^+$.

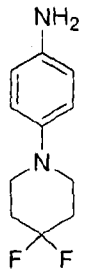
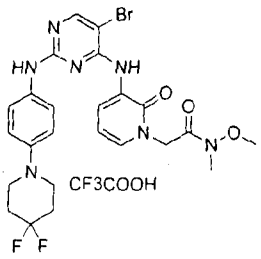
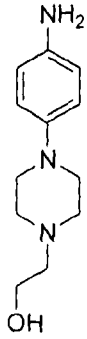
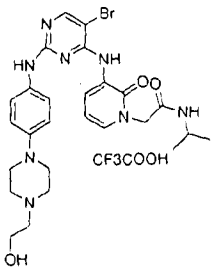
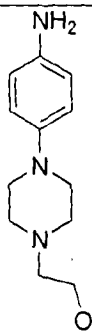
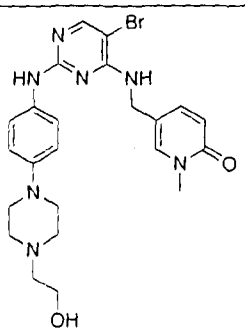
D.1.55			232	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.27 (s, 1H), 8.55 (bs, 2H), 8.23 (s, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 5.6 Hz, 1H), 6.90 (d, J = 9.2 Hz, 2H), 6.24 (t, J = 6.8 Hz, 1H), 4.42 (t, J = 5.2 Hz, 1H), 3.82 (d, J = 7.2 Hz, 2H), 3.54 (q, J = 6.0 Hz, 2H), 3.08 (t, J = 4.4 Hz, 4H), 2.56 (t, J = 4.4 Hz, 4H), 2.43 (t, J = 6.4Hz, 2H), 2.13 (m, 1H), 0.87 (d, J = 6.4 Hz, 6H). MS m/z : 542.2 $(M+H)^+$.
D.1.56			275	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.53 (s, 1H), 10.45 (s, 1H), 9.35 (s, 1H), 8.61 (s, 1H), 8.54 (bs, 1H), 8.25 (s, 1H), 7.46 - 7.44 (bs, 1H), 7.35 (s, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.27 (bs, 1H), 5.13 (m, 1H), 1.34 (d, J = 6.9 Hz, 6H). MS m/z : 456.1 $(M+H)^+$.
D.1.57			255	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.27 (s, 1H), 8.52 (bs, 2H), 8.23(s, 1H), 7.53 (dd, J_1 = 6.8 Hz, J_2 = 1.4 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.37 - 7.27 (m, 7H), 6.92 (d, J = 8.8Hz, 2H), 6.29 (t, J = 6.8 Hz,

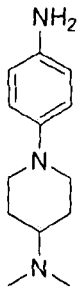
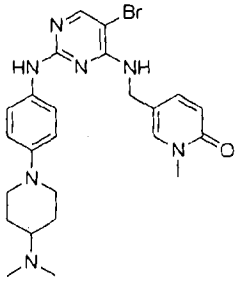
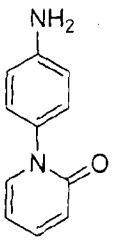
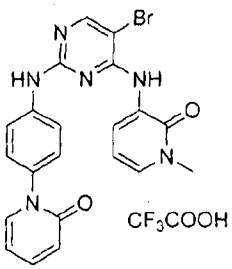
					1H), 5.22 (s, 2H), 3.65 (d, *J* = 2.2 Hz, 2H), 2.67 - 2.59 (m, 3H) , 2.29 (bs, 6H), 1.87 (d, *J* = 11.2 Hz, 2H), 1.56 - 1.48 (m, 2H). MS m/z : 576.2 (M+2).
D.1.58			258	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.27 (s, 1H), 9.38 (s, 1H), 8.54 (bs, 2H), 8.25 (s, 1H), 7.56 - 7.53 (m, 2H), 7.35 - 7.29 (m, 6H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.32 (t, *J* = 7.3 Hz, 1H), 5.22 (s, 2H), 3.46 (s, 2H). MS m/z : 505.1 (M+2).
D.1.59			243	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.28 (s, 1H), 8.60 - 8.52 (bs, 2H), 8.23 (s, 1H), 7.52 (dd, J_1 = 6.8 Hz, J_2 = 1.5 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.35 - 7.29 (m, 5H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.30 (t, *J* = 4.0 Hz, 1H), 5.22 (s, 2H), 4.41 (t, *J* = 5.1 Hz, 1H), 3.55 - 3.51 (m, 2H), 3.07 (t, *J* = 4.6 Hz, 4H), 2.67 - 2.52 (m, 4H), 2.45 - 2.41 (m, 2H). MS m/z : 576.2 $(M+H)^+$.

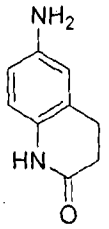
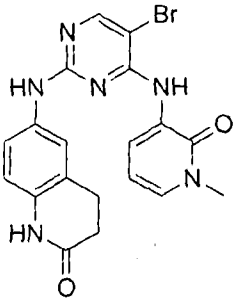
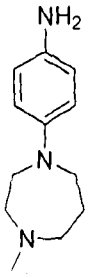
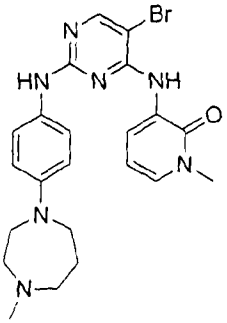
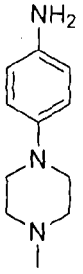
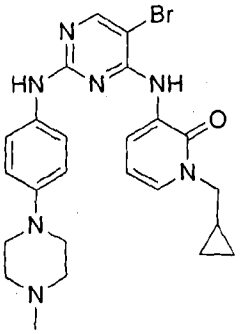
D.1.60			208	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.27 (s, 1H), 8.53 (bs, 2H), 8.23 (s, 1H), 7.51 (dd, J_1 = 6.9 Hz, J_2 = 1.5Hz, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 4H), 6.27 (t, J = 6.6 Hz, 1H), 5.13 (s, 2H), 3.72 (s, 3H), 3.08 (t, J = 4.9 Hz, 4H), 2.46 - 2.44 (m, 4H), 2.22 (s, 3H). MS m/z : 576.2 $(M+H)^+$.
D.1.61			156	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.90 (bs, 1H), 9.84 (s, 1H), 8.64 (s, 2H), 8.35 (s, 1H), 7.82 - 7.73 (m, 4H), 7.45 (d, J = 5.4 Hz, 1H), 6.35 (t, J = 7.1 Hz, 1H), 3.57 - 3.51 (m, 7H), 1.92 - 2.00 (m, 4H), 1.87 - 1.40 (m, 2H). MS m/z : 457.1 $(M+2)^+$.
D.1.62			157	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.53 (bs, 1H), 8.65 (s, 1H), 8.50 (bs, 1H), 8.27 (s, 1H), 7.50 (d, J = 7.4 Hz, 2H), 7.43 (d, J = 5.4 Hz, 1H), 7.07 (bs, 2H), 6.27 (t, J = 6.8 Hz, 1H), 3.81 - 3.80 (m, 4H), 3.20 - 3.10 (m, 4H). MS m/z : 457.1 $(M+H)^+$.

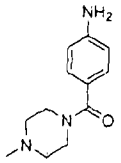
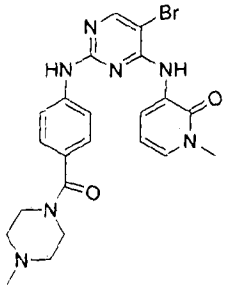
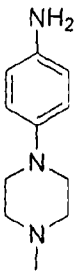
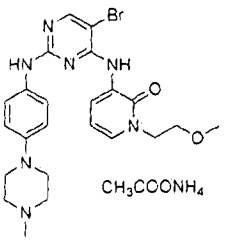
D.1.63			160	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.31 (bs, 1H), 9.67 (s, 1H), 8.62 (s, 1H), 8.56 (bs, 1H), 8.33 (s, 1H), 7.71 (d, J = 5.2 Hz, 1H), 7.44 (dd, J_1 = 6.8 Hz, J_2 = 1.4 Hz, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.08 (t, J = 9.3 Hz, 1H), 3.55 - 3.40 (m, 6H), 3.25 - 3.18 (m, 3H), 3.06 (t, J = 11.5 Hz, 2H), 2.83 (d, J = 4.9 Hz, 3H). MS m/z: 488.1 $(M+H)^+$.
D.1.64			274	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.44 (s, 1H), 8.38 (s, 2H), 8.22 (bs, 1H), 8.14 (s, 1H), 7.48 (dd, J_1 = 6.8 Hz, J_2 = 1.4 Hz, 1H), 7.36 - 7.27 (m, 6H), 6.62 (d, J = 2.4 Hz, 1H), 6.49 (dd, J_1 = 8.3 Hz, J_2 = 2.4 Hz, 1H), 6.12 (bs, 1H), 5.19 (s, 2H), 4.42 (t, J = 5.3 Hz, 1H), 3.73 (s, 3H), 3.56 - 3.52 (m, 2H), 3.15 (t, J = 4.6 Hz, 4H), 2.67 (t, J = 2.0 Hz, 2H), 2.57(t, J = 4.6 Hz, 4H), 2.44 (t, J = 6.4 Hz, 2H). MS m/z : 606.2 $(M+H)^+$.

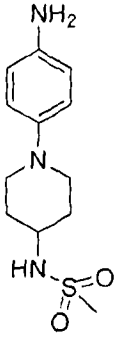
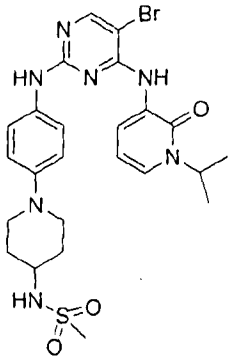
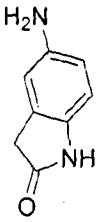
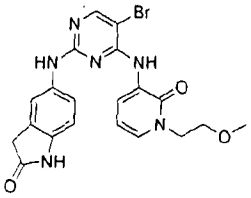
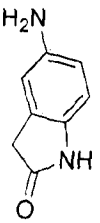
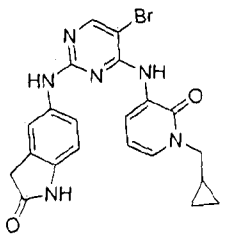
D.1.65			181	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.25 (s, 1H), 8.52 (s, 2H), 8.22 (s, 1H), 7.43 - 7.38 (m, 3H), 6.90 (d, J = 8.8 Hz, 2H), 6.24 (t, J = 4.0 Hz, 1H), 4.46 (t, J = 5.2 Hz, 1H), 3.61 (d, J = 2.2 Hz, 2H), 3.56 (s, 3H), 3.29 - 3.28 (m, 2H), 2.61 - 2.52 (m, 2H), 1.75 (d, J = 1.8 Hz, 2H), 1.3 (m, 1H), 1.27 - 1.26 (m, 2H). MS m/z : 485.1 $(M+H)^+$.
D.1.66			190	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.41 (bs, 1H), 9.45 (s,1H), 8.60 (s, 1H), 8.55 (bs, 1H), 8.26 (s, 1H), 7.55 (dd, J_1 = 6.8 Hz, J_2 = 1.4 Hz, 1H), 7.49 (d, J = 8.3 Hz, 2H), 7.37 - 7.29 (m, 5H), 6.99 (d, J = 9.3 Hz, 2H), 6.32 (t, J = 7.1Hz, 1H), 5.23 (s, 2H), 3.75 (d, J = 1.8 Hz, 2H), 3.49 (d, J = 11.7 Hz, 2H), 3.20 - 3.12 (m, 2H), 3.04 - 3.01 (m, 2H), 2.82 (d, J = 4.4 Hz, 3H). MS m/z : 546.2 $(M+H)^+$.

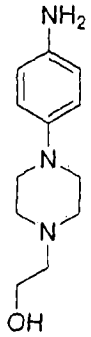
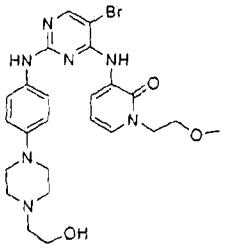
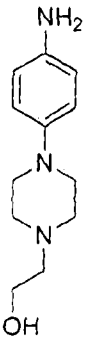
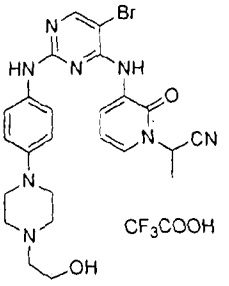
D.1.67			237	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.85 (s, 1H), 8.67 (s, 1H), 8.49 (bs, 1H), 8.32 (s, 1H), 7.55 -7.41 (m, 3H), 7.29 (bs, 2H), 6.33 -6.29 (t, J = 6.8 Hz, 1H), 3.81 (s, 3H), 3.45 - 3.38 (m, 5H), 3.155 (s, 3H), 2.33 - 2.25 (m, 5H). MS m/z: 578.2 $(M+H)^+$.
D.1.68			259	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.56 (bs,1H), 9.39 (s, 1H), 8.55 (bs, 1H), 8.48 (s,1H), 8.25 (s, 1H), 8.41 - 8.13 (d, J = 8.0 Hz,1H), 7.53 - 7.51 (d, J = 8.8 Hz, 1H), 7.33 - 7.31 (dd, J = 8 Hz, 1H), 7.00 - 6.98 (d, J = 8.8 Hz, 1H), 6.28-6.25 (m, 1H), 4.61 (s, 2H), 3.87 - 3.74 (m, 6H), 3.61 - 3.58 (d, J = 11.6 Hz, 2H), 3.26 - 3.21 (m, 4H), 3.06 - 3.00 (m, 2H), 1.09 - 1.08 (m, 6H). MS m/z : 585.5 $(M+H)^+$.
D.1.69			314	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.98 (s, 1H), 7.96 (s, 1H), 7.56 (s, 1H), 7.49 - 7.36 (m, 4H), 6.88 - 6.86 (d, J = 8.8 Hz, 1H), 6.34 - 6.32 (d, J = 9.2 Hz,1H), 4.6 (bs, 2H), 3.17 - 3.11 (m, 7H), 2.89 - 2.67

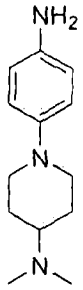
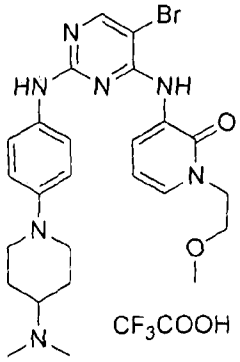
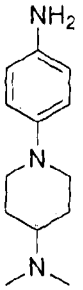
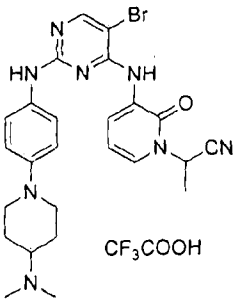
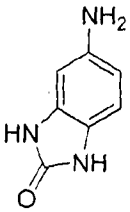
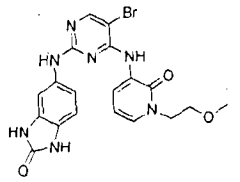
					(m, 6H). MS m/z : 514.3 $(M+H)^+$.
D.1.70			320	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.94 (s, 1H), 7.95 (s, 1H), 7.55 (s, 1H), 7.38 - 7.35 (t, *J* = 5.6 Hz, 1H), 6.87 - 6.85 (d, *J* = 8.8 Hz, 1H), 6.33 - 6.31 (d, *J* = 9.2 Hz, 1H), 4.27 - 4.25 (d, *J* = 5.6 Hz, 2H), 3.60 - 3.57 (d, *J* = 12 Hz, 2H), 3.32 - 3.28 (m, 3H), 2.19 (m, 8H), 1.83 - 1.80 (d, *J* = 11.6 Hz), 1.52 - 1.43 (m, 2H). MS m/z: 512.1 $(M+H)^+$.
D.1.71			158	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.75 (s, 1H), 8.62 (s, 1H), 8.59 (s,1H), 8.34 (s, 1H), 7.78 - 7.76 (d, *J* = 8.4 Hz, 2H), 7.66 - 7.64 (d, *J* = 5.2 Hz, 1H), 7.52 - 7.48 (m, 1H), 7.44 - 7.42 (d, *J* = 8.8 Hz, 2H), 6.49 - 6.47 (d, *J* = 9.2 Hz, 1H), 6.38 - 6.34 (t, *J* = 7.2 Hz,1H), 6.32 - 6.29 (t, *J* = 6.4 Hz, 1H), 3.57 (s, 3H). MS m/z : 465.1 $(M+H)^+$.

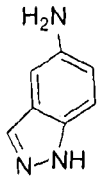
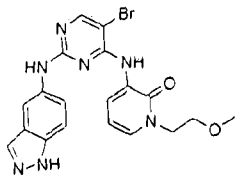
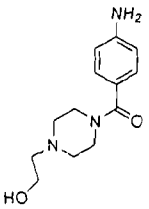
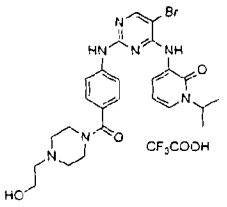
D.1.72			169	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.98 (s, 1H), 9.39 (s, 1H), 8.55 (s, 1H), 8.52 (s, 1H), 8.26 (s, 1H), 7.48 (s, 1H), 7.41 - 7.39 (d, J = 6.4 Hz, 1H), 7.31 - 7.29 (d, J = 7.6 Hz, 1H), 6.81 - 6.79 (d. J = 8.0 Hz, 1H), 6.27 - 6.23 (t, J = 6.8 Hz, 1H), 3.56 (s, 3H), 2.87 - 2.83 (t, J = 7.6 Hz, 2H), 2.50 - 2.43 (t, J = 7.6 Hz, 2H). MS m/z : 441.3 $(M+H)^+$.
D.1.73			177	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.11 (s, 1H), 8.50 (s, 1H), 8.19 (s, 1H), 7.39 - 7.38 (d, J = 6.0 Hz, 2H), 7.31 - 7.29 (m, 1H), 6.68 - 6.65 (d, J = 7.2 Hz, 2H). 6.20 (m, 1H), 3.6 (s, 3H), 3.42 - 3.55 (m, 4H), 2.67 - 2.61 (m, 4H), 2.26 (s, 3H), 1.89 (m, 2H). MS m/z :484.3 $(M+H)^+$.
D.1.74			183		^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.29 (s, 1H), 8.55 (s, 2H), 8.23 (s, 1H), 7.45 (m, 3H), 6.93 - 6.91 (d, J = 7.6 Hz, 2H), 6.27 (m, 1H), 3.87 - 3.85 (d, J = 6.0 Hz, 2H), 3.12 (m, 4H), 2.67 (m, 4H), 2.31 (s, 3H), 1.26 (m, 1H), 0.54 - 0.41 (m, 4H). MS m/z:

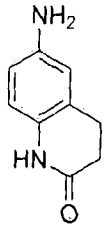
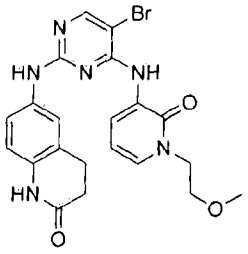
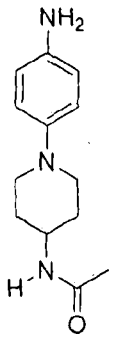
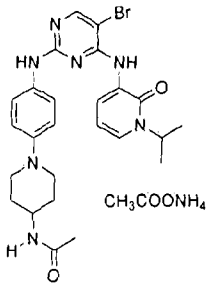
					510.2 $(M+H)^+$.
D.1.75			196	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.77 (s, 1H), 8.62 (s, 1H), 8.59 (s, 1H), 8.35 (s, 1H), 7.77 - 7.74 (d, J = 8.8 Hz, 2H), 7.45 - 7.45 (d, J = 1.6 Hz, 1H), 7.44 - 7.43 (d, J = 1.6 Hz, 2H), 6.33 - 6.30 (t, J = 6.8 Hz, 3H), 3.57 (s, 3H), 3.54 (s, 3H), 2.66 (m, 4H), 2.49 (m, 4H). MS m/z : 498.3 $(M+H)^+$.
D.1.76			209	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.28 (s, 1H), 8.51 (s, 1H), 8.23 (s, 1H), 7.44 - 7.42 (d, J = 8.4 Hz, 2H) 7.34 - 7.32 (d, J = 6.0 Hz, 1H), 6.92 - 6.90 (d, J = 8.8 Hz, 2H), 6.26 - 6.23 (t, J = 7.2 Hz, 1H), 4.18 - 4.16 (t, J = 4.8 Hz, 2H), 3.64 -3.17 (t, J = 4.8 Hz 2H), 3.24 (s, 3H), 3.09 - 3.07 (m, 4H), 2.47 - 2.45 (m, 4H), 2.24 (s, 3H), MS m/z : 514.1 $(M+H)^+$.

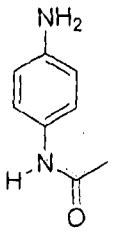
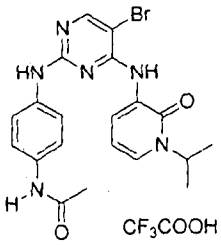
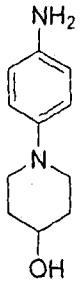
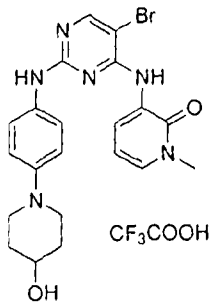
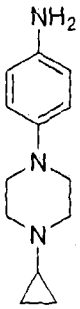
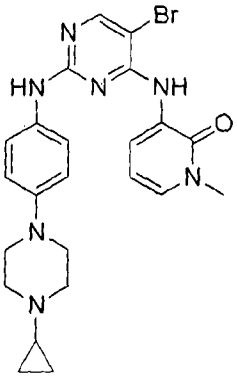
D.1.77			220	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.27 (s, 1H), 8.59 (s, 1H), 8.51 (s, 1H), 8.23 (s, 1H), 7.46 - 7.44 (m, 3H), 7.13 - 7.12 (d, *J* = 1.6 Hz, 1H), 6.93 - 6.91 (d, *J* = 7.6 Hz, 2H), 6.30 - 6.29 (t, *J* = 6.8 Hz, 1H), 5.10 - 5.15 (m, 1H), 3.59 -3.56 (d, *J* = 12.8 Hz, 2H), 2.95 (s, 3H), 2.74 - 2.67 (t, *J* = 2.8 Hz, 2H), 1.93 - 1.91 (d, *J* = 11.2 Hz, 2H), 1.58 -1.56 (m, 2H), 1.33 (s, 6H). MS m/z : 576.2 $(M+H)^+$.
D.1.78			221	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.28 (s, 1H), 9.40 (s, 1H), 8.54 (s, 2H), 8.25 (s, 1H), 7.56 (s, 1H), 7.36 - 7.34 (t, *J* = 2.0 Hz, 1H), 6.78 - 6.76 (t, *J* = 8.0 Hz, 1H), 6.28 - 6.25 (t, *J* = 6.8 Hz, 1H), 4.19 - 4.16 (t, *J* = 5.6 Hz, 2H), 3.65 - 3.62 (t, *J* = 5.6 Hz, 2H), 3.47 (s, 2H), 3.25 (s, 3H), MS m/z : 471.1 $(M+H)^+$.
D.1.79			226	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.27 (s, 1H), 9.38 (s, 1H), 8.57 (s, 1H), 8.52 (s, 1H), 8.25 (s, 1H), 7.573 (s, 1H), 7.47 - 7.46 (d, *J* = 1.6 Hz, 1H), 7.48 - 7.44 (d, *J* = 2.0 Hz, 1H), 6.77

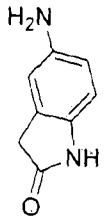
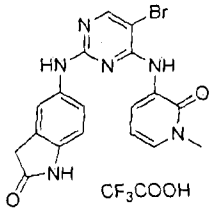
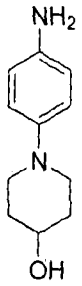
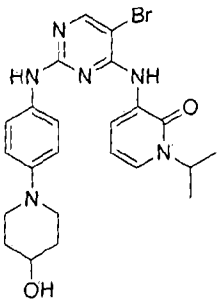
					- 6.75 (d, J = 8.4 Hz, 1H), 6.30 - 6.27 (t, J = 6.8 Hz, 1H), 3.87 - 3.86 (d, J = 6.8 Hz, 2H), 3.47 (s, 2H), 1.28 - 1.26 (m, 1H), 0.51 - 0.47 (m, 4H). MS m/z : 467.4 $(M+H)^+$.
D.1.80			233	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.29 (s, 1H), 8.52 (s, 2H), 8.23 (s, 1H), 7.46 - 7.44 (d, J = 7.2 Hz, 1H), 7.35 - 7.34 (d, J = 1.5 Hz, 2H), 6.93 - 6.91 (d, J = 8.0 Hz, 2H), 6.26 - 6.23 (t, J = 6.8 Hz, 1H), 4.18 - 4.16 (t, J = 4.8 Hz, 2H), 3.64 - 3.62 (t, J = 5.2 Hz, 2H), 3.57 (m, 3H), 3.27 (s, 3H), 3.08 - 3.01 (m, 6H), 2.57 - 2.50 (m, 4H), MS m/z: 544.2 $(M+H)^+$.
D.1.81			234	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.4 (s, 1H), 8.59 (s, 1H), 8.45 (s, 1H), 8.28 (s, 1H), 7.53 - 7.51 (m, 2H), 7.52 - 7.51 (m, 1H), 6.99 - 6.97 (d, J = 9.2 Hz, 2H), 6.45 - 6.41 (t, J = 7.6 Hz, 1H), 5.95 - 5.90 (m, 1H), 5.38 (s, 1H), 3.80 - 3.72 (m, 4H), 3.61 - 3.58 (m, 2H), 3.26 - 3.25 (m, 4H), 3.18 - 3.07 (t, J = 11.6 Hz, 2H), 1.75 - 1.74 (m,

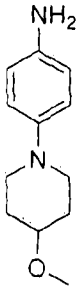
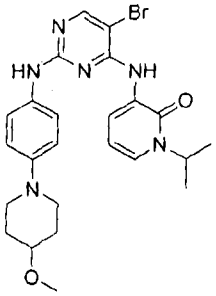
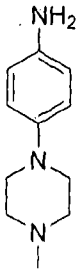
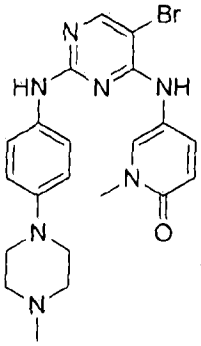
					3H), MS m/z : 539.2 $(M+H)^+$.
D.1.82			238	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.6 (s, 1H), 9.63 (s,1H), 8.63 (s, 2H), 8.52 (s, 1H), 8.29 (s, 1H), 7.59 (bs, 2H), 7.38 - 7.36 (m, 2H), 7.25 - 7.23(m, 1H), 6.30 - 6.27 (t, J = 7.2 Hz, 1H), 4.19 - 4.17 (t, J = 4.8 Hz, 2H), 3.64 - 3.61 (t, J = 5.2 Hz, 2H), 3.38 (m, 1H), 3.25 (s, 3H), 2.77 (s, 6H), 2.3 - 1.8 (m, 4H). MS m/z : 542.1 $(M+H)^+$.
D.1.83			239	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.2 (s, 1H), 9.47 (s, 1H), 8.58 (s, 1H), 8.48 (s, 1H), 8.28 (s, 1H), 7.54 - 7.52 (m, 3H), 7.07 (m, 2H), 6.45 - 6.41 (t, J = 7.2 Hz, 1H), 5.95 - 5.90 (m, 1H), 3.79 - 3.76 (d, J = 12.0 Hz, 2H), 3.31 (m, 2H), 2.77 - 2.76 (s, 6H), 2.14 - 2.12 (m, 2H), 1.83 (m, 2H), 1.75 - 1.74 (d, J = 5.6 Hz, 3H). MS m/z : 537.2 $(M+H)^+$.
D.1.84			264	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.56 (s, 1H), 10.48 (s, 1H), 9.45 (s, 1H), 8.59 (s, 1H) 8.56 (s, 1H), 7.36 - 7.35 (s, 2H), 7.10 - 7.08 (d, 1H), 6.88 -

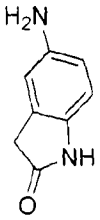
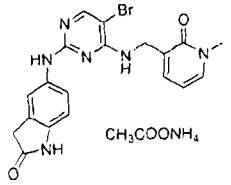
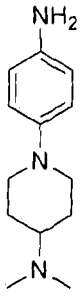
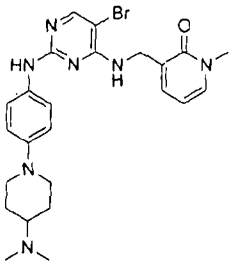
					6.85 (d, J = 8.4 Hz, 1H), 6.21 (m, 1H), 4.18 - 4.16 (t, J = 4.8 Hz, 2H), 3.64 - 3.62 (t, J = 5.6 Hz, 2H), 3.24 (s, 3H). MS m/z : 474.1 (M+2).
D.1.85			265	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.96 (s, 1H) 9.50 (s,1H), 8.54 (s, 2H), 8.29 (s, 1H), 8.07 - 8.00 (s, 2H), 7.51 - 7.49 (t, 2H), 7.34 - 7.32 (d, 1H), 6.15 (m, 1H), 4.18 - 4.15 (t, J = 5.2 Hz, 2H), 3.64 - 3.62 (t, J = 5.2 Hz, 2H), 3.24 (s, 3H), MS m/z : 456.1 $(M+H)^+$.
D.1.86			273	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.82 (s, 1H), 9.67 (s, 1H), 8.71 (s, 1H), 8.61 - 8.59 (d, J = 8.8 Hz, 1H), 8.36 (s, 1H), 7.80 - 7.78 (d, J = 8.8 Hz, 2H), 7.5 - 7.43 (m, 3H), 6.40 - 6.37 (t, J = 7.6 Hz, 1H), 5.18 - 5.11 (m, 1H), 4.20 (m, 2H), 3.76 - 3.73 (t, J = 4.8 Hz, 2H), 3.53 - 3.40 (m, 4H), 3.23 - 3.12 (m, 4H), 1.37 - 1.35 (d, J = 7.2 Hz, 6H). MS m/z: 558.2 (M+2).

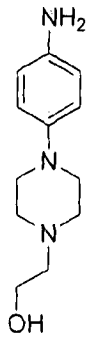
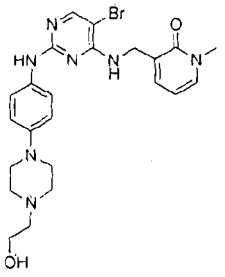
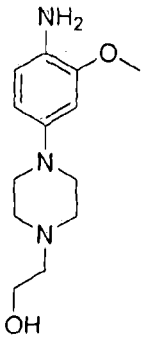
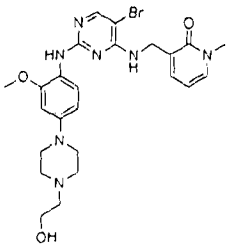
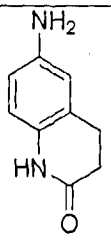
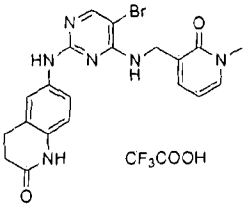
D.1.87			292	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.99 (s, 1H), 9.41 (s, 1H), 8.55 (s, 1H), 8.52 (s, 1H), 8.27 (s, 1H), 7.48 (s, 1H), 7.36 - 7.31 (m, 2H), 6.81 - 6.79 (d, *J* = 8.8 Hz, 1H), 6.27 - 6.23 (t, *J* = 7.2 Hz, 1H), 4.18 - 4.16 (t, *J* = 5.2 Hz, 2H), 3.65 - 3.62 (t, *J* = 5.6 Hz, 2H), 3.25 (s, 3H), 2.87 - 2.83 (t, *J* = 7.2 Hz, 2H), 2.45 - 2.43 (t, *J* = 1.6 Hz, 2H). MS m/z : 486.9 $(M+H)^+$.
D.1.88			294	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.26 (s, 1H), 8.58 (s, 2H), 8.23 (s, 1H), 7.83 - 7.81 (d, *J* = 7.2 Hz, 1H), 7.46 - 7.41 (m, 3H), 6.93 - 6.91 (d, *J* = 9.2 Hz, 2H), 6.30 (t, 1H), 5.15 - 5.12 (m, *J* = 6.8 Hz, 1H), 3.59 (m, 1H), 3.57 - 3.36 (m, 2H), 2.76 - 2.71 (t, *J* = 11.2 Hz, 2H), 1.91 (s, 3H), 1.82 - 1.80 (m, 2H), 1.50 - 1.47 (m, 2H), 1.35 - 1.33 (d, *J* = 6 Hz, 6H). MS m/z : 542.2 $(M+H)^+$.

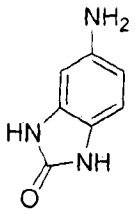
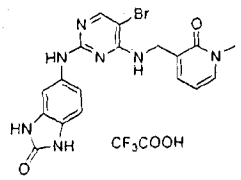
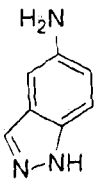
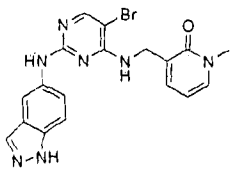
D.1.89			306	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.86 (s, 1H), 9.44 (s, 1H), 8.61 (s, 1H), 8.53 (s, 1H), 8.27 (s, 1H), 7.51 - 7.46 (m, 4H), 6.33 - 6.29 (t, *J* = 6.8 Hz, 1H), 5.15 - 5.12 (m, 1H), 2.00 (s, 3H), 1.36 - 1.34 (d. *J* = 6.8 Hz, 6H). MS m/z : 457.1 $(M+H)^+$.
D.1.90			170	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.73 (bs, 1H), 8.63 (s, 1H), 8.57 - 8.55 (d, *J* = 6.0 Hz, 1H), 8.33 (s, 1H), 7.74 (bs, 2H), 7.45 - 7.43 (m, 3H), 6.34 - 6.30 (t, *J* = 7.2 Hz, 1H), 3.85 (bs, 1H), 3.57 (bs, 5H), 3.39 - 3.37 (m, *J* = 6.8 Hz, 2H), 2.01 (bs, 2H), 1.77 (bs, 2H), MS m/z : 473.2 (M+2).
D.1.91			171	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.28 (bs, 1H), 8.53 (bs, 2H), 8.23 (s, 1H), 7.45 - 7.39 (m, *J* = 8.0 Hz, 3H), 6.92 - 6.90 (d, *J* = 8.8 Hz, 2H), 6.26 - 6.23 (t, *J* = 6.8 Hz, 1H), 3.56 (s, 3H), 3.05 (bs, 4H), 2.70 - 2.67 (m, *J* = 15.2 Hz, 3H), 1.65 (bs, 1H), 0.47 (m, 3H). MS m/z : 496.2 $(M+H)^+$.

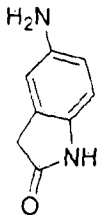
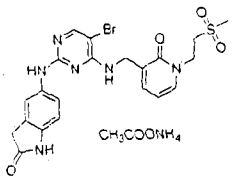
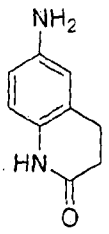
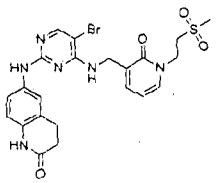
D.1.92			172	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.32 (bs, 1H), 9.61 (bs, 1H), 8.69 (s, 1H), 8.45 (bs, 1H), 8.27 (s, 1H), 7.52 (s, 1H), 7.45 - 7.43 (dd, *J* = 1.6 Hz, 1H), 7.31 - 7.29 (d, *J* = 8.0 Hz, 1H), 6.79 - 6.77 (d, *J* = 8.4 Hz, 1H), 6.27 - 6.24 (t, *J* = 7.2 Hz, 1H), 3.56 (s, 3H), 3.47 (s, 2H). MS m/z 429.1 $(M+H)^+$.
D.1.93			187	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.24 (s, 1H), 8.58 (bs, 1H), 8.49 (bs, 1H), 8.22 (s, 1H), 7.45 - 7.40 (m, *J* = 1.6 Hz, 3H), 6.92 - 6.89 (d, *J* = 9.2 Hz, 2H), 6.31 - 6.27 (t, *J* = 6.8 Hz, 1H), 5.16 - 5.10 (m, *J* = 6.8 Hz, 1H), 4.66 - 4.65 (m, *J* = 4 Hz, 1H), 3.63 - 3.57 (m, *J* = 4.4 Hz, 2H), 3.47 - 3.44 (m, *J* = 12.4 Hz, 2H), 2.81 - 2.75 (m, *J* = 2.4 Hz, 2H), 1.84 - 1.80 (m, *J* = 4.0 Hz, 2H), 1.53 - 1.44 (m, *J* = 3.2 Hz, 2H), 1.35 - 1.33 (d, *J* = 6.4 Hz, 6H). MS m/z : 499.2 $(M+H)^+$.

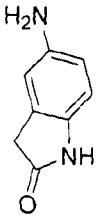
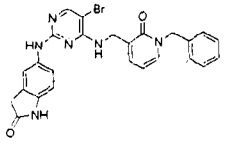
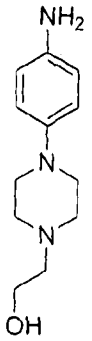
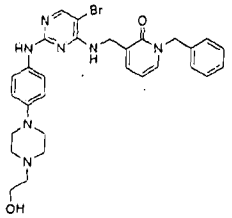
D.1.94			197	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.27 (bs, 1H), 8.58 (bs, 1H), 8.50 (bs, 1H), 8.23 (s, 1H), 7.46 - 7.42 (m, *J* = 2 Hz, 3H), 6.93 - 6.92 (d, *J* = 6.8 Hz, 2H), 6.31 - 6.28 (t, *J* = 6.8 Hz, 1H), 5.16 - 5.11 (m, *J* = 6.8 Hz, 1H), 3.44 - 3.41 (m, *J* = 6.8 Hz, 2H), 3.32 (s, 3H), 2.83 (m, 2H), 1.96 - 1.93 (m, *J* = 9.6 Hz, 2H), 1.55 - 1.53 (m, *J* = 9.2 Hz, 2H), 1.35 - 1.33 (d, *J* = 6.0 Hz, 6H). MS m/z 513.2 $(M+H)^+$.
D.1.95			125	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.03 (bs, 1H), 8.36 (s, 1H), 8.09 (s, 1H), 7.88 (bs, 1H), 7.55-7.51 (dd, *J* = 2.8 Hz, 1H), 7.38 - 7.35 (d, *J* = 8.8 Hz, 2H), 6.75 - 6.73 (d, *J* = 9.2 Hz, 2H), 6.43 - 6.40 (d, *J* = 10.0 Hz,1H), 3.40 (s, 3H), 3.02 - 3.00 (t, *J* = 4.0 Hz, 4H), 2.46 - 2.45 (t, *J* = 4.8 Hz, 4H), 2.22 (s, 3H), MS m/z : 472.2 (M+2).

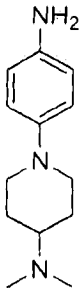
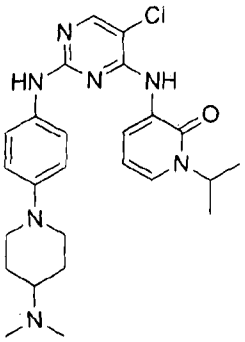
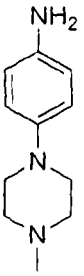
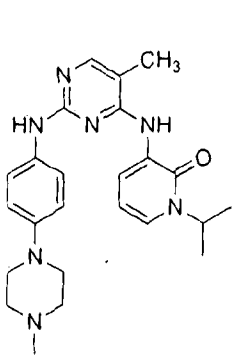
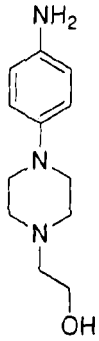
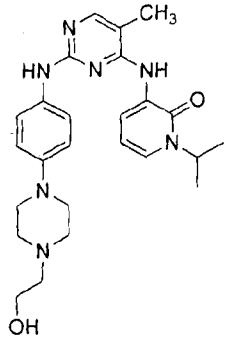
D.1.96			245	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.15 (bs, 1H), 9.04 (bs, 1H), 8.00 (s, 1H), 7.62 - 7.60 (dd, *J* = 1.2 Hz, 1H), 7.43 (bs, 1H), 7.33 - 7.30 (t, *J* = 5.6 Hz, 1H), 7.29 - 7.27 (d, *J* = 8.4 Hz, 1H), 7.10 - 7.08 (d, *J* = 6.0 Hz, 1H), 6.20 - 6.17 (t, *J* = 6.8 Hz, 1H), 4.37 - 4.36 (d, *J* = 5.6 Hz, 2H), 3.49 (s, 3H). MS m/z : 441.1 $(M+H)^+$.
D.1.97			251	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.91 (bs, 1H), 7.98 (s, 1H), 7.62 - 7.60 (dd, *J* = 2 Hz, 1H), 7.36 - 7.34 (d, *J* = 9.2 Hz, 2H), 7.25 (t, 1H), 7.11 - 7.10 (d, *J* = 5.2 Hz, 1H), 6.71 - 6.69 (d, *J* = 9.2 Hz, 2H), 6.19 - 6.16 (t, *J* = 6.8 Hz, 1H), 4.37 - 4.36 (d, *J* = 6.0 Hz, 2H), 3.54 (m, 2H), 3.49 (s, 3H), 2.57 (m, 2H), 2.19 (s, 6H), 1.83 - 1.80 (d, *J* = 12.0 Hz, 2H), 1.48 - 1.44 (m, 2H). MS m/z 512.2 $(M+H)^+$.

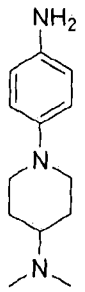
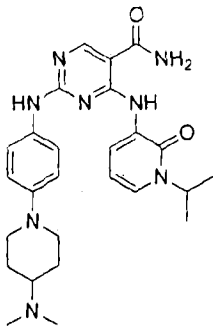
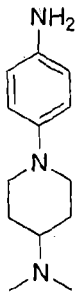
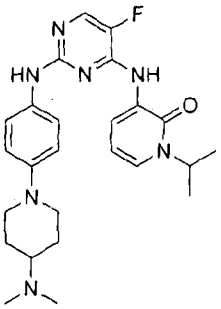
D.1.98			252	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.94 (bs, 1H), 7.99 (s, 1H), 7.62 - 7.60 (dd, *J* = 1.6 Hz, 1H), 7.39 - 7.37 (d, *J* = 8.4 Hz, 2H), 7.27 - 7.25 (t, *J* = 5.2 Hz, 1H), 7.12 - 7.10 (d, *J* = 6 Hz, 1H), 6.73 - 6.71 (d, *J* = 8.4 Hz, 2H), 6.20 - 6.16 (t, *J* = 6.8 Hz, 1H), 4.38 - 4.36 (d, *J* = 6 Hz, 2H), 3.57 (bs, 4H), 3.49 (s, 3H), 3.01 (bs, 4H). MS m/z: 516.2 (M+2).
D.1.99			267	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.96 (s, 1H), 7.63-7.59 (m, *J* = 7.2 Hz, 2H), 7.44(s, 1H), 7.26 - 7.23(t, *J* = 5.6 Hz, 1H), 7.08 - 7.07(d, *J* = 5.6 Hz, 2H), 6.58 - 6.58 (d, *J* = 1.2 Hz, 1H), 6.28-6.27 (d, *J* = 7.2 Hz, 1H), 6.18 - 6.15 (t, *J* = 6.8 Hz, 1H), 4.34 - 4.33(d, *J* = 5.2 Hz, 2H), 3.78(s, 1H), 3.57(m, 2H), 3.48 (s, 3H), 3.08 (m, 4H), 2.67-2.50 (m, 3H). MS m/z: 543.9 $(M+H)^+$.
D.1.100			268	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.02 (bs, 1H), 9.70 (bs, 1H), 8.14 (bs, 2H), 7.64 - 7.62 (dd, *J* = 1.6 Hz, 1H), 7.26 (bs, 1H), 7.16 - 7.08 (m, *J* = 2.0 Hz,

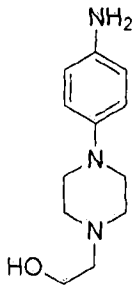
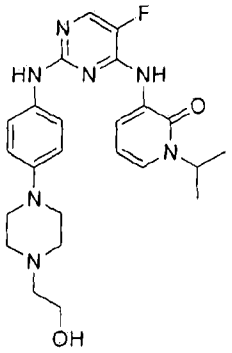
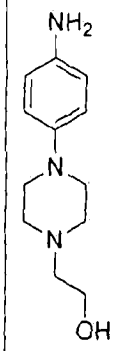
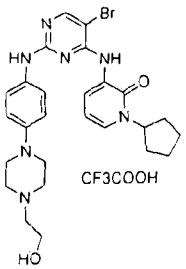
					2H), 6.67 - 6.65 (d, J = 8.4 Hz, 1H), 6.20 - 6.17 (t, J = 6.8 Hz, 1H), 4.39 - 4.38 (d, J = 5.6 Hz, 2H), 3.49 (s, 3H), 2.69 - 2.66 (m, J = 7.2 Hz, 2H), 2.40-2.32 (m, J = 8.0 Hz, 2H).; MS m/z : 455.1 $(M+H)^+$.
D.1.101			269	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.57 (bs, 1H), 10.52 (bs, 1H), 9.99 (bs, 1H), 8.41 (bs, 1H), 8.13 (s, 1H), 7.65 - 7.64 (d, J = 5.2 Hz, 1H), 7.16 - 7.15 (d, J = 5.2 Hz, 2H), 6.99 - 6.97 (d, J = 8.0 Hz, 1H), 6.79 - 6.77 (d, J = 8.4 Hz, 1H), 6.20 - 6.17 (t, J = 6.8 Hz, 1H), 4.43 - 4.425 (d, J = 5.6 Hz, 2H), 3.48 (s, 3H). MS m/z : 442.2 $(M+H)^+$.
D.1.102			270	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.80 (s, 1H), 9.18 (s, 1H), 8.07 - 8.04 (d, J = 10.0 Hz, 2H), 7.84 (s, 1H), 7.61 - 7.59 (d, J = 6.4 Hz, 1H), 7.41-7.36 (t, J = 8.8 Hz, 2H), 7.31 - 7.29 (d, J = 9.6 Hz, 1H), 7.12 - 7.10 (d, J = 6.8 Hz, 1H), 6.19 - 6.16 (t, J = 6.8 Hz, 1H), 4.44 - 4.43 (d, J = 4.8 Hz, 2H), 3.51

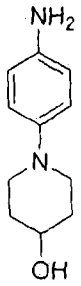
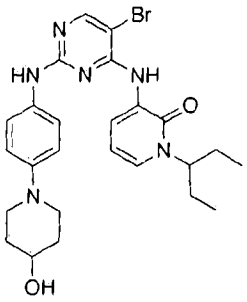
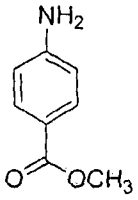
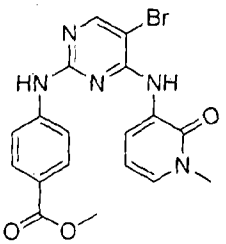
					(s, 3H). MS m/z: 428.1 (M+2).
D.1.103			271	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.03 (s, 1H), 8.01 (s, 1H), 7.64 - 7.63 (d, J = 5.6 Hz, 1H), 7.47 (s, 1H), 7.31 - 7.29 (d, J = 8.4 Hz, 2H), 7.14 - 7.13 (d, J = 6.4 Hz, 1H), 6.59 - 6.57 (d, J = 8.4 Hz, 1H), 6.25 - 6.22 (t, J = 6.8 Hz, 1H), 4.40 - 4.38 (d, J = 5.6 Hz, 2H), 4.36 - 4.32 (t, J = 6.4 Hz, 2H), 3.59 - 3.56 (t, J = 6.8 Hz, 2H), 3.04 (s, 4H). MS m/z : 535 (M+H)$^+$.
D.1.104			281	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.88 (s, 1H), 9.06 (s, 1H), 8.02 (s, 1H), 7.63 - 7.62 (d, J = 5.2 Hz, 1H), 7.40 (s, 1H), 7.32 - 7.25 (t, J = 2.6 Hz, 1H), 7.23 - 7.23 (d, J = 1.6 Hz, 1H), 7.13 - 7.11 (d, J = 6.4 Hz, 1H), 6.61 - 6.59 (d, J = 8.8 Hz, 1H), 6.25 - 6.22 (t, J = 6.8 Hz, 1H), 4.40 - 4.39 (d, J = 5.2 Hz, 2H), 4.36 - 4.32 (t, J = 6.8 Hz, 2H), 3.59 - 3.56 (t, J = 6.8 Hz, 2H), 3.05 (s, 1H), 2.69 - 2.65 (t, J = 7.2 Hz, 2H), 2.39 - 2.35 (t, J = 8.4 Hz, 2H). MS m/z :547.1 (M+H)$^+$.

D.1.105			293	2	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.16 (s, 1H), 9.04 (s, 1H), 8.01 (s, 1H), 7.72-7.70 (dd, *J* = 2.0 Hz, 1H), 7.49 (s, 1H), 7.34 - 7.25 (m, 7H), 7.12 - 7.11 (d, *J* = 5.2 Hz, 1H), 6.61 - 6.59 (d, *J* = 8.0 Hz, 1H), 6.25 - 6.22 (t, *J* = 6.8 Hz, 1H), 5.16 (s, 2H), 4.41 - 4.40 (d, *J* = 5.6 Hz, 2H), 3.34 (s, 2H). MS m/z : 517.2 $(M+H)^+$.
D.1.106			295	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.93 (bs, 1H), 7.99 (s, 1H), 7.73 - 7.71 (dd, *J* = 1.6 Hz, 1H), 7.41 - 7.39 (d, *J* = 8.8 Hz, 2H), 7.35 - 7.23 (m, 5H), 7.13 - 7.12 (d, *J* = 5.2 Hz, 1H), 6.72 - 6.70 (d, *J* = 9.2 Hz, 2H), 6.25 - 6.22 (t, *J* = 6.8 Hz, 1H), 5.17 (s, 2H), 4.41 - 4.39 (m, 3H), 3.54 - 3.50 (m, 2H), 2.99 - 2.97 (t, *J* = 4.4 Hz, 4H), 2.54 - 2.52 (t, *J* = 4.4 Hz, 4H), 2.43 - 2.40 (t, *J* = 6.4 Hz, 2H). MS m/z : 590.2 $(M+H)^+$

D.1.107			250	1	^{1}H NMR (400 MHz, CD_3OD) δ: 9.27 (s, 1H), 8.55 (s, 1H), 8.51 (bs, 1H), 8.17 (s, 1H), 7.44 (m, 3H), 6.92 (d, *J* = 9.2 Hz, 2H), 6.31 (t, *J* = 6.8 Hz, 1H), 5.14 (m, 1H), 3.66 (d, *J* = 12.8 Hz, 2H), 2.66 (m, 3H), 2.49 (bs, 6H), 1.88 (d, *J* = 11.6 Hz, 2H), 1.54 (bs, 2H), 1.34 (d, *J* = 6.8 Hz, 6H). MS m/z: 482.3 $(M+H)^+$.
D.1.108			229	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.89 (s, 1H), 8.58 (d, *J* = 6.8 Hz, 1H), 7.98 (s, 1H), 7.91 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.39 (dd, *J* = 7.6 Hz, 2 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.31 (t, *J* = 7.6 Hz, 1H), 5.14 (m, 1H), 3.06 (t, *J* = 4.8 Hz, 4H), 2.2 (s, 3H), 2.08 (s, 3H), 1.34 (d, *J* = 6.8 Hz, 6H). MS m/z : 434.1 $(M+H)^+$.
D.1.109			236	1	^{1}H NMR (400 MHz, CD_3OD) δ: 8.48 (dd, *J* = 7.2 Hz, 1.6 Hz, 1H), 7.73 (d, *J* = 0.8 Hz, 1H), 7.29 (d, 2H, *J* = 9.6 Hz), 7.21 (dd, *J* = 7.6 Hz, 2Hz, 1H), 6.89 (d, *J* = 9.6 Hz, 2H), 6.26 (t, *J* = 7.2 Hz, 1H), 5.15 (m, 1H), 3.65 (t, *J* = 5.6 Hz, 2H), 3.10 (m,

					4H), 2.65 (m, 4H), 2.53 (t, J = 5.6 Hz, 2H), 1.32 (d, J = 6.8 Hz, 6H). MS m/z: 464.3 $(M+H)^+$.
D.1.110			312	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.74 (s, 1H), 9.41 (s, 1H), 8.63 (s, 1H), 7.8 (bs, 1H), 7.43 (d, J = 8.0 Hz, 1H),δ 7.37 (d, J = 5.6 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 6.18 (t, J = 9.0 Hz, 6.8 Hz,1H), 5.16 (m, 1H), 3.67 (d, J = 6 Hz, 2H), 2.67 (t, J = 2.0 Hz, 2H), 2.22 (s, 6H), 1.9 (d, J = 6.0 Hz, 2H), 1.55 - 1.45 (m, 2H), 1.32 (d, J = 8.0 Hz, 6H). MS m/z : 491.4 $(M+H)^+$.
D.1.111			257	2	^{1}H NMR (400 MHz, DMSO-d_6) δ:9.09 (s, 1H), 8.47 (d, J = 7.4 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 8.12 (d, J = 3.0 Hz, 1H), 7.45 (dd, J_1 = 5.2, J_2 = 1.7 Hz, 3H), 6.89 (d, J =9.3 Hz, 2H), 6.33 (t, J = 7.3 Hz, 1H), 5.15 - 5.11 (m, 1H), 3.61 (d, J = 2.7 Hz, 2H), 2.70 - 2.55 (m, 2H), 2.19 (s, 6H), 2.16 - 2.15 (m, 1H), 1.82 (d, J = 1.8 Hz, 2H), 1.55 - 1.40 (m, 2H), 1.34 (d, J = 6.8 Hz, 6H).

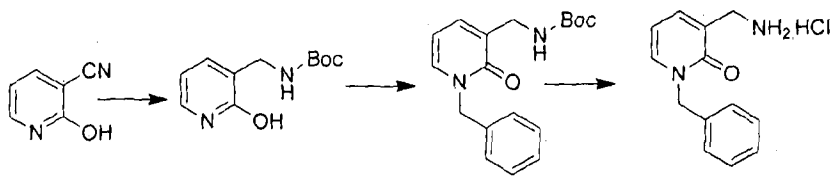
					MS m/z : 466.3 $(M+H)^+$.
D.1.112			256	2	^{1}H NMR (400 MHz, DMSO-d_6) δ:9.10 (s, 1H), 8.47 (d, J = 7.4 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 8.12 (d, J = 2.9 Hz, 1H), 7.47 - 7.44 (m, 3H), 6.88 (d, J = 8.8 Hz, 2H), 6.33 (t, J = 7.1 Hz, 1H), 5.17 - 5.10 (m, 1H), 4.42 (bs, 1H), 3.53 (q, J_1 = 5.8 Hz, J_2 = 5.9Hz, 2H), 3.07 - 3.05 (m, 4H), 2.56 - 2.52 (m, 4H), 2.45 - 2.42 (m, 2H), 1.34 (d, J = 6.8 Hz, 6H). MS m/z : 468.3 $(M+H)^+$.
D.1.113			216	1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.60 (bs, 1H), 9.39 (s, 1H), 8.63 (s, 1H), 8.53 (bs ,1H), 8.25 (s, 1H),7.51 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 4.4 Hz, 1H), 7.00 (d, J = 0.8 Hz, 1H), 6.31 (t, J = 7.6 Hz, 1H), 5.18-5.12 (m, 1H), 3.79-3.73 (m, 4H), 3.61-3.58 (m, 2H), 3.02-3.27 (m, 6H), 1.84-1.66 (m, 6H), 2.04 (m, 2H). MS m/z : 554.2 $(M+H)^+$.

D.1.114			315	1	^{1}HNMR (400MHz, DMSO): δ 9.272 (s,1H), 8.596 (s,1H), 8.527 (bs,1H), 8.227(s,1H), 7.428-7.336(m,3H), 6.930-6.908 (d, *J*=8.8, 2H), 6.291(m,1H), 4.806(bs,1H), 4.695-4.685(d, *J*=4,1H), 3.624-3.375(m,3H),2.811-2.759 (m,2H), 1.838-1.708 (m,6H), 1.531 -1.461 (m,2H), 0.715 (m,6H). MS m/z : 527.2 $(M+H)^+$.
D.1.115				1	^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.55 (s, 1H), 8.65 (s, 1H), 8.64 - 8.62 (m, 1H), 8.39 (s, 1H), 7.89 - 7.81 (m, 4H) 7.47-7.45 (m, 1H), 6.35 - 6.31 (m, 1H), 3.58 (s, 3H).

Preparation # 1 : 3-(aminomethyl)-1-benzylpyridin-2(1H)-one

3-(aminomethyl)-1-benzylpyridin-2(1H)-one synthesized using synthetic **Scheme II** starting from 2-oxo-1,2-dihydropyridine-3-carbonitrile

Scheme II

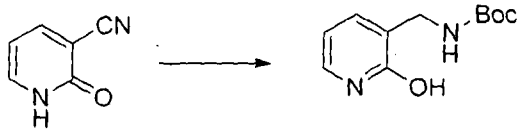


General procedure E: Formation of Boc protected amine from nitrile derivatives

To a mixture of appropriate nitrile derivative (1 equiv), nickel chloride hexahydate (0.1 to 0.5 equiv, preferably 0.1 equiv) and di-*tert*-butyldicarbonate (2-5equiv, preferably 2 equiv)in a protic solvent (such as MeOH, EtOH, preferably MeOH) is added sodium borohydride (3-5 equiv, preferably 4equiv) at 0°C. The reaction mixture is slowly warmed to RT and stirred for about 2 - 12 h (preferably 2 h). The reaction mixture is quenched with water filtered through a Celite® pad and washed with EtOAc. The organic layer is successively washed with water, brine and dried over sodium sulphate. The crude mass obtained upon concentration of the organic layer is purified to obtain the required material.

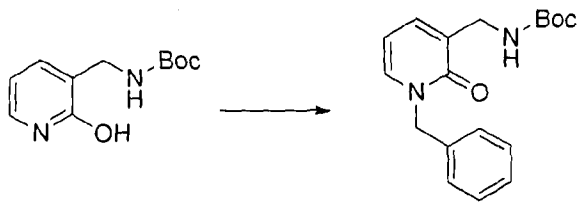
Illustration of General procedure E:

Step #.1 : tert-butyl ((2-hydroxypyridin-3-yl)methyl)carbamate



To a mixture of 2-oxo-1,2-dihydropyridine-3-carbonitrile (7.5 gm.,62.4mmol,Combi-Blocks), nickel chloride hexahydrate (1.48 gm.,6.24mmol, Spectrochem) and di-*tert*-butyldicarbonate (27.25 gm.,124.8mmol)in MeOH was added sodium borohydride (14.17 gm., 374mmol, Spectrochem) at 0°C. The reaction mixture was slowly warmed to RT, stirred for 4 hr and quenched with water. Further it was filtered through a Celite® pad and washed with EtOAc. The organic layer was successively washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure. Obtained crude material was purified by column chromatography eluting with 5-15% EtOAc in Hexane. The relevant fractions containing the product were collected and evaporated to dryness to afford *tert-butyl ((2-hydroxypyridin-3-yl)methyl)carbamate* . ^{1}H NMR (400 MHz, DMSO-d_6) : δ 11.582 (bs, 1H), 7.273-7.268 (d, *J*=2Hz,1H), 7.257-7.252(d, *J*=2Hz, 1H), 7.250-7.189 (m,1H), 6.193-6.160 (m,1H), 3.891-3.875 (d, *J*=6.4Hz,2H), 1.393(s,9H), MS m/z : 225.1 (M+H+).

Step#2: tert-butyl ((1-benzyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamate



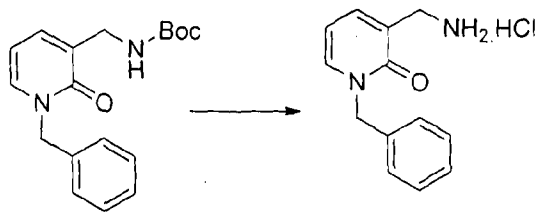
To a solution of tert-butyl ((2-hydroxypyridin-3-yl)methyl)carbamate (2.5 gm., 0.011mol, preparation #1, step-1) in DMF(15 ml), added K_2CO_3 (4.62 gm, 33.4mmol, Rankem) followed by benzyl bromide (1.9 gm., 0.011mol, Spectrochem) at 0°C. The reaction was stirred at RT for 12 hrs., diluted with Ice cold water (50ml) and the product was extracted with ethyl acetate(3x50ml). The combined organic layers were washed with brine, dried over sodium sulphate and concentrated under reduced pressure. Crude material was purified by column chromatography eluting with 5-10% EtOAc in Hexane. The relevant fractions containing the product was collected and evaporated to dryness to afford tert-*butyl ((1-benzyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamate* .2.6 g (74%) ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.222-7.00 (dd, *J*=1.6Hz, 1H), 7.352-7.127(m, 7H), 6.284-6.251(m,1H),5.166 (s,2H), 3.923-3.903 (d, *J*=8Hz, 2H) 1.39 (s,9H), MS m/z : 315.2 $(M+H)^+$.

General procedure F: Acidic cleavage of Boc protected amine

To flask containing appropriate Boc protected amine (1 equvi) in 4N Dioxane HCl and stirred at room temperature for about (2-12hr, preferably 3h). Excess of solvent was removed under reduced pressure and obtained crude material is optionally purified by precipitation, crystallization or trituration from an appropriate solvent or solvents or by column chromatography, preparative HPLC to get the target compound.

Illustration of General #F

Step #3 : 3-(aminomethyl)-1-benzylpyridin-2(1H)-one

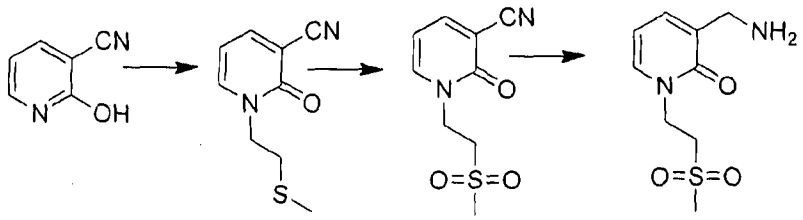


Tert-butyl ((1-benzyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamate (2.6 g, 0.00828 mol, Preparation #1,step-2) was dissolved in 4N 1,4-dioxane/HCl (20 mL) and stirred at RT for about 12 h. Excess solvent was removed *in vaccuo* and the crude material was triturated with ether (2 x 100 mL) to afford 3-(aminomethyl)-1-benzylpyridin-2(1H)-one 2.0 g (90 %) as off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.187 (bs,1H), 7.937-7.915 (dd, *J*=2Hz,1H), 7.648-7.628 (dd, *J*=2Hz,1H), 7.350-7.289 (m,5H), 6.382-6.348 (t, *J*=6.8Hz, 1H), 5.171 (s,2H), 3.858-3.815 (m,2H), MS m/z : 428.3$(M+H)^+$.

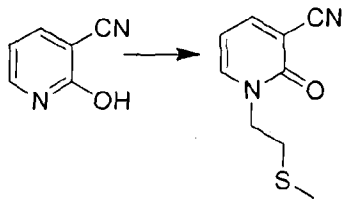
Preparation #2 : 3-(aminomethyl)-1-(2-(methylsulfonyl)ethyl)pyridin-2(1H)-one

3-(aminomethyl)-1-(2-(methylsulfonyl)ethyl)pyridin-2(1H)-one was synthesized using **Scheme III** starting from 2-oxo-1,2-dihydropyridine-3-carbonitrile

Scheme III



Step #1: Preparation of 1-(2-(methylthio)ethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile



To a cold solution of 2-oxo-1,2-dihydropyridine-3-carbonitrile (4 gm., 33.3mmol, combi blocks) in DMF (25ml) added K_2CO_3 (11.5 gm., 83.2mmol, Rankem) followed by 2-Chloroethyl methyl sulfide (4.05 gm., 36.6mmol, oakwood). The reaction mixture was slowly warmed to room temperature and stirred at room temperature for about 12hrs. Diluted the reaction mixture with ice cold water (75ml) and the product was extracted with ethyl acetate (2x50ml). The combined organic layers were successively washed with water (2x20ml), brine(2x20ml), dried over sodium sulphate and evaporated to dryness. Crude material was purified by column

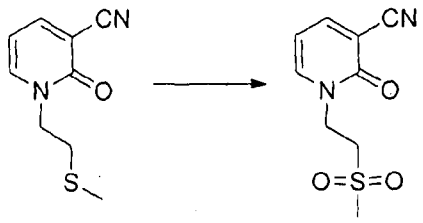
chromatography eluting with 10-30% EtOAc in Hexane. The relevant fractions containing the product were collected and evaporated to dryness to afforded *1-(2-(methylthio)ethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* 3.2g (49.53%) . ^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.172-8.149 (dd, *J*=1.6 Hz,1H), 8.127-8.105 (dd, *J*=2 Hz,1H), 6.448-6.414 (t, *J*=6.8 Hz,1H), 4.158-4.124 (t, *J*=6.8 Hz,2H), 2.828-2.793 (t, *J*=6.8 Hz,2H), 2.094 (s.3H), MS m/z : 195.1 $(M+H)^+$.

General procedure G: Preparation of sulfones

To a flask containing an appropriate sulphide derivative in an protic solvent (such as EtOH, MeOH, water preferably mixture of MeOH, water) is added an appropriate oxidizing agent (such as mCPBA, Oxone, H_2O_2 preferably oxone 2 to 5 equiv preferably 2.5 equiv) portion wise. The reaction mixture is allowed to stirred at room temperature for about 0.5 to 1hr (preferably 0.5hrs). Excess solvent is removed under reduced pressure and the crude material is basified with sat.$NaHCO_3$ solution. The product extracted with ethyl acetate. The combined organic layers dried over sodium sulphate and evaporate to dryness. The crude material is optionally purified by precipitation, crystallization or trituration from an appropriate solvent or solvents or by column chromatography to get the target compound.

Illustration of General procedure G:

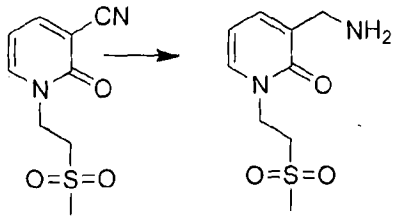
Step 2: 1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile



To a solution of 1-(2-(methylthio)ethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile(0.25 g , 1.28mmol preparation #2, step 1) in MeOH-H_2O (15ml, 2:1) was added oxone (0.988 gm., 3.21mmol,spectrochem) portion wise. Reaction Mixture was stirred at room temperature for 0.5hrs. Excess solvent was evaporated under reduced pressure. The crude material was basified with sat.$NaHCO_3$ solution (10ml). Product was extracted with ethylacetate (2x50ml) and combined organic layers were concentrated under pressure. The crude material was triturated with diethyl ether (20ml) afforded a 1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-

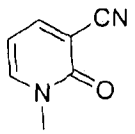
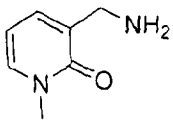
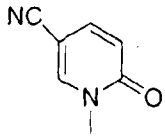
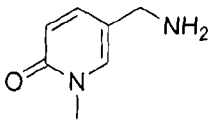
carbonitrile 0.2g (68.72%) as off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.190 -8.166 (dd, *J*=2 Hz,1H), 8.137-8.155 (dd, *J*=2 Hz,1H), 6.461-6.425 (t, *J*=7.2 Hz,1H), 4.386-4.353 (t, *J*=6.8 Hz,2H), 3.617-3.583 (t, *J*=6.8 Hz,2H), 3.066 (s,3H), MS m/z : 227.1 $(M+H)^+$.

Step #3: Preparation of 3-(aminomethyl)-1-(2-(methylsulfonyl)ethyl)pyridin-2(1H)-one



To a stirred solution of 1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (1 gm.,4.41mmol, preparation #2, step 2) in MeOH (50ml) was added Raney® nickel (0.2 gm., Rankem), ammonium hydroxide solution (10ml). The reaction mixture was hydrogenated at 40 psi for 12hrs. The reaction mixture was filtered through a Celite® pad and washed with MeOH (50ml). The filtrate was concentrated under reduced pressure. The crude material was carried out for further step without purification. MS m/z : 231.1 $(M+H)^+$.

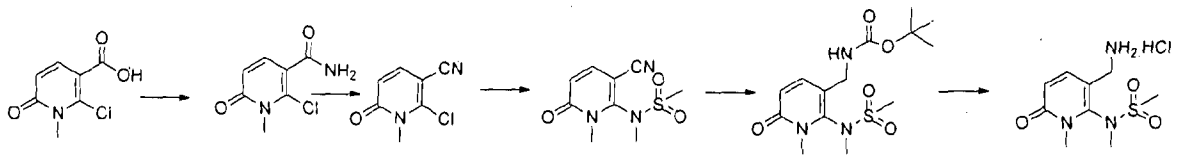
Below compounds are made from the above preparation#2, Step#3:

S. No	Starting material	Product	Analytical data
1			^{1}H NMR (400 MHz, DMSO-d_6): δ 7.575-7.554 (dd, *J*=1.6, 1H), 7.384-7.368 (d, *J*=6.4, 1H), 6.205-6.188 (t, *J*=3.2, 1H), 3.535 (s, 2H), 3.447 (s, 3H), MS m/z : 139.2 $(M+H)^+$.
2.			^{1}H NMR (400 MHz, DMSO-d_6): δ 7.535(s, 1H), 7.441-7.411 (dd, *J*=9.6, Hz ,1H), 6.357-6.333 (d, *J*=9.6 Hz,1H), 3.440 (s,2H), 2.00 (bs,2H)

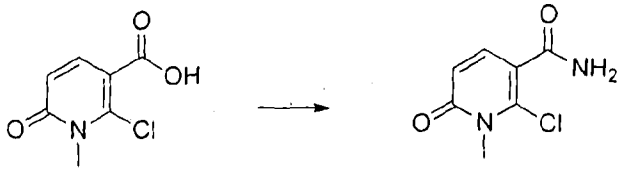
Preparation#3: N-(3-(aminomethyl)-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-N-methyl methanesulfonamide hydrochloride

N-(3-(aminomethyl)-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-N-methylmethanesulfonamide hydrochloride was synthesized using Scheme IV starting from 2-chloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid

Scheme-IV



Step #1: 2-chloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide



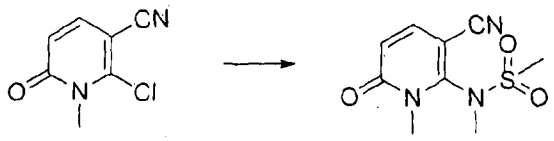
Oxalyl chloride (5.7g, 0.045mol, Spectrochem) was added drop wise to a cold solution of 2-chloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (2.8g, 0.015mol, US20080045511) in DCM (50ml) and DMF (0.1 ml). The reaction mixture was slowly warmed to room temperature and stirred at room temperature for about 2h. The reaction mixture was concentrated under vacuum. The crude material was dissolved in DCM (50ml) and added to cold solution of ammonium solution (50ml). The reaction mixture was stirred for 10-15min. The biphasic layer was separated and aqueous was extracted with DCM (2x50ml). The combined organic layers were dried over sodium sulphate and evaporated to dryness to afford *2-chloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide* 2g (72%) as brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.78(bs,1H), 7.52 (d,2H, *J*=9.2Hz), 6.42(d,1H, *J*=9.6Hz),3.59(s,3H). MS m/z : 187 $(M+H)^+$.

Step #2: 2-chloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile



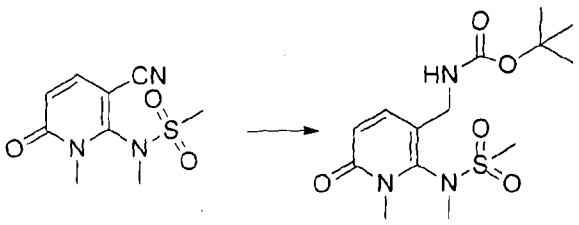
To a solution of 2-chloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (4.5g, 0.024mol, preparation #3,Step #1) in THF (50ml) was added $POCl_3$ (14.8g, 0.097mol, Spectrochem) and pyridine (8ml, 0.097mol, Spectrochem). The reaction mixture was heated to reflux for about 2hrs. Cooled the reaction mixture to room temperature and poured into ice cold water (50ml) and the product extracted with ethyl acetate (2x50ml). The combined organic layer were dried over sodium sulphate and concentrated under reduced pressure to afford *2-chloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile* 3g (75%) as brick red solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75(d, *J*=9.6Hz,1H), 6.52(d, *J*=10.0Hz,1H), 3.59(s,3H). MS m/z: 169.1 $(M+H)^+$.

Step#3: N-(3-cyano-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-N-methyl methanesulfonamide



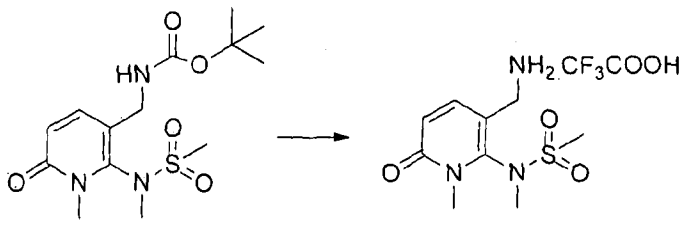
To a solution of 2-chloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (1.5g, 0.089 mol, preparation#3,step 2) in acetonitrile (20ml) was added CeCO3 (3.47g, 0.011mol) and N-methylmethanesulfonamide (0.92g, 0.089mol, Aldrich). The reaction was heated to reflux temperature for period of 8h. The reaction mixture was cooled to room temperature, filtered and washed with acetonitrile. The crude residue obtained upon concentration was purified by silica gel (60-120 mesh) column chromatography eluting with 40% ethyl acetate in hexane. The relevant fractions containing the product were concentrated and evaporated to dryness to afford *N-(3-cyano-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-N-methylmethanesulfonamide* 1.35g (62%) as brown liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.77(d,1H, *J*=9.6Hz), 6.62(d,1H, *J*=9.2Hz), 3.43(s,3H), 3.40(s, 3H), 2.86(s, 3H). MS m/z : 240(M-H).

Step#4: tert-butyl ((1-methyl-2-(N-methylmethylsulfonamido)-6-oxo-1,6-dihydropyridin-3-yl)methyl)carbamate:



Sodium borohydride (0.99g, 0.02 mol) was added slowly to a cold solution of *N-(3-cyano-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-N-methyl methane sulfonamide* (1.3 g, 0.005 mol, preparation#3, Step 3) in methanol (20 mL) containing $NiCl_2.6H20$ (128 mg, 0.5 mmol) and ditert. butyl pyrocarbonate (1.5 ml). The reaction mixture was slowly warmed to room temperature and stirred at room temperature for 8hrs. The reaction was quenched with saturated ammonium chloride solution (15 ml) and the product was extracted with ethyl acetate (50 ml). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to afford *tert-butyl ((1-methyl-2-(N-methylmethylsulfonamido)-6-oxo-1,6-dihydropyridin-3-yl)methyl)carbamate* (1.0 g, 54%) as brown liquid. ^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.51 (bs, 1H), 7.36 (d, *J*=9.6Hz,1H), 6.47(d, *J*=10Hz,1H), 3.38(s,3H), 3.20(s,3H), 3.15(s,3H), 1.41(s,9H). MS m/z: 346 $(M+H)^+$.

Step#5: N-(3-(aminomethyl)-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-N-methylmethane sulfonamide:

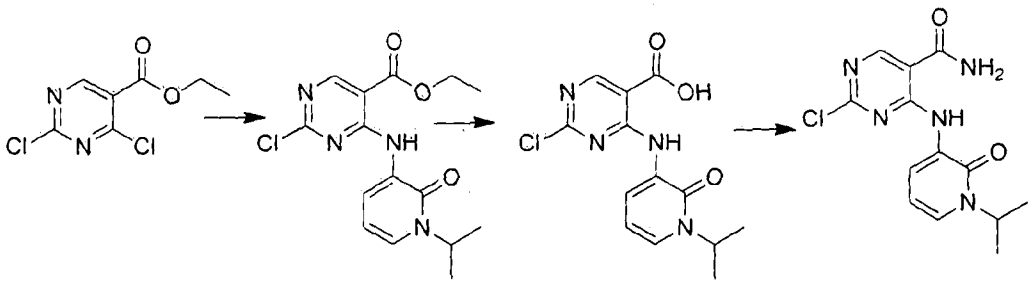


To a solution of *tert*-butyl ((1-methyl-2-(N-methylmethylsulfonamido)-6-oxo-1,6-dihydropyridin-3-yl)methyl)carbamate (1.0 g, 0.002 mol, preparation #3,Step #4) in DCM (20 ml) was added TFA(2 ml) and stirred overnight. The reaction mixture was concentrated under vacuum to afford *N-(3-(aminomethyl)-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-N-methylmethane sulfonamide* (0.6 g, 84.5%) as off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.13(bs,2H), 7.62 (d, *J*=10Hz,1H), 6.64 (d, *J*=9.2Hz1H), 3.87(bs,2H),3.41(s,3H), 3.37(s,3H), 3.21(s,3H), MS m/z : 244.1$(M+H)^+$.

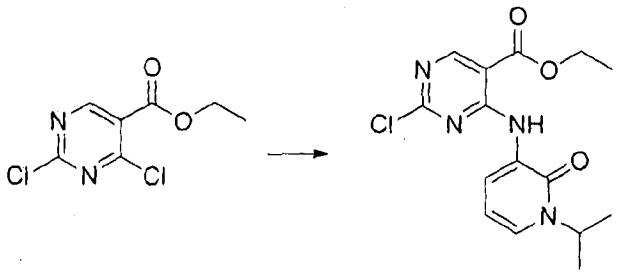
Preparation#4 : 2-chloro-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidine-5-carboxamide

2-chloro-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidine-5-carboxamide was synthesized using Scheme V starting from ethyl 2,4-dichloropyrimidine-5-carboxylate

Scheme V

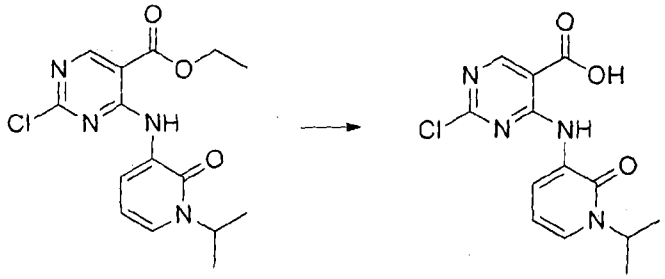


Step #1: ethyl 2-chloro-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidine-5-carboxylate



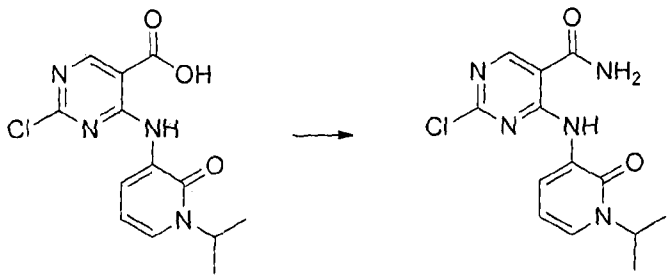
A 50 mL sealed tube was charged with ethyl 2,4-dichloropyrimidine-5-carboxylate (1.5g, 0.006mol, US20110251194), DIPEA (2.3ml, 0.013mol Spectrochem), 3-amino-1-isopropylpyridin-2(1H)-one (1g, 0.006mol, B.1.3) and IPA (10ml). The reaction mixture was heated to 120°C for about 12h. The reaction mixture was cooled to 0°C, obtained solids was filtered, washed with cold IPA (2ml) and dried under vacuum. The crude material was washed with hexane and dried under vacuum to afford *ethyl 2-chloro-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidine-5-carboxylate* 1.2g, (54%) as yellowish solids. ^{1}H NMR (400 MHz $CDCl_3$) : δ 400 MHz: 11.5(s, 1H), 8.85(s, 1H), 8.59(dd, *J*=2Hz, 2Hz, 1H), 7.12(m,1H), 6.38(t, *J*=7.2Hz,1H), 5.36(m,1H), 4.49 (d, *J*=6.8Hz, 2H) 1.44(m, 9H), MS m/z : 336 (M+H)+.

Step #2 : 2-chloro-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidine-5-carboxylic acid:



To a solution of ethyl 2-chloro-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidine-5-carboxylate (1g, 0.003mol, preparation #4,Step-I) in a mixture of methanol (10 mL) and THF (50 mL) was added lithium hydroxide (0.15g, 0.003mol, Spectrochem) dissolved in water (15 mL). The reaction mixture was stirred at RT for about 5 h. The reaction mixture was concentrated under vacuum and re-dissolved in water (10 mL). Acidified the reaction mixture to pH 2 with 2N HCl and the solids obtained were collected by filtration to afford *2-chloro-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidine-5-carboxylic acid* (0.8g,87%) as off white solids. ^{1}H NMR (400MHz, DMSO-d_6) : δ 14.1(bs, 1H), 11.35(s, 1H) 8.8(s, 1H), 8.45(dd, *J*=2Hz,1H), 7.55(dd, *J*=2Hz, 1H), 6.46(t, *J*= 3.2Hz,1H), 5.16(m, 1H), 1.35(d, *J*=6.8Hz, 6H), MS m/z : 308 (M+H+).

Step #3: 2-chloro-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidine-5-carboxamide

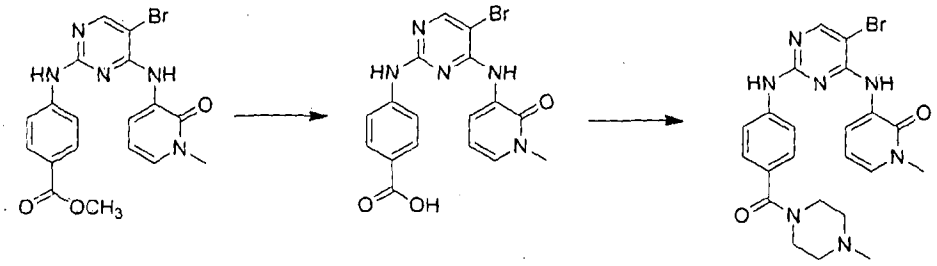


Oxalyl chloride (0.66g, 0.005mol,, Spectrochem) was added drop wise to a cold solution of 2-chloro-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidine-5-carboxylic acid (0.8g, 0.002mol, preparation #4,Step-2) in DCM (10ml) and DMF (0.1 ml). The reaction mixture was

slowly warmed to room temperature and stirred at room temperature for about 2h. The reaction mixture was concentrated under vacuum. The crude material was dissolved in DCM (50ml) and added to cold solution of ammonium solution (15ml). The reaction mixture was stirred for 15-30min. The biphasic layer was separated and aqueous was extracted with DCM (2x50ml). The combined organic layers were dried over sodium sulphate and evaporated to dryness to afford *2-chloro-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidine-5-carboxamide* (0.4g, 50%) as off white solid. ^{1}H NMR (400MHz, DMSO-d_6) : δ 11.8(s, 1H), 8.77(s,1H), 8.42(t, *J*=2Hz, 1H), 8.33(S, 1H) 7.86(S, 1H), 7.51(dd, *J*=2Hz, 1H), 6.43(t, *J*=7.2Hz,1H), 5.14(m, 1H), 1.34(d, *J*=6.8Hz, 6H), MS m/z : 308 $(M+H)^+$.

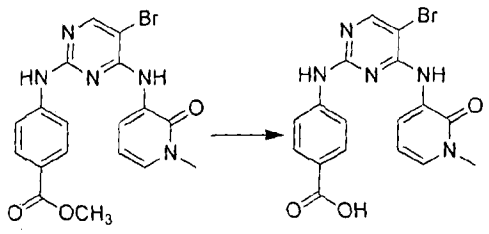
Preparation #5: 3-((5-bromo-2-((4-(4-methylpiperazine-1-carbonyl)phenyl)amino) pyrimidin-4-yl)amino)-1-methylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-methylpiperazine-1-carbonyl)phenyl)amino)pyrimidin-4-yl)amino)-1-methylpyridin-2(1H)-one was synthesized using Scheme **V** starting from 4-((5-bromo-4-((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino) pyrimidin-2-yl)amino)benzoic acid



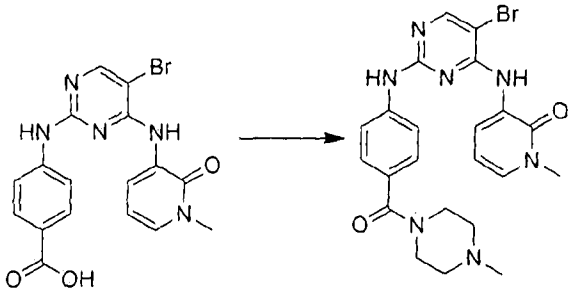
Scheme-V

Step #1: 4-((5-bromo-4-((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino) pyrimidin-2-yl)amino)benzoic acid:



To a solution of Methyl-4-((5-bromo-4-((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)benzoate (1 g, 2.32 mmol, D.1.115) in a mixture of methanol (5 mL) and THF (10 mL) was added a solution of potassium hydroxide (0.2 g, 3.4 mmol, Spectrochem) in water (2 mL). The reaction mixture was stirred at room temperature for about 12h. The reaction mixture was concentrated under vacuum and dissolved in water (10 mL). Further it was acidified to pH 2 with 2N HCl and the solids obtained were collected by filtration to afford *4-((5-bromo-4-((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)benzoic acid* 0.2g (21 %) as white solids. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.55 (s, 1H), 8.65 (s, 1H), 8.64 - 8.62 (m, 1H), 8.39 (s, 1H), 7.89 - 7.81 (m, 4H) 7.47-7.45 (m, 1H), 6.35 - 6.31 (m, 1H), 3.58 (s, 3H).

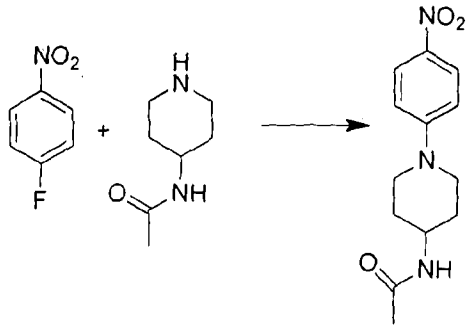
Step #2: 3-((5-bromo-2-((4-(4-methylpiperazine-1-carbonyl)phenyl)amino) pyrimidin-4-yl) amino)-1-methylpyridin-2(1H)-one:



To a solution of 4-((5-bromo-4-((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino) pyrimidin-2-yl)amino)benzoic acid (200 mg, 0.48 mmol Preparation #5,Step#1) in THF (6 mL) was added N-methylpiperazine (72 mg, 0.72 mmol, Spectrochem), *N*-ethyl-*N*-isopropylpropan-2-amine (167 mg, 0.96 mmol, Spectrochem) and followed by HATU (286 mg, 0.752 mmol, Molekule). The reaction mixture was stirred at room temperature for 16h and was quenched with ice cold water (10 mL). The product was extracted with DCM (3 x 20 mL). The combined organic layers were dried over sodium sulphate and evaporated to dryness under vacuum. The residue obtained was purified by silica gel column chromatography by eluting with 40-60% EtOAc in hexane. The relevant fractions containing the product were combined and evaporated under reduced pressure to afford 3-((5-bromo-2-((4-(4-methylpiperazine-1-carbonyl) phenyl) amino)pyrimidin-4-yl)amino)-1-methylpyridin-2(1H)-one 70 mg (29%) as pale yellow solids. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.77(s, 1H), 8.62 (s, 1H), 8.56 (s, 1H), 8.35 (s, 1H), 7.77 - 7.75 (d, J = 8.8 Hz, 2H),

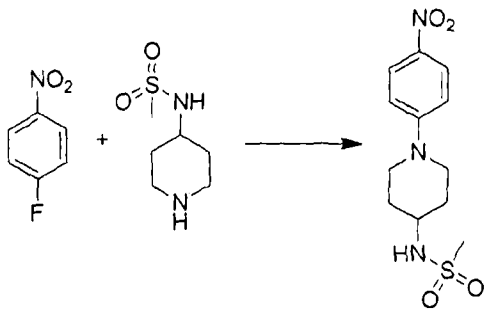
7.46 - 7.45 (d, J = 1.6 Hz, 1H), 7.44 - 7.43 (d, J = 1.6 Hz, 2H), 6.33 - 6.30 (t, J = 6.8 Hz, 3H), 3.57 (s, 3H), 3.54 (s, 3H), 2.67 (m, 4H), 2.50 (m, 4H). MS m/z : 500.1 (M+2).

Preparation #6: N-(1-(4-nitrophenyl)piperidin-4-yl)acetamide:



To a solution of N-(piperidin-4-yl)acetamide (1g, 7.04 mmol, Alfa-aesar) in DMF was added K_2CO_3 (1.6 g, 14.18 mmol, Rankem) followed by 1-fluoro-4-nitrobenzene (1 g, 7.04 mmol, AVRA) at 0 °C. The reaction mixture was heated at 80 °C for 12 h. The reaction mixture was cooled to room temperature and poured into ice cold water and the product was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulphate and evaporated to dryness to afford the target compound (67.5%).^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 - 8.06 (d, J = 2.4 Hz, 2H), 7.04 - 7.01 (d, J = 9.2 Hz, 2H), 3.99 - 3.85 (m, 3H), 3.15 (s, 3H), 1.84 (s, 4H), 1.38 (m, 2H).

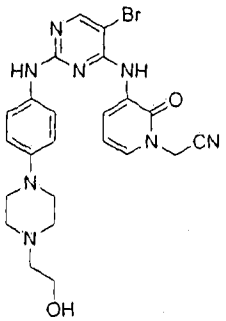
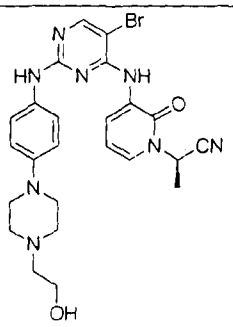
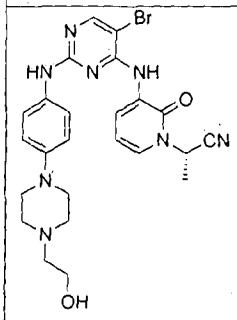
Preparation #7: N-(1-(4-nitrophenyl)piperidin-4-yl)methanesulfonamide:



To a solution of N-(piperidin-4-yl)methanesulfonamide (1 g, 5.6 mmol, Combi-blocks) in DMF was added K_2CO_3 (1.55 g, 11.2 mmol, Rankem) followed by 1-fluoro-4-nitrobenzene (0.79 g,

5.06 mmol, AVRA) at 0 °C. The reaction mixture was stirred at 80 °C for 12 h and was poured into ice cold water; the product was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulphate and evaporated to dryness to afford the target compound (59.7%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 - 8.05 (d, J = 4.0 Hz, 1H), 7.14 - 7.12 (d, J = 7.2 Hz, 1H), 7.04 - 7.01 (m, 2H), 3.99 - 3.95 (d, J = 13.6 Hz, 2H), 3.49 -3.46 (m, 1H),

Individual enantiomers of Example D.1.81 are separated using Chiral preparative HPLC (Method Table-E)

Example#	Structure	Pure Enantiomers	LCMs R_t Time in min	MS m/z: $(M+H)^+$
E.1	 D.1.81		R_t: 1.3*	542.2
E.2			R_t: 1.29*	542.2

Prep. HPLC method:

Column Chiral Pak IC (250 mm x 4.6 mm)5.0μM; Mobile Phase: A:-n-Hexane, B: EtOH (0.% DEA), Isocratic: A:D (10:90), Flow Rate: 0.8 mL/min. Diluent: EtOH+MP (Sonicated) UV□ =: 300nm

**LCMS conditions: Instrument : Agilent 6120 quadrapole; Column: Zorbax-SB-C18,4.6x50mm,3.5µm;Mobile Phase: A - 0.1% Formic acid in water B – ACN; Gradient: (T/%B): 0/30, 2/95, 5/95 & 5.1/30, Flow : 1.0 mL/min.*

ASSAYS:

JAK2 TR-FRET assay: The enzymatic assay was standardized using recombinant human JAK2 enzyme (Cat# 14-640) from Millipore using Ultra Light Poly GT (Cat# TRF 0100D) from Perkin Elmer as a substrate.TR-FRET (Time resolved fluorescence resonance energy transfer) detection technology was used for the read out. The final assay conditions were 2.5 ng JAK2 , 10 nM U-light pGT peptide substrate, 10 µM ATP (Km conc.), 1 nM Eu-Ab,W1024 (Cat# AD0203, Perkin Elmer) , 50mM Tris pH 7.5, 20 mM $MgCl_2$, 1mM EGTA, 2mM DTT, 0.01% Tween, 1 % DMSO (20 µl rxn volume: 30 min pre-incubation of enzyme with compound, 1 hr reaction time with substrate) in 384 well format. The TR-FRET signal (Excitation at 340 nm, Emission at 615 nm and 665 nm) was read with 50 µs delay time on Victor^3 V fluorimeter. The data is calculated using the ratio of reading at 665 nm to 615 nm. The final concentration of DMSO was 1 % in the assay. Each individual IC_{50} was determined using 10 point dose response curve generated by GraphPad Prism software Version 4 (San Diego, California, USA) using non-linear regression curve fit for sigmoidal dose response (variable slope).

FAK TR-FRET assay: The enzymatic assay was standardized using recombinant human FAK enzyme (Cat# 14-720) from Millipore using Ultra Light Poly GT (Cat# TRF 0100D) from Perkin Elmer as a substrate.TR-FRET (Time resolved fluorescence resonance energy transfer) detection technology was used for the read out. The final assay conditions were 5 ng FAK , 40 nM U-light pGT peptide substrate, 15 µM ATP (Km conc.), 1 nM Eu-Ab,W1024 (Cat# AD0203, Perkin Elmer) , 50mM Tris pH 7.5, 20 mM $MgCl_2$, 1mM EGTA, 2mM DTT, 0.01% Tween, 1 % DMSO (20 µl rxn volume: 30 min pre-incubation of enzyme with compound, 1 hr reaction time with substrate) in 384 well format. The TR-FRET signal (Excitation at 340 nm, Emission at 615 nm and 665 nm) was read with 50 µs delay time on Victor^3 V fluorimeter. The data is calculated using the ratio of reading at 665 nm to 615 nm. The final concentration of DMSO was 1 % in the assay. Each individual IC_{50} was determined using 10 point dose response curve generated by GraphPad Prism software Version 4 (San Diego, California, USA) using non- linear regression curve fit for sigmoidal dose response (variable slope).

pStat3 ICW protocol in A549 cells:

A549 cells are seeded at a density of 20,000 cells/well in a 96 well flat bottom plate. After 6 hours cells are serum starved and incubated overnight at 37°C/5% CO_2 . The dilutions of the compound to be tested are done in DMSO. 10µL of diluted compound is added to the cells. Final DMSO concentration less than 0.5%.The cells with compound are incubated for 3h at 37°C/5% CO_2. Cells are stimulated with 25ng/ml IL6 for 20 minutes. The cells are fixed with 100 µl/well of methanol. Then, cells are washed with 3x100µl of 1X PBST. Cells are incubated with blocking buffer, 5%BSA in 1X PBST for 1h at room temperature on plate shaker. The primary antibody pStat3 is diluted (1:100) in the blocking buffer. 50µl of the primary antibody is added to each wells and incubated at 4°C overnight on a rocking plate. The cells are washed with 3x100 µl 1X wash buffer. The Europium labeled rabbit secondary antibody is diluted (1:2000) in the assay buffer (Delfia Assay Buffer). 50µl of the secondary antibody is added to all wells of the plate. The plate is incubated at room temperature on plate shaker for 2h.The cells are washed with 3x100 µl 1X wash buffer. 50µl of the Delfia Enhancement solution is added to the plate and the plate is incubated at room temperature on plate shaker. The plate is read at the Europium settings on the Victor. Readings at taken at 5min and 20min. After the Europium is read, plate is washed with 1x 100µL of 1X PBS.100µL of the 0.5µg/ml Hoechst in 1XPBS is added to all wells containing cells. The plate is placed on a plate shaker at room temperature for 15min. The plate is read on Victor on the umbelliferone setting. Each well is assigned a correction factor. Correction factor = average Hoechst value of the plate/Hoechst value of the well. Normalized europium values are obtained by multiplying the raw values with the correction factor.

pFak ICW protocol in 4T1 cells:

4T1 cells are seeded at a density of 10000 cells/well in in a 96 well flat bottom plate. Cells are incubated at 37°C/5% CO_2 overnight. The dilutions of the compound to be tested and the standard compound are done in DMSO.10µL of diluted compound is added to the cells. Final DMSO concentration less than 0.5%.The cells with compound are incubated for 3h at 37°C/5% CO_2.The cells are fixed with 100 µl/well of 4% paraformaldehyde in PBS and incubated for 60 min at room temperature. The cells are washed with 3x100µl of 1X PBST. Cells are incubated with blocking buffer, 5%BSA in 1X PBST for 1h at room temperature on plate shaker. The primary antibody pFAK is diluted (1:100) in the blocking buffer.50µl of the primary antibody is

added to each wells and incubated at 4°C overnight on a rocking plate. The cells are washed with 3x100 µl 1X wash buffer (Delfia/Autodelfia wash concentrate). The Europium labeled rabbit secondary antibody is diluted (1:2000) in the assay buffer (Delfia Assay Buffer). 50µl of the secondary antibody is added to all wells of the plate. The plate is incubated at room temperature on plate shaker for 2h.The cells are washed with 3x100 µl 1X wash buffer. 50µl of the Delfia enhancement solution is added to the plate and the plate is incubated at room temperature on plate shaker. The plate is read at the Europium settings on the Victor. Readings at taken at 5min and 20min. After the Europium is read, plate is washed with 1x 100µL of 1X PBS.100µL of the 0.5µg/ml Hoechst in 1XPBS is added to all wells containing cells. The plate is placed on a plate shaker at room temperature for 15min. The plate is read on Victor on the umbelliferone setting. Each well is assigned a correction factor. Correction factor = average Hoechst value of the plate/Hoechst value of the well. Normalized europium values are obtained by multiplying the raw values with the correction factor.

Table D: cell free assay and cell based assay data for the examples described above

Comp. No.	Cell free assay data			Cell based assay data	
	FAK IC_{50} (nM)	JAK IC_{50} (nM)	AXL IC_{50} (nM)	pFAK ICW (nM)	pStat3 ICW (nM)
D.1.2	****	****	ND	**	**
D.1.3	***	****	**	**	**
D.1.4	****	****	**	**	**
D.1.5	***	****	ND	*	*
D.1.6	****	***	ND	ND	ND
D.1.8	***	***	ND	ND	ND
D.1.12	***	****	ND	ND	ND
D.1.13	****	****	ND	ND	ND
D.1.14	****	****	ND	ND	ND
D.1.17	***	****	ND	**	**

D.1.18	****	****	ND	ND	ND
D.1.19	***	****	ND	ND	ND
D.1.27	***	****	ND	*	**
D.1.30	****	***	ND	ND	ND
D.1.31	****	****	ND	ND	ND
D.1.32	****	****	ND	***	**
D.1.33	****	****	ND	ND	ND
D.1.34	**	***	ND	ND	ND
D.1.35	***	****	ND	ND	ND
D.1.37	***	***	ND	ND	ND
D.1.38	***	***	ND	ND	ND
D.1.39	***	***	ND	ND	ND
D.1.40	***	***	ND	*	*
D.1.41	***	***	ND	*	*
D.1.45	***	***	ND	ND	ND
D.1.46	****	****	ND	***	**
D.1.47	****	****	ND	*	*
D.1.50	****	****	ND	*	*
D.1.51	****	****	ND	*	***
D.1.52	***	ND	ND	ND	ND
D.1.53	***	****	ND	**	**
D.1.55	****	****	ND	***	**
D.1.57	****	****	ND	*	*
D.1.58	***	****	ND	ND	ND
D.1.59	***	****	ND	ND	ND

D.1.61	***	***	ND	ND	ND
D.1.62	***	****		*	*
D.1.63	***	***	ND	**	**
D.1.66	***	****	ND	ND	ND
D.1.67	***	**	ND	ND	ND
D.1.68	****	****	ND	ND	ND
D.1.71	***	***	ND	ND	ND
D.1.72	***	***	ND	**	**
D.1.73	****	****	ND	ND	
D.1.74	****	****	ND	**	**
D.1.75	***	***	ND	ND	ND
D.1.76	***	****	ND	ND	ND
D.1.80	****	****	ND	ND	ND
D.1.81	****	****	ND	***	***
D.1.82	***	****	ND	ND	ND
D.1.83	****	****		***	**
D.1.89	****	****	ND	*	**
D.1.90	****	***	ND	*	*
D.1.92	****	****	ND	*	*
D.1.93	****	****	ND	**	**
D.1.94	***	****	ND	ND	ND
D.1.95	**	****	ND	ND	ND
D.1.96	***	****	ND	*	*
D.1.97	***	****	ND	ND	ND
D.1.98	****	****	ND	*	**

D.1.100	***	***	ND	*	**
D.1.103	***	***	ND	ND	ND
D.1.104	***	***	ND	*	*
D.1.107	***	****	ND	ND	ND
D.1.109	***	****	ND	ND	ND
D.1.110	***	***	ND	*	*
D.1.111	***	****	ND	ND	ND
D.1.112	***	****	ND	ND	ND
D.1.114	***	****	ND	**	**
E.1	****	****	ND	ND	ND
E.2	****	****	ND	ND	ND

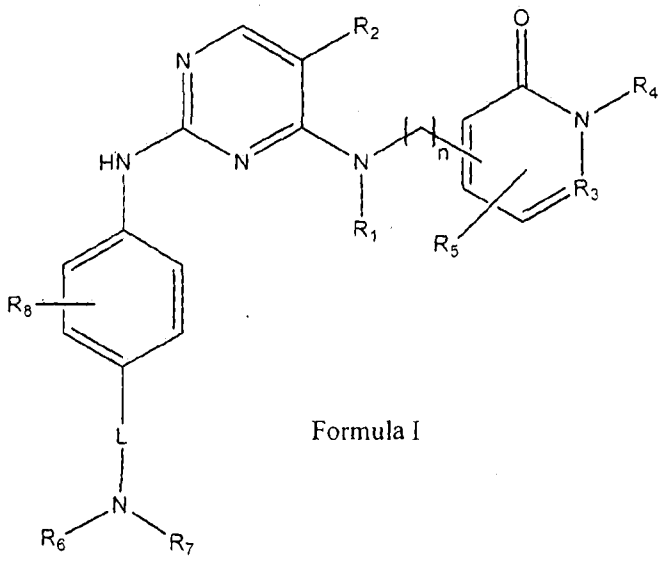
The details of the IC50 values range disclosed in Table D is illustrated in below table.

IC_{50}: >1000 nM	*
IC_{50}:100 nM-1000 nM	**
IC_{50}:10 nM-100 nM	***
IC_{50}:< 10 nM	****
Not done	ND

5

We claim:

1. A compound of formula I



Formula I

wherein

L is direct bond or group selected from $-(CH_2)_p-$, –CO- or $-SO_2-$;

R_1 is hydrogen or alkyl;

R_2 is hydrogen, halogen, optionally substituted alkyl, haloalkyl, cyano, $-CONHR_1$;

R_3 is CR_9 or N;

R_4 is independently selected from optionally substituted alkyl, cyanoalkyl , $-(CH_2)_qCONR_{10}R_{11}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted cycloalkylalkyl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl; wherein optionally substituent, in each occurrence is independently selected from $–OR_{12}$, $-SR_{12}$, $-S(O)_2R_{12}$ or $-NR_{13}R_{14}$;

R_5 is independently selected from hydrogen, halogen, optionally substituted alkyl or $-NR_{13}R_{14}$;

R_6 and R_7 are

i) independently selected from hydrogen, alkyl or acyl;

ii) taken together with the nitrogen to which they are attached may optionally form 3 to 7 membered saturated, partially saturated or unsaturated ring having 0-2 additional heteroatoms selected from N, O, S; wherein the said ring is optionally substituted with halo, alkyl, acyl, alkyloxy, hydroxyl, hydroxyalkyl, oxo, cycloalkyl, heterocycloalkyl or $-NR_{13}R_{14}$;

alternatively, when L is direct bond then R_6 or R_7 together with the nitrogen to which it is attached and adjacent carbon atom of the phenyl group may optionally form 3 to 7 membered saturated, partially unsaturated or fully unsaturated ring having 0-2 additional heteroatoms selected from N, O, S; wherein the said ring is optionally substituted with oxo;

R_8 is independently selected from hydrogen, halo or alkyloxy;

R_9 at each occurrence is independently selected from hydrogen, alkyl or $-NR_{13}R_{14}$;

R_{10} and R_{11} at each occurrence are independently selected from hydrogen, alkyl or alkyloxy;

R_{12} in each occurrence are independently selected from hydrogen or alkyl;

R_{13} and R_{14} in each occurrence are independently selected from hydrogen, alkyl, acyl or $-S(O)_2R_{12}$;

n is 0 or 1;

p is selected from 1 to 5; and

q is selected from 0 to 5;

or a pharmaceutically acceptable salts, stereoisomer's, polymorphs or prodrugs thereof.

2. A compound selected from

3-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-methylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-ethylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-cyclopentylpyridin-2(1H)-one

5-((5-bromo-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)indolin-2-one

3-((5-bromo-2-((4-(morpholinosulfonyl)phenyl)amino)pyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-phenylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-phenylpyridin-2(1H)-one hydrochloride

5-((5-bromo-4-((2-oxo-1-phenyl-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)indolin-2-one

2-(3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)acetonitrile

3-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-phenylpyridin-2(1H)-one

2-(3-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)acetonitrile

2-(3-((5-bromo-2-((2-oxoindolin-5-yl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)acetonitrile 2,2,2-trifluoroacetate

2-(3-((5-bromo-2-((2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)acetonitrile 2,2,2-trifluoroacetate

N-(3-(((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)methyl)-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-N-methylmethanesulfonamide

3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-ethylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4,4-difluoropiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one

(5-((5-bromo-4-((1-cyclopentyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)indolin-2-one

(N-(2-(3-((5-bromo-2-((2-oxoindolin-5-yl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)ethyl)methanesulfonamide 2,2,2-trifluoroacetate

3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methoxyphenyl)amino) pyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one 2,2,2-trifluoroacetate

3-((2-((1H-indazol-5-yl)amino)-5-bromopyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one

N2-(1H-benzo[d]imidazol-5-yl)-5-bromo-N4-(1-isopropyl-1,2-dihydropyridin-3-yl)pyrimidine-2,4-diamine

3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methoxyphenyl amino)pyrimidin-4-yl)amino)-1,6-dimethylpyridin-2(1H)-one

7-((5-bromo-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)-2H-benzo[b][1,4]oxazin-3(4H)-one

3-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1,6-dimethylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-(pentan-3-yl)pyridin-2(1H)-one

6-((5-bromo-4-((1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)-3,4-dihydroquinolin-2(1H)-one 2,2,2-trifluoroacetate

2,2,2-trifluoroacetic acid compound with 2-(3-((5-bromo-2-((2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)-N-methoxy-N-methylacetamide

3-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-(pentan-3-yl)pyridin-2(1H)-one

3-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1,6-dimethylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1,6-dimethylpyridin-2(1H)-one

4-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-phenylpyridazin-3(2H)-one

4-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-phenylpyridazin-3(2H)-one

4-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-phenylpyridazin-3(2H)-one

4-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-methylpyridazin-3(2H)-one

2-(3-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)-N-methoxy-N-methylacetamide

2-(3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)-N-methoxy-N-methylacetamide

2-(3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)-N,N-dimethylacetamide

2-(3-((5-bromo-2-((4-(4-(hydroxymethyl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)-N-methoxy-N-methylacetamide

2-(3-((2-((1H-indazol-5-yl)amino)-5-bromopyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)-N,N-dimethylacetamide

2-(3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)-N-methoxy-N-methylacetamide

2-(3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)-N,N-dimethylacetamide

2-(3-((5-bromo-2-((4-(4-(hydroxymethyl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)-N,N-dimethylacetamide

3-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-isobutylpyridin-2(1H)-one

5-((5-bromo-4-((1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)indolin-2-one

6-((5-bromo-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)-3,4-dihydroquinolin-2(1H)-one 2,2,2-trifluoroacetate

3-((2-((4-(4-acetylpiperazin-1-yl)phenyl)amino)-5-bromopyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one

6-((5-bromo-4-((1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)-3,4-dihydroquinolin-2(1H)-one 2,2,2-trifluoroacetate

(3-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-(2-(methylsulfonyl)ethyl)pyridin-2(1H)-one

3-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-isobutylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-(2-(methylthio)ethyl)pyridin-2(1H)-one

3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-isobutylpyridin-2(1H)-one

5-((5-bromo-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)-1H-benzo[d]imidazol-2(3H)-one

1-benzyl-3-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)pyridin-2(1H)-one

5-((4-((1-benzyl-2-oxo-1,2-dihydropyridin-3-yl)amino)-5-bromopyrimidin-2-yl)amino)indolin-2-one

1-benzyl-3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)pyridin-2(1H)-one

3-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-(4-methoxybenzyl)pyridin-2(1H)-one

3-((5-bromo-2-((4-(piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-methylpyridin-2(1H)-one

3-((5-bromo-2-((4-morpholinophenyl)amino)pyrimidin-4-yl)amino)-1-methylpyridin-2(1H)-one

3-((5-bromo-2-((3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-methylpyridin-2(1H)-one

1-benzyl-3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)pyridin-2(1H)-one

3-((5-bromo-2-((4-(4-(hydroxymethyl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-methylpyridin-2(1H)-one

1-benzyl-3-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)pyridin-2(1H)-one

2-(3-((5-bromo-2-((4-(4,4-difluoropiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)-N-methoxy-N-methylacetamide 2,2,2-trifluoroacetate

2,2,2-trifluoroacetic acid compound with 2-(3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)-N-isopropylacetamide

5-(((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)methyl)-1-methylpyridin-2(1H)-one

5-(((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)methyl)-1-methylpyridin-2(1H)-one

3-((5-bromo-2-((4-(2-oxopyridin-1(2H)-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-methylpyridin-2(1H)-one 2,2,2-trifluoroacetate

6-((5-bromo-4-((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)-3,4-dihydroquinolin-2(1H)-one

3-((5-bromo-2-((4-(4-methyl-1,4-diazepan-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-methylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-(cyclopropylmethyl)pyridin-2(1H)-one

3-((5-bromo-2-((4-(4-methylpiperazine-1-carbonyl)phenyl)amino)pyrimidin-4-yl)amino)-1-methylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-(2-methoxyethyl)pyridin-2(1H)-one

N-(1-(4-((5-bromo-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)phenyl)piperidin-4-yl)methanesulfonamide

5-((5-bromo-4-((1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)indolin-2-one

5-((5-bromo-4-((1-(cyclopropylmethyl)-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)indolin-2-one

3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-(2-methoxyethyl)pyridin-2(1H)-one

2-(3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)propanenitrile 2,2,2-trifluoroacetate

3-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-(2-methoxyethyl)pyridin-2(1H)-one 2,2,2-trifluoroacetate

2-(3-((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)propanenitrile 2,2,2-trifluoroacetate

5-((5-bromo-4-((1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)-1H-benzo[d]imidazol-2(3H)-one

3-((2-((1H-indazol-5-yl)amino)-5-bromopyrimidin-4-yl)amino)-1-(2-methoxyethyl)pyridin-2(1H)-one

3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazine-1-carbonyl)phenyl)amino)pyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one 2,2,2-trifluoroacetate

3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazine-1-carbonyl)phenyl)amino)pyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one 2,2,2-trifluoroacetate

6-((5-bromo-4-((1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)-3,4-dihydroquinolin-2(1H)-one

N-(1-(4-((5-bromo-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)phenyl)piperidin-4-yl)acetamide

N-(4-((5-bromo-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)phenyl)acetamide 2,2,2-trifluoroacetate

3-((5-bromo-2-((4-(4-hydroxypiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-methylpyridin-2(1H)-one 2,2,2-trifluoroacetate

3-((5-bromo-2-((4-(4-cyclopropylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-methylpyridin-2(1H)-one

5-((5-bromo-4-((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidin-2-yl)amino)indolin-2-one 2,2,2-trifluoroacetate

3-((5-bromo-2-((4-(4-hydroxypiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-methoxypiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one

5-((5-bromo-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-methylpyridin-2(1H)-one

5-((5-bromo-4-(((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)amino)pyrimidin-2-yl)amino)indolin-2-one

3-(((5-bromo-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)methyl)-1-methylpyridin-2(1H)-one

3-(((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)methyl)-1-methylpyridin-2(1H)-one

3-(((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methoxyphenyl) amino)pyrimidin-4-yl)amino)methyl)-1-methylpyridin-2(1H)-one

6-((5-bromo-4-(((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)amino)pyrimidin-2-yl)amino)-3,4-dihydroquinolin-2(1H)-one 2,2,2-trifluoroacetate

5-((5-bromo-4-(((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)amino)pyrimidin-2-yl)amino)-1H-benzo[d]imidazol-2(3H)-one 2,2,2-trifluoroacetate

3-(((2-((1H-indazol-5-yl)amino)-5-bromopyrimidin-4-yl)amino)methyl)-1-methylpyridin-2(1H)-one

5-((5-bromo-4-(((1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridin-3-yl)methyl)amino)pyrimidin-2-yl)amino)indolin-2-one

6-((5-bromo-4-(((1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridin-3-yl)methyl)amino)pyrimidin-2-yl)amino)-3,4-dihydroquinolin-2(1H)-one

5-((4-(((1-benzyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)amino)-5-bromopyrimidin-2-yl)amino)indolin-2-one

1-benzyl-3-(((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)methyl)pyridin-2(1H)-one

3-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one

1-isopropyl-3-((5-methyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)pyridin-2(1H)-one

3-((2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one

2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)-4-((1-isopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyrimidine-5-carboxamide

3-((2-((4-(4-(dimethylamino)piperidin-1-yl)phenyl)amino)-5-fluoropyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one

3-((5-fluoro-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-isopropylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-cyclopentylpyridin-2(1H)-one

3-((5-bromo-2-((4-(4-hydroxypiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-1-(pentan-3-yl)pyridin-2(1H)-one

(R)-2-(3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)propanenitrile

(S)-2-(3-((5-bromo-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-2-oxopyridin-1(2H)-yl)propanenitrile.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/002645

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 C07D401/12 C07D239/48 C07D213/46
ADD. A61K31/505 A61P35/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2008/079907 A1 (RIGEL PHARMACEUTICALS INC [US]; ARGADE ANKUSH [US]; SRAN ARVINDER [US]) 3 July 2008 (2008-07-03) tables II,III,XV	1,2
Y	WO 2007/027238 A2 (RIGEL PHARMACEUTICALS INC [US]; WONG BRIAN [US]) 8 March 2007 (2007-03-08) compounds 14,16,26,27,69,84	1,2
A	WO 2010/075558 A2 (RIGEL PHARMACEUTICALS INC [US]; BHAMIDIPATI SOMASEKHAR [US]; LI HUI [U) 1 July 2010 (2010-07-01) examples	1,2

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
20 August 2013	27/08/2013

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/002645

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