(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 October 2014 (02.10.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/155300 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/IB2014/060155

(22) International Filing Date:
26 March 2014 (26.03.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1398/CHE/2013 28 March 2013 (28.03.2013) IN
1403/CHE/2013 28 March 2013 (28.03.2013) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

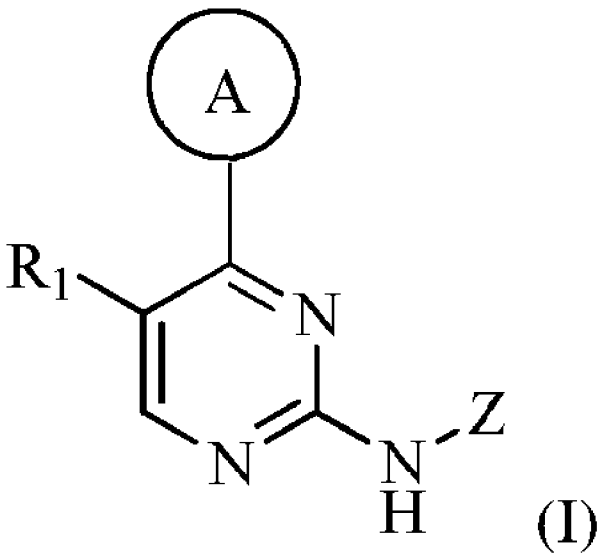
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: SUBSTITUED PYRIMIDINE AMINE DERIVATIVES AS TAK-1 INHIBITORS



(I)

(57) Abstract: The present invention relates to substituted pyrimidine amine derivatives of formula (I) and their pharmaceutically acceptable salts or pharmaceutically acceptable stereoisomers thereof, which are useful as TAK1 inhibitors. (I) In particular the invention also relates to the process for preparation thereof, pharmaceutical compositions comprising them, and their use for the treatment and prevention in diseases or disorder, in particular their use in diseases or disorder associated as TAK1 inhibitors.

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SUBSTITUED PYRIMIDINE AMINE DERIVATIVES AS TAK-1 INHIBITORS

This application claims the benefit of Indian provisional application number 1398/CHE/2013 filed on 28th March 2013 and 1403/CHE/2013 filed on 28th March 2013 which hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to substituted pyrimidine amine derivatives of formula (I), useful as TAK1 inhibitors. In particular the invention also relates to the process for preparation thereof, pharmaceutical compositions comprising them, and their use for the treatment and prevention in diseases or disorder, in particular their use in diseases or disorder associated as TAK1 inhibitors.

BACKGROUND OF THE INVENTION

Kinases are well known to regulate the majority of cellular pathways and constitute one of the largest and most functionally diverse gene families. Their participation in the signaling events controls 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.

Transforming growth factor (TGF)–β–activated kinase 1 (TAK1) is a serine/threonine kinase that was identified by Matsumoto and colleagues in 1995 and was characterized as mitogen-activated protein kinase (MAPK) family (MAP3K7), which is activated by TGF-β and bone morphogenetic protein (BMP), hence TAK1 has role in the control of morphogenesis and tissue homeostasis. TAKl is expressed in most tissues and cell types and has key role in pro-inflammatory cytokine signaling, including tumor necrosis factor-a (TNF-a), interleukin-1 (IL-1), and Toll-like receptor (TLR) ligands [Shirakabe, K. et al., J. Biol. Chem 272, 8141–8144 (1997); Sakurai H. et al., J. Biol. Chem 274 10641-10648 (1999)], hence TAK1 has a critical role in innate and adaptive immune response. Recently it has been shown that the Smad-independent non-canonical TAK1 pathway is involved in TGF-b signaling pathways [Landstro¨m, M. (2010) Int. J. Biochem. Cell Biol. 42, 585–589]. TAK1 interacts with TAK1-binding protein 1 and 2 (TAB1/2) to activate MAPK kinase 3/6 (MKK3/6) and p38, MKK4 and c-Jun N-terminal kinase (JNK), as well as the nuclear factor-kB NF-κB pathways. NF-kB and AP-1 are critical regulators of stress responses, immunity, inflammation and cancer in a variety of cell types.

Since TAK1 is a key molecule in the pro-inflammatory NF-kB signaling pathway a TAK1 inhibitor would be effective in diseases associated with inflammation and tissue destruction such as rheumatoid arthritis and inflammatory bowel disease (Crohn's), as well as in cellular processes such as stress responses, apoptosis, proliferation and differentiation. Various pro-inflammatory cytokines and endotoxins trigger the kinase activity of endogenous TAK1 (Ninomiya-Tsuji J et al., Nature 398 252-256 (999); Irie T et al., FEBS Lett. 467 60-164 (2000); Sakurai H. et al., J. Biol. Chem. 274 10641 -10648 (1999)). Blockade of TAK1 is potentially an attractive strategy to target the three main proinflammatory pathways (p38, JNK, and NF-kB) and the major profibrotic growth factor, TGF-1, in the development of kidney disease. Knock out data has shown that TAK1 deletion caused profound suppression of renal inflammation and fibrosis (Frank Y. Ma et al., Am J Physiol Renal Physiol 300: F1410–F1421, 2011). Cardiomyocyte hypertrophy and neuronal death in cerebral ischemia are also prevented by suppression of TAK1 [Neubert, M. et al., Cell Death Differ. 18, 1521–1530 (2011)]. TAK1 deletion in dendritic cells (DC) leads to a reduction in the hapten-elicited contact hypersensitivity response in the ear [Zhao, Y.G. et al., Cell. Mol. Immunol. 8, 315–324 (2011)]. A naturally occurring inhibitor of TAK1, 5Z-7-oxozeaenol, has been identified with an IC_{50} value of 8 nM. 5Z-7-oxozeaenol has been shown to be selective for TAK1 within the MAPKKK family and relieves inflammation in a picryl chloride-induced ear swelling mouse model (Ninomiya-Tsuji J. et al., J. Biol. Chem. 278 18485 (2003)). Systemic administration of TAK1 siRNA particles potently protects mice from arthritis progression, decreasing both systemic and local inflammatory features (i.e., proinflammatory key cytokines and joint destruction [Gabriel Courties et al., blood 116: 3505-3516 (2010)].

A potential mechanism of TAK1 mediated survival is driven by the ability of TAK1 to phosphorylate IKK and MKKs ultimately leading to the activation of both NF-kB and AP-1, transcription factors that play a role in cell survival. Others have reported that the TAB1: TAK1: IKK3: NF-kB signaling axis forms aberrantly in breast cancer cells, and consequently, enables oncogenic signaling by TGF-[beta] (Neil J et al., Cancer Res. 68 1462 (2008)). It has been reported that TGF-β signaling contributes to tumor angiogenesis and invasion via a mechanism involving matrix metalloproteinase 9 (MMP9) (Safina A et al., Oncogene 26 p2407 (2007)), and that TAK1 is required for TGFβl-mediated regulation of matrix metalloproteinase-9 and metastasis (Safina A et al., Oncogene 2008; 27(9):1 198- 12072008). Others have reported that

TGF-[beta] signaling can induce an epithelial-to- mesenchymal transition (EMT) and contributes to tumor invasion and progression (Ikushima H et al., Nature Reviews Cancer 10 p415 (2010)) and that TAK1 is required for this process (Neil J et al., Cancer Res. 68 1462 (2008)). Thus, TAK1 has been suggested as providing an opportunity for selective inhibition of pro-oncogenic function of TGF-β. TAK1 signaling pathways to EGFR via MAPKs in a tyrosine kinase-independent manner, suggesting a new paradigm for inflammation-related cancer progression. Genotoxic agents also induce TAK1-mediated NF-kB activation and hence TAK1 might have role in resistance to conventional chemotherapy. It has been shown that in human pancreatic cancer, TAK1 inhibition reduced chemoresistance LYTAK1, an orally active TAK1 inhibitor, significantly reduced NF-kB activity and sensitized cancer cells to gemcitabine, SN38 and oxaliplatin in vitro [72 and LYTAK1 in combination with gemcitabine reduced tumor volume and prolonged survival in a nude mouse model in vivo [Melisi, D. et al., J. Natl. Cancer Inst. 103, 1190–1204 (2011)]. TAK1 has also drives cell survival in KRAS-dependent cells, in which KRAS regulates TAK1 and Wnt signaling through BMP-7 receptor activation and 5Z-7-oxozeaenol can suppress tumor growth of KRAS-dependent cell lines in vivo [Anurag Singh et al., Cell 148, 639–650 (2012)]. Recently it has been shown that in a panel lymphoma cell lines, including mantle cell, anaplastic large cell, and Hodgkin lymphoma cell lines there is increase active TAK1 expression. Silencing TAK1 expression using small interfering RNA inhibited the activation of NF-κB and p38, and induced apoptosis in lymphoma cell lines (Daniela Buglio et al., Blood 2012).

TAK1 has been characterized as key regulator in inflammatory and immune signaling pathways, and in addition microbial proteins and components of host cell signaling scramble for the TAK1 complex in innate immunity. Hence the finding indicates that TAK1 inhibitors have therapeutic value for cancer and inflammatory diseases. Accordingly, there has been an interest in finding selective inhibitors of TAK1 that are effective as therapeutic agents. A challenge has been to find protein kinase inhibitors that act in a selective manner, targeting only TAK1. Since there are numerous protein kinases that are involved in a variety of cellular responses, non-selective inhibitors may lead to unwanted side effects. In this regard, the three-dimensional structure of the kinase would assist in the rational design of inhibitors. The determination of the amino acid residues in TAK1 binding pockets and the determination of the shape of those binding pockets would allow one to design selective inhibitors that bind favorably to this class of

enzymes. The determination of the amino acid residues in TAK1 binding pockets and the determination of the shape of those binding pockets would also allow one to determine the binding of compounds to the binding pockets and to, e.g., design inhibitors that can bind to TAK1.

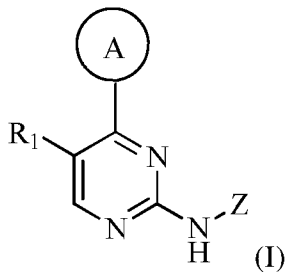
Hence the search targeting protein kinases raises the potential for new therapeutic options for cancer (such as proliferative disease, primary cancers and metastatic disease), and inflammatory disorders (rheumatoid arthritis, airway inflammation and fibrosis in particular kidney) and targeted therapies, including tyrosine kinase inhibitors, such as TAK1 inhibitors, including selective inhibitors, and for potent, orally bioavailable, and efficacious inhibitors continues with great intensity.

The substituted pyrimidine amine derivatives according to the present invention may possess inhibitory activity of one or more protein kinases including TAK1 and are, therefore, expected to be useful in the treatment of kinase-associated diseases or disorders.

SUMMARY OF THE INVENTION

The present invention provides substituted pyrimidine amine derivatives of the following formula (I), useful as TAK1 inhibitors.

In one aspect of the present invention relates to the compounds of formula (I)



(I)

or a pharmaceutically acceptable salt or a pharmaceutically acceptable stereoisomer thereof,

wherein,

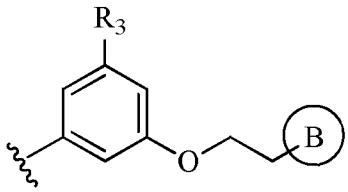
Ring 'A' is an optionally substituted C_4-C_{10} monocyclic or bicyclic ring containing 1-4 heteroatoms/groups independently selected from N, NH and CO; wherein the optional substituent at each occurrence is independently selected from one or more R_2;

R_1 is selected from hydrogen, halogen, alkyl, haloalkyl, cyano, hydroxy, amino and alkoxy;

R_2 is selected from halogen, alkoxy, alkyl, cyano, aryl, $-S(O)_2$aryl and arylalkyl;

Z represents:

i)

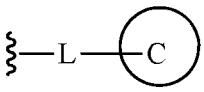


wherein,

R_3 is selected from hydrogen, alkyl, amino, hydroxy and alkoxy;

Ring 'B' is an optionally substituted N-linked C_4-C_8 monocyclic ring; wherein the optional substituent at each occurrence is independently selected from hydroxy and alkoxy;

ii)

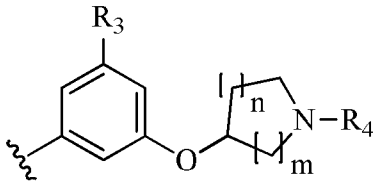


wherein,

L represents direct bond or aryl;

Ring 'C' is an optionally substituted C_{11}-C_{14} tricyclic heterocyclyl ring; wherein the optional substituent at each occurrence is independently selected from alkyl, halogen, hydroxyalkyl, -C(O)cycloalkyl and $-S(O)_2$alkyl;

iii)



wherein,

R_3 is selected from hydrogen, alkyl, amino, hydroxy, alkoxy and heterocyclyl;

R_4 is selected from hydrogen, alkyl and hydroxyalkyl;

'm' is selected from an integer 1 to 2, both inclusive; and

'n' is selected from an integer 0 to 2, both inclusive.

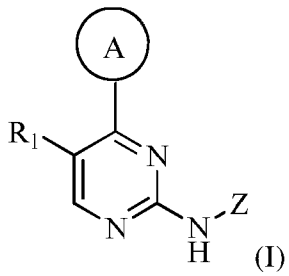
In further yet another aspect of the present invention, it provides processes for preparation of substituted pyrimidine amine derivatives of formula (I).

In further yet another aspect the present invention provides pharmaceutical composition comprising compounds of present invention and their pharmaceutically acceptable salts or pharmaceutically acceptable stereoisomers thereof, for use in the treatment and prevention of diseases and disorders for which TAK1 inhibitor is indicated.

DETAILED DESCRIPTION OF THE INVENTION

Embodiment of the present invention provides the substituted pyrimidine amine derivatives of formula (I), useful as TAK1 inhibitors.

In one embodiment of the present invention relates to the compounds of formula (I)



(I)

or a pharmaceutically acceptable salt or a pharmaceutically acceptable stereoisomer thereof, wherein,

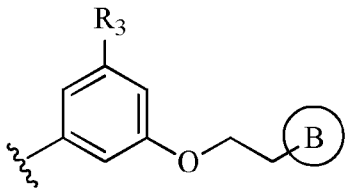
Ring 'A' is an optionally substituted C_4-C_{10} monocyclic or bicyclic ring containing 1-4 heteroatoms/groups independently selected from N, NH and CO; wherein the optional substituent at each occurrence is independently selected from one or more R_2;

R_1 is selected from hydrogen, halogen, alkyl, haloalkyl, cyano, hydroxy, amino and alkoxy;

R_2 is selected from halogen, alkoxy, alkyl, cyano, aryl, $-S(O)_2$aryl and arylalkyl;

Z represents:

i)

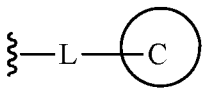


wherein,

R_3 is selected from hydrogen, alkyl, amino, hydroxy and alkoxy;

Ring 'B' is an optionally substituted N-linked C_4-C_8 monocyclic ring; wherein the optional substituent at each occurrence is independently selected from hydroxy and alkoxy;

ii)

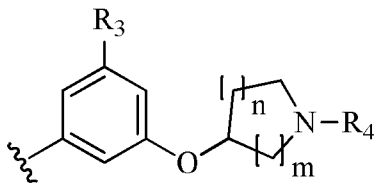


wherein,

L represents direct bond or aryl;

Ring 'C' is an optionally substituted C_{11}-C_{14} tricyclic heterocyclyl ring; wherein the optional substituent at each occurrence is independently selected from alkyl, halogen, hydroxyalkyl, -C(O)cycloalkyl and $-S(O)_2$alkyl;

iii)



wherein,

R_3 is selected from hydrogen, alkyl, amino, hydroxy, alkoxy and heterocyclyl;

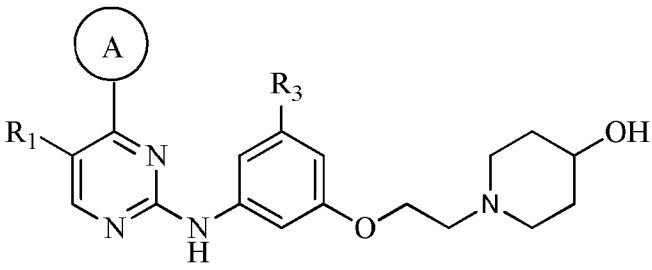
R_4 is selected from hydrogen, alkyl and hydroxyalkyl;

'm' is selected from an integer 1 to 2, both inclusive; and

'n' is selected from an integer 0 to 2, both inclusive.

The compounds of formula (I) may involve one or more embodiments. The embodiments below are illustrative of the compound of formula (I) of the present invention and are not intended to limit the claims to the specific embodiments exemplified.

According to one particular embodiment of the present invention, the compound of formula (I) is a compound of (Ia)



(Ia)

or a pharmaceutically acceptable salt or a pharmaceutically acceptable stereoisomer thereof, wherein,

Ring 'A' is an optionally substituted N-linked C_4-C_{10} monocyclic or bicyclic ring containing 1-4 heteroatoms and/or heterogroups selected from N, NH and C(O); wherein the optional substituent at each occurrence is independently selected from one or more R_2;

R_1 is selected from hydrogen, halogen, alkyl, haloalkyl, cyano, hydroxy, amino and alkoxy;

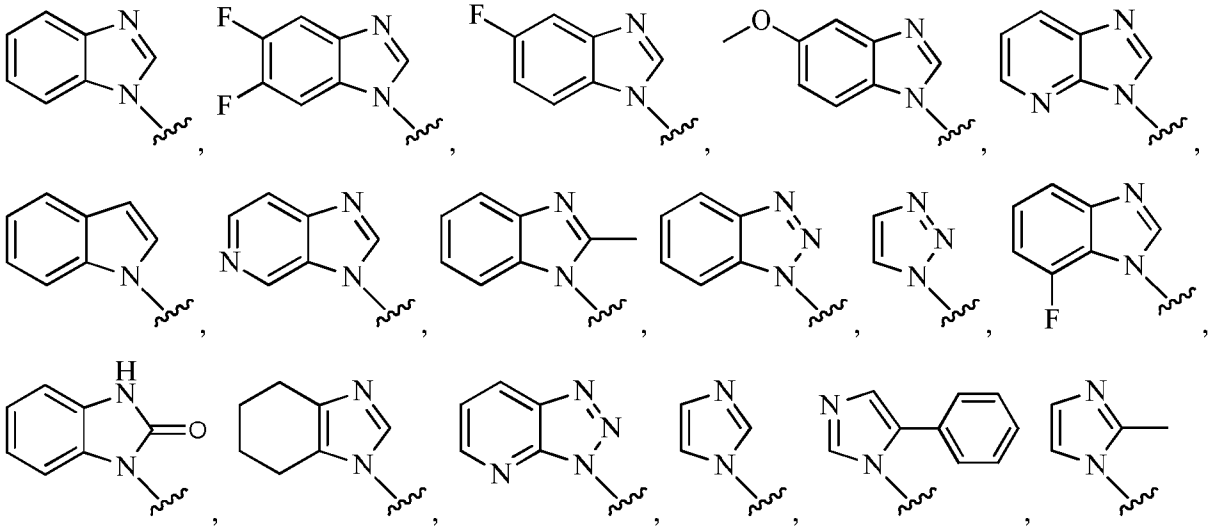
R_2 is selected from halogen, alkoxy, alkyl, cyano and aryl; and

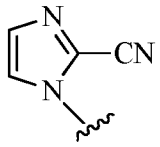
R_3 is selected from hydrogen, alkyl, amino, hydroxy and alkoxy.

According to preceding embodiment, specifically provided are compounds of formula (Ia), wherein R_1 is halogen; in particular halogen is fluoro.

According to one of the preceding embodiment, specifically provided are compound of formula (Ia), wherein R_3 is alkyl, in particular alkyl is ethyl.

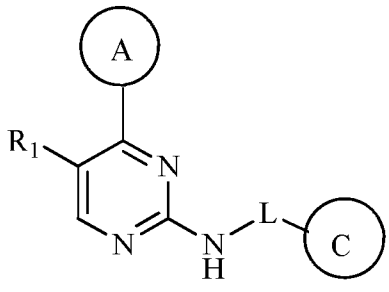
According to one of the preceding embodiment, specifically provided are compounds of formula (Ia), wherein Ring A is selected from





and .

According to another particular embodiment of the present invention, the compound of formula (I) is a compound of formula (Ib)



(Ib)

or a pharmaceutically acceptable salt or a pharmaceutically acceptable stereoisomer thereof, wherein,

Ring 'A' is an optionally substituted C_4-C_{10} monocyclic or bicyclic ring containing 1-3 heteroatoms; wherein the heteroatom is 'N' and the optional substituent at each occurrence is independently selected from one or more R_2;

Ring 'C' is an optionally substituted C_{11}-C_{14} tricyclic heterocyclyl ring containing 1-4 heteroatoms independently selected from N, O and NH; wherein the optional substituent at each occurrence is independently selected from alkyl, halogen, hydroxyalkyl, -C(O)cycloalkyl and $-S(O)_2$alkyl;

L represents direct bond or aryl;

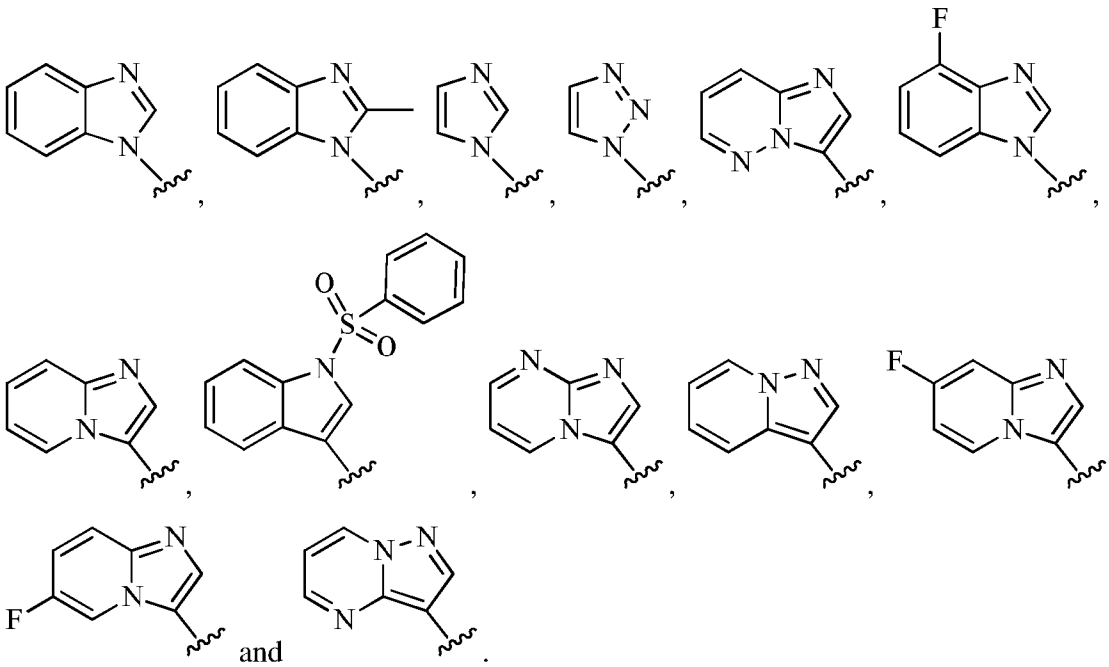
R_1 is selected from hydrogen, alkyl, halogen, haloalkyl, cyano, hydroxy, amino and alkoxy;

R_2 is selected from alkyl, halogen and $-S(O)_2$aryl.

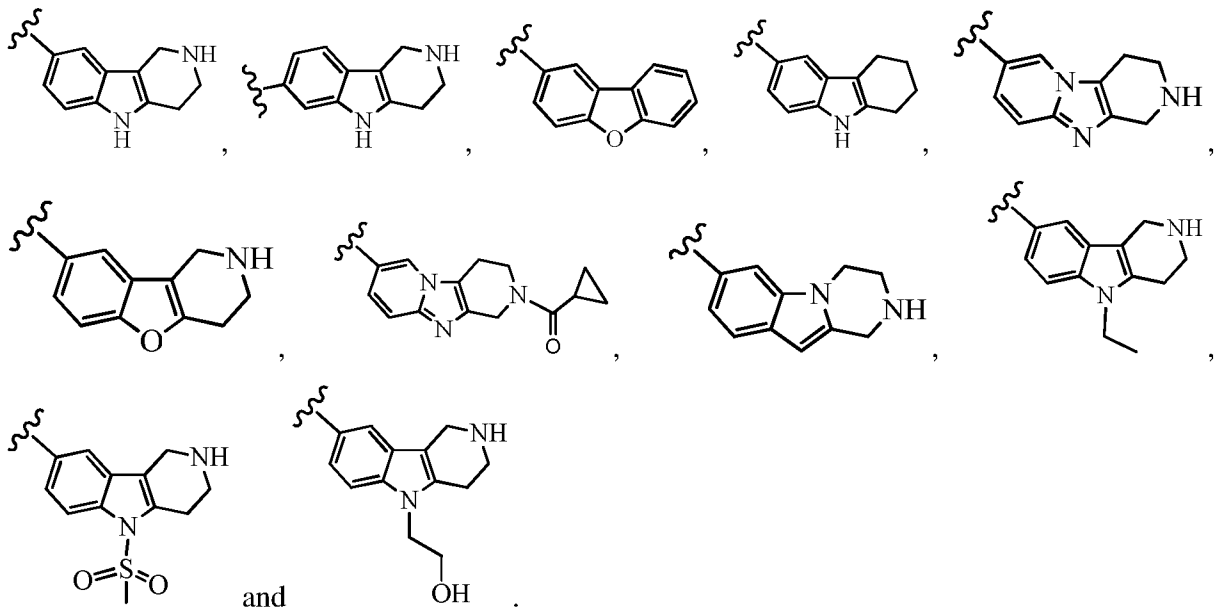
According to preceding embodiment, specifically provided are compounds of formula (Ib), wherein R_1 is halogen; in particular halogen is fluoro.

According to one of the preceding embodiment, specifically provided are compounds of formula (Ib), wherein L is direct bond or aryl; in particular aryl is phenyl.

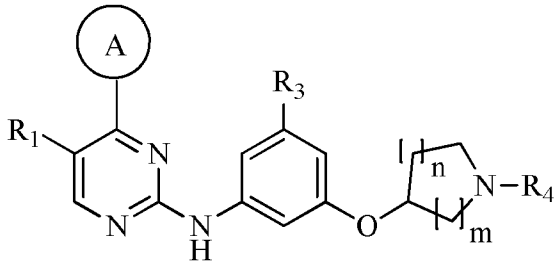
According to one of the preceding embodiment, specifically provided are compounds of formula (Ib), wherein Ring A is selected from



According to one of the preceding embodiment, specifically provided are compounds of formula (Ib), wherein Ring B is selected from



According to yet another particular embodiment of the present invention, the compound of formula (I) is a compound of formula (Ic)



(Ic)

or a pharmaceutically acceptable salt or a pharmaceutically acceptable stereoisomer thereof, wherein,

Ring 'A' is an optionally substituted C_4-C_{10} monocyclic or bicyclic ring containing 1-4 heteroatoms/groups independently selected from N, NH and CO; wherein the optional substituent is arylalkyl; with a proviso that ring A is not selected from oxazole and isoxazole;

R_1 is selected from hydrogen, halogen, alkyl, haloalkyl, cyano, hydroxy, amino and alkoxy;

R_3 is selected from hydrogen, alkyl, amino, hydroxy, alkoxy and heterocyclyl;

R_4 is selected from hydrogen, alkyl and hydroxyalkyl;

'm' is selected from an integer 1 to 2, both inclusive; and

'n' is selected from an integer 0 to 2, both inclusive.

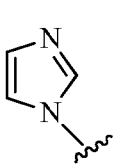
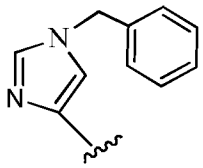
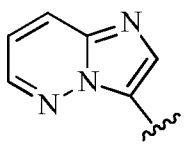
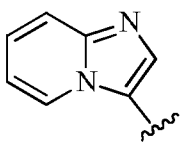
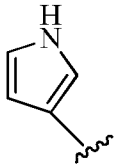
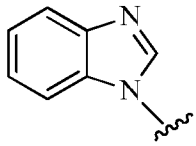
According to preceding embodiment, specifically provided are compounds of formula (Ic), wherein R_1 is halogen; in particular halogen is fluoro.

According to one of the preceding embodiment, specifically provided are compounds of formula (Ic), wherein R_3 is alkyl; in particular alkyl is ethyl.

According to one of the preceding embodiment, specifically provided are compounds of formula (Ic), wherein R_3 is heterocyclyl; in particular heterocyclyl is 2-thiophene and 1*H*-pyrazole.

According to one of the preceding embodiment, specifically provided are compounds of formula (Ic), wherein R_4 is hydrogen or hydroxyalkyl; in particular hydroxyalkyl is $-CH_2CH_2OH$.

According to one of the preceding embodiment, specifically provided are compounds of formula (Ic), wherein Ring A is selected from

 ,  ,  ,  ,  and  .

According to particular embodiment of the present invention, the compound of formula (I) is selected from the group consisting of

1-(2-(3-((4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)-5-ethylphenoxy) ethyl)piperidin-4-ol (Compound-1);

1-(2-(3-((4-(5,6-difluoro-1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)-5-ethylphenoxy)ethyl)piperidin-4-ol (Compound-2);

1-(2-(3-ethyl-5-((5-fluoro-4-(5-fluoro-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy)ethyl)piperidin-4-ol (Compound-3);

1-(2-(3-ethyl-5-((5-fluoro-4-(5-methoxy-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy)ethyl)piperidin-4-ol (Compound-4);

1-(2-(3-ethyl-5-((5-fluoro-4-(3H-imidazo[4,5-b]pyridin-3-yl)pyrimidin-2-yl)amino) phenoxy)ethyl)piperidin-4-ol (Compound-5);

1-(2-(3-ethyl-5-((5-fluoro-4-(1H-indol-1-yl)pyrimidin-2-yl)amino)phenoxy)ethyl) piperidin-4-ol (Compound-6);

1-(2-(3-ethyl-5-((5-fluoro-4-(3H-imidazo[4,5-c]pyridin-3-yl)pyrimidin-2-yl)amino) phenoxy)ethyl)piperidin-4-ol (Compound-7);

1-(2-(3-ethyl-5-((5-fluoro-4-(2-methyl-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy)ethyl)piperidin-4-ol (Compound-8);

1-(2-(3-((4-(1H-benzo[d][1,2,3]triazol-1-yl)-5-fluoropyrimidin-2-yl)amino)-5-ethyl phenoxy)ethyl)piperidin-4-ol (Compound-9);

1-(2-(3-ethyl-5-((5-fluoro-4-(7-fluoro-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)amino) phenoxy)ethyl)piperidin-4-ol (Compound-10);

1-(2-(3-((4-(1H-benzo[d]imidazol-1-yl)-5-chloropyrimidin-2-yl)amino)-5-ethylphenoxy) ethyl)piperidin-4-ol (Compound-11);

1-(2-(3-ethyl-5-((5-fluoro-4-(4,5,6,7-tetrahydro-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy)ethyl)piperidin-4-ol (Compound-12);

1-(2-(3-((4-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-5-fluoropyrimidin-2-yl)amino)-5-ethylphenoxy)ethyl)piperidin-4-ol (Compound-13);

1-(2-((3-ethyl-5-(2-(4-hydroxypiperidin-1-yl)ethoxy)phenyl)amino)-5-fluoropyrimidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (Compound-14);

1-(2-(3-ethyl-5-((5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy)ethyl) piperidin-4-ol (Compound-15);

1-(2-(3-ethyl-5-((5-fluoro-4-(5-phenyl-1H-imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy) ethyl)piperidin-4-ol (Compound-16);

1-(2-(3-ethyl-5-((5-fluoro-4-(2-methyl-1H-imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy) ethyl)piperidin-4-ol (Compound-17);

1-(2-(3-ethyl-5-((5-fluoro-4-(1H-1,2,3-triazol-1-yl)pyrimidin-2-yl)amino)phenoxy)ethyl) piperidin-4-ol (Compound-18);

1-(2-((3-ethyl-5-(2-(4-hydroxypiperidin-1-yl)ethoxy)phenyl)amino)-5-fluoropyrimidin-4-yl)-1H-imidazole-2-carbonitrile (Compound-19);

N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido [4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-20);

N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido [4,3-b]indol-7-amine 2,2,2-trifluoroacetate (Compound-21);

4-(1H-benzo[d]imidazol-1-yl)-N-(dibenzo[b,d]furan-3-yl)-5-fluoropyrimidin-2-amine (Compound-22);

N-(5-fluoro-4-(2-methyl-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-7-amine 2,2,2-trifluoroacetate (Compound-23);

N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-carbazol-7-amine (Compound-24);

N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-1,2,3,4-tetrahydroimidazo[1,2-a:4,5-c']dipyridin-7-amine 2,2,2-trifluoroacetate (Compound-25);

N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-5-ethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-7-amine 2,2,2-trifluoroacetate (Compound-26);

N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-1,2,3,4-tetrahydrobenzofuro [3,2-c]pyridin-7-amine 2,2,2-trifluoroacetate (Compound-27);

4-(1H-benzo[d]imidazol-1-yl)-5-fluoro-N-(3-(1,2,3,4-tetrahydroimidazo[1,2-a:4,5-c']dipyridin-7-yl)phenyl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-28);

4-(1H-benzo[d]imidazol-1-yl)-5-fluoro-N-(4-(1,2,3,4-tetrahydroimidazo[1,2-a:4,5-c']dipyridin-7-yl)phenyl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-29);

N-(5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-30);

N-(dibenzo[b,d]furan-3-yl)-5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-amine (Compound-31);

N-(5-fluoro-4-(1H-1,2,3-triazol-1-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-32);

5-fluoro-4-(imidazo[1,2-b]pyridazin-3-yl)-N-(4-(1,2,3,4-tetrahydroimidazo[1,2-a:4,5-c']dipyridin-7-yl)phenyl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-33);

N-(5-fluoro-4-(imidazo[1,2-b]pyridazin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-34);

N-(5-fluoro-4-(4-fluoro-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-35);

N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-36);

N-(5-fluoro-4-(imidazo[1,2-a]pyridin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-37);

N-(5-fluoro-4-(imidazo[1,2-b]pyridazin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-7-amine 2,2,2-trifluoroacetate (Compound-38);

N-(5-fluoro-4-(imidazo[1,2-a]pyridin-3-yl)pyrimidin-2-yl)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-7-amine acetate (Compound-39);

N-(5-fluoro-4-(imidazo[1,2-a]pyrimidin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-40);

N-(5-fluoro-4-(imidazo[1,2-a]pyrazin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-41);

N-(5-fluoro-4-(pyrazolo[1,5-a]pyridin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-42);

N-(5-fluoro-4-(7-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-43);

N-(5-fluoro-4-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-44);

N-(5-fluoro-4-(pyrazolo[1,5-a]pyrimidin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-45);

N-(5-fluoro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-46);

(7-(3-((4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)phenyl)-3,4-dihydroimidazo[1,2-a:4,5-c']dipyridin-2(1H)-yl)(cyclopropyl)methanone (Compound-47);

2-(8-((5-fluoro-4-(imidazo[1,2-b]pyridazin-3-yl)pyrimidin-2-yl)amino)-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)ethanol 2,2,2-trifluoroacetate (Compound-48);

N-(3-(azetidin-3-yloxy)-5-ethylphenyl)-5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-49);

N-(3-ethyl-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-50);

(S)-N-(3-ethyl-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-51);

(R)-N-(3-ethyl-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-52);

N-(3-ethyl-5-(piperidin-4-yloxy)phenyl)-5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-53);

N-(3-ethyl-5-(piperidin-3-yloxy)phenyl)-5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-54);

N-(3-ethyl-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro-4-(imidazo[1,2-b]pyridazin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-55);

N-(3-ethyl-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro-4-(imidazo[1,2-a]pyridin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-56);

5-fluoro-4-(1H-imidazol-1-yl)-N-(3-(pyrrolidin-3-yloxy)-5-(thiophen-2-yl)phenyl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-57);

5-fluoro-4-(imidazo[1,2-a]pyridin-3-yl)-N-(3-(pyrrolidin-3-yloxy)-5-(thiophen-2-yl)phenyl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-58);

N-(3-(1H-pyrazol-4-yl)-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro-4-(imidazo[1,2-a]pyridin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-59);

4-(1-benzyl-1H-imidazol-4-yl)-N-(3-ethyl-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-60);

N-(3-(azetidin-3-yloxy)-5-ethylphenyl)-5-fluoro-4-(1H-pyrrol-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-61);

4-(1H-benzo[d]imidazol-1-yl)-N-(3-ethyl-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-62);

2-(3-(3-((4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)-5-ethylphenoxy) pyrrolidin-1-yl)ethanol (Compound-63);

2-(3-(3-ethyl-5-((5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy) pyrrolidin-1-yl)ethanol (Compound-64);

(R)-2-(3-(3-ethyl-5-((5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy) pyrrolidin-1-yl)ethanol (Compound-65); and

(S)-2-(3-(3-ethyl-5-((5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy) pyrrolidin-1-yl)ethanol (Compound-66),

or a pharmaceutically acceptable salt or a pharmaceutically acceptable stereoisomer thereof.

In further yet another particular embodiment, the definition "compound of formula (I)" inherently includes all the all stereoisomers of the compound of formula (I) either as pure stereoisomer or as a mixture of two or more stereoisomers. The word stereoisomers include enantiomers, diasteroisomers, racemates, cis-isomers, trans-isomers and mixture thereof.

The absolute configuration at an asymmetric atom is specified by either R or S. Resolved compounds whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light. When a specific stereoisomer is identified, this means that said stereoisomer is substantially free, i.e. associated with less than 50%, preferably less than 20%, more preferably less than 5%, in particularly less than 2% or 1% of the other isomers. Thus when a compound of formula (I) is for instance specified as (R), this means that the compound is substantially free of (S) isomer; when the compound of formula (I) is for instance specified as E, this means that the compound is free of the Z isomer; when the

compound of formula (I) is for instance specified as cis-isomer, this means that the compound is free of the trans-isomer.

In further yet another particular embodiment, the present invention provides processes for preparing novel substituted pyrimidine amine derivatives of formula (I).

In further yet another particular embodiment, the present invention provides a pharmaceutical composition comprising the compound of formula (I) and at least one pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent). Preferably, the pharmaceutical composition comprises a therapeutically effective amount of at least one compound described herein.

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 herein, the following definitions are supplied in order to facilitate the understanding of the present invention.

“Alkyl” refers to a hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms; in particular alkyl is C_1-C_{10} alkyl group which may have 1 to 10 (inclusive) carbon atoms in it; in more particular alkyl is C_1-C_6 alkyl group which may have 1 to 6 (inclusive) carbon atoms in it and in more preferred particular alkyl is C_1-C_4 alkyl group which may have 1 to 4 (inclusive) carbon atoms in it. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, neopentyl, and isohexyl. An alkyl group can be unsubstituted or substituted with one or more suitable groups.

"Alkoxy” refers to the group alkyl-O- or –O-alkyl, where alkyl group is as defined above. Exemplary alkoxy groups include but are not limited to methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy and *t*-butoxy. An alkoxy group can be unsubstituted or substituted with one or more suitable groups.

"Halogen" or "halo" includes fluorine, chlorine, bromine or iodine.

"Haloalkyl" refers to an alkyl group, as defined above, wherein one or more of the alkyl group's hydrogen atoms has been replaced with - F,- Cl,- Br or -I. Representative examples of an haloalkyl group include, but are not limited to -CH_2F, -CCl_3, -CF_3, -CH_2Cl, -CH_2CH_2Br, -CH_2CH_2I, -$CH_2CH_2CH_2F$, -$CH_2CH_2CH_2Cl$, -$CH_2CH_2CH_2CH_2Br$, -$CH_2CH_2CH_2CH_2I$, -

$CH_2CH_2CH_2CH_2CH_2Br$, $-CH_2CH_2CH_2CH_2CH_2I$, $-CH_2CH(Br)CH_3$, $-CH_2CH(Cl)CH_2CH_3$, and $-CH(F)CH_2CH_3$.

"Cyano" refers to –CN group.

"Hydroxy" or "Hydroxyl" refers to -OH group.

"Hydroxyalkyl" refers to the an alkyl group substituted with one or more hydroxy groups; the alkyl group and hydroxy group are same as defined above. Representative examples of an hydroxyalkyl group includes but are not limited to $–CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH(OH)CH_3$, $-CH_2CH(OH)CH_2CH_3$ and the like.

"Amino" refers to an –N- group, the nitrogen atom of said group being attached to a hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl or any suitable groups. Representative examples of an amino group include, but are not limited to $–NH_2$, $-NHCH_3$ and -NH-cyclopropyl. An amino group can be unsubstituted or substituted with one or more of the suitable groups.

"Aryl" refers to an optionally substituted monocylic, bicyclic or polycyclic aromatic hydrocarbon ring system of about 6 to 14 carbon atoms. Examples of a C_6-C_{14} aryl group include, but are not limited to phenyl, naphthyl, biphenyl, anthryl, tetrahydronaphthyl, fluorenyl, indanyl, biphenylenyl and acenaphthyl. Aryl group can be unsubstituted or substituted with one or more suitable groups;

"Cycloalkyl" refers to a non-aromatic, saturated, monocyclic, bicyclic or polycyclic hydrocarbon ring system. Representative examples of a cycloalkyl include, but are not limited to cyclopropyl, cyclopentyl, cycloheptyl, cyclooctyl, decahydronaphthalen-1-yl, octahydro-1H-inden-2-yl and decahydro-1H-benzo[7] annulen-2-yl. A cycloalkyl can be unsubstituted or substituted with one or more suitable groups.

The term "Heterocyclyl" includes the definitions of "heterocycloalkyl" and "heteroaryl". The term "Heterocycloalkyl" refers to a non-aromatic, saturated or partially saturated, monocyclic or polycyclic ring system of 3 to 10 member having at least one heteroatom or heterogroup selected from O, N, S, S(O), $S(O)_2$, NH and C(O). Exemplary heterocycloalkyl groups include piperdinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,3-dioxolanyl, 1,4-dioxanyl and the like. A heterocycloalkyl group can be unsubstituted or substituted with one or more suitable groups;

"Heteroaryl" refers to an unsaturated, monocyclic, bicyclic, or polycyclic aromatic ring system containing at least one heteroatoms selected from oxygen, sulfur and nitrogen. Examples

of C_5-C_{10} heteroaryl groups include furan, thiophene, indole, azaindole, oxazole, thiazole, thiadiazole, isoxazole, isothiazole, imidazole, N-methylimidazole, pyridine, pyrimidine, pyrazine, pyrrole, N-methylpyrrole, pyrazole, N-methylpyrazole, 1,3,4-oxadiazole, 1,2,4-triazole, 1-methyl-1,2,4-triazole, 1H-tetrazole, 1-methyltetrazole, benzoxazole, benzothiazole, benzofuran, benzisoxazole, benzimidazole, N-methylbenzimidazole, azabenzimidazole, indazole, quinazoline, quinoline, and isoquinoline. Bicyclic heteroaryl groups include those where a phenyl, pyridine, pyrimidine or pyridazine ring is fused to a 5 or 6-membered monocyclic heterocyclyl ring having one or two nitrogen atoms in the ring, one nitrogen atom together with either one oxygen or one sulfur atom in the ring, or one O or S ring atom. A heteroaryl group can be unsubstituted or substituted with one or more suitable groups.

"Hetero atom" refers to a sulfur, nitrogen or oxygen atom.

"Hetero group" refers to –C(O)-, -S(O), -NH and $S(O)_2$.

The terms "monocyclic", "bicyclic" or "tricyclic" ring refers to a saturated, partially saturated or unsaturated 4-16 membered ring, in which 1 to 4 of the ring carbon atoms have been independently replaced with a heteroatom/heterogroups such as N, O, S, –C(O)-, -S(O), -NH and $S(O)_2$. Representative examples of a 4 to 16 membered ring include, but are not limited to 1H-imidazole, 1H-pyrrole, 1H-1,2,3-triazole, 1H-benzo[d]imidazole, 3H-imidazo[4,5-b]pyridine, 1H-indole, 3H-imidazo[4,5-c]pyridine, 1H-benzo[d][1,2,3]triazole, 1H-benzo[d]imidazol-2(3H)-one, 4,5,6,7-tetrahydro-1H-benzo[d]imidazole, 3H-[1,2,3]triazolo[4,5-b]pyridine, imidazo[1,2-b]pyridazine, imidazo[1,2-a]pyridine, imidazo[1,2-a]pyrimidine, pyrazolo[1,5-a]pyridine, pyrazolo[1,5-a]pyrimidine, 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole, dibenzo[b,d]furan, 2,3,4,9-tetrahydro-1H-carbazole, 1,2,3,4-tetrahydroimidazo[1,2-a:4,5-c']dipyridine, 1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine, 1,2,3,4-tetrahydropyrazino[1,2-a]indole and the like

"Optionally substituted or substituted" as used herein means that at least one or two hydrogen atoms of the optionally substituted group has been substituted with suitable groups as exemplified but not limited to alkyl, alkenyl, alkoxy, alkynyl, aryl, amido, amino, carboxy, cyano, cycloalkyl, guanidine, halogen, imidamide, hydroxy, nitro, haloalkyl, alkoxyalkyl, haloalkoxy, heterocyclyl, oxo(=O), thio(=S), $-P(O)_3H$, $-P(O)_2NH_2$, $-P(O)_2NH$(alkyl), $-P(O)_2NH$(cycloalkyl),$-P(O)_2NH$(heterocyclyl), $-P(O)_2NH$(aryl), -C(O)(alkyl), -C(O)(aryl), -C(O)(cycloalkyl), -C(O)(heterocyclyl), or two substituents on the same carbon atom combined

together to form an optionally substituted 3-8 member ring containing 0-3 heteroatoms independently selected form N, O and S in any stable combination.

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.

The use of the term “including” as well as other forms, such as “include”, “includes”, and “included”, is not limiting.

As used herein, the terms “treat”, "treating" or "treatment" encompass either or both responsive and prophylaxis measures, e.g., measures designed to inhibit or delay the onset of the disease or disorder, achieve a full or partial reduction of the symptoms or disease state, and/or to alleviate, ameliorate, lessen, or cure the disease or disorder and/or its symptoms. The terms “treat,” “treating” or “treatment”, include, but are not limited to, prophylactic and/or therapeutic treatments.

As used herein the terms "subject" or "patient" are well-recognized in the art, and, are used interchangeably herein to refer to a mammal, including dog, cat, rat, mouse, monkey, cow, horse, goat, sheep, pig, camel, and, most preferably, a human. In some embodiments, the subject is a subject in need of treatment or a subject with a disease or disorder. However, in other embodiments, the subject can be a normal subject. The term does not denote a particular age or sex. Thus, adult and new-born subjects, whether male or female, are intended to be covered.

As used herein the term “therapeutically effective amount,” refers to a sufficient amount of a compound or a composition being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. The term “therapeutically effective amount” includes, for example, a prophylactically effective amount.

"Pharmaceutically acceptable" means that, which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and “Pharmaceutically acceptable salt” or “pharmaceutically acceptable derivatives” is taken to mean an active ingredient, which comprises a compound of the present invention of formula (I) in the form of one of its salts, in particular if this salt form imparts improved pharmacokinetic properties on the active ingredient compared with the free form of the active ingredient or any other salt form of the active ingredient used earlier. The pharmaceutically acceptable salt form of

the active ingredient can also provide this active ingredient for the first time with a desired pharmacokinetic property which it did not have earlier and can even have a positive influence on the pharmacodynamics of this active ingredient with respect to its therapeutic efficacy in the body.

In one particular embodiment, the compounds of the present invention and their pharmaceutically compositions are used in the treatment and/or prevention of diseases and/or disorders in which aberrant, abnormal or deregulated activity of TAK-1, AAK-1, BIKE, CDK (CDK-1,2,3,4,5,9), Syk, ALK , BTK, FLT (FLT-3,4), JAK (JAK-1,2,3), KDR, VEGR-2, ZAP-70, INSR, Aurora, p38, AXL, MUSK, Trk A, GSK-3, c-SRC, PDGFR, IRAK-4, GLK, Erk, FLT, GAK, KIT, MAP2K, MNK, NIK, NLK, PBK, PKD, PRP4, RSK, SPEG, TGFR or ZAK 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.

Diseases and/or disorders associated with aberrant, abnormal or deregulated activity of TAK-1, AAK-1, BIKE, CDK (CDK-1,2,3,4,5,9), Syk, ALK , BTK, FLT (FLT-3,4), JAK (JAK-1,2,3), KDR, VEGR-2, ZAP-70, INSR, Aurora, p38, AXL, MUSK, Trk A, GSK-3, c-SRC, PDGFR, IRAK-4, GLK, Erk, FLT, GAK, KIT, MAP2K, MNK, NIK, NLK, PBK, PKD, PRP4, RSK, SPEG, TGFR or ZAK kinases include, but are not limited to allergic disorders and/or autoimmune and/or inflammatory diseases and/or conditions associated with inflammation and pain, cancers, proliferative diseases, hematopoietic disorders, hematological 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.

In particular, the compounds according to the present invention possess potential of providing cancer cell growth inhibiting effects and are effective in treating cancers, autoimmune and inflammatory diseases; in particular cancer includes all types of solid cancers and malignant lymphomas but not limited to leukaemia, skin cancer, bladder cancer, breast cancer, uterus cancer, ovary cancer, prostate cancer, lung cancer, colon cancer, pancreas cancer, renal cancer, gastric cancer, brain tumour & etc; and particularly the compounds according to the present invention are used in the treatment of autoimmune and/or inflammatory diseases and/or

conditions associated with inflammation and pain include, but are not limited to acid reflux, heart burn, acne, allergies and allergen sensitivities, bronchitis, carditis, celiac disease, chronic pain, cirrhosis, colitis, dementia, dermatitis, diabetes, dry eyes, edema, emphysema, eczema, fibromyalgia, gastroenteritis, gingivitis, heart disease, hepatitis, high blood pressure, insulin resistance, interstitial cystitis, joint pain/arthritis/rheumatoid arthritis, atherosclerosis, sarcoid, spinal cord injury, stroke, chronic inflammatory demyelinating neuropathy, radiation induced demyelination, hereditary demyelinating condition, a prion-induced demyelination, encephalitis induced demyelination, Sjogren's disease, tissue graft rejection, and hyperacute rejection of transplanted organs, Kaposi's sarcoma associated with HIV, asthma, systemic lupus erythematosus (and associated glomerulonephritis), juvenile cystic kidney disease, and type I nephronophthisis (NPHP), dermatomyositis, multiple sclerosis, scleroderma, vasculitis (ANC Aassociated and other vasculitides), autoimmune hemolytic and thrombocytopenic states, Good pasture's syndrome (and associated glomerulonephritis and pulmonary hemorrhage), chronic idiopathic thrombocytopenic purpura (ITP), Addison's disease, Parkinson's disease, Guam-Parkinson dementia, supranuclear palsy, Alzheimer's disease, diabetes, septic shock and myasthenia gravis, Kuf's disease, and Pick's disease, as well as memory impairment, brain ischemia, and schizophrenia, periodontal disease, polyarteritis, polychondritis, psoriasis, scleroderma, sinusitis, Sjogren's syndrome, spastic colon, systemic candidiasis, tendonitis, urinary tract infections, vaginitis, inflammatory cancer (e.g., inflammatory breast cancer) and the like.

The subject treated in the present methods is a mammal, preferably mice, rat, rabbit, dog, horse, monkey or a human being, male or female, in whom modulation of TAK-1, AAK-1, BIKE, CDK (CDK-1,2,3,4,5,9), Syk, ALK , BTK, FLT (FLT-3,4), JAK (JAK-1,2,3), KDR, VEGR-2, ZAP-70, INSR, Aurora, p38, AXL, MUSK, Trk A, GSK-3, c-SRC, PDGFR, IRAK-4, GLK, Erk, FLT, GAK, KIT, MAP2K, MNK, NIK, NLK, PBK, PKD, PRP4, RSK, SPEG, TGFR or ZAK receptor activity may be desired. "Modulation" as used herein is intended to encompass antagonism, agonism, partial antagonism, inverse agonism and/or partial agonism. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The compounds and pharmaceutically compositions of the present invention may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of the present invention may be useful. Such other drugs may be administered, by a route and in an amount commonly used there for, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention may also be preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

A pharmaceutical composition of the invention may be formulated as being compatible with its intended route of administration, which may preferably be an oral administration. For example the pharmaceutical compositions of the invention may be formulated for administration by inhalation, such as aerosols or dry powders; for oral administration, such in the form of tablets, capsules, gels, syrups, suspensions, emulsions, elixirs, solutions, powders or granules; for rectal or vaginal administration, such as suppositories; or for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular, or infusion) such as a sterile solution, suspension or emulsion.

The compounds of the present invention may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethyl cellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, *Osol, A. Ed.* (1980).

The substituted pyrimidine amine derivatives of formula (I) according to the present invention may be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred experimental conditions (i.e. reaction temperatures, time, moles of reagents, solvents etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by

the person skilled in the art, using routine optimization procedures. The specifics of the processes according to the present invention are detailed in the example section mentioned below.

In a further aspect, the compounds of the present invention can also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the present invention also embraces isotopically-labeled variants of the present invention which are identical to those recited herein, but for the fact that one or more atoms of the compound are replaced by an atom having the atomic mass or mass number different from the predominant atomic mass or mass number usually found in nature for the atom. All isotopes of any particular atom or element as specified are contemplated within the scope of the compounds of the invention, and their uses. Exemplary isotopes that can be incorporated in to compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine and iodine, such as ^{2}H ("D"), ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I and ^{125}I. Isotopically labeled compounds of the present inventions can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

The abbreviations used in the entire specification may be summarized herein below with their particular meaning.

atm (atmosphere); Boc anhydride/Boc_2O (Di-*tert*-butyl dicarbonate); NaH (sodium hydride); brine (NaCl solution); bs (broad singlet); J (coupling constant); ^{o}C (degree Celsius); DBU (2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine); DMF (N,N-dimethyl formamide); DIPEA/DIEA (N, N- Diisopropyl ethyl amine); DEAD (Diethyl azodicarboxylate); DPPA (Diphenylphosphoryl azide); DMAP (4-Dimethylaminopyridine); CH_2Cl_2/DCM (dichloromethane); $CDCl_3$ (deuteriated chloroform); $CHCl_3$ (chloroform); d (doublet); dd (doublet of doublet); EDC.HCl (1-(3-Dimethyl aminopropyl)-3-carbodiimide hydrochloride); H_2 (hydrogen gas); HPLC(High-performance liquid chromatography); HOBT (1-Hydroxy benzotriazole); HBr (Hydrogen bromide); EtOAc (Ethyl acetate); MeOH (methanol); EtOH (ethanol); Et_2O (diethyl ether); g (gram); IPA (Isopropanol): H (hydrogen); HCl (hydrochloric acid); $HClO_4$ (perchloric acid); h (hours); mmol (milli mole); M (molar); mL (milli litre); mg (milli gram); m (multiplet); MHz (mega hertz); Hz (hertz); MS (ES) (mass spectroscopy-electro spray); min (minutes); N_2 (nitrogen); $MgSO_4$ (Magnesium sulfate); NMR (nuclear magnetic

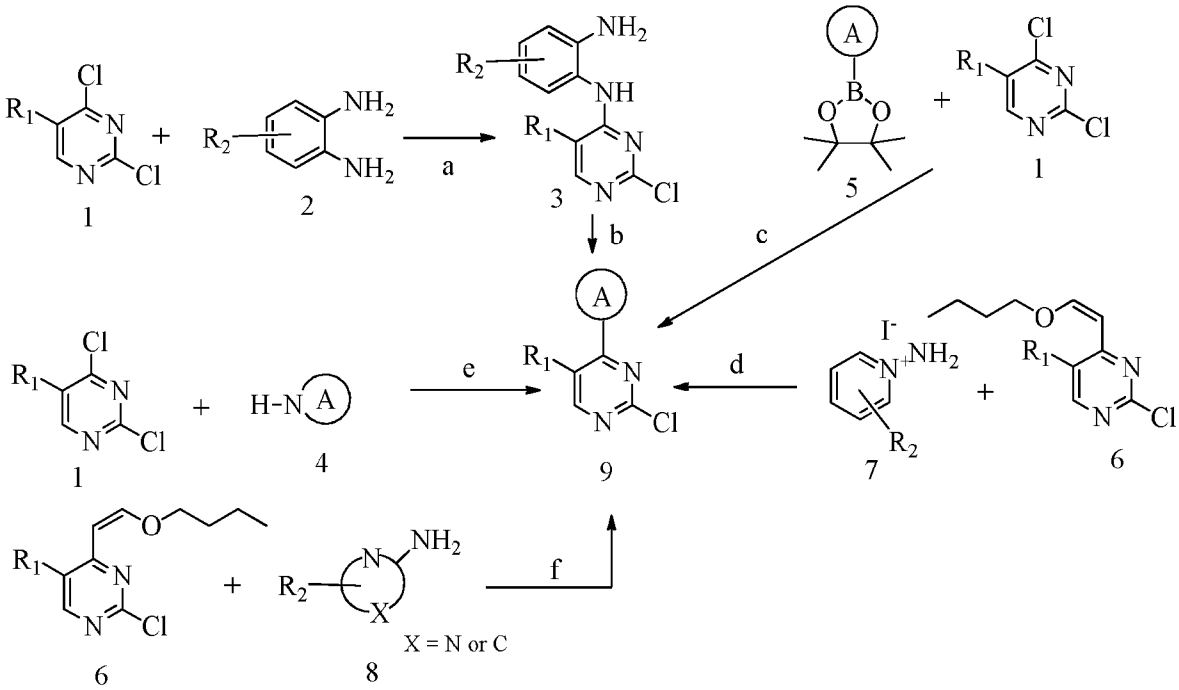
resonance spectroscopy); K_2CO_3 (potassium carbonate); LAH (Lithium aluminium hydride); Pd/C (Palladium carbon); $Pd_2(dba)_3$ (trisdibenzylideneacetone)dipalladium; $Pd(OAc)_2$ (Palladium diacetate); Na_2SO_4 (Sodium sulphate); $NaHCO_3$ (Sodium bicarbonate); NaOMe (Sodium methoxide); $LiBH_4$ (Lithium borohydride); NaOH (Sodium hydroxide); NH_4OH (Ammonium hydroxide); s (singlet); TsOH (*p*-toluenesulfonic acid); TLC (Thin Layer Chromatography); THF (tetrahydrofuran); TEA (triethylamine); TFA (trifluoro acetic acid); t (triplet); H_2O (water); RT (Room temperature: 20-35°C); NBS (N-Bromosuccinamide); $NaHCO_3$ (Sodium bicarbonate); $Pd(PPh_3)_4$ (Tetrakis(triphenylphosphine)palladium(0)); PPh_3 (triphenylphosphine); Conc. (Concentrated); DMSO (Dimethyl sulfoxide); nM (nanomolar); ppm-δ (parts per million); Hz (Hertz); MeOH (methanol); µM (micro molar); LC/MS (Liquid chromatography–mass spectrometry); m/z (molecular weight).

GENERAL MODES OF PREPARATION

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.

A general approach for the synthesis of compounds of general formula (I) is depicted in below schemes. As used herein the below schemes the terms 'R_1', 'R_2', 'R_3', 'R_4', 'A', 'L', 'C' 'm' and 'n' represents all the possible substitutions as disclosed in formula Ia, Ib and Ic.

A general approach for the synthesis of critical intermediate of the present invention is depicted in schemes-a, b, c, d, e, and f.



Scheme-a: Substituted 2,4-dichloro pyrimidine derivatives (1) are treated with 1,2-diamines (2) using organic solvents such as (*i*PrOH, *n*BuOH), base (TEA, DIPEA) at 100°C to 120°C for about 12 to 16 h to get the compound of general formula (3).

Scheme-b: Compound of general formula (3) are treated with acid (such as *p*-toluenesulfonic acid), trimethyl orthoformate at about 100°C for 2 h to get the compound of general formula (9).

Scheme-c: Substituted 2,4-dichloro pyrimidine derivatives (1) are treated with boronate esters (5) using base (such as tripotassium phosphate, cesium carbonate, potassium carbonate, sodium carbonate), palladium(0) catalyst and tricyclohexylphosphine using solvents (such as DMF, DME, dioxane, acetonitrile) at 90°C to 100°C for about 1 h to 2 h to get the compound of general formula (9).

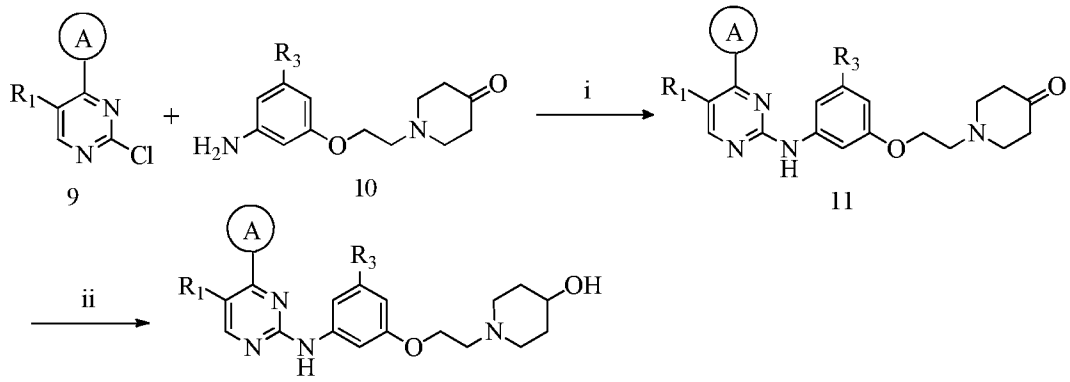
Scheme-d: An appropriate amine like 1-aminopyridin-1-ium iodide (7) was reacted with compound of general formula (6) in presence of NBS at room temperature to 60°C for about 1 h to 5 h using solvent (such as DMF, dioxane, acetonitrile) in combination of water to get the compound of general formula (9).

Scheme-e: Substituted 2,4-dichloro pyrimidine derivatives (1) are treated with appropriate amines (4) in presence of base such as NaH, DIPEA, *t*BuOk and the like, in suitable organic solvents such as DMF, THF, n-butanol and the like were reacted at the suitable

temperature range of about 0°C to room temperature for about 30 minute to 1 h to get the compound of general formula (9).

Scheme-f: An appropriate heteroaryl amines (8) was reacted with compound of general formula (6) in presence of a base (such as cesium carbonate, potassium carbonate, sodium carbonate) at 90°C to 100°C for about 1 h to 2 h using solvent (such as DMF, dioxane, acetonitrile) to get the compound of general formula (9).

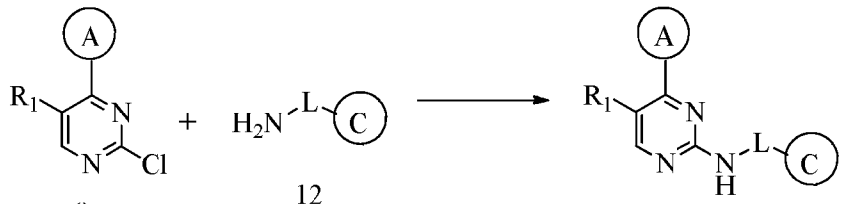
Scheme-I:



Formula Ia

Substituted 2-chloro pyrimidine derivatives (9) and appropriate amines (10) were reacted in presence of organic solvents (such as dioxane, acetonitrile, DME, DMF, THF), base (such as cesium carbonate, potassium carbonate, sodium carbonate), palladium(0) catalysts and xantphos at about 60°C for about 30 min to 1 h under microwave condition to get the compound of general formula 11. Compound of general formula 11 are treated with $NaBH_4$, $LiAlH_4$ and the like, solvents used such as (MeOH, EtOH, *i*PrOH, in combination of THF) at RT for about 30 min to 1 h to get the compound of general formula Ia.

Scheme-II:

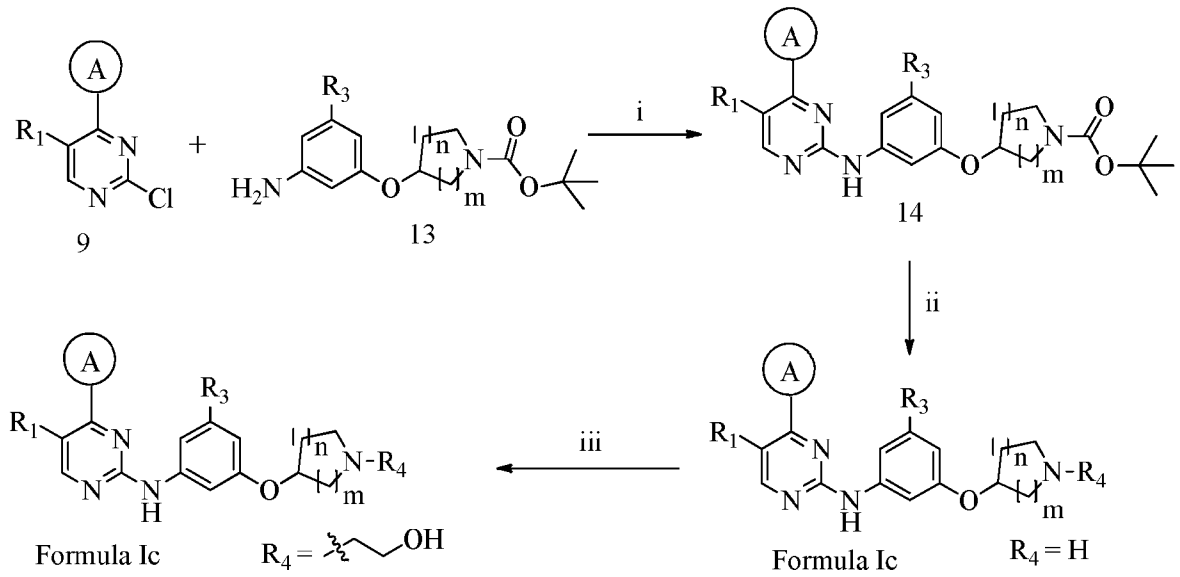


Formula Ib

Substituted 2-chloro pyrimidine derivatives (9) are treated with appropriate amines (12) in presence of organic solvents (such as dioxane, acetonitrile, DME, DMF, THF), base (such as cesium carbonate, potassium carbonate, sodium carbonate), palladium(0) catalyst and xantphos

at about 80°C to 100°C for about 30 min to 1 h to get the compound of general formula Ib. Alternatively the general formula Ib can be prepared from substituted 2-chloro pyrimidine derivatives (9) and appropriate amines (12) in presence of organic solvents (such as *i*PrOH, *t*BuOH), base (such as triethylamine, diisopropylethylamine, DBU) at about 90°C to 110°C for about 12 h to 16 h.

Scheme-III:



Substituted 2-chloro pyrimidine derivatives (9) are treated with appropriate amines (13) in presence of organic solvents (such as dioxane, acetonitrile, DME, DMF, THF), base (such as Cs_2CO_3, K_2CO_3, Na_2CO_3 and the like), palladium(0) catalysts and xantphos at about 80°C to 100°C for about 30 min to 1 h to get the compound of general formula 14. Compound of general formula 14 is treated with trifluoroacetic acid, HCl in dioxane/diethyl ether, acetic acid and the like in suitable organic solvents such as DCM, dioxane, acetonitrile, DME, DMF, THF at about 25°C to 35°C for about 1 h to 4 h to get the compound of general formula Ic (wherein R_4 is H). Compound of general formula Ic (wherein R_4 is H) is treated with 2-bromoethanol, solvents used such as (such as dioxane, acetonitrile, DME, DMF, THF), base (such as TEA, DIPEA and the like) at 30°C to 40°C for about 1 h to 2 h to get the compound of general formula Ic (wherein R_4 is hydroxy alkyl).

EXAMPLES

Although the invention has been illustrated by certain of the preceding examples, it is not to be construed as being limited thereby; but rather, the invention encompasses the generic area

as hereinbefore disclosed. Various modifications and embodiments can be made without departing from the spirit and scope thereof.

The MS data provided in the examples described below were obtained as follows:

Mass spectrum: LC/MS Agilent 6120 Quadrapole LC/MS.

The NMR data provided in the examples described below were obtained as follows:

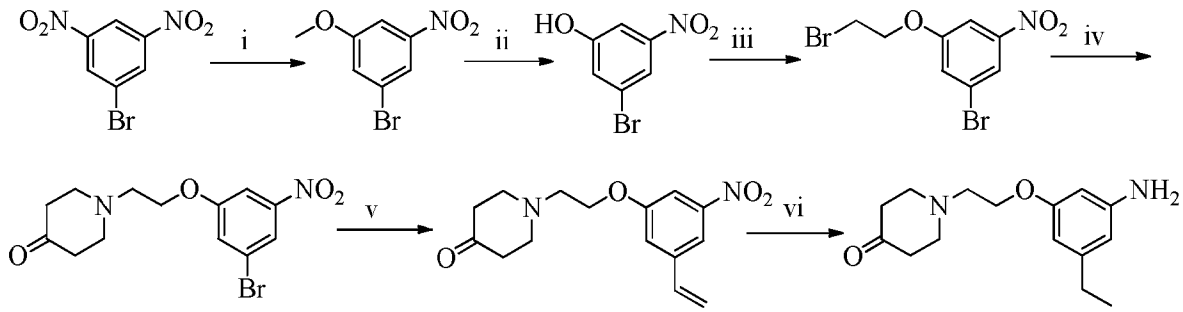
^{1}H-NMR: Varian 400 MHz.

The microwave chemistry was performed on a CEM Explorer.

The procedure for the compounds of formula (I) are detailed herein below stepwise including the synthesis of various intermediates involved in process of manufacture of the compounds according to the present invention.

Experimental:

Intermediate-1: Synthesis of 1-(2-(3-amino-5-ethylphenoxy)ethyl)piperidin-4-one:



Step-i: Synthesis of 1-bromo-3-methoxy-5-nitrobenzene:

To a stirred solution of 3,5-dinitrobromobenzene (12.5 g, 50.6 mmol) in methanol (120 mL) was added solution of sodium methoxide (0.5 M in methanol, 126 mL). This mixture was heated to 60°C for 2h. After completion of the reaction, the reaction mixture was cooled to RT and quenched with 1N HCl solution. The reaction mixture was extracted with dichloromethane. The organic layer washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (silica gel, 9:1 *n*-hexane/EtOAc) to afford the desired product as an off-white solid (10 g, 80%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (s, 1H), 7.67 (s, 1H), 7.37 (s, 1H), 3.89 (s, 3H).

Step-ii: Synthesis of 3-bromo-5-nitrophenol:

A solution of 3-bromo-5-nitroanisole (9.6 g, 41.2 mmol) in DCM (200 mL) was cooled to 0°C and treated with boron tribromide (1M in CH_2Cl_2, 158 mL, 158 mmol), giving a clear purple solution. The reaction mixture heated to reflux for 2.5 hours. The reaction was poured into

ice/water, the layers were separated and extracted with methylene chloride. The aqueous layer was neutralized with aqueous saturated $NaHCO_3$ and extracted with DCM. The organic layer washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (silica gel, 10:1 to 5:1 *n*-hexane/EtOAc) to afford desired product as a yellow solid (8 g, 91%). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 10.92 (bs, 1H), 7.79 (s, 1H), 7.55 (s, 1H), 7.39 (s, 1H) and MS (ES) m/e 216 $(M–H)^+$.

Step-iii: Synthesis of 1-bromo-3-(2-bromoethoxy)-5-nitrobenzene:

To a stirred solution of 3-bromo-5-nitrophenol (9 g, 41 mmol) in acetone (90 mL), was added K_2CO_3 (17 g, 123 mmol) and allowed to stirred at room temperature for 30 min. To mixture 1,2-dibromoethane (11.5 g, 61 mmol) was added drop wise and heated at 80°C for 5 h. After completion of reaction, reaction mixture was poured on ice, solid obtained was filtered and dried to afford the desired product as a brown solid (7.5 g, 56%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (s, 1H), 7.69 (s, 1H), 7.40 (s, 1H), 4.37 (t, *J* = 12 Hz, 2H), 3.67 (t, *J* = 12 Hz, 2H) and MS (ES) m/e 216 $(M–H)^+$.

Step-iv: Synthesis of 1-(2-(3-bromo-5-nitrophenoxy) ethyl) piperidin-4-one:

To a mixture of 4-piperidone hydrochloride (7.44 g, 48 mmol) in DMF (70 mL), was added K_2CO_3 (9.5 g, 69 mmol) and stirred at room temperature for 30 min. To the above mixture 1-bromo-3-(2-bromoethoxy)-5-nitrobenzene (7.5 g, 23 mmol) was added drop wise by dissolving in DMF (10 mL). Reaction was stirred at room temperature for 12 h. After completion of reaction, reaction mixture was poured on ice, obtained solid was filtered and dried under vacuum to get the desired product (6.8 g, 87%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (s, 1H), 7.76 (s, 1H), 7.70 (s, 1H), 4.29 (t, *J* = 12 Hz, 2H), 2.87 (t, *J* = 12 Hz, 2H), 2.84-2.73 (m, 4H), 2.50-2.49 (m, 4H) and MS (ES) m/e 345 $(M+2H)^{2+}$.

Step-v: Synthesis of 1-(2-(3-nitro-5-vinylphenoxy) ethyl) piperidin-4-one:

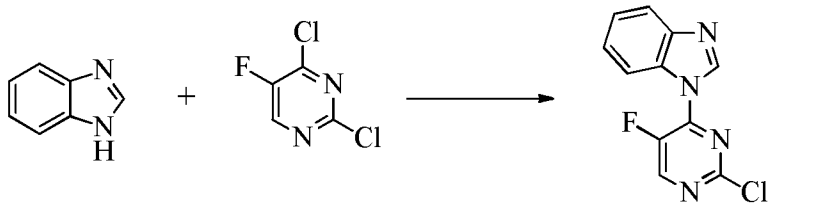
Reaction flask was charged with 1-(2-(3-bromo-5-nitrophenoxy)ethyl)piperidin-4-one (6.8 g, 19.8 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (6.1 g, 39.6 mmol) and K_2CO_3 (8.2 g, 59 mmol) in 70 mL of 1,4-dioxane in water (7:3) was degassed with nitrogen for 30 min. To the above mixture $Pd(PPh_3)_4$ (1.1 g, 0.99 mmol) was added and again degassed for 30 min, reaction mixture was heated at 90°C for 2h. After completion of reaction, reaction mixture was cooled to room temperature, diluted with ethyl acetate and passed through celite. The filtrate was washed with water followed by brine. The organic layer was dried over anhydrous sodium

sulphate and concentrated under reduced pressure. The obtained crude was purified by column chromatography (2:8 EtOAc/*n*-hexane) to obtain the title product as an off-white solid (4 g, 67%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (s, 1H), 7.66 (s, 1H), 7.56 (s, 1H), 6.87-6.80 (dd, *J* = 8.0 Hz, 12 Hz, 1H), 6.12 (d, *J* = 17.6 Hz, 1H), 5.47 (d, *J* = 11.2 Hz, 1H), 4.29 (t, *J* = 12 Hz, 2H), 2.89 (t, *J* = 12 Hz, 2H), 2.85-2.82 (m, 4H), 2.50-2.49 (m, 4H) and MS (ES) m/e 291 $(M+H)^+$.

Step-vi: Synthesis of 1-(2-(3-amino-5-ethylphenoxy)ethyl)piperidin-4-one:

1-(2-(3-nitro-5-vinylphenoxy)ethyl)piperidin-4-one (4 g, 13.7 mmol) was dissolved in methanol (130 mL). To the above solution 10% Pd/C (0.4 g) was added at room temperature and stirred under hydrogen atmosphere for 2h. After completion of reaction, reaction mixture was filtered through celite bed and washed with methanol. Filtrate was concentrated under reduced pressure to afford a crude compound (3.2 g, crude). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.00 (s, 1H), 5.97-5.95 (m, 2H), 4.93 (bs, 2H), 3.99 (t, *J* = 5.6 Hz, 2H), 2.80 (t, *J* = 5.9 Hz, 6H), 2.42-2.33 (m, 6H), 1.11 (t, *J* = 7.5 Hz, 3H) and MS (ES) m/e 263 $(M+H)^+$.

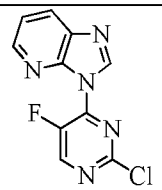
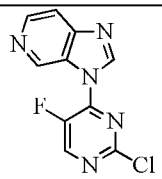
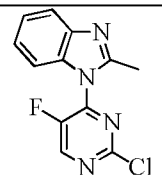
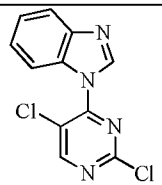
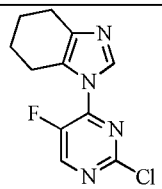
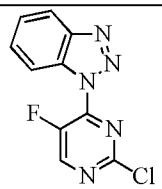
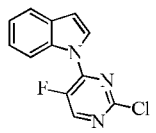
Intermediate-2: Synthesis of 1-(2-chloro-5-fluoropyrimidin-4-yl)-1*H*-benzo[*d*]imidazole:

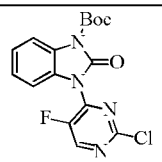
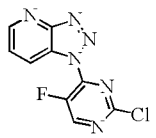
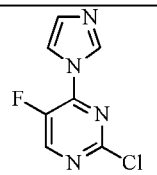
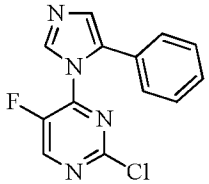
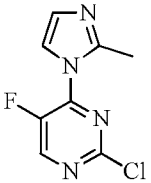
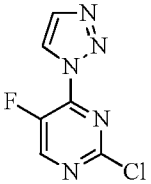
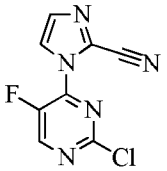
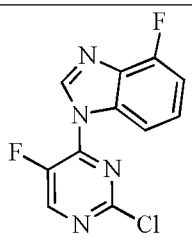


Intermediate-2

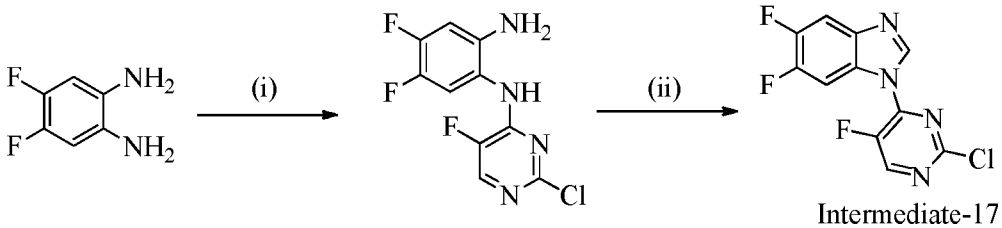
To a suspension of NaH (28 mg, 0.71 mmol) in dry THF (5 mL), was added benzimidazole (70 mg, 0.59 mmol) in portion wise and stirred at 0°C for 30 min. To the above mixture 2,4-dichloro-5-fluoropyrimidine (100 mg, 0.59 mmol) was added and stirred at room temperature for 30 min. After completion of reaction, excess of NaH was quenched with ice cold water and extracted with EtOAc. The organic phase was washed with water followed by brine, dried over Na_2SO_4 and concentrated. The crude was purified by column chromatography on silica gel eluting with DCM:MeOH (95:5) as eluent to obtain the titled product as an off-white solid (0.14 g, 94%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.10 (d, *J* = 3.6 Hz, 1H), 8.82 (d, *J* = 2.0 Hz, 1H), 8.25 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.52-7.42 (m, 2H) and MS (ES) m/e 249 $(M+H)^+$.

Below intermediates were prepared by following similar procedure as depicted in intermediate 2, by using approprite raw materials at suitable conditions.

Int No.	Structure	Characterization Data
3		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.14 (d, J = 3.6 Hz, 1H), 9.09 (d, J = 2.0 Hz, 1H), 8.62-8.56 (m, 2H), 7.56-7.53 (m, 1H) and MS (ES) m/e 250 $(M+H)^+$.
4		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.17-9.15 (m, 2H), 8.95 (d, J = 1.6 Hz, 1H), 8.62 (d, J = 6.0 Hz, 1H), 8.16 (d, J = 5.6 Hz, 1H) and MS (ES) m/e 250 $(M+H)^+$.
5		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25 (d, J = 1.6 Hz, 1H), 7.68 (d, J = 2.4 Hz, 1H), 7.49-7.46 (m, 1H), 7.33-7.28 (m, 2H), 2.61 (s, 3H) and MS (ES) m/e 263 $(M+H)^+$.
6		^{1}H NMR (400 MHz, DMSO-d$_6$): δ 9.20 (s, 1H), 8.85 (s, 1H), 7.87-7.81 (m, 2H), 7.44-7.40 (m, 2H) and MS (ES) m/e 265 $(M+H)^+$.
7		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.04 (d, J = 3.6 Hz, 1H), 8.06 (d, J = 3.2 Hz, 1H), 2.80 (bs, 2H), 2.52-2.51 (m, 2H), 1.77-1.75 (m, 4H) and MS (ES) m/e 253 $(M+H)^+$.
8		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.76 (d, J = 2.9 Hz, 1H), 8.49 (d, J = 8.8 Hz, 1H), 8.21 (d, J = 8.3 Hz, 1H), 7.76-7.72 (m, 1H), 7.60-7.53 (m, 1H) and MS (ES) m/e 250 $(M+H)^+$.
9		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (d, J = 3.9 Hz, 1H), 8.34 (d, J = 8.4 Hz, 1H), 7.89 (t, J = 3.2 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.38 (t, J = 7.1 Hz, 1H), 7.36-7.29 (m, 1H), 6.93 (d, J = 3.4 Hz, 1H) and MS (ES) m/e 248 $(M+H)^+$.

10		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 (d, J = 2.0 Hz, 1H), 7.78-7.76 (m, 1H), 7.47-7.45 (m, 1H), 7.31-7.29 (m, 1H), 7.26-7.24 (m, 1H), 1.62 (s, 9H) and MS (ES) m/e 265 (M-boc).
11		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.27 (d, J = 3.5 Hz, 1H), 8.93 (dd, J = 1.2, 4.6 Hz, 1H), 8.77 (dd, J = 1.5, 8.3 Hz, 1H), 7.92-7.88 (m, 1H) and MS (ES) m/e 251 (M+H)$^+$.
12		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.06 (d, J = 4.0 Hz, 1H), 8.48 (s, 1H), 7.90 (d, J = 1.2 Hz, 1H), 7.24 (s, 1H) and MS (ES) m/e 199 (M+H)$^+$.
13		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63 (d, J = 4.0 Hz, 1H), 8.54 (s, 1H), 8.12 (s, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.46-7.32 (m, 3H); MS (ES) m/e 275 (M+H)$^+$.
14		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63 (d, J = 2.4 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 7.08 (s, 1H), 2.70 (s, 3H) and MS (ES) m/e 213 (M+H)$^+$.
15		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 (d, J = 2.4 Hz, 1H), 8.6 (d, J = 1.2 Hz, 1H), 7.91 (d, J = 1.6 Hz, 1H) and MS (ES) m/e 200 (M+H)$^+$.
16		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.79 (d, J = 2 Hz, 1H), 7.74 (d, J = 4 Hz, 1H), 7.44 (d, J = 1.2 Hz, 1H) and MS (ES) m/e 224 (M+H)$^+$.
16a		MS (ES) m/e 267 (M+H)$^+$.

Intermediate-17: Synthesis of 1-(2-chloro-5-fluoropyrimidin-4-yl)-5,6-difluoro-1H-benzo[d] imidazole:



Intermediate-17

Step-i: Synthesis of N^1-(2-chloro-5-fluoropyrimidin-4-yl)-4,5-difluorobenzene-1,2-diamine:

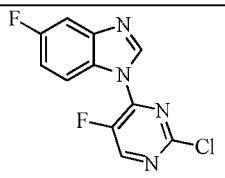
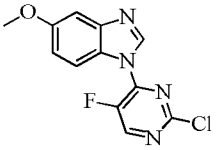
To a stirred solution of 4,5-difluorobenzene-1,2-diamine (0.3 g, 2.08 mmol) in n-butanol (10 mL) was added DIPEA (1.8 mL, 10.41 mmol) followed by 2,4-dichloro-5-fluoropyrimidine (0.347 g, 2.08 mmol) and heated to 120°C for 16 h. After completion of the reaction, the reaction mixture was cooled to RT and diluted with EtOAc. The organic phase was washed with water followed by brine, dried over Na_2SO_4 and concentrated. The crude was further purified by column chromatography on silica gel eluting with *n*-hexane: EtOAc (7:3) as eluent to obtain N^1-(2-chloro-5-fluoropyrimidin-4-yl)-4,5-difluorobenzene-1,2-diamine (0.42 g, 73%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.33 (s, 1H), 8.21 (s, 1H), 7.18-7.13 (m, 1H), 6.70-6.65 (m, 1H), 5.23 (bs, 2H) and MS (ES) m/e 275 $(M+H)^+$.

Step-ii: Synthesis of 1-(2-chloro-5-fluoropyrimidin-4-yl)-5,6-difluoro-1H-benzo[d] imidazole:

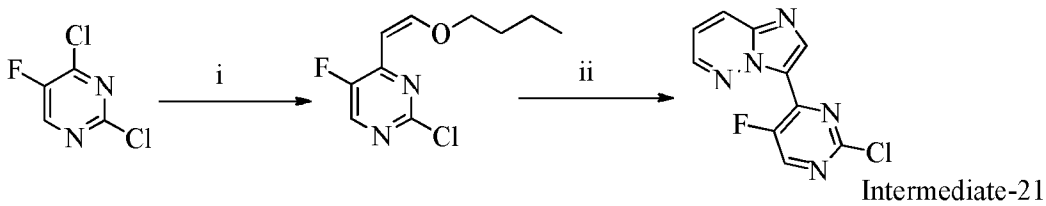
N^1-(2-chloro-5-fluoropyrimidin-4-yl)-4,5-difluorobenzene-1,2-diamine (0.42 g, 1.53 mmol), *p*-toluenesulfonic acid (0.026 g, 0.153 mmol) were dissolved in 10 mL of trimethyl orthoformate and heated to 100°C for 2 h. After completion of reaction, reaction mixture was cooled to RT, diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The crude was then purified by triturating with *n*-pentane to obtain the titled compound as a brown solid (0.32 g, 73%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.15 (d, J = 4 Hz, 1H), 8.91 (d, J = 4 Hz, 1H), 8.21-8.17 (m, 1H), 8.03-7.98 (m, 1H) and MS (ES) m/e 285 $(M+H)^+$.

Below intermediates were prepared by following similar procedure as depicted in intermediate 17, by using approprite raw materials at suitable conditions.

Int No.	Structure	Characterization Data

18		^{1}H NMR (400 MHz, DMSO-d$_6$): δ 9.12 (d, *J* = 4 Hz, 1H), 8.89 (d, *J* = 2 Hz, 1H), 8.27-8.23 (m, 1H), 7.71-7.68 (m, 1H), 7.42-7.37 (m, 1H).
19		^{1}H NMR (400 MHz, DMSO-d$_6$): δ 9.06 (d, *J* = 4 Hz, 1H), 8.78 (d, *J* = 2 Hz, 1H), 8.17-8.14 (m, 1H), 7.37 (s, 1H), 7.12-7.10 (m, 1H), 3.8 (s, 3H) and MS (ES) m/e 279 (M+H)$^+$.
20		^{1}H NMR (400 MHz, DMSO-d$_6$): δ 9.15 (d, *J* = 4 Hz, 1H), 8.85 (s, 1H), 8.07 (d, *J* = 8 Hz, 1H), 7.53-7.48 (m, 1H), 7.33-7.28 (m, 1H) and MS (ES) m/e 267 (M+H)$^+$.

Intermediate-21: Synthesis of 3-(2-chloro-5-fluoropyrimidin-4-yl)imidazo[1,2-b]pyridazine:



Intermediate-21

Step-i: Synthesis of (Z)-4-(2-butoxyvinyl)-2-chloro-5-fluoropyrimidine:

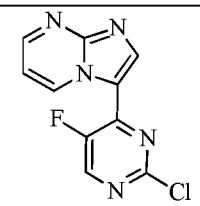
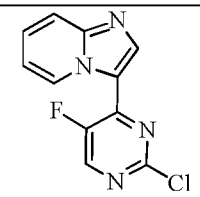
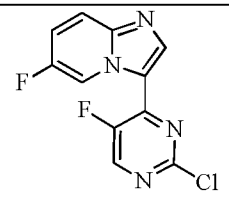
2,4-dichloro-5-fluoropyrimidine (1 g, 7.19 mmol) was added in single portion, to a stirred solution of butyl vinyl ether (0.76 g, 7.6 mmol), Pd(II) acetate (0.16 g, 0.72 mmol) and triethyl amine (0.76 g, 7.6 mmol) in polyethylene glycol (15 mL). Reaction mixture was stirred at 80°C for 2 h. After completion of reaction, reaction mixture was cooled to room temperature and diluted with diethyl ether. Organic layer was washed with water followed by brine and dried over anhydrous Na_2SO_4. Desired compound was obtained by concentrating the dried organic layer under reduced pressure as a gummy brown solid (0.85 g, 51%). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.61 (d, *J* = 2.4 Hz, 1H), 7.98 (d, *J* = 12.3 Hz, 1H), 5.94 (d, *J* = 12.2 Hz, 1H), 4.09 (t, *J* = 6.6 Hz, 2H), 1.69-1062 (m, 2H), 1.43-1.33 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H) and MS (ES) m/e 230 (M+H)$^+$.

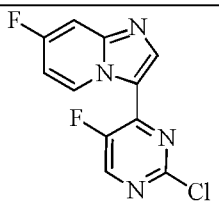
Step-ii: Synthesis of 3-(2-chloro-5-fluoropyrimidin-4-yl)imidazo[1,2-b]pyridazine:

To a stirred solution of (Z)-4-(2-butoxyvinyl)-2-chloro-5-fluoropyrimidine (0.85 g, 3.6 mmol) in 1,4-dioxane (18 mL) and water (7 mL) at room temperature was added NBS (0.65 g, 3.6 mmol) and stirred at room temperature for 1 h. To the above reaction mixture 3-

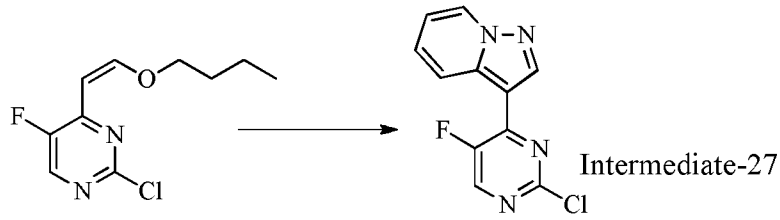
aminopyridazine (0.35 g, 3.6 mmol) was added slowly and heated at 60°C for 5 h. After completion of reaction, excess of 1,4-dioxane was removed under reduced pressure. pH of the reaction mixture was adjusted to 7 by using 5% sodium bi-carbonate solution and extracted with DCM. Organic layer was washed with water followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain crude compound. Crude material was purified by column chromatography (1:9 MeOH/DCM) to obtain pure compound as a solid (0.35 g, 38%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.01 (d, J = 2.5 Hz, 1H), 8.79 (dd, J = 1.5 & 4.4 Hz, 1H), 8.46 (d, J = 2.4 Hz, 1H), 8.36 (dd, J = 1.4 & 9.2 Hz, 1H), 7.52 (dd, J = 4.4 & 9.3 Hz, 1H) and MS (ES) m/e 250 $(M+H)^+$.

Below intermediates were prepared by following similar procedure as depicted in intermediate 21, by using approprite raw materials at suitable conditions.

Int No.	Structure	Characterization Data
22		^{1}H NMR (400 MHz, DMSO-d_6): δ 10.01-9.99 (m, 1H), 8.93 (d, J = 3.4 Hz, 1H), 8.87-8.86 (m, 1H), 8.68 (d, J = 4.0 Hz, 1H), 7.52-7.49 (m, 1H) and MS (ES) m/e: 250 $(M+H)^+$.
23		MS (ES) m/e: 250 $(M+H)^+$.
24		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.76 (d, J = 6.8 Hz, 1H), 8.87 (d, J = 3.4 Hz, 1H), 8.54 (d, J = 4.4 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.69-7.64 (m, 1H), 7.39-7.35 (m, 1H).
25		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.80 (s, 1H), 9.98 (s, 1H),8.58 (s, 1H), 8.00-7.98 (m, 1H), 7.78-7.80 (m, 1H)MS (ES) m/e: 267 $(M+H)^+$.

26		^{1}H NMR (400 MHz, DMSO-d_6): 10.01 (d, J = 7.9 Hz, 1H), 8.58 (d, J = 4.0 Hz, 1H), 8.46 (d, J = 2.9 Hz, 1H), 7.48-7.45 (m, 1H), 7.06-7.01 (m, 1H).

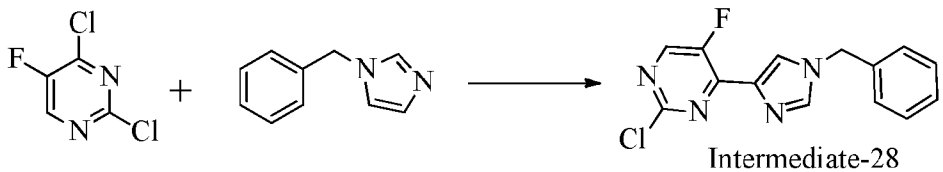
Intermediate-27: Synthesis of 3-(2-chloro-6-fluoropyrimidin-4-yl)pyrazolo[1,5-a]pyridine:



Intermediate-27

To a stirred solution of 1-aminopyridin-1-ium iodide (0.518 g, 2.25 mmol) in dry DMF (10 mL) was potassium carbonate (0.310 g, 2.25 mmol) at 0°C over a period of 15-20 min. A solution of (Z)-4-(2-butoxyvinyl)-2-chloro-6-fluoropyrimidine (0.518 g, 2.25 mmol) in dry DMF (5 mL) was added. The resultant reaction mixture was heated at 110°C for 2 h. After completion of the reaction, reaction mixture was cooled to room temperature, diluted with EtOAc. Organic layer was washed with water followed by brine and dried over anhydrous Na_2SO_4, concentrated under reduced pressure, crude compound was purified by column chromatography, eluting with EtOAc/*n*-hexane (1:3) to give title product as a pale yellow solid (245 mg, 44%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (d, J = 6.9 Hz, 1H), 8.77 (d, J = 3.4 Hz, 1H), 8.68 (d, J = 3.4 Hz, 1H), 8.53 (t, J = 8.8 Hz, 1H), 7.75-7.71 (m, 1H), 7.29-7.25 (m, 1H) and MS (ES) m/e: 249 $(M+H)^+$.

Intermediate-28: Synthesis of 4-(1-benzyl-1H-imidazol-4-yl)-2-chloro-5-fluoropyrimidine:

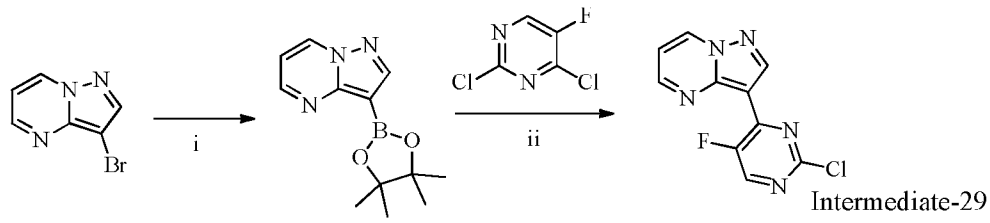


Intermediate-28

To a stirred solution of 2,4-dichloro-5-fluoropyrimidine (0.2 g, 0.75 mmol) in 1,4-dioxane (10 mL), were added 1-benzyl-1*H*-imidazole (0.12 g, 0.75 mmol) and cesium carbonate (0.36 g, 1.12 mmol) and degassed with nitrogen for 15 min. To this palladium acetate (8.3 mg, 0.037 mmol) and triphenyl phosphine (39 mg, 0.15 mmol) were added and again degassed with nitrogen for 15 min. Then the reaction mixture was allowed to stir at 100°C for 1 h. After completion of reaction, the reaction mixture was filtered through celite, filterate was

concentrated under reduced pressure. The obtained crude material was purified by column chromatography, eluting with 15% EtOAc/*n*-hexane to obtain titled product (80 mg, 23%). MS (ES): m/e 289.1 $(M+H)^+$.

Intermediate-29: Synthesis of 3-(2-chloro-5-fluoropyrimidin-4-yl)pyrazolo[1,5-a]pyrimidine:



Intermediate-29

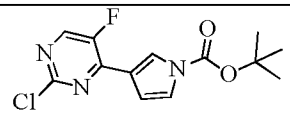
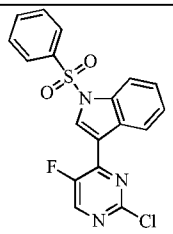
Step-i: Synthesis of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine:

To a stirred solution of 3-bromopyrazolo[1,5-a]pyrimidine (0.2 g, 1.01 mmol) in 1,4-dioxane (10 mL), was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.12 g, 4.4 mmol), potassium acetate (0.35 g, 3.5 mmol), and degassed for 20 min. To the degassed reaction mixture catalyst Bis(triphenylphosphine)palladium(II)dichloride (0.035 g, 0.05 mmol) was added and heated at 90°C for 16 h. After completion of reaction, reaction mixture was cooled to room temperature and diluted with pentane passed through celite and washed with 2:3 (EtOAc : Ether) and concentrated under reduced pressure to obtain crude product. Crude material was purified by column chromatography (50% EtOAc: hexane) to obtain pure compound (0.1 g, 40%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J = 6.9 Hz, 1H), 8.63-8.49 (m, 1H), 8.15 (s, 1H), 6.72 (s, 1H), 1.39-1.19 (m, 12H).

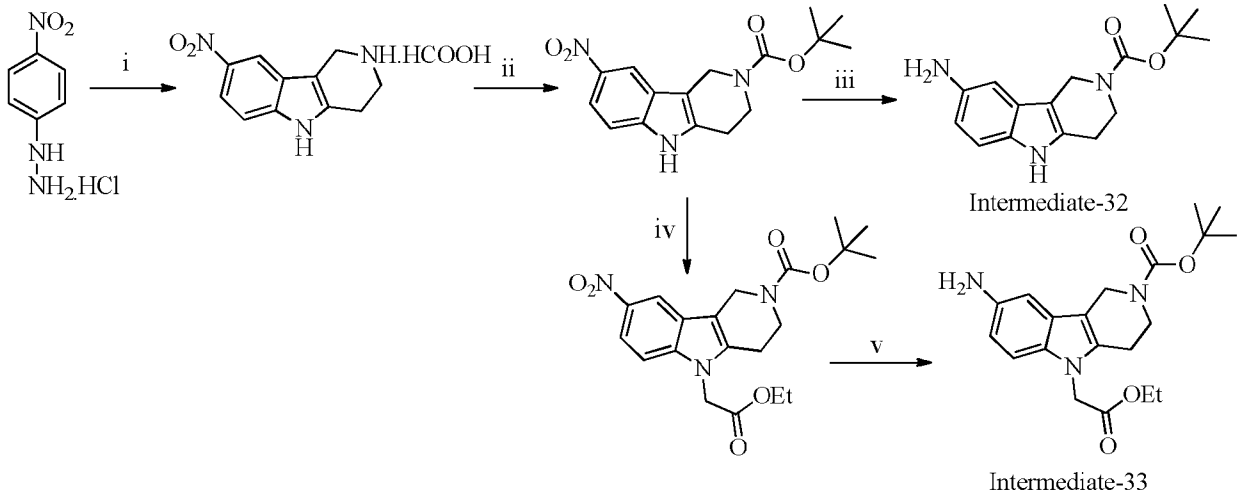
Step-ii: Synthesis of 3-(2-chloro-5-fluoropyrimidin-4-yl)pyrazolo[1,5-a]pyrimidine:

To a stirred solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine (0.1 g, 0.40 mmol) in DMF (10 mL), were added 2,4-dichloro-5-fluoropyrimidine (0.068 g, 0.40 mmol), tripotassium phosphate (0.25 g, 1.2 mmol) and degassed for 15 min. To the reaction mixture tris(dibenzylideneacetone)dipalladium(0) (0.018 g, 0.02 mmol), and tricyclohexylphosphine (0.011 g, 0.04 mmol) were added and heated at 90°C for 1h. After completion of the reaction, reaction mixture was cooled to room temperature, diluted with EtOAc. Organic layer was washed with water followed by brine and dried over anhydrous Na_2SO_4. Organic layer was concentrated under reduced pressure to obtain crude compound, which was purified by column chromatography, eluting with a gradient (EtOAc/hexane 1:1) to give the title compound (0.020 g, 19%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78-8.69 (m, 1H), 8.49 (s, 1H), 8.14 (s, 1H), 7.11-7.08 (m, 1H), 6.84-6.72 (m, 1H).

Below intermediates were prepared by following similar procedure as depicted in step-ii of intermediate 29, by using approprite raw materials at suitable conditions.

Int No.	Structure	Characterization Data
30		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.84 (d, J = 2.9 Hz, 1H), 7.95 (d, J = 1.9 Hz, 1H), 7.46 (dd, J = 2.2 Hz and 3.2 Hz, 1H), 6.88 (s, 1H), 1.60 (s, 9H).
31		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.97 (s, 1H), 8.51 (s, 1H), 8.49-8.48 (m, 1H), 8.18-8.16 (m, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.78-7.74 (m, 1H), 7.66-7.62 (m, 2H), 7.53-7.45 (m, 2H).

Intermediate-32 and 33: Synthesis of tert-butyl 8-amino-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate and tert-butyl 8-amino-5-(2-ethoxy-2-oxoethyl)-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate:



Step-i: Synthesis of 8-nitro-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole formate:

To a stirred solution of (4-nitrophenyl)hydrazine hydrochloride (1 g, 5.2 mmol) in formic acid (5 mL), was added piperidin-4-one hydrochloride (0.79 g, 5.8 mmol) and heated at 90°C for 6 h. After completion of reaction, the reaction mixture was cooled to room temperature and diluted with 1,4-dioxane. The separated solid was filtered and dried, used in the next step without further purification (0.5 g, 36%).

Step-ii: Synthesis of tert-butyl 8-nitro-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate:

8-Nitro-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole formate (0.4 g, 1.5 mmol) was dissolved in dry DCM (10 mL), TEA (1 mL, 7.6 mmol) was added and stirred at room temperature for 30 min. To the above reaction mixture Boc anhydride (0.36 mL, 1.6 mmol) was added and stirred at room temperature for 6 h. After completion of reaction, the reaction mixture was diluted with water (50 mL) and extracted with DCM (50 mL). The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was triturated with diethyl ether to afford the desired product as a pale yellow solid (0.25 g, 42%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.73 (s, 1H), 8.45 (d, J = 2.0 Hz, 1H), 7.97-7.94 (m, 1H), 7.46 (d, J = 9.3 Hz, 1H), 4.61 (bs, 2H), 3.72 (t, J = 5.6 Hz, 2H), 2.82 (t, J = 5.4 Hz, 2H), 1.45 (s, 9H).

Step-iii: Synthesis of tert-butyl 8-amino-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate:

tert-butyl 8-nitro-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (0.25 g, 0.76 mmol) was dissolved in methanol (10 mL). To the above solution 10% Pd/C (25 mg) was added at room temperature and stirred under hydrogen atmosphere for 5h. After completion of reaction, the reaction mixture was filtered through celite and washed with methanol. The filtrate was concentrated under reduced pressure and crude material was triturated with diethyl ether to afford the desired product as a brown solid (0.16 g, 73%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.35 (s, 1H), 6.97 (d, J = 8.8 Hz, 1H), 6.51 (s, 1H), 6.42 (dd, J = 1.4 Hz, 8.3 Hz, 1H), 4.50 (bs, 2H), 4.40 (s, 2H), 3.66 (t, J = 5.6 Hz, 2H), 2.69 (t, J = 5.4 Hz, 2H), 1.43 (s, 9H).

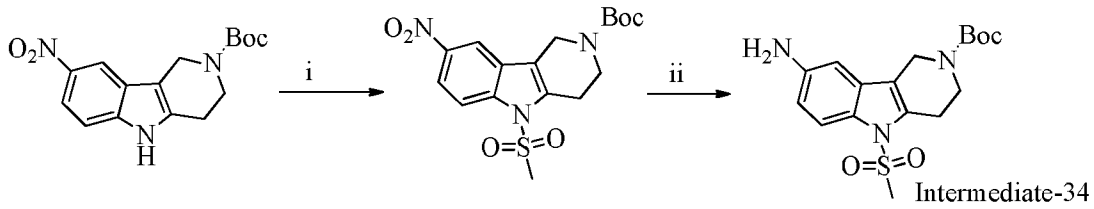
Step-iv: Synthesis of tert-butyl 5-(2-ethoxy-2-oxoethyl)-8-nitro-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate:

To a solution of tert-butyl 8-nitro-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (0.35 g, 0.0011 mol) in dry DMF, was added NaH (88 mg, 0.00221 mol) at 0°C, stirred at same temperature for 30 min. Ethyl bromoacetate (0.15 ml, 0.00132 mol) was added drop wise stirred at RT for 2 h. After completion of reaction, reaction mixture was diluted with water and extracted with EtOAc. Organic layer was washed with brine and dried over anhydrous Na_2SO_4. Organic layer was concentrated under reduced pressure, crude compound was purified by column over 230-400 mesh silica gel by eluting with EtOAc/*n*-hexane (3:7) to give title compound as a pale yellow solid (380 mg, 85%); MS (ES) m/e 404 $(M+H)^+$.

Step-v: Synthesis of tert-butyl 8-amino-5-(2-ethoxy-2-oxoethyl)-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate:

The process of this step was adopted from step-iii of intermediate-32. MS (ES) m/e 374 $(M+H)^+$.

Intermediate-34: Synthesis of tert-butyl 8-amino-5-(methylsulfonyl)-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate:



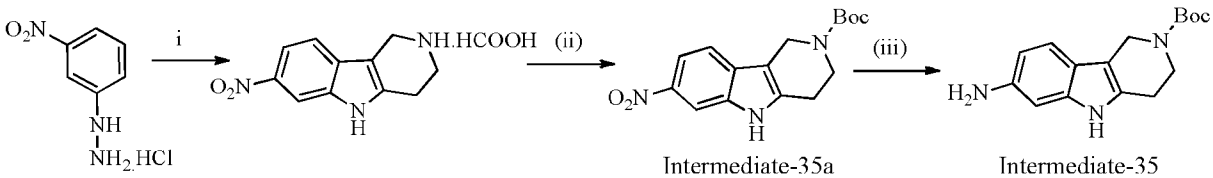
Intermediate-34

Step-i: Synthesis of tert-butyl 5-(methylsulfonyl)-8-nitro-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate:

To a solution of tert-butyl 8-nitro-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (0.5 g, 0.001582 mol) in dry DMF, was added NaH (125 mg, 0.00316 mol) at 0°C, stirred at same temperature for 30 min. Methanesulfonyl chloride (0.217 mg, 0.00186 mol) was added drop wise, stirred at RT for 2 hrs. After completion of reaction, reaction mixture was diluted with water and extracted with EtOAc. Organic layer was washed with brine and dried over anhydrous Na_2SO_4. Organic layer was concentrated under reduced pressure, crude compound was purified by column over 230-400 mesh silica gel by eluting with EtOAc/*n*-hexane (3:7) to give title compound as a pale yellow solid (450 mg, 72%); MS (ES) m/e 396 $(M+H)^+$.

Step-ii: The process of this step was adopted from step-iii of Intermediate-32. The desired product obtained as a pink solid (400 mg, 86%); MS (ES) m/e 366 $(M+H)^+$.

Intermediate-35: Synthesis of tert-butyl 7-amino-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate:

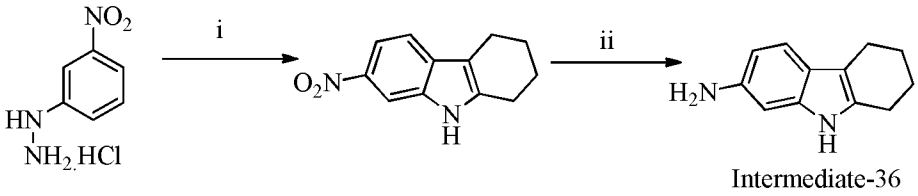


Intermediate-35a Intermediate-35

Step-(i, ii and iii): The process of these steps were adapted from step-i to step-iii of Intermediate-32. The desired product obtained as an off-white solid (0.5 g, 85%); ^1H NMR (400 MHz,

DMSO-d_6): δ 10.25 (s, 1H), 6.74 (d, J = 8.3 Hz, 1H), 6.47 (d, J = 1.9 Hz, 1H), 6.35-6.31 (m, 1H), 4.64 (bs, 2H), 4.41 (bs, 2H), 3.65 (t, J = 5.9 Hz, 2H), 2.65 (t, J = 5.6 Hz, 2H), 1.43 (s, 9H).

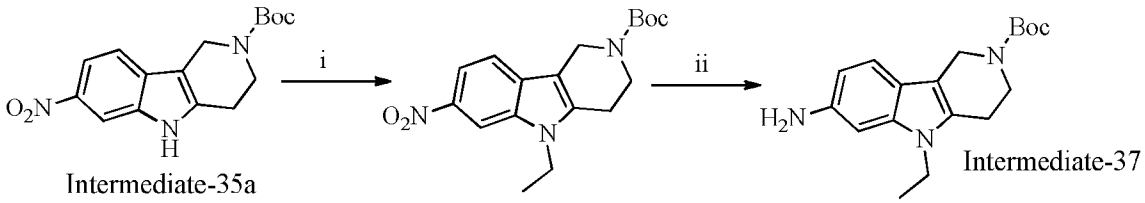
Intermediate-36: Synthesis of 2,3,4,9-tetrahydro-1H-carbazol-7-amine:



Intermediate-36

Step-i and ii: The process of these steps was adopted from step-i and step-iii of Intermediate-32. The desired product obtained as dark brown semi-solid (0.2 g, 23%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.96 (bs, 1H), 6.97 (d, J = 8 Hz, 1H), 6.44 (s, 1H), 6.29 (d, J = 8 Hz, 1H), 5.75 (bs, 2H), 2.59-2.49 (m, 4H), 1.78-1.72 (m, 4H) and MS (ES) m/e 187 $(M+H)^+$.

Intermediate-37: Synthesis of *tert*-butyl 7-amino-5-ethyl-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate:



Intermediate-35a

Intermediate-37

Step-i: Synthesis of *tert*-butyl 5-ethyl-7-nitro-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate:

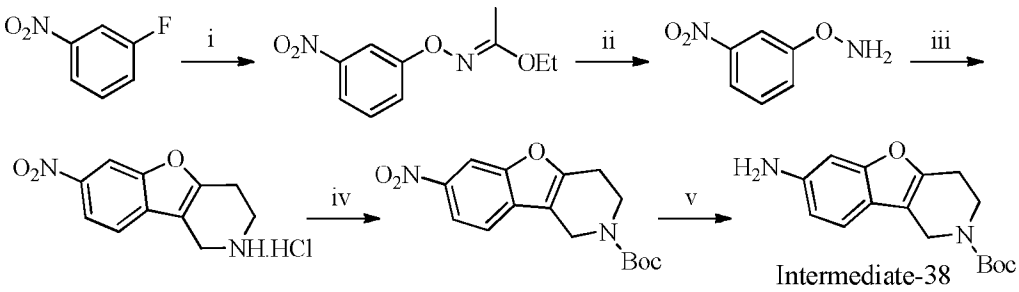
To a stirred solution of intermediate-35a (0.2 g, 0.63 mmol) in dry THF (5 mL) was added NaH (37 mg, 0.94 mmol) and stirred at 0°C for 30 min. To the above suspension, ethyl iodide (0.07 mL, 0.94 mmol) was added drop wise stirred at room temperature for 2 h. The reaction mixture was poured in ice and extracted with EtOAc, dried and concentrated to afford the desired product as an off-white solid (0.2 g, 92%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (d, J = 1.9 Hz, 1H), 7.92-7.89 (m, 1H), 7.63 (d, J = 8.8 Hz, 1H), 4.59 (s, 2H), 4.29 (q, J = 7.2 Hz, 2H), 3.75 (t, J = 5.6 Hz, 2H) 2.91 (t, J = 5.6 Hz, 2H), 1.44 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H).

Step-ii: Synthesis of *tert*-butyl 7-amino-5-ethyl-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate:

The process of this step was adopted from step-iii of Intermediate-32. The desired product obtained as an off-white solid (0.18 g, 98%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.05 (d, J = 8.3 Hz, 1H), 6.51 (d, J = 1.4 Hz, 1H), 6.38-6.36 (m, 1H), 4.73 (bs, 2H), 4.42 (bs, 2H), 3.91

(q, *J* = 7.0 Hz, 2H), 3.68 (t, *J* = 5.9 Hz, 2H), 2.71-2.70 (m, 2H), 1.43 (s, 9H), 1.18 (t, *J* =7.1 Hz, 3H).

Intermediate-38: Synthesis of tert-butyl 7-amino-3,4-dihydrobenzofuro[3,2-c]pyridine-2(1H)-carboxylate:



Intermediate-38

Step-i: Synthesis of (E)-ethyl N-3-nitrophenoxyacetimidate:

A solution of ethyl acetohydroximate (0.5 g, 6.37 mmol) in dry THF (5 mL) was stirred under nitrogen at 0°C. Potassium tert-butoxide (0.6 g, 10.62 mmol) was added over a period of 30 min and the resulting mixture was stirred at below -10°C for 1.5 h. A solution of 1-fluoro-3-nitrobenzene (0.75 g, 5.31 mmol) in dry THF (5 mL) was added in a single portion. Then the mixture was heated at 80°C for 4 h and room temperature for overnight. The reaction mixture was quenched with ice water and resulted reaction mixture was extracted with ethyl acetate, washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The obtained crude material was purified by column chromatography, eluting with 0-5% ethyl acetate in n-hexane to afford the titled product (0.5 g, 42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (s, 1H), 7.83-7.80 (m, 1H), 7.42-7.26 (m, 2H), 4.22 (q, *J* = 10.8 Hz, 2H), 1.38 (t, *J* = 14 Hz, 3H) and MS (ES) m/e 225 $(M+H)^+$.

Step-ii: Synthesis of O-(3-nitrophenyl)hydroxylamine:

To a stirred solution of (E)-ethyl N-3-nitrophenoxyacetimidate (0.5 g, 2.23 mmol) in 1,4-dioxane (5 mL) was added 70% $HClO_4$ drop wise at 0°C. After completion of the addition, cooling bath was removed and stirring was continued at room temperature for 2 h. Reaction mixture was poured into ice/water, pH of the aqueous solution was adjusted to > 11 with 2M NaOH and was extracted with EtOAc. The combined organic extracts were washed with brine and dried over anhydrous sodium sulphate and were concentrated in vacuo. The obtained crude was purified by column chromatography, eluting with 0-100% ethyl acetate in n-hexane to afford

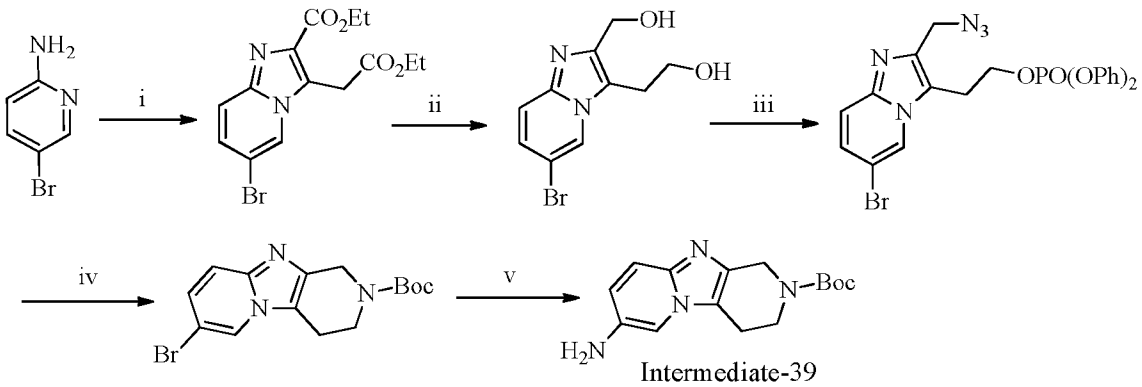
the desired product (0.3 g, 87%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98-7.97 (m, 1H), 7.77-7.75 (m, 1H), 7.55-7.44 (m, 2H), 7.26 (bs, 2H).

Step-iii: Synthesis of 7-nitro-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine hydrochloride:

To a stirred solution of O-(3-nitrophenyl)hydroxylamine (0.3 g, 1.94 mmol) in ethanol (5 mL) was added 4-piperidone hydrochloride (0.31 g, 2.33 mmol) and conc. HCl (5 mL). Then the reaction mixture was refluxed for 48 h. After completion of reaction, excess of ethanol and HCl were removed under reduced pressure. The obtained solid was used in next step without purification (0.4 g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.15 (d, J = 8 Hz, 1H), 7.71 (d, J = 8 Hz, 1H), 3.85 (s, 2H), 3.08 (t, J = 12 Hz, 2H), 2.78-2.76 (m, J = 8 Hz, 2H) and MS (ES) m/e 219 $(M+H)^+$.

Step-iv and v: The process of these steps was adopted from step-ii and step-iii of Intermediate-32. The desired product obtained as a brown color semi-solid (0.15 g, 66%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.81 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 8 Hz, 1H), 6.29 (s, 1H), 5.37 (bs, 2H), 3.93 (bs, 2H), 3.52 (bs, 2H), 2.49 (bs, 2H), 1.42 (s, 1H) and MS (ES) m/e 289 $(M+H)^+$.

Intermediate-39: Synthesis of tert-butyl 7-amino-3,4-dihydroimidazo[1,2-a:4,5-c']dipyridine-2(1*H*)-carboxylate:



Step-i: Synthesis of ethyl 6-bromo-3-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridine-2-carboxylate:

A mixture of 5-bromopyridin-2-amine (74 g, 0.428 mol) and 3-bromo-2-oxopentanedioic acid dimethyl ester (170 g, 0.6 mol) in ethanol (1.5 L) was heated at 100°C for 2 h. After completion of reaction, excess of solvent was removed under reduced pressure, the obtained crude product was purified by flash chromatography ($CHCl_3$/methanol 20:1) to afford the title product as a brown solid (80 g, 52%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 8 Hz, 1H), 8.00

(s, 1H), 7.24 (d, J = 8, 1H), 4.45 (s, 2H), 4.29 (q, J = 10 Hz, 2H), 4.09 (q, J = 10 Hz, 2H), 1.30 (t, J = 12 Hz, 3H), 1.17 (t, J = 12 Hz, 3H); MS (ES) m/e 355 $(M+H)^+$ and 356 $(M+2H)^{2+}$.

Step-ii: Synthesis of 2-(6-bromo-2-(hydroxymethyl)imidazo[1,2-a]pyridin-3-yl)ethanol:

To a stirred solution of ethyl 6-bromo-3-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridine-2-carboxylate (80 g, 0.22 mol) in dry THF (800 mL) was added sodium borohydride (50 g, 1.35 mol) portion wise at 0°C. To the above reaction mixture, boron trifluoride diethyl etherate (166 mL, 1.35 mol) was added drop wise at 0°C over a period of 30 min. After being stirred for 12 h, the mixture was diluted with a saturated solution of ammonium chloride and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The resultant crude was purified by flash chromatography ($CHCl_3$/methanol 9:1) to afford the desired product as a brown oily liquid (27 g, 44%). ^1H NMR (400 MHz, DMSO-d_6): δ 8.67 (s, 1H), 7.46 (d, J = 12 Hz, 1H), 7.28 (d, J = 12 Hz, 1H), 4.98 (t, J = 12 Hz, 1H), 4.80 (t, J = 12 Hz, 1H), 4.56 (d, J = 4 Hz, 2H), 3.62 (dt, J = 12 Hz, 8 Hz, 2H), 3.13 (t, J = 12 Hz, 2H) and MS (ES) m/e 273 $(M+2H)^{2+}$.

Step-iii: Synthesis of 2-(2-(azidomethyl)-6-bromoimidazo[1,2-a]pyridin-3-yl)ethyl diphenyl phosphate:

To a stirred mixture of 2-(6-bromo-2-(hydroxymethyl)imidazo[1,2-a]pyridin-3-yl)ethanol (27 g, 99 mmol) and DBU (33 g, 217 mmol) in THF (270 mL) was added DPPA (46 mL, 217 mmol) at 0°C. After being stirred at room temperature for 2 h, the mixture was diluted with EtOAc, washed with H_2O, dried over $MgSO_4$ and concentrated. The obtained crude product was purified by flash chromatography (n-hexane/EtOAc 2:1) to afford title product as a brown oily liquid (14 g, 26%). ^1H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, J = 0.8 Hz, 1H), 7.55 (d, J = 12 Hz, 1H), 7.37-7.03 (m, 11H), 4.46-4.41 (m, 4H), 3.47 (t, J = 12 Hz, 2H).

Step-iv: Synthesis of tert-butyl 7-bromo-3,4-dihydroimidazo[1,2-a:4,5-c']dipyridine-2(1H)-carboxylate:

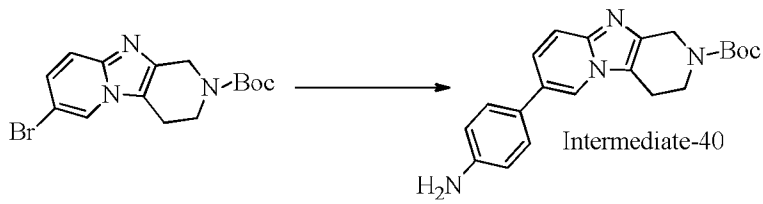
A stirred mixture of 2-(2-(azidomethyl)-6-bromoimidazo[1,2-a]pyridin-3-yl)ethyl diphenyl phosphate (14 g, 26.7 mmol) and PPh_3 (9.7 g, 34.7 mmol) in THF:H_2O/10:1 (155 mL) was heated at 60°C for 4 h. After the mixture was cooled to room temperature, Boc_2O (11.65 g, 53.4 mmol) and DMAP (0.325 g, 2.67 mmol) were added to the mixture, which was then stirred at room temperature for 12 h. The mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated. The obtained residue was purified by flash chromatography (n-hexane/EtOAc 1:1) to afford the desired product as a white solid (6 g, 63%). ^1H NMR (400

MHz, DMSO-d_6) δ 8.605 (d, J = 1.6 Hz, 1H), 7.50 (d, J = 8 Hz, 1H), 7.33 (d, J = 12 Hz, 1H), 4.54 (s, 2H), 3.75 (t, J = 12 Hz, 2H), 2.89 (t, J = 12 Hz, 2H), 1.43 (s, 9H); MS (ES) m/e 354 $(M+2H)^{2+}$, 298 (M-*t*-butyl) and 254 $(M\text{-Boc})^{+}$.

Step-v: Synthesis of tert-butyl 7-amino-3,4-dihydroimidazo[1,2-a:4,5-c']dipyridine-2(1*H*)-carboxylate:

To a stirred solution of tert-butyl 7-bromo-3,4-dihydroimidazo[1,2-a:4,5-c']dipyridine-2(1H)-carboxylate (500 mg, 1.42 mmol) in DMSO (25 mL), was added L-proline (65 mg, 0.5 mmol), copper(I)iodide (50 mg, 0.28 mmol) and K_2CO_3 (290 mg, 2.13 mmol). Reaction mixture was degassed with argon for 15 min, to the above mixture 5 mL of ammonium hydroxide was added and heated in a seal tube at 90°C for 12 h. After completion of reaction, the reaction mixture was cooled to room temperature and diluted with EtOAc, washed with brine, dried over $MgSO_4$ and the residue was purified by flash chromatography (DCM/MeOH 9:1) to afford the desired product (0.2 g, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.345 (d, J = 0.8 Hz, 1H), 7.27 (d, J = 12 Hz, 1H), 6.819 (d, J = 2 Hz, 1H), 4.86 (bs, 2H), 4.46 (s, 2H), 3.74 (t, J = 11.2 Hz, 2H), 2.72 (t, J = 10.4 Hz, 2H), 1.42 (s, 9H); MS (ES) m/e 289 $(M+H)^{+}$, 233 (M-*t*-butyl) and 189 $(M\text{-Boc})^{+}$.

Intermediate-40: Synthesis of tert-butyl 7-(4-aminophenyl)-3,4-dihydroimidazo[1,2-a:4,5-c']dipyridine-2(1H)-carboxylate:

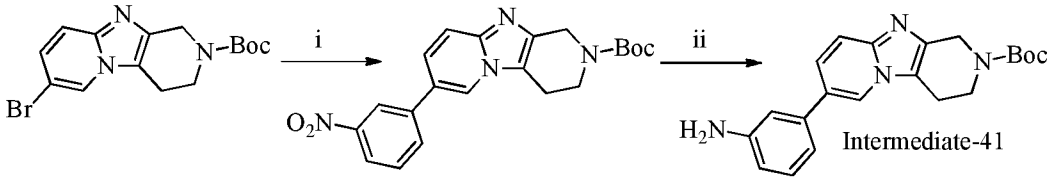


Intermediate-40

To a stirred solution of tert-butyl 7-bromo-3,4-dihydroimidazo[1,2-a:4,5-c']dipyridine-2(1*H*)-carboxylate (0.35 g, 1 mmol) in 1,4-dioxane (15 mL), was added 4-aminophenylboronic acid pinacol ester (0.263 g, 1.2 mmol), 1M sodium carbonate solution (5 mL) and degassed for 30 min. To the degassed reaction mixture catalyst $Pd(PPh_3)_4$ (0.1 g, 0.1 mmol) was added and heated at 90°C for 2 h. After completion of reaction, the reaction mixture was cooled to room temperature and diluted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The obtained crude material was purified by column chromatography (5% MeOH in DCM) to afford the desired product (0.3 g, 82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.64-7.40 (m, 4H), 6.67 (d,

J = 8 Hz, 2H), 5.75 (bs, 2H), 4.54 (bs, 2H), 3.92 (bs, 2H), 2.95 (bs, 2H), 1.43 (s, 9H) and MS (ES) m/e 365 $(M+H)^+$.

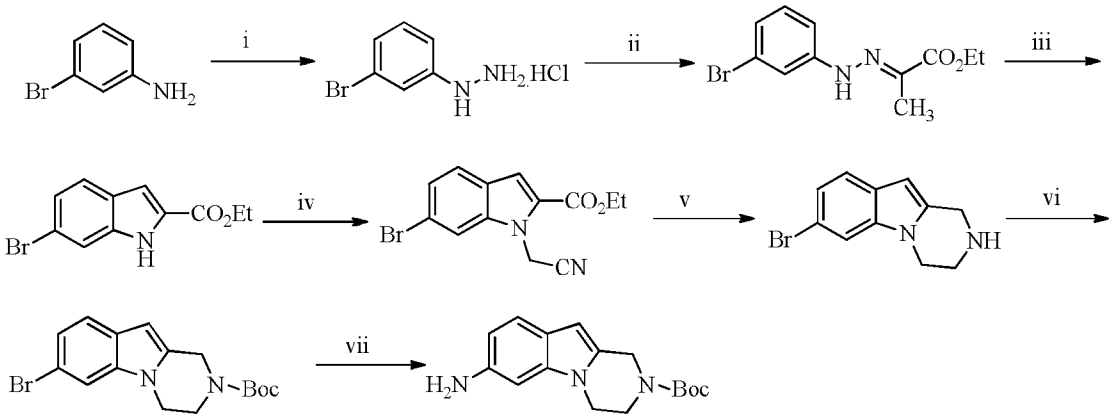
Intermediate-41: Synthesis of *tert*-butyl 7-(3-aminophenyl)-3,4-dihydroimidazo[1,2-a:4,5-c']dipyridine-2(1H)-carboxylate:



Step-i: The process of this step was adopted from Intermediate-40. The desired product obtained as a yellow solid (0.5 g, 89%). MS (ES) m/e 395 $(M+H)^+$ and 339 (M-*t*-buytl).

Step-ii: The process of this step was adopted from step-iii of Intermediate-32. The desired product obtained as a brown solid (0.14 g, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.55-6.56 (m, 6H), 5.18 (bs, 2H), 4.54 (bs, 2H), 3.77 (bs, 2H), 2.93 (bs, 2H), 1.42 (s, 9H); MS (ES) m/e 365 $(M+H)^+$ and 309 (M-*t*-buytl).

Intermediate-42: Synthesis of tert-butyl 7-amino-3,4-dihydropyrazino[1,2-a]indole-2(1H)-carboxylate:



Interemdiate-42

Step-i: Synthesis of (3-bromophenyl) hydrazine hydrochloride:

3-bromoaniline (50 g, 290 mmol) was dissolved in a mixture of water and HCl (1:1, 100 mL). To this added sodium nitrite (20 g, 289 mmol) in water (90 mL) at 0°C. Sn(II) chloride (165 g, 870 mmol) in HCl (100mL) solution was added drop wise and stirred for 30 minutes at 0°C. The generated solid in the reaction mixture was filtered and washed with water and then

dried under vacuum to give the title product (58.98 g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.25-7.18 (m, 2H), 7.11 (d, J = 8.3 Hz, 1H), 6.97 (d, J = 7.9 Hz, 1H).

Step-ii: Synthesis of (E)-ethyl 2-(2-(3-bromophenyl)hydrazono)propanoate:

A solution of (3-bromophenyl)hydrazine hydrochloride (58.98 g, 264 mmol) in ethanol (800 mL) was added ethyl pyruvate (36.17 g, 311 mmol) and stirred at room temperature for 4 h. Removed the solvent dried under vacuum to give the title product (87.7 g). The obtained crude material was used in the next step without purification. MS (ES) m/e: 285 (M+1, 16%).

Step-iii: Synthesis of ethyl 6-bromo-1H-indole-2-carboxylate:

A solution of (E)-ethyl 2-(2-(3-bromophenyl)hydrazono)propanoate (77.7 g, 272 mmol) in toluene (800 mL) was added Polyphosphoric acid (233 g, 83.0 mmol) and stirred at 120°C for 12-14 h. Diluted the reaction mixture with EtOAc. The organic layer was washed with saturated $NaHCO_3$ and NaCl solutions. The organic layer was dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by silica gel column chromatography eluting with a gradient of EtOAc (6%) in hexane to give the title product (17 g, 23%).^{1}H NMR (400 MHz, DMSO-d_6): δ 12.01 (bs, 1H), 7.62 (t, J = 8.8 Hz, 1H), 7.23-7.20 (m, 1H), 7.17 (s, 1H), 4.35 (q, J = 7.16 Hz, 2H), 1.34 (t, J = 7.10 Hz, 3H). MS (ES) m/e: 266 (M-1, 100%).

Step-iv: Synthesis of ethyl 6-bromo-1-(cyanomethyl)-1H-indole-2-carboxylate:

A solution of ethyl 6-bromo-1H-indole-2-carboxylate (15.0 g, 55.97 mmol) in DMF (150 mL) was added to a suspension of sodium hydride (2.0 g, 83.0 mmol) in DMF at 0°C and stirred for 45 minutes. Chloroacetonitrile (7.06 mL, 112 mmol) was added drop wise and continued stirring at 75°C for 1 h .After completion of reaction quenched the excess of NaH with ice, precipitated solid was filtered and washed with water and then dried under vacuum to give the title product (15.92 g, 94%).^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (s, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.43 (s, 1H), 7.38 (d, J = 8.8 Hz, 1H), 5.76 (s, 2H), 4.37 (q, J = 7.0 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H).

Step-v: Synthesis of 7-bromo-1,2,3,4-tetrahydropyrazino[1,2-a]indole:

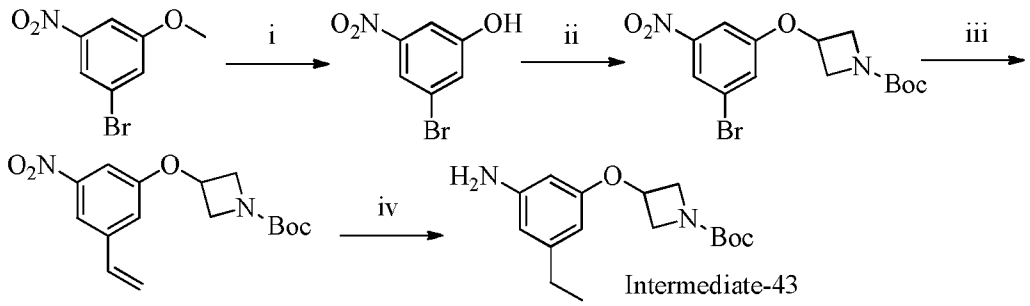
Ethyl 6-bromo-1-(cyanomethyl)-1H-indole-2-carboxylate (0.50 g, 1.6 mmol) in THF (10 mL) was added to LAH powder (0.153 g, 4.03 mmol) in THF (10 mL) at 0°C. The reaction mixture was refluxed for 6.5 h. After completion of reaction, reaction mixture was cooled to room temperature and then to 0°C. Quenched LAH with saturated Na_2SO_4 solution, diluted with ethyl acetate, filtered through celite. Filtrate was washed with water followed by brine solution.

Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude compound. The crude residue was purified by column chromatography (DCM/MeOH 97:3.0) to give the title product (0.128 g, 76%).^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72 (s, 1H), 7.45-7.43 (m, 1H), 7.12-7.09 (m, 1H), 6.38 (s, 1H), 4.16 (d, J = 4.9 Hz, 2H), 4.17-4.07 (m, 2H), 2.88-2.82 (m, 2H).

Step-vi and vii: Synthesis of tert-butyl 7-amino-3,4-dihydropyrazino[1,2-a]indole-2(1H)-carboxylate:

The process of these steps was adopted from step-ii and step-iii of Intermediate-32. The desired product obtained as a brown semi-solid (160 mg, 49%); MS (ES) m/e 288 $(M+H)^+$.

Intermediate-43: Synthesis of *tert*-butyl 3-(3-amino-5-ethylphenoxy)pyrrolidine-1-carboxylate:



Step-i: Synthesis of 3-bromo-5-nitrophenol:

A solution of 1-bromo-3-methoxy-5-nitrobenzene (15 g, 0.064 mol) was cooled to 0°C and treated with aqueous HBr (80 mL) and HBr in acetic acid (80 mL). The reaction was warmed slowly to room temperature and stirred at 110°C for overnight. The reaction was poured into ice/water, solid separated was filtered and dried under reduced pressure to obtain title product as an off-white solid (12.5 g, 89%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.93 (bs, 1H), 7.79 (s, 1H), 7.55 (s, 1H), 7.40 (s, 1H) and MS (ES) m/e 218 $(M+H)^+$.

Step-ii: Synthesis of *tert*-butyl 3-(3-bromo-5-nitrophenoxy)azetidine-1-carboxylate:

To a stirred solution of *N*-boc-azitidinol (4 g, 0.023 mol) was added DEAD (4.5 mL, 0.023 mol), TPP (6 g, 0.023 mol) in dry THF (40 mL) at 0°C. A solution of 3-bromo-5-nitrophenol (3.5 g, 0.015 mol) in dry THF (10 mL) was added drop wise over a period of 15 min. Reaction mixture was stirred at room temperature for 12 h. After completion of reaction, the reaction mixture was diluted with water, extracted with EtOAc and dried over anhydrous Na_2SO_4. The resultant organic layer was concentrated and purified by column chromatography over 230-400 mesh silica gel by eluting with EtOAc/*n*-hexane (1:9) to afford desired product (4

g, 66%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (s, 1H), 7.62 (s, 1H), 7.55 (s, 1H), 5.21 (m. 1H), 4.33 (bs, 2H), 3.82 (bs, 2H), 1.39 (s, 9H).

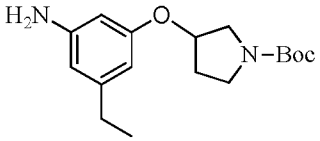
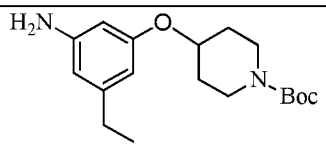
Step-iii: Synthesis of *tert*-butyl 3-(3-nitro-5-vinylphenoxy)azetidine-1-carboxylate:

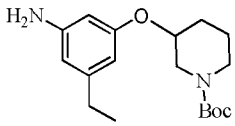
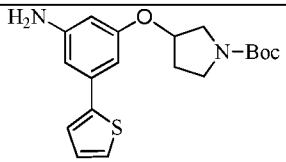
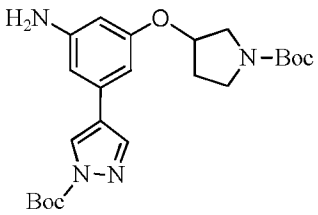
Reaction flask was charged with tert-butyl 3-(3-bromo-5-nitrophenoxy)azetidine-1-carboxylate (4 g, 0.01 mol), vinylboronic acid pinacol ester (2.5 g, 0.016 mol), K_2CO_3 (4.4 g, 0.032 mol) in 28 mL of 1,4-dioxane and 12 mL of H_2O was degassed with nitrogen for 30 min. To the above mixture $Pd(PPh_3)_4$ (0.6 g, 0.0005 mol) was added and again degassed for 30 min, reaction mixture was stirred at 90°C for 2 h. After completion of reaction, the reaction mixture was cooled to room temperature, diluted with EtOAc and passed through celite. Filtrate was washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained crude material was purified by column chromatography over 230-400 mesh silica gel by eluting with EtOAc/*n*-hexane (2:8) to afford the title product (3 g, 87%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (s, 1H), 7.48 (s, 1H), 7.42 (s, 1H), 6.88-6.81 (dd, *J* = 7.2 Hz, 1H), 6.11 (d, *J* = 17.6 Hz, 1H), 5.47 (d, *J* = 11.6 Hz, 1H), 5.20-5.17 (m, 1H), 4.35 (bs, 2H), 3.85-3.82 (m, 1H), 1.39 (s, 9H)

Step-iv: Synthesis of *tert*-butyl 3-(3-amino-5-ethylphenoxy)azetidine-1-carboxylate:

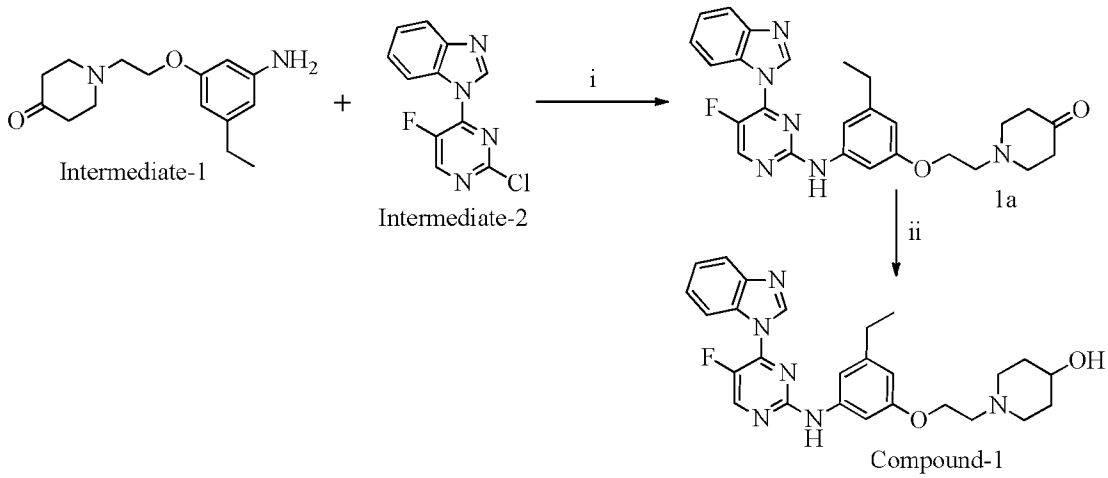
The process of this step was adopted from step-iii of intermediate-32. (2.5 g, 97%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.03 (s, 1H), 5.81 (s, 2H), 4.99 (bs, 2H), 4.83-4.80 (m, 1H), 4.22 (t, *J* = 13.6 Hz, 2H), 3.73 (t, *J* = 8.8 Hz, 2H), 2.38 (q, *J* = 5.8 Hz, 2H), 1.38 (s, 9H), 1.18 (t, *J* = 15.2 Hz, 3H) and MS (ES) m/e 291 $(M-H)^+$.

Below intermediates were prepared by following similar procedure as depicted in intermediate 43, by using approprite raw materials at suitable conditions..

Int No.	Structure	Characterization data
44		^{1}H NMR (400 MHz, DMSO-d_6): δ 6.04 (s, 1H), 5.95 (d, *J* = 1.9, 2H), 5.23 (bs, 2H), 4.82 (bs, 1H), 3.50-3.41 (m, 3H), 3.39-3.30 (m, 2H), 2.45-2.40 (m, 2H), 2.10-1.98 (m, 2H), 1.10 (t, *J* = 7.6 Hz, 3H) and MS (ES): m/z 207.1 $(M+H)^+$.
45		^{1}H NMR (400 MHz, DMSO-d_6): δ 5.99-5.96 (m, 3H), 4.91 (s, 2H), 4.39-4.33 (m, 1H), 3.64-3.59 (m, 4H), 3.16 (t, *J* = 9.6 Hz, 2H), 2.49-2.32 (m, 2H), 1.87-1.82 (m, 2H),

		1.402 (s, 9H), 1.10 (t, J = 8.0 Hz, 3H) and MS (ES): m/z 319.3 $(M–H)^-$.
46		MS (ES): m/z 321.2 $(M+H)^+$.
47		MS (ES): m/z 361.0 $(M+H)^+$.
48		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.12 (s, 1H), 6.48 (d, J = 1.6 Hz, 2H), 6.08 (s, 1H), 5.13 (s, 2H), 4.95-4.93 (m, 1H), 3.43-3.36 (m, 4H), 2.13-1.99 (m, 2H), 1.59 (s, 9H), 1.13 (s, 9H) and MS (ES): m/z 445.3 $(M+H)^+$.

Example-I: Synthesis of 1-(2-(3-((4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)-5-ethylphenoxy)ethyl)piperidin-4-ol (Compound-1):



Step-i: Synthesis of 1-(2-(3-((4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)-5-ethylphenoxy)ethyl)piperidin-4-one:

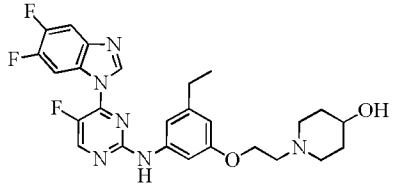
To a mixture of intermediate-1 (198 mg, 0.78 mmol), intermediate-2 (207 mg, 078 mmol) in 1,4-dioxane (5 mL), cesium carbonate (900 mg, 0.8 mmol) was added and degassed with argon for 30 min. To the above mixture tris(dibenzylideneacetone)dipalladium(0) (20 mg, 0.078 mmol) and xantphos (45 mg, 0.078 mmol) were added, again degassed with argon for 30 min

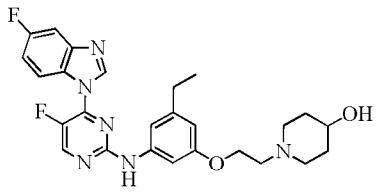
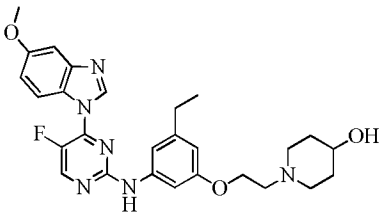
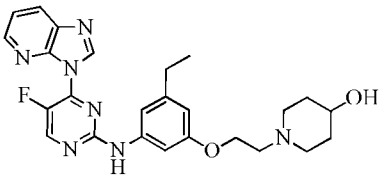
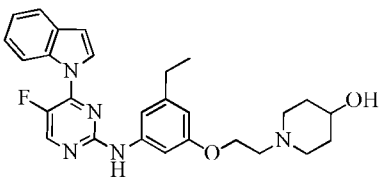
and heated to 60°C for 30 min under microwave condition. After completion of reaction, the reaction mixture was cooled to room temperature, diluted with EtOAc and passed through celite. Filtrate was washed with water followed by brine. The organic phase was separated, dried over Na_2SO_4 and concentrated. The crude was then purified by column chromatography on silica gel eluting with DCM: MeOH (9.5:0.5) as eluent to afford the desired compound-1a (75 mg, 19%). MS (ES) m/e 475 $(M+H)^+$.

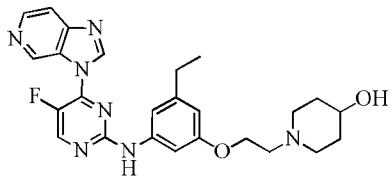
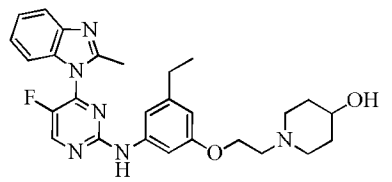
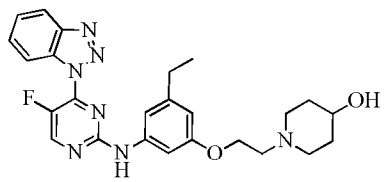
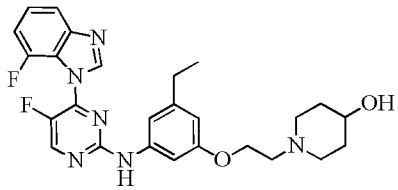
Step-ii: Synthesis of 1-(2-(3-((4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)-5-ethylphenoxy)ethyl)piperidin-4-ol:

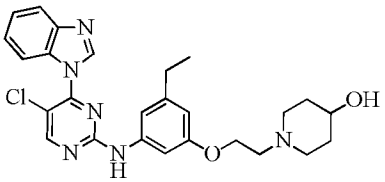
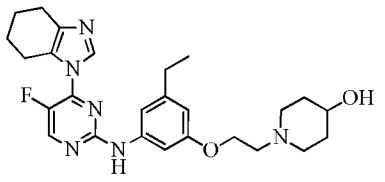
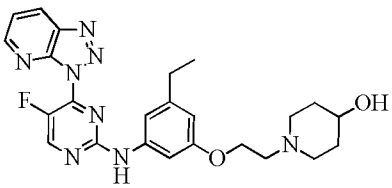
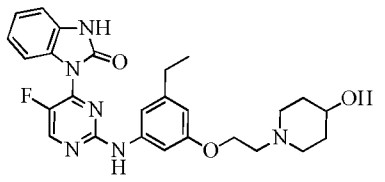
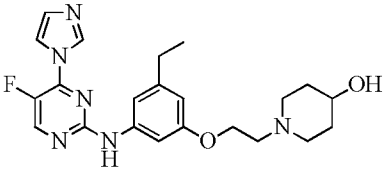
To a solution of 1-(2-(3-((4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)-5-ethylphenoxy)ethyl)piperidin-4-one (75 mg, 1.5 mmol) in MeOH:THF (2 mL, 1:1), was added $NaBH_4$ (9.4 mg, 2.25 mmol) portion wise at 0°C and stirred at RT for 30 min. After completion of reaction, excess of sodium borohydride was quenched with acetone and excess of solvent was removed under reduced pressure and extracted with EtOAc. The organic phase was separated, dried over Na_2SO_4 and concentrated. The obtained crude was purified by column chromatography on silica gel eluting with DCM:MeOH (9.5:0.5) as eluent to obtain the titled compound as a white solid (2.3 mg, 3%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.87 (s, 1H), 8.81 (d, J = 3.4 Hz, 1H), 8.77 (d, J = 2.5 Hz, 1H), 8.34 (s, 1H), 7.81 (dd, J = 3.2, 6.1 Hz, 1H), 7.41 (d, J = 3.4 Hz, 1H), 7.39 (d, J = 3.5 Hz, 1H), 7.25 (s, 1H), 7.16 (s, 1H), 6.47 (s, 1H), 4.54 (bs, 1H), 3.98 (s, 2H), 3.41-3.37 (m, 1H), 2.73- 2.67 (m, 1H), 2.66-2.62 (m, 1H), 2.56-2.49 (m, 4H), 2.08 (bs, 2H), 1.68 (bs, 2H), 1.36 (d, J = 9.3 Hz, 2H), 1.16 (t, J = 7.6 Hz, 3H); MS (ES) m/e 477.3 $(M+H)^+$.

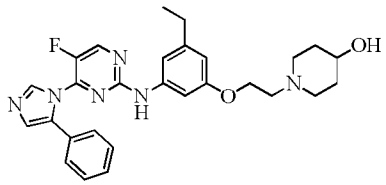
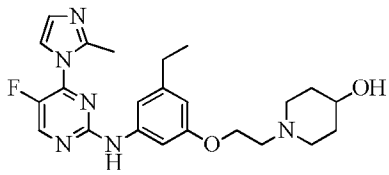
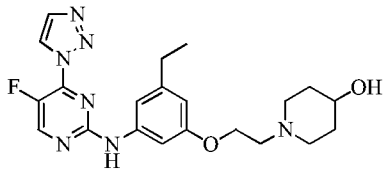
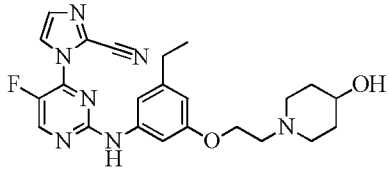
The below compounds were prepared by procedure similar to the one described in Example-I with appropriate variations in reactants, quantities of reagents and reaction conditions. The physiochemical characteristics of the compounds are summarized herein below table.

Comp No.	Structure	Characterization Data ^{1}H NMR (400 MHz, DMSO-d_6)
2		δ 9.33 (bs, 1H), 8.89 (s, 1H), 8.81 (d, J = 3.6 Hz, 1H), 8.51 (m, 1H), 7.96 (dd, J = 7.6, 10.4 Hz, 1H), 7.27 (s, 1H), 7.20 (s, 1H), 6.57 (s, 1H), 5.00-5.20 (m, 1H), 4.30 (d, J = 4.8 Hz, 2H), 3.93 (m, 1H), 3.40-3.35 (m, 2H), 3.30-3.25 (m, 2H), 2.58 (q, J = 8

		Hz, 2H), 1.73-1.98 (m, 4H), 1.62-1.58 (m, 2H), 1.18 (t, *J* = 6 Hz, 3H) and MS (ES) m/e 513.2 $(M+H)^+$.
3		δ 9.89 (bs, 1H), 8.84-8.83 (m, 2H), 8.38 (bs, 1H), 7.67-7.64 (m, 1H), 7.29-7.13 (m, 3H), 6.47 (s, 1H), 4.53 (bs, 1H), 4.02 (bs, 2H), 3.98 (bs, 1H), 2.73-2.55 (m, 6H), 2.88 (bs, 2H), 1.68 (bs, 2H), 1.38 (bs, 2H), 1.14 (q, *J* = 4.5 Hz, 3H) and MS (ES) m/e 495.2 $(M+H)^+$.
4		δ 9.83 (s, 1H), 8.78 (d, *J* = 4.0 Hz, 1H), 8.73 (d, *J* = 1.6 Hz, 1H),8.28 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.24 (s, 1H), 7.15 (s, 1H), 6.99-6.96 (m, 1H), 6.47 (s, 1H), 4.52 (d, *J* = 4 Hz, 1H), 3.98 (t, *J* = 6 Hz, 2H), 3.84 (s, 3H), 3.4 (bs, 1H), 2.77-2.71 (m, 2H), 2.62 (t, *J* = 5.8 Hz, 2H), 5.56-5.50 (m, 2H), 2.08 (t, *J* = 9.8 Hz, 2H), 1.68 (d, *J* = 9.2 Hz, 2H), 1.36 (d, *J* = 10 Hz, 2H), 1.17 (t, *J* = 7.6 Hz, 3H) and MS (ES) m/e 507.3 $(M+H)^+$.
5		δ 9.90 (s, 1H), 9.04 (d, *J* = 2.0 Hz, 1H), 8.83 (d, *J* = 4.0 Hz , 1H), 8.75 (d, *J* = 8.4 Hz 1H), 8.58 (dd, *J* = 1.6, 4.8 Hz, 1H), 7.45 (dd, *J* = 4.6 , 8.2 Hz, 1H), 7.23 (s, 1H), 7.12 (s, 1H), 6.48 (s, 1H), 4.53 (s, 1H), 3.98 (s, 2H), 3.46-3.34 (m, 1H), 2.73 (d, *J* = 8.0 Hz, 2H), 2.67-2.62 (m, 2H), 2.57-2.52 (m, 2H), 2.08 (s,2H), 1.97-1.67 (m, 2H), 1.37-1.23 (m, 2H), 1.16 (t, *J* = 7.6 Hz, 3H) and MS (ES) m/e 478.2 $(M+H)^+$.
6		δ 9.74 (s, 1H), 8.70 (d, *J* = 4.4 Hz, 1H), 8.36 (d, *J* = 7.6 Hz, 1H), 7.86 (t, *J* = 3.2 Hz, 1H), 7.68 (dd, *J* = 2, 6.4 Hz, 1H), 7.30- 7.23 (m, 3H), 7.17 (s, 1H), 6.86 (d, *J* = 3.6 Hz, 1H), 6.44 (s, 1H), 4.54 (bs, 1H), 3.96 (t, *J* = 6.0 Hz, 2H), 3.38-3.28 (m, 1H), 2.73-2.67 (m,

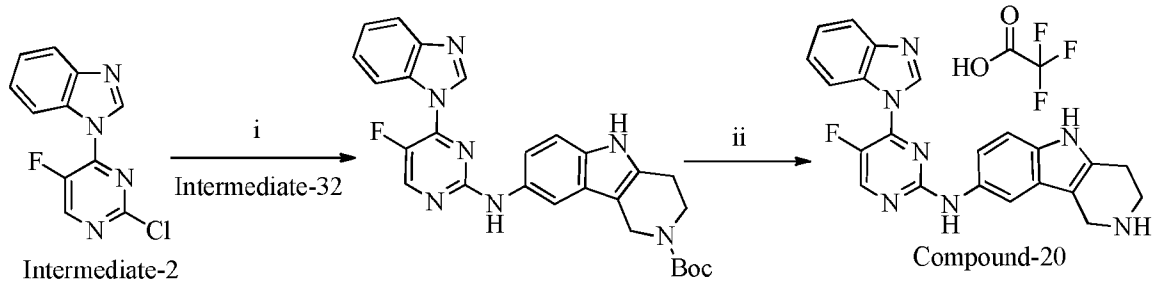
		2H), 2.61 (t, *J* = 6.0 Hz, 2H), 2.55-2.49 (m, 2H), 2.10 (t, *J* = 9.8 Hz, 2H), 1.68 (d, *J* = 9.2 Hz, 2H), 1.36 (q, *J* = 9.3 Hz, 2H), 1.15 (t, *J* = 7.6 Hz, 3H) and MS (ES) m/e 476.3 $(M+H)^+$.
7		δ 9.92 (s, 1H), 9.12 (s, 1H), 8.90 (s, 1H), 8.85 (d, *J* = 2.8 Hz, 1H), 8.53 (d, *J* = 5.6 Hz , 1H), 8.31 (d, *J* = 4.8 Hz 1H), 7.24 (s, 1H), 7.13 (s, 1H), 6.48 (s, 1H), 4.52 (d, *J* = 4.0 Hz, 1H), 3.98 (t, *J* = 5.8 Hz, 2H), 3.42 (d, *J* = 4.0 Hz, 1H), 2.72 (d, *J* = 11.2 Hz, 2H), 2.67-2.53 (m, 4H), 2.08 (t, *J* = 10.4 Hz, 2H), 1.68 (d, *J* = 10.4 Hz, 2H), 1.36 (q, *J* = 9.3 Hz, 2H), 1.16 (t, *J* = 7.6 Hz, 3H) and MS (ES) m/e 478.4 $(M+H)^+$.
8		δ 9.95 (s, 1H), 8.91 (s, 1H), 7.67 (d, *J* = 2.4, 1H), 7.47 (d, *J* = 4.8 Hz , 1H), 7.28 (d, *J* = 4.0 Hz, 2H), 7.22 (s, 1H), 7.10 (s, 1H), 6.43 (s, 1H), 4.51 (bs, 1H), 3.92 (s, 2H), 3.31 (s, 1H), 2.69-2.50 (m, 7H), 2.06 (bs, 2H), 1.66-1.23 (m, 6H), 1.12 (t, *J* = 7.6 Hz, 3H) and MS (ES) m/e 491.3 $(M+H)^+$.
9		δ 10.07 (s, 1H), 9.29 (bs, 1H), 8.54 (d, *J* = 8.8 Hz, 1H), 8.88 (s, 1H), 8.20-8.42 (s, 2H), 7.73 (s, 1H), 7.62 (s, 1H), 6.56 (s, 1H), 4.26 -3.92 (m, 4H), 3.71-3.48 (m, 6H), 3.21-3.01 (m, 2H), 1.94-1.86 (m, 4H), 1.15 (s, 3H) and MS (ES) m/e 478.1 $(M+H)^+$.
10		δ 9.91 (s, 1H), 8.84 (d, *J* = 3.2 Hz, 2H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.42-7.37 (m, 1H), 7.24 (s, 2H), 7.14 (s, 1H), 6.47 (s, 1H), 4.53 (d, *J* = 3.2 Hz, 1H), 3.96 (t, *J* = 5.2 Hz, 2H), 3.42 (bs, 1H), 2.72 (d, *J* = 11.2 Hz, 2H), 2.61 (t, *J* = 5.5 Hz, 2H), 2.54-2.44 (m, 2H), 2.09-2.05 (m, 2H), 1.68 (d, *J* = 10.4 Hz, 2H), 1.37-1.32 (m, 2H), 1.56 (t, *J* = 7.6 Hz, 3H) and MS (ES) m/e 495.2 $(M+H)^+$.

11		δ 10.08 (s, 1H), 8.85 (s, 1H), 8.80 (s, 1H), 7.87 (d, *J* = 4.8 Hz, 1H), 7.81 (d, *J* = 5.2 Hz, 1H), 7.38 (d, *J* = 3.6 Hz, 2H), 7.23 (s, 1H), 7.15 (s, 1H), 6.45 (s, 1H), 4.53 (d, *J*= 4.4 Hz, 1H), 3.91 (t, *J* = 5.4 Hz, 2H), 3.40 (bs, 1H), 2.71-2.67 (m, 2H), 2.57-2.56 (m, 2H), 2.51-2.49 (m, 2H), 2.05 (bs, 2H), 1.68 (d, *J* = 9.6 Hz, 2H), 1.36 (d, *J* = 14 Hz, 2H), 1.11 (t, *J* = 7.6 Hz, 3H) and MS (ES) m/e 493.4 $(M+H)^+$.
12		δ 9.72 (s, 1H), 8.73 (d, *J* = 3.2 Hz, 1H), 7.99 (d, *J*= 3.6 Hz , 1H), 7.16 (s, 1H), 7.08 (s, 1H), 6.44 (s, 1H), 4.53 (d, *J* = 3.6 Hz, 1H), 3.99 (t, *J* = 5.8 Hz, 2H), 3.43 (d, *J* = 3.6 Hz, 1H), 2.81-2.74 (m, 4H), 2.67 (t, *J* = 1.8 Hz, 2H), 2.63 (t, *J* = 5.8 Hz , 4H), 2.18 (t, *J* = 9.8 Hz , 2H), 1.76-1.67 (m, 6H), 1.41 (d, *J* = 3.6 Hz , 2H) 1.16 (t, *J* = 7.6 Hz, 3H) and MS (ES) m/e 481.4 $(M+H)^+$.
13		δ 10.00 (s, 1H), 8.98-8.94 (m, 3H), 7.82-7.80 (m, 1H), 7.25 (s, 1H), 7.18 (s, 1H), 6.45 (s, 1H), 4.62 (s, 1H), 3.99 (t, *J* = 5.8 Hz, 2H), 3.41 (m, 1H), 2.92-2.45 (m, 6H), 2.08 (t, *J* = 9.8 Hz, 2H), 1.82 (m, 2H), 1.42 (m, 2H), 1.12 (m, 3H) and MS (ES) m/e 477.4 $(M–H)^-$.
14#		δ 11.39 (s, 1H), 9.92 (s, 1H), 9.41 (bs, 1H), 8.78 (s, 1H), 7.30-7.13 (m, 6H), 6.44 (s, 1H), 5.01 (bs, 1H), 4.21 (s, 2H), 3.92-3.62 (m, 6H), 3.24 (s, 2H), 1.99-1.75 (m, 4H), 1.16 (s, 3H) and MS (ES) m/e 493.0 $(M+H)^+$.
15		δ 9.83 (s, 1H), 8.76 (d, J = 3.6 Hz, 1H), 8.41 (s, 1H), 7.84 (d, J = 1.2 Hz, 1H), 7.22 (d, J = 2.8 Hz, 2H), 7.12 (s, 1H), 6.45 (s, 1H), 4.54 (s, 1H), 4.03 (s, 2H), 3.43 (s, 1H), 2.78 (s, 2H), 2.66 (d, J = 8.0 Hz, 2H),

		2.52-2.49 (m, 2H), 2.13 (s, 2H), 1.71 (d, J = 9.2 Hz, 2H), 1.39-1.33 (m, 2H), 1.18 (t, J = 7.6 Hz, 3H) and MS (ES): m/e 427.3 $(M+H)^+$.
16		δ 9.88 (s, 1H), 8.79 (d, *J* = 4.0 Hz, 1H), 8.50 (s, 1H), 8.27 (s, 1H), 8.89 (d, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.25 (s, 1H), 7.17 (s, 1H), 6.47 (s, 1H), 4.54 (d, *J* = 4.0 Hz, 1H), 4.04 (t, *J* = 5.8 Hz, 2H), 3.42-3.40 (m, 1H), 3.78-3.75 (m, 2H), 2.65 (t, *J* = 6.2 Hz, 2H), 2.56-2.60 (m, 2H), 2.10 (t, *J* = 9.8 Hz, 2H), 1.68 (d, *J* = 9.2 Hz, 2H), 1.41-1.32 (m, 2H), 1.20 (t, *J* = 7.8 Hz, 3H) and MS (ES) m/e 503.4 $(M+H)^+$.
17		δ 10.02 (s, 1H), 9.61 (bs, 1H), 8.86 (d, *J* = 1.6 Hz, ,1H), 7.88 (s, 1H), 7.58 (s, 1H), 7.20 (s, 1H), 7.17 (s, 1H), 6.58 (s, 1H), 4.30 (bs, 3H), 3.97-3.80 (m, 1H), 3.80-3.35 (m, 2H), 3.30-3.08 (m, 2H), 2.72 (s, 3H), 2.61-2.44 (m, 2H), 2.03-2.79 (m, 4H), 2.45 (d, *J* = 10.8 Hz, 2H), 1.18 (t, *J* = 7.6 Hz, 3H) and MS (ES) m/e 441.4 $(M+H)^+$.
18		δ 10.11 (s, 1H), 9.51 (bs, 1H), 8.92 (s, 1H), 8.74 (s, 1H), 8.09 (s, 1H), 7.38-7.01 (m, 2H), 6.54 (s, 1H), 5.03 (m, 1H), 4.32 (bs, 1H), 3.95 (bs, 1H), 3.65-3.11 (m, 4H), 2.67-2.50 (m, 2H), 1.99-1.90 (m, 2H), 1.79-1.60 (m, 4H), 1.21-1.19 (m, 3H) and MS (ES) m/e 428.4 $(M+H)^+$.
19		δ 10.01 (s,1H), 8.93-8.92 (m, 1H), 8.09-8.08 (m, 1H), 7.51 (s, 1H), 7.22 (s, 2H), 7.46 (s, 1H), 4.53 (bs, 1H), 4.02 (s, 2H), 3.44 (bs, 1H), 2.76 (bs, 2H), 2.67 (d, *J* = 2.0 Hz, 2H), 2.64-2.54 (m, 2H), 2.11 (bs, 2H), 1.70 (bs, 2H), 1.39 (bs, 2H), 1.17 (t, *J* = 7.6 Hz, 3H) and MS (ES) m/e 452.2 $(M+H)^+$.

Boc deprotection-conditions: Boc-protected compound dissolved in DCM (5 mL) and cooled at 0°C. To the above solution trifluoroacetic acid (0.5 mL) was added dropwise over a period of 10 min and stirred at RT for 3 h. Excess of TFA and DCM was removed under vacuo and the crude compound was triturated with diethyl ether to afford the compound-14 as an off-white solid (20 mg, 25%).

Example-II: Synthesis of N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine.trifluoroacetic acid (Compound-20).



Step-i: Synthesis of tert-butyl 8-((4-(1*H*-benzo[*d*]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate:

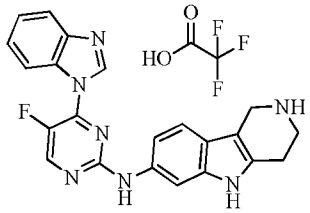
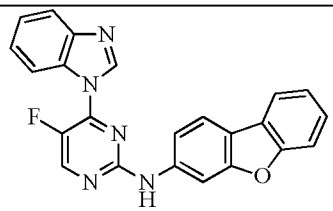
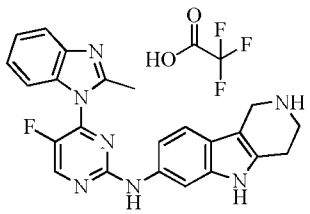
To a mixture of tert-butyl 8-amino-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (115 mg, 0.4 mmol), 1-(2-chloro-5-fluoropyrimidin-4-yl)-1*H*-benzo[*d*]imidazole (100 mg, 0.4 mmol)) and cesium carbonate (260 mg, 0.8 mmol) in 1,4-dioxane (5 mL) was degassed with argon in a seal tube for 30 min. To the above reaction mixture tris(dibenzylideneacetone)dipalladium(0) (15 mg, 0.016 mmol) and xantphos (28 mg, 0.048 mmol) were added and again degassed with argon for 30 min. Then the reaction mixture was heated at 90°C for 30 min. After completion of reaction, reaction mixture was cooled to room temperature, diluted with ethyl acetate and passed through celite. The resultant filtrate was washed with water, brine solution, organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography (3:7 MeOH/DCM) to afford the desired product as a pale yellow solid (50 mg, 25%). MS (ES) m/e 500 $(M+H)^+$ and 400 $(M\text{-}Boc)^+$.

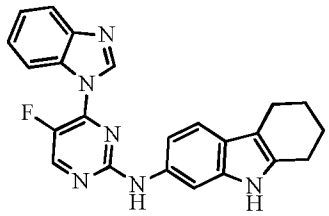
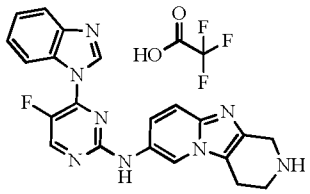
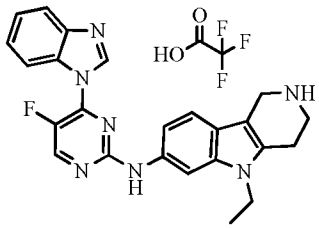
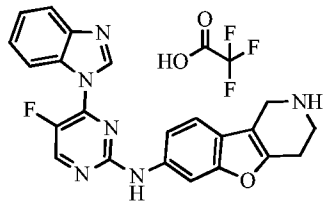
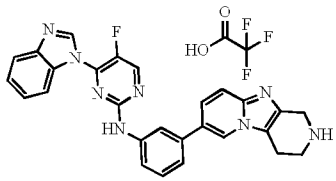
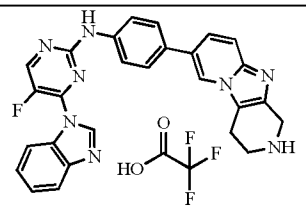
Step-ii: Synthesis of N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine trifluoro acetic acid:

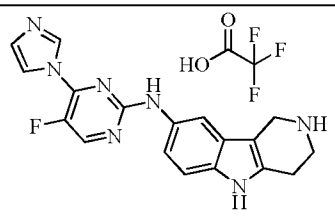
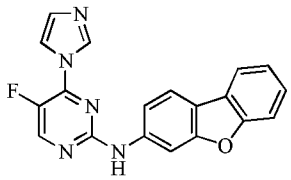
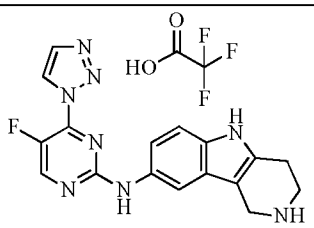
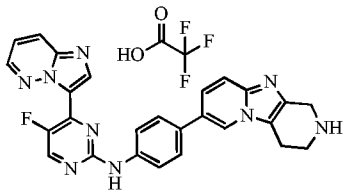
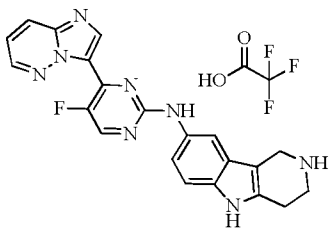
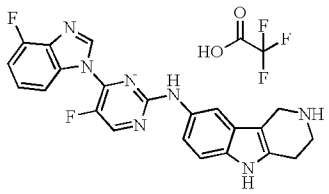
tert-butyl 8-((4-(1*H*-benzo[*d*]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (50 mg, 0.1 mmol) was dissolved in DCM (5 mL)

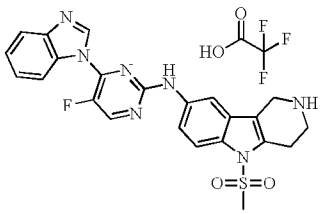
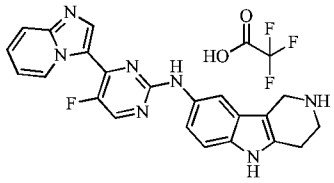
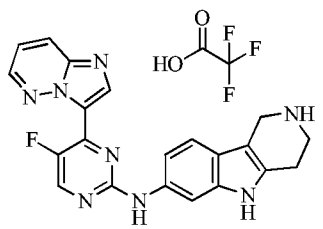
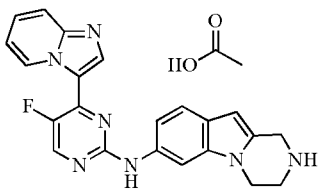
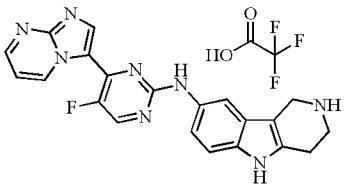
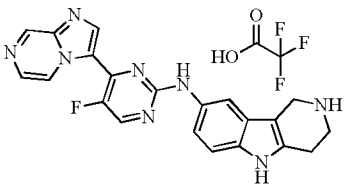
and cooled at 0°C. To the above solution trifluoro acetic acid (0.5 mL) was added dropwise over a period of 10 min. Reaction mixture was stirred at room temperature for 3 h. After completion of reaction, excess of TFA and DCM was removed under reduced pressure and was triturated with diethyl ether to afford the desired product as an off-white solid (10 mg, 25%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.10 (s, 1H), 9.78 (s, 1H), 8.97 (bs, 2H), 8.78 (d, J = 2.0 Hz, 1H), 8.75 (d, J = 4.0 Hz, 1H), 8.27 (bs, 1H), 7.85 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.40-7.27 (m, 4H) 4.22 (s, 2H), 3.60 (t, J = 6.6 Hz, 2H), 3.02 (t, J = 5.6 Hz, 2H) and MS (ES) m/e 400 $(M+H)^+$.

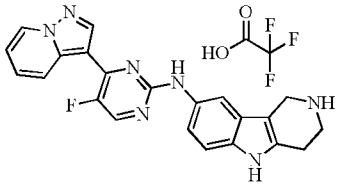
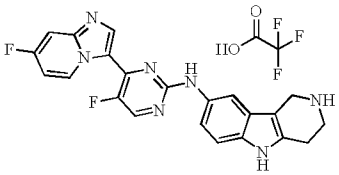
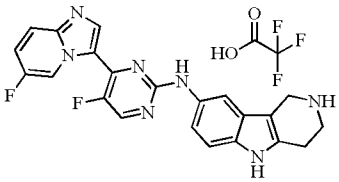
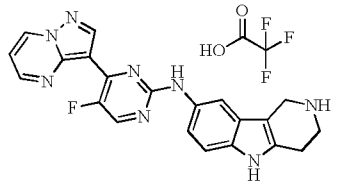
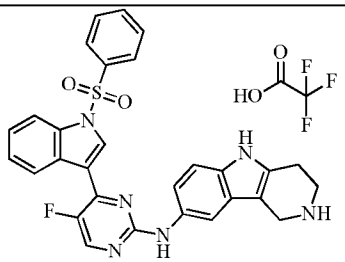
The below compounds were prepared by procedure similar to the one described in Example-II with appropriate variations in reactants, quantities of reagents and reaction conditions. The physiochemical characteristics of the compounds are summarized herein below table.

Comp. No	Structure	Characterization data ^{1}H NMR (400 MHz, DMSO-d_6)
21		δ 11.07 (s, 1H), 9.88 (s, 1H), 9.88 (s, 1H), 8.97 (s, 1H), 8.78 (d, J = 3.2 Hz, 2H), 8.31 (bs, 1H), 7.89 (s, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.41-7.36 (m, 3H), 7.29-7.27 (m, 1H), 4.31 (bs, 2H), 3.49 (d, J = 5.2 Hz , 2H), 3.00 (t, J = 5.6 Hz , 2H) and MS (ES) m/e 400 $(M+H)^+$.
22		δ 10.34 (s, 1H), 8.89 (d, J = 3.6 Hz, 1H), 8.82 (d, J = 2.0 Hz, 1H), 8.39-8.37 (m, 1H), 8.30 (d, J = 1.6 Hz, 1H), 8.07-8.05 (m, 2H), 7.85-7.83 (m, 1H), 7.69-7.64 (m, 2H), 7.47-7.36 (m, 4H) and MS (ES) m/e 396 $(M+H)^+$.
23		δ 10.62 (s, 1H), 9.87 (s, 1H), 8.85 (d, J = 2.4 Hz, 1H), 7.82 (s, 1H), 7.66 (dd, J_1 = 2.8 Hz, J_2 = 6.0 Hz, 1H), 7.42 (d, J = 4.0 Hz, 1H), 7.28 (dd, J_1 = 2.2 Hz, J_2 = 5.0 Hz, 2H), 7.20 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 1.6 Hz, 1H), 3.81 (bs, 1H), 3.44 (d, J = 6.8 Hz, 2H), 2.70 (s, 3H), 2.66 (d, J = 2 Hz, 2H), 2.64 (s, 1H) and MS (ES) m/e 412.3 $(M-H)^+$.

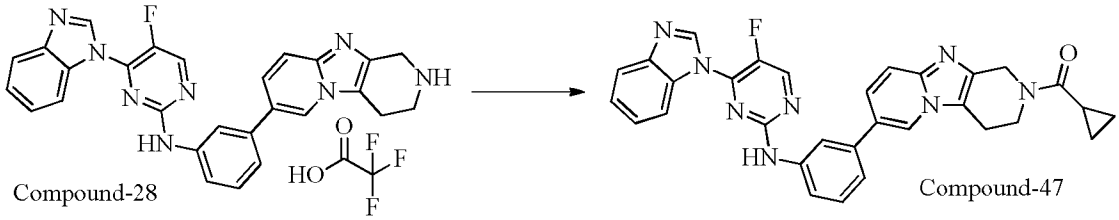
24		δ 10.55 (s, 1H), 9.76 (s, 1H), 8.77 (d, *J* = 2.0 Hz, 1H), 8.75 (d, *J* = 3.6 Hz, 1H), 8.32 (bs, 1H), 7.81-7.79 (m, 1H), 7.75 (s, 1H), 7.41-7.25 (m, 2H), 7.19 (d, *J* = 2.0 Hz, 1H), 7.17 (d, *J* = 1.6 Hz, 1H), 2.68-2.66 (m, 2H), 2.62-2.61 (m, 2H), 1.84-1.78 (m, 4H) and MS (ES) m/e 399.1 $(M+H)^+$.
25		δ 10.24 (s, 1H), 9.3 (bs, 1H), 8.97-8.84 (m, 3H), 8.25 (s, 1H), 7.85-7.40 (m, 5H), 4.40 (bs, 2H), 3.55 (bs, 2H), 2.98 (bs, 2H) and MS (ES) m/e 401 $(M+H)^+$.
26		δ 9.95 (s, 1H), 9.04 (s, 2H), 8.80 (dd, *J* = 2.8 Hz, 5.0 Hz, 2H), 8.27 (s, 1H), 7.96 (s, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.41-7.30 (m, 3H), 4.33 (s, 2H), 4.04 (q, *J* = 7.0 Hz, 2H), 3.53 (d, *J* = 5.8 Hz, 2H), 3.05 (t, *J* = 5.6 Hz, 2H), 1.14 (t, *J* = 6.8 Hz, 3H) and MS (ES) m/e 428.0 $(M+H)^+$.
27		δ 10.2 (s, 1H), 9.18 (bs, 2H), 8.84 (d, *J* = 3.4 Hz, 1H), 8.79 (d, *J* = 1.9 Hz, 1H), 8.32 (d, *J* = 6.3 Hz, 1H), 8.17 (s, 1H), 7.83 (dd, *J* = 2.9 Hz, 5.9 Hz, 1H), 7.54 (s, 2H), 7.43-7.37 (m, 2H), 4.34 (s, 2H), 3.56 (s, 2H), 3.06 (s, 2H) and MS (ES) m/e 401.2 $(M+H)^+$.
28		δ 10.14 (s, 1H), 9.34 (bs, 1H), 8.85-8.64 (m, 3H), 8.30-8.28 (d, *J* = 8.0 Hz, 1H), 8.20 (s, 1H), 7.81-7.19 (m, 8H), 4.44 (bs, 2H), 3.60 (bs, 2H), 3.11 (bs, 2H) and MS (ES) m/e 477 $(M+H)^+$.
29		δ 10.16 (s, 1H), 9.3 (bs, 1H), 8.82-8.69 (m, 3H), 8.34 (s, 1H), 7.93-7.46 (m, 9H), 4.43 (bs, 2H), 3.65 (bs, 2H), 3.26 (bs, 2H) and MS (ES) m/e 477 $(M+H)^+$.

30		δ 11.08 (s, 1H), 9.76 (s, 1H), 9.02 (s, 2H), 8.72 (d, *J* = 3.6 Hz, 1H), 8.54 (s, 1H), 7.87 (s, 1H), 7.80 (s, 1H), 7.33-7.23 (s, 3H), 4.32 (s, 2H), 3.42-3.3.37 (m, 2H), 3.02 (s, 2H) and MS (ES) m/e 321.2 $(M+H)^+$.
31		δ 10.31 (s, 1H), 8.84 (d, *J* = 3.2 Hz, 1H), 8.48 (s, 1H), 8.26 (d, *J* = 1.2 Hz, 1H), 8.07-8.03 (m, 2H), 7.91 (s, 1H), 7.68-7.62 (m, 2H), 7.45 (t, *J* = 7.0 Hz, 1H), 7.43-7.35 (m, 1H), 7.27 (s, 1H) and MS (ES) m/e 346.0 $(M+H)^+$.
32		δ 9.30 (d, *J* = 2.4 Hz, 1H), 9.29-9.25 (m, 2H), 8.92 (s, 1H), 8.40 (d, *J* = 8.8 Hz, 1H), 8.19 (s, 1H), 7.25 (s, 1H), 7.12 (s, 1H), 6.99 (s, 1H), 4.39 (s, 2H), 3.52 (s, 4H) and MS (ES) m/e 294.1 $(M+H)^+$.
33		δ 10.03 (s, 1H), 9.26 (bs, 2H), 8.91(d, *J* = 3.6 Hz, 1H), 8.75 (d, *J* = 2.4 Hz, 1H), 8.64 (s, 1H), 8.42-8.36 (m, 2H), 8.18 (d, *J* = 8.4 Hz, 2H), 7.78-7.76 (m, 4H), 7.52-7.40 (m, 1H), 4.40 (bs, 2H), 3.62 (bs, 2H) 3.23 (bs, 2H); MS (ES) m/e 478.3 $(M+H)^+$.
34		δ 10.99 (s, 1H), 9.61 (s, 1H), 8.96 (bs, 2H), 8.77-8.75 (m, 1H), 8.65 (d, *J* = 2.4 Hz, 1H), 8.35-8.32 (m, 2H), 7.95 (s, 1H), 7.51-7.43 (m, 1H), 7.29-7.21 (m, 2H), 4.26 (bs, 2H), 3.48 (d, *J* = 4.4 Hz, 2H), 3.00 (t, *J* = 5.6 Hz, 2H); MS (ES): m/z 401.1 $(M+H)^+$.
35		δ 11.09 (s, 1H), 9.81 (s, 1H), 8.98 (bs, 2H), 8.81 (d, *J* = 1.2 Hz, 1H), 8.77 (d, *J* = 3.2 Hz, 1H), 8.06 (bs, 1H), 7.84 (s, 1H), 7.33-7.20 (m, 4H), 4.21 (s, 2H), 3.49 (s, 2H), 3.02 (t, *J* = 5.4 Hz, 2H); MS (ES): m/z 418.1 $(M+H)^+$.

36		δ 10.09 (s, 1H), 9.06 (bs, 2H), 8.81-8.80 (m, 2H), 8.30 (d, *J* = 3.2 Hz, 1H), 8.04 (d, *J* = 2.0 Hz, 1H), 7.86-7.82 (m, 2H), 7.59-7.56 (m, 1H), 7.43-7.39 (m, 2H), 4.23 (s, 2H), 3.50 (s, 2H), 3.39 (s, 3H), 3.20 (s, 2H); MS (ES): m/z 478.3 $(M+H)^+$.
37		δ 11.10 (s, 1H), 10.04 (bs, 1H), 9.54 (s, 1H), 9.00 (bs, 2H), 8.46 (s, 1H), 8.42 (d, *J* = 2.8 Hz, 1H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.75 (s, 1H), 7.58 (t, *J* = 6.0 Hz, 1H), 7.37-7.28 (m, 2H), 6.99 (bs, 1H), 4.27 (s, 2H), 3.51-3.50 (m, 2H), 3.04 (t, *J* = 4.4 Hz, 2H); MS (ES): m/z 400 $(M+H)^+$.
38		δ 10.93 (s, 1H), 9.75 (s, 1H), 8.96 (bs, 2H), 8.79-8.78 (m, 1H), 8.68 (d, *J* = 3.2 Hz, 1H), 8.35-8.33 (m, 2H), 8.11 (d, *J* = 1.2 Hz, 1H), 7.49-7.43 (m, 2H), 7.37-7.34 (m, 1H), 4.29 (s, 2H), 3.51-3.42 (m, 2H), 3.00 (t, *J* = 3.6 Hz, 2H); MS (ES): m/z 401.2 $(M+H)^+$.
39		δ 10.05 (s, 1H), 9.61 (s, 1H), 8.55 (d, *J* = 4.0 Hz, 1H), 8.41 (d, *J* = 4.0 Hz, 1H), 7.81 (d, *J* = 9.2 Hz, 1H), 7.72 (s, 1H), 7.56-7.52 (m, 1H),7.42 (d, *J* = 8.4 Hz, 1H), 7.25 (d, *J* = 1.6 Hz, 1H), 6.97 (bs, 1H), 6.10 (s, 1H), 4.03 (s, 2H), 3.86 (t, *J* = 5.4 Hz, 2H), 3.15 (t, *J* = 5.4 Hz, 2H), 1.81 (s, 3H); MS (ES): m/z 400.2 $(M+H)^+$.
40		δ 11.11 (s, 1H), 10.30 (bs, 1H), 9.58 (s, 1H), 9.01 (bs, 2H), 8.75-8.74 (m, 1H), 8.57-8.54 (m, 2H), 7.75 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 1.2 Hz, 1H), 7.12 (bs, 1H), 4.27 (s, 2H), 3.52-3.50 (m, 2H), 3.04 (d, *J* = 5.6 Hz, 2H); MS (ES): m/z 401.2 $(M+H)^+$.
41		δ 11.13 (s, 1H), 9.82 (bs, 1H), 9.65 (bs, 1H), 9.31 (bs, 1H), 9.06 (bs, 2H), 8.63 (d, *J* = 3.4 Hz, 1H), 8.54 (d, *J* = 3.9 Hz, 1H), 7.97 (bs, 1H), 7.76 (s, 1H), 7.38-7.36 (m, 1H), 7.26-7.28 (m, 1H), 4.20-4.28 (m, 2H), 3.51-3.52

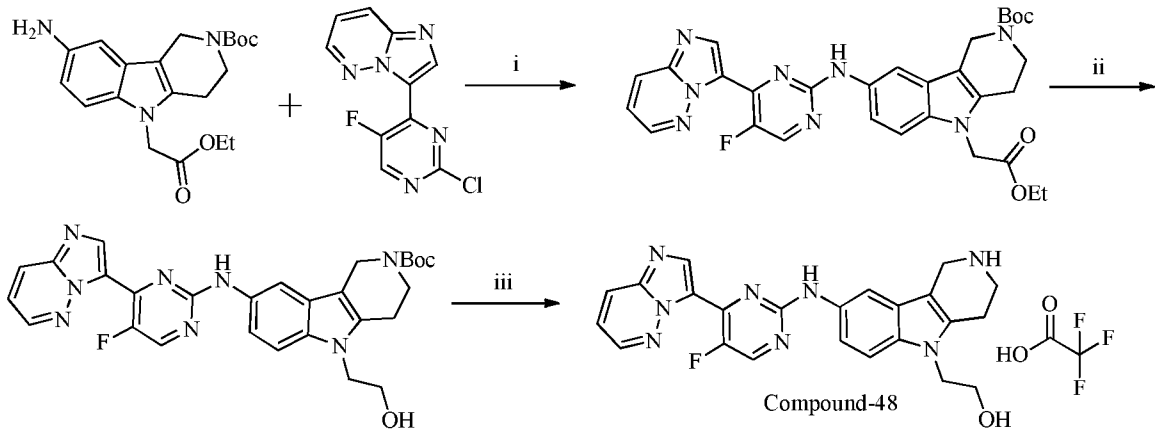
		(m, 2H), 3.03-3.06 (m, 2H); MS (ES): m/z 401.2 $(M+H)^+$.
42		δ 10.83 (s, 1H), 9.29 (s, 1H), 8.88 (s, 1H), 8.72 (s, 1H), 8.69 (s, 1H), 8.43 (d, *J* = 3.3 Hz, 1H), 8.35 (bs, 1H), 7.71 (bs, 1H) ,7.43-7.39 (m, 1H), 7.28-7.21 (m, 2H), 7.16-7.12 (m, 1H), 3.98 (bs, 2H), 3.22 (bs, 2H), 2.84 (bs, 2H); MS (ES): m/z 400 $(M+H)^+$.
43		δ 11.1 (s, 1H), 10.08 (bs, 1H), 9.56 (s, 1H), 9.02 (s, 1H), 8.54 (d, *J* = 3.2 Hz, 1H), 8.41 (d, *J* = 4.0 Hz, 1H), 7.75-7.73 (m, 2H), 7.37-7.35 (m, 2H), 7.29-7.27 (m, 1H), 7.00-6.97 (m, 1H), 4.28 (s, 2H), 3.50 (s, 2H), 3.04 (s, 2H); MS (ES): m/z 418 $(M+H)^+$.
44		δ 11.12 (s, 1H), 10.09 (bs, 1H), 9.63 (bs, 1H), 9.07 (bs, 1H), 8.54 (d, *J* = 3.9 Hz, 1H), 8.47 (d, *J* = 3.9 Hz, 1H), 7.63-7.66 (m, 2H), 7.35 (bs, 2H), 4.29 (bs, 2H), 3.50 (bs, 2H), 3.04 (bs, 2H); MS (ES): m/z 418 $(M+H)^+$.
45		δ 10.97 (s, 1H), 9.44 (s, 1H), 9.31 (dd, J_1= 1.8 Hz & J_2= 7.2 Hz, 1H), 9.01 (bs, 2H), 8.86 (dd, J_1= 1.8 Hz & J_2= 4.2 Hz, 1H), 8.73 (d , *J* = 1.6 Hz, 1H), 8.52 (d , *J* = 2.4 Hz, 1H), 8.09 (s, 1H), 7.54 (dd, J_1= 1.2 Hz & J_2= 4.8 Hz, 1H), 7.28-7.26 (m, 2H), 4.29 (s, 2H), 3.50 (s, 2H), 3.01 (s, 2H); MS (ES): m/z 401 $(M+H)^+$.
46		δ 11.05 (s, 1H), 9.48 (s, 1H), 8.93 (bs, 2H), 8.58 (d, *J* = 2.8 Hz, 2H), 8.43 (d, *J* = 2.0 Hz, 1H), 8.13 (d, *J* = 7.2 Hz, 2H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.80-7.75 (m, 2H), 7.65-7.62 (m, 2H), 7.44-7.25 (m, 4H), 4.21 (s, 2H), 3.49 (s, 2H), 3.02 (s, 2H); MS (ES): m/z 539.1 $(M+H)^+$.

Example-III: Synthesis of (7-(3-((4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)phenyl)-3,4-dihydroimidazo[1,2-a:4,5-c']dipyridin-2(1H)-yl)(cyclopropyl)methanone (Compound-47):



To a stirred solution of cyclopropyl carboxylic acid (0.1 g, 1.16 mmol) in DCM (10 mL), EDCI.HCl (0.26 g, 1.39 mmol), HOBT (0.18 g, 1.39 mmol) and DIPEA (0.4 mL, 2.32 mmol) were added and stirred at room temperature for 10 min. To the above reaction mixture, solution of compound-28 (0.1 g, 0.17 mmol) in DCM (10 mL) was added and stirred at room temperature for 12 h. Reaction mixture was diluted with water (20 mL) and extracted with DCM (50 mL). Organic layer was washed with water followed by brine and dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The obtained crude compound was purified by column chromatography (7:3, DCM/MeOH) to afford the desired product as a white solid (20 mg, 21%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 8.86-8.81 (m, 3H), 8.27-8.25 (m, 2H), 7.79-7.26 (m, 8H), 5.08 (bs, 1H), 4.81 (bs, 1H), 4.16 (bs, 2H), 3.84 (bs, 1H), 2.96 (s, 2H), 0.80 (bs, 4H); MS (ES) m/e 545 $(M+H)^+$.

Example-IV: Synthesis of 2-(8-((5-fluoro-4-(imidazo[1,2-b]pyridazin-3-yl)pyrimidin-2-yl)amino)-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)ethanol 2,2,2-trifluoroacetate (Compound-48):



Step-i: Synthesis of tert-butyl 5-(2-ethoxy-2-oxoethyl)-8-((5-fluoro-4-(imidazo[1,2-b]pyridazin-3-yl)pyrimidin-2-yl)amino)-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate:

To a solution of tert-butyl 8-amino-5-(2-ethoxy-2-oxoethyl)-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (0.3 g, 0.804 mol) in IPA (2.5 mL) and DIPEA (2.5 mL) mixture, 3-(2-chloro-5-fluoropyrimidin-4-yl)imidazo[1,2-b]pyridazine (0.2 g, 0.804 mol) was added and stirred at 110°C for 16 hrs in a seal tube. After completion of reaction, reaction mixture was concentrated under reduced pressure, crude material was diluted with EtOAc washed with water. Organic layer was washed with brine and dried over anhydrous Na_2SO_4, concentrated under reduced pressure, crude compound was purified by column over 230-400 mesh silica gel by eluting with EtOAc/*n*-hexane (3:7) to give title compound as a pale yellow solid (160 mg, 34%); MS (ES) m/e 587 $(M+H)^+$.

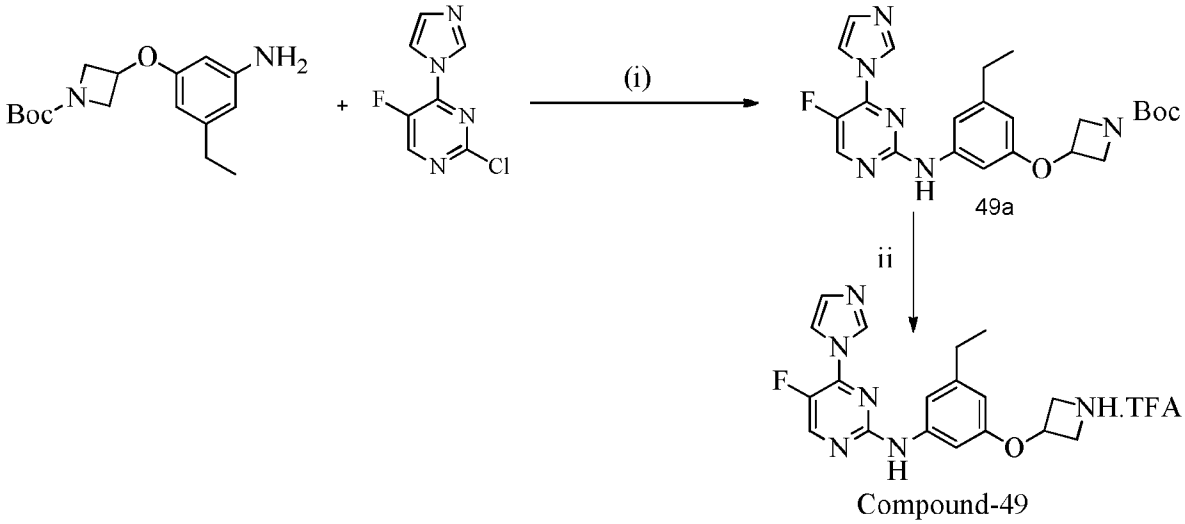
Step-ii: Synthesis of tert-butyl 8-((5-fluoro-4-(imidazo[1,2-b]pyridazin-3-yl)pyrimidin-2-yl)amino)-5-(2-hydroxyethyl)-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate:

To a stirred solution of tert-butyl 5-(2-ethoxy-2-oxoethyl)-8-((5-fluoro-4-(imidazo[1,2-b]pyridazin-3-yl)pyrimidin-2-yl)amino)-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (170 mg. 0.00029 mol) in dry THF (10 mL) at 0°C. $LiBH_4$ was added at same temperature. Reaction mass was stirred at room temperature for 12 hrs. After completion of reaction, reaction mass was poured in ice then extracted with EtOAc. Organic layer was washed with brine and dried over anhydrous Na_2SO_4. Organic layer was concentrated under reduced pressure, crude compound was purified by column over 230-400 mesh silica gel by eluting with MeOH/DCM (1:9) to give title compound as an off-white solid (70 mg, 50%); MS (ES) m/e 544 $(M+H)^+$.

Step-iii: Synthesis of 2-(8-((5-fluoro-4-(imidazo[1,2-b]pyridazin-3-yl)pyrimidin-2-yl)amino)-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)ethanol 2,2,2-trifluoroacetate (Compound-48):

The process of this step was adopted from step-ii of compound-20. The desired product obtained as a brown solid (8 mg, 10%); ^1H NMR (400 MHz, DMSO-d_6): δ 9.52 (s, 1H), 8.75 (d, J = 4.0 Hz, 1H) , 8.63 (d, J = 2.0 Hz, 1H), 8.42 (bs, 2H), 8.34-8.29 (m, 2H), 7.83 (s, 1H), 7.32-7.30 (m, 2H), 7.50-7.40 (m, 2H), 4.06 (d, J = 5.6 Hz, 2H), 3.83 (s, 2H), 3.61 (t, J=5.6 Hz, 2H) 3.08 (s, 2H), 2.78 (s, 2H); MS (ES): m/z 445.3 $(M+H)^+$.

Example-V: Synthesis of *N*-(3-(azetidin-3-yloxy)-5-ethylphenyl)-5-fluoro-4-(1*H*-imidazol-1-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound 49):



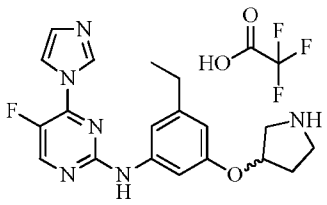
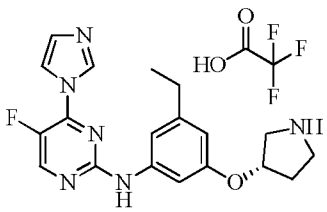
Step-i: Synthesis of *tert*-butyl 3-(3-ethyl-5-((5-fluoro-4-(1*H*-imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy)azetidine-1-carboxylate:

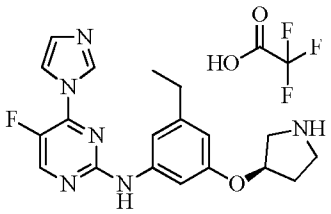
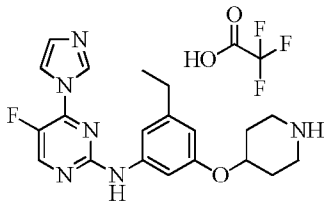
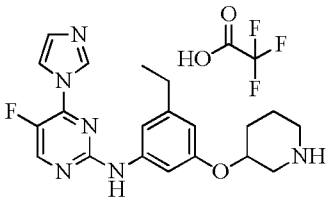
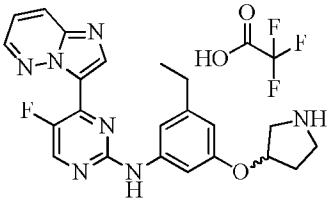
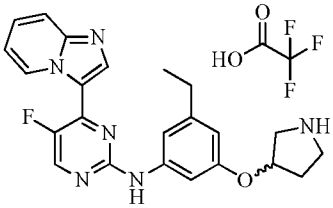
To a mixture of tert-butyl 3-(3-amino-5-ethylphenoxy)azetidine-1-carboxylate (0.175 g, 0.6 mmol), 2-chloro-5-fluoro-4-(1*H*-imidazol-1-yl)pyrimidine (0.095 g, 0.48 mmol) and cesium carbonate (0.394 g, 1.21 mmol) in 1,4-dioxane (5 mL) was degassed with argon in a seal tube for 30 min. To the above reaction mixture tris(dibenzylideneacetone)dipalladium(0) (22 mg, 0.024 mmol) and xantphos (35 mg, 0.06 mmol) were added and again degassed with argon for 30 min. Reaction mixture was stirred at 90°C for 30 min. After completion of reaction, reaction mixture was cooled to room temperature, diluted with EtOAc and passed through celite. Filtrate was washed with water followed by brine. Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude compound. Crude material was purified by column using 3% MeOH:DCM as a mobile phase over 230-400 mesh silica gel to obtain pure title compound *tert*-butyl 3-(3-ethyl-5-((5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-yl)amino) phenoxy)azetidine-1-carboxylate (0.13 g, 47%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.86 (s, 1H), 8.77 (d, J = 3.2 Hz, 1H), 8.42 (s, 1H), 7.84 (d, J = 1.6 Hz, 1H), 7.24 (d, J = 8.8 Hz, 2H), 7.04 (s, 1H), 6.32 (s, 1H), 4.96-4.91 (p, J = 4.2 Hz, 1H), 4.28 (t, J = 15.2 Hz, 2H), 3.81 (d, J = 4 Hz, 1H), 3.7 (d, J = 3.2 Hz, 1H), 2.5 (q, J = 5.8 Hz, 2H), 1.39 (s, 9H) 1.2 (t, J = 5 Hz, 3H).

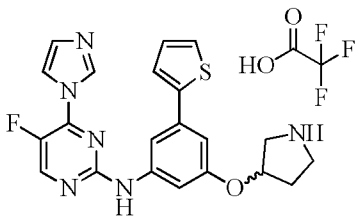
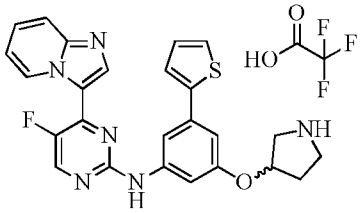
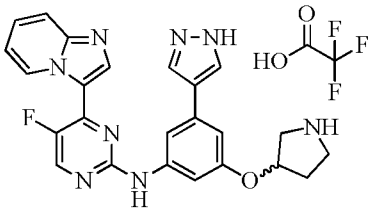
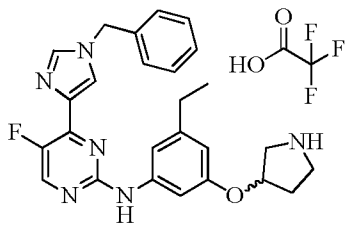
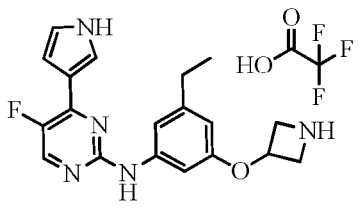
Step-ii: Synthesis of N-(3-(azetidin-3-yloxy)-5-ethylphenyl)-5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate:

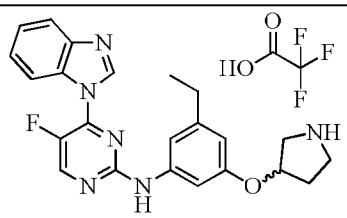
tert-butyl 3-(3-ethyl-5-((5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy) azetidine-1-carboxylate (0.13 g, 0.26 mmol) was dissolved in DCM (10 mL) and cooled at 0°C. To the above solution trifluoroaceticacid (0.2 mL) was added dropwise. Reaction mixture was stirred at room temperature for 3 h. After completion of reaction, excess of TFA and DCM was removed under reduced pressure to obtain crude compound. Crude material was triturated with di-ethyl ether to obtain pure compound as an off-white solid (90 mg, 86%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.93 (s, 1H), 9.07 (d, J = 3.5 Hz, 1H), 8.81-8.80 (m, 2H), 8.60 (bs, 1H), 7.89 (s, 1H), 7.34 (s, 1H), 7.29 (s, 1H), 7.07 (s, 1H), 6.34 (s, 1H), 5.04 (t, J = 5.6 Hz, 1H), 4.45-4.41 (m, 2H), 4.02-4.00 (d, J = 2.4 Hz, 2H), 2.57 (q, J = 7.7 Hz, 2H), 1.19 (t, J = 11.3 Hz, 3H). MS (ES): m/e 355.2 (M+1, 100%).

The below compounds were prepared by procedure similar to the one described in Example-V with appropriate variations in reactants, quantities of reagents and reaction conditions. The physiochemical characteristics of the compounds are summarized herein below table.

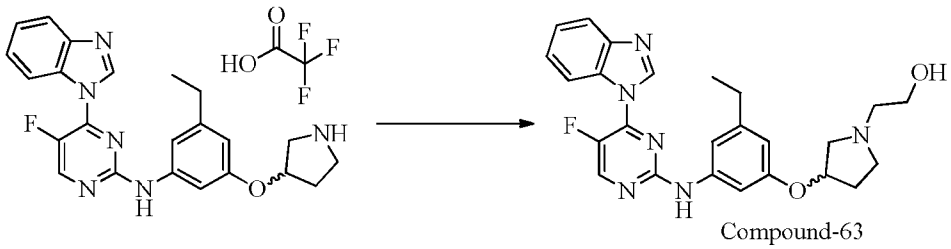
Comp No.	Structure	Characterization data ^{1}H NMR (400 MHz, DMSO-d_6)
50		δ 9.91 (s, 1H), 9.09 (bs, 2H), 8.78 (d, J = 3.6 Hz, 2H), 8.49 (s, 1H), 7.86 (s, 1H), 7.27 (s, 1H), 7.22 (s, 1H), 7.19 (s, 1H), 6.48 (s, 1H), 5.09 (bs, 1H), 3.48-3.43 (m, 4H), 2.60-2.55 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H) and MS (ES): m/e 369.1 $(M+H)^+$.
51		δ 9.89 (bs, 1H), 8.77 (s, 1H), 8.76 (s, 1H), 8.42 (s, 1H), 7.84 (s, 1H), 7.24 (s, 1H), 7.22 (s, 1H), 7.19 (s, 1H), 6.48 (s, 1H), 5.08 (s, 1H), 3.46-3.32 (m, 2H), 2.92 (d, J = 6.8 Hz, 1H), 2.60-2.50 (m, 3H), 2.22-2.15 (m, 3H), 1.23-1.17 (m, 3H) and MS (ES): m/e 367.3 $(M-H)^+$.

52		δ 9.91 (s, 1H), 9.08 (bs, 1H), 8.96 (bs, 1H), 8.78 (d, *J* = 3.4 Hz, 1H), 8.52 (s, 1H), 7.87 (s, 1H), 7.29 (s, 1H), 7.23 (s, 1H), 7.19 (s, 1H), 6.48 (s, 1H), 5.09 (s, 1H), 3.48-3.41 (m, 2H), 3.39-3.31 (m, 2H), 2.58 (q, *J* = 7.5 Hz, 2H), 2.46-2.15 (m, 2H), 1.19 (t, *J* = 7.6 Hz, 3H) and MS (ES) m/e 369.1 $(M+H)^+$.
53		δ 9.88 (bs, 1H), 8.78 (d, *J* = 3.6 Hz, 1H), 8.53 (s, 1H), 8.47 (bs, 2H), 7.87 (s, 1H), 7.30 (s, 1H), 7.22 (s, 1H), 7.09 (s, 1H), 6.53 (s, 1H), 4.61-4.57 (m, 1H), 4.61-4.60 (s, 1H), 3.39-3.37 (m, 4H), 2.51-2.50 (m, 2H), 2.21-2.11 (m, 2H), 1.80-1.78 (m, 2H), 1.21-1.19 (m, 3H) and MS (ES): m/e 382.9 $(M+H)^+$.
54		δ 9.89 (s, 1H), 8.78-8.77 (m, 2H), 8.59 (bs, 1H), 8.50 (s, 1H), 7.87 (s, 1H), 7.28-7.20 (m, 3H), 6.56 (s, 1H), 4.65 (s, 1H), 3.32-3.26 (m, 2H), 3.09 (s, 2H), 2.61-2.55 (m, 2H), 1.91-1.88 (m, 3H), 1.67 (bs, 1H), 1.20 (t, *J* = 7.3 Hz, 3 H) and MS (ES): m/e 383.2 $(M+H)^+$.
55		δ 9.78 (s, 1H), 9.05 (bs, 1H), 8.92 (bs, 1H), 8.74 (s, 1H), 8.72 (s, 1H), 8.36-8.34 (m, 2H), 7.54 (s, 1H), 7.50-7.48 (m, 1H), 7.36 (s, 1H), 5.42 (s, 1H), 5.06 (s, 1H), 3.43-3.33 (m, 4H), 2.67-2.55 (m, 2H), 2.18 (s, 2H), 1.17 (t, *J* = 7.6 Hz, 3H) and MS (ES) m/e 420.2 $(M+H)^+$.
56		δ 10.16 (d, *J* = 6.8 Hz, 1H), 9.77 (s, 1H), 9.08 (bs,1H), 8.96 (bs, 1H), 8.61 (d, *J* = 4 Hz, 1H), 8.49 (d, *J* = 3.2 Hz, 1H), 7.87 (d, *J* = 4 Hz, 1H), 7.64 (d, *J* = 4 Hz, 1H), 7.35 (s, 1H), 7.23-7.20 (m, 1H), 7.11 (s, 1H), 6.49 (s, 1H), 5.1 (s, 1H), 3.49-3.30 (m, 4H), 2.67-2.56 (m, 2H), 2.32-2.18 (m, 2H), 1.2 (t, *J* = 7.6 Hz, 3H) and MS (ES): m/e 419.2 $(M+H)^+$.

57		δ 10.07 (s, 1H), 9.03 (bs, 2H), 8.81 (d, *J* = 3.6 Hz, 1H), 8.46 (s, 1H), 7.88-7.75 (m, 1H), 7.78 (bs, 1H), 7.58 (d, *J* = 4.8 Hz, 1H), 7.52 (d, *J* = 3.4 Hz, 1H), 7.31 (bs, 1H), 7.25 (bs, 1H), 7.17-7.15 (m, 1H), 6.92 (bs, 1H), 5.18-5.21 (m, 1H), 3.52-3.41 (m, 4H), 2.39-2.22 (m, 2H) and MS (ES): m/e 423.3 $(M+H)^+$.
58		δ 10.17 (d, *J* = 6.8 Hz, 1H), 9.94 (s, 1H), 9.09-8.95 (bs, 2H), 8.65 (d, *J* = 3.4 Hz, 1H), 8.50 (d, *J* = 3.4 Hz, 1H), 7.87 (d, *J* = 8.9 Hz, 1H), 7.63-7.53 (m, 5H), 7.17-7.12 (m, 2H), 6.91 (s, 1H), 5.24 (s, 1H), 3.49-3.46 (m, 2H), 3.36-3.34 (m, 2H), 2.27-2.22 (m, 2H) and MS (ES): m/e 473.2 $(M+H)^+$.
59		δ 10.17 (d, *J* = 8.0 Hz, 1H), 9.82 (s, 1H), 9.05 (bs, 2H), 8.63 (d, *J* = 3.2, 1H), 8.50 (d, *J* = 4.0 Hz, 1H), 8.02 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.62-7.60 (m, 1H), 7.58-7.41 (m, 2H), 7.11-7.05 (m, 2H), 6.98 (s, 1H), 5.43 (s, 1H), 3.75-3.51 (m, 4H), 2.27-2.25 (m, 2H) and MS (ES): m/e 457.3 $(M+H)^+$.
60		δ 9.67 (s, 1H), 9.07 (bs, 2H), 8.95 (s, 1H), 7.55 (s, 1H), 7.2 (m, 5H), 7.26 (s, 1H), 7.01 (m, 2H), 6.46 (s, 1H), 5.80 (s, 2H), 5.08 (s, 1H), 3.37 (m, 4H), 2.67 - 2.58 (m, 2H), 2.30-2.20 (m, 2H), 1.98-1.90 (m, 3H) and MS (ES): m/e 459.2 $(M+H)^+$.
61		δ 11.52 (s, 1H), 9.41(s, 1H), 8.40 (s, 1H), 7.56 (s, 1H), 7.44 (s, 1H), 740-7.01 (m, 2H), 6.97 (s, 1H), 6.77 (s, 1H), 6.25 (s, 1H), 5.05-5.02 (m, 1H), 4.46-4.41 (m, 2H), 4.03-3.99 (m, 2H), 2.59-2.50 (m, 2H), 1.20 (t, *J* = 7.6 Hz, 3H) and MS (ES): m/e 354.2 $(M+H)^+$.

62		MS (ES): m/e 419.2 $(M+H)^+$.

Example-VI: Synthesis of 2-(3-(3-((4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)-5-ethylphenoxy)pyrrolidin-1-yl)ethanol 2,2,2-trifluoroacetate (Compound-63):

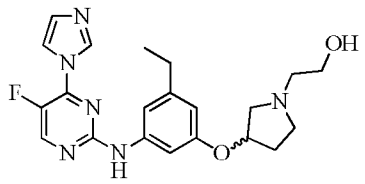
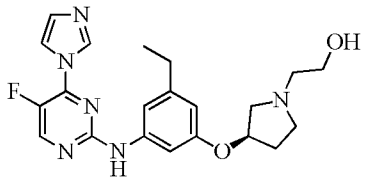
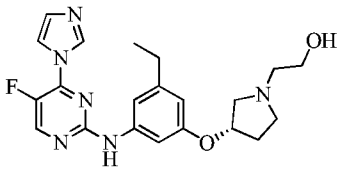


Compound-63

To a stirred solution of 4-(1H-benzo[d]imidazol-1-yl)-N-(3-ethyl-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoropyrimidin-2-amine 2,2,2-trifluoroacetate (0.1 g, 0.24 mmol) in DMF (2 mL), was added TEA (0.12 g, 1.19 mmol) and stirred at room temperature for 30 min. To the above mixture 2-bromoethanol (0.06 g, 0.48 mmol) was added drop wise and heated at 40°C for 2 h. After completion of reaction, the reaction mixture was poured on crushed ice, solid obtained was filtered and dried to afford the crude (0.1 g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.95 (s, 2H), 8.81-8.80 (d, J = 3.2 Hz, 1H), 8.79 (s, 1H), 8.33 (s, 1H), 7.84-7.81 (m, 1H), 7.43-7.41 (m, 2H), 7.27-7.22 (m, 2H), 6.48 (s, 1H), 5.10 (m, 1H), 5.04 (m, 1H), 3.72-3.63 (m, 5H), 3.31-3.24 (m, 4H), 2.67-2.55 (m, 2H), 1.17 (t, J = 8.0 Hz, 3H) and MS (ES): m/e 463.2 $(M+H)^+$.

The below compounds were prepared by procedure similar to the one described in Example-VI with appropriate variations in reactants, quantities of reagents and reaction conditions. The physiochemical characteristics of the compounds are summarized herein below table.

Comp No.	Structure	Characterization data ^{1}H NMR (400 MHz, DMSO-d_6)

64		δ 9.93 (bs, 2H), 8.79 (d, *J* = 3.2 Hz, 1H), 8.57 (s, 1H), 7.88 (s, 1H), 7.32 (s, 1H), 7.23-7.18 (m, 2H), 6.47 (s, 1H), 5.2-5.0 (bs, 2H), 4.02-3.96 (m, 2H), 3.73-3.71 (m, 4H), 3.04-3.28 (m, 2H), 2.67-2.57 (m, 3H), 1.19 (t. *J* = 7.2 Hz, 3H) and MS (ES): m/e 413.3 $(M+H)^+$.
65		δ 9.82 (s, 1H), 8.76 (d, *J* = 3.6 Hz, 1H), 8.41 (s, 1H), 7.84 (s, 1H), 7.23 (s, 1H), 7.17 (s, 1H), 7.10 (s, 1H), 6.38 (bs, 1H), 4.79 (bs, 1H), 4.45 (bs, 1H), 3.48 (d, *J*= 5.6 Hz, 2H), 2.85 (t, *J* = 10.4 Hz, 1H), 2.73-2.66 (m, 3H), 2.25-2.22 (m, 2H), 1.76 (d, *J* = 4.4 Hz, 2H), 1.18 (t, *J* = 7.6 Hz, 3H) and MS (ES): m/e 413.1 $(M+H)^+$.
66		δ 10.01 (bs, 1H), 9.91 (s, 1H), 8.78 (s, 1H), 8.78 (s, 1H), 8.50 (s, 1H), 7.86 (s, 1H), 7.28 (s, 1H), 7.23 (s, 1H), 7.18 (s, 1H), 6.47 (s, 1H), 5.09 (bs, 2H), 4.02-3.88 (m, 2H), 3.34-3.27 (m, 2H), 2.61-2.55 (m, 4H), 2.40-2.08 (m, 3H), 1.20 (t, *J* = 7.2 Hz, 3H) and MS (ES): m/e 413.1 $(M+H)^+$.

Biology: In vitro biochemical assay for TAK1 kinase.

This in vitro assay tests the ability of TAK1-TAB1 fusion protein to phosphorylate a substrate in the presence of ATP. TAK1 radiometric kinase assay was performed by incubating 250ng of TAK1-TAB1 fusion protein with the compound in the assay buffer (50mM Tris-HCl, pH: 7.5, 10mM Magnesium chloride, 10mM dithiotreitol, 0.1mM EGTA) for 30 min at room temperature. 3µg of Mylein basic protein (MBP), 10µM unlabelled ATP and 1µCi $\gamma^{32}P$ labeled ATP diluted in assay buffer were added and incubated for additional 15mins at room temperature. The reaction was quenched with 13µL of 100mM ATP in 8N HCl. 30µl of the sample was spotted onto a P81 Whatman Chromatography paper. The strips were washed several times with 0.5% Ortho Phosphoric acid and acetone. The p81 filter strips were then dried and placed in a 96well plate. 100µL of Microscint-O scintillation fluid was added and incubated for

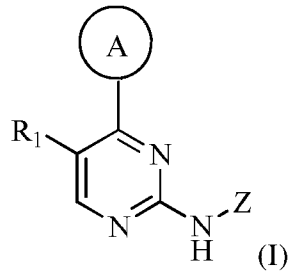
10mins at room temperature and read in Perkin Elmer NXL-Top Count. The percent inhibition of activity of the enzyme is calculated by comparing counts in the presence and absence of compounds. Dose response curves were generated for compound with 12 concentrations using GraphPad Prism software Version 5 (San Diego, California, USA) using non linear regression curve fit for sigmoidal dose response (variable slope).

The selected compounds were screened at 1 μM concentration and the results are summarized in below table. The IC_{50} values of the compounds are set forth in below Table, wherein Group "A" refers to an IC_{50} value in less than 0.2 μM, Group "B" refers to IC_{50} value in range of 0.2 to 0.5 μM and Group "C" refers to IC_{50} value in greater than 0.5.

Group	Compounds
A	1, 5, 9, 10, 12, 13, 15, 18, 19, 34, 37, 39, 42, 43, 44, 45, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 64, 65, 66.
B	3, 4, 11, 14, 20, 21, 26, 30, 35, 38, 40,
C	6, 7, 8, 16, 17, 28, 36, 41,

We claim:

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt or a pharmaceutically acceptable stereoisomer thereof,

wherein,

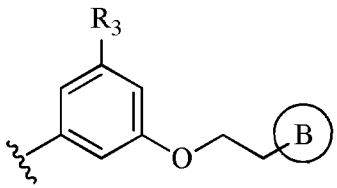
Ring 'A' is an optionally substituted C_4-C_{10} monocyclic or bicyclic ring containing 1-4 heteroatoms/groups independently selected from N, NH and CO; wherein the optional substituent at each occurrence is independently selected from one or more R_2;

R_1 is selected from hydrogen, halogen, alkyl, haloalkyl, cyano, hydroxy, amino and alkoxy;

R_2 is selected from halogen, alkoxy, alkyl, cyano, aryl, $-S(O)_2$aryl and arylalkyl.

Z represents:

i)

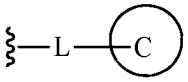


wherein,

R_3 is selected from hydrogen, alkyl, amino, hydroxy and alkoxy;

Ring 'B' is an optionally substituted N-linked C_4-C_8 monocyclic ring; wherein the optional substituent at each occurrence is independently selected from hydroxy and alkoxy;

ii)

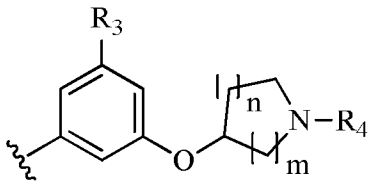


wherein,

L represents direct bond or aryl;

Ring 'C' is an optionally substituted C_{11}-C_{14} tricyclic heterocyclyl ring; wherein the optional substituent at each occurrence is independently selected from alkyl, halogen, hydroxyalkyl, -C(O)cycloalkyl and $-S(O)_2$alkyl;

iii)



wherein,

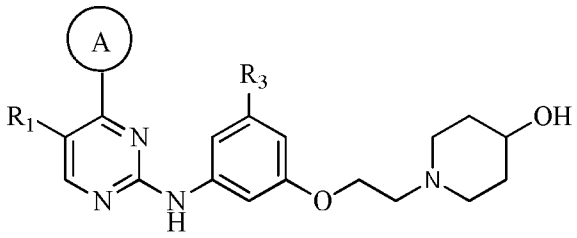
R_3 is selected from hydrogen, alkyl, amino, hydroxy, alkoxy and heterocyclyl;

R_4 is selected from hydrogen, alkyl and hydroxyalkyl;

'm' is selected from an integer 1 to 2, both inclusive; and

'n' is selected from an integer 0 to 2, both inclusive.

2. A compound according to claim 1 is a compound of formula (Ia)



(Ia)

or a pharmaceutically acceptable salt or a pharmaceutically acceptable stereoisomer thereof,

wherein,

Ring 'A' is an optionally substituted N-linked C_4-C_{10} monocyclic or bicyclic ring containing 1-4 heteroatoms and/or heterogroups selected from N, NH and C(O); wherein the optional substituent at each occurrence is independently selected from one or more R_2;

R_1 is selected from hydrogen, halogen, alkyl, haloalkyl, cyano, hydroxy, amino and alkoxy;

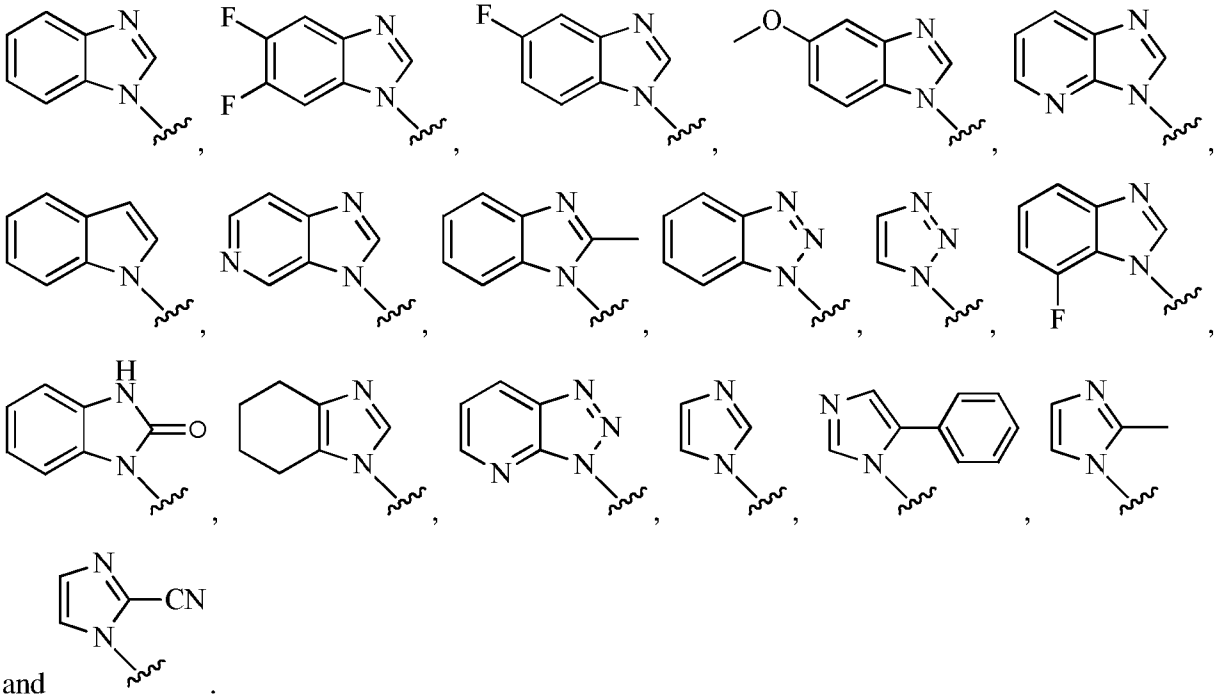
R_2 is selected from halogen, alkoxy, alkyl, cyano and aryl; and

R_3 is selected from hydrogen, alkyl, amino, hydroxy and alkoxy.

3. The compound according to claim 2, wherein R_1 is halogen.

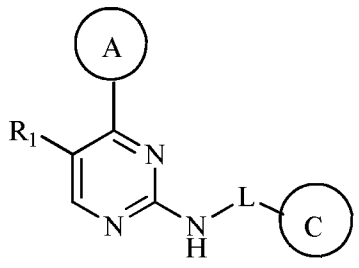
4. The compound according to claim 2, wherein R_3 is alkyl.

5. The compound according to claim 2, wherein Ring A is



and .

6. A compound according to claim 1 is a compound of formula (Ib)



(Ib)

or a pharmaceutically acceptable salt or a pharmaceutically acceptable stereoisomer thereof, wherein,

Ring 'A' is an optionally substituted C_4-C_{10} monocyclic or bicyclic ring containing 1-3 heteroatoms; wherein the heteroatom is 'N' and the optional substituent at each occurrence is independently selected from one or more R_2;

Ring 'C' is an optionally substituted C_{11}-C_{14} tricyclic heterocyclyl ring containing 1-4 heteroatoms independently selected from N, O and NH; wherein the optional substituent at each occurrence is independently selected from alkyl, halogen, hydroxyalkyl, -C(O)cycloalkyl and –$S(O)_2$alkyl;

L represents direct bond or aryl;

R_1 is selected from hydrogen, alkyl, halogen, haloalkyl, cyano, hydroxy, amino and alkoxy;

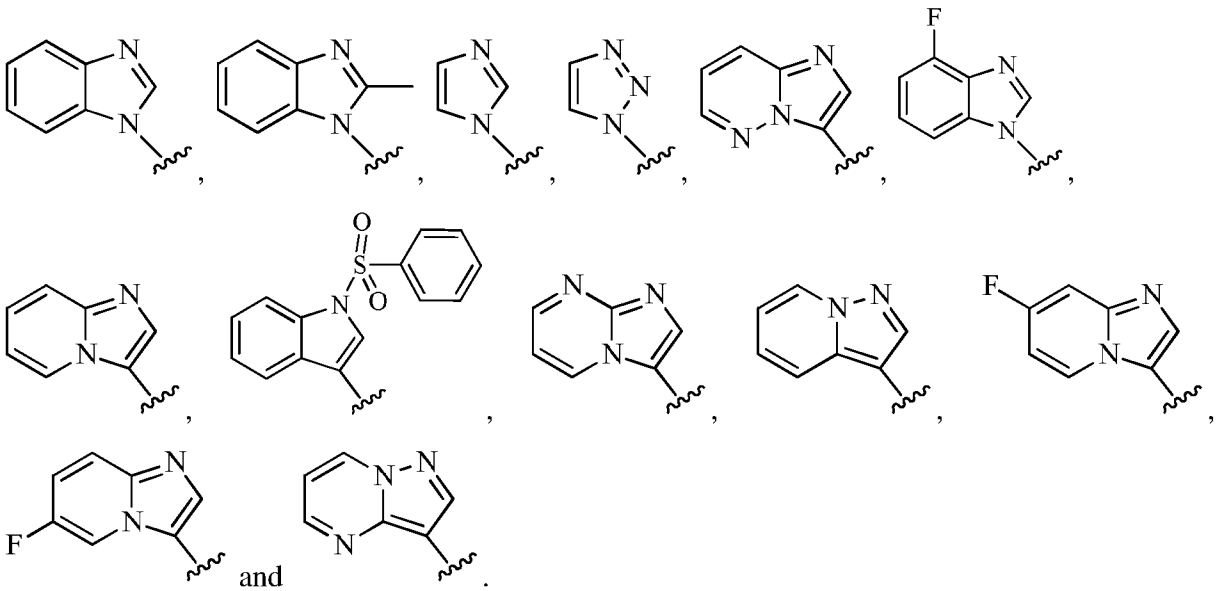
R_2 is selected from alkyl, halogen and $-S(O)_2$aryl.

7. The compound according to claim 6, wherein L is direct bond.

8. The compound according to claim 6, wherein L is phenyl.

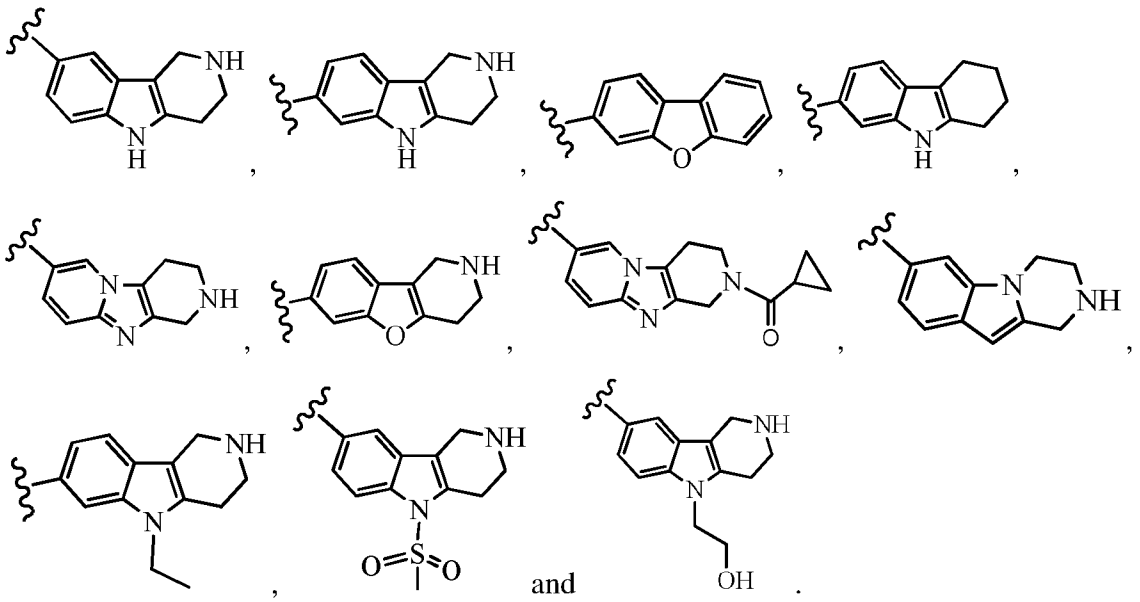
9. The compound according to claim 6, wherein R_1 is halogen.

10. The compound according to claim 6, wherein Ring A is



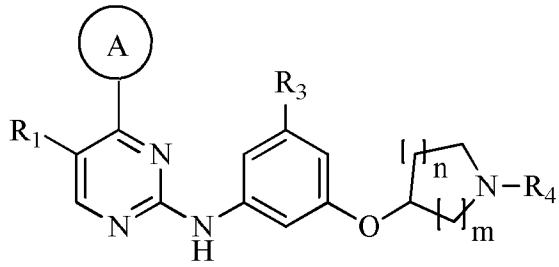
and .

11. The compound according to claim 6, wherein Ring C is



and .

12. A compound according to claim 1 is a compound of formula (Ic)



(Ic)

or a pharmaceutically acceptable salt or a pharmaceutically acceptable stereoisomer thereof, wherein,

Ring 'A' is an optionally substituted C_4-C_{10} monocyclic or bicyclic ring containing 1-4 heteroatoms/groups independently selected from N, NH and CO; wherein the optional substituent is arylalkyl;

R_1 is selected from hydrogen, halogen, alkyl, haloalkyl, cyano, hydroxy, amino and alkoxy;

R_3 is selected from hydrogen, alkyl, amino, hydroxy, alkoxy and heterocyclyl;

R_4 is selected from hydrogen, alkyl and hydroxyalkyl;

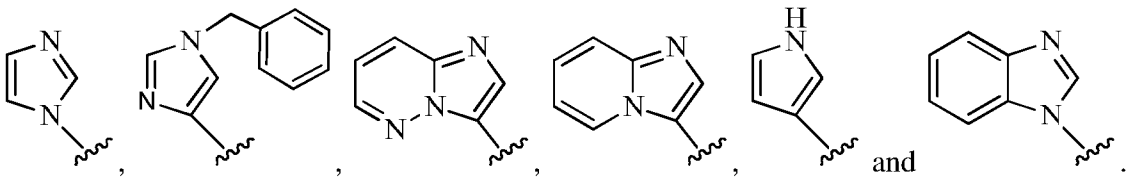
'm' is selected from an integer 1 to 2, both inclusive; and

'n' is selected from an integer 0 to 2, both inclusive.

13. The compound according to claim 12, wherein R_1 is halogen.

14. The compound according to claim 12, wherein R_3 is alkyl and heterocyclyl.

15. The compound according to claim 12, wherein Ring A is



and .

16. The compound according to claim 12, wherein R_4 is hydrogen and hydroxyalkyl.

17. A compound selected from the group consisting of

1-(2-(3-((4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)-5-ethylphenoxy) ethyl)piperidin-4-ol (Compound-1);

1-(2-(3-((4-(5,6-difluoro-1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)-5-ethylphenoxy)ethyl)piperidin-4-ol (Compound-2);

1-(2-(3-ethyl-5-((5-fluoro-4-(5-fluoro-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy)ethyl)piperidin-4-ol (Compound-3);

1-(2-(3-ethyl-5-((5-fluoro-4-(5-methoxy-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy)ethyl)piperidin-4-ol (Compound-4);

1-(2-(3-ethyl-5-((5-fluoro-4-(3H-imidazo[4,5-b]pyridin-3-yl)pyrimidin-2-yl)amino) phenoxy)ethyl)piperidin-4-ol (Compound-5);

1-(2-(3-ethyl-5-((5-fluoro-4-(1H-indol-1-yl)pyrimidin-2-yl)amino)phenoxy)ethyl) piperidin-4-ol (Compound-6);

1-(2-(3-ethyl-5-((5-fluoro-4-(3H-imidazo[4,5-c]pyridin-3-yl)pyrimidin-2-yl)amino) phenoxy)ethyl)piperidin-4-ol (Compound-7);

1-(2-(3-ethyl-5-((5-fluoro-4-(2-methyl-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy)ethyl)piperidin-4-ol (Compound-8);

1-(2-(3-((4-(1H-benzo[d][1,2,3]triazol-1-yl)-5-fluoropyrimidin-2-yl)amino)-5-ethyl phenoxy)ethyl)piperidin-4-ol (Compound-9);

1-(2-(3-ethyl-5-((5-fluoro-4-(7-fluoro-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)amino) phenoxy)ethyl)piperidin-4-ol (Compound-10);

1-(2-(3-((4-(1H-benzo[d]imidazol-1-yl)-5-chloropyrimidin-2-yl)amino)-5-ethylphenoxy) ethyl)piperidin-4-ol (Compound-11);

1-(2-(3-ethyl-5-((5-fluoro-4-(4,5,6,7-tetrahydro-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy)ethyl)piperidin-4-ol (Compound-12);

1-(2-(3-((4-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-5-fluoropyrimidin-2-yl)amino)-5-ethylphenoxy)ethyl)piperidin-4-ol (Compound-13);

1-(2-((3-ethyl-5-(2-(4-hydroxypiperidin-1-yl)ethoxy)phenyl)amino)-5-fluoropyrimidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (Compound-14);

1-(2-(3-ethyl-5-((5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy)ethyl) piperidin-4-ol (Compound-15);

1-(2-(3-ethyl-5-((5-fluoro-4-(5-phenyl-1H-imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy) ethyl)piperidin-4-ol (Compound-16);

1-(2-(3-ethyl-5-((5-fluoro-4-(2-methyl-1H-imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy) ethyl)piperidin-4-ol (Compound-17);

1-(2-(3-ethyl-5-((5-fluoro-4-(1H-1,2,3-triazol-1-yl)pyrimidin-2-yl)amino)phenoxy)ethyl) piperidin-4-ol (Compound-18); and

1-(2-((3-ethyl-5-(2-(4-hydroxypiperidin-1-yl)ethoxy)phenyl)amino)-5-fluoropyrimidin-4-yl)-1H-imidazole-2-carbonitrile (Compound-19),

or a pharmaceutically acceptable salt or a pharmaceutically acceptable stereoisomer thereof.

18. A compound selected from the group consisting of

N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido [4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-20);

N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido [4,3-b]indol-7-amine 2,2,2-trifluoroacetate (Compound-21);

4-(1H-benzo[d]imidazol-1-yl)-N-(dibenzo[b,d]furan-3-yl)-5-fluoropyrimidin-2-amine (Compound-22);

N-(5-fluoro-4-(2-methyl-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-7-amine 2,2,2-trifluoroacetate (Compound-23);

N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-carbazol-7-amine (Compound-24);

N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-1,2,3,4-tetrahydroimidazo[1,2-a:4,5-c']dipyridin-7-amine 2,2,2-trifluoroacetate (Compound-25);

N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-5-ethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-7-amine 2,2,2-trifluoroacetate (Compound-26);

N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-1,2,3,4-tetrahydrobenzofuro [3,2-c]pyridin-7-amine 2,2,2-trifluoroacetate (Compound-27);

4-(1H-benzo[d]imidazol-1-yl)-5-fluoro-N-(3-(1,2,3,4-tetrahydroimidazo[1,2-a:4,5-c']dipyridin-7-yl)phenyl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-28);

4-(1H-benzo[d]imidazol-1-yl)-5-fluoro-N-(4-(1,2,3,4-tetrahydroimidazo[1,2-a:4,5-c']dipyridin-7-yl)phenyl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-29);

N-(5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-30);

N-(dibenzo[b,d]furan-3-yl)-5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-amine (Compound-31);

N-(5-fluoro-4-(1H-1,2,3-triazol-1-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-32);

5-fluoro-4-(imidazo[1,2-b]pyridazin-3-yl)-N-(4-(1,2,3,4-tetrahydroimidazo[1,2-a:4,5-c']dipyridin-7-yl)phenyl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-33);

N-(5-fluoro-4-(imidazo[1,2-b]pyridazin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-34);

N-(5-fluoro-4-(4-fluoro-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-35);

N-(4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-36);

N-(5-fluoro-4-(imidazo[1,2-a]pyridin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-37);

N-(5-fluoro-4-(imidazo[1,2-b]pyridazin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-7-amine 2,2,2-trifluoroacetate (Compound-38);

N-(5-fluoro-4-(imidazo[1,2-a]pyridin-3-yl)pyrimidin-2-yl)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-7-amine acetate (Compound-39);

N-(5-fluoro-4-(imidazo[1,2-a]pyrimidin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-40);

N-(5-fluoro-4-(imidazo[1,2-a]pyrazin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-41);

N-(5-fluoro-4-(pyrazolo[1,5-a]pyridin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-42);

N-(5-fluoro-4-(7-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-43);

N-(5-fluoro-4-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-44);

N-(5-fluoro-4-(pyrazolo[1,5-a]pyrimidin-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-45);

N-(5-fluoro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-amine 2,2,2-trifluoroacetate (Compound-46);

(7-(3-((4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)phenyl)-3,4-dihydroimidazo[1,2-a:4,5-c']dipyridin-2(1H)-yl)(cyclopropyl)methanone (Compound-47); and

2-(8-((5-fluoro-4-(imidazo[1,2-b]pyridazin-3-yl)pyrimidin-2-yl)amino)-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)ethanol 2,2,2-trifluoroacetate (Compound-48),

or a pharmaceutically acceptable salt or a pharmaceutically acceptable stereoisomer thereof.

19. A compound selected from the group consisting of

N-(3-(azetidin-3-yloxy)-5-ethylphenyl)-5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-49);

N-(3-ethyl-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-50);

(S)-N-(3-ethyl-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-51);

(R)-N-(3-ethyl-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-52);

N-(3-ethyl-5-(piperidin-4-yloxy)phenyl)-5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-53);

N-(3-ethyl-5-(piperidin-3-yloxy)phenyl)-5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-54);

N-(3-ethyl-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro-4-(imidazo[1,2-b]pyridazin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-55);

N-(3-ethyl-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro-4-(imidazo[1,2-a]pyridin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-56);

5-fluoro-4-(1H-imidazol-1-yl)-N-(3-(pyrrolidin-3-yloxy)-5-(thiophen-2-yl)phenyl) pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-57);

5-fluoro-4-(imidazo[1,2-a]pyridin-3-yl)-N-(3-(pyrrolidin-3-yloxy)-5-(thiophen-2-yl)phenyl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-58);

N-(3-(1H-pyrazol-4-yl)-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro-4-(imidazo[1,2-a]pyridin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-59);

4-(1-benzyl-1H-imidazol-4-yl)-N-(3-ethyl-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-60);

N-(3-(azetidin-3-yloxy)-5-ethylphenyl)-5-fluoro-4-(1H-pyrrol-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-61);

4-(1H-benzo[d]imidazol-1-yl)-N-(3-ethyl-5-(pyrrolidin-3-yloxy)phenyl)-5-fluoro pyrimidin-2-amine 2,2,2-trifluoroacetate (Compound-62);

2-(3-(3-((4-(1H-benzo[d]imidazol-1-yl)-5-fluoropyrimidin-2-yl)amino)-5-ethylphenoxy) pyrrolidin-1-yl)ethanol (Compound-63);

2-(3-(3-ethyl-5-((5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy) pyrrolidin-1-yl)ethanol (Compound-64);

(R)-2-(3-(3-ethyl-5-((5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy) pyrrolidin-1-yl)ethanol (Compound-65); and

(S)-2-(3-(3-ethyl-5-((5-fluoro-4-(1H-imidazol-1-yl)pyrimidin-2-yl)amino)phenoxy) pyrrolidin-1-yl)ethanol (Compound-66),

or a pharmaceutically acceptable salt or a pharmaceutically acceptable stereoisomer thereof.

20. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of formula (I) according to any of claims 1 to 19, their pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers, in admixture with atleast one pharmaceutically acceptable carrier or excipient including mixtures thereof in all ratios, for use as a medicament.

21. The pharmaceutical composition of claim 20, further comprising a therapeutically effective amount of an active pharmaceutical ingredient selected from the group consisting of an anti-cancer drug, anti-proliferative agent and an anti-inflammatory drug.

22. A method of treating diseases or disease condition for which a TAK-1 inhibitor is indicated in a subject in need thereof which comprises administering an effective amount of a compound according to any of claims 1 to 19.

23. The method of claim 22, wherein the disease or disease condition for which a TAK-1 inhibitor is indicated is cancer, autoimmune or inflammatory.

24. Use of a compound according to any of claims 1 to 19, in the manufacture of a medicament for use in the treatment of diseases associated with TAK-1 in animals including humans.