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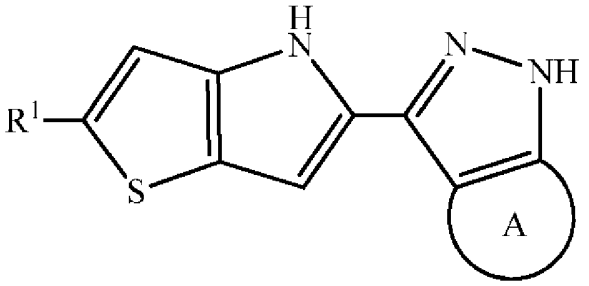
(54) Title: THIENOPYRROLE DERIVATIVES AS ITK INHIBITORS



(I)

(57) Abstract: The present invention is directed to thienopyrrole compounds of formula (I) as Tec kinase inhibitors, in particular ITK (interleukin-2 inducible tyrosine kinase) inhibitors. Also provided herein are processes for preparing compounds described herein, intermediates used in their synthesis, pharmaceutical compositions thereof, and methods for treating or preventing diseases, conditions and/or disorders mediated by ITK.

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THIENOPYRROLE DERIVATIVES AS ITK INHIBITORS

Related Applications

This application claims benefit of Indian provisional application No(s). 2686/MUM/2012 filed on September 14, 2012; 1836/MUM/2013 filed on May 24, 2013 and US provisional application No. 61/714,343 filed on October 16, 2012. All of which are hereby incorporated by reference in their entirety.

Technical Field of the Invention

The present patent application relates to thieno pyrrole compounds which are inhibitors of kinase activity, in particular ITK (interleukin-2 inducible tyrosine kinase) activity, processes for their preparation, pharmaceutical compositions comprising the compounds, and the use of the compounds or the compositions in the treatment or prevention of various diseases, conditions and/or disorders.

Background of the Invention

Protein kinases are enzymes which modulate fundamental cellular processes via protein phosphorylation. Protein kinases play a critical role in mediating the signaling events which control the activation, growth, differentiation and survival of cells in response to extracellular mediators or stimuli such as growth factors, cytokines or chemokines. Kinases are classified in two general groups, those that preferentially phosphorylate tyrosine residues and those that preferentially phosphorylate serine and/or threonine residues (S. K. Hanks and T. Hunter, *FASEB. J.,* 1995, 9, 576-596). Protein tyrosine kinases are a class of enzymes that catalyze the transfer of a phosphate group from ATP or GTP to a tyrosine residue located on a protein substrate. The tyrosine kinases include membrane-spanning growth factor receptors such as the epidermal growth factor receptor (EGFR), insulin receptor (INSR), and platelet derived growth factor receptor, and cytosolic non-receptor kinases such as Src family kinases (Lck and Lyn), the Syk family kinases (ZAP-70 and Syk) and the Tec family kinases (e.g. ITK).

The Tec family kinase includes ITK (IL2-inducible T-cell kinase, Gibson, S. et al., *Blood*, 1993, 82, 1561-1572), Txk (T-cell expressed kinase; Haire, R. N. et al., *Hum. Mol.*

Genet., 1994, 3, 897-901), Tec (tyrosine kinase expressed in hepatocellular carcinoma cells; Mano et al., *Oncogene*, 1990, 5, 1781-1786), Btk (Bruton's tyrosine kinase; Vetrie, D. et al., *Nature*, 1993, 361, 226-233), and Bmx (bone marrow kinase, X-linked; Tamagnon, L. et al., *Oncogene*, 1994, 9, 3683-3688). ITK or Tsk (T-cell- specific tyrosine kinase) is expressed solely in inflammation cells such as T cells, natural killer (NK) cells, and mast cells with a prominent role of T cell proliferation and production of critical cytokines such as IL2, IL4, IL5, IL10 and IL13. During T cell activation via T cell receptor (TCR) CD3 and CD28 interaction, a cascade of signal transduction events is triggered including Lck activation followed by ZAP70 and ITK phosphorylation. ITK subsequently activates phospholipase C γ (PLC-γ) that further cleaves phosphotidyli-nositol biphosphate to yield diacylgycerol (DAG) and inositol triphosphate (IP3). Finally these two components activate NFκB and NFAT pathways leading to cytokine production, T cell-proliferation and subsequent differentiation. Disruption of T cell signal transduction by inhibition of ITK in the cascade would attenuate T cell mediated inflammation responses, especially in the pathological stage.

The study of genetically manipulated mice in which the gene encoding the ITK protein is deleted reveal that mice lacking ITK have decreased numbers of mature thymocytes, especially CD4+ T cells. The T cells isolated from such mice are compromised in their proliferative response to allogeneic MHC stimulation, and to anti-TCR/CD3 cross-linking (Liao X. C. and Littman, D. R., *Immunity*, 1995, 3, 757-769). These T cells also exhibit defective PLCγ1 tyrosine phosphorylation, inositol triphosphate production, Ca^{2+} mobilization, and cytokine production (such as IL-2 and IFNγ) in response to TCR cross-linking (Schaeffer, E. M. et al., *Science*, 1999, 284, 638-641) This genetic evidence indicates that ITK activity plays a requisite role in TCR signal transduction; and selective inhibition of ITK should have immunosuppressive, anti-inflammatory, and anti-proliferative effects. Recent studies have shown that ITK deficient mice have drastically reduced lung inflammation, eosinophil infiltration, and mucous production in response to OVA induced allergic asthma (Mueller, C; August, A., *J. Immunol.*, 2003, 170, 5056). These studies support a key role for ITK in the activation of T cells, thus inhibitors of ITK should be useful as immunosuppressive or anti-inflammatory agents.

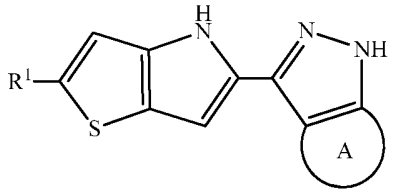
WO2002050071 relates to inhibitors of the Tec family tyrosine kinases, particularly, inhibitors of Emt [expressed mainly in T cells] as immunosuppressive, anti-inflammatory, anti-allergic & anti-cancer agents. WO2011065402, WO2003041708, WO2004016600, WO2004016609, WO2004016610, WO2005079791, WO2007058832, WO2008025820,

WO2007076228 and WO2008025822 disclose certain ITK inhibitors for the treatment of inflammation, immunological disorders, and allergic disorders.

Thus, an object of the present invention is to provide novel compounds which are inhibitors of kinase activity, in particular ITK activity. Compounds of the present invention may be useful in the treatment of disorders associated with inappropriate kinase activity, in particular inappropriate ITK activity, for example in the treatment and prevention of disorders mediated by ITK mechanisms. Such disorders include respiratory diseases including asthma, chronic obstructive pulmonary disease (COPD) and bronchitis; allergic diseases including allergic rhinitis and atopic dermatitis; autoimmune diseases including rheumatoid arthritis, multiple sclerosis, psoriasis, type I diabetes, T cell mediated hypersensitivities, Guillain-Barre Syndrome and Hashimoto's thyroiditis; transplant rejection; graft versus host disease; inflammatory disorders including conjunctivitis, contact dermatitis, inflammatory bowel disease and chronic inflammation; proliferative disorders; immunological disorders; HIV; aplastic anemia; and pain including inflammatory pain.

Summary of the Invention

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



(I)

or a pharmaceutically acceptable salt thereof,

wherein,

R^1 is selected from $-C(O)NR^aR^b$, $-NR^aC(O)R^b$ and $-(CH_2)_nNR^aR^b$;

ring 'A' is C_{3-12}cycloalkyl, C_{6-14}aryl or 5- to 14- membered heteroaryl each optionally substituted with one or more substituents independently selected from C_{1-8}alkyl, C_{1-8}alkoxy, 5- to 14- membered heteroaryl and $-NHC(O)R^c$;

at each occurrence, R^a is independently selected from hydrogen and C_{1-8}alkyl;

at each occurrence, R^b is independently selected from hydrogen, C_{1-8}alkyl, C_{3-12}cycloalkyl and 3- to 15- membered heterocyclylC_{1-8}alkyl;

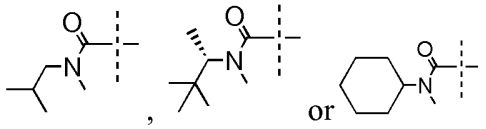
R^c is C_{1-8}alkyl; and

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

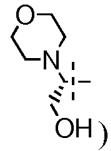
According to one embodiment, specifically provided are compounds of formula (I), in which R^1 is -C(O)NR^aR^b. In this embodiment, R^a is C_{1-8}alkyl (e.g. methyl); R^b is C_{1-8}alkyl (e.g. isobutyl or 3,3-dimethyl-but-2-yl) or C_{3-12}cycloalkyl (e.g. cyclohexyl).

According to another embodiment, specifically provided are compounds of formula (I), in which R^1 is -C(O)NR^aR^b. In this embodiment, R^a is methyl; R^b is isobutyl, 3,3-dimethyl-but-2-yl or cyclohexyl.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R^1 is

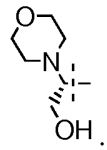


According to yet another embodiment, specifically provided are compounds of formula (I), in which R^1 is -$NR^aC(O)R^b$. In this embodiment, R^a is C_{1-8}alkyl (e.g. methyl or ethyl); R^b is C_{1-8}alkyl (e.g. methyl, 2,2-dimethyl-1-propyl), C_{3-12}cycloalkyl (e.g. cyclohexyl), or 3- to 15- membered heterocyclylC_{1-8}alkyl (e.g. morpholinylmethyl, morpholinylethyl or



).

According to yet another embodiment, specifically provided are compounds of formula (I), in which R^1 is -$NR^aC(O)R^b$. In this embodiment, R^a is methyl or ethyl; R^b is methyl, 2,2-dimethyl-1-propyl, cyclohexyl, morpholinylmethyl, morpholinylethyl or



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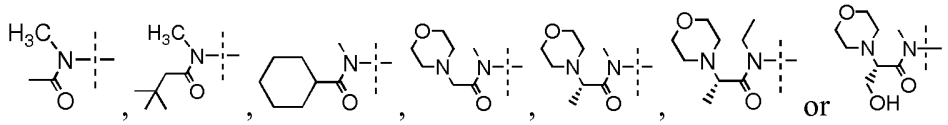
According to yet another embodiment, specifically provided are compounds of formula (I), in which R^1 is

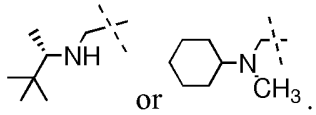


According to yet another embodiment, specifically provided are compounds of formula (I), in which R^1 is -$(CH_2)_nNR^aR^b$. In this embodiment, R^a is hydrogen or C_{1-8}alkyl

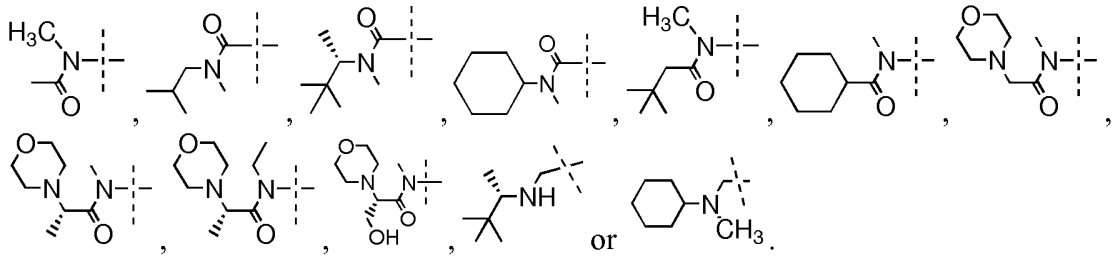
(e.g. methyl); R^b is C_{1-8}alkyl (e.g. 3,3-dimethyl-but-2-yl) or C_{3-12}cycloalkyl (e.g. cyclohexyl) and n is 1.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R^1 is $-(CH_2)_nNR^aR^b$. In this embodiment, R^a is hydrogen or methyl; R^b is 3,3-dimethyl-but-2-yl or cyclohexyl and n is 1.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R^1 is



According to yet another embodiment, specifically provided are compounds of formula (I), in which R^1 is



According to yet another embodiment, specifically provided are compounds of formula (I), in which ring 'A' is C_{3-12}cycloalkyl (e.g. cyclohexyl).

According to yet another embodiment, specifically provided are compounds of formula (I), in which ring 'A' is cyclohexyl.

According to yet another embodiment, specifically provided are compounds of formula (I), in which ring 'A' is C_{3-12}cycloalkyl (e.g. cyclohexyl) optionally substituted with one or more C_{1-8}alkyl (e.g. methyl).

According to yet another embodiment, specifically provided are compounds of formula (I), in which ring 'A' is cyclohexyl optionally substituted with one or more methyl.

According to yet another embodiment, specifically provided are compounds of formula (I), in which ring 'A' is C_{6-14}aryl (e.g. phenyl).

According to yet another embodiment, specifically provided are compounds of formula (I), in which ring 'A' is phenyl.

According to yet another embodiment, specifically provided are compounds of formula (I), in which ring 'A' is C_{6-14}aryl (e.g. phenyl) optionally substituted with one or more substituents independently selected from C_{1-8}alkoxy (e.g. methoxy), 5- to 14- membered

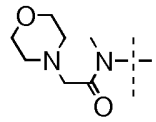
heteroaryl (e.g. 1*H*-pyrazol-4-yl, 1-methyl-1*H*-pyrazol-4-yl or pyridin-4-yl) and –NHC(O)R^c, in this embodiment R^c is C_{1-8}alkyl (e.g. ethyl).

According to yet another embodiment, specifically provided are compounds of formula (I), in which ring 'A' is phenyl optionally substituted with one or more substituents independently selected from methoxy, 1*H*-pyrazol-4-yl, 1-methyl-1*H*-pyrazol-4-yl or pyridin-4-yl) and –NHC(O)CH_2CH_3.

According to yet another embodiment, specifically provided are compounds of formula (I), in which ring 'A' is 5- to 14- membered heteroaryl (e.g. pyridinyl).

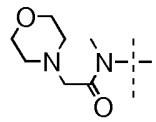
According to yet another embodiment, specifically provided are compounds of formula (I), in which ring 'A' is pyridinyl.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R^1 is



and ring 'A' is cyclohexyl optionally substituted with one or more methyl.

According to yet another embodiment, specifically provided are compounds of formula (I), in which R^1 is

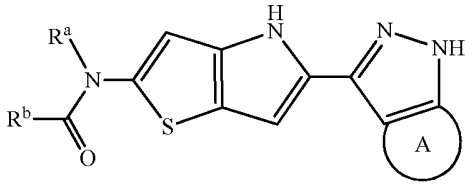


and ring 'A' is cyclohexyl.

According to an embodiment, specifically provided are compounds of formula (I) with an IC_{50} value of less than 500 nM, preferably, less than 100 nM, more preferably less than 50 nM, with respect to ITK activity.

The invention also provides a compound of formula (Ia), which is an embodiment of a compound of formula (I).

Accordingly the invention provides a compound of formula (Ia)



(Ia)

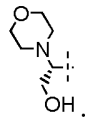
or a pharmaceutically acceptable salt thereof,

wherein,

ring 'A' is cyclohexyl optionally substituted with one or more methyl; phenyl optionally substituted with one or more substituents independently selected from methoxy, 1*H*-pyrazol-4-yl, 1-methyl-1*H*-pyrazol-4-yl, pyridine-4-yl and $-NHC(O)CH_2CH_3$ or pyridinyl;

R^a is selected from hydrogen, methyl and ethyl; and

R^b is selected from methyl, 2,2-dimethyl-1-propyl, cyclohexyl, morpholinylmethyl, morpholinylethyl and



According to an embodiment, specifically provided are compounds of formula (Ia) with an IC_{50} value of less than 500 nM, preferably, less than 100 nM, more preferably less than 50 nM, with respect to ITK activity.

It should be understood that the formulas (I) and (Ia) structurally encompasses all geometrical isomers, stereoisomers, enantiomers and diastereomers, pharmaceutically acceptable salts and solvates including hydrates that may be contemplated from the chemical structure of the genera described herein.

The present invention also provides a pharmaceutical composition that includes at least one compound described herein or a pharmaceutically acceptable salt thereof 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. The compounds described in the present patent application may be associated with a pharmaceutically acceptable excipient (such as a carrier or a diluent) or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container.

The compounds and pharmaceutical compositions described herein are useful for inhibiting kinase activity, in particular ITK activity.

The invention is still further directed to methods of inhibiting ITK activity and treatment of disorders associated therewith using a compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof. The invention is yet further directed towards processes for the preparation of the compounds of the invention.

In another aspect, the present patent application further provides a method for treating, controlling, delaying or preventing in a mammalian patient in need of treatment of one or more diseases, conditions and/or disorders selected from the group consisting of respiratory diseases, allergic diseases, autoimmune diseases, inflammatory disorders, proliferative disorders, transplant rejection, graft versus host disease, HIV, aplastic anemia, pain including inflammatory pain and other diseases and disorders associated with ITK, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound according to the present invention or a pharmaceutically acceptable salt thereof.

Detailed Description

Terms and Definitions:

The terms "halogen" or "halo" means fluorine (fluoro), chlorine (chloro), bromine (bromo), or iodine (iodo).

The term "alkyl" refers to a straight or branched hydrocarbon chain radical that includes solely carbon and hydrogen atoms in the backbone, containing no unsaturation, having from one to eight carbon atoms (i.e. C_{1-8}alkyl), and which is attached to the rest of the molecule by a single bond. "C_{1-6} alkyl" is an alkyl group that has from 1 to 6 carbon atoms. Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, 2-methylpropyl (isobutyl), n-pentyl, 1,1-dimethylethyl (t-butyl), and 2,2-dimethylpropyl. Unless set forth or recited to the contrary, all alkyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "alkenyl" refers to a hydrocarbon chain containing from 2 to 10 carbon atoms (i.e. C_{2-10} alkenyl) and including at least one carbon-carbon double bond. Non-limiting examples of alkenyl groups include ethenyl, 1-propenyl, 2-propenyl (allyl), *iso*-propenyl, 2-methyl-1-propenyl, 1-butenyl, and 2-butenyl. Unless set forth or recited to the contrary, all alkenyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "alkynyl" refers to a hydrocarbyl radical having at least one carbon-carbon triple bond, and having 2 to about 12 carbon atoms (with radicals having 2 to about 10 carbon atoms being preferred i.e. C_{2-10} alkynyl). Non-limiting examples of alkynyl groups include ethynyl, propynyl, and butynyl. Unless set forth or recited to the contrary, all alkynyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "alkoxy" denotes an alkyl group attached via an oxygen linkage to the rest of the molecule (i.e. C_{1-8}alkoxy). Representative examples of such groups are -OCH_3 and -

OC_2H_5. Unless set forth or recited to the contrary, all alkoxy groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "alkoxyalkyl" or "alkyloxyalkyl" refers to an alkoxy or alkyloxy group as defined above directly bonded to an alkyl group as defined above (i.e. C_{1-8}alkoxyC_{1-8}alkyl or C_{1-8}alkyloxyC_{1-8}alkyl). Example of such alkoxyalkyl moiety includes, but are not limited to, $-CH_2OCH_3$ and $-CH_2OC_2H_5$. Unless set forth or recited to the contrary, all alkoxyalkyl groups described herein may be straight chain or branched, substituted or unsubstituted.

The term "haloalkyl" refers to at least one halo group (selected from F, Cl, Br or I), linked to an alkyl group as defined above (i.e. haloC_{1-8}alkyl). Examples of such haloalkyl moiety include, but are not limited to, trifluoromethyl, trifluoroethyl, difluoromethyl and fluoromethyl groups. Unless set forth or recited to the contrary, all haloalkyl groups described herein may be straight chain or branched, substituted or unsubstituted.

The term "haloalkoxy" refers to an alkoxy group substituted with one or more halogen atoms (i.e. haloC_{1-8}alkoxy). Examples of "haloalkoxy" include but are not limited to fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy, pentachloroethoxy, chloromethoxy, dichlorormethoxy, trichloromethoxy and 1-bromoethoxy. Unless set forth or recited to the contrary, all haloalkoxy groups described herein may be straight chain or branched, substituted or unsubstituted.

The term "hydroxyalkyl" refers to an alkyl group as defined above wherein one to three hydrogen atoms on different carbon atoms is/are replaced by hydroxyl groups (i.e. hydroxyC_{1-8}alkyl). Examples of hydroxyalkyl moiety include, but are not limited to $-CH_2OH$, $-C_2H_4OH$ and $-CH(OH)C_2H_4OH$.

The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of 3 to about 12 carbon atoms, for example C_{3-12}cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of multicyclic cycloalkyl groups include, but are not limited to, perhydronaphthyl, adamantyl and norbornyl groups, bridged cyclic groups or spirobicyclic groups, e.g., spiro(4,4)non-2-yl. Unless set forth or recited to the contrary, all cycloalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "cycloalkylalkyl" refers to a cyclic ring-containing radical having 3 to about 8 carbon atoms directly attached to an alkyl group, for example C_{3-8}cycloalkylC_{1-8}alkyl. The cycloalkylalkyl group may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Non-limiting examples of such groups include cyclopropylmethyl, cyclobutylethyl, and cyclopentylethyl. Unless set forth or recited

to the contrary, all cycloalkylalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "cycloalkenyl" refers to a cyclic ring-containing radical having 3 to about 8 carbon atoms with at least one carbon-carbon double bond, for example C_{3-8}cycloalkenyl, such as cyclopropenyl, cyclobutenyl, and cyclopentenyl. Unless set forth or recited to the contrary, all cycloalkenyl groups described or claimed herein may be substituted or unsubstituted.

The term "cycloalkenylalkyl" refers to a cyclic ring-containing radical having 3 to about 8 carbon atoms with at least one carbon-carbon double bond, directly attached to an alkyl group, for example C_{3-8}cycloalkenylC_{1-8}alkyl. The cycloalkenylalkyl group may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Unless set forth or recited to the contrary, all cycloalkenylalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "aryl" refers to an aromatic radical having 6 to 14 carbon atoms (i.e. C_{6-14}aryl), including monocyclic, bicyclic and tricyclic aromatic systems, such as phenyl, naphthyl, tetrahydronapthyl, indanyl, and biphenyl. Unless set forth or recited to the contrary, all aryl groups described or claimed herein may be substituted or unsubstituted.

The term "aryloxy" refers to an aryl group as defined above attached via an oxygen linkage to the rest of the molecule (i.e. C_{6-14}aryloxy). Examples of aryloxy moiety include, but are not limited to phenoxy and naphthoxy. Unless set forth or recited to the contrary, all aryloxy groups described herein may be substituted or unsubstituted.

The term "arylalkyl" refers to an aryl group as defined above directly bonded to an alkyl group as defined above, i.e. C_{6-14}arylC_{1-8}alkyl, such as $-CH_2C_6H_5$ and $-C_2H_4C_6H_5$. Unless set forth or recited to the contrary, all arylalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "heterocyclyl" or "heterocyclic ring" unless otherwise specified refers to substituted or unsubstituted non-aromatic 3- to 15- membered ring radical which consists of carbon atoms and from one to five hetero atoms selected from nitrogen, phosphorus, oxygen and sulfur. The heterocyclic ring radical may be a mono-, bi- or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; also, unless otherwise constrained by the definition the heterocyclic ring or heterocyclyl may optionally contain one or more olefinic bond(s). Examples of such heterocyclic ring radicals include, but

are not limited to azepinyl, azetidinyl, benzodioxolyl, benzodioxanyl, chromanyl, dioxolanyl, dioxaphospholanyl, decahydroisoquinolyl, indanyl, indolinyl, isoindolinyl, isochromanyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, oxazolinyl, oxazolidinyl, oxadiazolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, octahydroindolyl, octahydroisoindolyl, perhydroazepinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, piperidinyl, phenothiazinyl, phenoxazinyl, quinuclidinyl, tetrahydroisquinolyl, tetrahydrofuryl, tetrahydropyranyl, thiazolinyl, thiazolidinyl, thiamorpholinyl, thiamorpholinyl sulfoxide and thiamorpholinyl sulfone. The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure. Unless set forth or recited to the contrary, all heterocyclyl groups described or claimed herein may be substituted or unsubstituted.

The term "heterocyclylalkyl" refers to a heterocyclic ring radical directly bonded to an alkyl group (i.e. heterocyclylC_{1-8}alkyl). The heterocyclylalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Unless set forth or recited to the contrary, all heterocyclylalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "heteroaryl" unless otherwise specified refers to substituted or unsubstituted 5- to 14- membered aromatic heterocyclic ring radical with one or more heteroatom(s) independently selected from N, O or S. The heteroaryl may be a mono-, bi- or tricyclic ring system. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure. Examples of such heteroaryl ring radicals include, but are not limited to oxazolyl, isoxazolyl, imidazolyl, furyl, indolyl, isoindolyl, pyrrolyl, pyrazolyl, triazolyl, triazinyl, tetrazoyl, thienyl, thiazolyl, isothiazolyl, pyridyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzofuranyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzothienyl, benzopyranyl, carbazolyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, naphthyridinyl, pteridinyl, purinyl, quinoxalinyl, quinolyl, isoquinolyl, thiadiazolyl, indazolyl, indolizinyl, acridinyl, phenazinyl and phthalazinyl. Unless set forth or recited to the contrary, all heteroaryl groups described or claimed herein may be substituted or unsubstituted.

The term "heteroarylalkyl" refers to a heteroaryl ring radical directly bonded to an alkyl group (i.e. heterarylC_{1-8}alkyl). The heteroarylalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Unless set forth or recited to the contrary, all heteroarylalkyl groups described or claimed herein may be substituted or unsubstituted.

Unless otherwise specified, the term "substituted" as used herein refers to substitution with any one or any combination of the following substituents: hydroxy, halogen, carboxyl, cyano, nitro, oxo (=O), thio (=S), substituted or unsubstituted alkyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted hydroxyl alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstiuted guanidine, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OC(O)NR^yR^z$, $-OC(O)OR^y$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$ and $-ONO_2$, wherein R^x, R^y and R^z are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, and substituted or unsubstituted heterocyclic ring. The substituents in the aforementioned "substituted" groups cannot be further substituted. For example, when the substituent on "substituted alkyl" is "substituted aryl", the substituent on "substituted aryl" can be unsubstituted alkenyl but cannot be "substituted alkenyl".

The term "pharmaceutically acceptable salt" includes salts prepared from pharmaceutically acceptable bases or acids including inorganic or organic bases and inorganic or organic acids. Examples of such salts include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate,

pamoate (embonate), palmitate, pantothenate, phosphate, diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate. Examples of salts derived from inorganic bases include, but are not limited to, aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, mangamous, potassium, sodium, and zinc.

The term "treating" or "treatment" of a state, disorder or condition includes: (a) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a subject that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition; (b) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof; or (c) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

The term "subject" includes mammals (especially humans) and other animals, such as domestic animals (e.g., household pets including cats and dogs) and non-domestic animals (such as wildlife).

A "therapeutically effective amount" means the amount of a compound that, when administered to a subject for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the subject to be treated.

The compound described in the present patent application may form salts. Non-limiting examples of pharmaceutically acceptable salts forming part of this patent application include salts derived from inorganic bases salts of organic bases salts of chiral bases, salts of natural amino acids and salts of non-natural amino acids.

Certain compounds of present patent application are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers). With respect to the overall compounds described by the general formula (I) the present patent application extends to these stereoisomeric forms and to mixtures thereof. To the extent prior art teaches synthesis or separation of particular stereoisomers, the different stereoisomeric forms of the present patent application may be separated from one another by the method known in the art, or a given isomer may be obtained by stereospecific or asymmetric synthesis. Tautomeric forms and mixtures of compounds described herein are also contemplated. It is also to be understood that

compounds of the invention may exist in solvated forms (such as hydrates) as well as unsolvated forms, and that the invention encompasses all such forms.

Pharmaceutical Compositions

The compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known in the pharmaceutical art and comprise at least one compound of the invention. The pharmaceutical composition of the present patent application comprises one or more compounds described herein and one or more pharmaceutically acceptable excipients. Typically, the pharmaceutically acceptable excipients are approved by regulatory authorities or are generally regarded as safe for human or animal use. The pharmaceutically acceptable excipients include, but are not limited to, carriers, diluents, glidants and lubricants, preservatives, buffering agents, chelating agents, polymers, gelling agents, viscosifying agents, solvents and the like.

Examples of suitable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid, lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethyl cellulose and polyvinyl pyrrolidone.

The pharmaceutical composition may also include one or more pharmaceutically acceptable auxiliary agents, wetting agents, emulsifying agents, suspending agents, preserving agents, buffers, sweetening agents, flavoring agents, colorants or any combination of the foregoing.

The pharmaceutical compositions may be in conventional forms, for example, capsules, tablets, aerosols, solutions, suspensions, injectables or products for topical application. Further, the pharmaceutical composition of the present invention may be formulated so as to provide desired release profile.

Administration of the compounds of the invention, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted routes of administration of pharmaceutical compositions. The route of administration may be any route which effectively transports the active compound of the patent application to the appropriate or desired site of action. Suitable routes of administration include, but are not limited to, oral,

nasal, pulmonary, buccal, dermal, intradermal, transdermal, parenteral, rectal, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic (such as with an ophthalmic solution) or topical (such as with a topical ointment).

Solid oral formulations include, but are not limited to, tablets, capsules (soft or hard gelatin), dragees (containing the active ingredient in powder or pellet form), troches and lozenges. Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, cornstarch and/or potato starch. A syrup or elixir is used in cases where a sweetened vehicle is employed.

Liquid formulations include, but are not limited to, syrups, emulsions, soft gelatin and sterile injectable liquids, such as aqueous or non-aqueous liquid suspensions or solutions.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Topical dosage forms of the compounds include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, eye ointments, eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The pharmaceutical forms suitable for injectable or infusing use include sterile aqueous solutions, suspensions or dispersions, and sterile powders for the extemporaneous preparation of sterile injectable or infusing solutions, suspension or dispersions.

The pharmaceutical compositions of the present patent application may be prepared by conventional techniques, e.g., as described in *Remington: The Science and Practice of Pharmacy*, 20th Ed., 2003 (Lippincott Williams & Wilkins).

Suitable doses of the compounds for use in treating the diseases and disorders described herein can be determined by those skilled in the relevant art. Therapeutic doses are generally identified through a dose ranging study in humans based on preliminary evidence derived from the animal studies. Doses must be sufficient to result in a desired therapeutic benefit without causing unwanted side effects. For example, the daily dosage of the ITK inhibitors can range from about 0.1 to about 200.0 mg/Kg. Mode of administration, dosage forms, and suitable pharmaceutical excipients can also be well used and adjusted by those skilled in the art. All changes and modifications are envisioned within the scope of the present patent application.

Methods of Treatment

The present invention provides compounds and pharmaceutical compositions which inhibit kinase activity, particularly ITK activity and are thus useful in the treatment or prevention of disorders associated with ITK. Compounds and pharmaceutical compositions of the present invention selectively inhibit ITK and are thus useful in the treatment or prevention of a range of disorders associated with the activation of ITK which includes, but are not limited to respiratory diseases, allergic diseases, autoimmune diseases, inflammatory disorders, immunological disorders, proliferative disorders, transplant rejection, graft versus host disease, HIV, aplastic anemia, pain including inflammatory pain and other diseases and disorders associated with ITK.

In particular, the compounds of the present invention may be used to prevent or treat airways diseases including chronic obstructive pulmonary disease (COPD) such as irreversible COPD; asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (for example, late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia; sinusitis, chronic rhinosinusitis, nasosinusal polyposis; pulmonary fibrosis; inflammatory bowel disease; Guillain-Barre syndrome, acute or chronic inflammation, rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis; psoriasis, atopic dermatitis, contact dermatitis and other eczematous dermitides, sebonhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythema, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis; Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, for example, migraine, rhinitis and eczema; multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, type II diabetes, nephritic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura; tuberculosis; organ and bone marrow transplant rejection; graft-versus-host disease.

The compounds of the present invention are useful for the treatment of cancer such as, but are not limited to breast cancer, skin cancer, bone cancer, prostate cancer, liver cancer, lung cancer, non- small cell lung cancer, brain cancer, cancer of the larynx, gall bladder, pancreas, rectum, parathyroid, thyroid, adrenal, neural tissue, head and neck, colon, stomach, bronchi, and kidney cancer, basal cell carcinoma, squamous cell carcinoma, metastatic skin carcinoma, osteo sarcoma, Ewing's sarcoma, myeloma, giant cell tumor, small-cell lung tumor, islet cell tumor, primary brain tumor, lymphocytic and granulocytic tumors, hairy-cell tumor, adenoma, hyperplasia, medullary carcinoma, pheochromocytoma, mucosal neuromas, intestinal ganglioneuromas, ovarian tumor, cervical dysplasia, neuroblastoma, retinoblastoma, soft tissue sarcoma, malignant carcinoid, topical skin lesion, rhabdomyosarcoma, Kaposi's sarcoma, osteogenic sarcoma, malignant hypercalcemia, renal cell tumor, adenocarcinoma, glioblastoma multiforma, leukemias, lymphomas, malignant melanomas, and epidermoid carcinomas.

Compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions may have potential utility in combination with other therapies for the treatment of immune, inflammatory, proliferative, and allergic disorders. Example includes but not limited to co-administration with steroids, leukotriene antagonists, anti-histamines, anti-cancer agents, protein kinase inhibitors, cyclosporine, or rapamycin.

Compounds of the invention are indicated both in the therapeutic and/or prophylactic treatment of the above-mentioned conditions. For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of the invention may be in the range from 0.05 mg/kg to 100 mg/kg.

General Methods of Preparation

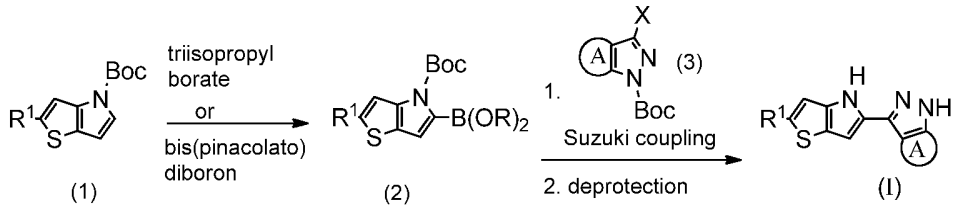
The compounds described herein, including compounds of general formula (I), (Ia), (Ib) and (Ic) and specific examples are prepared using techniques known to one skilled in the art through the reaction sequences depicted in scheme 1-5. Furthermore, in the following schemes, where specific acids, bases, reagents, coupling agents, solvents, etc. are mentioned, it is understood that other suitable acids, bases, reagents, coupling agents, solvents etc. may be used and are included within the scope of the present invention. Modifications to reaction conditions, for example, temperature, duration of the reaction or combinations thereof, are

envisioned as part of the present invention. The compounds obtained using the general reaction sequences may be of insufficient purity. These compounds can be purified using any of the methods for purification of organic compounds known to persons skilled in the art, for example, crystallization or silica gel or alumina column chromatography using different solvents in suitable ratios. All possible geometrical isomers and stereoisomers are envisioned within the scope of this invention.

The starting materials for the below reaction schemes are commercially available or can be prepared according to methods known to one skilled in the art or by methods disclosed herein. In general, intermediates and compounds of the present invention may be prepared through the reaction scheme as follows.

A general approach for the synthesis of indazolo thienopyrrole of the formula (I) [wherein R^1 and ring 'A' are as defined in description above in compound of formula (I)] can be prepared as described in synthetic scheme 1. An appropriately substituted and boc protected thieno pyrrole of formula (1) on reaction with triisopropyl borate or bis(pinacolato)diboron in the presence of a suitable base such as lithium diisopropyl amide in suitable solvent such as dry tetrahydrofuran can give the corresponding boronic acid of formula (2) [wherein R can be hydrogen, alkyl or cycloalkyl]. The Suzuki coupling reaction of thieno pyrrole boronic acid of formula (2) with appropriately substituted indazole halide of formula (3) [wherein X can be Cl, Br or I] using palladium catalyst such as tetrakis(triphenylphosphine)palladium (0) or [1,1′-bis(diphenylphosphino) ferrocene]dichloropalladium(II) in presence of suitable base gives coupled intermediate which on deprotection gives compound of the general formula (I).

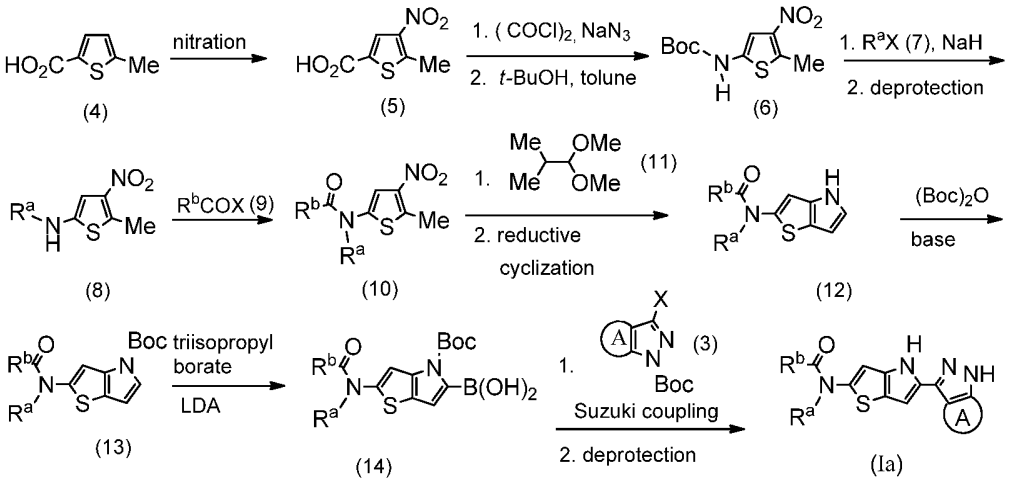
Synthetic scheme 1



An approach for the synthesis of indazolo thieno pyrrole derivative of the formula (Ia) [wherein R^a, R^b, ring 'A' are as defined above in compound of formula (Ia)] can be prepared as described in synthetic scheme 2. The nitration of 5-methylthiophene-2-carboxylic acid (4) affords 5-methyl-4-nitrothiophene-2-carboxylic acid (5). The Curtius rearrangement of (5) followed by Boc protection gives tert-butyl(5-methyl-4-nitrothiophen-2-yl)carbamate (6). The *N*-alkylation of tert-butyl(5-methyl-4-nitrothiophen-2-yl)carbamate (6) with appropriate alkyl

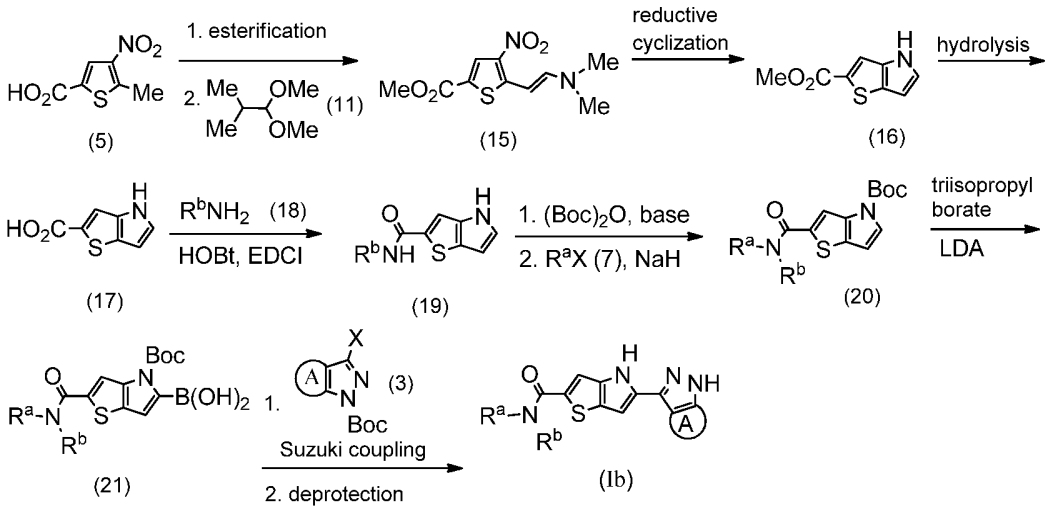
halide (7) [wherein X can be Cl, Br or I] followed by boc deprotection gives N-alkyl-5-methyl-4-nitrothiophene derivative (8). The coupling reaction of *N*-alkyl-5-methyl-4-nitrothiophene derivative (8) with appropriately substituted acid or acid chloride of formula (9) [wherein X can be OH or Cl] using standard amide coupling methods gives 4-nitro-5-methyl thiophene amide (10). Alternatively, 4-nitro-5-methyl thiophene amide (10) can be prepared by deprotection of (6) followed by coupling with acid or acid halide of the formula (9) [wherein X can be OH or Cl] and *N*-alkylation of corresponding amide with alkyl halide of the formula (7). The condensation of 4-nitro-5-methyl thiophene amide of formula (10) with N,N-dimethylformamide dimethyl acetal (11) in suitable solvent such as dry *N*,*N*-dimethylformamide, dry tetrahydrofuran gives enamine derivative which on reductive cyclization using suitable methods such as hydrogenation in the presence of palladium carbon under hydrogen atmosphere or sodium dithionate or zinc/AcOH using suitable solvent affords 4*H*-thieno[3,2-*b*]pyrrole-2-carboxylic amide derivative of formula (12). The boc protection of thienopyrrole amide of formula (12) using di-tert-butyl dicarbonate gives 4*H*-thieno[3,2-*b*]pyrrole-2-carboxylic amide of formula (13). The reaction of 4*H*-thieno[3,2-*b*]pyrrole-2-carboxylic amide of formula (13) with triisopropyl borate in presence of suitable base such as lithium diisopropyl amide (LDA) in suitable solvent such as dry tetrahydrofuran gives thieno pyrrole boronic acid of formula (14). The Suzuki coupling reaction of thienopyrrole boronic acid (14) with suitably substituted indazole halide of formula (3) using palladium catalyst such as tetrakis(triphenylphosphine)palladium (0) or [1,1′-bis(diphenylphosphino) ferrocene]dichloropalladium(II) in presence of suitable base such as sodium carbonate, potassium carbonate, cesium fluoride or cesium carbonate in suitable solvent such as tetrahydrofuran, *N*,*N*-dimethylformamide, mixture of toluene and methanol or 1,4-dioxane affords thienopyrrolo indazole amide followed by sequential deprotection furnishes compounds of formula (Ia). These indazole derivatives can be converted into its hydrochloride salts using saturated solution of hydrochloric acid in ethyl acetate.

Synthetic scheme 2



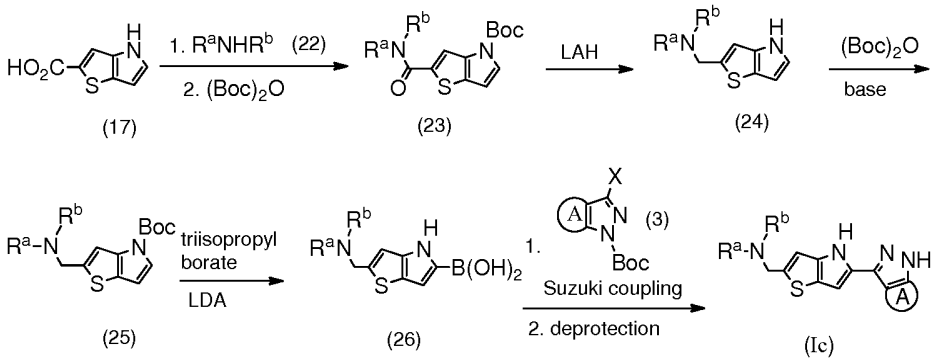
A general approach for the synthesis of indazolo thieno pyrrole derivative of the formula (Ib) [wherein R^a, R^b, ring 'A' are as defined above in compound of formula (I)] is shown in synthetic scheme 3. The esterification of 5-methyl-4-nitro-thiophene-2-carboxylic acid of formula (5) followed by the reaction with *N,N*-dimethylformamide dimethyl acetal (11) in suitable solvent such as dry DMF, dry DMA affords nitro thiophene enamine derivative (15). The reductive cyclization of (15) using suitable methods as described in synthetic scheme 2 gives 4*H*-thieno[3,2-*b*]pyrrole derivative (16). The hydrolysis of thienopyrrole ester (16) affords the corresponding acid of formula (17). The coupling reaction of thienopyrrole acid of formula (17) with appropriately substituted amine of formula (18) by using a standard amide coupling method gives 4*H*-thieno[3,2-*b*]pyrrole-2-carboxamide derivative of formula (19). The boc protection of thieno[3,2-*b*]pyrrole amide derivative of formula (19) using di-tert-butyl bicarbonate followed by *N*-alkylation of amide with suitable alkyl halide of formula (7) [wherein X is Cl, Br or I] affords boc protected-4*H*-thieno[3,2-b]pyrrole-4-carboxamide of formula (20). The reaction of thieno pyrrole carboxamide of formula (20) with triisopropyl borate in the presence of suitable base such as lithium diisopropyl amide gives thieno pyrrole boronic acid of formula (21). The Suzuki coupling reaction of thieno pyrrole boronic acid of formula (21) with appropriately substituted indazole halide of formula (3) [wherein X is Cl, Br or I] using palladium catalyst such as tetrakis(triphenylphosphine)palladium (0) or [1,1′-bis(diphenylphosphino) ferrocene]dichloropalladium(II) in presence of suitable base such as sodium carbonate, potassium carbonate, cesium fluoride or cesium carbonate in suitable solvent such as tetrahydrofuran, *N,N*-dimethylformamide, mixture of toluene and methanol or 1,4-dioxane afford the coupled intermediate which on deprotection gives compounds of the general formula (Ib).

Synthetic scheme 3



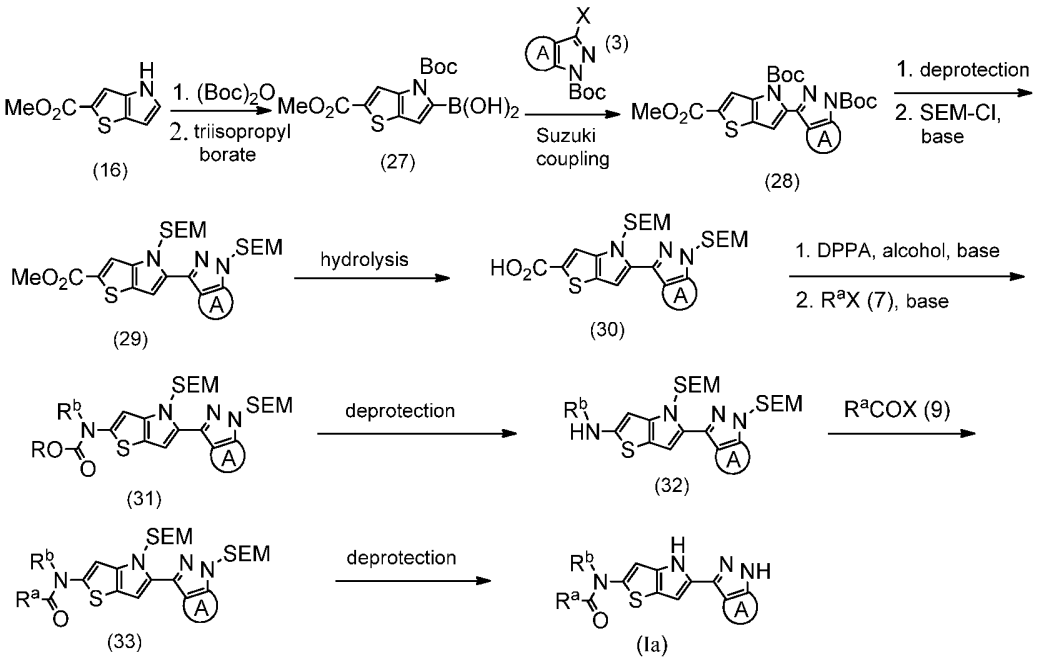
An approach for the synthesis of indazolo thieno pyrrole derivative of formula (Ic) [wherein R^a, R^b, ring 'A' are as defined above in compound of formula (I)] is depicted in synthetic scheme 4. The coupling reaction of 4*H*-thieno[3,2-*b*]pyrrole-2-carboxylic acid of formula (17) with appropriately substituted amine of formula (22) using standard amide coupling methods followed by Boc protection using di-tert-butyl bicarbonate gives Boc protected-4*H*-thieno[3,2-b]pyrrole-4-carboxamide of formula (23). The reduction of thieno pyrrole carboxamide of formula (23) using lithium aluminium hydride gives thieno pyrrole derivative of formula (24). The Boc protection of thieno pyrrole intermediate of formula (24) gives Boc thieno pyrrole derivative of formula (25). The conversion of thieno pyrrole amine (25) to thieno pyrrole amine boronic acid of the formula (26) is accomplished by using same procedure as described in synthetic scheme 2. The Suzuki coupling reaction of thieno pyrrole amine boronic acid (26) with appropriately substituted indazole halide of formula (3) [wherein X is Cl, Br or I] using palladium catalyst such as tetrakis(triphenylphosphine)palladium (0) or [1,1′-bis(diphenylphosphino) ferrocene]dichloropalladium(II) in presence of suitable base such as sodium carbonate, potassium carbonate, cesium fluoride or cesium carbonate in suitable solvent such as tetrahydrofuran, *N*,*N*-dimethylformamide, mixture of toluene and methanol or 1,4-dioxane affords the coupled intermediate which on deprotection furnishes compounds of formula (Ic).

Synthetic scheme 4



An alternative approach for the synthesis of indazolo thieno pyrrole derivative of formula (Ia) [wherein R^a, R^b, ring 'A' are as defined above in compound of formula (I)] is described in synthetic scheme 5. The boc protection of methyl 4*H*-thieno[3,2-b]pyrrole-2-carboxylate (16) followed by reaction with triisopropyl borate in the presence of suitable base such as lithium diisopropyl amide gives intermediate (27) which on Suzuki coupling reaction with appropriately substituted indazole halide of formula (3) affords indazolo thieno pyrrole of formula (28). The boc deprotection of formula (28) followed by reaction with 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) in the presence of suitable base gives intermediate of formula (29). The hydrolysis of indazolo thieno ester of formula (29) gives indazolo thienopyrrole carboxylic acid of formula (30). The Curtius rearrangement of thieno pyrrole acid of formula (30) using diphenylphosphoryl azide and suitable alcohol such as tertiary butyl alcohol or benzyl alcohol affords Boc or Cbz protected thieno pyrrole indazole which on *N*-alkylation using alkyl halide (7) in presence of suitable base gives thieno pyrrole of the formula (31). The deprotection of formula (31) under standard conditions gives thieno pyrrole amine of the formula (32). The coupling reaction of thieno pyrrole amine of formula (32) with appropriately substituted acid or acid halide of formula (9) affords the corresponding thieno pyrrole amide of formula (33). The deprotection of thieno pyrrole amide of formula (33) furnishes the indazolo thieno pyrrole of formula (Ia).

Synthetic scheme 5



(16) (27) (28) (29) (30) (31) (32) (33) (Ia)

Experimental

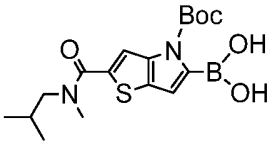
Unless otherwise stated, work-up implies the following operations: distribution of the reaction mixture between the organic and aqueous phase, separation of layers, drying the organic layer over sodium sulfate, filtration and evaporation of the organic solvent. Purification, unless otherwise mentioned, implies purification by silica gel chromatographic techniques, generally using ethyl acetate/petroleum ether mixture of a suitable polarity as the mobile phase. The following abbreviations are used in the text: DMSO-d_6: hexadeuterodimethyl sulfoxide; DMF: *N*,*N*-dimethylformamide, ^{1}H NMR: Proton Nuclear Magnetic Resonance; $CDCl_3$: Deuterated chloroform; THF: Tetrahydrofuran; *J*: coupling constant in units of Hz; RT or rt: room temperature (22-26°C); h: hour(s); DMSO: Dimethyl sulfoxide; HOBt: Hydroxybenzotriazole; EDCI: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide; DMA: *N*,*N*-dimethylacetamide.

The starting materials used herein are commercially available or were prepared by methods known in the art to those of ordinary skill or by methods disclosed herein.

The intermediates described below were prepared using synthetic schemes 1 to 5 depicted herein above.

Intermediate 1

(4-(*tert*-Butoxycarbonyl)-2-(isobutyl(methyl)carbamoyl)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid



Step 1: Methyl 5-methyl-4-nitrothiophene-2-carboxylate: A mixture of 5-methyl-4-nitrothiophene-2-carboxylic acid (15.9 g, 85.026 mmol) in dry methanol (160 ml) and sulfuric acid (2.8 ml) was refluxed overnight. The reaction mixture was cooled to room temperature, concentrated under reduced pressure and diluted with ice cold water (200 ml). The precipitated solid was collected by filtration and dried to yield 15 g of product as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.84 (s, 3H), 3.91 (s, 3H), 8.20 (s, 1H).

Step 2: Methyl 5-[2-(dimethylamino)ethenyl]-4-nitrothiophene-2-carboxylate: To a stirred solution of step 1 intermediate (15 g, 74.60 mmol) in dry *N,N*-dimethylformamide (44 ml), *N,N*-dimethylformamide dimethyl acetal (29.7 ml, 223.8 mmol) was added at room temperature and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was cooled to room temperature and quenched with cold water (350 ml). The precipitated solid was collected by filtration and dried to give 17.5 g of product as orange solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.07 (s, 6H), 3.86 (s, 3H), 6.49-6.58 (m, 1H), 7.28 (d, J = 6.3 Hz, 1H), 8.09 (s, 1H).

Step 3: Methyl 4*H*-thieno[3,2-*b*]pyrrole-2-carboxylate: A mixture of step 2 intermediate (8 g, 31.25 mmol), 5 % w/w palladium carbon (3 g) and acetic acid (8 ml) in dry tetrahydrofuran (150 ml) was stirred under hydrogen pressure (50 PSI) for 48 h. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was diluted with diethyl ether (300 ml) and the organic layer was washed with hydrochloric acid (1 N, 250 ml), water (100 ml) and aqueous saturated solution of sodium bicarbonate (200 ml). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue obtained was purified by column chromatography to yield 4.65 g of product as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H), 6.48 (s, 1H), 7.13-7.22 (m, 1H), 7.70 (s, 1H), 8.57 (s, 1H).

Step 4: 4*H*-Thieno[3,2-*b*]pyrrole-2-carboxylic acid: To a stirred solution of step 3 intermediate (3.6 g, 19.88 mmol) in ethanol (99 ml), potassium hydroxide (2.89 g, 51.688 mmol) in water (41 ml) was added drop wise and reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue obtained was stirred with hydrochloric acid (1 N, 200 ml) for 30 min. The solid obtained was filtered and dried to yield 3.15 g of product as an off-white solid. ^{1}H NMR (300

MHz, DMSO-d_6): δ 6.42 (s, 1H), 7.31 (t, J = 3.0 Hz, 1H), 7.62 (s, 1H), 11.44 (s, 1H), 12.67 (s, 1H).

Step 5: *N*-Isobutyl-4*H*-thieno[3,2-b]pyrrole-2-carboxamide: To a stirred solution of 4*H*-thieno[3,2-*b*]pyrrole-2-carboxylic acid (850 mg, 5.087 mmol), 2-methylpropan-1-amine (505 µl, 5.087 mmol) in dry 1,2-dichloroethane (28 ml), HOBt (254 mg, 1.881 mmol), *N*-methyl morpholine (650 µl, 5.899 mmol) was added followed by EDCI (1.32 g, 5.90 mmol) and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (100 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extract was washed with water (75 ml), dried over sodium sulphate and filtered. The mixture was concentrated under reduced pressure and purified by column chromatography to yield 1.03 g of product as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (d, J = 6.9 Hz, 6H), 1.81-1.95 (m, 1H), 3.26 (t, J = 7.2 Hz, 2H), 5.95 (br s, 1H), 6.46 (s, 1H), 7.12 (s, 1H), 7.50 (s, 1H), 8.68 (s, 1H).

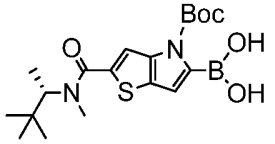
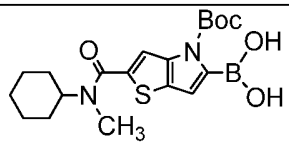
Step 6: *tert*-Butyl 2-(isobutylcarbamoyl)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: To a stirred solution of step 5 intermediate (1.0 g, 4.50 mmol) in dry tetrahydrofuran (11.2 ml), di-*tert*-butyl bicarbonate (991 mg, 4.54 mmol) was added followed by 4-dimethylaminopyridine (22 mg, 0.18 mmol) and the reaction mixture was stirred for 2 h at room temperature. The mixture was concentrated under reduced pressure and the product obtained was purified by column chromatography to yield 1.04 g of product as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (d, J = 6.3 Hz, 6H), 1.66 (s, 9H), 1.85-1.93 (m, 1H), 3.27 (t, J = 7.2 Hz, 2H), 6.01 (br s, 1H), 6.52 (s, 1H), 7.46 (s, 1H), 7.75 (s, 1H).

Step 7: *tert*-Butyl 2-(isobutyl(methyl)carbamoyl)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: To a stirred solution of step 6 intermediate (1 g, 3.103 mmol) in dry tetrahydrofuran (9 ml), sodium hydride (186 mg, 4.65 mmol) was added portion wise at 0 °C, and the reaction mixture was stirred at same temperature for 15 min. Methyl iodide (291 µl, 4.65 mmol) was added to reaction mixture and was stirred at room temperature overnight. The reaction mixture was quenched with aqueous solution of ammonium chloride (75 ml) and extracted with ethyl acetate (2 x 75 ml). The combined organic layer was washed with water (75 ml), dried over sodium sulphate and filtered. The mixture was concentrated under reduced pressure and purified by column chromatography to yield 770 mg of product as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, J = 6.3 Hz, 6H), 1.65 (s, 9H), 2.02-2.10 (m, 2H), 3.23 (s, 3H), 3.42 (d, J = 7.2 Hz, 6H), 6.52 (s, 1H), 7.45 (s, 1H), 7.62 (s, 1H).

Step 8: (4-(*tert*-Butoxycarbonyl)-2-(isobutyl(methyl)carbamoyl)-4H-thieno[3,2-b]pyrrol-5-yl)boronic acid: To a stirred solution of step 7 intermediate (750 mg, 2.23 mmol) in dry tetrahydrofuran (11.2 ml), triisopropyl borate (1.15 ml, 5.017 mmol) was added drop wise followed by lithium di-isopropyl amide (2.0 M solution in THF, 2.17 ml, 4.35 mmol) at -5 to 0 °C and the reaction mixture was stirred for 2 h at same temperature. The reaction was quenched with aqueous solution of ammonium chloride (150 ml) and extracted with ethyl acetate (3 x 75 ml). The combined organic layer was washed with water (75 ml), dried over sodium sulphate and filtered. The mixture was concentrated under reduced pressure to yield solid. The solid was stirred in n-hexane (100 ml), filtered and dried to yield 620 mg of product as a grey solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (d, J = 6.0 Hz, 6H), 1.04-1.14 (m, 2H), 1.96-2.10 (m, 1H), 3.18 (s, 3H), 6.71 (s, 1H), 7.60 (s, 1H), 8.25 (s, 2H).

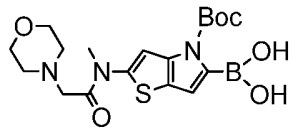
Intermediates 2 and 3 were prepared in similar manner as per procedure described in intermediate 1. The structural formulas, chemical names and ^{1}H NMR data are provided in table 1.

Table 1: Structure, Chemical Name and ^{1}H NMR data of Intermediate 2-3.

Structure and Intermediate No.	Chemical name and ^{1}H NMR data
 Intermediate 2	(*S*)-(4-(*tert*-Butoxycarbonyl)-2-((3,3-dimethylbutan-2-yl)(methyl)carbamoyl)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid: ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.80-0.90 (m, 9H), 1.59 (s, 9H), 2.70-2.79 (m, 4H), 6.71 (s, 1H), 7.57 (s, 1H).
 Intermediate 3	(4-(*tert*-Butoxycarbonyl)-2-(cyclohexyl(methyl)carbamoyl)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid: ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.10-1.29 (s, 9H), 1.55-1.80 (m, 10H), 2.99 (s, 3H), 4.10-4.19 (m, 1H), 6.72 (s, 1H), 7.53 (s, 1H), 8.24 (s, 2H). APCI (*m/z*) 307.31 $(M+H)^+$.

Intermediate 4

(4-(*tert*-Butoxycarbonyl)-2-(*N*-methyl-2-morpholinoacetamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid



Step 1: 5-Methyl-4-nitrothiophene-2-carbonyl azide: To a stirred solution of 5-methyl-4-nitrothiophene-2-carboxylic acid (10 g, 53.42 mmol) in dry dichloromethane (100 ml), dry *N,N*-dimethylformamide (1.5 ml) was added and cooled to 0 °C and oxalyl chloride (5.6 ml, 64.04 mmol) was drop wise added to the reaction mixture and stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and the residue obtained was diluted with 1,2-dichloroethane (100 ml). This solution was drop wise added to a stirred mixture of sodium azide (6.93 g, 106.74 mmol) in 1,2-dichloroethane (30 ml) and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure, diluted with water (150 ml) and extracted with dichloromethane (3 x 200 ml). The combined organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to yield 11.3 g of product as brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.86 (s, 3H), 8.23 (s, 1H).

Step 2: *tert*-Butyl (5-methyl-4-nitrothiophen-2-yl)carbamate: To a stirred solution of step 1 intermediate (11.2 g, 52.78 mmol) in toluene (66 ml), *tert*-butanol (88 ml) was added and the reaction mixture was stirred at 85 °C overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure, diluted with water (250 ml) and extracted with ethyl acetate (3 x 150 ml). The combined organic extract was washed with water (250 ml), dried over sodium sulfate and filtered. The organic mixture was concentrated under reduced pressure and purified by column chromatography to yield 10.9 g of product as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.63 (s, 9H), 2.75 (s, 3H), 6.95 (s, 1H), 11.75 (br s, 1H).

Step 3: *tert*-Butyl methyl(5-methyl-4-nitrothiophen-2-yl)carbamate: This intermediate was prepared by *N*-methylation of step 2 intermediate (10 g, 38.71 mmol) using methyl iodide (12.1 ml, 193.57 mmol) in presence of sodium hydride (1.7 g, 42.58 mmol) in dry *N,N*-dimethylformamide (129 ml) as described in step 7 of intermediate 1 to afford 8 g of product as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (s, 9H), 2.68 (s, 3H), 3.33 (s, 3H), 6.86 (s, 1H).

Step 4: *N*,5-Dimethyl-4-nitrothiophen-2-amine: To a stirred solution of step 3 intermediate (7.9 g, 29.01 mmol) in ethyl acetate (39.5 ml), concentrated hydrochloric acid (11.65 N, 79 ml) at 0 °C was drop wise added and reaction mixture was stirred at room temperature for 2 h. The reaction mixture was slowly poured on ice cooled aqueous solution of sodium

bicarbonate and the mixture was stirred for 30 min. The precipitated solid was collected by filtration and dried to yield 4.2 g of product as an orange solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.63 (s, 3H), 2.85 (s, 3H), 3.80-3.87 (m, 1H), 6.37 (s, 3H).

Step 5: *N*-Methyl-*N*-(5-methyl-4-nitrothiophen-2-yl)-2-(morpholin-4-yl)acetamide: To a stirred solution of morpholin-4-ylacetic acid (4.04 g, 27.90 mmol) in dry dichloromethane (40 ml), catalytic amount of dry *N*,*N*-dimethylformamide (1.2 ml) was added followed by drop wise addition of oxalyl chloride (4.0 ml, 46.50 mmol) at 0 °C and the reaction mixture was stirred for 4 h at room temperature. The reaction mixture was concentrated under reduced pressure, diluted with dry tetrahydrofuran (65 ml) and to this reaction mixture a solution of *N*,5-dimethyl-4-nitrothiophen-2-amine (4.0 g, 23.25 mmol) and dry pyridine (8 ml) in dry tetrahydrofuran (65 ml) was drop wise added at 0 °C. The reaction mixture was stirred overnight at room temperature. The mixture was diluted with ethyl acetate (300 ml) and washed with hydrochloric acid (1 N, 100 ml). The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain 3.3 g of product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44-2.59 (m, 4H), 2.69 (s, 3H), 3.41 (s, 3H), 3.56 (s, 3H), 3.65-3.80 (m, 4H), 7.06 (s, 1H).

Step 6: *N*-(5-(2-(Dimethylamino)vinyl)-4-nitrothiophen-2-yl)-*N*-methyl-2-morpholinoacetamide: This intermediate was prepared by the reaction of step 5 intermediate (3.3 g, 11.00 mmol) with *N*,*N*-dimethylformamide dimethyl acetal (4.37 ml, 33.00 mmol) in dry *N*,*N*-dimethylformamide (16 ml) at room temperature as described in step 2 of intermediate 1 to yield 3.91 g of product as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.49-2.65 (m, 4H), 2.93-3.10 (m, 6H), 3.21 (s, 3H), 3.41 (s, 2H), 3.50 (s, 2H), 3.67-3.77 (m, 4H), 6.44 (d, J = 14.1 Hz, 1H), 6.57 (d, J = 12.6 Hz, 1H), 6.91 (s, 1H).

Step 7: *N*-Methyl-2-(morpholin-4-yl)-*N*-(4*H*-thieno[3,2-*b*]pyrrol-2-yl)acetamide:

The title compound can be prepared by following methods.

Method A: using zinc and acetic acid

To a stirred solution of step 6 intermediate (3.9 g, 11.00 mmol) in 1,2-dichloroethane (110 ml), zinc dust (7.1 g, 110 mmol) was added followed by acetic acid (6.1 ml) and reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with aqueous saturated solution of sodium bicarbonate (100 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic layer was washed with water (100 ml), dried over sodium sulphate and filtered. The mixture was concentrated under reduced pressure and purified by column chromatography to yield 1.73 g of the product as grey semi-solid. ^{1}H NMR (300 MHz,

$CDCl_3$): δ 2.45-2.56 (m, 4H), 3.21 (s, 2H), 3.30 (s, 3H), 3.65-3.79 (m, 4H), 6.46 (s, 1H), 6.83 (s, 1H), 7.07 (t, *J* = 3.0 Hz, 1H), 8.63 (br s, 1H).

Method B: using sodium dithionate:

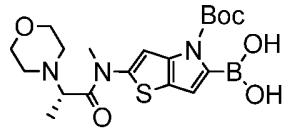
To a stirred solution of step 6 intermediate (1 mmol) in tetrahydrofuran (1 ml), ethanol (1 ml), water (3 ml) was added followed by sodium dithionate (5 mmol) and reaction mixture was stirred at 100 °C for 48 h. The reaction mixture was filtered through celite and filtrate was concentrated under reduced pressure. The residue obtained was treated with aqueous saturated solution of sodium bicarbonate and the mixture was extracted with ethyl acetate. The combined organic extract was washed with water, dried over sodium sulfate and filtered. The organic mixture was concentrated under reduced pressure and purified by column chromatography to yield a product.

Step 8: *tert*-Butyl 2-(*N*-methyl-2-morpholinoacetamido)-4H-thieno[3,2-b]pyrrole-4-carboxylate: This intermediate was prepared by the reaction of step 7 intermediate (1.73 g, 6.192 mmol) with di-*tert*-butyl bicarbonate (1.36 g, 6.248 mmol) using 4-dimethylaminopyridine (30 mg, 0.247 mmol) in dry tetrahydrofuran (15 ml) as described in step 6 of intermediate 1 to yield 2.18 g of product as off white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65 (s, 9H), 2.41-2.53 (m, 4H), 3.18 (s, 2H), 3.31 (s, 3H), 3.65-3.75 (m, 4H), 6.49 (d, *J* = 3.0 Hz, 1H), 7.19-7.28 (m, 1H), 7.43 (s, 1H).

Step 9: (4-(*tert*-Butoxycarbonyl)-2-(N-methyl-2-morpholinoacetamido)-4H-thieno[3,2-b]pyrrol-5-yl)boronic acid: This intermediate was prepared by the reaction of step 8 intermediate (2.1 g, 5.53 mmol) with triisopropyl borate (2.87 ml, 12.45 mmol) using lithium di-isopropyl amide (2.0 M in THF, 5.39 ml, 10.78 mmol) in dry tetrahydrofuran (28 ml) as described in step 8 of intermediate 1 to yield 2.1 g of product as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54-1.75 (m, 9H), 2.92-3.01 (m, 2H), 3.34 (s, 3H), 3.55-3.75 (m, 4H), 3.85-4.03 (m, 4H), 6.85-6.95 (m, 1H), 7.05-7.16 (m, 1H).

Intermediate 5

(*S*)-(4-(*tert*-Butoxycarbonyl)-2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid



Step 1: 5-Methyl-4-nitrothiophen-2-amine: To a stirred solution of *tert*-butyl (5-methyl-4-nitrothiophen-2-yl)carbamate (3 g, 11.622 mmol) in ethyl acetate (15 ml), concentrated hydrochloric acid (11.5 N, 15 ml) was added at 0 °C and the reaction mixture was stirred for 2

h at room temperature. The reaction mixture was quenched with aqueous saturated solution of sodium bicarbonate (200 ml) and the product was extracted with ethyl acetate (3 x 150 ml). The combined organic extract was dried over sodium sulphate, filtered and concentrated under reduced pressure to yield 1.9 g of product as red solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.49-2.57 (m, 3H), 5.92 (s, 2H), 6.19 (s, 1H).

Step 2: (2*S*)-*N*-(5-Methyl-4-nitrothiophen-2-yl)-2-(morpholin-4-yl)propanamide: This intermediate is prepared by the coupling reaction of 5-methyl-4-nitrothiophen-2-amine (6.0 g, 37.974 mmol) with (2*S*)-2-(morpholin-4-yl)propanoic acid (7.42 g, 37.974 mmol) using HOBt (1.89 g, 14.05 mmol) and EDCI (10.89 g, 56.971 mmol) in presence of *N*-methyl morpholine (10.45 ml, 94.935 mmol) in dry 1,2-dichloroethane (189 ml) as described in step 5 of intermediate 1 to yield 5.3 g of the product as yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (d, *J* = 6.6 Hz, 3H), 2.55-2.63 (m, 4H), 2.71 (s, 3H), 3.27-3.36 (m, 1H), 3.74-3.83 (m, 4H), 7.10 (s, 1H), 9.68 (s, 1H).

Step 3: (*S*)-*N*-Methyl-*N*-(5-methyl-4-nitrothiophen-2-yl)-2-(morpholin-4-yl)propanamide: To a stirred solution of step 2 intermediate (9.8 g, 32.737 mmol) in dry *N,N*-dimethylformamide (98 ml), potassium carbonate (6.8 g, 49.106 mmol) was added followed by methyl iodide (3.07 ml, 49.106 mmol) at 0 °C and the reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with water (300 ml) and extracted with ethyl acetate (3 x 200 ml). The combined organic layer was washed with water (200 ml), brine (200 ml), dried over sodium sulphate and filtered. The reaction mixture was concentrated under reduced pressure and residue obtained was purified by column chromatography to yield 6.47 g of product as yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (d, *J* = 6.9 Hz, 3H), 2.45-2.53 (m, 4H), 2.69 (s, 3H), 3.63 (s, 3H), 3.65-3.73 (m, 4H), 3.75-3.83 (m, 1H), 7.08 (s, 1H).

Step 4: (*S*)-*N*-(5-(2-(Dimethylamino)vinyl)-4-nitrothiophen-2-yl)-*N*-methyl-2-morpholinopropanamide: This intermediate was prepared by the reaction of step 3 intermediate (6.4 g, 10.73 mmol) with *N,N*-dimethylformamide dimethyl acetal (8.1 ml, 61.14 mmol) in dry *N,N*-dimethylformamide (29 ml) as described in step 2 of intermediate 1 to yield 7.5 g of product as a dark red semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21-1.30 (m, 4H), 2.55-2.69 (m, 3H), 2.99 (s, 3H), 3.06 (s, 3H), 3.24 (s, 1H), 3.58 (s, 1H), 3.63 (s, 1H), 3.64-3.90 (m, 7H), 7.21-7.30 (m, 1H).

Step 5: (*S*)-*N*-Methyl-2-morpholino-*N*-(4*H*-thieno[3,2-b]pyrrol-2-yl)propanamide: This intermediate is prepared by cyclization reaction of step 4 intermediate (7.4 g, 20.084 mmol) using acetic acid (10 ml) in presence of zinc dust (13 g, 200.80 mmol) in 1,2-dichloroethane

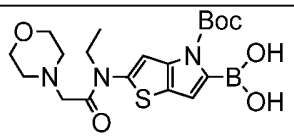
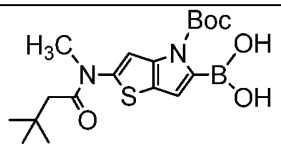
(200 ml) as described in step 7 (Method A) of intermediate 4 to yield 3.5 g of product as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (d, *J* = 6.9 Hz, 3H), 2.41-2.53 (m, 2H), 2.59-2.71 (m, 2H), 3.32 (s, 3H), 3.58 (q, *J* = 6.6 Hz, 1H), 3.64-3.72 (m, 4H), 6.45 (s, 1H), 6.83 (s, 1H), 7.02-7.09 (m, 1H), 8.65 (s, 1H).

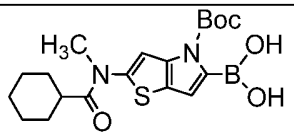
Step 6: (*S*)-*tert*-Butyl 2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: This intermediate was prepared by the reaction of step 5 intermediate (3.45 g, 11.76 mmol) with di-tert-butyl bicarbonate (3.17 g, 11.87 mmol) in presence of 4-dimethylaminopyridine (58 mg, 0.47 mmol) in dry tetrahydrofuran (36 ml) as described in step 6 of intermediate 1 to yield 4.56 g of product as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (d, *J* = 6.3 Hz, 3H), 1.64 (s, 9H), 2.35-2.43 (m, 2H), 2.59-2.69 (m, 2H), 3.31 (s, 3H), 3.53 (q, *J* = 6.6 Hz, 1H), 3.63-3.70 (m, 4H), 6.46 (d, *J* = 3.9 Hz, 1H), 7.19-7.26 (m, 1H), 7.41 (s, 1H).

Step 7: (S)-(4-(*tert*-Butoxycarbonyl)-2-(*N*-methyl-2-morpholinopropanamido)-4H-thieno[3,2-b]pyrrol-5-yl)boronic acid: This intermediate was prepared by the reaction of step 6 intermediate (4.5 g, 11.44 mmol) with triisopropyl borate (6 ml, 25.74 mmol) using lithium di-isopropyl amide (2.0 M in THF, 11.16 ml, 22.31 mmol) in dry tetrahydrofuran (57 ml) as described in step 8 of intermediate 1 to yield 5.03 g of product as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.70 (s, 9H), 2.44-2.50 (m, 2H), 2.61-2.68 (m, 2H), 3.34 (s, 3H), 3.65-3.76 (m, 4H), 7.01-7.09 (m, 2H), 7.31-7.40 (m, 2H).

Intermediate 6-8 were prepared in similar manner as procedure described in intermediate 4. The structural formulas, chemical names and ^{1}H NMR data are provided in table 2.

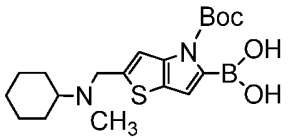
Table 2: Structure, Chemical Name and ^{1}H NMR data of Intermediate 6-8.

Structure and Intermediate No.	Chemical name and ^{1}H NMR data
 Intermediate 6	(4-(*tert*-Butoxycarbonyl)-2-(*N*-ethyl-2-morpholinoacetamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.15-1.27 (m, 9H), 1.47 (d, *J* = 6.6 Hz, 2H), 2.69-2.78 (m, 4H), 3.29-3.35 (m, 2H), 3.69-3.84 (m, 4H), 6.99-7.10 (m, 3H), 7.36 (s, 1H).
	(4-(*tert*-Butoxycarbonyl)-2-(*N*,3,3-trimethylbutanamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid: ^{1}H NMR (300 MHz, DMSO-d_6): δ

Structure and Intermediate No.	Chemical name and ^{1}H NMR data
Intermediate 7	0.83-1.10 (m, 9H), 1.57 (s, 9H), 2.17 (s, 2H), 3.18 (s, 3H), 6.68 (s, 1H), 7.20 (s, 1H), 8.15-8.23 (m, 2H).
 Intermediate 8	(4-(*tert*-Butoxycarbonyl)-2-(*N*-methylcyclohexanecarboxamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid: ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.81-1.60 (m, 20H), 3.17 (s, 3H), 6.69 (s, 1H), 7.24 (s, 1H), 8.21 (s, 2H).

Intermediate 9

(4-(*tert*-Butoxycarbonyl)-2-((cyclohexyl(methyl)amino)methyl)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid



Step 1: *N*-Cyclohexyl-*N*-methyl-4*H*-thieno[3,2-*b*]pyrrole-2-carboxamide: This intermediate was prepared by coupling reaction of 4*H*-thieno[3,2-*b*]pyrrole-2-carboxylic acid (1.0 g, 5.985 mmol) with *N*-methylcyclohexanamine (780 µl, 5.985 mmol) using HOBt (300 mg, 2.214 mmol) and EDCI (1.33 g, 6.943 mmol) in presence of *N*-methyl morpholine (766 µl, 6.943 mmol) in dry 1,2-dichloroethane (20 ml) as described in step 5 of intermediate 1 to yield 1.42 g of product as brown solid. ESI (*m/z*): 263.18 $(M+H)^+$.

Step 2: *tert*-Butyl 2-(Cyclohexyl(methyl)carbamoyl)-4H-thieno[3,2-b]pyrrole-4-carboxylate: This intermediate was prepared by reaction of step 1 intermediate (1.4 g, 5.335 mmol) with di-tert-butyl bicarbonate (1.175 g, 5.384 mmol) using 4-dimethylaminopyridine (26 mg, 0.213 mmol) in dry tetrahydrofuran (20 ml) as described in step 6 of intermediate 1 to yield 1.94 g of product as a brown viscous liquid. APCI (*m/z*): 363.08 $(M+H)^+$.

Step 3: *N*-((4*H*-Thieno[3,2-b]pyrrol-2-yl)methyl)-*N*-methylcyclohexanamine: To a stirred solution of lithium aluminium hydride (2.0 g, 52.486 mmol) in dry tetrahydrofuran (20 ml), a solution of step 2 intermediate (1.9 g, 5.248 mmol) in dry tetrahydrofuran (30 ml) was drop wise added at room temperature and the reaction mixture was stirred at same temperature overnight. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride (200 ml), filtered through celite and celite bed was washed with ethyl acetate (200 ml). The filtrate was collected, dried over sodium sulphate, filtered and concentrated under

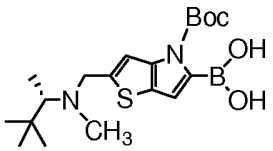
reduced pressure to yield 1.4 g of the product as brown viscous liquid. ESI (*m/z*): 249.03 $(M+H)^+$.

Step 4: *tert*-Butyl 2-((Cyclohexyl(methyl)amino)methyl)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: This intermediate was prepared by the reaction of step 3 intermediate (1.4 g, 5.642 mmol) with di-tert-butyl bicarbonate (1.24 g, 5.693 mmol) using 4-dimethylaminopyridine (28 mg, 0.225 mmol) in dry tetrahydrofuran (14 ml) as described in step 6 of intermediate 1 to yield 815 mg of product as a brown viscous liquid. ESI (*m/z*): 348.92 $(M+H)^+$.

Step 5: (4-(*tert*-Butoxycarbonyl)-2-((cyclohexyl(methyl)amino)methyl)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid: The title intermediate was prepared by the reaction of step 4 intermediate (800 mg, 2.298 mmol) with triisopropyl borate (1.2 ml, 5.172 mmol) using lithium di-isopropyl amide (2.0 M in THF, 2.3 ml, 4.597 mmol) in dry tetrahydrofuran (12 ml) as described in step 8 of intermediate 1 to yield 907 mg of product as a brown solid. ESI (*m/z*): 392.96 $(M+H)^+$.

Intermediate 10

(*S*)-(4-(*tert*-Butoxycarbonyl)-2-(((3,3-dimethylbutan-2-yl)(methyl)amino)methyl)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid



Step 1: (*S*)-*N*-(3,3-Dimethylbutan-2-yl)-4*H*-thieno[3,2-b]pyrrole-2-carboxamide: This intermediate was prepared by coupling reaction of 4*H*-thieno[3,2-*b*]pyrrole-2-carboxylic acid (1.3 g, 7.774 mmol) with (2*S*)-3,3-dimethylbutan-2-amine (1.1 ml, 7.774 mmol) using HOBt (385 mg, 2.851 mmol) and EDCI (1.71 g, 8.92 mmol) in presence of *N*-methyl morpholine (990 µl, 8.93 mmol) in dry 1,2-dichloroethane (30 ml) as described in step 5 of intermediate 1 to yield 1.85 g of product as yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88 (s, 9H), 1.07 (d, J = 7.2 Hz, 3H), 3.85-3.93 (m, 1H), 6.37 (s, 1H), 7.22 (d, J = 3.0 Hz, 1H), 7.80 (d, J = 9.3 Hz, 1H), 11.40 (s, 1H); ESI (*m/z*) 251.20 $(M+H)^+$.

Step 2: (*S*)-*tert*-Butyl 2-((3,3-dimethylbutan-2-yl)carbamoyl)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: This intermediate was prepared by the reaction of step 1 intermediate (1.8 g, 7.20 mmol) with di-tert-butyl dicarbonate (1.58 g, 7.26 mmol) using 4-dimethylaminopyridine (10 mg, 0.072 mmol) in dry tetrahydrofuran (18 ml) as described in step 6 of intermediate 1 to yield 2.55 g of product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (s, 9H), 1.16 (d,

J = 6.9 Hz, 3H), 1.61-1.70 (m, 9H), 4.04-4.14 (m, 1H), 5.78-5.84 (m, 1H), 6.52 (d, *J* = 3.6 Hz, 1H), 7.46 (s, 1H), 7.74 (s, 1H); APCI (*m/z*) 351.11 $(M+H)^+$.

Step 3: (*S*)-*tert*-Butyl 2-((3,3-dimethylbutan-2-yl)(methyl)carbamoyl)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: This intermediate was prepared by *N*-methylation of step 2 intermediate (2.5 g, 7.142 mmol) with methyl iodide (670 µl, 10.714 mmol) in presence of sodium hydride (430 mg, 10.417 mmol) in dry tetrahydrofuran (21 ml) as described in step 7 of intermediate 1 to afford 2.1 g of product as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (s, 9H), 1.21-1.30 (m, 9H), 1.79 (s, 3H), 3.20 (s, 3H), 4.79-4.85 (m, 1H), 6.51 (d, *J* = 3.6 Hz, 1H), 7.46 (s, 1H), 7.66 (s, 1H); ESI (*m/z*) 365.02 $(M+H)^+$.

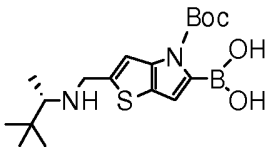
Step 4: (*S*)-*N*-((4*H*-Thieno[3,2-b]pyrrol-2-yl)methyl)-*N*,3,3-trimethylbutan-2-amine: This intermediate is prepared by reduction of step 2 intermediate (2.05 g, 5.631 mmol) using lithium aluminium hydride (2.14 g, 56.318 mmol) in dry tetrahydrofuran (60 ml) as described in step 3 of intermediate 9 to yield 1.3 g of the product as brown viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91-1.02 (m, 9H), 2.15-2.30 (m, 5H), 2.41-2.51 (m, 3H), 4.19-4.30 (m, 1H), 6.41 (s, 1H), 6.78 (s, 1H), 6.91 (s, 1H), 8.15 (s, 1H); ESI (*m/z*) 251.01 $(M+H)^+$.

Step 5: (*S*)-*tert*-Butyl 2-(((3,3-dimethylbutan-2-yl)(methyl)amino)methyl)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: This intermediate was prepared by the reaction of step 1 intermediate (1.2 g, 4.8 mmol) with di-tert-butyl dicarbonate (1.14 g, 5.232 mmol) using 4-dimethylaminopyridine (6 mg, 0.048 mmol) in dry tetrahydrofuran (12 ml) as described in step 6 of intermediate 1 to yield 1.55 g of product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89-1.02 (m, 18H), 1.15 (s, 3H), 2.41 (s, 3H), 2.45-2.53 (m, 1H), 3.61 (d, *J* = 9.0 Hz, 1H), 3.91 (d, *J* = 9.0 Hz, 1H), 6.45 (s, 1H), 7.14 (s, 1H), 7.30 (s, 1H); APCI (*m/z*) 351.00 $(M+H)^+$.

Step 6: (*S*)-(4-(*tert*-Butoxycarbonyl)-2-(((3,3-dimethylbutan-2-yl)(methyl)amino)methyl)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid: The title intermediate was prepared by the reaction of step 2 intermediate (730 mg, 2.0857 mmol) with triisopropyl borate (1.082 ml, 4.693 mmol) using lithium di-isopropyl amide (2.0 M in THF, 2.03 ml, 4.067 mmol) in dry tetrahydrofuran (10 ml) as described in step 8 of intermediate 1 to yield 900 mg of product as a brown solid which was used directly for next step.

Intermediate 11

(*S*)-(4-(*tert*-Butoxycarbonyl)-2-(((3,3-dimethylbutan-2-yl)amino)methyl)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid



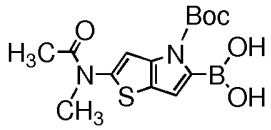
Step 1: (*S*)-*N*-((4*H*-Thieno[3,2-b]pyrrol-2-yl)methyl)-3,3-dimethylbutan-2-amine: This intermediate is prepared by reduction reaction of (*S*)-*tert*-butyl 2-((3,3-dimethylbutan-2-yl)carbamoyl)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate (1.5 g, 4.29 mmol) using lithium aluminium hydride (1.63 g, 42.9 mmol) in dry tetrahydrofuran (60 ml), as described in step 3 intermediate 9 to yield 980 mg of the product as brown viscous liquid. APCI (*m/z*): 235.22 $(M-H)^-$.

Step 2: (*S*)-*tert*-Butyl 2-(((3,3-dimethylbutan-2-yl)amino)methyl)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: This intermediate was prepared by reaction of step 1 intermediate (930 mg, 3.94 mmol) with di-*tert*-butyl bicarbonate (867 mg, 3.976 mmol) using 4-dimethylaminopyridine (10 mg, 0.08 mmol) in dry tetrahydrofuran (10 ml) as described in step 6 of intermediate 1 to yield 970 g of product as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.16 (d, *J* = 6.6 Hz, 3H), 1.59-1.65 (m, 1H), 1.66 (s, 9H), 4.01-4.13 (m, 2H), 5.71-5.80 (m, 1H), 6.51 (d, *J* = 6.3 Hz, 1H), 7.46 (s, 1H), 7.74 (s, 1H).

Step 3: (*S*)-(4-(*tert*-Butoxycarbonyl)-2-(((3,3-dimethylbutan-2-yl)amino)methyl)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid: The reaction of step 2 intermediate (950 mg, 2.827 mmol) with triisopropyl borate (1.47 ml, 6.36 mmol) using lithium di-isopropyl amide (2.0 M in THF, 2.75 ml, 5.51 mmol) in dry tetrahydrofuran (15 ml) as described in step 8 of intermediate 1 to yield 900 mg of product as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.61-1.67 (m, 1H), 1.72 (s, 9H), 3.99-4.09 (m, 2H), 5.71 (d, *J* = 10.2 Hz, 1H), 6.87-6.94 (m, 1H), 7.21-7.29 (m, 1H), 7.37 (s, 1H), 7.73 (s, 1H).

Intermediate 12

(4-(*tert*-Butoxycarbonyl)-2-(*N*-methylacetamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid



Step 1: *N*-Methyl-*N*-(5-methyl-4-nitrothiophen-2-yl)acetamide: To a stirred solution of *N*,5-dimethyl-4-nitrothiophen-2-amine (5 g, 29.02 mmol) and dry pyridine (5 ml) in dry tetrahydrofuran (100 ml), acetyl chloride (2.47 ml, 34.82 mmol) was added drop wise at 0 °C and the reaction mixture was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced pressure; acidfied with 1 N HCl, precipitated solid was

collected by filtration to yield 5.82 g of product as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.69 (s, 3H), 3.48 (s, 3H), 7.01 (s, 1H).

Step 2: *N*-{5-[2-(Dimethylamino)ethenyl]-4-nitrothiophen-2-yl}-*N*-methylacetamide: This intermediate was prepared by the reaction of step 1 intermediate (6.4 g, 81.372 mmol) with *N,N*-dimethylformamide dimethyl acetal (12.5 ml, 94.117 mmol) in dry *N,N*-dimethylformamide (44 ml) as described in step 2 of intermediate 1 to yield 7.85 g of product as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.04 (s, 3H), 3.20 (s, 3H), 3.43 (s, 3H), 6.45, 6.58 (2d, J = 4.4 Hz, 1H), 6.87 (s, 1H), 7.11, 7.19 (2d, J = 7.8 Hz, 1H).

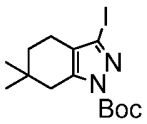
Step 3: *N*-Methyl-*N*-(4*H*-thieno[3,2-b]pyrrol-2-yl)acetamide: This intermediate is prepared by reductive cyclization of step 2 intermediate (7.8 g, 28.961 mmol) using acetic acid (16 ml) in presence of zinc dust (18.9 g, 289.61 mmol) in 1,2-dichloroethane (289 ml) as described in step 7 (Method A) of intermediate 4 to yield 3.54 g of product as an brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07 (s, 3H), 3.30 (s, 3H), 6.45 (s, 1H), 6.81 (s, 1H), 7.05 (s, 1H), 8.59-8.67 (m, 1H). APCI (m/z) 195.21 $(M+H)^+$.

Step 4: *tert*-Butyl 2-(*N*-methylacetamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by the reaction of step 3 intermediate (3.5 g, 18.0189 mmol) with di-tert-butyl dicarbonate (3.97 g, 18.199 mmol) using 4-dimethylaminopyridine (87.8 mg, 0.720 mmol) in dry tetrahydrofuran (45 ml) as described in step 6 of intermediate 1 to yield 4.83 g of product as off white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65 (s, 9H), 2.07 (s, 3H), 3.30 (s, 3H), 6.48 (s, 1H), 7.15 (br, s, 1H), 7.42 (br, s, 1H).

Step 5: (4-(*tert*-Butoxycarbonyl)-2-(*N*-methylacetamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid: The title intermediate was prepared by the reaction of step 4 intermediate (2.77 g, 9.421 mmol) with triisopropyl borate (4.9 ml, 21.19 mmol) using lithium di-isopropyl amide (2.0 M in THF, 9.1 ml, 18.37 mmol) in dry tetrahydrofuran (47 ml) as described in step 8 of intermediate 1 to yield 3.0 g of product as a brown solid. The crude bornic acid was directly used without purification in the next step.

Intermediate 13

tert-Butyl 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole-1-carboxylate



Step 1: 4,4-Dimethyl-2-oxocyclohexanecarbaldehyde: A solution of 3,3-dimethylcyclohexanone (10 g, 79.23 mmol) in dry tetrahydrofuran (30 ml), a stirred suspension of sodium hydride (3.48 g, 87.15 mmol) in dry tetrahydrofuran (60 ml) was drop

wise added at 0 °C and reaction mixture was stirred at room temperature for 1 h. A solution of ethyl formate (12.8 ml, 158.46 mmol) in dry tetrahydrofuran (30 ml) was drop wise added to the reaction mixture and stirred for 2 h at room temperature. The reaction was quenched with hydrochloric acid (1 N, 100 ml) and extracted with ethyl acetate (3 x 200 ml). The combined organic layer was washed with brine (200 ml), dried sodium sulphate and filtered. The mixture was concentrated under reduced pressure to obtain 13.3 g of product as a brown viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 6H), 1.46 (t, J = 6.9 Hz, 2H), 2.09 (s, 2H), 2.38 (t, J = 6.3 Hz, 2H), 8.77 (s, 1H), 14.37 (s, 1H).

Step 2: 6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazole: To a stirred solution of step 1 intermediate (13.3 g, 88.54 mmol) in methanol (177 ml), hydrazine hydrate (5 ml, 106.25 mmol) was added at room temperature and the reaction mixture was stirred at reflux temperature for 1 h. The reaction mixture was cooled at room temperature and concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (3 x 150 ml). The combined organic layer was washed with water (150 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure to yield 13.35 g of product as a brown viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 6H), 1.52 (t, J = 6.9 Hz, 2H), 2.39 (s, 2H), 2.53 (t, J = 6.3 Hz, 2H), 7.31 (s, 1H), 11.51 (s, 1H).

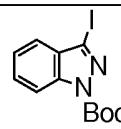
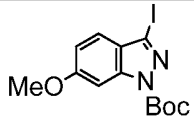
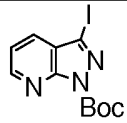
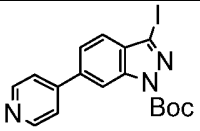
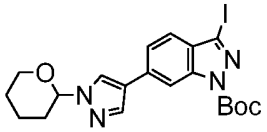
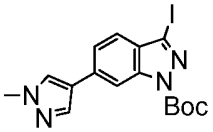
Step 3: 3-Iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazole: To a stirred solution of step 2 intermediate (13.3 g, 88.54 mmol) in dry *N*,*N*-dimethylformamide (177 ml), iodine (15.74 g, 61.98 mmol) was added followed by addition of potassium hydroxide (13.88 g, 247.9 mmol) at room temperature and the reaction mixture was stirred for 5 h at room temperature. The reaction mixture was cooled in ice bath, saturated solution of sodium thiosulfate (100 ml) was added and the mixture was extracted with ethyl acetate (3 x 200 ml). The combined organic layer was washed with water (200 ml), dried over sodium sulfate and filtered. The mixture was concentrated under reduced pressure and purified by column chromatography to yield 3.95 g of product as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (s, 6H), 1.54 (t, J = 6.9 Hz, 2H), 2.34 (t, J = 6.3 Hz, 2H), 2.49 (s, 2H), 11.89 (s, 1H).

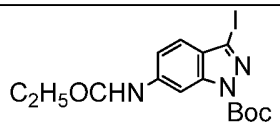
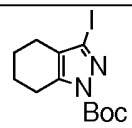
Step 4: *tert*-Butyl 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazole-1-carboxylate: To a stirred solution of step 3 intermediate (3.9 g, 14.124 mmol) in dry tetrahydrofuran (20 ml), triethylamine (2.08 ml, 14.83 mmol), 4-dimethylaminopyridine (68 mg, 0.565 mmol) were added followed by addition of di-tert-butyl bicarbonate (3.23 g, 14.83 mmol) at room temperature and reaction mixture was stirred for 1 h at same temperature. The solvent was evaporated under reduced pressure and product was purified by column chromatography to

yield 5.24 g of product as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (s, 6H), 1.50 (t, *J* = 6.6 Hz, 2H), 1.59-1.69 (m, 9H), 2.31 (t, *J* = 6.3 Hz, 2H), 2.67 (s, 2H).

The intermediates 14-20 were prepared according to the procedures reported in literature. The intermediate 21 was obtained in the similar manner as described above in intermediate 11. The structural formulas, chemical names and ^{1}H NMR data are provided in table 3.

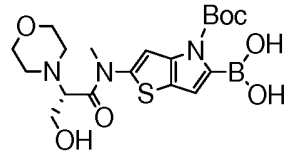
Table 3: Structure, Chemical Name and ^{1}H NMR data of Intermediate 12-19.

Structure and Intermediate No.	Chemical name and ^{1}H NMR analysis
 Intermediate 14	*tert*-Butyl 3-iodo-1*H*-indazole-1-carboxylate: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72 (s, 9H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 8.12 (d, *J* = 8.1 Hz, 1H).
 Intermediate 15	*tert*-Butyl 3-iodo-6-methoxy-1*H*-indazole-1-carboxylate: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72 (s, 9H), 3.91 (s, 3H), 6.93-7.03 (m, 1H), 7.29-7.40 (m, 1H), 7.60 (s, 1H).
 Intermediate 16	*tert*-Butyl 3-iodo-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.73 (s, 9H), 7.31-7.41 (m, 1H), 7.86 (d, *J* = 7.2 Hz, 1H), 8.78 (d, *J* = 5.1 Hz, 1H).
 Intermediate 17	*tert*-Butyl 3-iodo-6-(pyridin-4-yl)-1*H*-indazole-1-carboxylate: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.74 (s, 9H), 7.55-7.70 (m, 4H), 8.48 (s, 1H), 8.75 (d, *J* = 5.1 Hz, 2H).
 Intermediate 18	*tert*-Butyl 3-iodo-6-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)-1*H*-indazole-1-carboxylate: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.73 (s, 9H), 1.95-2.20 (m, 8H), 3.69-3.76 (m, 1H), 7.41-7.55 (m, 2H), 7.95 (s, 1H), 8.02 (s, 1H), 8.28 (s, 1H).
 Intermediate 19	*tert*-Butyl 3-iodo-6-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indazole-1-carboxylate: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.73 (s, 9H), 3.99 (s, 3H), 7.41-7.50 (m, 2H), 7.75 (s, 1H), 7.88 (s, 1H),

Structure and Intermediate No.	Chemical name and ^{1}H NMR analysis
	8.25 (s, 1H).
 Intermediate 20	*tert*-Butyl 3-iodo-6-(propionamido)-1*H*-indazole-1-carboxylate: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.8 Hz, 3H), 1.72 (s, 9H), 2.45 (q, *J* = 7.2 Hz, 2H), 7.35-7.50 (m, 3H), 8.56 (s, 1H).
 Intermediate 21	*tert*-Butyl 3-iodo-4,5,6,7-tetrahydro-1*H*-indazole-1-carboxylate: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (s, 9H), 1.65-1.90 (m, 4H), 2.30 (t, *J* = 5.7 Hz, 2H), 2.87 (t, *J* = 5.7 Hz, 2H).

Intermediate 22

(*S*)-(4-(tert-butoxycarbonyl)-2-(3-hydroxy-*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid

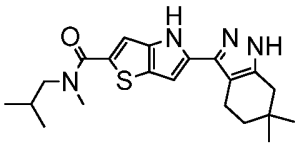


Examples

The compounds of the present invention shown below are prepared from intermediates described above using synthetic schemes 1 to 5.

Example 1

5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-*N*-isobutyl-*N*-methyl-4*H*-thieno[3,2-b]pyrrole-2-carboxamide



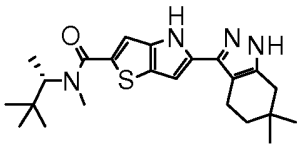
Step 1: *tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-2-(isobutyl(methyl)carbamoyl)-4*H*-thieno[3,2-*b*]pyrrole-4-carboxylate: A mixture of (4-(*tert*-butoxycarbonyl)-2-(isobutyl(methyl)carbamoyl)-4H-thieno[3,2-b]pyrrol-5-yl)boronic acid (500 mg, 1.315 mmol), *tert*-butyl 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole-1-carboxylate (495 mg, 1.315 mmol) and tetrakis(triphenylphosphine)palladium (31 mg, 0.026 mmol) was stirred in degassed toluene (13 ml) and methanol (1.6 ml) under nitrogen

atmosphere for 10 min. To the reaction mixture aqueous solution of sodium carbonate (2.0 M, 1.6 ml) was added and stirred at 90 ° C for 18 h. The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 x 100 ml). The combined organic extract was washed with water (100 ml), dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to afford 84 mg of product as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84-0.90 (m, 2H), 0.99 (s, 6H), 1.17-1.60 (m, 15H), 1.64 (s, 9H), 2.04 (s, 1H), 2.37 (s, 2H), 2.75 (s, 2H), 3.24 (s, 3H), 3.43 (d, *J* = 6.9 Hz, 2H), 6.68 (s, 1H), 7.66 (s, 1H).

Step 2: 5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-*N*-isobutyl-*N*-methyl-4*H*-thieno[3,2-b]pyrrole-2-carboxamide: To the stirred solution of step 1 intermediate (80 mg, 0.137 mmol) in dichloromethane (1.14 ml), trifluoroacetic acid (0.7 ml) was added at 0 °C and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure, poured into saturated aqueous solution of sodium bicarbonate (100 ml) and extracted with ethyl acetate (2 x 150 ml). The combined organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure. The solid was purified by column chromatography to afford 14 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (d, *J* = 6.9 Hz, 6H), 0.99 (s, 6H), 1.51-1.59 (m, 2H), 1.95-2.05 (m, 1H), 2.38 (s, 2H), 2.57-2.66 (m, 2H), 3.16 (br.s, 5H), 6.55 (s, 1H), 7.30 (s, 1H), 11.41 (s, 1H), 12.43 (s, 1H). APCI (*m/z*): 385.23 $(M+H)^+$.

Example 2

(*S*)-5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-*N*-(3,3-dimethylbutan-2-yl)-*N*-methyl-4*H*-thieno[3,2-*b*]pyrrole-2-carboxamide



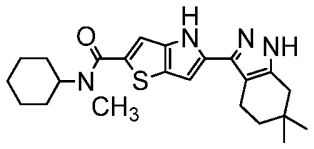
Step 1 (*S*)-*tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-2-((3,3-dimethylbutan-2-yl)(methyl)carbamoyl)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: This intermediate is prepared by Suzuki coupling reaction of (*S*)-(4-(*tert*-butoxycarbonyl)-2-((3,3-dimethylbutan-2-yl)(methyl)carbamoyl)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid (1.3 g, 3.183 mmol) with *tert*-butyl 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole-1-carboxylate (1.197 g, 3.183 mmol) using tetrakis(triphenylphosphine)palladium (74 mg, 0.064 mmol), aqueous solution of sodium carbonate (2.0 M, 4 ml) in degassed toluene (31.8 ml) and methanol (4 ml) as described in step 1 of example 1 to afford 305 mg of product as a yellow

solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93, 0.99 (2s, 15H), 1.45 (s, 11H), 1.56 (s, 9H), 2.15-2.76 (s, 2H), 2.23 (br, s, 3H), 2.68 (s, 2H), 3.16 (br s, 3H), 6.91 (s, 1H), 7.48-7.68 (m, 1H).

Step 2: (*S*)-5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-*N*-(3,3-dimethylbutan-2-yl)-*N*-methyl-4*H*-thieno[3,2-b]pyrrole-2-carboxamide: To a stirred solution of step 1 intermediate (300 mg) in ethanol (4 ml), aqueous solution of sodium hydroxide (1 *N*, 4 ml) was added at room temperature and reaction mixture was stirred at reflux temperature for 1 h. The reaction mixture was cooled to 0 °C and hydrochloric acid (1 *N*, 10 ml) was added and stirred for 30 min. The mixture was extracted with ethyl acetate (2 x 100 ml), dried over sodium sulphate, filtered and concentrated under reduced pressure. The solid was purified by column chromatography to afford 36 mg of product as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.91 (br s, 9H), 0.99 (br s, 6H), 1.13-1.26 (m, 3H), 1.55 (t, *J* = 4.2 Hz, 2H), 2.38 (s, 2H), 2.55-2.66 (m, 2H), 3.08 (br s, 3H), 4.51-4.61 (m, 1H), 6.53 (s, 1H), 7.29 (s, 1H), 11.43 (s, 1H), 12.42 (s, 1H). APCI (*m/z*): 413.18 $(M+H)^+$.

Example 3

N-Cyclohexyl-5-(6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-*N*-methyl-4*H*-thieno[3,2-b]pyrrole-2-carboxamide



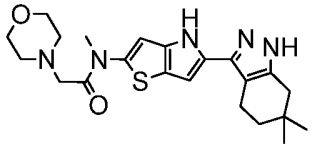
Step 1: *tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-2-(cyclohexyl(methyl)carbamoyl)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: This intermediate was prepared by Suzuki coupling reaction of (4-(*tert*-butoxycarbonyl)-2-(cyclohexyl(methyl)carbamoyl)-4H-thieno[3,2-b]pyrrol-5-yl)boronic acid (400 mg, 0.985 mmol) with *tert*-butyl 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole-1-carboxylate (371 mg, 0.985 mmol) using tetrakis(triphenylphosphine)palladium (23 mg, 0.02 mmol), aqueous solution of sodium carbonate (2.0 M, 1.2 ml) in degassed toluene (10 ml) and methanol (1.2 ml) as described in step 1 of example 1 to afford 125 mg of product as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (s, 6H), 1.39 (s, 9H), 1.64 (s, 9H), 0.84-1.95 (m, 12H), 2.35-2.40 (m, 2H), 2.75 (s, 2H), 3.07 (s, 3H), 4.15-4.35 (m, 1H), 6.68 (s, 1H), 7.60 (s, 1H).

Step 2: *N*-Cyclohexyl-5-(6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-*N*-methyl-4*H*-thieno[3,2-b]pyrrole-2-carboxamide: The title compound was prepared by deprotection reaction of step 1 intermediate (120 mg, 0.196 mmol) using trifluoroacetic acid (0.8 ml) in

dichloromethane (1.7 ml) as described in step 2 of example 1 to afford 45 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.99 (s, 6H), 1.04-1.95 (m, 12H), 2.38 (s, 2H), 2.45-2.75 (m, 2H), 3.00 (s, 3H), 4.14-4.24 (m, 1H), 6.54 (s, 1H), 7.24 (s, 1H), 11.42 (s, 1H), 12.43 (s, 1H). ESI (*m/z*): 411.33 $(M+H)^+$.

Example 4

N-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinoacetamide

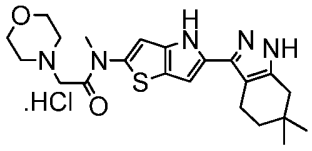


Step 1: *tert*-Butyl 5-(1-(tert-butoxycarbonyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-2-(N-methyl-2-morpholinoacetamido)-4H-thieno[3,2-b]pyrrole-4-carboxylate: A mixture of (4-(*tert*-butoxycarbonyl)-2-(N-methyl-2-morpholinoacetamido)-4H-thieno[3,2-b]pyrrol-5-yl)boronic acid (1 g, 2.346 mmol), *tert*-butyl 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazole-1-carboxylate (1.07 g, 2.839 mmol), aqueous solution of potassium carbonate (2 M, 1.46 ml) in dry tetrahydrofuran (7.14 ml) was degassed for 30 min. To this mixture tetrakis(triphenylphosphine)palladium (135 mg, 0.117 mmol) was added and stirred at 65 ° C for 18 h. The reaction mixture was cooled at room temperature, diluted with water (100 ml) and extracted with ethyl acetate (3 x 150 ml). The combined organic extract was washed with brine (100 ml), dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to yield 250 mg of product as a dark brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (s, 6H), 1.46 (s, 9H), 1.44-1.55 (m, 2H), 1.64 (s, 9H), 2.35-2.40 (m, 2H), 2.60-2.80 (m, 6H), 3.33 (br. s, 5H), 3.68-3.85 (m, 4H), 6.64 (s, 1H), 7.26 (s, 1H). APCI (*m/z*): 628.78 $(M+H)^+$.

Step 2: *N*-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinoacetamide: The title compound was prepared by deprotection reaction of step 1 intermediate (240 mg) using aqueous solution of sodium hydroxide (1*N*, 5 ml) in ethanol (5 ml) as described in step 2 of example 2 to afford 18 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98 (s, 6H), 1.49-1.57 (m, 2H), 2.35-2.47 (m, 4H), 2.52-2.65 (m, 2H), 3.12 (s, 2H), 3.17 (s, 3H), 3.42-3.65 (m, 6H), 6.50 (s, 1H), 6.96 (s, 1H), 11.44 (s, 1H), 12.34 (s, 1H). APCI (*m/z*): 428.30 $(M+H)^+$.

Example 5

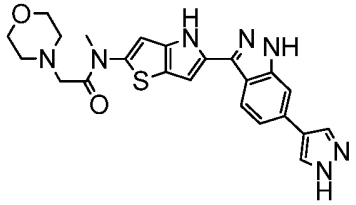
N-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinoacetamide hydrochloride



To a stirred solution of example 4 (125 mg, 0.292 mmol) in dry ethyl acetate (1 ml), a saturated solution of hydrochloride in ethyl acetate (3 ml) was added at 0 °C and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the solid residue was diluted with ethyl acetate (10 ml). The mixture was again concentrated and the solid obtained was stirred in n-hexane (10 ml), filtered and dried to yield 110 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98 (s, 6H), 1.51-1.61 (m, 2H), 2.38-2.50 (m, 2H), 2.58-2.65 (m, 2H), 3.10-3.18 (m, 2H), 3.26 (s, 3H), 3.31-3.3.46 (m, 2H), 3.65-3.95 (m, 4H), 4.18 (s, 2H), 6.73 (s, 1H), 7.19 (s, 1H), 10.38 (s, 1H), 11.88 (s, 1H). APCI (*m/z*): 428.30 $(M+H)^+$.

Example 6

N-(5-(6-(1*H*-Pyrazol-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinoacetamide



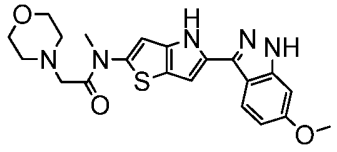
Step 1: *tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-6-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)-1*H*-indazol-3-yl)-2-(*N*-methyl-2-morpholinoacetamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: This intermediate was prepared by Suzuki coupling reaction of (4-(*tert*-butoxycarbonyl)-2-(*N*-methyl-2-morpholinoacetamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid (400 mg, 1.058 mmol) with *tert*-butyl 3-iodo-6-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)-1*H*-indazole-1-carboxylate (470 mg, 0.952 mmol) using tetrakis(triphenylphosphine)palladium (61 mg, 0.052 mmol) in presence of aqueous solution of potassium carbonate (2.0 M, 1.35 ml) in dry tetrahydrofuran (7 ml) as described in step 1 of example 4 to afford 143 mg of product as an viscous liquid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.18 (s, 9H), 1.39-1.50 (m, 2H), 1.75 (s, 9H), 2.12-2.20 (m, 4H), 3.39 (s, 3H), 3.69-3.76 (m, 6H), 4.03-4.13 (m, 6H), 5.39-5.47 (m, 1H), 6.85 (s, 1H), 7.39-7.55 (m, 2H), 7.59-7.68 (m, 1H), 7.95 (s, 1H), 8.03 (s, 1H), 8.37 (s, 1H); APCI (*m/z*): 746.25 $(M+H)^+$.

Step 2: *N*-Methyl-2-morpholino-*N*-(5-(6-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)acetamide: The title compound was prepared by deprotection of step 1 intermediate (138 mg) using aqueous solution of sodium hydroxide (1*N*, 2 ml) in ethanol (2 ml) as described in step 2 of example 2 to afford 77 mg of product as an grey solid which was directly used in next step.

Step 3: *N*-(5-(6-(1*H*-Pyrazol-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinoacetamide: To a stirred solution of step 2 intermediate (75 mg, 0.137 mmol) in ethanol (2.5 ml), p-toluenesulfonic acid (53 mg, 0.275 mmol) was added and the reaction mixture was stirred at 90 °C for 1 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. To the obtained residue, a aqueous saturated solution of sodium bicarbonate (75 ml) was added and the mixture was stirred for 15 min. The precipitated solid was collected by filtration and dried. The solid was then purified by column chromatography to yield 13 mg of product as a grey solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.35-2.55 (m, 4H), 3.21 (s, 3H), 3.45-3.62 (m, 6H), 7.07 (d, J = 4.2 Hz, 2H), 7.48 (d, J = 5.1 Hz, 1H), 7.69 (s, 1H), 8.04 (d, J = 6.3 Hz, 2H), 8.30-8.37 (m, 1H), 11.82 (s, 1H), 12.98 (s, 1H), 13.08 (s, 1H); APCI (*m/z*): 462.47 $(M+H)^+$.

Example 7

N-(5-(6-Methoxy-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinoacetamide



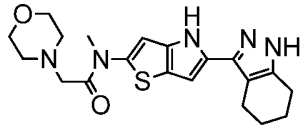
Step 1: *tert*-Butyl 5-(1-(tert-butoxycarbonyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-2-(N,3,3-trimethylbutanamido)-4H-thieno[3,2-b]pyrrole-4-carboxylate: This intermediate was prepared by Suzuki coupling reaction of (4-(*tert*-butoxycarbonyl)-2-(*N*-methyl-2-morpholinoacetamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid (250 mg, 0.590 mmol) with *tert*-butyl 3-iodo-6-methoxy-1*H*-indazole-1-carboxylate (267 mg, 0.714 mmol) using tetrakis(triphenylphosphine)palladium (34 mg, 0.029 mmol) in presence of aqueous solution of potassium carbonate (2.0 M, 770 µl) in dry tetrahydrofuran (3.7 ml) as described in step 1 of example 4 to afford 84 mg of product as a brown solid. APCI (*m/z*): 626.24 $(M+H)^+$.

Step 2: *N*-(5-(6-Methoxy-1H-indazol-3-yl)-4H-thieno[3,2-b]pyrrol-2-yl)-N-methyl-2-morpholinoacetamide: The title compound was prepared by deprotection of step 1 intermediate (84 mg) using aqueous solution of sodium hydroxide (1*N*, 2 ml) in ethanol (2 ml) as described in step 2 of example 2 to afford 14 mg of product as an grey solid. ^{1}H NMR (300

MHz, DMSO-d_6): δ 2.35-2.46 (m, 4H), 3.20 (s, 3H), 3.40-3.65 (m, 6H), 3.84 (s, 3H), 6.82 (d, J = 7.8 Hz, 1H), 6.93 (s, 1H), 7.03 (d, J = 6.0 Hz, 2H), 7.95 (d, J = 8.7 Hz, 1H), 11.77 (s, 1H), 12.92 (s, 1H). APCI (m/z): 426.14 $(M+H)^+$.

Example 8

N-Methyl-2-morpholino-*N*-(5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)acetamide

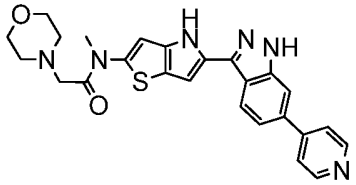


Step 1: *tert*-Butyl 5-(1-(tert-butoxycarbonyl)-4,5,6,7-tetrahydro-1H-indazol-3-yl)-2-(N-methyl-2-morpholinoacetamido)-4H-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by Suzuki coupling reaction of (4-(*tert*-butoxycarbonyl)-2-(*N*-methyl-2-morpholinoacetamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid (600 mg, 1.417 mmol) with *tert*-Butyl 3-iodo-4,5,6,7-tetrahydro-1*H*-indazole-1-carboxylate (597 mg, 1.715 mmol) using tetrakis(triphenylphosphine)palladium (82 mg, 0.070 mmol) in presence of aqueous solution of potassium carbonate (2.0 M, 1.8 ml) in dry tetrahydrofuran (9 ml) as described in step 1 of example 4 to afford 122 mg of product as a brown solid which was directly used in next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (s, 9H), 1.64 (s, 9H), 1.69-1.79 (m, 2H), 1.81-1.93 (m, 2H), 2.35-2.42 (m, 2H), 2.80-3.10 (m, 6H), 3.35 (s, 3H), 3.42-3.60 (m, 2H), 3.84-4.00 (m, 4H), 6.63 (s, 1H), 7.26 (s, 1H).

Step 2: *N*-Methyl-2-morpholino-N-(5-(4,5,6,7-tetrahydro-1H-indazol-3-yl)-4H-thieno[3,2-b]pyrrol-2-yl)acetamide: The title compound was prepared by deprotection reaction of step 1 intermediate (115 mg) using aqueous solution of sodium hydroxide (1*N*, 2 ml) in ethanol (2 ml) as described in step 2 of example 2 to afford 26 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.71-1.80 (m, 4H), 2.33-2.43 (m, 4H), 2.54-2.65 (m, 4H), 3.17 (s, 3H), 3.46-3.57 (m, 6H), 6.47 (s, 1H), 6.96 (s, 1H), 11.43 (s, 1H), 12.36 (s, 1H). APCI (m/z): 400.24 $(M+H)^+$.

Example 9

N-Methyl-2-morpholino-*N*-(5-(6-(pyridin-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)acetamide

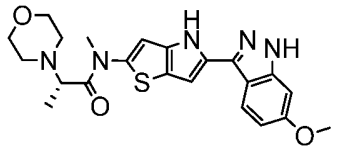


Step 1: *tert*-Butyl 5-(1-(tert-butoxycarbonyl)-6-(pyridin-4-yl)-1H-indazol-3-yl)-2-(N-methyl-2-morpholinoacetamido)-4H-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by Suzuki coupling reaction of (4-(*tert*-butoxycarbonyl)-2-(N-methyl-2-morpholinoacetamido)-4H-thieno[3,2-b]pyrrol-5-yl)boronic acid (450 mg, 1.063 mmol) with *tert*-butyl 3-iodo-6-(pyridin-4-yl)-1*H*-indazole-1-carboxylate (448 mg, 1.063 mmol) using tetrakis(triphenylphosphine)palladium (62 mg, 0.053 mmol) in presence of aqueous solution of potassium carbonate (2.0 M, 1.36 ml) in dry tetrahydrofuran (7 ml) as described in step 1 of example 4 to afford 95 mg of product as a brown solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.27 (s, 9H), 1.75 (s, 9H), 3.40 (s, 3H), 3.45-3.57 (m, 4H), 3.91 (s, 2H), 4.09-4.20 (m, 4H), 6.89 (s, 1H), 7.26 (s, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.89 (d, *J* = 7.2 Hz, 2H), 7.92-8.05 (m, 2H), 8.67 (s, 1H), 8.81 (d, *J* = 6.0 Hz, 1H). APCI (*m/z*): 673.10 $(M+H)^+$.

Step 2: *N*-Methyl-2-morpholino-*N*-(5-(6-(pyridin-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)acetamide: The title compound was prepared by deprotection of step 1 intermediate (90 mg) using aqueous solution of sodium hydroxide (1*N*, 2 ml) in ethanol (2 ml) as described in step 2 of example 2 to afford 18 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.36-2.55 (m, 6H), 3.21 (s, 3H), 3.40-3.62 (m, 4H), 7.06 (s, 1H), 7.13 (s, 1H), 7.61 (d, *J* = 6.3 Hz, 1H), 7.82 (d, *J* = 5.4 Hz, 2H), 7.93 (s, 1H), 8.25 (d, *J* = 8.7 Hz, 1H), 8.67 (d, *J* = 6.0 Hz, 2H), 11.89 (s, 1H), 13.39 (s, 1H). APCI (*m/z*): 473.12 $(M+H)^+$.

Example 10

(S)-*N*-(5-(6-Methoxy-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinopropanamide



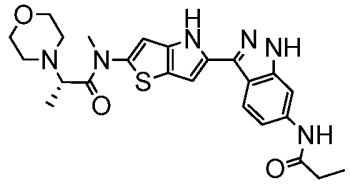
Step 1: (*S*)-*tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-6-methoxy-1*H*-indazol-3-yl)-2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: This intermediate was prepared by Suzuki coupling reaction of (*S*)-(4-(*tert*-butoxycarbonyl)-2-(*N*-methyl-2-morpholinopropanamido)-4H-thieno[3,2-b]pyrrol-5-yl)boronic acid (500 mg, 1.143 mmol), with *tert*-butyl 3-iodo-6-methoxy-1*H*-indazole-1-carboxylate (518 mg, 1.383 mmol), using tetrakis(triphenylphosphine)palladium (66 mg, 0.057 mmol) in presence of aqueous solution of potassium carbonate (2.0 M, 1.46 ml) in dry tetrahydrofuran (7.14 ml) as described in step 1 of example 4 to afford 250 mg of product as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 9H), 1.15-1.35 (m, 3H), 1.73 (s, 9H), 2.41-2.50 (m, 2H), 2.63-2.70 (m,

2H), 3.37 (s, 3H), 3.67-3.76 (m, 5H), 3.94 (s, 3H), 6.83 (s, 1H), 6.96 (d, *J* = 6.9 Hz, 1H), 7.40 (s, 1H), 7.42-7.50 (m, 1H), 7.70 (s, 1H).

Step 2: (*S*)-*N*-(5-(6-Methoxy-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinopropanamide: The title compound was prepared by deprotection reaction of step 1 intermediate (240 mg) using aqueous solution of sodium hydroxide (1*N*, 5 ml) in ethanol (5 ml) as described in step 2 of example 2 to afford 38 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.10 (d, *J* = 6.6 Hz, 3H), 2.31-2.55 (m, 4H), 3.21 (s, 3H), 3.45-3.65 (m, 5H), 3.84 (s, 3H), 6.82 (d, *J* = 8.7 Hz, 1H), 6.93 (s, 1H), 6.95-7.06 (m, 2H), 7.94 (d, *J* = 8.7 Hz, 1H), 11.75 (s, 1H), 12.91 (s, 1H). APCI (*m/z*): 440.35 $(M+H)^+$.

Example 11

(*S*)-*N*-Methyl-2-morpholino-*N*-(5-(6-propionamido-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)propanamide

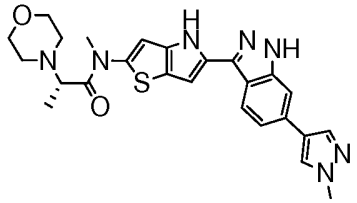


Step 1: (*S*)-*tert*-Butyl 5-(1-(tert-butoxycarbonyl)-6-propionamido-1*H*-indazol-3-yl)-2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by Suzuki coupling reaction of (*S*)-(4-(*tert*-butoxycarbonyl)-2-(*N*-methyl-2-morpholinopropanamido)-4H-thieno[3,2-b]pyrrol-5-yl)boronic acid (300 mg, 0.686 mmol) with *tert*-Butyl 3-iodo-6-(propionamido)-1*H*-indazole-1-carboxylate (256 mg, 0.617 mmol) using tetrakis(triphenylphosphine)palladium (39 mg, 0.031 mmol) in presence of aqueous solution of potassium carbonate (2.0 M, 0.8 ml) in dry tetrahydrofuran (4.2 ml) as described in step 1 of example 4 to afford 105 mg of product as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (s, 9H), 1.29 (t, *J* = 7.8 Hz, 3H), 1.61 (s, 9H), 1.74 (s, 3H), 2.38-2.55 (m, 4H), 2.59-2.66 (m, 2H), 3.37 (s, 3H), 3.68-3.75 (m, 5H), 6.84 (s, 1H), 7.35-7.44 (m, 3H), 7.48-7.57 (m, 1H), 8.59 (s, 1H). APCI (m/z): 681.09 $(M+H)^+$.

Step 2: *N*-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-4H-thieno[3,2-b]pyrrol-2-yl)-N,3,3-trimethylbutanamide: The title compound was prepared by deprotection of step 1 intermediate (95 mg) using aqueous solution of sodium hydroxide (1*N*, 1.5 ml) in ethanol (1.5 ml) as described in step 2 of example 2 to afford 24 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-*d6*): δ 1.02-1.16 (m, 6H), 2.32-2.60 (m, 6H), 3.22 (s, 3H), 3.40-3.64 (m, 5H), 7.00-7.06 (m, 2H), 7.17 (d, J = 5.1 Hz, 1H), 7.98 (d, *J* = 8.7 Hz, 1H), 8.17 (s, 1H), 10.06 (s, 1H), 11.76 (s, 1H), 12.96 (s, 1H). APCI (m/z): 481.04 $(M+H)^+$.

Example 12

(*S*)-*N*-Methyl-*N*-(5-(6-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-2-morpholinopropanamide

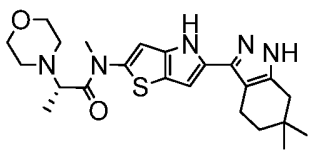


Step 1: (*S*)-*tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-6-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indazol-3-yl)-2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by Suzuki coupling reaction of (*S*)-(4-(*tert*-butoxycarbonyl)-2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid (400 mg, 0.686 mmol) with *tert*-butyl 3-iodo-6-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indazole-1-carboxylate (469 mg, 1.107 mmol) using tetrakis(triphenylphosphine)palladium (53 mg, 0.045 mmol) in presence of aqueous solution of potassium carbonate (2.0 M, 1.17 ml) in dry tetrahydrofuran (5.7 ml) as described in step 1 of example 4 to afford 150 mg of product as a brown solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.15-1.30 (m, 12H), 1.75 (s, 9H), 2.55-2.63 (m, 2H), 2.75-2.89 (m, 2H), 3.35 (s, 3H), 3.69-3.76 (m, 5H), 3.98 (s, 3H), 6.86 (s, 1H), 7.41 (s, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.55-7.63 (m, 1H), 7.77 (s, 1H), 7.89 (s, 1H), 8.35 (s, 1H). APCI (*m/z*): 690.12 $(M+H)^+$.

Step 2: (*S*)-*N*-Methyl-*N*-(5-(6-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-2-morpholinopropanamide: The title compound was prepared by deprotection of step 1 intermediate (145 mg) using aqueous solution of sodium hydroxide (1*N*, 2.5 ml) in ethanol (2.5 ml) as described in step 2 of example 2 to afford 34 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.10 (d, *J* = 6.9 Hz, 3H), 2.27-2.60 (m, 4H), 3.22 (s, 3H), 3.45-3.65 (m, 5H), 3.89 (s, 3H), 7.06 (d, *J* = 7.2 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.65 (s, 1H), 7.98 (s, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 8.27 (s, 1H), 11.80 (s, 1H), 13.09 (s, 1H). APCI (*m/z*): 490.07 $(M+H)^+$..

Example 13

(*S*)-*N*-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinopropanamide

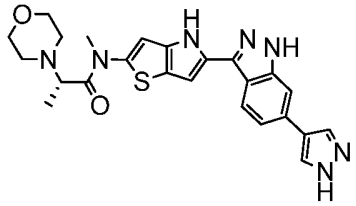


Step 1: (*S*)-*tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by Suzuki coupling reaction of (*S*)-(4-(*tert*-butoxycarbonyl)-2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid (510 mg, 1.166 mmol) with *tert*-butyl 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole-1-carboxylate (530 mg, 1.411 mmol) using tetrakis(triphenylphosphine)palladium (67 mg, 0.058 mmol) in presence of aqueous solution of potassium carbonate (2.0 M, 1.5 ml) in dry tetrahydrofuran (7.3 ml) as described in step 1 of example 4 to afford 135 mg of product as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (s, 6H), 1.49 (s, 9H), 1.10-1.68 (m, 9H), 1.64 (s, 9H), 2.31-2.40 (m, 3H), 2.76 (s, 2H), 3.35 (s, 3H), 3.65-3.85 (m, 4H), 6.64 (s, 1H), 7.26 (s, 1H); APCI (*m/z*): 642.19 $(M+H)^+$.

Step 2: (*S*)-*N*-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinopropanamide: The title compound was prepared by deprotection of step 1 intermediate (130 mg) using aqueous solution of sodium hydroxide (1*N*, 2 ml) in ethanol (2 ml) as described in step 2 of example 2 to afford 21 mg of product as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (s, 6H), 1.17-1.28 (m, 5H), 1.63 (t, J = 5.4 Hz, 2H), 2.42 (s, 2H), 2.50-2.80 (m, 4H), 3.32 (s, 3H), 3.67-3.75 (m, 5H), 6.60 (s, 1H), 6.83 (s, 1H), 9.77 (s, 1H); APCI (*m/z*): 442.16 $(M+H)^+$.

Example 14

(*S*)-*N*-(5-(6-(1*H*-Pyrazol-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinopropanamide



Step 1: *tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-6-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)-1*H*-indazol-3-yl)-2-((*S*)-*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by Suzuki coupling reaction of (*S*)-(4-(*tert*-butoxycarbonyl)-2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid (400 mg, 0.915 mmol) with *tert*-butyl 3-iodo-6-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)-1*H*-indazole-1-carboxylate (370 mg, 0.748 mmol) using tetrakis(triphenylphosphine)palladium (52 mg, 0.045 mmol) in presence of aqueous solution of potassium carbonate (2.0 M, 1.2 ml) in dry tetrahydrofuran (0.16 M, 6 ml) as described in

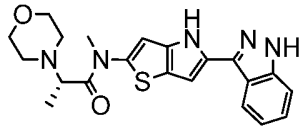
step 1 of example 4 to afford 254 mg of product as an viscous liquid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.19 (s, 9H), 1.20-1.26 (m, 3H), 1.75 (s, 9H), 2.05-2.15 (m, 2H), 2.41-2.65 (m, 8H), 3.37 (s, 3H), 3.69-3.78 (m, 6H), 4.05-4.11 (m, 1H), 5.38-5.47 (m, 1H), 6.87 (s, 1H), 7.42 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.55-7.64 (m, 1H), 7.95 (s, 1H), 8.03 (s, 1H), 8.38 (s, 1H). ESI (*m/z*): 760.24 $(M+H)^+$.

Step 2: (*S*)-*tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-6-(1*H*-pyrazol-4-yl)-1*H*-indazol-3-yl)-2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by deprotection of step 1 intermediate (250 mg, 0.329 mmol) using p-toluenesulfonic acid (250 mg, 1.317 mmol) in ethanol (5 ml) as described in step 3 of example 6 to yield 200 mg of product as a brown solid which was directly used in next step.

Step 3: (*S*)-*N*-(5-(6-(1*H*-Pyrazol-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinopropanamide: The title compound was prepared by deprotection reaction of step 2 intermediate (190 mg) using aqueous solution of sodium hydroxide (1*N*, 2 ml) in ethanol (2 ml) as described in step 2 of example 2 to afford 60 mg of product as brown solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08 (t, *J* = 6.6 Hz, 3H), 2.33-2.55 (m, 4H), 3.22 (s, 3H), 3.35-3.65 (m, 5H), 7.06 (d, *J* = 6.6 Hz, 2H), 7.49 (d, *J* = 9.6 Hz, 1H), 7.70 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 8.32 (s, 1H), 11.80 (s, 1H), 12.99 (s, 1H), 13.09 (s, 1H). APCI (*m/z*): 476.23 $(M+H)^+$.

Example 15

(*S*)-*N*-(5-(1*H*-Indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinopropanamide



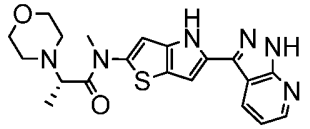
Step 1: (*S*)-*tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-1*H*-indazol-3-yl)-2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by Suzuki coupling reaction of (*S*)-(4-(*tert*-butoxycarbonyl)-2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid (780 mg, 1.783 mmol) with *tert*-butyl 3-iodo-1*H*-indazole-1-carboxylate (742 mg, 2.158 mmol) using tetrakis(triphenylphosphine)palladium (103 mg, 0.089 mmol) in the presence of aqueous solution of potassium carbonate (2.0 M, 1.4 ml) in dry tetrahydrofuran (11 ml) as described in step 1 of example 4 to afford 170 mg of product as a brown solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17 (s, 9H), 1.17-1.29 (m, 3H), 1.74 (s, 9H), 2.41-2.50 (m, 2H), 2.59-2.67 (m, 2H), 3.37 (s, 3H), 3.52-3.60 (m, 1H), 3.65-3.75 (m, 4H), 6.86 (s, 1H), 7.37 (t, *J* = 8.1 Hz, 1H),

7.41 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 8.23 (d, *J* = 8.7 Hz, 1H). APCI (*m/z*): 610.13 $(M+H)^+$.

Step 2: (*S*)-*N*-(5-(1*H*-Indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinopropanamide: The title compound was prepared by deprotection of step 1 intermediate (160 mg) using aqueous solution of sodium hydroxide (1 *N*, 2 ml) in ethanol (2 ml) as described in step 2 of example 2 to afford 21 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.24 (d, *J* = 6.6 Hz, 3H), 2.43-2.54 (m, 2H), 2.62-2.78 (m, 2H), 3.35 (s, 3H), 3.44-3.51 (m, 1H), 3.60-3.75 (m, 4H), 6.86 (s, 1H), 7.03 (s, 1H), 7.25-7.32 (m, 2H), 7.41-7.56 (m, 2H), 8.03 (d, *J* = 7.8 Hz, 1H), 9.47 (s, 1H). APCI (*m/z*): 410.16 $(M+H)^+$.

Example 16

(*S*)-*N*-(5-(1*H*-Pyrazolo[3,4-*b*]pyridin-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinopropanamide

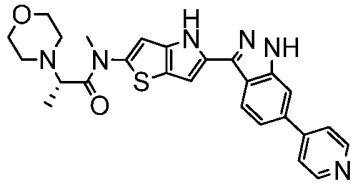


Step 1: (*S*)-*tert*-Butyl 5-(1-(tert-butoxycarbonyl)-1*H*-pyrazolo[3,4-b]pyridin-3-yl)-2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by Suzuki coupling reaction of (*S*)-(4-(*tert*-butoxycarbonyl)-2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid (500 mg, 1.143 mmol) with *tert*-butyl 3-iodo-1*H*-pyrazolo[3,4-*b*]pyridine-1-carboxylate (477 mg, 1.383 mmol) using tetrakis(triphenylphosphine)palladium (66 mg, 0.057 mmol) in the presence of aqueous solution of potassium carbonate (2.0 M, 1.46 ml) in dry tetrahydrofuran (7 ml) as described in step 1 of example 4 to afford 154 mg of product as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (s, 9H), 1.61 (s, 3H), 1.74 (s, 9H), 2.55-2.63 (m, 4H), 3.38 (s, 3H), 3.68-3.75 (m, 5H), 6.85 (s, 1H), 7.31-7.43 (m, 2H), 8.03 (s, 1H), 8.81 (s, 1H). APCI (*m/z*): 611.09 $(M+H)^+$.

Step 2: (*S*)-*N*-(5-(1*H*-Pyrazolo[3,4-b]pyridin-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinopropanamide: The title compound was prepared by deprotection of step 1 intermediate (145 mg) using aqueous solution of sodium hydroxide (1 *N*, 2 ml) in ethanol (2 ml) as described in step 2 of example 2 to afford 29 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.09 (d, *J* = 6.9 Hz, 3H), 2.31-2.59 (m, 4H), 3.22 (s, 3H), 3.46-3.65 (m, 5H), 7.06 (s, 1H), 7.14 (s, 1H), 7.20-7.35 (m, 1H), 8.47-8.65 (m, 2H), 11.93 (s, 1H), 13.71 (s, 1H). APCI (*m/z*): 411.20 $(M+H)^+$.

Example 17

(*S*)-*N*-Methyl-2-morpholino-*N*-(5-(6-(pyridin-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-*b*]pyrrol-2-yl)propanamide

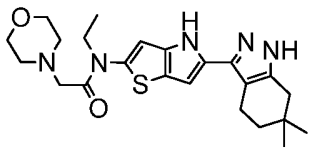


Step 1: (*S*)-*tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-6-(pyridin-4-yl)-1*H*-indazol-3-yl)-2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by Suzuki coupling reaction of (*S*)-(4-(*tert*-butoxycarbonyl)-2-(*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid (500 mg, 1.143 mmol) with *tert*-butyl 3-iodo-6-(pyridin-4-yl)-1*H*-indazole-1-carboxylate (582 mg, 1.382 mmol) using tetrakis(triphenylphosphine)palladium (66 mg, 0.057 mmol) in presence of aqueous solution of potassium carbonate (2.0 M, 1.46 ml) in dry tetrahydrofuran (7 ml) as described in step 1 of example 4 to afford 135 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.23 (s, 9H), 1.65 (d, *J* = 6.3 Hz, 3H), 1.76 (s, 9H), 3.20-3.45 (m, 4H), 3.42 (s, 3H), 4.32-4.45 (m, 5H), 6.88 (s, 1H), 7.42 (s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.79-7.94 (m, 3H), 8.61 (s, 1H), 8.76 (d, *J* = 6.0 Hz, 2H). APCI (*m/z*): 687.21 $(M+H)^+$.

Step 2: (*S*)-*N*-Methyl-2-morpholino-*N*-(5-(6-(pyridin-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)propanamide: The title compound was prepared by deprotection of step 1 intermediate (125 mg) using aqueous solution of sodium hydroxide (1*N*, 2 ml) in ethanol (2 ml) as described in step 2 of example 2 to afford 20 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.10 (d, *J* = 6.3 Hz, 3H), 2.34-2.46 (m, 2H), 2.49-2.56 (m, 2H), 3.22 (s, 3H), 3.46-3.67 (m, 5H), 7.06 (s, 1H), 7.13 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 3.9 Hz, 2H), 7.93 (s, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.66 (d, *J* = 3.9 Hz, 2H), 11.88 (s, 1H), 13.39 (s, 1H). APCI (*m/z*): 485.43 $(M-H)^-$.

Example 18

N-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-ethyl-2-morpholinoacetamide



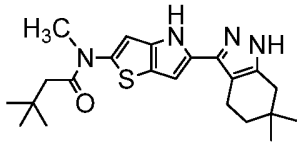
Step 1: *tert*-Butyl 5-(1-(tert-butoxycarbonyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-2-(*N*-ethyl-2-morpholinoacetamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title

intermediate was prepared by Suzuki coupling reaction of (4-(*tert*-butoxycarbonyl)-2-(N-ethyl-2-morpholinoacetamido)-4H-thieno[3,2-b]pyrrol-5-yl)boronic acid (1.0 g, 1.063 mmol) with *tert*-butyl 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole-1-carboxylate (1.04 g, 2.76 mmol) using tetrakis(triphenylphosphine)palladium (132 mg, 0.114 mmol) in presence of aqueous solution of potassium carbonate (2.0 M, 2.92 ml) in dry tetrahydrofuran (14.3 ml) as described in step 1 of example 4 to afford 70 mg of product as a brown solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.04 (s, 6H), 1.15-1.25 (m, 3H), 1.45 (s, 9H), 1.48-1.56 (m, 4H), 1.64 (s, 9H), 2.40 (t, J = 4.8 Hz, 2H), 2.70-2.81 (m, 4H), 3.25-3.43 (m, 2H), 3.81-3.95 (m, 6H), 6.64 (s, 1H), 7.23 (s, 1H); APCI (*m/z*): 642.17 $(M+H)^+$.

Step 2: *N*-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-ethyl-2-morpholinoacetamide: The title compound was prepared by deprotection of step 1 intermediate (125 mg) using aqueous solution of sodium hydroxide (1 *N*, 2.4 ml) in ethanol (2.4 ml) as described in step 2 of example 2 to afford 27 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98 (s, 6H), 1.09 (t, J = 4.8 Hz, 3H), 1.50-1.62 (m, 2H), 2.34-2.43 (m, 6H), 2.55-2.64 (m, 2H), 3.09 (s, 2H), 3.47-3.66 (m, 6H), 6.51 (s, 1H), 6.92 (s, 1H), 11.43 (s, 1H), 12.35 (s, 1H); APCI (*m/z*): 442.26 $(M+H)^+$.

Example 19

N-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*,3,3-trimethylbutanamide

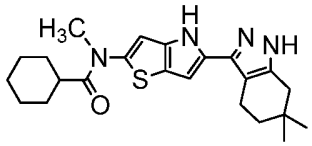


Step 1: *tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-2-(*N*,3,3-trimethylbutanamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by Suzuki coupling reaction of (4-(*tert*-butoxycarbonyl)-2-(N,3,3-trimethylbutanamido)-4H-thieno[3,2-b]pyrrol-5-yl)boronic acid (530 g, 1.344 mmol) with *tert*-butyl 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole-1-carboxylate (506 g, 1.344 mmol) using tetrakis(triphenylphosphine)palladium (31 mg, 0.03 mmol) in presence of aqueous solution of sodium carbonate (2.0 M, 1.7 ml) in degassed toluene (13.5 ml) and methanol (1.7 ml) as described in step 1 of example 1 to afford 205 mg of product as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (s, 15H), 1.24-1.69 (m, 20H), 2.25 (s, 2H), 2.35-2.42 (m, 2H), 2.76 (s, 2H), 3.30 (s, 3H), 6.64 (s, 1H), 7.14 (s, 1H).

Step 2: *N*-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*,3,3-trimethylbutanamide: The title compound was prepared by deprotection of step 1 intermediate (200 mg) using aqueous solution of sodium hydroxide (1*N*, 3 ml) in ethanol (3 ml) as described in step 2 of example 2 to afford 90 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.94, 0.98 (2s, 15H), 1.50-1.60 (m, 2H), 2.21 (s, 2H), 2.38 (s, 2H), 2.55-2.65 (m, 2H), 3.17 (s, 3H), 6.49 (s, 1H), 6.86 (s, 1H), 11.41 (s, 1H), 12.34 (s, 1H). ESI (*m/z*): 399.26 $(M+H)^+$.

Example 20

N-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methylcyclohexanecarboxamide

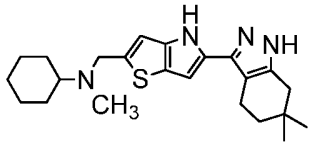


Step 1: *tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-2-(*N*-methylcyclohexanecarboxamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by Suzuki coupling reaction of (4-(*tert*-butoxycarbonyl)-2-(*N*-methylcyclohexanecarboxamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid (440 mg, 1.083 mmol) with *tert*-butyl 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole-1-carboxylate (408 mg, 1.083 mmol) using tetrakis(triphenylphosphine)palladium (25 mg, 0.021 mmol) in presence of aqueous solution of sodium carbonate (2.0 M, 1.35 ml) in degassed toluene (10.8 ml) and methanol (1.35 ml) as described in step 1 of example 1 to afford 159 mg of brown viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99, 1.04 (2s, 15H), 0.95-2.40 (m, 23H), 2.76 (s, 2H), 3.30 (s, 3H), 4.10-4.20 (m, 1H), 6.64 (s, 1H), 7.17 (s, 1H). APCI (*m/z*): 611.06 $(M+H)^+$.

Step 2: *N*-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methylcyclohexanecarboxamide: The title compound was prepared by deprotection reaction of step 1 intermediate (150 mg, 0.245 mmol) using trifluoroacetic acid (1.22 ml) in dichloromethane (2 ml) as described in step 2 of example 1 to afford 21 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.96 (s, 6H), 1.04-1.65 (m, 12H), 2.36 (s, 2H), 2.47-2.62 (m, 3H), 3.14 (s, 3H), 6.49 (s, 1H), 6.92 (s, 1H), 11.38 (s, 1H), 12.33 (s, 1H). APCI (*m/z*): 411.20 $(M+H)^+$.

Example 21

N-((5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)methyl)-*N*-methylcyclohexanamine

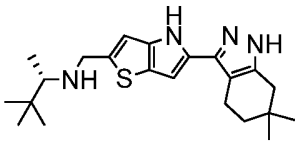


Step 1: *tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-2-((cyclohexyl(methyl)amino)methyl)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by Suzuki coupling reaction of (4-(*tert*-butoxycarbonyl)-2-((cyclohexyl(methyl)amino)methyl)-4H-thieno[3,2-b]pyrrol-5-yl)boronic acid (900 mg, 2.295 mmol) with *tert*-butyl 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole-1-carboxylate (863 mg, 2.295 mmol) using tetrakis(triphenylphosphine)palladium (53 mg, 0.045 mmol) in presence of aqueous solution of sodium carbonate (2.0 M, 3 ml) in degassed toluene (23 ml) and methanol (3 ml) as described in step 1 of example 1 to afford 330 mg of product as a yellow viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (br s, 9H), 1.21-1.30 (m, 6H), 1.49 (br s, 9H), 1.63 (br s, 6H), 1.94-2.04 (m, 4H), 2.30-2.45 (m, 6H), 2.75 (s, 3H), 3.98-4.05 (m, 2H), 4.86 (s, 1H), 6.64 (s, 1H), 6.98-7.09 (m, 1H). ESI (*m/z*): 596.84 $(M)^+$.

Step 2: *N*-((5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)methyl)-*N*-methylcyclohexanamine: The title compound was prepared by deprotection of step 1 intermediate (320 mg, 0.536 mmol) using sodium hydroxide (1 N, 5 ml) in ethanol (5 ml) as described in step 2 of example 2 to afford 18 mg of product as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (br s, 6H), 1.17-2.73 (m, 20H), 3.95 (s, 2H), 6.56 (s, 1H), 6.94-7.05 (m, 1H), 9.65-9.75 (m, 2H). APCI (*m/z*): 395.51 $(M-H)^-$.

Example 22

(*S*)-*N*-((5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)methyl)-3,3-dimethylbutan-2-amine



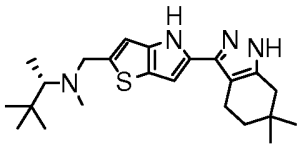
Step 1: (*S*)-*tert*-Butyl 5-(1-(tert-butoxycarbonyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-2-(((3,3-dimethylbutan-2-yl)amino)methyl)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by Suzuki coupling reaction of (*S*)-(4-(*tert*-butoxycarbonyl)-2-(((3,3-dimethylbutan-2-yl)amino)methyl)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid (980 mg, 2.258 mmol) with *tert*-butyl 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole-1-carboxylate (970 mg, 2.258 mmol) using tetrakis(triphenylphosphine)palladium (59 mg,

0.052 mmol) in presence of aqueous solution of sodium carbonate (2.0 M, 2.95 ml) in degassed toluene (23 ml) and methanol (2.95 ml) as described in step 1 of example 1 to afford 135 mg of product as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (s, 9H), 1.04 (br s, 6H), 1.17 (d, *J* = 6.9 Hz, 4H), 1.46 (s, 9H), 1.49-1.55 (m, 2H), 1.85-1.95 (m, 9H), 2.36 (t, *J* = 6.0 Hz, 3H), 2.76 (s, 2H), 4.06-4.15 (m, 1H), 5.75-5.83 (m, 1H), 6.67 (s, 1H), 7.77 (s, 1H).

Step 2: (*S*)-*N*-((5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)methyl)-3,3-dimethylbutan-2-amine: The title compound was prepared by deprotection of step 1 intermediate (130 mg, 0.222 mmol) using sodium hydroxide (1 N, 1.95 ml) in ethanol (1.95 ml) as described in step 2 of example 2 to afford 35 mg of product as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$+ DMSO-d_6): δ 0.78 (br s, 9H), 0.85 (br s, 6H), 0.97 (d, *J* = 5.1 Hz, 3H), 1.45 (t, *J* = 4.8 Hz, 2H), 2.27 (s, 2H), 2.51 (t, *J* = 4.8 Hz, 2H), 3.81-3.90 (m, 2H), 4.51-5.52 (m, 1H), 6.18 (d, *J* = 7.2 Hz, 1H), 6.45 (s, 1H), 7.39 (s, 1H), 10.63 (s, 1H).

Example 23

(*S*)-*N*-((5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)methyl)-*N*,3,3-trimethylbutan-2-amine



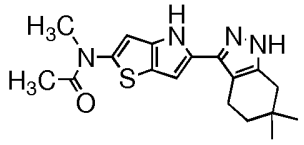
Step 1: (*S*)-*tert*-Butyl 5-(1-(tert-butoxycarbonyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-2-(((3,3-dimethylbutan-2-yl)(methyl)amino)methyl)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by Suzuki coupling reaction of (*S*)-(4-(*tert*-butoxycarbonyl)-2-(((3,3-dimethylbutan-2-yl)(methyl)amino)methyl)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid (890 mg, 2.257 mmol) with *tert*-butyl 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole-1-carboxylate (850 mg, 2.257 mmol) using tetrakis(triphenylphosphine)palladium (52 mg, 0.045 mmol) in presence of aqueous solution of sodium carbonate (2.0 M, 2.8 ml) in degassed toluene (23 ml) and methanol (2.8 ml) as described in step 1 of Example 1 to afford 430 mg of product as a yellow viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91-1.01 (m, 11H), 1.48 (s, 9H), 1.55-1.64 (m, 8H), 1.67-1.75 (s, 14H), 3.24-3.36 (m, 6H), 6.62 (s, 1H), 7.17 (s, 1H); APCI (*m/z*): 599.71 $(M+H)^+$.

Step 2: (*S*)-*N*-((5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)methyl)-*N*,3,3-trimethylbutan-2-amine: The title compound was prepared by deprotection reaction of step 1 intermediate (420 mg, 0.702 mmol) using sodium hydroxide (1 *N*, 6 ml) in ethanol (6 ml) as described in step 2 of example 2 to afford 15 mg of product as an off-white

solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93-1.04 (m, 12H), 1.05 (s, 6H), 1.59-1.66 (m, 2H), 2.28 (s, 3H), 2.40-2.2.47 (m, 3H), 2.65-2.72 (m, 2H), 3.53-3.65 (m, 1H), 3.83-3.90 (m, 1H), 6.59 (s, 1H), 6.76 (s, 1H), 9.15 (s, 1H). APCI (*m/z*): 397.35 $(M-H)^-$.

Example 24

N-[5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl]-*N*-methylacetamide

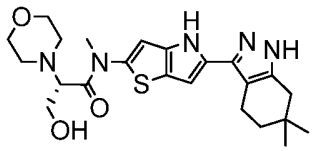


Step 1: *tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-2-(*N*-methylacetamido)-4*H*-thieno[3,2-b]pyrrole-4-carboxylate: The title intermediate was prepared by Suzuki coupling reaction of (4-(*tert*-butoxycarbonyl)-2-(*N*-methylacetamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid (3.0 g, 8.870 mmol) with *tert*-Butyl 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole-1-carboxylate (4.03 g, 10.73 mmol) using tetrakis(triphenylphosphine)palladium (512 mg, 0.443 mmol) in presence of aqueous solution of potassium carbonate (2.0 M, 11.3 ml) in dry tetrahydrofuran (56 ml) as described in step 1 of example 4 to afford 390 mg of product as a dark brown semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (s, 6H), 1.47 (s, 9H), 1.40-1.50 (m, 2H), 1.64 (m, 9H), 1.97-2.38 (m, 5H), 2.76 (s, 2H), 3.37 (s, 3H), 6.65 (s, 1H), 7.26 (s, 1H). APCI (m/z) 541.74 $(M-H)^-$.

Step 2: *N*-[5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl]-*N*-methylacetamide: To a stirred solution of step 1 intermediate (380 mg) in 0.62 M solution of tetrahydrofuran (1.7 ml) and 0.41M solution of methanol (1.1 ml), aqueous solution of sodium hydroxide (2N, 1.4 ml) was added at 0 °C and stirred at room temperature for 2h. The reaction mixture was evaporated under reduced pressure, acidified with 1N Hall and extracted with ethyl acetate (50 ml x 3). The combined organic layer washed with water and dried over Na_2SO_4. The reaction mixture was concentrated under reduced pressure and residue obtained was purified by column chromatography to yield 70 mg of product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98 (s, 6H), 1.40-1.48 (m, 2H), 1.50-1.60 (m, 3H), 2.37 (s, 2H), 2.54-2.64 (m, 2H), 3.20 (s, 3H), 6.51 (s, 1H), 6.92 (s, 1H), 11.47 (br, s, 1H), 12.35 (br, s, 1H). APCI (m/z) 343.42 $(M+H)^+$.

Example 25

(*S*)-*N*-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-3-hydroxy-*N*-methyl-2-morpholinopropanamide



The title compound was prepared by (*S*)-(4-(tert-butoxycarbonyl)-2-(3-hydroxy-*N*-methyl-2-morpholinopropanamido)-4*H*-thieno[3,2-b]pyrrol-5-yl)boronic acid with *tert*-Butyl 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole-1-carboxylate using tetrakis (triphenylphosphine) palladium in presence of aqueous solution of potassium carbonate in tetrahydrofuran as described in step 1 of example 4. The obtained intermediate further treated with aqueous sodium hydroxide to obtain the desired product.

Pharmacological Activity

In-vitro ITK inhibition assay of compounds of the invention:

The compounds of the present invention were evaluated as inhibitors of human recombinant ITK using TR-FRET (time resolved fluorescence resonance energy transfer) based LANCE (Lanthanide chelate excite) *Ultra* assay.

LANCE *Ultra* Assay Principle: The phosphorylation of an U*Light* peptide substrate is detected with a specific anti phospho- peptide antibody (Ab) labeled with europium chelate molecules (Eu). The binding of the Eu-antibody to the phosphorylated U*Light* peptide substrate brings both the donor and acceptor dye molecules into close proximity.

Upon irradiation at 320 nm or 340 nm, the excited europium chelate donor dye transfers its energy to the nearby U*Light* acceptor dye molecule that will in turn emit light at 665 nm.

The intensity of light emission is proportional to the level of the U*Light* peptide phosphorylation.

The ITK assay utilized recombinant human ITK fused with GST (Glutathione *S*-transferase). The assay was carried out in the 384 well white optiplates on the automated robotic system. 2.5 µl of test compounds (or controls at final 1% DMSO concentration) were added to 384 well plate, followed by 2.5 µl of ITK enzyme in the kinase assay buffer and the reaction was started by adding 5 µl of ATP / peptide substrate mix in the kinase assay buffer. The kinase assay components contained 50 mM Hepes pH 7.5, 5 mM $MgCl_2$ (Magnesium Chloride), 1 mM EGTA (Ethylene glycol tetraacetic acid), 2 mM DTT (Dithiothreitol), 0.01% Tween 20, 0.75 nM ITK enzyme, 100 nM U*light*-PolyGT substrate and 3 µM ATP (Adenosine-5'-triphosphate) in 10 µl volume. Incubation was carried out at 23°C for 15 minutes on the shaker. The assay was stopped by adding EDTA (Ethylenediaminetetraacetic

acid). This was followed by the addition of detection reagent Europium anti-phospho-substrate antibody. The fluorescence was measured at 665/620 nm on htrf reader (Homogenous time resolved fluorescence) after incubation for 1 hour at RT. IC_{50} values were calculated from non-linear regression analysis of the initial rate data using the GraphpadPrism software.

The compounds of present invention were tested using the above assay procedure and the results obtained are given in Table 4. Percentage inhibition of ITK enzyme at compound concentrations of 1.0 µM and 10.0 µM is given in the table 4.

The IC_{50} (nM) values of the compounds are set forth in table 4 wherein "A" refers to an IC_{50} value of less than 10 nM, "B" refers to IC_{50} value in range of 10.01 to 50 nM, "C" refers to an IC_{50} value in range of 50.01 to 100 nM and "D" refers to an IC_{50} value more than 100.01 nM.

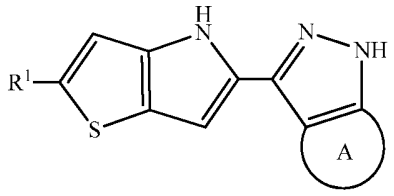
Table 4: Result of the *In-vitro* screening of compounds of present invention.

Example No.	% inhibition of ITK at (Concentration)		IC_{50} (nM)
	1.0 µM	10.0 µM	
1	83.46	81.17	B
2	84.63	92.03	B
4	87.99	89.70	A
6	85.98	87.46	A
7	85.55	87.54	B
8	87.01	88.25	B
9	88.01	91.39	A
10	89.88	90.98	A
11	77.97	86.17	C
12	89.32	88.19	A
13	87.80	89.57	A
14	88.56	90.06	A
15	91.42	91.90	A
16	81.32	86.72	B
17	87.13	91.00	A
18	89.52	91.71	A
19	80.48	89.94	C
20	79.91	88.30	C
21	84.98	88.90	B

Example No.	% inhibition of ITK at (Concentration)		IC_{50} (nM)
	1.0 μM	10.0 μM	
22	67.63	85.17	D
23	71.62	89.40	D

Claims:

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof,

wherein,

R^1 is selected from $-C(O)NR^aR^b$, $-NR^aC(O)R^b$ and $-(CH_2)_nNR^aR^b$;

ring 'A' is C_{3-12}cycloalkyl, C_{6-14}aryl or 5- to 14- membered heteroaryl each optionally substituted with one or more substituents independently selected from C_{1-8}alkyl, C_{1-8}alkoxy, 5- to 14- membered heteroaryl and $-NHC(O)R^c$;

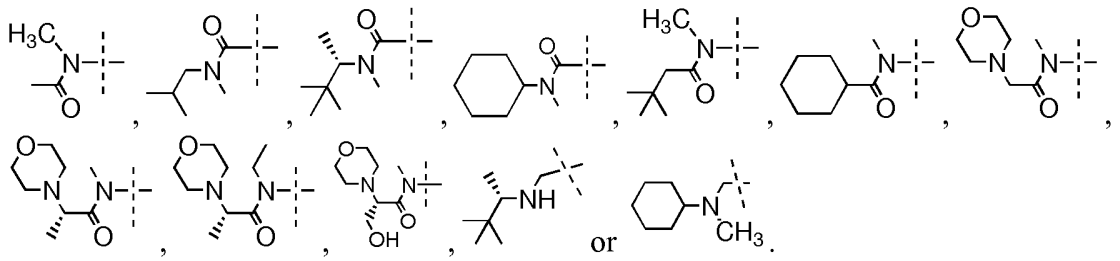
at each occurrence, R^a is independently selected from hydrogen and C_{1-8}alkyl;

at each occurrence, R^b is independently selected from hydrogen, C_{1-8}alkyl, C_{3-12}cycloalkyl and 3- to 15- membered heterocyclylC_{1-8}alkyl;

R^c is C_{1-8}alkyl; and

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

2. The compound according to claim 1, wherein R^1 is



or

3. The compound according to claim 1 or 2, wherein ring 'A' is cyclohexyl.

4. The compound according to claim 1 to 3, wherein ring 'A' is cyclohexyl substituted with one or more methyl.

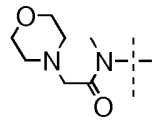
5. The compound according to claim 1 or 2, wherein ring 'A' is phenyl.

6. The compound according to claim 1 or 2, wherein ring 'A' is phenyl substituted with one or more substituents independently selected from methoxy, 1*H*-pyrazol-4-yl, 1-methyl-1*H*-pyrazol-4-yl or pyridin-4-yl) and $-NHC(O)CH_2CH_3$.

7. The compound according to claim 1 or 2, wherein ring 'A' is pyridinyl.

8. The compound according to claim 1, wherein

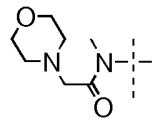
R^1 is



and ring 'A' is cyclohexyl substituted with one or more methyl.

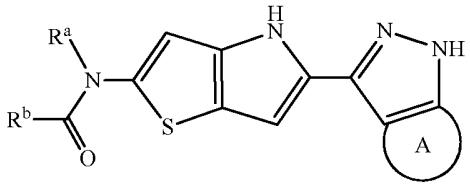
9. The compound according to claim 1, wherein

R^1 is



and ring 'A' is cyclohexyl.

10. A compound of formula (Ia)



(Ia)

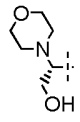
or a pharmaceutically acceptable salt thereof,

wherein,

ring 'A' is cyclohexyl optionally substituted with one or more methyl; phenyl optionally substituted with one or more substituents independently selected from methoxy, 1*H*-pyrazol-4-yl, 1-methyl-1*H*-pyrazol-4-yl, pyridine-4-yl and $-NHC(O)CH_2CH_3$ or pyridinyl;

R^a is selected from hydrogen, methyl and ethyl; and

R^b is selected from methyl, 2,2-dimethyl-1-propyl, cyclohexyl, morpholinylmethyl, morpholinylethyl and



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11. A compound selected from

5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-*N*-isobutyl-*N*-methyl-4*H*-thieno[3,2-b]pyrrole-2-carboxamide;

(*S*)-5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-*N*-(3,3-dimethylbutan-2-yl)-*N*-methyl-4*H*-thieno[3,2-*b*]pyrrole-2-carboxamide;

N-Cyclohexyl-5-(6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-*N*-methyl-4*H*-thieno[3,2-b]pyrrole-2-carboxamide;

N-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinoacetamide;

N-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinoacetamide hydrochloride;

N-(5-(6-(1*H*-Pyrazol-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinoacetamide;

N-(5-(6-Methoxy-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinoacetamide;

N-Methyl-2-morpholino-*N*-(5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)acetamide;

N-Methyl-2-morpholino-*N*-(5-(6-(pyridin-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)acetamide;

(*S*)-*N*-(5-(6-Methoxy-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinopropanamide;

(*S*)-*N*-Methyl-2-morpholino-*N*-(5-(6-propionamido-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)propanamide;

(*S*)-*N*-Methyl-*N*-(5-(6-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-2-morpholinopropanamide;

(*S*)-*N*-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinopropanamide;

(*S*)-*N*-(5-(6-(1*H*-Pyrazol-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinopropanamide;

(*S*)-*N*-(5-(1*H*-Indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinopropanamide;

(*S*)-*N*-(5-(1*H*-Pyrazolo[3,4-*b*]pyridin-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methyl-2-morpholinopropanamide;

(*S*)-*N*-Methyl-2-morpholino-*N*-(5-(6-(pyridin-4-yl)-1*H*-indazol-3-yl)-4*H*-thieno[3,2-*b*]pyrrol-2-yl)propanamide;

N-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-ethyl-2-morpholinoacetamide;

N-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*,3,3-trimethylbutanamide;

N-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-*N*-methylcyclohexanecarboxamide;

N-((5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)methyl)-*N*-methylcyclohexanamine;

(*S*)-*N*-((5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)methyl)-3,3-dimethylbutan-2-amine;

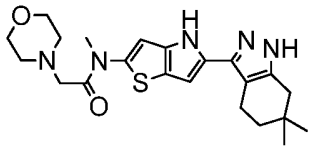
(*S*)-*N*-((5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)methyl)-*N*,3,3-trimethylbutan-2-amine;

N-[5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl]-*N*-methylacetamide;

(*S*)-*N*-(5-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-thieno[3,2-b]pyrrol-2-yl)-3-hydroxy-*N*-methyl-2-morpholinopropanamide

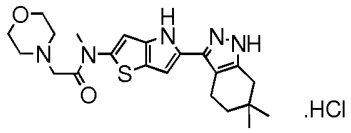
or a pharmaceutically acceptable salt thereof.

12. A compound of formula



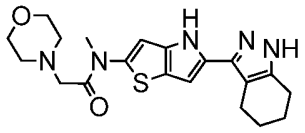
or a pharmaceutically acceptable salt thereof.

13. A compound of formula



.HCl

14. A compound of formula



or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 14 and a pharmaceutically acceptable excipient.

16. The pharmaceutical composition according to claim 15, wherein the pharmaceutically acceptable excipient is a carrier or diluent.

17. A method of treating ITK mediated disease, disorder or syndrome in a subject comprising administering an effective amount of a compound according to any one of claims 1 to 14.

18. A method of treatment of disorder or disease selected from the group consisting of respiratory disease, an allergic disease, an autoimmune disease, an inflammatory disorder, a proliferative disorder, diabetes, transplant rejection, graft versus host disease, HIV, aplastic anemia, and pain comprising administering an effective amount of a compound according to any one of claims 1 to 14.

19. A method of treatment of disorder or disease selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), bronchitis, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, multiple sclerosis, psoriasis, type I diabetes, type II diabetes, T cell mediated hypersensitivity, Guillain-Barre Syndrome, Hashimoto's thyroiditis, cancer, transplant rejection, graft versus host disease, conjunctivitis, contact dermatitis, inflammatory bowel disease, chronic inflammation, HIV, aplastic anemia, and inflammatory pain comprising administering an effective amount of a compound according to any one of claims 1 to 14.

20. A method according to claim 19, wherein the disorder or disease is asthma or chronic obstructive pulmonary disease (COPD).

21. A method according to claim 19, wherein the disorder or disease is allergic rhinitis.

22. A method according to claim 19, wherein the disorder or disease is atopic dermatitis.

23. A method according to claim 19, wherein the disorder or disease is rheumatoid arthritis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2013/058538

A. CLASSIFICATION OF SUBJECT MATTER

See the extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D 495/-, A61K 31/-, A61P 11/-, A61P 19/-, A61P 35/-, A61P 37/-

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

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

WPI, EPODOC, CNPAT, CNKI, CA, ISI Web of Knowledge, Registry, interleukin, ITK, kinase, thieno, pyrro+

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/076228 A2 (BOEHRINGER INGELHEIM INTERNATIONAL GMBH), 05 July 2007 (05.07.2007) see the whole document	1-23
A	WO 2005/026175 A1 (AVENTIS PHARMACEUTICALS INC.), 24 March 2005 (24.03.2005) see the whole document	1-23
A	WO 03/024969 A1 (MERCK & CO., INC.), 27 March 2003 (27.03.2003) see the whole document	1-23
A	WO 01/53268 A2 (AGOURON PHARMACEUTICALS, INC.), 26 July 2001 (26.07.2001) see the whole document	1-23

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 December 2013 (12.12.2013)	**06 Feb. 2014 (06.02.2014)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer DAI, Nianzhen Telephone No. (86-10)82245540

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2013/058538

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17-23
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 17-23 are directed to methods of treatment of the human/animal body, and the search is based on the use of the claimed compound for manufacturing medicaments for treating the alleged diseases.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2013/058538

Continuation of **A. CLASSIFICATION OF SUBJECT MATTER**

C07D 495/04 (2006.01) i

A61K 31/407 (2006.01) i

A61P 11/08 (2006.01) i

A61P 19/02 (2006.01) i

A61P 35/00 (2006.01) i

A61P 37/02 (2006.01) i

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2013/058538

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2013/058538

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2013/058538

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
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		IN 202735 B	13.04.2007
		WO 0153268 A3	27.12.2001