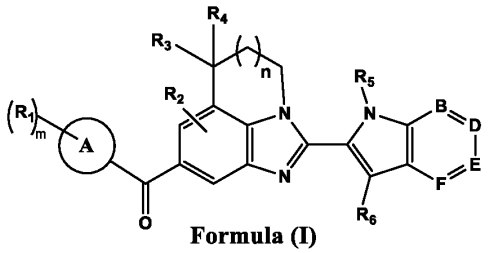
POLYHETEROCYCLIC COMPOUNDS AS PEPTIDYL ARGININE DEIMINASE 4 (PAD4) INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefits of the Indian provisional patent application number 202411015473, filed on 01 March 2024; the specifications of which are hereby incorporated by reference in their entirely and for all purposes.

FIELD OF THE INVENTION

The present disclosure relates to heterocyclic compounds and in particular relates to polyheterocyclic compounds of Formula (I). The compounds of the present disclosure are Peptidyl Arginine Deiminase 4 (PAD4) inhibitors. The present disclosure also relates to process of preparing the compounds of Formula (I).



Formula (I)

The compounds of the present disclosure are useful in treating and/or preventing diseases and disorders mediated by PAD4 such as rheumatoid arthritis, vasculitis, systemic lupus erythematosus, cutaneous lupus erythematosus, ulcerative colitis, cystic fibrosis, asthma, multiple sclerosis, atopic dermatitis, and psoriasis. The compounds of the present disclosure are also useful in treating and/or preventing diseases and disorders mediated by PAD4 such as cancer, cancer metastasis, immune disorder, inflammatory disorder, and transplant rejection.

BACKGROUND OF THE INVENTION

Post-translational modifications (PTM) play a major role in the integrity of proteins, the activity of enzymes, and the expression of genes. This PTM are carried out through phosphorylation, acetylation, methylation, and citrullination. Protein arginine deiminase (PAD) consists of a unique family of calcium-dependent enzymes that catalyzes the hydrolysis of peptidyl-arginine on physiologically significant proteins to peptidyl-citrulline. (Nava-Quiroz, K.J *et al,* Cells 2023, *12*, 2829). The PAD family consists of five enzymes: PAD1, PAD2, PAD3, PAD4, and PAD6. Each has its own tissue distribution and functional activities

which regulate many physiological and pathological process including cellular differentiation, gene regulation, inflammation, and embryonic development. (Horibata S, *et al*, J Reprod Dev. 2012;58(3):274-82). The dysregulation of these enzymes has been implicated in various ailments, for example, cell differentiation (K. Nakashima *et al.,* J. Biol. Chem., 1999, 274, 27786-27792), stem cell pluripotency (M. A. Christophorou *et al.*, Nature, 2014, 507, 104-108), apoptosis (G. Y. Liu, Apoptosis, 2006, 11, 183-196), neutrophil extracellular trap (NET) formation (Y. Wang *et al.*, J. Cell Biol., 2009, 184, 205-213), transcriptional regulation (P. Li *et al.*, Mol. Cell Biol., 2008, 28, 4745-4758), antigen processing in autophagy (J. M. Ireland *et al.,* J. Exp. Med., 2011, 208, 2625-2632), inflammation (D. Makrygiannakis *et al.*, Ann. Rheum. Dis., 2006, 65, 1219-1222), the cornification of skin (E. Candi *et al.*, Nat. Rev. Mol. Cell Biol., 2005, 6, 328-340), demyelination in multiple sclerosis (F. G. Mastronardi *et al.*, J. Neurosci., 2006, 26, 11387-11396), chemokine regulation (T. Loos *et al.*, Blood, 2008, 112, 2648-2656), spinal cord injury repair (S. Lange *et al.*, Dev. Biol., 2011, 355, 205-214), and various normal cellular processes. Neutrophils are known to be recruited to the sites of infection where they kill numerous pathogens such as bacteria, fungi, and viruses by oxidative burst and phagocytosis (Schonrich *et al.,* Front. Immunol., 2016, 7, 1-7). However, neutrophils have another mechanism of removing pathogens through the production of NETs (Brinkmann *et al.,* Science., 2004, 303 (5663), 1532-1535).

Protein arginine deiminases (PADs) catalyses the citrullination process and this process either activates or repress gene transcription. The process of citrullination is catalyzed by the peptidyl arginine deiminases, a family of enzymes that is dependent on calcium (Ca2+) and is caused by closely related PADs which are PAD1, PAD2, PAD3, PAD4 and PAD6. The citrullination or hypercitrullination affects various physiological and pathological processes (Nat Chem Biol. 2015 March; 11(3): 189–191).

PADs especially PAD4 are expressed in granulocytes and is strongly linked to diverse diseases. In rheumatoid arthritis antibodies against PADs occurs at the advanced stage of the disease. Increased PAD activities are observed in numerous diseases such as cancer, asthma, vasculitis, colitis, ulcerative colitis, multiple sclerosis, lupus, Parkinson's disease, and Alzheimer's disease (Biopolymers. 2013 Feb; 99(2): 155–163).

PAD4 and PAD2 enzymes are more strongly associated. PAD2 are observed in skeletal muscle, brain, spleen, secretory glands and pancreas, spinal cord, kidney, schwann cells, uterus and ovaries macrophages, neutrophils, T cells, oligodendrocytes, whereas, PAD4 are seen in granulocytes such as eosinophils and neutrophils, monocytes, T cells, and in oligodendrocytes.

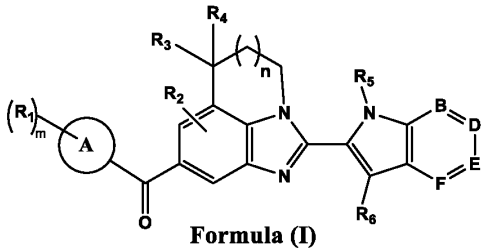
Therefore, inhibition of PADs is essential in treating diseases affecting the said organs or cells, which in turn treats related diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, cancer, Alzheimer's, and prion's diseases. Also, PAD1 enzymes are expressed in Epidermis and uterus, hair follicles and inhibition of PAD1 will facilitate the treatment and prevention of skin related diseases such as psoriasis (Nature Reviews Rheumatology, 16(6), 301–315). Further, it has been identified that PAD2 and PAD4 have been linked to tumor progression. PADs inactivate antithrombin and inhibition of antithrombin promotes angiogenesis, increased tumor growth, and distant metastasis (Rheumatology, Volume 44, Issue 3, March 2005, Pages 293–298).

PADs were also found to be involved in inflammatory reactions and neutrophil extracellular trap (NET) formation under different pathological conditions. PAD4 plays an important enzymatic role in increasing chromatin decondensation and neutrophil extracellular trap (NET) production, which is associated with a variety of immune-mediated ailments. Specifically, inhibition of PAD4 alleviates arthritis via reducing the development of neutrophil extracellular traps (NETs) (Gajendran C, *et al.*, Sci Rep. 2023 Feb 23;13(1):3189) and decreased remote lung injury by decreasing NET formation, apoptosis, and inflammatory factor secretion. Acute kidney injury, lung injury, renal ischemia reperfusion injury can be treated by inhibition of PAD (*Mediators Inflamm.* 2020; 2020: 1724206).

From the above, it is evident that PAD4 inhibition is a viable strategy for the treatment of numerous diseases. The use of PAD4 inhibitors in various diseases where dysregulated PAD4 activity is implicated needs to be explored. Overexpression of PAD4 can significantly be a root cause for wide spectrum of diseases and thus, the PAD4 inhibition can largely treat and prevent the severity of these diseases. Although a definitive role for dysregulated PAD4 activity in these diseases has not been established, a direct link is plausible. Therefore, there remains a need to develop compounds that are effective PAD4 inhibitors, which can efficiently exhibit therapeutic properties in treating and preventing the severity of diseases mediated by PAD4.

SUMMARY OF THE INVENTION

In an aspect of the present disclosure, there is provided a compound of Formula (I) as described herein,



Formula (I)

or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof; wherein, B is selected from N or CR_7; D is selected from N or CR_8; E is selected from N or CR_9; F is selected from N or CR_{10}; Ring A is selected from 5-12 membered monocyclic, bicyclic or tricyclic heterocyclyl with 1-3 heteroatoms selected from N, S or O; R_1 at each occurrence is independently selected from alkyl, alkoxy, alkylamino, acylamino, cycloalkyl, halogen, haloalkyl, hydroxy, $-NR_aR_b$, $-NHC(NH)CH_2Cl$, or $-NH(CO)CH=CH-CH_2-N(CH_3)_2$; R_2 is selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, haloalkyl or hydroxy; R_3 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl or heteroaryl; R_4 is selected from the group consisting of $-NR_cR_d$, $-O-(CO)-NR_cR_d$, $-NR_c(CO)-R_d$, $-NR_c(SO)_2-R_d$, $-NR_c-(CO)-O-R_e$, or $-OR_e$; alternatively, R_3 and R_4 on the same carbon atom together form an oxo (=O), =N-OR_e, or =N-NR_cR_d group; R_5 is selected from the group consisting of hydrogen, alkyl, haloalkyl, alkoxy, cycloalkyl, aryl or heteroaryl; wherein, alkyl, alkoxy, cycloalkyl, aryl, and heteroaryl, is optionally substituted with one or more groups selected from alkyl, alkoxy, cycloalkyl, aryl, heteroaryl, halogen, hydroxy or cyano; R_6 is selected from the group consisting of hydrogen, hydroxy, cyano, halogen, alkyl, alkoxy, haloalkyl, haloalkoxy, acylamino, alkylamino, aryl or heteroaryl; R_7, R_8, R_9 and R_{10} are independently selected from the group consisting of hydrogen, hydroxy, cyano, halogen, alkyl, alkoxy, haloalkyl, haloalkoxy, acylamino, alkylamino, aryl or heterocyclyl; wherein, aryl and heterocyclyl, is optionally substituted with one or more of the groups selected from alkyl, alkoxy, haloalkyl, alkylhydroxy, cyano, hydroxy or COR_{11}; R_{11} is selected from the group consisting of alkyl, hydroxy or cycloalkyl; wherein, alkyl and cycloalkyl is optionally substituted with one or more groups selected from alkyl, alkoxy, cycloalkyl or hydroxy; R_a, R_b, R_c, R_d and R_e are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl or heteroaryl; m is selected from 0-4; and n is selected from 0-2.

In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound of Formula (I) as described herein, or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof and at least one pharmaceutically acceptable carrier.

In one another aspect of the present disclosure, there is provided a method for inhibiting PAD4 in a cell with an effective amount of a compound of Formula (I) as described herein, or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof.

In one more aspect of the present disclosure, there is provided a method of treating and/or preventing a disease or disorder mediated by PAD4, the method comprising administering to a subject suffering from a disease or disorder mediated by PAD4, a therapeutically effective amount of a compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof or the pharmaceutical composition as described herein.

In further aspect of the present disclosure, there is provided a compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof as described herein, for use in the treatment of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cystic fibrosis, asthma, atopic dermatitis, cutaneous lupus erythematosus, or psoriasis.

In one more aspect of the present disclosure, there is provided a method for the treatment and/or prevention of a disease or disorder mediated by PAD4, comprising administering to a subject suffering from the disease or disorder mediated by PAD4 a therapeutically effective amount of a compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof, or the pharmaceutical composition as described herein.

In another aspect of the present disclosure, there is provided a method for the treatment of rheumatoid arthritis, said method comprising administering a combination of the compounds of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof or the pharmaceutical composition as described herein, with other clinically relevant cytotoxic agents or non-cytotoxic agents to a subject in need thereof.

In one more aspect of the present disclosure, there is provided a method of treatment and/or prevention of cancer, said method comprising administering a combination of the compounds of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof, or the pharmaceutical composition as described herein, with other clinically relevant immune modulator agents or anti-inflammatory agents to a subject in need of thereof.

These and other features, aspects and advantages of the present subject matter will become better understood with reference to the following description. This summary is provided to introduce a selection of concepts in a simplified form. This summary is not intended to identify key features or essential features of the disclosure, nor is it intended to be used to limit the scope of the subject matter.

DESCRIPTION

Those skilled in the art will be aware that the present disclosure is subject to variations and modifications other than those specifically described. It is to be understood that the present disclosure includes all such variations and modifications. The disclosure also includes all such steps, features, compositions, and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any or more of such steps or features.

Definitions

For convenience, before further description of the present disclosure, certain terms employed in the specification, and examples are collected here. These definitions should be read in the light of the remainder of the disclosure and understood as by a person of skill in the art. The terms used herein have the meanings recognized and known to those of skill in the art, however, for convenience and completeness, particular terms and their meanings are set forth below.

The term "compound(s)" comprises the compounds disclosed in the present disclosure.

The articles “a”, “an” and “the” are used to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article.

Throughout the description and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

The term “including” is used to mean “including but not limited to”. “including” and “including but not limited to” are used interchangeably.

In the structural formulae given herein and throughout the present disclosure, the following terms have been indicated meaning, unless specifically stated otherwise.

Furthermore, the compound of Formula (I) can be its derivatives, analogs, stereoisomer's, diastereomers, geometrical isomers, polymorphs, solvates, co-crystals, intermediates, metabolites, prodrugs or pharmaceutically acceptable salts and compositions.

The compounds according to Formula (I) contain one or more asymmetric centres (also referred to as a chiral centres) and may, therefore, exist as individual enantiomers, diastereoisomers or other stereoisomeric forms, or as mixtures thereof. All such single stereoisomers, and mixtures thereof are intended to be within the scope of the subject matter described. Chiral centres, such as chiral carbon atoms, may also be present in a substituent such as an alkyl group. Where the stereochemistry of a chiral centre present in Formula (I) or in any chemical structure illustrated herein, is not specified, the structure is intended to encompass any stereoisomer and all mixtures thereof. Thus, compounds according to Formula (I) containing one or more chiral centres may be used as racemic modifications including racemic mixtures and racemates, enantiomerically-enriched mixtures, or as enantiomerically-pure individual stereoisomers.

Individual stereoisomers of a compound according to Formula (I), which contain one or more asymmetric centres may be resolved by methods known to those skilled in the art. For example, such resolution may be carried out (1) by formation of diastereoisomeric salts, complexes, or other derivatives; (2) by selective reaction with a stereoisomer-specific reagent, for example by enzymatic oxidation or reduction; or (3) by gas-liquid or liquid chromatography in a chiral environment, for example, on a chiral support such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired stereoisomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired form.

Alternatively, specific stereoisomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts, or solvents, or by converting one enantiomer to the other by asymmetric transformation.

It is to be understood that the references herein to compounds of Formula (I) and salts thereof covers the compounds of Formula (I) as free bases, or as salts thereof, for example as pharmaceutically acceptable salts thereof. Thus, in one embodiment, the disclosure is directed to compounds of Formula (I) as the free base. In another embodiment, the disclosure is directed to compounds of Formula (I) and salts thereof. In a further embodiment, the disclosure is directed to compounds of Formula (I) and pharmaceutically acceptable salts thereof.

It will be appreciated that pharmaceutically acceptable salts of the compounds according to Formula (I) may be prepared. Indeed, in certain embodiments of the disclosure, pharmaceutically acceptable salts of the compounds according to Formula (I), may be preferred over the respective free base because such salts impart greater stability or solubility to the molecule thereby facilitating formulation into a dosage form. Accordingly, the disclosure is further directed to compounds of Formula (I) and pharmaceutically acceptable salts thereof.

The compounds of the present disclosure shall also exist as tautomers, wherein the one or more forms of the compounds of Formula (I) shall exist in equilibrium and are in interchangeable by migration of an atom or group within the compound. Tautomers are structural isomers wherein more frequently there is transfer of protons from one group to another within the compound.

"Enantiomeric excess" (ee) is the excess of one enantiomer over the other expressed as a percentage. In a racemic modification, since both enantiomers are present in equal amounts, the enantiomeric excess is zero (0% ee). However, if one enantiomer was enriched such that it constitutes 95% of the product, then the enantiomeric excess would be 90% ee (the amount of the enriched enantiomer, 95%, minus the amount of the other enantiomer, 5%).

Included within the scope of the 'compounds of the disclosure' are all solvates (including hydrates), complexes, polymorphs, prodrugs, radiolabeled derivatives, and stereoisomers of the compounds of Formula (I), and salts thereof.

The compounds of the disclosure may exist in solid or liquid form. In the solid state, the compounds of the disclosure may exist in crystalline or non-crystalline form, or as a mixture thereof. For compounds of the disclosure that are in crystalline form, the skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed wherein solvent molecules are incorporated into the crystalline lattice during crystallization. Solvates may involve non-aqueous solvents such as ethanol, iso-propyl alcohol, N, N- dimethylsulfoxide (DMSO), acetic acid, ethanolamine, and EtOAc, or they may involve water as the solvent that is incorporated into the crystalline lattice. Solvates wherein water is the solvent that is incorporated into the crystalline lattice are typically referred to as 'hydrates'. Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water. The disclosure includes all such solvates.

It will be further appreciated that certain compounds of the disclosure that exist in crystalline form, including the various solvates thereof, may exhibit polymorphism (i.e. the capacity to occur in different crystalline structures). These different crystalline forms are

typically known as 'polymorphs'. The disclosure includes such polymorphs. Polymorphs have the same chemical composition but differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state. Polymorphs, therefore, may have different physical properties such as shape, density, hardness, deformability, stability, and dissolution properties. Polymorphs typically exhibit different melting points, IR spectra, and X-ray powder diffraction patterns, which may be used for identification. It will be appreciated that different polymorphs may be produced, for example, by changing or adjusting the reaction conditions or reagents, used in making the compound. For example, changes in temperature, pressure, or solvent may result in polymorphs. In addition, one polymorph may spontaneously convert to another polymorph under certain conditions.

The disclosure also includes isotopically-labelled compounds, which are identical to the compounds of Formula (I) and salts thereof, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Examples of isotopes that can be incorporated into the compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, and fluorine, such as ^{3}H, ^{11}C, ^{14}C and ^{18}F.

The term “substituted” in reference to a group indicates that a hydrogen atom attached to a member atom within a group is replaced. It should be understood that the term 'substituted' includes the implicit provision that such substitution be in accordance with the permitted valence of the substituted atom and the substituent and that the substitution results in a stable compound (i.e. one that does not spontaneously undergo transformation such as rearrangement, cyclisation, or elimination). In certain embodiments, a single atom may be substituted with more than one substituent as long as such substitution is in accordance with the permitted valence of the atom. Suitable substituents are defined herein for each substituted or optionally substituted group.

The present disclosure discloses “intermediates” of the compounds of the Formula (I), wherein the intermediate compounds are prepared to obtain the compounds of Formula (I). The intermediate are compounds which have the same core structure as the compound of Formula (I) as disclosed herein. The intermediates are useful in obtaining the compounds of the present disclosure and possess similar physical and chemical properties as that of the compounds of Formula (I).

The term “alkyl” refers to a saturated hydrocarbon chain having the specified number of carbon atoms. For example, which are not limited, $C_{1\text{-}10}$ alkyl refers to an alkyl group having

from 1 – 10 carbon atoms or C_{1-6} alkyl refers to an alkyl group having from 1 – 6 carbon atoms. Alkyl groups may be straight or branched chained groups. Representative branched alkyl groups have one, two, or three branches. Preferred alkyl groups include, without limitation, methyl, ethyl, n-propyl, isopropyl, butyl, and isobutyl. The alkyl groups may be optionally substituted.

The term "C(O) alkyl" or "acyl" refers to an alkyl group as defined above attached via carbonyl linkage to the rest of the molecule. For example, $C(O)C_{1-6}$ alkyl refers to an alkyl group having from 1 – 6 carbon atoms attached via carbonyl linkage to the rest of the molecule. Preferred C(O) alkyl groups include, without limitation, $-C(O)CH_3$, $-C(O)CH_2CH_3$, and the like. The C(O) alkyl group may be optionally substituted.

The term "alkoxy" refers to an alkyl group attached via an oxygen linkage to the rest of the molecule. For example, C_{1-6} alkoxy refers to an alkyl group having from 1 – 6 carbon atoms attached via an oxygen linkage to the rest of the molecule. Preferred alkoxy groups include, without limitation, $–OCH_3$ (methoxy), $–OC_2H_5$ (ethoxy) and the like. The alkoxy group is optionally substituted.

The term "alkylamino" refers to an alkyl group as defined above attached via amino linkage to the rest of the molecule. For example, C_{1-6} alkylamino refers to an alkyl group having from 1 – 6 carbon atoms attached via amino linkage to the rest of the molecule. Preferred alkylamino groups include, without limitation, $-NHCH_3$, $-N(CH_3)_2$, and the like. The alkylamino group is optionally substituted.

The term "acylamino" refers to an acyl group as defined above attached via amino linkage to the rest of the molecule. For example, C_{1-6} acylamino refers to an acyl group having from 1 – 6 carbon atoms attached via amino linkage to the rest of the molecule. Preferred acylamino groups include, without limitation, $-NHCOCH_3$, $-NHCOC_2H_5$, and the like. The acylamino group is optionally substituted.

The term "haloalkyl" refers to an alkyl group as defined above wherein at least one hydrogen of the alkyl group is replaced with halogen atom. For example, C_{1-6} haloalkyl refers to an alkyl group having from 1 – 6 carbon atoms having one or more same or different halogen atoms. Preferred haloalkyl groups include, without limitation, $-CH_2Cl$, $-CHCl_2$, $-CH_2CH_2Cl$, and the like. The haloalkyl may be optionally substituted.

The term "alkylhydroxy" refers to an alkyl group as defined above wherein at least one hydrogen of the alkyl group is replaced with hydroxy group. For example, C_{1-6}

alkylhydroxy refers to an alkyl group having from 1 – 6 carbon atoms having one or more hydroxy groups. The alkylhydroxy may be optionally substituted.

The term "haloalkoxy" refers to an alkoxy group as defined above wherein at least one hydrogen of the alkoxy group is replaced with halogen atom. For example, C_{1-6} haloalkoxy refers to an alkoxy group having from 1 – 6 carbon atoms having one or more same or different halogen atoms. The haloalkoxy may be optionally substituted.

The term "amino" refers to -NH_2 group.

The term "cyano" refers to -CN group.

The term "halo" or "halogen" refers to a halogen radical, for example, fluoro, chloro, bromo or iodo.

The term "hydroxy/hydroxyl" refers to –OH group.

The term "oxo" refers to =O group.

The term "heteroatom" as used herein designates a sulfur, nitrogen or oxygen atom.

The term "cycloalkyl" refers to a saturated hydrocarbon ring having a specified number of carbon atoms. For example, C_{3-8} cycloalkyl refers to a cycloalkyl group having from 3 to 8 member atoms. Preferred cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, groups and the like. The cycloalkyl group can be optionally substituted.

The term "aryl" refers to aromatic ring having a specified number of carbon atoms. For example, C_{6-12} aryl refers to an aryl group having 6 to 12 members atoms. Preferred aryl groups include, without limitation, C_6 aryl such as phenyl. 6-12 membered monocyclic or bicyclic aryl refers to the aryl group having 6 to 12 carbon atoms which could be monocyclic or polycyclic. The polycyclic or bicyclic aryl group can be of fused, bridged, or spiral structures. The aryl group can be optionally substituted.

The term "heteroaryl" refers to aromatic rings containing from 1 to 5 heteroatoms in the ring. "Heteroaryl" groups may be substituted with one or one or more substituents if so, defined herein. The "C_{1-6} heteroaryl" rings having 1 to 6 carbon as member atoms. The "heteroaryl" includes pyridinyl, tetrazolyl and pyrazolyl. "Heteroatom" refers to a nitrogen, sulfur, or oxygen atom, for example a nitrogen atom or an oxygen atom. The heteroaryl may also be unsaturated, or partially saturated. The heteroaryl group can be monocyclic, polycyclic with 5 to 14 membered rings which may be of fused, bridged, or spiral, structures. The heteroaryl group having 5 to 14 membered rings have 1 to 7 or preferable 1

to 3 heteroatoms selected from N, S, or O. The heteroaryl group may be optionally substituted.

The term "heterocyclyl" refers to a heterocyclic ring radical which may be optionally substituted by one or more substituents. The heterocyclyl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

Furthermore, the term "heterocyclyl" refers to a stable 3 to 20 membered rings radical, which consists of carbon atoms and heteroatoms selected from nitrogen, phosphorus, oxygen, and sulfur. For purposes of this disclosure the heterocyclic ring radical may be monocyclic, bicyclic or tricyclic ring systems, and the nitrogen, phosphorus, carbon, 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; and the ring radical may be partially or fully saturated. Preferred heterocyclyl groups include, without limitation, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazolyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pyridyl, pteridinyl, purinyl, quinazolinyl, qunioxalinyl, quinolinyl, isoquinolinyl, tetrazolyl, thiazinane dioxide, imidazolyl, tetrahydroisoquinolinyl, piperidinyl, piperazinyl, homopiperazinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, triazolyl, indanyl, isoxazolyl, isoxazolidinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzooxazolyl, thienyl, morpholinyl, thiomorpholinyl, thiamorpholinyl sulfoxide, furyl, tetrahydrofuryl, tetrahydropyranyl, chromanyl, and isochromanyl.

The term "heterocyclyl" refers to monocyclic or polycyclic ring, polycyclic ring system refers to a ring system containing 2 or more rings, preferably bicyclic or tricyclic rings, in which rings can be fused, bridged or spiro rings or any combinations thereof. A fused ring as used herein means that the two rings are linked to each other through two adjacent ring atoms common to both rings. The fused ring can contain 1-4 hetero atoms independently selected from N, O, or S. The rings can be either fused by nitrogen or -CH-group.

The phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, and dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. These pharmaceutically acceptable salts may be prepared in situ during the final isolation and purification of the compound, or by separately reacting the purified compound in its free base form with a suitable acid. The pharmaceutically acceptable salt selected derived from inorganic bases such as like Li, Na, K, Ca, Mg, Fe, Cu, Zn and Mn; salts of organic bases such as N, N'-diacetylethylenediamine, glucamine, triethylamine, choline, dicyclohexylamine, benzylamine, trialkylamine, thiamine, guanidine, diethanolamine, α-phenylethylamine, piperidine, morpholine, pyridine, hydroxyethylpyrrolidine, hydroxyethylpiperidine, ammonium, substituted ammonium salts, aluminum salts and the like. Salts also include amino acid salts such as glycine, alanine, cystine, cysteine, lysine, arginine, phenylalanine, and guanidine. Salts may include acid addition salts where appropriate which are sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, trifluoroacetates, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, tosylates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, and ketoglutarates.

Salts and solvates having non-pharmaceutically acceptable counter-ions or associated solvents are within the scope of the present disclosure, for example, for use as intermediates in the preparation of other compounds of Formula (I), and their pharmaceutically acceptable salts. Thus, one embodiment of the disclosure embraces compounds of Formula (I) and salts thereof. Compounds according to Formula (I) contain a basic functional group and are therefore capable of forming pharmaceutically acceptable acid addition salts by treatment with a suitable acid. Suitable acids include pharmaceutically acceptable inorganic acids and pharmaceutically acceptable organic acids. Representative pharmaceutically acceptable acid addition salts include hydrochloride, hydrobromide, nitrate, methylnitrate, sulfate, bisulfate, sulfamate, phosphate, acetate, trifluoroacetate, hydroxyacetate, phenyl acetate, propionate, butyrate, iso-butyrate, valerate, maleate, hydroxymaleate, acrylate,

fumarate, malate, tartrate, citrate, salicylate, glycollate, lactate, heptanoate, phthalate, oxalate, succinate, benzoate, o-acetoxybenzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, naphthoate, hydroxynaphthoate, mandelate, tannate, formate, stearate, ascorbate, palmitate, oleate, pyruvate, pamoate, malonate, laurate, glutarate, glutamate, estolate, methanesulfonate (mesylate), ethanesulfonate (esylate), 2-hydroxyethanesulfonate, benzenesulfonate (besylate), aminobenzenesulfonate, p- toluenesulfonate (tosylate), and naphthalene-2-sulfonate.

The term "PAD inhibitor" or "inhibitor of PAD" as used herein, refers to compounds of Formula (I) which can effectively inhibit PAD enzymes. PAD inhibitors are capable of interacting with neutrophil extracellular traps (NETs) and more specifically in the histone citrullination that occurs during NETosis. Inhibiting PAD enzymatic activity means reducing the ability of PADs enzyme so as to inhibit the formation of citrulline through citrullination process. The inhibition refers to inhibition of PAD1, or PAD2 or PAD3 or PAD4 or PAD6, preferably inhibition of PAD4 enzyme.

Described herein are prodrugs of the compound of Formula (I), which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of a compounds of the present disclosure, which are readily convertible *in vivo* into a compound of present disclosure.

The compounds described herein can also be prepared in any solid or liquid physical form, for example the compound can be in a crystalline form, in amorphous form and have any particle size. Furthermore, the compound particles may be micronized or nanonized, or may be agglomerated, particulate granules, powders, oils, oily suspensions or any other form of solid or liquid physical forms.

The term "cytotoxic agents" or "inhibitors" is used to identify any agents or drugs which are capable of killing cells including cancer cells. These agents or inhibitors may stop cancer cells from growing and dividing and may cause tumors to shrink in size.

The term "non-cytotoxic agents" or "inhibitors" is used to identify any agents or inhibitors are which does not directly kill cells, but instead affects cellular transport and metabolic functions to ultimately produce cell death.

The term "immune checkpoint inhibitors agents" or "immune modulators agents" are used to identify any agents or inhibitors that blocks certain proteins made by some types of immune system cells, such as T cells, and some cancer cells. These proteins help keep

immune responses in check and can keep T cells from killing cancer cells. When these proteins are blocked, the “brakes” on the immune system are released and T cells are able to kill cancer cells better. The immune checkpoint inhibitors include inhibitors against immune checkpoint molecules such as CD27, CD28, CD40, CD 122, CD96, CD73, CD47, 0X40, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM arginase, CD137 (also known as 4-1BB), ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, VISTA, PD-1, PD-L1 and PD-L2. The terms “immune modulators agents” and “immune checkpoint inhibitors” are used interchangeably throughout the present disclosure.

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

The term "pharmaceutical composition" refers to a composition(s) containing a therapeutically effective amount of at least one compound of formula (I) or its pharmaceutically acceptable salt; and a conventional pharmaceutically acceptable carrier.

The pharmaceutical composition(s) of the present disclosure can be administered orally, for example in the form of tablets, coated tablets, pills, capsules, granules, suspension, emulsion, elixirs, powder, syrup, or solution. Administration, however, can also be carried out rectally, for example in the form of suppositories, or parenterally, for example intravenously, intramuscularly or subcutaneously, in the form of injectable sterile solutions or suspensions, or topically, for example in the form of gel, hydrogel, lotion, ointments, foam or creams or transdermals, in the form of patches, or in other ways, for example in the form of aerosols or nasal sprays.

The pharmaceutical composition(s) usually contain(s) about 1% to 99%, for example, about 5% to 75%, or from about 10% to about 30% by weight of the compound of formula (I) or pharmaceutically acceptable salts thereof. The amount of the compound of formula (I) or pharmaceutically acceptable salts thereof in the pharmaceutical composition(s) can range from about 1 mg to about 1000 mg or from about 2.5 mg to about 500 mg or from about 5 mg to about 250 mg or in any range falling within the broader range of 1 mg to 1000 mg or higher or lower than the afore mentioned range.

The term "treat", "treating" and "treatment" refer to any treatment of a disease in a mammal, including: (a) Inhibiting the disease, i.e., slowing or arresting the development of clinical symptoms; and/or (b) relieving the disease, i.e., causing the regression of clinical symptoms and/or (c) alleviating or abrogating a disease and/or its attendant symptoms.

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

The term "therapeutically effective amount" refers to that amount of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof; or a composition comprising the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, effective in producing the desired therapeutic response in a particular patient suffering from a diseases or disorder, in particular their use in diseases or disorder associated with cancer. Particularly, the term “therapeutically effective amount” includes the amount of the compound of formula (I) or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof, when administered, that induces a positive modification in the disease or disorder to be treated or is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disease or disorder being treated in a subject. In respect of the therapeutic amount of the compound, the amount of the compound used for the treatment of a subject is low enough to avoid undue or severe side effects, within the scope of sound medical judgment can also be considered. The therapeutically effective amount of the compound or composition will be varied with the particular condition being treated, the severity of the condition being treated or prevented, the duration of the treatment, the nature of concurrent therapy, the age and physical condition of the end user, the specific compound or composition employed the particular pharmaceutically acceptable carrier utilized.

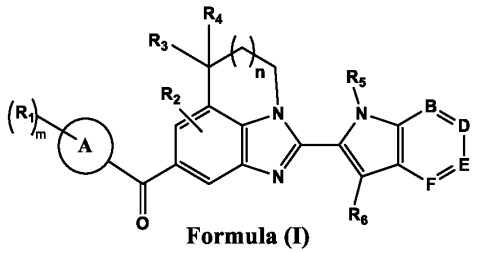
A term once described, the same meaning applies for it, throughout the patent.

As discussed in the background, PAD enzymes are widely over-expressed covering various diseased pathological conditions or disorders and thus, the inhibition of PADs will prevent the disease or lessen/affect the severity of such diseases.

Accordingly, the present disclosure provides compounds of Formula (I) or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof

which act as effective PAD inhibitors. The present disclosure also provides a process for preparing the compounds of the present disclosure.

In an embodiment of the present disclosure, there is provided a compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates or pharmaceutically acceptable salts thereof as disclosed herein,



Formula (I)

wherein, B is selected from N or CR_7; D is selected from N or CR_8; E is selected from N or CR_9; F is selected from N or CR_{10}; Ring A is selected from 5-12 membered monocyclic, bicyclic or tricyclic heterocyclyl with 1-3 heteroatoms selected from N, S or O; R_1 at each occurrence is independently selected from alkyl, alkoxy, alkylamino, acylamino, cycloalkyl, halogen, haloalkyl, hydroxy, $-NR_aR_b$, $-NHC(NH)CH_2Cl$, or $-NH(CO)CH=CH-CH_2-N(CH_3)_2$; R_2 is selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, haloalkyl or hydroxy; R_3 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl or heteroaryl; R_4 is selected from the group consisting of $-NR_cR_d$, $-O-(CO)-NR_cR_d$, $-NR_c(CO)-R_d$, $-NR_c(SO)_2-R_d$, $-NR_c-(CO)-O-R_e$, or $-OR_e$; alternatively, R_3 and R_4 on the same carbon atom together form an oxo (=O), $=N-OR_e$, or $=N-NR_cR_d$ group; R_5 is selected from the group consisting of hydrogen, alkyl, haloalkyl, alkoxy, cycloalkyl, aryl or heteroaryl; wherein, alkyl, alkoxy, cycloalkyl, aryl and heteroaryl, is optionally substituted with one or more groups selected from alkyl, alkoxy, cycloalkyl, aryl, heteroaryl, halogen, hydroxy or cyano; R_6 is selected from the group consisting of hydrogen, hydroxy, cyano, halogen, alkyl, alkoxy, haloalkyl, haloalkoxy, acylamino, alkylamino, aryl or heteroaryl; R_7, R_8, R_9 and R_{10} are independently selected from the group consisting of hydrogen, hydroxy, cyano, halogen, alkyl, alkoxy, haloalkyl, haloalkoxy, acylamino, alkylamino, aryl or heterocyclyl; wherein, aryl and heterocyclyl is optionally substituted with one or more of the groups selected from alkyl, alkoxy, haloalkyl, alkylhydroxy, cyano, hydroxy or COR_{11}; R_{11} is selected from the group consisting of alkyl, hydroxy or cycloalkyl; wherein, alkyl and cycloalkyl is optionally substituted with one or more groups selected from alkyl, alkoxy, cycloalkyl or hydroxy; R_a, R_b, R_c, R_d and R_e are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl or heteroaryl; m is selected from 0-4; and n is selected from 0-2.

In an embodiment of the present disclosure, there is provided a compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates or pharmaceutically acceptable salts thereof as disclosed herein,

wherein,

B is selected from N or CR_7; D is selected from N or CR_8; E is selected from N or CR_9; F is selected from N or CR_{10};

Ring A is selected from 5-12 membered monocyclic or bicyclic heterocyclyl with 1-3 heteroatoms selected from N, S or O;

R_1 at each occurrence is independently selected from alkyl, halogen or $-NR_aR_b$;

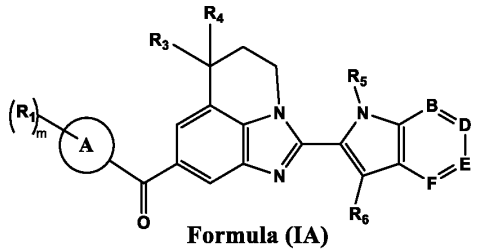
R_2 is selected from hydrogen or alkyl; R_3 is selected from hydrogen or C_{1-6} alkyl;

R_4 is selected from $-NR_aR_b$, or $-OR_e$; alternatively, R_3 and R_4 on the same carbon atom together form an oxo (=O) group; R_5 is selected from the group consisting of hydrogen, alkyl or haloalkyl; wherein, alkyl is optionally substituted with cycloalkyl; R_6 is selected from the group consisting of hydrogen or alkyl; R_7, R_8, R_9 and R_{10} are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, or heterocyclyl; wherein, heterocyclyl, is optionally substituted with alkyl or COR_{11}; R_{11} is selected from the group consisting of alkyl, or cycloalkyl; wherein, alkyl, and cycloalkyl, is optionally substituted with one or more groups selected from alkyl, or hydroxy; R_a, R_b, R_c, R_d and R_e are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl or heteroaryl; m is selected from 0-4.

In an embodiment of the present disclosure, there is provided a compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof as disclosed herein, wherein, B is selected from N or CR_7; D is selected from N or CR_8; E is selected from N or CR_9; F is selected from N or CR_{10}; Ring A is selected from 5-12 membered monocyclic, bicyclic or tricyclic heterocyclyl with 1-3 heteroatoms selected from N, S or O; R_1 at each occurrence is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} acylamino, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, hydroxy, $-NR_aR_b$, $-NHC(NH)CH_2Cl$, or $-NH(CO)CH=CH-CH_2-N(CH_3)_2$; R_2 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, halogen, C_{1-6} haloalkyl, or hydroxy; R_3 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{6-12} aryl, or C_{1-6} heteroaryl; R_4 is selected from the group consisting of $-NR_cR_d$, $-O-(CO)-NR_cR_d$, $NR_c(CO)-R_d$, $-NR_c(SO)_2-R_d$, $-NR_c-(CO)-O-R_e$, or $-OR_e$; alternatively, R_3 and R_4 on the same carbon atom together form an oxo (=O), =N-OR_e, or =N-NR_cR_d group; R_5 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{6-12} aryl, or C_{1-6} heteroaryl; wherein, C_{1-6} alkyl, C_{1-6}

alkoxy, C_{3-6} cycloalkyl, C_{6-12} aryl, and C_{1-6} heteroaryl, is optionally substituted with one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{6-12} aryl, C_{1-6} heteroaryl, halogen, hydroxy or cyano; R_6 is selected from the group consisting of hydrogen, hydroxy, cyano, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} acylamino, C_{1-6} alkylamino, C_{6-12} aryl, or C_{1-6} heteroaryl; R_7, R_8, R_9 and R_{10} are independently selected from the group consisting of hydrogen, hydroxy, cyano, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} acylamino, C_{1-6} alkylamino, C_{6-12} aryl, or C_{1-6} heterocyclyl; wherein, C_{6-12} aryl, and C_{1-6} heterocyclyl, is optionally substituted with one or more of the groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} alkylhydroxy, cyano, hydroxy, or COR_{11}; R_{11} is selected from the group consisting of C_{1-6} alkyl, hydroxy, or C_{3-6} cycloalkyl; wherein, C_{1-6} alkyl, and C_{3-6} cycloalkyl, is optionally substituted with one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or hydroxy; R_a, R_b, R_c, R_d and R_e are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-12} aryl, or C_{1-6} heteroaryl; m is selected from 0-4; and n is selected from 0-2.

In an embodiment of the present disclosure, there is provided a compound of Formula (IA):



Formula (IA)

or its stereoisomer, tautomers, intermediates, solvates or pharmaceutically acceptable salt thereof;

wherein,

B is selected from N or CR_7;

D is selected from N or CR_8;

E is selected from N or CR_9;

F is selected from N or CR_{10};

Ring A is selected from 5-12 membered monocyclic, bicyclic or tricyclic heterocyclyl with 1-3 heteroatoms selected from N, S or O;

R_1 at each occurrence is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} acylamino, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, hydroxy, $-NR_aR_b$, $-NHC(NH)CH_2Cl$, or $-NH(CO)CH=CH-CH_2-N(CH_3)_2$;

R_3 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{6-12} aryl, or C_{1-6} heteroaryl;

R_4 is selected from the group consisting of $-NR_cR_d$, $-O-(CO)-NR_cR_d$, $NR_c(CO)-R_d$, $-NR_c(SO)_2-R_d$, $-NR_c-(CO)-O-R_e$, or $-OR_e$;

alternatively, R_3 and R_4 on the same carbon atom together form an oxo (=O), $=N-OR_e$, or $=N-NR_cR_d$ group;

R_5 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{6-12} aryl, or C_{1-6} heteroaryl; wherein, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{6-12} aryl, and C_{1-6} heteroaryl, is optionally substituted with one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{6-12} aryl, C_{1-6} heteroaryl, halogen, hydroxy or cyano;

R_6 is selected from the group consisting of hydrogen, hydroxy, cyano, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} acylamino, C_{1-6} alkylamino, C_{6-12} aryl, or C_{1-6} heteroaryl;

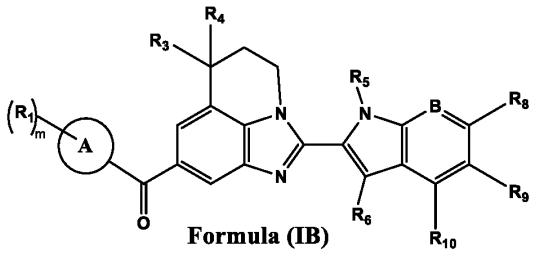
R_7, R_8, R_9 and R_{10} are independently selected from the group consisting of hydrogen, hydroxy, cyano, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} acylamino, C_{1-6} alkylamino, C_{6-12} aryl, or C_{1-6} heterocyclyl; wherein, C_{6-12} aryl, and C_{1-6} heterocyclyl, is optionally substituted with one or more of the groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} alkylhydroxy, cyano, hydroxy, or COR_{11};

R_{11} is selected from the group consisting of C_{1-6} alkyl, hydroxy, or C_{3-6} cycloalkyl; wherein, C_{1-6} alkyl, and C_{3-6} cycloalkyl, is optionally substituted with one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or hydroxy;

R_a, R_b, R_c, R_d and R_e are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-12} aryl, or C_{1-6} heteroaryl; and

m is selected from 0-4.

In an embodiment of the present disclosure, there is provided a compound of Formula (IB):



Formula (IB)

or its stereoisomers, tautomers, intermediates, solvates or pharmaceutically acceptable salts thereof as disclosed herein,

wherein,

B is selected from N or CR_7;

Ring A is selected from 5-12 membered monocyclic or bicyclic heterocyclyl with 1-3 heteroatoms selected from N, S or O;

R_1 at each occurrence is independently selected from C_{1-6} alkyl, halogen or $-NH_2$;

R_3 is selected from hydrogen or C_{1-6} alkyl;

R_4 is selected from $-NH_2$, or hydroxy;

alternatively, R_3 and R_4 on the same carbon atom together form an oxo (=O) group;

R_5 is selected from the group consisting of hydrogen, C_{1-6} alkyl or C_{1-6} haloalkyl; wherein, C_{1-6} alkyl is optionally substituted with C_{3-6} cycloalkyl;

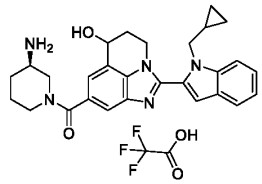
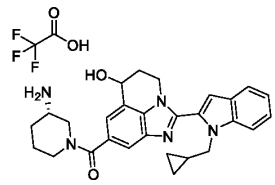
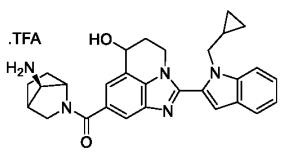
R_6 is selected from the group consisting of hydrogen or C_{1-6} alkyl;

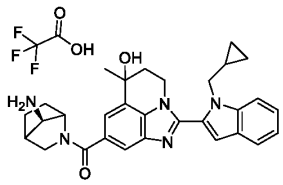
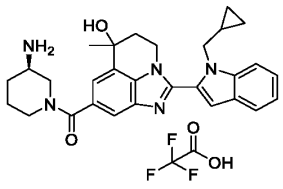
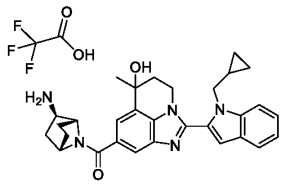
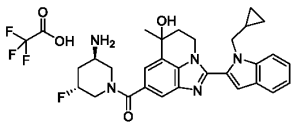
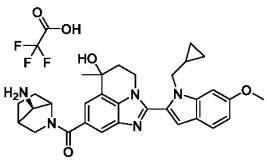
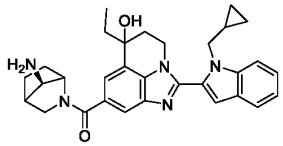
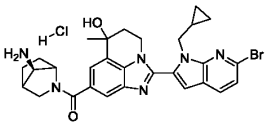
R_7, R_8, R_9 and R_{10} are independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} heterocyclyl; wherein, C_{1-6} heterocyclyl, is optionally substituted with C_{1-6} alkyl or COR_{11};

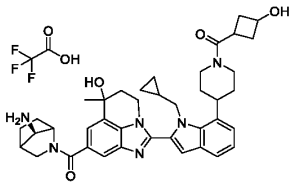
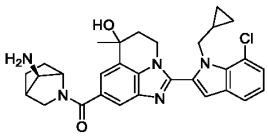
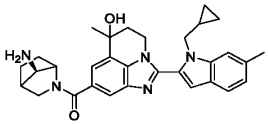
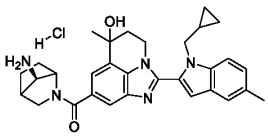
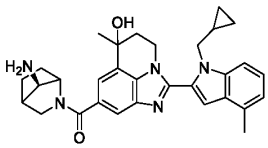
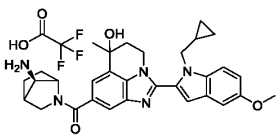
R_{11} is selected from the group consisting of C_{1-6} alkyl, or C_{3-6} cycloalkyl; wherein, C_{1-6} alkyl, and C_{3-6} cycloalkyl, is optionally substituted with one or more groups selected from C_{1-6} alkyl, or hydroxy; and

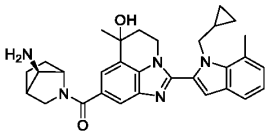
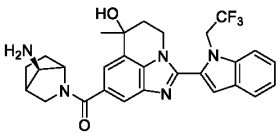
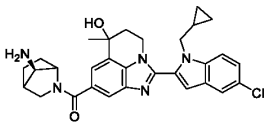
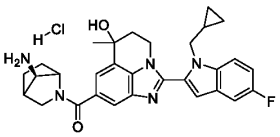
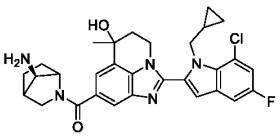
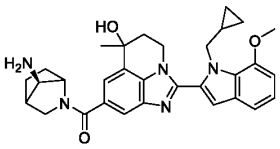
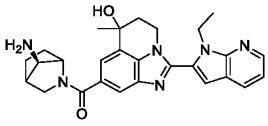
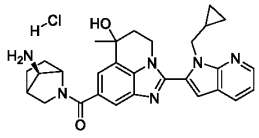
m is selected from 1-2.

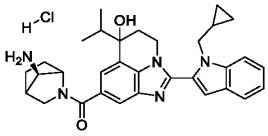
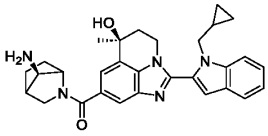
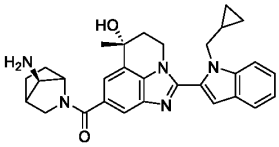
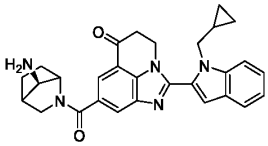
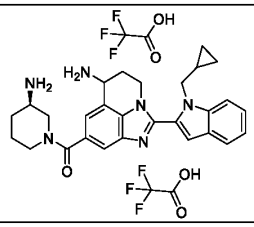
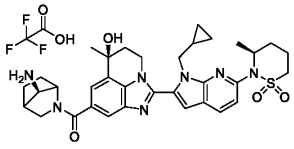
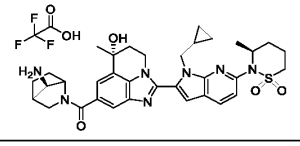
In an embodiment, the present disclosure provides a compound selected from:

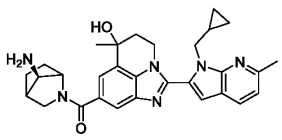
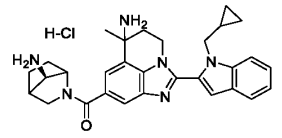
Example No	Structure	IUPAC
1		(R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
2		((S)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
3		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;

4		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
5		((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
6		((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
7		((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
8		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
9		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-ethyl-6-hydroxy-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
10		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-

		methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone hydrochloride;
11		(4-(2-(8-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)(3-hydroxycyclobutyl)methanone trifluoroacetate;
12		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(7-chloro-1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
13		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
14		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-5-methyl-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone hydrochloride;
15		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-4-methyl-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
16		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-5-methoxy-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;

17		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-7-methyl-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
18		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(6-hydroxy-6-methyl-2-(1-(2,2,2-trifluoroethyl)-1H-indol-2-yl)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
19		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(5-chloro-1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
20		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone hydrochloride;
21		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(7-chloro-1-(cyclopropylmethyl)-5-fluoro-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
22		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-7-methoxy-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
23		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
24		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-

		dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone hydrochloride;
25		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-isopropyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone hydrochloride;
26		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((S)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
27		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((R)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
28		8-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4,5-dihydro-6H-imidazo[4,5,1-ij]quinolin-6-one;
29		(6-amino-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)((R)-3-aminopiperidin-1-yl)methanone di-trifluoroacetate;
30		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((S)-2-(1-(cyclopropylmethyl)-6-((S)-3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
31		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((R)-2-(1-(cyclopropylmethyl)-6-((S)-3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-

		pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
32		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone; and
33		(6-amino-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)methanone hydrochloride.

or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof.

In an embodiment of the present disclosure, there is provided a process for preparing the compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof as disclosed herein.

In an embodiment of the present disclosure, there is provided a pharmaceutical composition comprising the compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof as disclosed herein, and at least one pharmaceutically acceptable carrier.

In an embodiment of the present disclosure, there is provided a pharmaceutical composition comprising a compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof as disclosed herein, together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

In an embodiment of the present disclosure, there is provided a pharmaceutical composition as disclosed herein, wherein the composition is in the form selected from the group consisting of a tablet, capsule, powder, syrup, solution, aerosol, ointment, lotion, cream, transdermal patches, gel, hydrogel, foam and suspension.

In an embodiment of the present disclosure, there is provided a compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof as disclosed herein, for use in the manufacture of a medicament for inhibiting one or more PADs in a cell. In another embodiment of the present disclosure, wherein the PAD is selected from PAD1, PAD2, PAD3, PAD4, and PAD6. In yet another embodiment of the present disclosure, wherein the PAD is PAD4.

In an embodiment of the present disclosure, there is provided a compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof as disclosed herein, for use in the manufacture of a medicament for inhibiting PAD4 in a cell.

In an embodiment of the present disclosure, there is provided a compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof as disclosed herein, for use in the treatment of PAD4 mediated disease or disorder.

In an embodiment of the present disclosure, there is provided a method for inhibiting PAD4 in a cell with an effective amount of the compound of Formula (I) as disclosed herein.

In an embodiment of the present disclosure, there is provided a method of inhibiting PAD4 in a subject, comprising administering to a subject suffering from a disease or disorder mediated by PAD4, a therapeutically effective amount of the compound of Formula (I) or the pharmaceutical composition as disclosed herein.

In an embodiment of the present disclosure, there is provided a method of treating and/or preventing a disease or disorder mediated by one or more PAD's, the method comprising administering to a subject suffering from a condition mediated by one or more PAD family, a therapeutically effective amount of the compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof or the pharmaceutical composition as disclosed herein.

In an embodiment of the present disclosure, there is provided a method of the treatment and/or prevention of a disease or disorder associated with NETosis, the method comprising administering to a subject a therapeutically effective amount of the compound of Formula (I), or its stereoisomer, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof.

In an embodiment of the present disclosure, there is provided a method of the treatment and/or prevention of a disease or disorder mediated by PAD4, the method comprising administering to a subject suffering from the disease or disorder mediated by PAD4 a

therapeutically effective amount of the compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof, or the pharmaceutical composition as disclosed herein.

In an embodiment of the present disclosure, there is provided a method of treatment and/or prevention of a disease or disorder, wherein the disease or disorder is selected from cancer, cancer metastasis, immune disorder, inflammatory disorder, or transplant rejection.

In an embodiment of the present disclosure, there is provided a method of treatment and/or prevention of a disease or disorder, wherein the disease or disorder is selected from rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cystic fibrosis, asthma, cutaneous lupus erythematosus, or psoriasis.

In an embodiment of the present disclosure, there is provided a method of treatment and/or prevention of rheumatoid arthritis, said method comprising administering a combination of the compounds of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof or the pharmaceutical composition as disclosed herein, with other clinically relevant cytotoxic agents or non-cytotoxic agents to a subject in need thereof.

In an embodiment of the present disclosure, there is provided a method of treatment and/or prevention of a disease or disorder, wherein the disease or disorder is selected from cancer, cancer metastasis, immune disorder, inflammatory disorder, and transplant rejection, said method comprising administering a combination of the compounds of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof or the pharmaceutical composition as disclosed herein, with other clinically relevant immune modulator agents or anti-inflammatory agents to a subject in need of thereof.

In an embodiment of the present disclosure, there is provided a method of treatment and/or prevention of cancer as described herein, wherein, the cancer is selected from breast cancer, prostate cancer, pancreatic cancer, gastric cancer, lung cancer, colon cancer, rectal cancer, esophagus cancer, duodenal cancer, tongue cancer, pharyngeal cancer, brain tumor, neurinoma, clear cell carcinoma, non-small cell lung cancer, small cell lung cancer, liver cancer, kidney cancer, bile duct cancer, uterine body cancer, cervical cancer, ovarian cancer, urinary bladder cancer, skin cancer, hemangioma, malignant lymphoma, malignant melanoma, thyroid cancer, bone tumor, vascular fibroma, glioblastoma, sarcoma, neuroendocrine tumors, retinoblastoma, penile cancer, pediatric solid cancer, renal cell carcinoma, lymphoma, myeloma, leukemia, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic

neutrophilic leukemia (CNL), chronic eosinophilic leukemia (CEL), chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), hairy cell leukemia, cutaneous T-cell lymphoma (CTCL), multiple myeloma (MM), myeloproliferative neoplasms (MPN), polycythemia vera (PV), essential thrombocythemia, essential thrombocytosis (ET) or myelofibrosis (MF).

In an embodiment of the present disclosure, there is provided a method of treatment and/or prevention of cancer metastasis as described herein, wherein the cancer metastasis is selected from liver cancer metastasis, lung cancer metastasis, and omentum cancer metastasis.

In an embodiment of the present disclosure, there is provided a method of treatment and/or prevention of cancer metastasis as described herein, wherein the cancer metastasis is selected from liver cancer metastasis originating from colorectal cancer and pancreatic cancer, lung cancer metastasis originating from breast cancer, and omentum cancer metastasis originating from ovarian cancer.

In an embodiment of the present disclosure, there is provided a method of treatment and/or prevention of a disease or disorder, wherein disease or disorder is selected from acid-induced lung injury, respiratory distress syndrome, allergen induced asthma, allergic bronchopulmonary disease, chronic lung disease of prematurity, chronic obstructive pulmonary disease, colitis, cystic fibrosis, gouty arthritis, inflammatory bowel disease, inflammatory lung disease, inflammatory pain, juvenile rheumatoid arthritis, kidney disease, kidney injury caused by parasitic infections, kidney transplant rejection prophylaxis, lung injury, lupus, lupus nephritis, multiple sclerosis, muscular dystrophy, non-allergen induced asthma, osteoarthritis, periodontitis, peritoneal endometriosis, psoriasis, pulmonary disease, pulmonary fibrosis, idiopathic pulmonary fibrosis, pyogenic sterile arthritis, renal disease, rheumatic disease, rheumatoid arthritis, sepsis, severe pain, ulcerative colitis, systemic inflammatory response syndrome, decreasing neutrophil extra cellular traps (NETs) release, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), COVID-19 (corona virus disease-2019) related lung infection, multi-organ failure or multi-organ dysfunction syndrome from ARDS, anti neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), hidradenitis suppurativa (HS), infections, cytokine storms induced by drugs or any agent, ischemic or haemorrhagic stroke, ischemic or drug-induced haemorrhagic transformation in the brain, haemorrhagic encephalopathy, traumatic brain injury, anoxic brain injury, diabetes, deep vein thrombosis, systemic microthrombosis, atherosclerotic thrombosis,

thromboembolism, systemic lupus erythematosus (SLE), crohn's disease, indeterminate colitis, or alzheimer's disease.

In an embodiment of the present disclosure, there is provided a compound of Formula (I) or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof as disclosed herein, for use in the treatment of a disease or disorder ameliorated by inhibition of NETosis thereof.

In an embodiment of the present disclosure, there is provided a compound of Formula (I) or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof as disclosed herein, for use in the treatment of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cystic fibrosis, asthma, atopic dermatitis, cutaneous lupus erythematosus, or psoriasis.In an embodiment of the present disclosure, there is provided a use of the compound of Formula (I) or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof as disclosed herein, for the treatment of a disease or disorder mediated by PAD4; or treatment and/or prevention of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cystic fibrosis, asthma, atopic dermatitis, cutaneous lupus erythematosus, or psoriasis together with other clinically relevant cytotoxic agents or non-cytotoxic agents.

In an embodiment of the present disclosure, there is provided a use of the pharmaceutical composition disclosed herein, for the treatment of a disease or disorder mediated by PAD4; or treatment and/or prevention of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cystic fibrosis, asthma, atopic dermatitis, cutaneous lupus erythematosus, or psoriasis together with other clinically relevant cytotoxic agents or non-cytotoxic agents.

In an embodiment of the present disclosure, there is provided a use of the compound of Formula (I) or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of a disease or disorder mediated by PAD4; or treatment and/or prevention of of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cystic fibrosis, asthma, atopic dermatitis, cutaneous lupus erythematosus, or psoriasis.

In an embodiment of the present disclosure, there is provided a use of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a disease or disorder mediated by PAD4; or treatment and/or prevention of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cystic fibrosis, asthma, atopic dermatitis, cutaneous lupus erythematosus, or psoriasis.

In an embodiment of the present disclosure, there is provided a use of the compound of Formula (I) or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a disease or disorder mediated by PAD4; or treatment and/or prevention of disease or disorder selected from cancer, cancer metastasis, immune disorder, inflammatory disorder, and transplant rejection.

In an embodiment of the present disclosure, there is provided a use of the compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof or pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a disease or disorder mediated by PAD4; or treatment and/or prevention of cancer as described herein, wherein the disease or disorder is cancer and cancer is selected from breast cancer, prostate cancer, pancreatic cancer, gastric cancer, lung cancer, colon cancer, rectal cancer, esophagus cancer, duodenal cancer, tongue cancer, pharyngeal cancer, brain tumor, neurinoma, clear cell carcinoma, non-small cell lung cancer, small cell lung cancer, liver cancer, kidney cancer, bile duct cancer, uterine body cancer, cervical cancer, ovarian cancer, urinary bladder cancer, skin cancer, hemangioma, malignant lymphoma, malignant melanoma, thyroid cancer, bone tumor, vascular fibroma, glioblastoma, sarcoma, neuroendocrine tumors, retinoblastoma, penile cancer, pediatric solid cancer, renal cell carcinoma, lymphoma, myeloma, and leukemia, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia (CEL), chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), hairy cell leukemia, cutaneous T-cell lymphoma (CTCL), multiple myeloma (MM), myeloproliferative neoplasms (MPN), polycythemia vera (PV), essential thrombocythemia, essential thrombocytosis (ET) or myelofibrosis (MF).

In an embodiment of the present disclosure, there is provided a use of the compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof or pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a disease or disorder mediated by PAD4; or treatment and/or prevention of treatment of cancer metastasis as described herein, wherein the cancer metastasis is selected from liver cancer metastasis, lung cancer metastasis, and omentum cancer metastasis.

In an embodiment of the present disclosure, there is provided use of the compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically

acceptable salts thereof or pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a disease or disorder mediated by PAD4; or treatment and/or prevention of treatment of cancer metastasis as described herein, wherein the cancer metastasis is selected from liver cancer metastasis originating from colorectal cancer and pancreatic cancer, lung cancer metastasis originating from breast cancer, and omentum cancer metastasis originating from ovarian cancer.

In an embodiment of the present disclosure, there is provided a use of the compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof or pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a disease or disorder mediated by PAD4; or treatment and/or prevention of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cystic fibrosis, asthma, atopic dermatitis, cutaneous lupus erythematosus, or psoriasis.

In an embodiment of the present disclosure, there is provided use of the compound of Formula (I), or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof or the pharmaceutical composition as disclosed herein, for the treatment of a disease or disorder mediated by PAD4; or treatment and/or prevention of disease or disorder selected from acid-induced lung injury, respiratory distress syndrome, allergen induced asthma, allergic bronchopulmonary, chronic lung disease of prematurity, chronic obstructive pulmonary disease, colitis, cystic fibrosis, gouty arthritis, inflammatory bowel disease, inflammatory lung disease, inflammatory pain, juvenile rheumatoid arthritis, kidney disease, kidney injury caused by parasitic infections, kidney transplant rejection prophylaxis, chronic kidney disease, lung injury, lupus, lupus nephritis, multiple sclerosis, muscular dystrophy, non-allergen induced asthma, osteoarthritis, periodontitis, peritoneal endometriosis, atopic dermatitis, psoriasis, pulmonary disease, pulmonary fibrosis, idiopathic pulmonary fibrosis, pyogenic sterile arthritis, renal disease, rheumatic disease, rheumatoid arthritis, sepsis, severe pain, ulcerative colitis, systemic inflammatory response syndrome, decreasing neutrophil extra cellular traps (NETs) release, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), COVID related lung infection, multi-organ failure or multi-organ dysfunction syndrome from ARDS, anti neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), hidradenitis suppurativa (HS), infections, cytokine storms induced by drugs or any agent, ischemic or haemorrhagic stroke, ischemic or drug-induced haemorrhagic transformation in the brain, haemorrhagic encephalopathy, traumatic brain injury, anoxic brain injury, diabetes, deep vein thrombosis, systemic microthrombosis, atherosclerotic thrombosis,

thromboembolism, systemic lupus erythematosus (SLE), crohn's disease, indeterminate colitis, or alzheimer's disease.

Although the subject matter has been described in considerable detail with reference to certain examples and implementations thereof, other implementations are possible.

EXAMPLES

The disclosure will now be illustrated with working examples, which is intended to illustrate the working of disclosure and not intended to take restrictively to imply any limitations on the scope of the present disclosure. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice of the disclosed compounds, compositions and methods, the exemplary illustrations are described herein. It is to be understood that this disclosure is not limited to particular methods, and experimental conditions described, as such methods and conditions may apply.

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

Abbreviations:

The following abbreviations refer respectively to the definitions herein:

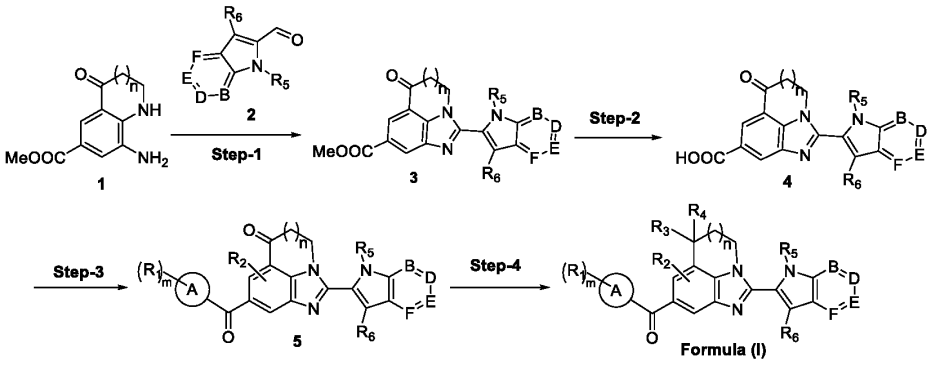
rt (Retention time); RT (Room temperature); RM (Reaction mixture); °C (degree Celsius); DMF (N,N-Dimethyl formamide); h (hour); THF (tetrahydrofuran); HCl (Hydrochloric acid); DCM, CH_2Cl_2 (Dichloromethane); TFA (Trifluoroacetic acid); H_2O (Water); TLC (Thin layer chromatography); Na_2SO_4 (Sodium sulphate); ACN/CH_3CN (acetonitrile); MeOH (Methanol); DMSO-d_6 (Hexadeuterodimethyl sulfoxide); HPLC (High pressure liquid chromatography); LCMS (Liquid chromatography mass spectrometry); NMR (Nuclear magnetic resonance); Cs_2CO_3 (Cesium carbonate); MHz (megahertz); s (singlet); m (multiplet); d (doublet); Fe (Ferrum); EtOH (Ethyl alcohol/Ethanol); EtOAc (Ethyl Acetate); LAH (Lithium aluminium hydride); LDA (Lithium diisopropylamide); $NaBH_3CN$ (Sodium cyanoborohydride); $NaBH_4$ (Sodium borohydride); HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate /Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium); DIPEA (N,N-

Diisopropylethylamine); TBAF (Tetra-n-butylammonium fluoride); NaH (Sodium hydride); NH_4Cl (Ammonium Chloride); K_2CO_3 (Potassium carbonate); K_3PO_4 (Potassium phosphate); $LiAlH_4$ (Lithium aluminium hydride); MnO_2 (Manganese dioxide); NAOH (Sodium hydroxide); T3P (Propylphosphonic anhydride); NH_4OAc (Ammonium acetate); NaCl (Sodium Chloride); and $CaCl_2$ (Calcium Chloride); DMA (N,N-Dimethyl Acetamide); IPA (Isopropyl alcohol); MeOH (methanol); $LiOH.H_2O$ (Lithium Hydroxide monohydrate); KOH (Potassium Hydroxide); EDC (N-Ethyl-N′-(3-dimethylaminopropyl)carbodiimide); HOBt (1-Hydroxybenzotriazole); DCC (N,N′-Dicyclohexylcarbodiimide); CDI (1,1′-Carbonyldiimidazole); BOP-Cl (Bis(2-oxo-3-oxazolidinyl)phosphinic chloride); STAB (Sodium Tri Acetoxy Borohydride); DIBAL-H (Diisobutylaluminum hydride); MeMgI (Methyl magnesium iodide); JackiePhos Pd G3 ([(2-{Bis[3,5-bis(trifluoromethyl)phenyl]phosphine}-3,6-dimethoxy- 2′,4′,6′- triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate); $Pd(PPh_3)_4$ (Tetrakis(triphenylphosphine)palladium(0)).

The following examples provide the details about the synthesis, activities, and applications of the compounds of the present disclosure. It should be understood the following is representative only, and that the present disclosure is not limited by the details set forth in these examples.

The compounds of the present disclosure may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out in the following schemes and can be readily adapted to prepare other compounds of the disclosure.

General Synthetic scheme:

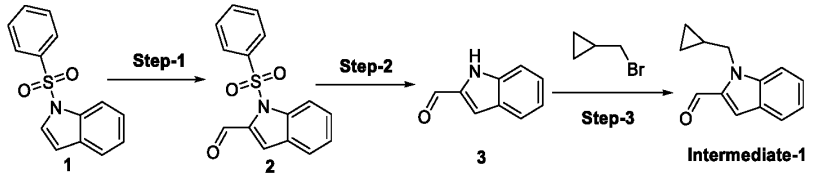


The diamino derivative **1** is reacted with substituted heterocyclic aldehyde derivative **2** in the presence of oxidizing agents like sodium metabisulfite or oxone and solvent such as DMF,

DMSO, DMA, IPA, MeOH, EtOH at -20 °C to 150 °C, in order to produce cyclised derivative **3**. The cyclized derivative **3** on acid or base mediated hydrolysis with reagents like HCl, TFA, $LiOH.H_2O$, NaOH, KOH etc., in the presence of solvents like dioxane, THF, EtOH, MeOH, water etc resulted in the formation of acid derivative **4**. The acid derivative **4** is treated with substituted and protected amine bearing derivatives in the presence of coupling agents like HATU, T3P, EDC, HOBt, DCC, CDI, BOP-Cl etc. and bases like TEA, DIPEA etc., using solvents like DCM, DMF, THF, EtOAc etc. resulted in amide derivative **5**. Intermediate **5** was finally converted into compounds of **Formula (I)** by reduction using reducing agents like $NaBH_4$, STAB, DIBAL-H etc., or by treating with alkyl/aryl Grignard agents or by reductive amination followed by deprotection of protecting groups by appropriate conditions (HCl, TFA etc).

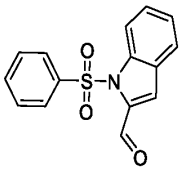
SYNTHESIS OF INTERMEDIATES

Synthesis of 1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde (Intermediate-1)



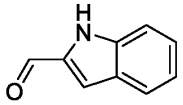
Reagents & conditions: 1. LDA, THF, -78°C, 0 °C, 2 h; **2.** TBAF, THF, 0°C, 0 °C, 2 h; **3.** $CsCO_3$, DMF, 0°C-RT, 16 h.

Step-1: Preparation of 1-(phenylsulfonyl)-1H-indole-2-carbaldehyde **(2)**



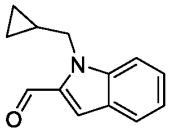
To a solution of 1-(phenylsulfonyl)-1H-indole (**1**, 15 g, 58.3 mmol) in THF (150 mL, 1.84 mol) was added LDA (31.2 g, 291 mmol) at -78 °C. After 30 min, DMF (12.8 g, 175 mmol) was added to the above solution. The RM was stirred for 2 h at 0 °C. After completion as monitored by TLC, the RM was quenched with EtOAc and solvent was removed under reduced pressure to get crude compound. The crude was purified by column chromatography to give title product (**2**, 10 g, 60%) as a light yellow solid. LCMS (ES) m/z = 286.2 $[M+H]^+$

Step-2: Preparation of 1H-indole-2-carbaldehyde **(3)**



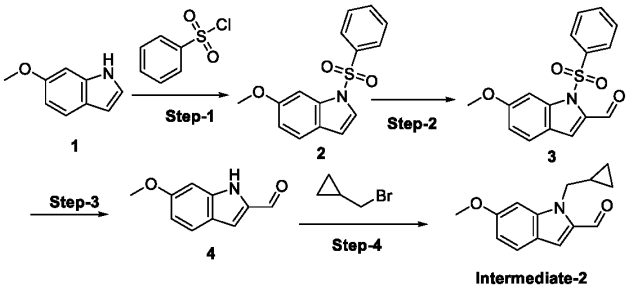
To a stirred solution of 1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (**2**, 10 g, 35 mmol) in THF (0.3 L) was added tetrabutylammonium fluoride (27.5 g, 105 mmol) at 0°C. The RM was stirred at the same temperature for 2 h. After completion of reaction as monitored by TLC, RM was quenched with ice cold water and extracted with EtOAc, the combined organic layer was washed with cold water followed by brine wash, solvent was removed under reduced pressure to get the crude material, which was purified by column chromatography to give title product (**3**, 4.2 g, 84%). LCMS (ES) m/z = 146 $[M+H]^+$

Step-3: Preparation of 1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde **(Intermediate-1)**



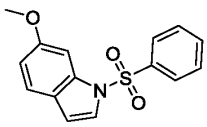
To a stirred solution of 1H-indole-2-carbaldehyde (**3**, 4.2 g, 28.9 mmol), 1-(bromomethyl)cyclopropane (4.69 g, 34.7 mmol) in DMF (80 mL) was added cesium carbonate (18.9 g, 57.9 mmol). The reaction was allowed to stir for 16 h at RT. After completion of reaction as monitored by TLC, RM was diluted with water and extracted with EtOAc, solvent was removed under reduced pressure to get the crude compound. The crude was purified by column chromatography to give title product (**Intermediate-1**, 3.5 g, 61%). LCMS (ES) m/z = 200 $[M+H]^+$

Synthesis of 1-(cyclopropylmethyl)-6-methoxy-1H-indole-2-carbaldehyde (Intermediate-2)



Reagents & conditions: 1. NaH, DMF, 0°C, 1 h; **2.** LDA, THF, DMF, -78°C, 1 h; **3.** TBAF, THF, RT, 16 h; **4.** $CsCO_3$, DMF, 80°C, 1 h.

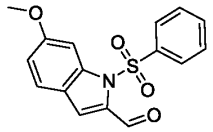
Step-1: Preparation of 6-methoxy-1-(phenylsulfonyl)-1H-indole **(2)**



To a stirred suspension of sodium hydride (1.3 g, 27.2 mmol) in DMF (20 mL), a solution of 6-methoxy-1H-indole (**1**, 2 g, 13.6 mmol) in DMF was added dropwise at 0 °C. To this benzene

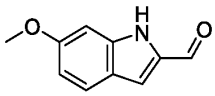
sulfonyl chloride (2.2 mL, 16.3 mmol) was added. The reaction was stirred at room temperature for 1 h. The progress of the reaction was monitored by TLC. After completion, the RM was quenched with ice-cold water. The obtained solid was filtered through a sinter funnel and dried to give title product (**2**, 3.5 g, 80.6%) as a yellow solid. LCMS (ES): *m/z* =288.3 $[M+H]^+$

Step-2: Preparation of 6-methoxy-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde **(3)**



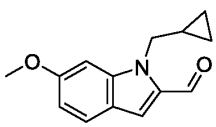
To a stirred solution of LDA (37 mL, 37.6 mmol) in THF (20 mL), solution of 6-methoxy-1-(phenylsulfonyl)-1H-indole (**2**, 3 g, 9.4 mmol) in THF (10 mL) was added dropwise at -78 °C. The reaction was stirred at -78 °C for 45 mins. To this DMF (30 mL) was added dropwise. The reaction was stirred at -78 °C for 1 h. The progress of reaction was monitored by TLC. After completion, the RM was quenched with saturated solution of ammonium chloride (70 mL) and extracted with EtOAc (2 X 100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give title product (**3**, 2.5 g, 37.12%) as a yellow solid. LCMS (ES): *m/z* =316.4 $[M+H]^+$

Step-3: Preparation of 6-methoxy-1H-indole-2-carbaldehyde **(4)**



To a stirred solution of 6-methoxy-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (**3**, 2 g, 2.79 mmol) in THF (20 mL), tetrabutylammonium fluoride (2.19 g, 8.37 mmol) was added. The reaction was stirred at room temperature for 16 h. The reaction was monitored by TLC. After completion, the RM was quenched with water (50 mL) and extracted with EtOAc (2 X 70 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude was purified by neutral alumina column chromatography using 10% EtOAc in heptane to give title product (**4**, 0.3 g, 57%) as a brown solid. LCMS (ES): *m/z* =176.06 $[M+H]^+$

Step-4: Preparation of 1-(cyclopropylmethyl)-6-methoxy-1H-indole-2-carbaldehyde **(Intermediate-2)**

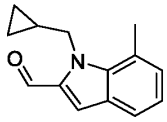
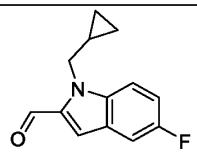
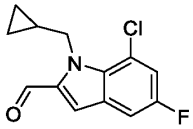
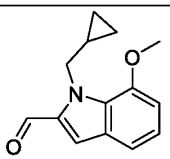
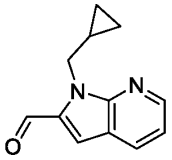


To a stirred solution of 6-methoxy-1H-indole-2-carbaldehyde (**4**, 0.2 g, 1.14 mmol) in DMF (2 mL), cesium carbonate (1.12 g, 3.42 mmol) and 1-(Bromomethyl)cyclopropane (0.2 g, 1.48

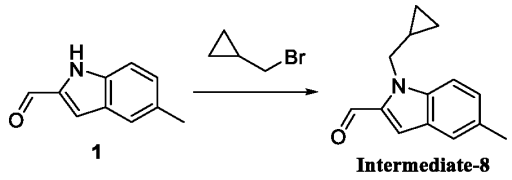
mmol) were added. The reaction was stirred at 80 °C for 1 h. The reaction was monitored by TLC. After completion, RM was quenched with water (50 mL) and extracted with EtOAc (2 X 70 mL). The organic layer was washed with ice cold saturated solution of sodium chloride (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give title product (**Intermediate-2**, 0.2 g, 71%) as a brown solid. LCMS (ES): *m/z* =230.3 $[M+H]^+$

The Intermediates in below **Table I** were prepared using the procedure described above for the synthesis of intermediate-2 with appropriate variations in reactants, quantity of reagents, protections & deprotections, solvents & reaction conditions. The characterization data of the compounds are summarized herein below **Table I**.

Table I:

Intermediate	Structure	IUPAC Name	LCMS (ES) m/z $[M+H]^+$
3		1-(cyclopropylmethyl)-7-methyl-1H-indole-2-carbaldehyde	214.20
4		1-(cyclopropylmethyl)-5-fluoro-1H-indole-2-carbaldehyde	218.18
5		7-chloro-1-(cyclopropylmethyl)-5-fluoro-1H-indole-2-carbaldehyde	252.21
6		1-(cyclopropylmethyl)-7-methoxy-1H-indole-2-carbaldehyde	230.20
7		1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carbaldehyde	201.21

Synthesis of 1-(cyclopropylmethyl)-5-methyl-1H-indole-2-carbaldehyde (Intermediate-8):



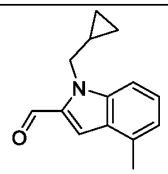
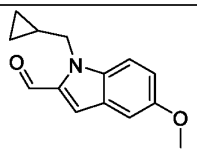
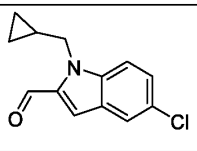
1 Intermediate-8

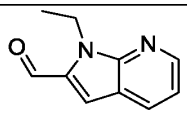
Reagents & conditions: 1. $CsCO_3$, DMF, 0°C-RT, 16 h.

To a stirred solution of 5-methyl-2-indolecarbaldehyde (**1**, 3 g, 18.8 mmol) in DMF (60 mL), cesium carbonate (12.3 g, 37.7 mmol) was added followed by the addition of 1-(bromomethyl)cyclopropane (3.05 g, 22.6 mmol) and the RM was stirred at RT for 16 h. After completion of reaction, as monitored by TLC, the RM was diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with cold water (3 x 60 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated to get the crude material, which was purified by silica gel column chromatography eluting with 10% EtOAc in hexane to afford title product (**Intermediate-8**, 3 g, 75%) as yellow gummy material. LCMS (ES) m/z = 214.21 $[M+H]^+$

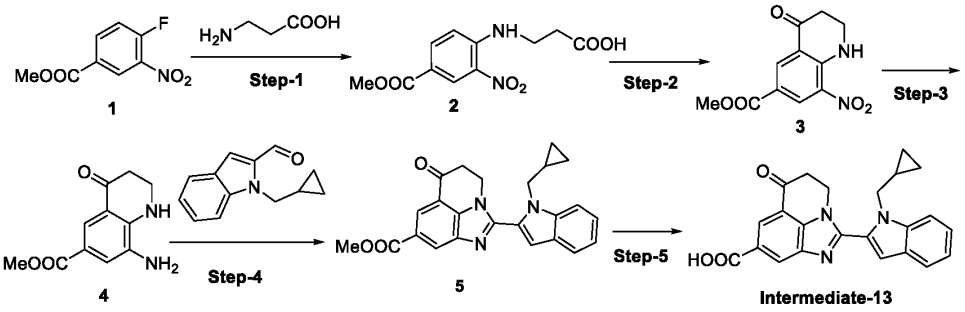
The Intermediates in below **Table II** were prepared using the procedure described above for the synthesis of intermediate-8 with appropriate variations in reactants, quantity of reagents, protections & deprotections, solvents & reaction conditions. The characterization data of the compounds are summarized herein below **Table II**.

Table II:

Intermediate	Structure	IUPAC Name	LCMS (ES) m/z $[M+H]^+$
9		1-(cyclopropylmethyl)-4-methyl-1H-indole-2-carbaldehyde	214.20
10		1-(cyclopropylmethyl)-5-methoxy-1H-indole-2-carbaldehyde	230.18
11		5-chloro-1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde	234.20

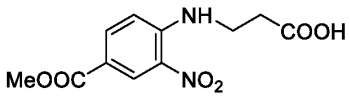
12		1-ethyl-1H-pyrrolo[2,3-b]pyridine-2-carbaldehyde	175.13

Synthesis of 2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylic acid (Intermediate-13):



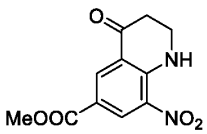
Reagents & conditions: 1. DIPEA, 100 °C, 3 h; **2.** Etons Reagent, 60 °C, 2 h; **3.** Fe, NH_4Cl, EtOH, H_2O, 80 °C, 6 h; **4.** Oxone, DMF: H_2O, 80 °C, 3 h; **5.** 6N HCl, 1,4-dioxane, 90 °C, 16 h.

Step-1: Preparation of 3-((4-(methoxycarbonyl)-2-nitrophenyl)amino)propanoic acid **(2)**



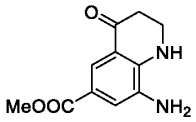
To a stirred solution of methyl 4-fluoro-3-nitrobenzoate (**1,** 5 g, 25.1 mmol) in acetonitrile (50 mL), 3-aminopropanoic acid (2.68 g, 30.1 mmol) and DIPEA (13.9 mL, 75.3 mmol) were added. The reaction was stirred at 100 °C for 3 h. The reaction was monitored by TLC. After completion, the RM was concentrated under reduced pressure. The obtained residue was triturated with diethyl ether (2 x 50 mL). Then, residue was dissolved in water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give title product (**2**, 3 g, 40%) as a yellow solid. LCMS (ES): *m/z* =269.2 $[M+H]^+$

Step-2: Preparation of methyl 8-nitro-4-oxo-1,2,3,4-tetrahydroquinoline-6-carboxylate **(3)**



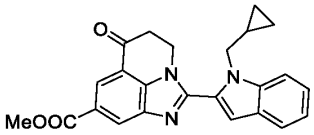
3-((4-(methoxycarbonyl)-2-nitrophenyl)amino)propanoic acid (**2**, 3 g, 10.1 mmol) was taken in round bottom flask. Then, Eaton's reagent (30 mL) was added and the RM was stirred at 60 °C for 2 h. Progress of the reaction was monitored by TLC. After completion, RM was quenched with ice cold water (50 ml) and extracted with EtOAc (2 x 70 ml). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give title product (**3**, 2 g, 63.5%) as a yellow solid. LCMS (ES): *m/z* =251.2 $[M+H]^+$

Step-3: Preparation of methyl 8-amino-4-oxo-1,2,3,4-tetrahydroquinoline-6-carboxylate **(4)**



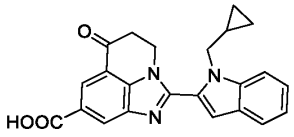
To a stirred solution of methyl 8-nitro-4-oxo-1,2,3,4-tetrahydro-6-quinolinecarboxylate (**3**, 2 g, 6.39 mmol) in ethanol (14 mL), water (6 mL), iron powder (1.79 g, 32 mmol) and NH_4Cl (3.42 g, 63.9 mmol) were added. The RM was stirred at 80 °C for 6 h. Progress of the reaction was monitored by TLC. After completion, RM was filtered and the filtrate was concentrated under reduced pressure. The obtained residue was triturated with pentane (2 x 30 mL) and dried to give title product (**4**, 1 g, 31.2%) as a brown solid. LCMS (ES): *m/z* =221.2 $[M+H]^+$

Step-4: Preparation of methyl 2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylate **(5)**



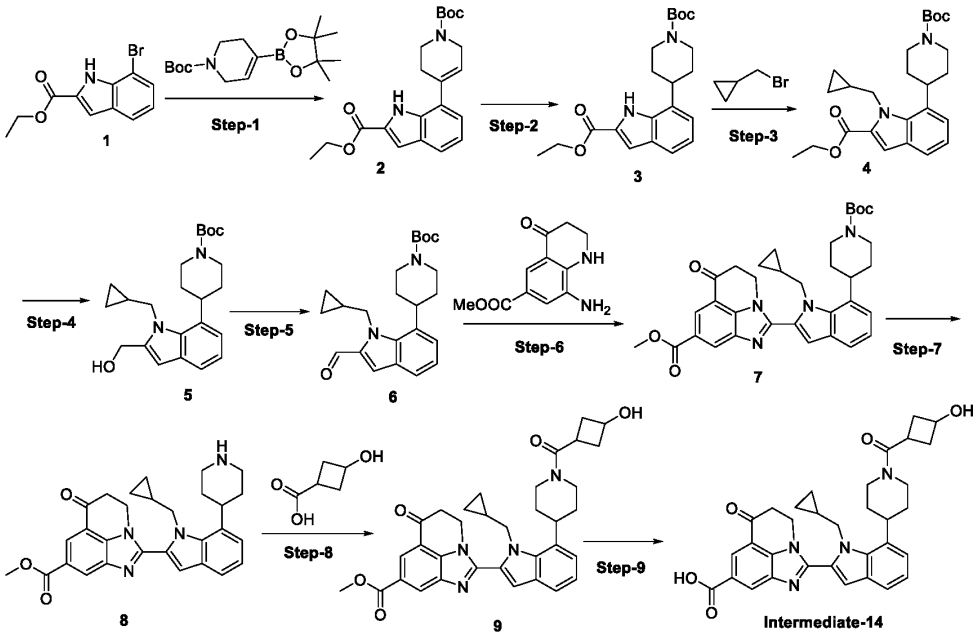
To the stirred solution of methyl 8-amino-4-oxo-1,2,3,4-tetrahydro-6-quinolinecarboxylate (**4**, 1 g, 2 mmol) in DMF (8 mL) and water (2 mL), 1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde (**6**, 0.398 g, 2 mmol) and oxone (0.92 g, 3 mmol) were added. The RM was stirred at 80 °C for 3 h. The progress of the reaction was monitored by TLC. After completion, the RM was quenched with water (50 mL) and extracted with EtOAc (2 X 70 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude was purified by neutral alumina flash column chromatography using 30% EtOAc in heptane to give title product (**5**, 0.3 g, 36.4%) as a yellow solid. LCMS (ES): *m/z* =400 $[M+H]^+$

Step-5: Preparation of 2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylic acid **(Intermediate-13)**



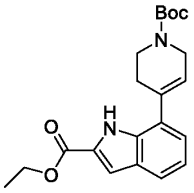
To a stirred solution of methyl 2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylate (**5**, 0.25 g, 0.626 mmol) in 1,4-dioxane (0.5 mL), 6N hydrogen chloride (0.6 mL) was added at 0 °C. The reaction was stirred at 90 °C for 16 h. The reaction was monitored by TLC. After completion, the RM was concentrated under reduced pressure. The obtained solid was triturated with diethyl ether (2 X 30 mL) and dried to give title product (**Intermediate-13**, 0.15 g, 48.7%) as a yellow solid. LCMS (ES): *m/z* =386.4 $[M+H]^+$

Synthesis of 2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylic acid (Intermediate-14)



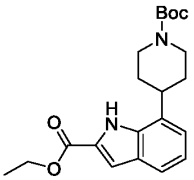
Reagents & conditions: 1. CataCXium-A-Pd-G_3, K_3PO_4, THF, water, 110 °C, 3 h; **2.** Pd/C, MeOH, RT, 2 h; **3.** Cs_2CO_3, DMF, 90 °C, 3 h; **4.** $LiAlH_4$, THF, -78 °C, 3 h; **5.** MnO_2, THF, RT, 6 h; **6.** Oxone, DMF : H_2O, 115 °C, 16 h; **7.** 4M HCl, DCM, 0 °C-RT, 1 h; **8.** HATU, DIPEA, DMF, RT, 1 h; **9.** NaOH, THF, 70 °C, 2 h.

Step-1: Preparation of ethyl 7-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole-2-carboxylate **(2)**



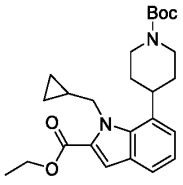
To a stirred solution of ethyl 7-bromo-1H-indole-2-carboxylate (**1**, 1 g, 3.73 mmol) in THF (9 mL), water (1 mL), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydro-1-pyridinecarboxylate (1.27 g, 4.1 mmol) and potassium phosphate (2.38 g, 11.2 mmol) were added. The RM was purged with nitrogen gas for 5 minutes. Then, cataCXium-A-Pd-G3 (0.272 g, 0.373 mmol) was added. The reaction was stirred at 110 °C for 3 h. The progress of the reaction was monitored by TLC. After completion, the RM was filtered through a sintered funnel and concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography using 5% EtOAc in heptane to give title product (2, 1.3 g, 75.2%) as a yellow solid. LCMS (ES): *m/z* =371.4 $[M+H]^+$

Step-2: Preparation of ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indole-2-carboxylate **(3)**



To a stirred solution of ethyl 7-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole-2-carboxylate (**2**, 1.2 g, 2.7 mmol) in methanol (15 mL), 10% palladium on carbon (50%wet in H_2O, 1.2 g) was added. The RM was stirred at room temperature for 2 h. The progress of the reaction was monitored by LCMS. After completion, the RM was filtered through celite bed and the filtrate was concentrated under reduced pressure to give title product (**3**, 1 g, 72.6%) as a yellow solid. LCMS (ES): *m/z* =373.2 $[M+H]^+$

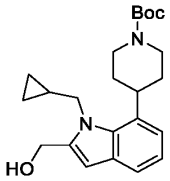
Step-3: Preparation of ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-indole-2-carboxylate **(4)**



To a stirred solution of ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-indole-2-carboxylate (**3**, 1 g, 1.9 mmol) in DMF (10 mL), cesium carbonate (1.85 g, 5.69 mmol) and 1-

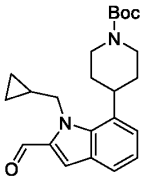
(bromomethyl)cyclopropane (0.38 g, 2.28 mmol) were added. The reaction was stirred at 90 °C for 3 h. The reaction was monitored by TLC. After completion, the RM was quenched with ice cold water (30 mL) and extracted with EtOAc (2 x 50 mL). The organic layer was washed with ice cold saturated solution of sodium chloride (50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give title product (**4**, 1 g, 86.6%) as a yellow solid. LCMS (ES): *m/z* =427.2 $[M+H]^+$

Step-4: Preparation of tert-butyl 4-(1-(cyclopropylmethyl)-2-(hydroxymethyl)-1H-indol-7-yl)piperidine-1-carboxylate **(5)**



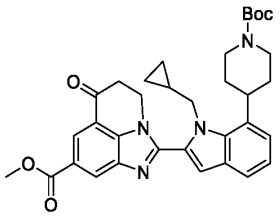
To a stirred solution of ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-indole-2-carboxylate (**4**, 1 g, 1.99 mmol) in THF (10 mL), LAH (4 mL; 1M in THF) was added dropwise at -78 °C. The reaction was stirred at -78 °C for 3 h. The reaction was monitored by TLC. After completion, the RM was quenched with saturated solution of ammonium chloride (50 mL) and extracted with EtOAc (2 X 70 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give title product (**5**, 0.85 g, 91%) as a yellow semi-solid. LCMS (ES): *m/z* =385.4 $[M+H]^+$

Step-5: Preparation of tert-butyl 4-(1-(cyclopropylmethyl)-2-formyl-1H-indol-7-yl)piperidine-1-carboxylate **(6)**



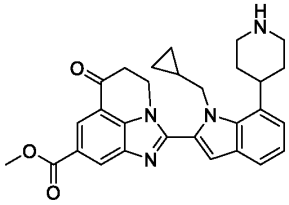
To a stirred solution of tert-butyl 4-(1-(cyclopropylmethyl)-2-(hydroxymethyl)-1H-indol-7-yl)piperidine-1-carboxylate (**5**, 0.85 g, 1.81 mmol) in THF (10 mL), manganese dioxide (1.58 g, 18.1 mmol) was added. The reaction was stirred at room temperature for 6 h. The reaction was monitored by TLC. After completion, the RM was filtered through sintered funnel. The filtrate was concentrated under reduced pressure to give title product (**6**, 0.7 g, 79.1%) as a yellow semi-solid. LCMS (ES): *m/z* =383.2 $[M+H]^+$

Step-6: Preparation of methyl 2-(7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylate (**7**)



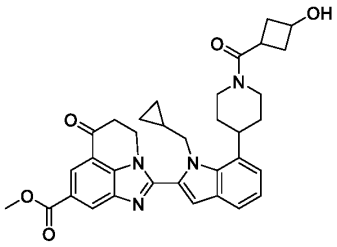
To a stirred solution of tert-butyl 4-(1-(cyclopropylmethyl)-2-formyl-1H-indol-7-yl)piperidine-1-carboxylate (**6**, 0.7 g, 1.43 mmol) in DMSO (10 mL), methyl 8-amino-4-oxo-1,2,3,4-tetrahydroquinoline-6-carboxylate (**6**, 0.39 g, 1.43 mmol) and oxone (0.67 g, 3.57 mmol) were added. The reaction was stirred at 115 °C for 16 h. The progress of reaction was monitored by TLC. After completion, the RM was quenched with water (20 mL) and extracted with EtOAc (2 X 50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude was purified by neutral alumina flash column chromatography using 20% EtOAc in heptane to give title product (**7**, 0.4 g, 38.4%) as a yellow solid. LCMS (ES): *m/z* =583.4 $[M+H]^+$

Step-7: Preparation of methyl 2-(1-(cyclopropylmethyl)-7-(piperidin-4-yl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylate (**8**)



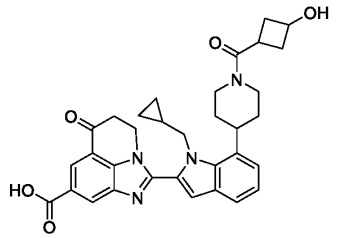
To a stirred solution of methyl 2-(7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-(cyclopropylmethyl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylate (**7**, 0.2 g, 0.343 mmol) in DCM (2 mL), hydrogen chloride (1 mL, 4M in 1,4-dioxane) was added at 0 °C. The reaction was stirred at room temperature for 1 h. The reaction was monitored by TLC. After completion, the RM was concentrated under reduced pressure. The obtained solid was triturated with diethyl ether and dried to give title product (**8**, 0.11 g, 73.8%) as a yellow solid. LCMS (ES): *m/z* =483.2 $[M+H]^+$

Step-8: Preparation of methyl 2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylate (**9**)



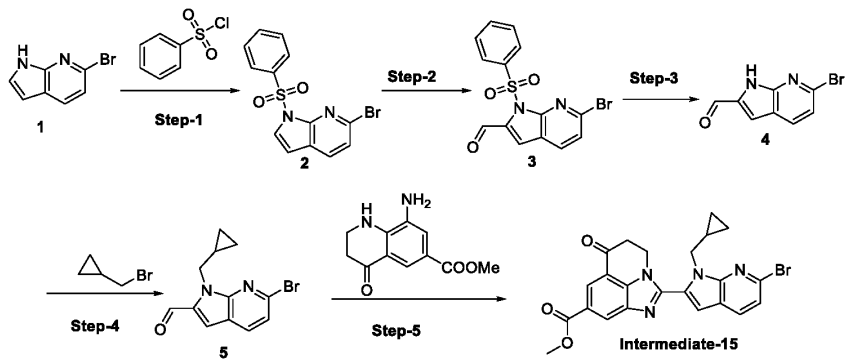
To a stirred solution of 3-hydroxycyclobutanecarboxylic acid (0.033 g, 0.288 mmol) in DMF (1 mL), DIPEA (0.1 mL) and HATU (0.14 g, 0.36 mmol) were added. Then, methyl 2-(1-(cyclopropylmethyl)-7-(piperidin-4-yl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylate (**8**, 0.13 g, 0.24 mmol) was added. The reaction was stirred at room temperature for 1 h. The reaction was monitored by TLC. After completion, the RM was quenched with water (10 mL) and extracted with EtOAc (2 x30 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give title product (**9**, 0.18 g, 38.7%) as a yellow solid. LCMS (ES): *m/z* =581.2 $[M+H]^+$

Step-9: Preparation of 2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylic acid **(Intermediate-14)**



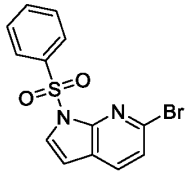
To a stirred solution of methyl 2-(1-(cyclopropylmethyl)-7-(1-(3-hydroxycyclobutane-1-carbonyl)piperidin-4-yl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylate (**9,** 0.18 g, 0.108 mmol) in methanol (0.5 mL), THF (2 mL) and sodium hydroxide (0.013 g, 0.32 mmol) was added. The RM was stirred at 70 °C for 2 h. The reaction was monitored by TLC. After completion, the RM was concentrated under reduced pressure, neutralised with 1N HCl and extracted with EtOAc (2 X 50 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give title product (**Intermediate-14**, 0.12 g, 58.5%) as a yellow solid. LCMS (ES): *m/z* =567.4 $[M+H]^+$

Synthesis of methyl 2-(6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylate (Intermediate-15)



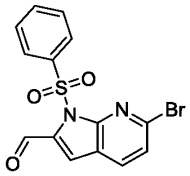
Reagents & conditions: 1. NaH, THF, 0 °C to RT, 2 h; **2.** DMF, LDA, THF, -78 °C, 2 h; **3.** TBAF, THF, RT, 2 h; **4.** Cs_2CO_3, DMF, RT, 12 h; **5.** $Na_2S_2O_5$ (2.5 eq.), DMSO (15 V), 90 °C, 16 h.

Step-1: Preparation of 6-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine **(2)**



To a stirred solution of 6-bromo-1H-1,7-diazaindene (**1**, 15 g, 76.1 mmol) in THF (300 mL), sodium hydride (6.09 g,152 mmol, 60% in mineral oil) was added portion wise at 0 °C. Then (chlorosulfonyl)benzene (12.7 mL, 99 mmol) was added and the RM was stirred at RT for 2 h. After completion of reaction, as monitored by TLC, The RM was poured into cold water (500 mL) slowly and extracted with EtOAc (300 mL x 3). The combined organic layer was washed with brine (300 mL), dried over Na_2SO_4 and concentrated to afford title product (**2**, 24 g, 93%) as off white solid. LCMS (ES) m/z = 337.2 $[M+H]^+$

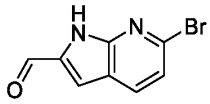
Step-2: Preparation of 6-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine-2-carbaldehyde **(3)**



To a stirred solution of 6-bromo-1-(phenylsulfonyl)-1H-1,7-diazaindene (**2**, 24 g, 71.2 mmol) in THF (240 mL), LDA (71 mL, 142 mmol, 2M in THF) was added dropwise at -78 °C and the RM was stirred at the same temperature for 30 mins. Then DMF (16.5 mL, 214 mmol) was added drop wise and reaction was continued for 1 h. After completion of reaction, as monitored by TLC, the RM was quenched with saturated solution of NH_4Cl and extracted with

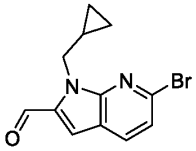
EtOAc (300 mL X 3), the combined organic layer was washed with brine (300 mL), dried over Na_2SO_4 and concentrated to get the crude compound, which was washed with diethyl ether to afford title product (**3**, 13 g, 50%) as light brown solid. LCMS (ES) m/z = 365.21 $[M+H]^+$

Step-3: Preparation of 6-bromo-1H-pyrrolo[2,3-b]pyridine-2-carbaldehyde **(4)**



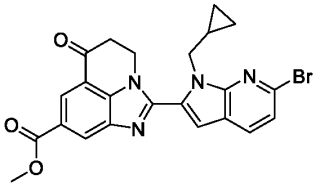
To a stirred solution of 6-bromo-1-(phenylsulfonyl)-1H-1,7-diazaindene-2-carbaldehyde (**3**, 13 g, 35.6 mmol) in THF (325 mL), TBAF (107 mL, 107 mmol, 1M in THF) was added at 0 °C and the RM was stirred at RT for 2 h. After completion of reaction monitored by LCMS, RM was diluted with water (500 mL) and extracted with EtOAc (300 mL X 3). The combined organic layer was washed with brine (250 mL), dried over Na_2SO_4 and concentrated to get the crude title product (**4**, 8 g, crude) as brown solid, which was used as such for next step. LCMS (ES) m/z = 224.94 $[M+H]^+$

Step-4: Preparation of 6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-2-carbaldehyde **(5)**



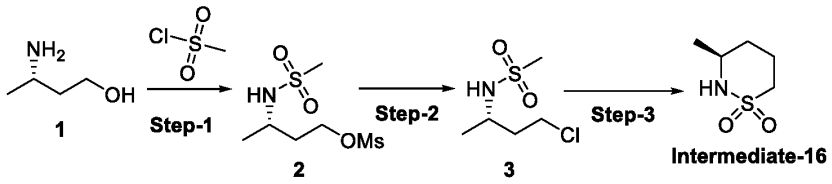
To a stirred solution of 6-bromo-1H-1,7-diazaindene-2-carbaldehyde (**4**, 8 g, 35.5 mmol) in DMF (120 mL), cesium carbonate (23.2 g, 71.1 mmol) was added followed by the addition of 1-(bromomethyl)cyclopropane (3.8 mL, 39.1 mmol) and the RM was stirred at RT for 12 h. After completion of reaction, as monitored by TLC, the RM was diluted with water (300 mL) and extracted with EtOAc (250 mL X 3). The combined organic layer was washed with cold water (250 mL) brine (250 mL), dried over Na_2SO_4 and concentrated to get the crude material, which was purified by silica gel column chromatography eluting with 10 % EtOAc in hexane to afford title product (**5**, 6 g, 60%) as light yellow solid. LCMS (ES) m/z = 279.16 $[M+H]^+$

Step-5: Preparation of methyl 2-(6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylate **(Intermediate-15)**



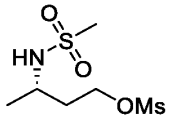
To a stirred solution of 6-bromo-1-(cyclopropylmethyl)-1H-1,7-diazaindene-2-carbaldehyde (**5**, 1.5 g, 5.37 mmol) in DMSO (60 mL), disodium disulfite (2.55 g, 13.4 mmol) and methyl 8-amino-4-oxo-1,2,3,4-tetrahydro-6-quinolinecarboxylate (1.78 g, 8.06 mmol) were added and the RM was stirred at 90 °C for 16 h. After completion of reaction, as monitored by TLC, the RM was diluted with water (100 mL) and extracted with EtOAc (100 mL X 3). The combined organic layer was washed with cold water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated to get crude material, which was purified by silica gel column chromatography eluting with 20% EtOAc in hexane to afford title product (**Intermediate-15,** 0.6 g, 23%) as yellow solid. LCMS (ES) m/z = 479.20 $[M+H]^+$

Synthesis of (S)-3-methyl-1,2-thiazinane 1,1-dioxide (Intermediate-16)



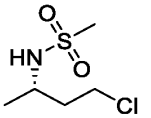
Reagents & conditions: 1. Et_3N, THF, RT, 16 h; **2.** NaCl, DMF, 80°C, 16 h; **3.** n-BuLi, DIPEA, 4,5-diazaphenanthrene, THF, RT, 16 h.

Step-1: Preparation of (S)-3-(methylsulfonamido)butyl methanesulfonate **(2)**



To a stirred solution of (S)-3-amino-1-butanol (**1**, 5 g, 56.1 mmol) in THF (150 mL), triethylamine (19.5 mL, 140 mmol) was added followed by the addition of (chlorosulfonyl)methane (10.7 mL, 139 mmol) slowly at 0 °C and the RM was stirred at RT for 16 h. After completion of reaction, as monitored by TLC, the RM was filtered, washed with THF and the filtrate was concentrated to afford title product (**2**, 13 g, 94%) as yellowish liquid, which was used as such for next step.

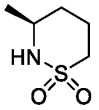
Step-2: Preparation of (S)-N-(4-chlorobutan-2-yl)methanesulfonamide **(3)**



To a stirred solution of (S)-3-(methylsulfonamido)butyl methanesulfonate (**2**, 13 g, 53 mmol) in DMF (130 mL), sodium chloride (13 g, 223 mmol) was added and the RM was stirred at 80 °C for 16 h. After completion of reaction, monitored by TLC, the RM was diluted with water (150 mL) and extracted with EtOAc (300 mL X 3). The combined organic layer was

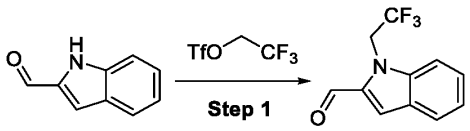
washed with cold water (200 mL), brine (200 mL), dried over Na_2SO_4 and concentrated to afford title product (**3**, 8 g, 81%) as yellowish liquid, which was used as such for next step.

Step-3: Preparation of (S)-3-methyl-1,2-thiazinane 1,1-dioxide **(Intermediate-16)**



To a stirred solution of (S)-N-(4-chlorobutan-2-yl)methanesulfonamide (**3**, 4 g, 21.5 mmol) in THF (80 mL), 4,5-diazaphenanthrene (15.5 mg, 86.2 µmol) and DIPEA (0.94 mL, 5.41 mmol) were added and the RM was cooled to -78 °C. Then N-butyllithium (30 mL, 75.4 mmol, 2.5 M in hexane) was added dropwise and the RM was allowed to warm to RT and stirred for 16 h. After completion of reaction, as monitored by TLC, the RM was quenched with saturated solution of NH_4Cl (100 mL), and extracted with EtOAc (100 mL x 3). The combined organic layer was dried over Na_2SO_4 and concentrated to get the crude compound, which was purified by silica gel column chromatography eluting 40% EtOAc in hexane to afford title product (**Intermediate-16,** 1.5 g, 47%) as off white solid. LCMS (ES) m/z = 148.1 [M-H]

Synthesis of 1-(2,2,2-trifluoroethyl)-1H-indole-2-carbaldehyde (Intermediate-17)

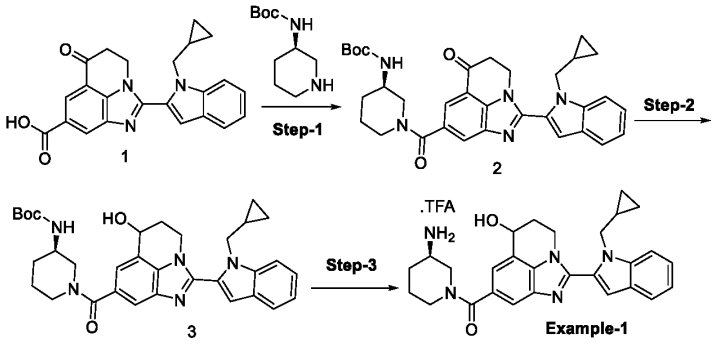


1 **Intermediate-17**

Reagents & conditions: 1. Cs_2CO_3, DMF, RT, 4 h.

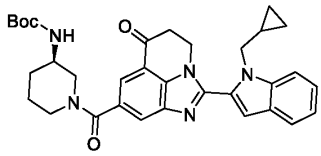
To a stirred solution of 2-indolecarbaldehyde (**1**, 2 g, 13.8 mmol) in DMF (20 mL), cesium carbonate (8.98 g, 27.6 mmol) was added followed by the addition of 1,1,1-trifluoro-2-(trifluoromesyloxy)ethane (3.2 g, 13.8 mmol) and the RM was stirred at RT for 12 h. After completion of reaction, as monitored by TLC, the RM was diluted with water (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with cold water (3 x 50 mL), brine, (50 mL), dried over Na_2SO_4 and concentrated to get the crude material, which was purified by silica gel column chromatography eluting with 10% EA in hexane to afford title product (**Intermediate-17,** 1.4 g, 75%) as light brown solid LCMS (ES) m/z = 228.21 $[M+H]^+$

Example-1: Synthesis of (R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl) methanone trifluoroacetate



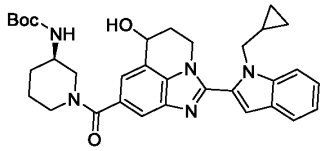
Reagents & conditions: 1. T_3P, DCM, 0 °C, RT, 3 h; **2.** $NaBH_4$, EtOH, RT, 16 h; **3.** 4M HCl in dioxane, RT, 1 h.

Step-1: Preparation of tert-butyl (R)-(1-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)piperidin-3-yl)carbamate **(2)**



To a solution of 2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylic acid (**1,** 0.3 g, 0.778 mmol) and tert-butyl (R)-piperidin-3-ylcarbamate (0.17 g, 0.856 mmol) in DCM (15 mL) was added DIPEA (0.503 g, 3.89 mmol). After stirring for 5 min at 0 °C, T3P (50% w/w in EtOAc, 0.743 g, 2.34 mmol) was added and the RM was allowed to stir at room temperature for 3 h. The progress of reaction was monitored by TLC and LCMS. After completion, the RM was quenched with water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over sodium sulphate and concentrated to get crude compound, which was further purified by neutral alumina column chromatography using 40% EtOAc in heptane to give title product (**2,** 0.2 g, 45.26%) as semisolid. LCMS (ES): m/z = 568.15 $[M+H]^+$.

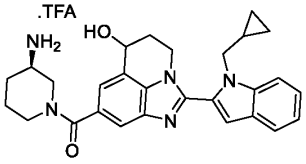
Step-2: Preparation of tert-butyl ((3R)-1-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)piperidin-3-yl)carbamate **(3)**



To a mixture of tert-butyl (R)-(1-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)piperidin-3-yl)carbamate (**2**, 0.030 g, 0.528 mmol) in EtOH (2 mL) was added $NaBH_4$ (0.004 g, 0.106 mmol) and stirred for 16 h at

room temperature. The progress of the reaction was monitored by LCMS and TLC. After completion of the reaction, the RM was diluted with water (5 mL) and extracted with 5% MeOH in DCM (3 x 50 mL). The combined organic layer was dried over sodium sulphate and concentrated to get crude compound which was purified by silica gel column chromatography using 40% EtOAc in heptane to get title product (**3**, 0.030 g, crude) which was used as such in next step without further purification. LCMS (ES): m/z = 570.20[M+H]$^+$.

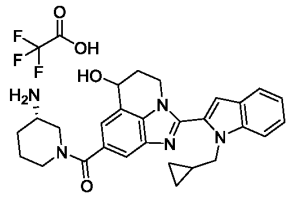
Step-3: Preparation of ((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate **(Example-1)**



To a stirred solution of tert-butyl ((3R)-1-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)piperidin-3-yl)carbamate (**3**, 0.030 g, 0.527 mmol) in DCM (2 mL) was added 4M HCl in dioxane (0.2 mL) at 0 °C and the RM was stirred room temperature for 1 h. After completion of the reaction, the reaction was concentrated under reduced pressure to get crude compound which was further purified by reverse phase preparative HPLC (Symmetry Atlantis T3, 19 mm × 250 mm, 10 µM, ACN and 0.02% trifluoroacetic acid in water, flow rate of 18 mL/min) to afford title product (**Example-1**, 0.015 g, 56%) as white solid. LCMS (ES) *m/z* = 470.35 [M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.94 (bs, 3H), 7.73-7.67 (m, 3H), 7.33-7.27 (m, 2H), 7.18-7.13 (m, 2H), 5.68 (bs, 1H), 5.10-5.00 (m, 1H), 4.70-4.60 (m, 2H), 4.54-4.44 (m, 2H), 4.20-4.10 (m, 1H), 3.30-3.10 (m, 4H), 2.30-2.15 (m, 2H), 2.18-2.05 (m, 1H), 1.80-1.70 (m, 1H), 1.60-1.50 (m, 2H), 1.20 (m, 1H), 0.35-0.30 (m, 2H), 0.23-0.19 (m, 2H).

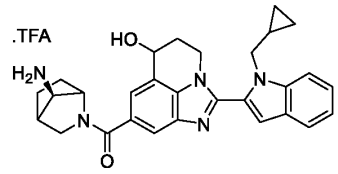
The following compounds were prepared following procedure described above.

Example-2: Synthesis of ((S)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate



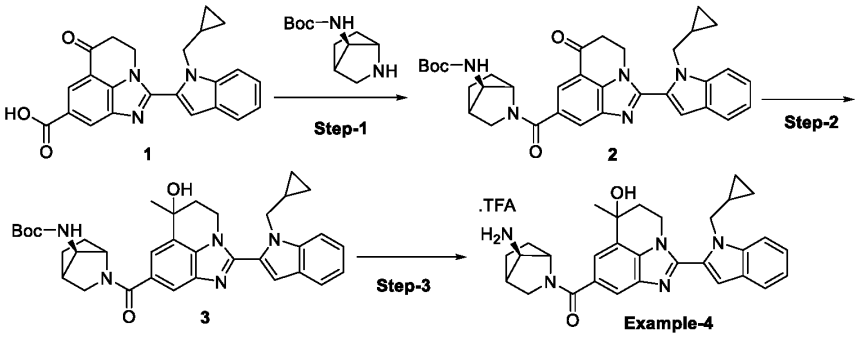
LCMS (ES) *m/z* = 470.30 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.94 (bs, 3H), 7.73-7.68 (m, 3H), 7.33-7.28 (m, 2H), 7.18-7.12 (m, 2H), 5.70 (bs, 1H), 5.05 (s, 1H), 4.70 (d, *J* = 9.8 Hz, 2H), 4.55-4.40 (m, 2H), 4.21 (m, 1H), 3.30-3.10 (m, 4H), 2.32-2.15 (m, 2H), 2.10-2.00 (m, 1H), 1.80-1.70 (m, 1H), 1.60-1.50 (m, 2H), 1.25-1.15 (m, 1H), 0.32 (d, *J* = 6.8 Hz, 2H), 0.21 (d, *J* = 5.2 Hz, 2H).

Example-3: Synthesis of ((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate



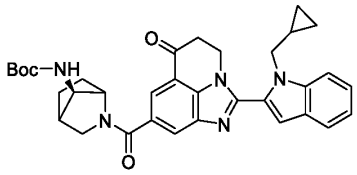
LCMS (ES) *m/z* = 482.17 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.20-7.8 (m, 4H), 7.69 (bs, 2H), 7.45-7.23 (m, 2H), 7.21-7.10 (m, 2H), 5.70 (bs, 1H), (5.05 (bs, 1H), 4.67 (bs, 2H), 4.53 (bs, 2H), 4.22-3.72 (m, 1H), 3.63-3.52 (m, 2H), 3.25-3.10 (m, 2H), 2.30-2.12 (bs, 2H), 1.90 (bs, 3H), 1.67 (bs, 1H), 1.26-1.13 (m, 1H), 0.40-0.25 (m, 2H), 0.20 (bs, 2H).

Example-4: Synthesis of ((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate



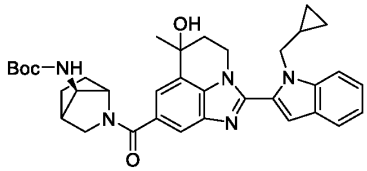
Reagents & conditions: 1. HATU, DIPEA, DMF, RT, 1 h**; 2.** MeMgBr, THF, 0 °C - RT, 3 h; **3.** 4M HCl in dioxane, DCM, 0°C-RT, 2 h.

Step-1: Preparation of tert-butyl ((7R)-2-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate **(2)**



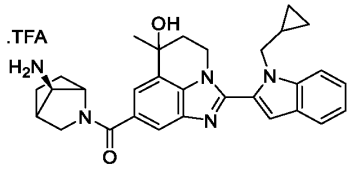
To a stirred solution of 2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylic acid (**1,** 0.12 g, 0.31 mmol) in DMF (1 mL), DIPEA (0.2 mL, 0.934 mmol) and HATU (0.178 g, 0.46 mmol) were added. To this tert-butyl ((7R)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (0.066 g, 0.311 mmol) was added. The reaction was stirred at room temperature for 1 h. The reaction was monitored by TLC. After completion, the RM was quenched with water (30 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give title product (**2**, 0.090 g, 45.3%) as a yellow solid. LCMS (ES): *m/z* =580.2 $[M+H]^+$

Step-2: Preparation of tert-butyl ((7R)-2-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate **(3)**



To a stirred solution of tert-butyl ((7R)-2-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (**2**, 0.090 g, 0.14 mmol) in THF (1.5 mL), methyl magnesium bromide (1.4 mL, 0.419 mmol, 3M in diethyl ether) was added at 0 °C. The reaction was stirred at room temperature for 3 h. Progress of the reaction was monitored by TLC. After completion, the RM was quenched with saturated solution of ammonium chloride (20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give title product (**3**, 0.120 g, crude) as a yellow solid. LCMS (ES): *m/z* =596.7 $[M+H]^+$

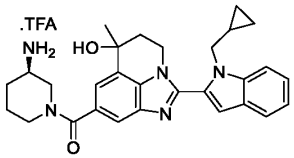
Step-3: Preparation of ((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate **(Example-4)**

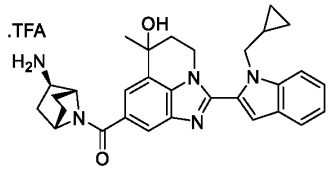
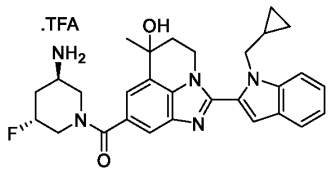
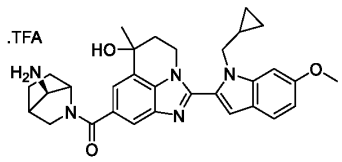


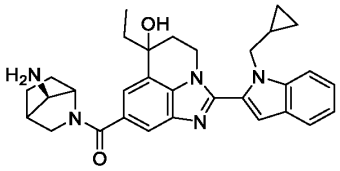
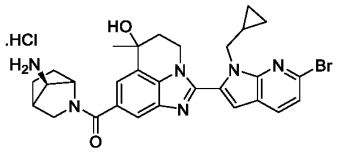
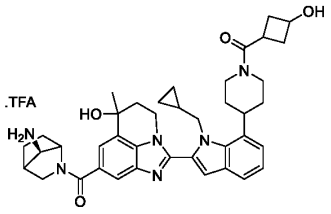
To a stirred solution of tert-butyl ((7R)-2-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (**2**, 0.12 g, 0.090 mmol) in DCM (1 mL), 4M HCl in 1,4 -dioxane (1 mL) was added at 0 °C. The reaction was stirred at room temperature for 2 h. Progress of the reaction was monitored by TLC. After completion, RM was concentrated under reduced pressure. The obtained solid was triturated with diethyl ether and dried. The residue was purified by reverse phase preparative HPLC (XBRIDGE C-8, 10 µm, ACN and 0.1% TFA in water) to give title product (**Example-4**, 0.030 g, 65.4%) as an off-white solid. LCMS (ES) *m/z* = 496.4 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.07 (bs, 1H), 7.93 (bs, 2H), 7.70-7.67 (m, 3H), 7.49-7.42 (m, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.19 (s, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 5.49 (bs, 1H), 4.72-4.60 (m, 2H), 4.49 (bs, 2H), 4.22-4.20 (m, 1H), 3.70-3.50 (m, 2H), 3.23-2.15 (m, 1H), 2.57 (bs, 1H), 2.21-2.14 (m, 2H), 2.00-1.80 (m, 3H), 1.70-1.64 (m, 4H), 1.18 (bs, 1H), 0.31 (d, *J* = 8 Hz, 2H), 0.19 (bs, 2H).

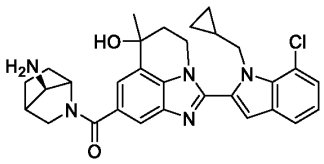
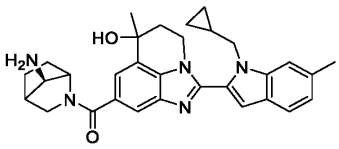
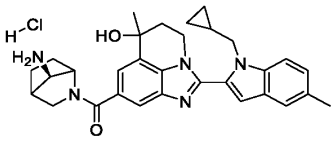
The compounds listed in below **Table III** were prepared by a procedure similar to the one described in **Example-4** with appropriate variations in reactants, quantity of reagents, protections & deprotections, solvents & reaction conditions. The characterization data of the compounds are summarized herein below **Table III**.

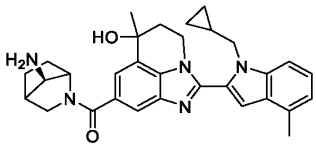
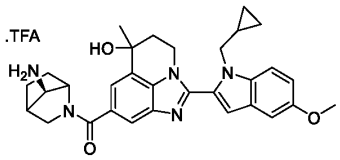
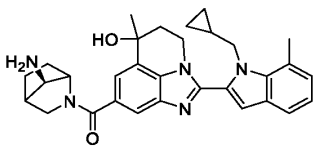
Table III:

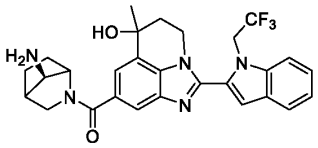
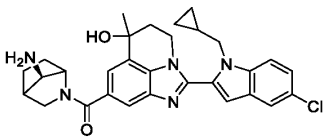
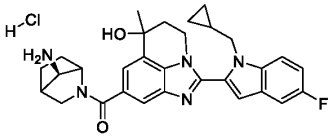
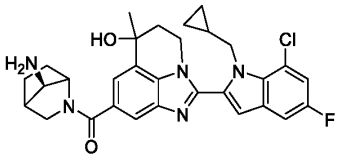
Example No.	Structure	Characterization data
5		LCMS (ES) *m/z* = 484.35 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.95 (bs, 3H), 7.72-7.65 (m, 3H), 7.38 (s, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.19 (s, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 5.48 (bs, 1H), 4.72-4.60 (m, 2H), 4.50 (s, 2H), 4.21-4.19 (m, 1H), 3.30-3.10 (m, 4H), 2.28-2.01 (m, 3H), 1.80-1.70 (m, 1H), 1.64 (s, 3H), 1.60-1.50 (m, 2H), 1.25-1.15 (m, 1H), 0.33 (d, *J* = 6.8 Hz, 2H), 0.21 (d, *J* = 5.2 Hz, 2H).

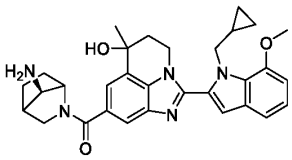
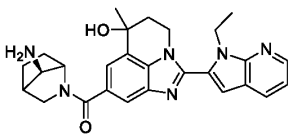
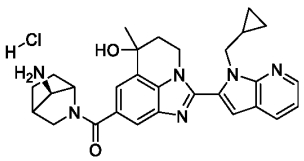
6		LCMS (ES): *m/z* =496.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.08 (bs, 3H), 7.86 (s, 1H), 7.69 (t, *J* = 7.6 Hz, 2H), 7.55 (s, 1H), 7.30 (t, *J* = 8.0. Hz, 1H), 7.21 (s, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 5.51 (bs. 1H), 4.78-4.60 (m, 2H), 4.58-4.40 (m, 4H), 3.80-3.70 (m, 2H), 2.28-2.10 (m, 2H), 1.90-1.80 (m, 3H), 1.65 (s, 3H), 1.62 (bs, 1H), 1.38-1.30 (m, 1H), 1.25-1.14 (m, 1H), 0.32 (d, *J* = 8.0 Hz, 2H), 0.25-0.15 (m, 2H).
7		LCMS (ES): *m/z* =502.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.01 (bs, 3H), 7.70-7.66 (m, 3H), 7.38 (s, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.19 (s, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 5.48 (bs, 1H), 5.10-4.85 (m, 1H), 4.73-4.60 (m, 2H), 4.54-4.50 (m, 2H), 4.08 (s, 1H), 3.44-3.42 (bs, 3H), 2.96 (bs, 1H), 2.40-2.33 (m, 1H), 2.28-2.18 (m, 1H), 2.17-2.09 (m, 1H), 1.93-1.72 (m, 1H), 1.64-1.63 (m, 3H), 1.23-1.17 (m, 1H), 0.32 (d, *J* = 8 Hz, 2H), 0.25-0.19 (m, 2H).
8		LCMS (ES): *m/z* =526.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.05 (bs, 1H), 7.97 (bs, 2H), 7.80-7.65 (m, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.47-7.40 (m, 1H), 7.17 (s, 1H), 7.11 (s, 1H), 6.81-6.78 (m, 1H), 5.47 (bs, 1H), 4.80-4.55 (m, 2H), 4.53-4.15 (m, 3H), 3.85 (s, 3H), 3.75 (bs, 1H), 3.65 (bs, 1H), 3.22-3.18 (m, 1H), 2.56 (bs, 1H), 2.25-2.15 (m, 2H), 2.01-1.80 (m, 3H), 1.71-1.55 (m, 4H), 1.17 (bs, 1H), 0.31 (d, *J* = 8 Hz, 2H), 0.06 (bs, 2H).

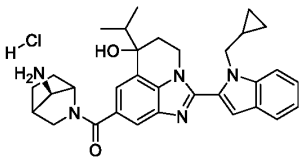
9		LCMS (ES): *m/z* =510.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.72-7.61 (m, 3H), 7.40-7.27 (m, 2H), 7.19-7.12 (m, 2H), 5.36-5.33 (m, 1H), 4.70-4.60 (m, 2H), 4.45-4.40 (m, 2H), 3.73 (d, *J* = 16.4 Hz, 1H), 3.66-3.50 (m, 1H), 3.16-2.97 (m, 2H), 2.20-2.10 (m, 3H), 2.01-1.90 (m, 4H), 1.84 (s, 2H), 1.72-1.63 (m, 1H), 1.49-1.40 (m, 1H), 1.20-1.15 (m, 1H), 1.00-0.90 (m, 3H), 0.35-0.26 (m, 2H), 0.25-0.10 (m, 2H).
10		LCMS (ES): *m/z* =575.26 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.25 (bs, 1H), 8.15-8.05 (m, 3H), 7,78 (d, *J* = 58 Hz, 1H), 7.55-7.42 (m, 1H), 7.40 (d, *J* = 8 Hz, 1H), 7.28 (s, 1H), 4.74-4.58 (m, 2H), 4.52 (bs, 2H), 3.82-3.77 (m, 2H), 3.58-3.48 (m, 2H), 3.22-3.14 (m, 1H), 2.57 (bs, 2H), 2.25-2.08 (m, 2H), 2.00-1.83 (bs, 3H), 1.66-1.64 (m, 3H), 1.27-1.23 (m, 1H), 0.35-0.30 (m, 4H).
11		LCMS (ES): *m/z* =677.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.06 (bs, 1H), 7.91 (bs, 2H), 7.67 (bs, 1H) 7.56 (d, *J* = 7.6 Hz, 1H), 7.50-7.43 (m, 1H), 7.22-7.15 (m, 2H), 7.14-7.10 (m, 1H), 5.60-5.40 (m, 1H), 4.80-4.70 (m, 2H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.50-4.40 (m, 2H), 4.21-4.18 (m, 1H), 4.00-3.92 (m, 2H), 3.80-3.70 (m, 1H), 3.69-3.60 (m, 2H), 3.20-3.12 (m, 2H), 3.99-3.90 (m, 1H), 3.85-3.80 (m, 2H), 2.60-2.55 (m, 1H), 2.40-230 (m, 2H), 2.29-2.10 (m, 2H), 2.09-1.84 (m, 7H), 1.75-1.60 (m, 6H), 1.00-0.90 (m, 1H), 0.23 (d, *J* = 8.0 Hz, 2H), -0.26-(-0.20) (m, 2H).

12		LCMS (ES): *m/z* =530.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.74-7.63 (m, 2H), 7.48-7.39 (m, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.25 (s, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 5.49 (d, *J* = 16.0 Hz, 1H), 5.03-4.93 (m, 2H), 4.41 (bs, 2H), 3.72 (d, *J* = 21.2 Hz, 1H), 3.52-3.50 (m, 1H), 3.14 (bs, 1H), 3.06-3.03 (m, 1H), 2.50-2.45 (m, 1H), 2.18-2.09 (m, 3H), 2.01-1.90 (m, 1H), 1.88 (s, 2H), 1.80-1.70 (m, 1H), 1.63-1.60 (m, 3H), 1.45-1.38 (m, 1H), 1.10-1.00 (m, 1H), 0.25-0.21 (m, 2H), -0.05-(-0.12) (m, 2H).
13		LCMS (ES): *m/z* =510.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.71-7.61 (m, 1H), 7.56 (d, *J* = 8 Hz, 1H), 7.47-7.38 (m, 2H), 7.11 (s, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.50-5.46 (m, 1H), 4.73-4.55 (m, 2H), 4.47 (bs, 2H), 3.74 (d, *J* = 22.4 Hz, 1H), 3.53-3.50 (m, 1H), 3.15 (bs, 1H), 3.08-3.04 (m, 1H), 2.47 (s, 3H), 2.23-2.08 (m, 3H), 2.03-1.87 (m, 2H), 1.83 (s, 3H), 1.78-1.68 (m, 1H), 1.65-1.60 (m, 2H), 1.45-1.39 (m, 1H), 1.20-1.13 (m, 1H), 0.35-0.25 (m, 2H), 0.24-0.10 (m, 2H).
14		LCMS (ES): *m/z* =510.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.35-8.21 (m, 3H), 7.76 (d, *J* = 54 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.52-7.45 (m, 2H), 7.14-7.11 (m, 2H), 4.67-4.54 (m, 2H), 4.49 (bs, 2H), 4.22 (bs, 1H), 3.80-3.72 (m, 1H), 3.65-3.58 (m, 1H), 3.54-3.48 (m, 1H), 3.21-3.10 (m, 1H), 2.69-2.65 (m, 1H), 2.42 (s, 3H), 2.25-2.13 (m, 2H), 2.03-1.82 (m, 3H), 1.68-1.58 (m, 4H), 1.20-1.10 (m, 1H), 0.30 (d, *J* = 8.4 Hz, 2H), 0.16-0.15 (m, 2H).

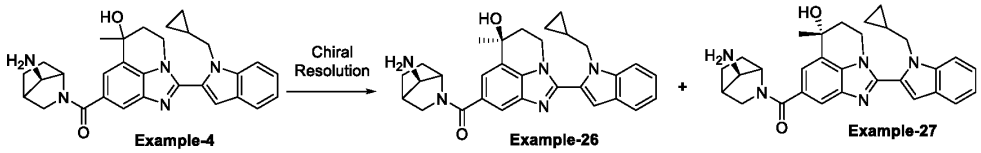
15		LCMS (ES): *m/z* =510.29 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.67 (d, *J* = 44 Hz, 1H), 7.49-7.39 (m, 2H), 7.20-7.16 (m, 2H), 6.93 (d, *J* = 7.2 Hz, 1H), 5.50-5.46 (m, 1H), 4.70-4.58 (m, 2H), 4.52 (bs, 2H), 3.80-3.72 (m, 1H), 3.65-3.52 (m, 1H), 3.17 (bs, 1H), 3.09-2.99 (m, 1H), 2.56 (s, 3H), 2.25-2.10 (m, 3H), 2.03-1.82 (m, 2H), 1.90 (s, 2H), 1.78-1.60 (m, 4H), 1.48-1.30 (m, 1H), 0.20-0.10 (m, 1H), 0.29 (d, *J* = 8 Hz, 2H), 0.17-0.15 (m, 2H).
16		LCMS (ES): *m/z* =526.41 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.05 (bs, 1H), 7.91 (bs, 2H), 7.81-7.67 (m, 1H), 7.58 (d, *J* = 9.2 Hz, 1H), 7.47-7.41 (m, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 7.08 (s, 1H), 6.95-6.92 (m, 1H), 5.47 (bs, 1H), 4.71-4.53 (m, 2H), 4.49 (bs, 2H), 4.21 (d, *J* = 8.4 Hz, 1H), 3.80 (s, 3H), 3.75 (bs, 2H), 3.22-3.15 (m, 1H), 2.57 (bs, 1H), 2.25-2.15 (m, 2H), 2.00-1.80 (m, 3H), 1.71-1.64 (m, 4H), 1.17-1.14 (m, 1H), 0.30 (d, *J* = 8.4 Hz, 2H), 0.17 (bs, 2H).
17		LCMS (ES): *m/z* =510.36 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.73-7.62 (m, 1H), 7.54-7.52 (m, 1H), 7.45-7.40 (m, 1H), 7.13-7.12 (m, 1H), 7.06-7.01 (m, 2H), 5.52-5.49 (m, 1H), 4.89-4.80 (m, 2H), 4.43 (bs, 2H), 3.76-3.71 (m, 1H), 3.54-3.51 (m, 1H), 3.15 (bs, 1H), 3.07-3.04 (m, 1H), 2.80 (s, 3H), 2.25-2.10 (m, 3H), 2.02-1.90 (m, 1H), 1.86 (s, 3H), 1.77-1.70 (m, 1H), 1.65-1.63 (m, 3H), 1.45-1.41 (m, 1H), 0.95-0.89 (m, 1H), 0.19 (d, *J* = 8 Hz, 2H), -0.22-(-0.33) (m, 2H).

18		LCMS (ES): *m/z* =524.33 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.79-7.73 (m, 3H), 7.46-7.35 (m, 3H), 7.22 (t, *J* = 7.6 Hz, 1H), 6.12-5.90 (m, 2H), 5.51-5.45 (m, 1H), 4.57 (bs, 2H), 4.10-3.51 (m, 2H), 3.54-3.51 (m, 1H), 3.16 (bs, 1H), 3.08-3.00 (m, 1H), 2.26-2.10 (m, 3H), 2.04-1.83 (m, 3H), 1.76-1.70 (m, 1H), 1.64 (d, *J* = 6 Hz, 3H), 1.45-1.31 (m, 1H).
19		LCMS (ES): *m/z* =530.32 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.74-7.63 (m, 3H), 7.45-7.40 (m, 1H), 7.30-7.27 (m, 1H), 7.17 (s, 1H), 5.51-5.45 (m, 1H), 4.75-4.58 (m, 2H), 4.47 (bs, 2H), 4.10-3.50 (m, 3H), 3.16 (bs, 1H), 3.08-2.97 (m, 1H), 2.25-2.09 (m, 3H), 2.00-1.68 (m, 4H), 1.64 (d, *J* = 5.2 Hz, 3H), 1.45-1.28 (m, 1H), 1.18-1.14 (m, 1H), 0.32 (d, *J* = 8 Hz, 2H), 0.21-0.16 (m, 2H).
20		LCMS (ES): *m/z* =514.35 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.31 (bs, 1H), 8.17 (bs, 2H), 7.83-7.69 (m, 2H), 7.51-7.45 (m, 2H), 7.18-7.13 (m, 2H), 4.69-4.61 (m, 2H), 4.54-4.48 (m, 2H), 4.22 (bs, 1H), 3.63-3.52 (m, 2H), 3.21-3.11 (m, 1H), 2.69-2.58 (m, 2H), 2.25-2.07 (m, 2H), 1.95 (bs, 3H), 1.64 (d, *J* = 6 Hz, 4H), 1.23-1.16 (m, 1H), 0.31 (d, *J* = 8 Hz, 2H), 0.18-0.17 (m, 2H).
21		LCMS (ES): *m/z* =548.33 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.76-7.65 (m, 1H), 7.54-7.51 (m, 1H), 7.47-7.42 (m, 1H), 7.38-7.35 (m, 1H), 7.25 (s, 1H), 5.51-5.46 (m, 1H), 5.00-4.96 (m, 2H), 4.42 (bs, 2H), 3.74 (d, *J* = 20.4 Hz, 1H), 3.65-3.51 (m, 1H), 3.17 (bs, 1H), 3.09-3.00 (m, 1H), 2.25-2.08 (m, 3H),

		2.01-1.90 (m, 4H), 1.67-1.63 (m, 4H), 1.48-1.30 (m, 1H), 1.12-1.03 (m, 1H), 0.27-0.20 (m, 2H), -0.03-(-0.16) (m, 2H).
22		LCMS (ES): *m/z* =526.32 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.73-7.62 (m, 1H), 7.44-7.39 (m, 1H), 7.26 (d, *J* = 8 Hz, 1H), 7.10 (s, 1H), 7.05 (t, *J* = 8 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 5.46 (d, *J* = 15.2 Hz, 1H), 4.90-4.79 (m, 2H), 4.42 (bs, 2H), 3.96 (s, 3H), 3.74 (d, *J* = 20.8 Hz, 1H), 3.65-3.50 (m, 1H), 3.16 (bs, 1H), 3.08-2.98 (m, 1H), 2.24-2.10 (m, 3H), 2.01-1.93 (m, 1H), 1.89 (s, 3H), 1.76-1.66 (m, 1H), 1.63 (d, *J* = 5.2 Hz, 3H), 1.48-1.30 (m, 1H), 1.10-1.00 (m, 1H), 0.21 (d, *J* = 8 Hz, 2H), 0.02-(-0.04) (m, 2H).
23		LCMS (ES): *m/z* =471.32 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.43-8.41 (m, 1H), 8.13-8.11 (m, 1H), 7.76-7.65 (m, 1H), 7.45-7.41 (m, 1H), 7.23-7.20 (m, 2H), 5.48 (d, *J* = 13.6 Hz, 1H), 4.92-4.80 (m, 2H), 4.54-4.53 (m, 2H), 3.75 (d, *J* = 20.8 Hz, 1H), 3.54-3.53 (m, 1H), 3.17 (bs, 1H), 3.09-3.05 (m, 1H), 2.24-2.10 (m, 3H), 2.01-1.93 (m, 1H), 1.90 (s, 3H), 1.75-1.69 (m, 1H), 1.64 (d, *J* = 4.4 Hz, 3H), 1.45-1.40 (m, 1H), 1.31 (t, *J* = 6.8 Hz, 3H).
24		LCMS (ES): *m/z* =497.30 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.41 (d, *J* = 4 Hz, 1H), 8.38 (bs, 1H), 8.24 (bs, 2H), 8.15 (d, *J* = 7.6 Hz, 1H), 7.86-7.71 (m, 1H), 7.53-7.46 (m, 1H), 7.25-7.21 (m, 2H), 4.77-4.65 (m, 2H), 4.53 (bs, 2H), 4.23 (bs, 1H), 3.80-3.75 (m, 1H), 3.65-3.48 (m, 2H), 3.21-3.13 (m, 1H), 2.66-2.58 (m, 1H), 2.22-2.15 (m, 2H), 1.97 (bs, 3H), 1.72-

		1.58 (m, 4H), 1.36-1.23 (m, 1H), 0.31-0.28 (m, 4H).
25		LCMS (ES): *m/z* =524.32 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.06-7.91 (m, 2H), 7.79-7.68 (m, 3H), 7.42-7.33 (m, 1H), 7.31-7.12 (m, 3H), 7.02 (d, *J* = 51.2 Hz, 1H), 5.28 (bs, 1H), 4.67 (bs, 2H), 4.54 (bs, 1H), 4.41 (bs, 1H), 4.17 (d, *J* = 28.4 Hz, 1H), 3.76 (bs, 1H), 3.48 (bs, 1H), 3.22-3.15 (m, 1H), 2.49 (bs, 1H), 2.41-2.37 (m, 1H), 2.23 (bs, 1H), 2.09-2.02 (m, 1H), 1.91 (bs, 3H), 1.69-1.60 (bs, 1H), 1.23-1.19 (m, 1H), 1.05 (bs, 3H), 0.95-0.94 (m, 3H), 0.32-0.31 (m, 2H), 0.22-0.17 (m, 2H).

Example-26: Synthesis of ((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((S)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone and Example-27: ((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((R)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone

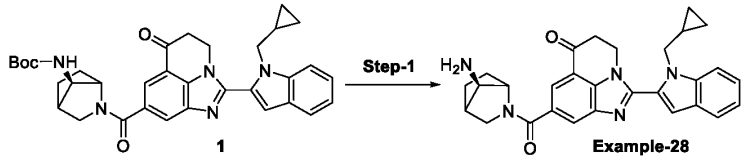


((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone(Examaple-4, 0.09 g) was purified by chiral SFC (Column: CHIRALPAK IG (30.0 mm x 250 mm) 5µm, Mobile phase: 0.1% Ammonium Hydroxide in MeOH) to afford title product ((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((S)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone (**Example-26**, 0.014 g) as off-white solid & title product ((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((R)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone (**Example-27**, 0.02 g) as off-white solid.

Analytical data of Example-26: LCMS (ES): m/z = 496.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.73-7.62 (m, 3H), 7.44-7.39 (m, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.17-7.12 (m, 2H), 5.45 (d, *J* = 7.2 Hz, 1H), 4.76-4.68 (m, 1H), 4.68-4.59 (m, 1H), 4.48 (bs, 2H), 4.10-3.72 (m, 1H), 3.65-3.48 (m, 1H), 3.16-2.98 (m, 2H), 2.20-2.11 (m, 3H), 2.00-1.82 (m, 3H), 1.75-1.68 (m, 1H), 1.65 (s, 3H), 1.45-1.43 (m, 1H), 1.37-1.20 (m, 1H), 1.19-1.15 (m, 1H), 0.31 (d, *J* = 8 Hz, 2H), 0.21-0.15 (m, 2H).

Analytical data of Example-27: LCMS (ES): m/z = 496.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.73-7.63 (m, 3H), 7.45-7.41 (m, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.17-7.12 (m, 2H), 5.48 (d, *J* = 15.6 Hz, 1H), 4.75-4.58 (m, 2H), 4.49 (bs, 2H), 4.10-3.78 (m, 1H), 3.65-3.52 (m, 1H), 3.17-3.00 (m, 2H), 2.23-2.11 (m, 3H), 2.02-1.82 (m, 3H), 1.75-1.68 (m, 1H), 1.63 (s, 3H), 1.45-1.43 (m, 1H), 1.37-1.20 (m, 1H), 1.19-1.15 (m, 1H), 0.31 (d, *J* = 8 Hz, 2H), 0.21-0.15 (m, 2H).

Example-28: Synthesis of 8-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4,5-dihydro-6H-imidazo[4,5,1-ij]quinolin-6-one

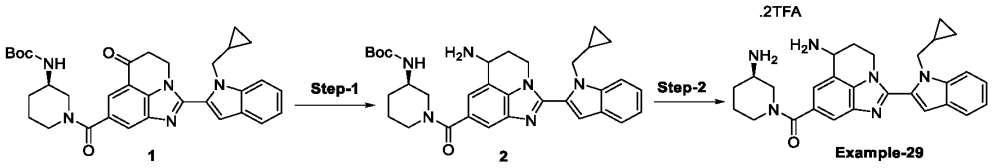


Reagents & conditions: 1. 4M HCl in dioxane, DCM, 0°C-RT, 1 h.

To a stirred solution of tert-butyl ((7R)-2-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (**1**, 0.045 g, 0.38 mmol) in DCM (0.5 mL), 4M HCl in dioxane (0.5 mL) was added at 0 °C. The reaction was stirred at room temperature for 1 h. The reaction was monitored by TLC. After completion, RM was concentrated under reduced pressure. The obtained solid was triturated with diethyl ether and dried. The residue was purified by reverse phase preparative HPLC (Xbridge Shield C18, 19 mm x 250 mm, 10µm, mobile phase: ACN in water containing 5 mM Ammonium acetate) to give title product (**Example-28**, 0.005 g, 28.8%) as a white solid.

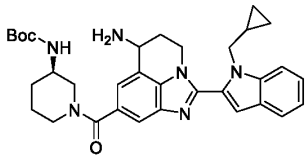
LCMS (ES): m/z = 480.25 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.10-8.02 (m, 1H), 7.72-7.60 (m, 3H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.22 (s, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 4.78 (s, 2H), 4.62 (d, *J* = 7.6 Hz, 2H), 3.70-3.60 (m, 1H), 3.53 (d, *J* = 7.6 Hz, 1H), 3.20-3.00 (m, 4H), 2.30-2.10 (m, 1H), 2.00-1.90 (m, 2H), 1.70-1.65 (m, 1H), 1.50-1.30 (m, 1H), 1.20-1.10 (m, 1H), 0.33 (d, *J* = 8.0 Hz, 2H), 0.190 (d, *J* = 4.0 Hz, 2H).

Example-29: Synthesis of (6-amino-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)((R)-3-aminopiperidin-1-yl)methanone di-trifluoroacetate



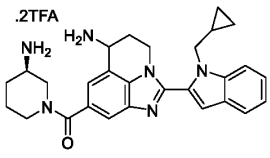
Reagents & conditions: 1. i) NH_4OAc, MeOH, 60 °C, 16 h, ii) $NaBH_3CN$, 60 °C, 1 h; **2.** 4M HCl in dioxane, 0 °C, RT, 1 h.

Step-1: Preparation of tert-butyl ((3R)-1-(6-amino-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)piperidin-3-yl)carbamate **(2)**



To a stirred solution of tert-butyl (R)-(1-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)piperidin-3-yl)carbamate (**1,** 0.1 g, 0.176 mmol) in methanol (2 mL), acetic acid (0.06 g, 0.176 mmol) and ammonium acetate (0.013 g, 0.176 mmol) were added and the RM was allowed to stir at 60 °C for 16 h. Then $NaBH_3CN$ (3.32 mg, 0.528 mmol) was added at 0 °C and the RM was stirred at 60 °C for 1 h. After completion (monitored by TLC), the RM was quenched with water (5 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried (sodium sulphate) and concentrated to get crude compound, which was further purified by neutral alumina column chromatography using 15% EtOAc in hexane to give the title product (**2,** 0.080 g, crude) as brown semisolid. LCMS (ES): m/z = 569.20 $[M+H]^+$

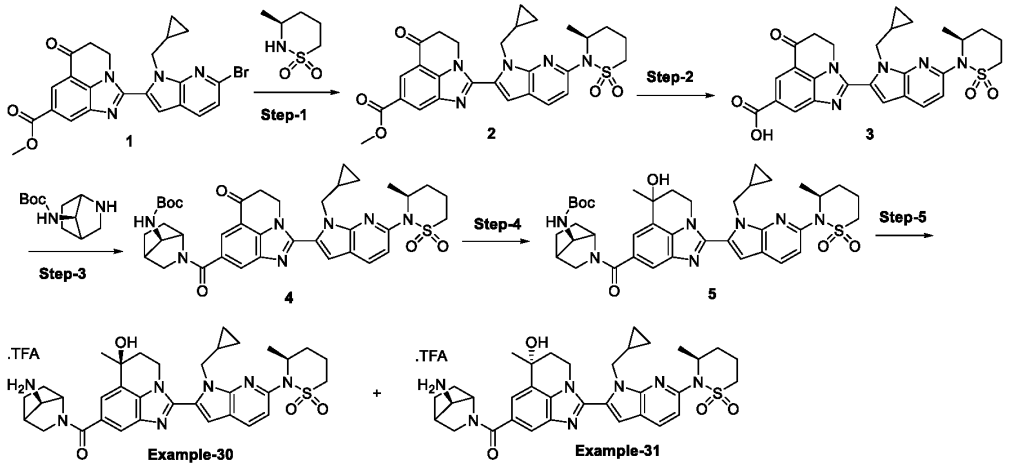
Step-2: Preparation of (6-amino-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)((R)-3-aminopiperidin-1-yl)methanone di-trifluoroacetate **(Example-29)**



To a stirred solution of tert-butyl ((3R)-1-(6-amino-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)piperidin-3-yl)carbamate (**2,** 0.08 g,

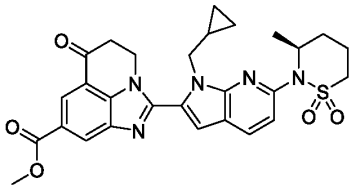
0.137 mmol) in DCM (2 mL) was added 4M HCl in 1,4-dioxane (0.2 mL) at 0 °C. The RM was stirred at room temperature for 1 h. After completion (monitored by TLC), the RM was concentrated to get crude compound, which was further purified by reverse phase preparative HPLC (Atlantis-T3, 19 mm x 250 mm, 10 µm, using ACN and 0.02% trifluoroacetic acid in water) to afford title product (**Example-29**, 0.021 g, 29.5%) as white solid. LCMS (ES): m/z = 469.40 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.64 (bs, 3H), 8.02 (bs, 3H), 7.88 (s, 1H), 7.71 (t, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 4.4 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.17-7.12 (m, 2H), 4.89 (bs, 1H), 4.70-4.40 (m, 4H), 4.30-4.20 (m, 1H), 3.30-3.10 (m, 4H), 2.40-2.30 (m, 2H), 2.10-2.00 (m, 1H), 1.80-1.70 (m, 1H), 1.60-1.50 (m, 2H), 1.25-1.15 (m, 1H), 0.33 (d, *J* = 6.8 Hz, 2H), 0.22 (d, *J* = 5.2 Hz, 2H).

Example-30 and Example-31: Synthesis of ((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((S)-2-(1-(cyclopropylmethyl)-6-((S)-3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate and ((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((R)-2-(1-(cyclopropylmethyl)-6-((S)-3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate



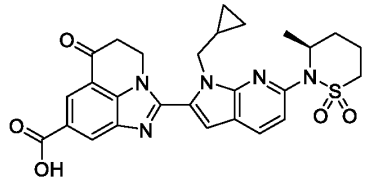
Reagents & conditions: 1. JackiePhos Pd G3, Cs_2CO_3, toluene, 90 °C, 2 h **2.** LiOH, THF: MeOH:H_2O, RT, 4 h; **3.** HATU, DIPEA, DMF, RT, 16 h; **4.** MeMgI, THF, 0 °C, 2 h; **5.** 4M HCl in Dioxane, DCM, 0 °C-RT, 5 h.

Step-1: Preparation of methyl (S)-2-(1-(cyclopropylmethyl)-6-(3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylate **(2)**



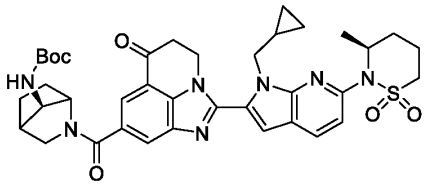
To a stirred solution of methyl 2-(6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylate (**1**, 0.9 g, 1.88 mmol) and (S)-3-methyl-1,2-thiazinane 1,1-dioxide (0.84 g, 5.63 mmol) in toluene (45 mL), cesium carbonate (1.84 g, 5.63 mmol) was added and RM was purged with N_2 for 5 mins. Then JackiePhos Pd G3 (0.110 g, 93.9 µmol) was added and the RM was heated at 90 °C for 2 h. After completion of reaction, as monitored by TLC, the RM was filtered through celite, washed with EtOAc (100 mL X 3) and the filtrate was concentrated to get the crude material, which was purified by silica gel column chromatography eluting with 15% EtOAc in hexane to afford title product (**2**, 0.155 g, 15%) as light yellow solid. LCMS (ES) m/z = 548.21 $[M+H]^+$

Step-2: Preparation of (S)-2-(1-(cyclopropylmethyl)-6-(3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylic acid **(3)**



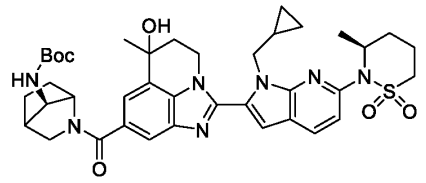
To a stirred solution of methyl (S)-2-(1-(cyclopropylmethyl)-6-(3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylate (**2**, 0.250 g, 0.45 mmol) in THF (6 mL), MeOH (4 mL) and water (2 mL) mixture (3:2:1), lithium hydroxide monohydrate (0.095 g, 2.28 mmol) was added and the RM was stirred at RT for 4 h. After completion of reaction, as monitored by TLC, the RM was concentrated and the residue obtained was diluted with water (50 mL), acidified with 1N HCl (25 mL) and extracted with EtOAc (30 mL X 3). The combined organic layer was washed with brine (25 mL), dried over Na_2SO_4 and concentrated to afford title product (**3**, 0.240 g, 98%) as yellow solid. LCMS (ES) m/z = 534.20 $[M+H]^+$

Step-3: Preparation of tert-butyl ((7R)-2-(2-(1-(cyclopropylmethyl)-6-((S)-3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate **(4)**



To a stirred solution of (S)-2-(1-(cyclopropylmethyl)-6-(3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylic acid (**3**, 0.240 g, 0.450 mmol) in dimethylformamide (10 mL), DIPEA (0.23 mL, 1.35 mmol) was added followed by the addition of HATU (0.257 g, 0.675 mmol) and tert-butyl ((7R)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (0.095 g, 0.45 mmol). Then the RM was stirred at RT for 16 h. After completion of reaction, as monitored by TLC, the RM was diluted with water (30 mL) and extracted with EtOAc (30 mL X 3). The combined organic layer was washed with cold water (25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated to get the crude material, which was purified by silica gel column chromatography eluting with 40% EA in hexane to afford title product (**4**, 0.1 g, 30%) as yellow solid. LCMS (ES) m/z = 728.20 $[M+H]^+$

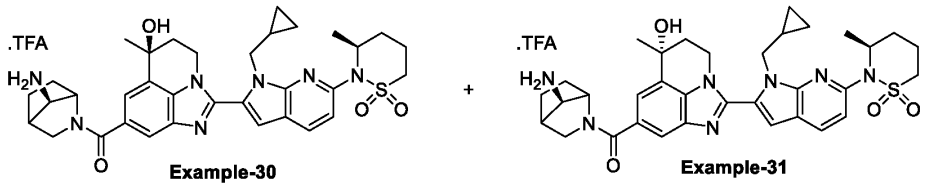
Step-4: Preparation of tert-butyl ((7R)-2-(2-(1-(cyclopropylmethyl)-6-((S)-3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate **(5)**



To a stirred solution of tert-butyl ((7R)-2-(2-(1-(cyclopropylmethyl)-6-((S)-3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (**4**, 0.1 g, 0.137 mmol) in THF (10 mL), MeMgI (2 mL, 1.37 mmol, 2M in diethyl ether) was added at 0 °C and the RM was stirred at the same temperature for 2 h. The RM was quenched with saturated solution of NH_4Cl and extracted with EtOAc (25 mL X 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated to get title product (**5**, 0.1 g, 97%) as crude material, which was used as such for next step. LCMS (ES) m/z = 744.21 $[M+H]^+$

Step-5: Preparation of ((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((S)-2-(1-(cyclopropylmethyl)-6-((S)-3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-

yl)methanone trifluoroacetate and ((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((R)-2-(1-(cyclopropylmethyl)-6-((S)-3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate **(Example-30 and Example-31)**



To a stirred solution of tert-butyl ((7R)-2-(2-(1-(cyclopropylmethyl)-6-((S)-3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (**5**, 0.1 g, 0.164 mmol) in dichloromethane (5 mL), 4M HCl in 1,4-dioxane (2 mL) was added at 0 °C and the RM was stirred at RT for 5 h. After completion of reaction, as monitored by TLC, the RM was evaporated and purified by Prep-HPLC to afford title product Example-30 (8 mg, 9%) and Example-31 (10.8 mg, 12%) as white solids.

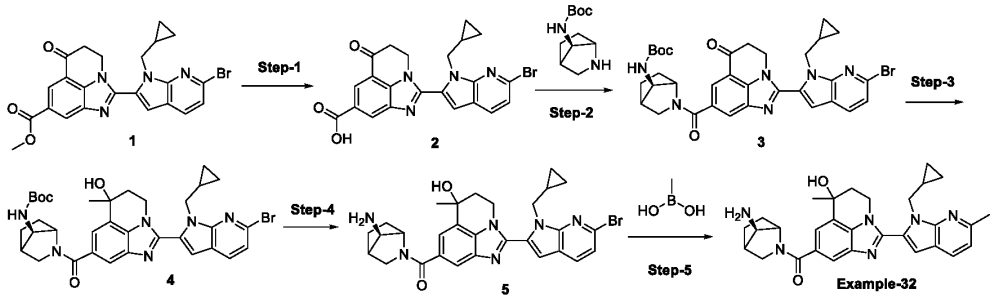
Example-30:

LCMS (ES) m/z = 644.31 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.17 (d, *J* = 8.4 Hz, 1H), 8.09 (bs, 1H), 7.95-7.87 (m, 2H), 7.62 (d, *J* = 92 Hz, 1H), 7.37 (d, *J* = 60 Hz, 1H), 7.21-6.96 (m, 2H), 5.50 (bs, 1H), 4.80-4.60 (m, 2H), 4.55 (bs, 2H), 4.21 (bs, 2H), 3.78-3.77 (m, 1H), 3.62 (bs, 1H), 3.42 (bs, 1H), 3.33-3.29 (m, 1H), 3.24-3.13 (m, 1H), 2.66 (bs, 1H), 2,57 (bs, 1H), 2.32 (bs, 1H), 2.22-2.13 (m, 4H), 1.96-1.87 (m, 2H), 1.70-1.65 (m, 5H), 1.33 (bs, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.36-0.31 (m, 4H).

Example-31:

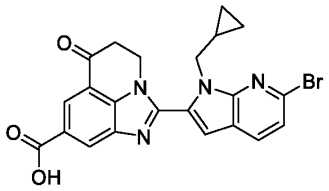
LCMS (ES) m/z = 644.29 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.17 (d, *J* = 8.0 Hz, 1H), 8.09 (bs, 1H), 7.94-7.88 (m, 2H), 7.62 (d, *J* = 88 Hz, 1H), 7.37 (d, *J* = 63 Hz, 1H), 7.21-6.96 (m, 2H), 5.54 (bs, 1H), 4.77-4.69 (m, 2H), 4.54 (bs, 2H), 4.23 (bs, 2H), 3.79-3.77 (m, 1H), 3.62 (bs, 1H), 3.46 (bs, 1H), 3.33-3.29 (m, 1H), 3.22-3.15 (m, 1H), 2.66 (bs, 1H), 2,56 (bs, 1H), 2.31 (bs, 1H), 2.22-2.13 (m, 4H), 1.96-1.87 (m, 2H), 1.70-1.65 (m, 5H), 1.33 (bs, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.36-0.31 (m, 4H).

Example-32: Synthesis of ((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone



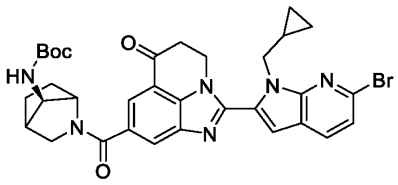
Reagents & conditions: 1. $LiOH.H_2O$, THF:MeOH:H_2O (3:2:1), RT, 4 h; **2.** HATU, DIPEA, DMF, RT, 16 h; **3.** MeMgI, THF, 0 °C, 2 h; **4.** 4M HCl in Dioxane, DCM, 0 °C-RT, 5 h; **5.** K_2CO_3, $Pd(PPh_3)_4$, Dioxane:Water, 90 °C, 4 h.

Step-1: Preparation of 2-(6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylic acid **(2)**



To a stirred solution of methyl 2-(6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylate (**1**, 0.32 g, 0.668 mmol) in mixture of THF (6 mL), MeOH (4 mL) and water (2 mL) (3:2:1), lithium hydroxide monohydrate (0.14 g, 3.34 mmol) was added and the RM was stirred at RT for 4 h. After completion of reaction, as monitored by TLC, the RM was concentrated and the residue obtained was diluted with water (25 mL), acidified with 1N HCl (20 mL) and extracted with EtOAc (30 mL X 3). The combined organic layer was washed with brine (25 mL), dried over Na_2SO_4 and concentrated to afford title product (**2**, 0.3 g, 96%) as brown solid. LCMS (ES) m/z = 465.21 $[M+H]^+$

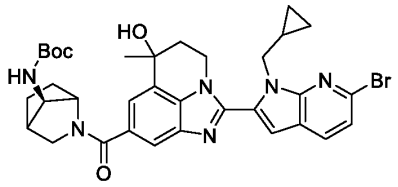
Step-2: Preparation of tert-butyl ((7R)-2-(2-(6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate **(3)**



To a stirred solution of 2-(6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carboxylic acid (**2**, 0.3 g, 0.645

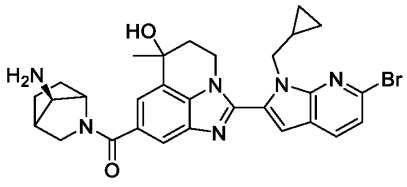
mmol) in DMF (10 mL), DIPEA (0.33 mL,1.93 mmol) was added followed by the addition of HATU (368 mg, 1.5 eq., 967 µmol) and tert-butyl ((7R)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (0.151 g, 0.709 mmol) and the RM was stirred at RT for 16 h. After completion of reaction, as monitored by TLC, the RM was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with cold water (25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated to get the crude material, which was purified by silica gel column chromatography eluting with 40% EA in hexane to afford title product (**3**, 0.3 g, 70%) as yellow solid. LCMS (ES) m/z = 659.20 $[M+H]^+$

Step-3: Preparation of tert-butyl ((7R)-2-(2-(6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate **(4)**



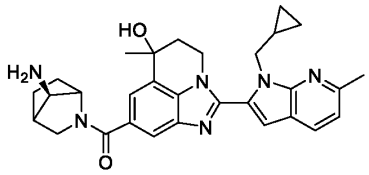
To a stirred solution of tert-butyl ((7R)-2-(2-(6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (**3**, 0.2 g, 0.303 mmol) in THF (6 mL), MeMgI (1.5 mL, 3.03 mmol, 2M in Diethyl ether) was added at 0 °C and the RM was stirred at the same temperature for 1 h. Additional 5 equivalent of MeMgI was addded and reaction was continued for 1 h. The RM was quenched with saturated solution of NH_4Cl (25 mL) and extracted with EA (3 x 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated to get crude material, which was purified by silica gel column chromatography eluting with 3% MeOH in DCM to afford title product (**4**, 0.1 g, 49%) as light yellow solid. LCMS (ES) m/z = 675.21 $[M+H]^+$

Step-4: Preparation of ((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone **(5)**



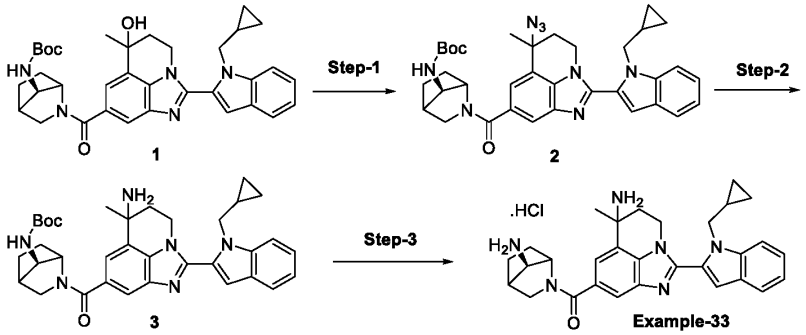
To a stirred solution of tert-butyl ((7R)-2-(2-(6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (**4**, 0.1 g, 0.152 mmol) in dichloromethane (4 mL), 4M HCl in dioxane (2 mL) was added at 0 °C and the RM was stirred at RT for 5 h. After completion of reaction, as monitored by TLC, the RM was evaporated and the residue obtained was triturated with diethyl ether to afford title product (**5**, 0.08 g, 94%) as light brown solid. LCMS (ES) m/z = 575.3 $[M+H]^+$

Step-5: Preparation of ((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone **(Example-32)**



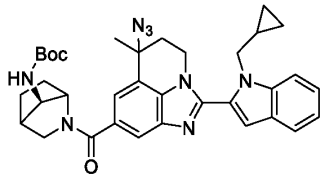
To a stirred solution of ((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone (0.05 g, 0.086 mmol) and methylboronic acid (0.015 g, 0.261 mmol) in solution of 1,4-dioxane (4.5 mL) and water (0.5 mL), K_2CO_3 (0.036 g, 0.261 mmol) was added and the RM was purged with nitrogen for 5 minutes. Then $Pd(PPh_3)_4$ (0.015 g, 0.013 mmol) was added and the RM was heated at 90 °C for 4 h. After completion of reaction, as monitored by TLC, the RM was filtered through celite and washed with EtOAc (20 mL X 3). The filtrate was concentrated to get the crude product, which was purified by preparative HPLC to afford title product (**Example-32,** 0.008 g, 18%) as white solid. LCMS (ES) m/z = 511.21 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.99 (d, *J* = 7.6 Hz, 1H), 7.64 (s, 1H), 7.45-7.40 (m, 1H), 7.14 (s, 1H), 7.09 (d, *J* = 8 Hz, 1H), 5.49 (d, *J* = 14.8 Hz, 1H), 4.77-4.55 (m, 2H), 4.50 (bs, 2H), 3.74 (d, *J* = 21.6 Hz, 1H), 3.66-3.51 (m, 1H), 3.16 (bs, 1H), 3.08-3.05 (m, 1H), 2.60 (s, 3H), 2.25-2.05 (m, 4H), 2.03-1.88 (m, 3H), 1.78-1.62 (m, 4H), 1.45-1.41 (m, 1H), 1.30-1.19 (m, 1H), 0.30-0.28 (m, 4H).

Example-33: Synthesis of (6-amino-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)methanone hydrochloride



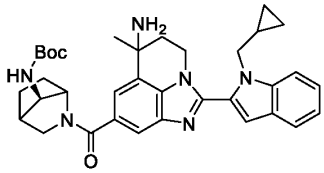
Reagents & conditions: 1. DPPA, DBU, Toluene, RT, 6 h; **2.** Pd/C, H_2, MeOH, RT, 6 h; **3.** 4M HCl in Dioxane, DCM, 0°C, 2 h.

Step-1: Preparation of tert-butyl ((7R)-2-(6-azido-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate **(2)**



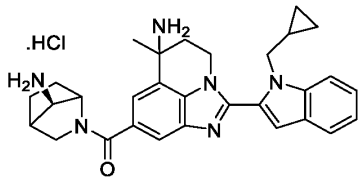
To a solution of tert-butyl ((7R)-2-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (**1**, 0.8 g, 1.34 mmol) in toluene (8 mL) was added diphenylphosphoryl azide (1.11 g, 4.03 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.511 g, 3.36 mmol). The RM was stirred at RT for 16 h. After completion of reaction as monitored by TLC, the RM was quenched with saturated ammonium chloride solution (20 mL) and extracted with EtOAc (25 mL X 3). The combined organic layer was concentrated under reduced pressure to get crude compound. The crude was purified by silica gel column chromatography to give title product (**2**, 0.7 g, 87%) as off white solid. LCMS (ES) m/z = 621.21 $[M+H]^+$

Step-2: Preparation of tert-butyl ((7R)-2-(6-amino-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate **(3)**



To a stirred solution of tert-butyl ((7R)-2-(6-azido-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (**2**, 0.7 g, 1.12 mmol) in methanol (7 mL) was added Pd/C (0.359 g, 3.38 mmol) under hydrogen gas atmosphere. The RM was stirred at RT for 4 h. After completion of reaction as monitored by TLC, the RM was filtered over celite bed and celite was washed with methanol. The obtained filtrate was concentrated to get crude title product as off white solid. LCMS (ES) m/z = 595.20 $[M+H]^+$

Step-3: Preparation of (6-amino-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)methanone hydrochloride **(Example-33)**



To a solution of tert-butyl ((7R)-2-(6-amino-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-8-carbonyl)-2-azabicyclo[2.2.1]heptan-7-yl)carbamate (**3**, 0.5 g, 0.84 mmol) in DCM (5 mL) was added 4M HCl in dioxane (5 mL) at 0 °C. Then the RM was stirred at the same temperature for 2 h. After completion of reaction as monitored by TLC, DCM was removed under reduced pressure. The obtained crude was washed with diethyl ether to afford title product (**Example-33**, 0.35 g, 84%) as off-white solid. LCMS (ES) m/z = 495.29 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.68 (bs, 2H), 8.09-7.97 (m, 3H), 7.71 (t, J = 8 Hz, 2H), 7.32 (t, J = 7.6 Hz, 1H), 7.20-7.08 (m, 2H), 4.73-4.51 (m, 4H), 4.25-4.22 (m, 1H), 3.67-3.61 (m, 2H), 3.24-3.13 (m, 1H), 2.70 (bs, 1H), 2.59 (bs, 1H), 2.46-2.42 (m, 4H), 2.07-1.89 (m, 2H), 1.79 (s, 3H), 1.70-1.55 (m, 1H), 1.23-1.19 (m, 1H), 0.34-0.31 (m, 2H), 0.28-0.24 (m, 2H).

BIOLOGICAL ASSAYS:

Ammonia Release Biochemical assay

Citrullination assay was detected via ammonia release. PAD4 enzyme was diluted to 120 nM in assay buffer (100 mM HEPES, 50 mM NaCl, 2 mM DDT, 0.6 mg/mL BSA, pH 7.4) and was added to wells containing various concentration of compound or DMSO vehicle (1 % final) in black 384 well plate. Following a 60-min preincubation at room temperature, the reaction was initiated by the addition of substrate (1.5 mM BAEE in 200 mM HEPES, 50 mM NaCl, 350 uM $CaCl_2$, 2 mM, pH 7.4). The reaction was stopped after 60 min by addition of

stop/detection buffer containing 50 mM EDTA, 2.6 mM of o-phthalaldehyde and 2.6 mM DTT. Assay was incubated at room temperature for 90 min before measuring fluorescence's (λ_{ex} 405/λ_{em} 460 nm) on Tecan reader. IC_{50} was calculated using XL-fit software model 205.

Citrullination ELISA:

Freshly isolated neutrophils from human donor were seeded at a density of 0.5 x 10^6 cells in 400 µL cell suspension/well in a 24-well plate and cells were pre-incubated with the compound for 30 minutes by adding 50 µL of the 10x concentration to achieve the final 1x concentration of compound (10 µM, 1 µM and 0.1 µM). 1% DMSO was added in control wells. Then, the cells were stimulated in the presence and absence of calcium ionophore by adding 50 µL/well to achieve the final concentration of 25 µM. Upon incubation for 30 minutes with calcium ionophore, S7 nuclease was added to the wells and incubated for 10 minutes to disrupt NET DNA. Following incubation, 10 µL of 1 mM EDTA was added to inactivate nuclease. Cells were scrapped gently and transferred to the tubes, followed by centrifugation at 1500 rpm for 5 minutes. After centrifugation, supernatant was discarded, and 200 µL of lysis buffer containing PBS and 1x Protease inhibitor was added to the tubes. The obtained lysis was then subjected to mechanical shearing using Geno grinder by spin the plate at 2500 rpm for 10 minutes, followed by collection of supernatant and stored at -20 °C or immediately used for ELISA.

ELISA was performed as per Citrullinated Histone H3 ELISA Kit. All the buffer components from the kit were dissolved according to the manufactures protocol. ELISA Buffer Concentrate (10X) (Item No. 400060) and Wash Buffer Concentrate (400X) (Item No. 400060) along with polysorbate 20 (2000x) (Item No. 400035) was diluted to 1x with MilliQ water. The standard for use in the ELISA was prepared as follows:

- Obtain eight clean test tubes and label them, #1 through #8. Aliquot 4.9 mL of ELISA Buffer into tube #1.
- Aliquot 500 µL of ELISA Buffer into the tubes #2-8. Then, transfer 0.1 mL of freshly prepared stock standard (500 ng/mL) to tube #1.
- Mix gently and serially dilute the standard by removing 500 µL from tube #1 and adding into tube #2; Repeat this process for tubes #3-7.
- Do not add any CitH3 ELISA Standard to tube #8. This tube is considered as blank, the lowest point on the standard curve.

100 µL of standards or diluted sample was added to the appropriate wells on the 96-well plate. Plates were covered with 96-well cover sheet and incubated for two hours at room

temperature on an orbital shaker. The samples and standard were removed from the wells and washed four times with Wash Buffer. After the last wash, Anti-Histone H3 HRP Conjugate (Item No. 501441) (10X) stock solution was diluted in 1x ELISA buffer and 100 µL of the HRP Conjugate working solution was added to each well of the plate and incubated for one hour at room temperature on an orbital shaker. Repeated the wash steps and after the last wash, 100 µL of TMB substrate solution was added to each well of the plate and incubated for 30 minutes at room temperature in the dark on an orbital shaker. After incubation, 100 µL of HRP stop solution was added to each well of the plate. The plates were allowed to develop yellow colour from blue and then they were read at a wavelength of 450 nm in a microplate reader. The IC_{50} values were subsequently determined using a sigmoidal dose-response curve (variable slope) in GraphPad Prism® 5 software.

Exemplary compounds of the present disclosure were screened by the above mentioned assays and the results are tabulated. The IC_{50} values (in range) of the selected compounds are set forth below in **Table IV**; wherein "**A**" refers to $IC_{50} < 0.5$ µM; "**B**" refers to IC_{50} 0.5 µM – 5 µM; and **"C"** refers to $IC_{50} > 5$ µM.

Table IV: PAD4 enzymatic and Citrullination in Neutrophils activity

Example No.	NH_3 release; PAD4 IC_{50} (µM)	Citrullination in Neutrophils IC_{50} (µM)	Example No.	NH_3 release; PAD4 IC_{50} (µM)	Citrullination in Neutrophils IC_{50} (µM)
1	A	A	**18**	B	ND
2	A	A	**19**	B	ND
3	ND	A	**20**	B	ND
4	A	A	**21**	B	ND
5	A	A	**22**	A	A
6	A	nd	**23**	C	ND
7	A	A	**24**	A	ND
8	A	nd	**25**	A	ND
9	ND	A	**26**	A	A
10	ND	A	**27**	B	B
11	A	nd	**28**	ND	A
12	A	A	**29**	B	A
13	A	A	**30**	A	ND
14	B	ND	**31**	B	ND
15	C	ND	**32**	A	ND

16	B	ND	**33**	B	ND
17	B	ND			

ND= not determined

Collagen induced arthritis model in DBA/1 mice

Protein arginine deiminases (PADs), a key set of enzymes involved in triggering the autoimmune responses required for the development of RA, may be targets for the treatment of RA. Collagen-induced arthritis (CIA) mouse model is the most commonly studied autoimmune model of rheumatoid arthritis. All mice were housed in the animal facility of Jubilant Biosys Ltd, a AAALAC (Association for Assessment and Accreditation of Lab Animal Care International) accredited facility where the experiments were carried out. Six- to eight-week-old DBA/1 male mice were purchased from Taconic (USA) and housed under standard laboratory conditions with a 12-h light/dark cycle and access to food and water ad libitum. Prior to the study's conduct, the Institutional Animal Care and Use Committee (IAEC/JDC/2023-292) reviewed and approved the procedures involving the care and use of animals.

Induction of arthritis: Animals from study group, except the normal control (N=10) received immunization. Primary immunization was done on day 0, followed by a booster immunization on day 21, by intradermal injection at the base of tail. For primary immunization, bovine type II collagen (2 mg/ml) was dissolved in 0.05 M acetic acid. Complete freund's adjuvant (CFA) was prepared by suspending M. tuberculosis (5 mg/ml) in incomplete freund's adjuvant (IFA). Emulsion was prepared by emulsifying equal volume of Bovine type II collagen with CFA. For booster immunization, bovine type II collagen (2 mg/ml) was dissolved in 0.05 M acetic acid. Emulsion was prepared by emulsifying equal volume of Bovine type II collagen with IFA. On day 28 lipopolysaccharide (LPS; 25 µg/100 µl/ animal, LPS prepared in saline) was administered intraperitoneally to accelerate the onset of disease.

Arthritic (Clinical) score: An arthritic (clinical) score was determined by grading the severity of disease in each hindpaw and forepaw according to a 0-4 point scale. Arthritic (clinical) scoring was based on the degree of peri-articular erythema and edema as well as deformity of the joints. The arthritic (clinical) score for each mouse was the sum of score of four paws with highest possible score being 16 for each mouse. Animals were dosed with Vehicle (0.5% Methyl cellulose in water + 0.5% Tween-80), Compound, 3, 10 and 30 mg/kg, PO, BID respectively. Clinical score (from day 28) and body weights (from day 1) were measured on

alternate days throughout the study. Mice treated with vehicle control showed disease progression as expected when disease induction was observed from day 28. The maximum clinical score was reached on day 33 and was sustained until the end of the study (day 45). Semi-prophylactic treatment with the compound at the dose of 3, 10 and 30 mg/kg PO, BID respectively from day 28 to day 45 significantly decreased the clinical score when compared to the disease control, thus attenuating the development of arthritic symptoms.

Incorporation by Reference

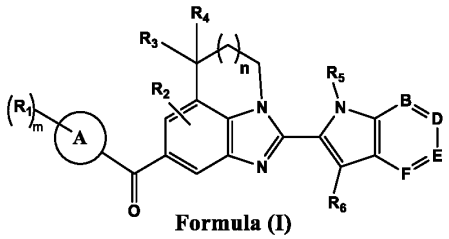
All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent were specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

Equivalents

While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the disclosure will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the disclosure should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

We claim:

1. A compound of Formula (I):



Formula (I)

or its stereoisomer, tautomers, intermediates, solvates or pharmaceutically acceptable salt thereof;

wherein,

B is selected from N or CR_7;

D is selected from N or CR_8;

E is selected from N or CR_9;

F is selected from N or CR_{10};

Ring A is selected from 5-12 membered monocyclic, bicyclic or tricyclic heterocyclyl with 1-3 heteroatoms selected from N, S or O;

R_1 at each occurrence is independently selected from alkyl, alkoxy, alkylamino, acylamino, cycloalkyl, halogen, haloalkyl, hydroxy, $-NR_aR_b$, $-NHC(NH)CH_2Cl$, or $-NH(CO)CH=CH-CH_2-N(CH_3)_2$;

R_2 is selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, haloalkyl or hydroxy;

R_3 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl or heteroaryl;

R_4 is selected from the group consisting of $-NR_cR_d$, $-O-(CO)-NR_cR_d$, $-NR_c(CO)-R_d$, $-NR_c(SO)_2-R_d$, $-NR_c-(CO)-O-R_e$, or $-OR_e$;

alternatively, R_3 and R_4 on the same carbon atom together form an oxo (=O), $=N-OR_e$, or $=N-NR_cR_d$ group;

R_5 is selected from the group consisting of hydrogen, alkyl, haloalkyl, alkoxy, cycloalkyl, aryl or heteroaryl; wherein, alkyl, alkoxy, cycloalkyl, aryl and heteroaryl, is optionally substituted with one or more groups selected from alkyl, alkoxy, cycloalkyl, aryl, heteroaryl, halogen, hydroxy or cyano;

R_6 is selected from the group consisting of hydrogen, hydroxy, cyano, halogen, alkyl, alkoxy, haloalkyl, haloalkoxy, acylamino, alkylamino, aryl or heteroaryl;

R_7, R_8, R_9 and R_{10} are independently selected from the group consisting of hydrogen, hydroxy, cyano, halogen, alkyl, alkoxy, haloalkyl, haloalkoxy, acylamino, alkylamino, aryl, or heterocyclyl; wherein, aryl and heterocyclyl is optionally substituted with one or more of the groups selected from alkyl, alkoxy, haloalkyl, alkylhydroxy, cyano, hydroxy or COR_{11};

R_{11} is selected from the group consisting of alkyl, hydroxy or cycloalkyl; wherein, alkyl and cycloalkyl is optionally substituted with one or more groups selected from alkyl, alkoxy, cycloalkyl or hydroxy;

R_a, R_b, R_c, R_d and R_e are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl or heteroaryl;

m is selected from 0-4; and n is selected from 0-2.

2. The compound of Formula (I) as claimed in claim 1, or its stereoisomer, tautomers, intermediates, solvates or pharmaceutically acceptable salt thereof;

wherein,

B is selected from N or CR_7;

D is selected from N or CR_8;

E is selected from N or CR_9;

F is selected from N or CR_{10};

Ring A is selected from 5-12 membered monocyclic, bicyclic or tricyclic heterocyclyl with 1-3 heteroatoms selected from N, S or O;

R_1 at each occurrence is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} acylamino, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, hydroxy, $-NR_aR_b$, $-NHC(NH)CH_2Cl$, or $-NH(CO)CH=CH-CH_2-N(CH_3)_2$;

R_2 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, halogen, C_{1-6} haloalkyl, or hydroxy;

R_3 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{6-12} aryl, or C_{1-6} heteroaryl;

R_4 is selected from the group consisting of $-NR_cR_d$, $-O-(CO)-NR_cR_d$, $NR_c(CO)-R_d$, $-NR_c(SO)_2-R_d$, $-NR_c-(CO)-O-R_e$, or $-OR_e$; alternatively, R_3 and R_4 on the same carbon atom together form an oxo (=O), $=N-OR_e$, or $=N-NR_cR_d$ group;

R_5 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{6-12} aryl, or C_{1-6} heteroaryl; wherein, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{6-12} aryl, and C_{1-6} heteroaryl, is optionally substituted with one or more groups

selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{6-12} aryl, C_{1-6} heteroaryl, halogen, hydroxy or cyano;

R_6 is selected from the group consisting of hydrogen, hydroxy, cyano, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} acylamino, C_{1-6} alkylamino, C_{6-12} aryl, or C_{1-6} heteroaryl;

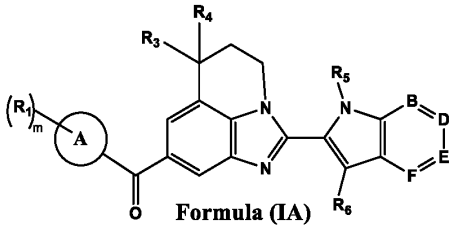
R_7, R_8, R_9 and R_{10} are independently selected from the group consisting of hydrogen, hydroxy, cyano, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} acylamino, C_{1-6} alkylamino, C_{6-12} aryl, or C_{1-6} heterocyclyl; wherein, C_{6-12} aryl, and C_{1-6} heterocyclyl, is optionally substituted with one or more of the groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} alkylhydroxy, cyano, hydroxy, or COR_{11};

R_{11} is selected from the group consisting of C_{1-6} alkyl, hydroxy, or C_{3-6} cycloalkyl; wherein, C_{1-6} alkyl, and C_{3-6} cycloalkyl, is optionally substituted with one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or hydroxy;

R_a, R_b, R_c, R_d and R_e are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-12} aryl, or C_{1-6} heteroaryl;

m is selected from 0-4; and n is selected from 0-2.

3. A compound of Formula (IA):



Formula (IA)

or its stereoisomer, tautomers, intermediates, solvates or pharmaceutically acceptable salt thereof;

wherein,

B is selected from N or CR_7;

D is selected from N or CR_8;

E is selected from N or CR_9;

F is selected from N or CR_{10};

Ring A is selected from 5-12 membered monocyclic, bicyclic or tricyclic heterocyclyl with 1-3 heteroatoms selected from N, S or O;

R_1 at each occurrence is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} acylamino, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, hydroxy, $-NR_aR_b$, $-NHC(NH)CH_2Cl$, or $-NH(CO)CH=CH-CH_2-N(CH_3)_2$;

R_3 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{6-12} aryl, or C_{1-6} heteroaryl;

R_4 is selected from the group consisting of $-NR_cR_d$, $-O-(CO)-NR_cR_d$, $NR_c(CO)-R_d$, $-NR_c(SO)_2-R_d$, $-NR_c-(CO)-O-R_e$, or $-OR_e$; alternatively, R_3 and R_4 on the same carbon atom together form an oxo (=O), $=N-OR_e$, or $=N-NR_cR_d$ group;

R_5 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{6-12} aryl, or C_{1-6} heteroaryl; wherein, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{6-12} aryl, and C_{1-6} heteroaryl, is optionally substituted with one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{6-12} aryl, C_{1-6} heteroaryl, halogen, hydroxy or cyano;

R_6 is selected from the group consisting of hydrogen, hydroxy, cyano, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} acylamino, C_{1-6} alkylamino, C_{6-12} aryl, or C_{1-6} heteroaryl;

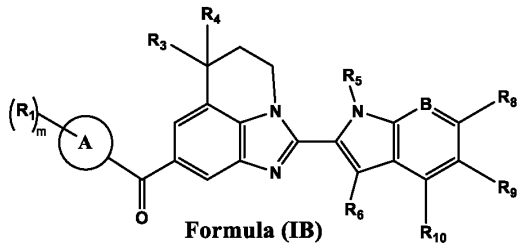
R_7, R_8, R_9 and R_{10} are independently selected from the group consisting of hydrogen, hydroxy, cyano, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} acylamino, C_{1-6} alkylamino, C_{6-12} aryl, or C_{1-6} heterocyclyl; wherein, C_{6-12} aryl, and C_{1-6} heterocyclyl, is optionally substituted with one or more of the groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} alkylhydroxy, cyano, hydroxy, or COR_{11};

R_{11} is selected from the group consisting of C_{1-6} alkyl, hydroxy, or C_{3-6} cycloalkyl; wherein, C_{1-6} alkyl, and C_{3-6} cycloalkyl, is optionally substituted with one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or hydroxy;

R_a, R_b, R_c, R_d and R_e are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-12} aryl, or C_{1-6} heteroaryl; and

m is selected from 0-4.

4. A compound of Formula (IB):



Formula (IB)

or its stereoisomer, tautomers, intermediates, solvates or pharmaceutically acceptable salt thereof;

wherein,

B is selected from N or CR_7;

Ring A is selected from 5-12 membered monocyclic or bicyclic heterocyclyl with 1-3 heteroatoms selected from N, S or O;

R_1 at each occurrence is independently selected from C_{1-6} alkyl, halogen or $-NH_2$;

R_3 is selected from hydrogen or C_{1-6} alkyl;

R_4 is selected from $-NH_2$, or hydroxy;

alternatively, R_3 and R_4 on the same carbon atom together form an oxo (=O) group;

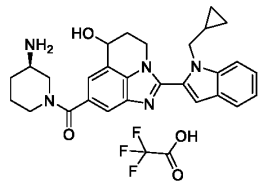
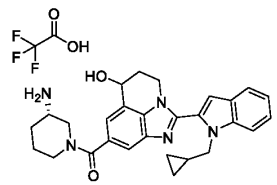
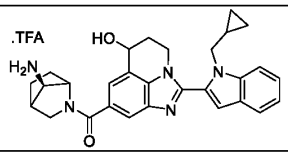
R_5 is selected from the group consisting of hydrogen, C_{1-6} alkyl or C_{1-6} haloalkyl; wherein, C_{1-6} alkyl is optionally substituted with C_{3-6} cycloalkyl;

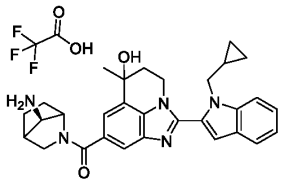
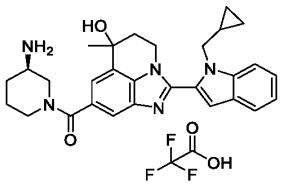
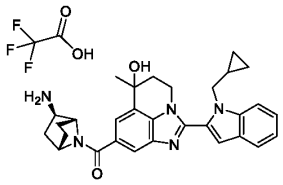
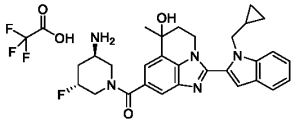
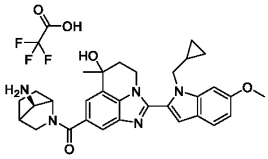
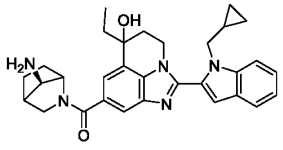
R_6 is selected from the group consisting of hydrogen or C_{1-6} alkyl;

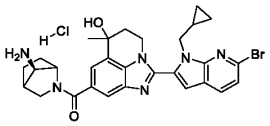
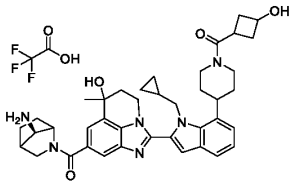
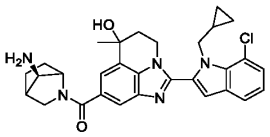
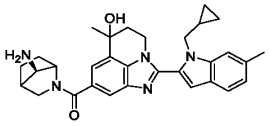
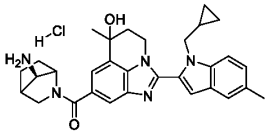
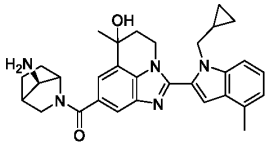
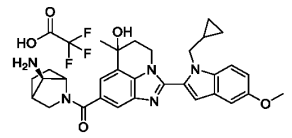
R_7, R_8, R_9 and R_{10} are independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} heterocyclyl; wherein, C_{1-6} heterocyclyl, is optionally substituted with C_{1-6} alkyl or COR_{11};

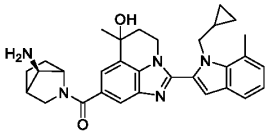
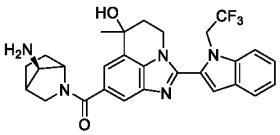
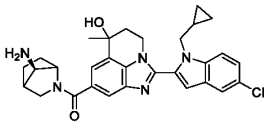
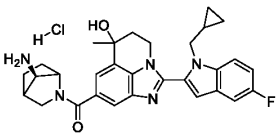
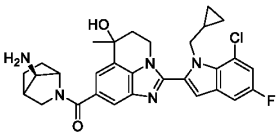
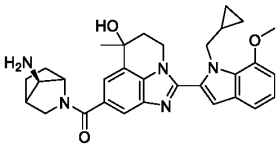
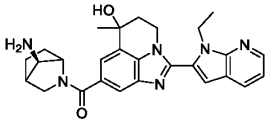
R_{11} is selected from the group consisting of C_{1-6} alkyl, or C_{3-6} cycloalkyl; wherein, C_{1-6} alkyl, and C_{3-6} cycloalkyl, is optionally substituted with one or more groups selected from C_{1-6} alkyl, or hydroxy; and m is selected from 1-2.

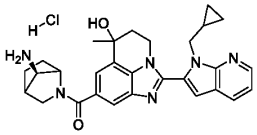
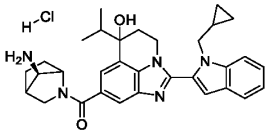
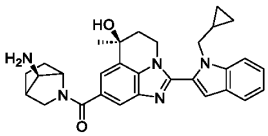
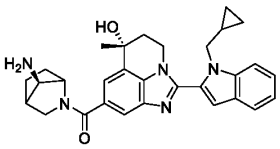
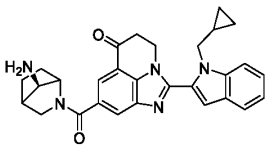
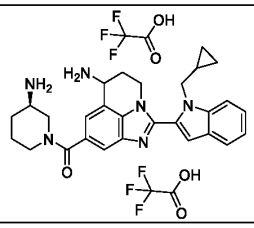
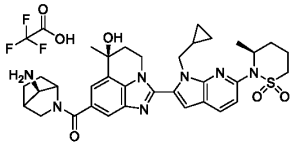
5. A compound selected from:

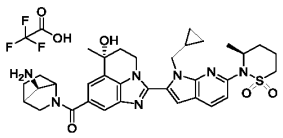
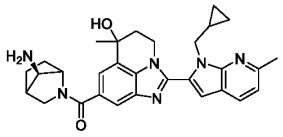
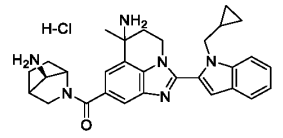
Example No	Structure	IUPAC
1		(R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
2		((S)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
3		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-

		hydroxy-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
4		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
5		((R)-3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
6		((1R,2R,4S)-2-amino-7-azabicyclo[2.2.1]heptan-7-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
7		((3R,5R)-3-amino-5-fluoropiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
8		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
9		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-ethyl-6-hydroxy-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;

10		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(6-bromo-1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone hydrochloride;
11		(4-(2-(8-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-2-yl)-1-(cyclopropylmethyl)-1H-indol-7-yl)piperidin-1-yl)(3-hydroxycyclobutyl)methanone trifluoroacetate;
12		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(7-chloro-1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
13		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
14		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-5-methyl-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone hydrochloride;
15		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-4-methyl-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
16		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-5-methoxy-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-

		4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
17		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-7-methyl-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
18		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(6-hydroxy-6-methyl-2-(1-(2,2,2-trifluoroethyl)-1H-indol-2-yl)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
19		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(5-chloro-1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
20		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone hydrochloride;
21		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(7-chloro-1-(cyclopropylmethyl)-5-fluoro-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
22		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-7-methoxy-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
23		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;

24		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone hydrochloride;
25		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-isopropyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone hydrochloride;
26		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((S)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
27		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((R)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone;
28		8-((7R)-7-amino-2-azabicyclo[2.2.1]heptane-2-carbonyl)-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-4,5-dihydro-6H-imidazo[4,5,1-ij]quinolin-6-one;
29		(6-amino-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)((R)-3-aminopiperidin-1-yl)methanone di-trifluoroacetate;
30		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((S)-2-(1-(cyclopropylmethyl)-6-((S)-3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;

31		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)((R)-2-(1-(cyclopropylmethyl)-6-((S)-3-methyl-1,1-dioxido-1,2-thiazinan-2-yl)-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone trifluoroacetate;
32		((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)(2-(1-(cyclopropylmethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-6-hydroxy-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)methanone; and
33		(6-amino-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-6-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-8-yl)((7R)-7-amino-2-azabicyclo[2.2.1]heptan-2-yl)methanone hydrochloride.

or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof.

6. A pharmaceutical composition comprising the compound of any one of the claims 1 to 5, or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof and at least one pharmaceutically acceptable carrier.

7. The pharmaceutical composition as claimed in claim 6, wherein the composition is in a form selected from the group consisting of a tablet, capsule, powder, syrup, solution, aerosol, ointment, lotion, cream, transdermal patches, gel, hydrogel, foam and suspension.

8. The compounds as claimed in any one of the claims 1-5 or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof for use in the manufacture of a medicament for inhibiting PAD4 in a cell.

9. The compounds as claimed in any one of the claims 1-5 or its stereoisomers, tautomers, intermediates, solvates, or pharmaceutically acceptable salts thereof for use in the treatment of PAD4 mediated disease or disorder.

10. A method of inhibiting PAD4 in a subject, comprising administering to a subject suffering from a disease or disorder mediated by PAD4, a therapeutically effective amount of the compound as claimed in any one of the claims 1-5 or the pharmaceutical composition as claimed in claim 6 or 7.

11. A method of the treatment and/or prevention of a disease or disorder mediated by PAD4, the method comprising administering to a subject suffering from the disease or disorder mediated by PAD4 a therapeutically effective amount of the compound as claimed in any one of the claims 1-5, or the pharmaceutical composition as claimed in claim 6 or 7.

12. The method as claimed in claim 11, wherein the disease or disorder is selected from cancer, cancer metastasis, immune disorder, inflammatory disorder, and transplant rejection.

13. The method as claimed in claim 11, wherein the disease or disorder is selected from rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cystic fibrosis, asthma, cutaneous lupus erythematosus, or psoriasis.

14. A method of treatment and/or prevention of rheumatoid arthritis, said method comprising administering a combination of the compounds as claimed in any one of the claims 1-5 or the pharmaceutical composition as claimed in claim 6 or 7, with other clinically relevant cytotoxic agents or non-cytotoxic agents to a subject in need thereof.

15. A method of treatment and/or prevention of cancer, cancer metastasis, immune disorder, inflammatory disorder, and transplant rejection, said method comprising administering a combination of the compounds as claimed in any one of the claims 1-5 or the pharmaceutical composition as claimed in claim 6 or 7, with other clinically relevant immune modulator agents or anti-inflammatory agents to a subject in need of thereof.

16. The method of treatment as claimed in claim 12 or 15, wherein the disease or disorder is cancer and cancer is selected from breast cancer, prostate cancer, pancreatic cancer, gastric cancer, lung cancer, colon cancer, rectal cancer, esophagus cancer, duodenal cancer, tongue cancer, pharyngeal cancer, brain tumor, neurinoma, clear cell carcinoma, non-small cell lung cancer, small cell lung cancer, liver cancer, kidney cancer, bile duct cancer, uterine body cancer, cervical cancer, ovarian cancer, urinary bladder cancer, skin cancer, hemangioma, malignant lymphoma, malignant melanoma, thyroid cancer, bone tumor, vascular fibroma, glioblastoma, sarcoma, neuroendocrine tumors, retinoblastoma, penile cancer, pediatric solid cancer, renal cell carcinoma, lymphoma, myeloma, leukemia, acute myelogenous leukemia

(AML), chronic myelogenous leukemia (CML), chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia (CEL), chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), hairy cell leukemia, cutaneous T-cell lymphoma (CTCL), multiple myeloma (MM), myeloproliferative neoplasms (MPN), polycythemia vera (PV), essential thrombocythemia, essential thrombocytosis (ET) or myelofibrosis (MF).

17. The method of treatment as claimed in claim 12 or 15, wherein the disease or disorder is cancer metastasis, and the cancer metastasis is selected from liver cancer metastasis, lung cancer metastasis, and omentum cancer metastasis.

18. The method as claimed in claim 12 or 15, wherein the cancer metastasis is selected from liver cancer metastasis originating from colorectal cancer and pancreatic cancer, lung cancer metastasis originating from breast cancer, and omentum cancer metastasis originating from ovarian cancer.

19. The method as claimed in claim 11, wherein disease or disorder selected from acid-induced lung injury, respiratory distress syndrome, allergen induced asthma, allergic bronchopulmonary disease, chronic lung disease of prematurity, chronic obstructive pulmonary disease, colitis, cystic fibrosis, gouty arthritis, inflammatory bowel disease, inflammatory lung disease, inflammatory pain, juvenile rheumatoid arthritis, kidney disease, kidney injury caused by parasitic infections, kidney transplant rejection prophylaxis, lung injury, lupus, lupus nephritis, multiple sclerosis, muscular dystrophy, non-allergen induced asthma, osteoarthritis, periodontitis, peritoneal endometriosis, psoriasis, pulmonary disease, pulmonary fibrosis, idiopathic pulmonary fibrosis, pyogenic sterile arthritis, renal disease, rheumatic disease, rheumatoid arthritis, sepsis, severe pain, ulcerative colitis, systemic inflammatory response syndrome, decreasing neutrophil extra cellular traps (NETs) release, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), COVID-19 (corona virus disease-2019) related lung infection, multi-organ failure or multi-organ dysfunction syndrome from ARDS, anti neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), hidradenitis suppurativa (HS), infections, cytokine storms induced by drugs or any agent, ischemic or haemorrhagic stroke, ischemic or drug-induced haemorrhagic transformation in the brain, haemorrhagic encephalopathy, traumatic brain injury, anoxic brain injury, diabetes, deep vein thrombosis, systemic microthrombosis, atherosclerotic thrombosis, thromboembolism, systemic lupus erythematosus (SLE), crohn's disease, indeterminate colitis, or alzheimer's disease.

20. Use of the compound as claimed in claims 1-5, or the pharmaceutical composition as claimed in claim 6 or 7 in the manufacture of a medicament for the treatment of a disease or disorder mediated by PAD4; or treatment and/or prevention of disease or disorder selected from cancer, cancer metastasis, immune disorder, inflammatory disorder, and transplant rejection.

21. Use of the compound as claimed in claim 20, wherein, the disease or disorder is cancer and cancer is selected from breast cancer, prostate cancer, pancreatic cancer, gastric cancer, lung cancer, colon cancer, rectal cancer, esophagus cancer, duodenal cancer, tongue cancer, pharyngeal cancer, brain tumor, neurinoma, clear cell carcinoma, non-small cell lung cancer, small cell lung cancer, liver cancer, kidney cancer, bile duct cancer, uterine body cancer, cervical cancer, ovarian cancer, urinary bladder cancer, skin cancer, hemangioma, malignant lymphoma, malignant melanoma, thyroid cancer, bone tumor, vascular fibroma, glioblastoma, sarcoma, neuroendocrine tumors, retinoblastoma, penile cancer, pediatric solid cancer, renal cell carcinoma, lymphoma, myeloma, and leukemia, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia (CEL), chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), hairy cell leukemia, cutaneous T-cell lymphoma (CTCL), multiple myeloma (MM), myeloproliferative neoplasms (MPN), polycythemia vera (PV), essential thrombocythemia, essential thrombocytosis (ET) or myelofibrosis (MF).

22. Use of the compound as claimed in claim 20, wherein the disease or disorder is cancer metastasis, and the cancer metastasis is selected from liver cancer metastasis, lung cancer metastasis, and omentum cancer metastasis.

23. Use of the compound as claimed in claim 20, wherein the cancer metastasis is selected from liver cancer metastasis originating from colorectal cancer and pancreatic cancer, lung cancer metastasis originating from breast cancer, and omentum cancer metastasis originating from ovarian cancer.

24. Use of the compound as claimed in any one of the claims 1-5, or the pharmaceutical composition as claimed in claim 6 or 7 in the manufacture of a medicament for the treatment of a disease or disorder mediated by PAD4; or treatment and/or prevention of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cystic fibrosis, asthma, cutaneous lupus erythematosus, or psoriasis.

25. Use of the compound as claimed in any one of the claims 1-5, or the pharmaceutical composition as claimed in claim 6 or 7, for the treatment of a disease or disorder mediated by PAD4; or treatment and/or prevention of disease or disorder selected from acid-induced lung injury, respiratory distress syndrome, allergen induced asthma, allergic bronchopulmonary disease, chronic lung disease of prematurity, chronic obstructive pulmonary disease, colitis, cystic fibrosis, gouty arthritis, inflammatory bowel disease, inflammatory lung disease, inflammatory pain, juvenile rheumatoid arthritis, kidney disease, kidney injury caused by parasitic infections, kidney transplant rejection prophylaxis, lung injury, lupus, lupus nephritis, multiple sclerosis, muscular dystrophy, non-allergen induced asthma, osteoarthritis, periodontitis, peritoneal endometriosis, psoriasis, pulmonary disease, pulmonary fibrosis, idiopathic pulmonary fibrosis, pyogenic sterile arthritis, renal disease, rheumatic disease, rheumatoid arthritis, sepsis, severe pain, ulcerative colitis, systemic inflammatory response syndrome, decreasing neutrophil extra cellular traps (NETs) release, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), COVID-19 (corona virus disease-2019) related lung infection, multi-organ failure or multi-organ dysfunction syndrome from ARDS, anti neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), hidradenitis suppurativa (HS), infections, cytokine storms induced by drugs or any agent, ischemic or haemorrhagic stroke, ischemic or drug-induced haemorrhagic transformation in the brain, haemorrhagic encephalopathy, traumatic brain injury, anoxic brain injury, diabetes, deep vein thrombosis, systemic microthrombosis, atherosclerotic thrombosis, thromboembolism, systemic lupus erythematosus (SLE), crohn's disease, indeterminate colitis, or alzheimer's disease.