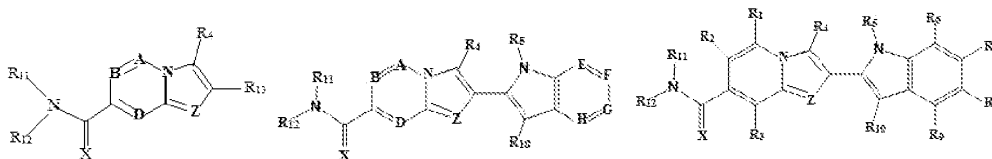


IMIDAZO-PYRIDINE COMPOUNDS AS PAD INHIBITORS

TECHNICAL FIELD OF THE INVENTION

[0001] The present disclosure relates to imidazo-pyridine compounds of Formula (I), (II), and (III) along with their polymorphs, stereoisomers, prodrugs, solvates, co-crystals, intermediates, pharmaceutically acceptable salts, and metabolites thereof which inhibit PAD4 enzyme.



Formula (I)

Formula (II)

Formula (III)

- 10 The process for the preparation of the above said heterocyclic compounds of the Formula (I), (II), and (III), their polymorphs, stereoisomers, prodrugs, solvates, co-crystals, intermediates, pharmaceutically acceptable salts, pharmaceutical compositions, and metabolites useful in the preparation of such compounds, are also described herein which are useful in the preparation of such compounds.
- 15 [0002] The compounds described herein inhibit PAD4 enzyme of the PAD family and may be used in the treatment of various disorders associated with cell division or inflammation.

BACKGROUND OF THE INVENTION

- [0003] The PAD (protein arginine deiminase) consists of a family of enzymes that afford the process of citrullination in living tissues (J. E. Jones, et al. Curr. Opin. Drug Discov. Devel., 2009, 12, 616-627). The PAD family consists of PAD1, PAD2, PAD3, PAD4, and PAD6 individual enzymes. The enzymes of PAD family affect and regulate various physiological and pathological processes in human body and thus are important.
- 20 [0004] The elevation in the levels 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
5 normal cellular processes. The elevation in the PAD enzyme levels become a direct cause of the above-mentioned ailments by enhancing the rate of citrullination process.

[0005] The enzymes not only catalyze citrullination but also produce autoantibodies that recognize the citrullinated proteins. The introduction of citrulline, resultant of PAD activity, changes both the structure and function of proteins. At physiological activity
10 levels, PADs regulate many cell signaling pathways like cell differentiation, apoptosis, and gene transcription (György et al. Int. J. Biochem. Cell Biol., 2006, 38, 1662-1677). Thus, these enzymes play a crucial role on the pathogenesis of the above-mentioned diseases.

[0006] PAD4 has also been known for their involvement in the formation of neutrophil extracellular traps (NETs) and more specifically in the histone citrullination that occurs during NETosis (J. Cedervall, A. -K. Olsson, Oncoscience, 2015, 2(11), 900-901). Thus, PAD4 enzyme is linked to diseases characterized by abnormal levels of neutrophil extracellular traps (NETs). The proposed role of PAD4 in NETosis is
15 pertinent for rheumatoid arthritis (RA) as NETs are deficient in the absence of PAD4 and PAD4 is released extracellularly in RA joints, probably due to the pathological status of RA neutrophils. Therefore, PAD inhibitor drugs would provide significant therapeutic potential because of the fact that NETs are implicated in many diseases.

[0007] Examples of some PAD inhibitor compounds are chloro-amidine, fluoro-chloridine and their related analogs that are known and act as mechanism-based
25 inhibitors that irreversibly inactivate PAD4 and other PAD isozymes (H. D. Lewis *et al.*, Nature Chemical Biology, 2015, 11, 189-191). These compounds have utility against rheumatoid arthritis (RA). PAD4, detected in synovial tissue, has been found to be responsible for citrullination of a variety of joint proteins. These citrullinated protein substrates produce anti-citrullinated antibodies which are responsible for disease
30 pathogenesis (Y. Kochi et al., Ann. Rheum. Dis., 2011, 70, 512-515).

[0008] Since the compounds that inhibit PAD4 enzyme activity have also been known for reducing pathological activity in numerous ailments, therefore such compounds can be utilized in injuries and disease pathologies. In this way PAD4

inhibitors have wider applicability in the treatment of ailments, specially those related with NETs.

[0009] US20050159334 discloses the treatment of RA with the administration of suitable PAD inhibitor, thus the PAD inhibitor compounds have a direct implication in treating RA.

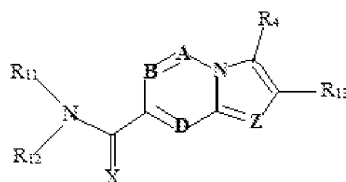
[0010] The PAD inhibitor compounds like chloro-amidine has been widely studied to demonstrate their efficacy in a number of animal disease models like, collagen-induced arthritis (V. C. Willis et al., J. Immunol., 2011, 186(7), 4396-4404), dextran sulfate sodium (DSS)-induced experimental colitis (A. A. Chumanevich et al., Am. J. Physiol. Gastrointest. Liver Physiol., 2011, 300(6), G929-G938), lupus-prone MRL/lpr mice atherosclerosis and arterial thrombosis (J. S. Knight et al., Circ. Res., 2014, 114(6), 947-956), spinal cord injury repair (S. Lange et al., Dev. Biol., 2011, 355(2), 205-214), and experimental autoimmune encephalomyelitis (EAE).

[0011] Similar to RA, the use of PAD4 inhibitors in the treatment of cancers (J. L. Slack et al., Cellular and Molecular Life Sciences, 2011, 68(4), 709-720) has also been studied earlier. It is suggested that PAD4 inhibitors have an anti-proliferative role as well. PAD4 deiminases arginine residues in histones at the promoters of p53- target genes such as p21, which are involved in cell cycle arrest and induction of apoptosis (P. Li et al., Molecular & Cell Biology, 2008, 28(15), 4745-4758).

[0012] The PAD4 inhibitory compounds, as described above, have vast utility. Therefore, the identification of a chemical moiety that facilitates PAD inhibition is necessary. However, the use of PAD inhibitors in various other ailments where dysregulated PAD activity is implicated still needs to be explored. Identification and development of new PAD4 inhibitor compounds treating PAD4 mediated disorders are direly required to treat diseases like example rheumatoid arthritis, vasculitis, systemic lupus erythematosus, cutaneous lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, multiple sclerosis and psoriasis efficiently.

SUMMARY OF INVENTION

[0013] The present disclosure discloses a compound of Formula I



Formula (I)

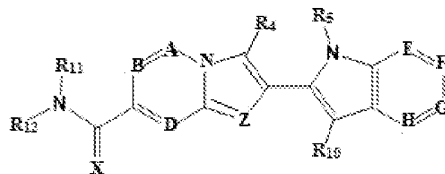
X is selected from O or S; Z is N; A is selected from N or CR₁;

B is selected from N or CR₂; D is selected from N or CR₃; R₁, R₂, R₃, and R₄ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆

- 5 alkylamino, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ heteroaryl, and C₁₋₆ haloalkoxy, is optionally substituted with one or more of the groups selected from
- 10 hydrogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, and hydroxyl; R₁₁ is hydrogen; R₁₂ is selected from C₁₋₆ alkylamino, and 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O, or R₁₁ and R₁₂ can be taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic
- 15 ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, -NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, or hydroxyl; R₁₃ is selected from hydrogen, 5-10 membered monocyclic or bicyclic aryl,
- 20 and 5-10 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl,
- 25 C₁₋₁₀ heterocyclyl, C₁₋₁₀ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, and C₁₋₁₀ heteroaryl, is optionally substituted with one or more of the
- 30 groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, hydroxyl, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen,

hydroxyl, $-\text{CH}_2\text{OH}$, and cyano; and R_{15} is selected from the group consisting of hydrogen, C_{1-6} alkyl, and combinations thereof.

[00014] The present disclosure also describes compound of Formula II



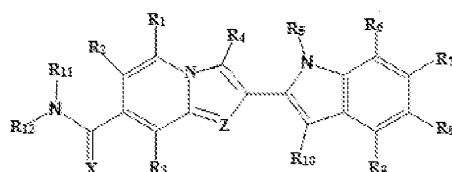
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Formula (II)

X is selected from O or S; Z is N; A is selected from N or CR_1 ; B is selected from N or CR_2 ; D is selected from N or CR_3 ; E is selected from N or CR_6 ; F is absent or is selected from N, and CR_7 ; G is absent or is selected from N, and CR_8 ; H is absent or is selected from N, and CR_9 ; R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 and R_{10} are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} acylamino, C_{1-6} alkylamino, C_{5-10} aryl, C_{1-10} heterocyclyl, C_{1-10} heteroaryl, $\text{C}(\text{O})\text{C}_{1-6}$ alkyl, $\text{C}(\text{O})\text{C}_{1-6}$ haloalkyl, $\text{C}(\text{O})\text{NR}_{15}$, $\text{C}(\text{O})\text{C}_{1-6}$ alkylamino, $\text{C}(\text{O})\text{C}_{5-6}$ aryl, $\text{C}(\text{O})\text{C}_{1-6}$ heteroaryl, $\text{SO}_2\text{C}_{1-6}$ alkyl, $\text{SO}_2\text{C}_{1-6}$ haloalkyl, $\text{SO}_2\text{C}_{3-6}$ cycloalkyl, $\text{SO}_2\text{NR}_{15}$, $\text{SO}_2\text{NC}_{1-6}$ alkylamino, $\text{SO}_2\text{C}_{5-6}$ aryl, or $\text{SO}_2\text{C}_{1-6}$ heteroaryl, wherein C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-10} heteroaryl, and C_{1-6} haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} alkylhydroxy, C_{3-6} cycloalkyl, C_{5-9} aryl, C_{1-6} heterocyclyl, C_{1-6} heteroaryl, cyano, halogen, and hydroxyl, wherein C_{5-9} aryl, C_{1-6} heteroaryl, and C_{1-6} heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, oxo, halogen, hydroxyl, $-\text{CH}_2\text{OH}$, and cyano;

R_{11} and R_{12} are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C_{1-6} alkylamino, C_{1-6} acylamino, $-\text{NHC}(\text{NH})\text{CH}_2\text{Cl}$, $\text{NH}(\text{CO})\text{CH}=\text{CH}-\text{CH}_2-\text{N}(\text{CH}_3)_2$, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, or hydroxyl; and R_{15} is selected from the group consisting of hydrogen, C_{1-6} alkyl, and combinations thereof.

[00015] The present disclosure further describes compound of Formula III

**Formula (III)**

X is selected from O or S; Z is N; R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉ and R₁₀ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, C₁₋₁₀ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₁₀ heteroaryl, and C₁₋₆ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ alkylhydroxy, C₃₋₆ cycloalkyl, C₅₋₉ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl, wherein C₅₋₉ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano;

R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, or hydroxyl; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[00016] The present disclosure further describes the process of preparation of compounds of Formula (I), Formula (II), and Formula (III) or its polymorphs, stereoisomers, prodrugs, solvates, co-crystals, intermediates, pharmaceutically acceptable salts, and metabolites thereof.

[00017] The present disclosure further discloses a pharmaceutical composition comprising a compound of Formula (I), Formula (II), and Formula (III) or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

[00018] The present disclosure further discloses a method for inhibiting one or more PAD family in a cell with an effective amount of the compound of the present disclosure.

5 [00019] The present disclosure further discloses a method of treating a condition 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), Formula (II), and Formula (III) or the pharmaceutical composition of the present disclosure with other clinically relevant agents or biological agents to a subject in need thereof.

10 [00020] The present disclosure further discloses a compound of Formula (I), Formula (II) and Formula (III) used for the treatment of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, cutaneous lupus erythematosus, and psoriasis.

[00021] 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.

DETAILED DESCRIPTION

20 [00022] 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

[00023] 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.

30 [00024] 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.

[00025] 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.

[00026] The term “including” is used to mean “including but not limited to”. “Including” and “including but not limited to” are used interchangeably.

[00027] In the structural formulae given herein and throughout the present disclosure, the following terms have been indicated meaning, unless specifically stated otherwise.

10 [00028] Furthermore, the compound of Formula (I), Formula (II), and Formula (III) can be its derivatives, analogs, stereoisomer's, diastereomers, geometrical isomers, polymorphs, solvates, co-crystals, intermediates, metabolites, prodrugs or pharmaceutically acceptable salts and compositions.

15 [00029] The compounds of Formula (I), Formula (II), and Formula (III) and their polymorphs, stereoisomers, prodrugs, solvates, co-crystals, intermediates, pharmaceutically acceptable salts, and metabolites thereof can also be referred as “compounds of the present disclosure”.

20 [00030] The compounds according to Formula (I), Formula (II), and Formula (III) 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. 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), Formula (II), and Formula (III), 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), Formula (II), and Formula (III) 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.

25 [00031] Individual stereoisomers of a compound according to Formula (I), Formula (II), and Formula (III) 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.

- 5 [00032] Alternatively, specific stereoisomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

- [00033] It is to be understood that the references herein to compounds of Formula (I), Formula (II), and Formula (III) and salts thereof covers the compounds of Formula (I),
10 Formula (II), and Formula (III) as free bases, or as salts thereof, for example as pharmaceutically acceptable salts thereof. Thus, in one embodiment, the invention is directed to compounds of Formula (I), Formula (II), and Formula (III) as the free base. In another embodiment, the invention is directed to compounds of Formula (I), Formula (II), and Formula (III) and salts thereof. In a further embodiment, the invention is
15 directed to compounds of Formula (I), Formula (II), and Formula (III) and pharmaceutically acceptable salts thereof.

- [00034] It will be appreciated that pharmaceutically acceptable salts of the compounds according to Formula (I, II, and III) may be prepared. Indeed, in certain embodiments of the invention, pharmaceutically acceptable salts of the compounds according to
20 Formula (I), Formula (II), and Formula (III) 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 invention is further directed to compounds of Formula (I), Formula (II), and Formula (III) and pharmaceutically acceptable salts thereof.

- 25 [00035] "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 were enriched such that it constitutes 95% of the product, then the enantiomeric excess would be 90% ee (the amount of the enriched enantiomer, 95%,
30 minus the amount of the other enantiomer, 5%).

[00036] "Enantiomerically enriched" refers to products whose enantiomeric excess (ee) is greater than zero. For example, 'enantiomerically enriched' refers to products whose enantiomeric excess is greater than 50% ee, greater than 75% ee, and greater

than 90% ee. 'Enantiomerically pure' refers to products whose enantiomeric excess is 99% or greater.

[00037] Included within the scope of the 'compounds of the invention' are all solvates (including hydrates), complexes, polymorphs, prodrugs, radiolabelled derivatives, and stereoisomers of the compounds of Formula (I), Formula (II), and Formula (III) and salts thereof.

[00038] The compounds of the invention may exist in solid or liquid form. In the solid state, the compounds of the invention may exist in crystalline or non-crystalline form, or as a mixture thereof. For compounds of the invention 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 ethyl acetate, 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 invention includes all such solvates.

[00039] It will be further appreciated that certain compounds of the invention 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 invention 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.

[00040] The invention also includes isotopically-labelled compounds, which are identical to the compounds of Formula (I, II, and III) 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 invention include isotopes of hydrogen, carbon, nitrogen, oxygen and fluorine, such as ^3H , ^{11}C , ^{14}C and ^{18}F .

[00041] The term “co-crystals” refers to solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts.

[00042] 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.

[00043] The term “polymorphs” refers to crystal forms of the same molecule, and different polymorphs may have different physical properties such as, for example, melting temperatures, heats of fusion, solubilities, dissolution rates and/or vibrational spectra as a result of the arrangement or conformation of the molecules in the crystal lattice.

[00044] The term “prodrugs” refers to the precursor of the compound of Formula (I, II, and III) which on administration undergoes chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of a compound of the invention, which are readily convertible *in vivo* into a compound of the invention.

[00045] The term “alkyl” refers to a saturated hydrocarbon chain having the specified number of carbon atoms. For example, which are not limited, C_{1-6} alkyl refers to an alkyl group having from 1 – 6 carbon atoms, or 1 – 3 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.

[00046] The term “C(O) alkyl” refers to an alkyl group as defined above attached via carbonyl linkage to the rest of the molecule. For example, C(O)C₁₋₆ alkyl refers to an alkyl group having from 1 – 6 carbon atoms, or 1 – 3 carbon atoms attached via carbonyl linkage to the rest of the molecule. Preferred C(O) alkyl groups include, without limitation, -C(O)CH₃, -C(O)CH₂CH₃, and the like.

[00047] The term “SO₂ alkyl” refers to an alkyl group as defined above attached via sulfonyl linkage to the rest of the molecule. For example, SO₂C₁₋₆ alkyl refers to an alkyl group having from 1 – 6 carbon atoms, or 1 – 3 carbon atoms attached via sulfonyl linkage to the rest of the molecule. Preferred SO₂ alkyl groups include, without limitation, -SO₂CH₃, -SO₂CH₂CH₃, and the like.

[00048] The term “alkoxy” refers to an alkyl group attached via an oxygen linkage to the rest of the molecule. For example, C₁₋₆ alkoxy refers to an alkyl group having from 1 – 6 carbon atoms, or 1 – 3 carbon atoms attached via an oxygen linkage to the rest of the molecule. Preferred alkoxy groups include, without limitation, -OCH₃ (methoxy), -OC₂H₅ (ethoxy) and the like.

[00049] The term “alkylamino” refers to an alkyl group as defined above attached via amino or alkyl linkage to the rest of the molecule. For example, C₁₋₆ alkylamino refers to an alkyl group having from 1 – 6 carbon atoms, or 1 – 3 carbon atoms attached via amino linkage to the rest of the molecule. Preferred alkylamino groups include, without limitation, -NHCH₃, -N(CH₃)₂, and the like.

[00050] The term “C(O)NR” refers to an alkylamino group as defined above attached via a carbonyl linkage to the rest of the molecule. Preferred C(O)NR groups include, C(O)NCH₃, C(O)NCH₂CH₃, and the like.

[00051] The term “SO₂NR” refers to an alkylamino group as defined above attached via a sulfonyl linkage to the rest of the molecule. Preferred SO₂NR groups include, SO₂NCH₃, SO₂NCH₂CH₃, and the like.

[00052] The term “C(O) alkylamino” refers to an alkylamino group as defined above attached via carbonyl linkage to the rest of the molecule. For example, C(O)C₁₋₆ alkylamino refers to an alkylamino group having from 1 – 6 carbon atoms, or 1 – 3 carbon atoms attached via carbonyl linkage to the rest of the molecule. Preferred C(O) alkylamino groups include, without limitation, -C(O)NHCH₃, -C(O)N(CH₃)₂, and the like.

[00053] The term “SO₂ alkylamino” refers to an alkylamino group as defined above attached via sulfonyl linkage to the rest of the molecule. For example, SO₂C₁₋₆

alkylamino refers to an alkylamino group having from 1 – 6 carbon atoms, or 1 – 3 carbon atoms attached via sulfonyl linkage to the rest of the molecule. Preferred SO₂ alkylamino groups include, without limitation, -SO₂NHCH₃, -SO₂N(CH₃)₂, and the like.

5 [00054] The term “acylamino” refers to an acyl group attached via carbonyl linkage to the rest of the molecule. For example, C₁₋₆ acylamino refers to an acyl group having from 1 – 6 carbon atoms, or 1 – 3 carbon atoms attached via amino linkage to the rest of the molecule. Preferred acylamino groups include, without limitation, -(CO)NHCH₃, -(CO)N(CH₃)₂, and the like.

10 [00055] The term “haloalkyl” refers to an alkyl group as defined above containing halogen and attached via alkyl linkage to the rest of the molecule. For example, C₁₋₆ haloalkyl refers to an alkyl group having from 1 – 6 carbon atoms, or 1 – 3 carbon atoms attached via halo linkage to the rest of the molecule. Preferred haloalkyl groups include, without limitation, -CH₂Cl, -CHCl₂, and the like.

15 [00056] The term “C(O) haloalkyl” refers to an haloalkyl group as defined above attached via carbonyl linkage to the rest of the molecule. For example, C(O)C₁₋₆ haloalkyl refers to an haloalkyl group having from 1 – 6 carbon atoms, or 1 – 3 carbon atoms attached via carbonyl linkage to the rest of the molecule. Preferred C(O) haloalkyl groups include, without limitation, -(CO)CH₂Cl, -C(O)CHCl₂, and the like.

20 [00057] The term “SO₂ haloalkyl” refers to an haloalkyl group as defined above attached via sulfonyl linkage to the rest of the molecule. For example, SO₂C₁₋₆ haloalkyl refers to an haloalkyl group having from 1 – 6 carbon atoms, or 1 – 3 carbon atoms attached via sulfonyl linkage to the rest of the molecule. Preferred SO₂ haloalkyl groups include, without limitation, -SO₂CH₂Cl, -SO₂CHCl₂, and the like.

25 [00058] The term “haloalkoxy” refers to an alkoxy group as defined above attached via oxygen linkage to the rest of the molecule. For example, C₁₋₆ haloalkoxy refers to an alkoxy group having from 1 – 6 carbon atoms, or 1 – 3 carbon atoms attached via halo linkage to the rest of the molecule. Preferred haloalkoxy groups include, without limitation, -OCH₂Cl, -OCHCl₂, and the like.

30 [00059] The term “halogen” refers to a halogen radical, for example, fluoro, chloro, bromo, or iodo. “Haloalkyl” refers to an alkyl group, as herein before defined, in which at least one of the hydrogen atoms has been replaced with a halogen radical. “C₁₋₆ haloalkyl” refers to a C₁₋₆ alkyl group in which at least one of the hydrogen atoms has been replaced with a halogen radical. An example of 'haloalkyl' is trifluoromethyl or 2,2,2-trifluoroethyl.

[00060] The term “cycloalkyl” refers to a saturated hydrocarbon ring having a specified number of carbon atoms. For example, which are not limited, C₃₋₆ cycloalkyl refers to a cycloalkyl group having from 3 to 6 member atoms, or 3 member atoms. Preferred cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, groups and the like.

[00061] The term “SO₂C₃₋₆ cycloalkyl” refers to an cycloalkyl group as defined above attached via sulfonyl linkage to the rest of the molecule. For example, SO₂C₃₋₆ cycloalkyl refers to a cycloalkyl group having from 3 – 6 carbon atoms attached via sulfonyl linkage to the rest of the molecule. Preferred SO₂ cycloalkyl groups include, without limitation, -SO₂C₃ cycloalkyl, and the like.

[00062] The term “aryl” refers to aromatic ring having a specified number of carbon atoms. For example, C₅₋₆ aryl refers to an aryl group having 5 or 6 member atoms, or 6 member atoms. Preferred aryl groups include, without limitation, phenyl, and the like.

[00063] The term “C(O) aryl” refers to an aryl group as defined above attached via carbonyl linkage to the rest of the molecule. For example, C(O)C₅₋₆ aryl refers to an alkyl group having from 5 – 6 carbon atoms attached via carbonyl linkage to the rest of the molecule. Preferred C(O) aryl groups include, without limitation, -C(O) C₆H₅, -C(O) C₅H₅, and the like.

[00064] The term “SO₂ aryl” refers to an aryl group as defined above attached via sulfonyl linkage to the rest of the molecule. For example, SO₂C₅₋₆ aryl refers to an aryl group having from 5 – 6 carbon atoms attached via sulfonyl linkage to the rest of the molecule. Preferred SO₂ aryl groups include, without limitation, -SO₂ C₆H₅, -SO₂ C₅H₅, and the like.

[00065] The term “heteroaryl” refers to aromatic rings containing from 1 to 3 heteroatoms in the ring. “Heteroaryl” groups may be substituted with one or one or more substituents if so defined herein. The “C₁₋₆ heteroaryl” rings having 1 or 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.

[00066] The term “C(O) heteroaryl” refers to an heteroaryl group as defined above attached via carbonyl linkage to the rest of the molecule. For example, C(O)C₁₋₆ heteroaryl refers to an alkyl group having from 1 – 6 carbon atoms attached via carbonyl linkage to the rest of the molecule. Preferred C(O) heteroaryl groups include, without limitation, -C(O) pyridinyl, -C(O) pyrazolyl, and the like.

5 [00067] The term “SO₂ heteroaryl” refers to an aryl group as defined above attached via sulfonyl linkage to the rest of the molecule. For example, SO₂C₁₋₆ heteroaryl refers to an aryl group having from 1 – 6 carbon atoms attached via sulfonyl linkage to the rest of the molecule. Preferred SO₂ heteroaryl groups include, without limitation, -SO₂ pyridinyl, -SO₂ pyrazolyl, and the like.

10 [00068] The term “heterocyclic” and “heterocyclyl” refer to saturated or unsaturated monocyclic aliphatic rings containing 5, 6, or 7 ring members including 1 or 2 heteroatoms or to saturated or unsaturated bicyclic aliphatic rings containing 5, 6 or 7 ring members including 1 or 2 heteroatoms. In certain embodiments, 'heterocyclyl' groups are saturated. In other embodiments, 'heterocyclyl' groups are unsaturated. 'Heterocyclyl' groups containing more than one heteroatom may contain different heteroatoms. 'Heterocyclyl' groups may be substituted with one or more substituents as defined herein. 'Heterocyclyl' includes piperidinyl, tetrahydropyranyl, azepinyl, oxazepinyl, azabicyclo[3.1.0]hexanyl.

15 [00069] 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.

20 [00070] 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.

25 [00071] Salts and solvates having non-pharmaceutically acceptable counter-ions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of Formula (I), Formula (II), and Formula (III) and their pharmaceutically acceptable salts. Thus one embodiment of the invention embraces compounds of Formula (I), Formula (II), and Formula (III) and salts thereof. Compounds according to Formula (I), Formula (II), and Formula (III) 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

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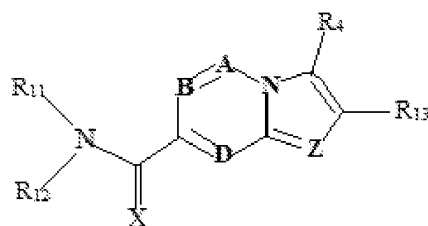
hydrochloride, hydrobromide, nitrate, methylnitrate, sulfate, bisulfate, sulfamate, phosphate, acetate, hydroxyacetate, phenyl acetate, propionate, butyrate, iso-butyrate, valerate, maleate, hydroxymaleate, acrylate, fumarate, malate, tartrate, citrate, salicylate, glycollate, lactate, heptanoate, phthalate, 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.

[00072] The term "PAD inhibitor" or "inhibitor of PAD" is used to identify a compound, which is capable of interacting with neutrophil extracellular traps (NETs) and more specifically in the histone citrullination that occurs during NETosis. Inhibiting PAD4 enzymatic activity means reducing the ability of PAD4 enzyme so as to inhibit the formation of citrulline through citrullination process. Preferably, such inhibition is specific to PAD4 enzyme.

[00073] A term once described, the same meaning applies for it, throughout the patent.

[00074] Despite of the vast utility of the PAD4 inhibitory compounds, as described above, the identification of a chemical moiety that facilitates PAD inhibition still remains a problem. Identification and development of new PAD4 inhibitor compounds treating PAD4 mediated disorders are direly required to treat diseases like example rheumatoid arthritis, vasculitis, systemic lupus erythematosus, cutaneous lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, multiple sclerosis and psoriasis.

[00075] In an embodiment of the present disclosure, there is provided a compound of Formula I their polymorphs, stereoisomers, prodrugs, solvates, co-crystals, intermediates, pharmaceutically acceptable salts, and metabolites thereof, wherein



Formula (I)

X is selected from O or S; Z is N; A is selected from N or CR₁;

B is selected from N or CR₂; D is selected from N or CR₃; R₁, R₂, R₃, and R₄ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₆ alkyl, C₁₋

- 5 6 alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ heteroaryl, and
- 10 C₁₋₆ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, and hydroxyl; R₁₁ is hydrogen; R₁₂ is selected from C₁₋₆ alkylamino, and 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O, or R₁₁ and R₁₂ can be taken together to
- 15 form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, -NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, or
- 20 hydroxyl; R₁₃ is selected from hydrogen, 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆
- 25 cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, C₁₋₁₀ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₁₀
- 30 heterocyclyl, and C₁₋₁₀ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, hydroxyl, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen,

hydroxyl, $-\text{CH}_2\text{OH}$, and cyano; and R_{15} is selected from the group consisting of hydrogen, C_{1-6} alkyl, and combinations thereof.

- [00076]** In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is selected from N or CR_1 ; B is selected from N or CR_2 ; D is selected from N or CR_3 ; R_1 , R_2 , R_3 , and R_4 are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{1-4} acylamino, C_{1-4} alkylamino, C_{5-6} aryl, C_{1-6} heterocyclyl, C_{1-6} heteroaryl, $\text{C}(\text{O})\text{NR}_{15}$, $\text{C}(\text{O})\text{C}_{1-4}$ alkylamino, $\text{C}(\text{O})\text{C}_{5-6}$ aryl, $\text{C}(\text{O})\text{C}_{1-6}$ heteroaryl, $\text{C}(\text{O})\text{C}_{1-4}$ alkyl, $\text{C}(\text{O})\text{C}_{1-4}$ haloalkyl, $\text{SO}_2\text{C}_{1-4}$ alkyl, $\text{SO}_2\text{C}_{1-4}$ haloalkyl, $\text{SO}_2\text{C}_{3-6}$ cycloalkyl, $\text{SO}_2\text{NR}_{15}$, $\text{SO}_2\text{NC}_{1-4}$ alkylamino, $\text{SO}_2\text{C}_{5-6}$ aryl, or $\text{SO}_2\text{C}_{1-6}$ heteroaryl, wherein C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-6} heteroaryl, and C_{1-4} haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{1-6} heterocyclyl, C_{1-6} heteroaryl, cyano, and hydroxyl; R_{11} is hydrogen; R_{12} is selected from C_{1-6} alkylamino, and 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O, or R_{11} and R_{12} can be taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C_{1-6} alkylamino, C_{1-6} acylamino, $-\text{NHC}(\text{NH})\text{CH}_2\text{Cl}$, $\text{NH}(\text{CO})\text{CH}=\text{CH}-\text{CH}_2-\text{N}(\text{CH}_3)_2$, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, and hydroxyl; R_{13} is selected from hydrogen, 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} acylamino, C_{1-6} alkylamino, C_{5-10} aryl, C_{1-10} heterocyclyl, C_{1-10} heteroaryl, $\text{C}(\text{O})\text{C}_{1-6}$ alkyl, $\text{C}(\text{O})\text{C}_{1-6}$ haloalkyl, $\text{C}(\text{O})\text{NR}_{15}$, $\text{C}(\text{O})\text{C}_{1-6}$ alkylamino, $\text{C}(\text{O})\text{C}_{5-6}$ aryl, $\text{C}(\text{O})\text{C}_{1-6}$ heteroaryl, $\text{SO}_2\text{C}_{1-6}$ alkyl, $\text{SO}_2\text{C}_{1-6}$ haloalkyl, $\text{SO}_2\text{C}_{3-6}$ cycloalkyl, $\text{SO}_2\text{NR}_{15}$, $\text{SO}_2\text{NC}_{1-6}$ alkylamino, $\text{SO}_2\text{C}_{5-6}$ aryl, and $\text{SO}_2\text{C}_{1-6}$ heteroaryl, wherein C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{5-10} aryl, C_{1-10} heterocyclyl, and C_{1-10} heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{1-6} heteroaryl, C_{1-6} heterocyclyl, oxo, halogen, hydroxyl, and cyano, wherein

C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

- 5 **[00077]** In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is selected from N or CR₁; B is selected from N or CR₂; D is selected from N or CR₃; R₁, R₂ and R₃, are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₆ aryl, C₁₋₆ heterocyclyl, or C₁₋₆ heteroaryl; R₄ is selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₁₋₄ acylamino, C₁₋₄ alkylamino, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)NR₁₅, C(O)C₁₋₄ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, C(O)C₁₋₄ alkyl, C(O)C₁₋₄ haloalkyl, SO₂C₁₋₄ alkyl, SO₂C₁₋₄ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₄ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₆ heteroaryl, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, and hydroxyl; R₁₁ is hydrogen; R₁₂ is selected from C₁₋₆ alkylamino, and 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O, or R₁₁ and R₁₂ can be taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, or hydroxyl; R₁₃ is selected from hydrogen, 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, C₁₋₁₀ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆

heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, and C₁₋₁₀ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, hydroxyl, and cyano, wherein

5 C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[00078] In an embodiment of the present disclosure, there is provided a compound of

10 Formula I as described herein, wherein X is selected from O or S; Z is N; A is selected from N or CR₁; B is selected from N or CR₂; D is selected from N or CR₃; R₁, R₂, R₃, and R₄ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₁₋₄ acylamino, C₁₋₄ alkylamino, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)NR₁₅, C(O)C₁₋₄

15 alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, C(O)C₁₋₄ alkyl, C(O)C₁₋₄ haloalkyl, SO₂C₁₋₄ alkyl, SO₂C₁₋₄ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₄ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₆ heteroaryl, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆

20 heterocyclyl, C₁₋₆ heteroaryl, cyano, and hydroxyl; R₁₁ is hydrogen; R₁₂ is selected from C₁₋₆ alkylamino, and 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O, or R₁₁ and R₁₂ can be taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered

25 monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, and hydroxyl; R₁₃ is selected from hydrogen, 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected

30 from N, S or O, wherein 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from cyano, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, or C₁₋₁₀ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, and C₁₋₁₀ heteroaryl, is optionally

substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, hydroxyl, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[00079] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is selected from N or CR₁; B is selected from N or CR₂; R₁, R₂, and R₃ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₆ aryl, C₁₋₆ heterocyclyl, or C₁₋₆ heteroaryl; R₄ is selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₆ aryl, C₁₋₄ heterocyclyl, C₁₋₄ heteroaryl, C(O)C₁₋₄ alkyl, C(O)C₁₋₄ haloalkyl, C(O)NR₁₅, C(O)C₁₋₄ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₄ heteroaryl, SO₂C₁₋₄ alkyl, SO₂C₁₋₄ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₄ alkylamino, SO₂C₅₋₆ aryl, SO₂C₁₋₄ heteroaryl, C₁₋₄ acylamino, or C₁₋₄ alkylamino, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ heteroaryl, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₄ heterocyclyl, C₁₋₄ heteroaryl, cyano, and hydroxyl; R₁₁ is hydrogen; R₁₂ is selected from C₁₋₄ alkylamino, and 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O, or R₁₁ and R₁₂ can be taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, or hydroxyl; R₁₃ is selected from hydrogen, 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, C₁₋₁₀ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅,

C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, or C(O)C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, and C₁₋₁₀ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, hydroxyl, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[00080] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is selected from N or CR₁; B is selected from N or CR₂; R₁, R₂, and R₃ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₆ aryl, C₁₋₆ heterocyclyl, and C₁₋₆ heteroaryl; R₄ is selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₆ aryl, C₁₋₄ heterocyclyl, C₁₋₄ heteroaryl, C(O)C₁₋₄ alkyl, C(O)C₁₋₄ haloalkyl, C(O)NR₁₅, C(O)C₁₋₄ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₄ heteroaryl, SO₂C₁₋₄ alkyl, SO₂C₁₋₄ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₄ alkylamino, SO₂C₅₋₆ aryl, SO₂C₁₋₄ heteroaryl, C₁₋₄ acylamino, or C₁₋₄ alkylamino, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ heteroaryl, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₄ heterocyclyl, C₁₋₄ heteroaryl, cyano, and hydroxyl; R₁₁ is hydrogen; R₁₂ is selected from C₁₋₄ alkylamino, and 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O, or R₁₁ and R₁₂ can be taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₄ alkylamino, C₁₋₄ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₄ alkyl, halogen, C₁₋₄ alkoxy, or hydroxyl; R₁₃ is selected from hydrogen, 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆

haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, C₁₋₁₀ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, or C(O)C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, and C₁₋₁₀ heteroaryl, is optionally substituted
5 with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, hydroxyl, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; and R₁₅ is selected
10 from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[00081] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is selected from N or CR₁; B is selected from N or CR₂; R₁, R₂, and R₃ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅
15 cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₆ aryl, C₁₋₆ heterocyclyl, or C₁₋₆ heteroaryl, and combinations thereof; R₄ is selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₆ aryl, C₁₋₄ heterocyclyl, C₁₋₄ heteroaryl, C(O)C₁₋₄ alkyl, C(O)C₁₋₄ haloalkyl, C(O)NR₁₅, C(O)C₁₋₄ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₄ heteroaryl, SO₂C₁₋₄ alkyl,
20 SO₂C₁₋₄ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₄ alkylamino, SO₂C₅₋₆ aryl, SO₂C₁₋₄ heteroaryl, C₁₋₄ acylamino, or C₁₋₄ alkylamino, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ heteroaryl, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₄ heterocyclyl, C₁₋₄ heteroaryl, cyano, and hydroxyl; R₁₁ is
25 hydrogen; R₁₂ is selected from C₁₋₄ alkylamino, and 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O, or R₁₁ and R₁₂ can be taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated
30 heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, and hydroxyl, and combinations thereof; R₁₃ is selected from hydrogen, 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O,

wherein 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, C₁₋₁₀ heteroaryl, C(O)C₁₋₄ alkyl, C(O)C₁₋₄ haloalkyl, C(O)NR₁₅, C(O)C₁₋₄ alkylamino, C(O)C₅₋₆ aryl, and C(O)C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, and C₁₋₁₀ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, hydroxyl, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; and R₁₅ is independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[00082] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is selected from N or CR₁; B is selected from N or CR₂; D is selected from N or CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₆ aryl, C₁₋₆ heterocyclyl, or C₁₋₆ heteroaryl; R₄ is selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)C₁₋₄ alkyl, C(O)C₁₋₄ haloalkyl, C(O)NR₁₅, C(O)C₁₋₄ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₄ alkyl, SO₂C₁₋₄ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₄ alkylamino, SO₂C₅₋₆ aryl, SO₂C₁₋₆ heteroaryl, C₁₋₄ acylamino, or C₁₋₄ alkylamino, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₆ heteroaryl, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, and hydroxyl; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₄ alkylamino, C₁₋₄ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₄ alkyl, halogen, C₁₋₄ alkoxy, or hydroxyl; R₁₃ is selected from hydrogen, 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl with 1-5

heteroatoms selected from N, S or O, wherein 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₁₋₄ acylamino, C₁₋₄ alkylamino, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, hydroxyl, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[00083] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is CR₁; B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₆ aryl, C₁₋₆ heterocyclyl, or C₁₋₆ heteroaryl; R₄ is selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)C₁₋₄ alkyl, C(O)C₁₋₄ haloalkyl, C(O)NR₁₅, C(O)C₁₋₄ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₄ alkyl, SO₂C₁₋₄ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₄ alkylamino, SO₂C₅₋₆ aryl, SO₂C₁₋₆ heteroaryl, C₁₋₄ acylamino, or C₁₋₄ alkylamino, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₆ heteroaryl, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, and hydroxyl; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₄ alkylamino, C₁₋₄ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₄ alkyl, halogen, C₁₋₄ alkoxy, or hydroxyl; R₁₃ is selected from hydrogen, 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl are optionally substituted

with 1-5 substituents selected from halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₁₋₄ acylamino, C₁₋₄ alkylamino, C₅₋₉ aryl, C₁₋₉ heterocyclyl, or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₆ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, hydroxyl, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[00084] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is selected from N or CR₁; B is selected from N or CR₂; D is selected from N or CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy; R₄ is selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)C₁₋₄ alkyl, C(O)C₁₋₄ haloalkyl, C(O)NR₁₅, C(O)C₁₋₄ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₄ alkyl, SO₂C₁₋₄ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₄ alkylamino, SO₂C₅₋₆ aryl, SO₂C₁₋₆ heteroaryl, C₁₋₄ acylamino, or C₁₋₄ alkylamino, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₆ heteroaryl, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, and hydroxyl; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₄ alkylamino, C₁₋₄ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₄ alkyl, halogen, C₁₋₄ alkoxy, or hydroxyl; R₁₃ is selected from hydrogen, 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₁₋₄ acylamino, C₁₋₄ alkylamino, C₅₋₉ aryl, C₁₋₉ heterocyclyl,

and C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, hydroxyl, and cyano, wherein

5 C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[00085] In an embodiment of the present disclosure, there is provided a compound of

10 Formula I as described herein, wherein X is selected from O or S; Z is N; A is selected from N or CR₁; B is selected from N or CR₂; D is selected from N or CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₆ aryl, C₁₋₆ heterocyclyl, or C₁₋₆ heteroaryl; R₄ is selected from hydrogen, hydroxyl, cyano, amino,

15 halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, and C₅₋₆ aryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, cyano, and hydroxyl; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated

20 heterocyclic ring with 1-5 heteroatoms selected from N or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₄ alkylamino, C₁₋₄ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₄ alkyl, halogen, C₁₋₄ alkoxy, or hydroxyl; R₁₃ is selected from hydrogen, 5-10 membered monocyclic or

25 bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₁₋₄ acylamino, C₁₋₄ alkylamino, C₅₋₉ aryl, C₁₋₉ heterocyclyl,

30 or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, hydroxyl, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or

more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

- [00086] In an embodiment of the present disclosure, there is provided a compound of
- 5 Formula I as described herein, wherein X is selected from O or S; Z is N; A is selected from N or CR₁; B is selected from N or CR₂; D is selected from N or CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₆ aryl, C₁₋₆ heterocyclyl, or C₁₋₆ heteroaryl; R₄ is selected from hydrogen, hydroxyl, cyano, amino,
- 10 halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)C₁₋₄ alkyl, C(O)C₁₋₄ haloalkyl, C(O)NR₁₅, C(O)C₁₋₄ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₄ alkyl, SO₂C₁₋₄ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₄ alkylamino, SO₂C₅₋₆ aryl, SO₂C₁₋₆ heteroaryl, C₁₋₄ acylamino, or C₁₋₄ alkylamino, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₆
- 15 heteroaryl, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, and hydroxyl; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N or O, wherein the 5-10
- 20 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₄ alkylamino, C₁₋₄ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₄ alkyl, halogen, C₁₋₄ alkoxy, or hydroxyl; R₁₃ is selected from hydrogen, 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl with 1-5
- 25 heteroatoms selected from N, S or O, wherein 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted
- 30 with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, hydroxyl, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆

alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[00087] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is CR₁;

- 5 B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, or C₁₋₂ alkyl; R₄ is selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, or C₅₋₆ aryl, wherein C₁₋₄ alkyl, and C₁₋₄ alkoxy, is optionally substituted with one or more of the groups selected from C₁₋₄ alkyl, and C₁₋₄ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5
- 10 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with the substituents selected from amino, NH(CO)CH=CH-CH₂-N(CH₃)₂, or C₁₋₂ alkylamino; and R₁₃ is selected from hydrogen, 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O,
- 15 wherein 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally
- 20 substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano.

- 25 **[00088]** In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is CR₁; B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, or C₁₋₂ alkyl; R₄ is selected from hydrogen, C₁ alkyl, C₁ alkoxy, C₃ cycloalkyl, or C₆ aryl, wherein C₁ alkyl, and C₁ alkoxy, is optionally substituted with one or more of the groups selected
- 30 from C₁ alkyl, and C₁ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with the substituents selected from amino, NH(CO)CH=CH-CH₂-N(CH₃)₂, or C₁₋₂ alkylamino; and R₁₃ is selected from hydrogen,

5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano.

[00089] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is CR₁; B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, and C₁₋₂ alkyl; R₄ is selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, and C₅₋₆ aryl, wherein C₁₋₄ alkyl, and C₁₋₄ alkoxy, is optionally substituted with one or more of the groups selected from C₁₋₄ alkyl, and C₁₋₄ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with amino, and NH(CO)CH=CH-CH₂-N(CH₃)₂; and R₁₃ is selected from hydrogen, 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano.

[00090] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is CR₁; B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, and C₁ alkyl; R₄ is selected from hydrogen, C₁ alkyl, C₁ alkoxy, C₃ cycloalkyl, and C₆ aryl, wherein C₁ alkyl, and C₁ alkoxy, is optionally substituted with one or more of the groups selected from C₁ alkyl, and C₁ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with amino, and NH(CO)CH=CH-CH₂-N(CH₃)₂; and R₁₃ is selected from hydrogen, 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano.

[00091] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is CR₁; B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, or C₁ alkyl; R₄ is selected from hydrogen, C₁ alkyl, C₁ alkoxy, C₃ cycloalkyl, or C₆ aryl, wherein C₁ alkyl, and C₁ alkoxy, is optionally substituted with one or more of the groups selected from C₁ alkyl, and C₁ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-6 membered monocyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-6 membered monocyclic saturated heterocyclic ring is optionally substituted with amino, and NH(CO)CH=CH-CH₂-N(CH₃)₂; and R₁₃ is selected from hydrogen, 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic

heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano.

10 **[00092]** In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is CR₁; B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, or C₁ alkyl; R₄ is selected from hydrogen, C₁ alkyl, C₁ alkoxy, C₃ cycloalkyl, or C₆ aryl, wherein C₁ alkyl, and C₁ alkoxy, is optionally substituted with one or more of the groups selected from C₁ alkyl, and C₁ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-10 membered bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O; and R₁₃ is selected from hydrogen, 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano.

25 **[00093]** In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is CR₁; B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, or C₁ alkyl; R₄ is selected from hydrogen, C₁ alkyl, C₁ alkoxy, C₃ cycloalkyl, or C₆ aryl, wherein C₁ alkyl, and C₁ alkoxy, is optionally substituted with one or more of the groups selected from C₁ alkyl, and C₁ alkoxy; R₁₁ and R₁₂ are taken together to form a 5 membered

monocyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5 membered monocyclic saturated heterocyclic ring is optionally substituted with amino; and R₁₃ is selected from hydrogen, 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano.

[00094] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is CR₁; B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, or C₁ alkyl; R₄ is selected from hydrogen, C₁ alkyl, C₁ alkoxy, C₃ cycloalkyl, or C₆ aryl, wherein C₁ alkyl, and C₁ alkoxy, is optionally substituted with one or more of the groups selected from C₁ alkyl, and C₁ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with amino, and NH(CO)CH=CH-CH₂-N(CH₃)₂; and R₁₃ is selected from hydrogen, 5-9 membered monocyclic aryl, wherein 5-9 membered monocyclic aryl, is optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heterocyclyl, or C₁₋₆ heteroaryl.

[00095] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is CR₁; B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, or C₁ alkyl; R₄ is selected from hydrogen, C₁ alkyl, C₁ alkoxy, C₃ cycloalkyl, or C₆ aryl, wherein C₁ alkyl, and C₁ alkoxy, is optionally substituted with one or more of the groups selected from C₁ alkyl, and C₁ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-6 membered

monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-6 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with amino; and R₁₃ is selected from hydrogen, 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl with 1 heteroatoms selected from S or O, wherein 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heterocyclyl, or C₁₋₆ heteroaryl.

10 **[00096]** In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is selected from O or S; Z is N; A is CR₁; B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, or C₁ alkyl; R₄ is selected from hydrogen, C₁ alkyl, C₁ alkoxy, C₃ cycloalkyl, or C₆ aryl, wherein C₁ alkyl, and C₁ alkoxy, is optionally substituted with one or more of the groups selected
15 from C₁ alkyl, and C₁ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-6 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-6 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with amino; and R₁₃ is indole, wherein indole is optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro,
20 C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, and cyano, wherein C₅₋₆ aryl, C₁₋₆
25 heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano.

[00097] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is O; Z is N; A is CR₁; B is CR₂; D is CR₃;
30 R₁, R₂, and R₃ are independently selected from hydrogen, or C₁₋₂ alkyl; R₄ is selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, or C₅₋₆ aryl, wherein C₁₋₄ alkyl, and C₁₋₄ alkoxy, is optionally substituted with one or more of the groups selected from C₁₋₄ alkyl, and C₁₋₄ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from

N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₂ alkylamino, and NH(CO)CH=CH-CH₂-N(CH₃)₂; and R₁₃ is selected from hydrogen, 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano.

[00098] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is O; Z is N; A is CR₁; B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, or C₁₋₂ alkyl; R₄ is selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, or C₅₋₆ aryl, wherein C₁₋₄ alkyl, and C₁₋₄ alkoxy, is optionally substituted with one or more of the groups selected from C₁₋₄ alkyl, and C₁₋₄ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₂ alkylamino, and NH(CO)CH=CH-CH₂-N(CH₃)₂; and R₁₃ is selected from hydrogen, 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, or O, wherein 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, and cyano,

wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano.

[00099] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is O; Z is N; A is CR₁; B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, or C₁₋₂ alkyl; R₄ is selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, and C₅₋₆ aryl, wherein C₁₋₄ alkyl, and C₁₋₄ alkoxy, is optionally substituted with one or more of the groups selected from C₁₋₄ alkyl, and C₁₋₄ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₂ alkylamino, and NH(CO)CH=CH-CH₂-N(CH₃)₂; and R₁₃ is selected from hydrogen, 5-9 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-9 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano.

[000100] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is O; Z is N; A is CR₁; B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, or C₁₋₂ alkyl; R₄ is selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, or C₅₋₆ aryl, wherein C₁₋₄ alkyl, and C₁₋₄ alkoxy, is optionally substituted with one or more of the groups selected from C₁₋₄ alkyl, and C₁₋₄ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₂ alkylamino, and NH(CO)CH=CH-CH₂-N(CH₃)₂; and R₁₃ is selected from hydrogen, 5-

9 membered monocyclic aryl, and 5-9 membered bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-9 membered monocyclic aryl, and 5-9 membered bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano.

[000101] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X selected from O or S; Z is N; A is CR₁; B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, or C₁₋₂ alkyl; R₄ is selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, or C₅₋₆ aryl, wherein C₁₋₄ alkyl, and C₁₋₄ alkoxy, is optionally substituted with one or more of the groups selected from C₁₋₄ alkyl, and C₁₋₄ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₂ alkylamino, and NH(CO)CH=CH-CH₂-N(CH₃)₂; and R₁₃ is selected from hydrogen, 5-9 membered bicyclic heteroaryl with 1-5 heteroatoms selected from N, or O, wherein 5-9 membered bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano.

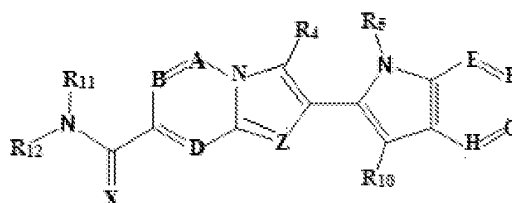
[000102] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is O; Z is N; A is CR₁; B is CR₂; D is CR₃;

R₁, R₂, and R₃ are independently selected from hydrogen, or C₁₋₂ alkyl; R₄ is selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, or C₅₋₆ aryl, wherein C₁₋₄ alkyl, and C₁₋₄ alkoxy, is optionally substituted with one or more of the groups selected from C₁₋₄ alkyl, and C₁₋₄ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₂ alkylamino, or NH(CO)CH=CH-CH₂-N(CH₃)₂; and R₁₃ is selected from hydrogen, 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl with 1 heteroatom selected from N, S or O, wherein 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro, bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano.

[000103] In an embodiment of the present disclosure, there is provided a compound of Formula I as described herein, wherein X is S; Z is N; A is CR₁; B is CR₂; D is CR₃; R₁, R₂, and R₃ are independently selected from hydrogen, or C₁₋₂ alkyl; R₄ is selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, or C₅₋₆ aryl, wherein C₁₋₄ alkyl, and C₁₋₄ alkoxy, is optionally substituted with one or more of the groups selected from C₁₋₄ alkyl, and C₁₋₄ alkoxy; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₂ alkylamino, or NH(CO)CH=CH-CH₂-N(CH₃)₂; and R₁₃ is selected from hydrogen, 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-9 membered monocyclic or bicyclic aryl, and 5-9 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, fluoro,

bromo, chloro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₅ cycloalkyl, C₅₋₉ aryl, C₁₋₉ heterocyclyl, and C₁₋₉ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano.

[000104] In an embodiment of the present disclosure, there is provided a compound of Formula II their polymorphs, stereoisomers, prodrugs, solvates, co-crystals, intermediates, pharmaceutically acceptable salts, and metabolites thereof, wherein



Formula (II)

X is selected from O or S; Z is N; A is selected from N or CR₁; B is selected from N or CR₂; D is selected from N or CR₃; E is selected from N or CR₆; F is absent or is selected from N, and CR₇; G is absent or is selected from N, and CR₈; H is absent or is selected from N, and CR₉; R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉ and R₁₀ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, C₁₋₁₀ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₁₀ heteroaryl, and C₁₋₆ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ alkylhydroxy, C₃₋₆ cycloalkyl, C₅₋₉ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl, wherein C₅₋₉ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano;

R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, or hydroxyl; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[000105] In an embodiment of the present disclosure, there is provided a compound of Formula II as described herein, wherein X is selected from O or S; Z is N; A is selected from N or CR₁; B is selected from N or CR₂; D is selected from N or CR₃; E is selected from N or CR₆; F is absent or is selected from N, and CR₇; G is absent or is selected from N, and CR₈; H is absent or is selected from N, and CR₉; R₁, R₂, R₃, R₆, R₇, R₈, R₉, and R₁₀ are independently selected from hydrogen, hydroxyl, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₃₋₅ cycloalkyl, or C₅₋₆ aryl; R₄, and R₅ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₁₋₄ acylamino, C₁₋₄ alkylamino, C₅₋₉ aryl, C₁₋₉ heterocyclyl, C₁₋₉ heteroaryl, C(O)C₁₋₄ alkyl, C(O)C₁₋₄ haloalkyl, C(O)NR₁₅, C(O)C₁₋₄ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₄ alkyl, SO₂C₁₋₄ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₄ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₉ heteroaryl, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ alkylhydroxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, or hydroxyl; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

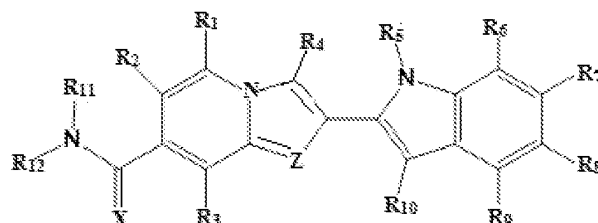
[000106] In an embodiment of the present disclosure, there is provided a compound of Formula II as described herein, wherein X is selected from O or S; Z is N; A is CR₁; B

is CR₂; D is CR₃; E is selected from N or CR₆; F is absent or is CR₇; G is absent or is CR₈; H is absent or is CR₉; R₁, R₂, R₃, R₆, R₇, R₈, R₉, and R₁₀ are independently selected from hydrogen, halogen, C₁₋₂ alkyl, C₁₋₂ alkoxy, or C₅₋₆ aryl; R₄, and R₅ are independently selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₉ aryl, C₁₋₉ heterocyclyl, or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₉ heteroaryl, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ alkylhydroxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with the substituents selected from amino, NH(CO)CH=CH-CH₂-N(CH₃)₂, or C₁₋₂ alkylamino.

[000107] In an embodiment of the present disclosure, there is provided a compound of Formula II as described herein, wherein X is selected from O or S; Z is N; A is CR₁; B is CR₂; D is CR₃; E is selected from N or CR₆; F is absent or is CR₇; G is absent or is CR₈; H is absent or is CR₉; R₁, R₂, R₃, R₆, R₇, R₈, R₉, and R₁₀ are independently selected from hydrogen, halogen, C₁ alkyl, or C₁ alkoxy; R₄ is selected from hydrogen, C₁ alkyl, C₁ alkoxy, C₃ cycloalkyl, or C₆ aryl, wherein C₁ alkyl, and C₁ alkoxy, is optionally substituted with one or more of the groups selected from C₁ alkyl, and C₁ alkoxy; R₅ is selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₉ aryl, C₁₋₉ heterocyclyl, or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₉ heteroaryl, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ alkylhydroxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; and R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10

membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with the substituents selected from amino, and $\text{NH}(\text{CO})\text{CH}=\text{CH}-\text{CH}_2-\text{N}(\text{CH}_3)_2$.

[000108] In an embodiment of the present disclosure, there is provided a compound of Formula III their polymorphs, stereoisomers, prodrugs, solvates, co-crystals, intermediates, pharmaceutically acceptable salts, and metabolites thereof, wherein



Formula (III)

X is selected from O or S; Z is N; R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉ and R₁₀ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, C₁₋₁₀ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₁₀ heteroaryl, and C₁₋₆ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ alkylhydroxy, C₃₋₆ cycloalkyl, C₅₋₉ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl, wherein C₅₋₉ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, or hydroxyl; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[000109] In an embodiment of the present disclosure, there is provided a compound of Formula III as described herein, wherein X is selected from O or S; Z is N; R₁, R₂, R₃, R₆, R₇, R₈, R₉ and R₁₀ are independently selected from hydrogen, hydroxyl, cyano,

amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₃₋₅ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heterocyclyl, or C₁₋₆ heteroaryl; R₄, and R₅ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₁₀ heterocyclyl, C₁₋₁₀ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₁₀ heteroaryl, and C₁₋₆ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ alkylhydroxy, C₃₋₆ cycloalkyl, C₅₋₉ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl, wherein C₅₋₉ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, or hydroxyl; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[000110] In an embodiment of the present disclosure, there is provided a compound of Formula III as described herein, wherein X is selected from O or S; Z is N; R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉ and R₁₀ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₁₋₄ acylamino, C₁₋₄ alkylamino, C₅₋₉ aryl, C₁₋₉ heterocyclyl, C₁₋₉ heteroaryl, C(O)C₁₋₄ alkyl, C(O)C₁₋₄ haloalkyl, C(O)NR₁₅, C(O)C₁₋₄ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₄ alkyl, SO₂C₁₋₄ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₄ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₉ heteroaryl, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ alkylhydroxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; R₁₁ and

R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, and hydroxyl; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[000111] In an embodiment of the present disclosure, there is provided a compound of Formula III as described herein, wherein X is selected from O or S; Z is N; R₁, R₂, R₃, R₆, R₇, R₈, R₉, and R₁₀ are independently selected from hydrogen, hydroxyl, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₃₋₅ cycloalkyl, or C₅₋₆ aryl; R₄, and R₅ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₁₋₄ acylamino, C₁₋₄ alkylamino, C₅₋₉ aryl, C₁₋₉ heterocyclyl, C₁₋₉ heteroaryl, C(O)C₁₋₄ alkyl, C(O)C₁₋₄ haloalkyl, C(O)NR₁₅, C(O)C₁₋₄ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₄ alkyl, SO₂C₁₋₄ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₄ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₉ heteroaryl, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ alkylhydroxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, or hydroxyl; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[000112] In an embodiment of the present disclosure, there is provided a compound of Formula III as described herein, wherein X is selected from O or S; Z is N; R₁, R₂, R₃, R₆, R₇, R₈, R₉, and R₁₀ are independently selected from hydrogen, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, or C₅₋₆ aryl; R₄, and R₅ are independently selected from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₅₋₉ aryl, C₁₋₉

heterocyclyl, or C₁₋₉ heteroaryl, wherein C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₉ heteroaryl, and C₁₋₄ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ alkylhydroxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; and R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₄ alkylamino, and NH(CO)CH=CH-CH₂-N(CH₃)₂.

[000113] In an embodiment of the present disclosure there is provided a compound of Formula (I) or its polymorphs, stereoisomers, prodrugs, solvates, co-crystals, intermediates, pharmaceutically acceptable salts, and metabolites thereof, which is selected from a group consisting of:

- 1) (R)-(3-aminopiperidin-1-yl)(2-(3-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 2) (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 3) (R)-(3-aminopiperidin-1-yl)(2-(1-benzyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 4) (R)-(3-aminopiperidin-1-yl)(2-(1-ethyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 5) (R)-(3-aminopiperidin-1-yl)(2-(1-ethyl-3-phenyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 6) (R)-(3-aminopyrrolidin-1-yl)(2-(1-ethyl-3-phenyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 7) (R)-(3-aminopyrrolidin-1-yl)(2-(1-ethyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 8) (R)-(3-aminopyrrolidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 9) (2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)(hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6(5H)-yl)methanone,

- 10) (R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-(pyridin-4-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone,
- 11) (R)-(3-Aminopiperidin-1-yl)(3-methyl-2-(1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone,
- 5 12) (R)-(3-aminopiperidin-1-yl)(2-(1-(4-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 13) (R)-(3-aminopiperidin-1-yl)(2-(1-(4-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 14) (R)-4-((2-(7-(3-aminopiperidine-1-carbonyl)-3-methylimidazo[1,2-a]pyridin-2-yl)-1H-indol-1-yl)methyl)benzonitrile,
- 10 15) (R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-(pyridin-3-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone,
- 16) (R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-(pyridin-2-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone,
- 15 17) (R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-(2,2,2-trifluoroethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone,
- 18) (R)-4-((2-(7-(3-aminopiperidine-1-carbonyl)-3-methylimidazo[1,2-a]pyridin-2-yl)-1H-indol-1-yl)methyl)-1-methylpyridin-2(1H)-one,
- 19) (R)-(3-aminopiperidin-1-yl)(2-(3-ethylbenzo[b]thiophen-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 20 20) (R)-(3-aminopiperidin-1-yl)(2-(1-(4-chlorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 21) (R)-(3-aminopiperidin-1-yl)(2-(1-(2-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 25 22) (R)-(3-aminopiperidin-1-yl)(2-(1-ethyl-5-phenyl-1H-pyrrol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 23) (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 24) (R)-(3-aminopiperidin-1-yl)(2-(1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 30 25) (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3,5-dimethylimidazo[1,2-a]pyridin-7-yl)methanone,
- 26) (R)-(3-aminopiperidin-1-yl)(2-(1-benzyl-1H-indol-2-yl)-3,5-dimethylimidazo[1,2-a]pyridin-7-yl)methanone,

- 27) (R)-(3-aminopiperidin-1-yl)(3,5-dimethyl-2-(1-(pyridin-2-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone,
- 28) (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-fluoro-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 5 29) (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 30) (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-methyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 31) (R)-(3-aminopiperidin-1-yl)(2-(2-ethylphenyl)-3-methylimidazo[1,2-a]pyridin-10 7-yl)methanone,
- 32) (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-phenylimidazo[1,2-a]pyridin-7-yl)methanone,
- 33) (R)-(3-aminopiperidin-1-yl)(3-cyclopropyl-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone,
- 15 34) (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridin-7-yl)methanone,
- 35) (R)-(3-aminopiperidin-1-yl)(2-(1-(3-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 36) (R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-(thiophen-3-ylmethyl)-1H-indol-2-20 yl)imidazo[1,2-a]pyridin-7-yl)methanone,
- 37) (R)-(3-aminopiperidin-1-yl)(2-(1-(furan-3-ylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 38) (R)-(3-aminopiperidin-1-yl)(2-(1-(1-(4-fluorophenyl)ethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 25 39) (R)-(3-aminopiperidin-1-yl)(2-(1-ethyl-5-fluoro-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 40) (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-4-fluoro-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 41) (R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-((4-methylthiazol-2-yl)methyl)-1H-30 indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone,
- 42) (R)-(3-aminopiperidin-1-yl)(2-(1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 43) (R)-(3-aminopiperidin-1-yl)(2-(5-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,

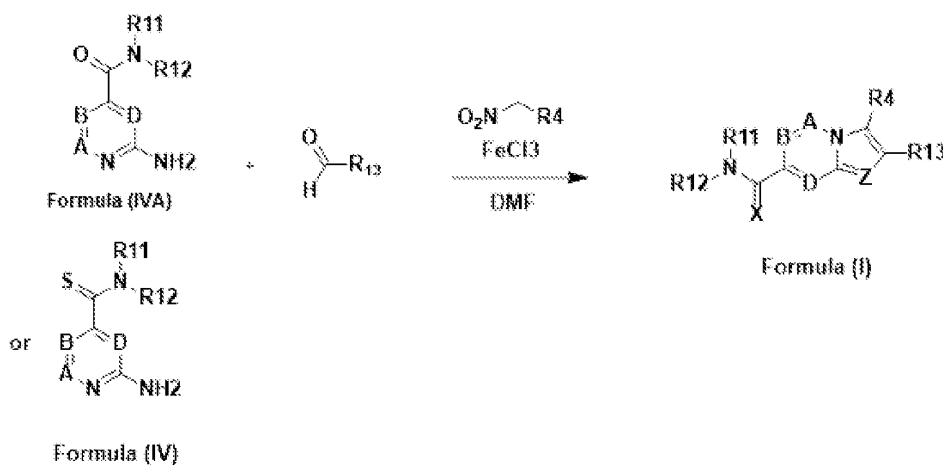
- 44) (R)-(3-aminopiperidin-1-yl)(2-(7-chloro-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 45) (R)-(3-aminopiperidin-1-yl)(2-(1-(4-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanethione,
- 5 46) (R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-methyl-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone,
- 47) (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-methoxy-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 48) (R)-(3-aminopiperidin-1-yl)(2-(1-((2,4-dimethylthiazol-5-yl)methyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 10 49) (R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-((2-methylthiazol-5-yl)methyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone,
- 50) (R)-(3-aminopiperidin-1-yl) (2-(1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone trifluoroacetic acid salt,
- 15 51) (R)-(3-aminopiperidin-1-yl)(2-(6-methoxy-1-(pyridin-3-ylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 52) (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-fluoro-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone trifluoroacetic acid salt,
- 53) (R)-(3-aminopiperidin-1-yl)(2-(5-fluoro-1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 20 54) (R)-(3-aminopiperidin-1-yl)(2-(6-fluoro-1-(4-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 55) (R)-(3-aminopiperidin-1-yl)(2-(5,6-difluoro-1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 25 56) (R,E)-4-(dimethylamino)-N-(1-(2-(1-(4-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)but-2-enamide,
- 57) (R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-(pyrazin-2-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone,
- 58) (R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-(pyrimidin-5-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone trifluoroacetic acid salt,
- 30 59) (R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-(pyridazin-3-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone,
- 60) (R)-(3-aminopiperidin-1-yl)(2-(1-isobutyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,

- 61) (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclobutylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 62) (R)-(3-aminopiperidin-1-yl)(2-(1-((3-fluoropyridin-2-yl)methyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 5 63) (R)-(3-aminopiperidin-1-yl)(2-(1-((5-methoxypyridin-2-yl)methyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 64) (R)-(3-aminopiperidin-1-yl)(2-(1-(2-methoxyethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 65) (R)-(3-aminopiperidin-1-yl)(2-(1-(2-hydroxyethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 10 66) (R)-(3-aminopiperidin-1-yl)(2-(6-methoxy-1-(pyridin-4-ylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 67) (R)-(3-aminopiperidin-1-yl)(2-(1-ethyl-6-methoxy-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 15 68) (R)-(3-aminopiperidin-1-yl)(2-(6-fluoro-1-(pyridin-4-ylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 69) (R)-(3-aminopiperidin-1-yl)(2-(6-fluoro-1-(pyridin-3-ylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 70) (R)-(3-aminopiperidin-1-yl)(2-(6-fluoro-1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 20 71) (R)-(3-aminopiperidin-1-yl)(2-(6-fluoro-1-(4-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 72) (R)-(3-aminopiperidin-1-yl)(2-(1-ethyl-6-fluoro-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 25 73) (R)-(3-aminopiperidin-1-yl)(2-(6-fluoro-1-isobutyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 74) (R)-(3-aminopiperidin-1-yl)(2-(5-fluoro-1-(pyridin-4-ylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 75) (R)-(3-aminopiperidin-1-yl)(2-(5-fluoro-1-(4-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 30 76) (R)-(3-aminopiperidin-1-yl)(2-(5-fluoro-1-(4-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 77) (R)-(3-aminopiperidin-1-yl)(2-(7-chloro-1-(4-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,

- 78) (R)-(3-aminopiperidin-1-yl)(2-(1-(2,2-difluoroethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone trifluoroacetic acid salt,
- 79) (R)-(3-aminopiperidin-1-yl)(2-(1-((5-fluoropyridin-2-yl)methyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 5 80) (R)-(3-aminopiperidin-1-yl)(2-(1-(4-fluorobenzyl)-6-methoxy-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 81) (R)-(3-aminopiperidin-1-yl)(2-(1-(4-(hydroxymethyl)benzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 82) (R)-(3-aminopiperidin-1-yl)(2-(1-isobutyl-6-methoxy-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 10 83) (R)-(3-aminopiperidin-1-yl)(2-(1-(2,2-difluoroethyl)-6-methoxy-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone,
- 84) (R)-(3-aminopiperidin-1-yl)(2-(5-fluoro-1-isobutyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone and
- 15 85) (R)-(3-aminopiperidin-1-yl)(2-(1-(4-fluoro-3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone, and
- 86) (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridin-7-yl)methanone.

[000114] In an embodiment, the disclosure relates to a process of preparation of compounds of Formula (I), Formula (II), and Formula (III) as claimed in any of claims 1-11 or its polymorphs, stereoisomers, prodrugs, solvates, co-crystals, intermediates, pharmaceutically acceptable salts, and metabolites thereof.

[000115] In an embodiment, the disclosure relates to a process of preparation of compounds of Formula (I), or its polymorphs, stereoisomers, prodrugs, solvates, co-crystals, intermediates, pharmaceutically acceptable salts, and metabolites thereof, the process comprising reacting $R_{13}CH(O)$ and $R_4CH_2NO_2$ with a compound selected from Formula (IVA) or Formula (IV)

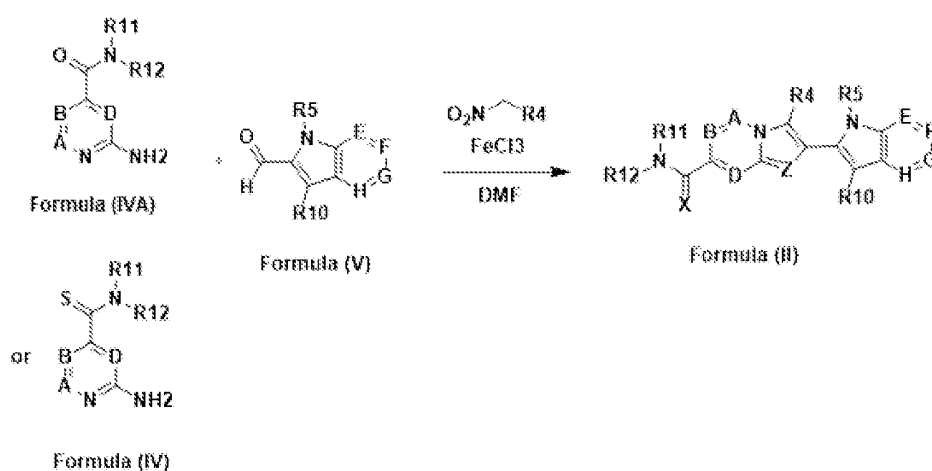


- wherein R₁₃ of R₁₃CH(O) is selected from hydrogen, 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from the group consisting of hydroxyl, cyano, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, and C₁₋₆ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, hydroxyl, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; A of Formula (IVA) and (IV) is selected from N or CR₁; B is selected from N or CR₂; D is selected from N or CR₃; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring optionally with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, -NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, or hydroxyl; R₄ of R₄CH₂NO₂ is selected from hydrogen, hydroxyl, cyano,

amino, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ heteroaryl, and C₁₋₆ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ alkylhydroxy, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl, wherein C₅₋₁₀ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; X of Formula (I) is selected from O or S; Z is N; A is selected from N or CR₁; B is selected from N or CR₂; D is selected from N or CR₃; R₁, R₂, R₃, and R₄ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ heteroaryl, and C₁₋₆ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, and hydroxyl; R₁₁ is hydrogen; R₁₂ is selected from C₁₋₆ alkylamino, and 5-10 membered monocyclic or bicyclic saturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O, or R₁₁ and R₁₂ can be taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, -NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, or hydroxyl; R₁₃ is selected from hydrogen, 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl with 1-5 heteroatoms selected from N, S or O, wherein 5-10 membered monocyclic or bicyclic aryl, and 5-10 membered monocyclic or bicyclic heteroaryl are optionally substituted with 1-5 substituents selected from hydroxyl, cyano, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy,

C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, and C₁₋₆ heteroaryl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ heteroaryl, C₁₋₆ heterocyclyl, oxo, halogen, hydroxyl, and cyano, wherein C₅₋₆ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[000116] In an embodiment, the disclosure relates to a process of preparation of compounds of Formula (II), or its polymorphs, stereoisomers, prodrugs, solvates, co-crystals, intermediates, pharmaceutically acceptable salts, and metabolites thereof, the process comprising reacting Formula (V) and R₄CH₂NO₂ with a compound selected from Formula (IVA) or Formula (IV)

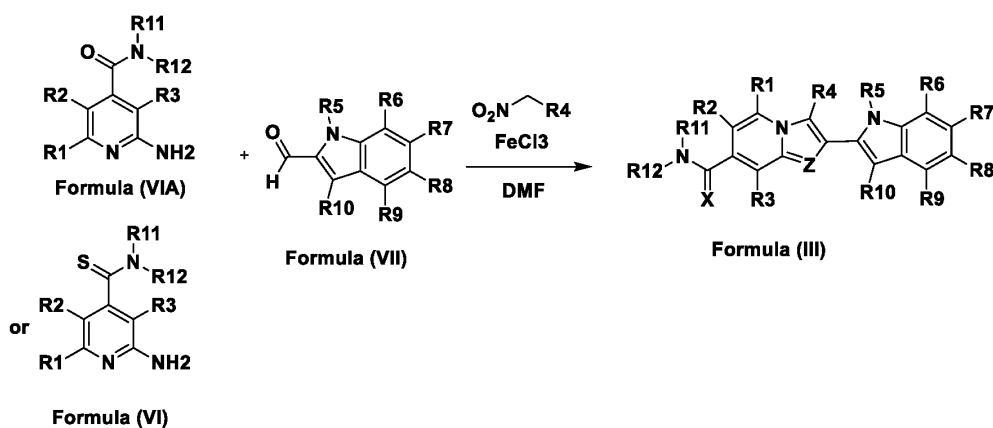


wherein A of Formula (IVA) and (IV) is selected from N or CR₁; B is selected from N or CR₂; D is selected from N or CR₃; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring optionally with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, -

NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, or hydroxyl; R₄ of
 R₄CH₂NO₂ is selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₆ alkyl, C₁₋₆
 alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆
 alkylamino, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆
 5 haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₆
 alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆
 aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ heteroaryl, and C₁₋₆
 haloalkoxy, is optionally substituted with one or more of the groups selected from
 hydrogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ alkylhydroxy, C₃₋₆
 10 cycloalkyl, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl,
 wherein C₅₋₁₀ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with
 one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen,
 hydroxyl, -CH₂OH, and cyano; E of Formula (V) is selected from N, C₅₋₆ aryl or CR₆; F
 is absent or is selected from N, and CR₇; G is absent or is selected from N, and CR₈; H
 15 is absent or is selected from N, and CR₉; R₁, R₂, R₃, R₅, R₆, R₇, R₈, R₉ and R₁₀ are
 independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₆ alkyl, C₁₋₆
 alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆
 alkylamino, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆
 haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₆
 20 alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆
 aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ heteroaryl, and C₁₋₆
 haloalkoxy, is optionally substituted with one or more of the groups selected from
 hydrogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ alkylhydroxy, C₃₋₆
 cycloalkyl, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl,
 25 wherein C₅₋₁₀ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with
 one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen,
 hydroxyl, -CH₂OH, and cyano; X of Formula (II) is selected from O or S; Z is N; A is
 selected from N or CR₁; B is selected from N or CR₂; D is selected from N or CR₃; E is
 selected from N or CR₆; F is absent or is selected from N, and CR₇; G is absent or is
 30 selected from N, and CR₈; H is absent or is selected from N, and CR₉; R₁, R₂, R₃, R₄,
 R₅, R₆, R₇, R₈, R₉ and R₁₀ are independently selected from hydrogen, hydroxyl, cyano,
 amino, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy,
 C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)C₁₋₆
 alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆

heteroaryl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ heteroaryl, and C₁₋₆ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ alkylhydroxy, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl, wherein C₅₋₁₀ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring optionally with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, -NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, or hydroxyl; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[000117] In an embodiment, the disclosure relates to a process of preparation of compounds of Formula (III), or its polymorphs, stereoisomers, prodrugs, solvates, co-crystals, intermediates, pharmaceutically acceptable salts, and metabolites thereof, the process comprising reacting Formula (VII) R₄CH₂NO₂ with a compound selected from Formula (VIA) or Formula (VI)



wherein R₁, R₂, and R₃ of Formula (VIA) and Formula (VI) are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅,
5 C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ heteroaryl, and C₁₋₆ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ alkylhydroxy, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl, wherein C₅₋₁₀ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; R₅, R₆, R₇, R₈, R₉ and R₁₀ of Formula (VII) and R₄ of R₄CH₂NO₂ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₆ alkyl,
15 C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino, C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ heteroaryl, and C₁₋₆ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ alkylhydroxy, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl, wherein C₅₋₁₀ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen,
20 hydroxyl, -CH₂OH, and cyano; X of Formula (III) is selected from O or S; Z is N; R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉ and R₁₀ are independently selected from hydrogen, hydroxyl, cyano, amino, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ acylamino, C₁₋₆ alkylamino, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl, C₁₋₆ heteroaryl, C(O)C₁₋₆ alkyl, C(O)C₁₋₆ haloalkyl, C(O)NR₁₅, C(O)C₁₋₆ alkylamino,
25 C(O)C₅₋₆ aryl, C(O)C₁₋₆ heteroaryl, SO₂C₁₋₆ alkyl, SO₂C₁₋₆ haloalkyl, SO₂C₃₋₆ cycloalkyl, SO₂NR₁₅, SO₂NC₁₋₆ alkylamino, SO₂C₅₋₆ aryl, or SO₂C₁₋₆ heteroaryl, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ heteroaryl, and C₁₋₆ haloalkoxy, is optionally substituted with one or more of the groups selected from hydrogen, oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ alkylhydroxy, C₃₋₆ cycloalkyl, C₅₋₁₀ aryl, C₁₋₆ heterocyclyl,
30

C₁₋₆ heteroaryl, cyano, halogen, and hydroxyl, wherein C₅₋₁₀ aryl, C₁₋₆ heteroaryl, and C₁₋₆ heterocyclyl, is optionally substituted with one or more of the groups selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, halogen, hydroxyl, -CH₂OH, and cyano; R₁₁ and R₁₂ are taken together to form a 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring optionally with 1-5 heteroatoms selected from N, S or O, wherein the 5-10 membered monocyclic or bicyclic saturated or unsaturated heterocyclic ring is optionally substituted with the substituents selected from amino, C₁₋₆ alkylamino, C₁₋₆ acylamino, -NHC(NH)CH₂Cl, -NH(CO)CH=CH-CH₂-N(CH₃)₂, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, or hydroxyl; and R₁₅ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and combinations thereof.

[000118] In another embodiment, the disclosure relates to pharmaceutical composition comprising a compound of Formula (I), Formula (II), and Formula (III) or a pharmaceutically acceptable salt thereof as claimed in any of claims 1-11 together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

[000119] In yet another embodiment, the disclosure relates to the pharmaceutical composition as described herein, wherein the composition is in the form selected from a tablet, capsule, powder, syrup, solution, aerosol and suspension.

[000120] In an embodiment of the present disclosure, there is provided compounds of Formula (I), Formula (II), and Formula (III) or a pharmaceutically acceptable salt thereof as described herein, wherein 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'-diacetylenediamine, 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, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, tosylates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates.

[000121] In an embodiment of the present disclosure, there is provided compounds of Formula (I), Formula (II), and Formula (III) or a pharmaceutically acceptable salt

thereof for use in the manufacture of a medicament for inhibiting one or more PADs in a cell.

[000122] In an embodiment, the present disclosure relates to a method for inhibiting one or more PAD family in a cell with an effective amount of the compounds of Formula (I), Formula (II), and Formula (III) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

[000123] In an embodiment, the present disclosure relates to a method for the treating a condition mediated by one or more PADs, the method comprising administering to a subject suffering from a condition mediated by one or more PAD family, a therapeutically effective amount of the compounds of Formula (I), Formula (II), and Formula (III) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

[000124] In an embodiment of the present disclosure, there is provided a compound of Formula (I), Formula (II) and Formula (III) used for the treatment of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, cutaneous lupus erythematosus, and psoriasis.

[000125] In an embodiment, the present disclosure relates to the use of the compound of Formula (I), Formula (II) and Formula (III) or a pharmaceutically acceptable salt or composition for the treatment of a condition mediated by one or more PAD family; or treatment and/or prevention of treatment of rheumatoid arthritis, vasculitis, systemic lupus erythematosus, ulcerative colitis, cancer, cystic fibrosis, asthma, cutaneous lupus erythematosus, and psoriasis together with other clinically relevant agents or biological agents.

[000126] In an embodiment, the present disclosure relates to the use of the compound of Formula (I), Formula (II) and Formula (III) or a pharmaceutically acceptable salt or composition for treatment of a condition mediated by one or more PAD family; or treatment and/or prevention of 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, lung injury, lupus, lupus nephritis,

multiple sclerosis, muscular dystrophy, non-allergen induced asthma, osterarthritis, periodontitis, peritoneal endometriosis, psoriasis, pulmonary disease, pulmonary fibrosis, pyogenic sterile arthritis, renal disease, rheumatic disease, rheumatoid arthritis, sepsis, severe pain and ulcerative colitis, together with other clinically relevant agents or biological agents.

[000127] In an embodiment, the disclosure relates to a method for the treatment and/or prevention of a condition mediated by one or more PAD family disorder, comprising administering to a subject suffering from the condition mediated by one or more PAD family a therapeutically effective amount of the compound of Formula (I), Formula (II), and Formula (III) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

[000128] In an embodiment, the invention relates to a method for the treatment of rheumatoid arthritis, said method comprising administering a combination of the compounds of Formula (I), Formula (II), and Formula (III) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions, with other clinically relevant agents or biological agents to a subject in need thereof.

[000129] In an embodiment, the disclosure relates to a method for the treatment of cancer, said method comprising administering a combination of compounds of Formula (I), Formula (II), and Formula (III) or a pharmaceutically acceptable salts thereof together with a pharmaceutically acceptable carrier, with other clinically relevant immune modulators agents to a subject in need of thereof.

EXAMPLES

[000130] As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society. 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:

AcOH	Acetic acid
BOC ₂ O	Di-tert-butyl dicarbonate
nBuLi	n-Butyllithium

	BuOH	Butanol
	Bz	Benzyl
	Cbz	Carboxybenzyl
	cHex	Cyclohexane
5	CS ₂ CO ₃	Caesium carbonate
	DCM / CH ₂ Cl ₂	Dichloromethane
	DIAD	Diisopropyl azodicarboxylate
	Dioxane	1,4-dioxane
	DIPEA	N, N-diisopropylethylamine
10	DMSO	Dimethylsulfoxide
	DMF	N,N-dimethylformamide
	Et ₃ N	Tri ethyl amine
	Ether	Diethyl ether
	EtOAc	Ethyl acetate
15	HATU	o-(7-Azabenzotriazol- 1 -yl)-N,N,N' ,N' -tetramethyluronium hexafluorophosphate
	HPLC	High performance liquid chromatography
	IPA	Isopropyl alcohol
	K ₂ CO ₃	Potassium carbonate
20	KOH	Potassium hydroxide
	LiOH	Lithium hydroxide
	LCMS or LC/MS	Liquid chromatography- mass spectroscopy
	MeOH	Methanol
	min	Minutes
25	Na ₂ SO ₄	Sodium sulfate
	NaHCO ₃	Sodium bicarbonate
	NH ₄ Cl	Ammonium chloride
	Palladium tetrakis	palladium tetrakis(triphenylphosphine)
	Pd/C	Palladium on carbon
30	PTSA	p-Toluenesulfonic acid
	rb	round-bottomed (flask)
	r.t / rt.	Room temperature
	Rt	Retention time
	TFA	Trifluoroacetic acid

TFAA	Trifluoroacetic anhydride
THF / thf	Tetrahydrofuran
TLC / tic	Thin layer chromatography
TMEDA	Tetramethyl ethyl enediamine
5 HOBt	Hydroxybenzotriazole
EDC.HCl	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide Hydrochloride

[000131] 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 invention is not limited by the details set forth in these examples.

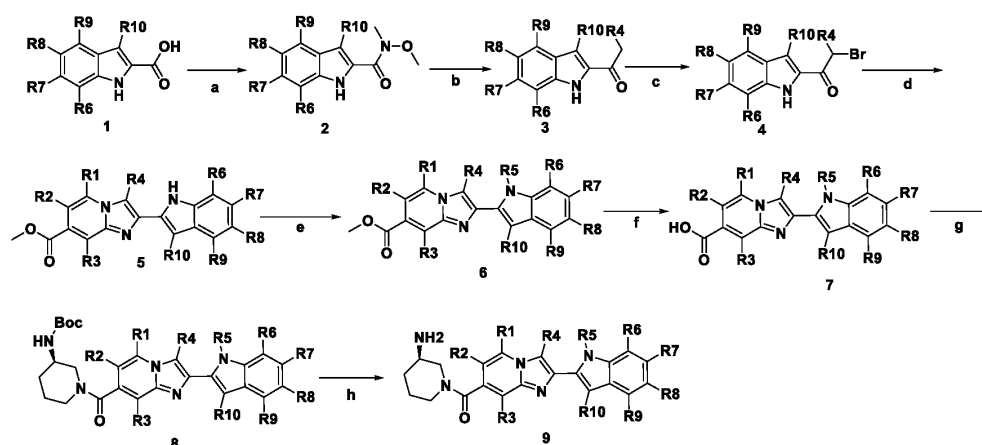
[000132] The compounds of the invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out in the following schemes, and can be readily adapted to prepare other compounds of the invention.

[000133] There is also provided a process as shown in the following Scheme-1, for the preparation of compounds of the Formula (I, II, and III), wherein all the groups are as defined earlier.

Example 1

General Procedure for synthesis of compounds of Formula I, Formula II, and Formula III

Scheme-1:



The said process for the preparation of the compounds of Formula (I, II, and III) comprises of the following steps:

Step 1: Compound **1** was converted to compound **2** under standard conditions using N,O-dimethylhydroxylamine hydrochloride, triethylamine, HOBt and EDC.HCl (Reaction condition **a**).

Step 2: Treatment of compound **2** with ethyl magnesium bromide (Reaction condition **b**) gave intermediate **3**.

Step 3: Intermediate **3** was converted to compound **4** using phenyl trimethyl ammonium tribromide (Reaction condition **c**).

Step 4: Treatment of compound **4** with methyl 2-aminoisonicotinate or ethyl 2-chloro-6-methylisonicotinate and NaHCO₃ (Reaction condition **d**) gave intermediate **5**.

Step 5: Intermediate **5** was converted to compound **6** by reacting with substituted bromides (bromomethyl cyclopropane) and Cs₂CO₃ (Reaction condition **e**).

Step 6: Compound **6** was hydrolysed to give compound **7** under reaction condition **f**.

Step 7: Coupling of compound **7** with substituted carbamates, like tert-butyl (R)-piperidin-3-yl carbamate, (Reaction condition **g**) gave compound **8**.

Step 8: Compound **8** was converted to final compound **9** by Boc deprotection (Reaction condition **h**).

General considerations and Analytical Methods:

[000134] The compounds used in the reaction processes, if not mentioned otherwise, were commercially available and purchased from Combi-Blocks, India.

[000135] NMR data were obtained on Varian 400 MHz spectrometer. All compounds were characterized by ¹H NMR, as well as, mass spectrometry (MS-ESI, Electrospray ionization Mass spectrometry). All ¹H chemical shifts were reported in parts per million (ppm) and were measured relative to TMS or residual deuterated DMSO as solvent. MS (ESI) measurements were performed on Waters Mass spectrometer. The yields of the compounds provided refer to isolated compounds.

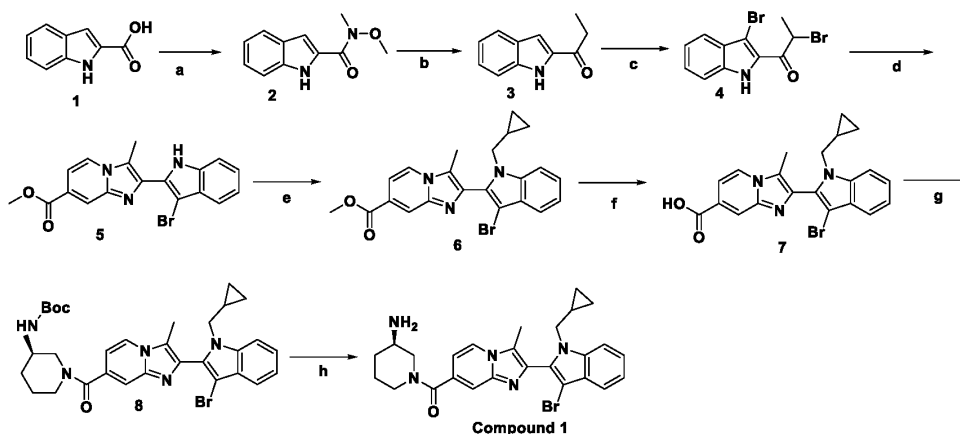
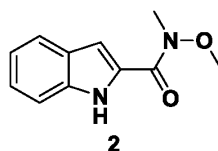
[000135] The examples given below are provided by the way of illustration only and therefore should not be construed to limit the scope of the invention.

[000136] Further, a class of compounds of Formula I, Formula II, and Formula III were prepared using the general procedure as described above.

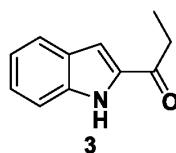
30 Compound-1:

Synthesis of (R)-(3-Aminopiperidin-1-yl)(2-(3-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone (Compound -1)

Scheme-2:

**Step 1: Preparation of N-Methoxy-N-methyl-1H-indole-2-carboxamide (2)**

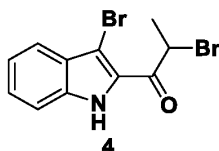
[000137] To a stirred solution of 1H-indole-2-carboxylic acid (**1**, 25 g, 155.5 mmol) and N,O-dimethylhydroxylamine hydrochloride (30.26 g, 310.2 mmol) in DCM (500 mL), was added triethylamine (107 mL, 775.6 mmol) and HOBt (36.7 g, 232.9 mmol), followed by EDC.HCl (44.4 g, 232.6 mmol) at 0°C (Reaction condition a). The reaction mixture was stirred at rt for 4 h. To the reaction mixture, water and DCM were added. DCM layer was separated and washed with brine, dried over sodium sulphate and concentrated under reduced pressure. To the resulting crude, was added diethyl ether (200 mL), stirred for 30 min and filtered to give white solid. This solid was dissolved in EtOAc, passed through celite bed and evaporated to give title compound as off white solid (**2**) (27 g, 87% Yield). MS (ESI): Mass calcd. for C₁₁H₁₂N₂O₂, 204.23; m/z found, 205.1 [M+H]⁺.

Step 2: Preparation of 1-(1H-Indol-2-yl)propan-1-one (3)

[000138] To a stirred solution of N-methoxy-N-methyl-1H-indole-2-carboxamide (**2**, 10 g, 49.01 mmol) in THF (200 mL), was added 3M solution of ethyl magnesium bromide (49 mL, 147 mmol) drop wise at 0°C (Reaction condition b). The reaction mixture was stirred at rt for 16 h. The reaction mixture was quenched with saturated

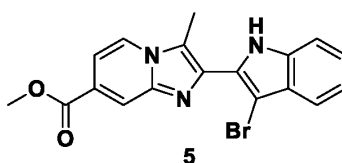
NH₄Cl (100 mL) solution at 0 °C and extracted with EtOAc (500 mL). Organic layer was separated, washed with brine, dried over sodium sulphate and concentrated under reduced pressure. The crude was purified by flash column chromatography to give the title compound as off white solid (**3**) (53%, 4.5 g, 53% Yield). MS (ESI): Mass calcd. for C₁₁H₁₁NO, 173.22; m/z found, 174.1 [M+H]⁺.

Step 3: Preparation of 2-Bromo-1-(3-bromo-1H-indol-2-yl)propan-1-one (4)



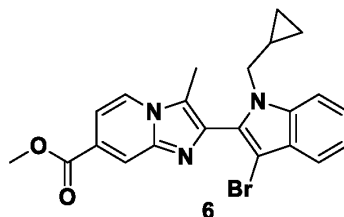
[000139] To the stirred solution of 1-(1H-indol-2-yl)propan-1-one (**3**, 2.5 g, 14.45 mmol) in THF (50 mL), was added phenyl trimethyl ammonium tribromide (16.3 g, 43.35 mmol) and stirred at reflux for 16 h (Reaction condition **c**). The reaction mixture was cooled to rt, added water (25 mL) and extracted with EtOAc (100 mL). Organic layer was washed with saturated NaHCO₃ (20 mL) solution, brine (20 mL) and evaporated. Crude product was purified by column chromatography to give the title compound as brown solid (**4**) (4 g, 86% Yield). MS (ESI): Mass calcd. for C₁₁H₉Br₂NO, 331.01; m/z found, 333.9 [M+2H]⁺.

Step 4: Preparation of Methyl 2-(3-bromo-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate (5)



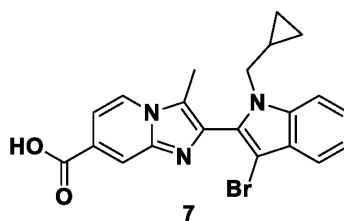
[000140] To the stirred solution of 2-bromo-1-(3-bromo-1H-indol-2-yl)propan-1-one (**4**, 2 g, 5.24 mmol) and methyl 2-aminoisonicotinate (0.92 g, 5.24 mmol) in EtOH (20 mL), was added NaHCO₃ (1.52 g, 26.2 mmol) and stirred at 90 °C for 16 h in seal tube (Reaction condition **d**). The reaction mixture was cooled to rt, added water (50 mL) and extracted with EtOAc (2 X 50 mL). Combined organic extracts were washed with brine, dried over sodium sulfate and evaporated to give the crude product. The crude product was purified by flash column chromatography using 25-30% EtOAc in hexane to afford title product as brown solid (**5**) (0.45 g, 20.5% Yield). MS (ESI): Mass calcd. for C₁₈H₁₄BrN₃O₂, 384.23; m/z found, 385.0 [M+H]⁺.

Step 5: Preparation of Methyl 2-(3-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate (6)



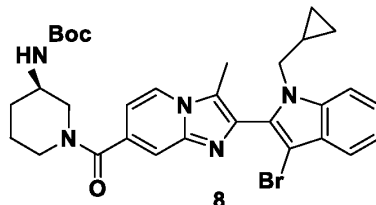
[000141] To the stirred solution of methyl 2-(3-bromo-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate (**5**, 0.4 g, 1.01 mmol) in DMF (8 mL), was added Cs₂CO₃ (0.98 g, 3.01 mmol) followed by (bromomethyl) cyclopropane (0.24 mL, 1.51 mmol) and stirred at 80 °C for 16 h (Reaction condition e). The reaction mixture was cooled to rt, added water (20 mL) and extracted with EtOAc (50 mL). Combined organic extracts were washed with brine, dried over sodium sulfate and evaporated to give the crude product. The crude product was purified by flash column chromatography using 25-30% EtOAc in hexane to afford title product as brown gum (**6**) (0.42 g, 90% Yield). MS (ESI): Mass calcd. for C₂₂H₂₀BrN₃O₂, 438.33; m/z found, 440.1 [M+2H]⁺.

Step 6: Preparation of 2-(3-Bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylic acid (7)



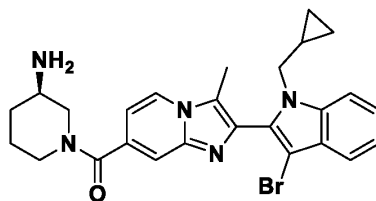
[000142] To the stirred solution of methyl 2-(3-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate (**6**, 0.42 g, 0.98 mmol) in MeOH (10 mL), was added 5N NaOH solution (0.2 mL, 4.51 mmol) and stirred at reflux for 1 h (Reaction condition f). The reaction mixture was cooled to rt, evaporated to dryness. Resulting crude was dissolved in water (10 mL), acidified using saturated citric acid solution and the compound was extracted with EtOAc (2 X 30 mL). Organic layer was separated, washed with brine (10 mL) solution, dried over anhydrous Na₂SO₄ and evaporated under vacuum to give the product as brown solid (**7**) (0.34 g, 83% Yield). MS (ESI): Mass calcd. for C₂₁H₁₈BrN₃O₂, 424.30; m/z found, 426.1 (M+2H)⁺.

Step 7: Preparation of Tert-butyl (R)-(1-(2-(3-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (8)



- 5 **[000143]** To a solution of tert-butyl (R)-piperidin-3-yl-12-azanecarboxylate (0.018 g, 0.09 mmol) and 2-(3-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylic acid (**7**, 0.04 g, 0.09 mmol) in DCM (10 mL) at rt was added triethylamine (0.037 mL, 0.27 mmol) and propylphosphonic anhydride (T3P, 50 % in ethylacetate solvent) (0.05 mL, 0.18 mmol). The reaction mixture was stirred at rt for 12 h (Reaction condition **g**). It was diluted with DCM and washed with saturated sodium bicarbonate solution. Organic layer was separated, dried over sodium sulphate and evaporated under reduced pressure to obtain crude. The crude product was purified by flash column chromatography using 5% methanol in DCM to afford desired product (**8**) (0.035 g, 82.5% Yield). MS (ESI): Mass calcd. for $C_{31}H_{36}BrN_5O_3$, 605.0; m/z found 606.3 $[M+H]^+$.

Step 8: Preparation of (R)-(3-Aminopiperidin-1-yl)(2-(3-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone (Compound-1)



20 **Compound-1**

- [000144]** To a stirred solution tert-butyl (R)-(1-(2-(3-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (**8**, 0.035 g, 0.005 mmol) in DCM (10 mL) was added trifluoroacetic acid (0.5 mL) at 0 °C, then it was stirred at rt for 2 h (Reaction condition **h**). After completion of reaction, solvent was evaporated. The crude was dissolved in water (10 mL) and neutralized with saturated $NaHCO_3$ solution to give the crude product. The crude was purified by flash column chromatography using 3-5% methanol

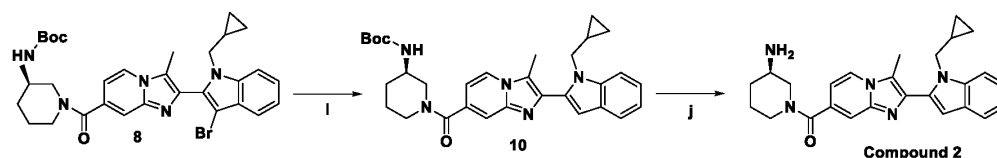
in DCM to afford desired product (**Compound-1**) (0.012 g, 60 % Yield). ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.45 (d, *J* = 7.2 Hz, 1H), 7.67-7.61 (m, 2H), 7.49 (d, *J* = 8 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 6.8 Hz, 1H), 4.49 (bs, 1H), 4.17 (d, *J* = 7.2 Hz, 2H), 2.99 (bs, 1H), 1.97 (m, 2H), 1.69 (m, 2H), 1.50 (m, 2H), 1.31 (m, 1H), 1.26 (s, 3H), 1.00 (m, 1H), 0.87-0.84 (m, 2H), 0.26-0.25 (m, 2H), 0.04 (m, 2H). MS (ESI): Mass calcd. for C₂₆H₂₈BrN₅O, 506.1; *m/z* found 508.3 [M+2H]⁺.

Compound-2:

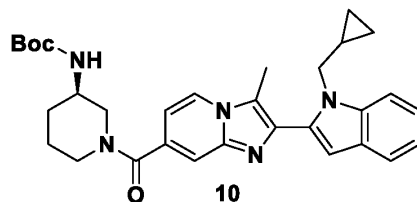
Synthesis of (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone (Compound -2)

[000145] Intermediate **8** was synthesized using the procedure outlined in above scheme-2.

Scheme-3:

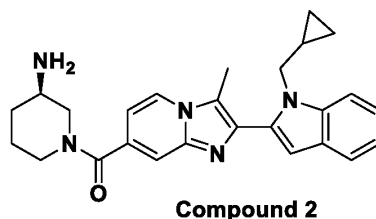


Step 1: Preparation of Tert-butyl (R)-(1-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (10)



[000146] To the stirred solution of tert-butyl (R)-(1-(2-(3-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (**8**, 0.07 g, 0.33 mmol) in MeOH (6 mL), was added zinc powder (0.1 g, 3.33 mmol) followed by ammonium hydroxide (2 mL) and stirred at 90 °C for 16 h (Reaction condition **i**). The reaction mixture was cooled to rt, filtered through celite and the filtrate was evaporated. To the crude product water (10 mL) was added and extracted with DCM (30 mL). Organic layer was separated, dried over sodium sulfate and evaporated to give the crude product. The crude product was purified by flash column chromatography using 2-6% MeOH in DCM to afford the product as off white solid (**10**) (0.03 g, 35% Yield). MS (ESI): Mass calcd. for C₃₁H₃₇N₅O₃, 527.29; *m/z* found, 528.3 (M+H)⁺.

Step 2: Preparation of (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone (Compound 2)



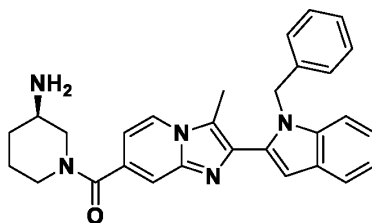
[000147] To a stirred solution tert-butyl (R)-(1-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (**10**, 0.03 g, 0.05 mmol) in 1,4-dioxane (1 mL), was added 4M HCl in dioxane (0.5 mL) and the reaction mixture was stirred at rt for 2 h (Reaction condition **j**). The reaction mixture was evaporated, dissolved in water (5 mL) and basified using saturated NaHCO₃ solution. Compound was extracted with EtOAc (2 X 15 mL). Combined organic layer was dried over anhydrous Na₂SO₄. The crude product was purified by flash column chromatography using 2-8% MeOH in DCM to afford the product as brown solid (**Compound-2**) (0.005 g, 20% Yield).

[000148] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.42 (d, *J* = 6.8 Hz, 1H), 7.57 (t, *J* = 6.8 Hz, 2H), 7.16-7.14 (m, 2H), 7.06-6.99 (m, 2H), 6.64 (s, 1H), 4.46 (d, *J* = 6.8 Hz, 2H), 2.91 (s, 3H), 2.65-2.59 (m, 2H), 2.00-1.95 (m, 3H), 1.69-1.55 (m, 2H), 1.43-1.35 (m, 2H), 1.10 (m, 1H), 0.83-0.81 (m, 2H), 0.27-0.25 (m, 2H), 0.15-0.13 (m, 2H). MS (ESI): Mass calcd. for C₂₆H₂₉N₅O, 427.55; *m/z* found, 428.3 [M+H]⁺.

[000149] Following compounds (Compounds 3, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 35, 36, 37, 38, 41, 42, 45, 46, 48 and 49) were synthesized using the above procedure as exemplified for **Compound-2** above.

Compound-3:

(R)-(3-Aminopiperidin-1-yl)(2-(1-benzyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone

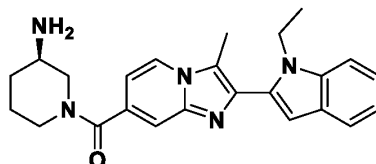


[000150] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.40 (d, *J* = 6.8 Hz, 1H), 7.61-7.59 (m, 2H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.16-7.02 (m, 5H), 6.95-6.93 (m, 3H), 6.75 (s,

1H), 5.89 (s, 2H), 2.97-2.88 (m, 2H), 2.69-2.59 (m, 3H), 2.58-2.50 (m, 3H), 1.82-1.75 (m, 1H), 1.66-1.59 (m, 1H), 1.33-1.25 (m, 1H), 1.21-1.15 (m, 3H). MS (ESI): Mass calcd. for C₂₉H₂₉N₅O, 463.59; m/z found, 464.2 (M+H)⁺.

Compound-4:

- 5 **(R)-(3-Aminopiperidin-1-yl)(2-(1-ethyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone**



- [000151] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.42 (d, *J* = 6.8 Hz, 1H), 7.63 (s, 1H), 7.58 (d, *J* = 8 Hz, 1H), 7.51 (d, *J* = 8 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 8 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.63 (s, 1H), 4.54 (t, *J* = 7.2 Hz, 2H), 3.01 (bs, 1H), 2.84 (bs, 2H), 2.65 (s, 3H), 1.99-1.97 (m, 2H), 1.88 (bs, 1H), 1.69 (bs, 1H), 1.45 (bs, 2H), 1.33-1.31 (m, 2H), 1.32 (t, *J* = 6.8 Hz, 3H). MS (ESI): Mass calcd. for C₂₄H₂₇N₅O, 401.22; m/z found, 402.2 [M+H]⁺.

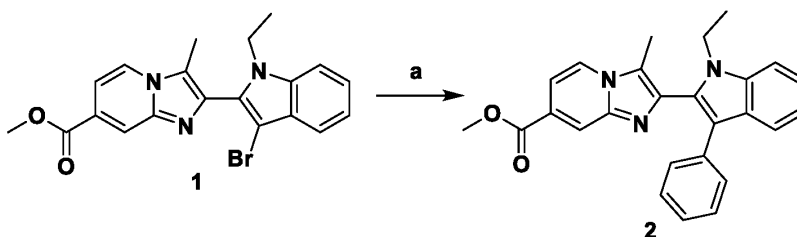
- 15 **Compound-5:**

Synthesis of (R)-(3-Aminopiperidin-1-yl)(2-(1-ethyl-3-phenyl-1H-indol-2-yl)-3-methylimidazo [1,2-a]pyridin-7-yl)methanone (Compound-5)

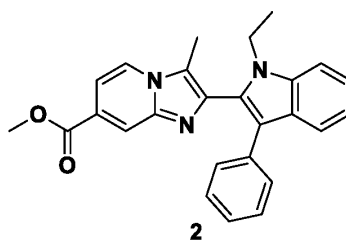
[000152] Intermediate 1 is synthesized using the procedure outlined for Intermediate 6 in Scheme-2 above.

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Scheme-4



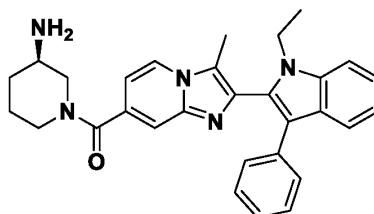
Step 6: Preparation of Methyl 2-(1-ethyl-3-phenyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate (2)



[000153] To the stirred solution of methyl 2-(3-bromo-1-ethyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate (**1**, 0.27 g, 0.65 mmol) in dioxane: water (8:2, 10 mL), was added phenylboronic acid (0.12 g, 0.98 mmol), K₂CO₃ (0.27 g, 1.96 mmol), Pd(PPh₃)₄ (0.04 g, 0.03 mmol) and stirred at 85°C for 16 h. The reaction mixture was cooled to rt, filtered through celite and dioxane was evaporated. To the resulting crude product was added water (10 mL), acidified using saturated citric acid solution and the compound was extracted with EtOAc (50 mL). Organic layer was washed with brine (10 mL) solution, dried over anhydrous Na₂SO₄ and evaporated under vacuum. The crude residue was purified by gradient column chromatography using 15-30% EtOAc in hexane to afford title product as brown gummy (**2**) (0.22 g, 78% Yield). MS (ESI): Mass calcd. for C₂₆H₂₃N₃O₂, 409.49; m/z found, 410.2 (M+H)⁺.

[000154] Further steps for **Compounds-5 and 6** were carried using the procedure as exemplified for **Compound-1**.

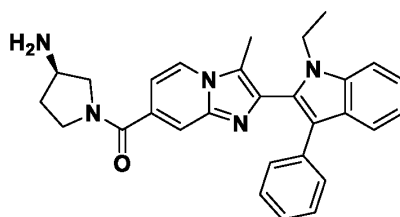
15 **Compound-5:**



[000155] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.26 (d, *J* = 7.2 Hz, 1H), 7.71-7.66 (m, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.30-7.24 (m, 3H), 7.20-7.16 (m, 2H), 7.13-7.11 (m, 2H), 6.95-6.93-7.01 (m, 1H), 4.30-4.28 (m, 2H), 3.65-3.62 (m, 2H), 3.02-2.98 (m, 2H), 3.27-3.23 (m, 1H), 1.85 (s, 3H), 1.69-1.65 (m, 1H), 1.47-1.44 (m, 1H), 1.26-1.24 (m, 5H), 1.18-1.15 (m, 2H). MS (ESI): Mass calcd. for C₃₀H₃₁N₅O, 477.61; m/z found, 478.3 (M+H)⁺.

Compound-6:

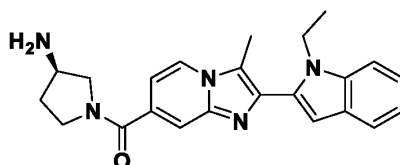
(R)-(3-Aminopyrrolidin-1-yl)-(2-(1-ethyl-3-phenyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-yl)methanone



[000156] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.25 (d, J = 7.2 Hz, 1H), 7.81-7.78 (m, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.30-7.24 (m, 3H), 7.19-7.13 (m, 4H), 7.06-7.01 (m, 1H), 4.31-4.28 (m, 2H), 3.65-3.62 (m, 2H), 3.51-3.47 (m, 2H), 3.27-3.23 (m, 1H), 1.96-1.94 (m, 2H), 1.86 (s, 3H), 1.65-1.62 (m, 1H), 1.26-1.24 (m, 3H), 1.18-1.15 (m, 1H). MS (ESI): Mass calcd. for $\text{C}_{29}\text{H}_{29}\text{N}_5\text{O}$, 463.59; m/z found, 464.2 ($\text{M}+\text{H}$) $^+$.

Compound-7:

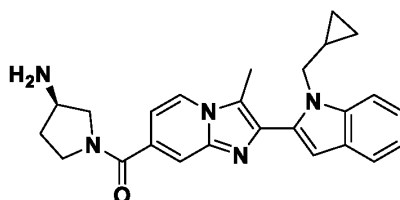
(R)-(3-Aminopyrrolidin-1-yl)(2-(1-ethyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000157] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.41 (d, J = 6.8 Hz, 1H), 7.76-7.74 (m, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.11-7.03 (m, 2H), 6.64 (s, 1H), 4.58-4.53 (m, 2H), 3.67-3.63 (m, 2H), 3.55-3.49 (m, 2H), 3.27 (br s, 2H), 3.10-2.99 (m, 2H), 2.88-2.81 (m, 2H), 2.63 (s, 3H), 1.99-1.95 (m, 1H), 1.22 (t, J = 6.8 Hz, 1H). MS (ESI): Mass calcd. for $\text{C}_{23}\text{H}_{25}\text{N}_5\text{O}$, 387.49; m/z found, 388.2 ($\text{M}+\text{H}$) $^+$.

Compound-8:

(R)-(3-Aminopyrrolidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone

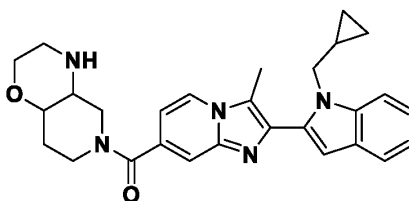


[000158] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.41 (d, J = 7.2 Hz, 1H), 7.77-6.73 (m, 1H), 7.57 (t, J = 7.6 Hz, 2H), 7.18-7.14 (m, 1H), 7.11-7.09 (m, 1H), 7.06-7.03

(m, 1H), 6.65 (s, 1H), 4.49 (d, $J = 6.8$ Hz, 2H), 3.67-3.60 (m, 2H), 3.57-3.50 (m, 2H), 3.23-3.19 (m, 1H), 2.63 (s, 3H), 1.96-1.89 (m, 1H), 1.65-1.60 (m, 1H), 1.23-1.15 (m, 2H), 1.09 (m, 1H), 0.26-0.25 (m, 2H), 0.15-0.13 (m, 2H). MS (ESI): Mass calcd. for $C_{25}H_{27}N_5O$, 413.53; m/z found, 414.2 ($M+H$)⁺.

5 **Compound-9:**

(2-(1-(Cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)
(hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6(5H)-yl)methanone



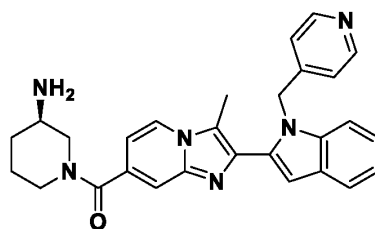
10

[000159] ¹HNMR (400 MHz, DMSO- d_6) δ (ppm): 8.41 (d, $J = 7.2$ Hz, 1H), 7.62 (s, 1H), 7.57 (t, $J = 6.8$ Hz, 2H), 7.18-7.14 (m, 1H), 7.06-6.99 (m, 2H), 6.64 (s, 1H), 4.48 (d, $J = 7.2$ Hz, 2H), 3.76-3.72 (m, 2H), 3.44-3.40 (m, 2H), 2.85-2.78 (m, 2H), 2.65 (s, 3H), 2.01-1.97 (m, 2H), 1.85-1.81 (m, 1H), 1.67-1.61 (m, 1H), 1.21-1.19 (m, 3H), 1.10-1.05 (m, 1H), 0.27-0.25 (m, 2H), 0.15-0.13 (m, 2H). MS (ESI): Mass calcd. for $C_{28}H_{31}N_5O_2$, 469.59; m/z found, 470.3 ($M+H$)⁺.

15

Compound-10:

(R)-(3-Aminopiperidin-1-yl)(3-methyl-2-(1-(pyridin-4-ylmethyl)-1H-indol-2-yl)
imidazo[1,2-a]pyridin-7-yl)methanone



20

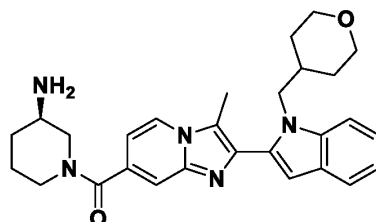
[000160] ¹HNMR (400 MHz, DMSO- d_6) δ (ppm): 8.40 (d, $J = 6.8$ Hz, 1H), 7.35-7.33 (m, 2H), 7.63 (d, $J = 7.6$ Hz, 1H), 7.57 (s, 1H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.13-7.07 (m, 2H), 6.98-6.96 (m, 1H), 6.90-6.88 (m, 2H), 6.78 (s, 1H), 5.95 (s, 2H), 4.19-4.11 (m, 1H), 3.65-3.61 (m, 2H), 2.99-2.95 (m, 1H), 2.80-2.79 (m, 2H), 2.64 (s, 3H), 1.86-1.83

25

(m, 1H), 1.66-1.63 (m, 1H), 1.45-1.42 (m, 1H), 1.31-1.29 (m, 1H), 1.21-1.18 (m, 1H). MS (ESI): Mass calcd. for C₂₈H₂₈N₆O, 464.57; m/z found, 465.3 (M+H)⁺.

Compound-11:

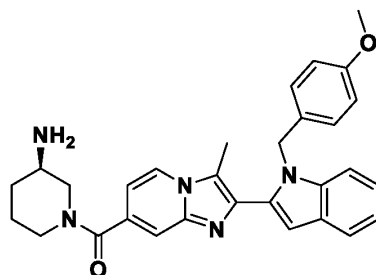
- (R)-(3-Aminopiperidin-1-yl)(3-methyl-2-(1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone



- [000161] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.41 (d, *J* = 6.8 Hz, 1H), 7.62 (s, 1H), 7.56 (t, *J* = 7.2 Hz, 2H), 7.18-7.14 (m, 1H), 7.06-7.00 (m, 1H), 6.98-6.95 (m, 1H), 6.65 (s, 1H), 4.52 (d, *J* = 7.2 Hz, 1H), 4.19-4.11 (m, 1H), 3.65-3.62 (m, 2H), 3.48-3.41 (m, 1H), 3.07-3.01 (m, 2H), 2.78-2.75 (m, 2H), 2.67-2.63 (m, 2H), 2.61 (s, 3H), 1.99-1.95 (m, 2H), 1.70-1.67 (m, 1H), 1.165-1.61 (m, 1H), 1.28-1.21 (m, 1H), 1.18-1.11 (m, 4H), 1.03-1.00 (m, 2H). MS (ESI): Mass calcd. for C₂₈H₃₃N₅O₂, 471.61; m/z found, 472.3 (M+H)⁺.

- 15 **Compound-12:**

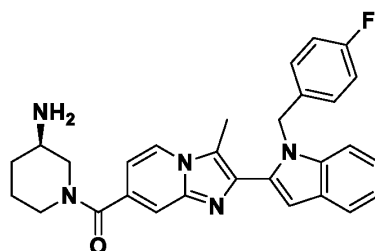
(R)-(3-Aminopiperidin-1-yl)(2-(1-(4-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



- [000162] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.40 (s, 1H), 7.60-7.57 (m, 2H), 7.41-7.39 (m, 2H), 7.11-7.07 (m, 1H), 7.05-7.01 (m, 1H), 6.99-6.97 (m, 1H), 6.92-6.90 (m, 2H), 6.72-6.70 (m, 2H), 5.80 (s, 2H), 3.63 (s, 3H), 2.83-2.81 (m, 2H), 2.68-2.65 (m, 2H), 2.64 (s, 3H), 2.06-2.01 (m, 2H), 1.88-1.85 (m, 1H), 1.68-1.65 (m, 1H), 1.44-1.41 (m, 1H), 1.21-1.18 (m, 2H). MS (ESI): Mass calcd. for C₃₀H₃₁N₅O₂, 493.61; m/z found, 494.3 (M+H)⁺.

- 25 **Compound-13:**

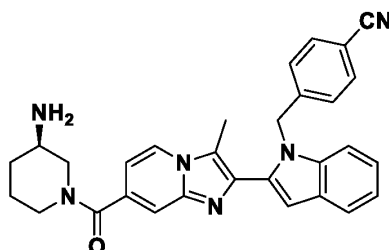
(R)-(3-Aminopiperidin-1-yl)(2-(1-(4-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000163] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.40 (d, *J* = 7.2 Hz, 1H), 7.61-7.59 (m, 2H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.12-7.08 (m, 1H), 7.02-6.98 (m, 6H), 6.75 (s, 1H), 5.86 (s, 2H), 4.05-4.01 (m, 1H), 3.57-3.51 (m, 1H), 2.97-2.94 (m, 1H), 2.78-2.71 (m, 1H), 2.62 (s, 3H), 2.02-1.98 (m, 2H), 1.84-1.81 (m, 1H), 1.67-1.61 (m, 1H), 1.44-1.41 (m, 1H), 1.25-1.21 (m, 2H). MS (ESI): Mass calcd. for C₂₉H₂₈FN₅O, 481.58; *m/z* found, 482.2 (M+H)⁺.

10 Compound-14:

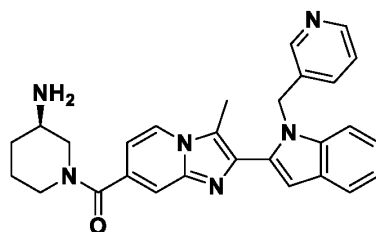
(R)-4-((2-(7-(3-Aminopiperidine-1-carbonyl)-3-methylimidazo[1,2-a]pyridin-2-yl)-1H-indol-1-yl)methyl)benzonitrile



[000164] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.41 (d, *J* = 7.2 Hz, 1H), 7.66-7.59 (m, 4H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.14-7.12 (m, 2H), 7.08-7.05 (m, 2H), 6.97 (d, *J* = 7.2 Hz, 1H), 6.81 (s, 1H), 5.99 (s, 2H), 2.93-2.89 (m, 2H), 2.64 (s, 3H), 1.99-1.97 (m, 1H), 1.88-1.85 (m, 1H), 1.68-1.65 (m, 1H), 1.45-1.41 (m, 3H), 1.33-1.29 (m, 1H), 1.22-1.19 (m, 2H). MS (ESI): Mass calcd. for C₃₀H₂₈N₆O, 488.60; *m/z* found, 489.2 (M+H)⁺.

Compound-15:

20 (R)-(3-Aminopiperidin-1-yl)(3-methyl-2-(1-(pyridin-3-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone

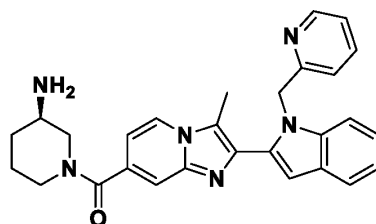


[000165] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.41 (d, J = 6.8 Hz, 1H), 8.32 (d, J = 4.0 Hz, 1H), 8.26 (s, 1H), 7.62-7.59 (m, 2H), 7.46-7.44 (m, 1H), 7.37-7.35 (m, 1H), 7.20-7.18 (m, 1H), 7.13-7.07 (m, 2H), 6.99-6.97 (m, 1H), 6.78 (s, 1H), 5.93 (s, 2H), 4.19-4.11 (m, 1H), 3.65-3.61 (m, 2H), 2.98-2.95 (m, 1H), 2.70-2.67 (m, 2H), 2.63 (s, 3H), 1.85-1.83 (m, 1H), 1.66-1.63 (m, 1H), 1.45-1.42 (m, 1H), 1.27-1.21 (m, 2H). MS (ESI): Mass calcd. for $\text{C}_{28}\text{H}_{28}\text{N}_6\text{O}$, 464.23; m/z found, 465.2 ($\text{M}+\text{H}$) $^+$.

Compound-16:

(R)-(3-Aminopiperidin-1-yl)(3-methyl-2-(1-(pyridin-2-ylmethyl)-1H-indol-2-yl)

10 **imidazo[1,2-a]pyridin-7-yl)methanone**

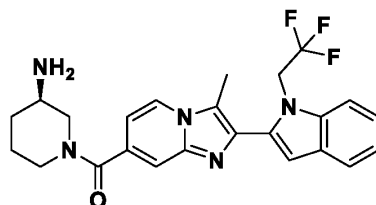


[000166] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.42-8.38 (m, 2H), 7.62 (d, J = 6.8 Hz, 1H), 7.57-7.52 (m, 2H), 7.34 (d, J =8.0 Hz, 1H), 7.15-7.05 (m, 3H), 7.04-6.95 (m, 1H), 6.78 (s, 1H), 6.64 (d, J = 8.0 Hz, 1H), 5.96 (s, 2H), 4.19-4.11 (m, 1H), 3.55-3.49 (m, 1H), 2.97-2.95 (m, 2H), 2.79-2.73 (m, 2H), 2.63 (s, 3H), 1.87-1.82 (m, 1H), 1.66-1.63 (m, 1H), 1.45-1.42 (m, 1H), 1.28-1.22 (m, 2H). MS (ESI): Mass calcd. for $\text{C}_{28}\text{H}_{28}\text{N}_6\text{O}$, 464.23; m/z found, 465.2 ($\text{M}+\text{H}$) $^+$.

Compound-17:

(R)-(3-Aminopiperidin-1-yl)(3-methyl-2-(1-(2,2,2-trifluoroethyl)-1H-indol-2-yl)

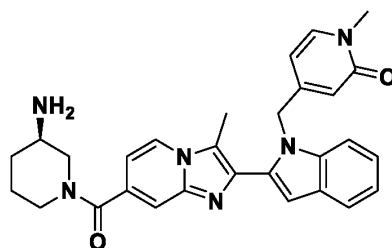
20 **imidazo[1,2-a]pyridin-7-yl)methanone**



- [000167] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.43 (d, *J* = 7.2 Hz, 1H), 7.66 - 7.61 (m, 3H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.83 (s, 1H), 5.85-5.80 (m, 2H), 4.1 (bs, 1H), 3.60 (bs, 1H), 3.00 (bs, 1H), 2.66 - 2.63 (m, 4H), 1.88 - 1.83 (m, 2H), 1.67 (bs, 2H), 1.46 (bs, 1H), 1.27 - 1.22 (m, 2H). MS (ESI): Mass calcd. for C₂₄H₂₄F₃N₅O, 455.49; *m/z* found, 456.2 (M+H)⁺.

Compound-18:

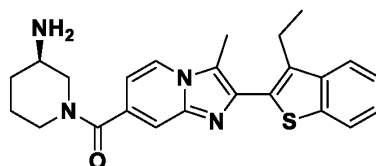
(R)-4-((2-(7-(3-Aminopiperidine-1-carbonyl)-3-methylimidazo[1,2-a]pyridin-2-yl)-1H-indol-1-yl)methyl)-1-methylpyridin-2(1H)-one



- 10 [000168] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.41 (d, *J* = 6.8 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.47 (d, *J* = 6.8 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.16-7.10 (m, 2H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.80 (s, 1H), 5.87 (d, *J* = 5.6 Hz, 1H), 5.77 (s, 2H), 5.65 (s, 1H), 4.19-4.11 (m, 1H), 3.65-3.61 (m, 1H), 3.24 (s, 3H), 2.97-2.93 (m, 1H), 2.65 (s, 3H), 2.64-2.61 (m, 2H), 1.86-1.83 (m, 2H), 1.66-1.63 (m, 2H), 1.44-1.41 (m, 1H), 1.24-1.19 (m, 1H). MS (ESI): Mass calcd. for C₂₉H₃₀N₆O₂, 494.24; *m/z* found, 495.4 (M+H)⁺.

Compound-19:

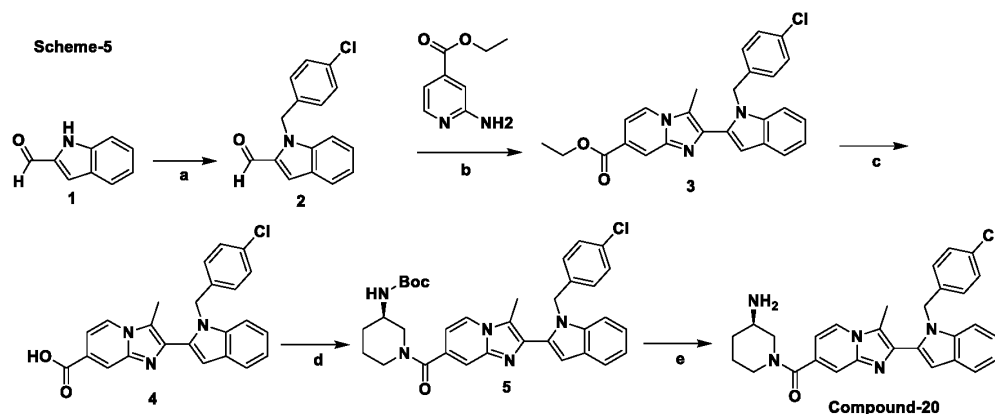
(R)-(3-Aminopiperidin-1-yl)(2-(3-ethylbenzo[b]thiophen-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



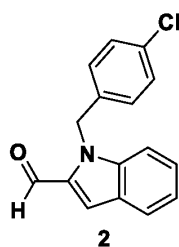
- 20 [000169] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.38 (d, *J* = 6.8 Hz, 1H), 7.96 (d, *J* = 7.2 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.59 (s, 1H), 7.45-7.36 (m, 2H), 6.97 (d, *J* = 7.2 Hz, 1H), 4.02-3.99 (m, 1H), 3.49-3.45 (m, 1H), 3.03-2.97 (m, 3H), 2.69-2.60 (m, 2H), 2.58 (s, 3H), 2.14-2.08 (m, 1H), 1.88-1.83 (m, 1H), 1.69-1.61 (m, 1H), 1.46-1.39 (m, 1H), 1.31-1.26 (m, 2H), 1.19-1.12 (m, 3H). MS (ESI): Mass calcd. for C₂₄H₂₆N₄OS, 418.56; *m/z* found, 419.2 (M+H)⁺.

Compound-20:

Synthesis of (R)-(3-Aminopiperidin-1-yl)(2-(1-(4-chlorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone (Compound-20)

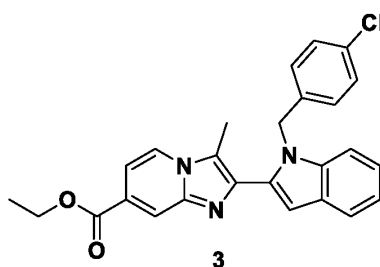


5 Step 1: Preparation of Ethyl 2-(1-(4-chlorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate (2)



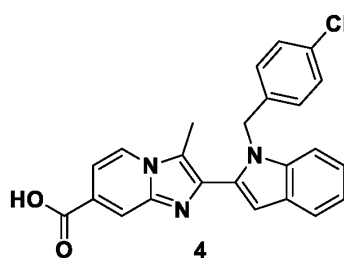
[000170] To a stirred solution 1H-indole-2-carbaldehyde (**1**, 0.5 g, 3.44 mmol) in
 10 DMF (10 mL), was added potassium carbonate (1.42 g, 10.3 mmol) followed by 1-
 (bromomethyl)-4-chlorobenzene (0.84 g, 4.13 mmol) and then the reaction mixture was
 stirred at rt for 4 h (Reaction condition **a**). Reaction mixture was poured into crushed
 ice which resulted in the formation of precipitate. The precipitate was filtered through
 sintered funnel and dried over vacuum to get the title compound as beige colour solid
 15 (**2**) (0.86 g, 93.4% Yield). MS (ESI): Mass calcd. for C₁₆H₁₂ClNO, 269.73; *m/z* found
 270.1 (M+H)⁺.

Step 2: Preparation of Ethyl 2-(1-(4-chlorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate (3)



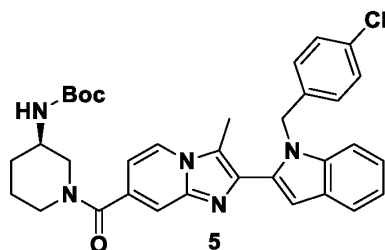
[000171] To the stirred solution of 1-(4-chlorobenzyl)-1H-indole-2-carbaldehyde (**2**, 0.38 g, 1.44 mmol) and ethyl 2-aminoisonicotinate (0.2 g, 1.2 mmol) in DMF was added nitro ethane (1.1 g, 14.3 mmol) followed by FeCl₃ (0.04 g, 0.28 mmol) and stirred at 90 °C under air for 5 h (Reaction condition **b**). The reaction mixture was cooled to rt, diluted with ethyl acetate and evaporated under vacuum to get crude compound. Crude was purified by flash column chromatography using ethylacetate in hexane as an eluent to afford the product as pale yellow gummy solid (**3**) (0.07 g, 10.9% Yield). MS (ESI): Mass calcd. for C₂₆H₂₂ClN₃O₂, 443.93; m/z found, 444.1 (M+H)⁺.

Step 3: Preparation of 2-(1-(4-Chlorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylic acid (4**)**



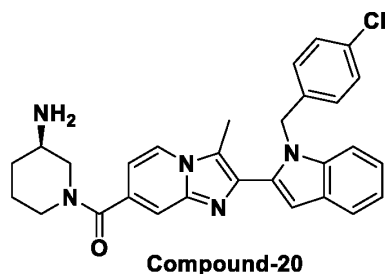
[000172] To the stirred solution of ethyl 2-(1-(4-chlorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate (**3**, 0.08 g, 0.18 mmol) in ethanol (5 mL), was added 5N sodium hydroxide solution (0.18 mL, 9.0 mmol) and was heated at 80 °C for 1 h (Reaction condition **c**). The reaction mixture was cooled to rt and evaporated to dryness. Resulting crude product was dissolved in water (10 mL), acidified using saturated citric acid solution and extracted with dichloromethane (40 mL). Organic layer was dried over anhydrous sodium sulfate and evaporated under vacuum to afford the product as colourless gummy solid (**4**) (0.06 g, 80.3% Yield). MS (ESI): Mass calcd. for C₂₄H₁₈ClN₃O₂, 415.88; m/z found, 416.1(M+H)⁺.

Step 4: Preparation of Tert-butyl (R)-(1-(2-(1-(4-chlorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxyl)piperidin-3-yl)carbamate (5**)**



[000173] To a stirred solution 2-(1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylic acid (**4**, 0.06 g, 0.144 mmol) in DCM (3 mL), was added tert-butyl (R)-piperidin-3-ylcarbamate (0.043 g, 0.216 mmol), Et₃N (0.06 mL, 0.432 mmol), 50% solution of T3P in ethyl acetate (0.068 mL, 0.216 mmol) and the reaction mixture was stirred at rt for 5 h (Reaction condition **d**). The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (25 mL). Organic layer was dried over anhydrous Na₂SO₄ and evaporated under vacuum. Crude was purified by column chromatography using ethylacetate in hexane to afford the product as off white solid (**5**) (0.09 g, 61% Yield). MS (ESI): Mass calcd. for C₃₄H₃₆ClN₅O₃, 598.14; m/z found, 599.2 (M+H)⁺.

Step 5: Preparation of (R)-(3-Aminopiperidin-1-yl)(2-(1-(4-chlorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone (6, Compound-20)



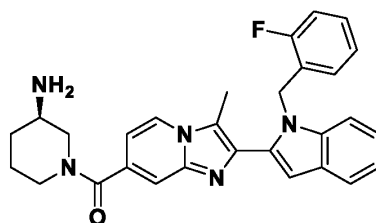
[000174] To a stirred solution tert-butyl (R)-(1-(2-(1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate)piperidin-3-yl)carbamate (**5**, 0.05 g, 0.083 mmol) in DCM (3 mL), was added TFA (0.5 mL) and the reaction mixture was stirred at rt for 2 h (Reaction condition **e**). The reaction mixture was basified using saturated sodium bicarbonate solution and extracted with MeOH/DCM (2 X 25 mL). Combined organic layer was dried over anhydrous sodium sulphate. Crude product was purified by flash column chromatography using 7% MeOH in DCM to give the title compound as brown colour solid (0.007 g, 26.8% Yield) (**6, Compound-20**) ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.41 (d, *J* = 6.8 Hz, 1H), 7.62 -7.59 (m,

2H), 7.37 (d, $J = 8.0$ Hz, 1H), 7.23 (d, $J = 8.4$ Hz, 2H), 7.12 - 7.00 (m, 2H), 6.99 - 6.98 (m, 3H), 6.76 (s, 1H), 5.91 (s, 2H), 4.12 (bs, 1H), 3.6 (bs, 1H), 3.00 (bs, 1H), 2.79 (bs, 1H), 2.65 - 2.63 (m, 1H), 1.88 - 1.84 (m, 2H), 1.68 (bs, 2H), 1.46 - 1.43 (m, 2H), 1.28 - 1.12 (m, 3H). MS (ESI): Mass calcd. for $C_{29}H_{28}ClN_5O$, 498.03; m/z found, 499.2(M+H)⁺.

[000175] Following compounds (Compounds 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 39, 40, 43, 44 and 47) were synthesized using the above procedure as exemplified for **Compound-20**.

Compound-21:

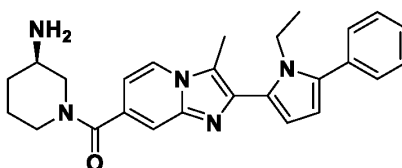
10 **(R)-(3-Aminopiperidin-1-yl)(2-(1-(2-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo [1,2-a]pyridin-7-yl)methanone**



[000176] ¹HNMR (400 MHz, DMSO- d_6) δ (ppm): 8.39 (d, $J = 7.2$ Hz, 1H), 7.62 - 7.59 (m, 2H), 7.37 (d, $J = 8$ Hz, 1H), 7.17 - 7.05 (m, 4H), 7.14 (d, $J = 6.8$ Hz, 1H), 6.96 - 6.89 (m, 1H), 6.78 (s, 1H), 6.52 - 6.48 (m, 1H), 5.97 (s, 2H), 4.10 (bs, 1H), 2.99 (bs, 1H), 2.80 (bs, 2H), 2.62 (s, 3H), 1.88 (bs, 2H), 1.68 (bs, 1H), 1.46 1.68 (bs, 1H), 1.31-1.21 (m, 3H). MS (ESI): Mass calcd. for $C_{29}H_{28}FN_5O$, 481.58; m/z found, 482.4 (M+H)⁺.

Compound-22:

20 **(R)-(3-Aminopiperidin-1-yl)(2-(1-ethyl-5-phenyl-1H-pyrrol-2-yl)-3-methylimidazo [1,2-a]pyridin-7-yl)methanone**

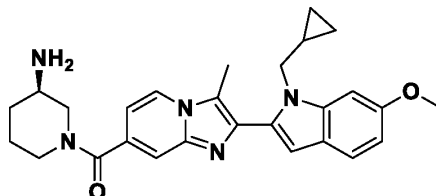


[000177] ¹HNMR (400 MHz, DMSO- d_6) δ (ppm): 8.35 (d, $J = 7.2$ Hz, 1H), 7.56 (s, 1H), 7.46 - 7.44 (m, 4H), 7.36 - 7.34 (m, 1H), 6.95 (d, $J = 6.8$ Hz, 1H), 6.30 (d, $J = 3.6$ Hz, 1H), 6.21 (d, $J = 3.6$ Hz, 1H), 4.40 - 4.38 (m, 2H), 3.05 (bs, 1H), 2.73 (bs, 2H), 2.57 (s, 3H), 1.88 - 1.84 (m, 2H), 1.68 (bs, 2H), 1.46 (bs, 1H), 1.28 - 1.22 (m, 3H), 0.90

- 0.83 (m, 3H). MS (ESI): Mass calcd. for $C_{26}H_{29}N_5O$, 427.55; m/z found, 428.3(M+H)⁺.

Compound-23:

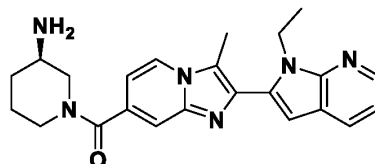
(R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000178] ¹HNMR (400 MHz, DMSO- d_6) δ (ppm): 8.41 (d, J = 6.8 Hz, 1H), 7.63 (s, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.08 (s, 1H), 6.99 (d, J = 6.4 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 6.55 (s, 1H), 5.15 (bs, 2H), 4.46 (d, J = 6.8 Hz, 2H), 3.82 (s, 3H), 3.08 - 2.92 (m, 3H), 2.61 (s, 3H), 1.97 - 1.88 (m, 2H), 1.71 (bs, 1H), 1.48 - 1.36 (bs, 3H), 1.09 (m, 1H), 0.26 (d, J = 7.6 Hz, 2H), 0.13 (d, J = 4 Hz, 2H). MS (ESI): Mass calcd. for $C_{27}H_{31}N_5O_2$, 457.58; m/z found, 458.58 (M+H).

Compound-24:

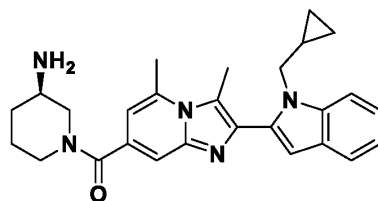
(R)-(3-Aminopiperidin-1-yl)(2-(1-ethyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000179] ¹HNMR (400 MHz, DMSO- d_6) δ (ppm): 8.43 (d, J = 6.4 Hz, 1H), 8.28-8.25 (m, 1H), 7.98 (d, J = 7.2 Hz, 1H), 7.63 (s, 1H), 7.13-7.11 (m, 1H), 7.01-6.99 (m, 1H), 6.67 (s, 1H), 4.71-4.65 (m, 2H), 4.24-4.21 (m, 1H), 3.55-3.49 (m, 1H), 3.00-2.96 (m, 1H), 2.69-2.66 (m, 1H), 2.65 (s, 3H), 2.21-2.19 (m, 2H), 1.87-1.83 (m, 2H), 1.68-1.65 (m, 1H), 1.45-1.42 (m, 1H), 1.35-1.33 (m, 1H), 1.26-1.24 (m, 3H). MS (ESI): Mass calcd. for $C_{23}H_{26}N_6O$, 402.22; m/z found, 403.1(M+H)⁺.

Compound-25:

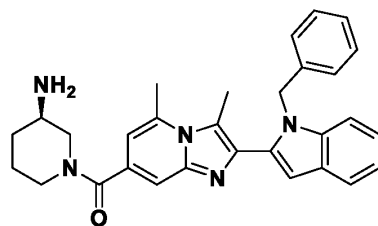
(R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3,5-dimethylimidazo[1,2-a]pyridin-7-yl)methanone



[000180] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 7.57 (t, *J* = 7.2 Hz, 2H), 7.40 (s, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.66 (s, 1H), 6.53 (s, 1H), 4.33 (d, *J* = 6.8 Hz, 2H), 4.09-4.04 (m, 1H), 2.95 (s, 3H), 2.88 (s, 3H), 2.65-2.61 (m, 2H),
 5 1.88-1.85 (m, 2H), 1.67-1.64 (m, 1H), 1.43-1.39 (m, 1H), 1.27-1.24 (m, 2H), 1.21-1.19 (m, 2H), 1.06-1.02 (m, 1H), 0.27-0.25 (m, 2H), 0.11-0.09 (m, 2H). MS (ESI): Mass calcd. for C₂₇H₃₁N₅O, 441.25; *m/z* found, 442.3 (M+H)⁺.

Compound-26:

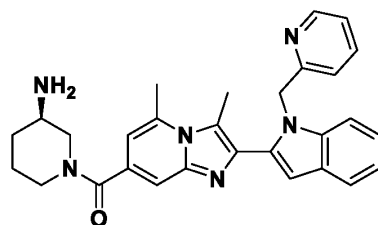
(R)-(3-Aminopiperidin-1-yl)(2-(1-benzyl-1H-indol-2-yl)-3,5-dimethylimidazo[1,2-
 10 a]pyridin-7-yl)methanone



[000181] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 7.62 (d, *J* = 8.0 Hz, 1H), 7.40-7.37 (m, 2H), 7.19-7.09 (m, 5H), 6.94 (d, *J* = 6.8 Hz, 2H), 6.66 (s, 2H), 5.75 (s, 2H), 4.19-4.14 (m, 1H), 3.75-3.71 (m, 1H), 2.94 (s, 3H), 2.89 (s, 3H), 1.89-1.87 (m, 2H),
 15 1.86-1.85 (m, 2H), 1.67-1.64 (m, 1H), 1.43-1.39 (m, 2H), 1.27-1.24 (m, 2H). MS (ESI): Mass calcd. for C₃₀H₃₁N₅O, 477.25; *m/z* found, 478.5 (M+H)⁺.

Compound-27:

(R)-(3-Aminopiperidin-1-yl)(3,5-dimethyl-2-(1-(pyridin-2-ylmethyl)-1H-indol-2-
 yl)imidazo[1,2-a]pyridin-7-yl)methanone



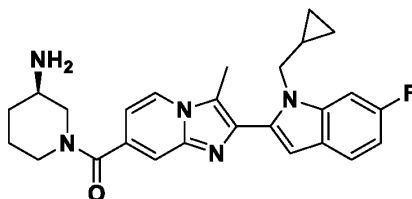
20

[000182] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.40 (d, *J* = 6.8 Hz, 1H), 7.63-7.61 (m, 1H), 7.55-7.51 (m, 1H), 7.37-7.35 (m, 2H), 7.15-7.10 (m, 4H), 6.67-6.64 (m,

2H), 5.80 (s, 2H), 3.75-3.71 (m, 1H), 2.92 (s, 3H), 2.88 (s, 3H), 2.65-2.61 (m, 1H), 2.01-1.98 (m, 1H), 1.97-1.94 (m, 2H), 1.88-1.85 (m, 2H), 1.43-1.39 (m, 2H), 1.27-1.24 (m, 2H). MS (ESI): Mass calcd. for $C_{29}H_{30}N_6O$, 478.25; m/z found, 479.2 ($M+H$)⁺.

Compound-28:

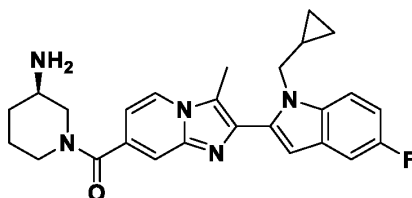
- 5 **(R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-fluoro-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone**



- [000183] ¹HNMR (400 MHz, DMSO- d_6) δ (ppm): 8.41 (d, J = 6.4 Hz, 1H), 7.60-7.55 (m, 2H), 7.44 (d, J = 9.6 Hz, 1H), 6.9 (d, J = 7.2 Hz, 1H), 6.92-6.88 (m, 1H), 6.54 (s, 1H), 4.46 (d, J = 6.8 Hz, 2H), 4.25 (m, 1H), 3.28 (m, 2H), 2.83 (m, 1H), 2.62 (s, 3H), 1.99-1.95 (m, 1H), 1.82(m, 2H), 1.68 (m, 2H), 1.46 (m, 2H), 1.07 (m, 1H), 0.27-0.25 (m, 2H), 0.14-0.13 (m, 2H). MS (ESI): Mass calcd. for $C_{26}H_{28}FN_5O$, 445.23; m/z found, 446.2 ($M+H$)⁺.

Compound-29:

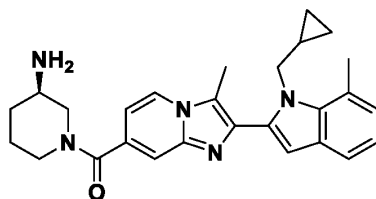
- 15 **(R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-5-fluoro-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone**



- [000184] ¹HNMR (400 MHz, DMSO- d_6) δ (ppm): 8.41 (d, J = 7.2 Hz, 1H), 7.61-7.57 (m, 2H), 7.35-7.32 (m, 1H), 7.03-6.98 (m, 2H), 6.64 (s, 1H), 4.48 (d, J = 6.8 Hz, 2H), 4.21-4.11 (m, 2H), 3.63-3.60 (m, 1H), 2.99-2.95 (m, 1H), 2.78-2.74 (m, 1H), 2.65 (s, 3H), 1.86-1.83 (m, 1H), 1.71-1.68 (m, 3H), 1.46-1.43 (m, 1H), 1.28-1.25 (m, 1H), 1.09-1.03 (m, 1H), 0.27-0.25 (m, 2H), 0.14-0.11 (m, 2H). MS (ESI): Mass calcd. for $C_{26}H_{28}FN_5O$, 445.23; m/z found, 446.2 ($M+H$)⁺.

Compound-30:

- 25 **(R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-methyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone**

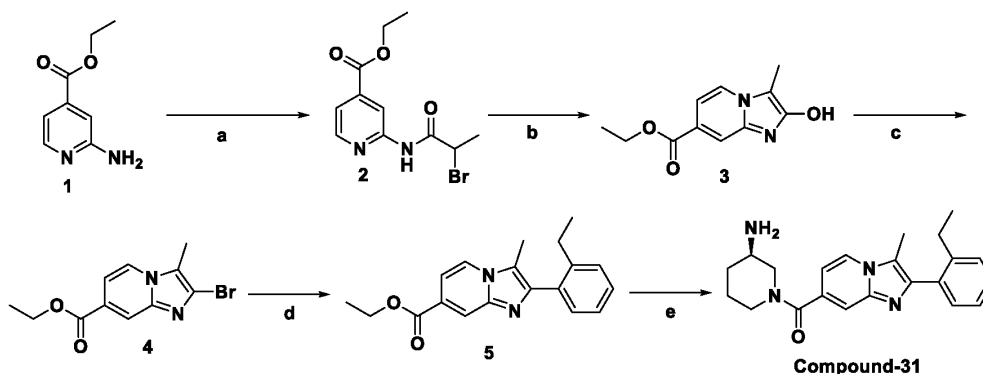


[000185] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.41 (d, $J = 7.2$ Hz, 1H), 7.60 (s, 1H), 7.42 (d, $J = 6.4$ Hz, 1H), 7.00-6.98 (m, 1H), 6.96-6.93 (m, 2H), 6.60 (s, 1H), 4.65 (d, $J = 6.0$ Hz, 2H), 4.21-4.11 (m, 2H), 3.01-2.98 (m, 1H), 2.79-2.77 (m, 2H), 2.76 (s, 3H), 2.65 (s, 3H), 1.89-1.85 (m, 2H), 1.69-1.66 (m, 1H), 1.46-1.43 (m, 1H), 1.32-1.27 (m, 2H), 0.89-0.85 (m, 1H), 0.15-0.14 (m, 2H), 0.24 -0.25 (m, 2H). MS (ESI): Mass calcd. for $\text{C}_{27}\text{H}_{31}\text{N}_5\text{O}$, 441.25; m/z found, 442.4 ($\text{M}+\text{H}$) $^+$.

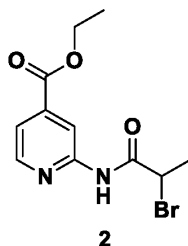
Compound-31:

Synthesis of (R)-(3-Aminopiperidin-1-yl)(2-(2-ethylphenyl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone (Compound-31)

Scheme-6:



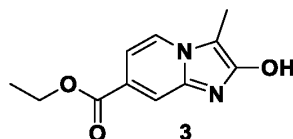
Step 1: Ethyl 2-(2-bromopropanamido)isonicotinate



[000186] To the stirred solution of ethyl 2-aminoisonicotinate (**1**, 2 g, 12.0 mmol) in DCM (20 mL) was added 2-bromopropanoic acid (2.2 g, 14.4 mmol), Et_3N (3.3 mL, 24.1 mmol), 50% solution of T3P in ethyl acetate (12.1 mL, 18.1 mmol) and the reaction mixture was stirred at rt for 16 h. To the reaction mixture, water (50 mL) was

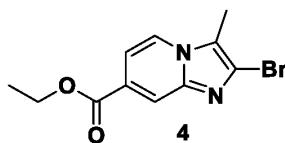
added and the compound was extracted with DCM (100 mL). Organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum. Crude product was purified by column chromatography using 20-30% EtOAc in hexane to afford the product as yellow solid (2.3 g, 64% Yield). MS (ESI): Mass calcd. for $\text{C}_{11}\text{H}_{13}\text{BrN}_2\text{O}_3$, 301.14; m/z found, 303.0 ($\text{M}+2\text{H}$)⁺.

Step 2: Ethyl 2-hydroxy-3-methylimidazo[1,2-a]pyridine-7-carboxylate



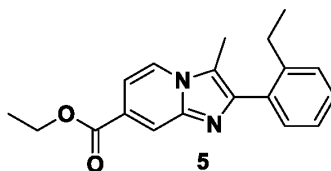
[000187] To the stirred solution of ethyl 2-(2-bromopropanamido)isonicotinate (**2**, 1 g, 3.33 mmol) in EtOH (20 mL), was added K_2CO_3 (1.37 g, 9.99 mmol) and stirred at 80°C for 5 h. The reaction mixture was evaporated to dryness, triturated with diethyl ether and dried to get crude product as brown gummy solid (1.0 g, 80% Yield). MS (ESI): Mass calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_3$, 220.08; m/z found, 221.1 ($\text{M}+\text{H}$)⁺.

Step 3: Ethyl 2-bromo-3-methylimidazo[1,2-a]pyridine-7-carboxylate



[000188] To the stirred solution of ethyl 2-hydroxy-3-methylimidazo[1,2-a]pyridine-7-carboxylate (**4**, 1.0 g, 5.45 mmol) in 1,2-dichloroethane (20 mL), was added POBr_3 (4.6 g, 16.3 mmol) and stirred at 90°C for 16 h. The reaction mixture was cooled to rt, quenched with saturated Na_2CO_3 solution (50 mL) and extracted with EtOAc (100 mL). Organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum. Crude product was purified by column chromatography using 30-40% EtOAc in hexane to afford the product as brown solid (0.2 g, 21% Yield). MS (ESI): Mass calcd. for $\text{C}_{11}\text{H}_{11}\text{BrN}_2\text{O}_2$, 283.13; m/z found, 285.0 ($\text{M}+2\text{H}$)⁺.

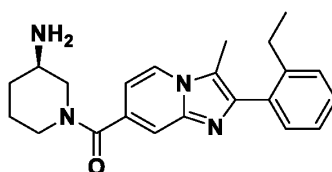
Step 4: Ethyl 2-(2-ethylphenyl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate



[000189] To a stirred solution ethyl 2-bromo-3-methylimidazo[1,2-a]pyridine-7-carboxylate (**5**, 0.2 g, 0.70 mmol) in dioxane (5 mL), was added (2-ethylphenyl)boronic

acid (0.16 g, 1.06 mmol), K_2CO_3 (0.3 g, 2.12 mmol), $Pd(dppf)Cl_2 \cdot DCM$ (0.03 g, 0.03 mmol) and the reaction mixture was stirred at 85°C for 16 h. The reaction mixture was filtered through celite and the solvent was evaporated. To the resulting crude product, water (10 mL) was added and the compound was extracted with EtOAc (25mL).
5 Organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum. Crude product was purified by column chromatography using 25-30% EtOAc in hexane to afford the product as brown solid (0.15 g, 71% Yield). MS (ESI): Mass calcd. for $C_{19}H_{20}N_2O_2$, 308.15; m/z found, 309.1 ($M+H$)⁺.

[000190] Remaining steps for **Compound-31** were carried using the procedure as exemplified for **Compound-20**.
10



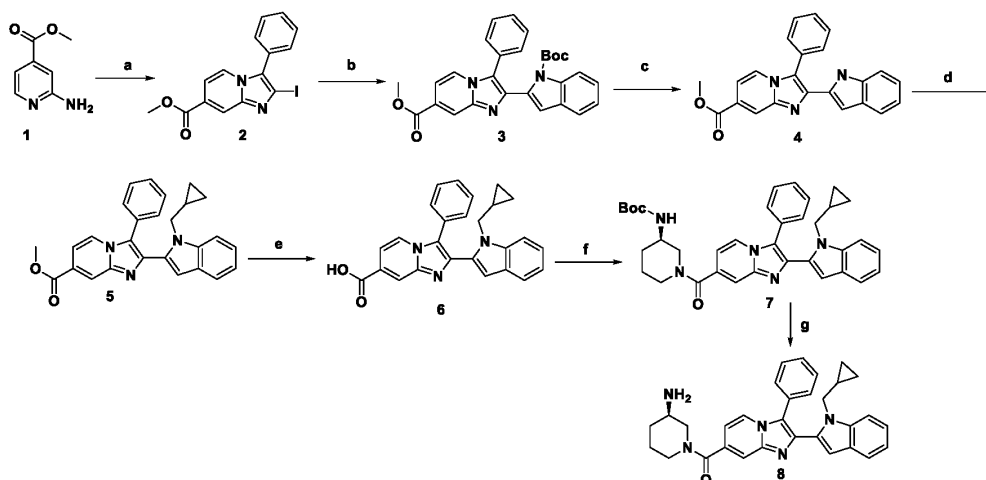
Compound-31

[000191] ¹HNMR (400 MHz, DMSO- d_6) δ (ppm): 8.34 (d, J = 6.8 Hz, 1H), 7.57 (s, 1H), 7.35-7.31 (m, 2H), 7.27-7.24 (m, 2H), 6.96 (d, J = 6.4 Hz, 1H), 4.01-3.98 (m, 2H), 3.66-3.61 (m, 1H), 3.49-3.41 (m, 1H), 3.02-2.97 (m, 1H), 2.83-2.79 (m, 2H), 2.67-2.61 (m, 1H), 2.38 (s, 3H), 1.88-1.82 (m, 1H), 1.69-1.62 (m, 1H), 1.48-1.42 (m, 1H), 1.33-1.29 (m, 1H), 1.21-1.19 (m, 1H), 1.02-0.98 (m, 3H). MS (ESI): Mass calcd. for $C_{22}H_{26}N_4O$, 362.21; m/z found, 363.2 ($M+H$)⁺.
15

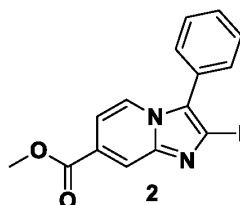
Compound-32:

Synthesis of (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-phenyl imidazo[1,2-a]pyridin-7-yl)methanone (Compound-32)
20

Scheme-7:

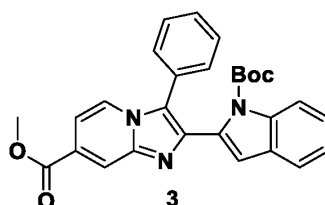


Step-1: Methyl 2-iodo-3-phenylimidazo[1,2-a]pyridine-7-carboxylate



[000192] To a stirred solution of methyl 2-aminoisonicotinate (**1**, 1 g, 6.5 mmol) and phenyl acetylene (0.79 mL, 7.8 mmol) in 1, 2-dichlorobenzene (20 mL), was added iodine (1.6 g, 6.5 mol) and copper (II)acetate (0.1 g, 0.65 mmol).The reaction mixture was filled with 5 kg/cm² oxygen in steel bomb and stirred at 120 °C for 12 h. Then the reaction mixture was filtered and evaporated to give residue which was dissolved in water (50 mL). It was extracted with ethyl acetate (2 x 20 mL) and the organic layer was dried over Na₂SO₄, filtered, and concentrated to give the crude product. The crude product was purified by gradient column chromatography using 20% EtOAc/hexane as the eluent to yield desired product as pale yellow solid (0.3 g, 12.2% Yield). MS (ESI): Mass calcd for C₁₅H₁₁IN₂O₂, 377.99; m/z found, 380.0 [M+H]⁺.

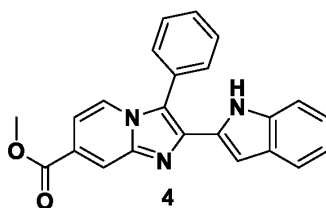
[000193] **Step-2: Methyl 2-(1-(tert-butoxycarbonyl)-1H-indol-2-yl)-3-phenylimidazo[1,2-a]pyridine-7-carboxylate**



[000194] To a solution of methyl 2-iodo-3-phenylimidazo[1,2-a]pyridine-7-carboxylate (**2**, 0.17 g, 0.44 mmol) and (1-(tert-butoxycarbonyl)-1H-indol-2-yl)boronic acid (0.17 g, 0.66 mmol) in 1,4-dioxane (10 mL) and water (2 mL), was added sodium carbonate (0.13 g, 1.3 mmol) and the mixture was purged with argon gas for 20 min.

- 5 Then added $\text{Pd}(\text{PPh}_3)_4$ (0.015 g, 0.002 mmol) and continued purging for 5 min. Then the reaction mixture was stirred for 12 h at 90 °C in sealed tube. To the reaction mixture, water (10 mL) was added and extracted with EtOAc (2 x 20 mL). Organic layer was washed with saturated NH_4Cl solution and brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by
- 10 gradient column chromatography using 20 % EtOAc/hexane as the eluent to yield desired product as pale yellow solid (0.1 g, 53.5 % Yield). MS (ESI): Mass calcd for $\text{C}_{28}\text{H}_{25}\text{N}_3\text{O}_4$, 467.18; m/z found, 468.3 $[\text{M}+\text{H}]^+$.

[000195] **Step-3: Methyl 2-(1H-indol-2-yl)-3-phenylimidazo[1,2-a]pyridine-7-carboxylate**



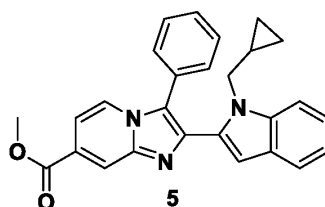
15

[000196] To a solution of methyl 2-(1-(tert-butoxycarbonyl)-1H-indol-2-yl)-3-phenylimidazo[1,2-a]pyridine-7-carboxylate (**3**, 0.08 g, 0.1 mmol) in DCM (2 mL) was added trifluoroacetic acid (0.04 mL, 0.5 mmol) at 0 °C. Mixture was stirred for 2 h at rt under N_2 atmosphere. The reaction mixture was concentrated under vacuum and

20 neutralized using aqueous sodium bicarbonate. The aqueous phase was then extracted with DCM (2 x 20 mL). Organic layer was dried over Na_2SO_4 and concentrated to give desired product as pale yellow solid (**4**; 0.06 g, 99 % Yield). MS (ESI): Mass calcd for $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O}_2$, 367.13; m/z found, 368.3 $[\text{M}+\text{H}]^+$.

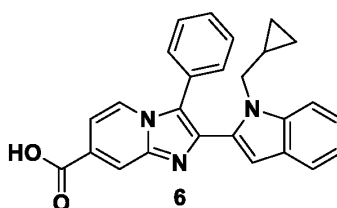
Step-4: Methyl 2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-phenylimidazo[1,2-a]pyridine-7-carboxylate

25



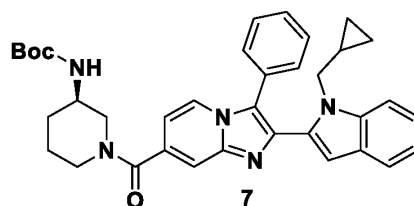
[000197] To a solution of methyl 2-(1H-indol-2-yl)-3-phenylimidazo[1,2-a]pyridine-7-carboxylate (**4**, 0.06 g, 0.16 mmol) in DMF (10 mL) was added cesium carbonate (0.025 g, 0.19 mmol) followed by (bromo methyl)cyclopropane (0.025 g, 0.19 mmol). Mixture was stirred for 12 h at rt. To the reaction mixture, water (20 mL) was added and extracted with EtOAc (2 x 20 mL). Organic layer was washed with water and brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain pale yellow solid (**5**; 0.06 g, 88.9% Yield). MS (ESI): Mass calcd for C₂₇H₂₃N₃O₂, 421.8; m/z found, 422.3 [M+H]⁺.

Step-5: 2-(1-(Cyclopropylmethyl)-1H-indol-2-yl)-3-phenylimidazo[1,2-a]pyridine-7-carboxylic acid



[000198] To a solution of methyl 2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-phenylimidazo[1,2-a]pyridine-7-carboxylate (**5**, 0.06 g, 0.14 mmol) in ethanol (20 mL), was added 5M sodium hydroxide solution (0.14 mL, 0.72 mmol). The reaction mixture was allowed to stir at 80 °C for 45 min. After the completion of the reaction, the reaction mixture was evaporated to dryness. Then crude product was dissolved in water, neutralized with citric acid to precipitate the product. The mixture was filtered to obtain the desired product as off white solid (**6**; 0.04 g, 70.2 % Yield). MS (ESI): Mass calcd for C₂₆H₂₁N₃O₂, 407.16; m/z found, 408.3 [M+H]⁺.

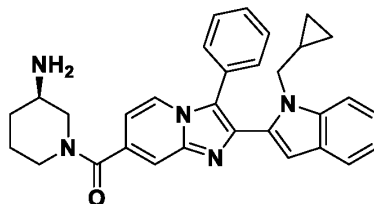
Step-6: Tert-butyl (R)-(1-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-phenylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate



[000199] To a solution of tert-butyl (R)-piperidin-3-yl-12-azanecarboxylate (0.02 g, 0.1 mmol) 2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-phenylimidazo[1,2-a]pyridine-7-carboxylic acid (**6**, 0.04 g, 0.09 mmol) in DCM (10 mL) at rt was added triethylamine (0.04 mL, 0.2 mmol) and propylphosphonic anhydride (T₃P, 50 % in ethyl acetate) (0.67 mL, 0.2 mmol). The reaction mixture was stirred at rt for 12 h. It was diluted with

DCM and washed with saturated sodium bicarbonate solution. Organic layer was separated, dried over sodium sulphate and evaporated under reduced pressure to obtain crude. The crude residue was purified by gradient column chromatography using 5% methanol in DCM to afford desired product (**7**; 0.04 g, 69.2% Yield). MS (ESI): Mass calcd for $C_{36}H_{39}N_5O_3$, 589.3; m/z found, 590.3 $[M+H]^+$.

Step-7: (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-phenylimidazo[1,2-a]pyridin-7-yl)methanone (Compound-32)

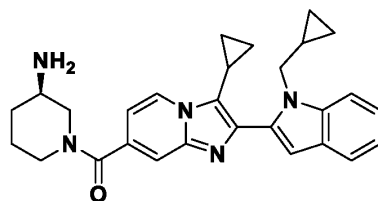


[000200] To a stirred solution tert-butyl (R)-(1-(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-phenylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (**7**, 0.04 g, 0.06 mmol) in DCM (10 mL) was added TFA (0.02 mL, 0.3 mmol) at 0°C, then it was stirred at rt for 2 h. After completion of reaction, solvent was evaporated. The crude was dissolved in water (10 mL) and neutralized with saturated $NaHCO_3$ solution to get crude. The crude product was purified by gradient column chromatography using 5% methanol in DCM followed by preparative HPLC Column: Inertsil ODS 3V (250mm X 4.6mm X 5mic) Mobile phase(A): 0.1% ammonia in water, Mobile phase(B) : acetonitrile, Flow rate : 1.0 mL/min to afford desired product as off white solid (0.02g, 68.9 % Yield). ^1H NMR (400 MHz, $DMSO-d_6$) δ (ppm): 8.21 (d, $J = 7.2$ Hz, 1H), 7.21 (s, 1H), 7.52 (m, 6H), 7.39 (d, $J = 8$ Hz, 1H), 7.13 (d, $J = 7.2$ Hz, 1H), 6.98-6.94 (m, 2H), 6.19 (s, 1H), 4.46 (d, $J = 8$ Hz, 2H), 2.78 (m, 2H), 1.86 (m, 2H), 1.72 (m, 2H), 1.45 (m, 2H), 1.30 (m, 2H), 1.12 (m, 2H), 0.30 (d, $J = 7.6$ Hz, 2H), 0.16 (d, $J = 3.6$ Hz, 2H). MS (ESI): Mass calcd. for $C_{31}H_{31}N_5O$, 489.25; m/z found, 490.3 $[M+H]^+$.

[000201] Following compounds (**Compounds-33 and 34**) were synthesized using the above procedure as exemplified for **Compound-32**.

Compound-33:

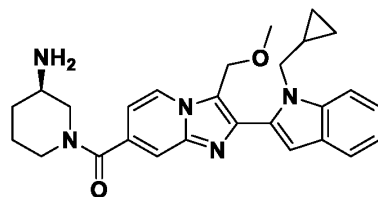
(R)-(3-Aminopiperidin-1-yl)(3-cyclopropyl-2-(1-(cyclopropylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone



[000202] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.55 (d, *J* = 7.2 Hz, 1H), 7.63 (s, 1H), 7.58 (t, *J* = 7.6 Hz, 2H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 8 Hz, 2H), 6.73 (s, 1H), 4.47 (d, *J* = 7.2 Hz, 2H), 3.9 (bs, 2H), 3.03 (bs, 1H), 2.85 (m, 2H), 2.12-2.08 (m, 1H), 2.01-1.95 (m, 2H), 1.88 (m, 1H), 1.73-1.69 (m, 1H), 1.45-1.44 (m, 2H), 1.08-1.06 (m, 2H), 0.85-0.81 (m, 1H), 0.39 (d, *J* = 4.4 Hz, 2H), 0.21 (d, *J* = 8 Hz, 2H), 0.01 (d, *J* = 4.4 Hz, 2H). MS (ESI): Mass calcd. for C₂₈H₃₁N₅O, 453.25; *m/z* found, 454.3 [M+H]⁺.

Compound-34:

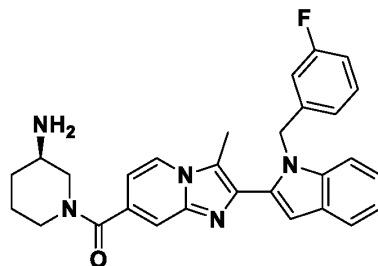
10 (R)-(3-Aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methoxymethylimidazo[1,2-a]pyridin-7-yl)methanone



[000203] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.52 (d, *J* = 7.2 Hz, 1H), 7.66 (s, 1H), 7.59 (t, *J* = 8.8 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.07-7.02 (m, 2H), 6.47 (s, 1H), 4.87 (s, 2H), 4.47 (d, *J* = 6.8 Hz, 2H), 3.8 (m, 3H), 3.04 (bs, 1H), 2.96-2.92 (m, 3H), 2.81 (s, 1H), 2.01-1.95 (m, 2H), 1.88 (m, 1H), 1.73-1.69 (m, 2H), 1.45-1.44 (m, 2H), 0.21 (d, *J* = 8 Hz, 2H), 0.01 (d, *J* = 4.4 Hz, 2H). MS (ESI): Mass calcd. for C₂₇H₃₁N₅O₂, 457.25; *m/z* found, 458.2 [M+H]⁺.

Compound-35:

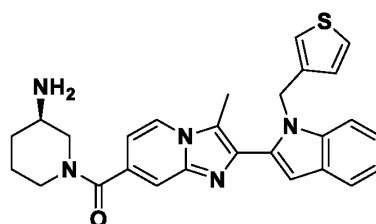
20 (R)-(3-aminopiperidin-1-yl)(2-(1-(3-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000204] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.41 (d, *J* = 6.8 Hz, 1H), 7.61-7.59 (m, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.23-7.18 (m, 1H), 7.13-7.04 (m, 2H), 6.99-6.97 (m, 1H), 6.93-6.91 (m, 1H), 6.80-6.76 (m, 3H), 5.91 (s, 2H), 4.05-4.01 (m, 1H), 3.49-3.45 (m, 1H), 2.99-2.95 (m, 1H), 2.73-2.71 (m, 2H), 2.63 (s, 3H), 1.86-1.83 (m, 2H),
 5 1.67-1.61 (m, 1H), 1.44-1.41 (m, 1H), 1.26-1.21 (m, 2H). MS (ESI): Mass calcd. for C₂₉H₂₈FN₅O, 481.23; *m/z* found, 482.2 (M+H)⁺.

Compound-36:

(R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-(thiophen-3-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone

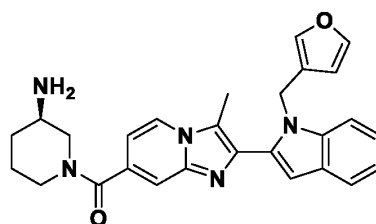


10

[000205] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.43 (d, *J* = 7.2 Hz, 1H), 7.63 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.31-7.29 (m, 1H), 7.13-7.11 (m, 2H), 7.06-7.00 (m, 2H), 6.76 (d, *J* = 4.4 Hz, 1H), 6.71 (s, 1H), 5.85 (s, 2H), 4.22-4.16 (m, 1H), 3.66-3.61 (m, 1H), 2.97-2.95 (m, 1H), 2.64-2.61 (m, 5H), 1.84-1.81 (m,
 15 2H), 1.66-1.59 (m, 2H), 1.44-1.42 (m, 2H). MS (ESI): Mass calcd. for C₂₇H₂₇N₅OS, 469.19; *m/z* found, 470.2 (M+H)⁺.

Compound-37:

(R)-(3-aminopiperidin-1-yl)(2-(1-(furan-3-ylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone

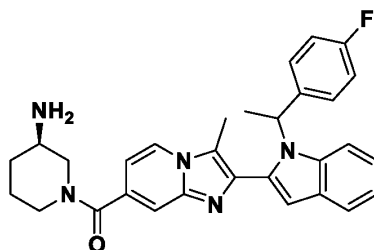


20

[000206] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.43 (d, *J* = 7.2 Hz, 1H), 7.65 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.48 (s, 1H), 7.40 (s, 1H), 7.16-7.12 (m, 1H), 7.06-7.00 (m, 2H), 6.69 (s, 1H), 6.15 (s, 1H), 5.67 (s, 2H), 4.22-4.16 (m, 1H), 3.57-3.55 (m, 1H), 3.02-2.99 (m, 1H), 2.76-2.73 (m, 2H), 2.64 (s, 3H), 1.84-1.81 (m, 2H), 1.69-1.65 (m, 2H), 1.30-1.28 (m, 1H), 1.21-1.18 (m, 1H). MS (ESI): Mass calcd. for C₂₇H₂₇N₅O₂,
 25 453.22; *m/z* found, 454.2 (M+H)⁺.

Compound-38:

(R)-3-aminopiperidin-1-yl(2-(1-(1-(4-fluorophenyl)ethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



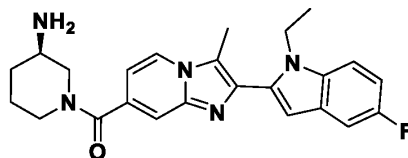
5

[000207] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.42 (d, J = 6.4 Hz, 1H), 7.61-7.57 (m, 2H), 7.32-7.30 (m, 2H), 7.11-7.08 (m, 2H), 6.98-6.95 (m, 4H), 6.74 (s, 1H), 6.48-6.45 (m, 1H), 4.22-4.18 (m, 1H), 3.59-3.55 (m, 1H), 2.97-2.94 (m, 1H), 2.72-2.70 (m, 2H), 2.63 (s, 3H), 1.88-1.86 (m, 4H), 1.68-1.65 (m, 2H), 1.44-1.41 (m, 1H), 1.27-1.25 (m, 2H). MS (ESI): Mass calcd. for $\text{C}_{30}\text{H}_{30}\text{FN}_5\text{O}$, 495.24; m/z found, 496.2 (M+H) $^+$.

10

Compound-39:

(R)-(3-aminopiperidin-1-yl)(2-(1-ethyl-5-fluoro-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



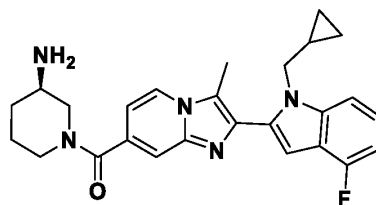
15

[000208] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.36 (d, J = 7.2 Hz, 1H), 7.60 (s, 1H), 7.5-7.750 (m, 1H), 7.33 (d, J = 9.6 Hz, 1H), 7.02-6.97 (m, 2H), 6.62 (s, 1H), 4.7-4.46 (m, 2H), 4.20 (m, 2H), 2.65 (s, 4H), 1.84 (m, 2H), 1.69 (m, 1H), 1.41 (m, 1H), 1.29-1.13 (m, 7H). MS (ESI): Mass calcd. for $\text{C}_{24}\text{H}_{26}\text{FN}_5\text{O}$, 419.2; m/z found 420.2 (M+H) $^+$.

20

Compound-40:

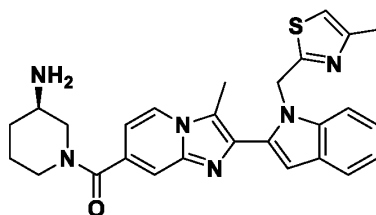
(R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-4-fluoro-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000209] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.43 (d, J = 6.8 Hz, 1H), 7.63 (s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.17-7.11 (m, 1H), 7.01 (d, J = 6.4 Hz, 1H), 6.82 (t, J = 8.4 Hz, 1H), 6.69 (s, 1H), 4.50 (d, J = 6.4 Hz, 2H), 4.20 (m, 1H), 3.49 (m, 1H), 3.02 (m, 1H), 2.79 (m, 2H), 2.63 (s, 3H), 1.88 (m, 2H), 1.70 (m, 2H), 1.48-1.45 (m, 1H), 1.31-1.28 (m, 1H), 1.10 (m, 1H), 0.27 (m, 2H), 0.15 (m, 2H). MS (ESI): Mass calcd. for $\text{C}_{26}\text{H}_{28}\text{FN}_5\text{O}$, 445.2; m/z found, 446 ($\text{M}+\text{H}$) $^+$.

Compound-41:

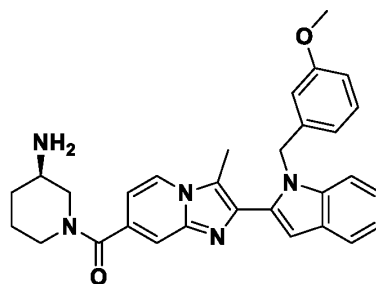
(R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-((4-methylthiazol-2-yl)methyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone



[000210] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.43 (d, J = 4.4 Hz, 1H), 7.61 (d, J = 8 Hz, 2H), 7.52 (d, J = 8.4 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.0 (d, J = 7.2 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.17-7.11 (m, 1H), 7.01 (d, J = 6.4 Hz, 1H), 6.80 (s, 1H), 3.02 (m, 2H), 2.80 (m, 2H), 2.65 (s, 3H), 2.23 (s, 3H), 1.68 (m, 2H), 1.47-1.45 (m, 2H), 1.1-1.22 (m, 3H). MS (ESI): Mass calcd. for $\text{C}_{27}\text{H}_{28}\text{N}_6\text{O}_2$, 484.2; m/z found, 485.2 ($\text{M}+\text{H}$) $^+$.

Compound-42:

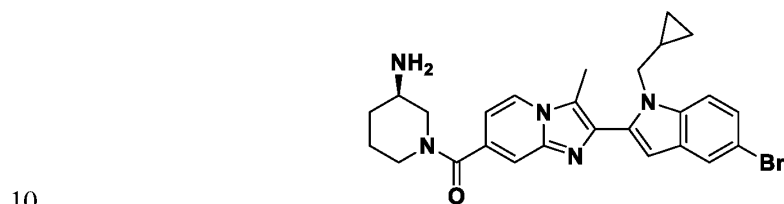
(R)-(3-aminopiperidin-1-yl)(2-(1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



- 5 [000211] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.41 (d, *J* = 6.8 Hz, 1H), 7.61 (t, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.12-7.03 (m, 3H), 6.69 (d, *J* = 5.2 Hz, 1H), 6.75 (s, 1H), 6.67-6.64 (m, 1H), 6.51 (s, 2H), 5.86 (s, 2H), 4.71-4.67 (m, 1H), 4.22-4.19 (m, 1H), 3.55 (s, 3H), 3.09-2.99 (m, 1H), 2.91-2.88 (m, 2H), 2.63 (s, 3H), 1.89-1.86 (m, 1H), 1.68-1.65 (m, 1H), 1.48-1.41 (m, 2H), 1.21-1.18 (m, 2H). MS (ESI): mass calcd. for C₃₀H₃₁N₅O₂, 493.25; *m/z* found, 494.2 (M+H)⁺.

Compound-43:

(R)-(3-aminopiperidin-1-yl)(2-(5-bromo-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



- 15 [000212] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.45 (d, *J* = 7.2 Hz, 1H), 7.77 (s, 1H), 7.70 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.28 (bs, 1H), 6.71 (bs, 1H), 6.65 (s, 1H), 4.49 (bs, 2H), 3.16 (bs, 3H), 2.06 – 1.89 (m, 2H), 1.53 (bs, 2H), 1.31 – 1.28 (m, 5H), 1.09 (bs, 1H), 0.83 (bs, 2H), 0.28 (bs, 2H), 0.15 (bs, 2H). MS (ESI): Mass calcd. for C₂₆H₂₈BrN₅O, 506.45; *m/z* found, 508.1 [M+H]²⁺.

Compound-44:

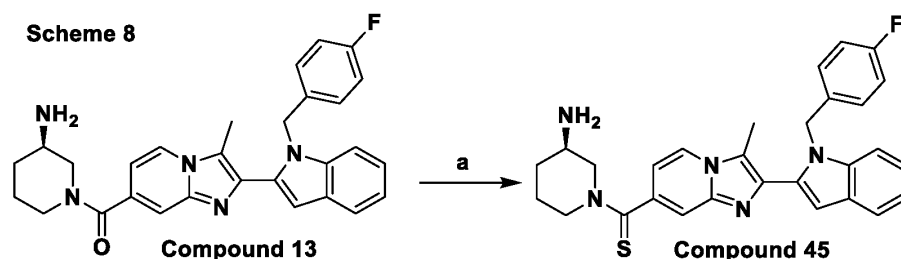
(R)-(3-aminopiperidin-1-yl)(2-(7-chloro-1-(cyclopropylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone

- 20
- 25 [000213] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.41 (d, *J* = 7.2 Hz, 1H), 7.67 (s, 1H), 7.58 (d, *J* = 8 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.08-7.02 (m, 2H), 6.74 (s, 1H), 4.80 (d, *J* = 6.8 Hz, 2H), 4.0 (bs, 2H), 2.98 (m, 3H), 2.61 (s, 3H), 1.89 (m, 2H), 1.71 (m, 1H), 1.48-1.46 (m, 2H), 1.22 (m, 1H), 1.02 (m, 1H), 0.20-0.18 (m, 2H), -0.08 (m, 2H). MS (ESI): mass calcd. for C₂₆H₂₈ClN₅O, 461.20; *m/z* found, 462.1 (M+H)⁺.

Compound-45:

Synthesis of (R)-(3-aminopiperidin-1-yl)(2-(1-(4-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone

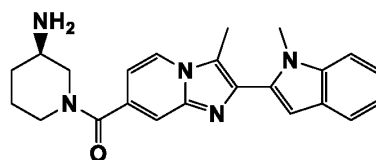
[000214] Compound-45 was prepared from Compound-13 according to the step provided below.



[000215] To the stirred solution of (R)-(3-aminopiperidin-1-yl)(2-(1-(4-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone (**Compound-13**, 0.05 g, 0.11 mmol) in toluene (2 mL), was added Lawesson's reagent (0.06 g, 0.15 mmol) and stirred at 100°C for 16 h (Reaction condition **a**). The reaction mixture was cooled to rt, added saturated NaHCO₃ (10 mL) and compound was extracted with EtOAc (30 mL). Organic extract was washed with brine solution (10 mL), dried over sodium sulfate and evaporated. Crude product was purified by column chromatography using 2-6% MeOH in DCM followed by prep. HPLC (Analytical Conditions:- Column :Inertsil ODS 3V(250mm X 4.6mm X 5mic), Mobile phase (A) : 0.1% ammonium acetate in water, Mobile phase(B) : ACN, Flow rate : 1.0 mL/min, Rt: 14.43) to afford the product as yellow solid (**Compound-45**) (0.015 g, 29% Yield).
¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.36 (d, *J* = 5.2 Hz, 1H), 7.61-7.59 (m, 1H), 7.42-7.38 (m, 2H), 7.12-7.00 (m, 6H), 6.92-6.90 (m, 1H), 6.74 (s, 1H), 5.86 (s, 2H), 5.08-4.90 (m, 2H), 3.84-3.76 (m, 1H), 3.45-3.42 (m, 1H), 3.10-3.05 (m, 1H), 2.84-2.81 (m, 1H), 2.62 (s, 3H), 1.85-1.81 (m, 2H), 1.67-1.59 (m, 2H), 1.32-1.29 (m, 1H). MS (ESI): Mass calcd. for C₂₉H₂₈FN₅S, 497.20; *m/z* found, 498.1 (M+H)⁺.

20 **Compound-46:**

(R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-methyl-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone

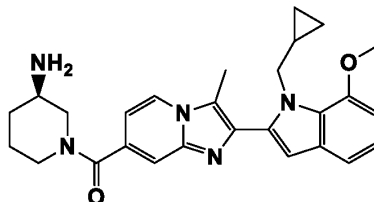


[000216] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.42 (d, *J* = 7.2 Hz, 1H), 7.64 (s, 1H), 7.59 (d, *J* = 8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.20 (t, *J* = 6.4 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 6.8 Hz, 1H), 6.66 (s, 1H), 4.12 (m, 1H), 3.96 (s, 3H),

2.65 (s, 3H), 1.87 (m, 1H), 1.68 (m, 2H), 1.47 (m, 1H), 1.26-1.22 (m, 4H), 0.88-0.84 (m, 2H). MS (ESI): Mass calcd. for C₂₃H₂₅N₅O, 387.20; *m/z* found 388.2 (M+H)⁺.

Compound-47:

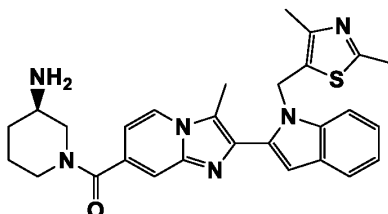
(R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-7-methoxy-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000217] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.41 (d, *J* = 7.2 Hz, 1H), 7.67 (s, 1H), 7.58 (d, *J* = 8 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.08-7.02 (m, 2H), 6.74 (s, 1H), 4.80 (d, *J* = 6.8 Hz, 2H), 4.0 (bs, 2H), 3.95 (s, 3H), 2.98 (m, 3H), 2.61 (s, 3H), 1.89 (m, 2H), 1.71 (m, 1H), 1.48-1.46 (m, 2H), 1.22 (m, 1H), 1.02 (m, 1H), 0.20-0.18 (m, 2H), -0.08 (m, 2H). MS (ESI): Mass calcd. for C₂₇H₃₁N₅O₂, 457.2; *m/z* found, 458.1 (M+H)⁺.

Compound-48:

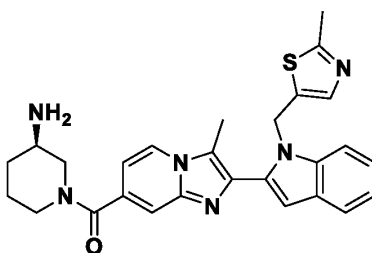
(R)-(3-aminopiperidin-1-yl)(2-(1-((2,4-dimethylthiazol-5-yl)methyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000218] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.43 (d, *J* = 6.8 Hz, 1H), 7.62-7.58 (m, 2H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 6.8 Hz, 1H), 7.07 (t, *J* = 6.8 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.72 (s, 1H), 6.00 (s, 2H), 4.22-4.16 (m, 1H), 3.66-3.61 (m, 1H), 2.99-2.95 (m, 1H), 2.64-2.63 (m, 1H), 2.62 (s, 3H), 2.56 (s, 3H), 2.17 (s, 3H), 2.01-1.95 (m, 1H), 1.84-1.81 (m, 2H), 1.66-1.59 (m, 2H), 1.44-1.42 (m, 1H), 1.22-1.20 (m, 1H). MS (ESI): Mass calcd. for C₂₈H₃₀N₆OS, 498.22; *m/z* found, 499.2 (M+H)⁺.

Compound- 49:

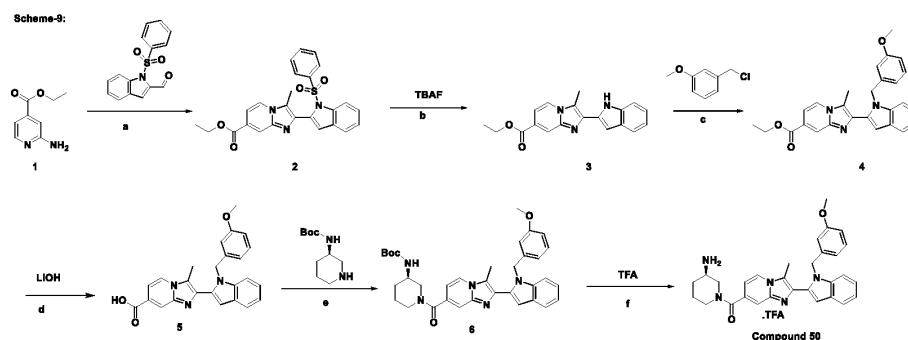
(R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-((2-methylthiazol-5-yl)methyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone



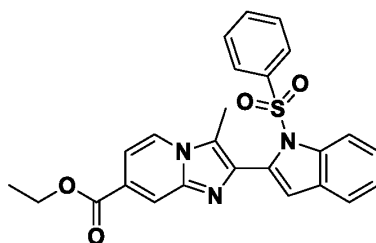
[000219] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.46 (d, J = 7.2 Hz, 1H), 7.67-7.64 (m, 2H), 7.58 (d, J = 7.6 Hz, 1H), 7.51 (s, 1H), 7.17 (t, J = 7.2 Hz, 1H), 7.08-7.02 (m, 2H), 6.74 (s, 1H), 6.07 (s, 2H), 4.66-4.61 (m, 1H), 4.12-4.08 (m, 1H), 3.05-3.01 (m, 1H), 2.94-2.91 (m, 2H), 2.66 (s, 3H), 2.41 (s, 3H), 1.90-1.87 (m, 1H), 1.70-1.67 (m, 1H), 1.49-1.45 (m, 1H), 1.37-1.33 (m, 1H), 1.26-1.21 (m, 2H). MS (ESI): Mass calcd. for $\text{C}_{27}\text{H}_{28}\text{N}_6\text{OS}$, 484.20; m/z found 485.1 ($\text{M}+\text{H}$) $^+$.

Compound- 50:

Synthesis of (R)-(3-aminopiperidin-1-yl) (2-(1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone trifluoroacetic acid salt (Compound-50)



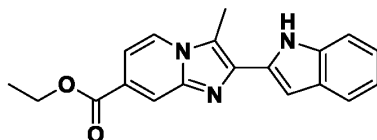
Step-1: Synthesis of ethyl-3-methyl-2-(1-(phenylsulfonyl)-1H-indol-2-yl)imidazo[1,2-a]pyridine-7-carboxylate (2)



[000220] To a stirred solution of ethyl-2-aminoisonicotinate (**1**, 6.0 g, 36.11 mmol) and 1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (11.3 g, 40.44 mmol) in nitro ethane (60 mL), ferric chloride (0.55 g, 3.37 mmol) was added and then reaction

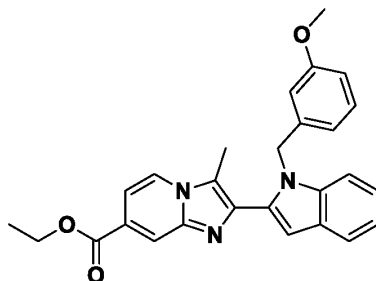
mixture was reflux at 90 °C for 5 h. After completion of reaction, ice cold water was added and the reaction mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the crude. The crude was purified by CombiFlash using 12.0 g RediSep column and 0-30% ethyl acetate in hexane as eluent. The desired fractions were concentrated under reduced pressure to afford ethyl-3-methyl-2-(1-(phenylsulfonyl)-1H-indol-2-yl)imidazo[1,2 a]pyridine-7-carboxylate (**2**) as yellow solid. Yield: 3.4 g (35%). MS (ESI): 459.22; m/z found: 460.39 [M+H]⁺.

Step-2: Synthesis of ethyl-2-(1H-indol-2-yl)-3-methylimidazo[1, 2-a]pyridine-7-carboxylate (3)



[000221] To a stirred solution of ethyl-3-methyl-2-(1-(phenylsulfonyl)-1H-indol-2-yl)imidazo[1,2 a]pyridine-7-carboxylate (**2**, 3.40 g 7.40 mmol) in tetrahydrofuran (10 mL), 1M tetra butyl ammonium fluoride in tetrahydrofuran (30 mL) was added under 0 °C slowly. The reaction mixture was refluxed at 60 °C for about 12 h. After completion of reaction, ice cold water was added and the reaction mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the crude. The crude was purified by CombiFlash using 12.0 g RediSep column and 30% ethyl acetate in hexane as eluent to afford of ethyl-2-(1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate (**3**) as yellow solid. Yield: 2.2 g (93%), MS (ESI): 319.11; m/z found, 320.34 [M+H]⁺.

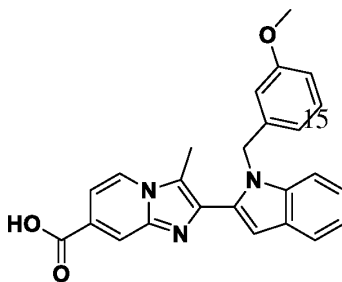
Step-3: Synthesis of ethyl-2-(1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate (4)



[000222] To a stirred solution of ethyl-2-(1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate (**3**, 2.20 g, 6.89 mmol) in *N,N*-dimethylformamide (20 mL),

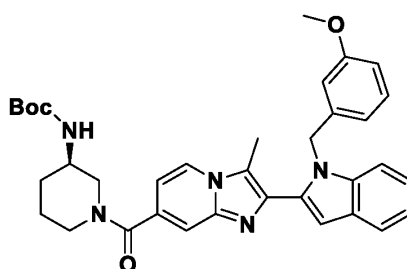
cesium carbonate (6.72 g, 20.68 mmol) was added at rt. 1-(chloromethyl)-3-methoxybenzene (1.20 g, 20.68 mmol) was added and stirred for about 10 min at rt and then resulting mixture was heated to 90 °C for 3 h. After completion of reaction, the reaction mixture was cooled to rt and diluted with ethyl acetate (50 mL × 3). The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude compound. The crude was purified by CombiFlash using 12.0 g RediSep column and 30-50% ethyl acetate in hexane as eluent to afford ethyl-2-(1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate (**4**) as yellow solid. Yield: 1.2 g (40%). MS (ESI): 439.50; m/z found, 440.04 [M+H]⁺.

Step-4: Synthesis of 2-(1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylic acid (5**)**



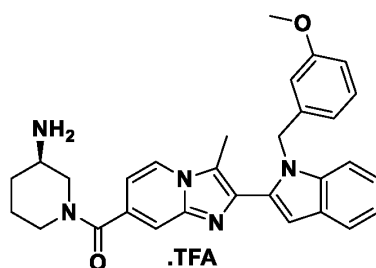
To a stirred solution of ethyl-2-(1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate (1.20 g, 2.73 mmol) in tetrahydrofuran (10 mL) was added methanol (4 mL) and 5N sodium hydroxide solution (4 mL) and the resulting mixture was heated to 60 °C for 3 h. After completion of reaction, the reaction mixture was evaporated under reduced pressure and acidify to pH 2-3 with citric acid at 0 °C. The crude was extracted with dichloromethane (30 mL × 2), washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to 2-(1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylic acid (**5**) as pale yellow color solid. Yield: 0.850 g (78%). MS (ESI): 412; m/z found, 413 [M+H]⁺.

Step-5: Synthesis of tert-butyl (R)-(1-(2-(1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (6**)**



- [000224] To a stirred solution of 2-(1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylic acid (**5**, 0.85 g, 2.06 mmol) in dichloromethane (20 mL), tert-butyl (R)-piperidin-3-ylcarbamate (0.49 g, 2.47 mmol), triethylamine (0.8 mL, 6.18 mmol) and propyl phosphoric anhydride in 50% ethyl acetate (2.1 mL, 6.80 mmol) were added at 0 °C. The reaction mixture was allowed to stir at rt for 1 h. After completion of reaction, the reaction mixture was quenched with sodium bicarbonate solution (20 mL) and extracted with dichloromethane (20 mL × 2). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude product. The crude was purified by CombiFlash using 40.0 g Redisep column and 30-50% ethyl acetate in hexane as eluent to tert-butyl (R)-1-(2-(1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxyl)piperidin-3-ylcarbamate (**6**) as brown solid. Yield: 0.640 g (86%). MS (ESI): 594.30; m/z found, 595.41[M+H]⁺.

Step-6: Synthesis of (R)-(3-aminopiperidin-1-yl)(2-(1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone trifluoroacetic acid salt (Compound 50)



20

- [000225] To the stirred solution of mixture tert-butyl (R)-1-(2-(1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxyl)piperidin-3-ylcarbamate (0.64 g, 1.08 mmol) in dichloromethane (60 mL), trifluoroacetic acid (10 mL) was added at 0 °C. The reaction mixture was stirred at rt for 2h. After

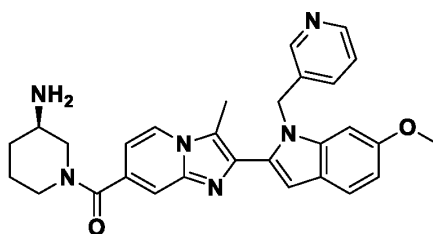
completion of reaction, the reaction mixture was concentrated under reduced pressure to remove trifluoroacetic acid. The crude was dissolved in minimum volume of water and basified by saturated sodium bicarbonate solution (20 mL) and was extracted with dichloromethane (50 mL $\times$ 2). The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated to get crude product. The crude was purified by reverse prep HPLC to afford (R)-(3-aminopiperidin-1-yl)(2-(1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone trifluoroacetate as off yellow solid. Yield: 0.49 g (93%).

[000226] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.49 (d, J = 7.0 Hz, 1H), 7.76 (s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 8.04 Hz, 1H), 7.15-7.07 (m, 4H), 6.80 (s, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.53 (s, 2H), 5.83 (s, 2H), 4.11 (bs, 2H), 3.57 (s, 3H), 3.27 (bs, 3H), 2.65 (s, 3H), 1.98 (m, 1H), 1.73 (m, 1H), 1.58 (m, 2H). MS (ESI): Mass calcd. for $\text{C}_{30}\text{H}_{31}\text{N}_5\text{O}_2$, 494.11; m/z found, 495.07 $[\text{M}+\text{H}]^+$.

[000227] Following compounds were synthesized using the above procedure as exemplified for **Compound-50**.

Compound- 51:

(R)-(3-aminopiperidin-1-yl) (2-(6-methoxy-1-(pyridin-3-ylmethyl)-1H-indol-2-yl)-3-methylimidazo [1,2-a]pyridin-7-yl)methanone

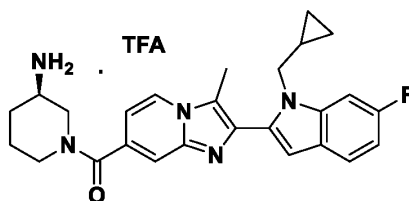


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[000228] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.41 (d, J = 7.08 Hz, 1H), 8.33 (d, J = 4.52 Hz, 1H), 8.26 (s, 1H), 7.59 (s, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.36 (d, J = 7.81 Hz, 1H), 7.22-7.19 (m, 1H), 7.03 (s, 1H), 6.98 (d, J = 7.08 Hz, 1H), 6.74 (d, J = 8.01 Hz, 1H), 6.70 (s, 1H), 5.92 (bs, 2H), 4.27-4.10 (m, 1H), 3.75 (s, 3H), 3.56 (bs, 1H), 2.98-2.95 (m, 2H), 2.66 (m, 1H), 2.62 (s, 3H), 1.85-1.82 (m, 1H), 1.71-1.67 (m, 3H), 1.44-1.42 (m, 1H), 1.27-1.23 (m, 1H). MS (ESI): Mass calcd. for $\text{C}_{29}\text{H}_{30}\text{N}_6\text{O}_2$, 494.43; m/z found, 495.07 $[\text{M}+\text{H}]^+$.

Compound- 52:

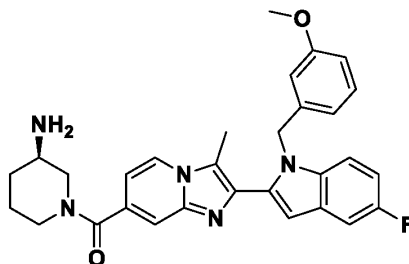
(R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-fluoro-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone trifluoroacetic acid salt



- 5 **[000229]** ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.51(d, J = 7.08 Hz, 1H), 7.95 (s, 1H), 7.76 (s, 1H), 7.62-7.58 (m, 1H), 7.49 (d, J = 10.3 Hz, 1H), 7.10 (d, J = 6.56 Hz, 1H), 6.94 (t, J = 8.04 Hz, 1H), 6.70 (s, 1H), 4.45(d, J = 6.64 Hz, 2H), 3.29 (s, 4H), 2.64 (s, 3H), 2.01 (s, 1H), 1.75 (s, 1H), 1.60 (s, 2H), 1.06 (s, 1H), 0.28(d, J = 7.48 Hz, 2H), 0.15 (d, J = 3.88 Hz, 2H). MS (ESI): Mass calcd. for $\text{C}_{26}\text{H}_{28}\text{FN}_5\text{O}$, 445; m/z found, 446.45[M+H] $^+$.

Compound-53:

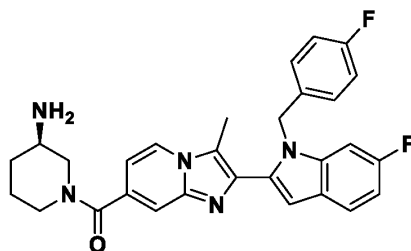
(R)-(3-aminopiperidin-1-yl)(2-(5-fluoro-1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



- 15 **[000230]** ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.42 (d, J = 6.9 Hz, 1H), 7.62 (s, 1H), 7.43-7.36 (m, 2H), 7.08 (t, J = 7.3 Hz, 1H), 7.01-6.94 (m, 2H), 6.76 (s, 1H), 6.67 (d, J = 6.9 Hz, 1H), 6.53-6.51 (m, 2H), 5.87 (s, 2H), 4.30-4.08 (m, 1H), 3.57 (s, 4H), 2.98 (s, 1H), 2.80 (s, 1H), 2.64 (s, 5H), 2.01 (bs, 1H), 1.85-1.83 (m, 1H), 1.68 (m, 1H), 1.45-1.42 (m, 1H), 1.26-1.23 (s, 1H). MS (ESI): Mass calcd. for $\text{C}_{30}\text{H}_{30}\text{FN}_5\text{O}_2$, 511.51; m/z found 512.67 [M+1] $^{+1}$.

Compound- 54:

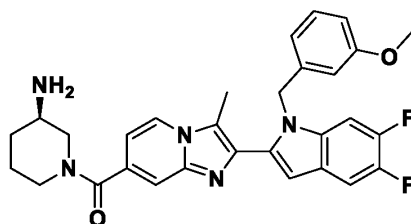
(R)-(3-aminopiperidin-1-yl)(2-(6-fluoro-1-(4-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000231] ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.42 (d, *J* = 6.96 Hz, 1H), 7.63-7.60 (m, 2H), 7.31 (d, *J* = 10.04 Hz, 1H), 7.03-6.99 (m, 5H), 6.93 (t, *J* = 8.6 Hz, 1H), 6.78 (s, 1H), 5.86 (s, 2H), 4.25-4.10 (m, 1H), 3.56 (m, 1H), 2.98 (bs, 1H), 2.82 (m, 1H), 2.62 (m, 5H), 1.85-1.82 (m, 1H), 1.69 (bs, 2H), 1.45-1.42 (m, 1H), 1.24-1.22 (m, 1H). MS (ESI): Mass calcd. for C₂₉H₂₇F₂N₅O, 499.22; *m/z* found, 500.37 [M+H]⁺.

Compound-55:

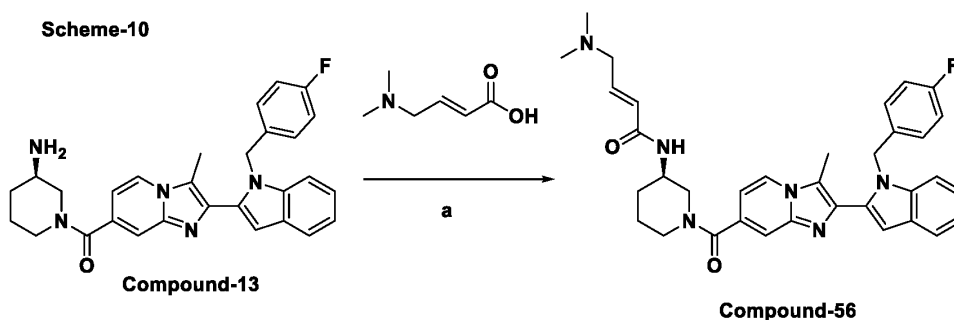
(R)-(3-aminopiperidin-1-yl)(2-(5,6-difluoro-1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000232] ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.42 (d, *J* = 6.84 Hz, 1H), 7.63-7.54 (m, 2H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 6.76 Hz, 1H), 6.77 (s, 1H), 6.69 (d, *J* = 7.56 Hz, 2H), 6.50 (m, 2H), 5.86 (s, 2H), 4.24-4.01 (bs, 2H), 3.56 (s, 3H), 2.97 (bs, 2H), 2.62 (m, 4H), 1.82 (m, 1H), 1.69 (m, 2H), 1.43 (d, *J* = 9.08 Hz, 1H), 1.23-1.09 (m, 2H). MS (ESI): Mass calcd. for C₃₀H₂₉F₂N₅O₂, 529.59; *m/z* found, 530.29 [M+H]⁺.

Compound-56:

Synthesis of (R,E)-4-(dimethylamino)-N-(1-(2-(1-(4-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)but-2-enamide



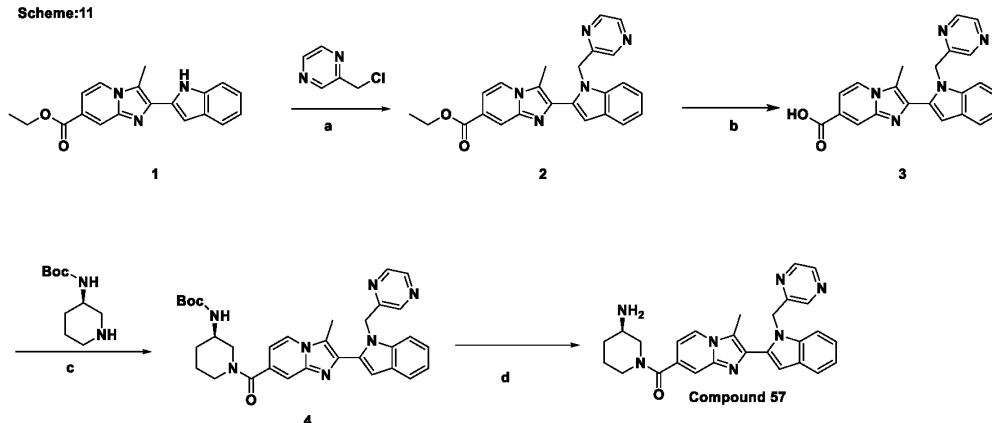
[000233] To a stirred solution of (E)-4-(dimethylamino)but-2-enoic acid (0.103 g, 0.623 mmol) in dichloromethane (10 mL), (R)-(3-aminopiperidin-1-yl)(2-(1-(4-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone (0.200 g, 0.415 mmol), triethylamine (0.18 mL, 1.28 mmol), propyl phosphonic anhydride in 50% ethyl acetate (0.85 mL, 1.33 mmol) were added at 0 °C. The reaction mixture was allowed to stir at rt for 2 h. After completion of reaction, the reaction mixture was quenched with sodium bicarbonate solution (20 mL) and extracted with dichloromethane (50 mL x 2). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude product. The crude product was purified by prep HPLC to afford (R,E)-4-(dimethylamino)-N-(1-(2-(1-(4-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)but-2-enamide as off-white solid. Yield: 0.12 g (49%).

[000234] ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.40 (s, 1H), 8.01 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.14-7.11 (m, 1H), 7.06-6.99 (m, 6H), 6.76 (s, 1H), 6.55-6.43 (m, 1H), 6.06 (d, *J* = 14.2 Hz, 1H), 5.88 (s, 2H), 4.13-3.68 (m, 3H), 3.11-2.94 (m, 4H), 2.63 (s, 3H), 2.11 (s, 6H), 1.87 (d, *J* = 9.2 Hz, 1H), 1.79 (m, 1H), 1.53-1.51 (m, 2H). MS (ESI): Mass calcd. for C₃₅H₃₇FN₆O₂, 592.30; *m/z* found 593.4 [M+H]⁺.

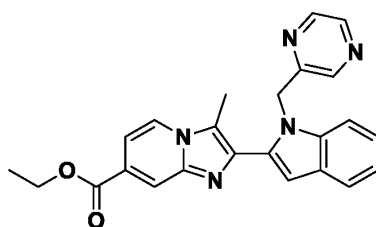
Compound-57:

Synthesis of (R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-(pyrazin-2-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone (Compound-57)

Scheme:11



Step-1: ethyl-3-methyl-2-(1-(pyrazin-2-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridine-7-carboxylate (2)

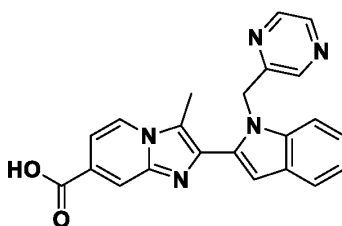


5

[000235] To a stirred solution of ethyl-2-(1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carboxylate (**1**, 0.3 g, 0.94 mmol) in *N,N*-dimethylformamide (10 mL), was added cesium carbonate (1.5 g, 4.7 mmol) and 2-(chloromethyl)pyrazine (0.15 g, 1.13 mmol), and stirred at 60 °C for 3 h. After completion of reaction, the reaction mixture was cooled to rt and diluted with ethyl acetate (10 mL × 3). The organic phase was washed with water, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude compound. The crude was purified by using CombiFlash, 12 g RediSep and 50-70% ethyl acetate in hexane as eluent to afford ethyl 3-methyl-2-(1-(pyrazin-2-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridine-7-carboxylate (**2**) as light brown solid. Yield: 0.108 g (28%). MS (ESI): 411.17; *m/z* found, 412.21.

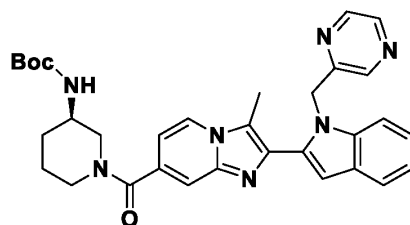
Step-2: Synthesis of 3-methyl-2-(1-(pyrazin-2-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridine-7-carboxylic acid (3)

20



[000236] To a stirred solution of ethyl 3-methyl-2-(1-(pyrazin-2-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridine-7-carboxylate (**2**, 0.108 g, 0.267 mmol) in tetrahydrofuran (4 mL), was added methanol (2 mL) and 5N sodium hydroxide solution in water (2 mL) and the resulting mixture was heated to 60 °C for 1 h. After completion of reaction, the reaction mixture was evaporated under reduced pressure and acidified to pH 2-3 with citric acid at 0 °C. The crude was extracted with dichloromethane (50 mL × 2), washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 3-methyl-2-(1-(pyrazin-2-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridine-7-carboxylic acid (**3**) as off white solid. Yield: 0.10 g, 99%. MS (ESI): 383.14; m/z found, 382.11 [M-H]⁻¹.

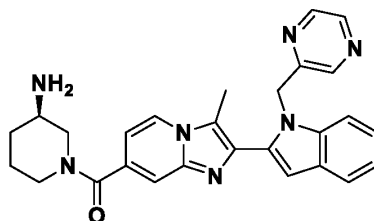
Step-3: Synthesis of tert-butyl (R)-(1-(3-methyl-2-(1-(pyrazin-2-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (4)



[000237] To a stirred solution of 3-methyl-2-(1-(pyrazin-2-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridine-7-carboxylic acid (**3**, 0.10 g, 0.261 mmol) in dichloromethane (10 mL), tert-butyl (R)-piperidin-3-ylcarbamate (0.06 g, 0.313 mmol), triethylamine (0.11 mL, 0.80 mmol), propyl phosphonic anhydride in 50% ethyl acetate (0.50 mL, 0.83 mmol) were added at 0 °C. The reaction mixture was allowed to stir at rt for 3 h. After completion of reaction, the reaction mixture was quenched with sodium bicarbonate solution (20 mL) and extracted with dichloromethane (5 mL × 2). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude product. The crude was

purified by using CombiFlash, 4.0 g RediSep and 1-5% methanol in dichloromethane as eluent to afford tert-butyl (R)-(1-(3-methyl-2-(1-(pyrazin-2-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (**4**) as off white solid. Yield: 0.07 g, 47%. MS (ESI): 565.28; m/z found, 566.18 [M+H]⁺.

5 **Step-4: Synthesis of (R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-(pyrazin-2-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanon (Compound 57).**



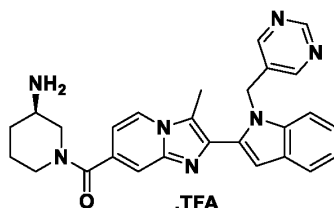
[000238] To the stirred solution of mixture tert-butyl (R)-(1-(3-methyl-2-(1-(pyrazin-2-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (**4**, 0.07 g, 0.123 mmol) in dichloromethane (2.0 mL), trifluoroacetic acid (0.5 mL) was added at 0 °C. The reaction mixture was stirred at rt for 3 h. After completion of reaction, the reaction mixture was concentrated under reduced pressure to remove trifluoroacetic acid. The crude was dissolved in minimum volume of water and basified by saturated sodium bicarbonate solution (20 mL) and was extracted with dichloromethane (10 mL × 2). The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated to afford (R)-(3-aminopiperidin-1-yl)(3-methyl-2-(1-(pyrazin-2-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone as white solid. Yield: 0.05 g (87%).

[000239] ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.49 (s, 1H), 8.43-8.40 (m, 2H), 8.15 (s, 1H), 7.64 (d, *J* = 7.56 Hz, 1H), 7.57 (s, 1H), 7.47 (d, *J* = 8.12 Hz, 1H), 7.16-7.07 (m, 2H), 6.99 (d, *J* = 7.04 Hz, 1H), 6.82 (s, 1H), 6.05 (s, 2H), 4.26-4.09 (m, 2H), 3.59-3.51 (m, 2H), 3.00 (bs, 2H), 2.64 (s, 3H), 1.85 (bs, 1H), 1.68 (bs, 1H), 1.46-1.43 (m, 1H), 1.35-1.23 (m, 2H). MS (ESI): Mass calcd. for C₂₇H₂₇N₇O, 465.23; m/z found, 466.17[M+H]⁺.

25 [000240] Following compounds were synthesized using the above procedure as exemplified for **Compound-57**.

Compound-58:

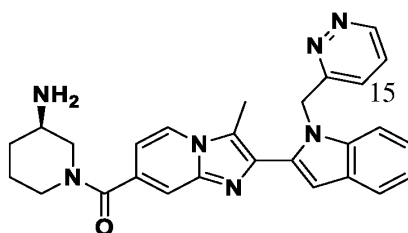
(R)-(3-aminopiperidin-1-yl) (3-methyl-2-(1-(pyrimidin-5-ylmethyl)-1H-indol-2-yl)imidazo [1,2-a]pyridin-7-yl)methanone trifluoroacetic acid salt



[000241] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.99 (s, 1H), 8.54 (s, 2H), 8.48 (d, $J = 6.5$ Hz, 1H), 7.70 (s, 1H), 7.65 (d, $J = 7.6$ Hz, 1H), 7.55 (d, $J = 8.0$ Hz, 1H), 7.20-7.16 (m, 1H), 7.13-7.09 (m, 1H), 7.05 (d, $J = 11.4$ Hz, 1H), 6.84 (s, 1H), 5.93 (s, 2H), 4.09 (s, 2H), 3.29 (m, 3H), 2.67 (s, 3H), 1.99 (s, 2H), 1.74 (s, 1H), 1.58 (m, 2H), 1.23 (s, 1H). MS (ESI): Mass calcd. for $\text{C}_{27}\text{H}_{27}\text{N}_7\text{O}$, 465.11; m/z found, 466.07 $[\text{M}+\text{H}]^+$.

10 Compound-59:

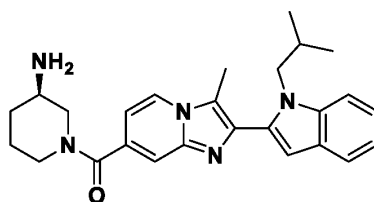
(R)-(3-aminopiperidin-1-yl) (3-methyl-2-(1-(pyridazin-3-ylmethyl)-1H-indol-2-yl)imidazo[1,2-a]pyridin-7-yl)methanone



20 [000242] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 9.06 (d, $J = 4.76$ Hz, 1H), 8.43 (d, $J = 7.0$ Hz, 1H), 7.64 (d, $J = 7.25$ Hz, 1H), 7.57 (s, 1H), 7.55-7.51 (m, 1H), 7.43 (d, $J = 7.68$ Hz, 1H), 7.18 (d, $J = 7.31$ Hz, 1H), 7.13-7.07 (m, 2H), 7.00 (d, $J = 6.96$ Hz, 1H), 6.83 (s, 1H), 6.17 (s, 2H), 4.25-4.08 (s, 1H), 3.54 (bs, 1H), 2.96 (bs, 1H), 2.66 (s, 3H), 1.88-1.83 (m, 4H), 1.70 (m, 2H), 1.44-1.41 (m, 1H), 1.28-1.23 (m, 1H). MS (ESI):
25 Mass calcd. for $\text{C}_{27}\text{H}_{27}\text{N}_7\text{O}$, 465.34; m/z found, 466.67 $[\text{M}+\text{H}]^+$.

Compound-60:

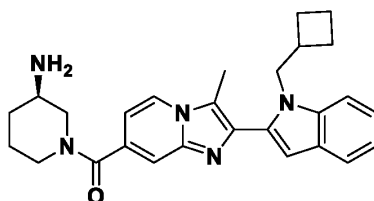
(R)-(3-aminopiperidin-1-yl)(2-(1-isobutyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000243] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.45 (d, $J = 2.9$ Hz, 1H), 7.71 (s, 1H), 7.59 (d, $J = 7.8$ Hz, 1H), 7.54 (d, $J = 8.2$ Hz, 1H), 7.17 (t, $J = 7.2$ Hz, 1H), 7.07-7.02 (m, 2H), 6.65 (s, 1H), 4.45 (d, $J = 7.0$ Hz, 2H), 4.18 (m, 2H), 3.12 (bs, 2H), 2.63 (s, 3H), 1.98-1.95 (m, 2H), 1.73 (m, 1H), 1.53 (m, 2H), 1.23 (s, 2H), 0.84 (m, 1H), 0.64 (d, $J = 6.4$ Hz, 6H). MS (ESI): Mass calcd. for $\text{C}_{26}\text{H}_{31}\text{N}_5\text{O}$, 429.31; m/z found, 430.24 $[\text{M}+\text{H}]^+$.

Compound- 61:

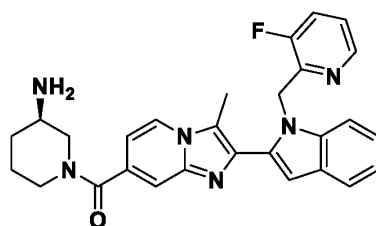
10 **(R)-(3-aminopiperidin-1-yl)(2-(1-(cyclobutylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone**



[000244] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.43 (d, $J = 6.92$ Hz, 1H), 7.65 (s, 1H), 7.57 (t, $J = 7.56$ Hz, 2H), 7.17 (t, $J = 7.20$ Hz, 1H), 7.07-7.00 (m, 2H), 6.63 (s, 1H), 4.67 (d, $J = 6.76$ Hz, 2H), 4.30-4.14 (m, 1H), 3.63 (bs, 1H), 3.01 (bs, 2H), 2.72 (m, 1H), 2.63 (s, 3H), 2.59-2.55 (m, 1H), 1.87 (d, $J = 9.8$ Hz, 1H), 1.70-1.62 (m, 6H), 1.53-1.48 (m, 4H), 1.35-1.23 (m, 1H). MS (ESI): Mass calcd. for $\text{C}_{27}\text{H}_{31}\text{N}_5\text{O}$, 441.25; m/z found, 442.27 $[\text{M}+\text{H}]^{+1}$.

20 **Compound-62:**

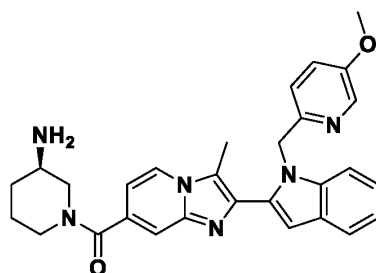
(R)-(3-aminopiperidin-1-yl)(2-(1-((3-fluoropyridin-2-yl)methyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



- [000245]** ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.39 (d, $J = 6.92$ Hz, 1H), 8.14 (d, $J = 4.44$ Hz, 1H), 7.61-7.54 (m, 3H), 7.44 (d, $J = 8.08$ Hz, 1H), 7.27-7.23 (m, 1H), 7.13-7.09 (m, 1H), 7.07-7.03 (m, 1H), 6.97 (d, $J = 6.04$ Hz, 1H), 6.73 (s, 1H), 6.09 (s, 2H), 4.25-4.07 (m, 1H), 3.57 (bs, 1H), 2.98 (m, 2H), 2.66 (m, 1H), 2.61 (s, 3H), 1.85 (d, $J = 9.68$ Hz, 1H), 1.69-1.58 (m, 2H), 1.45-1.42 (m, 1H), 1.23 (m, 2H). MS (ESI): Mass calcd. for $\text{C}_{27}\text{H}_{31}\text{N}_5\text{O}$, 482.22; m/z found, 483.30 $[\text{M}+\text{H}]^+$.

Compound- 63:

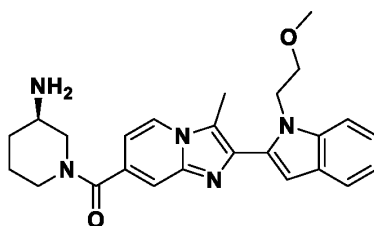
- (R)-(3-aminopiperidin-1-yl)(2-(1-((5-methoxypyridin-2-yl)methyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone**



- [000246]** ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.42 (d, $J = 6.96$ Hz, 1H), 8.13 (d, $J = 2.72$ Hz, 1H), 7.63-7.60 (m, 1H), 7.38 (d, $J = 7.96$ Hz, 1H), 7.19-7.16 (dd, $J = 2.8$ Hz, 8.6 Hz, 1H), 7.13-7.04 (m, 2H), 7.00 (d, $J = 6.24$ Hz, 1H), 6.77 (s, 1H), 6.70 (d, $J = 8.64$ Hz, 2H), 5.90 (s, 2H), 4.26-4.01 (s, 2H), 3.71 (s, 3H), 3.58 (m, 1H), 2.96 (bs, 2H), 2.65 (s, 3H), 1.85-1.69 (m, 4H), 1.45-1.42 (m, 1H), 1.26-1.23 (m, 1H). MS (ESI): Mass calcd. for $\text{C}_{29}\text{H}_{30}\text{N}_6\text{O}_2$, 494.23; m/z found, 495.29 $[\text{M}+\text{H}]^+$.

Compound-64:

(R)-(3-aminopiperidin-1-yl) (2-(1-(2-methoxyethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone

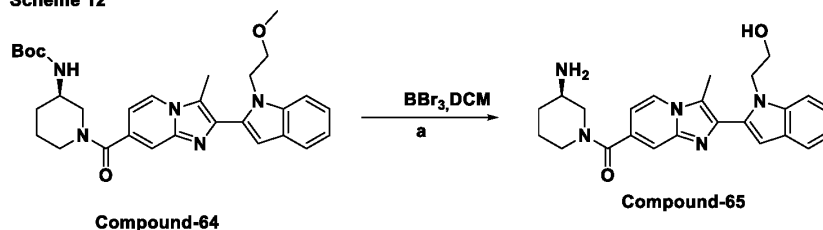


[000247] ^1H NMR(400 MHz, DMSO- d_6) δ (ppm): 8.43 (d, $J = 7.0$ Hz, 1H), 7.62 (s, 1H), 7.60-7.54 (m, 2H), 7.18 (t, $J = 7.6$ Hz, 1H), 7.06 (t, $J = 7.4$ Hz, 1H), 7.00 (d, $J = 6.8$ Hz, 1H), 6.67 (s, 1H), 4.72 (t, $J = 5.6$ Hz, 2H), 4.28-4.12 (m, 1H), 3.58 (t, $J = 5.8$ Hz, 2H), 3.07 (s, 3H), 2.98-2.74 (m, 2H), 2.64 (s, 5H), 1.86-1.84 (m, 1H), 1.72 (m, 2H), 1.47-1.44 (m, 1H), 1.29-1.24 (m, 1H). MS (ESI): Mass calcd. for $\text{C}_{25}\text{H}_{29}\text{N}_5\text{O}_2$, 431.23; m/z found, 432.27 $[\text{M}+\text{H}]^+$.

Compound-65:

10 Synthesis of (R)-(3-aminopiperidin-1-yl)(2-(1-(2-hydroxyethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone

Scheme 12



15 [000248] To the stirred solution of tert-butyl (R)-(1-(2-(1-(2-methoxyethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (4, 0.20 g, 0.30 mmol) in dichloromethane (4 mL), boron tribromide (1M solution in dichloromethane) (5 mL) was added at 0 °C. The reaction mixture was stirred at rt for 3 h. After completion of reaction, the reaction mixture was concentrated under reduced pressure to remove boron tribromide. The crude product was dissolved in minimum volume of water and basified by saturated sodium bicarbonate solution (20 mL) and was extracted with dichloromethane (20 mL $\times$ 2). The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated to get crude product. The crude product was purified by prep HPLC to afford (R)-(3-aminopiperidin-1-yl)(2-(1-

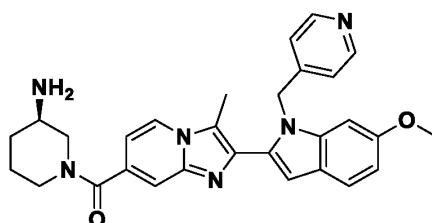
20

(2-hydroxyethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone as off-white solid.

[000249] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.45 (d, J = 6.8 Hz, 1H), 7.64 (s, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.55 (d, J = 6.9 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 7.08 (d, J = 7.44 Hz, 1H), 7.05-7.02 (m, 1H), 6.66 (s, 1H), 5.24 (bs, 1H), 4.56 (t, J = 5.80 Hz, 2H), 4.25-4.06 (m, 1H), 3.69 (t, J = 5.8 Hz, 2H), 3.07 (bs, 1H), 2.80 (bs, 2H), 2.64 (s, 3H), 1.87 (s, 4H), 1.75-1.72 (m, 1H), 1.49 (m, 1H), 1.32 (m, 1H). MS (ESI): Mass calcd. for $\text{C}_{24}\text{H}_{27}\text{N}_5\text{O}_2$, 417.22; m/z found, 418.39 $[\text{M}+\text{H}]^+$.

Compound-66:

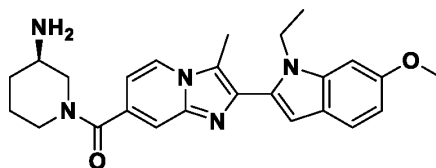
10 **(R)-(3-aminopiperidin-1-yl)(2-(6-methoxy-1-(pyridin-4-ylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone**



[000250] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.35 (s, 2H), 7.55 (s, 2H), 6.90 (s, 4H), 6.74 (s, 3H), 5.94 (s, 2H), 4.21-4.05 (m, 1H), 3.72 (s, 3H), 2.97 (bs, 2H), 2.63-2.49 (m, 4H), 1.84 (m, 2H), 1.69 (m, 2H), 1.44 (bs, 1H), 1.24 (m, 2H). MS (ESI): Mass calcd. for $\text{C}_{29}\text{H}_{30}\text{N}_6\text{O}_2$, 494.22; m/z found, 495.07 $[\text{M}+\text{H}]^+$.

Compound-67:

20 **(R)-(3-aminopiperidin-1-yl)(2-(1-ethyl-6-methoxy-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone**

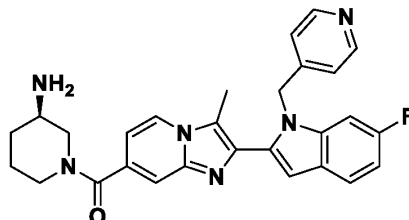


[000251] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.41 (d, J = 6.96 Hz, 1H), 7.61 (s, 1H), 7.46 (d, J = 8.56 Hz, 1H), 7.04 (s, 1H), 6.99 (d, J = 6.56 Hz, 1H), 6.72 (d, J = 8.56 Hz, 1H), 6.56 (s, 1H), 4.54 (d, J = 7.0 Hz, 2H), 4.28-4.08 (m, 2H), 3.83 (s, 3H), 3.63 (m, 1H), 3.00 (bs, 2H), 2.67 (m, 1H), 2.62 (s, 3H), 1.85 (d, J = 9.80 Hz, 1H), 1.71

(bs, 2H), 1.45 (d, $J = 10.08$ Hz, 2H), 1.23-1.20 (t, $J = 6.8$ Hz, 3H). MS (ESI): Mass calcd. for $C_{25}H_{29}N_5O_2$, 431.23; m/z found, 432.32 $[M+H]^+$.

Compound-68:

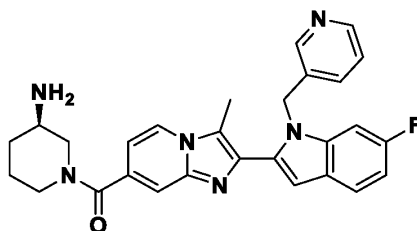
(R)-(3-aminopiperidin-1-yl)(2-(6-fluoro-1-(pyridin-4-ylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000252] ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.36 (s, 3H), 7.65 (s, 1H), 7.56 (s, 1H), 7.28 (d, $J = 8.4$ Hz, 1H), 6.97-6.84 (m, 5H), 5.95 (s, 2H), 4.21-4.10 (m, 2H), 3.50 (m, 1H), 2.97 (bs, 2H), 2.64 (s, 3H), 1.83 (m, 2H), 1.67 (m, 2H), 1.23 (s, 2H). MS (ESI): Mass calcd. for $C_{28}H_{27}FN_6O$, 482; m/z found, 483.33 $[M+H]^+$.

Compound-69:

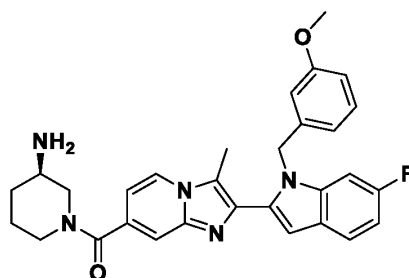
(R)-(3-aminopiperidin-1-yl)(2-(6-fluoro-1-(pyridin-3-ylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000253] ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.43 (d, $J = 7.0$ Hz, 1H), 8.34 (d, $J = 3.8$ Hz, 1H), 8.27 (s, 1H), 7.63 (t, $J = 6.2$ Hz, 2H), 7.39-7.36 (m, 2H), 7.23-7.19 (m, 1H), 7.02 (d, $J = 7.0$ Hz, 1H), 6.94 (t, $J = 6.3$ Hz, 1H), 6.81 (s, 1H), 5.92 (s, 2H), 4.08 (bs, 2H), 3.5 (bs, 1H), 3.02 (bs, 1H), 2.85 (bs, 2H), 2.63 (s, 3H), 1.88-1.87 (m, 1H), 1.69 (bs, 1H), 1.48-1.45 (m, 1H), 1.35-1.33 (m, 1H), 1.22 (s, 1H). MS (ESI): Mass calcd. for $C_{28}H_{27}FN_6O$, 482.22; m/z found, 483.14 $[M+H]^+$.

Compound-70:

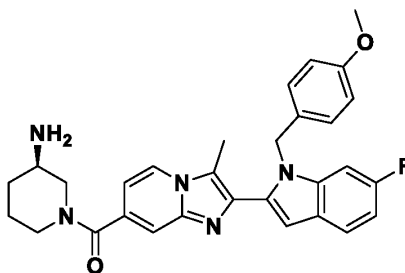
(R)-(3-aminopiperidin-1-yl)(2-(6-fluoro-1-(3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000254] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.42 (d, J = 7.96 Hz, 1H), 7.63-7.60 (m, 2H), 7.29 (d, J = 9.36 Hz, 1H), 7.08 (t, J = 8.12 Hz, 1H), 6.99 (d, J = 6.4 Hz, 1H), 6.92 (t, J = 8.3 Hz, 1H), 6.78 (s, 1H), 6.69 (d, J = 7.04 Hz, 1H), 6.53 (s, 2H),
 5 5.85 (s, 2H), 4.26-4.08 (m, 1H), 3.56 (s, 4H), 2.98 (m, 1H), 2.62 (s, 3H), 1.84-1.83 (m, 2H), 1.71-1.70 (m, 2H), 1.46-1.42 (m, 1H), 1.23 (s, 3H). MS (ESI): Mass calcd. for $\text{C}_{30}\text{H}_{30}\text{FN}_5\text{O}_2$, 511.24; m/z found, 512.38 $[\text{M}+\text{H}]^+$.

Compound-71:

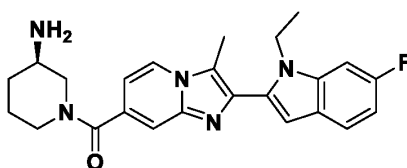
(R)-(3-aminopiperidin-1-yl)(2-(6-fluoro-1-(4-methoxybenzyl)-1H-indol-2-yl)-3-
 10 methylimidazo[1,2-a]pyridin-7-yl)methanone



[000255] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.43 (d, J = 6.96 Hz, 1H), 7.62-7.58 (m, 2H), 7.29 (d, J = 10.24 Hz, 1H), 7.00 (d, J = 6.72 Hz, 1H), 6.94-6.88 (m, 3H), 6.75-6.72 (m, 3H), 5.79 (s, 2H), 4.27-4.08 (m, 1H), 3.62 (s, 3H), 2.98 (bs, 2H),
 15 2.63 (m, 5H), 1.85-1.73 (m, 4H), 1.45-1.42 (m, 1H), 1.25-1.22 (m, 1H). MS (ESI): Mass calcd. for $\text{C}_{30}\text{H}_{30}\text{FN}_5\text{O}_2$, 511.24; m/z found, 512.25 $[\text{M}+\text{H}]^+$.

Compound-72:

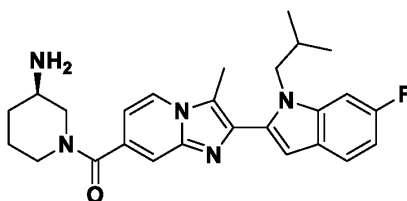
(R)-(3-aminopiperidin-1-yl)(2-(1-ethyl-6-fluoro-1H-indol-2-yl)-3-
 20 methylimidazo[1,2-a]pyridin-7-yl)methanone



[000256] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.43 (d, J = 6.96 Hz, 1H), 7.62-7.57 (m, 2H), 7.42 (d, J = 9.2 Hz, 1H), 7.00 (d, J = 6.52 Hz, 1H), 6.92 (t, J = 8.24 Hz, 1H), 6.66 (s, 1H), 4.54 (d, J = 7.04 Hz, 2H), 4.28-4.03 (m, 2H), 3.60 (bs, 1H), 3.00 (bs, 2H), 2.80 (m, 1H), 2.63 (s, 3H), 1.86-1.83 (m, 1H), 1.68-1.56 (m, 2H), 1.46-1.44 (m, 1H), 1.23-1.19 (s, 4H). MS (ESI): Mass calcd. for $\text{C}_{24}\text{H}_{26}\text{FN}_5\text{O}$, 419.21; m/z found, 420.31 $[\text{M}+\text{H}]^+$.

Compound- 73:

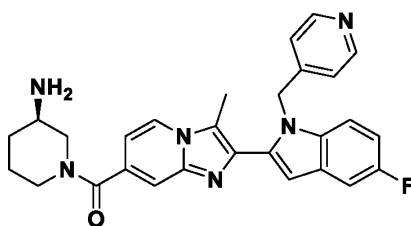
10 **(R)-(3-aminopiperidin-1-yl)(2-(6-fluoro-1-isobutyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone**



[000257] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.42 (d, J = 7.0 Hz, 1H), 7.63 (s, 1H), 7.60-7.56 (m, 1H), 7.43 (d, J = 9.44 Hz, 1H), 7.00 (d, J = 6.16 Hz, 1H), 6.91 (t, J = 7.6 Hz, 1H), 6.66 (s, 1H), 4.41 (d, J = 7.28 Hz, 2H), 4.27-4.11 (m, 1H), 3.00 (bs, 2H), 2.83-2.66 (m, 2H), 2.62 (s, 3H), 1.93-1.92 (m, 1H), 1.88 (s, 2H), 1.75-1.72 (m, 2H), 1.47-1.45 (m, 1H), 1.28-1.25 (m, 1H), 0.64 (d, J = 6.64 Hz, 6H). MS (ESI): Mass calcd. for $\text{C}_{26}\text{H}_{30}\text{FN}_5\text{O}$, 447.24; m/z found, 448.45 $[\text{M}+\text{H}]^+$.

20 **Compound-74:**

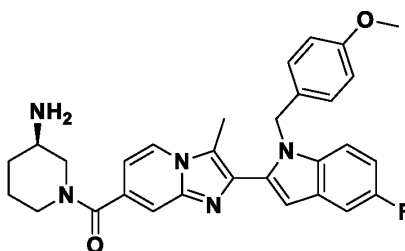
(R)-(3-aminopiperidin-1-yl)(2-(5-fluoro-1-(pyridin-4-ylmethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000258] ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.42 (d, *J* = 6.9 Hz, 1H), 8.37 (d, *J* = 4.8 Hz, 2H), 7.57 (s, 1H), 7.36-7.42 (m, 2H), 6.99-6.96 (m, 2H), 6.91 (d, *J* = 4.7 Hz, 2H), 6.82 (s, 1H), 5.97 (s, 2H), 4.24-4.08 (m, 1H), 3.50 (m, 1H), 3.38 (m, 1H), 2.96 (bs, 1H), 2.65 (s, 3H), 1.82 (m, 2H), 1.71 (m, 1H), 1.60 (m, 1H), 1.41 (m, 1H), 1.23 (m, 2H). MS (ESI): Mass calcd. for C₂₈H₂₇FN₆O, 482.21; m/z found, 483.21[M+H]⁺.

Compound-75:

(R)-(3-aminopiperidin-1-yl)(2-(5-fluoro-1-(4-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



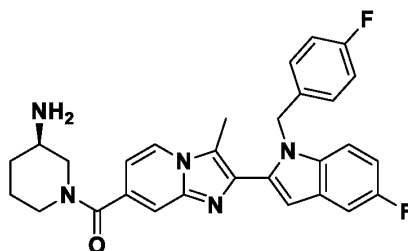
10

[000259] ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.44 (d, *J* = 6.96 Hz, 1H), 7.63 (s, 1H), 7.44-7.41 (m, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.01-6.91 (m, 4H), 6.74-6.72 (m, 3H), 5.82 (s, 2H), 4.27-4.10 (m, 1H), 3.62 (s, 3H), 2.97 (bs, 2H), 2.79 (m, 2H), 2.64 (s, 3H), 1.83 (m, 1H), 1.70 (m, 2H), 1.45-1.43 (m, 1H), 1.27-1.24 (m, 1H). MS (ESI): Mass calcd. for C₃₀H₃₀FN₅O₂, 511.32; m/z found, 512.32 [M+H]⁺.

15

Compound-76:

(R)-(3-aminopiperidin-1-yl)(2-(5-fluoro-1-(4-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



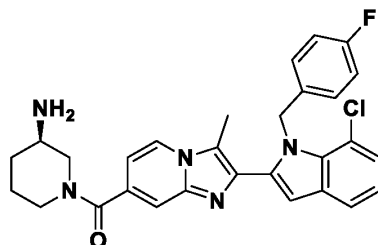
20

[000260] ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.43 (d, *J* = 6.92 Hz, 1H), 7.61 (s, 1H), 7.44-7.37 (m, 2H), 7.03-7.37 (m, 6H), 6.77 (s, 1H), 5.88 (s, 2H), 4.27-4.09 (m, 1H), 3.60 (bs, 1H), 2.98 (bs, 1H), 2.83 (bs, 1H), 2.64 (s, 3H), 1.85-1.83 (m, 1H), 1.69 (bs, 3H), 1.45-1.42 (m, 1H), 1.31-1.20 (m, 2H). MS (ESI): Mass calcd. for C₂₉H₂₇F₂N₅O, 499.22; m/z found, 500.38 [M+H]⁺.

25

Compound-77:

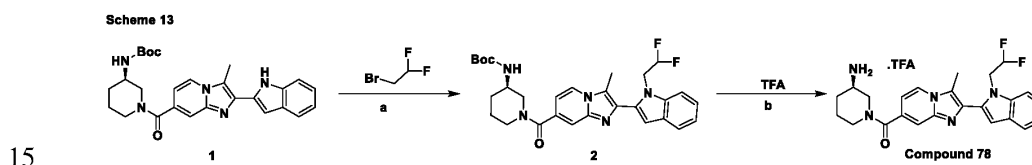
(R)-(3-aminopiperidin-1-yl)(2-(7-chloro-1-(4-fluorobenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



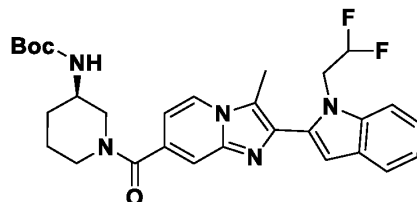
- 5 **[000261]** ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.41 (d, J = 6.96 Hz, 1H), 7.63 (d, J = 7.72 Hz, 1H), 7.61 (s, 1H), 7.16 (d, J = 7.44 Hz, 1H), 7.08 (t, J = 7.68 Hz, 1H), 6.99-6.97 (m, 3H), 6.89 (s, 1H), 6.73-6.70 (m, 2H), 6.15 (s, 2H), 4.26-4.09 (m, 2H), 2.98 (bs, 2H), 2.66 (m, 1H), 2.59 (s, 3H), 1.88 (s, 2H), 1.83 (m, 1H), 1.75-1.65 (m, 1H), 1.45-1.42 (m, 1H), 1.28-1.23 (m, 1H). MS (ESI): Mass calcd. for $\text{C}_{29}\text{H}_{27}\text{ClFN}_5\text{O}$,
10 515.19; m/z found, 516.18 $[\text{M}+\text{H}]^+$.

Compound-78:

Synthesis of (R)-(3-aminopiperidin-1-yl)(2-(1-(2,2-difluoroethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone trifluoroacetic acid salt



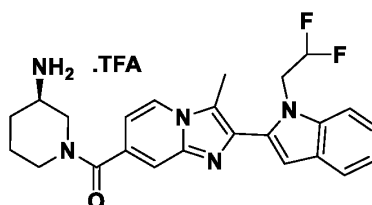
Step-1: Synthesis of *tert*-butyl (R)-(1-(2-(1-(2,2-difluoroethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (2)



- 20 **[000262]** To a stirred solution of *tert*-butyl (R)-(1-(2-(1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (**1**, 0.50 g, 1.05 mmol) in *N,N*-dimethylformamide (5.0 mL), cesium carbonate (1.7 g, 5.28 mmol) and 2-bromo-1,1-difluoroethane (0.22 mL, 2.64 mmol) were added at rt. The reaction

mixture was stirred at 60 °C for 4 h. After completion of reaction, reaction mixture was diluted with water and extracted with ethyl acetate (200 mL × 2). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by CombiFlash using 12.0 g RediSep column and 70% ethyl acetate in hexane as eluent to afford the *tert*-butyl (R)-(1-(2-(1-(2,2-difluoroethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate as brown solid (**2**). Yield: 0.13 g (26%), MS (ESI): 537; *m/z* found 538.32 [M+1]⁺.

Step-2: Synthesis of (R)-(3-aminopiperidin-1-yl)(2-(1-(2,2-difluoroethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone trifluoroacetic acid salt (Compound-78)



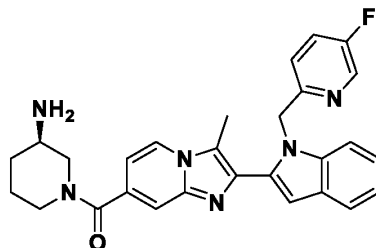
[000263] To a stirred solution of *tert*-butyl (R)-(1-(2-(1-(2,2-difluoroethyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (**2**, 0.13 g, 0.24 mmol) in dichloromethane (2.0 mL), trifluoroacetic acid (1.0 mL) was added at 0 °C. The reaction mixture was stirred at rt for 2 h. After completion of reaction, the reaction mixture was concentrated under reduced pressure to remove trifluoroacetic acid. The crude was dissolved in minimum volume of water and basified by saturated sodium bicarbonate solution and was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated to get the crude. The crude was purified by prep HPLC to afford (R)-(3-aminopiperidin-1-yl) (2-(1-(2,2-difluoroethyl)-1H-indol-2-yl)-3-methylimidazo [1,2-a]pyridin-7-yl)methanone trifluoroacetic acid salt as white solid. Yield: 0.007 g (7%).

[000264] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.50 (d, *J* = 6.9 Hz, 1H), 7.75 (s, 1H), 7.64-7.60 (m, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.14 -7.07 (m, 2H), 6.81 (s, 1H), 6.47 (t, *J* = 55.6 Hz, 1H), 5.05 (t, *J* = 14.4 Hz, 2H), 3.29 (m, 4H), 2.68 (s, 3H), 2.58 (s, 1H), 2.00 (m, 2H), 1.76 (m, 2H), 1.60-1.59 (m, 2H). MS (ESI): Mass calcd. for C₂₄H₂₅F₂N₅O, 437.23; *m/z* found, 438.27 [M+1]⁺.

[000265] Following **compounds 79-82** were synthesized using the above procedure as exemplified for Compound-78.

Compound- 79:

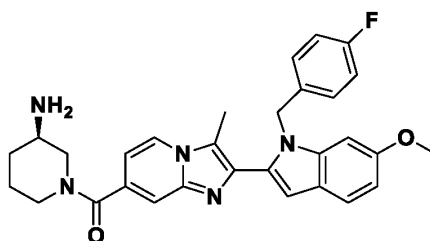
(R)-(3-aminopiperidin-1-yl)(2-(1-((5-fluoropyridin-2-yl)methyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



- 5 [000266] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.44 (s, 1H), 8.42 (s, 1H), 7.62 (t, $J = 7.96$ Hz, 2H), 7.53 (t, $J = 9.00$ Hz, 1H), 7.38 (d, $J = 7.92$ Hz, 1H), 7.14-7.06 (m, 2H), 7.00 (d, $J = 6.96$ Hz, 1H), 6.84-6.80 (m, 2H), 5.97 (s, 2H), 4.14 (s, 2H), 3.65 (bs, 1H), 3.12 (bs, 2H), 2.96 (m, 2H), 2.65 (s, 3H), 1.90-1.87 (m, 1H), 1.69 (bs, 1H), 1.48-1.46 (m, 1H), 1.36-1.23 (m, 1H). MS (ESI): Mass calcd. for $\text{C}_{28}\text{H}_{27}\text{FN}_6\text{O}$, 482; m/z found, 483.30 $[\text{M}+1]^+$.
- 10

Compound- 80:

(R)-(3-aminopiperidin-1-yl)(2-(1-(4-fluorobenzyl)-6-methoxy-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone

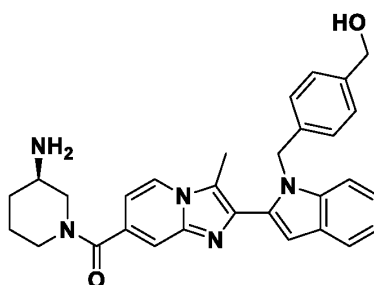


15

- [000267] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.41 (d, $J = 6.96$ Hz, 1H), 7.60 (s, 1H), 7.49 (d, $J = 8.6$ Hz, 1H), 7.03-6.96 (m, 6H), 6.73 (d, $J = 8.56$ Hz, 1H), 6.68 (s, 1H), 5.85 (s, 2H), 4.29-4.08 (m, 2H), 3.73 (s, 3H), 3.00 (bs, 2H), 2.71 (m, 1H), 2.61 (s, 3H), 1.8-1.84 (m, 2H), 1.68 (bs, 2H), 1.45-1.43 (m, 1H), 1.27-1.23 (m, 1H). MS (ESI): Mass calcd. for $\text{C}_{30}\text{H}_{30}\text{FN}_5\text{O}_2$, 511; found m/z 512.35 $[\text{M}+1]^+$.
- 20

Compound-81:

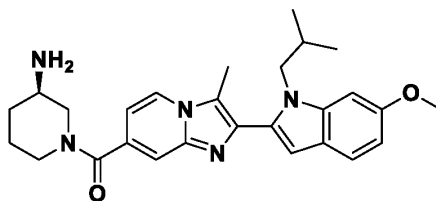
(R)-(3-aminopiperidin-1-yl)(2-(1-(4-(hydroxymethyl)benzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000268] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.42 (d, J = 6.96 Hz, 1H), 7.61 (s, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.11-7.03 (m, 4H), 6.99 (d, J = 6.72 Hz, 1H), 6.91 (d, J = 7.88 Hz, 2H), 6.76 (s, 1H), 5.89 (s, 2H), 5.02 (t, J = 5.44 Hz, 1H), 4.33 (s, 2H), 4.09 (bs, 1H), 3.59 (bs, 1H), 3.00-2.95 (m, 2H), 2.65 (s, 3H), 2.17-1.99 (m, 2H), 1.83 (m, 1H), 1.69 (m, 1H), 1.45 (m, 1H), 1.26-1.24 (m, 1H). MS (ESI): Mass calcd. for $\text{C}_{30}\text{H}_{31}\text{N}_5\text{O}_2$, 493.25; m/z found, 494.39 $[\text{M}+\text{H}]^+$.

Compound-82:

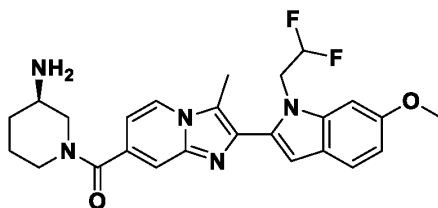
(R)-(3-aminopiperidin-1-yl)(2-(1-isobutyl-6-methoxy-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000269] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.40 (d, J = 7.0 Hz, 1H), 7.61 (s, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.04 (s, 1H), 6.98 (d, J = 6.9 Hz, 1H), 6.72 (dd, J = 8.7, 1.5 Hz, 1H), 6.55 (s, 1H), 4.41 (d, J = 7.1 Hz, 2H), 4.11 (bs, 1H), 3.82 (s, 3H), 3.61 (bs, 1H), 2.98 (bs, 1H), 2.66 (m, 1H), 2.61 (s, 3H), 1.98-1.91 (m, 1H), 1.88 (m, 3H), 1.75-1.70 (m, 1H), 1.47-1.44 (m, 1H), 1.29-1.24 (m, 1H), 0.64 (d, J = 6.6 Hz, 6H). MS (ESI): Mass calcd. for $\text{C}_{27}\text{H}_{33}\text{N}_5\text{O}_2$, 459.59; m/z found, 460.41 $[\text{M}+\text{H}]^+$.

Compound-83:

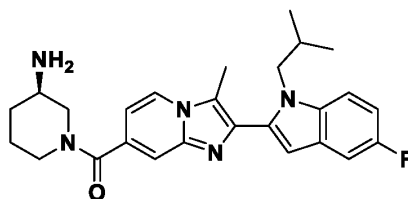
(R)-(3-aminopiperidin-1-yl)(2-(1-(2,2-difluoroethyl)-6-methoxy-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone



[000270] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.44 (d, $J = 7.0$ Hz, 1H), 7.63 (s, 1H), 7.49 (d, $J = 8.5$ Hz, 1H), 7.16 (s, 1H), 7.02 (d, $J = 6.8$ Hz, 1H), 6.78-6.75 (m, 1H), 6.70 (s, 1H), 6.45 (t, $J = 56.0$ Hz, 1H), 5.03 (t, $J = 14.5$ Hz, 2H), 4.17 (bs, 1H), 3.83 (s, 3H), 3.04 (bs, 1H), 2.81 (m, 2H), 2.65 (s, 3H), 1.90 (m, 4H), 1.75-1.70 (m, 1H), 1.48-1.46 (m, 1H), 1.32-1.01 (m, 1H). MS (ESI): Mass calcd. for $\text{C}_{25}\text{H}_{27}\text{F}_2\text{N}_5\text{O}_2$, 467.52; m/z found, 468.17 $[\text{M}+\text{H}]^+$.

Compound-84:

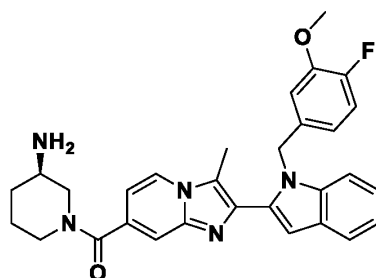
10 **(R)-(3-aminopiperidin-1-yl)(2-(5-fluoro-1-isobutyl-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone**



[000271] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.42 (d, $J = 7.0$ Hz, 1H), 7.63 (s, 1H), 7.58-7.55 (m, 1H), 7.36-7.33 (dd, $J = 2.3$ Hz, 7.0 Hz, 1H), 7.03-6.99 (m, 2H), 6.64 (s, 1H), 4.44 (d, $J = 7.2$ Hz, 2H), 4.28-4.11 (m, 1H), 3.60 (bs, 1H), 2.99-2.78 (m, 2H), 2.66 (m, 1H), 2.62 (s, 3H), 1.98-1.91 (m, 1H), 1.87-1.73 (m, 4H), 1.47-1.44 (m, 1H), 1.29-1.23 (m, 1H), 0.63 (d, $J = 6.6$ Hz, 6H). MS (ESI): Mass calcd. for $\text{C}_{26}\text{H}_{30}\text{FN}_5\text{O}$, 447.24; m/z found, 448.39 $[\text{M}+\text{H}]^+$.

Compound-85:

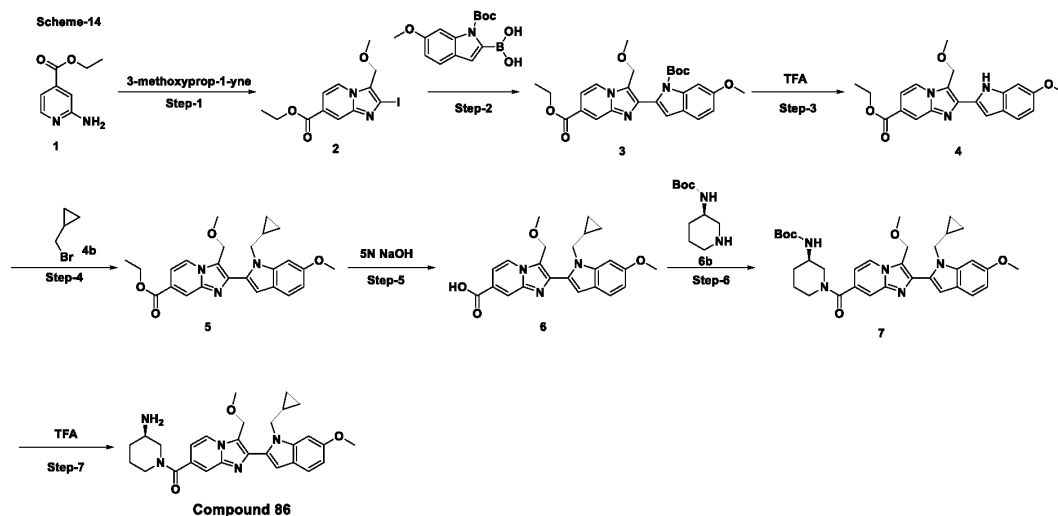
20 **(R)-(3-aminopiperidin-1-yl)(2-(1-(4-fluoro-3-methoxybenzyl)-1H-indol-2-yl)-3-methylimidazo[1,2-a]pyridin-7-yl)methanone**



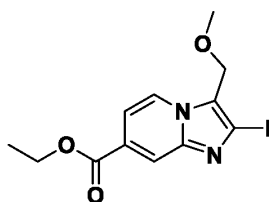
[000272] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.43 (d, $J = 7.0$ Hz, 1H), 7.62 (d, $J = 7.9$ Hz, 2H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.13 (t, $J = 7.84$ Hz, 1H), 7.06 (t, $J = 7.32$ Hz, 1H), 7.01-6.96 (m, 3H), 6.76 (s, 1H), 6.49 (bs, 1H), 5.83 (s, 2H), 4.29-4.10 (m, 1H), 3.62 (s, 3H), 2.98 (bs, 2H), 2.63 (s, 3H), 1.82 (m, 1H), 1.66 (m, 3H), 1.45 (m, 1H), 1.23 (m, 3H). MS (ESI): Mass calcd. for $\text{C}_{26}\text{H}_{30}\text{FN}_5\text{O}$, 511.24; m/z found, 512.48 $[\text{M}+\text{H}]^+$.

Compound-86:

10 (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridin-7-yl)methanone

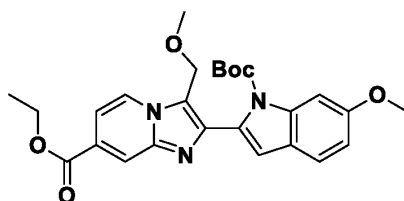


15 Step-1: Synthesis of ethyl-2-iodo-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carboxylate (2)



- [000273] To a stirred solution of methyl-2-aminoisonicotinate (**1**, 5.0 g, 30.0 mmol) and 3-methoxyprop-1-yne (2.53 g, 36.1 mmol) in 1, 2-dichlorobenzene (100 mL), were added iodine (7.63 g, 30.0 mol) and copper (II) acetate (0.54 g, 3.0 mmol). The reaction mixture was filled with 5 kg/cm² oxygen in steel bomb and stirred at 120 °C for 12 h. After completion of reaction, The reaction mixture directly passed through 100-200 mesh size silica gel and eluted with hexane (2000 m L) followed by 20% ethyl acetate in hexane as eluent to afford ethyl 2-iodo-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carboxylate (**2**) as white solid. Yield 7.40 g (68.1%). MS (ESI): Mass 360.15; m/z found, 361.01 [M+H]⁺.

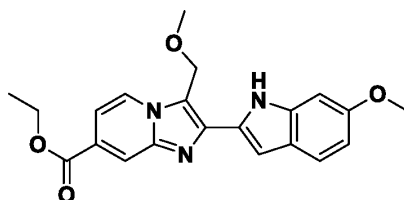
Step-2: Synthesis of ethyl-2-(1-(tert-butoxycarbonyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carboxylate (3)



- [000274] To a solution of ethyl-2-iodo-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carboxylate (**2**, 0.8 g, 2.22 mmol) and (1-(tert-butoxycarbonyl)-6-methoxy-1H-indol-2-yl)boronic acid (0.97 g, 3.33 mmol) in 1, 4 dioxane (40 mL) and water (8 mL), was added potassium phosphate (1.4 g, 6.66 mmol) and the mixture was purged with argon gas for 20 min. Then added tetrakis(triphenylphosphine)palladium(0) (0.12 g, 0.11 mmol) and continued purging for 5 min. The reaction mixture was stirred for 4 h at 90 °C in sealed tube. After completion of reaction, water (100 mL) was added and extracted with ethyl acetate (200 mL × 2). Organic layer was washed with saturated ammonium chloride solution, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified CombiFlash using 40.0 g RediSep column and 30-40% ethyl acetate in hexane as eluent to afford ethyl-2-(1-(tert-butoxycarbonyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridine-

7-carboxylate (**3**) as oily liquid. Yield 0.8 g (80%). MS (ESI): Mass 479.21; m/z found, 480.19 $[M+H]^+$.

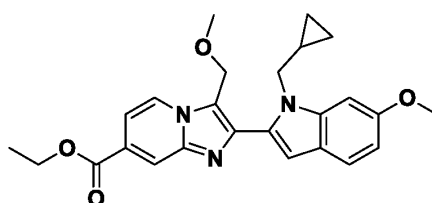
Step-3: Synthesis of ethyl-2-(6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carboxylate (4**)**



5

[000275] To a solution of ethyl-2-(1-(tert-butoxycarbonyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carboxylate (**3**, 0.8 g, 1.64 mmol) in dichloromethane (50 mL) was added trifluoroacetic acid (8.0 mL) at 0 °C. The reaction mixture was stirred for 5h at room temperature. After completion of reaction, mixture was concentrated under vacuum and neutralized using aqueous sodium bicarbonate. The aqueous phase was then extracted with dichloromethane (2 × 20 mL). Organic layer was dried over sodium sulfate and concentrated to afford ethyl-2-(6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carboxylate (**4**) as pale yellow solid. Yield 0.55 g. MS (ESI): Mass 379.15; m/z found, 380.24 $[M+H]^+$.

15 Step 4: Synthesis of ethyl 2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carboxylate (5**)**

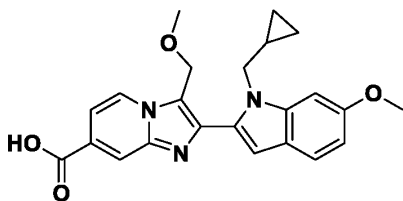


[000276] To a stirred solution of ethyl-2-(6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carboxylate (**4**, 0.5 g, 1.32 mmol) in *N,N*, dimethylformamide (10 mL), was added cesium carbonate (1.23 g, 3.95 mmol) and (bromomethyl)cyclopropane (0.21 g, 1.58 mmol). The reaction mixture was stirred at 60 °C for 3 h. After completion of reaction, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (100 mL × 3). The organic phase was washed with water, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude compound. The crude was purified CombiFlash using 40.0 g RediSep column and 10-15% ethyl acetate in hexane as eluent to afford ethyl-2-(1-

25

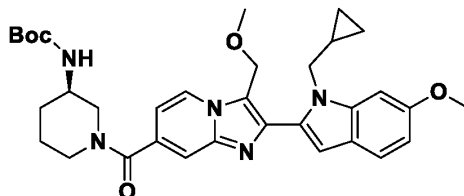
(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carboxylate (**5**) as yellow solid. Yield: 0.30 g (52%). MS (ESI): 433.20; m/z found, 434.14 [M+H]⁺.

Step 5: Synthesis of 2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carboxylic acid (6)



[000277] To a stirred solution of ethyl-2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carboxylate (**5**, 0.30 g, 0.629 mmol) in tetrahydrofuran (10 mL) were added methanol (5 mL) and 5N sodium hydroxide solution in water (5 mL) and the resulting mixture was heated to 60 °C for 3 h. After completion of reaction, the reaction mixture was evaporated under reduced pressure and acidified up to pH 2-3 with citric acid at 0 °C. The crude was extracted with dichloromethane (10 mL × 2), washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carboxylic acid (**6**) as yellow solid. Yield: 0.20 g (71%). MS (ESI): 405.17; m/z found, 404.12 [M-H]⁻.

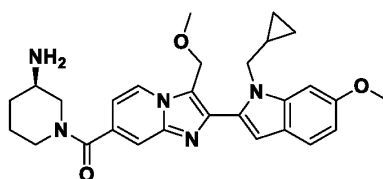
Step 6: Synthesis of tert-butyl (R)-(1-(2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (7)



[000278] To a stirred solution of 2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carboxylic acid (**6**, 0.20 g, 0.508

mmol) in dichloromethane (10 mL) were added tert-butyl (R)-piperidin-3-ylcarbamate (0.122 g, 0.61 mmol), triethylamine (0.22 mL, 1.57 mmol) and propyl phosphonic anhydride in 50% ethyl acetate (1.2 mL, 1.62 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 1h. After completion of reaction, the reaction mixture was quenched with sodium bicarbonate solution (20 mL) and extracted with dichloromethane (20 mL × 2). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude product. The crude was purified by CombiFlash using 12.0 g RediSep column and 2-5% methanol in dichloromethane as eluent to afford tert-butyl (R)-(1-(2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (**7**) as off-white solid. Yield: 0.14 g (48%). MS (ESI): 587.31; m/z found, 588.27 [M+H]⁺.

Step 7: Synthesis of (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridin-7-yl)methanone (Example 86)



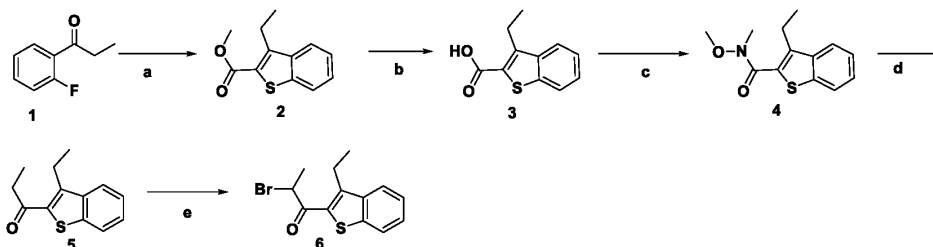
[000279] To a stirred solution of mixture of tert-butyl (R)-(1-(2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridine-7-carbonyl)piperidin-3-yl)carbamate (**7**, 0.14 g, 0.24 mmol) in dichloromethane (5 mL), trifluoroacetic acid (1.0 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 2h. After completion of reaction, the reaction mixture was concentrated under reduced pressure to remove trifluoroacetic acid. The crude was dissolved in minimum volume of water and basified by saturated sodium bicarbonate solution (20 mL) and was extracted with dichloromethane (20 mL × 2). The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated and was purified by reverse prep to afford (R)-(3-aminopiperidin-1-yl)(2-(1-(cyclopropylmethyl)-6-methoxy-1H-indol-2-yl)-3-(methoxymethyl)imidazo[1,2-a]pyridin-7-yl)methanone as yellow solid. Yield: 0.03 g (30%).

[000280] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.54 (d, J = 7.0 Hz, 1H), 7.66 (s, 1H), 7.48 (d, J = 8.56 Hz, 1H), 7.1 (s, 1H), 7.03 (d, J = 7.21 Hz, 1H), 6.72 (d, J = 8.56 Hz, 1H), 6.58 (s, 1H), 4.88 (s, 2H), 4.49 (d, J = 6.64 Hz, 2H), 4.28-4.09 (m, 1H), 3.83 (s, 3H), 3.76-3.53 (m, 1H), 3.34-3.32 (m, 4H), 3.00-2.85 (m, 2H), 2.65 (s, 1H), 1.83 (m, 1H), 1.72 (bs, 2H), 1.47-1.44 (m, 1H), 1.26-1.23 (m, 1H), 1.09 (m, 1H), 0.27 (d, J = 7.64 Hz, 2H), 0.15 (d, J = 3.96 Hz, 2H). MS (ESI): Mass calculated for $\text{C}_{28}\text{H}_{33}\text{N}_5\text{O}_3$, 487.26; m/z found, 488.41 $[\text{M}+\text{H}]^+$.

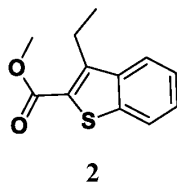
10

SYNTHESIS OF INTERMEDIATES

Synthesis of 2-bromo-1-(3-ethylbenzo[*b*]thiophen-2-yl)propan-1-one (Intermediate for Compound-19):

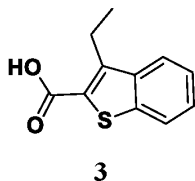


Step-1: Preparation of Methyl 3-ethylbenzo[*b*]thiophene-2-carboxylate (2)

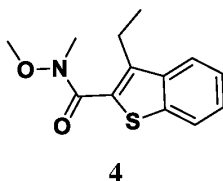


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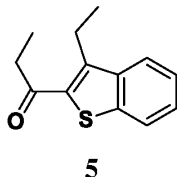
[000281] To a suspension of NaH (60% in oil, 1.7 g, 42.7 mmol) in THF (50 mL) was added methyl 2-mercaptoacetate (4.1 g, 39.4 mmol) at rt and stirred for 30 min. To the reaction was added solution of 1-(2-fluorophenyl)propan-1-one (**1**, 5.0 g, 32.8 mmol) in THF and allowed to reflux for 16 h (Reaction condition a). Completion of the reaction was monitored by LCMS since starting material and product come very close in TLC (2:8 EtOAc:Hexane). The reaction mixture was cooled to rt, diluted with EtOAc (100 mL) and washed with 1N NaOH (20 mL) and water (20 mL). Organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure. The obtained crude is purified by column chromatography to obtain the product as brown oil (**2**) (4.0 g, 57.14% Yield). MS (ESI): Mass calcd. for $\text{C}_{12}\text{H}_{12}\text{O}_2\text{S}$, 220.06; m/z found, 221.1 $(\text{M}+\text{H})^+$.

Step 2: Preparation of 3-Ethylbenzo[b]thiophene-2-carboxylic acid (3)

[000282] To a solution of methyl 3-ethylbenzo[b]thiophene-2-carboxylate (**2**, 4.0 g, 18.1 mmol) in THF:MeOH:H₂O (8:2:1, 40 mL) was added LiOH (1.7 g, 72.7 mmol) at 0 °C and stirred at rt for 3 h (Reaction condition **b**). The reaction mixture was evaporated, dissolved in water (20 mL) and acidified using saturated citric acid solution. The white precipitate formed was collected by filtration and dried to obtain the product (**3**) (2.7 g, 73% Yield). MS (ESI): Mass calcd. for C₁₁H₁₀O₂S, 206.04; m/z found, 207.1 (M+H)⁺.

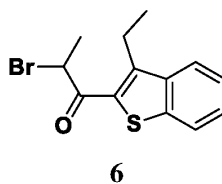
Step 3: Preparation of 3-Ethyl-N-methoxy-N-methylbenzo[b]thiophene-2-carboxamide (4)

[000283] To a stirred solution of 3-ethylbenzo[b]thiophene-2-carboxylic acid (**3**, 2.5 g, 12.1 mmol) and N,O-dimethylhydroxylamine hydrochloride (1.8 g, 18.2 mmol) in DCM (30 mL), was added triethylamine (8.4 mL, 60.6 mmol), HOBT (2.4 g, 18.2 mmol) followed by EDC.HCl (2.8 g, 18.2 mmol) at 0°C and the reaction mixture was stirred at rt for 4h (Reaction condition **c**). To the reaction mixture, was added water (50 ml) and DCM layer was separated. The organic layer was washed with brine solution (20 mL), dried and evaporated to give the crude product. The crude was purified by gradient column chromatography using 20-25% ethyl acetate in hexane to afford the product as off white solid (**4**) (2.15 g, 72% Yield). MS (ESI): Mass calcd. for C₁₃H₁₅NO₂S, 249.08; m/z found, 250.2 [M+H]⁺.

Step 4: Preparation of 1-(3-Ethylbenzo[b]thiophen-2-yl)propan-1-one (5)

[000284] To a stirred solution of 3-ethyl-N-methoxy-N-methylbenzo[b]thiophene-2-carboxamide (**4**, 2.1 g, 8.43 mmol) in THF (20 mL), was added 3M solution of ethyl magnesium bromide (8.4 mL, 25.3 mmol) drop wise at 0°C and the reaction mixture was stirred at rt for 16 h (Reaction condition **d**). The reaction mixture was quenched with saturated NH₄Cl (10 mL) solution at 0°C and extracted with EtOAc (50 mL). The organic layer was evaporated, purified by flash column chromatography to give the title compound as brown oil (**5**) (1.7g, 92% Yield). MS (ESI): Mass calcd. for C₁₃H₁₄OS, 218.08; m/z found, 219.1 [M+H]⁺.

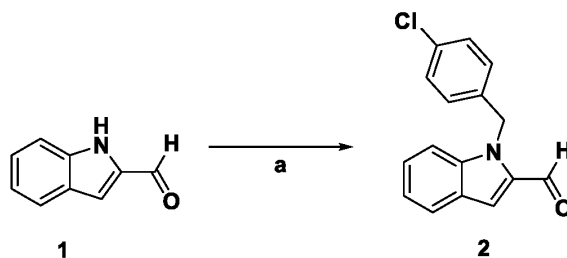
Step 5: Preparation of 2-Bromo-1-(3-ethylbenzo[b]thiophen-2-yl)propan-1-one (6**)**



[000285] To the stirred solution of 1-(3-ethylbenzo[b]thiophen-2-yl)propan-1-one (**5**, 0.5 g, 2.29 mmol) in THF (5 mL), was added trimethylphenylammonium tribromide (0.95 g, 2.52 mmol) and stirred at 80°C for 3 h (Reaction condition **e**). The reaction mixture was cooled to rt, added water (20 mL) and compound was extracted with EtOAc (50 mL). Organic extract was washed with saturated NaHCO₃ (20 mL), dried over sodium sulfate and evaporated. Crude was purified by column chromatography using 0-25% EtOAc in hexane to afford the product as pale yellow gummy solid (**6**) (0.6 g, 88% Yield). MS (ESI): mass calcd. for C₁₃H₁₃BrOS, 295.99; m/z found, 297.0 (M+H)⁺.

[000286] Rest of the steps are similar to that given for Compound-1 (Step 4 onwards).

Synthesis of 1-(4-chlorobenzyl)-1H-indole-2-carbaldehyde (Intermediate for Compound-20)

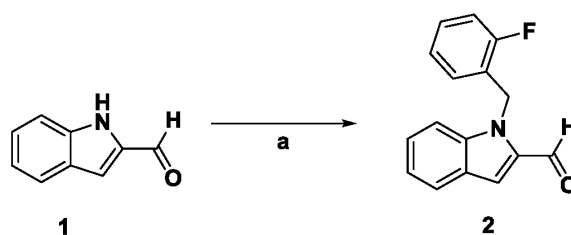


[000287] To a stirred solution 1H-pyrrolo[2,3-b]pyridine-2-carbaldehyde (**1**, 0.5 g, 3.44 mmol) in DMF (10 mL), was added potassium carbonate (1.42 g, 10.3 mmol)

followed by 1-(bromomethyl)-4-chlorobenzene (0.84 g, 4.13 mmol) and the reaction mixture was stirred at same temperature for 4 h (Reaction condition **a**). The reaction mixture was quenched with water and extracted with ethyl acetate (30 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulfate, filtered and evaporated to give the crude product. Crude residue was purified by gradient column chromatography using 10-15% ethyl acetate in hexane to give the product as off white solid (**2**) (0.86 g, 93.4%, Yield). ¹HNMR (400 MHz, DMSO) δ (ppm): 9.9 (s, 1H), 7.79 (d, J = 8 Hz, 1H), 7.60-7.56 (m, 2H), 7.39-7.36 (m, 1H), 7.31 (d, J = 8 Hz, 2H), 7.18-7.14 (m, 1H), 7.06 (d, J = 8 Hz, 2H), 5.8 (s, 2H). MS (ESI): Mass calcd. for C₁₆H₁₂ClNO, 269.73; m/z found, 270.1 (M+H)⁺.

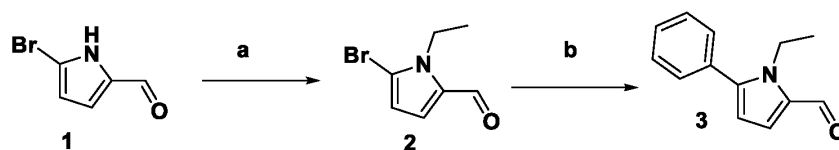
[000288] Following compound below was synthesized using the above procedure as exemplified for 1-(4-chlorobenzyl)-1H-indole-2-carbaldehyde (**Intermediate for Compound-20**).

Synthesis of 1-(2-fluorobenzyl)-1H-indole-2-carbaldehyde (Intermediate for Compound-21)

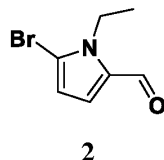


[000289] To a stirred solution 1H-indole-2-carbaldehyde (**1**, 1 g, 6.89 mmol) in DMF (15 mL), was added potassium carbonate (2.85 g, 20.6 mmol) followed by 1-(chloromethyl)-2-fluorobenzene (1.19 g, 8.26 mmol) and the reaction mixture was stirred at same temperature for 4 h (Reaction condition **a**). Reaction mixture was poured into crushed ice, diluted with water and extracted with ethyl acetate. Organic layer was dried over anhydrous sodium sulfate, evaporated under vacuum to give the crude. Crude was purified by flash column chromatography using ethyl acetate and hexane to afford the 1-(2-fluorobenzyl)-1H-indole-2-carbaldehyde as grey color solid (**2**) (Yield: 1.8g, 96.5%). ¹HNMR (400 MHz, DMSO) δ (ppm): 9.90 (s, 1H), 7.81 (d, J = 8 Hz, 1H), 7.58-7.54 (m, 2H), 7.40-7.36 (m, 1H), 7.28-7.15 (m, 3H), 7.01-6.97 (m, 1H), 6.55-6.51 (m, 1H), 5.88 (s, 2H). MS (ESI): mass calcd. for C₁₆H₁₂FNO, 253.09; m/z found, 254.0 (M+H)⁺.

Synthesis of 1-ethyl-5-phenyl-1H-pyrrole-2-carbaldehyde (Intermediate for Compound-22)

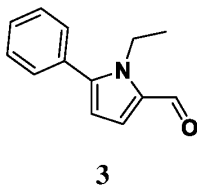


Step 1: Preparation of 5-Bromo-1-ethyl-1H-pyrrole-2-carbaldehyde (2)



- 5 **[000290]** To a stirred solution 5-bromo-1H-pyrrole-2-carbaldehyde (**1**, 1g, 5.7 mmol) in DMF (15 mL), was added potassium carbonate (3.14 g, 22 mmol) followed by ethyl iodide (1.33 g, 8.6 mmol) and the reaction mixture was stirred at same temperature for 16 h (Reaction condition **a**). Reaction mixture was diluted with water and extracted with ethyl acetate. Organic layer was dried over anhydrous sodium sulfate and evaporated under vacuum to obtain the crude. Crude was purified by flash column chromatography using ethylacetate in Hexane as an elutant to afford the title compound as orange color liquid (0.9 g, 77.58% Yield) (**2**) MS (ESI): Mass calcd. for C_7H_8BrNO , 202.05; m/z found 204.0 ($M+2H$)⁺.
- 10

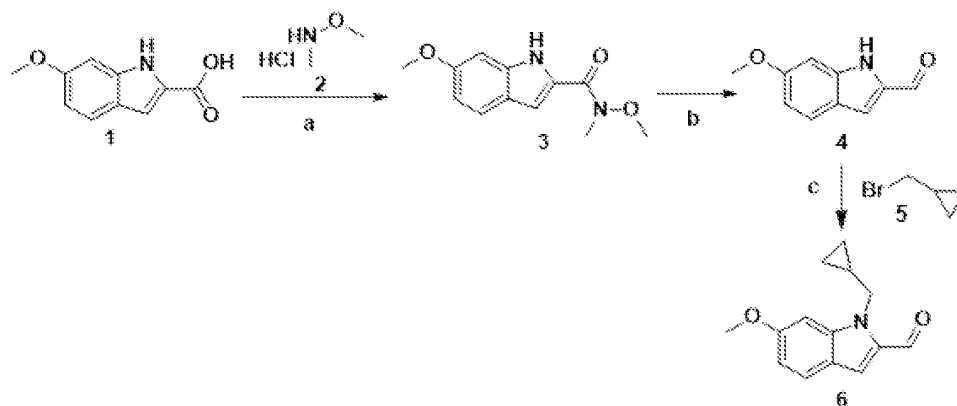
Step 2: Preparation of 1-Ethyl-5-phenyl-1H-pyrrole-2-carbaldehyde (3)



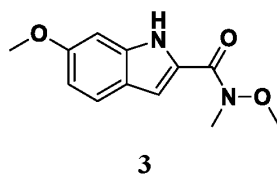
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- [000291]** To a stirred solution of 5-bromo-1-ethyl-1H-pyrrole-2-carbaldehyde (**2**, 0.9g, 4.45 mmol), in 1,4-dioxane in a seal tube was added phenyl boronic acid (0.8g, 6.67 mmol), potassium carbonate (1.84 g, 13.3 mmol) then the reaction mixture was purged with nitrogen. After purging for few minutes, [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (0.18g, 0.22 mmol) was added and then heated to 80°C for 12 h (Reaction condition **b**). After completion of the reaction, reaction mixture was filtered through celite bed, filtrates were evaporated to dryness to give the crude product. The crude was purified by gradient column chromatography using 12% ethyl acetate in hexane to give the title compound as pale yellow colour solid (**3**) (0.52 g, 59.09% Yield). MS (ESI): Mass calcd. for $C_{13}H_{13}NO$, 199.25; m/z found 200.0 ($M+H$)⁺.
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- 25

Synthesis of 1-(cyclopropylmethyl)-6-methoxy-1H-indole-2-carbaldehyde (Intermediate for Compound-23)



Step-1: Preparation of N,6-dimethoxy-N-methyl-1H-indole-2-carboxamide (3)



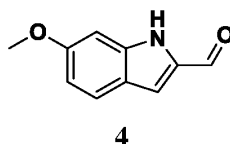
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[000292] To a stirred solution 6-methoxy-1H-indole-2-carboxylic acid (**1**, 3 g, 15.69 mmol) in DCM (20 mL), was added N,O-dimethylhydroxylamine hydrochloride (**2**, 3 g, 31.38 mmol), followed by hydroxybenzotriazole (3.6 g, 23.5 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (4.5 g, 23.5 mmol) and TEA (11.3 mL, 120.7 mmol), and the reaction mixture was stirred at same temperature for 5 h (Reaction condition **a**). The reaction mixture was quenched with water, extracted with ethyl acetate (50 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulfate, filtered and evaporated to get crude product. Crude residue was purified by gradient column chromatography using 25-30% ethyl acetate in hexane to get the product as beige colour solid (**3**) (Yield: 75%, 0.86 g). MS (ESI): mass calcd. for C₁₂H₁₄N₂O₃, 234.10; *m/z* found, 235 (M+H)⁺.

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

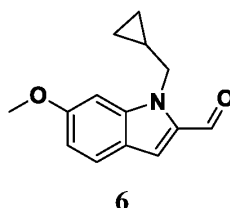


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[000293] To a stirred solution of N,6-dimethoxy-N-methyl-1H-indole-2-carboxamide (**3**, 2 g, 8.54 mmol) in THF (20 mL), was added LAH 1M soln. in THF (12.8 mL, 12.75 mmol) slowly under cooling condition, and then the reaction mixture

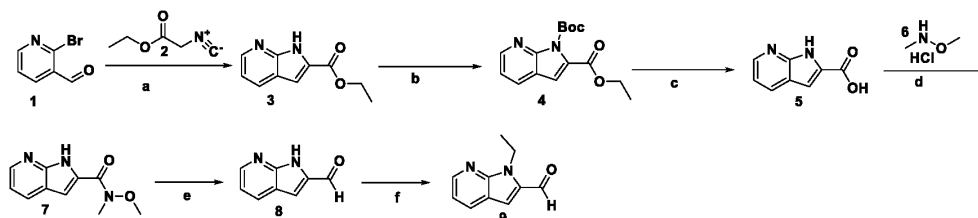
was allowed to stir at rt for 1h (Reaction condition **b**). The reaction mixture was quenched with ammonium chloride, extracted with ethyl acetate (50 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulfate, filtered and evaporated to get crude product. Crude residue was purified by gradient column chromatography using 5-10% ethyl acetate in hexane to get the product as white solid (**4**) (Yield: 60%, 0.9 g). MS (ESI): mass calcd. for C₁₀H₉NO₂, 175.06; *m/z* found, 176.1 (M+H)⁺.

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

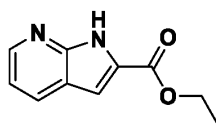


[000294] To a stirred solution of 6-methoxy-1H-indole-2-carbaldehyde (**4**, 0.28 g, 1.6 mmol) in DMF (5 mL), was added potassium carbonate (1.1 g, 8 mmol) followed by (bromomethyl)cyclopropane (**5**, 0.23 mL, 1.72 mmol) and the reaction mixture was stirred at same temperature for 4h (Reaction condition **c**). The reaction mixture was quenched with water, extracted with ethyl acetate (20 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulfate, filtered and evaporated to get crude product. Crude residue was purified by gradient column chromatography using 5-10% ethyl acetate in hexane to get the product as brown liquid (**6**) (Yield: 63%, 0.23 g). ¹HNMR (400 MHz, DMSO) δ (ppm): 9.72 (s, 1H), 7.62 (d, *J* = 8 Hz, 1H), 7.3 (s, 1H), 7.07 (s, 1H), 6.78 (d, *J* = 8 Hz, 1H), 4.43 (d, *J* = 8 Hz, 2H), 3.84 (s, 3H), 1.26-1.21 (m, 1H), 0.40-0.38 (m, 4H). MS (ESI): mass calcd. for C₁₄H₁₅NO₂, 229.1; *m/z* found, 230.2 (M+H)⁺.

Synthesis of 1-ethyl-1H-pyrrolo[2,3-b]pyridine-2-carbaldehyde (Intermediate for Compound-24):



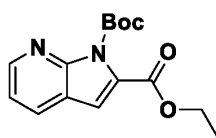
Step-1: Preparation of Ethyl 1H-pyrrolo[2,3-b]pyridine-2-carboxylate (3)



3

[000295] To the stirred solution of 2-bromonicotinaldehyde (**1**, 10.0 g, 53.7 mmol) in DMSO (100 mL), was added Cs_2CO_3 (35.0 g, 107 mmol), CuI (1.05 g, 5.37 mmol) followed by ethyl-2- isocyanoacetate (**2**, 7.9 mL, 69.8 mmol) and stirred at 80°C for 16 h (Reaction condition **a**). The reaction mixture was cooled to rt and filtered through celite. To this water (100 mL) was added and the compound was extracted with EtOAc (200 mL). Organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum. Crude was purified by column chromatography using 30-50% EtOAc in Hexane to afford the product as brown gummy solid (**3**) (4.5 g, 45% Yield). MS (ESI): Mass calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2$, 190.20; m/z found 191.0 ($\text{M}+\text{H}$)⁺.

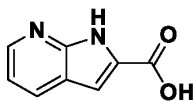
Step-2: Preparation of 1-(Tert-butyl) 2-ethyl 1H-pyrrolo[2,3-b]pyridine-1,2-dicarboxylate (4)



4

[000296] To the stirred solution of ethyl 1H-pyrrolo[2,3-b]pyridine-2-carboxylate (**3**, 34.5 g, 23.6 mmol) in THF (50 mL), was added triethylamine (6.5 mL, 47.3 mmol) followed by Boc anhydride (3.6 g, 35.5 mmol) and stirred at rt for 16 h (Reaction condition **b**). To the reaction mixture was added water (100 mL) and extracted with EtOAc (200 mL). Organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum. Crude was purified by column chromatography using 20-30% EtOAc in Hexane to afford the product as brown gum (**4**) (5.5 g, 81% Yield). MS (ESI): Mass calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_4$, 290.32; m/z found, 291.1 ($\text{M}+\text{H}$)⁺.

Step-3: Preparation of 1H-Pyrrolo[2,3-b]pyridine-2-carboxylic acid (5)

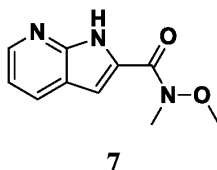


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[000297] To a stirred solution 1-(tert-butyl) 2-ethyl 1H-pyrrolo[2,3-b]pyridine-1,2-dicarboxylate (**4**, 5.5 g, 18.9 mmol) in THF (40 mL), was added LiOH (3.9 g, 94.8

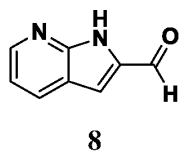
mmol) in water (10 mL) and stirred at rt for 4 h (Reaction condition **c**). The reaction mixture was evaporated, dissolved in minimum amount of water. To this added saturated citric acid solution till acidic and the precipitate formed was collected by filtration and dried to afford the product as white solid (**5**) (2.5 g, 81% Yield). MS (ESI): Mass calcd. for $C_8H_6N_2O_2$, 162.04; m/z found, 163.1 ($M+H$)⁺.

Step-4: Preparation of N-Methoxy-N-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (7)



[000298] To the stirred solution of 1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (**5**, 2.5 g, 15.4 mmol) and N,O-dimethylhydroxylamine hydrochloride (**6**, 1.8 g, 18.5 mmol) in DCM (50 mL), was added triethylamine (10.6 mL, 77.1mmol), HOBt (3.54 g, 23.14 mmol) followed by EDC.HCl (4.42 g, 23.18 mmol) at 0°C and the reaction mixture was stirred at rt for 16 h (Reaction condition **d**). The reaction mixture was cooled to rt, filtered through celite and the filtrate was evaporated. To the crude, water (10 mL) was added and the compound was extracted with DCM (30mL). Organic layer was dried over sodium sulfate and evaporated to give the crude product. The crude residue was purified by gradient column chromatography using 2-4% MeOH in DCM to afford the product as off white solid (**7**) (2.6 g, 82% Yield). MS (ESI): Mass calcd. for $C_{10}H_{11}N_3O_2$, 205.09; m/z found 206.1 ($M+H$)⁺.

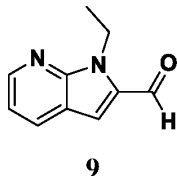
Step-5: Preparation of 1H-Pyrrolo[2,3-b]pyridine-2-carbaldehyde (8)



[000299] To a stirred solution N-methoxy-N-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (**7**, 0.5 g, 2.43 mmol) in THF (10 mL), was added 1M LAH in THF (3.6 mL, 3.65 mmol) at -78°C and the reaction mixture was stirred at same temperature for 3 h (Reaction condition **e**). The reaction mixture was basified using saturated Na_2CO_3 solution and extracted with DCM (2 X 25mL). The reaction was quenched with saturated NH_4Cl (10mL) solution and the compound was extracted with EtOAc (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give the crude product. Crude was purified by flash column chromatography using 25-30%

EtOAc in hexane to get the compound as white solid (**8**) (0.3g, 85% Yield). MS (ESI): Mass calcd. for $C_8H_6N_2O$, 146.15; m/z found, 147.1 ($M+H$)⁺.

Step_6: Preparation of 1-Ethyl-1H-pyrrolo[2,3-b]pyridine-2-carbaldehyde (9**)**

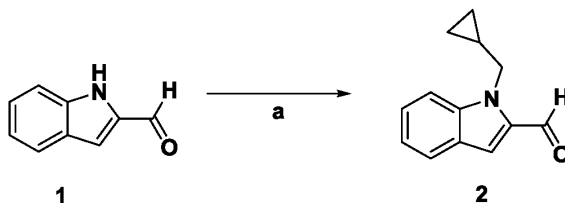


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[000300] To a stirred solution 1H-pyrrolo[2,3-b]pyridine-2-carbaldehyde (**8**, 0.3 g, 2.19 mmol) in DMF(10 mL), was added K_2CO_3 (0.91 g, 6.57 mmol) followed by ethyl iodide (0.5 g, 3.28 mmol) and the reaction mixture was stirred at same temperature for 16 h (Reaction condition f). To the reaction mixture was added water (15 mL) and extracted with EtOAc (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give the crude product. Crude was purified by flash column chromatography using 15-20% EtOAc in hexane to give the compound as colorless oil (**9**) (0.34 g, 95% Yield). MS (ESI): Mass calcd. for $C_{10}H_{10}N_2O$, 174.08; m/z found, 175.2 ($M+H$)⁺.

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15 Synthesis of 1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde (Intermediate for Compound-25)



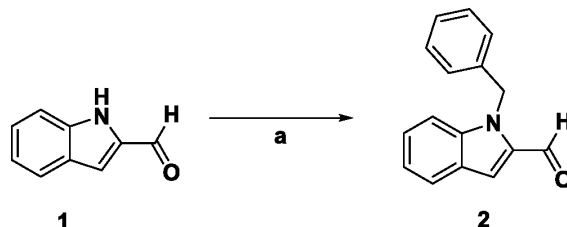
[000301] To the stirred solution of 1H-indole-2-carbaldehyde (**1**, 1 g, 6.89 mmol) in DMF (20 mL), were added potassium carbonate (2.8 g, 20.67 mmol) and (bromomethyl)cyclopropane (0.678 mL, 7.58 mmol) at rt. The reaction mixture was stirred at rt for 12 h (Reaction condition a). The reaction mixture was diluted with water and extracted with ethyl acetate (50 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulfate and evaporated to get crude product. The crude residue was purified by gradient column chromatography using 3-7% ethyl acetate in hexane to afford the 1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde as yellow solid (**2**) (1 g, 76 Yield). ¹HNMR (400 MHz, DMSO) δ (ppm): 9.88 (s, 1H), 7.75 (d, J = 8 Hz, 1H), 7.64 (d, J = 8 Hz, 1H), 7.46 (s, 1H), 7.41-7.37 (m, 1H), 7.16-7.12 (m, 1H),

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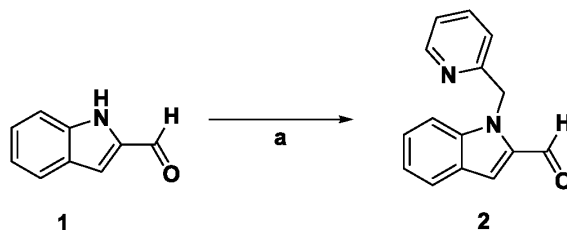
4.45 (d, $J = 8$ Hz, 2H), 1.24-1.14 (m, 1H), 0.39-0.35 (m, 4H). MS (ESI): mass calcd. for $C_{13}H_{13}NO$, 199.1; m/z found, 200.1 (M+H)⁺.

Synthesis of 1-benzyl-1H-indole-2-carbaldehyde (Intermediate for Compound-26)



- 5 **[000302]** To the stirred solution of 1H-indole-2-carbaldehyde (**1**, 1 g, 6.89 mmol) in DMF (20 mL), were added potassium carbonate (2.8 g, 20.68 mmol) and (bromomethyl)benzene (1.2 g, 7.58 mmol) at rt (Reaction condition **a**). The reaction mixture was stirred at rt for 12 h. The reaction mixture was diluted with water and extracted with ethyl acetate (50 mL x 2). Combined organic extracts were washed with
- 10 brine, dried over sodium sulfate and evaporated to give the crude product. The crude residue was purified by gradient column chromatography using 3-7% ethyl acetate in hexane to afford the 1-benzyl-1H-indole-2-carbaldehyde as viscous liquid (**2**) (0.5 g, 33% Yield). ¹HNMR (400 MHz, DMSO) δ (ppm): 9.92 (s, 1H), 7.78 (d, $J = 8$ Hz, 1H), 7.58 (d, $J = 8$ Hz, 1H), 7.54 (s, 1H), 7.38-7.35 (m, 1H), 7.26-7.20 (m, 2H), 7.18-7.13
- 15 (m, 2H), 7.05 (d, $J = 4$ Hz, 2H), 5.82 (s, 2H). MS (ESI): mass calcd. for $C_{16}H_{13}NO$, 235.10; m/z found, 236.1 (M+H)⁺.

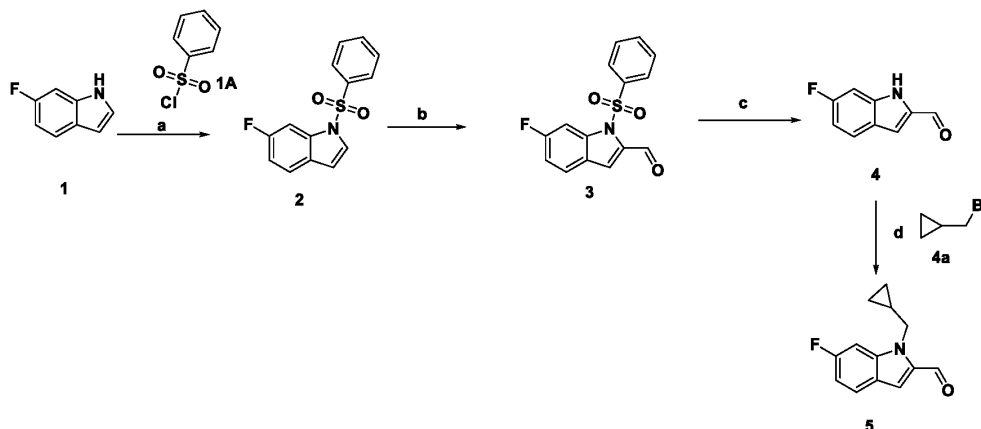
Synthesis of 1-(pyridin-2-ylmethyl)-1H-indole-2-carbaldehyde (Intermediate for Compound-27)



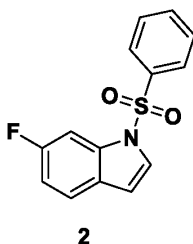
- 20 **[000303]** To the stirred solution of 1H-indole-2-carbaldehyde (**1**, 1 g, 6.89 mmol) in DMF (20 mL), were added cesium carbonate (6.7g, 20.68 mmol) and 2-(bromomethyl)pyridine (1.1g, 6.89 mmol) at rt (Reaction condition **a**). The reaction mixture was refluxed at 80°C for 12 h. The reaction mixture was diluted with water and extracted with ethyl acetate (50 mL x 2). Combined organic extracts were washed with
- 25 brine, dried over sodium sulfate and evaporated to get crude product. The crude residue was purified by gradient column chromatography using 3-7% ethyl acetate in hexane to

afford the 1-(pyridin-2-ylmethyl)-1H-indole-2-carbaldehyde as yellow solid (**2**) (0.8 g, 50% Yield). ¹HNMR (400 MHz, DMSO) δ (ppm): 9.92 (s, 1H), 8.45 (d, J = 4 Hz, 1H), 7.79 (d, J = 8 Hz, 1H), 7.66 (m, 1H), 7.56 (d, J = 12 Hz, 2H), 7.37-7.33 (m, 1H), 7.22-7.19 (m, 1H), 7.17-7.13 (m, 1H), 6.88 (d, J = 8 Hz, 1H), 5.89 (s, 2H). MS (ESI): mass calcd. for C₁₆H₁₂ClNO, 269.73; m/z found, 270.1 (M+H)⁺.

Synthesis of 1-(cyclopropylmethyl)-6-fluoro-1H-indole-2-carbaldehyde (Intermediate for Compound-28)



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

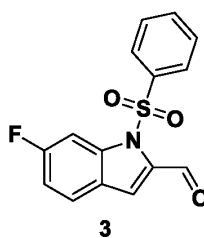


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[000304] To a solution of sodium hydride (0.88 g, 22.2 mmol) in DMF (50 mL) was added solution of 6-fluoro-1H-indole (**1**, 3.0 g, 22.2 mmol) in DMF at 0°C, dropwise over 15 min. Benzenesulfonyl chloride in DMF (2.86 mL, 22.2 mmol) was added at 0°C and stirred for 2 h at rt under N₂ atmosphere (Reaction condition a). To the reaction mixture was added ice cold water (50 mL), then filtered off the precipitate and washed with ice cold water to obtain white solid (**2**) (6.0 g, 98.19 %).

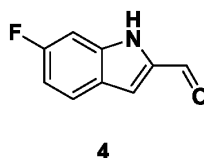
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Step 2: preparation 6-fluoro-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (3) (Intermediate for Compound-52, 54, 68, 69, 70, 71, 72 & 73)



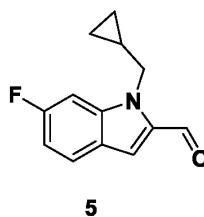
[000305] To a solution of 6-fluoro-1-(phenylsulfonyl)-1H-indole (**2**, 6.0 g, 22.0 mmol) in dry THF (60 mL) was added lithium diisopropylamide 2M in THF (10.9 mL g, 22.0 mmol) at -78 °C and stirred for 5-8 min, followed by addition of dry DMF (2.5 mL, 33.0 mmol) at -78 °C and stirred for 10 min at -78 °C under N₂ atmosphere (Reaction condition **b**). To the reaction mixture was added aqueous ammonium chloride (20 mL), then extracted in to EtOAc. Organic layer was washed with saturated NH₄Cl solution and brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain yellow solid (**3**) (6.0 g, 90.90%). MS (ESI): *m/z* 304.2 (M+H)⁺.

10 Step 3: Preparation of 6-fluoro-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (4)



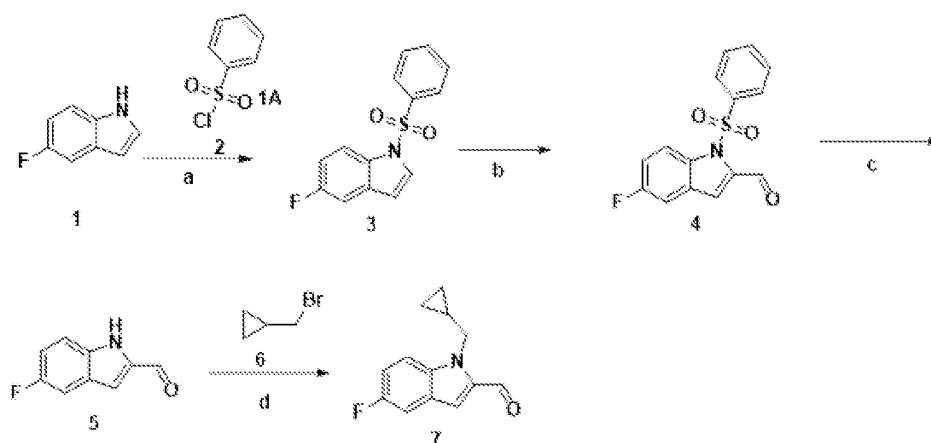
[000306] To the stirred solution of 6-Difluoro-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (**3**, 1g, 3.3 mmol) in THF (50 mL), was added TBAF (1M in THF) (9.15 mL, 16.5mmol) at rt. The reaction mixture was stirred at rt for 12 h (Reaction condition **c**). The reaction mixture was diluted with water and extracted with ethyl acetate (50 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulfate and evaporated to get crude product. The crude residue was purified by gradient column chromatography using 15-25% ethyl acetate in hexane to afford 6-fluoro-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde as sticky solid (**4**) (0.45 g, 90% Yield) MS (ESI): Mass calcd. for C₉H₆FNO, 163 *m/z*; found, 164 (M+H)⁺.

Step 4: Preparation of 1-(cyclopropylmethyl)-6-fluoro-1H-indole-2-carbaldehyde (5)

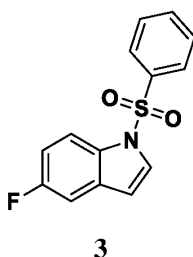


[000307] To a stirred solution 6-fluoro-1H-indole-2-carbaldehyde (**4**, 0.5 g, 3.44 mmol) in DMF (10 mL), was added potassium carbonate (1.42 g, 10.3 mmol) followed by (bromomethyl)cyclopropane (0.84 g, 4.13 mmol) and the reaction mixture was stirred at same temperature for 4 h (Reaction condition **d**). The reaction mixture was quenched with water, extracted with ethyl acetate (30 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulfate, filtered and evaporated to get crude product. Crude residue was purified by gradient column chromatography using 10-15% ethyl acetate in hexane to get the product as half white solid (**5**) (Yield: 93.4%, 0.86 g). ¹HNMR (400 MHz, DMSO) δ (ppm): 9.81 (s, 1H), 7.69-7.66 (m, 1H), 7.25 (d, J = 6.8 Hz, 1H), 7.07 (d, J = 8 Hz, 1H), 6.97-6.91 (m, 1H), 4.43 (d, J = 8 Hz, 2H), 1.32-1.25 (m, 1H), 0.5-0.45 (m, 2H), 0.42-0.38 (m, 2H). MS (ESI): mass calcd. for C₁₃H₁₂FNO, 217.09; m/z found, 218.0 (M+H)⁺.

Synthesis of 1-(cyclopropylmethyl)-5-fluoro-1H-indole-2-carbaldehyde (Intermediate for Compound-29)



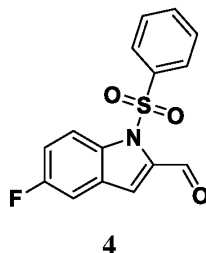
Step 1: Preparation of 5-fluoro-1-(phenylsulfonyl)-1H-indole (3)



[000308] To a solution of sodium hydride (0.06 g, 15 mmol) in DMF (10 mL) was added a solution of 5-fluoro-1H-indole (**1**, 0.2 g, 15 mmol) in DMF at 0 °C, drop wise over 15 min. followed by addition of a solution of benzenesulfonyl chloride (**2**, 0.26 g,

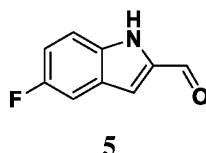
15 mmol) in DMF at 0 °C and the reaction mixture was stirred for 2 h at rt under N₂ atmosphere (Reaction condition **a**). To the reaction mixture was added ice cold water (50 mL), then the precipitate was filtered off and washed with ice cold water to obtain brown solid (**3**) (0.25 g, 62.50 % Yield). MS (ESI) *m/z* 275.0 (M+H)⁺.

5 **Step 2: Preparation of 5-fluoro-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (4)**
(Intermediate for Compound-53, 74, 75, 76, & 84)



- 10 **[000309]** To a solution of 5-fluoro-1-(phenylsulfonyl)-1H-indole (**3**, 0.250 g, 1.0 mmol) in dry THF (50 mL) was added lithium diisopropylamide 1M in THF (0.5 mL g, 1.0 mmol) at -78 °C, followed by addition of dry DMF (0.11 mL, 1.5 mmol) at -78 °C and stirred for 10 min at -78 °C under N₂ atmosphere (Reaction condition **b**). To the reaction mixture was added aqueous ammonium chloride (20 mL) and extracted with
- 15 EtOAc. Organic layer was washed with saturated NH₄Cl solution and brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain brown solid (**4**) (0.150 g, 54.54 % Yield). MS (ESI) *m/z* 304.1 (M+H)⁺.

Step 3: Preparation of 5-fluoro-1H-indole-2-carbaldehyde (5)

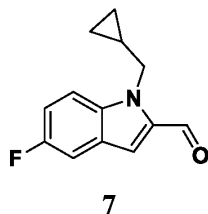


20

- [000310]** To the stirred solution of 5-fluoro-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (**4**, 1.85 g, 6.105 mmol) in THF (50 mL), was added TBAF (1M in THF) (9.15 mL, 9.158 mmol) at rt (Reaction condition **c**). The reaction mixture was stirred at
- 25 rt for 12 h. The reaction mixture was diluted with water and extracted with ethyl acetate (50 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulfate and evaporated to get crude product. The crude residue was purified by gradient column chromatography using 15-25% ethyl acetate in hexane to afford the 5-fluoro-

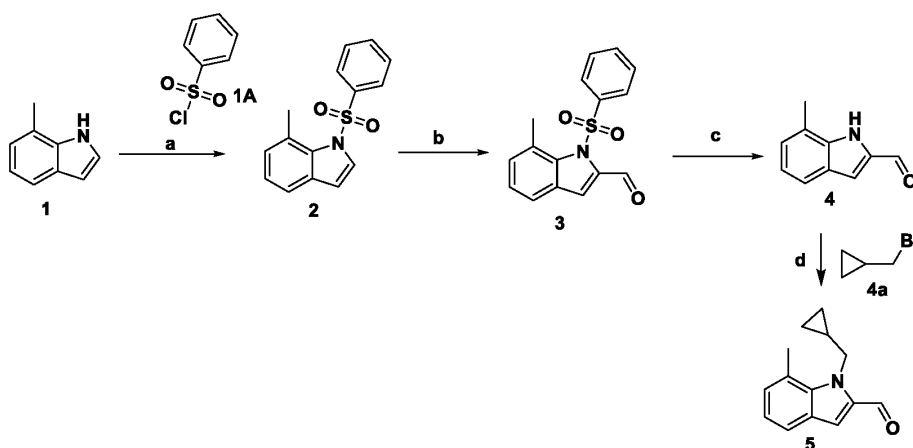
1H-indole-2-carbaldehyde as sticky solid (**5**) (0.65 g, 65% Yield) MS (ESI): Mass calcd. for C_9H_6FNO , 163.15; m/z found, 162.0 $[M-H]^-$.

Step 4: Preparation of 1-(cyclopropylmethyl)-5-fluoro-1H-indole-2-carbaldehyde (7**)**

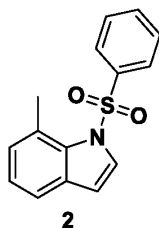


[000311] To the stirred solution of 5-fluoro-1H-indole-2-carbaldehyde (**5**, 0.65 g, 3.98 mmol) in DMF (50 mL), were added potassium carbonate (1.64 g, 11.94 mmol) and (bromomethyl)cyclopropane (**6**, 0.58 mL, 5.98 mmol) at rt. The reaction mixture was stirred at rt for 12 h (Reaction condition **d**). The reaction mixture was diluted with water and extracted with ethyl acetate (50 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulphate and evaporated to get crude product. The crude residue was purified by gradient column chromatography using 3-7% ethyl acetate in hexane to afford the 1-(cyclopropylmethyl)-5-fluoro-1H-indole-2-carbaldehyde as sticky solid (**7**) (0.76 g, 88% Yield). ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 9.90 (s, 1H), 7.73-7.69 (m, 1H), 7.55-7.52 (m, 1H), 7.44 (s, 1H), 7.29-7.24 (m, 1H), 4.50 (d, $J = 7.2$ Hz, 2H), 1.23-1.16 (m, 1H), 0.41-0.32 (m, 4H). MS (ESI): Mass calcd. for $C_{13}H_{12}FNO$, 217.24; m/z found, 218.1 $[M+H]^+$.

Synthesis of 1-(cyclopropylmethyl)-7-methyl-1H-indole-2-carbaldehyde (Intermediate for Compound-30)

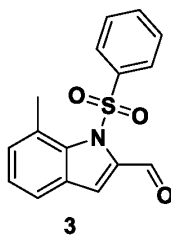


Step 1: Preparation of 7-methyl-1-(phenylsulfonyl)-1H-indole (2**)**



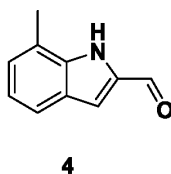
[000312] To a solution of sodium hydride (0.92 g, 23 mmol) in DMF (10 mL) was added solution of 7-methyl-1H-indole (**1**, 3.0 g, 23 mmol) in DMF at 0 °C, dropwise over 15 min. Benzenesulfonyl chloride in DMF (2.96 mL, 23 mmol) was added at 0°C and stirred for 2 h at rt under N₂ atmosphere (Reaction condition **a**). To the reaction mixture was added ice cold water (50 mL), then filtered off the precipitate and washed with ice cold water to obtain brown solid (**2**) (5.30 g, 85.50%). MS (ESI) *m/z* 272.1 (M+H)⁺.

Step 2: Preparation 7-methyl-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (3)



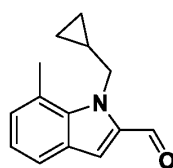
[000313] To a solution of 7-methyl-1-(phenylsulfonyl)-1H-indole (**2**, 5.3 g, 20.0 mmol) in dry THF (50 mL) was added lithium diisopropylamide 1.5M in THF (13.0 mL, 20.0 mmol) at -78 °C and stirred for 5-8 min, followed by addition of dry DMF (2.33 mL, 30.0 mmol) at -78 °C and stirred for 10 min at -78 °C under N₂ atmosphere (Reaction condition **b**). To the reaction mixture was added aqueous ammonium chloride (20 mL), then extracted in to EtOAc. Organic layer was washed with saturated NH₄Cl solution and brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain red viscous liquid (**3**) (5.0 g, 85.47 %). MS (ESI) *m/z* 300.2 (M+H)⁺.

Step 3: Preparation of 7-methyl-1H-indole-2-carbaldehyde (4)



[000314] To the stirred solution of 7-methyl-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (**3**, 2 g, 6.68 mmol) in THF (20 mL), was added 1M solution of tetrabutyl ammonium fluoride in THF (10 mL, 10.2 mmol) and stirred at 80 °C for 1h (Reaction condition **c**). Reaction mixture was cooled to rt, added water (20 mL) and extracted with EtOAc (100 mL). Organic layer was dried over anhydrous Na₂SO₄ and evaporated under vacuum. Crude was purified by column chromatography using 15-20% EtOAc in Hexane to afford the product as brown solid (**4**). (0.8 g, 58% Yield). MS (ESI): Mass calcd. for C₁₀H₉NO, 159.07; *m/z* found 160.1 (M+H)⁺.

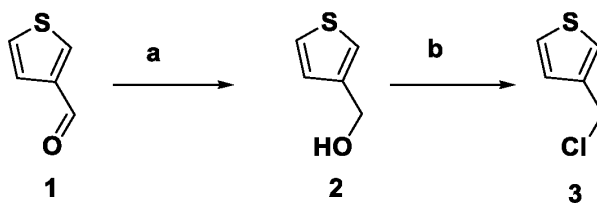
Step 4: Preparation of 1-(cyclopropylmethyl)-7-methyl-1H-indole-2-carbaldehyde (5**)**



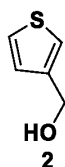
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[000315] To the stirred solution of 7-methyl-1H-indole-2-carbaldehyde (**4**, 0.85 g, 5.345 mmol) in DMF (20 mL), were added potassium carbonate (2.21 g, 16.035 mmol) and (bromomethyl)cyclopropane (4a, 0.78 mL, 8.018 mmol) at rt. The reaction mixture was stirred at rt for 12 h (Reaction condition **d**). The reaction mixture was diluted with water and extracted with ethyl acetate (50 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulfate and evaporated to get crude product. The crude residue was purified by gradient column chromatography using 3-7% ethyl acetate in hexane to afford the 1-(cyclopropylmethyl)-7-methyl-1H-indole-2-carbaldehyde as sticky solid (**5**) (0.52 g, 45% Yield). ¹HNMR (400 MHz, CDCl₃) δ (ppm): 9.82 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 7.13 (d, *J* = 6.8 Hz, 1H), 6.26 (m, 1H), 4.83 (d, *J* = 6.8 Hz, 2H), 2.77 (s, 3H), 1.15-1.10 (m, 1H), 0.41-0.33 (m, 4H). MS (ESI): Mass calcd. for C₁₄H₁₅NO, 213.28; *m/z* found, 214.1 [M+H]⁺.

Synthesis of 3-(chloromethyl)thiophene (Intermediate for Compound-36)

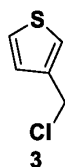


Step 1: Preparation of Thiophen-3-ylmethanol (2)



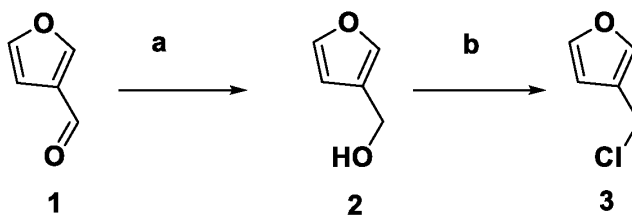
[000316] To the stirred solution of thiophene-3-carbaldehyde (**1**, 1 g, 8.92 mmol) in MeOH (10 mL), was added NaBH₄ (0.5 g, 13.3 mmol) portion wise at 0 °C and stirred at rt for 1 h (Reaction condition **a**). The reaction mixture was quenched with ice and the MeOH was evaporated. To the resulting crude added water (5 mL) and extracted with EtOAc (2 X 20 mL). Organic layer was washed with brine (5 mL) solution, dried over anhydrous Na₂SO₄ and evaporated under vacuum to give the product as brown oil (**2**) (0.9 g, 90%, Yield). ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 7.45-7.43 (m, 1H), 7.26 (s, 1H), 7.03 (d, *J* = 4.4 Hz, 1H), 5.05 (t, *J* = 6.0 Hz, 1H), 4.45 (d, *J* = 5.6 Hz, 2H).

Step 2: Preparation of 3-(chloromethyl)thiophene (**3**)

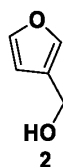


[000317] To a stirred solution thiophen-3-ylmethanol (**2**, 0.5 g, 4.38 mmol) in DCM (5 mL), was added SOCl₂ (0.6 mL, 8.77 mmol) drop wise at 0 °C and the reaction mixture was stirred at rt for 1 h (Reaction condition **b**). The reaction mixture was evaporated under vacuum and dried to afford the product as brown oil (**3**) (0.5 g, 80%, Yield). ¹HNMR (400 MHz, DMSO-d₆): δ 7.45-7.43 (m, 1H), 7.26 (s, 1H), 7.03 (d, *J* = 4.4 Hz, 1H), 4.78 (s, 2H).

Synthesis of 3-(chloromethyl)furan (Intermediate for Compound-37)

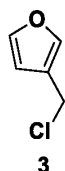


Step 1: Preparation of Furan-3-ylmethanol (**2**)



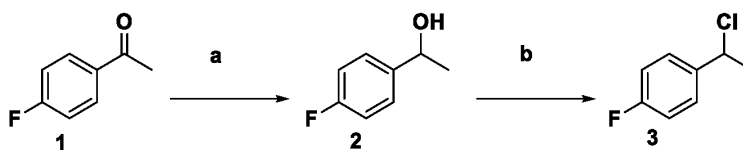
[000318] To the stirred solution of furan-3-carbaldehyde (**1**, 1 g, 10.4 mmol) in MeOH (10 mL), was added NaBH₄ (0.6 g, 15.6 mmol) portion wise at 0 °C and stirred
 5 at rt for 1 h (Reaction condition **a**). The reaction mixture was quenched with ice and the MeOH was evaporated. To the resulting crude added water (5 mL) and extracted with EtOAc (2 X 20 mL). Organic layer was washed with brine (5 mL) solution, dried over anhydrous Na₂SO₄ and evaporated under vacuum to give the product as brown oil (**2**)
 (0.6 g, 60%, Yield). ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 7.56-7.50 (m, 2H), 6.41
 10 (s, 1H), 4.90 (t, *J* = 5.2 Hz, 1H), 4.31 (d, *J* = 6.0 Hz, 2H).

Step 2: Preparation of 3-(chloromethyl)furan (3**)**

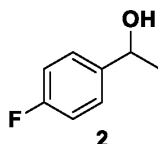


[000319] To a stirred solution furan-3-ylmethanol (**2**, 0.5 g, 5.10 mmol) in DCM (5 mL), was added SOCl₂ (0.7 mL, 10.2 mmol) drop wise at 0 °C and the reaction
 15 mixture was stirred at rt for 1 h (Reaction condition **b**). The reaction mixture was evaporated under vacuum and dried to afford the product as brown oil (**3**) (0.5 g, 84%, Yield). ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 7.75-7.65 (m, 2H), 6.53 (s, 1H), 4.68 (s, 2H).

Synthesis of 1-(1-chloroethyl)-4-fluorobenzene (Intermediate for Compound-38)

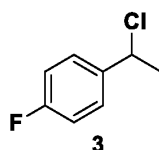


Step 1: Preparation of 1-(4-fluorophenyl)ethan-1-ol (2**)**



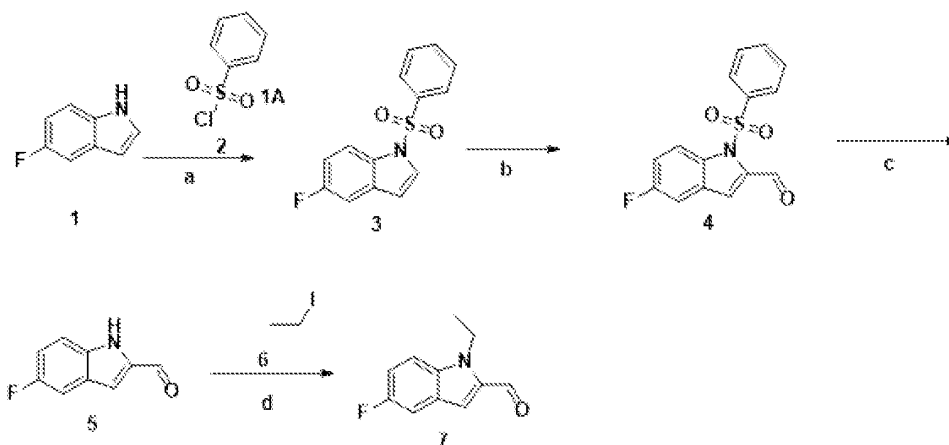
[000320] To the stirred solution of 1-(4-fluorophenyl)ethan-1-one (**1**, 2.0 g, 17.6 mmol) in MeOH (20 mL), was added NaBH₄ (1.0 g, 26.5 mmol) portion wise at 0 °C and stirred at rt for 1 h (Reaction condition **a**). The reaction mixture was quenched with ice and the MeOH was evaporated. To the resulting crude added water (10 mL) and extracted with EtOAc (2 X 25 mL). Organic layer was washed with brine (10 mL) solution, dried over anhydrous Na₂SO₄ and evaporated under vacuum to give the product as colourless oil (**2**) (1.9 g, 95%, Yield). ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 7.36-7.33 (m, 2H), 7.14-7.07 (m, 2H), 5.12 (d, *J* = 4.0 Hz, 1H), 4.72-4.67 (m, 1H), 1.28 (d, *J* = 6.8 Hz, 3H).

10 **Step 2: Preparation of 1-(1-chloroethyl)-4-fluorobenzene (3)**



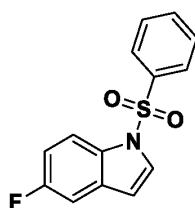
[000321] To a stirred solution 1-(4-fluorophenyl)ethan-1-ol (**2**, 0.5 g, 3.57 mmol) in DCM (5 mL), was added SOCl₂ (0.7 mL, 7.10 mmol) drop wise at 0 °C and the reaction mixture was stirred at rt for 1 h (Reaction condition **b**). The reaction mixture was evaporated under vacuum and dried to afford the product as brown oil (**3**) (0.5 g, 89%, Yield). ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 7.53-7.51 (m, 2H), 7.21-7.16 (m, 2H), 5.36-5.33 (m, 1H), 1.76 (d, *J* = 6.8 Hz, 3H).

Synthesis of 1-ethyl-5-fluoro-1H-indole-2-carbaldehyde (Intermediate for Compound-39)



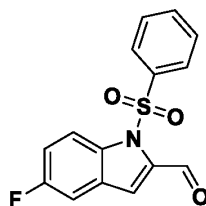
20

Step 1: Preparation of 5-fluoro-1-(phenylsulfonyl)-1H-indole (3)

**3**

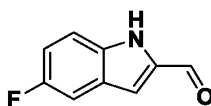
[000322] To a solution of sodium hydride (0.06 g, 15 mmol) in DMF (10 mL) was added a solution of 5-fluoro-1H-indole (**1**, 0.2 g, 15 mmol) in DMF at 0°C, drop wise over 15 min. followed by addition of a solution of benzenesulfonyl chloride (**2**, 0.26 g, 15 mmol) in DMF at 0°C and the reaction mixture was stirred for 2 h at rt under N₂ atmosphere (Reaction condition **a**). To the reaction mixture was added ice cold water (50 mL), then the precipitate was filtered off and washed with ice cold water to obtain brown solid (**3**) (0.25 g, 62.50 % Yield). MS (ESI) *m/z* 275.0 (M+H)⁺.

10 Step 2: Preparation of 5-fluoro-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (4)

**4**

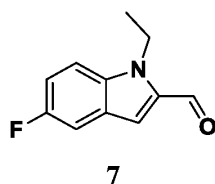
[000323] To a solution of 5-fluoro-1-(phenylsulfonyl)-1H-indole (**3**, 0.250 g, 1.0 mmol) in dry THF (50 mL) was added lithium diisopropylamide 1M in THF (0.5 mL g, 1.0 mmol) at -78 °C, followed by addition of dry DMF (0.11 mL, 1.5 mmol) at -78 °C and stirred for 10 min at -78 °C under N₂ atmosphere (Reaction condition **b**). To the reaction mixture was added aqueous ammonium chloride (20 mL) and extracted with EtOAc. Organic layer was washed with saturated NH₄Cl solution, brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain brown solid (**4**) (0.150 g, 54.54 % Yield). MS (ESI) *m/z* 304.1 (M+H)⁺.

Step 3: Preparation of 5-fluoro-1H-indole-2-carbaldehyde (5)

**5**

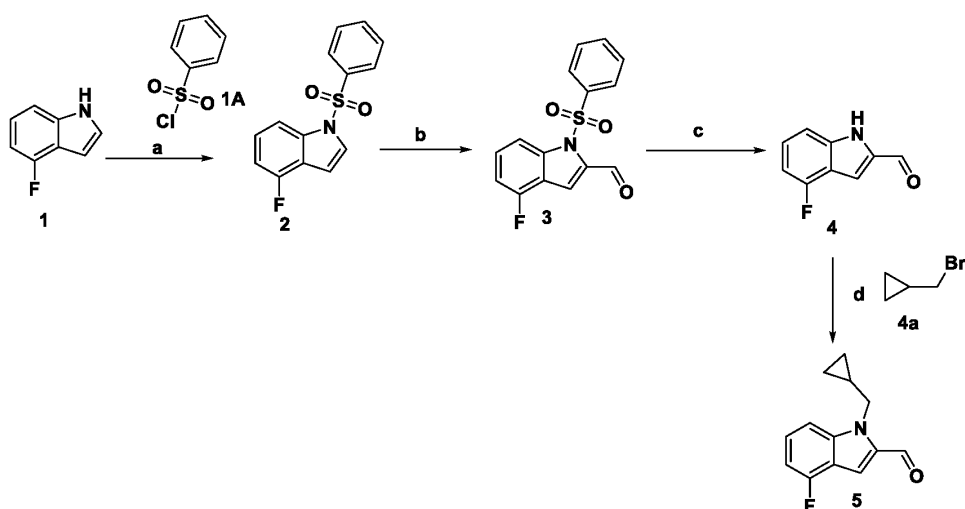
[000324] To the stirred solution of 5-fluoro-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (**4**, 1.85 g, 6.105 mmol) in THF (50 mL), was added TBAF (1M in THF) (9.15 mL, 9.158 mmol) at rt (Reaction condition **c**). The reaction mixture was stirred at rt for 12 h. The reaction mixture was diluted with water and extracted with ethyl acetate (50 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulfate and evaporated to get crude product. The crude residue was purified by gradient column chromatography using 15-25% ethyl acetate in hexane to afford the 5-fluoro-1H-indole-2-carbaldehyde as sticky solid (**5**) (0.65 g, 65% Yield) MS (ESI): Mass calcd. for C₉H₆FNO, 163.15; m/z found, 164.0 (M+H)⁺.

10 **Step 4: Preparation of 1-ethyl-5-fluoro-1H-indole-2-carbaldehyde (7)**

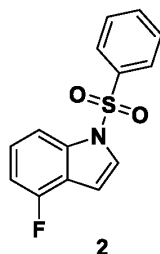


[000325] To the stirred solution of 5-fluoro-1H-indole-2-carbaldehyde (**5**, 0.6 g, 3.98 mmol) in DMF (50 mL), were added potassium carbonate (1.64 g, 11.94 mmol) and ethyliodide (**6**, 0.43 mL, 5.4 mmol) at rt (Reaction condition **d**). The reaction mixture was stirred at rt for 12 h. The reaction mixture was diluted with water and extracted with ethyl acetate (50 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulphate and evaporated to give the crude product. The crude residue was purified by gradient column chromatography using 3-7% ethyl acetate in hexane to afford the 1-(cyclopropylmethyl)-5-fluoro-1H-indole-2-carbaldehyde as sticky solid (**7**) (0.3 g, 43.6 % Yield). MS (ESI): Mass calcd. for C₁₁H₁₀FNO, 191.07; m/z found, 192.1 [M+H]⁺.

Synthesis of 1-(cyclopropylmethyl)-4-fluoro-1H-indole-2-carbaldehyde (Intermediate for Compound-40)

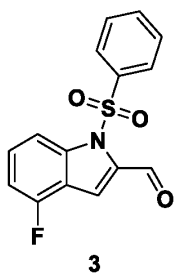


Step 1: Preparation of 4-fluoro-1-(phenylsulfonyl)-1H-indole (2)



[000326] To a solution of sodium hydride (0.88 g, 22.2 mmol) in DMF (50 mL) was added solution of 4-fluoro-1H-indole (**1**, 3.0 g, 22.2 mmol) in DMF at 0 °C, dropwise over 15 min. Benzenesulfonyl chloride in DMF (2.86 mL, 22.2 mmol) was added at 0°C and stirred for 2 h at rt under N₂ atmosphere (Reaction condition **a**). To the reaction mixture was added ice cold water (50 mL), then filtered off the precipitate and washed with ice cold water to obtain white solid (**2**). (7.0 g - crude).

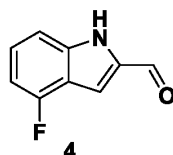
Step 2: Preparation of 4-fluoro-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (3)



[000327] To a solution of 4-fluoro-1-(phenylsulfonyl)-1H-indole (**2**, 7.0 g, 22.0 mmol) in dry THF (60 mL) was added lithium diisopropylamide 2M in THF (10.9 mL, 22.0 mmol) at -78 °C and stirred for 5-8 min, followed by addition of dry DMF (2.5

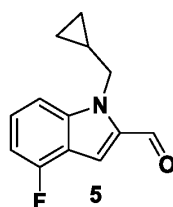
mL, 33.0 mmol) at -78 °C and stirred for 10 min at -78 °C under N₂ atmosphere (Reaction condition **b**). To the reaction mixture was added aqueous ammonium chloride (20 mL), then extracted in to EtOAc. Organic layer was washed with saturated NH₄Cl solution and brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain red liquid (**3**) (6.80 g, 88.31 %).

Step 3: Preparation of 4-fluoro-1H-indole-2-carbaldehyde (4)



[000328] To a solution of 4-fluoro-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (**4**, 3.0 g, 9.9 mmol) in dry THF (20 mL) was added tetrabutyl ammonium fluoride 1M in THF (14.8 mL) and the reaction mixture was stirred for about 12 h under rt (Reaction condition **c**). The reaction mixture was quenched with water and, then extracted with ethyl acetate (50 mL x 3). Combined organic extracts were washed with brine, dried over sodium sulfate, filtered and evaporated to get crude product. Crude residue was purified by gradient column chromatography using 5-10% ethyl acetate in hexane to get the product as yellow solid (**4**). (Yield: 99%, 1.6 g). MS (ESI): Mass calcd. for C₉H₆FNO, 163.04; *m/z* found 164 (M+H)⁺.

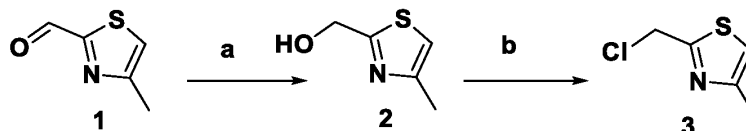
Step- 4: Preparation of 1-(cyclopropylmethyl)-4-fluoro-1H-indole-2-carbaldehyde (5)



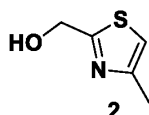
[000329] To a stirred solution of 4-fluoro-1H-indole-2-carbaldehyde (**4**, 1.6 g, 9.877 mmol) in DMF (10 mL), was added potassium carbonate (6.8g, 49.38mmol) followed by (bromomethyl)cyclopropane (6, 1.4 mL, 10.65 mmol) and the reaction mixture was stirred at rt for 12h (Reaction condition **d**). The reaction mixture was quenched with water, extracted with ethyl acetate (30 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulfate, filtered and evaporated to get crude product. Crude residue was purified by gradient column chromatography using 5-10% ethyl acetate in hexane to get the product as brown liquid (**5**). (Yield: 47.6%, 1 g). ¹HNMR (400 MHz, DMSO) δ (ppm): 9.90 (s, 1H), 7.55-7.50 (m, 2H),

7.40-7.35 (m, 1H), 6.95-6.90 (m, 1H), 4.46 (d, $J = 8$ Hz, 2H), 1.22-1.21 (m, 1H), 0.42-0.36 (m, 4H). MS (ESI): Mass calcd. for $C_{13}H_{12}FNO$, 217.24; m/z found, 218 $[M+H]^+$.

Synthesis of 2-(chloromethyl)-4-methylthiazole (Intermediate for Compound-41)

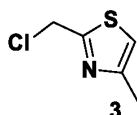


5 Step 1: Preparation of (4-methylthiazol-2-yl)methanol (2)



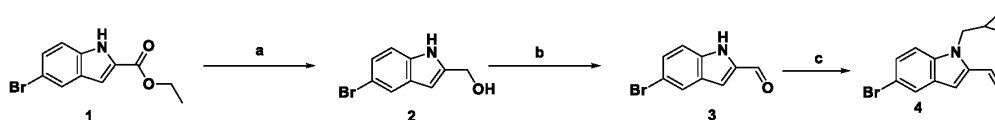
[000330] To the stirred solution of 4-methylthiazole-2-carbaldehyde (**1**, 1 g, 7.8 mmol) in MeOH (10 mL), was added $NaBH_4$ (0.5 g, 15.6 mmol) portion wise at 0 °C and stirred at rt for 1 h (Reaction condition **a**). The reaction mixture was quenched with ice and the MeOH was evaporated. To the resulting crude added water (5 mL) and extracted with EtOAc (2 X 20 mL). Organic layer was washed with brine (5 mL) solution, dried over anhydrous Na_2SO_4 and evaporated under vacuum to give the product as brown oil (**2**) (1 g, 79.5%, Yield). MS (ESI): mass calcd. for C_5H_7NOS 129.02; m/z found 130.1 $(M+H)^+$.

15 Step 2: Preparation of 2-(chloromethyl)-4-methylthiazole (3)

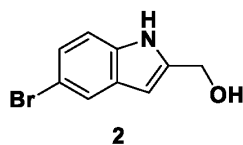


[000331] To a stirred solution (4-methylthiazol-2-yl)methanol (**2**, 1 g, 7.7 mmol) in DCM (20 mL), was added $SOCl_2$ (0.89 mL, 11.55 mmol) drop wise at 0 °C and the reaction mixture was stirred at rt for 1 h (Reaction condition **b**). The reaction mixture was evaporated under vacuum and dried to afford the product as brown oil (**3**) (1 g, 88.3 %, Yield). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.91 (s, 1H), 4.82 (s, 2H), 2.45 (s, 3H).

Synthesis of 5-bromo-1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde (Intermediate for Compound-43)

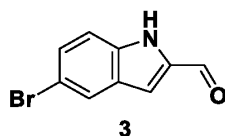


25 Step-1: Preparation of (5-bromo-1H-indol-2-yl)methanol (2)



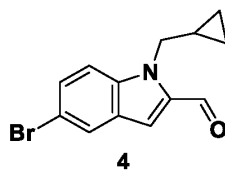
[000332] To a solution of ethyl 5-bromo-1H-indole-2-carboxylate (**1**, 5.0 g, 18.6 mmol) in THF (35 mL) was added solution of 1 M lithium aluminum hydride in THF (37.2 mL, 37.2 mmol) at 0 °C, dropwise over 20 min. Reaction mixture was stirred for 2 h at rt under N₂ atmosphere (Reaction condition **a**). To the reaction mixture ice cold aq.NH₄Cl (20 mL) was added drop wise at 0 °C, diluted with water and extracted with ethyl acetate (2 X 200 mL). Organic layer was dried using Na₂SO₄ and evaporated. The crude was purified by gradient column chromatography using 20% ethyl acetate in hexane to afford pink coloured solid (**2**) (4.1 g, 97% yield). MS (ESI): Mass calcd. for C₉H₈BrNO, *m/z* 226.07 found 228.0[M+H]²⁺.

Step-2: Preparation of 5-bromo-1H-indole-2-carbaldehyde (3)



[000333] To a solution of (5-bromo-1H-indol-2-yl) methanol (**2**, 4.1 g, 18.1 mmol) in chloroform (50 mL) was added MnO₂ (15.7 g, 181 mmol) and heated at 90°C for 2 h under N₂ atmosphere (Reaction condition **b**). Reaction mixture was filtered off and evaporated the filtrate to obtain crude. The crude was purified by gradient column chromatography using 20% ethyl acetate in hexane to afford pink coloured solid (**3**) (4.1 g, 97% yield). MS (ESI): Mass calcd. for C₉H₆BrNO, *m/z* 224.06 found 226.0[M+H]²⁺.

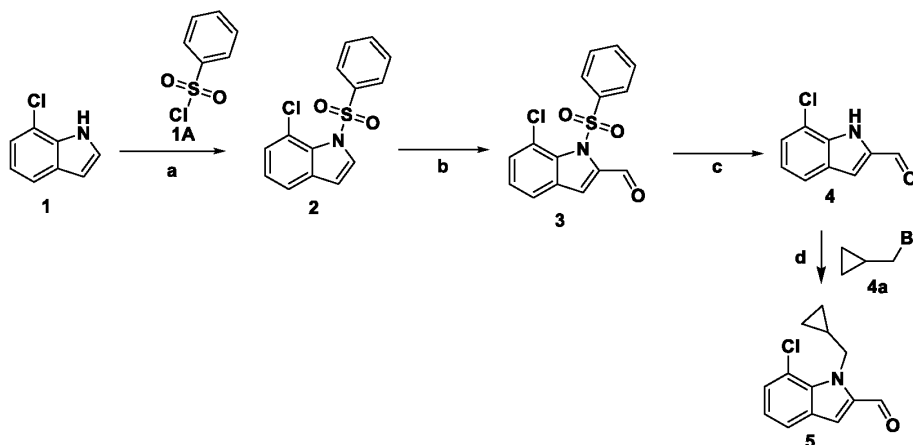
Step-3: 5-bromo-1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde (4)



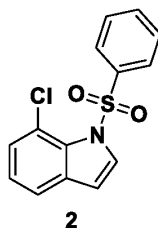
[000334] To the stirred solution of 5-bromo-1H-indole-2-carbaldehyde (**3**, 1.18 g, 5.22 mmol) in DMF (20 mL), were added potassium carbonate (1.4 g, 10.44 mmol) and (bromomethyl)cyclopropane (0.78 mL, 7.8 mmol) at rt. The reaction mixture was stirred at rt for 12 h (Reaction condition **c**). The reaction mixture was diluted with water and extracted with ethyl acetate (50 mL x 2). Combined organic extracts were washed

with brine, dried over sodium sulfate and evaporated to give the crude product. The crude was purified by gradient column chromatography using 20% ethyl acetate in hexane to afford the 5-bromo-1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde as sticky solid (**4**) (0.9 g, 62% Yield). MS (ESI): Mass calcd. for $C_{13}H_{12}BrNO$, 278.15; m/z found, 280.0 $[M+H]^+$.

Synthesis of 7-chloro-1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde (Intermediate for Compound-44)



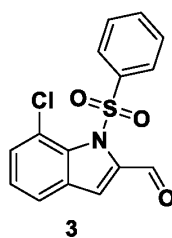
Step 1: Preparation of 7-chloro-1-(phenylsulfonyl)-1H-indole (2)



10

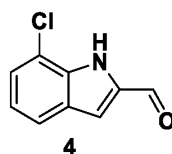
[000335] To a solution of sodium hydride (1.68 g, 42 mmol) in DMF (10 mL), was added solution of 7-chloro-1H-indole (**1**, 3.2 g, 21 mmol) in DMF at 0°C, dropwise over 15 min. Benzenesulfonyl chloride in DMF (2.8 mL, 23 mmol) was added at 0°C and stirred for 2 h at rt under N_2 atmosphere (Reaction condition **a**). To the reaction mixture, ice cold water (50 mL) was added and filtered off the precipitate. The precipitate was washed with ice cold water and purified by gradient column chromatography using 30% ethyl acetate in hexane to afford title compound as pale brown solid (**2**) (5 g, 81.8%). MS (ESI): Mass calcd. for $C_{14}H_{10}ClNO_2S$, 219.01; m/z found, 220.1 $[M+H]^+$.

Step 2: Preparation of 7-chloro-1-(cyclopropylmethyl)-1H-indole-2-carbaldehyde (3)



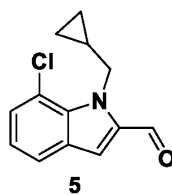
[000336] To a solution of 7-chloro-1-(phenylsulfonyl)-1H-indole (**2**, 5 g, 17 mmol) in dry THF (50 mL), was added lithium diisopropylamide 1.5 M in THF (17.0 mL, 34 mmol) at -78 °C and stirred for 30 min, followed by addition of dry DMF (1.65 mL, 20 mmol) at -78 °C. It was stirred for 10 min at -78 °C under N₂ atmosphere (Reaction condition **b**). To the reaction mixture was added aqueous ammonium chloride (20 mL) and extracted with EtOAc. Organic layer was washed with saturated NH₄Cl solution and brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude was purified by gradient column chromatography using 30% ethyl acetate in hexane to afford title compound as pale brown viscous liquid (**3**) (3.0 g, 55.3 %). MS (ESI): Mass calcd. for C₁₅H₁₀ClNO₃S, 319.01; *m/z* found, 320.1 [M+H]⁺.

Step 3: Preparation of 7-chloro-1H-indole-2-carbaldehyde (4)



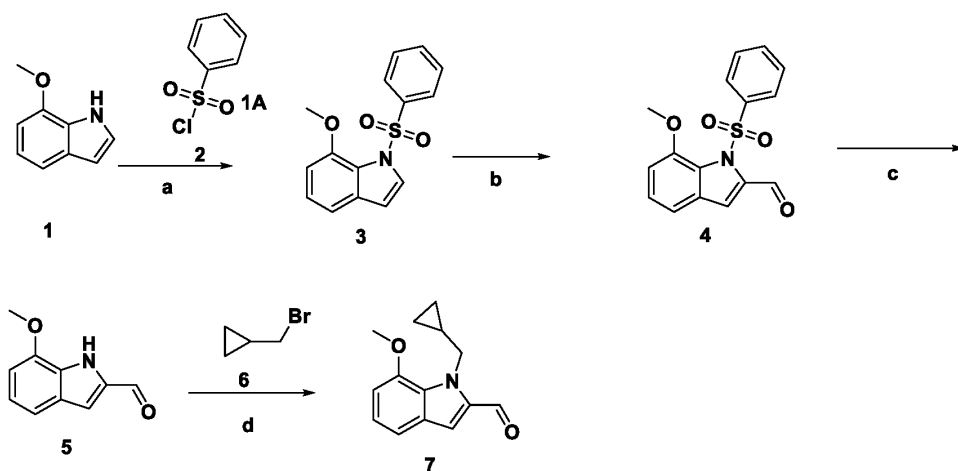
[000337] To the stirred solution of 7-chloro-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (**3**, 3 g, 9.40 mmol) in THF (20 mL), was added 1 M solution of tetrabutyl ammonium fluoride in THF (18.8 mL, 18.8 mmol) and stirred at 80°C for 1 h (Reaction condition **c**). Reaction mixture was cooled to rt, added water (20 mL) and extracted with EtOAc (100 mL). Organic layer was dried over anhydrous Na₂SO₄ and evaporated under vacuum. Crude was purified by column chromatography using 15-20% EtOAc in Hexane to afford the product as brown solid (**4**). (1.6 g, 95% Yield). MS (ESI): Mass calcd. for C₉H₆ClNO, 179.01; *m/z* found 180.1 (M+H)⁺.

Step 4: Preparation of 1-(cyclopropylmethyl)-7-chloro-1H-indole-2-carbaldehyde (5)

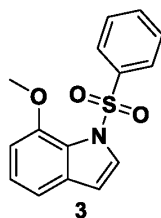


To the stirred solution of 7-chloro-1H-indole-2-carbaldehyde (**4**, 1 g, 5.5 mmol) in DMF (20 mL), were added cesium carbonate (3.5 g, 11 mmol) and (bromomethyl)cyclopropane (**4a**, 0.65 mL, 6.7 mmol) at rt (Reaction condition **d**). The reaction mixture was stirred at rt for 12 h. The reaction mixture was diluted with water and extracted with ethyl acetate (50 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulfate and evaporated to give the crude product. The crude was purified by gradient column chromatography using 20% ethyl acetate in hexane to afford the 1-(cyclopropylmethyl)-7-chloro-1H-indole-2-carbaldehyde as sticky solid (**5**) (0.7 g, 54% Yield). ¹HNMR (400 MHz, CDCl₃) δ (ppm): 9.87 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H) 7.29 (s, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 5.00-4.92 (m, 2H), 1.36-1.32 (m, 2H), 1.25 (m, 1H), 0.43-0.41 (m, 2H). MS (ESI): Mass calcd. for C₁₃H₁₂ClNO, 233.06; *m/z* found, 234.1 [M+H]⁺.

Synthesis of 1-(cyclopropylmethyl)-7-methoxy-1H-indole-2-carbaldehyde (Intermediate for Compound-47)



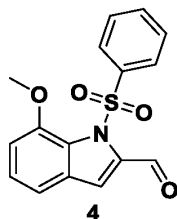
Step 1: Preparation of 7-methoxy-1-(phenylsulfonyl)-1H-indole



[000338] To a solution of sodium hydride (1.6 g, 40 mmol) in DMF (10 mL) was added a solution of 7-methoxy-1H-indole (**1**, 3 g, 20 mmol) in DMF at 0 °C, drop wise

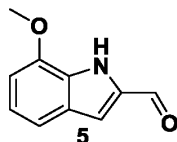
over 15 min. followed by addition of a solution of benzenesulfonyl chloride (**2**, 2.86 mL, 22 mmol) in DMF at 0 °C and the reaction mixture was stirred for 2 h at rt under N₂ atmosphere. To the reaction mixture was added ice cold water (50 mL), then the precipitate was filtered off and washed with ice cold water to obtain brown solid (**3**) (5.6 g, 97.5 % Yield). MS (ESI) m/z 288.1 (M+H)⁺.

Step 2: Preparation of 7-methoxy-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde



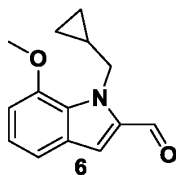
[000339] To a solution of 7-methoxy-1-(phenylsulfonyl)-1H-indole (**3**, 3 g, 10.4 mmol) in dry THF (50 mL) was added lithium diisopropylamide 1M in THF (5.2 mL, 20 mmol) at -78 °C and stirred for 45 min at same temperature. Dry DMF (1 mL, 12 mmol) was added at -78 °C and stirred for 10 min. To the reaction mixture was added aqueous ammonium chloride (20 mL) and extracted with EtOAc. Organic layer was washed with saturated NH₄Cl solution and brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain brown solid (**4**) (1.2 g, 37.5 % Yield). MS (ESI) m/z 304.1 (M+H)⁺.

Step 3: Preparation of 7-methoxy-1H-indole-2-carbaldehyde



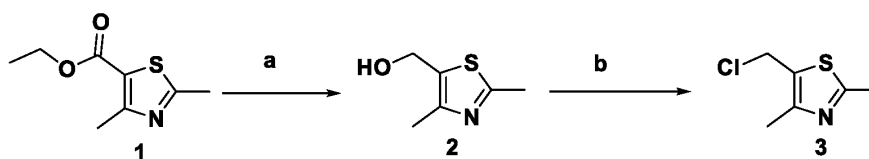
[000340] To the stirred solution of 7-methoxy-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (**4**, 1.1 g, 3.4 mmol) in THF (50 mL), was added TBAF (1M in THF) (6.9 mL, 6.9 mmol) at rt. The reaction mixture was stirred at rt for 12 h. The reaction mixture was diluted with water and extracted with ethyl acetate (50 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulfate and evaporated to get crude product. The crude residue was purified by gradient column chromatography using 15-25% ethyl acetate in hexane to afford the 5-fluoro-1H-indole-2-carbaldehyde as sticky solid (**5**) (0.47 g, 79.6% Yield). MS (ESI): Mass calcd. for C₁₀H₉NO₂, 175.06; m/z found, 176.1 [M+H]⁺.

Step 4: Preparation of 1-(cyclopropylmethyl)-7-methoxy-1H-indole-2-carbaldehyde

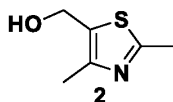


[000341] To the stirred solution of 7-methoxy-1H-indole-2-carbaldehyde (**5**, 0.47 g, 2.6 mmol) in DMF (50 mL), were added potassium carbonate (0.55 g, 5.2 mmol) and (bromomethyl)cyclopropane (**6**, 0.41 mL, 4.02 mmol) at rt. The reaction mixture was stirred at rt for 12 h. The reaction mixture was diluted with water and extracted with ethyl acetate (50 mL x 2). Combined organic extracts were washed with brine, dried over sodium sulphate and evaporated to get crude product. The crude residue was purified by gradient column chromatography using 3-7% ethyl acetate in hexane to afford title compound as sticky solid (**6**) (0.41 g, 68% Yield). MS (ESI): Mass calcd. for C₁₄H₁₅NO₂, 229.1; m/z found, 230.1 [M+H]⁺.

Synthesis of 5-(chloromethyl)-2,4-dimethylthiazole (Intermediate for Compound-48)

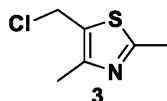


Step 1: (2,4-dimethylthiazol-5-yl)methanol



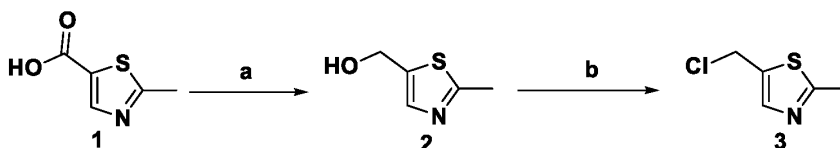
[000342] To the stirred solution of ethyl 2,4-dimethylthiazole-5-carboxylate (**1**, 0.5 g, 2.70 mmol) in THF (10 mL), was added 1M LAH in THF (4 mL, 4.05 mmol) drop wise at 0 °C and stirred at rt for 1 h. The reaction mixture was quenched with saturated NH₄Cl solution, filtered through celite and extracted with EtOAc (2 X 25 mL). Organic layer was washed with brine (5mL) solution, dried over anhydrous Na₂SO₄ and evaporate. The crude was purified by gradient column chromatography using 50-60% EtOAc in Hexane to afford the product as colourless oil. (0.3 g, 79% Yield). MS (ESI): Mass calcd. for C₆H₉NOS, 143.04; m/z found 144.1 (M+H)⁺.

Step 2: 5-(chloromethyl)-2,4-dimethylthiazole

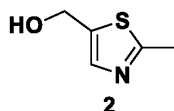


[000343] To a stirred solution of (2,4-dimethylthiazol-5-yl)methanol (**2**, 0.3 g, 2.09 mmol) in DCM (5 mL), was added SOCl₂ (0.3 mL, 4.19 mmol) drop wise at 0 °C and the reaction mixture was stirred at rt for 1 h. The reaction mixture was evaporated under vacuum and dried to afford the product as brown oil. (0.25 g, 75% Yield) (**3**).
¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 4.99 (s, 2H), 2.59 (s, 3H), 2.30 (s, 3H).

Synthesis of 2-bromo-1-(3-ethylbenzo[b]thiophen-2-yl)propan-1-one (Intermediate for Compound-49):

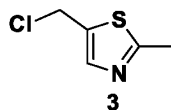


Step 1: (2-methylthiazol-5-yl)methanol



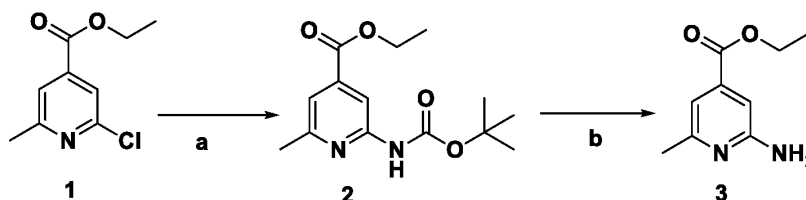
[000344] To the stirred solution of 2-methylthiazole-5-carboxylic acid (**1**, 1.0 g, 6.99 mmol) in THF (10 mL) at -10 °C, was added triethylamine (1.02 mL, 7.34 mmol) followed by ethyl chloroformate (0.66 mL, 6.99 mmol) in THF (2 mL) drop wise at -10 °C and stirred at same temperature for 1 h. The reaction mixture was filtered through celite and the filtrate was cooled to -10 °C. To the filtrate, suspension of NaBH₄ (0.68 g, 17.4 mmol) in water (2 mL) was added and allowed to attain rt and stirred for 2h. The reaction mixture was diluted with 2N NaOH (5 mL) and extracted with EtOAc (2 X 25 mL). Organic layer was washed with brine (5mL) solution, dried over anhydrous Na₂SO₄ and evaporated. The crude residue was purified by gradient column chromatography using 40-60% EtOAc in Hexane to afford the product as yellow oil (**2**) (0.2 g, 25%, Yield). MS (ESI): Mass calcd. for C₅H₇NOS, 129.02; *m/z* found 130.1 (M+H)⁺.

Step 2: 5-(chloromethyl)-2-methylthiazole

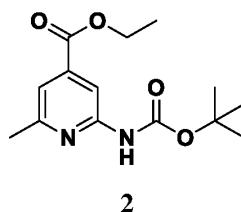


[000345] To a stirred solution of (2-methylthiazol-5-yl)methanol (**2**, 0.2 g, 1.55 mmol) in DCM (5 mL), was added SOCl₂ (0.23 mL, 3.10 mmol) drop wise at 0 °C and the reaction mixture was stirred at rt for 1 h. The reaction mixture was neutralized using cold NaHCO₃ (5 mL) solution and extracted with DCM (2 X 25 mL). Organic layer was washed with brine (5mL) solution, dried over anhydrous Na₂SO₄ and evaporated to afford the product as yellow oil. (0.2 g, 90%, Yield). MS (ESI): Mass calcd. for C₅H₆ClNS, 146.99; *m/z* found 148.1 (M+H)⁺.

10 Synthesis of ethyl 2-amino-6-methylisonicotinate (Intermediate for Compounds-25, 26 & 27)



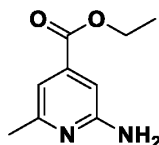
Step 1: Preparation of Ethyl 2-((tert-butoxycarbonyl)amino)-6-methylisonicotinate (2)



[000346] To the stirred solution of ethyl 2-chloro-6-methylisonicotinate (**1**, 5.2 g, 26.1 mmol) in 1,4-dioxane (50 mL), was added tert-butyl carbamate (4.6 g, 39.1 mmol), Cs₂CO₃ (21.3 g, 65.3 mmol), XPhos (1.24 g, 2.61 mmol) followed by Bis(dibenzylideneacetone)palladium (0) (0.75 g, 1.31 mmol) and stirred at 85°C for 16 h (Reaction condition **a**). The reaction mixture was cooled to rt, filtered through celite. To this added water (100 mL) and compound was extracted with EtOAc (200 mL). Organic layer was dried over anhydrous Na₂SO₄ and evaporated under vacuum. Crude was purified by column chromatography using 15-20% EtOAc in Hexane to afford the

product as brown gummy solid (**2**) (3.5g, 58% Yield). MS (ESI): mass calcd. for $C_{14}H_{20}N_2O_4$, 280.14; m/z found 281.2 (M+H)⁺.

Step 2: Preparation of Ethyl 2-amino-6-methylisonicotinate (3)



3

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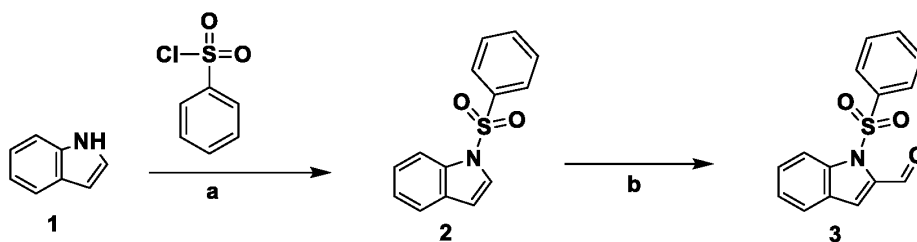
[000347] To the stirred solution of ethyl 2-((tert-butoxycarbonyl)amino)-6-methylisonicotinate (**2**, 3.5 g, 12.5 mmol) in DCM (30 mL), was added TFA (10 mL) and stirred at rt for 16 h (Reaction condition **b**). The reaction mixture was evaporated, added water (20 mL) and basified using saturated Na_2CO_3 solution. The precipitate formed was collected by filtration and dried to afford the product (**3**) as off white solid. (1.6 g, 72% Yield). MS (ESI): mass calcd. for $C_9H_{12}N_2O_2$, 180.09; m/z found 181.1 (M+H)⁺.

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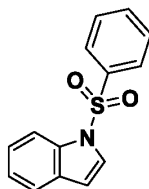
Synthesis of 1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (3) (Intermediate for

Compound-50, 57, 58, 59, 60, 61, 62, 63, 78, 79, 81& 85)

15



Step-a: Synthesis of 1-(phenylsulfonyl)-1H-indole (2)

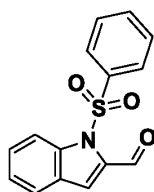


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[000348] To a stirred solution 1H-indole (**1**, 10.0 g, 85.36 mmol) in *N,N*-dimethylformamide (100 mL), sodium hydride (4.08 g, 170.94 mmol) was added slowly at 0 °C the reaction mixture was stirred at 0 °C for 40 min. Benzene sulphonyl

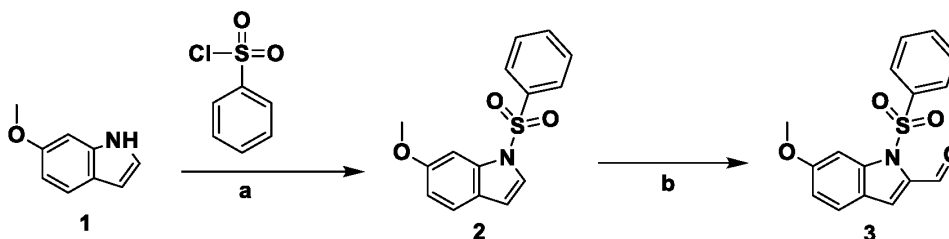
chloride (22.6 g, 128.20 mmol) was added drop wise then reaction mixture was stirred at rt for 1 h. After completion of reaction, the reaction mixture was quenched with ice, solid obtained filtered and dried. The crude was purified by column chromatography (100-200 silica gel) using 20% ethyl acetate in hexane as eluent. The desired fractions were concentrated under reduced pressure to afford 1-(phenylsulfonyl)-1H-indole (**2**) as white solid. Yield: 16.2 g (76%). MS (ESI): 257.12; m/z found, 258.23 [M+H]⁺.

Step-b: Synthesis of 1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (3**)**

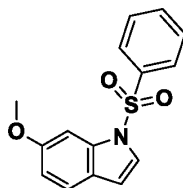


[000349] To a stirred solution 1-(phenylsulfonyl)-1H-indole (**2**, 16.2 g, 62.97 mmol) in tetrahydrofuran (150 mL), 2.5 M n-butyl lithium in hexane (35.5 ml, 89.07 mmol) was added drop wise at -78 °C. The reaction mixture was stirred at -78° for 1 h. *N,N*-Dimethylformamide (6.57 ml, 83.50 mmol) was added at -78 °C and the reaction mixture was further stirred at -78 °C for 1 h. After completion of reaction, the reaction mixture was quenched with ammonium chloride, extracted with ethyl acetate (100 mL × 2). Organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to get crude product. The crude was purified by CombiFlash, using 40.0 g RediSep column and 20% ethyl acetate in hexane as eluent. The desired fractions were concentrated under reduced pressure to afford 1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (**3**) as yellow solid. Yield: 12.6 g (73%). MS (ESI): 285.11; m/z found, 256.39 [M+H]⁺.

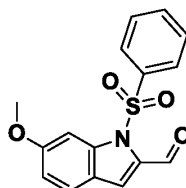
Synthesis of 6-methoxy-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (3**)**
(Intermediate for Compound-51, 67, 80, 82 & 83)



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Step-a: Synthesis of 6-methoxy-1-(phenylsulfonyl)-1H-indole (2)

[000350] To a stirred solution 6-methoxy-1H-indole (**1**, 10.0 g, 68.02 mmol) in
5 *N,N*-dimethylformamide (100 mL), sodium hydride (5.44 g, 136.05 mmol) was added
slowly at 0 °C, the reaction mixture was stirred at rt at 0°C for 40 min. Benzene
sulphonyl chloride (17.8 g, 102.03 mmol) was added drop wise then reaction mixture
was stirred at rt for 1 h. After completion of reaction, the reaction mixture was
quenched with ice, solid obtained filtered and dried. The crude was purified by column
10 chromatography (100-200 silica gel) using 20% ethyl acetate in hexane as eluent. The
desired fractions were concentrated under reduced pressure to afford 6-methoxy-1-
(phenylsulfonyl)-1H-indole (**2**) as white solid. Yield: 16.5 g (84%). MS (ESI): 286.11;
m/z found, 287.52 [M+H]⁺.

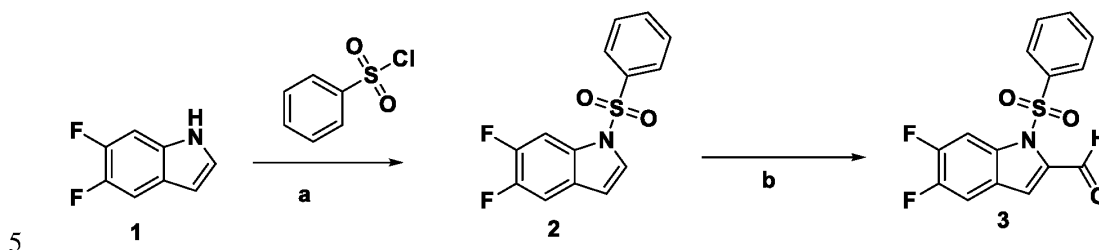
Step-b: 6-methoxy-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (3)

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[000351] To a stirred solution 6-methoxy-1-(phenylsulfonyl)-1H-indole (**2**, 6.0 g,
20.9 mmol) in tetrahydrofuran (60 mL), 2.5 M *n*-butyl lithium in hexane (13.37 ml,
33.44 mmol) was added drop wise at -78 °C and the reaction mixture was stirred at -78
20 °C for 1 h. *N,N*-dimethylformamide (2.3 ml, 31.3 mmol) was added at -78°C and the
reaction mixture was stirred at -78° for 1 h The reaction mixture was quenched with
saturated solution of ammonium chloride, extracted with ethyl acetate (50 mL × 2).
Organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and
evaporated to get crude product. The crude was purified by CombiFlash using 40.0 g
25 RediSep column and 20% ethyl acetate in hexane as eluent. The desired fractions were
concentrated under reduced pressure to afford 6-methoxy-1-(phenylsulfonyl)-1H-

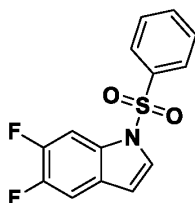
indole-2-carbaldehyde (**3**) as yellow solid. Yield: 5.1 g (78%). MS (ESI): 314.21; m/z found, 315.22 $[M+H]^+$.

Synthesis of 5,6-difluoro-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (Intermediate for Compound-55)



Step-1: Synthesis of 5,6-difluoro-1-(phenylsulfonyl)-1H-indole (2)

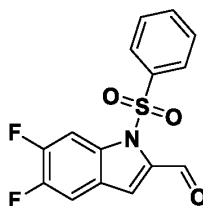
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[000352] To a solution of 5,6-difluoro-1H-indole (**1**, 5.0 g, 32.67 mmol) in *N,N*-dimethylformamide (50 mL), sodium hydride (60%, 3.1 g, 81.61 mmol) was added portion wise over 15 min at 0 °C. After 15 min benzenesulfonyl chloride (6.4 mL, 49.0 mmol) was added at 0 °C and stirred for 2 h at rt under N₂ atmosphere. After completion of reaction, ice cold water (150 mL) was added to reaction mixture. The solid precipitated was filtered off and washed with ice cold water. The crude was purified by CombiFlash using 40 g RediSep and 20% ethyl acetate in hexane as eluent to afford 5,6-difluoro-1-(phenylsulfonyl)-1H-indole (**2**) as off white solid. Yield: 8.8 g (92.63%). MS (ESI): 293; m/z found, 294.01 $[M+H]^+$.

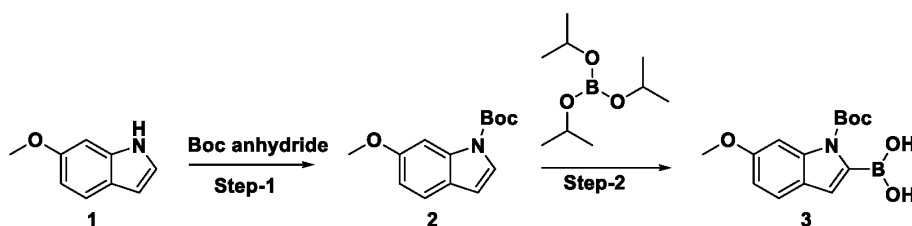
25 **Step-2: Synthesis of 5,6-difluoro-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (3)**



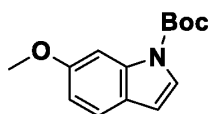
[000353] To a solution of 5,6-difluoro-1-(phenylsulfonyl)-1H-indole (**2**, 8.8 g, 30.12 mmol) in dry tetrahydrofuran (80 mL), was added 2.5 M n-butyllithium in hexane (20.0 mL, 45.37 mmol) at -78 °C and stirred for 45 min, followed by addition of anhydrous *N,N*-dimethylformamide (2.5 mL, 45.37 mmol) at -78 °C. The reaction mass was stirred for 30 min at -78 °C under N₂ atmosphere. After completion of reaction, reaction mixture was quenched with aqueous ammonium chloride (30 mL) and extracted with ethyl acetate (100 mL×2). The organic layer was washed with saturated ammonium chloride solution and brine (100mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by CombiFlash using 40 g RediSep and 30% ethyl acetate in hexane as eluent to afford 5,6-difluoro-1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (**3**) as yellow liquid. Yield: 7.0 g, (72.9 %). MS (ESI): 321.30; *m/z* found, 322.1 [M+H]⁺.

Synthesis of (1-(tert-butoxycarbonyl)-6-methoxy-1H-indol-2-yl)boronic acid

(Intermediate for Compound-86)



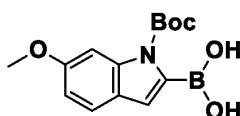
Step-1: Synthesis of tert-butyl-6-methoxy-1H-indole-1-carboxylate (2)



[000354] To a stirred solution of 6-methoxy-1H-indole (**1**, 2.0 g, 13.64 mmol) in dichloromethane (20 mL), was added triethylamine (5.60 mL, 40.8 mmol), *N,N*-dimethyl aminopyridine (0.08 g, 0.68 mmol) and boc-anhydride (3.9 mL, 16.3 mmol) at 0°C and then the reaction mixture was stirred at room temperature for 16h. After completion of reaction, the reaction mixture was diluted with dichloromethane (100 mL × 3). The organic phase was washed with water, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude compound. The

crude was purified by CombiFlash using 40.0 g RediSep column and 1-5% ethyl acetate in hexane as eluent to afford tert-butyl-6-methoxy-1H-indole-1-carboxylate (**2**) as oily liquid. Yield: 3.0 g (89%). MS (ESI): 247.12; m/z found, 246.01[M-H]⁻¹.

Step-2: Synthesis of (1-(tert-butoxycarbonyl)-6-methoxy-1H-indol-2-yl)boronic acid (3**)**



[000355] To a stirred solution of tert-butyl-6-methoxy-1H-indole-1-carboxylate (**2**, 2.5 g, 10.12 mmol), triisopropyl borate (**2**, 2.7 mL, 20.24 mmol) in tetrahydrofuran (25 mL), was added lithium diisopropylamide 1M in tetrahydrofuran (10 mL, 20.24 mmol) drop wise at 0°C and the reaction mixture was stirred at 0 °C for 3 h. After completion of reaction, the reaction mixture was quenched with saturated solution of ammonium chloride, extracted with ethyl acetate (50 mL × 2). Organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to get crude product. The crude was purified by CombiFlash using 40.0 g RediSep column and 10-20% ethyl acetate in hexane as eluent. The desired fractions were concentrated under reduced pressure to afford (1-(tert-butoxycarbonyl)-6-methoxy-1H-indol-2-yl)boronic acid (**3**) as off-white solid. Yield: 1.3 g, (44%).

[000356] ¹HNMR (400 MHz, DMSO-d₆) δ (ppm): 8.11 (s, 2H), 7.65 (s, 1H), 7.43 (d, *J* = 8.56 Hz, 1H), 6.82 (d, *J* = 8.56 Hz, 1H), 6.55 (s, 1H), 3.79 (s, 3H), 1.59 (s, 9H). MS (ESI): Mass calculated for C₁₄H₁₈BNO₅, 291.13; m/z found 191.01[M+H-100]⁺¹.

Example 2

General Procedure for biological Evaluation

FP Binding assay

[000357] Binding of compounds with PAD4 was detected by FP assay. PAD4 was diluted to 1 uM in assay buffer (100 mM HEPES, 50 mM NaCl, 1 mM DTT, 5% Glycerol and 1 mM CHAPS) and added to wells containing various concentration of compounds or DMSO vehicle (1%) in a 384 well black plate. 10 nM of fluorescein labelled probe (JPAD -00085) was added to the plate. Assay plate was incubated for 60 minutes at RT before measuring FP reading at FP module (λ_{ex} 485/λ_{em} 535 nm) on Pherastar. IC₅₀ was calculated using XL-fit software model 205. (Lewis et. al, Nat Chem Biol. 2015, 11(3), 189-91).

Ammonia Release Biochemical assay

[000358] Citrullination assay was detected via ammonia release. PAD4 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) added to wells containing various concentration of compound or DMSO vehicle (1 % final) in black 384 well plate. Following a 60-min preincubation at RT, the reaction was initiated by the addition of substrate (1.5 mM BAEE in 200 mM HEPES, 50 mM NaCl, 350 uM CaCl₂, 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 RT for 90 min before measuring fluorescence's (λ_{ex} 405/ λ_{em} 460 nm) on Tecan reader. IC₅₀ was calculated using XL-fit software model 205. (Lewis et. al Nat Chem Biol. 2015, 11(3), 189-91).

Anti-PAD4 activity:

[000359] Table 1, below, shows the activity of selected compounds of this invention in the PAD4 assays described above. Compounds having an activity designated as "A" provided IC₅₀ ≤ 1uM; compounds having an activity designated as "B" provided IC₅₀ 1 – 10 uM; and compounds having an activity designated as "C" provided IC₅₀ ≥10 uM.

Table 1: PAD4 activity

Compound No.	NH3 release biochemical assay PAD4 IC ₅₀ (uM)	FP binding assay PAD4 IC ₅₀ (uM)
1	C	nd
2	B	nd
3	A	B
4	A	nd
5	C	nd
6	C	nd
7	C	nd
8	C	nd
9	B	nd
10	A	B
11	B	B

12	A	B
13	A	A
14	B	B
15	A	B
16	A	A
17	A	B
18	B	B
19	B	B
20	B	B
21	A	B
22	B	B
23	A	A
24	A	B
25	A	B
26	A	B
27	B	C
28	A	A
29	A	A
30	A	A
31	B	C
32	C	C
33	B	A
34	A	B
35	A	nd
36	A	A
37	A	nd
38	B	B
39	A	A
40	B	nd
41	A	nd
42	A	nd
43	B	nd
44	A	nd

45	A	nd
46	C	nd
47	A	nd
48	B	nd
49	A	nd
50	B	nd
51	A	nd
52	A	nd
53	A	nd
54	A	nd
55	A	nd
56	B	nd
57	B	nd
58	A	nd
59	B	nd
60	A	nd
61	A	nd
62	A	nd
63	A	nd
64	A	nd
65	B	nd
66	C	nd
67	A	nd
68	A	nd
69	A	nd
70	A	nd
71	A	nd
72	A	nd
73	A	nd
74	A	nd
75	A	nd
76	A	nd
77	A	nd

78	A	nd
79	A	nd
80	A	nd
81	B	nd
82	A	nd
83	A	nd
84	B	nd
85	A	nd
86	nd	nd

nd= not determined

[000360] Table 1 illustrates that most of the tested compounds were found to be active against the PAD4 enzyme when evaluated through both Ammonia Release Biochemical and FP Binding assays. The IC₅₀ values display the efficacy of the compounds in inhibiting the PAD4 enzyme activity. IC₅₀ value indicates how much of a particular drug or a compound is needed to inhibit a given biological process or component of a process such as an enzyme. A low value of IC₅₀ denotes high inhibition efficacy of the test compound (Compounds 1-48 as described herein). However, in the above Table 1, high efficacy is denoted by “A”, “B”, and “C”, wherein “A” having least value of IC₅₀ and thus most effective.

[000361] The ammonia release biochemical assay showed that 55 out of 86 compounds have an IC₅₀ value of $\leq 1\mu\text{M}$ denoted by “A”. These 55 compounds were 3, 4, 10, 12, 13, 15-17, 21, 23-26, 28-30, 34-37, 39, 41, 42, 44, 45, 47, 49, 51-55, 58, 60-64, 67-80, 82, 83 & 85.

[000362] On the other hand, the FP Binding assay showed that 9 of the compounds to be actively inhibiting PAD4 enzyme activity. The individual compounds are 13, 16, 23, 28-30, 33, 36, and 39, respectively.

[000363] Therefore, it may be inferred that compounds- 3, 4, 10, 12, 13, 15-17, 21, 23-26, 28-30, 34-37, 39, 41, 42, 44, 45, 47, 49, 51-55, 58, 60-64, 67-80, 82, 83 & 85 can help in treating PAD4 mediated disorders.