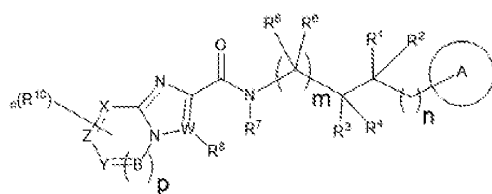


HETEROCYCLIC COMPOUNDS AS PRMT5 INHIBITORS

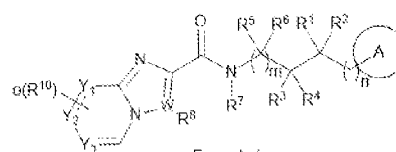
TECHNICAL FIELD OF THE INVENTION

[0001] The present disclosure relates to the field of pharmaceutical chemistry in general. In particular, the present disclosure relates to the development of PRMT5 inhibitory compounds of Formula I, Formula Ia, or Formula Ib their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites and prodrugs thereof, active against the PRMT5 protein.

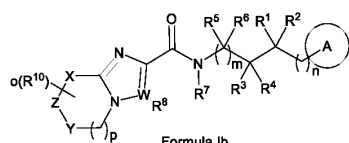
It further relates to the synthesis and characterization of aforementioned compounds to exhibit PRMT5 inhibitory activity.



Formula I



Formula Ia



Formula Ib

[0002] The compounds described herein are substituted heterocyclic compounds that inhibit PRMT5 enzyme and may be used in the treatment of a condition mediated by PRMT5 or a proliferative disorder or cancer.

BACKGROUND OF THE INVENTION

[0003] The methylation of arginine, carried out by argininemethyltransferases (PRMTs), is a modification which is as common as phosphorylation and ubiquitination (Larsen SC *et al.*, Science Signaling, 2016, 9(443): RS9). The family of PRMTs is a group of nine proteins, which are responsible for the catalytic transfer of a methyl group from S-adenosylmethionine (SAM) to the guanidine nitrogen atoms of arginine (Bedford M.T. *et al.*, Molecular Cell, 2009, 33:1-13; Yang Y *et al.*, Nature Review Cancer, 2013, 13:37-50).

[0004] There are three main categories according to the catalytic activity of PRMTs: Type I (PRMT1, PRMT2, PRMT3, PRMT4, PRMT6 and PRMT8), Type II (PRMT5 and

PRMT9), and Type III (PRMT7). Among these enzymes, PRMT5 is the major enzyme responsible for mono- and symmetric dimethylation of arginine. This protein is the regulatory protein possessing critical biological function in a wide range of cellular processes. The methylation by PRMT5 is known to regulate genome organization, transcription, stem cells, primordial germ cells, differentiation, the cell cycle, and spliceosome assembly. It forms an active complex with MEP50 and transfers methyl groups from S-adenosylmethionine (SAM) to histone proteins and transcription factors. These methylations form mono and symmetrically di-methylated arginine residues.

[0005] Human PRMT5 was first identified as Jak-binding protein 1 (JBP1) (Pollack B.P. *et al.*, J. Biological Chemistry, 1999, 274(44):31531-42; Branscombe T.L. *et al.*, J. Biological Chemistry, 2001, 276(35):32971-6) and shown to methylate Histones H2A, H4 on Arg3 (H2AR3, H4R3), and H3 on Arg8 (H3R8) along with a number of non-histone proteins including P53 (Jansson *et al.*, Nature Cell Biology, 2008, 10(12):1431-9), and epidermal growth factor receptor (EGFR) (Hsu J.M. *et al.*, Nature Cell Biology, 2011, 13(2):174-81), NF- κ B (Wei H. *et al.*, Proc. Natl. Acad. Sci, 2013, 110(13):13516-21).

[0006] The activity of PRMT5 has an important role in cell signaling, chromatin remodeling, and control of gene expression and thus in diseases like cancer, kidney and heart diseases, and neurological disorders. It mainly functions as a co-repressor (transcriptional repressor), wherein H4R3me2s antibody is recognized by the DNA methyltransferase DNMT3a. Once recruited, DNMT3a methylates neighboring DNA to further strengthen the associated gene repression by PMRT5 (Fabbri E. *et al.*, EMBO Reports, 2002, 3(7):641-5; Zhao Q. *et al.*, Nature Structural and Molecular Biology, 2009, 16:304-11). Besides being a transcriptional repressor, PRMT5, along with PRMT7, plays an important role in the splicing of mRNA through methylating spliceosomal proteins (Sm proteins D1, D3, B/B' etc.), which are then assembled into small nuclear ribonucleoproteins (snRNPs). Due to this reason, the PRMT5-deficient cells harbor numerous defects in splicing (Brahms H *et al.*, RNA, 2001, 7(11):1531-42; Meister G *et al.*, EMBO J, 2002, 21(21):5853-63; Stopa N. *et al.*, Cellular and Molecular Life Sciences, 2015, 72(11):2014-59).

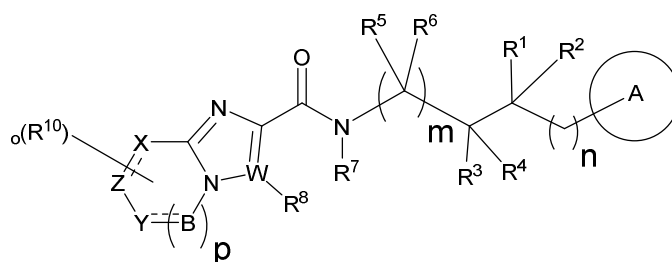
[0007] PRMT5 is emerging as an important enzyme involved in tumorigenesis and stem cell maintenance, as it is highly expressed in several cancer types, including ovarian, lung, lymphoid, glioblastoma, colon, melanoma, gastric, bladder cancers and germ cell tumors (Eckert D. *et al.*, BMC Developmental Biology, 2008, 8(106):1-11; Gu Z. *et al.*,

Biochemistry J, 2012, 446(2):235-41; Bao X. *et al.*, J.Histochem Cytochem, 2013, 61(3):206-17; Nicholas C. *et al.*, PLoS ONE, 2013, 8(9):e74710; Stopa N. *et al.*, Cellular and Molecular Life Sciences, 2015, 72(11):2014-59).

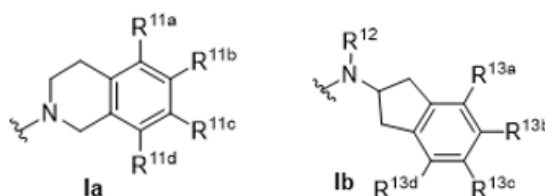
[0008] PRMT5 is therefore considered to be a clinically relevant target and potential. PRMT5 inhibitors are under development as specified in the applications, such as, WO 2017153518A1, WO 2017153186A1, WO2016034671A1, WO216034673A1, WO2016034675A1, WO2016022605A1, and WO2015200677A2. However, there is still a need for novel, potent, PRMT5 inhibitors as anti-cancer therapies.

SUMMARY

[0009] In one example, there is disclosed a compound of Formula I, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein



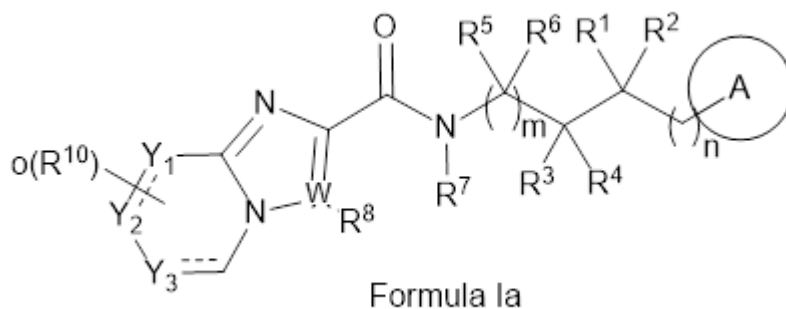
Formula I

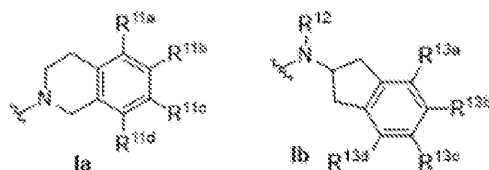


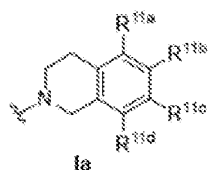
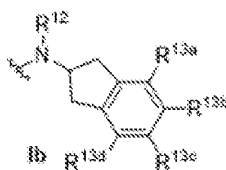
wherein A is selected from  or ; ---- represents optional single or double bond; n is 0 or 1; m is 0 - 2; p is 1 or 2; o is 1 - 3; R¹, R², R³, R⁴, R⁵, and R⁶ are independently selected from hydrogen, halogen, hydroxyl or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one or more groups selected from hydroxyl, or halogen; R⁷, and R¹² are independently selected from hydrogen or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O, or S; W, and B are independently selected from N or C; R⁸ is absent or is selected from hydrogen, halogen,

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SF₅, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a, or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl, or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00010] In another example, there is disclosed a compound of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein

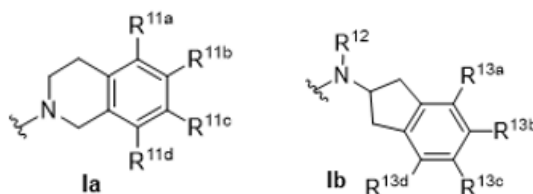
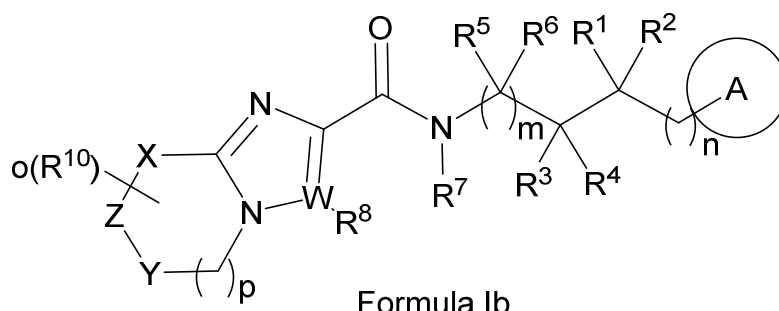




A is selected from  or  ; n is 0 or 1; m is 0 - 2; o is 1 - 3; R¹, R², R³, R⁴, R⁵, and R⁶ are independently selected from the group consisting of hydrogen, halogen, hydroxyl, or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one or more groups selected from hydroxyl, or halogen; R⁷ and R¹² are independently selected from hydrogen, and C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; Y¹, Y², and Y³ are independently selected from N or CH; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR_aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SF₅, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, or SO₂R_a, wherein C₅₋₆ aryl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, cyano, oxo, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl, and C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or or R_a and R_b can be taken

together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00011] In yet another example, there is disclosed a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein

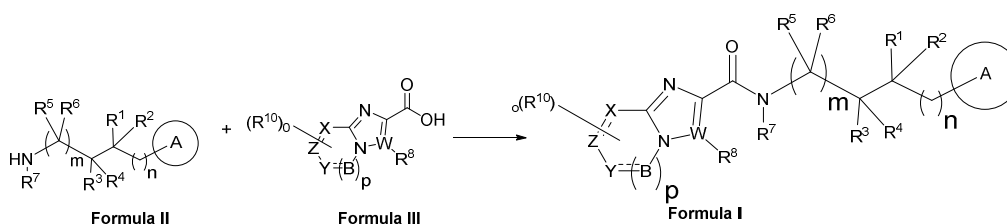


wherein A is selected from or ; n is 0 or 1; m is 0 - 2; p is 1; o is 1 - 3; R¹, R², R³, and R⁴ are independently selected from hydrogen, halogen, hydroxyl, or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, or halogen; R⁵, and R⁶ are independently selected from hydrogen, C₁₋₆ alkyl, or halogen, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, or halogen; R⁷, and R¹² are independently selected from hydrogen or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O, or S; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR_aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b,

NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a, or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

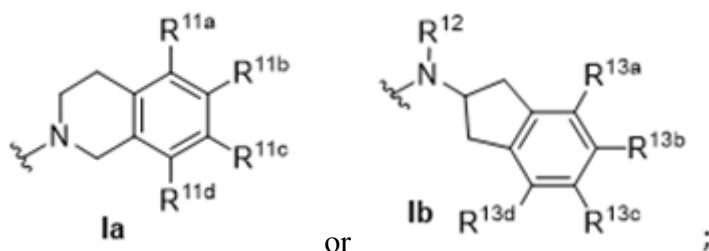
[00012] The present disclosure further describes the process of preparation of compounds of Formula I, Formula Ia, or Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof.

[00012a] In yet another example, there is disclosed a process of preparation of compounds of Formula I as disclosed herein, or its analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, the process comprising reacting Formula II, and Formula III

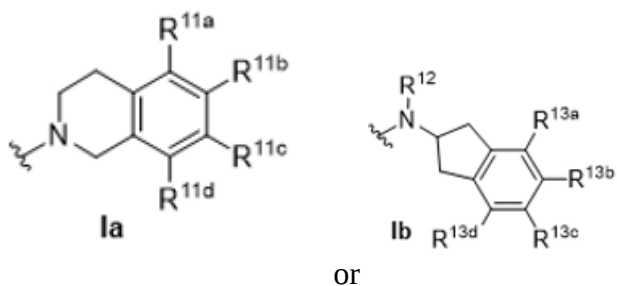


in presence of a coupling reagent and a solvent to obtain the compounds of Formula I, wherein X, Y, and Z of Formula III are independently selected from CR¹⁰, NR¹⁰, O or S; W and B are independently selected from N or C, p is 1 or 2; o is 1 – 3; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl, and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl,

C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, and C₃₋₁₅ heteroaryl are optionally substituted with C₁₋₆ alkyl; n is 0-1; A of Formula II is selected from



n is 0 - 1; m is 0 - 2; o is 1 - 3; R¹, R², R³, and R⁴ are independently selected from hydrogen, halogen, hydroxyl or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, halogen, and combinations thereof; R⁵, and R⁶ are independently selected from hydrogen, C₁₋₆ alkyl or halogen, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, halogen, and combinations thereof; R⁷, and R¹² are independently selected from hydrogen or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₁₋₆ alkoxy; A of Formula I is selected from



---- represents optional single or double bond; n is 0 or 1; m is 0 - 2; p is 1 or 2; o is 1 - 3; R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are independently selected from hydrogen, halogen, hydroxyl or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more groups selected from hydroxyl or halogen; R^7 , and R^{12} are independently selected from hydrogen or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with C_{5-6} aryl, and wherein C_{5-6} aryl is optionally substituted with one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, halogen, hydroxyl, or cyano; R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{13a} , R^{13b} , R^{13c} , and R^{13d} are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl or C_{1-6} alkoxy; X, Y, and Z are independently selected from CR^{10} , NR^{10} , O or S; W, and B are independently selected from N or C; R^8 is absent or is selected from hydrogen, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{3-15} heteroaryl or C_{3-15} heterocyclyl; and R^{10} is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{1-6} alkylamino, $COOR_a$, $C(O)R_b$, $C(S)R_a$, $C(O)NR_aR_b$, $C(S)NR_aR_b$, $NR^aC(O)NR_bR_c$, $N(R_a)SOR_b$, $N(R_a)SO_2R_b$, $NR_aC(O)OR_b$, NR_aR_b , $NR_aC(S)NR_bR_c$, $NR_aC(O)R_b$, $NR_aC(S)R_b$, $SONR_aR_b$, $SO_2NR_aR_b$, $OC(O)NR_aR_b$, $OR_aC(O)OR_b$, $OC(O)NR_aR_b$, $OC(O)R_a$, OR_a , $R_aNR_bR_c$, R_aOR_b , SR_a , SOR_a , SO_2R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C_{5-6} aryl, C_{3-6} cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, $C(O)R_b$, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with $C(O)R_b$, and wherein R_a , R_b , and R_c are independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{3-15} heterocyclyl or C_{3-15} heteroaryl, wherein C_{5-6} aryl, C_{3-6} cycloalkyl, and C_{3-15} heteroaryl are optionally substituted with one or more substituents selected from halogen,

cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00013] In one example, the present disclosure refers to subject matter as defined in the attached set of claims. In yet another example, the present disclosure refers to a pharmaceutical composition comprising a compound of Formula I, Formula Ia, or Formula Ib or a pharmaceutically acceptable salt thereof as disclosed herein together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

[00013a] In an aspect, there is provided a compound, its stereoisomers, pharmaceutically acceptable salts, and pharmaceutical compositions, thereof, which is selected from a group consisting of:

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 1),

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methylimidazo[1,2-a]pyridine-2-carboxamide (Example 2),

N-(2-(3,4-dihydroisoquinolin-2(1H)-yl)-1-hydroxyethyl)-7-(4-fluorophenyl) imidazo[1,2-a]pyridine-2-carboxamide (Example 3),

(S)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-ethyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 4),

(S)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-propyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 5),

(S)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 6),

(S)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 7),

(S)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 8),

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methoxyimidazo[1,2-a]pyridine-2-carboxamide (Example 9),

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-phenylimidazo[1,2-a]pyridine-2-carboxamide (Example 10),

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl) imidazo[1,2-a]pyridine-2-carboxamide (Example 11),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-isopropylimidazo [1,2-a]pyridine-2-carboxamide (Example 12),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 13),

(S)-6-(4-cyanophenyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl) imidazo[1,2-a]pyridine-2-carboxamide (Example 14),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(3,5-dimethyl isoxazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 15),

(S)-6-(3,5-difluorophenyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 16),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl) imidazo[1,2-a]pyridine-2-carboxamide (Example 17),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-isobutyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 18),

(S)-6-(3,6-dihydro-2H-pyran-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 19),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 20),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 21),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 22),

(S)-6-(1-(1-acetylazetidin-3-yl)-1H-pyrazol-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 23),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-isopropyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 24),

(S)-6-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 25),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example-26),

(S)-6-(1-acetylpiperidin-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 27),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2-methylpyrimidin-5-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 28),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(6-methylpyridin-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 29),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(6-methylpyridazin-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 30),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2-methylthiazol-5-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 31),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4,5-dimethylthiazol-2-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 32),

(S)-6-(5-chloropyridin-2-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 33),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 34),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 35),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 36),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-isopropyl-1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 37),

(S)-N-2-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-6-methylimidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 38),

(S)-6-acetamido-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 39),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-sulfamoylimidazo[1,2-a]pyridine-2-carboxamide (Example 40),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(methylsulfonamido)imidazo[1,2-a]pyridine-2-carboxamide (Example 41),

((S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyrimidine-2-carboxamide (Example 42),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrimidine-2-carboxamide (Example 43),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrimidine-2-carboxamide (Example 44),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 45),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 46),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 47),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 48),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 50),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 51),

(S)-6-(1-acetylpiperidin-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 52),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 53),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 57),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 62),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 63),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 64),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-methyl-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 65),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-methyl-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 66),

(S)-6-(azetidin-1-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 69),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(3-fluoropyrrolidin-1-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 70),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-methylpiperazin-1-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 71),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-morpholinoimidazo[1,2-a]pyridine-2-carboxamide (Example 72),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(3-fluoropyrrolidin-1-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 73),
 (S)-6-(4-cyanophenyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 74),
 (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 75),
 N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 76),
 N-((2R,3R)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 77),
 N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 78),
 N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 79),
 N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 80),
 N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 81),
 (S)-N-(3-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 82),
 (S)-N-(3-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 85),

 (S)-6-(difluoromethyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 86),

 (R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 88),
 (R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 89),
 (R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 92),
 (R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 93),
 (R)-6-(4-cyanophenyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methylimidazo[1,2-a]pyrazine-2-carboxamide (Example 95),

N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-trifluoromethylimidazo[1,2-a]pyridine-2-carboxamide (Example 96),

N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 97),

6-(1-acetylpiperidin-4-yl)-N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 98),

N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 99),

N-(4-(3,4-dihydroisoquinolin-2(1H)-yl)-1-hydroxybutan-2-yl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 100),

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 102),

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-7-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 103),

6-cyclopropyl-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 104),

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-7-propyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 105),

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-propyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 106),

(R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methoxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 107a),

(S)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methoxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 107b),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-isopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 108),

N-(2-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-7-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 109),

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 110),

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 111),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-phenyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine-2-carboxamide (Example 112),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 114),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 115),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl)-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine-2-carboxamide (Example 116),

N-((S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 117),

6-(1-acetylpiperidin-4-yl)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide-Isomer-1 (Example 118A),

N-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example-119),

(R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 120A),

(S)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 120B),

(S)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 121A),

(R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 121B),

(R)-6-bromo-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 122),

(S)-6-cyano-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example_123),

(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-fluoroimidazo[1,2-a]pyridine-2-carboxamide (Example 125),

(S)-N-6-(3,3-difluorocyclobutyl)-N2-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 128),

(S)-N-6-cyclohexyl-N2-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 130),

N-6-(3,3-difluorocyclobutyl)-N2-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 134),

(S)-6-benzamido-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 138),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2-fluorobenzamido)imidazo[1,2-a]pyridine-2-carboxamide (Example 139),
 (S)-6-(cyclohexanecarboxamido)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 140),
 (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-carboxamido)imidazo[1,2-a]pyridine-2-carboxamide (Example 141),
 (S)-6-(cyclopropanecarboxamido)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 142),
 (S)-6-(4-cyanobenzamido)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 144),
 6-(4-cyanobenzamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 145),
 6-benzamido-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 146),
 6-(cyclopentanecarboxamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 150),
 rac-(R)-6-(azetidine-1-carbonyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 156),
 (S)-N-(2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)isoxazole-3-carboxamide (Example 157),
 6-(bicyclo[2.2.1]heptane-2-carboxamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 158),
 (S)-N-(2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-5-carboxamide (Example 160),
 (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-ethylimidazo[1,2-a]pyridine-2-carboxamide (Example 165), and
 (S)-6-(1,1-difluoroethyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 166).

[00013b] In another aspect, there is provided a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof as defined above together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

[00014] In one example, the present disclosure further describes a method for the treatment and/or prevention of various diseases, including cancer and infectious diseases, comprising administering to a subject suffering from the proliferative disorder or cancer a therapeutically

effective amount of the compound of Formula I, Formula Ia, or Formula Ib or the pharmaceutical composition, with other clinically relevant cytotoxic agents or non-cytotoxic agents to a subject in need thereof. In yet another aspect, the present disclosure refers to use of the compound as disclosed herein or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treatment and/or prevention of various diseases, including cancer and infectious disease, wherein said medicament is to be administered in combination with other clinically relevant cytotoxic agents or non-cytotoxic agents, wherein the compound or the pharmaceutical composition is to be administered to a subject suffering from the proliferative disorder or cancer.

[00014a] In yet another aspect, the present disclosure refers to use of the compounds as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for the treatment and/or prevention of various diseases including proliferative disorder or cancer; or treatment of cancer, wherein said medicament is to be administered together in combination with other clinically relevant cytotoxic agents or non-cytotoxic agents.

[00014b] In yet another aspect, the present disclosure refers to use of the compounds as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treatment of cancer, wherein said medicament is to be administered in combination with other clinically relevant cytotoxic agents or non-cytotoxic agents.

[00014c] In yet another aspect, the present disclosure refers to use of the compounds as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treatment of cancer, wherein said medicament is to be administered in combination with other clinically relevant immune modulator agents.

[00014d] In yet another aspect, the present disclosure refers to use of the compounds as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treatment of a condition mediated by PRMT5; treatment and/or prevention of a proliferative disorder or cancer; or treatment of cancer selected from hematologic malignancy, solid tumor, B-cell lymphoma, T-cell lymphoma, breast cancer, prostate cancer, pancreatic cancer, gastric cancer, lung cancer, colon cancer, rectal cancer, esophagus cancer, duodenal cancer, tongue cancer, pharyngeal cancer, brain tumor, neurinoma, non-small cell lung cancer, small cell lung cancer, liver cancer, kidney cancer, bile duct cancer, uterine body cancer, cervical cancer, ovarian cancer, urinary bladder cancer, skin cancer, hemangioma, malignant lymphoma, malignant melanoma, thyroid cancer, bone tumor, vascular fibroma, retinoblastoma, penile cancer, pediatric solid cancer, lymphoma, myeloma, leukemia, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic neutrophilic leukemia, chronic eosinophilic leukemia, chronic lymphocytic leukemia (CLL), acute

lymphoblastic leukemia (ALL) or hairy cell leukemia, wherein said medicament is to be administered together in combination with other clinically relevant cytotoxic agents or non-cytotoxic agents.

[00014e] In yet another aspect, the present disclosure refers to use of the compound as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for the treatment and/or prevention of a condition mediated by PRMT5 or a proliferative disorder or cancer selected from hematologic malignancy, solid tumor, B-cell lymphoma, T-cell lymphoma, breast cancer, prostate cancer, pancreatic cancer, gastric cancer, lung cancer, colon cancer, rectal cancer, esophagus cancer, duodenal cancer, tongue cancer, pharyngeal cancer, brain tumor, neurinoma, non-small cell lung cancer, small cell lung cancer, liver cancer, kidney cancer, bile duct cancer, uterine body cancer, cervical cancer, ovarian cancer, urinary bladder cancer, skin cancer, hemangioma, malignant lymphoma, malignant melanoma, thyroid cancer, bone tumor, vascular fibroma, retinoblastoma, penile cancer, pediatric solid cancer, lymphoma, myeloma, leukemia, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic neutrophilic leukemia, chronic eosinophilic leukemia, chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL) or hairy cell leukemia.

[00015] 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

[00016] 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

[00017] 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.

[00018] 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.

[00019] 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.

[00020] The term “including” is used to mean “including but not limited to”. “Including” and “including but not limited to” are used interchangeably.

[00021] In the structural formulae given herein and throughout the present disclosure, the following terms have been indicated meaning, unless specifically stated otherwise.

[00022] The term “effective amount” refers to an amount or concentration of the compound of Formula Ib, Formula Ia, and Formula I that produces a biological response either individually or when present in a pharmaceutical composition. The term effective amount or effective dose can be used interchangeably when measurements are taken either *in vivo*, or *in vitro*.

[00023] The term “cytotoxic agents” or “inhibitors” is used to identify any agents or drugs which is capable of killing cells including cancer cells. These agents or inhibitors may stop cancer cells from growing and dividing and may cause tumors to shrink in size.

[00024] The term “non-cytotoxic agents” or “inhibitors” is used to identify any agents or inhibitors which does not directly kill cells, but instead affects cellular transport and metabolic functions to ultimately produce cell death.

[00025] The term “immune checkpoint inhibitors agents” or “immune modulators agents” are used to identify any agents or inhibitors that blocks certain proteins made by some types of immune system cells, such as T cells, and some cancer cells. These proteins help keep immune responses in check and can keep T cells from killing cancer cells. When these proteins are blocked, the “brakes” on the immune system are released and T cells are able to kill cancer cells better. The immune checkpoint inhibitors include inhibitors against immune checkpoint molecules such as CD27, CD28, CD40, CD122, CD96, CD73, CD47, OX40, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, aiginase, CD137 (also known as 4-1BB), ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, VISTA, PD-1, PD-L1 and PD-L2. The terms “immune modulators agents” and “immune checkpoint inhibitors” are used interchangeably throughout the present disclosure.

[00026] The term “alkyl” refers to straight or branched aliphatic hydrocarbon groups having the specified number of carbon atoms, which are attached to the rest of the molecule by a single atom, which may be optionally substituted by one or more substituents as described hereinafter in the disclosure. For example, which are not limited, C₁₋₆ alkyl refers to an alkyl group having from 1 – 6 carbon atoms, or 1 – 5, or 1 - 4 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, isobutyl, t-butyl, pentyl, hexyl, heptyl, octyl, and the like.

[00027] The term “alkenyl” refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched chain having about 2 – 6 carbon atoms, which may be optionally substituted by one or more substituents as described hereinafter in the disclosure. Preferred alkenyl groups include, without limitation, ethenyl, 1-propenyl, 2-propenyl, iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like.

[00028] The term “alkynyl” refers to a straight or branched hydrocarbyl radicals having at least one carbon-carbon triple bond and having in the range of 2 – 6 carbon atoms, which may be optionally substituted by one or more substituents as described hereinafter

in the disclosure. Preferred alkynyl groups include, without limitation, ethynyl, propynyl, butynyl, and the like.

[00029] The term “alkoxy” refers to an alkyl group as defined above attached via an oxygen linkage to the rest of the molecule, which may be optionally substituted by one or more substituents as described hereinafter in the disclosure. For example, C₁₋₆ alkoxy refers to an alkyl group having from 1 – 6 carbon atoms, or 1 – 4, 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.

[00030] The term “alkylamino” refers to an alkyl group as defined above attached via amino linkage to the rest of the molecule, which may be optionally substituted by one or more substituents as described hereinafter in the disclosure. For example, C₁₋₆ alkylamino refers to an alkyl group having from 1 – 6 carbon atoms, or 1 – 4 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.

[00031] The term “haloalkyl” refers to a halogen in an alkyl group as defined above 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 – 4 carbon atoms attached *via* halo linkage to the rest of the molecule. Preferred haloalkyl groups include, without limitation, –CH₂Cl, –CHCl₂, trifluoromethyl, 2,2,2-trifluoroethyl, and the like.

[00032] The term “haloalkoxy” refers to a halogen in 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 – 4 carbon atoms attached via oxygen linkage of the alkoxy group to the rest of the molecule. Preferred haloalkoxy groups include, without limitation, –OCH₂Cl, –OCHCl₂, and the like.

[00033] The term “halogen” refers to a halogen radical, for example, fluoro, chloro, bromo, or iodo.

[00034] The term “cycloalkyl” refers to non-aromatic mono or polycyclic ring system of about 3 to 6 carbon atoms, which may be optionally substituted by one or more substituents as described hereinafter in the disclosure. The polycyclic ring denotes hydrocarbon systems containing two or more ring systems with one or more ring carbon atoms in common i.e. a spiro, fused or bridged structures. For example, which are not limited, C₃₋₆ cycloalkyl refers to a cycloalkyl group having from 3 to 6 membered atoms. Preferred cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctanyl, perhydronaphthyl, adamantyl, noradamantyl and

norbornyl groups, bridged cyclic groups or spirobicyclic groups e.g spiro [4.4] non-2-yl, and the like.

[00035] The term “aryl” refers to aromatic ring having a specified number (5 to 6) of carbon atoms, which may be optionally substituted by one or more substituents as described hereinafter in the disclosure. For example, C₅₋₆ aryl refers to an aryl group having 5 or 6 membered atoms, or 6 membered atoms. Preferred aryl groups include, without limitation, phenyl, naphthyl, indanyl, biphenyl, and the like.

[00036] The term “heteroaryl” refers to an aromatic heterocyclic ring radical as defined above which may be optionally substituted by one or more substituents as described hereinafter in the disclosure. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of stable structure. The “heteroaryl” includes pyridinyl, tetrazolyl, and pyrazolyl.

[00037] The term “heterocyclyl” refers to a heterocyclic ring radical which may be optionally substituted by one or more substituents as described hereinafter in the disclosure. The heterocyclyl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure. Furthermore, the term “heterocyclyl” refers to a stable 3 to 15 membered rings radical, which consists of carbon atoms and from one to five heteroatoms selected from nitrogen, phosphorus, oxygen and sulfur. For purposes of this disclosure the heterocyclic ring radical may be monocyclic, bicyclic or tricyclic ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated. Preferred heterocyclyl groups include, without limitation, azetidiny, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazolyl, cinnoliny, dioxolanyl, indoliziny, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pyridyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinoliny, isoquinoliny, tetrazolyl, imidazolyl, tetrahydroisoquinoliny, piperidinyl, piperazinyl, homopiperazinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazoliny, triazolyl, indanyl, isoxazolyl, isoxazolidinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indoliny, isoindoliny, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl,

benzooxazolyl, thienyl, morpholinyl, thiomorpholinyl, thiomorpholinylsulfoxide, furyl, tetrahydrofuryl, tetrahydropyranyl, chromanyl and isochromanyl.

[00038] Furthermore, the compound of Formula I, Formula Ia, or Formula Ib can be its derivatives, analogs, stereoisomer's, diastereomers, geometrical isomers, polymorphs, solvates, co-crystals, intermediates, hydrates, metabolites, prodrugs or pharmaceutically acceptable salts and compositions.

[00039] It is understood that included in the family of compounds of Formula I, Formula Ia, or Formula Ib are isomeric forms including diastereoisomers, enantiomers, tautomers, and geometrical isomers in "E" or "Z" configurational isomer or a mixture of E and Z isomers. It is also understood that some isomeric forms such as diastereomers, enantiomers and geometrical isomers can be separated by physical and/or chemical methods by those skilled in the art.

[00040] Compounds disclosed herein may exist as single stereoisomers, racemates and or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the subject matter described.

[00041] Compounds disclosed herein include isotopes of hydrogen, carbon, oxygen, fluorine, chlorine, iodine and sulfur which can be incorporated into the compounds, such as, but not limited to, ^2H (D), ^3H (T), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{35}S , ^{36}Cl , and ^{125}I . Compounds of this disclosure wherein atoms were isotopically labeled for example radioisotopes such as ^3H , ^{13}C , ^{14}C , and the like can be used in metabolic studies, kinetic studies, and imaging techniques such as positron emission tomography used in understanding the tissue distribution of the drugs. Compounds of the disclosure where hydrogen is replaced with deuterium may improve the metabolic stability, and pharmacokinetics properties of the drug such as in vivo half-life. Compounds of the disclosure where isotopically labeled ^{18}F can be useful as PET imaging studies.

[00042] The compounds of Formula I, Formula Ia, or Formula Ib and their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof can also be referred as "compounds of the present disclosure".

[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. The compounds described herein may also exhibit polymorphism. This disclosure further includes different polymorphs of the compounds of the present disclosure. The term polymorph refers to a particular crystalline state of a substance, having particular physical properties such as X-ray diffraction, IR spectra, melting point, and the like.

[00044] 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.

[00045] The term “prodrugs” refers to the precursor of the compound of Formula I which on administration undergoes chemical conversion by metabolic processes before becoming active pharmacological substances. Described herein are prodrugs of the compound of Formula I, Formula Ia, or Formula Ib, 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 disclosure, which are readily convertible in vivo into a compound of the disclosure.

[00046] The compounds described herein can also be prepared in any solid or liquid physical form, for example the compound can be in a crystalline form, in amorphous form and have any particle size. Furthermore, the compound particles may be micronized or nanoized, or may be agglomerated, particulate granules, powders, oils, oily suspensions or any other form of solid or liquid physical forms.

[00047] The phrase “pharmaceutically acceptable” refers to compounds or compositions that are physiologically tolerable and do not typically produce allergic or similar untoward reactions, including but not limited to gastric upset or dizziness when administered to mammal.

[00048] 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. Pharmaceutically acceptable salts forming part of this disclosure include salts derived from inorganic bases such as Li, Na, K, Ca, Mg, Fe, Cu, Zn, Mn, ammonium, substituted ammonium salts, aluminum salts and the like; salts of

organic bases such as N, N'-diacetythylenediamine, glucamine, triethylamine, choline, dicyclohexylamine, benzylamine, trialkylamine, thiamine, guanidine, diethanolamine, α -phenylethylamine, piperidine, morpholine, pyridine, hydroxyethylpyrrolidine, hydroxyethylpiperidine, and the like. Salts also include amino acid salts such as glycine, alanine, cystine, cysteine, lysine, arginine, phenylalanine, guanidine etc. 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, and the like.

[00049] The terms "Protein arginine methyl transferase" and "PRMT" are intended to refer to any one of a family of enzymes that transfer methyl group to the arginines of histone or proteins.

[00050] The term "Protein arginine methyl transferase inhibitor" or "inhibitor of protein arginine methyl transferase" is used to identify a compound, which is capable of interacting with a protein arginine methyl transferase and inhibiting its activity, more particularly its enzymatic activity. Inhibiting protein arginine methyl transferase enzymatic activity means reducing the ability of a protein arginine methyl transferase for methylation of arginine residue of histone or other proteins.

[00051] The term "Protein arginine methyl transferase inhibitor-5" or "inhibitor of protein arginine methyl transferase-5 or inhibitors of PRMT5" is used to identify a compound, which is capable of interacting with a protein arginine methyl transferase and inhibiting its activity, more particularly its enzymatic activity. Inhibiting protein arginine methyl transferase-5 enzymatic activity means reducing the ability of a protein arginine methyl transferase-5 for symmetrical dimethylation of arginine residue of histone or other proteins.

[00052] The disclosure also provides a method of treatment of cancer in patients including administration of a therapeutically effective amount of a compound of Formula I, Formula Ia, or Formula Ib. The disclosure also provides a method for treatment of proliferative conditions or cancer, comprising administering to a subject suffering from proliferative conditions or cancer, a therapeutically effective amount of a compound of Formula I, Formula Ia, or Formula Ib, in the presence or absence of other clinically relevant cytotoxic agents or non-cytotoxic agents need thereof.

[00053] The present disclosure provides a method of treatment of a disorder caused by, associated with or accompanied by disruptions of cell proliferation and/or angiogenesis

and the subsequent metastasis including administration of a therapeutically effective amount of a compound of Formula I, Formula Ia, or Formula Ib.

[00054] The disclosure provides a method of treatment of cancer in patient including administration of effective amount of compounds of Formula I, Formula Ia, or Formula Ib. The cancer can be either a hematologic malignancy or solid tumor. Hematological malignancy is selected from the group consisting of B-cell lymphoma, T-cell lymphoma and leukemia. In the case of solid tumors, the tumors are selected from the group consisting of breast cancer, lung cancer, ovarian cancer, prostate cancer, head cancer, neck cancer, renal cancer, gastric cancer, colon cancer, pancreatic cancer, and brain cancer.

[00055] As discussed above, the compounds of the present disclosure are useful for treating proliferative diseases. Proliferative diseases include, for example, a tumor disease and/or metastases. Compounds of the present disclosure are useful for treating a proliferative disease that is refractory to the treatment with other chemotherapeutics; or a tumor that is refractory to treatment with other therapeutics due to multidrug resistance.

[00056] Compounds of the present disclosure are able to slow tumor growth, stop tumor growth or bring about the regression of tumors and to prevent the formation of tumor metastases (including micrometastases) and the growth of metastases (including micrometastases). In addition, they can be used in epidermal hyperproliferation.

[00057] The compound of Formula I of the present disclosure can be used as a prophylactic or therapeutic agent for cancer. Examples of the cancer include but are not restricted to, breast cancer, prostate cancer, pancreatic cancer, gastric cancer, lung cancer, colon cancer, rectal cancer, esophagus cancer, duodenal cancer, tongue cancer, pharyngeal cancer, brain tumor, neurinoma, non-small cell lung cancer, small cell lung cancer, liver cancer, kidney cancer, bile duct cancer, uterine body cancer, cervical cancer, ovarian cancer, urinary bladder, skin cancer, hemangioma, malignant lymphoma, malignant melanoma, thyroid cancer, bone tumor, vascular fibroma, retinoblastoma, penile cancer, pediatric solid cancer, lymphoma, myeloma and leukemia (including, for example acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic neutrophilic leukemia, chronic eosinophilic leukemia, chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL) or hairy cell leukemia).

[00058] "Combination therapy" includes the administration of the subject compounds in further combination with other biologically active ingredients (such as, but are not limited to, different antineoplastic agent) and non-drug therapies (such as, but are not limited to,

surgery or radiation treatment). The compounds described herein can be used in combination with other pharmaceutically active compounds, preferably, which will enhance the effect of the compounds of the disclosure. The compounds can be administered simultaneously or sequentially to the other drug therapy.

[00059] In an embodiment, the disclosure provides a method of inhibiting PRMT5 activity comprising administering, to a patient in need of treatment, an amount of a composition comprising a compound of Formula I, Formula Ia, or Formula Ib and a pharmaceutically acceptable carrier sufficient to inhibit PRMT5 activity.

[00060] In one aspect of this embodiment, the disclosure provides a compound of Formula I for use in inhibiting PRMT5. In a related aspect, the disclosure provides for the use of a compound of Formula I, Formula Ia, or Formula Ib for the manufacture of a medicament for inhibiting PRMT5.

[00061] In an embodiment, the disclosure provides a method of treating and/or preventing a neurodegenerative disease or disorder comprising administering, to a patient in need of treatment, a therapeutically effective amount of a composition comprising a compound of Formula I, Formula Ia, or Formula Ib and a pharmaceutically acceptable carrier.

[00062] In an aspect of this embodiment, the disclosure provides a compound of Formula I for use in treating and/or preventing a neurodegenerative disorder or condition. In a related aspect, the disclosure provides for the use of a compound of Formula I, Formula Ia, or Formula Ib for the manufacture of a medicament for treating and/or preventing a neurodegenerative disorder or condition.

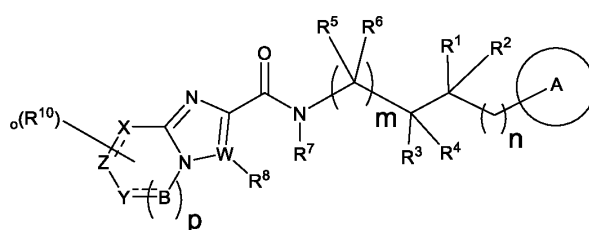
[00063] In another aspect, the compound may be administered in combination therapy by combining the compound of Formula I, Formula Ia, or Formula Ib with one or more separate agents, not limited to targets such as DNA methyltransferase, heat shock proteins (e.g. HSP90), kinase, epigenetic and other matrix metalloproteinases.

[00064] In another aspect, the subject compounds may be combined with the antineoplastic agents (e.g. small molecules, cytotoxic reagents, non-cytotoxic reagents, monoclonal antibodies, antisense RNA and fusion proteins) that inhibit one or more biological targets. Such combination may enhance therapeutic efficacy over the efficacy achieved by any of the agents alone and may prevent or delay the appearance of resistant variants.

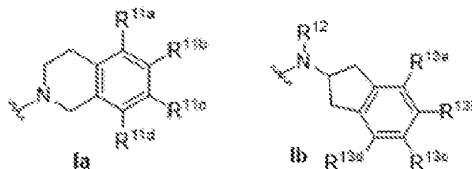
[00065] In yet another aspect, the subject compounds may be combined with immunoncology drugs not restricting to PDL-1, IDO, TDO, CTLA4 or any other drugs which is involved in the immune modulation.

[00066] As discussed in the background section, PRMT5 enzymes play an important role in cancer and other related diseases. Therefore, there is a requirement for PRMT5 inhibitors for treating cancer and other diseases or conditions associated with the over expression of PRMT5.

[00067] In an embodiment of the present disclosure, there is provided compounds of Formula I, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein



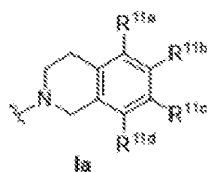
Formula I



wherein A is selected from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_5\text{-C}_6$ aryl, $\text{C}_3\text{-C}_{15}$ heteroaryl or $\text{C}_3\text{-C}_{15}$ heterocyclyl; or $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_2\text{-C}_6$ haloalkoxy, $\text{C}_3\text{-C}_6$ cycloalkoxy, $\text{C}_5\text{-C}_6$ aryloxy, $\text{C}_3\text{-C}_{15}$ heteroaryloxy or $\text{C}_3\text{-C}_{15}$ heterocycloryl; --- represents optional single or double bond; n is 0 or 1; m is 0 - 2; p is 1 or 2; o is 1 - 3; R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are independently selected from hydrogen, halogen, hydroxyl or $\text{C}_1\text{-C}_6$ alkyl, wherein $\text{C}_1\text{-C}_6$ alkyl is optionally substituted with one or more groups selected from hydroxyl, or halogen; R^7 , and R^{12} are independently selected from hydrogen or $\text{C}_1\text{-C}_6$ alkyl, wherein $\text{C}_1\text{-C}_6$ alkyl is optionally substituted with $\text{C}_5\text{-C}_6$ aryl, and wherein $\text{C}_5\text{-C}_6$ aryl is optionally substituted with one or more groups selected from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, halogen, hydroxyl, or cyano; R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{13a} , R^{13b} , R^{13c} , and R^{13d} are independently selected from hydrogen, halogen, cyano, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl or $\text{C}_1\text{-C}_6$ alkoxy; X, Y, and Z are independently selected from CR^{10} , NR^{10} , O, or S; W, and B are independently selected from N or C; R^8 is absent or is selected from hydrogen, halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_5\text{-C}_6$ aryl, $\text{C}_3\text{-C}_{15}$ heteroaryl or $\text{C}_3\text{-C}_{15}$ heterocyclyl; and R^{10} is selected from hydrogen, halogen, hydroxyl,

oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SF₅, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a, or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl, or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

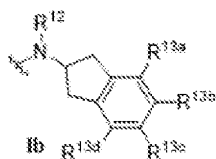
[00068] In an embodiment of the present disclosure, there is provided compounds of Formula I, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein



A is ; --- represents optional single or double bond; n is 0 or 1; m is 0 - 2; p is 1 or 2; o is 1 - 3; R¹, R², R³, R⁴, R⁵, and R⁶ are independently selected from hydrogen, halogen, hydroxyl or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one or more groups selected from hydroxyl, or halogen; R⁷, and R¹² are independently selected from hydrogen or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more

groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, and R^{11d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O, or S; W, and B are independently selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SF₅, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a, or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl, or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

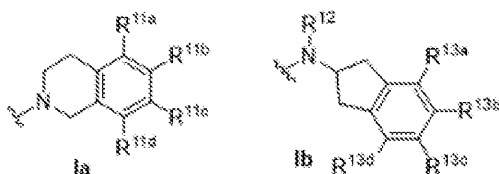
[00069] In an embodiment of the present disclosure, there is provided compounds of Formula I, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein



A is --- ; --- represents optional single or double bond; n is 0 or 1; m is 0 - 2; p is 1 or 2; o is 1 - 3; R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are independently selected from hydrogen, halogen, hydroxyl or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more groups selected from hydroxyl, or halogen; R^7 , and R^{12} are independently selected from hydrogen or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with C_{5-6} aryl, and wherein C_{5-6} aryl is optionally substituted with one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, halogen, hydroxyl, or cyano; R^{13a} , R^{13b} , R^{13c} , and R^{13d} are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl or C_{1-6} alkoxy; X, Y, and Z are independently selected from CR^{10} , NR^{10} , O, or S; W, and B are independently selected from N or C; R^8 is absent or is selected from hydrogen, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{3-15} heteroaryl or C_{3-15} heterocyclyl; and R^{10} is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{1-6} alkylamino, $COOR_a$, $C(O)R_b$, $C(S)R_a$, $C(O)NR_aR_b$, $C(S)NR_aR_b$, $NR^aC(O)NR_bR_c$, $N(R_a)SOR_b$, $N(R_a)SO_2R_b$, $NR_aC(O)OR_b$, NR_aR_b , $NR_aC(S)NR_bR_c$, $NR_aC(O)R_b$, $NR_aC(S)R_b$, SF_5 , $SONR_aR_b$, $SO_2NR_aR_b$, $OC(O)NR_aR_b$, $OR_aC(O)OR_b$, $OC(O)NR_aR_b$, $OC(O)R_a$, OR_a , $R_aNR_bR_c$, R_aOR_b , SR_a , SOR_a , SO_2R_a , or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C_{5-6} aryl, C_{3-6} cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, $C(O)R_b$, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with $C(O)R_b$, and wherein R_a , R_b , and R_c are independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{3-15} heterocyclyl, or C_{3-15} heteroaryl, wherein C_{5-6} aryl, C_{3-6} cycloalkyl, and C_{3-15} heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C_{1-6} alkyl; or R_a and R_b can be

taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00070] In an embodiment of the present disclosure, there is provided compounds of Formula I, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



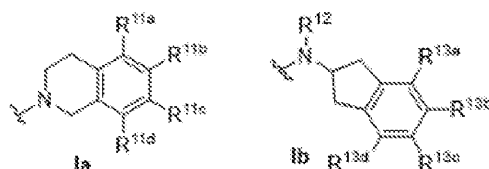
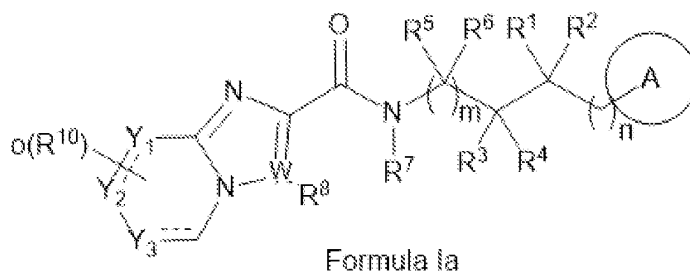
or

; ---- represents optional single or double

bond; n is 0 or 1; m is 0 - 2; p is 1; o is 1 or 2; R¹, R², R³, R⁴, R⁵, and R⁶ are independently selected from hydrogen, halogen, hydroxyl, or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one or more groups selected from hydroxyl and halogen; R⁷, and R¹² are independently selected from hydrogen, or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O, or S; W, and B are independently selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR_aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SF₅, SR_a, SOR_a, SO₂R_a, or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or

unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₆ cycloalkyl, C₃₋₁₅ heterocyclyl, or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

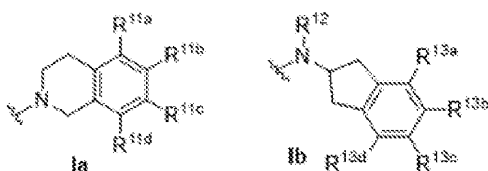
[00071] In an embodiment of the present disclosure, there is provided compounds of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein



A is selected from  or ; n is 0 or 1; m is 0 - 2; o is 1 - 3; R¹, R², R³, R⁴, R⁵, and R⁶ are independently selected from the group consisting of hydrogen, halogen, hydroxyl, or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one or more groups selected from hydroxyl, or halogen; R⁷ and R¹² are independently selected from hydrogen, and C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; Y¹, Y², and Y³ are independently selected from N or CH;

W is selected from N or C; R^8 is absent or is selected from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{3-15} heteroaryl, or C_{3-15} heterocyclyl; and R^{10} is selected from hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{5-6} aryl, 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, C_{1-6} alkylamino, $COOR_a$, $C(O)R_b$, $C(S)R_a$, $C(O)NR_aR_b$, $C(S)NR_aR_b$, $NR^aC(O)NR_bR_c$, $N(R_a)SOR_b$, $N(R_a)SO_2R_b$, $NR_aC(O)OR_b$, NR_aR_b , $NR_aC(S)NR_bR_c$, $NR_aC(O)R_b$, $NR_aC(S)R_b$, SF_5 , $SONR_aR_b$, $SO_2NR_aR_b$, $OC(O)NR_aR_b$, $OR_aC(O)OR_b$, $OC(O)NR_aR_b$, $OC(O)R_a$, OR_a , $R_aNR_bR_c$, R_aOR_b , SR_a , SOR_a , or SO_2R_a , wherein C_{5-6} aryl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, cyano, oxo, C_{3-6} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, $C(O)R_b$, 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with $C(O)R_b$, and wherein R_a , R_b , and R_c are independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{3-15} heterocyclyl, and C_{3-15} heteroaryl, wherein C_{5-6} aryl, C_{3-6} cycloalkyl, and C_{3-15} heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C_{1-6} alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00072] In an embodiment of the present disclosure, there is provided compounds of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



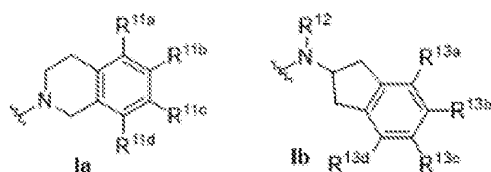
or

; n is 0 or 1; m is 0 – 2; o is 1 – 3; R^1 , R^2 ,

R^3 , R^4 , R^5 , and R^6 are independently selected from the group consisting of hydrogen, halogen, hydroxyl, and C_{1-5} alkyl, wherein C_{1-5} alkyl is optionally substituted with one or more groups selected from hydroxyl, or halogen; R^7 and R^{12} are independently selected

from hydrogen, and C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from the group consisting of hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; Y¹, Y², and Y³ are independently selected from N or CH; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SF₅, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a and SO₂R_a, wherein C₅₋₆ aryl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl, and C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00073] In an embodiment of the present disclosure, there is provided compounds of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



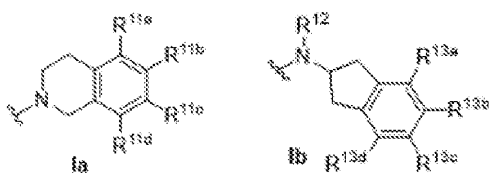
or

; n is 0 or 1; m is 0 – 2; o is 1 – 3; R¹, R²,

R³, R⁴, R⁵, and R⁶ are independently selected from the group consisting of hydrogen, halogen, hydroxyl, and C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more groups selected from hydroxyl, or halogen; R⁷ and R¹² are independently selected from hydrogen, and C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from the group consisting of hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; Y¹, Y², and Y³ are independently selected from N or CH; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SF₅, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a and SO₂R_a, wherein C₅₋₆ aryl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl, and C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be

taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00074] In an embodiment of the present disclosure, there is provided compounds of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



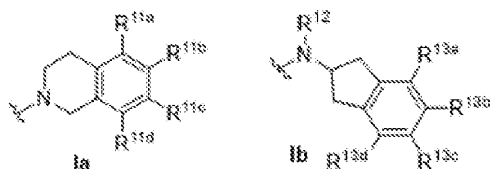
or

; n is 0 or 1; m is 0 - 2; o is 1 - 3; R¹, R²,

R³, R⁴, R⁵, and R⁶ are independently selected from the group consisting of hydrogen, halogen, hydroxyl, or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more groups selected from hydroxyl, or halogen; R⁷ and R¹² are independently selected from hydrogen, or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with C₆ aryl, and wherein C₆ aryl is optionally substituted with one or more groups selected from the group consisting of C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from the group consisting of hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; Y¹, Y², and Y³ are independently selected from N or CH; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, and C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR_aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SF₅, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a and SO₂R_a, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, and wherein

3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl, and C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00075] In an embodiment of the present disclosure, there is provided compounds of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



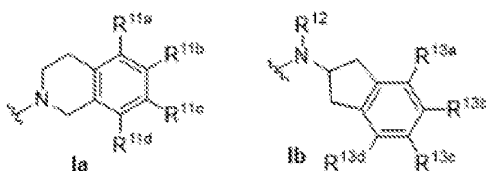
or

; n is 0 or 1; m is 0 or 1; o is 1 – 3; R¹, R²,

R³, R⁴, R⁵, and R⁶ are independently selected from the group consisting of hydrogen, halogen, hydroxyl, or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more groups selected from hydroxyl, or halogen; R⁷ and R¹² are independently selected from hydrogen, or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with C₆ aryl, and wherein C₆ aryl is optionally substituted with one or more groups selected from the group consisting of C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from the group consisting of hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; Y¹, Y², and Y³ are independently selected from N or CH; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, and C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SF₅, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b,

OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a and SO₂R_a, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, and wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl, and C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00076] In an embodiment of the present disclosure, there is provided compounds of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



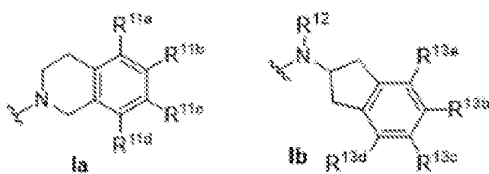
or

; n is 0 or 1; m is 0 or 1; o is 1 – 3; R¹, R²,

R³, R⁴, R⁵, and R⁶ are independently selected from the group consisting of hydrogen, halogen, hydroxyl, and C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more groups selected from hydroxyl, fluoro, chloro, or bromo; R⁷ and R¹² are independently selected from hydrogen, and C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with C₆ aryl, and wherein C₆ aryl is optionally substituted with one or more groups selected from the group consisting of C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from the group consisting of hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; Y¹, Y², and Y³ are independently selected from N or CH; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, and C₃₋₁₅ heterocyclyl;

and R^{10} is selected from hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{5-6} aryl, 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, C_{1-4} alkylamino, $COOR_a$, $C(O)R_b$, $C(S)R_a$, $C(O)NR_aR_b$, $C(S)NR_aR_b$, $NR^aC(O)NR_bR_c$, $NR_aC(S)NR_bR_c$, $N(R_a)SOR_b$, $N(R_a)SO_2R_b$, $NR_aC(O)OR_b$, NR_aR_b , $NR_aC(O)R_b$, $NR_aC(S)R_b$, SF_5 , $SONR_aR_b$, $SO_2NR_aR_b$, OR_a , $OR_aC(O)OR_b$, $OC(O)NR_aR_b$, $OC(O)R_a$, $OC(O)NR_aR_b$, $R_aNR_bR_c$, R_aOR_b , SR_a , SOR_a and SO_2R_a , wherein C_{5-6} aryl, C_{3-6} cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, cyano, oxo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, $C(O)R_b$, 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with $C(O)R_b$, and wherein R_a , R_b , and R_c are independently selected from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{3-6} cycloalkyl, C_{3-15} heterocyclyl, and C_{3-15} heteroaryl, wherein C_{5-6} aryl, and C_{3-15} heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C_{1-6} alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00077] In an embodiment of the present disclosure, there is provided compounds of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



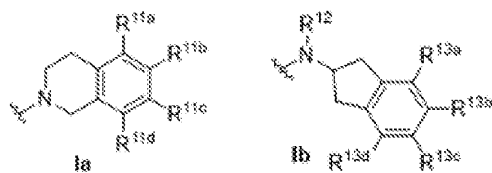
or

; n is 0; m is 0; o is 1 – 3; R^1 , R^2 , R^3 , R^4 ,

R^5 , and R^6 are independently selected from the group consisting of hydrogen, halogen, hydroxyl, and C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more groups selected from hydroxyl, fluoro, chloro, or bromo; R^7 and R^{12} are independently selected from hydrogen, and C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with C_6 aryl, and wherein C_6 aryl is optionally substituted with one or more groups selected

from the group consisting of C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from the group consisting of hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; Y¹, Y², and Y³ are independently selected from N or CH; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, and C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, C₁₋₄alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, NR_aC(S)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(O)R_b, NR_aC(S)R_b, SF₅, SONR_aR_b, SO₂NR_aR_b, OR_a, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OC(O)NR_aR_b, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a and SO₂R_a, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, cyano, oxo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₆ cycloalkyl, C₃₋₁₅ heterocyclyl, and C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00078] In an embodiment of the present disclosure, there is provided compounds of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



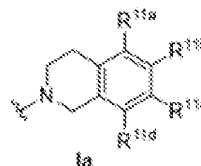
or

; n is 1; m is 1; o is 1 – 3; R¹, R², R³, R⁴,

R⁵, and R⁶ are independently selected from the group consisting of hydrogen, halogen, hydroxyl, and C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more groups selected from hydroxyl, fluoro, chloro, or bromo; R⁷ and R¹² are independently selected from hydrogen, and C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with C₆ aryl, and wherein C₆ aryl is optionally substituted with one or more groups selected from the group consisting of C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from the group consisting of hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; Y¹, Y², and Y³ are independently selected from N or CH; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, and C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, C₁₋₄alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, NR_aC(S)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(O)R_b, NR_aC(S)R_b, SF₅, SONR_aR_b, SO₂NR_aR_b, OR_a, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OC(O)NR_aR_b, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a and SO₂R_a, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, cyano, oxo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₆ cycloalkyl, C₃₋₁₅ heterocyclyl, and C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or

bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

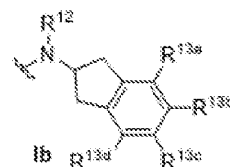
[00079] In an embodiment of the present disclosure, there is provided compounds of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical



compositions, metabolites, and prodrugs thereof, wherein A is C_n ; n is 0; m is 1; o is 1 – 3; R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are independently selected from the group consisting of hydrogen, halogen, hydroxyl, and C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more groups selected from hydroxyl, fluoro, chloro, or bromo; R^7 is selected from hydrogen, and C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with C_6 aryl, and wherein C_6 aryl is optionally substituted with one or more groups selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxyl, or cyano; R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{13a} , R^{13b} , R^{13c} , and R^{13d} are independently selected from the group consisting of hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy; Y^1 , Y^2 , and Y^3 are independently selected from N or CH; W is selected from N or C; R^8 is absent or is selected from hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{3-15} heteroaryl, and C_{3-15} heterocyclyl; and R^{10} is selected from hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{5-6} aryl, 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, C_{1-4} alkylamino, $COOR_a$, $C(O)R_b$, $C(S)R_a$, $C(O)NR_aR_b$, $C(S)NR_aR_b$, $NR^aC(O)NR_bR_c$, $NR_aC(S)NR_bR_c$, $N(R_a)SOR_b$, $N(R_a)SO_2R_b$, $NR_aC(O)OR_b$, NR_aR_b , $NR_aC(O)R_b$, $NR_aC(S)R_b$, SF_5 , $SONR_aR_b$, $SO_2NR_aR_b$, OR_a , $OR_aC(O)OR_b$, $OC(O)NR_aR_b$, $OC(O)R_a$, $OC(O)NR_aR_b$, $R_aNR_bR_c$, R_aOR_b , SR_a , SOR_a and SO_2R_a , wherein C_{5-6} aryl, C_{3-6} cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, cyano, oxo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, $C(O)R_b$, 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms

selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₆ cycloalkyl, C₃₋₁₅ heterocyclyl, and C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

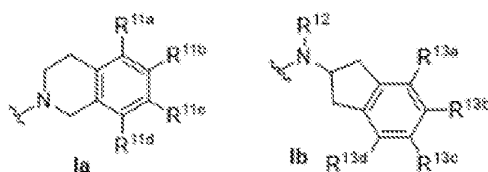
[00080] In an embodiment of the present disclosure, there is provided compounds of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical



compositions, metabolites, and prodrugs thereof, wherein A is ; n is 0; m is 1; o is 1 – 3; R¹, R², R³, R⁴, R⁵, and R⁶ are independently selected from the group consisting of hydrogen, halogen, hydroxyl, and C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more groups selected from hydroxyl, fluoro, chloro, or bromo; R⁷ and R¹² are independently selected from hydrogen, and C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with C₆ aryl, and wherein C₆ aryl is optionally substituted with one or more groups selected from the group consisting of C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from the group consisting of hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; Y¹, Y², and Y³ are independently selected from N or CH; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, and C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, C₁₋₄alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, NR_aC(S)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(O)R_b, NR_aC(S)R_b, SF₅, SONR_aR_b, SO₂NR_aR_b, OR_a, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OC(O)NR_aR_b, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a and SO₂R_a, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15

membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, cyano, oxo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₆ cycloalkyl, C₃₋₁₅ heterocyclyl, and C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00081] In an embodiment of the present disclosure, there is provided compounds of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



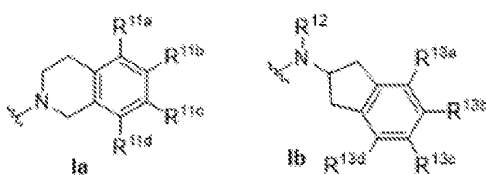
or

; n is 0 or 1; m is 0 or 1; o is 1 – 3; R¹, R²,

R³, R⁴, R⁵, and R⁶ are independently selected from the group consisting of hydrogen, halogen, hydroxyl, and C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more groups selected from hydroxyl, fluoro, chloro, or bromo; R⁷ and R¹² are independently selected from hydrogen, and C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with C₆ aryl, and wherein C₆ aryl is optionally substituted with one or more groups selected from the group consisting of C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from the group consisting of hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; Y¹, Y², and Y³ are independently selected from N or CH; W is C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, and C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, 3-15

membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, C_{1-4} alkylamino, $COOR_a$, $C(O)R_b$, $C(S)R_a$, $C(O)NR_aR_b$, $C(S)NR_aR_b$, $NR^aC(O)NR_bR_c$, $NR^aC(S)NR_bR_c$, $N(R_a)SOR_b$, $N(R_a)SO_2R_b$, $NR^aC(O)OR_b$, NR_aR_b , $NR^aC(O)R_b$, $NR^aC(S)R_b$, SF_5 , $SONR_aR_b$, $SO_2NR_aR_b$, OR_a , $OR^aC(O)OR_b$, $OC(O)NR_aR_b$, $OC(O)R_a$, $OC(O)NR_aR_b$, $R_aNR_bR_c$, R_aOR_b , SR_a , SOR_a and SO_2R_a , wherein C_{5-6} aryl, C_{3-6} cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, cyano, oxo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, $C(O)R_b$, 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with $C(O)R_b$, and wherein R_a , R_b , and R_c are independently selected from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{3-6} cycloalkyl, C_{3-15} heterocyclyl, and C_{3-15} heteroaryl, wherein C_{5-6} aryl, and C_{3-15} heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C_{1-6} alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00082] In an embodiment of the present disclosure, there is provided compounds of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



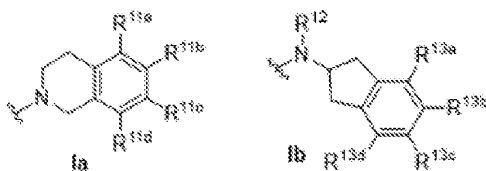
or

; n is 0 or 1; m is 0 or 1; o is 1 – 3; R^1 , R^2 ,

R^3 , R^4 , R^5 , and R^6 are independently selected from the group consisting of hydrogen, halogen, hydroxyl, and C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more groups selected from hydroxyl, or bromo; R^7 and R^{12} are independently selected from hydrogen, and C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with C_6 aryl, and wherein C_6 aryl is optionally substituted with one or more groups selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxyl, or cyano; R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{13a} , R^{13b} , R^{13c} , and R^{13d} are independently selected from the group consisting of

hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; Y¹, Y², and Y³ are independently selected from N or CH; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, and C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, C₁₋₄alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, NR_aC(S)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(O)R_b, NR_aC(S)R_b, SF₅, SONR_aR_b, SO₂NR_aR_b, OR_a, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OC(O)NR_aR_b, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a and SO₂R_a, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, cyano, oxo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₆ cycloalkyl, C₃₋₁₅ heterocyclyl, and C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00083] In an embodiment of the present disclosure, there is provided compounds of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



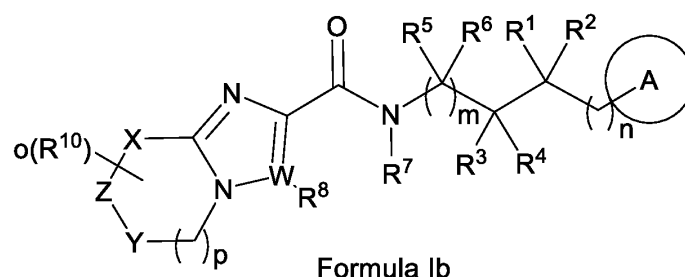
or

; n is 0 or 1; m is 0 or 1; o is 1 – 3; R¹, R²,

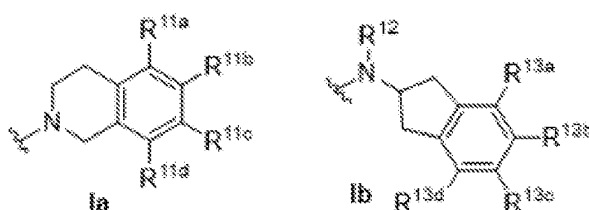
R³, R⁴, R⁵, and R⁶ are independently selected from the group consisting of hydrogen,

halogen, hydroxyl, and C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more groups selected from hydroxyl, fluoro, chloro, or bromo; R⁷ is selected from hydrogen, or C₁₋₄ alkyl; R¹² is selected from hydrogen, and C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with C₆ aryl, and wherein C₆ aryl is optionally substituted with one or more groups selected from the group consisting of C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from the group consisting of hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; Y¹, Y², and Y³ are independently selected from N or CH; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, and C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, C₁₋₄alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, NR_aC(S)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(O)R_b, NR_aC(S)R_b, SF₅, SONR_aR_b, SO₂NR_aR_b, OR_a, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OC(O)NR_aR_b, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a and SO₂R_a, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, cyano, oxo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₆ cycloalkyl, C₃₋₁₅ heterocyclyl, and C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00084] In an embodiment of the present disclosure, there is provided compounds of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein



wherein A is selected from



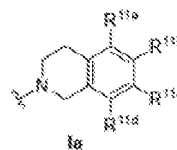
or

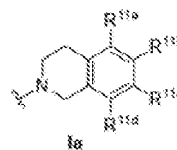
; n is 0 or 1; m is 0 - 2; p is 1; o

is 1 - 3; R^1 , R^2 , R^3 , and R^4 are independently selected from hydrogen, halogen, hydroxyl, or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with hydroxyl, or halogen; R^5 , and R^6 are independently selected from hydrogen, C_{1-6} alkyl, or halogen, wherein C_{1-6} alkyl is optionally substituted with hydroxyl, or halogen; R^7 , and R^{12} are independently selected from hydrogen or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with C_{5-6} aryl, and wherein C_{5-6} aryl is optionally substituted with one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, halogen, hydroxyl, or cyano; R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{13a} , R^{13b} , R^{13c} , and R^{13d} are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy; X, Y, and Z are independently selected from CR^{10} , NR^{10} , O, or S; W is selected from N or C; R^8 is absent or is selected from hydrogen, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{3-15} heteroaryl or C_{3-15} heterocyclyl; and R^{10} is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{1-6} alkylamino, $COOR_a$, $C(O)R_b$, $C(S)R_a$, $C(O)NR_aR_b$, $C(S)NR_aR_b$, $NR^aC(O)NR_bR_c$, $N(R_a)SOR_b$, $N(R_a)SO_2R_b$, $NR_aC(O)OR_b$, NR_aR_b , $NR_aC(S)NR_bR_c$, $NR_aC(O)R_b$, $NR_aC(S)R_b$, $SONR_aR_b$, $SO_2NR_aR_b$, $OC(O)NR_aR_b$, $OR_aC(O)OR_b$, $OC(O)NR_aR_b$, $OC(O)R_a$, OR_a , $R_aNR_bR_c$, R_aOR_b , SR_a , SOR_a , SO_2R_a , or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C_{5-6} aryl, C_{3-6} cycloalkyl, and 3-15

membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

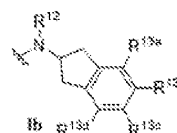
[00085] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical



compositions, metabolites, and prodrugs thereof, wherein A is ; n is 0 or 1; m is 0 - 2; p is 1; o is 1 - 3; R¹, R², R³, and R⁴ are independently selected from hydrogen, halogen, hydroxyl, or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, or halogen; R⁵, and R⁶ are independently selected from hydrogen, C₁₋₆ alkyl, or halogen, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, or halogen; R⁷ is selected from hydrogen or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, and R^{11d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O, or S; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a,

C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a, or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

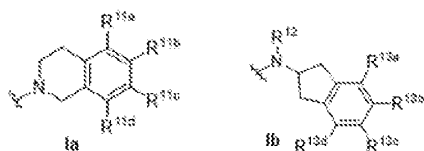
[00086] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical



compositions, metabolites, and prodrugs thereof, wherein A is ; n is 0 or 1; m is 0-2; p is 1; o is 1-3; R¹, R², R³, and R⁴ are independently selected from hydrogen, halogen, hydroxyl, or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, or halogen; R⁵, and R⁶ are independently selected from hydrogen, C₁₋₆ alkyl, or halogen, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, or halogen; R⁷, and R¹² are independently selected from hydrogen or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O, or S; W is selected from N or C; R⁸ is absent or is selected from hydrogen,

halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00087] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from

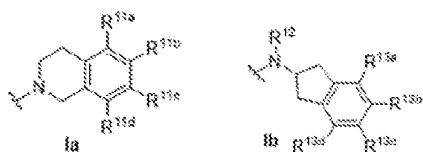


or ; n is 0; m is 0 -2; p is 1; o is 1 – 3; R¹, R², R³,

and R⁴ are independently selected from hydrogen, halogen, hydroxyl, or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, or halogen; R⁵, and R⁶ are independently selected from hydrogen, C₁₋₆ alkyl, or halogen, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, or halogen; R⁷, and R¹² are independently selected

from hydrogen or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O, or S; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a, or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00088] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



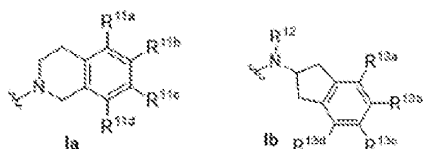
or

; n is 0 or 1; m is 1; p is 1; o is 1 – 3; R^1, R^2, R^3 ,

and R⁴ are independently selected from hydrogen, halogen, hydroxyl, or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, or halogen; R⁵, and R⁶ are independently selected from hydrogen, C₁₋₆ alkyl, or halogen, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, or halogen; R⁷, and R¹² are independently selected from hydrogen or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O, or S; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a, or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or

bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00089] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from

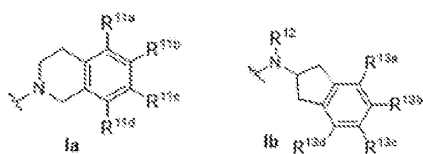


or ; n is 0 or 1; m is 0 - 2; p is 1; o is 1 - 3; R¹, R²,

R³, R⁴, R⁵, and R⁶ are independently selected from hydrogen, halogen, hydroxyl or C₁₋₆ alkyl; R⁷, and R¹² are independently selected from hydrogen or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O, or S; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR_aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a, or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl,

C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00090] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from

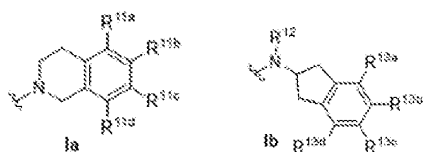


or ; n is 0 or 1; m is 0 - 2; p is 1; o is 1 - 3; R¹, R²,

R³, and R⁴ are independently selected from hydrogen, halogen, hydroxyl, or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, or halogen; R⁵, and R⁶ are independently selected from hydrogen, C₁₋₆ alkyl, or halogen, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, or halogen; R⁷, and R¹² are independently selected from hydrogen or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; X is CH₂, Y, and Z are independently selected from CR¹⁰, NR¹⁰, or O; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR_aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a, or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally

substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00091] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from

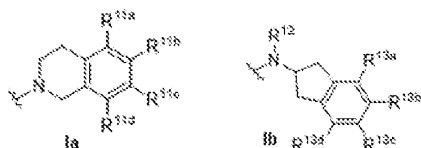


or ; n is 0 or 1; m is 0 - 2; p is 1; o is 1 - 3; R¹, R²,

R³, and R⁴ are independently selected from hydrogen, halogen, hydroxyl, or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, or halogen; R⁵, and R⁶ are independently selected from hydrogen, C₁₋₆ alkyl, or halogen, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, or halogen; R⁷, and R¹² are independently selected from hydrogen, or C₁₋₆ alkyl; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O, or S; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR_aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b,

OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a, or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

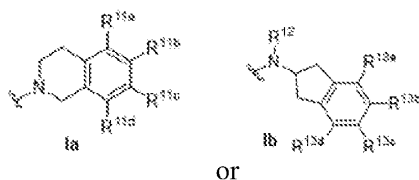
[00092] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



; n is 0 or 1; m is 0 or 1; p is 1; o is 1 – 3; R¹, R², R³, and R⁴ are independently selected from hydrogen, halogen, hydroxyl, or C₁₋₅ alkyl, wherein C₁₋₅ alkyl is optionally substituted with hydroxyl, or halogen; R⁵, and R⁶ are independently selected from hydrogen, C₁₋₅ alkyl, or halogen, wherein C₁₋₅ alkyl is optionally substituted with hydroxyl, or halogen; R⁷, and R¹² are independently selected from hydrogen or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR⁹, NR¹⁰, O, or S; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆

alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl, or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00093] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



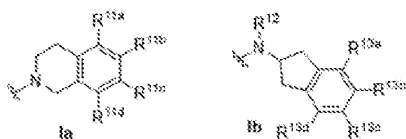
or

; n is 0 or 1; m is 0 or 1; p is 1; o is 1 – 3; R¹, R²,

R³, and R⁴ are independently selected from hydrogen, halogen, hydroxyl, or C₁₋₅ alkyl, wherein C₁₋₅ alkyl is optionally substituted with hydroxyl, or halogen; R⁵, and R⁶ are independently selected from hydrogen, C₁₋₅ alkyl, or halogen, wherein C₁₋₅ alkyl is optionally substituted with hydroxyl, or halogen; R⁷, and R¹² are independently selected

from hydrogen or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR⁹, NR¹⁰, O, or S; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl, or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[00094] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from

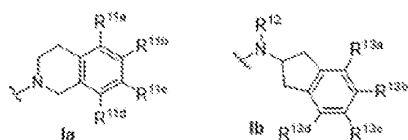


or ; n is 0 or 1; m is 0 or 1; p is 1; o is 1 – 3; R¹, R²,

R³, and R⁴ are independently selected from hydrogen, halogen, hydroxyl, or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more groups selected from hydroxyl, chloro, bromo, fluoro, or iodo; R⁵, and R⁶ are independently selected from hydrogen, C₁₋₄ alkyl, or halogen, wherein C₁₋₄ alkyl is optionally substituted with one or more groups selected from hydroxyl, chloro, bromo, fluoro, or iodo; R⁷, and R¹² are independently selected from hydrogen or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with C₆ aryl, and wherein C₆ aryl is optionally substituted with one or more groups selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O or S; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, or C₃₋₁₅ heterocyclyl; R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or

R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S, or O.

[00095] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from

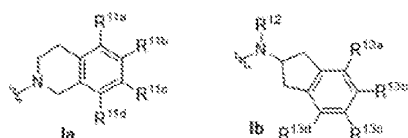


or ; n is 0 or 1; m is 0 or 1; p is 1; o is 1 – 3; R¹, R²,

R³, R⁴, R⁵, and R⁶ are independently selected from hydrogen, halogen, hydroxyl, or C₁₋₄ alkyl; R⁷, and R¹² are independently selected from hydrogen or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with C₆ aryl, and wherein C₆ aryl is optionally substituted with one or more groups selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O or S; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, or C₃₋₁₅ heterocyclyl; R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, and C₃₋

15 heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S, or O.

[00096] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from

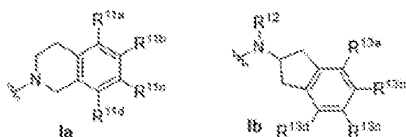


or ; n is 0 or 1; m is 0 or 1; p is 1; o is 1 – 3; R¹, R²,

R³, and R⁴ are independently selected from hydrogen, halogen, hydroxyl, or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more groups selected from hydroxyl, chloro, bromo, fluoro, or iodo; R⁵, and R⁶ are independently selected from hydrogen, C₁₋₄ alkyl, or halogen, wherein C₁₋₄ alkyl is optionally substituted with one or more groups selected from hydroxyl, chloro, bromo, fluoro, or iodo; R⁷, and R¹² are independently selected from hydrogen or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with C₆ aryl, and wherein C₆ aryl is optionally substituted with one or more groups selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O or S; W is C; R⁸ is selected from hydrogen, halogen, or C₁₋₆ alkyl; R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR_aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or

heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S, or O.

[00097] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



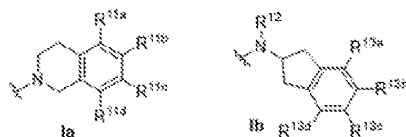
or

; n is 0 or 1; m is 0 or 1; p is 1; o is 1 – 3; R¹, R²,

R³, and R⁴ are independently selected from hydrogen, halogen, hydroxyl, or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more groups selected from hydroxyl, fluoro, or chloro; R⁵, and R⁶ are independently selected from hydrogen, C₁₋₄ alkyl or halogen, wherein C₁₋₄ alkyl is optionally substituted with one or more groups selected from hydroxyl, chloro, bromo, fluoro, or iodo; R⁷, and R¹² are independently selected from hydrogen or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with C₆ aryl, and wherein C₆ aryl is optionally substituted with one or more groups selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxyl or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O or S; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₄ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, NR_aC(S)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OR_a,

OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OC(O)NR_aR_b, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, cyano, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S, or O.

[00098] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



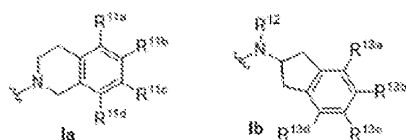
or

; n is 0 or 1; m is 0 or 1; p is 1; o is 1 – 3; R¹, R²,

R³, and R⁴ are independently selected from hydrogen, or hydroxyl; R⁵, and R⁶ are independently selected from hydrogen, C₁₋₄ alkyl, or halogen, wherein C₁₋₄ alkyl is optionally substituted with hydroxyl, chloro, bromo, fluoro, or iodo; R⁷, and R¹² are independently selected from hydrogen, or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with C₆ aryl, and wherein C₆ aryl is optionally substituted with one or more groups selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, hydroxyl or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O, or S; W is selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋

$_6$ alkoxy, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{1-6} alkylamino, $COOR_a$, $C(O)R_b$, $C(S)R_a$, $C(O)NR_aR_b$, $C(S)NR_aR_b$, $NR^aC(O)NR_bR_c$, $N(R_a)SOR_b$, $N(R_a)SO_2R_b$, $NR_aC(O)OR_b$, NR_aR_b , $NR_aC(S)NR_bR_c$, $NR_aC(O)R_b$, $NR_aC(S)R_b$, $SONR_aR_b$, $SO_2NR_aR_b$, $OC(O)NR_aR_b$, $OR_aC(O)OR_b$, $OC(O)NR_aR_b$, $OC(O)R_a$, OR_a , $R_aNR_bR_c$, R_aOR_b , SR_a , SOR_a , SO_2R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C_{5-6} aryl, C_{3-6} cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C_{3-6} cycloalkyl, $C(O)R_b$, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with $C(O)R_b$, and wherein R_a , R_b , and R_c are independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{3-15} heterocyclyl or C_{3-15} heteroaryl, wherein C_{5-6} aryl, and C_{3-15} heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C_{1-6} alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S, or O.

[00099] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from

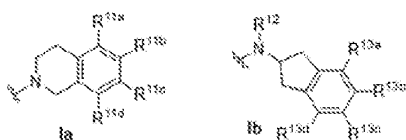


or ; n is 0 or 1; m is 0 or 1; p is 1; o is 1 – 3; R^1 , R^2 ,

R^3 , and R^4 are independently selected from hydrogen, halogen, hydroxyl or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more substituents selected from hydroxyl, fluoro, or chloro; R^5 , and R^6 are independently selected from hydrogen, C_{1-4} alkyl, or halogen, wherein C_{1-4} alkyl is optionally substituted with one or more substituents selected from hydroxyl, chloro, bromo, fluoro, or iodo; R^7 , and R^{12} are independently selected from hydrogen, or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with C_6 aryl, and wherein C_6 aryl is optionally substituted with one or more groups selected from C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxyl, or cyano; R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{13a} , R^{13b} , R^{13c} , and R^{13d} are independently selected from hydrogen, halogen, cyano,

C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰ or O or S; W is C; R⁸ is selected from hydrogen, halogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S, or O.

[000100] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected from



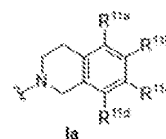
or

; n is 0 or 1; m is 0 or 1; p is 1; o is 1 – 3; R¹, R²,

R³, R⁴, R⁵, and R⁶ are independently selected from group consisting of hydrogen, hydroxyl, or C₁₋₄ alkyl; R⁷, and R¹² are independently selected from hydrogen, or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with C₆ aryl, and wherein C₆ aryl is optionally substituted with one or more groups selected from C₁₋₄ alkyl, C₁₋₄ alkoxy,

halogen or hydroxyl; R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{13a} , R^{13b} , R^{13c} , and R^{13d} are independently selected from hydrogen; X, and Y are independently selected from CR^{10} , NR^{10} or O; Z is O; W is C; R^8 is hydrogen; and R^{10} is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{1-6} alkylamino, $COOR_a$, $C(O)R_b$, $C(S)R_a$, $C(O)NR_aR_b$, $C(S)NR_aR_b$, $NR^aC(O)NR_bR_c$, $N(R_a)SOR_b$, $N(R_a)SO_2R_b$, $NR_aC(O)OR_b$, NR_aR_b , $NR_aC(S)NR_bR_c$, $NR_aC(O)R_b$, $NR_aC(S)R_b$, $SONR_aR_b$, $SO_2NR_aR_b$, $OC(O)NR_aR_b$, $OR_aC(O)OR_b$, $OC(O)NR_aR_b$, $OC(O)R_a$, OR_a , $R_aNR_bR_c$, R_aOR_b , SR_a , SOR_a , SO_2R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C_{5-6} aryl, C_{3-6} cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C_{3-6} cycloalkyl, $C(O)R_b$, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with $C(O)R_b$, and wherein R_a , R_b , and R_c are independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{3-15} heterocyclyl or C_{3-15} heteroaryl, wherein C_{5-6} aryl, and C_{3-15} heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C_{1-6} alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S, or O.

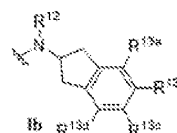
[000101] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical

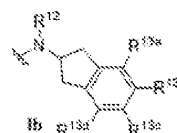


compositions, metabolites, and prodrugs thereof, wherein A is ; n is 0 or 1; m is 1; p is 1; o is 1 – 3; R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are independently selected from group consisting of hydrogen, hydroxyl, or C_{1-4} alkyl; R^7 is from hydrogen, or C_{1-4} alkyl; R^{11a} , R^{11b} , R^{11c} , and R^{11d} are independently selected from hydrogen; X is CR^{10} ; Y is selected from CR^{10} , or O; Z is selected from CR^{10} , NR^{10} or O; W is C; R^8 is hydrogen; and R^{10} is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-6}

cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C₃₋₆ cycloalkyl, C(O)R_b, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S, or O.

[000102] In an embodiment of the present disclosure, there is provided a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical



compositions, metabolites, and prodrugs thereof, wherein A is ; n is 0 or 1; m is 1; p is 1; o is 1 – 3; R¹, R², R³, R⁴, R⁵, and R⁶ are independently selected from group consisting of hydrogen, hydroxyl, or C₁₋₄ alkyl; R⁷, and R¹² are independently selected from hydrogen, or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with C₆ aryl, and wherein C₆ aryl is optionally substituted with one or more groups selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen or hydroxyl; R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen; X is CR¹⁰; Y is selected from CR¹⁰, or O; Z is selected from CR¹⁰, NR¹⁰ or O; W is C; R⁸ is hydrogen; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b,

$N(R_a)SO_2R_b$, $NR_aC(O)OR_b$, NR_aR_b , $NR_aC(S)NR_bR_c$, $NR_aC(O)R_b$, $NR_aC(S)R_b$, $SONR_aR_b$, $SO_2NR_aR_b$, $OC(O)NR_aR_b$, $OR_aC(O)OR_b$, $OC(O)NR_aR_b$, $OC(O)R_a$, OR_a , $R_aNR_bR_c$, R_aOR_b , SR_a , SOR_a , SO_2R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C_{5-6} aryl, C_{3-6} cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, oxo, C_{3-6} cycloalkyl, $C(O)R_b$, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with $C(O)R_b$, and wherein R_a , R_b , and R_c are independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-6} aryl, C_{3-15} heterocyclyl or C_{3-15} heteroaryl, wherein C_{5-6} aryl, and C_{3-15} heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C_{1-6} alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S, or O.

[000103] In an embodiment, the present disclosure relates to a compound of Formula I, Formula Ia, or Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, which is selected from a group consisting of: *N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 1), *N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methylimidazo[1,2-a]pyridine-2-carboxamide (Example 2), *N*-(2-(3,4-dihydroisoquinolin-2(1H)-yl)-1-hydroxyethyl)-7-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 3), (S)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-ethyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 4), (S)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-propyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 5), (S)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 6), (S)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 7),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 8),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methoxyimidazo[1,2-a]pyridine-2-carboxamide (Example 9),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-phenylimidazo[1,2-a]pyridine-2-carboxamide (Example 10),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 11),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-isopropylimidazo[1,2-a]pyridine-2-carboxamide (Example 12),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 13),
(S)-6-(4-cyanophenyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 14),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(3,5-dimethylisoxazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 15),
(S)-6-(3,5-difluorophenyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 16),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 17),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-isobutyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 18),
(S)-6-(3,6-dihydro-2H-pyran-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 19),
N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 20),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 21),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 22),
(S)-6-(1-(1-acetylazetidin-3-yl)-1H-pyrazol-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 23),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-isopropyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 24),
(S)-6-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 25),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example-26),
(S)-6-(1-acetylpiperidin-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 27),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2-methylpyrimidin-5-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 28),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(6-methylpyridin-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 29),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(6-methylpyridazin-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 30),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2-methylthiazol-5-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 31),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4,5-dimethylthiazol-2-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 32),
(S)-6-(5-chloropyridin-2-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 33),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 34),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 35),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 36),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-isopropyl-1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 37),
(S)-N2-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N6-methylimidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 38),
(S)-6-acetamido-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 39),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-sulfamoylimidazo[1,2-a]pyridine-2-carboxamide (Example 40),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(methylsulfonamido)imidazo[1,2-a]pyridine-2-carboxamide (Example 41),
((S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyrimidine-2-carboxamide (Example 42),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrimidine-2-carboxamide (Example 43),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrimidine-2-carboxamide (Example 44),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 45),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 46),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 47),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 48),
(S)-6-(1-acetylpiperidin-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 49),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 50),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 51),
(S)-6-(1-acetylpiperidin-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 52),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 53),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-methyl-6-(trifluoromethyl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 54),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3,6-dimethylimidazo[1,2-a]pyrazine-2-carboxamide (Example 55),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methylimidazo[1,2-b]pyridazine-2-carboxamide (Example 56),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 57),

(S)-6-(3,3-difluoroazetidin-1-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 58),
(S)-6-(3,3-difluoroazetidin-1-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 59),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 60),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 61),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 62),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 63),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 64),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-methyl-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 65),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-methyl-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 66),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5-methylpyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 67),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-fluoro-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 68),
(S)-6-(azetidin-1-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 69),
N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(3-fluoropyrrolidin-1-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 70),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-methylpiperazin-1-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 71),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-morpholinoimidazo[1,2-a]pyridine-2-carboxamide (Example 72),
N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(3-fluoropyrrolidin-1-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 73),
(S)-6-(4-cyanophenyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 74),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 75),
N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 76),
N-((2R,3R)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 77),
N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 78),
N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 79),
N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 80),
N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 81),
(S)-N-(3-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 82),
(S)-N-(3-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 83),
(S)-N-(3-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 84),
(S)-N-(3-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 85),
(S)-6-(difluoromethyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 86),
6-(difluoromethyl)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 87),
(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 88),
(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 89),
(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 90),

(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(trifluoromethyl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 91),
(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 92),
(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 93),
(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 94),
(R)-6-(4-cyanophenyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methylimidazo[1,2-a]pyrazine-2-carboxamide (Example 95), N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-trifluoromethylimidazo[1,2-a]pyridine-2-carboxamide (Example 96),
N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 97),
6-(1-acetylpiperidin-4-yl)-N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 98),
N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 99),
N-(4-(3,4-dihydroisoquinolin-2(1H)-yl)-1-hydroxybutan-2-yl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 100),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 101),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 102),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-7-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 103),
6-cyclopropyl-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 104),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-7-propyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 105),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-propyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 106),
(R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methoxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 7a) and (S)-N-((S)-3-(3,4-

dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methoxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 107b) (Examples 107a and 7b),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-isopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 108),

N-(2-(3,4-dihydroisoquinolin-2(1H)-yl)-1-hydroxyethyl)-7-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 109),

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 110),

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 111),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-phenyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine-2-carboxamide (Example 112),

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-7-isopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-2-carboxamide (Example 113),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 114),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 115),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl)-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine-2-carboxamide (Example 116),

N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 117),

(R)-6-(1-acetylpiperidin-4-yl)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (-Example 118A),

(S)-6-(1-acetylpiperidin-4-yl)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 118B),

N--3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 119),

(R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 120A),

(S)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (-(Example 120B),

(S)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 121A),

(R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 121B),

(R)-6-bromo-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 122),

(S)-6-cyano-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example_123),

(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 124),

(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-fluoroimidazo[1,2-a]pyridine-2-carboxamide (Example 125),

(R)-2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbonyl)imidazo[1,2-a]pyridine-6-carboxylic acid (Example 126),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(piperidine-1-carbonyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 127),

(S)-N6-(3,3-difluorocyclobutyl)-N2-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 128),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(piperazine-1-carbonyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 129),

(S)-N6-cyclohexyl-N2-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 130),

(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2,6-diazaspiro[3.3]heptane-2-carbonyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 131),

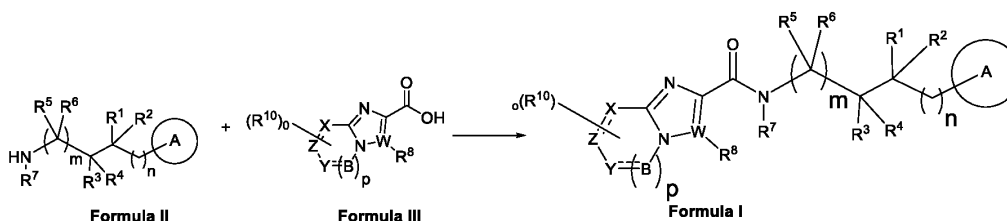
N-((R)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 132),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(piperidine-1-carbonyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 133),
N6-(3,3-difluorocyclobutyl)-N2-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 134),
N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(piperazine-1-carbonyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 135),
N-((R)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2,6-diazaspiro[3.3]heptane-2-carbonyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 136),
N-((R)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 137),
(S)-6-benzamido-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 138),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2-fluorobenzamido)imidazo[1,2-a]pyridine-2-carboxamide (Example 139),
(S)-6-(cyclohexanecarboxamido)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 140),
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-carboxamido)imidazo[1,2-a]pyridine-2-carboxamide (Example 141),
(S)-6-(cyclopropanecarboxamido)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 142),
(S)-6-(cyclobutanecarboxamido)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 143),
(S)-6-(4-cyanobenzamido)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 144),
6-(4-cyanobenzamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 145),
6-benzamido-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 146),
N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(isonicotinamido)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 147),

N-(2-(((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)oxazole-4-carboxamide (Example 148),
N-((R)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-carboxamido)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 149),
6-(cyclopentanecarboxamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 150),
6-(cyclopropanecarboxamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 151),
6-(cyclohexanecarboxamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 152),
6-(cyclobutanecarboxamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 153),
(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(phenylsulfonamido)imidazo[1,2-a]pyridine-2-carboxamide (Example 154),
N-((R)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(phenylsulfonamido)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 155),
rac-(R)-6-(azetidine-1-carbonyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 156),
(S)-N-(2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)isoxazole-3-carboxamide (Example 157),
6-(bicyclo[2.2.1]heptane-2-carboxamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 158),
(S)-N-(2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)oxazole-2-carboxamide (Example 159),
(S)-N-(2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-5-carboxamide (Example 160),

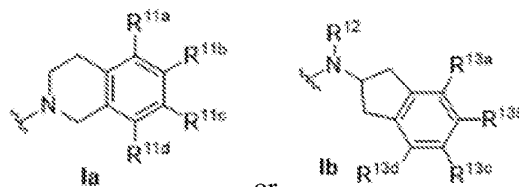
N-(2-(((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)isoxazole-3-carboxamide (Example 161),
 6-(bicyclo[2.2.1]heptane-2-carboxamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 162),
 N-(2-(((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)oxazole-2-carboxamide (Example 163),
 N-(2-(((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)thiazole-5-carboxamide (Example 164),
 (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-ethylimidazo[1,2-a]pyridine-2-carboxamide (Example 165),
 (S)-6-(1,1-difluoroethyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 166), and (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(pentafluoro-16-sulfaneyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 167).

[000104] In an embodiment, the present disclosure relates to a process of preparation of compounds of Formula I or its analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites and prodrugs thereof as described herein, wherein the process comprises reacting compounds of Formula II with Formula III in presence of a coupling reagent and a solvent to obtain the compounds of Formula I

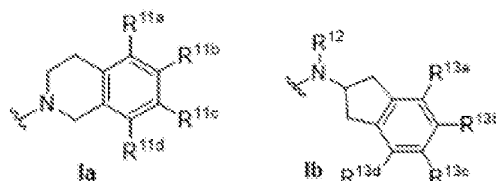


[000105] In an embodiment, the present disclosure relates to a process of preparation of compounds of Formula I or its analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites and prodrugs thereof as described herein, wherein the process comprises reacting compounds of Formula II with Formula III in presence of a coupling reagent and a solvent to obtain the compounds of Formula I,

wherein X, Y, and Z of Formula III are independently selected from CR¹⁰, NR¹⁰, O or S; W and B are independently selected from N or C, p is 1 or 2; o is 1 – 3; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl, and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, and C₃₋₁₅ heteroaryl are optionally substituted with C₁₋₆ alkyl; n is 0-1; A of Formula II



is selected from **Ia** or **Ib**; n is 0 - 1; m is 0 - 2; R¹, R², R³, and R⁴ are independently selected from hydrogen, halogen, hydroxyl or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, halogen, and combinations thereof; R⁵, and R⁶ are independently selected from hydrogen, C₁₋₆ alkyl or halogen, wherein C₁₋₆ alkyl is optionally substituted with hydroxyl, halogen, and combinations thereof; R⁷, and R¹² are independently selected from hydrogen or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₁₋₆



alkoxy; A of Formula I is selected from  ;
 --- represents optional single or double bond; n is 0 or 1; m is 0 - 2; p is 1 or 2; o is 1 - 3;
 R¹, R², R³, R⁴, R⁵, and R⁶ are independently selected from hydrogen, halogen, hydroxyl or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one or more groups selected from hydroxyl or halogen; R⁷, and R¹² are independently selected from hydrogen or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with C₅₋₆ aryl, and wherein C₅₋₆ aryl is optionally substituted with one or more groups selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, or cyano; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{13a}, R^{13b}, R^{13c}, and R^{13d} are independently selected from hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl or C₁₋₆ alkoxy; X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O or S; W, and B are independently selected from N or C; R⁸ is absent or is selected from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl or C₃₋₁₅ heterocyclyl; and R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR_aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a

5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[000106] In an embodiment, the present disclosure relates to a process of preparation of compounds of Formula I as described herein, wherein the coupling reagent is selected from the group consisting of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride, hydroxybenzotriazole, propane phosphonic acid anhydride, and combinations thereof.

[000107] In an embodiment, the present disclosure relates to a process of preparation of compounds of Formula I as described herein, wherein the solvent is a polar aprotic solvent selected from the group consisting of DMF, dioxane, acetonitrile, THF, and combinations thereof.

[000108] In an embodiment, the present disclosure relates to pharmaceutical composition comprising a compound of Formula I, Formula Ia, or Formula Ib as described herein, or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

[000109] In another embodiment, the present disclosure relates to the pharmaceutical composition as described herein, wherein the composition is in the form selected from the group consisting of a tablet, capsule, powder, syrup, solution, aerosol and suspension.

[000110] In an embodiment, the present disclosure relates to a method for the treatment and/or prevention of various diseases, including cancer and infectious diseases, comprising administering to a subject suffering from the proliferative disorder or cancer a therapeutically effective amount of the compounds of Formula I, Formula Ia, or Formula Ib or a pharmaceutically acceptable salt thereof or together with a pharmaceutically acceptable carrier, with other clinically relevant cytotoxic agents or non-cytotoxic agents to a subject in need thereof.

[000111] In an embodiment, the present disclosure relates to the use of compounds of Formula I, Formula Ia, or Formula Ib or pharmaceutically acceptable salts thereof together with a pharmaceutically acceptable carrier, for the treatment and/or prevention of various diseases including proliferative disorder or cancer; or treatment of cancer together with other clinically relevant cytotoxic agents or non-cytotoxic agents.

[000112] In an embodiment, the present disclosure relates to the use of compounds of Formula Ib, Formula Ia, Formula I or pharmaceutically acceptable salts thereof together with a pharmaceutically acceptable carrier, for the treatment and/or prevention of various

diseases including proliferative disorder or cancer; or treatment of cancer together with other clinically relevant cytotoxic agents or non-cytotoxic agents such as carboplatin, bortezomib, carfilzomib, lenalidomide, pomalidomide, doxorubicin, daunorubicin, decitabine, denileukin, denileukin diftitox, dexrazoxane, docetaxel, doxorubicin, dromostanolone propionate cyclophosphamide, 5-fluorouracil, imatinib, methotrexate, irinotecan, topotecan, vinblastine, etoposide, vincristine, carmustine, paclitaxel, vorinostat, belinostat, panbinostat, romidepsin, chiadamide, entinostat, mocetinostat, afatinib, bosutinib, cetuximab, enterctinib, lapatinib, nilotinib, pazopanib, ruxlotinib, sorafenib, sunitinib, vemurafenib, axitinib, gefitinib, cobimetinib, carbozantinib, temozolomide, idarubicin, abarelix, aldesleukin, alemtuzumab, allopurinol, altretamine, anastrozole, asparaginase, bexarotene, baricitinib, bleomycin, busulfan, capecitabine, cladribine, clofarabine, cytarabine, dacarbazine, dactinomycin, sodium, dasatinib, letrozole, tamoxifen, oxaliplatin, procarbazine and zoleronate.

[000113] In an embodiment, the present disclosure relates to a method for the treatment of cancer as described herein, wherein said method comprising administering a combination of the compounds of Formula I or pharmaceutically acceptable salts thereof, together with a pharmaceutically acceptable carrier, with other clinically relevant cytotoxic agents or non-cytotoxic agents to a subject in need thereof.

[000114] In an embodiment, the present disclosure relates to a method of treatment of cancer as described herein, wherein said method comprising administering a combination of the compounds of Formula I or the pharmaceutical composition with other clinically relevant immune modulator agents to a subject in need of thereof.

[000115] In an embodiment, the present disclosure relates to a method of treatment of cancer as described herein, wherein said method comprising administering a combination of the compounds of Formula I, Formula Ia, or Formula Ib or the pharmaceutical composition with other clinically relevant immune checkpoint inhibitors. In another embodiment of the present disclosure, the immune checkpoint inhibitors are selected from the group consisting of CD27, CD28, CD40, CD122, CD96, CD73, CD47, OX40, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, aiginase, CD137 (also known as 4-1BB), ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, VISTA, PD-1, PD-L1, PD-L2, and combinations thereof.

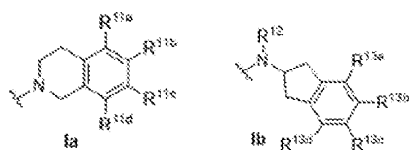
[000116] In an embodiment, the present disclosure relates to a method of treatment of cancer as described herein, wherein said method comprising administering a combination of the compounds of Formula I, Formula Ia, or Formula Ib or the pharmaceutical

composition with other clinically relevant immune checkpoint inhibitors such as nivolumab, pembrolizumab, pidilimumab, bms-986016, epacadostat, tremelimumab, CD73 inhibitors and arginase inhibitors to a subject in need of thereof.

[000117] In an embodiment, the present disclosure relates to the use of compounds of Formula I or the pharmaceutical composition for treatment of a condition mediated by PRMT5; treatment and/or prevention of a proliferative disorder or cancer; or treatment of cancer together with other clinically relevant cytotoxic agents or non-cytotoxic agents.

[000118] In an embodiment, the present disclosure relates to a method for the treatment and/or prevention of a condition mediated by PRMT5 or a proliferative disorder or cancer as described herein, wherein said method comprising administering to a subject suffering from the condition mediated by PRMT5 or the proliferative disorder or cancer, a therapeutically effective amount of the compound of Formula I or the pharmaceutical composition.

[000119] In an embodiment, the present disclosure relates to a compound of Formula I, Formula Ia, or Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein A is selected



[000120] In an embodiment, the present disclosure relates to a compound of Formula I, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein n is 0 or 1; m is 0-2; p is 1 or 2; and o is 1 - 3.

[000121] In an embodiment, the present disclosure relates to a compound of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein n is 0 or 1; and m is 0-2.

[000122] In an embodiment, the present disclosure relates to a compound of Formula I, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein n is 0 or 1; m is 0-2; and p is 1.

[000123] In an embodiment, the present disclosure relates to a compound of Formula I, or Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are independently selected from hydrogen, halogen, hydroxyl, or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more groups selected from hydroxyl, or halogen.

[000124] In an embodiment, the present disclosure relates to a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein R^1 , R^2 , R^3 , and R^4 are independently selected from hydrogen, halogen, hydroxyl, or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more groups selected from hydroxyl, or halogen; and R^5 , and R^6 are independently selected from hydrogen, C_{1-6} alkyl, or halogen, wherein C_{1-6} alkyl is optionally substituted with one or more groups selected from hydroxyl, or halogen.

[000125] In an embodiment, the present disclosure relates to a compound of Formula I, Formula Ia, or Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein R^7 is selected from hydrogen, or C_{1-4} alkyl.

[000126] In an embodiment, the present disclosure relates to a compound of Formula I, Formula Ia, or Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein R^{12} is absent or is selected from hydrogen, or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with C_6 aryl, and wherein C_6 aryl is optionally substituted with one or more groups selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxyl, or cyano.

[000127] In an embodiment, the present disclosure relates to a compound of Formula I, Formula Ia, or Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{13a} , R^{13b} , R^{13c} , and R^{13d} are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy.

[000128] In an embodiment, the present disclosure relates to a compound of Formula I, Formula Ia, or Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein X, Y, and Z are independently selected from CR¹⁰, NR¹⁰, O, or S.

[000129] In an embodiment, the present disclosure relates to a compound of Formula I, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SF₅, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a, or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl, or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[000130] In an embodiment, the present disclosure relates to a compound of Formula Ia, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein R¹⁰ is selected from hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, 3-15 membered

saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SF₅, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, or SO₂R_a, wherein C₅₋₆ aryl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, cyano, oxo, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O is optionally substituted with C(O)R_b, and wherein R_a, R_b, and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl, and C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[000131] In an embodiment, the present disclosure relates to a compound of Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein R¹⁰ is selected from hydrogen, halogen, hydroxyl, oxo, nitro, cyano, azido, nitroso, amino, hydrazino, formyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₁₋₆ alkylamino, COOR_a, C(O)R_b, C(S)R_a, C(O)NR_aR_b, C(S)NR_aR_b, NR^aC(O)NR_bR_c, N(R_a)SOR_b, N(R_a)SO₂R_b, NR_aC(O)OR_b, NR_aR_b, NR_aC(S)NR_bR_c, NR_aC(O)R_b, NR_aC(S)R_b, SONR_aR_b, SO₂NR_aR_b, OC(O)NR_aR_b, OR_aC(O)OR_b, OC(O)NR_aR_b, OC(O)R_a, OR_a, R_aNR_bR_c, R_aOR_b, SR_a, SOR_a, SO₂R_a, or 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-5 heteroatoms selected from N, S or O, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and 3-15 membered saturated or unsaturated heterocyclyl or heteroaryl ring are optionally substituted with one or more groups selected from halogen, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C(O)R_b, or 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring with 1-3 heteroatoms selected from N, S or O, wherein 3-6 membered saturated or unsaturated heterocyclyl or heteroaryl ring is optionally substituted with C(O)R_b, and wherein R_a, R_b,

and R_c are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heterocyclyl or C₃₋₁₅ heteroaryl, wherein C₅₋₆ aryl, C₃₋₆ cycloalkyl, and C₃₋₁₅ heteroaryl are optionally substituted with one or more substituents selected from halogen, cyano, or C₁₋₆ alkyl; or R_a and R_b can be taken together to form a 5-10 membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring with 1-3 heteroatoms selected from N, S or O.

[000132] In an embodiment, the present disclosure relates to a compound of Formula I, Formula Ia, or Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein W is selected from N or C.

[000133] In an embodiment, the present disclosure relates to a compound of Formula I, Formula Ia or Formula Ib, their analogs, tautomeric forms, stereoisomers, geometrical isomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, pharmaceutical compositions, metabolites, and prodrugs thereof, wherein R⁸ is absent or is selected from hydrogen, halogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₅₋₆ aryl, C₃₋₁₅ heteroaryl, and C₃₋₁₅ heterocyclyl.

EXAMPLES

[000134] 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* or the *Journal of Biological Chemistry*. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. 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:

BSA	Bovine serum albumin;
DCE	1,2-Dichloroethane;
DCM	Dichloromethane;
DME	1,2-Dimethoxyethane;
DMF	Dimethyl formamide;
Hünig's base	<i>N</i> -ethyl- <i>N</i> -(1-methylethyl)-2-propanamine;

Dioxane	1,4-Dioxane;
DMSO	Dimethylsulfoxide;
DTT	Dithiothreitol;
<i>N</i> -(3-Dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride;	
HPLC	High pressure liquid chromatography;
HOBt	Hydroxybenzotriazole;
LiOH.H ₂ O	Lithium hydroxide monohydrate;
NMR	Nuclear magnetic resonance;
DCMComplex	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II). dichloromethane complex;
tetrakis(triphenylphosphine)palladium(0);	(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate);
RT	Room temperature;
TCEP	(Tris(2-carboxyethyl)phosphine)
TLC	Thin layer chromatography;
TMS	Tetramethyl silane;
T ₃ P	Propane phosphonic acid anhydride;
TFA	Trifluoroacetic acid; and
THF	Tetrahydrofuran.

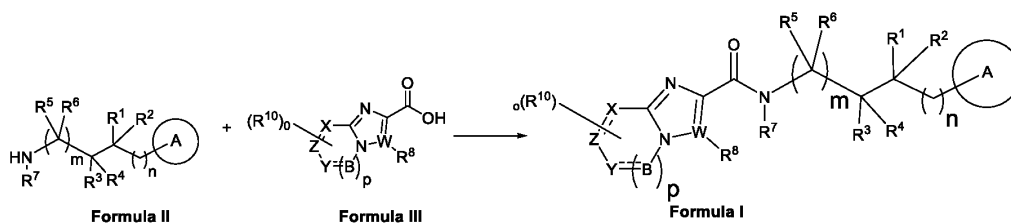
[000135] The following examples provide the details about the synthesis, activities, and applications of the compounds of the present disclosure. It should be understood the following is representative only, and that the disclosure is not limited by the details set forth in these examples.

[000136] The compounds of the disclosure may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out in the following schemes, and can be readily adapted to prepare other compounds of the disclosure.

[000137] There is also provided a process as shown in the following Scheme-1, for the preparation of compounds of the Formula I, wherein all the groups are as defined earlier.

Example 1

General Procedure for synthesis of compounds of Formula I



[000138] The said process for the preparation of the compounds of Formula I comprises: (a) Reacting compounds of Formula II with compounds of Formula III in the presence of a coupling reagent such as EDCI.HCl, HOBT, T₃P and the like in solvents like polar aprotic solvents such as DMF, dioxane and the like gives compound of Formula I.

[000139] Compounds of Formula I when isotopically labeled can be synthesized using the general protocol given in Scheme 1 by using the corresponding isotopically labeled starting materials.

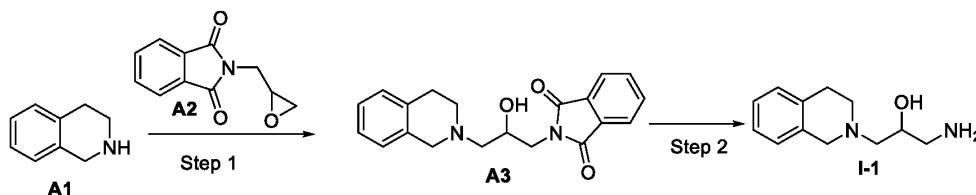
General considerations and Analytical Methods:

[000140] The compounds used in the reaction processes, if not mentioned otherwise, were commercially available and purchased from Aldrich. NMR data were obtained on Varian 400 MHz spectrometer. All compounds were characterized by ¹H NMR, HPLC and mass spectrometry (LCMS (ES)), Liquid chromatography-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. LCMS (ES) measurements were performed on Agilent and Waters Mass spectrometers. The yields of the compounds provided refer to isolated compounds.

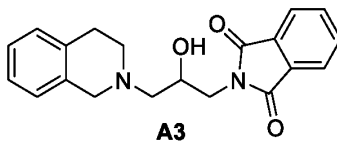
[000141] The examples given below are provided by the way of illustration only and therefore should not be construed to limit the scope of the disclosure.

General Procedure for synthesis of Intermediates

Synthesis of 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (I-1)

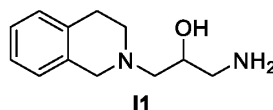


Step- 1: Preparation of 2-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)isoindoline-1,3-dione (A3)



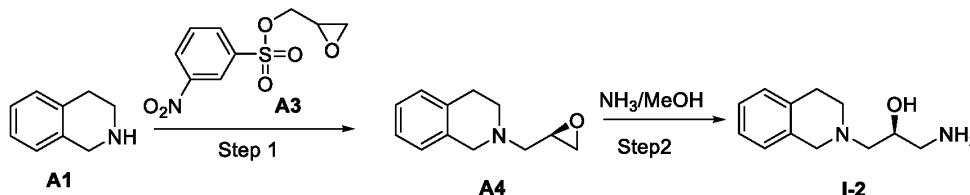
[000142] To a stirred suspension of compound 2-(oxiran-2-yl-methyl) isoindoline-1, 3-dione (**A2**, 20.0 g, 98.0 mmol) in ethanol (200 mL) was added 1, 2, 3, 4-tetrahydroisoquinoline (**A1**, 13.1 g, 98.0 mmol). The reaction mixture was heated at 80°C for 16 h and cooled to room temperature. The solvent was evaporated to afford the crude product **A3** (32.8 g) which was taken for the next step as such. MS (ESI) $m/z = 337.2$ $[M+H]^+$.

Step- 2: Preparation of 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (I-1)

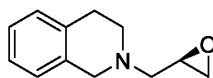


[000143] To a stirred solution of crude compound 2-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2 hydroxypropyl)isoindoline-1,3-dione (**A3**, 32.8 g, 97 mmol) in ethanol 200mL was added hydrazine hydrate (24mL, 488 mmol). An additional 800 mL of ethanol was added. The reaction mixture was stirred at 23-25°C until the disappearance of starting material. The solvent was filtered and the residue washed with dichloromethane (DCM). The filtrate was concentrated to dryness. The residue was taken in DCM and minimum amount of water was added (~50mL). The organic and aqueous layers were separated. The DCM layer was dried over anhydrous Na_2SO_4 , filtered and evaporated to dryness to get compound 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol **I-1** as a yellow syrupy liquid. Yield: 24.4 g (90%). MS (ESI) $m/z = 207.1$ $[M+H]^+$.

Synthesis of (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (I-2)



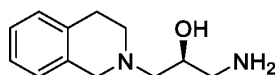
Step-1: Preparation of (R)-2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (A4)



A4

[000144] To a solution of 1,2,3,4-tetrahydroquinoline (**A1**, 1 g, 7.5 mmol) in THF (10 mL) at 0 °C was added KF (0.87 g, 15 mmol). After 1 h (S)-oxiran-2-yl-methyl-3-nitro benzenesulfonate (**A3**, 2.2 g, 8.49 mmol) was added and the resulting solution was stirred at room temperature for 16 h. The solid was removed by filtration and washed with THF. The solution was concentrated to afford to compound **A4** (1g) was used for next step without further purification. MS (ESI) $m/z = 190.2$ $[M+H]^+$.

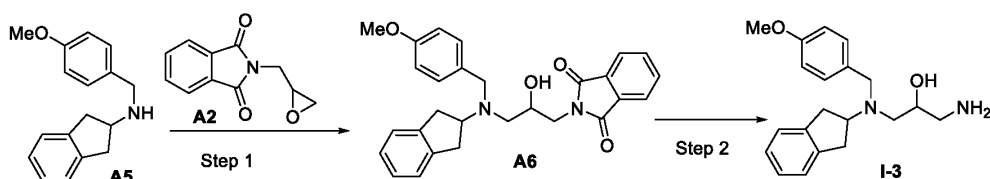
Step-2: Preparation of (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (I-2)



I-2

[000145] To a solution of crude (R)-2-(Oxiran-2-yl methyl)-1,2,3,4-tetrahydroisoquinoline (**A4**, 1g, 4.85 mmol) in ethanol (20 mL) at -78 °C was slowly bubbled ammonia for 30 min. The reaction mixture was sealed and heated at 80 °C for 3 h. The reaction mixture was concentrated and crude product **I-2** (1g, purity 80 %) was used for next step without further purification. MS (ESI) $m/z = 207.2$ $[M+H]^+$.

Synthesis of 1-amino-3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)propan-2-ol (I-3)



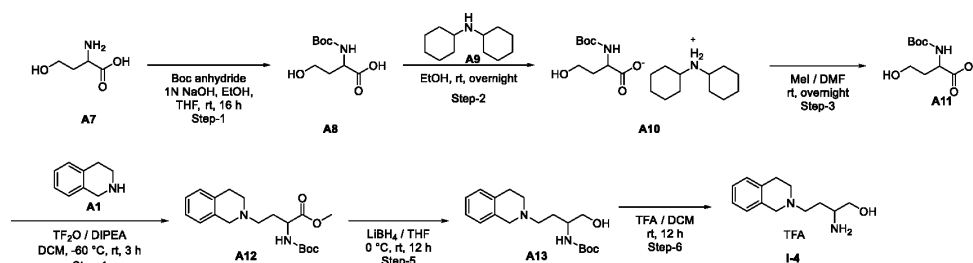
Step 1: Preparation of 2-(3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)-2-hydroxypropyl)isoindoline-1,3-dione (B3)

[000146] To a stirred solution of N-(4-methoxybenzyl)-2,3-dihydrobenzofuran-2-amine (**A4**, 7.1 g, 28.4 mmol) in EtOH (60 mL) was added 2-(oxiran-2-ylmethyl)-1H-indene-1,3(2H)-dione (**A2**, 5.7 g, 28.4 mmol). The reaction mixture was stirred for 16 h at 80 °C. The solvent was evaporated to get the product **B3** as a brown liquid (10.1 g, 78 %). MS (ESI) $m/z = 457.2$ $[M+H]^+$.

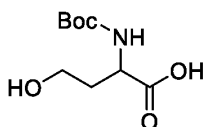
Step 2: Preparation of 1-amino-3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)propan-2-ol (I-3)

[000147] To a stirred solution 2-(3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)-2-hydroxypropyl)isoindoline-1,3-dione (**B3**, 11 g, 2.41 mmol) in EtOH was added hydrazine hydrate (50 mL, 6.03 mmol). Reaction mixture was stirred for 16 h at room temperature. The reaction mixture was concentrated. The residue was dissolved in ethylacetate/H₂O mixture. Organic layer was separated and dried over anhydrous Na₂SO₄. The organic layer was concentrated to afford yellow oily product **I-3** (5.6 g, 65%). MS (ESI) m/z = 327.1 [M+H]⁺.

Synthesis of tert-butyl (4-(3,4-dihydroisoquinolin-2(1H)-yl)-1-hydroxybutan-2-yl)carbamate (I-4)

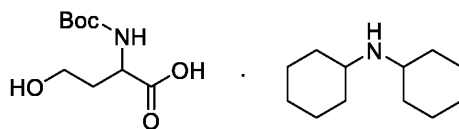


Step 1: Preparation of (tert-butoxycarbonyl)homoserine (**A8**)



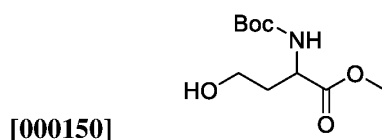
[000148] To a solution of DL-homosericine (**A7**, 12.12 g, 101.89 mmol) in 1N NaOH (111 mL) and EtOH (97 mL) was added a solution of Boc anhydride (24.43 g, 112 mmol) in THF (97 mL) over 15 minutes. The reaction mixture was stirred at room temperature for 16 h. The mixture was then washed with ether (3×200 mL), acidified with 1N HCl to pH 2 and extracted with ethyl acetate (6×250 mL). The combined organic extracts were washed with brine (250 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. To afford 5.9 g of **A8** as a colourless liquid. MS (ESI) m/z = 218.9 [M+H]⁺.

Step 2: Preparation of (tert-butoxycarbonyl)homoserinedicyclohexyl amine complex (**A10**)



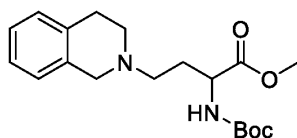
[000149] To a solution of (tert-butoxycarbonyl)homoserine (**A8**, 5.9 g, 26.9 mmol) in EtOH (41 mL) was added drop wise dicyclohexylamine (**A9**, 5.82 mL, 29.3 mmol). The mixture was stirred for 12 h at room temperature and then concentrated under reduced pressure. The white solid was dried under high vacuum and then triturated with ether (1000 mL). The fine white powder was collected by filtration, washed with ether and dried under high vacuum. (6.37 g, 59% yield). The crude material **A10** was as such taken for next step.

Step 3: Preparation of Methyl (tert-butoxycarbonyl)homoserinate (**A11**)



[000151] To a suspension of (tert-butoxycarbonyl)homoserinedicyclohexyl amine complex (**A10**, 6.37 g, 15.9 mmol) in DMF (52 mL) was added iodomethane (1.18 mL, 19.1 mmol). The mixture was stirred at room temperature for 16 h. The clear solution was concentrated under reduced pressure. The residue was diluted with water (200 mL) and extracted with ethyl acetate (2 x 100 mL) and stirred for 2 h before the layers were separated. The combined extracts were washed with brine (250 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide yellow oil. The crude was purified by column chromatography using silica gel eluting with ethyl acetate/hexane to afford methyl (tert-butoxycarbonyl)homoserinate **A11** as a colorless oil (2 g, 54% yield). The crude material was as such taken for next step.

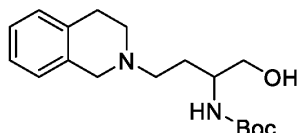
Step 4: Preparation of Methyl 2-((tert-butoxycarbonyl)amino)-4-(3,4-dihydroisoquinolin-2(1H)-yl)butanoate (**A12**)



[000152] To a solution of methyl (tert-butoxycarbonyl)homoserinate (**A11**, 0.2 g, 0.86 mmol) in dry dichloromethane (5 mL), diisopropyl ethyl amine (0.75 mL, 4.2 mmol) was added and cooled to -60 °C, triflic anhydride (0.21 mL, 1.28 mmol) was added to the reaction mixture slowly and allowed to stirred at room temperature for 3 h. Reaction mixture was quenched with water and extracted with dichloromethane. The combined

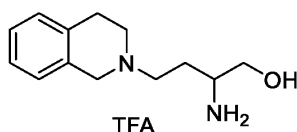
organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography using silica gel eluting with ethyl acetate/hexane to afford methyl 2-((tert-butoxycarbonyl)amino)-4-(3,4-dihydroisoquinolin-2(1H)-yl)butanoate **A11** as a colorless liquid (0.18 g, 60%). MS (ESI) m/z = 349.2 $[M+H]^+$.

Step 5: Preparation of tert-butyl (4-(3,4-dihydroisoquinolin-2(1H)-yl)-1-hydroxybutan-2-yl)carbamate (A13)



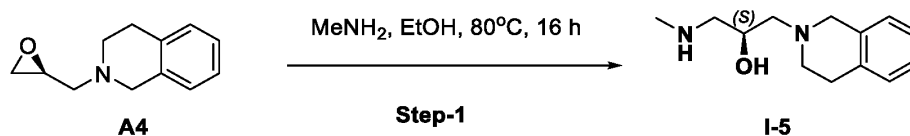
[000153] A solution of methyl 2-((tert-butoxycarbonyl)amino)-4-(3,4-dihydroisoquinolin-2(1H)-yl)butanoate methyl ester (**A12**, 0.18 g, 0.51 mmol) in 7 mL of THF was cooled to 0°C in an ice bath. (1.29 mL, 1.29 mmol) of a 1M solution of LiBH_4 in THF was then added at once. The ice bath was removed 2 min. later. The solution was allowed to warm to room temperature and stirred for 22 h. Reaction mixture was quenched with sat. NH_4Cl solution was then added carefully due to the resulting evolution of hydrogen. Once effervescence had ceased, the resulting mixture was extracted with dichloromethane and then an additional (3 x 20 mL) of dichloromethane. The organic extracts were dried over sodium sulfate and then filtered and concentrated. Purified by column chromatography using ethyl acetate/ hexane to afford **A13** as a colorless liquid (0.14 g, 84.8%). MS (ESI) m/z = 321.2 $[M+H]^+$.

Step 6: Preparation of TFA salt of 2-amino-4-(3,4-dihydroisoquinolin-2(1H)-yl)butan-1-ol (I-4)



[000154] To a solution of tert-butyl (4-(3,4-dihydroisoquinolin-2(1H)-yl)-1-hydroxybutan-2-yl)carbamate (**A13**, 0.14 g, 0.43 mmol) in DCM (5 mL), cooled to 0 °C, Trifluoro acetic acid (1 mL) and stirred at room temperature for 12 h. Reaction mixture was concentrated. The crude material **I-4** was as such taken for next step. MS (ESI) m/z = 221.1 $[M+H]^+$.

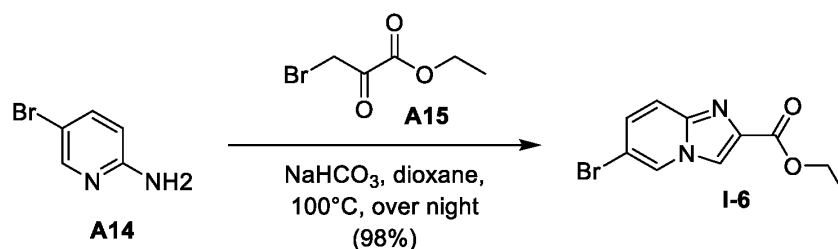
Synthesis of (S)-1-(3,4-dihydroisoquinolin-2(1H)-yl)-3-(methylamino)propan-2-ol (I-5)



Step- 1: (S)-1-(3,4-dihydroisoquinolin-2(1H)-yl)-3-(methylamino)propan-2-ol (I5)

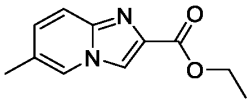
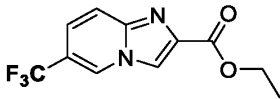
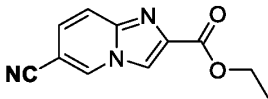
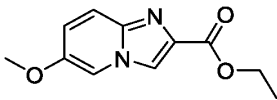
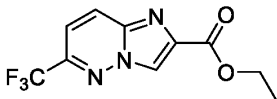
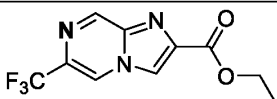
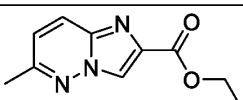
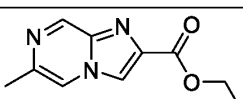
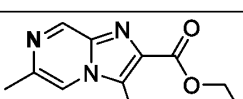
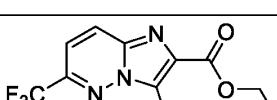
To a stirred solution of (S)-2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (**B2**, 1.0 g, 5.28 mmol) in EtOH (10 mL) and methylamine (2.0 M solution THF) (3.96 mL, 7.92 mmol) was added drop wise at room temperature and the reaction was stirred for 16 h at 80°C. The reaction mixture was concentrated under reduced pressure to afford (S)-1-(3,4-dihydroisoquinolin-2(1H)-yl)-3-(methylamino)propan-2-ol **I-5** as a light yellow liquid. Yield: 1.0 g (crude) LC-MS (ES) m/z : 221.16 [M+H]⁺

Synthesis of Ethyl 6-bromoimidazo[1,2-a]pyridine-2-carboxylate (I-6)

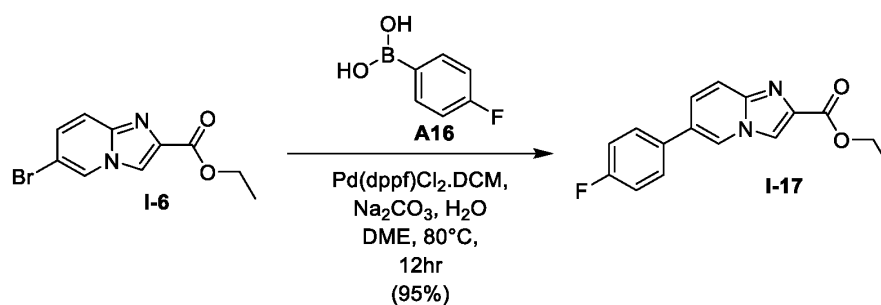


[000155] To a stirred solution of 5-bromopyridin-2-amine (**A14**, 10 g, 57.8 mmol) in 1,4-dioxane (120 mL) was added ethyl 3-bromo pyruvate (**A15**, 10.83 mL, 86.71 mmol), followed by NaHCO₃ (9.71 g, 115.6 mmol). The reaction mixture was heated for 12 h at 100 °C and then concentrated under reduced pressure. The crude product was washed with ethyl acetate/water 2:1 mixture (3x 75 mL) and the combined organic layer was concentrated. Purified by column chromatography using ethyl acetate/hexane to afford **I6** as blackish brown solid (15.3 g, 98%). MS (ESI) m/z =271 [M+H]⁺.

[000156] Further, the following intermediates were synthesized using the protocol exemplified for **I-6**.

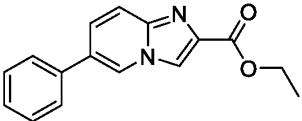
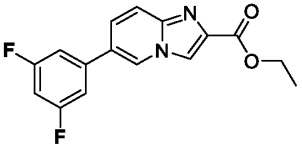
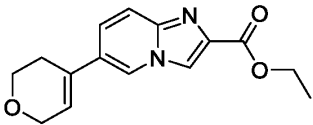
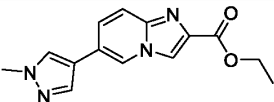
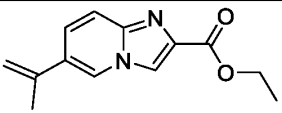
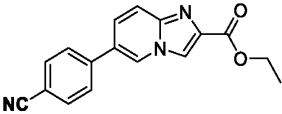
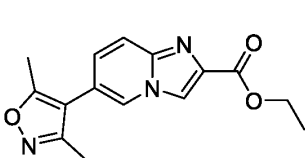
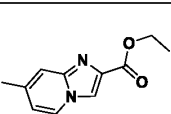
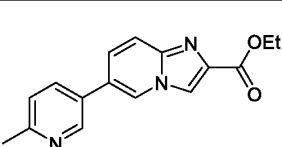
Intermediate No	Structure	LC/MS_m/z_ [M+H] ⁺
I-7		205.2
I-8		259.0
I-9		216.9
I-10		193.1
I-11		260.1
I-12		260.1
I-13		206.04
I-14		206.04
I-15		206.2
I-16		260.1

Synthesis of Ethyl 6-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxylate (I-17)



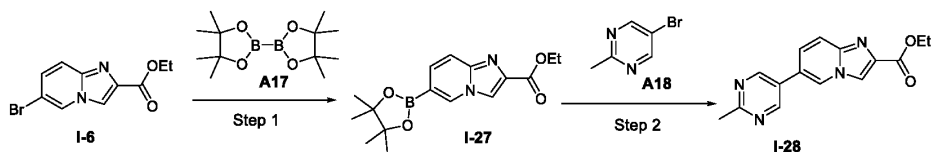
[000157] To a solution of ethyl 6-bromoimidazo[1,2-a]pyridine-2-carboxylate (**I-6**, 2 g, 7.43 mmol) in 1,2- DME (50 mL) was added (4-fluorophenyl)boronic acid (**A16**, 1.56 g, 11.15 mmol), followed by addition of Na_2CO_3 (2.34 g, 22.29 mmol) dissolved in H_2O (12 mL). The reaction mixture was purged with N_2 gas for 20 min followed by the addition of $\text{Pd(dppf)Cl}_2\cdot\text{DCM}$ (0.54 g, 0.743 mmol). It was further purged with N_2 gas for 10 more minutes and stirred for 16 h at 80°C . The reaction mixture was filtered through celite and extracted with ethyl acetate/water mixture. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purified using column chromatography using ethyl acetate/hexane to afford **I-17** as a blackish brown solid product (2.0 g, 95 %). MS (ESI) $m/z = 285.1$ $[\text{M}+\text{H}]^+$.

[000158] The following intermediates were synthesized using the protocol exemplified for **I-17**.

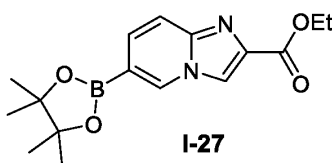
Intermediate No	Structure	LC/MS_m/z_ [M+H] ⁺
I-18		267.1
I-19		303.2
I-20		273.1
I-21		271.1
I-22		231.2
I-23		292.1
I-24		286.1
I-25		372.1
I-26		283.2

Synthesis of ethyl 6-(2-methylpyrimidin-5-yl)imidazo[1,2-a]pyridine-2-carboxylate

I-28

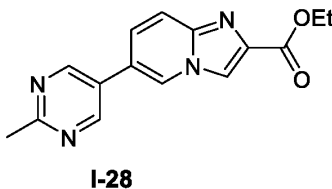


Step-1: ethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyridine-2-carboxylate (I-27)



[000159] A stirred solution of ethyl 6-bromoimidazo[1,2-a]pyridine-2-carboxylate (I-6, 4.0 g, 14.86 mmol), 4,4,4',4'',5,5,5',5''-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (A17, 6.42 g, 25.27 mmol) and KOAc (2.47 gm, 25.27 mmol) in dioxane (100 mL) was degassed with argon for 30 minutes. Then [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.761 g, 1.04 mmol) was added. The reaction mixture was heated at 90°C for 16 h. After completion, reaction mixture quenched with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain the crude. This crude washed with 30% diethyl ether in hexane and concentrated the filtrate to offered ethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyridine-2-carboxylate I-27 as brown gummy liquid. Yield: 7.8 g LC-MS(ES) $m/z = 235.09$ [M+H]⁺.

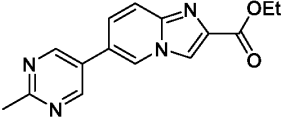
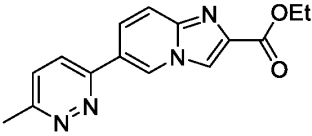
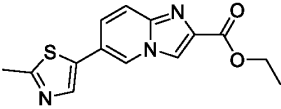
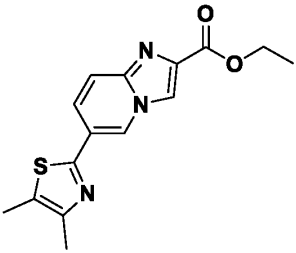
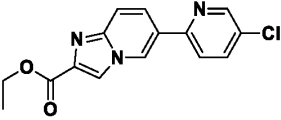
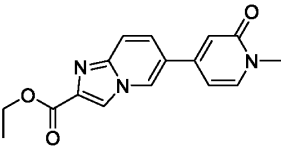
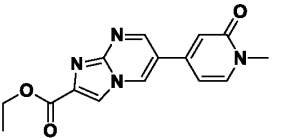
Step-2: ethyl 6-(2-methylpyrimidin-5-yl)imidazo[1,2-a]pyridine-2-carboxylate (I-28)



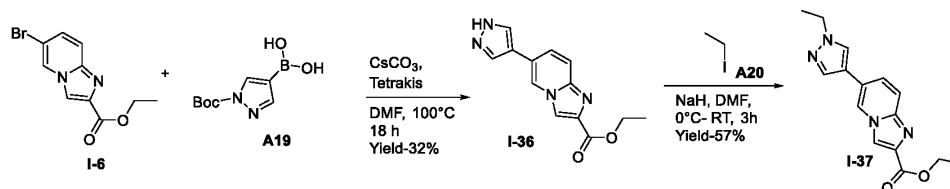
[000160] A stirred solution of 5-bromo-2-methylpyrimidine (A18, 0.5 g 2.8 mmol), ethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyridine-2-carboxylate (I-26, 1.55 g, 4.9 mmol) and sodium carbonate (0.612 g, 5.7 mmol) in

dioxane : water (4:1) 15 mL was degassed with argon for 20 minutes. Then [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.126 g, 0.17 mmol) was added. The reaction mixture was heated at 90°C for 16 h. After completion, reaction mixture quenched with water and extracted with 20% MeOH in DCM (3 times). The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain the crude. This crude purified by combiflash using 3% MeOH in DCM as eluent. The desired fractions were concentrated under reduced pressure to offered ethyl 6-(2-methylpyrimidin-5-yl)imidazo[1,2-a]pyridine-2-carboxylate **I-28** as dark solid. Yield: 0.64 g (78%) LC-MS (ES) $m/z = 283.3$ $[M+H]^+$.

[000161] The following intermediates were synthesized using the protocol exemplified for **I28**.

Intermediate No	Structure	LC/MS_m/z_ [M+H] ⁺
I-29		283.3
I-30		283.2
I-31		287.9
I-32		302.2
I-33		302.2
I-34		298.08
I-35		299.1

Synthesis of (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-isobutyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (I-37)



Step 1: Preparation of Ethyl 6-(1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (I-36)

[000162] A solution of ethyl 6-bromoimidazo[1,2-a]pyridine-2-carboxylate (**I-6**, 3 g, 11.15 mmol), cesium carbonate (7.3 g, 25.09 mmol) and boronic acid compound **A19** (4.92 g, 16.72 mmol) in DMF (60 mL) was purged with argon gas for 30 minutes at room temperature, tetrakis (0.427 g, 0.55 mmol) was added to the reaction mixture and purged argon for another 10 min. The reaction mixture was then heated to 100 °C for 18 h. The reaction mixture was filtered through celite pad and the filtrate was diluted with ice cold water and extracted with ethyl acetate. The organic layer was then washed with ice cold water (2x50 mL) and brine solution. Finally, the organic layer was dried over sodium sulfate and concentrated under reduced pressure to get the crude product. The crude product was then purified by column chromatography with 70% ethyl acetate/hexane as eluent to afford the compound **I-36** as white solid (0.9 g, 32%). MS (ESI) m/z = 256.9 $[M+H]^+$.

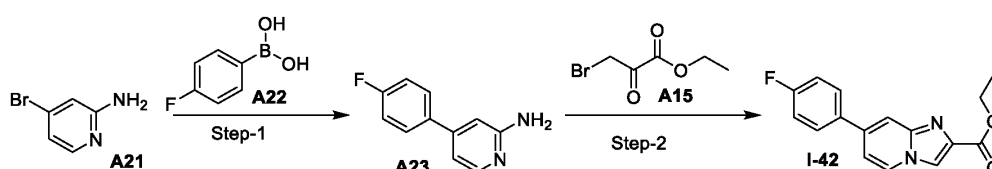
Step 2: Preparation of Ethyl 6-(1-ethyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (I-37)

[000163] To a solution of ethyl 6-(1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (**I-36**, 0.75 g, 2.9 mmol) in DMF (6 mL) at 0°C was added sodium hydride (0.13 g, 3.4 mmol) under inert atmosphere. To the reaction mixture was added ethyl iodide (**A20**, 0.28 mL, 3.5 mmol). The reaction mixture was stirred for 12 h, then quenched with ice and extracted with ethyl acetate/ice water, followed by brine, dried over Na₂SO₄ and concentrated under reduced pressure. The compound was purified using column chromatography using ethyl acetate/hexane to afford **I-37** brown solid product (0.35 g, 95 %). MS (ESI) m/z = 285.3 $[M+H]^+$.

[000164] The following intermediates were synthesized using the protocol exemplified for **I-37**. For intermediates **I-39- I-41** cycloalkyl tosylates were used in place of cycloalkyl bromide.

Intermediate No	Structure	LC/MS_m/z_ [M+H] ⁺
I-38		285.0
I-39		327.1
I-40		313.3
I-41		354.3

Synthesis of ethyl 7-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxylate (I-42)



Step 1: Preparation of 4-(4-fluorophenyl)pyridin-2-amine (A23)

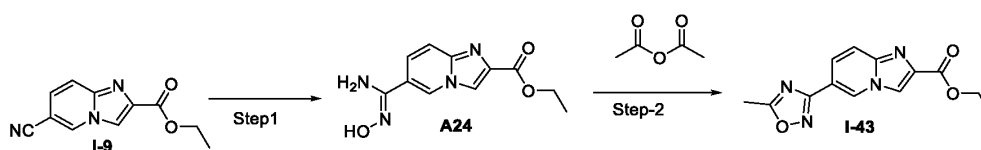
[000165] To a stirred solution of 4-bromopyridin-2-amine (**A21**, 3 g, 17.4 mmol) in 1,2- DME (80 mL) and (4-fluorophenyl)boronic acid (**A22**, 3.0 g, 20.9 mmol) was added Na_2CO_3 (3.7 g, 34.90 mmol) dissolved in H_2O (30 mL). The reaction mixture was purged with N_2 gas for 20 min. To the above reaction mixture was added $\text{Pd}(\text{PPh}_3)_4$ and the resulting solution was further purged with N_2 gas for 10 min then stirred for 1 h at 80-85 °C. The reaction mixture was filtered over celite bed and washed with ethyl acetate/water

mixture. The filtrate was washed with water, brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The compound was purified by column chromatography using 30% ethyl acetate/hexane as the eluent to afford the title product **A23** as a yellow solid (2.5 g, 76 %). MS (ESI) m/z = 189.1 $[\text{M}+\text{H}]^+$.

Step 2: Preparation of Ethyl 7-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxylate (I-42)

[000166] To a stirred solution of 4-(4-fluorophenyl)pyridin-2-amine (**B9**, 2.5 g, 13.2 mmol) in 1,2-DME (30 mL) was added ethyl 3-bromo pyruvate (**A8**, 3.4 mL, 26.5 mmol) and stirred at room temperature for 16 h. A white precipitate was observed and was filtered. The precipitate was washed with diethylether (10 mL x 2). The solid was taken in EtOH and heated for 4 h at 70-75 °C. Reaction mixture was cooled to room temperature and concentrated to remove ethanol. The crude **I-42** was a brown oil and used for the next step without further purification (2.0 g). MS (ESI) m/z = 285.1 $[\text{M}+\text{H}]^+$.

Synthesis of ethyl 6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxylate (I-43)



Step-1: ethyl (Z)-6-(N'-hydroxycarbamimidoyl)imidazo[1,2-a]pyridine-2-carboxylate (A24)

[000167] To a suspension of ethyl 6-cyanoimidazo[1,2-a]pyridine-2-carboxylate (**I9**, 0.3 g, 1.39 mmol) in isopropanol (25 mL) were added triethylamine (1.35 mL, 9.76 mmol) and hydroxylamine hydrochloride (0.579 g, 8.34 mmol). The reaction mixture was stirred at 90 °C for 16 h. The solvent was evaporated and the crude residue was diluted with sodium bicarbonate solution and extracted with ethyl acetate. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to give the title compound **B10** as light yellow solid (0.13 g, 37.5 %). MS (ESI) m/z = 249 $(\text{M}+\text{H})^+$.

Step-2: ethyl 6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxylate (I-43)

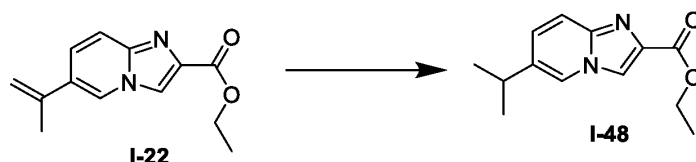
[000168] A suspension of ethyl (Z)-6-(N'-hydroxycarbamimidoyl)imidazo[1,2-a]pyridine-2-carboxylate **B10** (0.1 g, 0.402 mmol) in acetic anhydride (**A16**, 3 mL) was stirred at 100 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give crude residue and purified by column chromatography using 3 %

methanol/dichloromethane mixture as eluent to give the title compound **I-43** as oily mass (0.091 g, 83 %). ^1H NMR (CDCl_3 , 400 MHz, ppm) δ 8.91 (s, 1H), 8.25 (s, 1H), 7.89 (d, J = 9.2 Hz, 1H), 7.78 (d, J = 9.6 Hz, 1H), 4.50-4.45 (q, 2H), 2.68 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H); MS (ESI) m/z = 273.1 ($\text{M}+\text{H}$) $^+$.

[000169] The following intermediates were synthesized using the protocol exemplified for **I-43**.

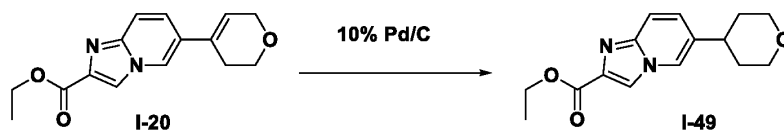
Intermediate No	Structure	LC/MS_ m/z _ [$\text{M}+\text{H}$]
I-44		301.1
I-45		327.9
I-46		301.82
I-47		299.3

Synthesis of ethyl 6-isopropylimidazo[1,2-a]pyridine-2-carboxylate (**I-48**)



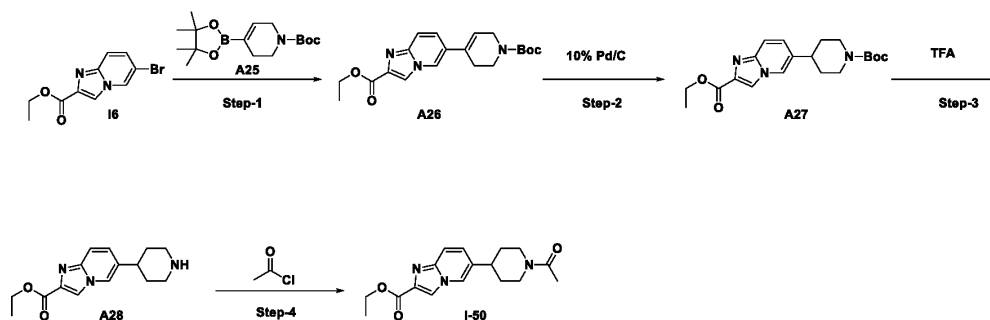
[000170] To a solution of ethyl 6-(prop-1-en-2-yl)imidazo[1,2-a]pyridine-2-carboxylate (**I-22**, 1.0 g, 4.35 mmol), PtO_2 in methanol (30 mL) in an autoclave, The reaction vessel was pressurized with H_2 and then stirred for 16 h at room temperature and filtered over wet celite pad. The filtrate was dried over anhydrous Na_2SO_4 and concentrated to afford **I-48** as a brown gummy liquid (0.065 g, 6.5%). MS (ESI) m/z = 233.1 [$\text{M}+\text{H}$] $^+$.

Ethyl 6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (**I-49**)



[000171] To a stirred solution of ethyl 6-(3,6-dihydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (**I14**, 0.40 g, 1.46 mmol) in methanol (10 mL) was added Pd/C (0.08 g, 0.471 mmol) under N₂ atmosphere and the reaction mixture was stirred under H₂ balloon pressure at room temperature for 4h. After completion of reaction mixture filtered through celite bed and washed with EtOAc. The filtrate was concentrated to dryness. The residue was washed with n-pentane dried to get ethyl 6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxylate **I-49** as a pale yellow solid. Yield: 0.30g (75%) LC-MS (ES) m/z : 274.74 [M+H]⁺.

Ethyl 6-(1-acetlylpiperidin-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (**I-50**)



Step- 1: ethyl 6-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (**A26**)

[000172] To a stirred solution of ethyl 6-bromoimidazo[1,2-a]pyridine-2-carboxylate (**I-6**, 0.50 g, 1.85 mmol) in 1,2-dimethoxyethane (10 mL) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**A25**, 0.86 g, 2.78 mmol) was added Na₂CO₃ (0.59 g, 5.57 mmol) dissolved in H₂O (2 mL). The reaction mixture was purged with N₂ gas for 20 min. To the above reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) with dichloromethane PdCl₂(dppf).DCM (0.15 g, 0.185 mmol), and the resulting solution was further purged with N₂ gas for 10 min then stirred for 16 h at 80°C. The reaction mixture was filtered over celite bed and washed with ethylacetate/water mixture. The filtrate was washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The compound was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford ethyl 6-(1-(tert-butoxycarbonyl)-

1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxylate **A26** as a white solid. Yield: 0.50 g (72%) LC-MS (ES) m/z : 372.06 $[M+H]^+$.

Step- 2: ethyl 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (A27)

[000173] To a stirred solution of ethyl 6-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (**A26**, 0.35 g, 0.942 mmol) in methanol (10 mL) was added Pd/C (0.05 g, 0.471 mmol) under N_2 atmosphere and the reaction mixture was stirred under H_2 balloon pressure at room temperature for 4h. After completion of reaction mixture filtered through celite bed and washed with EtOAc. The filtrate was concentrated to dryness. The residue was washed with n-pentane dried to get ethyl 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)imidazo[1,2-a]pyridine-2-carboxylate **B12** as a pale yellow solid. Yield: 0.27 g (77%) LC-MS (ES) m/z : 374.74 $[M+H]^+$.

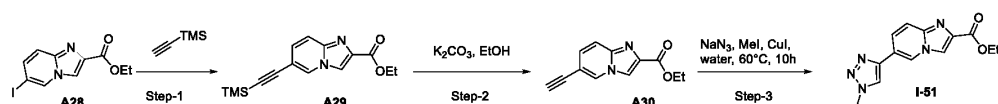
Step- 3: ethyl 6-(piperidin-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (A27)

[000174] To a solution of ethyl 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (**A26**, 0.25 g, 0.669 mmol) in DCM (5 mL) at 0 °C was added TFA (2.5 mL) and the resulting solution was stirred at room temperature for 2 h. After completion of reaction mixture concentrated under reduced pressure and washed with ether and dried to afford compound ethyl 6-(piperidin-4-yl)imidazo[1,2-a]pyridine-2-carboxylate **A27** as a brown solid. Yield: 0.25 g (crude) LC-MS (ES) m/z : 274.03 $[M+H]^+$.

Step- 4: ethyl 6-(1-acetylpiperidin-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (I-50)

[000175] To a solution of ethyl 6-(piperidin-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (**A27**, 0.250 g, 0.914 mmol) in DCM (10 mL) at 0 °C was added TEA (0.31 mL, 2.28 mmol) and acetyl chloride (0.10 mL, 1.37 mmol) was added and the resulting solution was stirred at room temperature for 4 h. After completion of reaction diluted with DCM and washed with water the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford ethyl 6-(1-acetylpiperidin-4-yl)imidazo[1,2-a]pyridine-2-carboxylate **I-50** as a brown solid. Yield: 0.21 g (98%) LC-MS (ES) m/z : 316.12 $[M+H]^+$.

Ethyl 6-(1-methyl-1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (I-51)



Step- 1: ethyl 6-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyridine-2-carboxylate (A29)

[000176] To a stirred solution of ethyl 6-iodoimidazo[1,2-a]pyridine-2-carboxylate (A28, 3.0 g, 9.49 mmol) in 1,4-dioxane (60 mL) was added ethynyltrimethylsilane (2.02 ml, 14.23 mmol), triethylamine (6.31 mL, 47.45 mmol), followed by CuI (9.03 g, 64.74 mmol) and PdCl₂(PPh₃)₂ (0.66 g, 0.949 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion of reaction, the mixture was filtered through celite bed and washed with EtOAc. The filtrate was diluted with water, organic layer separated, dried over sodium sulphate and concentrated under reduced pressure. The obtained crude was purified by column chromatography using 30% ethyl acetate in hexane as eluent to afford ethyl 6-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyridine-2-carboxylate A29 the desired product as yellow solid (2.2 g, 81%) .LC-MS m/z : 286.99 [M+H]⁺.

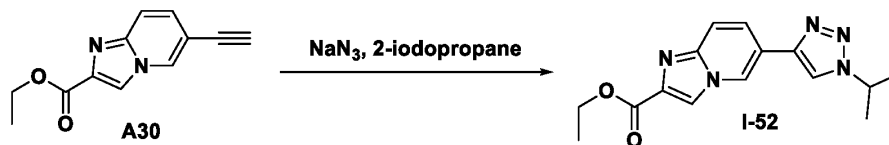
Step- 2: ethyl 6-ethynylimidazo[1,2-a]pyridine-2-carboxylate (A30)

[000177] To a stirred solution of ethyl 6-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyridine-2-carboxylate (A29, 2.20 g, 7.68 mmol) in THF (20 mL) was added tetra butyl ammonium fluoride (4.44 mL, 15.36 mmol) and the reaction mixture was stirred at room temperature for 2h. After completion of reaction mixture quenched with water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated under reduced pressure. The obtained crude was purified by column chromatography using 40% ethyl acetate in hexane as eluent to get compound ethyl 6-ethynylimidazo[1,2-a]pyridine-2-carboxylate A30 as a brown solid. Yield: 1.2 g (83%) LC-MS (ES) m/z : 214.99 [M+H]⁺.

Step- 3: ethyl 6-(1-methyl-1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (I-51)

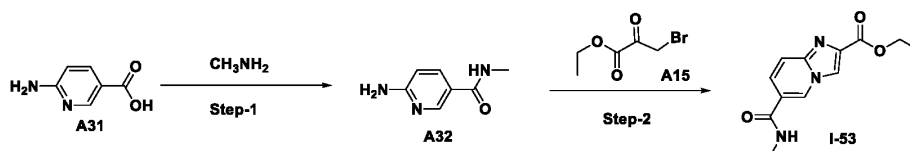
[000178] To a solution of 6-ethynylimidazo[1,2-a]pyridine-2-carboxylate (A30, 1 g, 4.66 mmol) in EtOH:H₂O(1:1) (15 mL) was added NaN₃ (0.36, 5.60 mmol), CuI (0.08, 0.466 mmol) and Iodomethane (0.46 mL, 4.67 mmol). The resulting solution was stirred in microwave for 1 h. After completion of reaction diluted with DCM and washed with water. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The obtained crude was purified by column chromatography 5.0% MeOH in DCM as eluent to afford ethyl 6-(1-methyl-1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-2-carboxylate I-51 as a white solid. Yield: 0.30 g (18%) LC-MS (ES) m/z : 271.22 [M+H]⁺.

Synthesis of ethyl 6-(1-isopropyl-1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (I-52)



[000179] To a solution of ethyl 6-ethynylimidazo[1,2-a]pyridine-2-carboxylate (A30, 1.0 g, 4.66 mmol) in EtOH:H₂O (1:1) (15 mL) was added NaN₃ (0.36 g, 5.60 mmol), CuI (0.08 g, 0.466 mmol) and 2-iodopropane (0.46 mL, 4.67 mmol) and the resulting solution was stirred in microwave for 1 h. After completion of reaction diluted with DCM and washed with water the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The obtained crude was purified by column chromatography using 0-60% ethyl acetate in hexanes to afford compound ethyl 6-(1-isopropyl-1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-2-carboxylate I-52 as a white solid. Yield: 0.30 g (18%) LC-MS (ES) m/z : 271.22 [M+H]⁺.

Synthesis of ethyl 6-(methylcarbamoyl)imidazo[1,2-a]pyridine-2-carboxylate (I-53)



Step- 1; 6-amino-N-methylnicotinamide (A32)

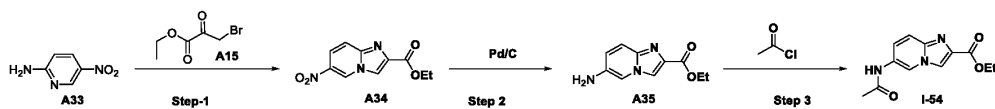
[000180] To a solution of 6-aminonicotinic acid (A31, 1.0 g, 7.24 mmol) in DMF (10 mL) was added DIPEA (3.89 mL, 21.73 mmol) followed by HATU (4.1 g, 10.86 mmol). The reaction mixture was stirred for 10 min followed by addition methyl amine (2.0 M in THF) (5.43 mL, 10.86 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was monitored till the completion of starting materials (LC/MS) and then concentrated under reduced pressure. The obtained crude was purified by column chromatography using 10% methanol in dichloromethane as eluent to afford 6-amino-N-methylnicotinamide **B18** as white solid, Yield: 0.12 g (13%) LC-MS (ES) m/z : 150.12 [M+H]⁺.

Step- 2: ethyl 6-(methylcarbamoyl)imidazo[1,2-a]pyridine-2-carboxylate (I-53)

[000181] To a stirred solution of 6-amino-N-methylnicotinamide (A31, 0.9 g, 5.96 mmol) in 1,4-dioxane (10 mL) was added Ethyl 3-bromo pyruvate (A15, 1.12 mL, 8.94 mmol), followed by NaHCO₃ (1.0 g, 11.92 mmol). The reaction mixture was heated for 12 h at 100 °C and then concentrated under reduced pressure. The crude product was triturated with water and washed with n-pentane and dried to afford ethyl 6-

(methylcarbamoyl)imidazo[1,2-a]pyridine-2-carboxylate I-53 as white solid Yield: 0.7 g, (50%). LC-MS m/z : 246.12 $[M-H]^-$.

Synthesis of ethyl 6-acetamidoimidazo[1,2-a]pyridine-2-carboxylate (I-54)



Step- 1: ethyl 6-nitroimidazo[1,2-a]pyridine-2-carboxylate (A34)

[000182] To a stirred solution of 5-nitropyridin-2-amine (A33, 4.50 g, 32.37 mmol) in 1,4-dioxane (100 mL) was added ethyl 3-bromo pyruvate (A15, 6.31 mL, 48.56 mmol), followed by NaHCO_3 (5.43 g, 64.74 mmol). The reaction mixture was heated for 12 h at 100 °C and then concentrated under reduced pressure. The crude product was triturated with water and washed with n-pentane and dried to afford ethyl 6-nitroimidazo[1,2-a]pyridine-2-carboxylate A34 as off white solid. Yield: 7.30 g, (96%). LC-MS m/z : 236.23 $[M+H]^+$.

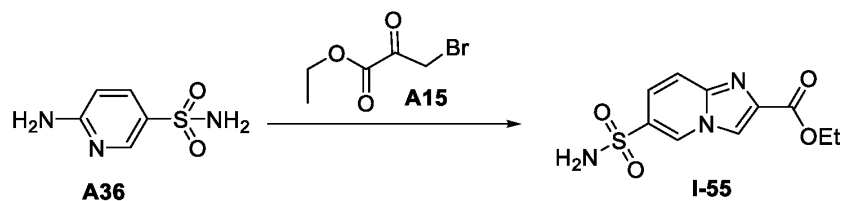
Step- 2: ethyl 6-aminoimidazo[1,2-a]pyridine-2-carboxylate (A35)

[000183] To a stirred solution of ethyl 6-nitroimidazo[1,2-a]pyridine-2-carboxylate (A34, 7.30 g, 31.73 mmol) in methanol (100mL) was added Pd/C (1.6 g, 15.86 mmol) under N_2 atmosphere and the reaction mixture was stirred under H_2 balloon pressure at room temperature for 4h. after completion of reaction mixture filtered through celite bed and washed with EtOAc. The filtrate was concentrated to dryness. The residue was washed with n-pentane dried to get compound ethyl 6-aminoimidazo[1,2-a]pyridine-2-carboxylate A35 as a green solid. Yield: 4.50 g (70%) LC-MS (ES) m/z : 205.99 $[M+H]^+$.

Step- 3: ethyl 6-acetamidoimidazo[1,2-a]pyridine-2-carboxylate (I-54)

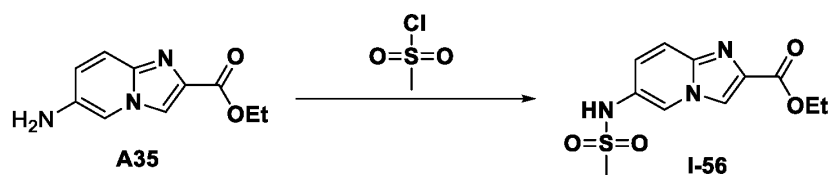
[000184] To a solution of ethyl 6-aminoimidazo[1,2-a]pyridine-2-carboxylate (A35, 0.50 g, 2.43 mmol) in DCM (10 mL) at 0 °C was added TEA (1.01 mL, 7.31 mmol) and acetyl chloride (0.26 mL, 3.65 mmol) was added and the resulting solution was stirred at room temperature for 4 h. after completion of reaction diluted with DCM and washed with water the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford compound ethyl 6-acetamidoimidazo[1,2-a]pyridine-2-carboxylate I-55 as a brown solid. Yield: 0.40 g (66%) LC-MS (ES) m/z : 248.11 $[M+H]^+$.

Synthesis of ethyl 6-sulfamoylimidazo[1,2-a]pyridine-2-carboxylate (I-55)



[000185] To a stirred solution of 6-aminopyridine-3-sulfonamide (**A36**, 0.80 g, 4.62 mmol) and NaHCO_3 (0.776 g, 9.24 mmol) in 1,4-dioxane, ethyl 3-bromo-2-oxopropanoate (2, 0.87 mL, 6.93 mmol) was added and reaction mixture heated to 100°C for 16 h. After completion, reaction mixture quenched with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to offered ethyl 6-sulfamoylimidazo[1,2-a]pyridine-2-carboxylate (**I-55**) as brown solid. Yield: 0.61 g (49%) LC-MS (ES) $m/z = 270.08$ $[\text{M}+\text{H}]^+$.

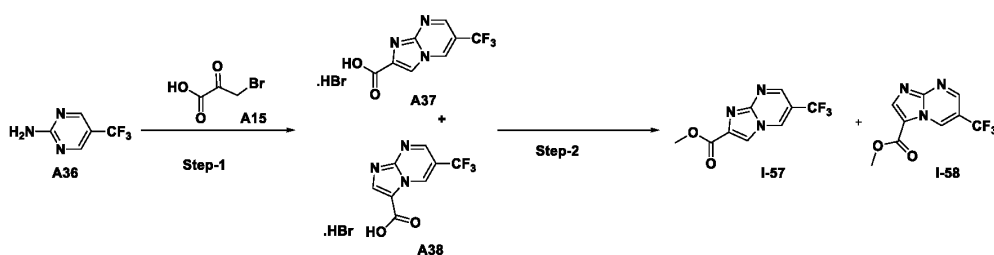
Synthesis of ethyl 6-(methylsulfonamido)imidazo[1,2-a]pyridine-2-carboxylate (**I-56**)



Synthesis of ethyl 6-(methylsulfonamido)imidazo[1,2-a]pyridine-2-carboxylate (**I-56**)

[000186] To a solution of ethyl 6-aminoimidazo[1,2-a]pyridine-2-carboxylate (**A35**, 1.0 g, 4.87 mmol) in pyridine (10 mL) methanesulfonyl chloride (0.37 mL, 4.87 mmol) was added and the resulting solution was stirred at room temperature for 2 h. After completion of reaction concentrated under reduced pressure to get crude. The crude was dissolved in DCM and washed with water and dried with anhydrous Na_2SO_4 , filtered and concentrated to afford ethyl 6-(methylsulfonamido)imidazo[1,2-a]pyridine-2-carboxylate **I-56** as a Light green solid. Yield: 0.70 g (crude) LC-MS (ES) $m/z : 284.08$ $[\text{M}+\text{H}]^+$.

Synthesis of methyl 6-(trifluoromethyl)imidazo[1,2-a]pyrimidine-2-carboxylate (**I-57** & **I-58**)



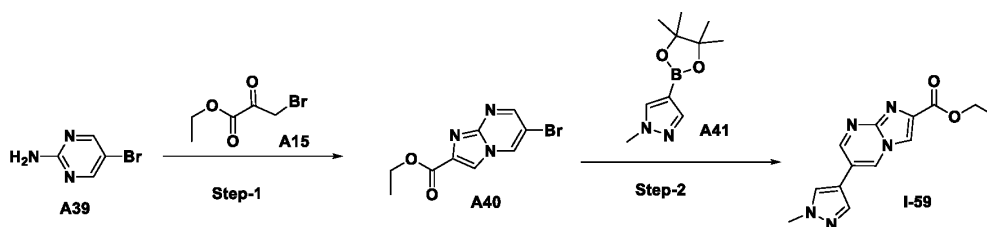
Step- 1: 6-(trifluoromethyl)imidazo[1,2-a]pyrimidine-2-carboxylic acid (A37 and A38)

[000187] To a stirred solution of 5-(trifluoromethyl)pyrimidin-2-amine (A36, 4.5 g, 27.60 mmol) in 1,4-dioxane (80 mL) was added 3-bromo-2-oxopropanoic acid (A15, 6.87 g, 41.4 mmol). The reaction mixture was heated at 100 °C for 16 h. After completion of reaction mixture was concentrated under reduced pressure. The crude product was triturated with ethyl acetate and dried to afford 6-(trifluoromethyl)imidazo[1,2-a]pyrimidine-2-carboxylic acid A37 and A38 as dark brown mixture. Yield: 7.0 g, (crude). LC-MS m/z : 229.96 $[M-H]^-$.

Step- 2: methyl 6-(trifluoromethyl)imidazo[1,2-a]pyrimidine-2-carboxylate (I-57 and I-58)

[000188] To a stirred solution of the mixture A37 and A38 (3, 4.5 g, 19.4 mmol) in methanol (100 mL) was added drop wise H_2SO_4 (10 mL) and the reaction mixture was stirred at 80 °C temperature for 16 h. After completion of reaction organic solvent was evaporated and the aqueous layer was basified with Sat. $NaHCO_3$ up to pH 8 to 9 and aqueous layer was extracted with 10% MeOH in DCM and then concentrated under reduced pressure. The obtained crude was purified by column chromatography using 10% methanol in dichloromethane as eluent to afford methyl 6-(trifluoromethyl)imidazo[1,2-a]pyrimidine-2-carboxylate I-57 and I-58 as pink solid. Yield: 0.5 g, (10%). LC-MS m/z : 245.97 $[M+H]^+$.

Synthesis of ethyl 6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrimidine-2-carboxylate (I-59)



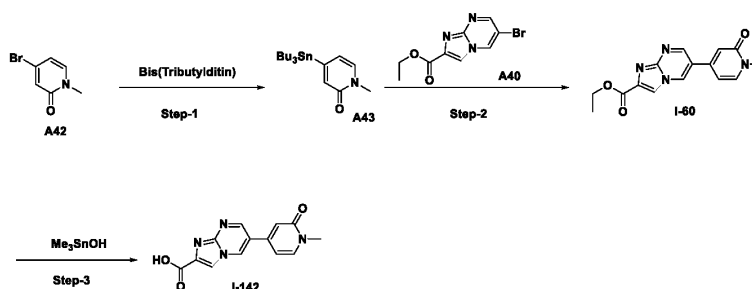
Step- 1: ethyl 6-bromoimidazo[1,2-a]pyrimidine-2-carboxylate (A40)

[000189] To a stirred solution of 5-bromopyrimidin-2-amine (A39, 1.0 g, 5.74 mmol) in DMF (20 mL) was added ethyl 3-bromo pyruvate (A15, 0.86 mL, 6.89 mmol). The reaction mixture was Stirred for 16 h at Room temp. and then concentrated under reduced pressure. The crude product was triturated with water and washed with n-pentane and dried to afford ethyl 6-bromoimidazo[1,2-a]pyrimidine-2-carboxylate A40 as light brown solid Yield: 1.50 g, (87%). LC-MS m/z : 268.20 [M-H]⁻.

Step- 2: ethyl 6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrimidine-2-carboxylate (I-59)

[000190] To a stirred solution of ethyl 6-bromoimidazo[1,2-a]pyrimidine-2-carboxylate (A40, 0.5 g, 1.85 mmol) in 1,4-dioxane (300 mL) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (A41, 0.57 g, 2.78 mmol) was added Na₂CO₃ (0.58 g, 5.57 mmol) dissolved in H₂O (2 mL). The reaction mixture was purged with N₂ gas for 20 min. To the above reaction mixture was added Pd(PPh₃)₄ (0.21 g, 0.185 mmol), and the resulting solution was further purged with N₂ gas for 10 min then stirred for 16 h at 80°C. The reaction mixture was filtered over celite bed and washed with ethylacetate/water mixture. The filtrate was washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The compound was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford ethyl 6-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrimidine-2-carboxylate I-59 as a brown solid. Yield: 0.4 g (86%) LC-MS (ES) m/z : 272.31 [M+H]⁺.

Synthesis of (6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a] pyrimidine-2-carboxylic acid (I61)



Step- 1: 1-methyl-4-(tributylstannyl)pyridin-2(1H)-one (A43)

[000191] To a stirred solution of 4-bromo-1-methylpyridin-2(1H)-one (A-42, 7.0 g, 37.23 mmol) in 1,4-dioxane (140 mL) and Bis(Tributyl)stannane (28.72 mL, 55.85 mmol).

The reaction mixture was purged with N₂ gas for 20 min. To the above reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) PdCl₂(dppf) (2.71 g, 3.72 mmol), and the resulting solution was further purged with N₂ gas for 10 min then stirred for 16 h at 80°C. The reaction mixture was filtered over celite bed and washed with ethylacetate. The filtrate was washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The compound was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford 1-methyl-4-(tributylstannyl)pyridin-2(1H)-one **A43** as a black liquid. Yield: 8.0 g (53%) LC-MS (ES) m/z : 400.17 [M+H]⁺.

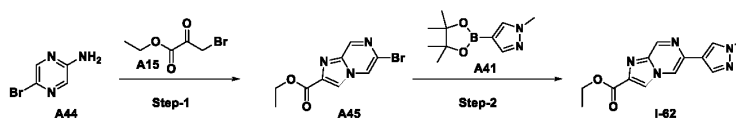
Step- 2: ethyl 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrimidine-2-carboxylate (I-60)

[000192] To a stirred solution of ethyl 6-bromoimidazo[1,2-a]pyrimidine-2-carboxylate (**A40**, 1.0 g, 3.70 mmol) in 1,4-dioxane (20 mL) and 1-methyl-4-(tributylstannyl)pyridin-2(1H)-one (**A43**, 2.20 g, 5.55 mmol). The reaction mixture was purged with N₂ gas for 20 min. To the above reaction mixture was added Bis(triphenylphosphine)palladium (II) dichloride PdCl₂(PPh₃)₂ (0.25 g, 0.372 mmol), and the resulting solution was further purged with N₂ gas for 10 min then stirred for 16 h at 80°C. The reaction mixture was filtered over celite bed and washed with ethylacetate. The filtrate was washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The compound was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford ethyl 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrimidine-2-carboxylate **I-141** as a brown solid. Yield: 0.45 g (63%) LC-MS (ES) m/z : 299.20 [M+H]⁺.

Step- 3: (6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrimidine-2-carboxylic acid (I61)

[000193] To a stirred solution of ethyl 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrimidine-2-carboxylate (**I-60**, 0.45 g, 1.51 mmol) in 1,2 dichloroethane (10 mL) was added trimethyl tin hydroxide Me₃SnOH (0.81 g, 4.53 mmol). The reaction mixture was stirred at 100 °C for 16h. After completion of reaction washed with saturated KF solution and the organic solvent was dried with Na₂SO₄, filtered and evaporated and the crude was acidified with 1N HCl up to pH 3 to 4 and concentrated to get desired product as a 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrimidine-2-carboxylic acid **I-61** as a white solid. Yield: 0.45 g (crude) LC-MS (ES) m/z : 271.09 [M+H]⁺.

Synthesis of ethyl 6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (I-62)



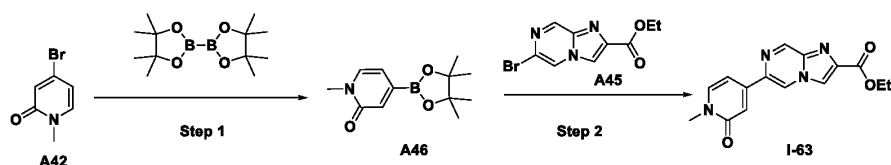
Step- 1: ethyl 6-bromoimidazo[1,2-a]pyrazine-2-carboxylate (A45)

[000194] To a stirred solution of 5-bromopyrazin-2-amine (A44, 2.0 g, 11.49 mmol) in 1,4-dioxane (40 mL) was added ethyl 3-bromo pyruvate (A15, 2.16 mL, 17.24 mmol), followed by NaHCO_3 (1.93 g, 22.98 mmol). The reaction mixture was heated for 12 h at 100 °C. After completion of reaction mixture concentrated under reduced pressure. The crude product was triturated with water and washed with n-pentane and dried to afford ethyl 6-bromoimidazo[1,2-a]pyrazine-2-carboxylate A45 as Off white solid Yield: 2.20 g, (71%). LC-MS m/z : 270.05 $[\text{M}+\text{H}]^+$.

Step- 2: ethyl 6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (I-62)

[000195] To a stirred solution of ethyl 6-bromoimidazo[1,2-a]pyrazine-2-carboxylate (A45, 1 g, 3.70 mmol) in 1,4-dioxane (20 mL) and DMF (1 mL) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (, 1.15 g, 5.55 mmol) was added Na_2CO_3 (1.17 g, 11.10 mmol) dissolved in H_2O (2 mL). The reaction mixture was purged with N_2 gas for 20 min. To the above reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) $\text{PdCl}_2(\text{dppf})$ (0.27 g, 0.37 mmol), and the resulting solution was further purged with N_2 gas for 10 min then stirred for 16 h at 80°C. The reaction mixture was filtered over celite bed and washed with ethylacetate/water mixture. The filtrate was washed with water, brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The compound was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford ethyl 6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate **I-62** as a brown solid. Yield: 0.70 g (70%) LC-MS (ES) m/z : 272.26 $[\text{M}+\text{H}]^+$.

Synthesis of ethyl 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (I-63)



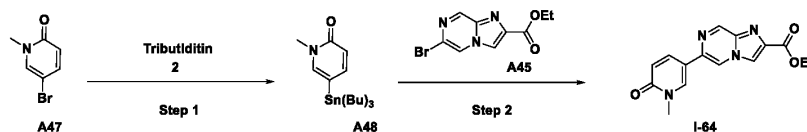
Step- 1: 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one (B27)

[000196] To a stirred solution of 4-boraneyl-1-methylpyridin-2(1H)-one (**A42**, 5.0 g, 41.33 mmol) in 1,4-dioxane (100 mL) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (15.74 g, 62.00 mmol) was added KOAc (8.10 g, 82.66 mmol). The reaction mixture was purged with N₂ gas for 20 min. To the above reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) PdCl₂(dppf) (3.02 g, 4.13 mmol), and the resulting solution was further purged with N₂ gas for 10 min then stirred for 16 h at 80°C. The reaction mixture was filtered over celite bed and washed with ethylacetate. The filtrate was washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. to afford 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one **A46** as a brown solid. Yield: 8.0 g (crude) LC-MS (ES) m/z : 154.18 [M+H]⁺ (corresponding boronic acid).

Step- 2: ethyl 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (I-63)

[000197] To a stirred solution of ethyl 6-bromoimidazo[1,2-a]pyrazine-2-carboxylate (**A45**, 0.60 g, 2.22 mmol) in 1,4-dioxane (12 mL) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one (**A46**, 1.04 g, 4.44 mmol) was added Na₂CO₃ (0.705 g, 6.66 mmol) dissolved in H₂O (2 mL). The reaction mixture was purged with N₂ gas for 20 min. To the above reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) PdCl₂(dppf) (0.16 g, 0.22 mmol), and the resulting solution was further purged with N₂ gas for 10 min then stirred for 16 h at 80°C. The reaction mixture was filtered over celite bed and washed with ethylacetate. The filtrate was washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The compound was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford ethyl 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate **I-63** as a off white solid. Yield: 0.50 g (45%) LC-MS (ES) m/z : 299.16 [M+H]⁺.

Synthesis of ethyl 6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxylate (I-64)



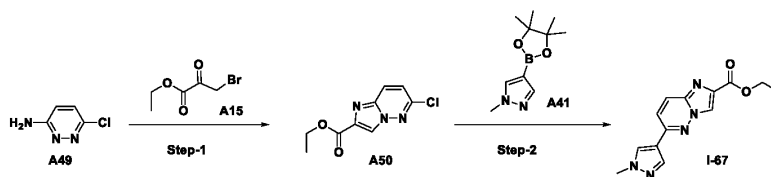
Step- 1: 1-methyl-5-(tributylstannyl)pyridin-2(1H)-one (A48)

[000198] To a stirred solution of 5-bromo-1-methylpyridin-2(1H)-one (**A47**, 1.0 g, 5.37 mmol) in 1,4-dioxane (10 mL) and tributyltin hydride (**2**, 4.0 mL, 8.06 mmol). The reaction mixture was purged with N₂ gas for 20 min. to the above reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) PdCl₂(dppf) (0.39 g, 0.537 mmol), and the resulting solution was further purged with N₂ gas for 10 min then stirred for 16 h at 100°C. The reaction mixture was filtered over celite bed and washed with ethylacetate. The filtrate was washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The compound was purified by column chromatography using 0-5% methanol/dichloromethane as the eluent to afford 1-methyl-5-(tributylstannyl)pyridin-2(1H)-one **A48** as colorless liquid. Yield: 0.90 g (42%) LC-MS (ES) m/z : 400.16 [M+H]⁺.

Step-2: ethyl 6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxylate (I64)

[000199] To a stirred solution of ethyl 6-bromoimidazo[1,2-a]pyrazine-2-carboxylate (**A45**, 1.0 g, 3.70 mmol) in N,N-dimethylformamide (10 mL) and 1-methyl-5-(tributylstannyl)pyridin-2(1H)-one (**A48**, 2.21 g, 5.55 mmol). The reaction mixture was purged with N₂ gas for 20 min. to the above reaction mixture was added Bis(triphenylphosphine)dichloropalladium(II) PdCl₂(PPh₃)₂ (0.23 g, 0.37 mmol), and the resulting solution was further purged with N₂ gas for 10 min then stirred for 6 h at 100°C. The reaction mixture was filtered over celite bed and washed with ethylacetate. The filtrate was washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The compound was purified by column chromatography using 0-5% methanol/dichloromethane as the eluent to afford ethyl 6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxylate **I-64** as brown solid, Yield: 0.19 g (18%) LC-MS (ES) m/z : 299.16 [M+H]⁺.

Synthesis of ethyl 6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate (I-67)



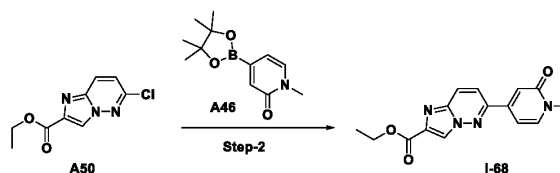
Step- 1: ethyl 6-chloroimidazo[1,2-b]pyridazine-2-carboxylate (A50)

[000200] To a stirred solution of 6-chloropyridazin-3-amine (A49, 2.0 g, 15.43 mmol) in 1,4-dioxane (40 mL) was added ethyl 3-bromo pyruvate (A15, 2.32 mL, 18.51 mmol), followed by NaHCO_3 (1.94 g, 23.14 mmol). The reaction mixture was heated for 12 h at 100 °C. After completion of reaction mixture concentrated under reduced pressure. The crude product was triturated with water and washed with n-pentane and dried to afford ethyl 6-chloroimidazo[1,2-b]pyridazine-2-carboxylate 3 as Off white solid Yield: 2.20 g, (64%). LC-MS m/z : 226.05 $[\text{M}+\text{H}]^+$.

Step- 2: ethyl 6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate (I-67)

[000201] To a stirred solution of ethyl 6-chloroimidazo[1,2-b]pyridazine-2-carboxylate (A50, 1 g, 4.43 mmol) in 1,4-dioxane (20 mL) and DMF (1 mL) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (A41, 1.38 g, 6.64 mmol) was added Na_2CO_3 (1.40 g, 13.29 mmol) dissolved in H_2O (2 mL). The reaction mixture was purged with N_2 gas for 20 min. To the above reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) $\text{PdCl}_2(\text{dppf})$ (0.32 g, 0.44 mmol), and the resulting solution was further purged with N_2 gas for 10 min then stirred for 16 h at 80°C. The reaction mixture was filtered over celite bed and washed with ethylacetate/water mixture. The filtrate was washed with water, brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The compound was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford ethyl 6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate I-67 as a brown solid. Yield: 0.70 g (59%) LC-MS (ES) m/z : 272.26 $[\text{M}+\text{H}]^+$.

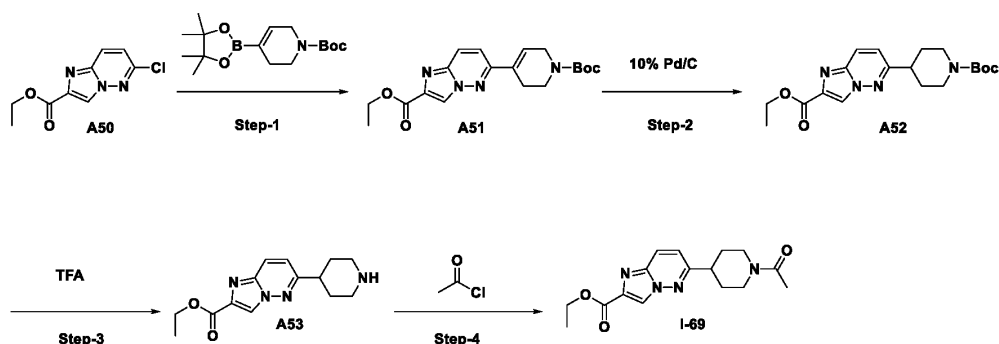
Synthesis of ethyl 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate (I-68)



Step-2: ethyl 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate (I-68)

[000202] To a solution of ethyl 6-chloroimidazo[1,2-b]pyridazine-2-carboxylate (A50, 1 g, 4.43 mmol) in 1,4 -Dioxane(8 mL) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one (A48, 2.08 g, 8.86 mmol), Na_2CO_3 (1.16 g, 13.29 mmol) dissolved in H_2O (2 mL). The reaction mixture was purged with N_2 gas for 20 min. To the above reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) with dichloromethane $\text{PdCl}_2(\text{dppf})\cdot\text{DCM}$ (0.15 g, 0.185 mmol), and the resulting solution was further purged with N_2 gas for 10 min then stirred for 16 h at 80°C . The reaction mixture was filtered over celite bed and washed with ethylacetate/water mixture. The filtrate was washed with water, brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude was purified by column chromatography using 0-10% MeOH-DCM as eluent to afford ethyl 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate 5 as white solid Yield: 0.32 g, (18%). LC-MS (ES) m/z : 299.16 $[\text{M}+\text{H}]^+$.

Synthesiis of ethyl 6-(1-acetylpiperidin-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate (I-69)



Step- 1: ethyl 6-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate (A51)

[000203] To a stirred solution of ethyl 6-chloroimidazo[1,2-b]pyridazine-2-carboxylate (A50, 1.5 g, 6.64 mmol) in 1,2-dimethoxy ethane (30 mL) and H₂O (6 mL) was added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1, 3.08 g, 9.97 mmol) and Na₂CO₃ (2.11 g, 19.94 mmol). The reaction mixture was purged with N₂ gas for 20 min. To the above reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) with dichloromethane PdCl₂(dppf).DCM (0.54 g, 0.664 mmol), and the resulting solution was further purged with N₂ gas for 10 min then stirred for 16 h at 80°C. The reaction mixture was filtered over celite bed and washed with ethylacetate/water mixture. The filtrate was washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained crude was purified by column chromatography using 0-10% MeOH in DCM as eluent to afford ethyl 6-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate A51 as a brown solid. Yield: 2.0 g (81%).LC-MS m/z: 370.98 [M-H]⁻.

Step-2: ethyl 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate (A52)

[000204] To a stirred solution of ethyl 6-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate (**A51**, 1.0 g, 2.68 mmol) in MeOH was added 10% Pd/C (0.20 g) and the resulting solution was stirred under H₂ gas atmosphere for 16 h at room temperature. The reaction mixture was filtered over celite bed and washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The crude was triturated with diethyl ether, decant and dried to afford ethyl 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate **A52** as a yellow liquid. Yield: 1.0 g (95%) LC-MS (ES) m/z: 375.27 [M+H]⁺.

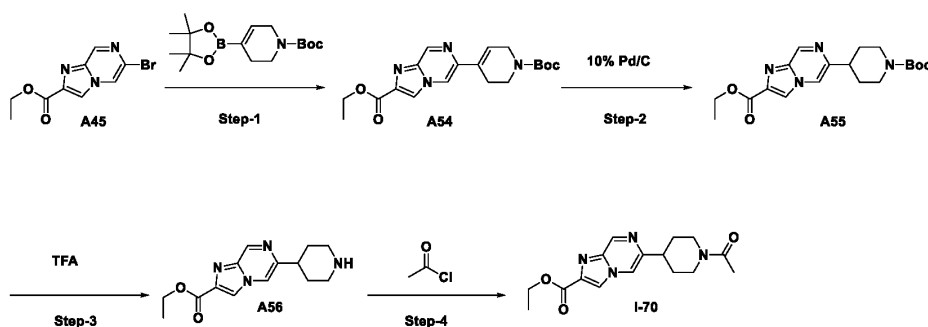
Step-3: ethyl 6-(piperidin-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate (A53)

[000205] To a solution of ethyl 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate (A52, 1.0 g, 2.67 mmol) in DCM:TFA (1:1 10mL) the resulting solution was stirred for 2 h at room temperature. The reaction mixture was basified with aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with water, brine solution, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The obtained crude washed with diethyl ether and dried to afford ethyl 6-(piperidin-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate A53 as white solid Yield: 0.8 g, (crude).LC-MS (ES) m/z :275.22 [M+H]⁺.

Step-4 ethyl 6-(1-acetylpiperidin-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate (I-69)

[000206] To a stirred solution of ethyl 6-(piperidin-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate (A53, 0.8 g, 2.91 mmol) in (10 mL) was added TEA (2.03 mL, 14.58 mmol) and acetyl chloride (0.312 mL, 4.37 mmol) at 0 °C. The reaction mixture was stirred for 1h at room temp. After completion of reaction diluted with H₂O and extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to get crude. Which was triturate with n-pentane and dried to afford ethyl 6-(1-acetylpiperidin-4-yl)imidazo[1,2-b]pyridazine-2-carboxylate I-69 as off white solid. Yield: 0.65 g (crude) LC-MS (ES) m/z: 317.23 [M+H]⁺.

Synthesis of ethyl 6-(1-acetylpiperidin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (I-70)



Step-1: ethyl 6-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (A54)

[000207] To a stirred solution of ethyl 6-bromoimidazo[1,2-a]pyrazine-2-carboxylate (A45, 0.50 g, 1.85 mmol) in 1,2-dimethoxyethane (10 mL) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.86 g, 2.78 mmol) was added Na₂CO₃ (0.59 g, 5.57 mmol) dissolved in H₂O (2 mL). The reaction mixture was purged with N₂ gas for 20 min. To the above reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) with dichloromethane PdCl₂(dppf).DCM (0.15 g, 0.185 mmol), and the resulting solution was further purged with N₂ gas for 10 min then stirred for 16 h at 80°C. The reaction mixture was filtered over celite bed and washed with ethylacetate/water mixture. The filtrate was washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The compound was purified by column chromatography using 0-10%

methanol/dichloromethane as the eluent to afford ethyl 6-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate **A54** as a white solid. Yield: 0.50 g (72%) LC-MS (ES) m/z : 373.06 $[M+H]^+$.

Step- 2: ethyl 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (A55)

[000208] To a stirred solution of ethyl 6-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (**A54**, 0.35 g, 0.942 mmol) in methanol (10 mL) was added Pd/C (0.05 g, 0.471 mmol) under N_2 atmosphere and the reaction mixture was stirred under H_2 balloon pressure at room temperature for 4h. After completion of reaction mixture filtered through celite bed and washed with EtOAc. The filtrate was concentrated to dryness. The residue was washed with n-pentane dried to get ethyl 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate **A55** as a pale yellow solid. Yield: 0.27 g (77%) LC-MS (ES) m/z : 375.74 $[M+H]^+$.

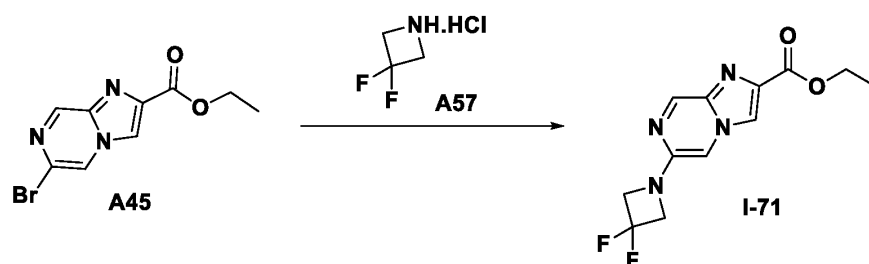
Step- 3: ethyl 6-(piperidin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (A56)

[000209] To a solution of ethyl 6-(1-(tert-butoxycarbonyl)piperidin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (**A55**, 0.25 g, 0.669 mmol) in DCM (5 mL) at 0 °C was added TFA (2.5 mL) and the resulting solution was stirred at room temperature for 2 h. After completion of reaction mixture concentrated under reduced pressure and washed with ether and dried to afford compound ethyl 6-(piperidin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate **B36** as a brown solid. Yield: 0.25 g (crude) LC-MS (ES) m/z : 275.03 $[M+H]^+$.

Step- 4: ethyl 6-(1-acetylpiperidin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (I-70)

[000210] To a solution of ethyl 6-(piperidin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (**A56**, 0.250 g, 0.914 mmol) in DCM (10 mL) at 0 °C was added TEA (0.31 mL, 2.28 mmol) and acetyl chloride (0.10 mL, 1.37 mmol) was added and the resulting solution was stirred at room temperature for 4 h. After completion of reaction diluted with DCM and washed with water the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford ethyl 6-(1-acetylpiperidin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate **I-70** as a brown solid. Yield: 0.21 g (98%) LC-MS (ES) m/z : 317.12 $[M+H]^+$.

Synthesis of ethyl 6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (I-71)



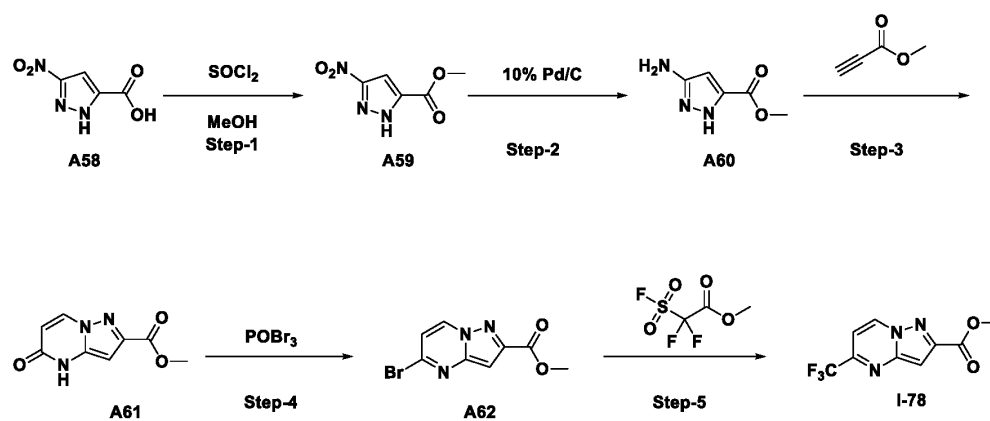
[000211] To a stirred solution of ethyl 6-bromoimidazo[1,2-a]pyrazine-2-carboxylate (**A45**, 1 g, 3.70 mmol) in 1,4-dioxane (20 mL) and 3,3-difluoroazetidine hydrochloride (**A56**, 0.95 g, 7.40 mmol) was added Cs_2CO_3 (3.60 g, 11.10 mmol). The reaction mixture was purged with N_2 gas for 20 min. To the above reaction mixture was added Tris(dibenzylideneacetone)dipalladium(0) $\text{Pd}_2(\text{dba})_3$ (0.16 g, 0.18 mmol), and 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos) (0.10 g, 0.018 mmol) and the resulting solution was further purged with N_2 gas for 10 min then stirred for 16 h at 80°C . The reaction mixture was filtered over celite bed and washed with ethylacetate/water mixture. The filtrate was washed with water, brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The compound was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford ethyl 6-(3,3-difluoroazetidin-1-yl)imidazo[1,2-a]pyrazine-2-carboxylate **I-71** as a brown solid. Yield: 0.60 g (59%) LC-MS (ES) m/z : 283.26 $[\text{M}+\text{H}]^+$

[000212] The following intermediates were synthesized using the protocol exemplified for **I-71**.

Intermediate	Structure	Mass
I-72		282.3
I-73		246.3

I-74		278.3
I-75		289.3
I-76		276.3
I-77		279.3

Synthesis of methyl 5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-2-carboxylate (I-78)



Step- 1: methyl 3-nitro-1H-pyrazole-5-carboxylate (BA59)

[000213] To a stirred solution of 3-nitro-1H-pyrazole-5-carboxylic acid (**A58**, 25.0 g, 159.14 mmol) in Methanol (250 mL) was added dropwise SOCl₂ (23.09 mL, 318.28 mmol) mL). The reaction mixture was stirred for 16 h at 80°C. After completion, addition of n-hexane (500 mL) solid precipitated, filtered and dried under reduced pressure to afford methyl 3-nitro-1H-pyrazole-5-carboxylate **A59** as a white solid. Yield: 26.0 g (95%) LC-MS (ES) m/z : 170.14 [M+H]⁺.

Step- 2: methyl 3-amino-1H-pyrazole-5-carboxylate (A60)

[000214] To a stirred solution of methyl 3-nitro-1H-pyrazole-5-carboxylate (**A59**, 25.0 g, 146.19 mmol) in methanol (500 mL) was added Pd/C (3.80 g, 36.54 mmol) under N₂ atmosphere and the reaction mixture was stirred under H₂ balloon pressure at room temperature for 4 h. After completion of reaction mixture filtered through celite bed and washed with EtOAc. The filtrate was concentrated to dryness. The residue was washed with n-pentane dried to get methyl 3-amino-1H-pyrazole-5-carboxylate **A60** as a pale yellow solid. Yield: 18.0 g (87%) LC-MS (ES) m/z : 142.16 [M+H]⁺.

Step-3: methyl 5-oxo-4,5-dihydropyrazolo[1,5-a]pyrimidine-2-carboxylate (A61)

[000215] To a stirred solution of methyl 3-amino-1H-pyrazole-5-carboxylate (**A60**, 22.0 g, 124.92 mmol) in 1,4-dioxane (440 mL) was added methyl propiolate (13.30 mL, 149.90 mmol) under N₂ atmosphere and the reaction mixture was stirred at 90 °C for 16 h. After completion of reaction mixture, the solvent was concentrated to dryness. The residue was purified by column chromatography using silica gel (100-200 mesh) 0-50% EtOAc/n-Hexanes as the eluent to afford methyl 5-oxo-4,5-dihydropyrazolo[1,5-a]pyrimidine-2-carboxylate **A61** as a yellow solid. Yield: 7.0 g (29%) LC-MS (ES) m/z : 194.13 [M+H]⁺.

Step-4: methyl 5-bromopyrazolo[1,5-a]pyrimidine-2-carboxylate (A62)

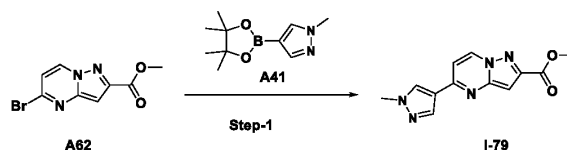
[000216] To a stirred solution of methyl 5-oxo-4,5-dihydropyrazolo[1,5-a]pyrimidine-2-carboxylate (**A61**, 7.0 g, 36.25 mmol) in 1,4-dioxane (140 mL) was added phosphorous oxybromide (51.90 g, 181.26 mmol) under N₂ atmosphere and the reaction mixture was stirred at 90 °C for 4 h. After completion of reaction mixture, the solvent was concentrated to dryness and basified with 1M Na₂CO₃ solution upto Ph-8, then extract with EtOAc the organic layer was dried over anhydrous Na₂SO₄ filtered, and concentrated under reduced pressure. The crude was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford methyl 5-

bromopyrazolo[1,5-a]pyrimidine-2-carboxylate **A62** as a light yellow solid. Yield: 3.0 g (32%) LC-MS (ES) m/z : 255.97 $[M+H]^+$.

Step-5: methyl 5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-2-carboxylate (I-78)

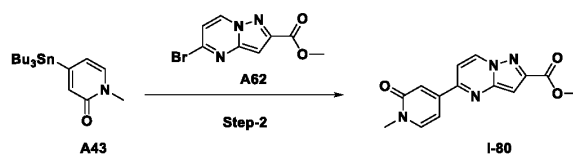
[000217] To a stirred solution of methyl 5-bromopyrazolo[1,5-a]pyrimidine-2-carboxylate (**A62**, 1.0 g, 3.92 mmol) in N,N-dimethyl formamide (20 mL) was added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (**7**, 1.10 mL, 7.84 mmol) and copper (I) iodide (0.074 g, 0.39 mmol), under N_2 atmosphere and the reaction mixture was stirred at 90 °C for 16 h. After completion of reaction mixture, quenched with water and extracted with EtOAc the organic layer was dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The crude was purified by column chromatography using 0-50% EtOAc/n-Hexanes as the eluent to afford methyl 5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-2-carboxylate **I-78** as a light yellow solid. Yield: 0.25 g (26%) LC-MS (ES) m/z : No ionization. ^1H NMR ($DMSO-d_6$, 400 MHz, ppm) δ 9.55 (d, J = 7.08 Hz, 1H), 7.68 (d, J = 7.0 Hz, 1H), 7.51 (s, 1H), 3.93 (s, 3H).

Synthesis of 1methyl 5-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxylate (I-79)



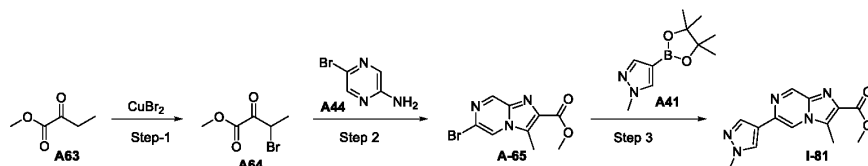
[000218] To a stirred solution of methyl 5-bromopyrazolo[1,5-a]pyrimidine-2-carboxylate (**A62**, 1 g, 3.90 mmol) in 1,4-dioxane (20 mL) and DMF (1 mL) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (**A41**, 1.21 g, 5.85 mmol) was added Na_2CO_3 (1.24 g, 11.70 mmol) dissolved in H_2O (2 mL). The reaction mixture was purged with N_2 gas for 20 min. To the above reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) $PdCl_2(dppf)$ (0.28 g, 0.39 mmol), and the resulting solution was further purged with N_2 gas for 10 min then stirred for 16 h at 80°C. The reaction mixture was filtered over celite bed and washed with ethylacetate/water mixture. The filtrate was washed with water, brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The compound was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford methyl 5-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxylate **I-79** as a brown solid. Yield: 0.51 g (51%) LC-MS (ES) m/z : 258.26 $[M+H]^+$.

Synthesis of methyl 5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxylate (I-80)



[000219] To a stirred solution of methyl 5-bromopyrazolo[1,5-a]pyrimidine-2-carboxylate (**A62**, 1.0 g, 3.90 mmol) in 1,4-dioxane (20 mL) and 1-methyl-4-(tributylstannyl)pyridin-2(1H)-one (**A43**, 2.33 g, 5.85 mmol). The reaction mixture was purged with N₂ gas for 20 min. To the above reaction mixture was added Bis(triphenylphosphine)palladium (II) dichloride PdCl₂(PPh₃)₂ (0.28 g, 0.392 mmol), and the resulting solution was further purged with N₂ gas for 10 min then stirred for 16 h at 80°C. The reaction mixture was filtered over celite bed and washed with ethyl acetate. The filtrate was washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The compound was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford methyl 5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxylate **I-80** as a brown solid. Yield: 0.35 g (32%) LC-MS (ES) m/z : 285.20 [M+H]⁺.

Synthesis of methyl 3-methyl-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (**I-81**)



Step-1: methyl 3-bromo-2-oxobutanoate (**A64**)

[000220] To a stirred solution of CuBr₂ (57.67 g, 258.6 mmol) in ethyl acetate, methyl 2-oxobutanoate (**A63**, 15.0 g, 9.17 mmol) was added dissolving in chloroform and reaction mixture heated to 80°C for 1.5 h. After completion, reaction mixture cooled to room temperature and filtered through celite and silica bed. Then concentrated the filtrate to obtain the crude. This crude diluted with dichloromethane and filtered through celite bed and concentrated the filtrate under reduced pressure to offered methyl 3-bromo-2-oxobutanoate (**2**) as brown liquid. Yield: 23.0 g (85%) ¹H NMR (400 MHz, DMSO-d₆) δ 5.31-5.26 (m, 1H), 3.84 (s, 3H), 1.69 (d, *J* = 6.4 Hz, 1H).

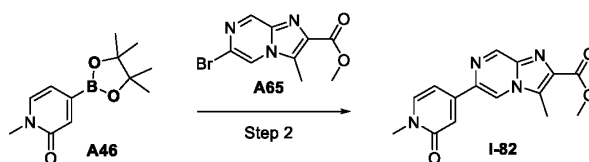
Step-2: methyl 6-bromo-3-methylimidazo[1,2-a]pyrazine-2-carboxylate (**65**)

[000221] To a stirred solution of 5-bromopyrazin-2-amine (3, 4.0 g, 22.98 mmol) and NaHCO_3 (5.79 g, 68.96 mmol) in 1,4-dioxane, methyl 3-bromo-2-oxobutanoate (**A44**, 26.89 g, 137.93 mmol) was added and reaction mixture heated to 100°C for 16 h. After completion, reaction mixture quenched with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated to obtain the crude. This crude purified by combiflash using 25% ethyl acetate in hexane as eluent. The desired fractions concentrated under reduced pressure to offered methyl 6-bromo-3-methylimidazo[1,2-a]pyrazine-2-carboxylate **A65** as brown solid. Yield: 1.3 g (20%) LC-MS (ES) $m/z = 269.96$ $[\text{M}+\text{H}]^+$.

Step-3: methyl 3-methyl-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (I-81)

[000222] A stirred solution of methyl 6-bromo-3-methylimidazo[1,2-a]pyrazine-2-carboxylate (4, 0.7 g 2.59 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (5, 0.808 g, 3.88 mmol) and sodium carbonate (0.824 g, 7.77 mmol) in dioxane : water (3:1) 17 mL was degassed with argon for 20 minutes. Then [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.189 g, 0.25 mmol) was added. The reaction mixture was heated at 100°C for 6 h. After completion, reaction mixture quenched with water and extracted with 10% MeOH in DCM (3 times). The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain the crude. This crude purified by combiflash using 3.5% MeOH in DCM as eluent. The desired fractions were concentrated under reduced pressure to offered methyl 3-methyl-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate **I-81** as brown solid. Yield: 0.36 g (50%) LC-MS (ES) $m/z = 272.19$ $[\text{M}+\text{H}]^+$.

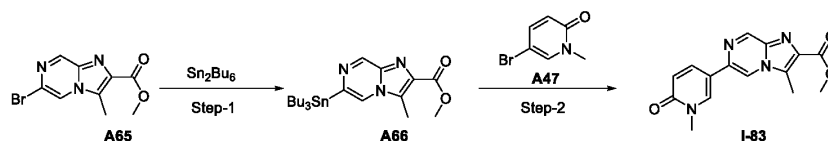
Synthesis of methyl 3-methyl-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate(I-82)



Synthesis of methyl 3-methyl-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate (I-82)

[000223] A stirred solution of methyl 6-bromo-3-methylimidazo[1,2-a]pyrazine-2-carboxylate (4, 0.7 g 2.59 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one (3, 3.04 g, 12.96 mmol) and Tripotassium phosphate (1.64 g, 7.7 mmol) in DMF: water (3:1) 12 mL was degassed with argon for 20 minutes. Then Bis(triphenylphosphine)palladium(II) dichloride (0.145 g, 0.2 mmol) was added. The reaction mixture was heated at 90°C for 16 h. After completion, evaporated the solvent from reaction mixture to obtain the residue. This residue quenched with water and extracted with 10% IPA in CHCl₃ (3 times). The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain the crude. This crude purified by combiflash using 4.3% MeOH in DCM as eluent. The desired fractions were concentrated under reduced pressure to offered methyl 3-methyl-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxylate **I-82** as brown solid. Yield: 0.61 g (79%) LC-MS (ES) m/z = 299.15 [M+H]⁺.

Synthesis of methyl 3-methyl-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxylate (I-83)



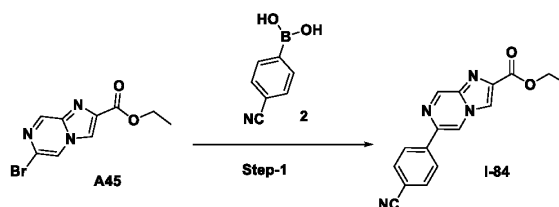
Step-1: methyl 3-methyl-6-(tributylstannyl)imidazo[1,2-a]pyrazine-2-carboxylate (2)

[000224] A stirred solution of methyl 6-bromo-3-methylimidazo[1,2-a]pyrazine-2-carboxylate (**A65**, 1.0 g, 3.7 mmol), hexabutylditin (2.83 mL, 5.5 mmol) in dioxane (10 mL), was degassed with argon for 30 minutes. Then tetrakis(triphenylphosphine)palladium(0) (0.429 g, 0.37 mmol) was added. The reaction mixture was heated at 100°C for 2 h. After completion, reaction mixture quenched with water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated under reduced pressure to obtain the crude. This crude purified by combiflash using 2.3% MeOH in DCM as eluent. The desired fractions were concentrated under reduced pressure to offered methyl 3-methyl-6-(tributylstannyl)imidazo[1,2-a]pyrazine-2-carboxylate **A66** as light brown gummy liquid. Yield: 0.3 g (16.6%) LC-MS (ES) m/z = 482.25 [M+H]⁺.

Step-2: methyl 3-methyl-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxylate (I-83)

[000225] A stirred solution of methyl 3-methyl-6-(tributylstannyl)imidazo[1,2-a]pyrazine-2-carboxylate (**2**, 0.3 g, 0.62 mmol) and 5-bromo-1-methylpyridin-2(1H)-one (**3**, 0.141 g, 0.75 mmol) in dioxane 15 mL was degassed with argon for 20 minutes. Then [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.045 g, 0.062 mmol) was added. The reaction mixture was heated at 100°C for 16 h. After completion, reaction mixture quenched with water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated under reduced pressure to offered methyl 3-methyl-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxylate **I-83** as brown solid. Yield: 0.2 g (71%) LC-MS (ES) $m/z = 299.01$ $[M+H]^+$.

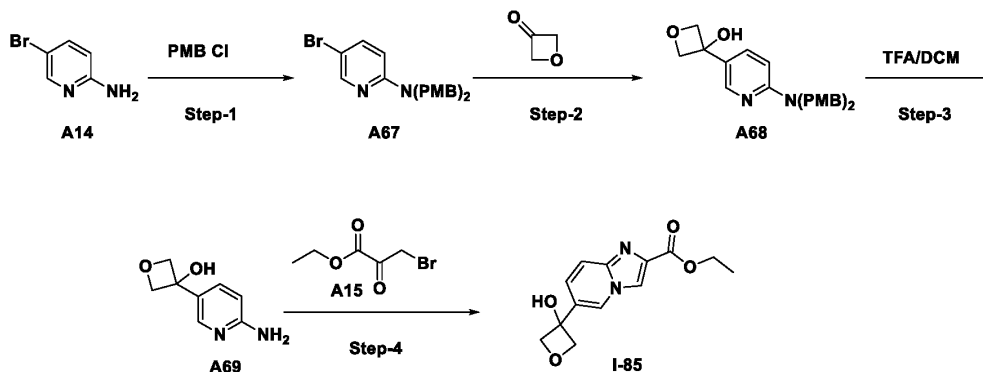
Synthesis of ethyl 6-(4-cyanophenyl)imidazo[1,2-a]pyrazine-2-carboxylate (I-84)



Step- 1: ethyl 6-(4-cyanophenyl)imidazo[1,2-a]pyrazine-2-carboxylate (3)

[000226] To a stirred solution of ethyl 6-bromoimidazo[1,2-a]pyrazine-2-carboxylate (**3**, 1 g, 3.70 mmol) in 1,4-dioxane (20 mL) and DMF (1 mL) and (4-cyanophenyl)boronic acid (**2**, 0.816 g, 5.55 mmol) was added K_3PO_4 (2.35 g, 11.10 mmol) dissolved in H_2O (2 mL). The reaction mixture was purged with N_2 gas for 20 min. To the above reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) $PdCl_2(dppf)$ (0.27 g, 0.37 mmol), and the resulting solution was further purged with N_2 gas for 10 min then stirred for 16 h at 80°C. The reaction mixture was filtered over celite bed and washed with ethylacetate/water mixture. The filtrate was washed with water, brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The compound was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford ethyl 6-(4-cyanophenyl)imidazo[1,2-a]pyrazine-2-carboxylate **3** as a brown solid. Yield: 0.50 g (50%) LC-MS (ES) $m/z : 293.26$ $[M+H]^+$.

Synthesis of ethyl 6-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridine-2-carboxylate (I-84)



Step- 1: 5-bromo-N,N-bis(4-methoxybenzyl)pyridin-2-amine (A67)

[000227] To a stirred solution of 5-bromopyridin-2-amine (**A14**, 2.0 g, 11.56 mmol) in N,N-dimethylformamide (40 mL) was added NaH (60% paraffin oil) (1.38 g, 34.68 mmol) at 0 °C. The reaction mixture stirred at room temperature for 1h. 4-methoxy benzyl chloride (3.10 mL, 23.12 mmol) was added at °C. The reaction mixture was stirred for 16 h at room temperature. After completion of reaction, quenched with ice water extracted with EtOAc. The organic layer was washed with water, brine solution, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by column chromatography using 0-30% EtOAc/n-hexanes as the eluent to afford 5-bromo-N,N-bis(4-methoxybenzyl)pyridin-2-amine **A67** as a white solid. Yield: 4.0 g (85%) LC-MS (ES) m/z : 413.08 [M+H]⁺.

Step- 2: 3-(6-(bis(4-methoxybenzyl)amino)pyridin-3-yl)oxetan-3-ol (A-68)

[000228] To a stirred solution of 5-bromo-N,N-bis(4-methoxybenzyl)pyridin-2-amine (**A-67**, 3.0 g, 7.28 mmol) in dry THF (60 mL) was added drop wise n-BuLi (1.6 M solution) (5.46 mL, 8.736 mmol) at -78 °C under N₂ atmosphere. The reaction mixture was stirred at -78 °C for 1h. A solution of in THF was added drop wise oxetan-3-one (0.65 g, 8.736 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 1h and slowly raised to temperature at room temperature then stirred for 3 h. After completion of reaction mixture, quenched with ice water and extracted with EtOAc. The organic layer was washed with water, brine solution, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by column chromatography using 0-30% EtOAc/n-hexanes as the eluent to afford 3-(6-(bis(4-

methoxybenzyl)amino)pyridin-3-yl)oxetan-3-ol **A-68** as a yellow sticky solid. Yield: 1.40 g (48%) LC-MS (ES) m/z : 407.16 $[M+H]^+$

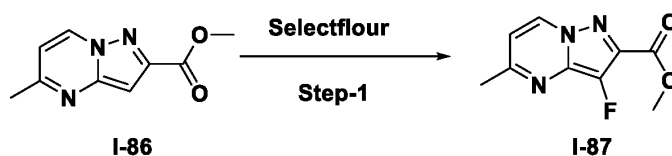
Step- 3: 3-(6-aminopyridin-3-yl)oxetan-3-ol (A69)

[000229] To a solution of 3-(6-(bis(4-methoxybenzyl)amino)pyridin-3-yl)oxetan-3-ol (A68, 5.30 g, 13.05 mmol) in DCM (20 mL) at 0 °C was added TFA (20 mL) and the resulting solution was stirred at room temperature for 16 h. After completion of reaction mixture concentrated under reduced pressure and washed with ether and dried to afford 3-(6-aminopyridin-3-yl)oxetan-3-ol **A69** as off white solid. Yield: 2.10 g (92%) LC-MS (ES) m/z : 167.18 $[M+H]^+$.

Step- 4: ethyl 6-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridine-2-carboxylate (I-85)

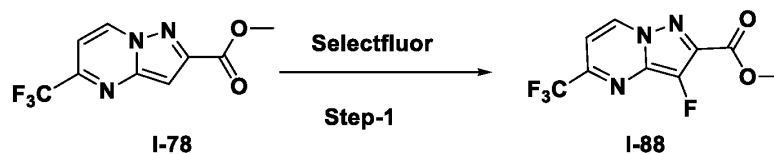
[000230] To a stirred solution of 3-(6-aminopyridin-3-yl)oxetan-3-ol (**B45**, 2.1 g, 12.64 mmol) in 1,4-dioxane (40 mL) was added ethyl 3-bromo-2-oxopropanoate (2, 3.31 mL, 18.96 mmol), followed by NaHCO_3 (1.59 g, 18.96 mmol), The reaction mixture was heated at 100 °C for 16 h. after completion of reaction mixture, the solvent was concentrated under reduced pressure. The crude product was triturated with water and washed with n-pentane and dried to afford ethyl 6-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridine-2-carboxylate **I-85** as brown solid. Yield: 3.10 g, (67%).LC-MS m/z : 263.07 $[M+H]^+$.

Synthesis of methyl 3-fluoro-5-methylpyrazolo[1,5-a]pyrimidine-2-carboxylate (I-87)



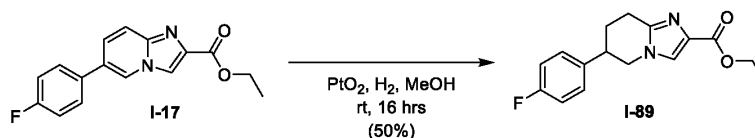
[000231] To a stirred solution of methyl 5-methylpyrazolo[1,5-a]pyrimidine-2-carboxylate (**I-86**, 1.0 g, 5.23 mmol) in acetonitrile (25 mL), was added 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis (4.63 g, 13.07 mmol) at room temperature. The reaction mixture was heated at 70 °C for 36 h. after completion of reaction diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to get crude. The crude was purified by column chromatography using 0-30% ethyl acetate in hexanes as eluent to afford methyl 3-fluoro-5-methylpyrazolo[1,5-a] pyrimidine-2-carboxylate **I-87** yellow solid Yield:0.3 g, (27%). LC-MS m/z : 210.07 $[M+H]^+$.

Synthesis of methyl 3-fluoro-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-2-carboxylate (I-88)



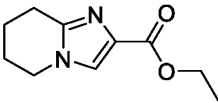
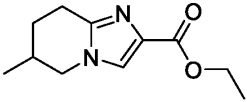
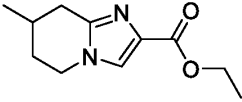
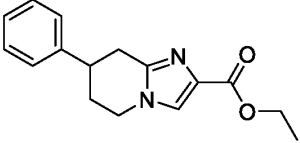
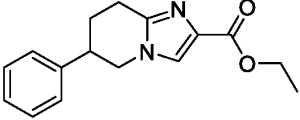
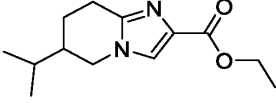
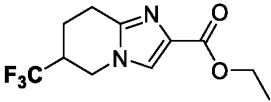
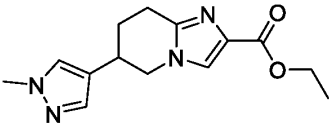
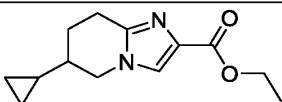
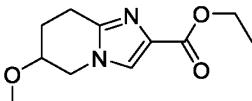
[000232] To a stirred solution of methyl 5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-2-carboxylate (I-78, 0.60 g, 2.44 mmol) in acetonitrile (15 mL), was added 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis (2.59 g, 7.32 mmol) at room temperature. The reaction mixture was heated at 70 °C for 36 h. after completion of reaction diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to get crude. The crude was purified by column chromatography using 0-60% ethyl acetate in hexanes as eluent to afford methyl 3-fluoro-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-2-carboxylate I-88 yellow solid Yield: 0.2 g, (31%). LC-MS m/z : 262.04 $[M-H]^-$.

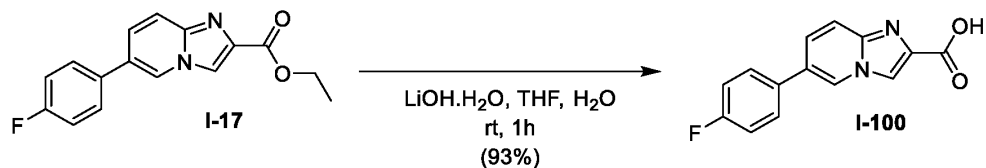
Synthesis of ethyl 6-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (I-89)



[000233] To an argon purged solution of ethyl 6-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxylate (**I-17** 0.1g, 0.35mmol) in methanol (30 mL) was added PtO₂ (10 wt%, 10mg). The resulting mixture was stirred for 16 h in an autoclave at room temperature under hydrogen atmosphere. The reaction mixture was then filtered through celite and concentrated. The crude product was purified by combi-flash purifier with 5 % MeOH in DCM as eluent to afford of intermediate **I-89** as a brown oily liquid (50%). MS (ESI) m/z = 289.1 $[M+H]^+$.

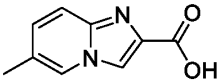
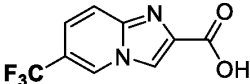
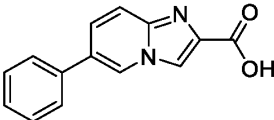
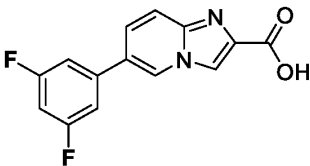
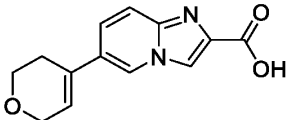
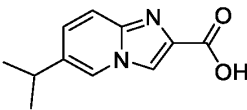
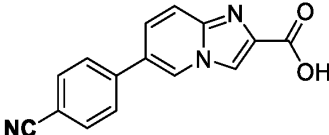
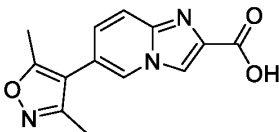
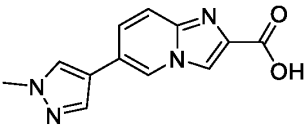
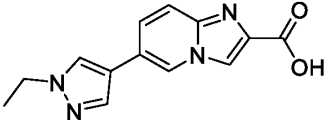
[000234] The following ester intermediates were synthesized using the protocol exemplified for **I-89**.

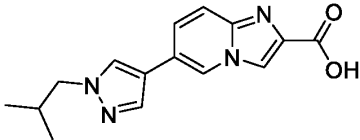
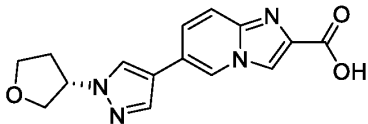
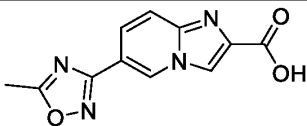
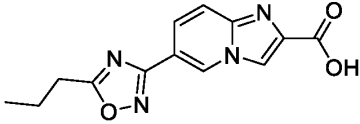
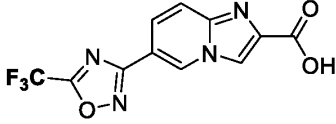
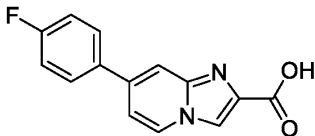
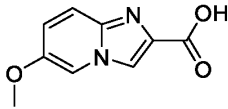
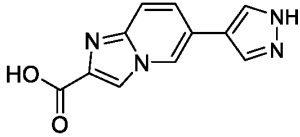
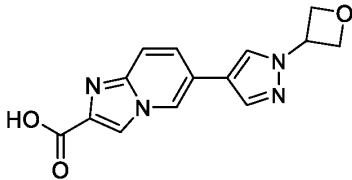
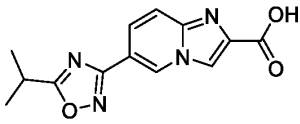
Intermediate No	Structure	LC/MS_m/z_ [M+H] ⁺
I-90		195.1
I-91		209.2
I-92		209.2
I-93		271.2
I-94		271.2
I-95		237.2
I-96		262.9
I-97		275.2
I-98		235.2
I-99		225.1

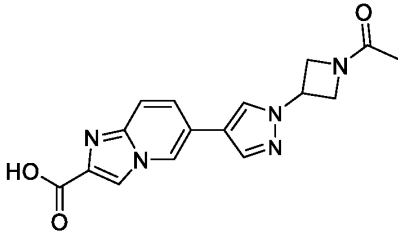
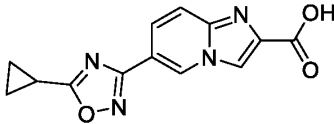
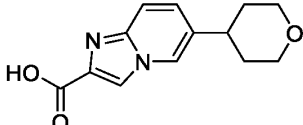
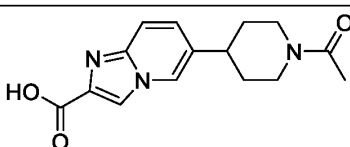
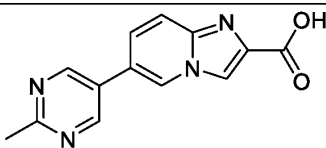
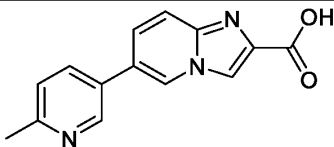
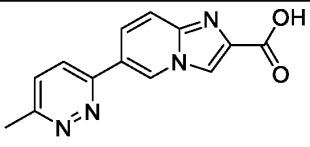
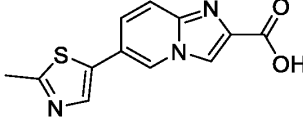
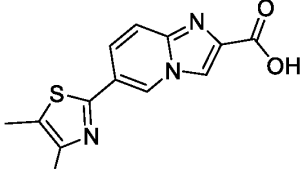
Synthesis of 6-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxylic acid (I-100)

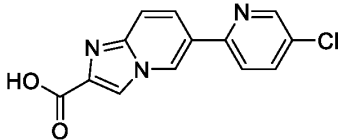
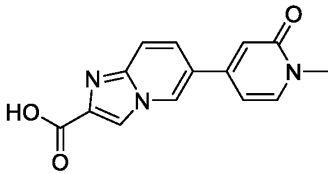
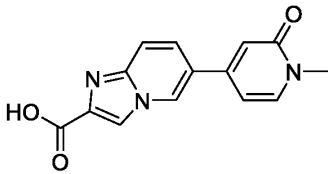
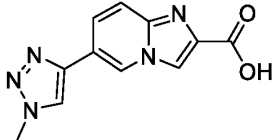
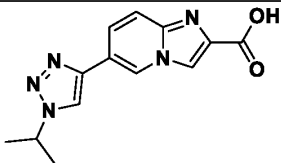
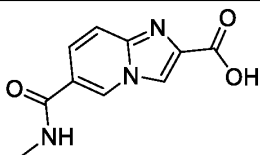
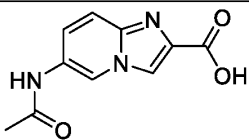
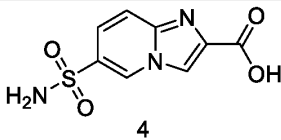
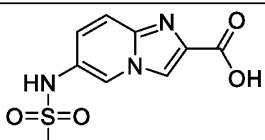
[000235] To a stirred solution of ethyl 6-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxylate (**I56**, 0.5 g, 1.76 mmol) in 10 mL of THF:H₂O (1:1) was added LiOH.H₂O (0.15 g, 3.52 mmol). The reaction mixture was stirred for 1 h at room temperature. Then pH of reaction mixture was brought in the range of 3 to 4 with 2N HCl and extracted with DCM/methanol mixture. The combined organic layer dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford **I-100** as a white solid (0.42 g, 93%). MS (ESI) $m/z = 257.1$ [M+H]⁺.

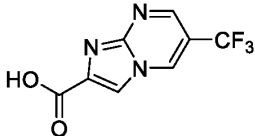
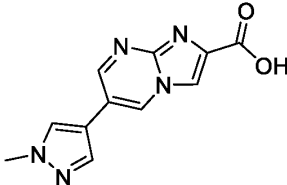
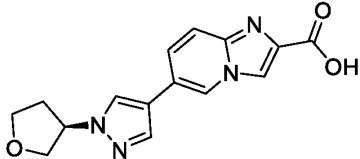
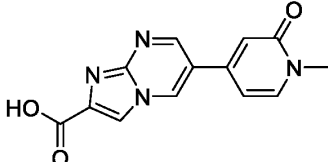
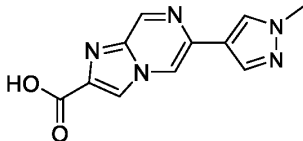
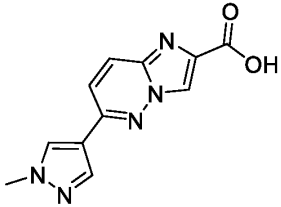
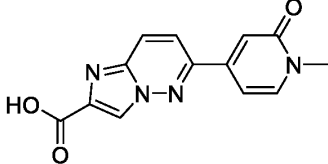
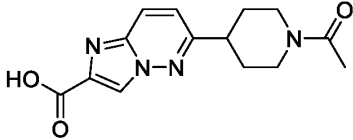
[000236] The following acid intermediates were synthesized using the protocol exemplified for **I98**.

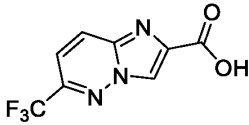
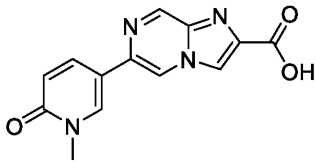
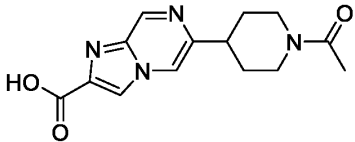
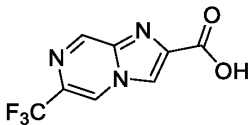
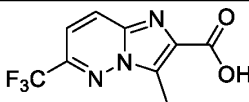
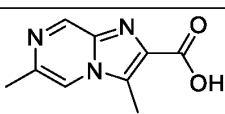
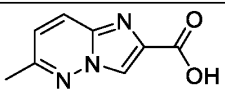
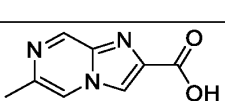
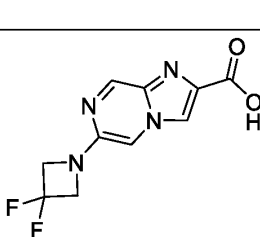
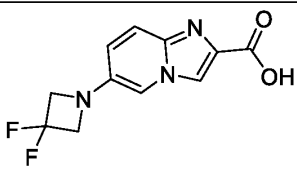
Intermediate No	Structure	LC/MS_m/z_ [M+H]
I-101		177.1
I-102		231.1
I-103		239.1
I-104		275.1
I-105		244.9
I-106		205.1
I-107		264.1
I-108		258.1
I-109		243.1
I-110		257.1

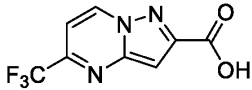
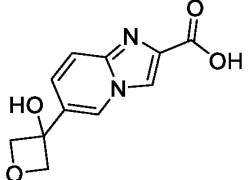
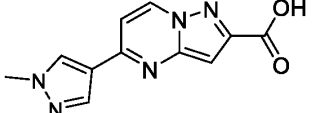
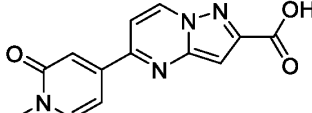
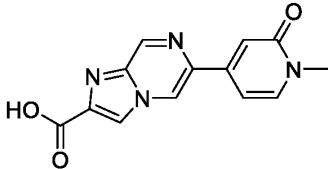
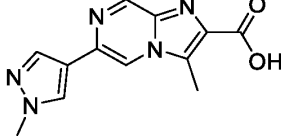
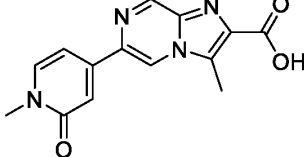
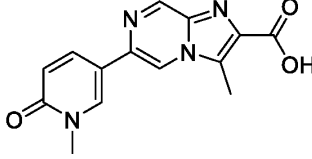
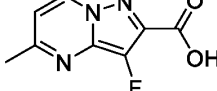
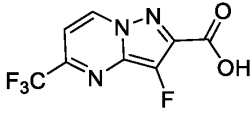
I-111		285.0
I-112		299.1
I-113		245.0
I-114		271.1
I-115		--
I-116		257.1
I-117		193.1
I-118		229.3
I-119		285.1
I-120		271

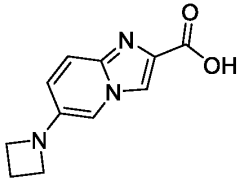
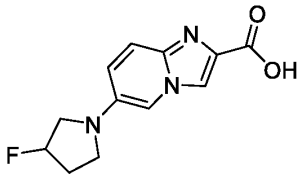
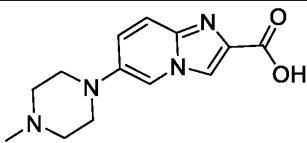
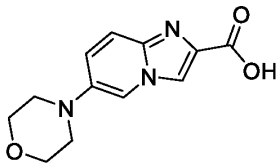
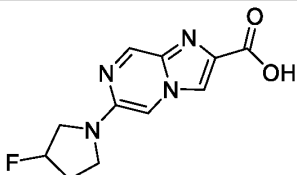
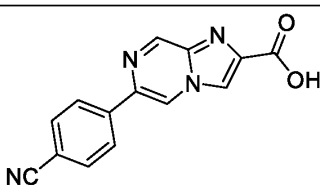
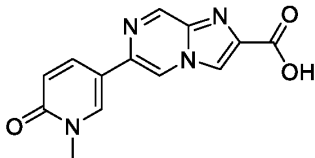
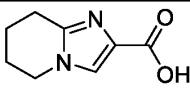
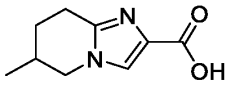
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I-122		271.3
I-123		247.3
I-124		288.3
I-125		255.2
I-126		254.2
I-127		255.2
I-128		260.2
I-129		274

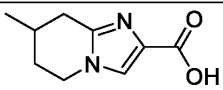
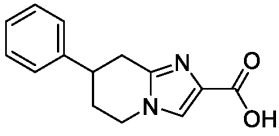
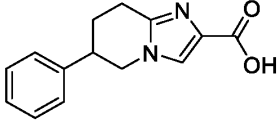
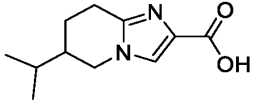
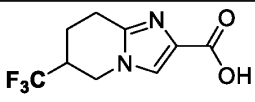
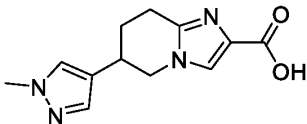
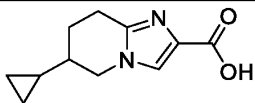
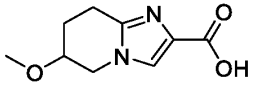
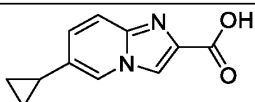
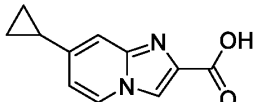
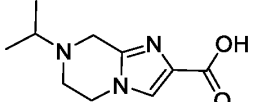
I-130		274
I-131		270.2
I-132		270.1
I-133		243.8
I-134		272.8
I-135		220.1
I-136		220.2
I-137	 4	241.8
I-138		254.2

I-139		229.9
I-140		242.1
I-141		299.1
I-142		271.1
I-144		244.08
I-145		244.08
I-146		271.2
I-147		289.2

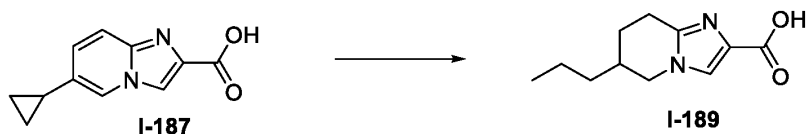
I-148		232.1
I-149		270.1
I-150		289.3
I-151		232.2
I-152		244.1
I-153		190.1
I-154		178.1
I-155		178.1
I-156		255.1
I-157		252.1

I-158		222.9
I-159		235.1
I-160		241.1
I-161		269.1
I-162		271.1
I-163		258.1
I-164		285.1
I-165		285.1
I-166		194.2
I-167		248.1

I-168		218.1
I-169		250.1
I-170		261.1
I-171		248.1
I-172		251.1
I-173		265.1
I-175		269.2
I-176		167.1
I-177		181.1

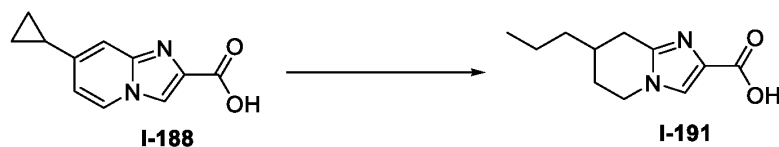
I-178		181.1
I-180		243.1
I-181		243.2
I-182		209.1
I-183		235.1
I-184		247.2
I-185		207.1
I-186		197.1
I-187		203.1
I-188		203.1
I-192		210.2

Synthesis of 6-propyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (I-189)



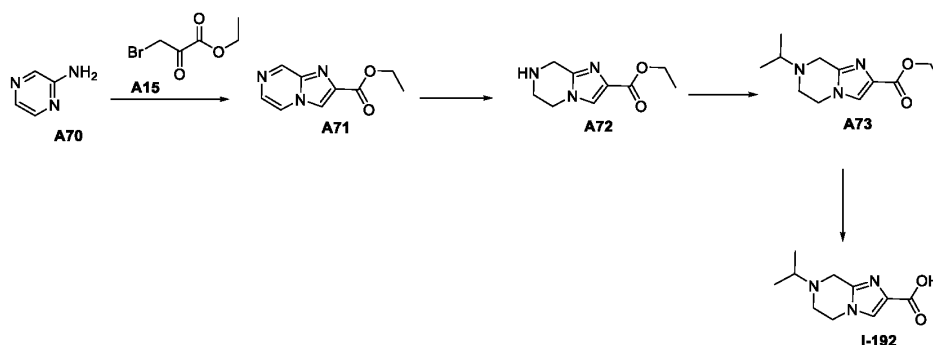
[000237] To a solution of 6-cyclopropylimidazo[1,2-a]pyridine-2-carboxylic acid (**I-187**, 0.05 g, 0.24 mmol) in ethanol (8 mL) was added 10 % Pd-C (0.03 g) and the resulting reaction mixture was stirred for 1 h under hydrogen atmosphere at room temperature. After completion of the reaction [monitored by LCMS], reaction mixture was filtered through diatomaceous earth and separated the organic layer. Organic layer was concentrated under reduced pressure to afford the desired product **I-189** as yellow semi solid (0.055 g) which was used for the next step without further purification. MS (ESI) $m/z = 209.2$ ($M+H$)⁺.

Synthesis of 7-propyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (I-190)

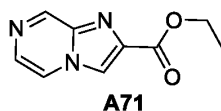


[000238] To a solution of 7-cyclopropylimidazo[1,2-a]pyridine-2-carboxylic acid (**I188**, 0.1 g, 0.49 mmol) in ethanol (10 mL) was added 10 % Pd-C (0.03 g) and the resulting reaction mixture was stirred for 1 h under hydrogen atmosphere at room temperature. After completion of the reaction [monitored by LCMS], reaction mixture was filtered through diatomaceous earth and separated the organic layer. Organic layer was concentrated under reduced pressure to afford the desired crude product **I-191** as yellow semi solid which was used for the next step without further purification (0.09 g). MS (ESI) $m/z = 209.1$ ($M+H$)⁺.

Synthesis of 7-isopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-2-carboxylic acid (I-192)

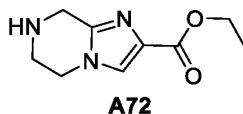


Step 1: Ethyl imidazo [1, 2-a] pyrazine-2-carboxylate (A71)



[000239] To a solution of pyrazin-2-amine (**A70**, 2.0 g, 2.10 mmol) and ethyl 3-bromo-2-oxopropanoate (**A15**, 3.0 mL, 2.30 mmol) in ethanol (15.0 mL) was added Conc., HCl (1.0 mL) at 0 °C and stirred for 12 h at 95 °C. The reaction mixture was concentrated under reduced pressure followed by addition of water (10 mL), the mixture was then extracted with DCM and the organic layer was washed with saturated NaHCO₃ solution and brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. The obtained crude was purified by combi-flash purifier with 3% methanol in dichloromethane as eluent to afford the desired product **A71** as yellow solid (0.4 g, 10 %). ¹H NMR (DMSO-d₆, 400 MHz) δ 1.31 (t, *J* = 7.2 Hz, 3H), 4.33 (q, *J* = 7.2 Hz, 2H), 7.96 (d, *J* = 4.4 Hz, 1H), 8.57 (d, *J* = 4.0 Hz, 1H), 8.66 (s, 1H), 9.15 (s, 1H); MS (ESI) *m/z* = 192.1 (M+H)⁺.

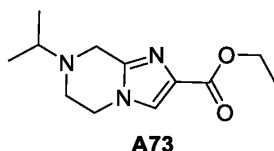
Step 2: Ethyl 5, 6, 7, 8-tetrahydroimidazo [1, 2-a] pyrazine-2-carboxylate (A-72)



[000240] To a solution of ethyl imidazo [1, 2-a] pyrazine-2-carboxylate (**A71**, 0.25 g, 1.30 mmol) in methanol (15.0 mL) was added PtO₂ (0.1 g). The reaction mixture was then stirred 12 hours under H₂ atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a celite pad and the organic layer was concentrated under reduced pressure to afford the desired product **A-72** as a viscous oil (0.22 g, 88 %). ¹H NMR (DMSO-d₆, 400 MHz) δ 1.22 (t, *J* = 7.2 Hz, 3H), 2.71 (bs, 1H),

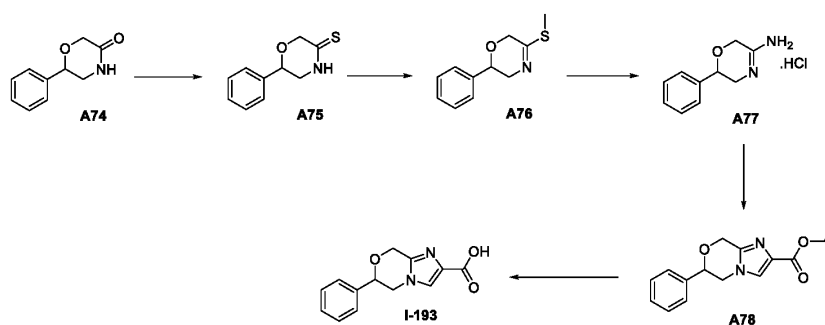
3.00 (t, $J = 6.0$ Hz, 2H), 3.80 (s, 2H), 3.90 (t, $J = 6.0$ Hz, 2H), 4.16 (q, $J = 7.2$ Hz, 2H), 7.71 (s, 1H), 9.15 (s, 1H); MS (ESI) $m/z = 196.2$ (M+H)⁺.

Synthesis of ethyl 7-isopropyl-5, 6, 7, 8-tetrahydroimidazo [1, 2-a] pyrazine-2-carboxylate (A73)

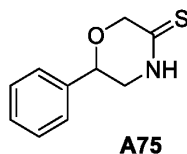


[000241] To a solution of ethyl 5, 6, 7, 8-tetrahydroimidazo [1, 2-a] pyrazine-2-carboxylate (**A72**, 0.2 g, 1.02 mmol) in methanol (10.0 mL) was added acetone (0.11 mL, 1.55 mmol) followed by catalytic amount of acetic acid (0.1 mL) at 0 °C and stirred at the same temperature for 30 mins. Sodium cyano borohydride (0.13 g, 2.05 mmol) was added slowly and it was further stirred for 12 h at room temperature. The reaction mixture was concentrated under reduced pressure followed by addition of water (10 mL) and then extracted into EtOAc. The organic layer was washed with saturated NaHCO₃ solution and brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. The obtained crude was purified by combi-flash purifier with 3% methanol in dichloromethane as eluent to afford the desired product **A73** as yellow oil (0.21 g, 86 %). ¹H NMR (DMSO-d₆, 400 MHz) δ 1.03 (d, $J = 7.6$ Hz, 6H), 1.22 (t, $J = 4.0$ Hz, 3H), 2.81-2.87 (m, 3H), 3.62 (s, 2H), 3.95 (t, $J = 6.0$ Hz, 2H), 4.17 (q, $J = 7.2$ Hz, 2H), 7.73 (s, 1H); MS (ESI) $m/z = 238.2$ (M+H)⁺.

Synthesis of 6-phenyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine-2-carboxylic acid (I-193)

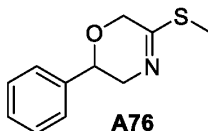


Step 1: 6-phenylmorpholine-3-thione (A75)



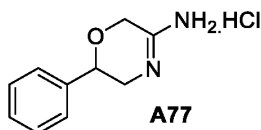
[000242] To a stirred solution of 6-phenylmorpholin-3-one (**A11**, 3.5 g, 20.0 mmol) in 100 mL of dry THF was added Lawesson's reagent (4.86 g, 12.0 mmol). The reaction mixture was stirred for 1.5 h at room temperature then 6N HCl (22.0 mL) was added and further stirred for another 10 min. The reaction mixture was concentrated and the concentrate was stirred with a mixture of DCM /sat. NaHCO₃. The separated organic layer was dried with anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by combiflash using 25% ethylacetate /hexane to afford product **B51** as an off white solid (2.5 g, 65.7%). MS (ESI) m/z = 194.0[M+H]⁺.

Step 2: 5-(methylthio)-2-phenyl-3,6-dihydro-2H-1,4-oxazine (A76)



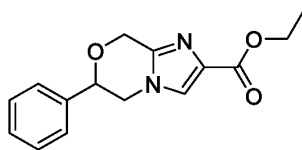
[000243] To a stirred solution of 6-phenylmorpholine-3-thione (**B51**, 1.0 g, 5.0 mmol) in 50 mL of dry DCM was added trimethyloxonium tetrafluoroborate (1.3 g, 8.6 mmol) at 0 °C. The reaction mixture was stirred for 1h at room temperature and quenched with saturated solution of K₂CO₃ (22.0 mL) at -10 °C and extracted with DCM. The separated organic layer was dried with anhydrous Na₂SO₄ and evaporated under reduced pressure to afford product **B52** as a yellow solid (0.950 g, 88.78%). MS (ESI) m/z = 208.1[M+H]⁺.

Step 3: 6-phenyl-5,6-dihydro-2H-1,4-oxazin-3-amine hydrochloride (B53)



[000244] To a stirred solution of 5-(methylthio)-2-phenyl-3,6-dihydro-2H-1,4-oxazine (**B52**, 0.950 g, 0.45 mmol) in 20 mL of MeOH (1.3 g, 8.6 mmol) was added ammonium chloride (0.294 g, 0.55 mmol). The reaction mixture was refluxed for 2 h. After the completion of reaction, it was concentrated to afford **A77** as an off white solid product (1.05 g) which was used with out further purification in the next step. MS (ESI) m/z = 177.1[M+H]⁺.

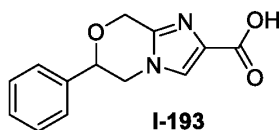
Step 4: ethyl 6-phenyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine-2-carboxylate (A78)



A78

[000245] To a stirred solution of 6-phenyl-5,6-dihydro-2H-1,4-oxazin-3-amine hydrochloride (**A77**, 0.65 g 0.30 mmol) in EtOH : dioxane (10:10 mL) was added ethyl bromopyruvate **A15** (0.5 mL, 0.36 mmol), followed by NaHCO₃ (0.772 g, 10.0 mmol). The reaction mixture was heated for 16 h at 100 °C and then concentrated. The concentrate was washed three times with 30 mL of ethyl acetate/water (8: 2). The separated organic layer was dried with anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by combiflash using 25% ethyl acetate/hexane to afford **A78** as a brown sticky solid (0.2 g). MS (ESI) m/z = 273.1[M+H]⁺.

Step 5: 6-phenyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine-2-carboxylic acid (I-193)

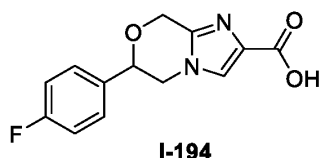


I-193

[000246] To a stirred solution of ethyl 6-phenyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine-2-carboxylate (**A78**, 0.2 g, 0.08 mmol) in 30 mL of MeOH:THF:H₂O (1:1:1) was added LiOH·H₂O (0.041 g, 10.0 mmol). The reaction mixture was stirred for 16h at room temperature and then evaporated to dryness. The pH of the aqueous solution was adjusted to 4 using dil HCl and then extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to afford the desired product **I-192** as pale yellow solid (0.2 g). MS (ESI): m/z = 245.0 [M+H]⁺.

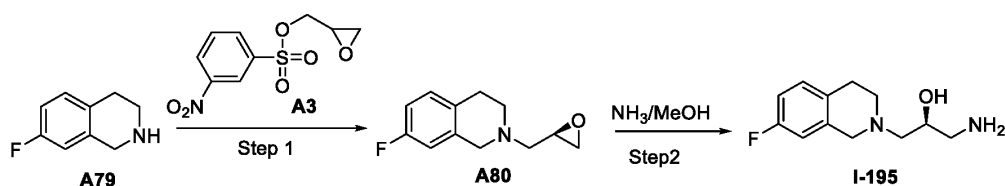
Synthesis of 6-(4-fluorophenyl)-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine-2-carboxylic acid (I193)

[000247] Using the procedure for the synthesis of **I193**, the compound **I194** was synthesized



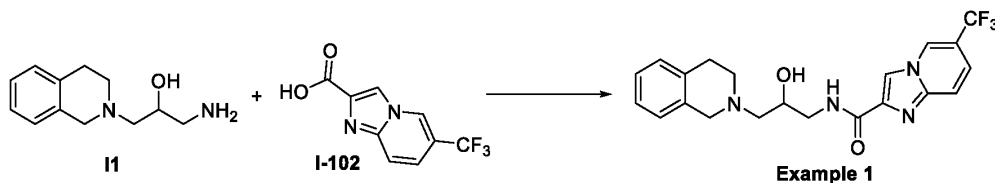
Synthesis of (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol(I-195)

Prepared according to the protocols followed for compound **I-2**



[000248] Further, the compounds of Formula I were prepared utilizing the intermediates above.

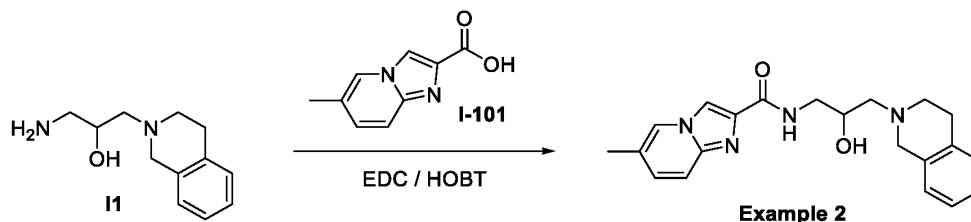
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 1)



[000249] To a solution of carboxylic acid (**I-102**, 0.2 g, 0.86 mmol) in DMF (8 mL) was added DIPEA (0.45 mL, 2.60 mmol) followed by EDC.HCl (0.333 g, 1.73 mmol) and HOBT (0.266 g, 1.73 mmol). The reaction mixture was stirred for 1 h followed by addition of 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (**I1**, 0.179 g, 0.86 mmol). The reaction mixture was stirred for 16 h. The reaction was monitored till the completion of starting materials (LC/MS) and then concentrated under reduced pressure. The obtained crude was purified by column chromatography using 10% methanol in dichloromethane as eluent to afford the desired product as white solid (27 mg, 8 %). ¹H NMR (DMSO-*d*₆, 400 MHz, ppm)- δ 9.23 (s, 1H), 8.42 (s, 1H), 8.36 (s, 1H), 7.68 (d, *J* = 9.2 Hz, 1H), 7.54 (d, *J* = 10 Hz, 1H), 7.12-7.04 (m, 3H), 6.99 (d, *J* = 5.6 Hz, 1H), 4.92 (d, *J* = 4.4 Hz, 1H), 3.90 (d, *J* = 5.2 Hz, 1H), 3.61 (s, 2H), 3.47 - 3.43 (m, 2H), (2

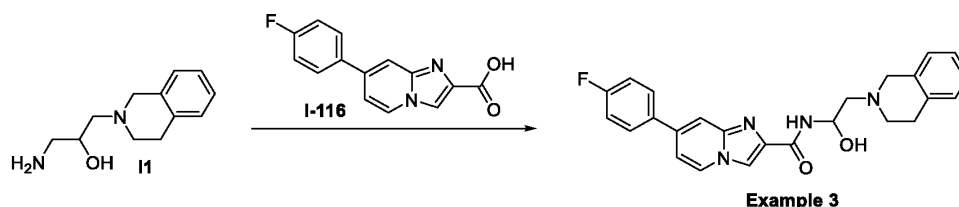
protons are merged with water-DMSO peak), 2.81 (d, $J = 4.8$ Hz, 2H), 2.77 - 2.73 (m, 1H), 2.69 - 2.65 (m, 1H); MS (ESI) $m/z = 419.2$ $[M+H]^+$.

***N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methylimidazo[1,2-a]pyridine-2-carboxamide (Example 2)**



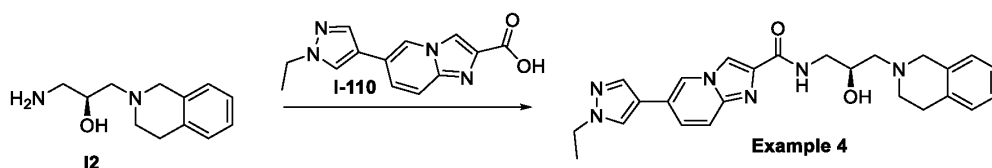
[000250] ^1H NMR (DMSO- d_6 , 400 MHz, ppm)- (TFA salt): δ 8.33 (bs, 1H), 8.16-8.23 (m, 1H, excluded the TFA proton), 7.40 (d, $J = 9.2$ Hz, 1H), 7.17 (d, $J = 8.4$ Hz, 1H), 7.01-7.09 (m, 3H), 6.96-7.04 (m, 1H), 6.42-6.46 (m, 1H), 4.89-4.91 (m, 1H), 3.83-3.89 (m, 1H), 3.55-3.61 (m, 2H), 3.41-3.47 (m, 1H), 2.78-2.84 (m, 2H), 2.65-2.73 (m, 2H), 2.25 (s, 3H) & 3 of the aliphatic protons merged underneath the DMSO/ H_2O peak; MS (ESI) $m/z = 365.3$ $[M+H]^+$.

***N*-(2-(3,4-dihydroisoquinolin-2(1H)-yl)-1-hydroxyethyl)-7-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 3)**



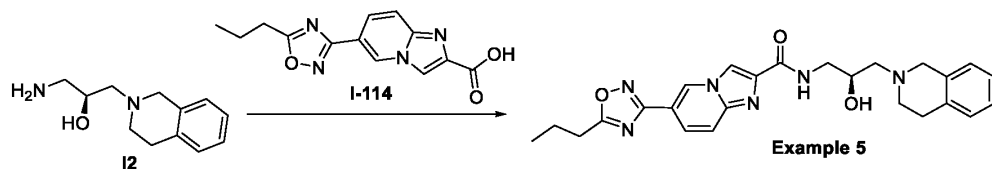
[000251] Yield 5.8%. ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 8.60 (d, $J = 6.8$ Hz, 1H), 8.28-8.37 (m, 2H), 7.82-7.85 (m, 2H), 7.69 (s, 1H), 7.32-7.36 (m, 3H), 7.04-7.12 (m, 3H), 7.00-7.02 (m, 1H), 4.94 (bs, 1H), 3.86-3.91 (m, 1H), 3.55-3.62 (m, 2H), 3.43-3.49 (m, 1H), 3.27-3.35 (m, 1H), 2.74-2.84 (m, 2H), 2.69-2.74 (m, 2H) & 2 of the aliphatic protons merged with the DMSO/ H_2O peak; MS (ESI) $m/z = 445.2$ $[M+H]^+$.

(S)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-ethyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 4)



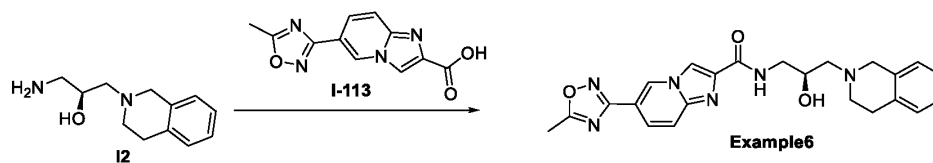
[000252] Yield 6 %. ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 8.80 (s, 1H), 8.22 (d, 2H, $J = 6.4$ Hz), 7.86 (s, 1H), 7.60 (d, 1H, $J = 9.2$ Hz), 7.54-7.50 (m, 1H), 7.14-7.06 (m, 3H), 7.06-6.98 (m, 2H), 4.20-4.10 (m, 2H), 3.70-3.64 (m, 1H), 3.48-3.40 (m, 1H), 2.82-2.75 (m, 2H), 2.91-2.87 (m, 1H), 1.42-1.38 (m, 3H), 1.30-1.20 (m, 3H), 1.15-1.10 (m, 1H), 0.90-0.80 (m, 3H); MS (ESI) $m/z = 445.2$ $[\text{M}+\text{H}]^+$.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-propyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 5)



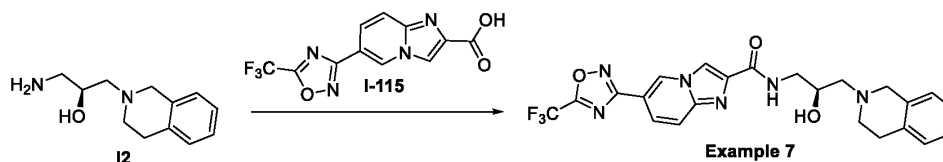
[000253] 13.75 %. ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 9.34 (s, 1H), 8.51 (s, 1H), 8.33 (s, 1H), 7.80 (d, $J = 9.2$ Hz, 1H), 7.64 (d, $J = 9.2$ Hz, 1H), 7.08 (bs, 3H), 7.00 (s, 1H), 4.92 (s, 1H), 3.90-3.89 (m, 1H), 3.61 (s, 2H), 3.47-3.43 (m, 1H), (2 H, proton merged with DMSO/ H_2O peak), 2.99 (t, $J = 6.8$ Hz, 2H), 2.82 (s, 2H), 2.73-2.64 (m, 3H), 1.84-1.78 (q, 2H), 0.98 (t, $J = 7.2$ Hz, 3H); MS (ESI) $m/z = 461.1$ $[\text{M}+\text{H}]^+$.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 6)



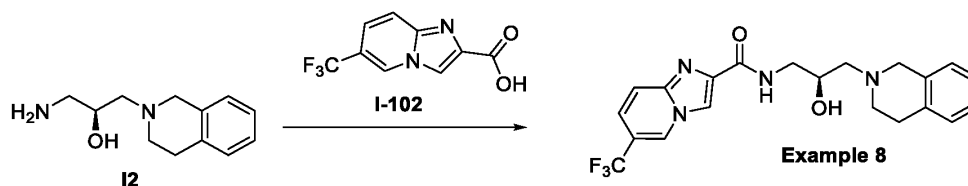
[000254] , 25 %. ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 9.34 (s, 1H), 8.51 (s, 1H), 8.33 (bs, 1H), 7.79 (d, $J = 9.6$ Hz, 1H), 7.64 (d, $J = 9.6$ Hz, 1H), 7.08-7.06 (m, 3H), 7.01 (d, $J = 6.8$ Hz, 1H), 4.93 (d, $J = 4.0$ Hz, 1H), 3.91-3.90 (m, 1H), 3.61 (s, 2H), 3.47-3.44 (m, 1H) (4H, proton merged with DMSO peak), 2.83 (s, 2H), 2.77-2.74 (m, 1H), 2.67 (s, 3H); MS (ESI) $m/z = 433.0$ $[\text{M}+\text{H}]^+$.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 7)



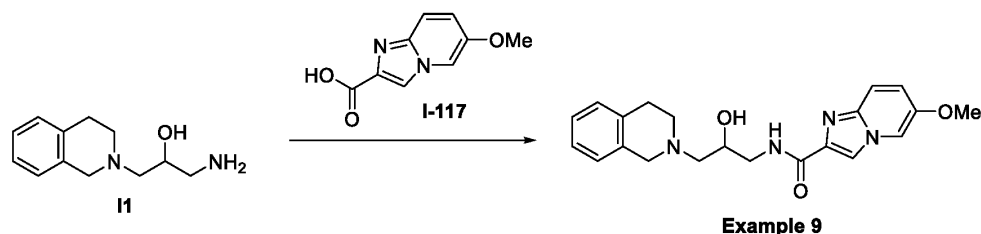
[000255] 3.2 %). ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 9.50 (s, 1H), 8.52 (s, 1H), 8.36 (t, $J = 7.6$ Hz, 1H), 7.84 (d, $J = 9.2$ Hz, 1H), 7.69 (d, $J = 9.2$ Hz, 1H), 7.08-7.06 (m, 3H), 7.00 (d, $J = 6.8$ Hz, 1H), 4.92 (d, $J = 4.4$ Hz, 1H), 3.91-3.90 (m, 1H), 3.61 (s, 2H), 3.47-3.44 (m, 1H), 3.4 (m, 3H, proton merged with DMSO/ H_2O peak), 2.82-2.77 (m, 2H), 2.73-2.64 (m, 2H); MS (ESI) $m/z = 487.1$ $[\text{M}+\text{H}]^+$.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 8)



[000256] 10 %). ^1H NMR (DMSO- d_6 , 400 MHz, ppm)- δ 9.24 (s, 1H), 8.42 (s, 1H), 8.38 (bs, 1H), 7.68 (d, $J = 9.6$ Hz, 1H), 7.54 (d, $J = 9.2$ Hz, 1H), 7.12-7.04 (m, 3H), 7.02-6.97 (m, 1H), 4.94 (bs, 1H), 3.96-3.87 (m, 1H), 3.66-3.55 (m, 2H), 3.50 - 3.42 (m, 2H), 2.87-2.80 (m, 2H), 2.78 - 2.72 (m, 2H), 2.70 - 2.64 (m, 2H); MS (ESI) $m/z = 419.2$.

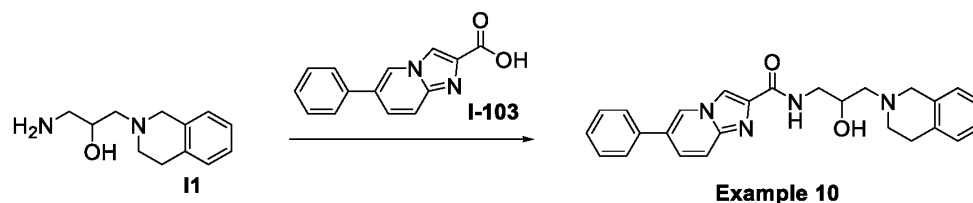
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methoxyimidazo[1,2-a]pyridine-2-carboxamide (Example 9)



[000257] 25%). ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 8.246 – 8.241 (m, 1H), 8.21 (s, 1H), 8.19 – 8.16 (m, 1H), 7.40 (d, $J = 8$ Hz, 1H), 7.10 – 7.04 (m, 4H), 7.00 – 6.99 (m,

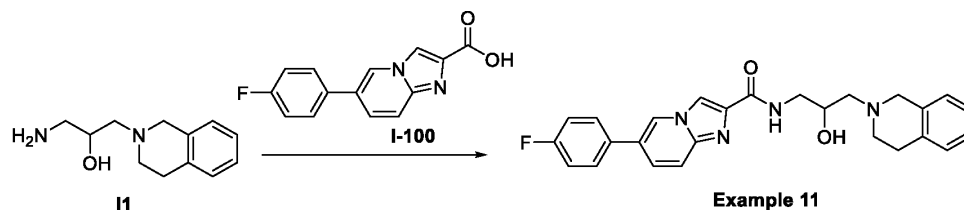
1H), 4.91 (d, $J = 8$ Hz, 1H), 3.90 – 3.86 (m, 1H), 3.77 (s, 3H), 3.58-3.60 (m, 2H), 3.48 – 3.41 (m, 1H), 3.30 – 3.24 (m, 1H) (1 proton is merged with water/DMSO peak), 2.88 – 2.82 (m, 2H), 2.76 – 2.71 (m, 1H), 2.69 - 2.63 (m, 1H), 2.50-2.40 (m, 1H); MS (ESI) $m/z = 381.2$ $[M+H]^+$.

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-phenylimidazo[1,2-a]pyridine-2-carboxamide (Example 10)



[000258] To a stirred solution of 6-phenylimidazo[1,2-a]pyridine-2-carboxylic acid (**I31**, 0.1 g, 0.42 mmol) in DMF was added compound (**I1**, 0.095 g, 0.46 mmol) followed by DIPEA (0.3 mL, 1.72 mmol), HATU (0.18 g, 0.46 mmol). The reaction mixture was stirred for 16 h at room temperature. The reaction mixture was diluted with ethyl acetate, washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated. Purification was done by preparative HPLC in to afford **Example10** as white solid (0.02 g, 11%). ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 8.94 (s, 1H), 8.54 (br, 1H), 8.42 (s, 1H), 7.76 (d, $J = 9.6$ Hz, 1H), 7.69 (d, $J = 6.8$ Hz, 3H), 7.50 (t, $J = 7.6$ Hz, 2H), 7.44 – 7.38 (m, 1H), 7.29-7.20 (m, 3H), 7.18-7.14 (m, 1H), 4.92 (d, $J = 5.2$ Hz, 1H), 4.58-4.47 (m, 2H), 4.40-4.30 (m, 1H), 4.27-4.17 (m, 1H), 3.45-3.38 (m, 3H), 3.36–3.28 (m, 1H), 3.24–3.12 (m, 2H), 3.11-2.94 (m, 2H); MS (ESI) $m/z = 427.2$ $[M+H]^+$.

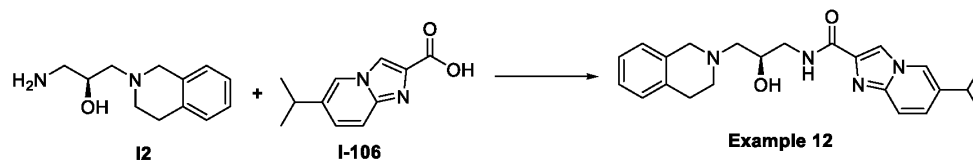
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 11)



[000259] 15%). ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 8.90 (br, 1H), 8.33-8.26 (m, 2H), 7.77-7.71 (m, 2H), 7.66 (d, $J = 9.2$ Hz, 1H), 7.57 (d, $J = 9.2$ Hz, 1H), 7.34 (t, $J = 8.6$ Hz, 2H), 7.11-7.05 (m, 3H), 7.04-6.99 (m, 1H), 4.93 (d, $J = 4.4$ Hz, 1H), 3.94-3.87 (m,

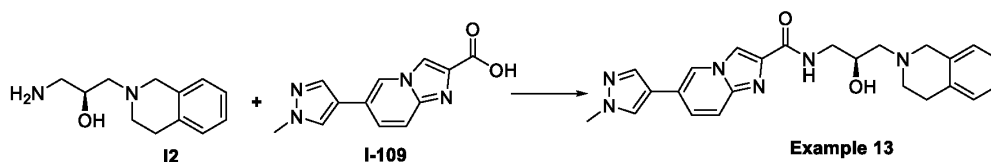
1H), 3.58-3.62 (m, 2H), 3.66-3.58 (m, 2H), 3.51-3.44 (m, 1H), 3.36-3.23 (m, 1H), 2.87-2.81 (m, 3H), 2.79-2.73 (m, 2H), 2.72-2.64 (m, 1H); MS (ESI) $m/z = 445.2$ $[M+H]^+$.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-isopropylimidazo[1,2-a]pyridine-2-carboxamide (Example 12)



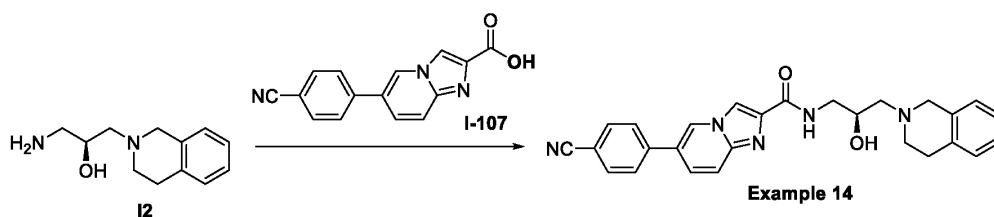
[000260] , 7%). ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 8.38 (s, 1H), 8.24 (bs, 2H), 7.43 (d, $J = 9.2$ Hz, 1H), 7.30 (d, $J = 8.8$ Hz, 1H), 7.11-7.04 (m, 3H), 7.03-6.98 (m, 1H), 4.92 (s, 1H), 3.89 (bs, 1H), 3.68-3.57 (m, 2H), 3.50-3.40 (m, 3H), 2.96-2.88 (m, 1H), 2.87-2.80 (m, 2H), 2.79-2.72 (m, 2H), 2.70-2.62 (m, 1H), 1.23 (d, $J = 5.6$ Hz, 6H); MS (ESI) $m/z = 393.1$ $[M+H]^+$.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 13)



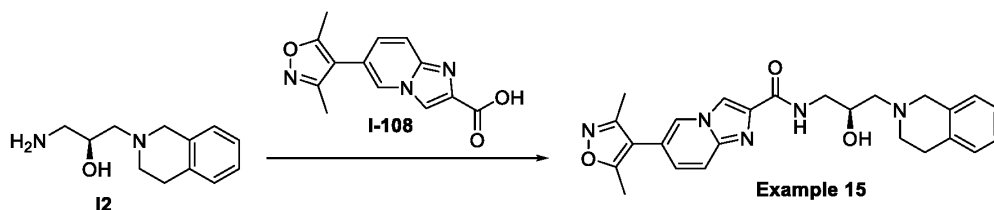
[000261] 22%). ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 8.21 (s, 1H), 8.13 (s, 1H), 7.85 (bs, 1H), 7.73 (s, 1H), 7.62 (s, 1H), 7.56 (d, $J = 9.2$ Hz, 1H), 7.35 (d, $J = 9.2$ Hz, 1H), 7.20-7.10 (m, 3H), 7.02 (d, $J = 6.8$ Hz, 1H), 4.23 (bs, 1H), 4.03 (d, $J = 14.8$ Hz, 1H), 3.97 (s, 3H), 3.87 (d, $J = 15.2$ Hz, 1H), 3.78-3.69 (m, 1H), 3.58-3.50 (m, 1H), 3.18-3.09 (m, 1H), 3.06-2.96 (m, 3H), 2.88-2.78 (m, 2H); MS (ESI) $m/z = 431.2$ $[M+H]^+$.

(S)-6-(4-cyanophenyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 14)



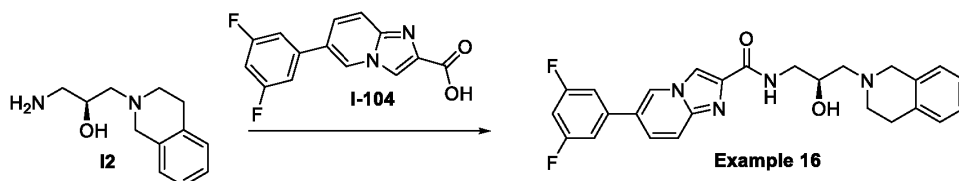
[000262] 21%). ^1H NMR (CDCl_3-d_6 , 400 MHz, ppm): δ 8.37 (s, 1H), 8.22 (s, 1H), 7.92 (bs, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.68 (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 9.2$ Hz, 1H), 7.28-7.24 (m, 2H), 7.21-7.12 (m, 3H), 7.04 (d, $J = 7.2$ Hz, 1H), 4.29 (bs, 1H), 4.10 (d, $J = 14.8$ Hz, 1H), 3.94 (d, $J = 14.8$ Hz, 1H), 3.80-3.72 (m, 1H), 3.60-3.51 (m, 1H), 3.24-3.16 (m, 1H), 3.12-3.02 (m, 3H), 2.94-2.82 (m, 2H); MS (ESI) $m/z = 452.2[\text{M}+\text{H}]^+$.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(3,5-dimethylisoxazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 15)



[000263] 19.29%). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz, ppm): δ 8.64 (s, 2H), 8.30 (s, 1H), 7.57 (d, $J = 8$ Hz, 1H), 7.36 (d, $J = 8.8$ Hz, 1H), 7.06-7.08 (m, 2H), 6.99 – 6.97 (m, 1H), 4.95 – 4.94 (m, 1H), 3.91–3.90 (m, 1H), 3.61 (s, 2H), 3.57 – 3.44 (m, 1H), (1 protons are merged with water-DMSO peak)2.83(bs, 2H), 2.48 (s, 4H), 2.25 (s, 3H); MS (ESI) $m/z = 446.2 [\text{M}+\text{H}]^+$.

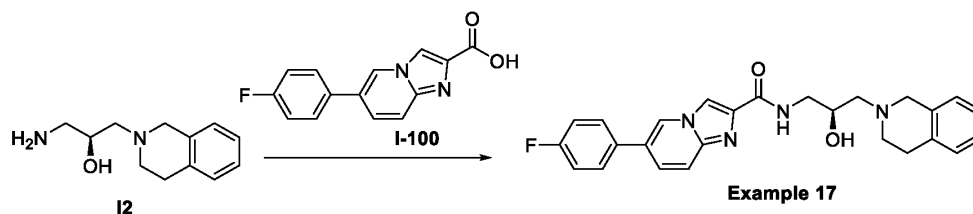
(S)-6-(3,5-difluorophenyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 16)



[000264] , 9%). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz, ppm): δ 8.65-8.34 (m, 2H), 7.73 (d, 1H, $J = 8$ Hz), 7.61 (d, 1H, $J = 12$ Hz), 7.51 (d, 2H, $J = 8.1$ Hz), 7.30-7.25 (m, 1H), 7.12-

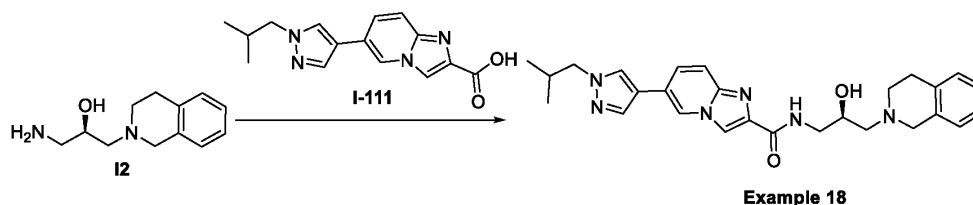
7.04 (m, 3H), 7.02-6.98 (m, 1H), 4.85-4.81 (m, 1H), 3.85-3.79 (m, 1H), 3.68-3.58 (m, 2H), 3.51-3.42 (m, 1H), 3.34-3.25 (m, 1H), 2.88-2.80 (m, 2H), 2.78-2.72 (m, 1H), 2.71-2.62 (m, 1H); MS (ESI) $m/z = 445.2$ $[M+H]^+$.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 17)



[000265] 10%). ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 8.90 (s, 1H), 8.33-8.26 (m, 2H), 7.78-7.71 (m, 2H), 7.66 (d, $J = 9.6$ Hz, 1H), 7.57 (d, $J = 9.6$ Hz, 1H), 7.34 (t, $J = 8.8$ Hz, 2H), 7.13-7.05 (m, 3H), 7.03-6.98 (m, 1H), 4.94 (d, $J = 4.4$ Hz, 1H), 3.98-3.86 (m, 1H), 3.68-3.58 (m, 2H), 3.50-3.42 (m, 2H), 3.36-3.24 (m, 1H), 2.84 (s, 2H), 2.80-2.72 (m, 1H), 2.70-2.62 (m, 2H); MS (ESI) $m/z = 445.2$ $[M+H]^+$.

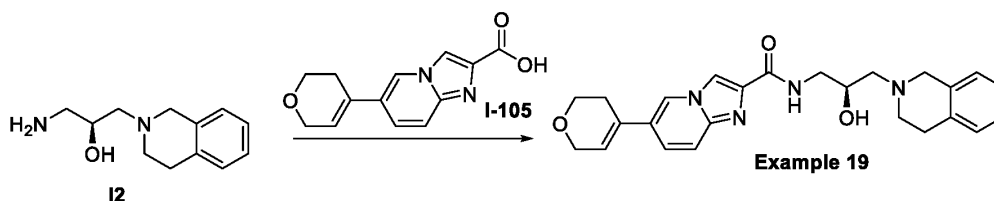
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-isobutyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 18)



[000266] To a stirred solution of 6-(1-isobutyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxylic acid (**I39**, 0.10 g, 0.35 mmol) in DCM (10 mL) was added compound **12** (0.093 g, 0.45 mmol) and triethylamine (0.16 g, 1.65 mmol). Then reaction mixture was cooled to 0°C and T₃P (0.28 g, 0.881 mmol) was added at the same temperature. The reaction mixture was then stirred at RT for 3 h. After completion of reaction, the reaction mixture was washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography with silica-gel column using methanol in DCM as the eluent to afford **Example 18** as an off white solid. Yield: 15.5 mg (9 %). ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 8.80 (s, 1H), 8.27 (bs, 1H), 8.22 (s, 1H), 8.18 (s, 1H), 7.87 (s, 1H), 7.58-7.49 (m, 2H), 7.09 (s, 3H), 7.02 (s, 1H), 4.94 (bs, 1H),

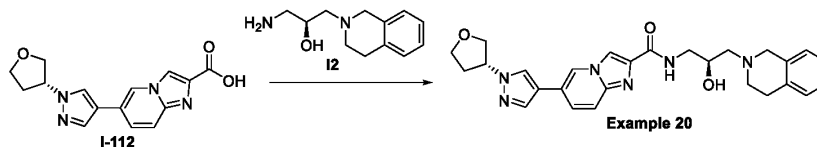
3.93 (d, $J = 6.8$ Hz, 3H), 3.63 (s, 2H), 3.49-3.43 (m, 1H), 2.84 (s, 4H), 2.16-2.09 (m, 2H), 0.85 (d, $J = 6$ Hz, 6H) (3 protons are merged with DMSO/H₂O peak); MS (ESI) $m/z = 473.3$ [M+H]⁺.

(S)-6-(3,6-dihydro-2H-pyran-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 19)



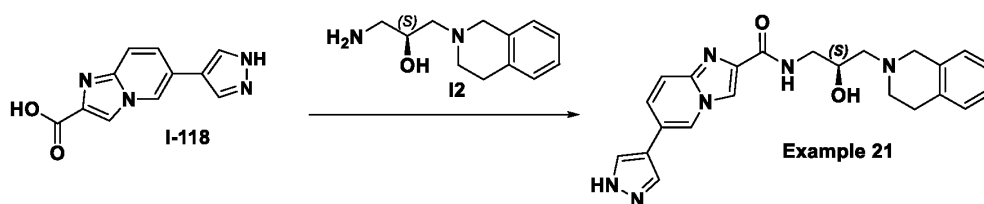
[000267] (3.2%). ¹H NMR (CD₃OD-*d*₆, 400 MHz, ppm): δ 8.44 (s, 1H), 8.21 (s, 1H), 7.62-7.57 (m, 1H), 7.44 (d, 1H, $J = 9.6$ Hz), 7.10-7.07 (m, 3H), 7.01 (d, 1H, $J = 6.8$ Hz), 4.32 (s, 2H), 4.13-4.10 (m, 1H), 3.94 (t, 2H, $J = 10.4$ Hz), 3.78 (s, 2H), 3.62-3.58 (m, 1H), 3.52-3.47 (m, 1H), 2.93-2.91 (m, 3H), 2.72-2.71 (m, 2H), 1.44-1.40 (m, 1H), 1.34-1.28 (m, 1H), 0.94-0.89 (m, 1H). MS (ESI) $m/z = 433.2$ [M+H]⁺.

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 20)



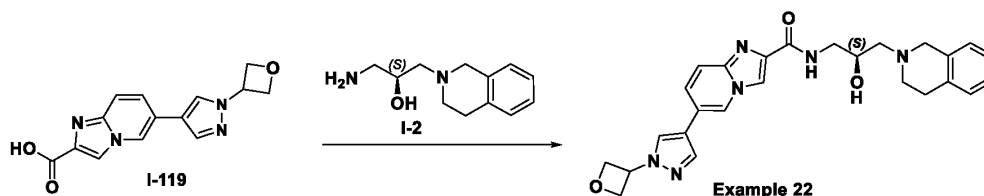
[000268] (3.2%). ¹H NMR (CD₃OD, 400 MHz) δ 8.68 (s, 1H), 8.22 (s, 1H), 8.12 (s, 1H), 7.90 (s, 1H), 7.60 (d, $J = 9.6$ Hz, 1H), 7.49 (d, $J = 9.2$ Hz, 1H), 7.08-7.06 (m, 3H), 7.01-7.00 (m, 1H), 5.09-5.06 (m, 1H), 4.17-4.11 (m, 2H), 4.09-4.06 (m, 2H), 3.95-3.90 (m, 1H), 3.74 (s, 2H), 3.63-3.58 (m, 1H), 3.52-3.47 (m, 1H), 2.93-2.91 (m, 2H), 2.88-2.87 (m, 2H), 2.68-2.64 (m, 2H), 2.53-2.47 (m, 1H), 2.40-2.36 (m, 1H); MS (ESI) $m/z = 487.2$ [M+H]⁺.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 21)



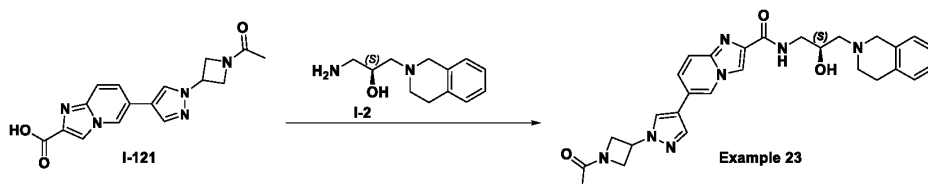
[000269] ^1H NMR (DMSO- d_6 , 400 MHz, ppm)- δ 13.05 (s, 1H), 8.84 (s, 1H), 8.29-8.23 (m, 3H), 7.94 (bs, 1H), 7.63 (d, 1H, $J = 9.96$ Hz), 7.52 (d, 1H, $J = 9.36$ Hz), 7.11-7.04 (m, 4H), 4.97 (bs, 1H), 3.93 (s, 1H), 3.64 (s, 1H), 3.48-3.45 (m, 2H), 3.40-3.30 (m, 2H), 2.86-2.77 (m, 5H). MS (ES) m/z : 417.12 $[\text{M}+\text{H}]^+$

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 22)



[000270] ^1H NMR (DMSO- d_6 , 400 MHz, ppm)- δ 8.86 (s, 1H), 8.43 (s, 1H), 8.3 (bs, 1H), 8.25 (s, 1H), 8.05 (s, 1H), 7.62 (d, $J = 8.2$ Hz, 1H), 7.53 (d, $J = 9.3$ Hz, 1H), 7.1 (bs, 3H), 7.03 (bs, 1H), 5.61 (t, $J = 6.7$ Hz, 1H), 4.97-4.9 (m, 5H), 3.92 (d, $J = 5.0$ Hz, 1H), 3.63 (bs, 2H), 3.5-3.44 (m, 1H), 3.29 (s, 1H), 2.85 (bs, 2H), 2.75-2.66 (m, 2H). LC-MS (ES) m/z : 473.19 $[\text{M}+\text{H}]^+$.

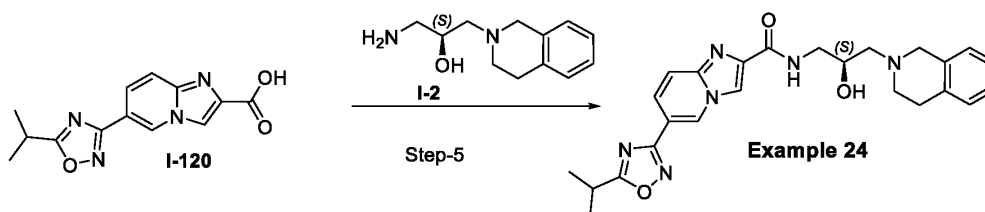
(S)-6-(1-(1-acetylazetidin-3-yl)-1H-pyrazol-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 23)



[000271] ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.82 (s, 1H), 8.89 (s, 1H), 8.57-8.52 (m, 1H), 8.46 (s, 1H), 8.31 (s, 1H), 8.05 (s, 1H), 7.64 (s, 1H), 7.26-7.19 (m, 4H), 5.92 (bs, 1H), 5.31-5.25 (m, 1H), 4.62-4.52 (m, 2H), 4.43-4.30 (m, 3H), 4.23-4.11 (m,

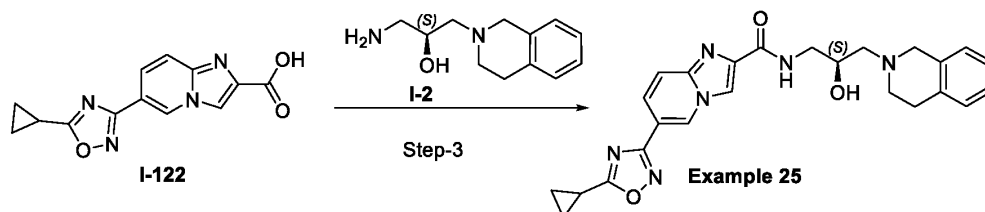
2H), 3.55-3.43 (m, 3H), 3.32-2.94 (m, 5H), 1.83 (s, 3H). LC-MS (ES) m/z : 514.26 $[M+H]^+$.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-isopropyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 24)



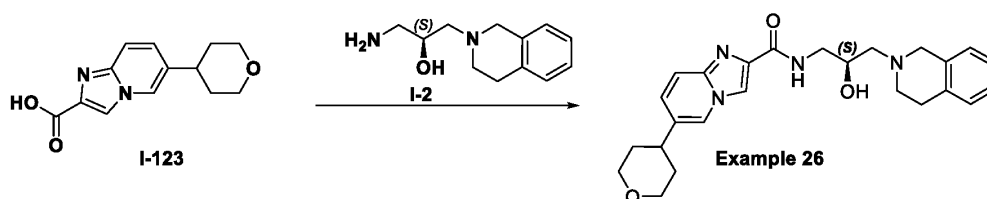
[000272] ^1H NMR (DMSO- d_6 , 400 MHz, ppm)- δ 9.79 (bs, 1H), 9.40 (s, 1H), 8.60 (bs, 2H), 7.85 (dd, $J = 9.4, 1.2$ Hz, 1H), 7.76 (d, $J = 9.4$ Hz, 1H), 7.28-7.17 (m, 4H), 5.9 (bs, 1H), 4.6-4.52 (m, 2H), 4.43-4.33 (m, 2H), 4.25 (bs, 2H), 3.75-3.69 (m, 1H), 3.43-3.36 (m, 2H), 3.23-3.19 (m, 1H), 3.06-3.02 (m, 1H), 1.4 (d, $J = 6.9$ Hz, 6H). LC-MS (ES) m/z : 461.16 $[M+H]^+$.

(S)-6-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 25)



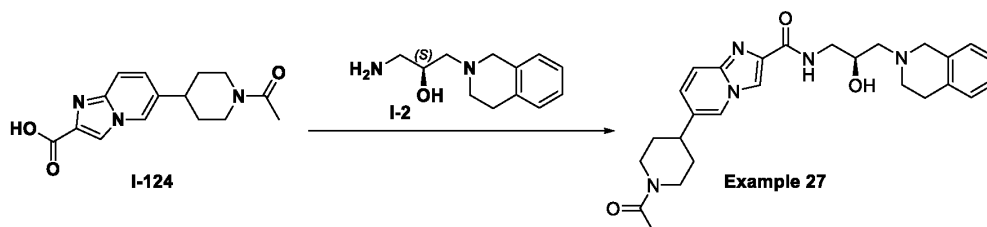
[000273] ^1H NMR (400 MHz, DMSO- d_6) δ 9.31 (s, 1H), 8.52 (s, 1H), 8.36 (t, $J = 5.4$ Hz, 1H), 7.77 (dd, $J = 9.4, 1.3$ Hz, 1H), 7.63 (d, $J = 9.4$ Hz, 1H), 7.1-7.01 (m, 4H), 4.95 (d, $J = 3.8$ Hz, 1H), 3.91 (d, $J = 4.8$ Hz, 1H), 3.62 (bs, 2H), 3.49-3.43 (m, 1H), 3.35-3.31 (m, 1H), 2.84 (s, 2H), 2.85-2.66 (m, 3H), 2.41-2.35 (m, 2H), 1.35-1.3 (m, 2H), 1.23-1.19 (m, 2H). LC-MS (ES) m/z = 459.14 $[M+H]^+$.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example-26)



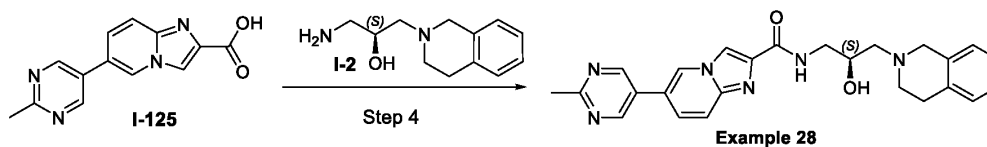
[000274] ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.42 (s, 1H), 8.26 (s, 2H), 7.46 (d, J = 8.96 Hz, 1H), 7.33 (d, J = 9.20 Hz, 1H), 7.12-7.05 (m, 4H), 4.99 (bs, 1H), 3.99-3.96 (dd, J = 7.28 Hz, 3.32 Hz, 3H), 3.78 (bs, 2H), 3.53-3.39 (m, 4H), 3.05-2.66 (m, 7H), 1.80 (d, J = 11.40 Hz, 2H), 1.74-1.64 (m, 2H). LC-MS (ES) m/z : 435.19 $[\text{M}+\text{H}]^+$.

(S)-6-(1-acetylpiperidin-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 27)



[000275] ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.40 (s, 1H), 8.24 (s, 1H), 8.17 (bs, 1H), 7.48 (d, 1H, J = 9.44 Hz), 7.31 (d, 1H, 9.36 Hz), 7.18-7.04 (m, 4H), 5.16 (bs, 1H), 4.54 (m, 4H), 3.52-3.41 (m, 1H), 3.40-3.38 (m, 1H), 3.05-3.00 (m, 3H), 3.00-2.87 (m, 3H), 2.86-2.76 (m, 3H), 2.73-2.66 (m, 1H), 2.08 (s, 3H), 1.69-1.49 (m, 2H). LC-MS (ES) m/z : 476.18 $[\text{M}+\text{H}]^+$.

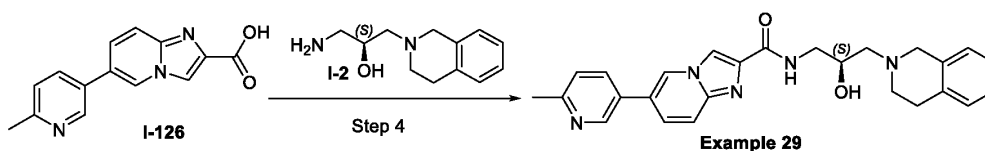
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2-methylpyrimidin-5-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 28)



[000276] ^1H NMR (400 MHz, DMSO- d_6) δ 9.07 (m, 2H), 8.34 (m, 2H), 7.77 (dd, J_{1-3} = 9.4 Hz, J_{1-2} = 1.4 Hz, 1H), 7.64 (d, J = 9.4 Hz, 1H), 7.09 (m, 3H), 7.03 (bs, 1H),

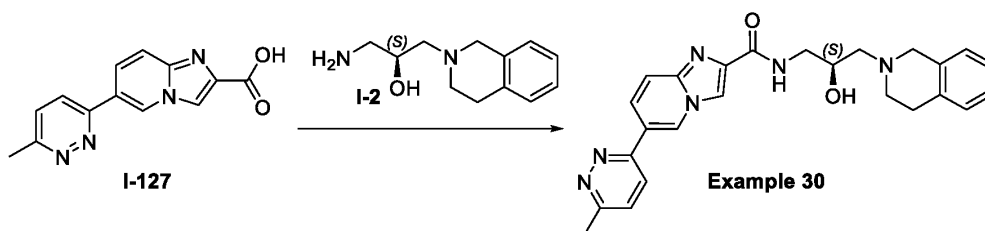
4.96 (d, $J = 4.6$ Hz, 1H), 3.92 (m, 1H), 3.63 (s, 2H), 3.48 (m, 1H), 3.35 (m, 1H), 2.85 (bs, 2H), 2.76 (m, 1H), 2.68 (bs, 5H), 2.54 (m, 1H). LC-MS (ES) $m/z = 443.14$ $[M+H]^+$.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(6-methylpyridin-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 29)



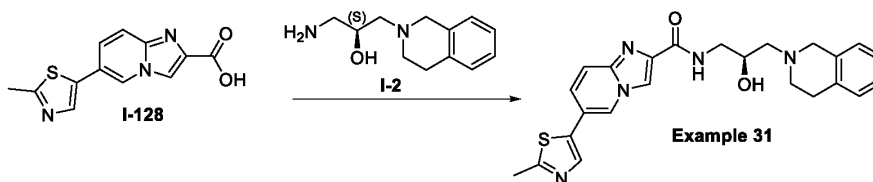
[000277] ^1H NMR (400 MHz, DMSO- d_6) δ 8.99 (s, 1H), 8.8 (d, $J = 1.9$ Hz, 1H), 8.32 (bs, 2H), 8.01 (dd, $J_{1-3} = 8.0$ Hz, $J_{1-2} = 2.2$ Hz, 1H), 7.71 (dd, $J_{1-3} = 9.4$ Hz, $J_{1-2} = 1.4$ Hz, 1H), 7.61 (d, $J = 9.4$ Hz, 1H), 7.39 (d, $J = 8.1$ Hz, 1H), 7.09 (m, 3H), 7.02 (bs, 1H), 5.0 (bs, 1H), 3.92 (t, $J = 5.6$ Hz, 1H), 3.63 (s, 2H), 3.5 (m, 1H), 3.35 to 3.25 (m, 3H), 2.85 (bs, 1H), 2.75-2.68 (m, 2H), 2.53 (s, 3H). LC-MS (ES) $m/z = 442.16$ $[M+H]^+$.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(6-methylpyridazin-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 30)



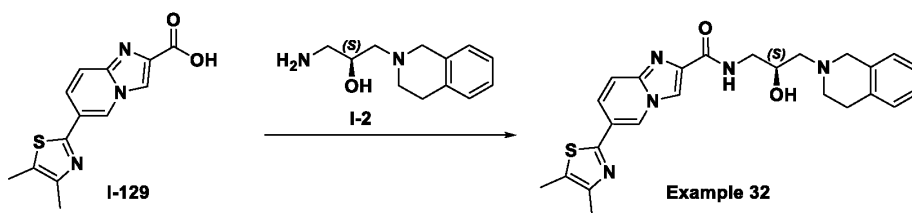
[000278] ^1H NMR (400 MHz, DMSO- d_6) δ 9.46 (s, 1H), 8.45 (s, 1H), 8.4 (s, 1H), 8.16 (d, $J = 8.7$ Hz, 1H), 8.1 (d, $J = 9.6$ Hz, 1H), 7.73 (d, $J = 8.8$ Hz, 1H), 7.68 (d, $J = 9.2$ Hz, 1H), 7.1 (m, 4H), 5.0 (bs, 1H), 3.98 (bs, 1H), 3.66 (bs, 2H), 3.5-3.3 (m, 4H), 2.89 (bs, 4H), 2.69 (s, 3H). LC-MS (ES) $m/z = 443.23$ $[M+H]^+$.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2-methylthiazol-5-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 31)



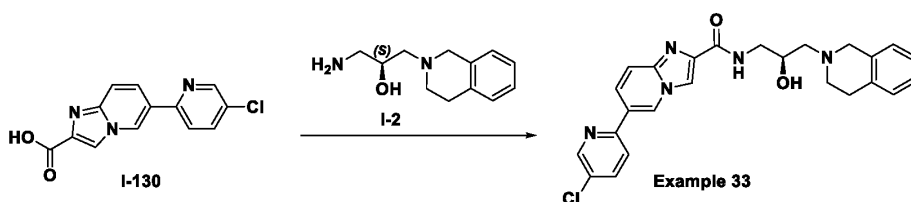
[000279] Yield: 0.05 g (8.2%); ^1H NMR (400 MHz, DMSO- d_6) δ 8.89 (s, 1H), 8.32 (bs, 2H), 8.29 (s, 1H), 8.08 (s, 1H), 7.67 (d, $J = 9.4$ Hz, 1H), 7.56 (d, $J = 9.4$ Hz, 1H), 7.1 (bs, 3H), 7.02 (bs, 1H), 4.98 (bs, 1H), 3.92 (bs, 1H), 3.64 (bs, 2H), 3.49-3.43 (m, 1H), 3.32 (bs, 2H), 2.85 (bs, 2H), 2.79-2.77 (m, 2H), 2.7-2.66 (m, 4H). LC-MS (ES) $m/z = 448$ $[\text{M}+\text{H}]^+$.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4,5-dimethylthiazol-2-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 32)



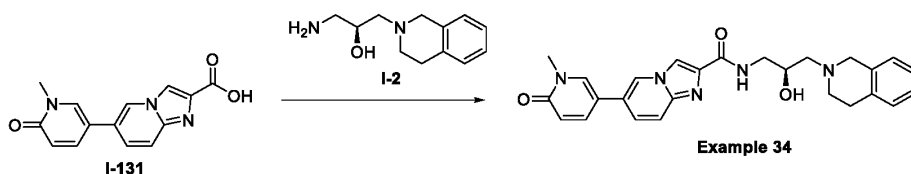
[000280] LC-MS (ES) m/z : 462.16 $[\text{M}+\text{H}]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm)- δ 9.19 (s, 1H), 8.43 (s, 1H), 8.32 (dd, 1H, $J = 11.0$ Hz, $J = 5.64$), 7.74 (d, 1H, $J = 9.44$ Hz), 7.57 (d, 1H, $J = 9.48$ Hz), 7.10-7.01 (m, 4H), 4.95 (bs, 1H), 3.92 (bs, 1H), 3.67 (s, 2H), 3.44-3.50 (m, 1H), 3.44-3.30 (m, 1H), 2.84-2.79 (m, 2H), 2.71-2.68 (m, 1H), 2.67-2.71 (m, 1H), 2.50-2.41 (m, 2H), 2.41 (s, 3H) 2.33 (s, 3H).

(S)-6-(5-chloropyridin-2-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 33)



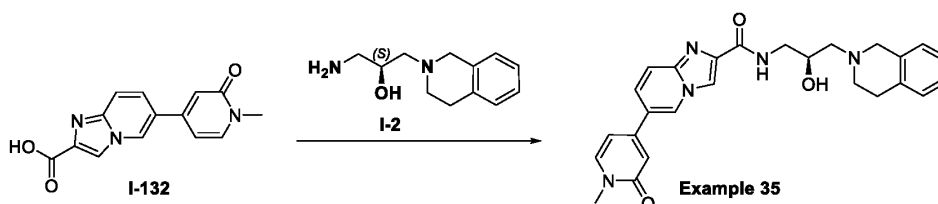
[000281] LC-MS (ES) m/z : 462.10 $[\text{M}+\text{H}]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.41 (s, 1H), 8.74 (d, 1H, $J = 2.0$ 8Hz), 8.58 (bs, 1H), 8.49 (s, 1H), 8.12-8.05 (m, 3H), 7.71 (d, 1H, $J = 9.48$ Hz), 7.28-7.17 (m, 4H), 5.93 (bs, 1H), 4.61-4.52 (m, 1H), 4.43-4.34 (m, 1H), 4.33-4.24 (m, 1H), 3.75-3.69 (m, 1H), 3.44-3.33 (m, 3H), 3.24-3.21 (m, 2H), 3.07-2.98 (m, 2H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 34)



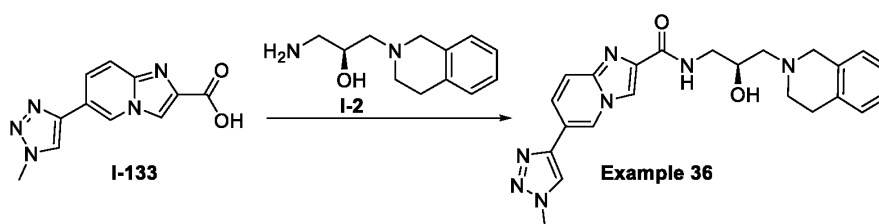
[000282] LC-MS (ES) m/z = 458.17 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.81 (s, 1H), 8.38 (s, 1H), 8.29 (s, 1H), 8.19 (d, J = 2.4 Hz, 1H), 7.81 (dd, J_{1-3} = 9.4 Hz, J_{1-2} = 2.6 Hz, 1H), 7.6 (s, 2H), 7.12 (bs, 4H), 6.53 (d, J = 9.4 Hz, 1H), 4.02 (bs, 4H), 3.51 (s, 3H), 3.47 (m, 1H), 3.4 (m, 2H), 2.92 (bs, 5H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 35)



[000283] LC-MS (ES) m/z : 458.16 $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.10 (s, 1H), 8.34-8.31 (m, 2H), 7.83 (d, J = 7.12 Hz, 1H), 7.70 (d, J = 1.52 Hz, 1H), 7.57 (d, J = 9.52 Hz, 1H), 7.10-7.09 (m, 3H), 7.03 (d, J = 5.28 Hz, 1H), 6.78 (s, 1H), 6.61 (d, J = 1.84 Hz, 1H), 4.96 (bs, 1H), 3.93 (d, J = 4.84 Hz, 1H), 3.63 (s, 2H), 3.49-3.46 (m, 6H), 2.84-2.76 (m, 5H).

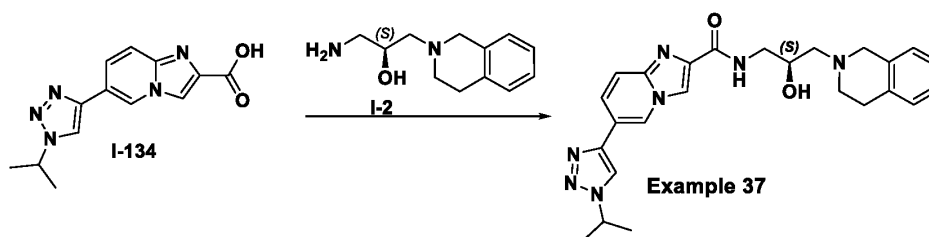
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 36)



[000284] LC-MS (ES) m/z : 432.11 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.12 (s, 1H), 8.56 (s, 1H), 8.42 (s, 1H), 8.31 (t, J = 5.2 Hz, 1H), 7.74 (d, J = 9.4 Hz, 1H), 7.6 (d, J = 9.4 Hz, 1H), 7.09 (bs, 3H), 7.02 (bs, 1H), 4.96 (d, J = 4.6 Hz, 1H), 4.12

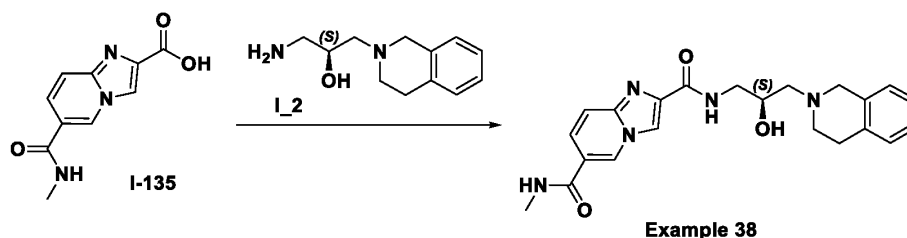
(s, 3H), 3.92-3.91 (m, 1H), 3.62 (bs, 2H), 3.49-3.46 (m, 1H), 3.32 (bs, 1H), 2.84 (bs, 2H), 2.77-2.72 (m, 1H), 2.71-2.66 (m, 1H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-isopropyl-1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 37)



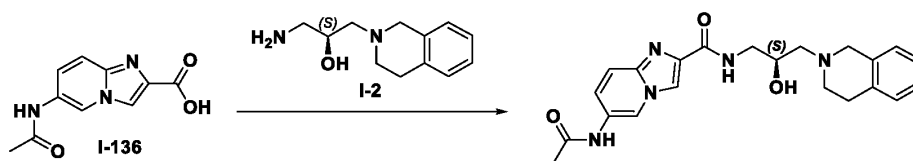
[000285] LC-MS (ES) m/z : 432.39 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm)- δ 9.12 (s, 1H), 8.718 (s, 1H), 8.42 (s, 1H), 8.312 (t, $J=5.2$ Hz, 1H), 7.75 (d, $J = 9.44$ Hz, 1H), 7.60 (d, $J = 9.4$ Hz, 1H), 7.10-7.01 (m, 4H), 4.95 (d, $J=4.6$ Hz, 1H), 4.91-4.84 (m, 1H), 3.94-3.90 (m, 1H), 3.59 (s, 2H), 3.49-3.44 (m, 2H), 2.84-2.70 (m, 5H), 2.18-2.15 (m, 1H), 1.55 (d, $J = 6.68$ Hz, 6H).

(S)-N2-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N6-methylimidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 38)



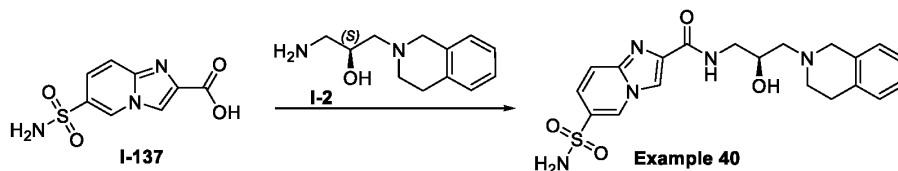
[000286] LC-MS (ES) m/z : 408.01 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.11 (s, 1H), 8.59 (dd, $J = 4.08$ Hz, 1H), 8.45 (s, 1H), 8.35 (d, $J = 4.92$ Hz, 1H), 7.70 (d, $J = 9.44$ Hz, 1H), 7.53 (d, $J = 9.44$ Hz, 1H), 7.09-7.01 (m, 4H), 4.95 (d, $J = 4.0$ Hz, 1H), 3.91 (d, $J = 4.96$ Hz, 1H), 3.66-3.58 (m, 2H), 3.49-3.45 (m, 1H), 3.32 (s, 3H), 2.84-2.80 (m, 1H), 2.77-2.73 (m, 3H), 2.69-2.50 (m, 3H).

(S)-6-acetamido-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 39)

**Example 39**

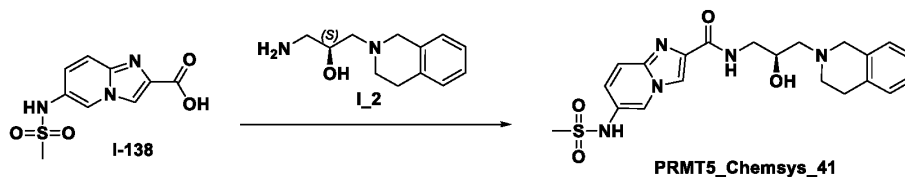
[000287] LC-MS (ES) m/z : 406.14 $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm)-
 δ 10.11 (s, 1H), 9.24 (s, 1H), 8.42 (s, 1H), 8.27 (bs, 1H), 7.50 (d, $J = 9.56$ Hz, 1H), 7.22
 (d, $J = 9.64$ Hz, 1H), 7.13-7.07 (m, 4H), 5.01 (bs, 1H), 3.97-3.42 (m, 5H), 2.89-2.66 (m,
 5H), 2.08 (s, 3H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-sulfamoylimidazo[1,2-a]pyridine-2-carboxamide (Example 40)

**Example 40**

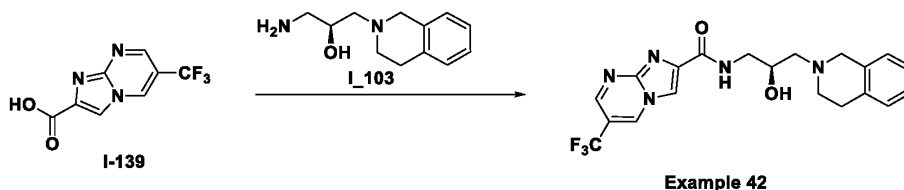
[000288] LC-MS (ES) m/z = 430.17 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ
 9.18 (s, 1H), 8.54 (s, 1H), 8.37 (bs, 1H), 7.68-7.59 (m, 4H), 7.09 (bs, 3H), 7.02 (bs, 1H),
 4.96 (bs, 1H), 3.92 (bs, 1H), 3.62 (bs, 2H), 3.48-3.45 (m, 1H), 2.84 (bs, 2H), 2.78-2.69
 (m, 4H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(methylsulfonylamido)imidazo[1,2-a]pyridine-2-carboxamide (Example 41)

**PRMT5_Chemsys_41**

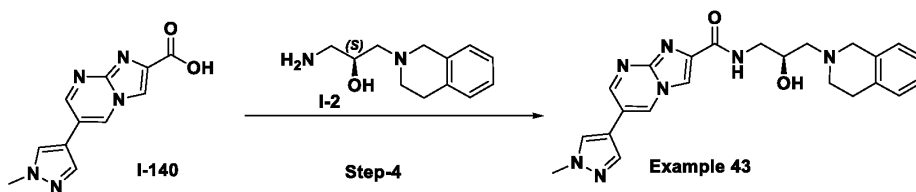
[000289] LC-MS (ES) m/z : 444.15 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm)
 δ 9.77 (s, 1H), 8.50 (s, 1H), 8.40 (s, 1H), 8.28 (bs, 1H), 7.51 (d, $J = 9.64$ Hz, 1H), 7.22
 (d, $J = 8.68$ Hz, 1H), 7.11-7.04 (m, 4H), 4.99 (bs, 1H), 3.92 (bs, 1H), 3.65 (bs, 2H), 3.47-
 3.42 (m, 1H), 3.32-3.30 (m, 1H), 3.04 (s, 3H), 2.85-2.58 (m, 6H).

((S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyrimidine-2-carboxamide (Example 42)



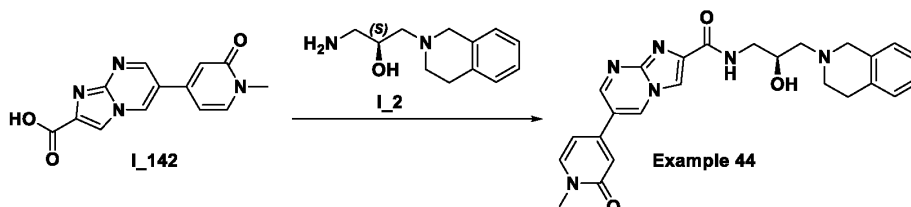
[000290] LC-MS (ES) m/z : 420.21 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.66 (s, 1H), 8.97 (d, J = 2.36Hz, 1H), 8.47 (dd, J = 12.04 Hz, 6.04Hz, 1H), 8.35 (s, 1H), 7.08-7.02 (m, 4H), 4.97 (bs, 1H), 3.94 (bs, 1H), 3.63 (bs, 2H), 3.53-3.47 (m, 1H), 3.32-3.25 (m, 1H), 2.82-2.66 (m, 6H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrimidine-2-carboxamide (Example 43)



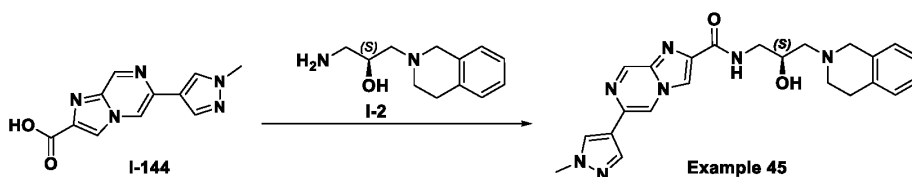
[000291] LC-MS (ES) m/z : 433.25 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.20 (d, J = 2.0 Hz, 1H), 8.95 (d, J = 2.24 Hz, 1H), 8.68 (bs, 1H), 8.26 (d, J = 11.0 Hz, 2H), 7.96 (s, 1H), 7.28-7.09 (m, 4H), 5.92 (bs, 1H), 4.61-4.56 (m, 1H), 4.52-4.39 (m, 1H), 4.25 (bs, 1H), 3.91 (s, 3H), 3.76-3.69 (m, 1H), 3.40 (m, 2H), 3.24-3.21 (m, 1H), 3.07-2.98 (m, 4H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrimidine-2-carboxamide (Example 44)



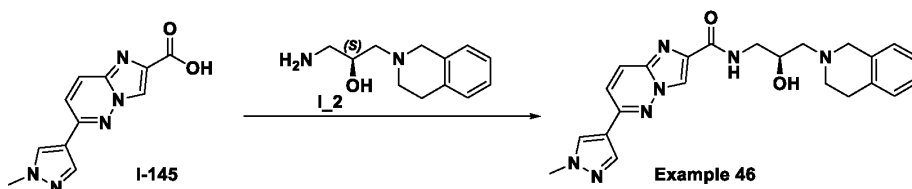
[000292] LC-MS (ES) m/z : 459.26 $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.46 (s, 1H), 9.03 (d, J = 1.96 Hz, 1H), 8.39 (bs, 1H), 8.25 (s, 1H), 7.88 (d, J = 7.08 Hz, 1H), 7.08-7.02 (m, 4H), 6.89 (s, 1H), 6.65 (d, J = 6.96 Hz, 1H), 4.95 (d, J = 4.56 Hz, 1H), 3.94 (d, J = 5.92 Hz, 1H), 3.62 (d, J = 3.16 Hz, 2H), 3.57-3.47 (m, 5H), 3.31-3.26 (m, 2H), 2.82-2.68 (m, 4H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 45)



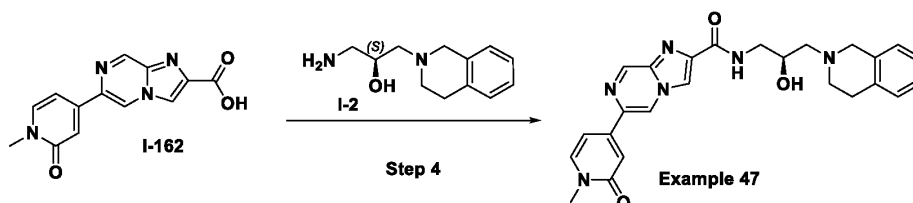
[000293] LC-MS (ES) m/z : 432.17 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.98 (s, 1H), 8.85 (s, 1H), 8.48 (dd, J = 12.24 Hz, J = 5.24 Hz, 1H), 8.37 (s, 1H), 8.20 (s, 1H), 7.92 (s, 1H), 7.10-7.00 (m, 4H), 4.97 (d, J = 3.72 Hz, 1H), 3.94-3.91 (m, 1H), 3.90 (s, 3H), 3.67-3.62 (m, 2H), 3.58-3.43 (m, 1H), 3.37-3.31 (m, 1H), 2.88-2.83 (m, 2H), 2.79-2.67 (m, 2H), 2.57-2.49 (m, 2H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 46)



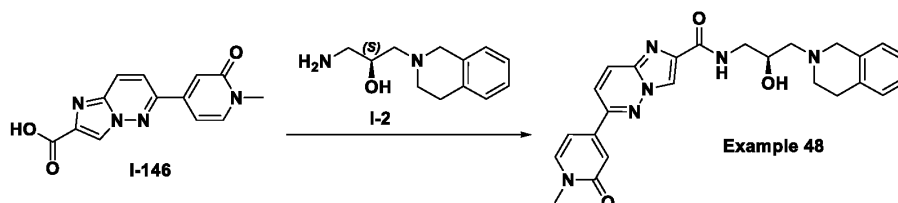
[000294] LC-MS (ES) m/z : 432.16 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.47 (d, J = 6.60 Hz, 2H), 8.35 (dd, J = 10.24 Hz, 1H), 8.09 (s, 1H), 8.02 (d, J = 9.56 Hz, 1H), 7.66 (d, J = 9.56 Hz, 1H), 7.10-7.01 (m, 4H), 4.97 (d, J = 3.32 Hz, 1H), 3.92 (s, 4H), 3.66-3.59 (m, 2H), 3.51-3.45 (m, 1H), 3.34-3.29 (m, 1H), 2.84-2.79 (m, 2H), 2.75-2.67 (m, 2H), 2.56-2.49 (m, 2H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 47)



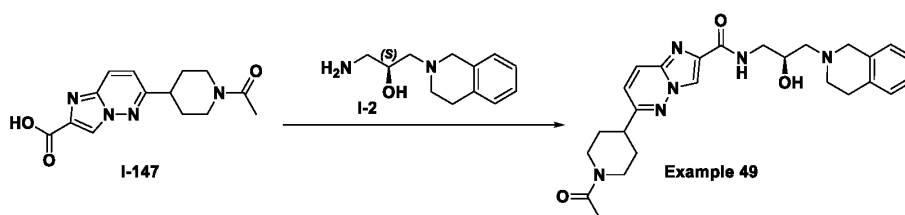
[000295] LC-MS (ES) m/z : 459.24 $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.33 (s, 1H), 9.09 (s, 1H), 8.54 (dd, J = 11.72 Hz, 5.52 Hz, 1H), 8.42 (s, 1H), 7.84 (d, J = 7.16 Hz, 1H), 7.10-7.06 (m, 4H), 7.01 (d, J = 6.7 Hz, 1H), 6.79 (dd, J = 7.12 Hz, 1.52 Hz, 1H), 4.96 (bs, 1H), 3.96-3.91 (m, 1H), 3.67-3.58 (m, 2H), 3.46 (s, 4H), 3.39-3.31 (m, 1H), 2.84 (d, J = 4.84 Hz, 2H), 2.76-2.70 (m, 2H), 2.57-2.50 (m, 2H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 48)



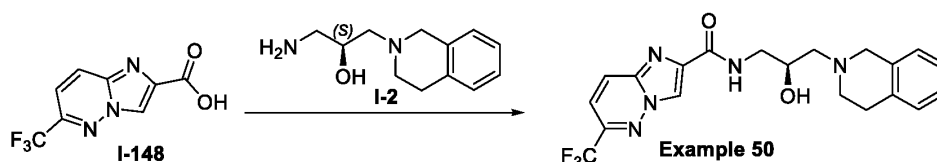
[000296] LC-MS (ES) m/z : 459.19 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm)- δ 8.69 (s, 1H), 8.43 (dd, J = 10.20 Hz, 1H), 8.15 (d, J = 9.68 Hz, 1H), 7.94 (d, J = 9.64 Hz, 1H), 7.88 (d, J = 7.04 Hz, 1H), 7.15 (s, 1H), 7.09 (s, 3H), 7.02 (d, J = 5.80 Hz, 1H), 6.88 (d, J = 6.88 Hz, 1H), 4.97 (d, J = 4.44 Hz, 1H), 3.94 (d, J = 5.52 Hz, 1H), 3.67-3.62 (m, 2H), 3.49 (s, 4H), 3.36-3.28 (m, 1H), 2.84 (d, J = 4.88 Hz, 2H), 2.79-2.69 (m, 2H), 2.54-2.5 (m, 2H).

(S)-6-(1-acetylpiperidin-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 49)



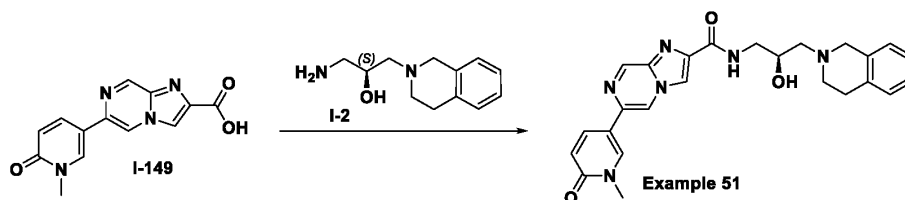
[000297] LC-MS (ES) m/z : 477.26 $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm)-
 δ 8.50 (s, 1H), 8.34 (t, J = 5.56 Hz, 1H), 7.98 (d, J = 9.56 Hz, 1H), 7.36 (d, J = 9.52 Hz, 1H), 7.09-7.01 (m, 4H), 4.96 (bs, 1H), 4.52 (d, J = 12.88 Hz, 1H), 3.95-3.92 (m, 2H), 3.62-3.57 (m, 2H), 3.49-3.44 (m, 1H), 3.31-3.07 m, 3H), 2.83-2.61 (m, 6H), 2.01 (s, 3H), 1.92 (t, J = 11.56 Hz, 2H), 1.70-1.64 (m, 1H), 1.52-1.47 (m, 1H), 1.07-1.02 (m, 1H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 50)



[000298] LC-MS (ES) m/z = 420.14 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ
 9.83 (bs, 1H), 8.96 (s, 1H), 8.74 (d, J = 4.2 Hz, 1H), 8.5 (d, J = 9.5 Hz, 1H), 7.8 (d, J = 9.5 Hz, 1H), 7.28-7.19 (m, 4H), 5.93 (bs, 1H), 4.6-4.52 (m, 1H), 4.41-4.35 (m, 1H), 4.25 (bs, 1H), 3.75-3.69 (m, 1H), 3.33 (bs, 2H), 3.24-3.21 (m, 2H), 3.06-2.98 (m, 2H).

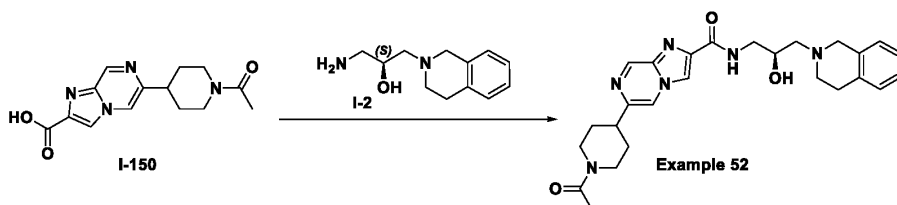
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 51)



[000299] LC-MS (ES) m/z : 459.23 $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm)
 δ 8.99 (s, 1H), 8.51 (bs, 1H), 8.43 (s, 1H), 8.39 (s, 1H), 8.01-7.98 (dd, J = 9.48 Hz, 2.04 Hz, 1H), 7.10-7.07 (m, 3H), 7.01 (d, J = 6.76 Hz, 1H), 6.55 (d, J = 9.48 Hz, 1H), 4.98

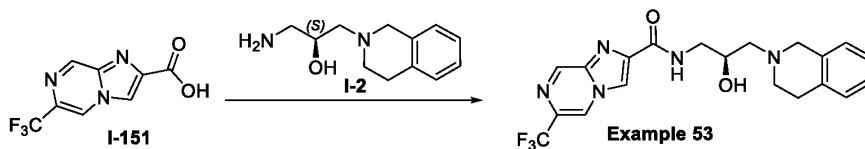
(bs, 1H), 3.93 (bs, 1H), 3.67-3.62 (m, 2H), 3.58 (s, 3H), 3.48-3.44 (m, 1H), 3.37-3.32 (m, 1H), 2.85-2.67 (m, 4H), 2.55-2.49 (m, 2H).

(S)-6-(1-acetylpiperidin-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 52)



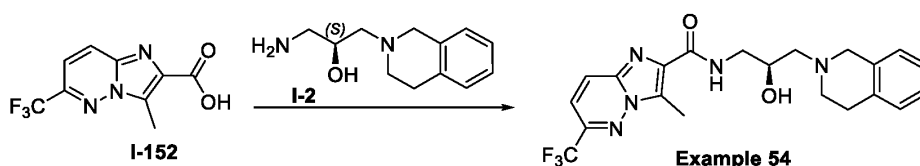
[000300] LC-MS (ES) m/z : 477.32 $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.11 (s, 1H), 8.66 (bs, 1H), 8.47 (d, J = 4.64 Hz, 2H), 7.26-7.18 (m, 4H), 5.90 (bs, 1H), 4.59-4.38 (m, 2H), 4.23 (bs, 1H), 3.95-3.92 (m, 1H), 3.75-3.68 (m, 1H), 3.34-2.92 (m, 8H), 2.66-2.62 (m, 1H), 2.03 (s, 3H), 1.96-1.89 (m, 2H), 1.69-1.61 (m, 1H), 1.61-1.49 (m, 1H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 53)



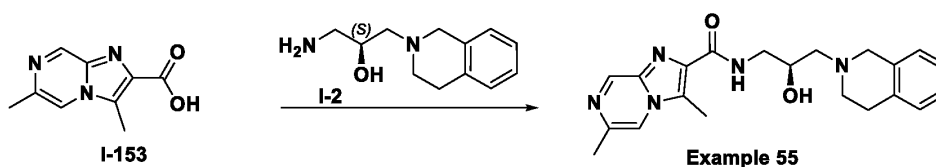
[000301] LC-MS (ES) m/z = 420.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.32 (s, 1H), 9.1 (s, 1H), 8.61 (bs, 1H), 8.56 (s, 1H), 7.1-7.0 (m, 4H), 4.97 (bs, 1H), 3.94 (bs, 1H), 3.63 (bs, 2H), 3.5-3.35 (m, 2H), 2.84 (bs, 2H), 2.76-2.63 (m, 2H), 2.54 (bs, 1H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-methyl-6-(trifluoromethyl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 54)



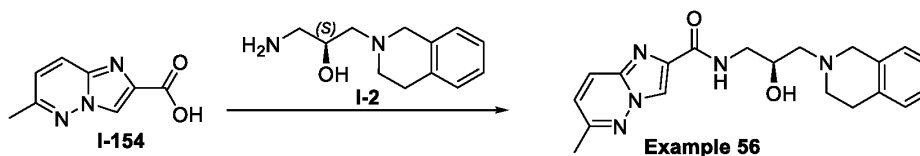
[000302] LC-MS (ES) m/z : 434.21 $[M-H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm)- δ 8.48 (t, $J=5.6$ Hz, 1H), 8.29 (d, $J=9.52$ Hz, 1H), 7.71 (d, $J=9.52$ Hz, 1H), 7.08-6.99 (m, 4H), 4.97 (d, $J=4.64$ Hz, 1H), 3.92 (t, $J=5.48$ Hz, 1H), 3.62 (d, $J=2.32$ Hz, 2H), 3.50-3.45 (m, 1H), 3.36 (t, $J=5.96$ Hz, 1H), 2.84-2.67 (m, 7H), 2.58-2.49 (m, 2H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3,6-dimethylimidazo[1,2-a]pyrazine-2-carboxamide (Example 55)



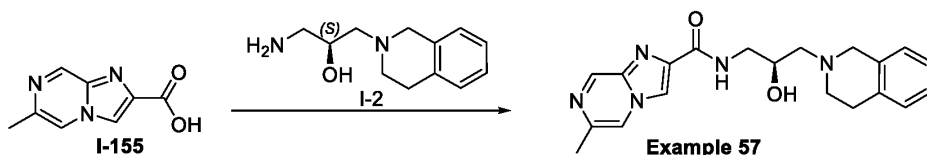
[000303] LC-MS (ES) m/z : 380.25 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm)- δ 8.83 (s, 1H), 8.43 (dd, $J=5.44$ Hz, 1H), 8.26 (s, 1H), 7.05-7.01 (m, 3H), 7.01 (d, $J=6.68$ Hz, 1H), 4.96 (d, $J=4.68$ Hz, 1H), 3.93-3.89 (m, 1H), 3.66-3.58 (m, 2H), 3.48-3.42 (m, 1H), 3.35-3.21 (m, 1H), δ 2.83 (d, $J=5.04$ Hz, 2H), 2.78-2.66 (m, 5H), 2.61-2.45 (m, 5H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methylimidazo[1,2-b]pyridazine-2-carboxamide (Example 56)



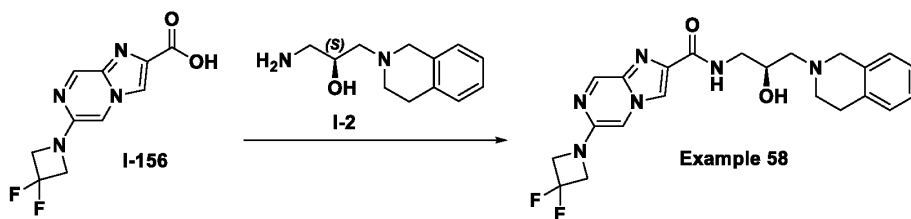
[000304] LC-MS (ES) m/z = 366.22 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.49 (s, 1H), 8.34 (t, $J=6.4$ Hz, 1H), 7.94 (d, $J=9.3$ Hz, 1H), 7.23 (d, $J=9.4$ Hz, 1H), 7.1 (bs, 3H), 7.03 (bs, 1H), 4.97 (bs, 1H), 3.93 (bs, 1H), 3.64 (bs, 2H), 3.49-3.45 (m, 1H), 2.84 (bs, 4H), 2.72 (bs, 2H), 2.53 (s, 3H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 57)



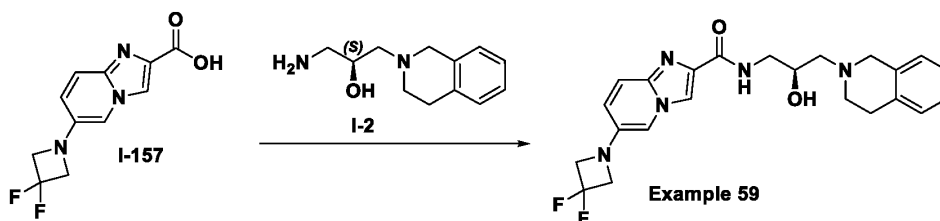
[000305] LC-MS (ES) $m/z = 366.19$ $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.91 (s, 1H), 8.47 (bs, 1H), 8.41 (s, 1H), 8.4 (s, 1H), 7.11-7.01 (m, 4H), 5.0 (bs, 1H), 3.94 (bs, 1H), 3.67 (bs, 2H), 3.48-3.42 (m, 1H), 3.37-3.34 (m, 1H), 2.85 (bs, 4H), 2.56 (bs, 2H), 2.42 (s, 3H).

(S)-6-(3,3-difluoroazetidin-1-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 58)



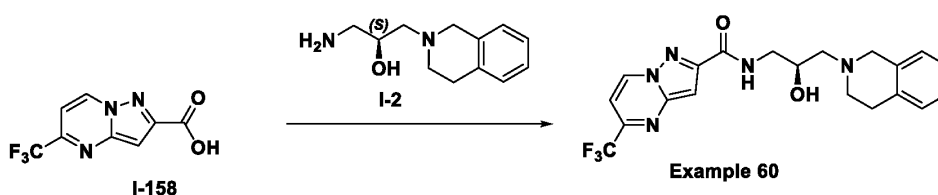
[000306] LC-MS (ES) $m/z : 443.16$ $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.78 (s, 1H), 8.41 (s, 1H), 8.32 (s, 1H), 7.88 (s, 1H), 7.10-7.00 (m, 5H), 4.96 (d, $J = 4.16$ Hz, 1H), 4.34 (t, $J = 24.6$ Hz, 12.32 Hz, 4H), 3.91 (d, $J = 5.28$ Hz, 1H), 3.66-3.62 (m, 2H), 3.48-3.28 (m, 2H), 2.84-2.49 (m, 6H).

(S)-6-(3,3-difluoroazetidin-1-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 59)



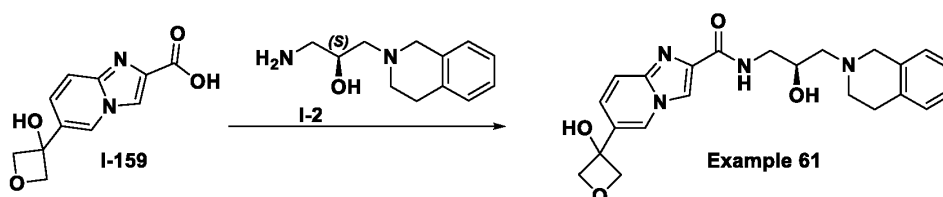
[000307] LC-MS (ES) m/z : 442.23 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.20 (dd, J = 10.96 Hz, 5.56 Hz, 1H), 8.15 (s, 1 H), 7.85 (s, 1H), 7.43 (d, J = 9.64 Hz, 1H), 7.10-7.08 (m, 4H), 7.02 (d, J = 4.56 Hz, 1H), 6.97-6.95 (dd, J = 9.72 Hz, 1.96 Hz, 1H), 4.95 (d, J = 4.12 Hz, 1H), 4.28 (t, J = 24.28 Hz, 12.16 Hz, 4H), 3.90 (d, J = 5.64 Hz, 1H), 3.66-3.62 (m, 2H), 3.48-3.44 (m, 1H), 3.31-3.26 (m, 1H), 2.83-2.69 (m, 4H), 2.49-2.43 (m, 2H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 60)



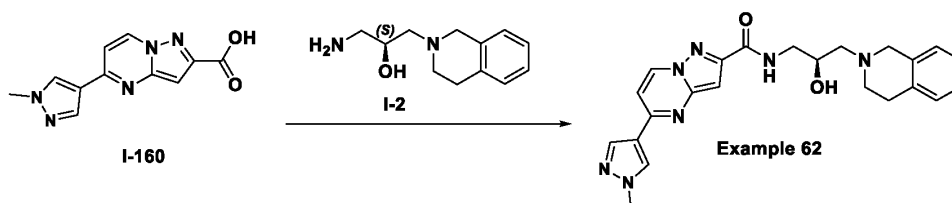
[000308] LC-MS (ES) m/z : 420.20 $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.24 (d, J = 7.36 Hz, 1H), 8.58 (dd, J = 10.76 Hz, 5.48 Hz, 1H), 7.59 (d, J = 7.32 Hz, 1H), 7.34 (s, 1H), 7.08-6.99 (m, 4H), 4.95 (d, J = 4.68 Hz, 1H), 3.97-3.93 (m, 1H), 3.62 (d, J = 6.16 Hz, 2H), 3.57-3.48 (m, 1H), 3.39-3.34 (m, 1H), 2.82-2.78 (m, 2H), 2.77-2.67 (m, 2H), 2.59-2.32 (m, 2H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 61)



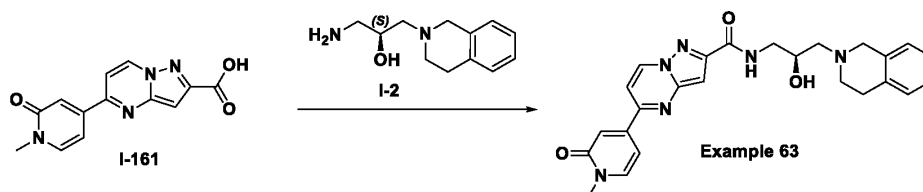
[000309] LC-MS (ES) m/z : 423.24 $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.70 (s, 1H), 8.37 (s, 1H), 8.26 (bs, 1H), 7.57 (d, J = 3.56 Hz, 2H), 7.10-7.01 (m, 4H), 4.96 (bs, 1H), 4.79 (d, J = 6.84 Hz, 2H), 4.72 (d, J = 6.56 Hz, 2H), 3.92 (d, J = 4.20 Hz, 1H), 3.62 (bs, 2H), 3.49-3.45 (m, 1H), 2.84 (bs, 2H), 2.79-2.66 (m, 2H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 62)



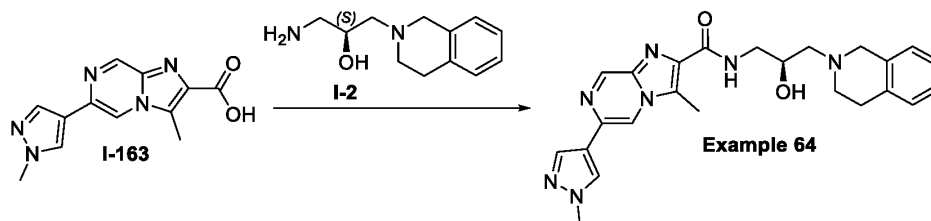
[000310] LC-MS (ES) m/z : 432.25 $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.82 (d, J = 7.28 Hz, 1H), 8.53 (s, 1H), 8.38 (bs, 1H), 8.16 (s, 1H), 7.42 (d, J = 7.36 Hz, 1H), 7.10-7.01 (m, 4H), 6.85 (s, 1H), 4.94 (bs, 1H), 3.91 (s, 4H), 3.63 (bs, 2H), 3.48-3.43 (m, 1H), 3.37-3.28 (m, 1H), 2.83-2.67 (m, 4H), 2.54-2.50 (m, 2H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 63)



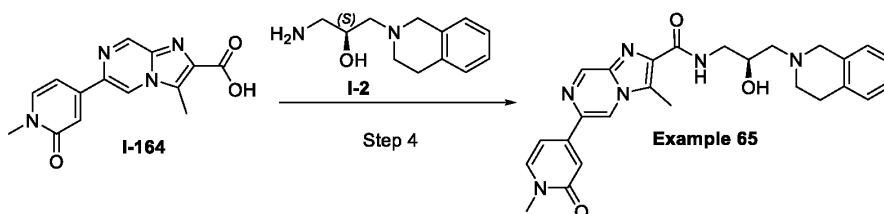
[000311] LC-MS (ES) m/z : 459.29 $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.01 (d, J = 7.32 Hz, 1H), 8.49 (dd, J = 9.76 Hz, 1H), 7.87-7.78 (dd, J = 6.88 Hz, 7.28 Hz, 2H), 7.24-7.00 (m, 7H), 4.95 (s, 1H), 3.95 (d, J = 5.20 Hz, 1H), 3.62-3.59 (m, 2H), 3.49-3.31 (m, 5H), 2.76-2.72 (m, 2H), 2.67-2.58 (m, 2H), 2.58-2.50 (m, 2H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 64)



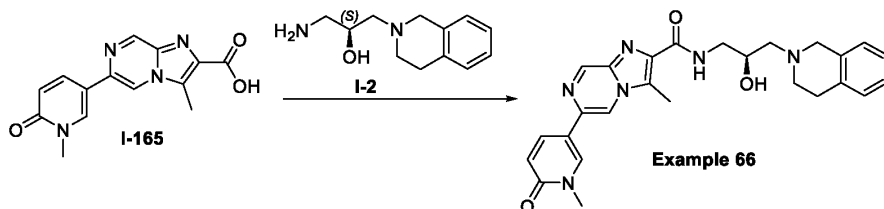
[000312] LC-MS (ES) $m/z = 446.34$ $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.91 (s, 1H), 8.66 (s, 1H), 8.45 (t, $J = 8.6$ Hz, 1H), 8.26 (s, 1H), 8.05 (s, 1H), 7.1 (bs, 3H), 7.01 (d, $J = 8.6$ Hz, 1H), 4.98 (bs, 1H), 3.95-3.93 (m, 2H), 3.9 (s, 3H), 3.63 (bs, 2H), 3.47-3.44 (m, 1H), 3.35-3.31 (m, 1H), 2.85 (bs, 2H), 2.79 (bs, 4H), 2.71 (bs, 1H), 2.56 (bs, 1H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-methyl-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide
(Example 65)



[000313] LC-MS (ES) $m/z = 473.38$ $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.03 (s, 1H), 9.01 (s, 1H), 8.49 (t, $J = 5.6$ Hz, 1H), 7.83 (d, $J = 7.2$ Hz, 1H), 7.22 (d, $J = 1.5$ Hz, 1H), 7.09-7.05 (m, 4H), 7.01 (d, $J = 7.0$ Hz, 1H), 4.98 (d, $J = 4.5$ Hz, 1H), 3.95-3.91 (m, 1H), 3.67-3.58 (m, 2H), 3.5-3.44 (m, 4H), 3.37-3.35 (m, 1H), 2.84 (bs, 5H), 2.79-2.67 (m, 2H), 2.57-2.53 (m, 2H).

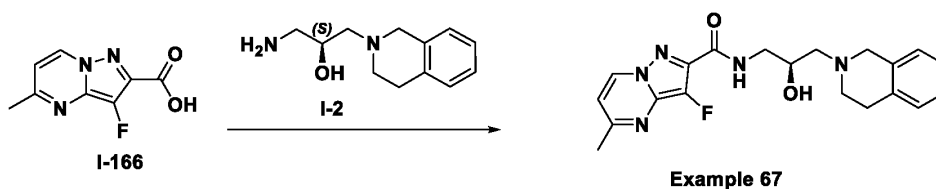
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-methyl-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxamide
(Example 66)



[000314] LC-MS (ES) $m/z = 473.35$ $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.93 (s, 1H), 8.73 (s, 1H), 8.49-8.45 (m, 2H), 8.2 (dd, $J = 9.4, 2.4$ Hz, 1H), 7.1-7.0 (m, 4H), 6.55 (d, $J = 9.4$ Hz, 1H), 4.98 (d, $J = 4.6$ Hz, 1H), 3.93-3.91 (m, 1H), 3.63 (bs, 2H),

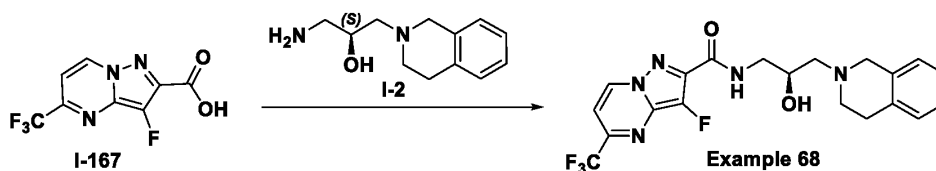
3.55 (s, 3H), 3.49-3.43 (m, 2H), 2.85 (bs, 2H), 2.83 (s, 3H), 2.78-2.67 (m, 2H), 2.55-2.53 (m, 2H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5-methylpyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 67)



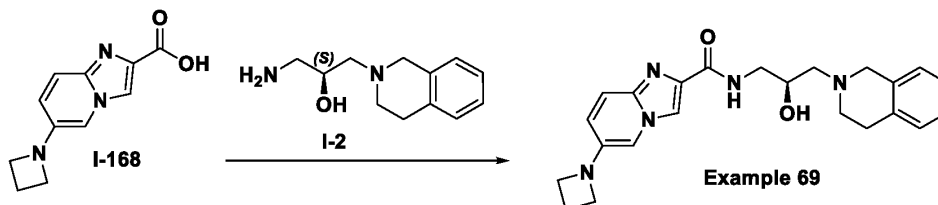
[000315] LC-MS (ES) m/z : 384.26 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.66 (d, J = 7.16 Hz, 1H), 8.34 (d, J = 5.52 Hz, 1H), 7.09-7.05 (m, 4H), 7.01-7.00 (d, J = 6.20 Hz, 1H), 4.94 (d, J = 4.08 Hz, 1H), 3.92 (t, J = 11.12 Hz, 5.48 Hz, 1H), 3.67-3.62 (m, 2H), 3.47-3.41 (m, 1H), 3.38-3.31 (m, 1H), 2.82 (d, J = 5.16 Hz, 1H), 2.76-2.71 (m, 3H), 2.62 (m, 4H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-fluoro-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 68)



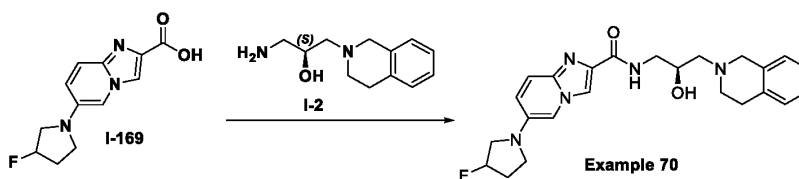
[000316] LC-MS (ES) m/z : 438.30 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.13 (d, J = 7.36 Hz, 1H), 8.53 (bs, 1H), 7.60 (d, J = 7.44 Hz, 1H), 7.07-6.98 (m, 4H), 4.95 (d, J = 4.72 Hz, 1H), 3.97-3.93 (m, 1H), 3.62 (d, J = 6.36 HZ, 2H), 3.57-3.43 (m, 1H), 3.40-3.34 (m, 1H), 2.82-2.69 (m, 2H), 2.77-2.67 (m, 4H), 2.59-2.49 (m, 2H).

(S)-6-(azetidin-1-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 69)



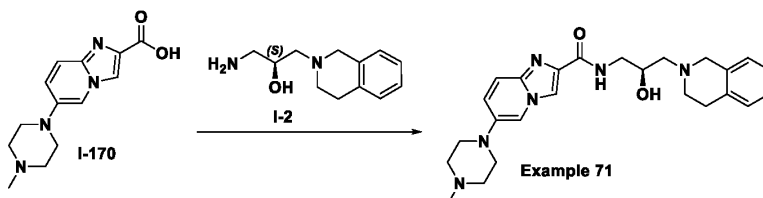
[000317] LC-MS (ES) m/z : 406.31 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.16 (dd, $J = 11.24$ Hz, 1H), 8.12 (s, 1H), 7.62 (s, 1H), 7.36 (d, $J = 9.60$ Hz, 1H), 7.09-7.01 (m, 4H), 6.86-6.83 (dd, $J = 9.68$ Hz, 1.88 Hz, 1H), 4.94 (d, $J = 4.60$ Hz, 1H), 3.88 (t, $J = 10.80$ Hz, 5.20 Hz, 1H), 3.81-3.77 (m, 4H), 3.65-3.61 (m, 2H), 3.48-3.42 (m, 1H), 3.31-3.23 (m, 1H), 2.83-2.65 (m, 4H), 2.56-2.49 (m, 2H), 2.34-2.26 (m, 2H).

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(3-fluoropyrrolidin-1-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 70)



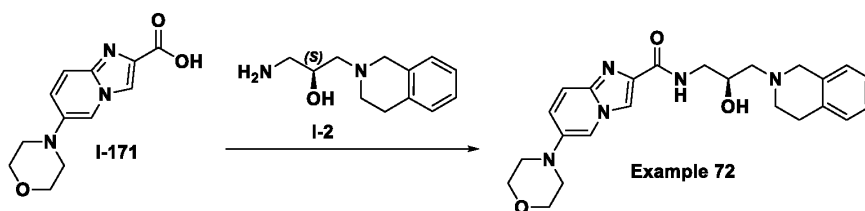
[000318] LC-MS (ES) m/z : 438.40 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.15 (dd, $J = 10.36$ Hz, 1H), 8.13 (s, 1H), 7.73 (s, 1H), 7.39 (d, $J = 9.76$ Hz, 1H), 7.15-7.01 (m, 5H), 5.53-5.39 (m, 1H), 4.95 (d, $J = 4.56$ Hz, 1H), 3.89 (d, $J = 5.32$ Hz, 1H), 3.62-3.55 (m, 3H), 3.49-3.23 (m, 5H), 2.83-2.64 (m, 6H), 2.282.17 (m, 2H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-methylpiperazin-1-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 71)



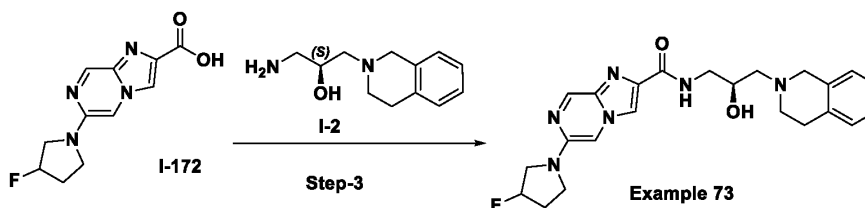
[000319] LC-MS (ES) m/z : 449.45 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.17 (dd, J = 12.52 Hz, 2H), 7.98 (s, 1H), 7.38-7.32 (m, 2H), 7.09-7.01 (m, 4H), 4.95 (d, J = 4.56 Hz, 1H), 3.89 (d, J = 5.68 Hz, 1H), 3.65-3.57 (m, 2H), 3.49-3.43 (m, 1H), 3.31-3.23 (m, 1H), 3.04 (s, 4H), 2.83-2.79 (m, 3H), 2.76-2.64 (m, 3H), 2.49-2.45 (m, 4H), 2.23 (s, 3H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-morpholinoimidazo[1,2-a]pyridine-2-carboxamide (Example 72)



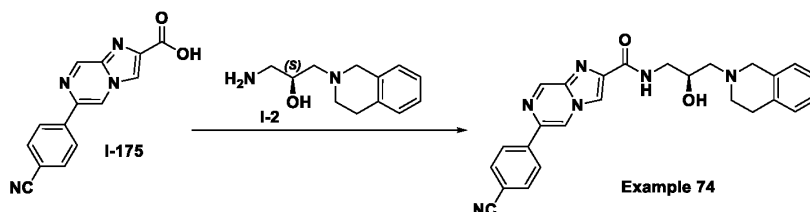
[000320] LC-MS (ES) m/z : 436.35 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.19 (dd, J = 8.96 Hz, 2H), 7.40-7.34 (m, 2H), 7.14-7.01 (m, 5H), 4.95 (d, J = 4.60 Hz, 1H), 3.89 (t, J = 11.0 Hz, 5.40 Hz, 1H), 3.75 (d, J = 4.56 Hz, 4H), 3.65-3.57 (m, 2H), 3.49-3.43 (m, 1H), 3.31-3.24 (m, 1H), 3.03 (d, J = 4.12 Hz, 4H), 2.83-2.79 (m, 2H), 2.78-2.66 (m, 2H), 2.54-2.44 (m, 2H).

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(3-fluoropyrrolidin-1-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 73)



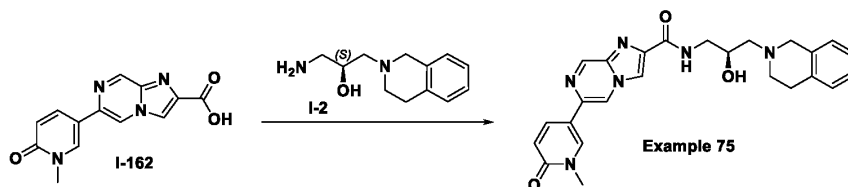
[000321] LC-MS (ES) m/z : 439.39 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.76 (s, 1H), 8.35 (dd, J = 10.76 Hz, 1H), 8.25 (s, 1H), 7.68 (s, 1H), 7.10-7.00 (m, 4H), 5.52-5.39 (m, 1H), 4.96 (d, J = 4.52 Hz, 1H), 3.90 (t, J = 10.60 Hz, 3.89 Hz, 2H), 3.69-3.59 (m, 3H), 3.58-3.35 (m, 4H), 2.83 (d, J = 5.28 Hz, 2H), 2.78-2.66 (m, 3H), 2.56-2.49 (m, 1H), 2.28-2.23 (m, 2H).

(S)-6-(4-cyanophenyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 74)



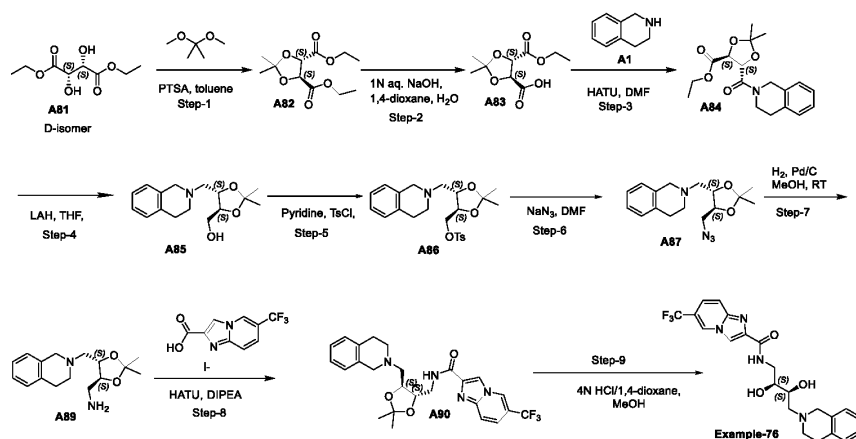
[000322] LC-MS (ES) m/z : 453.30 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.37 (s, 1H), 9.12 (s, 1H), 8.55 (dd, J = 10.80 Hz, 1H), 8.46 (s, 1H), 8.22 (d, J = 8.32 Hz, 2H), 8.00 (d, J = 8.32 Hz, 2H), 7.10-7.00 (m, 4H), 4.98 (d, J = 4.68 Hz, 1H), 3.95 (d, J = 5.80 Hz, 1H), 3.63 (d, J = 4.20 Hz, 2H), 3.50-3.48 (m, 1H), 3.46-3.38 (m, 1H), 2.84-2.78 (m, 2H), 2.76-2.66 (m, 2H), 2.55-2.50 (m, 2H).

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 75)



[000323] LC-MS (ES) m/z : 459.23 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.99 (s, 1H), 8.51 (bs, 1H), 8.43 (s, 1H), 8.39 (s, 1H), 8.01-7.98 (dd, J = 9.48 Hz, 2.04 Hz, 1H), 7.10-7.07 (m, 3H), 7.01 (d, J = 6.76 Hz, 1H), 6.55 (d, J = 9.48 Hz, 1H), 4.98 (bs, 1H), 3.93 (bs, 1H), 3.67-3.62 (m, 2H), 3.58 (s, 3H), 3.48-3.44 (m, 1H), 3.37-3.32 (m, 1H), 2.85-2.67 (m, 4H), 2.55-2.49 (m, 2H).

N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 76)



Step 1: diethyl (4S,5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (A82)

[000324] To the stirred solution of diethyl (2S, 3S)-2,3-dihydroxysuccinate (**A81**, 10.0 g, 48.50 mmol) in toluene was added PTSA (1.84 g, 4.80 mmol), and 2,2-dimethoxypropane (**2**, 15.4 ml, 63.0 mmol) at room temperature. The reaction mixture was heated at 100°C for 1h. The reaction mixture was cooled to room temperature and diluted with EtOAc. The organic layer was washed with sat. NaHCO₃ solution followed by water and brine solution. The organic layer was dried over anhydrous Na₂SO₄, and filtered. The organic layer was concentrated to get diethyl (4S,5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **A82** as pale brown oil. Yield: 9.0g, (75%). LC-MS (ES) m/z : 247.26 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 4.87-4.82 (m, 2H), 4.11-4.08 (q, 2H), 1.38 (s, 6H), 1.1 (t, 3H).

Step 2: (4S,5S)-5-(ethoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (A83)

[000325] To the stirred solution of diethyl (4S,5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (**A82**, 9.0 g, 36.50 mmol), in 1,4-dioxane (60 mL) and water (60mL) was added dropwise aq. 1N NaOH solution (55.0 mL, 54.80 mmol) at 0°C. The reaction mixture was allowed to stir at room temperature for 4h. After completion of reaction, reaction mixture was washed with DCM. The aqueous layer was acidified using conc.HCl to pH 2-3. The aqueous layer was extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, filtered.and concentrated to get (4S,5S)-5-(ethoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid **A83** as a pale yellow oil. Yield: 6.0 g, (75%). LC-MS (ES) m/z : 217.10 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.31 (bs, 1H), 4.71-4.69 (m 2H), 4.19-4.14 (q, 2H), 1.22 (s, 6H), 1.21 (t, 3H).

Step 3: ethyl (4S,5S)-2,2-dimethyl-5-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1,3-dioxolane-4-carboxylate (A84)

[000326] To the stirred solution of (4S, 5S)-5-(ethoxycarbonyl)-2, 2-dimethyl-1,3-dioxolane-4-carboxylic acid (**A83**, 6.0g, 27.40 mmol) in DCM (60 mL) at room temperature was added DMAP (0.33g, 2.70 mmol), and T₃P (24.70mL, 82.4 mmol). The reaction mixture was stirred for 20 min at room temperature. 1, 2, 3, 4-tetrahydroisoquinoline (**A1**, 4.4 g, 32.90mmol) was added at room temperature. Reaction mixture was stirred at room temperature for 16 h. After completion of reaction, diluted with DCM and washed with water and brine solution. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated. The crude was purified by combiflash with 0-30% EA/hexanes as eluent. The fractions were concentrated to get ethyl (4S,5S)-2,2-dimethyl-5-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1,3-dioxolane-4-carboxylate **A84** as pale yellow oil. Yield: 2.40 g, (26%). LCMS (ESI): m/z: 334.16 [M+H] +.

Step 4: ((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (A85)

[000327] To the stirred solution of ethyl (4S,5S)-2,2-dimethyl-5-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1,3-dioxolane-4-carboxylate (**A84**, 2.30g, 6.80 mmol) in dry THF at 0°C was added drop wise LAH (5.10 ml, 10.30 mmol). The reaction mixture was heated to 60 °C for 1h. After completion of reaction, was cooled to room temperature and quenched with ice-cold aq. Rochelle salt solution. The quenched mixture was filtered over celite bed and washed with EtOAc. The organic layer was washed with water, followed by. brine solution. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to get the ((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol **A85** as pale yellow oil. Yield: 1.3 g, (72%). LCMS (ESI): m/z, 278.19 [M+H] +.

Step 5: ((4S, 5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate (A86)

[000328] To the stirred solution of ((4S, 5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (**A85**, 1.3 g, 4.60 mmol) in THF and pyridine at 0 °C was added TsCl (1.30 g, 7.0 mmol). Reaction mixture was stirred at room temperature for 16 h. After completion of reaction was evaporated to get crude. The residue was diluted with EtOAc washed subsequently with cold aqueous 1M HCl solution, saturated aq. NaHCO₃ solution and brine solution. The organic layer was dried

over anhydrous Na₂SO₄, filtered and concentrated to get crude. The crude was purified by combiflash over silica gel with gradient using 20-30% EA/hexanes to afford the ((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol **A86** as a pale yellow oil which changes to a solid at low temperatures. Yield: 0.9 g, (45%). LCMS (ESI): m/z 432.08 [M+H] ⁺.

Step 6: 2-(((4S,5S)-5-(azidomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1,2,3,4-tetrahydroisoquinoline (A87)

[000329] To the stirred solution of 2-(((4S,5S)-5-(azidomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1,2,3,4-tetrahydroisoquinoline (**A86**, 0.9 g, 2.0 mmol) in DMF was added NaN₃ (0.20 g 3.10 mmol) at room temperature. Reaction was stirred at 70°C for 16 h. After completion of reaction, reaction mass was diluted with EtOAc washed subsequently with water and brine solution. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to get crude. The crude was purified by combiflash over silica gel with gradient elution 20-30% EA/hexanes to afford 2-(((4S,5S)-5-(azidomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1,2,3,4-tetrahydroisoquinoline **A87** as a pale yellow oil. Yield: 0.40 g, (66%). LCMS (ESI): m/z, 304.0[M+H] ⁺.

Step 7: ((4S, 5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (A88)

[000330] To a solution of ((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate (**A87**, 0.50 g, 1.60 mmol) in methanol was added Pd/C (50% moisture), and reaction mixture was maintained under hydrogen atmosphere (30 psi) for 1 h. After completion of reaction, reaction mass was filtered through celite and wash with methanol. The filtrate was concentrated to get ((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanamine **A88** as pale yellow oil. Yield: 0.40 g, (90%).. LCMS (ESI): m/z 277.06 [M+H] ⁺.

Step 8: N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (A89)

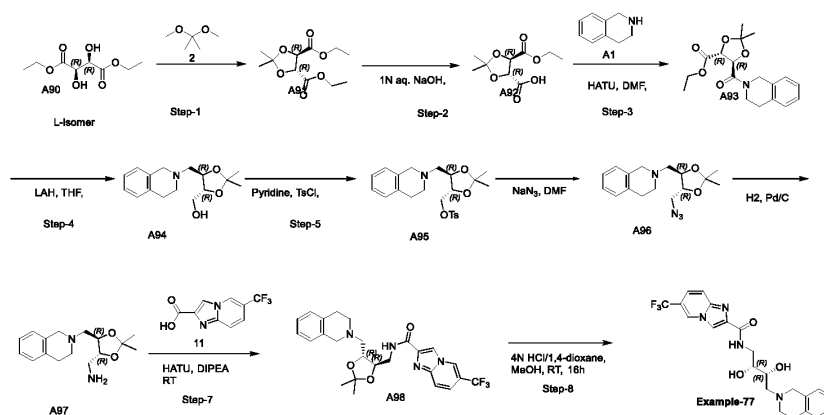
[000331] To a stirred solution of 6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxylic acid (**I-102**, 0.10 g, 0.46 mmol) in DMF (2.0 mL) was added ((4S, 5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (**A88**, 0.13 g, 0.46 mmol) at 0°C was added HATU (0.26 g, 0.70 mmol),

and DIPEA (0.25 mL, 1.40 mmol). Reaction mixture was stirred at room temperature for 16 h. After completion of reaction diluted with ethyl acetate and washed with water and brine solution. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated to afford the N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide **A89** as a pale yellow oil. Yield: 0.2 g, (90%). LCMS (ESI): m/z 489.18 $[\text{M}+\text{H}]^+$.

Step-9: N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 76)

[000332] To the stirred solution of N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (**12**, 0.2 g, 0.40 mmol) in MeOH (3 mL) and 1,4-dioxane (2.0 mL) was added dropwise 4N HCl at 0 °C. The reaction mixture was stirred at room temperature for 16 h. After completion of reaction concentrated to remove the solvent and basified using aq. ammonia solution. and extracted with 5% MeOH/DCM. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated and taturate with ether and pentane and dried to afford N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide as a beige solid Yield: 0.120 g (65%). LCMS (ESI): m/z 449.2, $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.27 (s, 1H), 8.45 (s, 1H), 8.29 (s, 1H), 7.79 (d, $J = 9.36$ Hz, 1H), 7.57 (d, $J = 9.32$ Hz, 1H), 7.08-7.01 (m, 4H), 4.87 (bs 1H), 4.60 (bs, 1H), 3.72-3.65 (m, 4H), 3.52 (t, $J = 13.0$ Hz, 1H), 2.79-2.49 (m, 7H).

N-((2R,3R)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 77)



Step 1: diethyl (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (A91)

[000333] To the stirred solution of diethyl (2R, 3R)-2,3-dihydroxysuccinate (**A90**, 20.0 g, 97.0 mmol) in toluene was added PTSA (1.84 g, 9.70 mol), and 2,2-dimethoxypropane (**2**, 15.4 mL, 126.10 mmol) at room temperature. The reaction mixture was heated to 100°C for 1h. The reaction mixture was heated at 100°C for 1h. The reaction mixture was cooled to room temperature and diluted with EtOAc. The organic layer was washed with sat. NaHCO₃ solution followed by water and brine solution. The organic layer was dried over anhydrous Na₂SO₄, and filtered. The organic layer was concentrated to get diethyl (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **A91** as pale brown oil. Yield: 18.0 g, (75%). MS (ESI): mass m/z 247.2 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 4.87-4.82 (m, 2H), 4.11-4.08 (q, 2H), 1.38 (s, 6H), 1.1 (t, 3H).

Step 2: (4R,5R)-5-(ethoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (A92)

[000334] To the stirred solution of diethyl (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (**A91**, 18.0 g, 73.40 mmol), in 1,4-dioxane (130 mL) and water (130 mL) was added dropwise aq. 1N NaOH solution (110.0 mL, 110.0 mmol) at 0°C. The reaction mixture was allowed to stir at room temperature for 4h. After completion of reaction, reaction mixture was washed with DCM. The aqueous layer was acidified using conc.HCl to pH 2-3. The aqueous layer was extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to get (4R,5R)-5-(ethoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid **A92** as a pale yellow oil. Yield: 8.0 g, (50%). LC-MS (ES) m/z : 217.10 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 13.31 (bs, 1H), 4.71-4.69 (m, 2H), 4.19-4.14 (q, 2H), 1.22 (s, 6H), 1.21 (t, 3H).

Step 3: ethyl (4R,5R)-2,2-dimethyl-5-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1,3-dioxolane-4-carboxylate (A93)

[000335] To the stirred solution of (4R, 5R)-5-(ethoxycarbonyl)-2, 2-dimethyl-1,3-dioxolane-4-carboxylic acid (**A92**, 5.0 g, 22.9 mmol) in DCM (50 mL) at room temperature was added DMAP (0.27 g, 2.2 mmol), and T₃P (20 mL, 34.3 mmol). The reaction mixture was stirred for 20 min at room temperature. 1, 2, 3, 4-tetrahydroisoquinoline (**5**, 3.60 g, 27.4 mmol) was added at room temperature. Reaction mixture was stirred at room temperature for 16 h. After completion of reaction, diluted with DCM and washed with water and brine solution. The organic layer was dried over

anhydrous Na₂SO₄, filtered and concentrated. The crude was purified by combiflash with 0-30% EA/hexanes as eluent. The fractions were concentrated to get ethyl (4R,5R)-2,2-dimethyl-5-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1,3-dioxolane-4-carboxylate **A93** as pale yellow oil. Yield: 3.0 g, (39%). LCMS (ESI): mass m/z: 334.30 [M+H] +.

Step 4: ((4R,5R)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (A94)

[000336] To the stirred solution of ethyl (4R, 5R)-2,2-dimethyl-5-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1,3-dioxolane-4-carboxylate (**A93**, 3.8 g, 11.30 mmol) in dry THF at 0°C was added LAH (8.5 mL, 17.0 mmol). The reaction mixture was heated to 60 °C for 1h. After completion of reaction, was cooled to room temperature and quenched with ice-cold aq. Rochelle salt solution. The quenched mixture was filtered over celite bed and washed with EtOAc. The organic layer was washed with water, followed by. brine solution. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to get the ((4R,5R)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol **A94** as pale yellow oil. Yield: 2.10 g, (67%). LCMS (ESI): mass m/z 278.30 [M+H] +.

Step 5: ((4R, 5R)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate (A95)

[000337] To the stirred solution of ((4R, 5R)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (**A94**, 2.0 g, 7.20 mmol) in pyridine at 0°C was added TsCl (2.0 g, 10.80 mmol). Reaction mixture was stirred at room temperature for 16 h. After completion of reaction was evaporated to get crude. The residue was diluted with EtOAc washed subsequently with cold aqueous 1M HCl solution, saturated aq. NaHCO₃ solution and brine solution. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to get crude. The crude was purified by combiflash over silica gel with gradient using 20-30% EA/hexanes to afford to afford the ((4R,5R)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate **A95** as a pale yellow oil which changes to a solid at low temperatures Yield: 0.7 g, (22%). LCMS (ESI): m/z 432.1 [M+H] +.

Step 5: 2-(((4R,5R)-5-(azidomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1,2,3,4-tetrahydroisoquinoline (A96)

[000338] To the stirred solution of 2-(((4R,5R)-5-(azidomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1,2,3,4-tetrahydroisoquinoline (**A945**, 0.7 g, 1.62 mmol) in DMF

was added NaN₃ (0.15g , 2.40 mmol) at room temperature. Reaction was stirred at 70°C for 16 h. After completion of reaction, reaction mass was diluted with EtOAc washed subsequently with water and brine solution. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to get crude. The crude was purified by combiflash over silica gel with gradient elution 20-30% EA/hexanes to afford 2-(((4R,5R)-5-(azidomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1,2,3,4-tetrahydroisoquinoline **A96** as a pale yellow oil. (0.25g, 52%). LCMS (ESI): mass; m/z , 304.17 [M+H] +.

Step 6: ((4R, 5R)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (A97)

[000339] To a solution of ((4R, 5R)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate (**A96**, 0.25 g, 0.8mmol) in methanol was added Pd/C (50% moisture), and reaction mixture was maintained under hydrogen atmosphere (30psi) for 1 h .after completion of reaction, reaction mass was filtered through cellite and washed with methanol. The methanol organic layer concentrated to get ((4R,5R)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (**A97**) as pale yellow oil. Yield: 0.2 g, (90%). LCMS (ESI): mass; m/z 277.2[M+H] +.

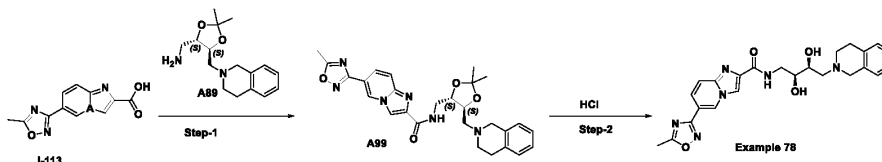
Step 7: N-(((4R,5R)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (A98)

[000340] To a stirred solution of 6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxylic acid (**I-102**, 0.16 g, 0.70 mmol) in DMF (3.0mL) was added ((4R, 5R)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (**A97**, 0.2 mg, 0.70 mmol).at 0°C was added HATU (0.41 g, 1.0 mmol), and DIPEA (0.3 mL, 2.10 mmol).). Reaction mixture was stirred at room temperature for 16 h. After completion of reaction diluted with ethyl acetate and washed with water and brine solution. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated to afford N-(((4R,5R)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide **A98** as a pale yellow oil. Yield: 0.30 g (88%). LCMS (ESI): mass, 488.2; m/z 489.2, [M+H] +.

Step-8: N-((2R,3R)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example77)

[000341] To the stirred solution of N-(((4R,5R)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (**A98**, 0.3g, 0.60mmol), in MeOH (5mL) was added dropwise 4N HCl at 0 °C. The reaction mixture was stirred at room temperature for 16 h. After completion of reaction concentrated to remove the solvent and basified using aq. ammonia solution. and extracted with 5% MeOH/DCM. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated and taturate with ether and pentane and dried to afford N-((2R,3R)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide as a white solid. Yield: 0.10 g (95% LCMS (ESI): m/z 449.13 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 9.27 (s, 1H), 8.45 (s, 1H), 8.28 (dd, J = 10.64 Hz, 1H), 7.79 (d, J = 9.52 Hz, 1H), 7.57 (d, J = 8.76 Hz, 1H), 7.08-7.00 (m, 4H), 4.87 (d, J = 5.16 Hz, 1H), 4.59 (d, J = 5.52 Hz, 1H), 3.70-3.61 (m, 5H), 3.55-3.49 (m, 1H), 2.79-2.49 (m, 6H).

N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 78)



Step-1: N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (A99)

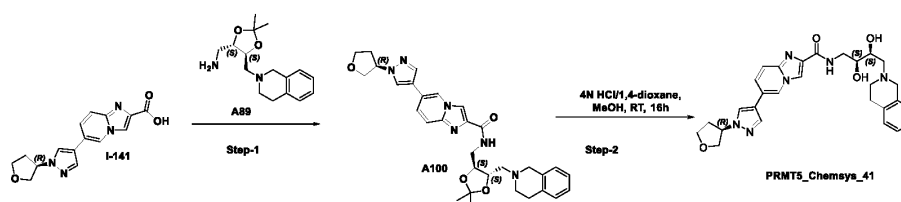
[000342] To a solution of 6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxylic acid (I-113, 0.12 g, 0.49 mmol) in DMF (10 mL) was added DIPEA (0.25 mL, 1.47 mmol) followed by HATU (0.28 g, 0.73 mmol) at 0 °C. The reaction mixture was stirred for 10 min followed by addition of ((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (A89, 0.13 g, 0.49 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was monitored till the completion of starting materials (LC/MS) and then concentrated under reduced pressure. The obtained crude was purified by combi-flash column using 0-10% MeOH/DCM as the eluent to afford N-(((4S,5S)-5-((3,4-

dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide A99 as white solid. Yield: 0.20 g, (83%). LC-MS (ES) m/z : 503.23 $[M+H]^+$.

Step-2: N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide

[000343] To a stirred solution of N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (A99, 0.20 g 0.39 mmol) in MeOH (3 mL) at 0°C, 4N HCl in dioxane was added and reaction mixture stirred at room temperature for 4h. After completion, evaporated the solvent from reaction mixture to obtain the residue. This residue quenched with NaHCO₃ solution and extracted with ethyl acetate (3 times). The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain the crude. This crude was washed with diethyl ether and dried to afford N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide as white solid. Yield: 0.011 g (6%) LC-MS (ES) m/z = 463.18 $[M+H]^+$ ¹H NMR (DMSO-*d*₆, 400 MHz, ppm)- δ 9.38 (s, 1H), 8.54 (s, 1H), 8.27 (s, 1H), 7.81 (d, J = 8.36 Hz, 1H), 7.74 (d, J = 9.52 Hz, 1H), 7.08-7.01 (m, 4H), 4.87 (s, 1H), 4.58 (s, 1H), 3.72-3.50 (m, 5H), 2.80 (s, 2H), 2.68 (d, J = 2.72 Hz, 2H), 2.50-2.32 (m, 5H).

N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 79)



Step-1: N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide(3)

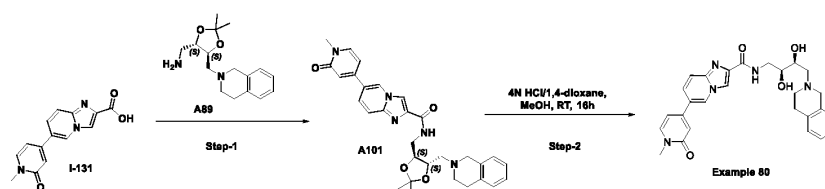
[000344] To a solution of (R)-6-(1-(tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxylic acid (I-141, 0.13 g, 0.471 mmol) in DMF (3 mL)

was added DIPEA (0.25 mL, 1.41 mmol) followed by HATU (0.268 g, 0.706 mmol). The reaction mixture was stirred for 10 min followed by addition of ((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (A89, 0.140 g, 0.471 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was monitored till the completion of starting materials (LC/MS) and then concentrated under reduced pressure. The obtained crude was purified by column chromatography using 0-10% methanol in dichloromethane as eluent to afford N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide A100 as a white solid. Yield: 0.22 g (83%) LC-MS (ES) m/z : 557.53 [M+H]⁺

Step-2: N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide

[000345] To a solution of N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (A100, 0.22 g, 39.49 μmol) in Methanol (4 mL) was added 4M HCL in Dioxane (2 mL) at 0°C. The reaction mixture was stirred at room temperature for 2 h After completion of reaction organic solvent was evaporated and the aqueous layer was basified with sat NaHCO₃ up to pH-10 and aqueous layer extracted by DCM and then concentrated under reduced pressure. The obtained crude was purified by column chromatography using 0-10% methanol in dichloromethane as eluent to afford N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide as a white solid. Yield: 0.10 g (49%). LC-MS (ES) m/z : 517.11 [M+H]⁺ ¹H NMR (DMSO-*d*₆, 400 MHz, ppm) δ 8.85 (s, 1H), 8.30 (s, 1H), 8.24 (s, 1H), 8.19 (dd, J = 11.40 Hz, 5.32Hz, 1H), 7.93 (s, 1H), 7.64-7.59 (m, 2H), 7.08-7.01 (m, 4H), 5.07-5.03 (m, 1H), 4.88 (bs, 1H), 4.59 (bs, 1H), 4.03-3.99 (m, 2H), 3.98-3.92 (m, 1H), 3.87-3.81 (m, 1H), 3.72-3.50 (m, 5H), 3.32-3.28 (m, 1H), 2.79-2.66 (m, 5H), 2.49-2.32 (m, 3H).

N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 80)



Step-1: N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (3)

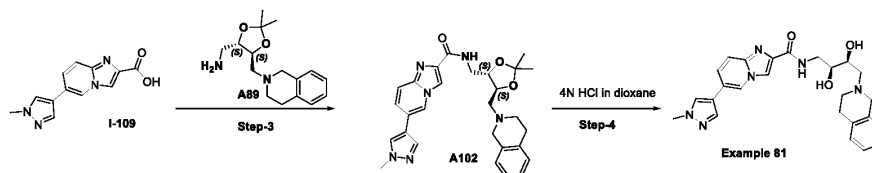
[000346] To a solution of 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxylic acid (I-131, 0.15 g, 0.55 mmol) in DMF (3 mL) was added DIPEA (0.27 mL, 1.67 mmol) followed by HATU (0.250 g, 0.66 mmol). The reaction mixture was stirred for 10 min followed by addition of ((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (A89, 0.15 g, 0.55 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was monitored till the completion of starting materials (LC/MS) and then concentrated under reduced pressure. The obtained crude was purified by column chromatography using 0-10% methanol in dichloromethane as eluent to afford N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide A101 as a white solid. Yield: 0.22 g (75%) LC-MS (ES) m/z : 528.53 [M+H]⁺

Step-2: N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide

[000347] To a solution of N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (A101, 0.22 g, 0.41 mmol) in Methanol (4 mL) was added 4M HCL in Dioxane (2 mL) at 0°C. The reaction mixture was stirred at room temperature for 2 h. After completion of reaction organic solvent was evaporated and the aqueous layer was basified with sat NaHCO₃ up to pH-10 and aqueous

layer extracted by DCM and then concentrated under reduced pressure. The obtained crude was purified by column chromatography using 0-10% methanol in dichloromethane as eluent to afford N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide as a white solid. Yield: 0.032 g (18%). LC-MS (ES) m/z : 488.0 [M+H]⁺ ¹H NMR (DMSO-*d*₆, 400 MHz, ppm) δ 9.11 (s, 1H), 8.32 (s, 1H), 8.25-8.22 (dd, J = 11.07 Hz, 5.68 Hz, 1H), 7.84 (d, J = 7.12 Hz, 1H), 7.73 (d, J = 9.64 Hz, 1H), 7.66 (d, J = 9.52 Hz, 1H), 7.08-6.99 (m, 4H), 6.78 (s, 1H), 6.61 (d, J = 7.04 Hz, 1H), 4.87 (s, 1H), 4.58 (d, J = 4.28 Hz, 1H), 3.71-3.50 (m, 5H), 3.49 (s, 3H), 3.32 (m, 1H), 2.79 (d, J = 4.72 Hz, 2H), 2.73 (d, J = 4.48 Hz, 2H), 2.63-2.50 (m, 1H).

N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 81)



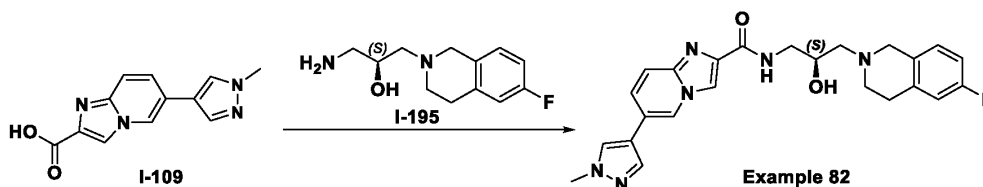
Step-3: N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (A102)

[000348] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxylic acid (I-109, 0.20 g, 0.82 mmol) in DMF (3 mL) was added DIPEA (0.43 mL, 2.47 mmol) followed by HATU (0.47 g, 1.23 mmol). The reaction mixture was stirred for 10 min followed by addition of ((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (A89, 0.27 g, 0.99 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was monitored till the completion of starting materials (LC/MS) and then concentrated under reduced pressure. The obtained crude was purified by column chromatography using 0-10% methanol in dichloromethane as eluent to afford N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide A102 as a white solid. Yield: 0.30 g (72%) LC-MS (ES) m/z : 501.24 [M+H]⁺

Step-4: N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide

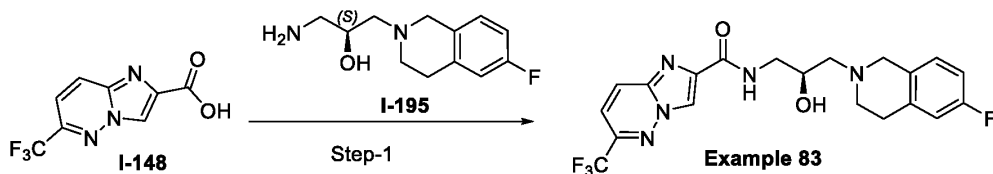
[000349] To a solution of N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (**A102**, 0.30 g, 0.60 mmol) in Methanol (4 mL) was added 4M HCL in Dioxane (2 mL) at 0°C. The reaction mixture was stirred at room temperature for 4 h. After completion of reaction, organic solvent was evaporated and the aqueous layer was basified with sat NaHCO₃ up to pH-10 and aqueous layer extracted by DCM and then concentrated under reduced pressure. The obtained crude was purified by column chromatography using 0-10% methanol in dichloromethane as eluent to afford N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide as a white solid. Yield: 0.06 g (21%). LC-MS (ES) m/z : 461.0 [M+H]⁺ ¹H NMR (DMSO-*d*₆, 400 MHz, ppm) δ 8.82 (s, 1H), 8.25 (s, 1H), 8.18 (s, 2H), 7.87 (s, 1H), 7.62-7.56 (m, 2H), 7.08-7.01 (m, 4H), 4.87 (d, J = 5.68 Hz, 1H), 4.58 (d, J = 4.96 Hz, 1H), 3.88 (s, 3H), 3.71 (s, 1H), 3.61 (s, 3H), 3.56-3.50 (m, 2H), 3.32-3.28 (m, 1H), 2.89 (d, J = 4.8 Hz, 2H), 2.73 (d, J = 5.0 Hz, 2H), 2.66-2.61 (m, 1H).

(S)-N-(3-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 82)



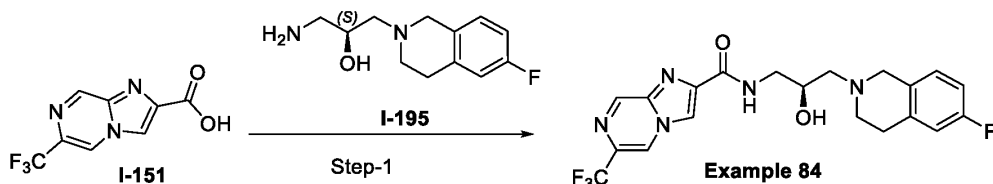
[000350] LC-MS (ES) m/z : 449.24 [M+H]⁺ ¹H NMR (DMSO-*d*₆, 400 MHz, ppm) δ 8.85 (s, 1H), 8.54 (dd, J = 5.24 Hz, 1H), 8.31 (s, 1H), 8.19 (s, 1H), 7.88 (s, 1H), 7.62 (s, 2H), 7.26 (d, J = 5.64 Hz, 1H), 7.13-7.09 (m, 2H), 5.92 (bs, 1H), 4.55-4.51 (m, 1H), 4.34-4.21 (m, 4H), 3.89 (s, 3H), 3.88-3.77 (m, 2H), 3.23-3.08 (m, 4H).

(S)-N-(3-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 83)



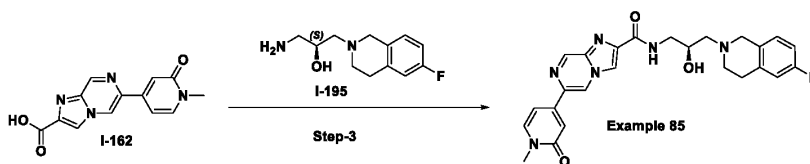
[000351] LC-MS (ES) m/z = 438.18 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.89 (s, 1H), 8.49 (bs, 1H), 8.39 (d, J = 9.5 Hz, 1H), 7.77 (d, J = 9.5 Hz, 1H), 7.0 (t, J = 6.3 Hz, 1H), 6.93-6.87 (m, 2H), 4.98 (bs, 1H), 3.93 (d, J = 4.4 Hz, 1H), 3.58 (bs, 2H), 3.51-3.46 (m, 1H), 3.36 (bs, 1H), 2.84 (bs, 2H), 2.72-2.67 (m, 2H), 2.54 (bs, 2H).

(S)-N-(3-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 84)



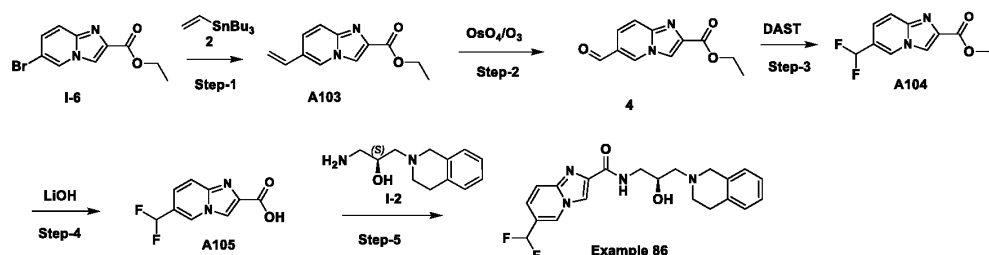
[000352] LC-MS (ES) m/z = 438.18 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.32 (s, 1H), 9.13 (s, 1H), 8.56 (bs, 2H), 7.03 (t, J = 6.3 Hz, 1H), 6.94-6.87 (m, 2H), 4.97 (d, J = 4.4 Hz, 1H), 3.92 (t, J = 5.4 Hz, 1H), 3.59 (bs, 2H), 3.49-3.43 (m, 1H), 3.38-3.35 (m, 1H), 2.84 (bs, 2H), 2.74-2.67 (m, 2H), 2.55 (bs, 2H).

(S)-N-(3-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 85)



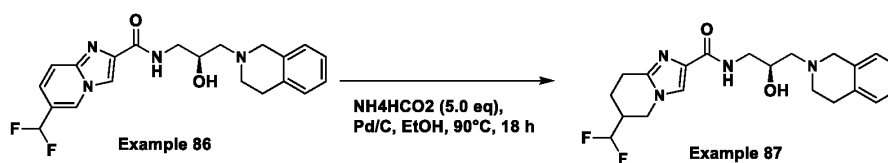
[000353] LC-MS (ES) m/z : 477.32 $[M+H]^+$

(S)-6-(difluoromethyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 86)



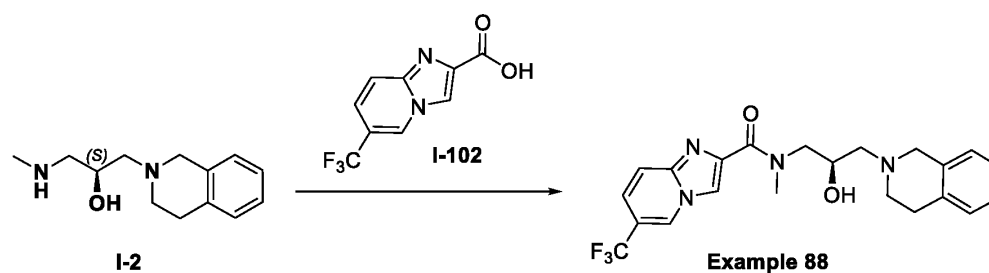
[000354] LC-MS (ES) m/z : 401.43 $[\text{M}+\text{H}]^+$

6-(difluoromethyl)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 87)



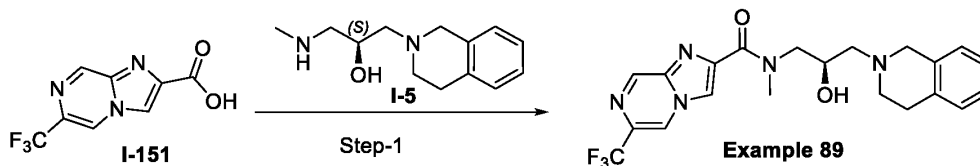
[000355] LC-MS (ES) m/z : 405.46 $[\text{M}+\text{H}]^+$

(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 88)



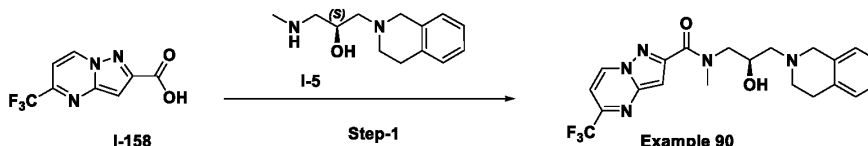
[000356] LC-MS (ES) m/z : 433.27 $[\text{M}+\text{H}]^+$ ^1H NMR ($\text{DMSO}-d_6$, 400 MHz, ppm) δ 9.14 (s, 1H), 8.34 (s, 1H), 7.69 (bs, 1H), 7.45 (d, $J = 9.44$ Hz, 1H), 7.06-6.97 (m, 4H), 4.70 (d, $J = 15.76$ Hz, 1H), 4.06-3.86 (m, 3H), 3.72-3.57 (m, 3H), 2.69-2.32 (m, 6H), 1.89-1.77 (m, 2H).

(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 89)



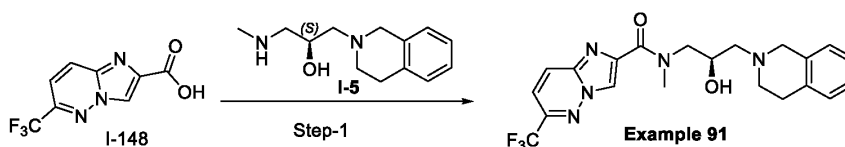
[000357] LC-MS (ES) $m/z = 434.21$ $[M+H]^+$. Note : compound is rotameric, two sets of peak appeared. ^1H NMR (400 MHz, DMSO- d_6) δ 9.33 & 9.26 (s, 1H), 9.17 & 9.11 (s, 1H), 8.53 & 8.43 (s, 1H), 7.08 & 7.03 (bs, 3H), 6.94 & 6.91 (bs, 1H), 4.93 & 4.85 (bs, 1H), 4.13 (s, 1H), 4.02-3.99 (m, 2H), 3.83-3.77 (m, 2H), 3.64 (bs, 1H), 3.45-3.42 (m, 4H), 3.26 (bs, 1H), 3.1 (s, 1H), 2.81-2.74 (m, 2H), 2.56 (bs, 3H), 2.37 (bs, 2H). At higher temperature: ^1H NMR (400 MHz, DMSO- d_6) δ 9.2 (bs, 2H), 8.46 (s, 1H), 7.05 (bs, 4H), 4.63 (bs, 1H), 4.06 (bs, 2H), 3.82-3.35 (m, 6H), 3.19-3.15 (m, 2H), 2.65 (bs, 3H).

(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 90)



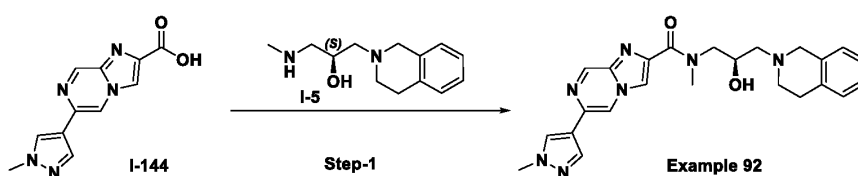
[000358] LC-MS (ES) $m/z : 434.24$ $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.38 (bs, 1H), 7.52 (d, $J = 7.16$ Hz, 1H), 7.27-7.21 (m, 5H), 5.72 (bs, 1H), 4.40 (bs, 3H), 3.72-3.60 (m, 2H), 3.44-3.15 (m, 9H).

(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(trifluoromethyl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 91)



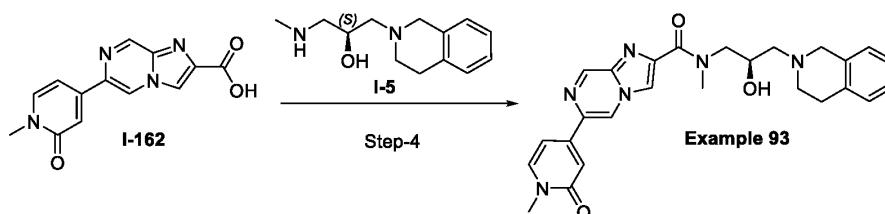
[000359] LC-MS (ES) $m/z = 434.24$ $[M+H]^+$. Note : compound is rotameric, two sets of peak appeared. ^1H NMR (400 MHz, DMSO- d_6) δ 8.83 & 8.73 (s, 1H), 8.51 & 8.33 (d, $J = 9.5$ Hz, 1H), 7.74 & 7.62 (d, $J = 9.5$ Hz, 1H), 7.08-6.86 (m, 4H), 4.96 & 4.84 (d, $J = 4.7$ Hz, 1H), 4.12-3.86 (m, 2H), 3.82-3.68 (m, 1H), 3.65-3.41 (m, 4H), 3.23 (bs, 1H), 3.1 (s, 2H), 2.81-2.72 (m, 2H), 2.56 (m, 1H), 2.36-2.34 (m, 1H). At higher temperature: ^1H NMR (400 MHz, DMSO- d_6) δ 8.67 (s, 1H), 8.35 (bs, 1H), 7.61 (bs, 1H), 7.05-6.9 (bs, 4H), 4.64 (bs, 1H), 4.05 (bs, 2H), 3.75-3.39 (m, 4H), 3.31-3.14 (m, 4H), 2.67 (bs, 3H).

(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 92)



[000360] LC-MS (ES) $m/z : 446.28$ $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.00 (s, 1H), 8.77 (s, 1H), 8.26 (s, 1H), 8.20 (d, $J = 4.96$ Hz, 1H), 7.92 (d, $J = 6.80$ Hz, 1H), 7.08-.93 (m, 4H), 5.01 (bs, 1H), 4.11-4.0 (m, 2H), 3.84 (s, 3H), 3.80-3.63 (m, 2H), 3.48 (d, $J = 7.32$ Hz, 3H), 3.37-3.26 (m, 1H), 3.09 (s, 2H), 2.81-2.57 (m, 4H), 2.40-2.32 (m, 2H).

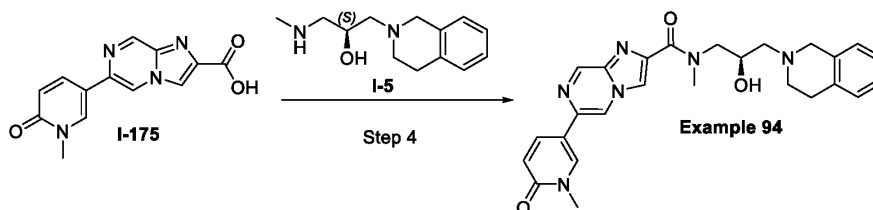
(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 93)



[000361] LC-MS (ES) $m/z = 473.38$ $[M+H]^+$. Note : compound is rotameric, two sets of peak appeared. ^1H NMR (400 MHz, DMSO- d_6) δ 9.33 & 9.2 (s, 1H), 9.23 & 9.08 (s, 1H), 8.39 & 8.3 (s, 1H), 7.84 (d, $J = 7.1$ Hz, 1H), 7.19-6.82 (m, 6H), 6.79 (d, $J = 7.1$

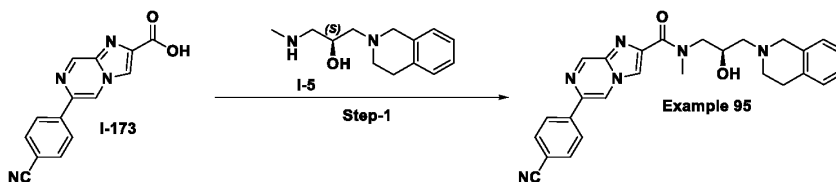
Hz, 1H), 4.96 & 4.84 (bs, 1H), 4.12-4.01 (m, 1H), 3.84-3.75 (m, 1H), 3.64-3.58 (m, 1H), 3.47-3.4374 (m, 4H), 3.1 (bs, 2H), 2.82-2.68 (m, 4H), 2.59 (bs, 2H), 2.39-2.37 (m, 2H).

(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 94)



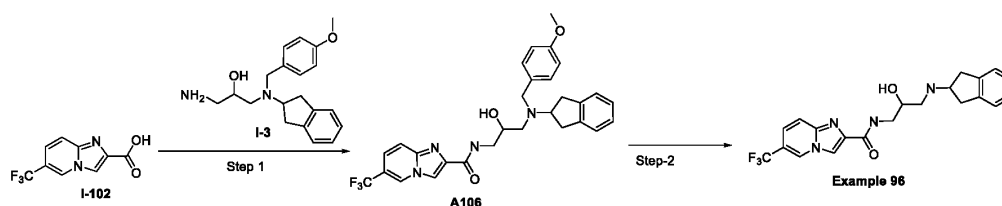
[000362] LC-MS (ES) $m/z = 473.38$ $[M+H]^+$. Note : compound is rotameric, two sets of peak appeared. ^1H NMR (400 MHz, DMSO- d_6) δ 9.17 & 9.04 (s, 1H), 8.99 & 8.71 (s, 1H), 8.44-8.27 (m, 2H), 7.98 (bs, 1H), 7.08-6.92 (m, 4H), 6.54 (d, $J = 9.0$ Hz, 1H), 5.0 & 4.84 (bs, 1H), 4.11-4.01 (m, 1H), 3.84-3.75 (m, 1H), 3.64 (bs, 1H), 3.55 (s, 3H), 3.49-3.44 (m, 3H), 3.09 (s, 2H), 2.81-2.73 (m, 2H), 2.59 (bs, 2H), 2.39 (bs, 2H).

(R)-6-(4-cyanophenyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methylimidazo[1,2-a]pyrazine-2-carboxamide (Example 95)



[000363] LC-MS (ES) $m/z : 467.36$ $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.23-9.13 (bs, 2H), 8.36 (s, 1H), 8.21 (d, $J = 8.16$ Hz, 2H), 7.95 (d, $J = 8.32$ Hz, 2H), 7.08-6.89 (m, 4H), 4.98 (d, $J = 4.88$ Hz, 1H), 4.13-4.03 (m, 2H), 3.86-3.78 (m, 1H), 3.64 (s, 1H), 3.49 (s, 3H), 3.31-3.24 (m, 1H), 3.10 (s, 2H), 2.81-2.58 (m, 5H), 2.39-2.32 (m, 2H).

Synthesis of N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 96)



Step 1: Preparation of N-(3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (A106)

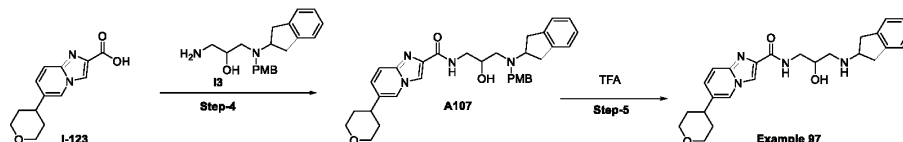
[000364] To a solution of 6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxylic acid (**I-102**, 0.1 g, 0.43 mmol) in DMF (5 ml) were added 1-amino-3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)propan-2-ol (**I3**, 0.17 g, 0.52 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.124 g, 0.651 mmol), N,N-Diisopropylethylamine (0.17 g, 13.03 mmol) and hydroxybenzotriazole (0.088 g, 0.65 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated and basified with sodium bicarbonate solution then extracted with dichloromethane. The combined organic layer was washed with brine solution and dried over anhydrous sodium sulphate, concentrated solvent under reduced pressure to give crude product. The compound was purified using column chromatography using 50 % ethyl acetate/hexane as eluent to give **A106** as a yellow sticky mass (0.08 g, 34.33 %). MS (ESI) $m/z = 539.2 [M+H]^+$.

Step 2: Preparation of N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 96)

[000365] A solution of N-(3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (**A102**, 0.08 g, 0.148 mmol) in trifluoroacetic acid (1 mL) was heated at 120 °C for 2 h in a microwave. The reaction mixture was concentrated, basified with sodium bicarbonate solution and was extracted with ethyl acetate. The combined organic layer washed with brine solution, dried over anhydrous sodium sulphate and then concentrated under reduced pressure to give crude product. The compound was purified by column chromatography using 7% methanol/dichloromethane as eluent to give the title **Example 96** as white solid (0.0085 g, 13.7 %). ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 9.26 (s, 1H), 8.44 (s, 1H), 8.38 (bs, 1H), 7.78 (s, $J = 9.2$ Hz 1H), 7.58 (d, $J = 9.2$ Hz, 1H),

7.14 (s, 2H), 7.08-7.07 (m, 2H), 4.94 (d, $J = 4.8$ Hz, 1H), 3.65-3.64 (m, 1H), 3.47-3.35 (m, 2H), 3.05-3.00 (m, 3H), 2.65 (s, 2H), 2.58-2.54 (m, 2H); MS (ESI) m/z 419.2 $[M+H]^+$.

N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 97)



Step-4: N-(3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (7)

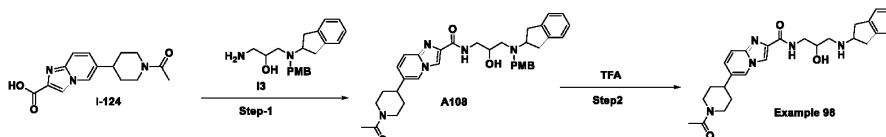
[000366] To a solution of 6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxylic acid (I-123, 0.30 g, 1.21 mmol) in DMF (15 mL) was added DIPEA (0.60 mL, 3.63 mmol) followed by HATU (0.55 g, 1.45 mmol). The reaction mixture was stirred for 10 min followed by addition of 1-amino-3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)propan-2-ol (I-3, 0.59 g, 1.81 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was monitored till the completion of starting materials (LC/MS) and then concentrated under reduced pressure. The obtained crude was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford N-(3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (A107) White solid Yield: 0.35 g, 53%). LC-MS (ES) m/z : 555.19 $[M+H]^+$

Step-5: N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxamide

[000367] To a solution of N-(3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (A107, 0.20 g, 0.36 mmol) in TFA (4 mL). The reaction mixture was stirred in a microwave at 120 °C. After completion of reaction organic solvent was evaporated. The obtained crude was purified by prep-HPLC to afford N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxamide Example 97 as off white solid Yield: 0.045 g (30%) LC-MS (ES) m/z : 435.20 $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.43 (s, 1H), 8.32 (bs, 1H), 8.29 (s, 1H), 7.53 (d, $J = 9.28$ Hz, 1H), 7.35 (d, $J = 9.28$ Hz, 1H), 7.18

(d, J = 3.08 Hz, 2H), 7.12 (d, J = 2.92 Hz, 2H), 5.43 (bs, 1H), 3.96 (d, J = 7.72 Hz, 1H), 3.80 (bs, 1H), 3.67 (bs, 1H), 3.44-3.32 (m, 5H), 3.15-3.10 (m, 2H), 2.81-2.67 (m, 5H), 1.77 (d, J = 11.36 Hz, 2H), 1.68-1.62 (m, 2H).

6-(1-acetylpiperidin-4-yl)-N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 98)



Step 1: 6-(1-acetylpiperidin-4-yl)-N-(3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (A108)

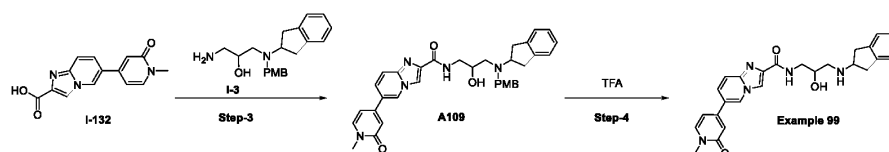
[000368] To a solution of 6-(1-acetylpiperidin-4-yl)imidazo[1,2-a]pyridine-2-carboxylic acid (I-124, 0.75 g, 2.61 mmol) in DMF (15 mL) was added DIPEA (1.4 mL, 7.83 mmol) followed by HATU (1.48 g, 3.91 mmol). The reaction mixture was stirred for 10 min followed by addition of 1-amino-3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)propan-2-ol (I-3, 1.28 g, 3.91 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was monitored till the completion of starting materials (LC/MS) and then concentrated under reduced pressure. The obtained crude was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford 6-(1-acetylpiperidin-4-yl)-N-(3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide A108 as Yellow solid (0.80 g, 53%). LC-MS (ES) m/z : 496.24 [M+H]⁺

Step-2: 6-(1-acetylpiperidin-4-yl)-N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide

[000369] To a solution of 6-(1-acetylpiperidin-4-yl)-N-(3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (A108, 0.140 g, 0.235 mmol) in TFA (2 mL). The reaction mixture was stirred in a microwave at 120 °C. After completion of reaction organic solvent was evaporated. The obtained crude was purified by prep-HPLC to afford 6-(1-acetylpiperidin-4-yl)-N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide Example 98 as off white solid

Yield: 0.035 g (30%) LC-MS (ES) m/z : 476.25 $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.44 (s, 1H), 8.39 (dd, J = 9.02 Hz, 5.04Hz, 1H), 8.29 (s, 1H), 7.53 (d, J = 9.40 Hz, 1H), 7.34 (d, J = 9.24 Hz, 1H), 7.20-7.13 (m, 4H), 5.43 (bs, 1H), 4.53 (d, J = 12.4 Hz, 1H), 3.93 (d, J = 4.84 HZ, 1H), 3.92-3.86 (m, 2H), 3.38-3.11 (m, 5H), 2.89-2.60 (m, 7H), 2.03 (s, 3H), 1.86 (t, J = 13.32 Hz, 2H), 1.62-1.49 (m, 2H).

N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 99)



Step-3: N-(3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (A109)

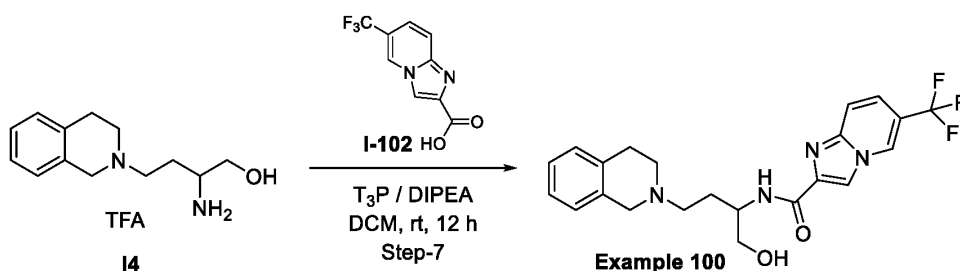
[000370] To a solution of 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxylic acid (I-132, 0.28 g, 1.03 mmol) in DMF (6 mL) was added DIPEA (0.51 mL, 3.11 mmol) followed by HATU (0.46 g, 1.23 mmol). The reaction mixture was stirred for 10 min followed by addition of 1-amino-3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)propan-2-ol (5, 0.50 g, 1.54 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was monitored till the completion of starting materials (LC/MS) and then concentrated under reduced pressure. The obtained crude was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford to N-(3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (A109) as off white solid (0.15 g, 25%).

Step-4: N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide

[000371] To a solution of N-(3-((2,3-dihydro-1H-inden-2-yl)(4-methoxybenzyl)amino)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (A109, 0.150 g, 0.235 mmol) in TFA (4 mL). The reaction mixture was stirred in a microwave at 120 °C. After completion of reaction organic solvent was evaporated. The obtained crude was purified by prep-HPLC to afford N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-

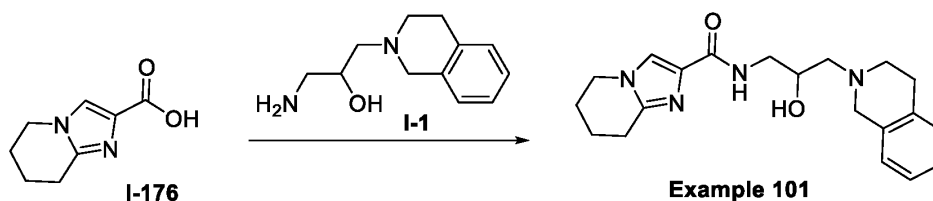
dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide Example 99 as off white solid Yield: 0.025 g (21%) LC-MS (ES) m/z : 458.0 $[M+H]^+$ ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.14 (s, 1H), 8.56 (bs, 1H), 8.37 (s, 1H), 7.85 (d, J = 7.12 Hz, 1H), 7.75 (d, J = 9.48 Hz, 1H), 7.67 (d, J = 9.56 Hz, 1H), 7.24 (d, J = 3.12 Hz, 2H), 7.18 (dd, J = 8.44 Hz, 5.36Hz, 2H), 6.79 (s, 1H), 6.62-6.60 (dd, J = 7.04 Hz, 1.72 Hz, 1H), 5.76 (bs, 1H), 4.01 (bs, 2H), 3.46 (s, 3H), 3.42-3.40 (m, 2H), 3.27-3.21 (m, 2H), 3.13-3.03 (m, 3H), 2.89 (t, J = 11.80 Hz, 1H).

Synthesis of N-(4-(3,4-dihydroisoquinolin-2(1H)-yl)-1-hydroxybutan-2-yl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 100)



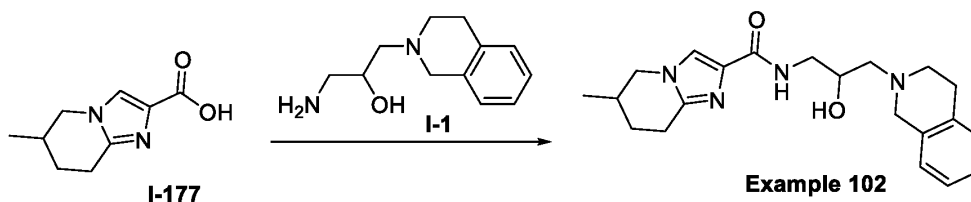
[000372] To a solution of 6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxylic acid (**I-102**, 0.043 g, 0.18 mmol) in dichloromethane (5 mL) was added N,N-diisopropylethylamine (0.19 g, 0.6 mmol). The resulting mixture was stirred at 0 °C for 15 minutes. 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (0.07 g, 0.2 mmol) was added into the reaction mixture and further reaction mixture was stirred for 10 minutes at 0 °C. TFA salt of 2-amino-4-(3,4-dihydroisoquinolin-2(1H)-yl)butan-1-ol (**14**, 0.299 g, 2.475 mmol) was added into the reaction mixture. The resulting mixture was stirred at RT or 16 h. The reaction mixture was diluted with dichloromethane and washed with ice cooled water. The organic layer dried over anhydrous sodium sulfate, concentrated to get crude residue. The crude residue was purified by column chromatography using ethyl acetate/n-hexane as eluent to afford N-(4-(3,4-dihydroisoquinolin-2(1H)-yl)-1-hydroxybutan-2-yl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide as off-white solid (0.01 g, 11%). ^1H NMR (DMSO- d_6 , 400 MHz, ppm): δ 9.26 (s, 1H), 8.36 (d, 1H, J = 4.4 Hz), 8.20 – 8.09 (m, 1H), 7.76 (t, 1H, J = 8.4 Hz), 7.56 (d, 1H, J = 9.6 Hz), 7.13 – 6.99 (m, 4H), 4.86 (s, 1H), 4.12 – 3.97 (m, 2H), 3.87 (s, 1H), 3.44 (s, 2H), 3.21 (s, 1H), 2.90 (s, 3H), 2.05 – 1.99 (m, 2H), 1.33 (s, 1H), 0.86 (d, 1H, J = 6 Hz); MS (ESI) m/z = 433.2 $[M+H]^+$.

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 101)



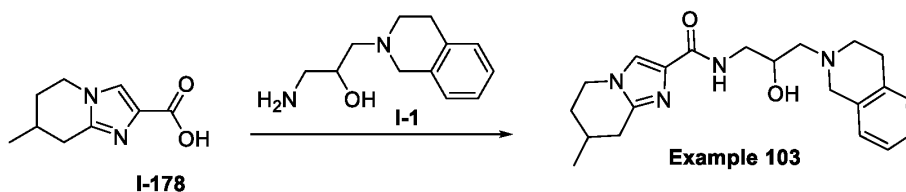
[000373] **Example 101** as an off-white solid (0.025 g, 14.5%). ¹H NMR (400 MHz, DMSO-d₆): δ 7.76 (t, *J* = 5.2Hz, 1H), 7.42 (s, 1H), 7.04-7.07 (m, 3H), 6.98-7.00 (m, 1H), 4.84 (d, *J* = 4.4Hz, 1H), 3.94 (t, *J* = 5.6Hz, 2H), 3.79-3.83 (m, 1H), 3.58 (s, 2H), 3.33-3.39 (m, 1H), 3.16-3.22 (m, 1H), 2.80-2.81 (m, 2H), 2.71-2.76 (m, 1H), 2.64-2.70 (m, 3H), 2.40-2.45 (m, 2H), 1.79-1.85 (m, 4H). LC-MS (ES) *m/z* = 355.5 [M+H]⁺.

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 102)



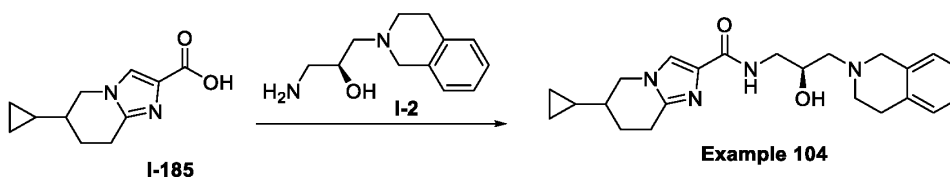
[000374] **Example 102** was prepared according to method exemplified for **Example 1** starting from the acid (**I-177**, 0.15 g, 0.83 mmol) and (**I1**, 0.15g, 0.7mmol) as an off white solid. (0.015 g, 5.8%). ¹H NMR (400 MHz, DMSO-d₆): δ 7.75 (t, *J* = 5.2Hz, 1H), 7.42 (s, 1H), 7.06-7.07 (m, 3H), 7.00-7.04 (m, 1H), 4.86 (bs, 1H), 4.03-4.06 (m, 1H), 3.81-3.82 (m, 1H), 3.54-3.59 (m, 2H), 3.44-3.49 (m, 1H), 3.33-3.39 (m, 1H), 3.16-3.22 (m, 1H), 2.77-2.80 (m, 2H), 2.59-2.75 (m, 4H), 2.02-2.05 (m, 1H), 1.87-1.91 (m, 1H), 1.44-1.54 (m, 1H), 1.00 (d, *J* = 6.4Hz, 3H)- 2 of the aliphatic protons merged. MS (ESI) *m/z* = 369.3 [M+H]⁺.

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-7-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 103)



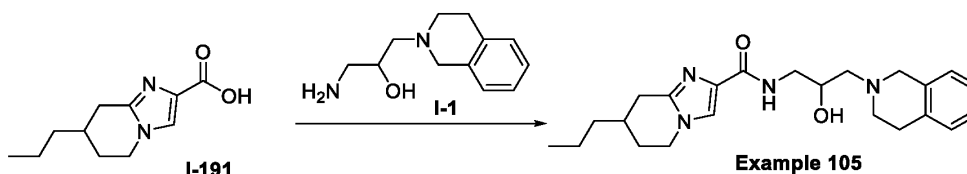
[000375] **Example 103** was prepared according to method exemplified for **Example 1** starting from the acid (**I-178**, 0.15 g, 0.83 mmol) and (**I1**, 0.15 g, 0.7 mmol) as an off white solid (0.02 g, 6.6%). ^1H NMR (400 MHz, DMSO-d_6): δ 7.76 (bs, 1H), 7.42 (s, 1H), 7.02-7.09 (m, 3H), 7.02-7.09 (m, 1H), 4.83 (bs, 1H), 4.02-4.06 (m, 1H), 3.82 (bs, 2H), 3.59 (bs, 1H), 3.44-3.49 (m, 1H), 3.32-3.37 (m, 1H), 3.18-3.21 (m, 1H), 2.76-2.87 (m, 2H), 2.59-2.72 (m, 5H), 2.02-2.05 (m, 2H), 1.89-1.90 (m, 1H), 1.44-1.54 (m, 1H), 1.00 (d, $J = 6.4\text{Hz}$, 3H). MS (ESI) $m/z = 369.2$ $[\text{M}+\text{H}]^+$.

6-cyclopropyl-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 104)



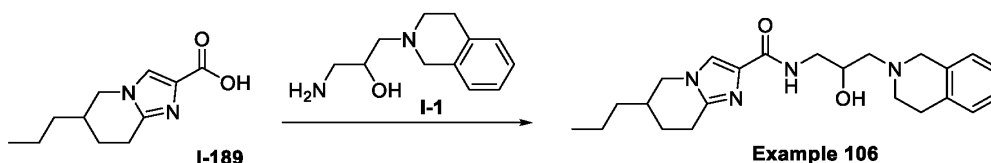
[000376] **Example 104** was prepared according to method exemplified for **Example 1** starting from the acid (**I-185**, 0.29 g, 1.4 mmol) and (**I2**, 0.29 g, 1.4mmol) as an off white solid (0.01 g, 8.7%). Compound was isolated as TFA salt since TFA was used as one of the eluent. ^1H NMR (400 MHz, DMSO-d_6): δ 9.79 (br, 1H), 8.2 (br, 1H), 7.75 (br, 1H), 7.27-7.18 (m, 4 H), 5.80 (br, 1H), 4.52 (br, 1H), 4.36 (br, 1H), 4.17 (br, 2H), 3.78 – 3.73 (m, 2H), 3.37 (s, 3H), 3.25 – 3.32 (m, 1H), 3.14 – 2.89 (m, 4H), 2.75 (br, 1H), 2.01 (br, 1H), 1.69 (d, 1H, $J = 6.8\text{ Hz}$), 1.22 (br, 1H), 0.68 (br, 1H), 0.46 (d, 2H, $J = 7.2\text{ Hz}$), 0.21 (t, 2H, $J = 9.6\text{ Hz}$). MS (ESI) $m/z = 395.2$ $(\text{M}+\text{H})^+$.

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-7-propyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 105)



[000377] To a stirred solution of 7-propyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (**I-191**, 0.09 g, 0.43 mmol) in DMF (6 mL) was added compound (**II**, 0.095 g, 0.46 mmol) followed by DIPEA (0.22 mL, 1.29 mmol), HATU (0.24 g, 0.64 mmol). The reaction mixture was stirred for 16h at room temperature. The reaction mixture was diluted with ethyl acetate, washed with water, brine, dried over anhydrous sodiumsulfate, filtered and concentrated. Purification was done by preparative HPLC to afford as white solid (0.05 g, 29 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.42 (s, 1H), 7.02-7.08 (m, 4H), 6.98-7.02 (m, 1H), 4.85 (bs, 1H), 4.06-4.09 (m, 1H), 3.75-3.85 (m, 2H), 3.55-3.60 (m, 2H), 3.32-3.33 (m, 1H), 3.20 (m, 1H merged with DMSO-H₂O peak), 2.65-2.82 (m, 5H), 1.95-2.05 (m, 1H), 1.65-1.75 (m, 1H), 1.50-1.65 (m, 2H), 1.25-1.35 (m, 1H), 1.10-1.20 (m, 1H), 0.90-0.92 (m, 3H), 0.65-0.75 (m, 1H), 0.41-0.43 (m, 1H), 0.16-0.17 (m, 1H); MS (ESI) *m/z* = 397.2 (M+H)⁺.

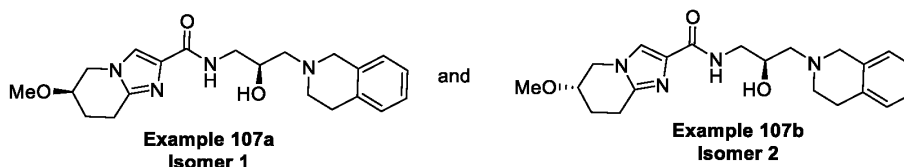
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-propyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 106)



[000378] **Example 106** was prepared according to method exemplified for **Example 105** starting from the acid (**I-189**, 0.05 g, 0.24 mmol) and (**I-1**, 0.74 g, 0.36 mmol) as an off white solid (0.007 g, 7 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.91 (bs, 1H), 7.44-7.50 (m, 1H), 7.14-7.24 (m, 3H), 5.40-5.82 (bs, 1H), 3.90-4.30 (m, 3H), 3.52-3.72 (m, 2H), 3.20-3.49 (m, 2H beneath under DMSO-H₂O peak), 2.65-2.83 (m, 5H), 1.81-2.06 (m, 2H), 1.58-1.67 (m, 1H), 1.45-1.55 (m, 1H), 1.30-1.40 (m, 2H), 0.83-0.94 (m, 3H), 0.65-0.75 (m, 1H), 0.41-0.45 (m, 1H), 0.20-0.21 (m, 1H); MS (ESI) *m/z* = 397.3 (M+H)⁺.

(R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methoxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 107a) and (S)-

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methoxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 107b)



[000379] **Example 107a and 107b** was prepared according to method exemplified for **Example 105** starting from the acid (**I-186**, 0.4 g, 2.0 mmol) and (**I2**, 0.516 g, 2.0 mmol) as white solids after purification through preparative HPLC using a chiral column **Example 107a** (0.020 g, 5.1 %) and **Example 107b** (0.045 g, 12.5 %).

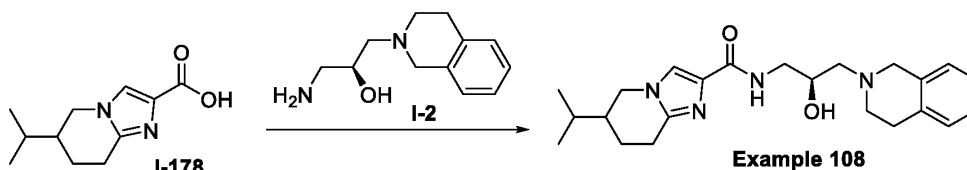
Example 1077a

[000380] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.77 (t, $J = 5.4$ Hz, 1H), 7.43 (s, 1H), 7.08 – 7.06 (m, 3H), 7.00 – 6.99 (m, 1H), 4.86 (s, 1H), 4.08 – 4.00 (m, 2H), 3.83 – 3.82 (m, 2H), 3.58 (s, 2H), 3.39 – 3.18 (m, 4H), 2.86 – 2.80 (m, 2H), 2.76 – 2.61 (m, 4H), 2.48 – 2.41 (m, 2H), 2.11 – 2.05 (m, 1H), 1.94 – 1.90 (m, 1H). MS (ESI) $m/z = 385.2[\text{M}+\text{H}]^+$.

Example 107b

[000381] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.77 (bs, 1H), 7.43 (s, 1H), 7.07 (bs, 3H), 7.00 (bs, 1H), 4.89 (bs, 1H), 4.04 (bs, 2H), 3.82 (bs, 2H), 3.64 (s, 2H), 3.45 – 3.18 (m, 6H), 2.84 – 2.67 (m, 6H), 2.11 – 2.10 (m, 1H), 1.94 – 1.87 (m, 1H). MS (ESI) $m/z = 385.2[\text{M}+\text{H}]^+$.

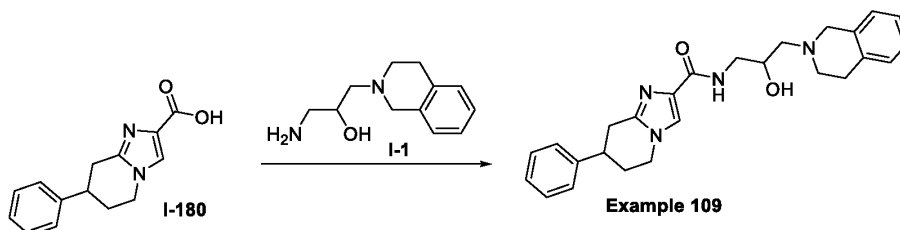
N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-isopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 108)



[000382] **Example 108** was prepared according to method exemplified for **Example 105** starting from the acid (**I-178**, 0.44 g, 2.12 mmol) and (**I2**, 0.52 g, 2.54 mmol) as an off white solid (0.125 g, 15%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.64 (s, 1H), 7.82 (s, 1H), 7.32-7.22 (m, 3H), 7.18 (d, $J = 6.8$ Hz, 1H), 4.94 (d, $J = 4.4$ Hz, 1H), 4.60-4.46 (m, 1H), 4.42-4.28 (m, 2H), 4.26-4.14 (m, 1H), 3.78-3.62 (m, 3H), 3.42-3.24 (m, 4H), 3.22-3.10 (m, 2H), 3.02-2.92 (m, 1H), 2.86-2.75 (m, 1H), 2.06-1.98 (m, 1H),

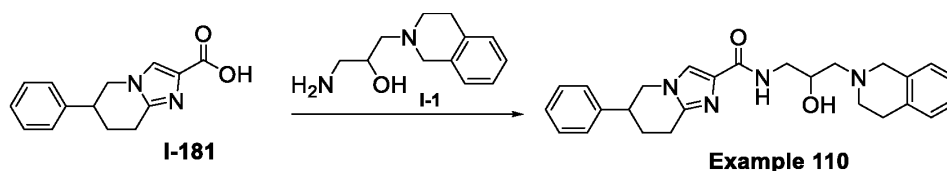
1.82-1.72 (m, 1H), 1.69-1.50 (m, 2H), 0.94 (d, $J = 6.8$ Hz, 6H). MS (ESI) $m/z = 397.3$ $[M+H]^+$.

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-7-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 109)



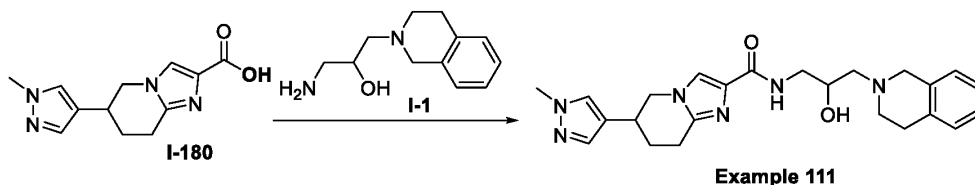
[000383] **Example 109** was prepared according to method exemplified for **Example 105** starting from the acid (**I-180**, 0.1 g, 0.41 mmol) and (**I1**, 0.13 g, 0.61mmol) as an off white solid (0.016 g, 9.5%). Compound was isolated as TFA salt since TFA was used as one of the eluent. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): (TFA salt) δ 9.76 (bs, 1H), 8.31 (bs, 1H), 7.71 (s, 1H), 7.33-7.35 (m, 4H), 7.23-7.25 (m, 4H), 7.15-7.19 (m, 1H), 5.83(bs, 1H), 4.32-4.36 (m, 1H), 4.13-4.18(m, 2H), 4.03-4.074 (m, 2H), 3.26-3.45 (m, 6H), 3.07-3.11 (m, 4H), 2.92-2.95(m, 2H). MS (ESI) $m/z = 431.3$ $[M+H]^+$.

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 110)



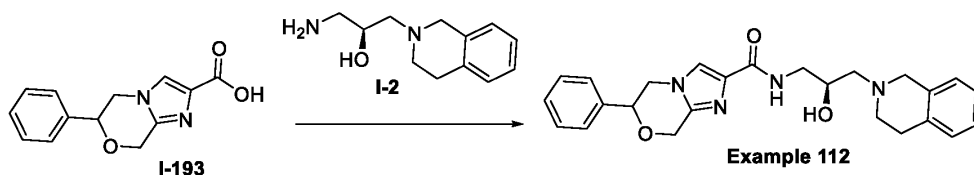
[000384] **Example 110** was prepared according to method exemplified for **Example 105** starting from the acid (**I-181**, 0.26 g, 1.074 mmol) and (**I1**, 0.243 g, 1.182 mmol) as a white solid (0.225 g, 49%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.60 (bs, 1H), 7.84 (s, 1H), 7.40-7.33 (m, 4H), 7.31-7.21 (m, 4H), 7.20-7.16 (m, 1H), 4.60-4.48 (m, 1H), 4.42-4.34 (m, 2H), 4.24-4.15 (m, 1H), 4.06 (t, $J = 12$ Hz, 1H), 3.80-3.62 (m, 1H), 3.50-3.42 (m, 1H), 3.38-3.34 (m, 2H), 3.32-3.26 (m, 2H), 3.22-3.12 (m, 2H), 3.06-2.96 (m, 3H), 2.20-2.10 (m, 2H). MS (ESI) $m/z = 431.2$ $[M+H]^+$.

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 111)



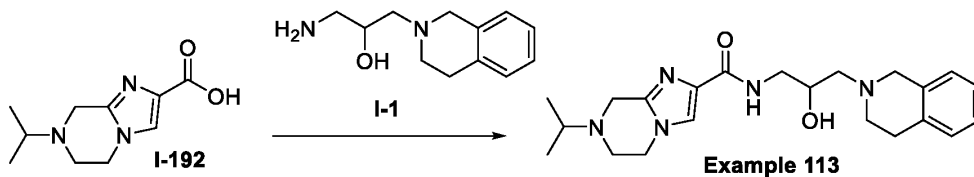
[000385] **Example 11** was prepared according to method exemplified for **Example 105** starting from the acid (**I-180**, 0.1 g, 0.41 mmol) and (**I1**, 0.1 g, 0.49 mmol) as a white solid (0.044 g, 25%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.78 (t, *J* = 5.2 Hz, 1H), 7.57 (s, 1H), 7.46 (s, 1H), 7.35 (s, 1H), 7.08 (d, *J* = 3.2 Hz, 3H), 7.02-6.98 (m, 1H), 4.86 (bs, 1H), 4.28-4.20 (m, 1H), 3.90-3.80 (m, 2H), 3.77 (s, 3H), 3.62-3.56 (m, 2H), 3.44-3.34 (m, 2H), 3.24-3.12 (m, 3H), 2.84-2.80 (m, 2H), 2.78-2.66 (m, 4H), 2.16-2.08 (m, 1H), 1.98-1.86 (m, 1H). MS (ESI) *m/z* = 435.2 [M+H]⁺.

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-phenyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine-2-carboxamide (Example 112)



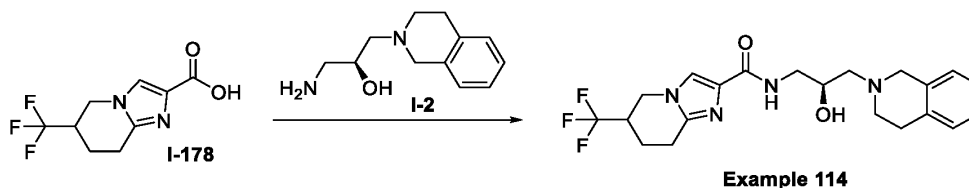
[000386] **Example 112** was prepared according to method exemplified for **Example 105** starting from the acid (**I-193**, 0.2 g, 0.8 mmol) and (**I2**, 0.329 g, 1.6 mmol) as a white solid (0.033 g, 9.3 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.86 (s, 1H), 7.58 (s, 1H), 7.46 – 7.42 (m, 2H), 7.39 - 7.35 (m, 3H), 7.07 (bs, 3H), 7.00 (bs, 1H), 5.01 - 4.99 (m, 1H), 4.91 - 4.82 (m, 3H), 4.37 – 4.34 (m, 1H), 3.98 (t, *J* = 12 Hz, 1H), 3.82 (bs, 1H), 3.59 (s, 2H), 3.36 - 3.22 (m, 2H), 2.86 - 2.81 (m, 3H), 2.77 - 2.64 (m, 2H). MS (ESI) *m/z* = 433.4[M+H]⁺.

N-(3-(3, 4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-7-isopropyl-5, 6, 7, 8-tetrahydroimidazo [1, 2-a] pyrazine-2-carboxamide (Example 113)



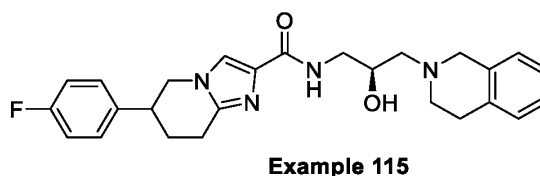
[000387] **Example 113** was prepared according to method exemplified for **Example 105** starting from the acid (**I-192**, 0.1 g, 0.47 mmol) and (**II**, 0.12 g, 0.574 mmol) as a white solid (0.02 g, 10 %). ^1H NMR (400 MHz, CDCl_3): δ 7.41-7.42 (m, 2H), 7.10-7.12 (m, 3H), 6.99 (d, $J = 5.2$ Hz, 1H), 3.79-3.82 (m, 1H), 3.75 (s, 2H), 3.59-3.67 (m, 3H), 3.40-3.47 (m, 1H), 2.89-2.96 (m, 6H), 2.73 (t, $J = 5.6$ Hz, 1H), 2.58 (d, $J = 6.4$ Hz, 2H), 1.13 (d, $J = 7.2$ Hz, 6H); MS (ESI) $m/z = 398.0$ ($\text{M}+\text{H}$) $^+$.

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 114)



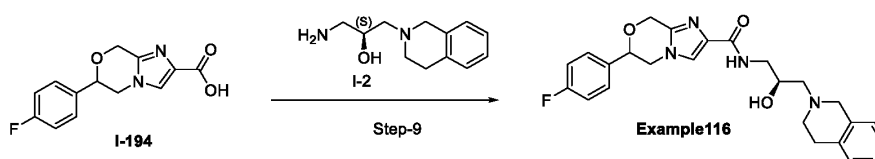
[000388] To a stirred solution of 6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (**I-178**, 0.64 g, 2.74 mmol) in DCM (10 mL) was added (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (**I2**, 0.68 g, 3.28 mmol) and triethylamine (1.14 mL, 8.21 mmol). Then reaction mixture was cooled to 0°C and T_3P (2.78 mL, 4.38 mmol) was added at the same temperature. The reaction mixture was then stirred at RT for 3 h. After completion of the reaction, the reaction mixture was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. Purification was done by Pre-HPLC in to afford **Example 114** as a white solid (0.032 g, 3%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.8 (t, $J = 5.2$ Hz, 1H), 7.53 (s, 1H), 7.10-6.98 (m, 4H), 4.85 (bs, 1H), 4.35-4.28 (m, 1H), 3.97 (t, $J = 10.4$ Hz, 1H), 3.86-3.78 (m, 1H), 3.58 (s, 2H), 3.42-3.32 (m, 1H), 3.24-3.12 (m, 3H), 2.88-2.78 (m, 4H), 2.69-2.61 (m, 3H), 2.2-2.12 (m, 1H), 1.95-1.82 (m, 1H). MS (ESI) $m/z = 423.2$ [$\text{M}+\text{H}$] $^+$.

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 115)



[000389] **Example 15** was prepared according to method exemplified for **Example 114** starting from the acid (**I-89**, 0.1 g, 0.39 mmol) and (**I2**, 0.1 g, 0.46 mmol) as a white solid (0.017 g, 10%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.80 (t, *J* = 5.6 Hz, 1H), 7.49 (s, 1H), 7.42-7.36 (m, 2H), 7.17 (t, *J* = 8.8 Hz, 2H), 7.10-7.04 (m, 3H), 7.02-6.98 (m, 1H), 4.87 (d, *J* = 3.6 Hz, 1H), 4.28-4.18 (m, 1H), 3.94 (t, *J* = 12 Hz, 1H), 3.88-3.80 (m, 1H), 3.60 (s, 2H), 3.42-3.16 (m, 5H), 2.90-2.80 (m, 4H), 2.78-2.70 (m, 1H), 2.68-2.62 (m, 1H), 2.14-2.02 (m, 2H). MS (ESI) *m/z* = 449.2 [*M*+H]⁺.

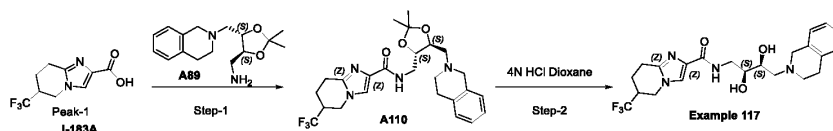
N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl)-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine-2-carboxamide (Example 116)



[000390] To a stirred solution of 6-(4-fluorophenyl)-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine-2-carboxylic acid (**11**, 0.3 g 1.14 mmol) in DMF (4 mL), HATU (0.652 g, 1.71 mmol) and DIPEA (0.99 mL, 5.72 mmol) were added and reaction mixture stirred at room temperature for 10 minutes. Then (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (**12**, 0.353 g, 1.71 mmol) was added dissolving in DMF (2 mL) and reaction mixture stirred at room temperature for 16 h. After completion, evaporated the solvent from reaction mixture to obtain the residue. This residue diluted with water and extracted with 10% MeOH in DCM (3 times). The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain the crude. This crude purified by combiflash using 5.0% MeOH in DCM as eluent. The desired fractions were concentrated under reduced pressure and again purified by prep HPLC to offered

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl)-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine-2-carboxamide as off white solid. Yield: 0.062 g (12%) LC-MS (ES) *m/z* = 451.16 [*M*+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.14 (bs, 1H), 7.68 (s, 1H), 7.53 (dd, *J* = 8.0, 5.6 Hz, 2H), 7.29-7.17 (m, 6H), 5.87 (bs, 1H), 5.06-4.92 (m, 3H), 4.59-4.51 (m, 1H), 4.42-4.32 (m, 3H), 4.17 (bs, 2H), 4.03 (t, *J* = 11.6 Hz, 1H), 3.68 (bs, 1H), 3.32 (bs, 3H), 3.21-3.08 (m, 2H).

N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 117)



Step-1: N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (A110)

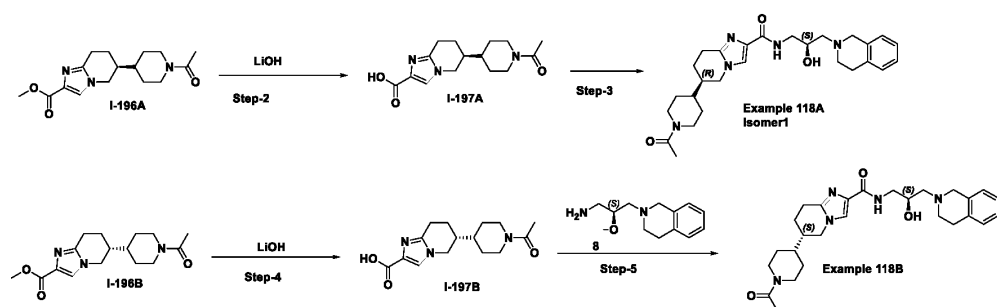
[000391] To a stirred solution of 6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (I-183A, 0.4 g 1.69 mmol) in DMF (3 mL), HATU (0.966 g, 2.54 mmol) and DIPEA (0.88 mL, 5.08 mmol) were added and reaction mixture stirred at room temperature for 10 minutes. Then ((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (A89, 0.467 g, 1.69 mmol) was added dissolving in DMF (2 mL) and reaction mixture stirred at room temperature for 16 h. After completion, reaction mixture quenched with water and extracted with ethyl acetate (3 times). The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain the crude. This crude purified by combiflash using 4.5% MeOH in DCM as eluent. The desired fractions were concentrated under reduced pressure to offered N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (A110) as brown gummy solid. Yield: 0.42 g (48%) LC-MS (ES) $m/z = 493.28$ $[M+H]^+$.

Step-2: N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide

[000392] To a stirred solution of N-(((4S,5S)-5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (3, 0.4 g 0.81 mmol) in MeOH (3 mL) at 0°C, 4N HCl in dioxane was added and reaction mixture stirred at room temperature for 4h. After completion, evaporated the solvent from reaction mixture to obtain the residue. This residue quenched with NaHCO₃ solution and extracted with ethyl acetate (3 times). The organic layer was separated, dried over anhydrous sodium sulphate and

concentrated under reduced pressure to obtain the crude. This crude washed with diethyl ether and on high vacuum pump to offered N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide as white solid. Yield: 0.124 g (32%) LC-MS (ES) m/z = 453.18 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 7.76 (t, J = 2.5 Hz, 1H), 7.55 (s, 1H), 7.09-7.0 (m, 4H), 4.8 (d, J = 5.6 Hz, 1H), 4.53 (d, J = 4.8 Hz, 1H), 4.33 (dd, J = 12.0, 4.7 Hz, 1H), 3.99 (t, J = 11.8 Hz, 1H), 3.64-3.56 (m, 4H), 3.43-3.4 (m, 1H), 3.21-3.19 (m, 2H), 2.91-2.84 (m, 2H), 2.78 (bs, 2H), 2.72-2.66 (m, 2H), 2.62-2.6 (m, 2H), 2.19-2.16 (m, 1H), 1.93-1.9 (m, 1H).

6-(1-acetylpiperidin-4-yl)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide- Isomer-1 (Example 118B)



Step-1: methyl 6-(1-acetylpiperidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (I196A and I196B)

[000393] To a solution of methyl 6-(piperidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (I-, 1.20 g, 4.55 mmol) in DCM (25 mL) at 0 °C was added TEA (1.90 mL, 13.67 mmol) and acetyl chloride (0.48 mL, 6.82 mmol) was added and the resulting solution was stirred at room temperature for 4 h. After completion of reaction diluted with DCM and washed with water the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude which was purified by prep-HPLC to afford methyl 6-(1-acetylpiperidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate 6 as a white solid. Yield: 0.25 g (15%) LC-MS (ES) m/z : 306.12 $[M+H]^+$ which was purified by chiral-HPLC to afford methyl 6-(1-acetylpiperidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate I196

: I196A and I196B & 2 as a white solid. (Peak-1) Yield: 0.090 g and (Peak-2) Yield: 0.12 g.

Step-2: 6-(1-acetylpiperidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (I197A)

[000394] To a stirred solution of methyl 6-(1-acetylpiperidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (**I196A**, 0.09 g, 0.29 mmol) in (6 mL) of THF:MeOH:H₂O (2:1:1) was added LiOH (0.022 g, 0.92 mmol). The reaction mixture was stirred for 3h at room temp. After completion of reaction organic solvent was evaporated and the aqueous layer was acidified with 1N HCl up to pH 3 to 4 and aqueous layer was concentrated to get crude as a 6-(1-acetylpiperidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid **I197A** as a white solid. Yield: 0.09 g (crude) LC-MS (ES) m/z : 292.16 [M+H]⁺

Step-3: 6-(1-acetylpiperidin-4-yl)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 118A)

[000395] To a solution of 6-(1-acetylpiperidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (**I197A**, 0.09 g, 0.30 mmol) in DMF (6 mL) was added DIPEA (0.15 mL, 0.90 mmol) followed by HATU (0.12 g, 0.33 mmol). The reaction mixture was stirred for 10 min followed by addition of (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (**8**, 0.092 g, 0.45 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was monitored till the completion of starting materials (LC/MS) and then concentrated under reduced pressure. The obtained crude was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford 6-(1-acetylpiperidin-4-yl)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide **118A** as white solid (0.015 g, 8%). LC-MS (ES) m/z : 480.37 [M+H]⁺ ¹H NMR (DMSO-*d*₆, 400 MHz, ppm) δ 7.79 (bs, 1H), 7.44 (d, J = 2.16 Hz, 1H), 7.08-7.02 (m, 4H), 4.89 (bs, 1H), 4.42 (d, J = Hz, 1H), 4.11-4.07 (dd, J = 7.84 Hz, 1H), 3.83 (d, J = 11.64 Hz, 2H), 3.71-3.65 (m, 1H), 3.59 (bs, 2H), 3.38-3.19 (m, 2H), 3.00-2.93 (m, 1H), 2.82-2.61 (m, 5H), 2.46-2.32 (m, 4H), 1.98 (s, 4H), 1.78-1.51 (m, 5H), 1.23-1.02 (m, 3H).

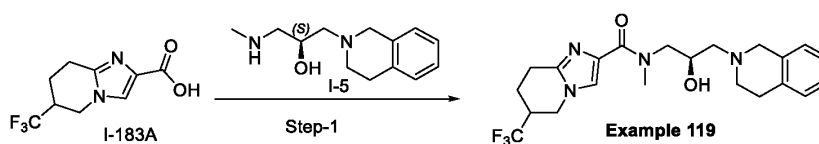
Step-4: 6-(1-acetylpiperidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (I197B)

[000396] To a stirred solution of methyl 6-(1-acetylpiperidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (**I196B** 0.12 g, 0.393 mmol) in (6 mL) of THF:MeOH:H₂O (2:1:1) was added LiOH (0.028 g, 1.18 mmol). The reaction mixture was stirred for 3h at room temp. After completion of reaction organic solvent was evaporated and the aqueous layer was acidified with 1N HCl up to pH 3 to 4 and aqueous layer was concentrated to get crude as a 6-(1-acetylpiperidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid **I197B** as a white solid. Yield: 0.12 g (crude) LC-MS (ES) m/z : 292.16 [M+H]⁺.

Step-5: 6-(1-acetylpiperidin-4-yl)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 118B)

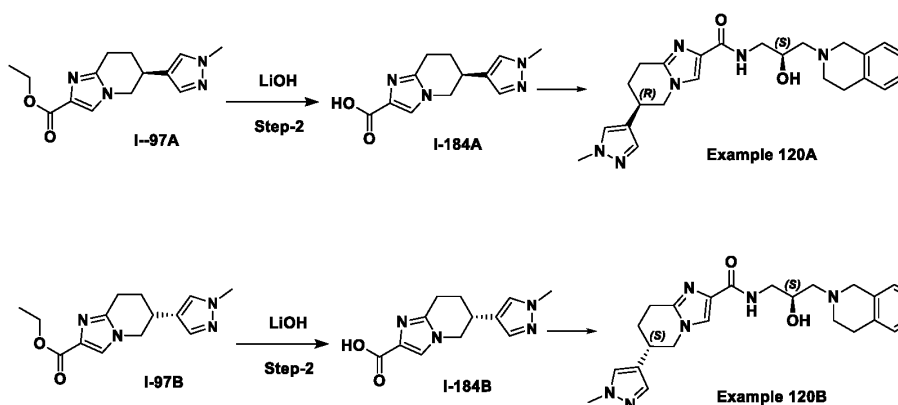
[000397] To a solution of 6-(1-acetylpiperidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (**I197B** 0.12 g, 0.41 mmol) in DMF (6 mL) was added DIPEA (0.20 mL, 1.23 mmol) followed by HATU (0.17 g, 0.45 mmol). The reaction mixture was stirred for 10 min followed by addition of (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (8, 0.120 g, 0.61 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was monitored till the completion of starting materials (LC/MS) and then concentrated under reduced pressure. The obtained crude was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford 6-(1-acetylpiperidin-4-yl)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide Example 118B as white solid (0.025 g, 13%). LC-MS (ES) m/z : 480.34 [M+H]⁺ ¹H NMR (DMSO-*d*₆, 400 MHz, ppm) δ 7.82 (bs, 1H), 7.45 (s, 1H), 7.11-7.04 (m, 4H), 4.91 (bs, 1H), 4.42 (d, J = 12.20 Hz, 1H), 4.09 (d, J = 7.84 Hz, 1H), 3.84 (d, J = 12.72 Hz, 2H), 3.71-3.61 (m, 2H), 3.38-3.28 (m, 2H), 3.07-2.77 (m, 5H), 2.66-2.59 (m, 5H), 1.98 (m, 4H), 1.78-1.52 (m, 5H), 1.23-1.10 (m, 3H).

N--3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example-119)



[000398] To a stirred solution of 6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (I-187, 0.2 g 0.85 mmol) in DMF (3 mL), HATU (0.487 g, 1.28 mmol) and DIPEA (0.74 mL, 4.27 mmol) were added and reaction mixture stirred at room temperature for 10 minutes. Then (S)-1-(3,4-dihydroisoquinolin-2(1H)-yl)-3-(methylamino)propan-2-ol (I-5, 0.225 g, 1.02 mmol) was added dissolving in DMF (2 mL) and reaction mixture stirred at room temperature for 16 h. After completion, reaction mixture quenched with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain the crude. This crude purified by combiflash using 3.0% MeOH in DCM as eluent. The desired fractions were concentrated under reduced pressure to offered N-((R)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide as white solid. Yield: 0.20 g (53%) LC-MS (ES) m/z = 437.28 $[M+H]^+$. Note : compound is rotameric, two sets of peak appeared. ^1H NMR (400 MHz, DMSO- d_6) δ 7.52 (s, 1H), 7.09-7.01 (m, 4H), 5.56 (bs, 1H), 4.75 (bs, 1H), 4.29 (bs, 1H), 4.03 (bs, 1H), 3.93 (bs, 2H), 3.73 (bs, 1H), 3.57 (bs, 2H), 3.47 (bs, 1H), 3.13 (bs, 2H), 2.97 (s, 2H), 2.76 (bs, 4H), 2.69 (d, J = 4.8 Hz, 2H), 2.44 (d, J = 5.7 Hz, 3H), 2.15 (bs, 1H), 1.87 (bs, 1H). At higher temperature: ^1H NMR (400 MHz, DMSO- d_6) δ 7.48 (s, 1H), 7.08 (d, J = 4.1 Hz, 3H), 7.01 (d, J = 4.3 Hz, 1H), 4.93 (bs, 1H), 4.33-4.28 (m, 1H), 4.03-3.94 (m, 2H), 3.84 (bs, 1H), 3.62 (s, 2H), 3.53 (bs, 1H), 3.12 (bs, 2H), 2.89-2.85 (m, 1H), 2.79-2.74 (m, 5H), 2.5 (s, 3H), 2.19-2.16 (m, 1H), 1.93-1.89 (m, 1H).

(R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 120A and 120B)



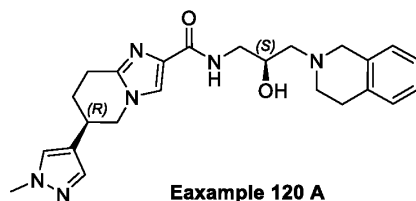
Step-1 ethyl 6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (2)

[000399] To a stirred solution of ethyl 6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxylate (0.7 g, 2.58 mmol) in MeOH (25 mL) was added ammonium formate (0.48 g, 7.76 mmol), followed by 10% Pd/C (0.21 g). The reaction mixture was heated for 16 h at 100 °C. after completion of reaction mixture filtered over celite bed and washed with EtOAc. The filtrate was washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained crude was purified by chiral prep-HPLC to afford ethyl 6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate I97A and B as white solid Yield: I97A 0.12g, (17%) & I97B 0.08g, (11%). LC-MS m/z: 275.17 [M+H]⁺.

Step-2: 6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (I-184-A)

[000400] To a stirred solution of ethyl 6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (I-197A, 0.12 g, 0.43 mmol) in (6 mL) of THF:MeOH:H₂O (2:1:1) was added LiOH (0.05 g, 1.31 mmol). The reaction mixture was stirred for 3h at room temp. After completion of reaction organic solvent was evaporated and the aqueous layer was acidified with 1N HCl up to pH 3 to 4 and aqueous layer was concentrated to get crude as 6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid I-184A as off white solid. Yield: 0.12 g (crude) (91%) LC-MS (ES) m/z : 247.08 [M+H]⁺.

Step-3: (R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 120 A)

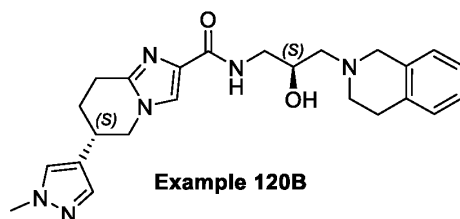
**Example 120 A**

[000401] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (I-184A, 0.12 g, 0.48 mmol) in DMF (10 mL) was added DIPEA (0.25 mL, 1.46 mmol) followed by HATU (0.27 g, 0.73 mmol). The reaction mixture was stirred for 10 min followed by addition of (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (I2, 0.12 g, 0.06 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was monitored till the completion of starting materials and then concentrated under reduced pressure. The obtained crude was purified by Prep HPLC to afford (R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide Example 120A as off white solid. Yield: 0.009 g, (4%). LC-MS (ES) m/z : 435.35 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm)- δ 7.80 (dd, J = 11.16 Hz, 1H), 7.58 (s, 1H), 7.47 (s, 1H), 7.36 (s, 1H), 7.09 (d, J = 3.68 Hz, 3H), 7.02 (bs, 1H), 4.90 (d, J = 4.60 Hz, 1H), 4.27-4.22 (dd, J = 12.36 Hz, 5.12 Hz, 1H), 3.89-3.83 (m, 2H), 3.78 (s, 3H), 3.59 (s, 2H), 3.39-3.17 (m, 5H), 2.82-2.62 (m, 6H), 2.13 (d, J = 11.56 Hz, 1H), 1.95-1.89 (m, 1H).

Step-2: 6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid I-184B

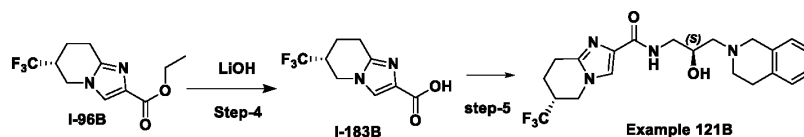
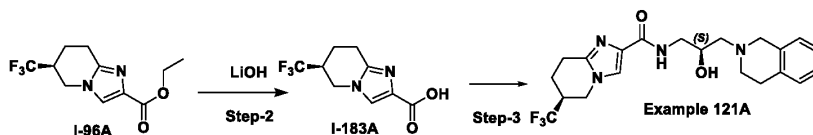
[000402] To a stirred solution of ethyl 6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (**5**, 0.08 g, 0.32 mmol) in (6 mL) of THF:MeOH:H₂O (2:1:1) was added LiOH (0.04 g, 0.97 mmol). The reaction mixture was stirred for 3h at room temp. After completion of reaction organic solvent was evaporated and the aqueous layer was acidified with 1N HCl up to pH 3 to 4 and aqueous layer was concentrated to get crude as 6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid **I-184B** as off white solid. Yield: 0.08 g crude (93%) LC-MS (ES) m/z : 247.08 $[M+H]^+$.

Step 3: (S)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 120B)



[000403] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (I-184B, 0.18 g, 0.32 mmol) in DMF (10 mL) was added DIPEA (0.17 mL, 0.97 mmol) followed by HATU (0.27 g, 0.48 mmol). The reaction mixture was stirred for 10 min followed by addition of (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (I2, 0.08 g, 0.38 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was monitored till the completion of starting materials and then concentrated under reduced pressure. The obtained crude was purified by Prep HPLC (S)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide Example 120B as off white solid Yield: 0.019 g, (13%). LC-MS (ES) m/z : 435.40 $[M+H]^+$. ^1H NMR (DMSO- d_6 , 400 MHz, ppm)- δ 7.81 (dd, J = 11.20 Hz, 1H), 7.58 (s, 1H), 7.47 (s, 1H), 7.36 (s, 1H), 7.09 (d, J = 4.60 Hz, 3H), 7.02 (d, J = 4.52 Hz, 1H), 4.90 (d, J = 4.52 Hz, 1H), 4.27-4.22 (dd, J = 12.36 Hz, 5.12 Hz, 1H), 3.88-3.80 (m, 2H), 3.78 (s, 3H), 3.59 (s, 2H), 3.39-3.18 (m, 3H), 2.82-2.64 (m, 6H), 2.49-2.42 (m, 2H), 2.14-2.12 (m, 1H), 1.95-1.89 (m, 1H).

(R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 121A and 121B)



Step-1: ethyl (R)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (I-96B) (peak1) and ethyl (S)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (I-96A) (peak2)

[000404] To a stirred solution of ethyl 6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxylate (10.0 g 38.75 mmol) in THF 200 mL, PtO₂ (1.4 g, 6.5 mmol) was added and reaction mixture stirred at room temperature under H₂ atmosphere for 48 h. After completion, reaction mixture filter through celite bed and evaporated the filtrate to obtain the crude. This crude purified by column chromatography using 30%ethyl acetate in hexane as eluent. The desired fractions were concentrated under reduced pressure to obtain the compound. This compound purified by chiral HPLC to offered ethyl (R)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (**I-96A**) as black solid. Yield: 3.2 g (31%) LC-MS (ES) m/z = 263.24 [M+H]⁺ and ethyl (S)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (**I-96B**) as black solid. Yield: 3.4 g (33.4%) LC-MS (ES) m/z = 263.24 [M+H]⁺.

Step-2: (R)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (I-183 A)

[000405] To a stirred solution of ethyl (R)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (4, 3.0 g 11.45 mmol) in MeOH : THF : H₂O (1:1:1) 30 mL, LiOH.H₂O (0.961 g, 22.9 mmol) was added and reaction mixture stirred at room temperature for 5 h. After completion, evaporated the solvent from reaction mixture to obtain the residue. This residue diluted with water and washed with diethyl ether twice. Then aqueous layer acidified with 1N HCl and concentrated to dryness under reduced pressure to offered (R)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (**I-183A**) as white gummy solid. Yield: 2.3 g (79%) LC-MS (ES) m/z = 235.22 [M+H]⁺.

[000406] **I-183B** was prepared using a process similar for synthesizing **I-183A**.

Step-3: (R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 121A)

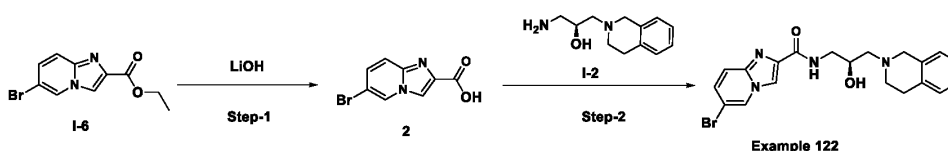
[000407] To a stirred solution of (R)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (6, 2.1 g 8.97 mmol) in DMF 15 mL, HATU (5.1 g, 13.46 mmol) and DIPEA (4.69 mL, 26.92 mmol) were added and reaction mixture stirred at room temperature for 10 minutes. Then (S)-1-amino-3-(3,4-

dihydroisoquinolin-2(1H)-yl)propan-2-ol (5, 2.77 g, 13.46 mmol) was added dissolving in DMF 5 mL and reaction mixture stirred at room temperature for 16 h. After completion, evaporated the solvent from reaction mixture to obtain the residue. This residue diluted with water and extracted with 10% MeOH in DCM (3 times). The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain the crude. This crude purified by combiflash using 5.0% MeOH in DCM as eluent. The desired fractions were concentrated under reduced pressure to offered (R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide

example121A as white solid. Yield: 1.4 g (37%) LC-MS (ES) $m/z = 423.17$ $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.82 (t, $J = 5.5$ Hz, 1H), 7.54 (s, 1H), 7.09–7.01 (m, 4H), 4.89 (bs, 1H), 4.32 (dd, $J_{1-3} = 12.4$ Hz, $J_{1-2} = 5.2$ Hz 1H), 3.98 (t, $J = 10.7$ Hz, 1H), 3.83 (bs, 1H), 3.59 (s, 2H), 3.37 (m, 1H), 3.21 (m, 2H), 2.82-2.62 (m, 7H), 2.45 (bs, 1H), 2.16 (bs, 1H), 1.9 (m, 1H).

[000408] Similarly (S)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide **Example121B** was prepared using the above protocol.

(R)-6-bromo-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 122)



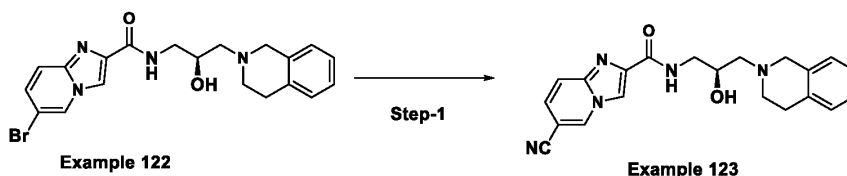
Step- 1: 6-bromoimidazo[1,2-a]pyridine-2-carboxylic acid (2)

[000409] To a stirred solution of ethyl 6-bromoimidazo[1,2-a]pyridine-2-carboxylate (**I-6**, 10.0 g 37.17 mmol) in (200 mL) of THF:MeOH:H₂O (2:1:1) was added LiOH (2.67 g, 111.52 mmol). The reaction mixture was stirred for 5h at room temp. After completion of reaction, the organic solvent was evaporated and the aqueous layer was acidified with 1N HCl up to pH 3 to 4 and aqueous layer was concentrated to get 6-bromoimidazo[1,2-a]pyridine-2-carboxylic acid **2** as a white solid. Yield: 8.0 g (crude) LC-MS (ES) m/z : 241.05 $[M+H]^+$

Step- 2: (S)-6-bromo-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 122)

[000410] To a solution of 6-bromoimidazo[1,2-a]pyridine-2-carboxylic acid (2, 8.0 g, 33.33 mmol) in DMF (160 mL) was added DIPEA (16.49 mL, 99.99 mmol) followed by HATU (13.93 g, 36.66 mmol). The reaction mixture was stirred for 10 min followed by addition of (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (**I-1**, 6.86 g, 33.33 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained crude was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford to (S)-6-bromo-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide as yellow solid. Yield: 8.0 g (56%) LC-MS (ES) m/z : 430.32 [M+H]⁺; δ 8.92 (s, 1H), 8.30 (s, 1H), 8.28 (s, 1H), 7.50-7.43 (m, 2H), 7.10-7.03 (m, 5H), 4.97 (s, 1H), 3.91 (s, 1H), 3.66 (d, J=12.24 Hz, 2H), 3.48-3.42 (m, 1H), 2.93 (s, 1H), 2.84-2.72 (m, 5H).

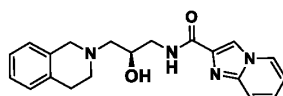
(S)-6-cyano-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 123)



[000411] To a solution of (S)-6-bromo-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (0.30 g, 0.692 mmol) in N,N-dimethylformamide (10 mL), zinc cyanide (0.24 g, 2.09 mmol) and zinc dust (0.0041 g, 0.034 mmol) were added at room temperature and the reaction mixture was degassed with argon for 15 min. 1,1'-Bis(diphenylphosphino)ferrocene (0.019 g, 0.034 mmol) and tris(dibenzylideneacetone)dipalladium (0.031 g, 0.034 mmol) were added to the reaction, degassed for additional 5 min and mixture was heated at 140 °C for 6 h. After completion, the reaction mass was diluted with ethyl acetate and washed with cold water. The organic layer was separated and dried over anhydrous sodium sulphate, filtered and concentrated to give crude. The crude was purified by silica gel column chromatography using 3-5%

methanol in dichloromethane as eluent. The desired fractions were concentrated and further purified by prep-HPLC to afford (S)-6-cyano-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide; off white solid. Yield: 0.04 g (20%). LC-MS (ES) m/z : 376.24 $[M+H]^+$, ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 9.38 (s, 1H), 8.65 (dd, J = 5.28 Hz, 1H), 8.45 (s, 1H), 7.77 (d, J = 9.44 Hz, 1H), 7.63 (d, J = 9.48 Hz, 1H), 7.29-7.17 (m, 4H), 5.90 (bs, 1H), 4.59-4.51 (m, 1H), 4.42-4.32 (m, 1H), 4.22 (bs, 1H), 3.74-3.67 (m, 2H), 3.47-3.42 (m, 2H), 3.31-3.20 (m, 2H), 3.05-2.97 (m, 2H).

(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 124)

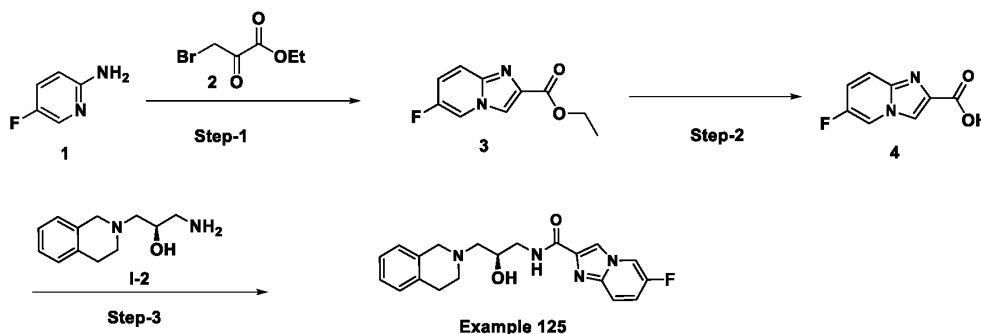


Example 124

[000412] **Example 124** was prepared according to method exemplified for **Example 122**. LC-MS (ES) m/z : 350.42 $[M+H]^+$

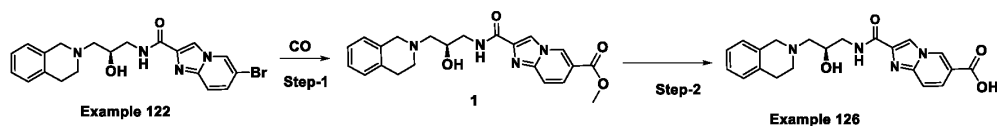
(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-fluoroimidazo[1,2-a]pyridine-2-carboxamide (Example 125)

[000413] **Intermediate 3** was prepared as I-6, and the **Example 125** was prepared according to method exemplified for **Example 122**



[000414] LC-MS (ES) m/z : 368.41 $[M+H]^+$.

(R)-2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridine-6-carboxylic acid (Example 126)



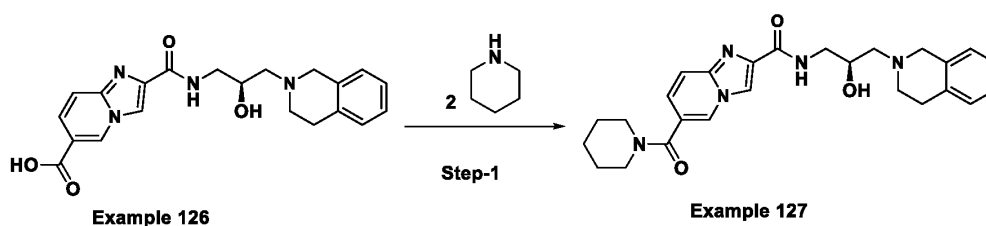
Step-1: methyl(S)-2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridine-6-carboxylate (1)

[000415] To a stirred solution of (S)-6-bromo-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (3.0 g, 6.98 mmol) in methanol (60 mL) was added triethylamine (2.12 mL, 20.96 mmol). The reaction mixture was purged with N₂ gas for 20 min. To the above reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.51 g, 0.698 mmol) and the resulting solution was filled with carbon monoxide (CO) at 100 psi in parr-vessel and reaction was stirred for 16 h at 80°C. The reaction mixture was filtered over celite bed and washed with ethyl acetate. The filtrate was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by column chromatography using 0-10% methanol/dichloromethane as the eluent to afford methyl(S)-2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridine-6-carboxylate **1** as off white solid. Yield: 1.51 g (53%) LC-MS (ES) m/z : 409.36 [M+H]⁺

Step-2: (S)-2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridine-6-carboxylic acid (Example 126)

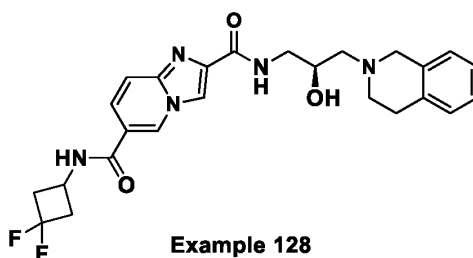
[000416] To a stirred solution of methyl (S)-2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridine-6-carboxylate (**1**, 1.50 g, 3.33 mmol) in (30 mL) of THF:MeOH:H₂O (2:1:1) was added LiOH (0.24 g, 9.99 mmol). The reaction mixture was stirred for 5h at room temp. After completion of reaction, the organic solvents were evaporated and the aqueous layer was acidified with 1N HCl up to pH 3 to 4 and aqueous layer was concentrated to get (S)-2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridine-6-carboxylic acid **Example 126** as a white solid. Yield: 1.40 g (crude) LC-MS (ES) m/z : 395.07 [M+H]⁺

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(piperidine-1-carbonyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 127)



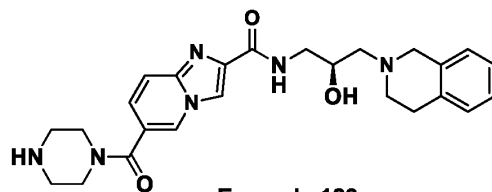
[000417] Step-1: To a solution of (S)-2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridine-6-carboxylic acid (0.25 g, 0.634 mmol) in DMF (6 mL) was added DIPEA (0.31 mL, 1.90 mmol) followed by HATU (0.24 g, 0.634 mmol). The reaction mixture was stirred for 10 min followed by addition of piperidine (**2**, 0.080 g 0.95 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained crude was purified by prep-HPLC to afford to (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(piperidine-1-carbonyl)imidazo[1,2-a]pyridine-2-carboxamide as off white solid. Yield: 0.18 g (62%) LC-MS (ES) m/z : 395.07 [M+H]⁺; ¹H NMR (DMSO-d₆, 400 MHz, ppm) δ 8.74 (s, 1H), 8.38 (s, 2H), 7.56 (d, J = 8.88 Hz, 1H), 7.33 (d, J = 9.28 Hz, 1H), 7.13-7.07 (m, 4H), 5.02 (bs, 1H), 4.00 (m, 1H), 3.75-3.44 (m, 6H), 3.15-2.89 (m, 4H), 2.66-2.07 (m, 2H), 1.62-1.53 (m, 6H), 1.23-1.21 (m, 2H).

(S)-N6-(3,3-difluorocyclobutyl)-N2-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 128)



[000418] Example 128 was prepared according to method exemplified for **Example 127**. LC-MS (ES) m/z : 484.37 [M+H]⁺, ¹H NMR (DMSO-d₆, 400 MHz, ppm) δ 9.13 (s, 1H), 9.01 (d, J = 4.96 Hz, 1H), 8.46 (s, 1H), 8.36 (dd, J = 11.04 Hz, 1H), 7.71 (d, J = 1.28 Hz, 1H), 7.54 (d, J = 9.52 Hz, 1H), 7.10-7.06 (m, 3H), 7.01 (d, J = 6.16 Hz, 1H), 4.98 (bs, 1H), 4.28 (bs, 1H), 3.93-3.90 (m, 1H), 3.66-3.58 (m, 2H), 3.49-3.43 (m, 1H), 3.33-3.27 (m, 1H), 3.00-2.96 (m, 2H), 2.84 (d, J = 5.16 Hz, 2H), 2.78-2.49 (m, 6H).

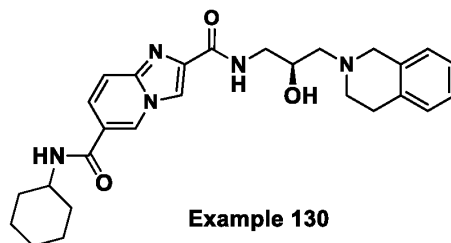
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(piperazine-1-carbonyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 129)



Example 129

[000419] Example 129 was prepared according to method exemplified for Example 127. LC-MS (ES) m/z : 463.46[M+H]⁺

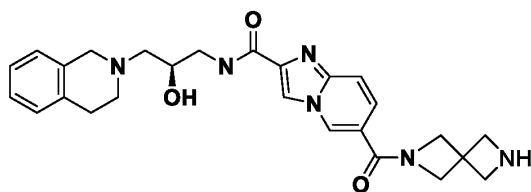
(S)-N6-cyclohexyl-N2-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 130)



Example 130

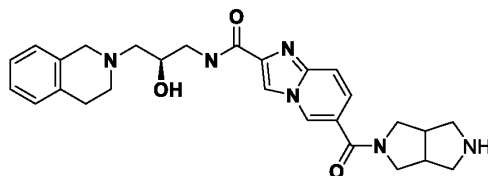
[000420] Example 130 was prepared according to method exemplified for Example 127. LC-MS (ES) m/z : 476.40 [M+H]⁺, ¹H NMR (DMSO-d₆, 400 MHz, ppm) δ 9.08 (s, 1H), 8.43 (s, 1H), 8.37-8.33 (m, 2H), 7.74-7.71 (dd, J = 9.56 Hz, 1.40 Hz, 1H), 7.51 (d, J = 9.48 Hz, 1H), 7.10-7.06 (m, 3H), 7.02 (d, J = 5.96 Hz, 1H), 4.95 (bs, 1H), 3.91 (bs, 1H), 3.78 (bs, 1H), 3.66-3.62 (m, 2H), 3.49-3.45 (m, 1H), 2.84-2.68 (m, 7H), 1.84-1.75 (m, 2H), 1.73-1.63 (m, 2H), 1.62-1.60 (m, 1H), 1.33-1.29 (m, 4H), 1.18-1.15 (m, 1H).

(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2,6-diazaspiro[3.3]heptane-2-carbonyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 131)

**Example 131**

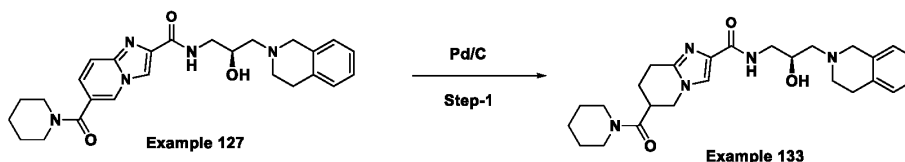
[000421] **Example 131** was prepared according to method exemplified for **Example 127**. LC-MS (ES) m/z : 475.24 $[M+H]^+$

N-((R)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 132)

**Example 132**

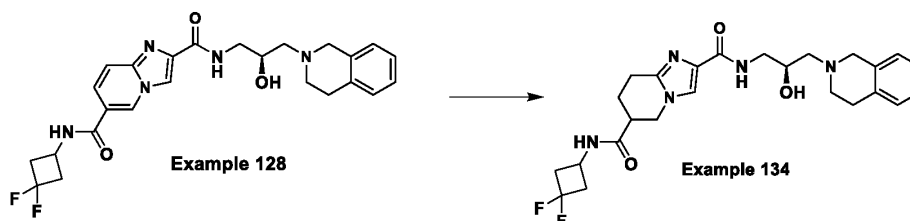
[000422] **Example 132** was prepared according to method exemplified for **Example 127**. LC-MS (ES) m/z : 489.25 $[M+H]^+$

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(piperidine-1-carbonyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 133)



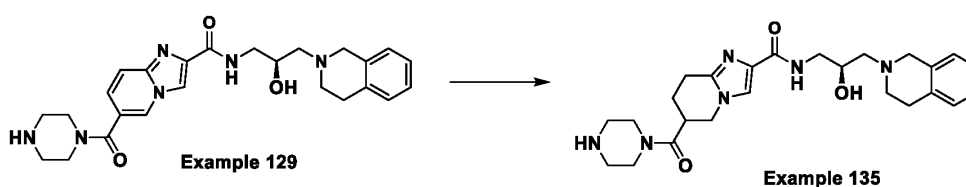
[000423] **Step- 1:** To a stirred solution of (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(piperidine-1-carbonyl)imidazo[1,2-a]pyridine-2-carboxamide (0.10 g, 0.21 mmol) in ethanol (3 mL) was added ammonium formate (0.068 g, 1.08 mmol) and Pd/C (0.011 g, 0.10 mmol) under N_2 atmosphere and the reaction mixture was stirred at 80 °C for 48 h. After completion, the reaction mixture was filtered through celite and washed with EtOAc. The filtrate was concentrated to dryness. The obtained crude was submitted to prep-HPLC for purification to afford N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(piperidine-1-carbonyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide as off white solid; LC-MS (ES) m/z : 466.26 $[M+H]^+$

N6-(3,3-difluorocyclobutyl)-N2-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 134)



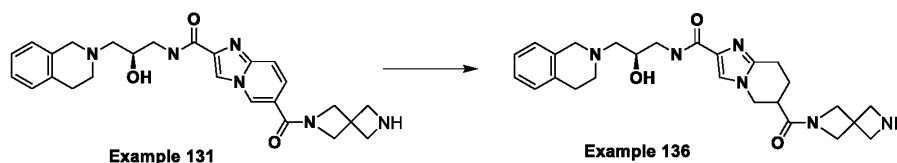
[000424] **Example 134** was prepared according to method exemplified for **Example 133**. LC-MS (ES) m/z : 488.24 $[M+H]^+$

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(piperazine-1-carbonyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 135)



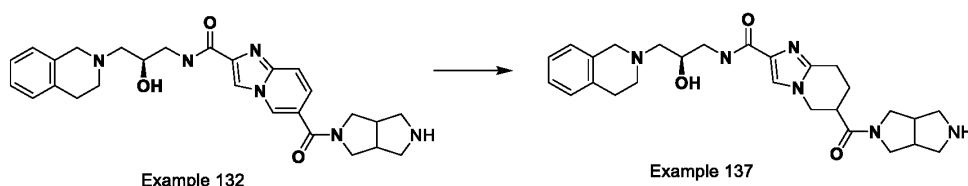
[000425] **Example 135** was prepared according to method exemplified for **Example 133**. LC-MS (ES) m/z : 467.27 $[M+H]^+$

N-((R)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2,6-diazaspiro[3.3]heptane-2-carbonyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 136)



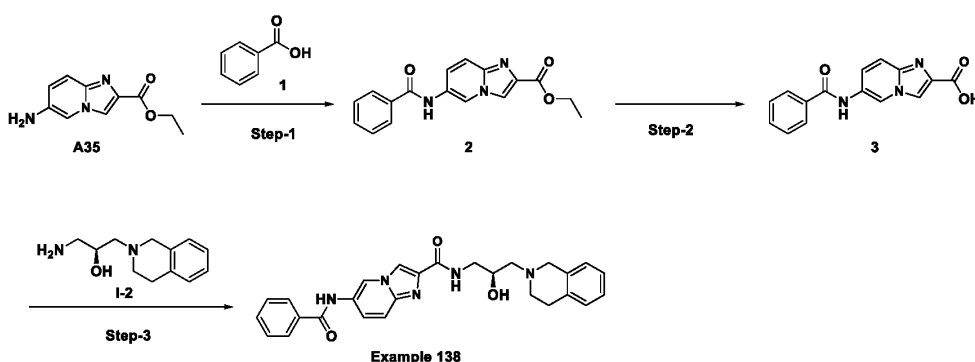
[000426] **Example 136** was prepared according to method exemplified for **Example 133**. LC-MS (ES) m/z : 479.27 $[M+H]^+$

N-((R)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 137)



[000427] **Example 137** was prepared according to method exemplified for **Example 133**. LC-MS (ES) m/z : 493.62 $[M+H]^+$

(S)-6-benzamido-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 138)



Step-1: Ethyl 6-benzamidoimidazo[1,2-a]pyridine-2-carboxylate (2)

[000428] To a solution of benzoic acid (**1**, 0.35 g, 2.92 mmol) in DMF (10 mL) was added DIPEA (1.27 mL, 7.31 mmol) followed by HATU (1.01 g, 2.68 mmol). The reaction mixture was stirred for 10 min followed by addition of ethyl 6-aminoimidazo[1,2-a]pyridine-2-carboxylate (**A35**, 0.50 g, 2.43 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with water, brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude was purified by column chromatography using 10% methanol in dichloromethane as eluent to afford the desired product ethyl 6-benzamidoimidazo[1,2-a]pyridine-2-carboxylate **2** as white solid. Yield: 0.44 g, (58%). LC-MS (ES) m/z : 310.10 $[M+H]^+$

Step- 2: 6-benzamidoimidazo[1,2-a]pyridine-2-carboxylic acid (3)

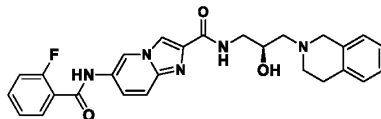
[000429] To a stirred solution of ethyl 6-benzamidoimidazo[1,2-a]pyridine-2-carboxylate (**2**, 0.44 g, 1.42 mmol) in (8 mL) of THF:MeOH:H₂O (2:1:1) was added LiOH (0.179 g, 4.27 mmol). The reaction mixture was stirred for 3h at room temp. After completion, reaction mixture was evaporated and the residue was acidified with 1N HCl

up to pH 3 to 4 and concentrated to get 6-acetamidoimidazo[1,2-a]pyridine-2-carboxylic acid 3 as an off white solid. Yield: 0.40 g, (crude). LC-MS (ES) m/z : 282.05 $[M+H]^+$

Step-3: (S)-6-benzamido-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 138)

[000430] To a solution of 6-benzamidoimidazo[1,2-a]pyridine-2-carboxylic acid (**7**, 0.40 g, 1.42 mmol) in DMF (10 mL) was added DIPEA (0.74 mL, 4.27 mmol) followed by HATU (0.59 g, 1.56 mmol). The reaction mixture was stirred for 10 min followed by addition of (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (**I-1**, 0.35 g, 1.70 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was monitored till the completion of starting materials (LC/MS) and then concentrated under reduced pressure. The obtained crude was purified by Prep HPLC to afford the desired product (S)-6-benzamido-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide as white solid. Yield: 0.25 g, (37%). LC-MS (ES) m/z : 470.34 $[M+H]^+$, ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 10.41 (s, 1H), 9.40 (s, 1H), 8.45 (s, 1H), 8.25-8.22 (dd, $J=5.72$ Hz, 1H), 7.98 (d, $H=7.2$ Hz, 2H), 7.64-7.54 (m, 5H), 7.10-7.01 (m, 4H), 4.95 (d, $J=4.68$ Hz, 1H), 3.3-3.89 (m, 1H), 3.66-3.31 (m, 4H), 2.84 (s, 2H), 2.78-2.67 (m, 2H), 2.57-2.40 (m, 2H).

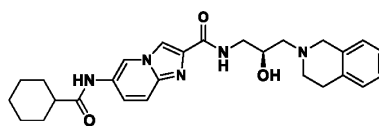
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2-fluorobenzamido)imidazo[1,2-a]pyridine-2-carboxamide (Example 139)



Example 139

[000431] **Example 139** was prepared according to method exemplified for **Example 138**. LC-MS (ES) m/z : 484.37 $[M+H]^+$, ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 10.61 (s, 1H), 9.40 (s, 1H), 8.46 (s, 1H), 8.24 (dd, $J = 11.36$ Hz, 1H), 7.70 (dd, $J = 14.44$ Hz, 1H), 7.62 (dd, $J = 13.52$ Hz, 1H), 7.53 (d, $J = 9.68$ Hz, 1H), 7.40-7.34 (m, 3H), 7.13-7.03 (m, 4H), 4.96 (d, $J = 4.04$ Hz, 1H), 3.91 (d, $J = 4.68$ Hz, 1H), 3.66-3.62 (m, 2H), 3.58-3.44 (m, 1H), 3.31-3.26 (m, 1H), 2.84-2.67 (m, 6H).

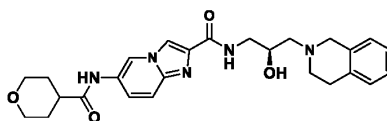
(S)-6-(cyclohexanecarboxamido)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 140)



Example 140

[000432] **Example 140** was prepared according to method exemplified for **Example 138**. LC-MS (ES) m/z : 476.34 $[M+H]^+$

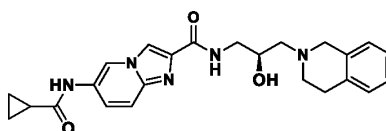
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-carboxamido)imidazo[1,2-a]pyridine-2-carboxamide (Example 141)



Example 141

[000433] **Example 141** was prepared according to method exemplified for **Example 138**. LC-MS (ES) m/z : 478.36 $[M+H]^+$, ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 10.11 (s, 1H), 9.28 (s, 1H), 8.38 (s, 1H), 8.22-8.19 (dd, $J=11.24$ Hz, 1H), 7.48 (d, $H=9.64$ Hz, 1H), 7.27-7.24 (dd, $J=9.71$, 1.6 Hz, 1H), 7.09-6.90 (m, 4H), 4.97 (bs, 1H), 3.91 (d, $J=11.2$ Hz, 3H), 3.65-3.24 (m, 7H), 2.83 (s, 2H), 2.77-2.59 (m, 4H), 1.71-1.62 (m, 4H).

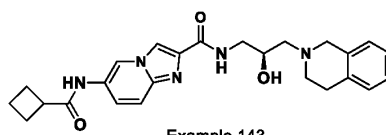
(S)-6-(cyclopropanecarboxamido)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 142)



Example 142

[000434] **Example 142** was prepared according to method exemplified for **Example 138**. LC-MS (ES) m/z : 434.30 $[M+H]^+$, ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 10.39 (s, 1H), 9.22 (s, 1H), 8.37 (s, 1H), 8.22-8.19 (dd, $J=5.68$ Hz, 1H), 7.48 (d, $H=9.6$ Hz, 1H), 7.26 (d, $J=9.64$ Hz, 1H), 7.09-7.01 (m, 4H), 4.98 (bs, 1H), 3.89 (t, $J=5.68$ Hz, 1H), 3.65-3.26 (m, 5H), 2.83 (s, 2H), 2.77-2.66 (m, 3H), 1.80 (t, $J=5.92$ Hz, 1H), 0.84-0.82 (m, 4H).

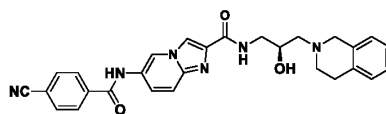
(S)-6-(cyclobutanecarboxamido)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 143)



Example 143

[000435] **Example 143** was prepared according to method exemplified for **Example 138**. LC-MS (ES) m/z : 448.54 $[M+H]^+$

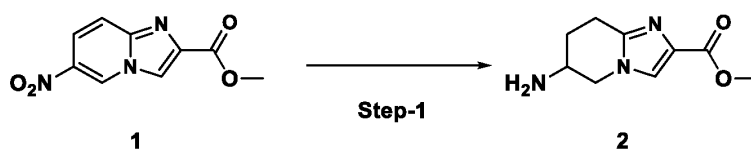
(S)-6-(4-cyanobenzamido)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 144)



Example 144

[000436] **Example 144** was prepared according to method exemplified for **Example 138**. LC-MS (ES) m/z : 495.21 $[M+H]^+$

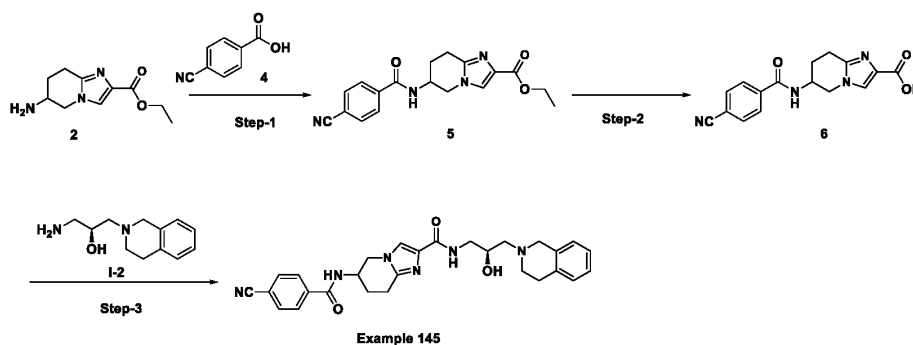
Methyl 6-aminoimidazo[1,2-a]pyridine-2-carboxylate (2)



Step- 1: Methyl 6-aminoimidazo[1,2-a]pyridine-2-carboxylate (2)

[000437] To a stirred solution of methyl 6-nitroimidazo[1,2-a]pyridine-2-carboxylate (**1**, 10.0 g, 42.55 mmol) in ethanol (150mL) was added ammonium formate (13.4 g, 212.76 mmol) and Pd/C (2.25 g, 21.27 mmol) under N_2 atmosphere and the reaction mixture was stirred at 80 °C for 48 h. After completion, the reaction mixture was filtered through celite and washed with EtOAc. The filtrate was concentrated to dryness. The residue was washed with n-pentane dried to get compound methyl 6-amino-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate **2** as a black solid. Yield: 7.50 g (84%) LC-MS (ES) m/z : 196.06 $[M+H]^+$.

6-(4-cyanobenzamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 145)



Step-1: ethyl 6-(4-cyanobenzamido)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (5)

[000438] To a solution of 4-cyanobenzoic acid (**4**, 0.42 g, 2.87 mmol) in DMF (10 mL) was added DIPEA (1.27 mL, 7.31 mmol) followed by HATU (1.01 g, 2.68 mmol). The reaction mixture was stirred for 10 min followed by addition of ethyl 6-amino-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (**2**, 0.50 g, 2.39 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained crude was purified by column chromatography using 10% methanol in dichloromethane as eluent to afford the desired product ethyl 6-(4-cyanobenzamido)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate **5** as white solid. Yield: 0.28 g, (35%). LC-MS (ES) m/z : 310.10 [M+H]⁺

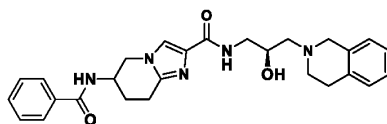
Step- 2: 6-(4-cyanobenzamido)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (6)

[000439] To a stirred solution of ethyl 6-(4-cyanobenzamido)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (**5**, 0.28 g, 0.82 mmol) in (8 mL) of THF:MeOH:H₂O (2:1:1) was added LiOH (0.10 g, 2.48 mmol). The reaction mixture was stirred for 3h at room temp. After completion of reaction, the organic solvents were evaporated and the aqueous layer was acidified with 1N HCl up to pH 3 to 4 and aqueous layer was concentrated to get 6-(4-cyanobenzamido)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid **6** as an off white solid. Yield: 0.28 g, (crude). LC-MS (ES) m/z : 282.05 [M+H]⁺

Step-3: 6-(4-cyanobenzamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 145)

[000440] To a solution of 6-(4-cyanobenzamido)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (**6**, 0.28 g, 0.90 mmol) in DMF (10 mL) was added DIPEA (0.47 mL, 2.70 mmol) followed by HATU (0.37 g, 0.99 mmol). The reaction mixture was stirred for 10 min followed by addition of (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (**7**, 0.22 g, 1.08 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was monitored till the completion of starting materials (LC/MS) and then concentrated under reduced pressure. The obtained crude was purified by Prep HPLC to afford 6-(4-cyanobenzamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide as white solid. Yield: 0.10 g, (22%). LC-MS (ES) m/z : 499.71 $[M+H]^+$, ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.85 (d, J = 5.64 Hz, 1H), 8.01-7.95 (m, 4H), 8.83 (d, J = 3.96 Hz, 1H), 7.51 (s, 1H), 7.09-7.08 (m, 3H), 7.01 (d, J = 5.16 Hz, 1H), 4.89 (bs, 1H), 4.43-4.31 (m, 1H), 4.30-4.27 (m, 1H), 3.92-3.82 (m, 2H), 3.24-3.21 (m, 2H), 2.90-2.64 (m, 7H), 2.47-2.44 (m, 3H), 2.08-2.02 (m, 2H).

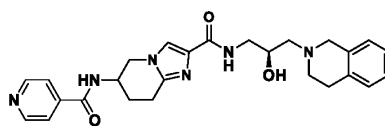
6-benzamido-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 146)



Example 146

[000441] **Example 146** was prepared according to method exemplified for **Example 145**. LC-MS (ES) m/z : 474.38 $[M+H]^+$, ^1H NMR (DMSO- d_6 , 400 MHz, ppm) δ 8.59 (d, J =5.44 Hz, 1H), 7.85-7.82 (m, 3H), 7.56-7.45 (m, 4H), 7.09-7.01 (m, 4H), 4.89 (t, J =4.28 Hz, 1H), 4.42 (bs, 1H), 4.30-4.26 (dd, J =12.52, 5.16 Hz, 1H), 3.90-3.81 (m, 2H), 3.60 (s, 2H), 3.41-3.33 (m, 1H), 3.27-3.25 (m, 1H), 2.92-2.63 (m, 6H), 2.47-2.42 (m, 2H), 2.07-2.01 (m, 2H).

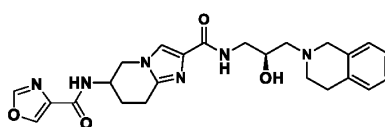
N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(isonicotinamido)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 147)



Example 147

[000442] Example 147 was prepared according to method exemplified for Example 145. LC-MS (ES) m/z : 475.24[M+H]⁺

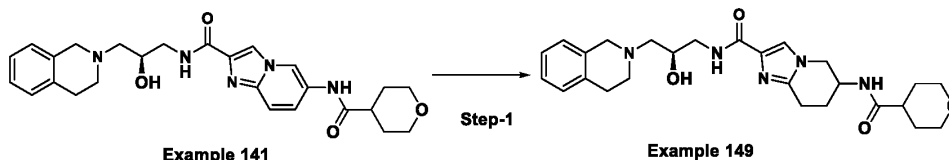
N-(2-(((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)oxazole-4-carboxamide (Example 148)



Example 148

[000443] Example 148 was prepared according to method exemplified for Example 145. LC-MS (ES) m/z : 465.24[M+H]⁺

N-((R)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-carboxamido)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 149)



Example 141

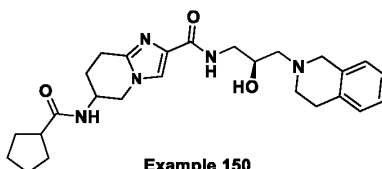
Example 149

Step- 1: N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-carboxamido)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 149)

[000444] To a stirred solution of (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-carboxamido)imidazo[1,2-a]pyridine-2-carboxamide (0.20 g, 0.41 mmol) in ethanol (5 mL) was added ammonium formate (0.13 g, 2.09 mmol) and Pd/C (0.021 g, 0.20 mmol) under N₂ atmosphere and the reaction mixture was stirred at 80 °C for 48 h. After completion, the reaction mixture was filtered through celite and washed with EtOAc. The filtrate was concentrated to dryness. The obtained crude was purified by prep-HPLC to afford N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-carboxamido)-5,6,7,8-

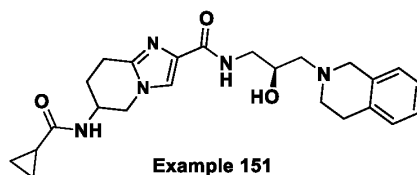
tetrahydroimidazo[1,2-a]pyridine-2-carboxamide as a brown solid. Yield: 0.050 g (25%)
LC-MS (ES) m/z : 482.26 [M+H]⁺

6-(cyclopentanecarboxamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 150)



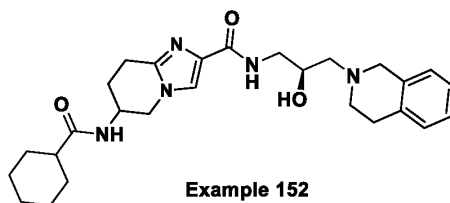
[000445] **Example 150** was prepared according to method exemplified for **Example 149**. LC-MS (ES) m/z : 482.26[M+H]⁺

6-(cyclopropanecarboxamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 151)



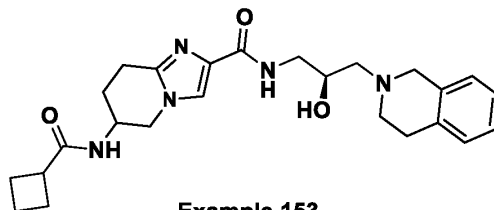
[000446] **Example 151** was prepared according to method exemplified for **Example 149**. LC-MS (ES) m/z : 438.26[M+H]⁺

6-(cyclohexanecarboxamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 152)



[000447] **Example 152** was prepared according to method exemplified for **Example 149**. LC-MS (ES) m/z : 480.30[M+H]⁺.

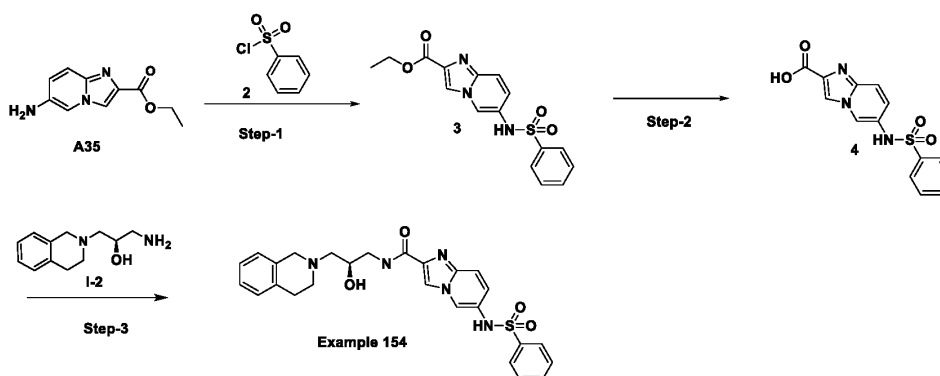
6-(cyclobutanecarboxamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 153)



Example 153

[000448] **Example 153** was prepared according to method exemplified for **Example 149**. LC-MS (ES) m/z : 452.57 $[M+H]^+$.

(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(phenylsulfonamido)imidazo[1,2-a]pyridine-2-carboxamide (Example 154)



Step- 1: ethyl 6-(phenylsulfonamido)imidazo[1,2-a]pyridine-2-carboxylate (3)

[000449] To a solution of ethyl 6-aminoimidazo[1,2-a]pyridine-2-carboxylate (A35, 1.0 g, 4.87 mmol) in pyridine (10 mL), benzenesulfonyl chloride (2, 0.75 mL, 5.84 mmol) was added and the resulting solution was stirred at room temperature for 16 h. After completion, the reaction mixture was concentrated under reduced pressure to get crude. The crude was dissolved in DCM and washed with water and dried with anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by column chromatography using silica gel (100-200 mesh) 0-80% EtOAc/n-hexanes as the eluent to afford ethyl 6-(phenylsulfonamido)imidazo[1,2-a]pyridine-2-carboxylate 3 as a Light green solid. Yield: 1.20 g (71%) LC-MS (ES) m/z : 346.08 $[M+H]^+$.

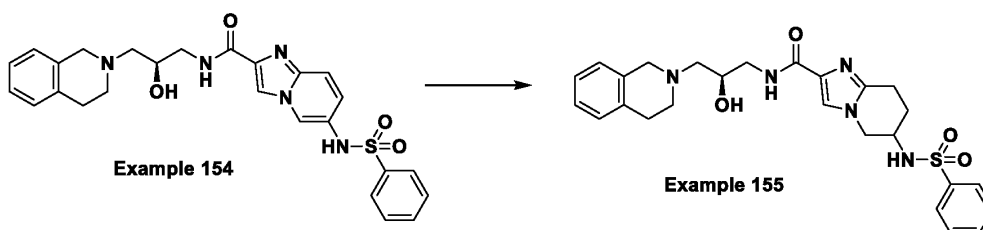
Step-2: 6-(phenylsulfonamido)imidazo[1,2-a]pyridine-2-carboxylic acid (4)

[000450] To a stirred solution of ethyl 6-(phenylsulfonamido)imidazo[1,2-a]pyridine-2-carboxylate (3, 0.8 g, 2.31 mmol) in (16 mL) of THF:MeOH:H₂O (2:1:1) was added LiOH (0.29 g, 6.95 mmol). The reaction mixture was stirred for 16h at room temp. After completion, organic solvents were evaporated and the aqueous layer was acidified with 1N HCl up to pH 3 to 4 and aqueous layer was concentrated to get crude as a 6-(phenylsulfonamido)imidazo[1,2-a]pyridine-2-carboxylic acid 4 as a white solid. Yield: 0.80 g (crude); LC-MS (ES) m/z : 318.02 [M+H]⁺.

Step-3:(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(phenylsulfonamido)imidazo[1,2-a]pyridine-2-carboxamide (Example 154)

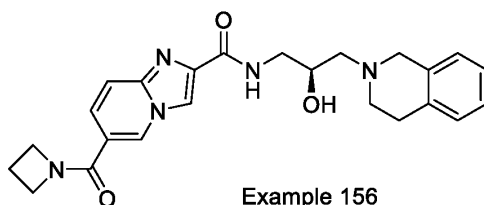
[000451] To a solution of 6-(phenylsulfonamido)imidazo[1,2-a]pyridine-2-carboxylic acid (4, 0.80 g, 2.52 mmol) in DMF (16 mL) was added DIPEA (1.24 mL, 7.57 mmol) followed by HATU (0.95 g, 2.52 mmol). The reaction mixture was stirred for 10 min followed by addition of (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (I-1, 0.62 g, 3.02 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by combiflash column chromatography using 0-10% MeOH/DCM as the eluent. The desired fractions were concentrated and submitted to prep HPLC for further purification to get Example 154 as a white solid. LC-MS (ES) m/z : 506.19 [M+H]⁺.

N-((R)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(phenylsulfonamido)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 155)



[000452] LC-MS (ES) m/z : 510.63 [M+H]⁺.

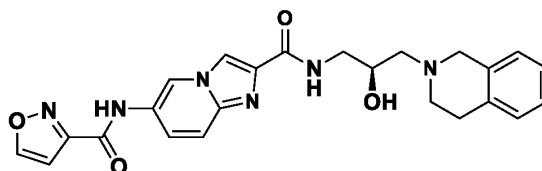
rac-(R)-6-(azetidine-1-carbonyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 156)



Example 156

[000453] **Example 156** was prepared according to method exemplified for **Example 127**. LC-MS (ES) m/z : 434.51 $[M+H]^+$.

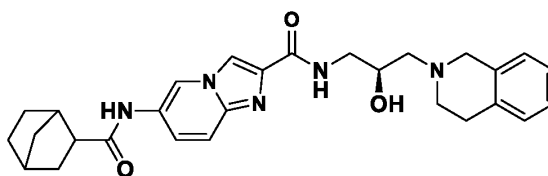
(S)-N-(2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)isoxazole-3-carboxamide (Example 157)



Example 157

[000454] **Example 157** was prepared according to method exemplified for **Example 138**. LC-MS (ES) m/z : 461.49 $[M+H]^+$.

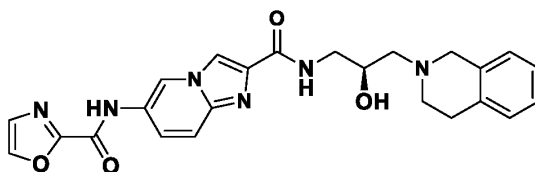
6-(bicyclo[2.2.1]heptane-2-carboxamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 158)



Example 158

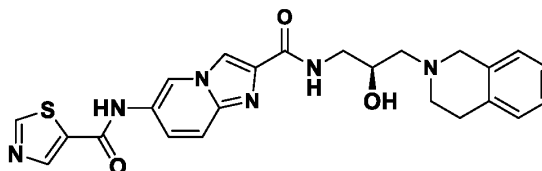
[000455] **Example 158** was prepared according to method exemplified for **Example 138**. LC-MS (ES) m/z : 488.60 $[M+H]^+$.

(S)-N-(2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)oxazole-2-carboxamide (Example 159)

**Example 159**

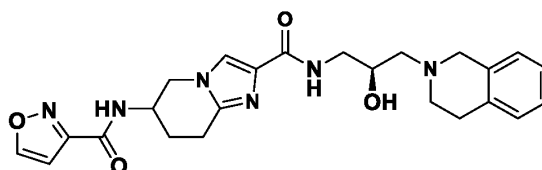
[000456] **Example 159** was prepared according to method exemplified for **Example 138**. LC-MS (ES) m/z : 461.49 $[M+H]^+$.

(S)-N-(2-(((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-5-carboxamide
(**Example 160**)

**Example 160**

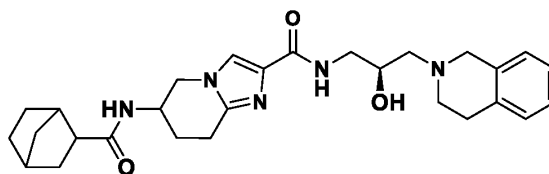
[000457] **Example 160** was prepared according to method exemplified for **Example 138**. LC-MS (ES) m/z : 477.56 $[M+H]^+$.

N-(2-(((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)isoxazole-3-carboxamide (**Example 161**)

**Example 161**

[000458] **Example 161** was prepared according to method exemplified for **Example 149**. LC-MS (ES) m/z : 465.53 $[M+H]^+$.

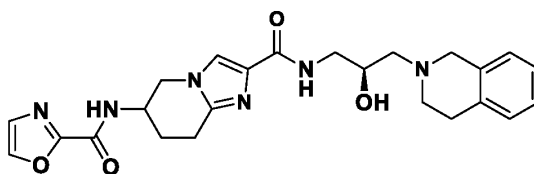
6-(bicyclo[2.2.1]heptane-2-carboxamido)-N-(((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide
(**Example 162**)



Example 162

[000459] **Example 162** was prepared according to method exemplified for **Example 149**. LC-MS (ES) m/z : 492.64 $[M+H]^+$.

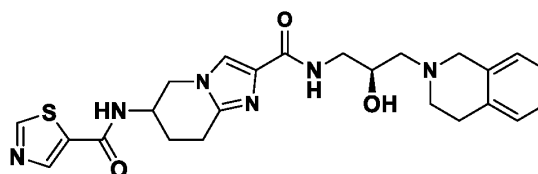
N-(2-(((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)oxazole-2-carboxamide (Example 163)



Example 163

[000460] **Example 163** was prepared according to method exemplified for **Example 149**. LC-MS (ES) m/z : 465.53 $[M+H]^+$.

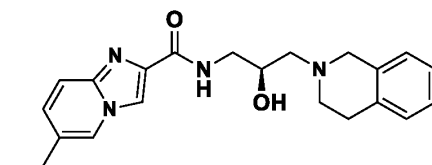
N-(2-(((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)thiazole-5-carboxamide (Example 164)



Example 164

[000461] **Example 164** was prepared according to method exemplified for **Example 149**. LC-MS (ES) m/z : 481.59 $[M+H]^+$.

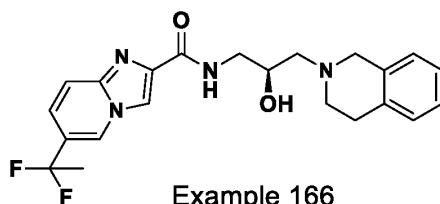
(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-ethylimidazo[1,2-a]pyridine-2-carboxamide (Example 165)



Example 165

[000462] LC-MS (ES) m/z : 379.48 [M+H]⁺.

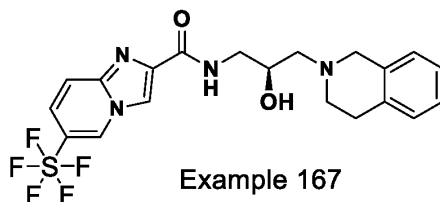
(S)-6-(1,1-difluoroethyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 166)



Example 166

[000463] LC-MS (ES) m/z : 415.46 [M+H]⁺.

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(pentafluoro-16-sulfaneyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 167)



Example 167

[000464] LC-MS (ES) m/z : 477.47 [M+H]⁺.

Biological Evaluation

Expression and Purification of PRMT5:MEP50 Complex

[000465] Full-length human PRMT5 (NP_006100) and Full-length human MEP50 (NP_077007) were synthesized at GenScript. PRMT5 subcloned into pFastBac1 with an amino terminal FLAG tag (MDYKDDDDK) and MEP50 subcloned into pFastBac HT A vector introducing an amino terminal tobacco etch virus cleavable His tag (MSYYHHHHHDYDIPTTENLYFQGA).

Protein Expression:

[000466] Recombinant baculovirus and Baculovirus– infected insect cell (BIIC) were generated according to the Bac-to-Bac® protocol (Life Technologies) and protein was expressed in baculovirus-infected Sf9 (*Spodoptera frugiperda*) insect cells grown in SF-900 II serum-free medium (Invitrogen) in a spinner flask. Protein overexpression was accomplished by infecting exponentially growing Sf9 cell culture at 1×10^6 cells/ml with a 5,000-fold dilution of PRMT5 and MEP50 (at 1:1 ratio) BIIC stock. Infections were carried out at 27 °C for 72 h, and cells were harvested by centrifugation and stored at –80 °C for purification.

Protein Purification:

[000467] Sf9 overexpressed full-length human FLAG-PRMT5–6×His-MEP50 protein complex were purified from cell paste in 2 steps: Nickel affinity chromatography followed by size exclusion chromatography. Frozen pellets were resuspended in 50 mM Tris, pH 8.0, 250 mM NaCl, 5% (v/v) glycerol, 0.1% (w/v) Triton X-100, 5 mM imidazole, 1 mM TCEP and cell lysis was performed by sonication. The homogenate was clarified by centrifugation at $39,000 \times g$ for 120 min and the supernatant was filtered through 0.8 µm filter membrane (Millipore). The clarified supernatant was loaded onto a 6 ml Ni-sepharose™ 6 fast flow beads from (GE Healthcare). The column was washed thoroughly with 12 CV of the wash buffer (50 mM Tris pH 8.0, 250 mM NaCl, 50 mM Imidazole, 1 mM TCEP, Tris(2-carboxyethyl)phosphine hydrochloride and 5% (v/v) Glycerol) at a flow rate of 1 mL/min until the elute UV absorbance was approximately zero. The PRMT5:MEP50 complex was then eluted with a 50 mM to 500 mM linear gradient of Imidazole in buffer (50 mM Tris–HCl pH 8.0, 250 mM NaCl, 1 mM TCEP, 500 mM Imidazole and 5% (v/v) Glycerol). Purity of the eluted fractions was examined on a 12% SDS-PAGE gel. Fractions containing protein of interest, for further purification collected from the protein elution peak and concentrated to 5 mL and injected onto a 26/60 Superdex 200 column (GE) equilibrated with 50 mM Tris–HCl pH 8.0, 250 mM NaCl, 3 mM TCEP, and 20% (v/v) Glycerol. The main peak that contains PRMT5:MEP50 complex eluted around 450 kDa position. Fractions containing PRMT5:MEP50 were concentrated to 2 mg/mL for Assay. All chromatographic steps were performed at 4 °C.

General Procedure for biological Evaluation

PRMT5 Biochemical Assay

[000468] General materials like S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), Tris-HCl, DTT, Bovine skin albumin (BSA) and Tween-

20 were purchased from Sigma-Aldrich. 3H-SAM and 384-well streptavidin Flashplates were purchased from Perkin Elmer. Substrates that were used were Peptide representative of human Histone 4 residues 1-15 which was purchased from Rockland antibodies and assays. The peptide was purified to greater than 95% purity and the sequence was Ac-SGRGKGGKGLGKGGGA[K-Biot]-amide.

PRMT5/MEP50 Enzyme assay on Peptide Substrates.

[000469] The assays were all performed in a buffer consisting of 50mMTris-HCl, pH 8, 1mM DTT, 0.01% BSA, 0.01% Tween-20, prepared on the day of use. Test compounds were diluted 3-fold in assay buffer (final DMSO concentration of 1%) and added into a 384-well OptiPlate (PerkinElmer, #6007290). A cocktail (10μL) of PRMT5/MEP50 enzyme and the peptide was added to the wells. The compounds were allowed to incubate with PRMT5/MEP50 for 30min at room temperature, then 5μL of ³H-SAM was added to initiate the reaction. The final concentrations of the components were as follows: PRMT5/MEP50 – 10nM, H4, 1-15aa peptide – 100nM, ³H-SAM – 1μM. The assays were stopped by the addition of 1mM SAH. 25μL of the reaction from the 384-well OptiPlate was then transferred to a 384-well Flashplate and the biotinylated peptides were allowed to bind to the streptavidin surface for at least 1h, before being washed twice with 50mMTris-HCl, pH 8, 0.1% Tween-20. The plates were then read in a PerkinElmer Topcount plate reader to measure the quantity of ³H-labeled peptide bound to the Flashplate surface measured as disintegrations per minute (dpm), also referred to as counts per minute (cpm).

$$\% \text{ inh} = 100 - \left[\frac{\text{cpmcmpd} - \text{cpmmin}}{\text{cpmmax} - \text{cpmmin}} * 100 \right]$$

[000470] The IC₅₀ values were calculated using a 4-parameter variable slope fit algorithm (cpm – counts per minute, cmpd – signal in assay well, and cpmmax and cpmmin are the respective minimum and maximum signal controls).

Z-138 Methylation Assay

[000471] General reagents. Z-138 suspension cells (Cat# CRL-3001) were purchased from ATCC. Iscove's Modified Dulbecco's Medium (IMDM), Horse serum, penicillin-streptomycin, PBS and TMB-ELISA substrate solution were purchased from ThermoFisher Scientific. Symmetric di-methyl arginine antibody was purchased from Cell Signaling Technologies. Anti-SNRPD3/SmD3 antibody was purchased from Sigma-Aldrich.

[000472] ELISA for detection of Symmetric di-methyl arginine. Exponentially growing Z-138 cells were plated in 96-well plates (Costar 3596) at a density of 150,000 cells/mL, in a volume of 80 μ L. A compound source plate was prepared by performing ten-point 3-fold dilution in DMSO, such that the final top concentration of the compound was 10 μ M, and DMSO was 0.3%. The total volume of compounds added was 20 μ L. The cells were incubated for 96h at 37°C, 5% CO₂. Z-138 cells were directly lysed in media with 3X Lysis Buffer (1X: 10mM HEPES pH7.9, 5mM MgCl₂, 1M NaCl, 0.25M Sucrose, 1% Triton X-100, 1mM PMSF, Protease & Phosphatase inhibitors). The lysates were diluted with Tris buffer to a final salt concentration of 100mM NaCl and appropriate amounts were added to each well of a 96-well titer plate (ThermoFisher, #3855). Plates were incubated at room temperature for a minimum of 3h and then washed with PBS-Tween 20 (0.05%). The plates were blocked with 5% BSA at room temperature for 1h, washed with PBS-Tween 20 and incubated with primary antibody at 4°C overnight. The next day, the plates were washed with PBST, followed by secondary antibody (anti-rabbit IgG horseradish peroxidase conjugate (CST, #7074) for 1h at room temperature. After a final wash, TMB solution was added to the wells, and color allowed to develop in the dark at room temperature. The reaction was stopped with 1N H₂SO₄, and the plates were read on a PerkinElmer EnVision reader scanning at 450nm.

Z-138 Long term Proliferation assays

[000473] Z-138 cells (ATCC, Cat# CRL-3001) were cultured in Iscove's Modified Dulbecco's Medium (IMDM), supplemented with horse serum to a final concentration of 10%. For the assessment of the effect of compounds on the proliferation of Z-138 cells, exponentially growing cells were plated in 96-well plates (Costar 3596) at a density of 150,000 cells/mL in a final volume of 80 μ L medium. A compound source plate was prepared by performing ten-point 3-fold dilution in DMSO, such that the final top concentration of the compound was 10 μ M, and DMSO was 0.3%. The total volume of compounds added was 20 μ L. The cells were incubated for 96h at 37°C, 5% CO₂. At this point, the DMSO-treated (Max) cells were counted and reseeded at similar seeding density. The cells were re-treated with the compounds and incubated for an additional four days. Cell viability was measured on both day 4 and day 8, by adding 25 μ L of Cell Titer Glo reagent to an equal volume of cell suspension. Luminescence was read on a PerkinElmer Victor3 multiplate reader. The concentration of compound inhibiting cell viability by 50% was determined using a 4-parameter, variable slope fit of the normalized dose response curves.

Evaluation of biological activity:

[000474] Table 1 below displays the biochemical data for PRMT5 inhibition of compounds of Formula I. Compounds having an activity designated as “A” provided IC₅₀ 0.01-1 μM; compounds having an activity designated as “B” provided IC₅₀=1-5 μM; and compounds having an activity designated as “C” provided IC₅₀>5 μM.

Table 1: Biochemical PRMT5 inhibiton data

Example	PRMT5 Enzyme_IC ₅₀ _μM	PRMT5_Z138_ GI ₅₀ _Day 8_μM	PRMT5_Z138_SDMA ELISA_Day 4_μM
1	A	A	A
2	A	A	A
3	nd	A	C
4	A	A	A
5	A	A	A
6	A	A	A
7	A	A	A
8	A	A	A
9	B	B	A
10	A	A	A
11	A	A	A
12	A	A	A
13	C	C	A

14	A	A	A
15	A	A	A
16	A	A	A
17	A	A	A
18	A	A	A
19	A	A	A
20	A	A	A
21	nd	nd	nd
22	A	A	nd
23	A	A	A
24	A	A	nd
25	A	A	nd
26	A	A	nd
27	A	A	nd
28	A	A	nd
29	A	A	nd
30	A	A	nd
31	A	A	nd

32	A	A	nd
33	A	A	nd
34	A	A	nd
35	A	A	nd
36	A	A	A
37	A	A	nd
38	A	A	nd
39	A	B	A
40	B	C	nd
41	C	A	A
42	A	B	A
43	C	C	A
44	A	A	nd
45	A	A	A
46	A	A	nd
47	A	A	A
48	A	A	A
49	A	A	nd

50	B	B	nd
51	A	A	nd
52	A	A	nd
53	A	B	nd
54	B	B	nd
55	B	B	nd
56	B	C	nd
57	B	B	nd
58	B	B	nd
59	B	B	nd
60	B	B	nd
61	B	B	nd
62	B	B	nd
63	A	B	nd
64	A	A	nd
65	A	A	nd
66	A	A	nd
67	B	C	nd

68	C	C	nd
69	A	B	A
70	A	B	nd
71	A	B	nd
72	A	B	nd
73	B	B	A
74	A	A	nd
75	A	A	nd
76	A	A	nd
77	A	A	nd
78	A	A	nd
79	A	A	nd
80	A	A	nd
81	A	A	nd
82	B	B	nd
83	C	C	nd
84	B	B	nd
85	B	B	nd

86	nd	nd	nd
87	nd	nd	nd
88	A	A	nd
89	A	A	nd
90	B	C	nd
91	B	C	nd
92	A	B	nd
93	A	B	A
94	B	B	nd
95	A	A	nd
96	A	A	A
97	A	A	nd
98	A	A	nd
99	A	A	nd
100	B	B	A
101	B	C	nd
102	B	A	A
103	B	A	A

104	nd	B	A
105	nd	B	A
106	A	B	A
107A	C	B	A
107B	nd	nd	nd
108	B	A	A
109	B	C	A
110	B	B	A
111	B	B	A
112	B	B	A
113	C	C	B
114	B	A	A
115	A	A	A
116	A	A	A
117	A	A	nd
118A	A	A	nd
118B	nd	nd	nd
119	A	A	nd

120A	A	A	nd
120B	A	B	nd
121A	A	A	A
121B	B	A	A
122	A	A	nd
123	A	A	nd

nd= not determined

[000475] Table 1 summarized the biological activity of the compounds. It was observed that Examples 1, 2, 4-8, 10-12, 14-20, 23, 36, 45, 47, 48, 96, 115, 116, 121A showed an IC₅₀ value in the range of 0.01-1 μ M for all the three assays and were found to be potent for inhibiting PRMT5 enzymes.

[000476] Optimal biological activity was obtained for Examples 124-167.

I/We claim:

1. A compound, its stereoisomers, pharmaceutically acceptable salts, and pharmaceutical compositions, thereof, which is selected from a group consisting of:
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 1),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methylimidazo[1,2-a]pyridine-2-carboxamide (Example 2),
N-(2-(3,4-dihydroisoquinolin-2(1H)-yl)-1-hydroxyethyl)-7-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 3),
(*S*)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-ethyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 4),
(*S*)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-propyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 5),
(*S*)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 6),
(*S*)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 7),
(*S*)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 8),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methoxyimidazo[1,2-a]pyridine-2-carboxamide (Example 9),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-phenylimidazo[1,2-a]pyridine-2-carboxamide (Example 10),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 11),
(*S*)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-isopropylimidazo[1,2-a]pyridine-2-carboxamide (Example 12),
(*S*)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 13),
(*S*)-6-(4-cyanophenyl)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 14),
(*S*)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(3,5-dimethylisoxazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 15),

(S)-6-(3,5-difluorophenyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 16),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4fluorophenyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 17),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-isobutyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 18),

(S)-6-(3,6-dihydro-2H-pyran-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 19),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 20),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 21),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 22),

(S)-6-(1-(1-acetylazetidin-3-yl)-1H-pyrazol-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 23),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(5-isopropyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 24),

(S)-6-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 25),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example-26),

(S)-6-(1-acetylpiperidin-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 27),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2-methylpyrimidin-5-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 28),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(6-methylpyridin-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 29),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(6-methylpyridazin-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 30),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2-methylthiazol-5-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 31),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4,5-dimethylthiazol-2-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 32),

(S)-6-(5-chloropyridin-2-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 33),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 34),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 35),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 36),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-isopropyl-1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 37),

(S)-N-2-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-6-methylimidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 38),

(S)-6-acetamido-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 39),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-sulfamoylimidazo[1,2-a]pyridine-2-carboxamide (Example 40),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(methylsulfonamido)imidazo[1,2-a]pyridine-2-carboxamide (Example 41),

((S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyrimidine-2-carboxamide (Example 42),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrimidine-2-carboxamide (Example 43),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrimidine-2-carboxamide (Example 44),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 45),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 46),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 47),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 48),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-b]pyridazine-2-carboxamide (Example 50),
 (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 51),
 (S)-6-(1-acetylpiperidin-4-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 52),
 (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 53),
 (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 57),
 (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 62),
 (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (Example 63),
 (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-methyl-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 64),
 (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-methyl-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 65),
 (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-methyl-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 66),
 (S)-6-(azetidin-1-yl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 69),
 N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(3-fluoropyrrolidin-1-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 70),
 (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-methylpiperazin-1-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 71),
 (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-morpholinoimidazo[1,2-a]pyridine-2-carboxamide (Example 72),
 N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(3-fluoropyrrolidin-1-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 73),
 (S)-6-(4-cyanophenyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 74),
 (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 75),

N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 76),
 N-((2R,3R)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 77),
 N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 78),
 N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 79),
 N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 80),
 N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 81),
 (S)-N-(3-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 82),
 (S)-N-(3-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 85),

 (S)-6-(difluoromethyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 86),
 (R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 88),
 (R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(trifluoromethyl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 89),
 (R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 92),
 (R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyrazine-2-carboxamide (Example 93),
 (R)-6-(4-cyanophenyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methylimidazo[1,2-a]pyrazine-2-carboxamide (Example 95),
 N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 96),

 N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 97),

6-(1-acetylpiperidin-4-yl)-N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 98),
N-(3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)imidazo[1,2-a]pyridine-2-carboxamide (Example 99),
N-(4-(3,4-dihydroisoquinolin-2(1H)-yl)-1-hydroxybutan-2-yl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 100),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 102),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-7-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 103),
6-cyclopropyl-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 104),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-7-propyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 105),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-propyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 106),
(R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methoxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 107a),
(S)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-methoxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 107b),
N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-isopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 108),
N-(2-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-7-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 109),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 110),
N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 111),
N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-phenyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine-2-carboxamide (Example 112),
N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 114),
N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 115),

N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(4-fluorophenyl)-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine-2-carboxamide (Example 116),

N-((2S,3S)-4-(3,4-dihydroisoquinolin-2(1H)-yl)-2,3-dihydroxybutyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 117),

6-(1-acetylpiperidin-4-yl)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide-Isomer-1 (Example 118A),

N-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-N-methyl-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 119),

(R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 120A),

(S)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 120B),

(S)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 121A),

(R)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 121B),

(R)-6-bromo-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 122),

(S)-6-cyano-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 123),

(R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-fluoroimidazo[1,2-a]pyridine-2-carboxamide (Example 125),

(S)-N-6-(3,3-difluorocyclobutyl)-N2-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 128),

(S)-N-6-cyclohexyl-N2-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 130),

N-6-(3,3-difluorocyclobutyl)-N2-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2,6-dicarboxamide (Example 134),

(S)-6-benzamido-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 138),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(2-fluorobenzamido)imidazo[1,2-a]pyridine-2-carboxamide (Example 139),

(S)-6-(cyclohexanecarboxamido)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 140),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(tetrahydro-2H-pyran-4-carboxamido)imidazo[1,2-a]pyridine-2-carboxamide (Example 141),

(S)-6-(cyclopropanecarboxamido)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 142),

(S)-6-(4-cyanobenzamido)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 144),

6-(4-cyanobenzamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 145),

6-benzamido-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 146),

6-(cyclopentanecarboxamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxamide (Example 150),

rac-(R)-6-(azetidine-1-carbonyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 156),

(S)-N-(2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)isoxazole-3-carboxamide (Example 157),

6-(bicyclo[2.2.1]heptane-2-carboxamido)-N-((S)-3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 158),

(S)-N-(2-((3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-5-carboxamide (Example 160),

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-ethylimidazo[1,2-a]pyridine-2-carboxamide (Example 165), and

(S)-6-(1,1-difluoroethyl)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)imidazo[1,2-a]pyridine-2-carboxamide (Example 166).

2. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof as claimed in claim 1 together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

3. The pharmaceutical composition as claimed in claim 2, wherein the composition is in the form selected from the group consisting of a tablet, capsule, powder, syrup, solution, aerosol and suspension.

4. Use of the compound in claim 1 or the pharmaceutical composition as claimed in claim 2 or 3, in the manufacture of a medicament for treatment and/or prevention of various diseases, including cancer and infectious disease, wherein said medicament is to be administered in combination with other clinically relevant cytotoxic agents or non-cytotoxic agents, wherein the compound or the pharmaceutical composition is to be administered to a subject suffering from the proliferative disorder or cancer.

5. Use of the compounds as claimed in claim 1 or the pharmaceutical composition as claimed in claim 2 or 3 in the manufacture of a medicament for the treatment and/or prevention of various diseases including proliferative disorder or cancer; or treatment of cancer, wherein said medicament is to be administered together in combination with other clinically relevant cytotoxic agents or non-cytotoxic agents.

6. Use of the compounds as claimed in claim 1 or the pharmaceutical composition as claimed in claim 2 in the manufacture of a medicament for treatment of cancer, wherein said medicament is to be administered in combination with other clinically relevant cytotoxic agents or non-cytotoxic agents.

7. Use of the compounds as claimed in claim 1 or the pharmaceutical composition as claimed in claim 2 in the manufacture of a medicament for treatment of cancer, wherein said medicament is to be administered in combination with other clinically relevant immune modulator agents.

8. Use of the compounds as claimed in claim 1 or the pharmaceutical composition as claimed in claim 2 in the manufacture of a medicament for treatment of a condition mediated by PRMT5; treatment and/or prevention of a proliferative disorder or cancer; or treatment of cancer selected from hematologic malignancy, solid tumor, B-cell lymphoma, T-cell lymphoma, breast cancer, prostate cancer, pancreatic cancer, gastric cancer, lung cancer, colon cancer, rectal cancer, esophagus cancer, duodenal cancer,

tongue cancer, pharyngeal cancer, brain tumor, neurinoma, non-small cell lung cancer, small cell lung cancer, liver cancer, kidney cancer, bile duct cancer, uterine body cancer, cervical cancer, ovarian cancer, urinary bladder cancer, skin cancer, hemangioma, malignant lymphoma, malignant melanoma, thyroid cancer, bone tumor, vascular fibroma, retinoblastoma, penile cancer, pediatric solid cancer, lymphoma, myeloma, leukemia, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic neutrophilic leukemia, chronic eosinophilic leukemia, chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL) or hairy cell leukemia, wherein said medicament is to be administered together in combination with other clinically relevant cytotoxic agents or non-cytotoxic agents.

9. Use of the compound as claimed in claim 1 or the pharmaceutical composition as claimed in claim 2 in the manufacture of a medicament for the treatment and/or prevention of a condition mediated by PRMT5 or a proliferative disorder or cancer selected from hematologic malignancy, solid tumor, B-cell lymphoma, T-cell lymphoma, breast cancer, prostate cancer, pancreatic cancer, gastric cancer, lung cancer, colon cancer, rectal cancer, esophagus cancer, duodenal cancer, tongue cancer, pharyngeal cancer, brain tumor, neurinoma, non-small cell lung cancer, small cell lung cancer, liver cancer, kidney cancer, bile duct cancer, uterine body cancer, cervical cancer, ovarian cancer, urinary bladder cancer, skin cancer, hemangioma, malignant lymphoma, malignant melanoma, thyroid cancer, bone tumor, vascular fibroma, retinoblastoma, penile cancer, pediatric solid cancer, lymphoma, myeloma, leukemia, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic neutrophilic leukemia, chronic eosinophilic leukemia, chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL) or hairy cell leukemia.