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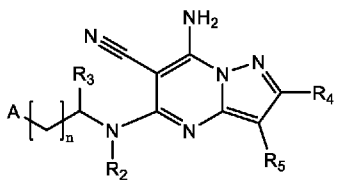
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(54) Title: DIAMINOPYRAZOLO[1,5-A]PYRIMIDINE-6-CARBONITRILE COMPOUNDS AS ADENOSINE 2A RECEPTOR AND ADENOSINE 2B RECEPTOR ANTAGONIST



Formula I

(57) **Abstract:** The present disclosure provides a compound of Formula I or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof. The compounds of Formula I act as antagonists to adenosine receptors. The present disclosure also provides a process for preparation of compounds of Formula I and pharmaceutical composition thereof.

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DIAMINOPYRAZOLO[1,5-a]PYRIMIDINE-6-CARBONITRILE COMPOUNDS AS ADENOSINE 2A RECEPTOR AND ADENOSINE 2B RECEPTOR ANTAGONIST

FIELD OF INVENTION

[0001] The present disclosure relates to the field of medicinal chemistry and particularly to the development of heterocyclic compounds and a process of preparation of the same. The present disclosure more particularly to the pyrazolopyrimidine compounds and in particular diaminopyrazolopyrimidine compounds which act as antagonists for adenosine receptors.

BACKGROUND

[0002] Adenosine is a purine nucleoside produced by cells for its intracellular physiological and extracellular signaling processes. It is synthesized from inosine monophosphate (IMP) as a nucleotide from adenosine monophosphate (AMP) or by the hydrolysis of adenosine triphosphate (ATP) via adenosine diphosphate (ADP) and AMP. Apart from being one of the building blocks of DNA, it is the primary energy source of cells as adenosine triphosphate (ATP) and is involved in the all-pervasive signal transduction processes as cyclic adenosine monophosphate (cAMP). Extracellular adenosine regulates inflammation, allostasis and cognitive functions in the brain, and vasodilation in the heart, lungs, and kidneys, all brought about by its binding to the adenosine receptors.

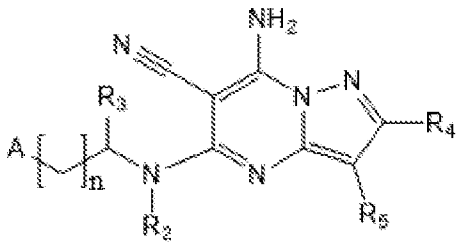
[0003] Adenosine receptors are members of the guanine nucleotide protein-coupled receptors (GPCR) family on the cell surface and consist of A_1R, $A_{2a}R$, $A_{2b}R$, and A_3R subtypes in humans (Jacobson *et al.*, 2012, PMID: 22371149). A_1 and A_3 receptor couple to $Ga_{i/o}$, in contrast, A_{2a} and A_{2b} receptors couple to Ga_s to inhibit or stimulate adenylate cyclase (AC) respectively and are distributed ubiquitously throughout the body (Borea *et al.*, 2018, DOI: 10.1007/978-3-319-90808-3; Cheng *et al.*, 2017, PMID: 28712806). Their agonist or antagonist ligands are used as pharmacological interventions of various pro- and anti-inflammatory mediators to

manage asthma, chronic pulmonary obstructive disease, heart failure, arrhythmia, diabetic kidney disease, glaucoma, stroke, sleep, anxiety, neurodegenerative disorders like Parkinson's, Alzheimer's and Huntington's diseases, epilepsy, pain, cognition and memory, and cancer (Sek *et al.*, 2018, PMID: 30513816).

[0004] During infection, injury, hypoxia, ischemia, or seizure, extracellular adenosine is upregulated in tissues as an allostatic measure to protect tissue damage from the inflammatory responses. Similar immunosuppressive mechanisms of elevated adenosine levels (in the tumor micro-environment, TME) have been identified in tumor immune evasion. In the TME, adenosine binds to $A_{2a}R$ and $A_{2b}R$ on various immune cells and suppresses them by activating the cAMP-dependent Protein Kinase A (PKA) and blockade of the nuclear factor-kB (NF-kB) and Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway (Allard *et al.,* 2020, PMID: 32514148). Relieving this inhibition of the $A_{2a}R$ and $A_{2b}R$ by selective antagonists can make the immune cells capable of killing tumor cells (Vijayan *et al.,* 2017; PMID: 29162946, Allard *et al.,* 2020, PMID: 32514148). Thus, in the present scenario of increasing proliferative disorders, or diseases or conditions, there is a huge need for antagonists of adenosine receptors. Hence there is a huge need for the antagonists of adenosine receptors, which will be useful in treating condition related to cancer or immune-related disorders mediated by these receptors.

SUMMARY OF THE INVENTION

[0005] In an aspect of the present disclosure, there is provided a compound of Formula I



Formula I

or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof,

wherein A is selected from C_{5-10} aryl, C_{2-10} heteroaryl, C_{3-6} cycloalkyl, or C_{1-10} heterocyclyl; wherein C_{5-10} aryl, C_{2-10} heteroaryl, C_{3-6} cycloalkyl, or C_{1-10} heterocyclyl is optionally substituted with one or more substituents selected from R_6, R_7, R_8, R_9, R_{9a}, or oxo;

R_2 is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl;

R_3 is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl; wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy;

R_4 and R_5 are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, -CO-N(R_{10} R_{11}), C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl are optionally substituted with one or more groups selected from C_{3-6} cycloalkyl, C_{1-6} alkoxy, or C_{1-10} heterocyclyl; or R_4 and R_5 are joined together to form C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{4-10} carbocyclyl or C_{1-10} heterocyclyl is optionally substituted with 1 to 3 groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

R_{10} and R_{11} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{3-6} halocycloalkyl, C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl;

R_6 is selected from hydrogen, halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, C_{3-6} halocycloalkyl, -Y-O-C_{1-6} alkyl, -Y-O-C_{3-6} cycloalkyl, -Y-CO-NH-R_{13}, -Y-Z, C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{1-6} alkylhydroxy, or C_{1-10} heterocyclyl is optionally substituted with one or more groups selected from halogen, hydroxyl, amine, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, C_{1-6} haloalkoxy, C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{3-6} cycloalkyl, or C_{1-6} aminoalkyl, is optionally further substituted with one or more groups independently selected from halogen,

hydroxyl, C_{1-6} alkylhydroxy, -C(O)C_{1-6} alkyl, -C(O)NH_2, -C(O)-C_{1-6}alkylhydroxy, or C_{1-10} heterocyclyl, and C_{1-10} heterocyclyl has 1 to 4 heteroatoms independently selected from O, N or S, and optionally substituted with 1 to 3 groups independently selected from halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

Y is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, or C_{3-6} cycloalkenyl; and C_{1-6} alkyl is optionally substituted with C_{3-6} cycloalkyl;

Z is selected from -OH, -NH_2, -COOH, -SO_2NH_2, -SO_2CH_3, -$SOCH_3$, -SCH_3, CH_2-NH-(C_{1-6} alkyl)-$SOCH_3$, -O-P(=O)$(OH)_2$, -$CONH_2$, -CONH(C_{1-6} alkyl), -SO_2NH(C_{1-6} alkyl), CON(C_{1-6} alkyl)$_2$, -NHCO(C_{1-6} alkyl), C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{1-10} heterocyclyl has 1 to 4 heteroatoms independently selected from O, N or S, and optionally substituted with 1 to 3 groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

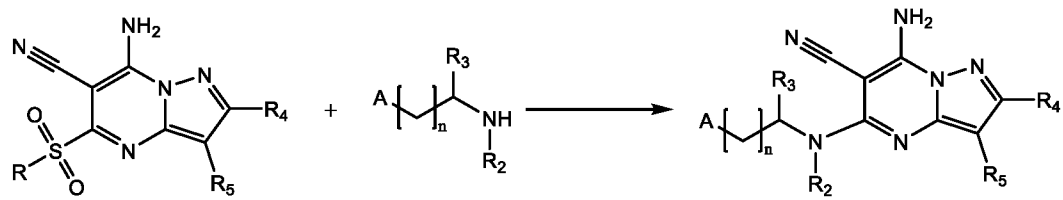
R_{13} is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or C_{3-6} halocycloalkyl;

R_7, R_8, R_9, and R_{9a} are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or C_{3-6} halocycloalkyl;

and

n is 0, 1, or 2.

[0006] In another aspect of the present disclosure, there is provided a process of preparation of compounds of Formula I or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof, said process comprising: reacting Formula (A), and Formula (B) in the presence of a base to obtain the compounds of Formula I,



Formula (A) Formula (B) Formula (I)

wherein R is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-10} aryl, C_{2-10} heteroaryl, or C_{1-10} heterocyclyl; and the substituents are as defined above.

[0007] In one another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound of Formula I as disclosed herein and one or more additional therapeutic agents.

[0008] In yet another aspect of the present disclosure, there is provided a method of treatment and/or prevention of a condition mediated by adenosine receptor or a proliferative disorder or cancer, comprising administering to a subject suffering from a condition mediated by adenosine receptor or a disease or proliferative disorder or cancer, a therapeutically effective amount of the compounds of Formula I as disclosed herein or the pharmaceutical composition comprising compounds of Formula I as disclosed herein and one or more additional therapeutic agent.

[0009] In further another aspect of the present disclosure, there is provided use of the compounds as disclosed herein or the pharmaceutical composition as disclosed herein for treatment of a condition mediated by adenosine receptor $A_{2a}R$, or $A_{2b}R$; treatment and/or prevention of a proliferative disorder or disease or cancer or immune-related disorder or disease or condition; or treatment of cancer together with other clinically relevant cytotoxic agents or non-cytotoxic agents.

[00010] In furthermore aspect of the present disclosure, there is provided use of the compounds as disclosed herein or the pharmaceutical composition as disclosed herein for treatment of a condition mediated by adenosine receptors $A_{2a}R$ and $A_{2b}R$; treatment and/or prevention of a proliferative disorder or disease or cancer or immune-related disorder or disease or condition; or treatment of cancer together with other clinically relevant cytotoxic agents or non-cytotoxic agents.

[00011] 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[00012] Figure 1 depicts the in vivo efficacy effect of Example-13 on Tumor volume, in accordance with an implementation of the present disclosure.

[00013] Figure 2 depicts Tumor Granzyme B expression compared to vehicle treatment in accordance with an implementation of the present disclosure.

DETAILED DESCRIPTION

[00014] 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 combinations of any or more of such steps or features.

Definitions

[00015] 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.

[00016] 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.

[00017] The terms "comprise" and "comprising" are used in the inclusive, open sense, meaning that additional elements may be included. Throughout this specification, 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 element or step or group of element or steps but not the exclusion of any other element or step or group of element or steps.

[00018] The term "including" is used to mean "including but not limited to". "Including" and "including but not limited to" are used interchangeably.

[00019] In the structural Formulae given herein and throughout the present disclosure, the following terms have been indicated meaning, unless specifically stated otherwise.

[00020] In this specification, the prefix C_{x-y} as used in terms such as C_{x-y} alkyl and the like (where x and y are integers) indicates the numerical range of carbon atoms that are present in the group; for example, C_{1-6}alkyl includes C_1alkyl (methyl(-CH_3), (-CH_2-)), C_2alkyl (ethyl(-C_2H_5, -CH_2CH_2-)), C_3alkyl (propyl and isopropyl) and C_4alkyl (butyl, 1-methylpropyl, 2-methylpropyl, and *t*-butyl). Unless specifically stated, the bonding atom of a group may be any suitable atom of that group; for example, propyl includes prop-1-yl and prop-2-yl.

[00021] The term "alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, t-butyl, n-hexyl, and the like. The groups may be optionally substituted.

[00022] The term "haloalkyl" as used herein refers to an alkyl group in which one or more hydrogen atoms are replaced by the same number of identical or different halogen atoms. The term "haloalkyl" is exemplified by groups such as chloromethyl, trifluoromethyl, 1-fluoroethyl, 2,2,2-trifluoroethyl, 2-fluoropropyl, 2,2-difluoropropyl, and the like. The term haloalkyl is exemplified by groups such as CF_3, CHF_2, CH_2F, and the like.

[00023] The term "aminoalkyl" refers to a group having an amine and an alkyl group and the amine may be primary, secondary or tertiary amine. The point of attachment may be N or C i.e amine or alkyl group. The term "aminoalkyl" and "alkylamino" may be used interchangeably. The term aminoalkyl is exemplified by groups such as -$CH(CH_3)_2NH_2$, -$CH_2CH_2NH_2$, -$CH_2CH_2NHCH_3$, -$CH_2CH(NH_2)CH_3$, -$CH_2CH_2N(CH_3)_2$, -$NHCH_3$, -$N(CH_3)_2$, -CH_2NH_2, -CH_2NHCH_3, -CH_2NHCH_2-, -$CH_2NHCH_2CH_2$- and the like.

[00024] The term "alkylhydroxy" or "alkylhydroxyl" refers to an alkyl group in which one or more hydrogen atoms are replaced by a hydroxyl(-OH) group. The

term alkylhydroxy is exemplified by groups such as $-CH_2CH(CH_3)_2OH$, $-CH(CH_3)_2OH$, $-CH_2OH$, CH_2CH_2OH and the like.

[00025] The term "alkenyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2, 3, 4, 5, or 6 carbon atoms and having 1, 2, or 3, double bond. The groups may be optionally substituted.

[00026] The term "alkynyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2, 3, 4, 5, or 6 carbon atoms and having 1, 2, or 3, triple bond. The groups may be optionally substituted.

[00027] The term "cycloalkyl" refers to carbocyclic groups with 3 to 6 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, and the like. The groups may be optionally substituted.

[00028] The term “cycloalkenyl” refers to carbocyclic groups of 3 to 6 carbon atoms having a single cyclic ring or multiple condensed rings which may be partially unsaturated.

[00029] The term “halocycloalkyl” as used herein refers to a cycloalkyl substituted with one or more halogen atoms. The halocycloalkyl refers to 3 to 6 carbon containing cycloalkyl substituted with one or more halogens.

[00030] The terms "alkoxyl" or "alkoxy" refers to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy, and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders an ether is or resembles an alkoxyl, such as can be represented by one of -O-alkyl, -O- alkenyl, -O-alkynyl. The alkoxy groups may be optionally substituted.

[00031] “Halo” or “Halogen”, alone or in combination with any other term means halogens such as chloro (Cl), fluoro (F), bromo (Br) and iodo (I).

[00032] The term “carbocyclyl” or “carbocycle” refers to a saturated, unsaturated ring having 4 to 10 carbon atoms forming cyclic systems. Carbocyclic groups may be spiral or bridged systems, may be saturated, unsaturated or partially saturated. Carbocyclyl groups may be optionally substituted with one or more heteroatoms. Carbocyclic groups may refer to heteroaryl groups with one or more heteroatoms. Representative carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, and the like.

[00033] The term “heterocyclyl” refers to a "carbocyclyl" as defined herein, wherein one or more carbon atoms have been replaced with a heteroatom selected from O, N, or S. The heterocyclyl group may contain 1 to 10 carbon in the ring structure, substituted with one to four heteroatoms selected from O, N, or S. The heterocyclyl may be saturated, unsaturated or partially saturated. Representative examples of heterocyclyl include oxiranyl, oxetanyl, oxolanyl, oxanyl, furanyl, dioxanyl, pyranyl, aziridinyl, piperidinyl, tetrahydropyranyl, azepinyl, oxazepinyl and the like.

[00034] The term “heteroaryl” refers to aromatic rings containing from 1 to 4 heteroatoms selected from N, O and S in the ring. “Heteroaryl” groups may be substituted with one or more substituents if so defined herein. The “$C_{2\text{-}6}$ heteroaryl” rings refers to a group having 2 or 6 carbon as ring member atoms with one to four heteroatoms.

[00035] The term “aryl” refers to aromatic ring having a specified number of carbon atoms. For example, $C_{5\text{-}10}$ aryl refers to an aryl group having 5 to 10 member atoms, or 6 member atoms. Preferred aryl groups include, without limitation, phenyl, and the like.

[00036] The term “haloalkoxy” refers to an alkoxy group as defined above further attached via halo linkage. For example, $C_{1\text{-}6}$ haloalkoxy refers to an alkoxy group having 1 – 6 carbon atoms further attached to one or more halogen. Preferred haloalkoxy groups include, without limitation, $-CH_2OCF_3$, $-CH_2CH_2OCF_3$, $-CH_2CH_2OCHF_2$, $-OCH_2Cl$, $-OCHCl_2$, $-CH_2OCF_3$ and the like.

[00037] As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms.

[00038] The term "effective amount" means an amount of a compound or composition which is sufficient enough to significantly and positively modify the symptoms and/or conditions to be treated (e.g., provide a positive clinical response). The effective amount of an active ingredient for use in a pharmaceutical composition will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular active ingredient(s) being employed, the particular pharmaceutically-acceptable excipient(s)/carrier(s) utilized, the route of administration, and like factors within the knowledge and expertise of the attending physician.

[00039] The compounds described herein may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), regioisomers, enantiomers, or diastereomers. Accordingly, the chemical structures depicted herein encompass all possible enantiomers and stereoisomers of the illustrated or identified compounds including the stereoisomerically pure form (e.g., geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the person skilled in the art. The compounds may also exist in several tautomeric forms including the enol form, the keto form, and mixtures thereof. Accordingly, the chemical structures depicted

herein encompass all possible tautomeric forms of the illustrated or identified compounds.

[00040] The term “racemates” refers to a mixture comprising a pair of optical isomers. Racemate refers to equimolar mixture of a pair of enantiomers. Racemate does not exhibit optical activity.

[00041] The term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00042] “Pharmaceutically acceptable salt” embraces salts with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids, for example hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic, hydroiodic and nitric acid and organic acids, for example citric, fumaric, maleic, malic, mandelic, ascorbic, oxalic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases, for example alkyl amines, arylalkyl amines and heterocyclic amines.

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

[00044] Salts and solvates having non-pharmaceutically acceptable counter-ions or associated solvents are within the scope of the present disclosure, for example, for use as intermediates in the preparation of other compounds of Formula I, and their pharmaceutically acceptable salts. Thus, one embodiment of the disclosure embraces compounds of Formula I, and salts thereof. Compounds according to and Formula I contain a basic functional group and are therefore

capable of forming pharmaceutically acceptable acid addition salts by treatment with a suitable acid. Suitable acids include pharmaceutically acceptable inorganic acids and pharmaceutically acceptable organic acids. Representative pharmaceutically acceptable acid addition salts include hydrochloride, hydrobromide, nitrate, methylnitrate, sulfate, bisulfate, sulfamate, phosphate, acetate, hydroxyacetate, phenyl acetate, propionate, butyrate, iso-butyrate, valerate, maleate, hydroxymaleate, acrylate, fumarate, malate, tartrate, citrate, salicylate, glycollate, lactate, heptanoate, phthalate, oxalate, succinate, benzoate, o-acetoxybenzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, naphthoate, hydroxynaphthoate, mandelate, tannate, formate, stearate, ascorbate, palmitate, oleate, pyruvate, pamoate, malonate, laurate, glutarate, glutamate, estolate, methanesulfonate (mesylate), ethanesulfonate (esylate), 2-hydroxyethanesulfonate, benzenesulfonate (besylate), aminobenzenesulfonate, p- toluenesulfonate (tosylate), and naphthalene-2-sulfonate.

[00045] The term “solvate”, as used herein, refers to a crystal form of a substance which contains solvent.

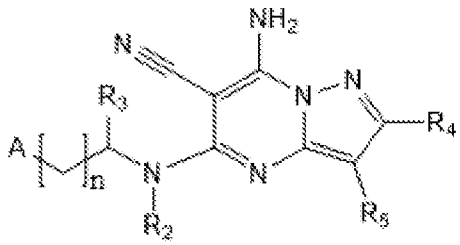
[00046] The term “complexes” as used herein, can be interchangeably used as "coordination complex," or "metal coordination complex," and the like. It refers to a complex of an organic compound with a metal that can be empirically differentiated from a simple metal salt of the organic compound based on physiochemical and/or spectroscopic properties, with a coordination complex typically having enhanced covalency as compared to a salt. Without limitation "complexes" as used herein also involve a combination of coordinate covalent bonds and/or ionic bonds. As used herein, the term "complexes" also includes molecules that lack an ionic component (e.g., such as a neutral coordination complex prior to deprotonation, where pKa of the coordination complex falls within a physiologically acceptable range).

[00047] The term “hydrate” refers to a solvate wherein the solvent is water.

[00048] A term once described, the same meaning applies for it, throughout the disclosure.

[00049] As discussed in the background, there has been enormous efforts for the identification and development of new compounds acting as antagonists for adenosine receptors for treating proliferative disorders or diseases or condition or diseases related to immune depression or cancer. Heterocyclic compounds have been found to act as such antagonists and in the present disclosure there is disclosed, compounds of Formula I, their synthetic preparation methods, and their biological activity towards the adenosine receptors. The compounds of Formula I are found to be adenosine receptor antagonists, in particular adenosine $A_{2a}R$ and $A_{2b}R$ receptor antagonists. The compounds of Formula I are suitably formulated with therapeutic agents to form the pharmaceutical composition. The pharmaceutical composition and the compounds of Formula I is used for the treatment of diseases or disorders or condition mediated by the adenosine receptors.

[00050] In an embodiment of the present disclosure, there is provided a compound of Formula I or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof,



Formula I

wherein A is selected from C_{5-10} aryl, C_{2-10} heteroaryl, C_{3-6} cycloalkyl, or C_{1-10} heterocyclyl; wherein C_{5-10} aryl, C_{2-10} heteroaryl, C_{3-6} cycloalkyl, or C_{1-10} heterocyclyl is optionally substituted with one or more substituents selected from R_6, R_7, R_8, R_9, R_{9a}, or oxo;

R_2 is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl;

R_3 is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl; wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy;

R_4 and R_5 are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, -CO-N(R_{10} R_{11}), C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl are optionally substituted with one or more groups selected from C_{3-6} cycloalkyl, C_{1-6} alkoxy, or C_{1-10} heterocyclyl; or R_4 and R_5 are joined together to form C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{4-10} carbocyclyl or C_{1-10} heterocyclyl is optionally substituted with 1 to 3 groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

R_{10} and R_{11} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{3-6} halocycloalkyl, C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl;

R_6 is selected from hydrogen, halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, C_{3-6} halocycloalkyl, -Y-O-C_{1-6} alkyl, -Y-O-C_{3-6} cycloalkyl, -Y-CO-NH-R_{13}, -Y-Z, C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{1-6} alkylhydroxy, or C_{1-10} heterocyclyl is optionally substituted with one or more groups selected from halogen, hydroxyl, amine, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, C_{1-6} haloalkoxy, C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{3-6} cycloalkyl, or C_{1-6} aminoalkyl, is optionally further substituted with one or more groups independently selected from halogen, hydroxyl, C_{1-6} alkylhydroxy, -C(O)C_{1-6} alkyl, -C(O)NH_2, -C(O)-C_{1-6}alkylhydroxy, or C_{1-10} heterocyclyl, and C_{1-10} heterocyclyl is optionally substituted with 1 to 3 groups independently selected from halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

Y is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, or C_{3-6} cycloalkenyl; and C_{1-6} alkyl is optionally substituted with C_{3-6} cycloalkyl;

Z is selected from -OH, -NH_2, -COOH, -SO_2NH_2, -SO_2CH_3, -$SOCH_3$, -SCH_3, CH_2-NH-(C_{1-6} alkyl)-$SOCH_3$, -O-P(=O)$(OH)_2$, -$CONH_2$, -CONH(C_{1-6} alkyl), -SO_2NH(C_{1-6} alkyl), CON(C_{1-6} alkyl)$_2$, -NHCO(C_{1-6} alkyl), C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{1-10} heterocyclyl has 1 to 4 heteroatoms independently

selected from O, N or S, and optionally substituted with 1 to 3 groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

R_{13} is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or C_{3-6} halocycloalkyl;

R_7, R_8, R_9, and R_{9a} are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or C_{3-6} halocycloalkyl;

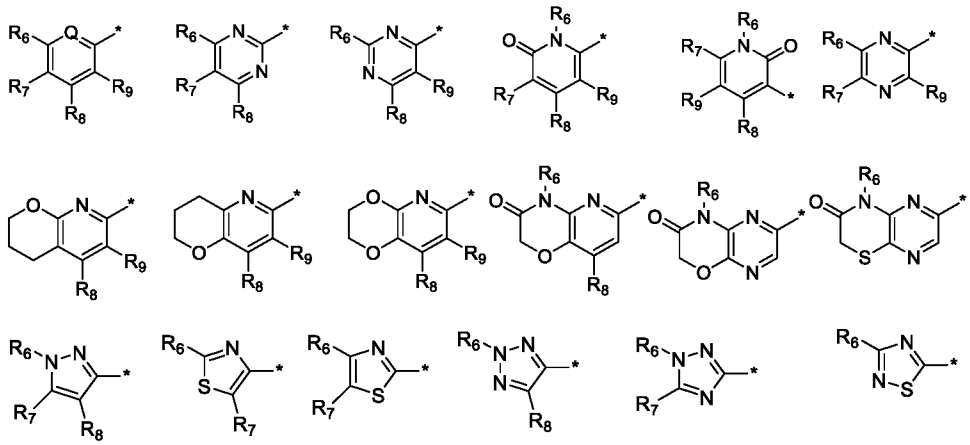
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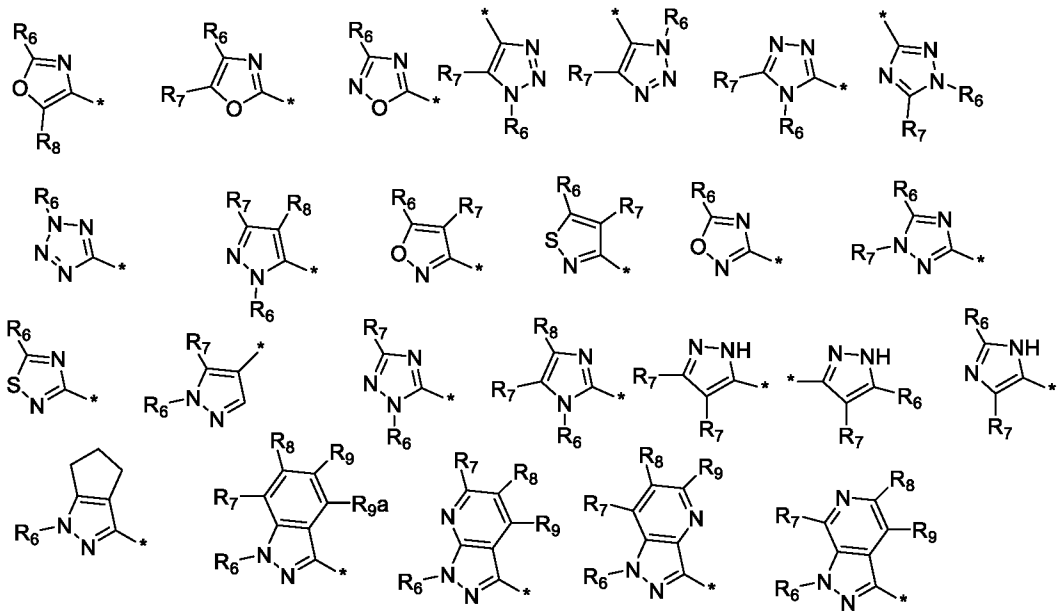
n is 0, 1, or 2.

[00051] In an embodiment of the present disclosure, there is provided a compound of Formula I or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof, A is selected from C_{5-10} aryl, C_{2-10} heteroaryl, or C_{1-10} heterocyclyl; C_{5-10} aryl, C_{2-10} heteroaryl, or C_{1-10} heterocyclyl is optionally substituted with one or more substituents selected from R_6, R_7, R_8, R_9, R_{9a}, or oxo; R_2 is selected from hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl; R_3 is selected from hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl and wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy; R_4 and R_5 are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, is optionally substituted with one or more groups selected from C_{3-6} cycloalkyl, C_{1-6} alkoxy, or C_{1-10} heterocyclyl; wherein C_{1-10} heterocyclyl has 1 to 3 heteroatoms independently selected from O, N or S, and optionally substituted with 1 to 3 groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy; R_6 is selected from hydrogen, halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, C_{3-6} halocycloalkyl, -Y-O-C_{1-6} alkyl, -Y-O-C_{3-6} cycloalkyl, -Y-CO-NH-R_{13}, -Y-Z, or C_{1-10} heterocyclyl, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, C_{3-6} halocycloalkyl or C_{1-10} heterocyclyl is optionally substituted with one or more groups selected from halogen, hydroxyl, amine, C_{1-6} alkoxy, C_{3-6}

cycloalkyl, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, C_{1-6} haloalkoxy, or C_{1-10} heterocyclyl, wherein C_{3-6} cycloalkyl, or C_{1-6} aminoalkyl, is optionally further substituted with one or more groups selected from halogen, hydroxyl, C_{1-6} alkylhydroxy, -C(O)C_{1-6} alkyl, -C(O)NH_2, -C(O)-C_{1-6}alkylhydroxy, or C_{1-10} heterocyclyl; Y is selected from C_{1-6} alkyl, or C_{3-6} cycloalkyl; and C_{1-6} alkyl is optionally substituted with C_{3-6} cycloalkyl; Z is selected from -OH, -NH_2, -COOH, -SO_2NH_2, -SO_2CH_3, -$SOCH_3$, , -SCH_3, CH_2-NH-(C_{1-6} alkyl)-$SOCH_3$,-O-P(=O)$(OH)_2$, -$CONH_2$, -CONH(C_{1-6} alkyl), -SO_2NH(C_{1-6} alkyl), CON(C_{1-6} alkyl)$_2$, NHCO(C_{1-6} alkyl), or C_{1-10} heterocyclyl, wherein C_{1-10} heterocyclyl has 1 to 3 heteroatoms independently selected from O, N, or S, and optionally substituted with 1 to 3 groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy; R_{13} is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or C_{3-6} halocycloalkyl; R_7, R_8, R_9, and R_{9a} are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or C_{3-6} halocycloalkyl; and n is 0, 1, or 2.

[00052] In an embodiment of the present disclosure, there is provided a compound of Formula I or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof, wherein A is selected from

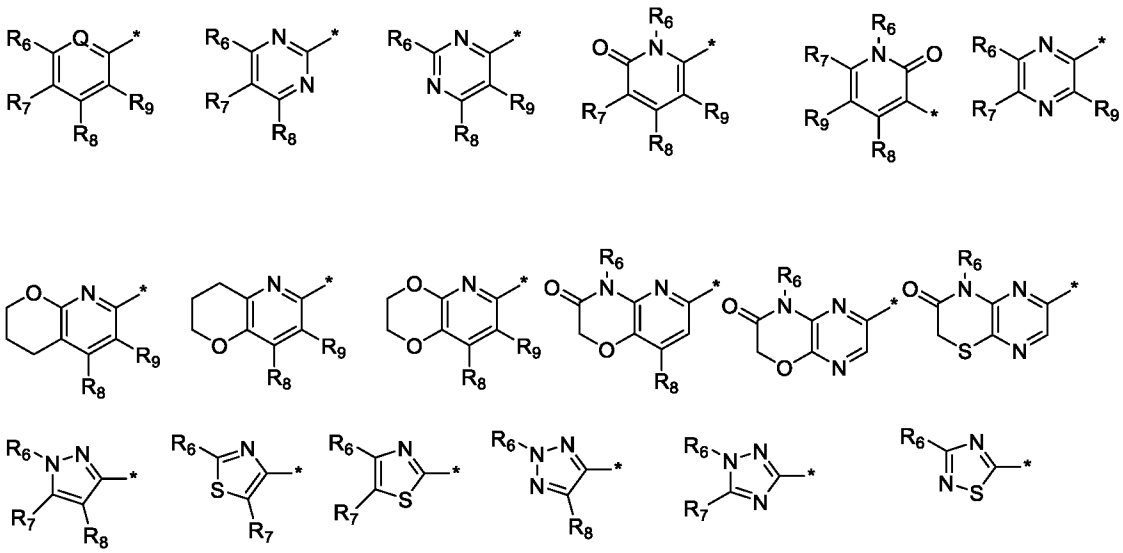


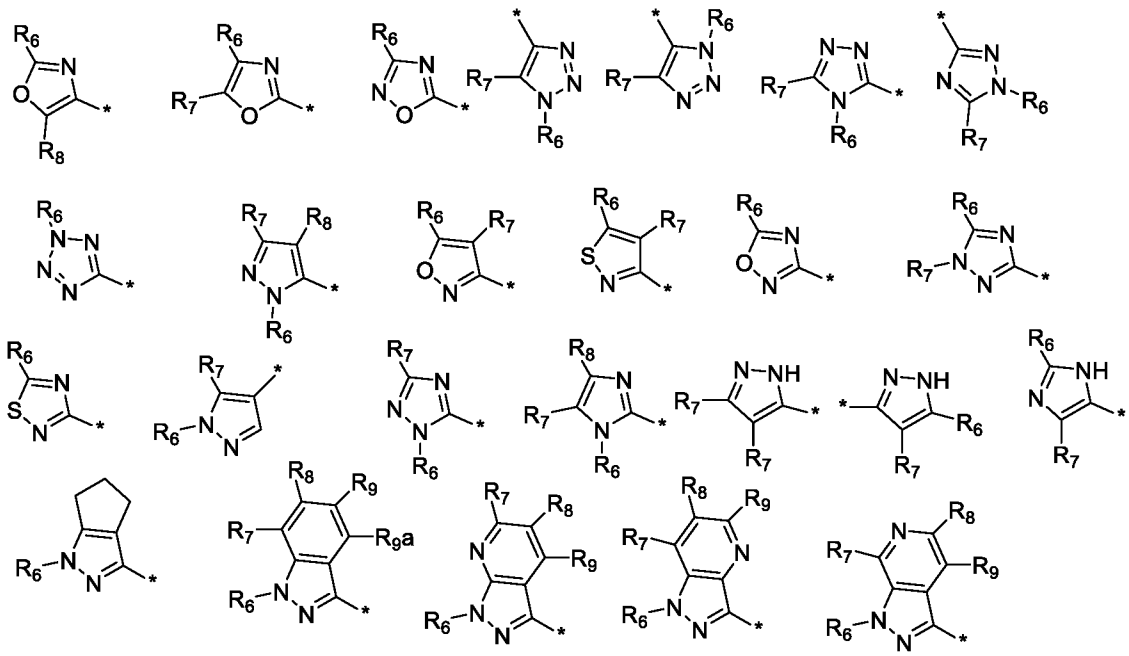


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wherein Q is N or CR_1; and R_1 is selected from cyano, hydrogen, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy; and C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with C_{1-6}alkoxy.

[00053] In an embodiment of the present disclosure, there is provided a compound of Formula I or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof, wherein A is selected from





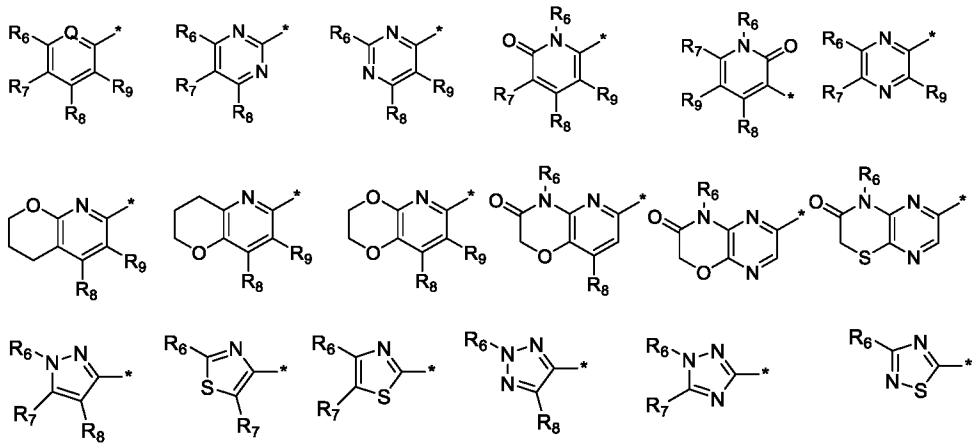
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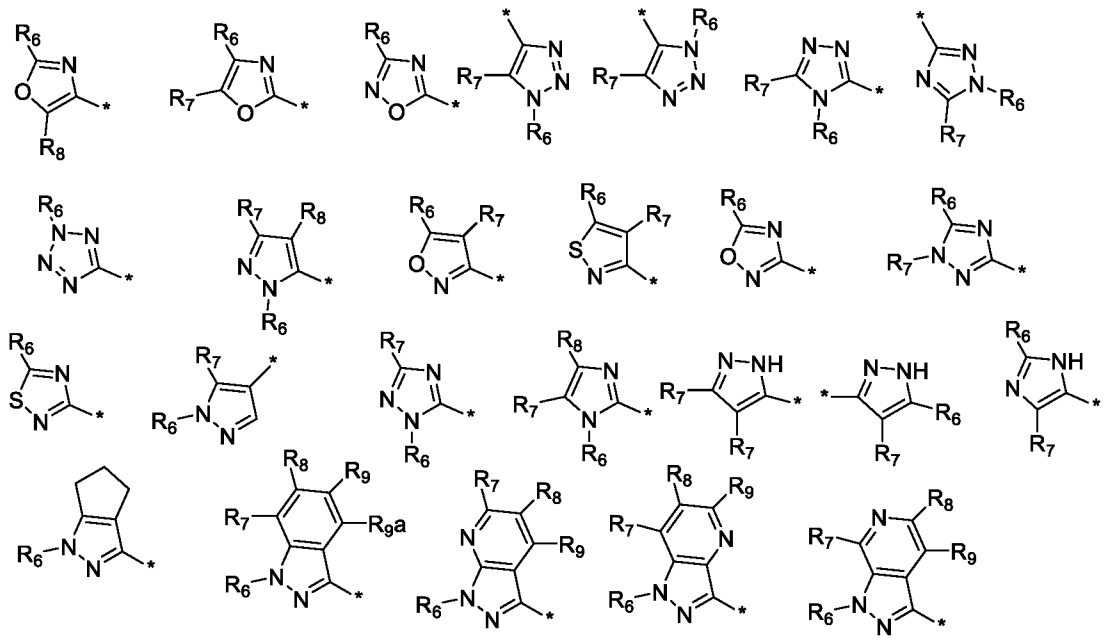
Q is N or CR_1;

R_1 is selected from cyano, hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy; R_2 is hydrogen or C_{1-6} alkyl; R_3 is hydrogen or C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy; R_4 and R_5 are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-10} heterocyclyl; wherein C_{1-6} alkyl is optionally substituted with one or more groups selected from C_{3-6} cycloalkyl, C_{1-6} alkoxy, or C_{1-10} heterocyclyl, wherein C_{1-10} heterocyclyl has 1 to 3 heteroatoms independently selected from O, N or S and optionally substituted with 1 to 3 groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy; R_6 is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, -Y-CO-NH-R_{13}, -Y-Z, or C_{1-10} heterocyclyl, wherein C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} alkylhydroxy, or C_{1-10} heterocyclyl is optionally substituted with one or more groups selected from halogen, hydroxyl, amine, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, C_{1-6} haloalkoxy, or C_{1-10} heterocyclyl having 1 to 4 heteroatoms independently selected from O, N or S, wherein C_{3-6} cycloalkyl, or C_{1-6} aminoalkyl optionally substituted with 1 to 3 groups independently selected from

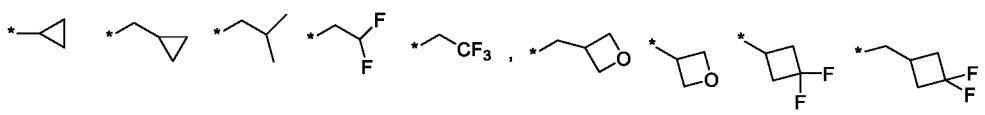
halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylhydroxy, -$C(O)C_{1-6}$ alkyl, -$C(O)NH_2$, -$C(O)$-C_{1-6}alkylhydroxy, or C_{1-10} heterocyclyl; Y is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein C_{1-6} alkyl optionally substituted with C_{3-6} cycloalkyl; Z is selected from -OH, -NH_2, -COOH, -SO_2NH_2, -SO_2CH_3, -$S(=O)CH_3$, -SCH_3, CH_2-NH-(C_{1-6} alkyl)-$SOCH_3$, -O-$P(=O)(OH)_2$, $CONH_2$, $CON(C_{1-6}$ alkyl$)_2$ -$CONH(C_{1-6}$ alkyl), -$SO_2NH(C_{1-6}$ alkyl), or -$NHCO(C_{1-6}$ alkyl); R_{13} is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or C_{3-6} halocycloalkyl; R_7, R_8, R_9, and R_{9a} are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or C_{3-6} halocycloalkyl; and n is 0, 1 or 2.

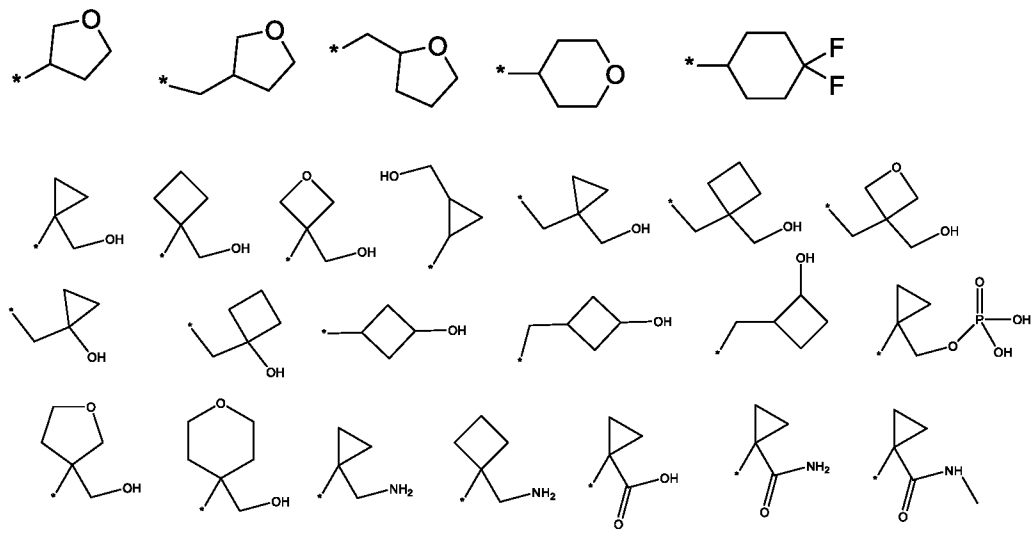
[00054] In an embodiment of the present disclosure, there is provided a compound of Formula I or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof, wherein A is selected from





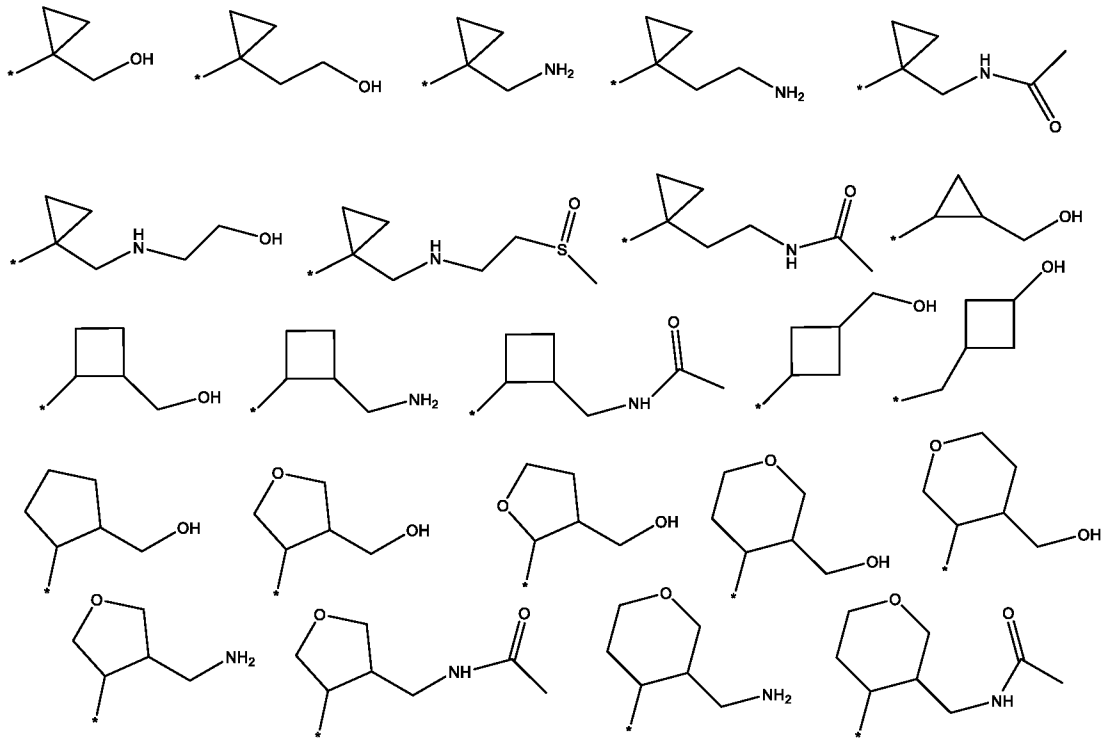
* is the point of attachment, wherein Q is N or CR_1; R_1 is selected from cyano, hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy; R_2 is hydrogen or C_{1-6} alkyl; R_3 is hydrogen or C_{1-6} alkyl and wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy; R_4 and R_5 are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, -CO-N(R_{10} R_{11}), C_{1-10} heterocyclyl, wherein C_{1-6} alkyl optionally substituted with one or more groups selected from C_{3-6} cycloalkyl, C_{1-6} alkoxy, or C_{1-10} heterocyclyl, wherein the C_{1-10} heterocyclyl has 1 to 4 heteroatoms independently selected from O, N or S and optionally substituted with 1 to 3 groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy; R_{10} is hydrogen or C_{1-6} alkyl; R_{11} is selected from hydrogen, C_{1-6} alkyl, or C_{1-10} heterocyclyl, wherein C_{1-6} alkyl is optionally substituted with one or more groups selected from halogen, C_{3-6} cycloalkyl or C_{1-10} heterocyclyl; C_{1-10} heterocyclyl has 1 to 4 heteroatoms independently selected from O, N or S, and optionally substituted with 1 to 3 groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy,





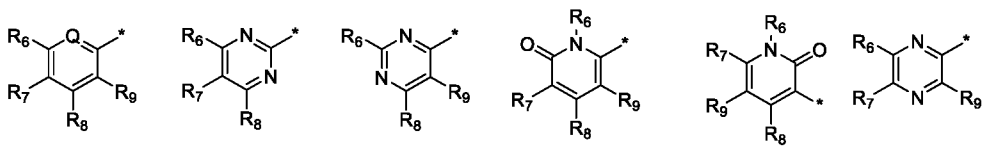
R_6 is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, -Y-CO-NH-R_{13}, -Y-Z, or C_{1-10} heterocyclyl, wherein C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} alkylhydroxy, or C_{1-10} heterocyclyl is optionally substituted with one or more groups selected from halogen, hydroxyl, amine, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, C_{1-6} haloalkoxy, C_{1-10} heterocyclyl having 1 to 4 heteroatoms independently selected from O, N or S; wherein C_{3-6} cycloalkyl, or C_{1-6} aminoalkyl is optionally further substituted with one or more groups selected from halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylhydroxy, -$C(O)C_{1-6}$ alkyl, -$C(O)NH_2$, -$C(O)$-C_{1-6}alkylhydroxy, C_{1-10} heterocyclyl, cyclopropyl, cyclobutyl, CH_2CF_3, CH_2CHFCH_3, $CH_2CF_2CH_3$, $CH_2C(CH_3)_2OH$, $C(CH_3)_2OH$, $C(CD_3)_2OH$, CH_2OH, CH_2OCH_3, CH_2OCF_3, $C(CH_3CF_3)OH$, CH_2CH_2OH, $CH_2CH_2OCH_3$, $CH_2CH(OCH_3)CH_3$, $C(CH_3)_2NH_2$, CH_2NH_2, $CH_2CH_2NH_2$, $CH_2CH_2NHCH_3$, $CH_2CH(NH_2)CH_3$, $CH_2CH_2N(CH_3)_2$, $CH_2CHFCH_2NH_2$, OCH_3, OCF_3, OCH_2CF_3, $OCH_2CH_2OCH_3$, $OCH_2CH_2OCHCF_2$, OCH_2CH_2OH, $OCH_2CH_2OCF_3$, $CH_2CF_2CH_2OH$, $CH_2C(CH_3)_2CH_2OH$, $CHCF_3OH$, $CHOHCH_2OH$, $CHOHCH_2OCH_3$, $CH_2CH_2CH_2OH$, $CH_2CH_2NHCH_2CH_2OH$, $CH_2NHCH_2CH_2OH$,$CH_2CH_2NHCOCH_3$,

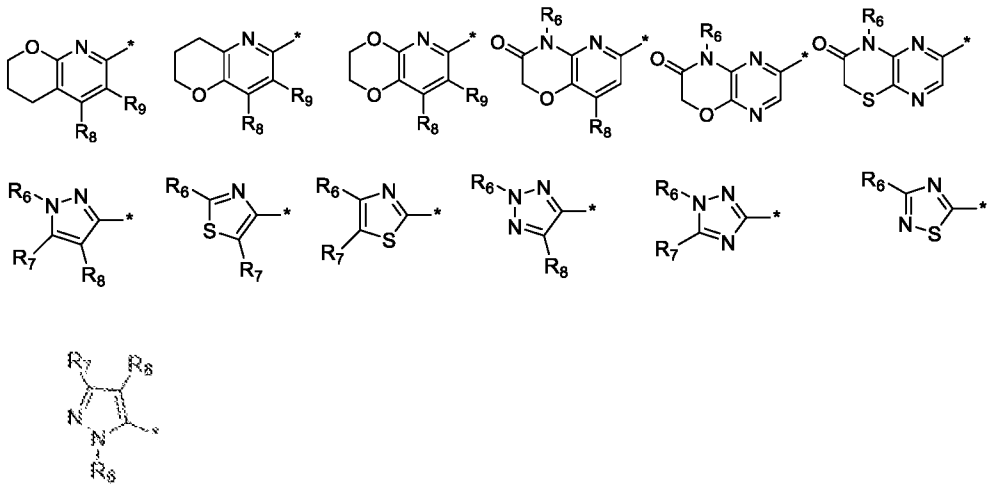
$CH_2CH_2S(=O)CH_3$, $CH_2CH_2CH_2S(=O)CH_3$,



; Y is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein C_{1-6} alkyl optionally substituted with C_{3-6} cycloalkyl; Z is selected from -OH, $-NH_2$, -COOH, $-SO_2NH_2$, $-SO_2CH_3$, $-S(=O)CH_3$, $-SCH_3$, CH_2-NH-(C_{1-6} alkyl)-$SOCH_3$, -O-P(=O)$(OH)_2$, $CONH_2$, CON(C_{1-6} alkyl)$_2$ -CONH(C_{1-6} alkyl), $-SO_2NH(C_{1-6}$ alkyl), or -NHCO(C_{1-6} alkyl); and R_{13} is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or C_{3-6} halocycloalkyl; R_7, R_8, R_9, and R_{9a} are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or C_{3-6} halocycloalkyl; and n is 0, 1 or 2.

[00055] In an embodiment of the present disclosure, there is provided a compound of Formula I or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof, wherein A is selected from

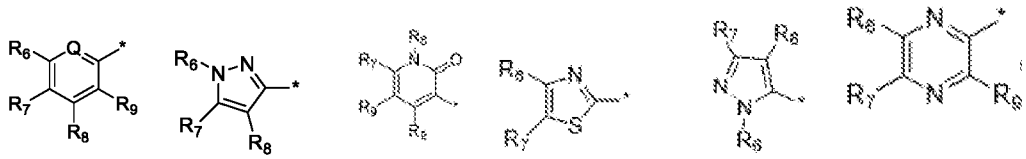




Q is N or CR_1; R_1 is selected from cyano, hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} alkoxy; R_2 is hydrogen or C_{1-6} alkyl; R_3 is hydrogen or C_{1-6} alkyl; R_4 and R_5 are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy; wherein C_{1-6} alkyl optionally substituted with one or more groups selected from C_{3-6} cycloalkyl, or C_{1-6} alkoxy; R_6 is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, -Y-CO-NH-R_{13}, -Y-Z, or C_{1-10} heterocyclyl, wherein C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} alkylhydroxy, or C_{1-10} heterocyclyl is optionally substituted with one or more groups independently selected from halogen, hydroxyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, C_{1-6} haloalkoxy, C_{1-10} heterocyclyl, wherein C_{3-6} cycloalkyl, or C_{1-6} aminoalkyl is optionally further substituted with one or more groups independently selected from halogen, hydroxyl, C_{1-6} alkylhydroxy, -C(O)C_{1-6} alkyl, -C(O)NH_2, or -C(O)-C_{1-6}alkylhydroxy; Y is C_{1-6} alkyl or C_{3-6} cycloalkyl; Z is selected from -OH, -NH_2, -COOH, -SO_2NH_2, -SO_2CH_3, -$SOCH_3$, -SCH_3, CH_2-NH-(C_{1-6} alkyl)-$SOCH_3$, -$CONH_2$, -CONH(C_{1-6} alkyl), -SO_2NH(C_{1-6} alkyl), CON(C_{1-6} alkyl)$_2$, or -NHCO(C_{1-6} alkyl); R_{13} is selected from hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl; R_7, R_8, R_9, and R_{9a} are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, or C_{1-6} alkoxy; and n is 0, 1, or 2.

[00056] In an embodiment of the present disclosure, there is provided a compound of Formula I or its pharmaceutically acceptable salts, complexes,

hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof, wherein A is selected from



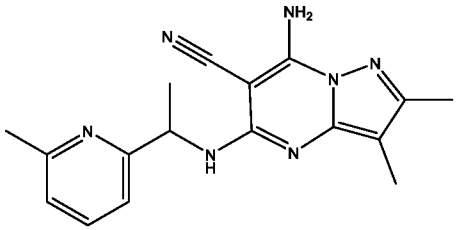
Q is N;

R_2 is hydrogen or C_{1-6} alkyl; R_3 is hydrogen or C_{1-6} alkyl; R_4 and R_5 are independently selected from halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{1-6} haloalkyl; wherein C_{1-6} alkyl is optionally substituted with C_{3-6} cycloalkyl; R_6 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, -Y-CO-NH-R_{13}, -Y-Z, or C_{1-10} heterocyclyl, wherein C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{1-6} alkylhydroxy, or C_{1-10} heterocyclyl is optionally substituted with one or more groups selected from halogen, hydroxyl, amine, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, or C_{1-10} heterocyclyl; , wherein C_{3-6} cycloalkyl, or C_{1-6} aminoalkyl, is optionally further substituted with one or more groups independently selected from halogen, hydroxyl, C_{1-6} alkylhydroxy, -C(O)C_{1-6} alkyl, -C(O)NH_2, or -C(O)-C_{1-6}alkylhydroxy; Y is C_{1-6} alkyl, or C_{3-6} cycloalkyl;

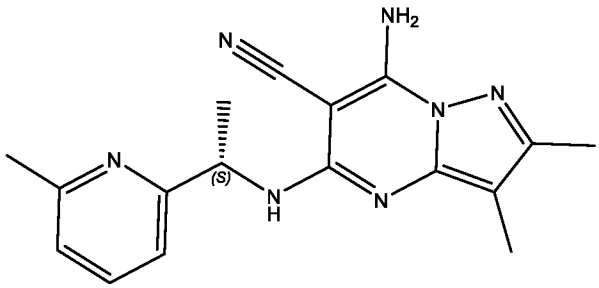
Z is selected from -$SOCH_3$, -SCH_3, CH_2-NH-(C_{1-6} alkyl)-$SOCH_3$, or -NHCO(C_{1-6} alkyl); R_{13} is selected from hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl; R_7, R_8, R_9, and R_{9a} are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl or C_{1-6} alkoxy; and n is 0, or 1.

[00057] In an embodiment of the present disclosure, there is provided a compound of Formula I or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof, is selected from a group consisting of:

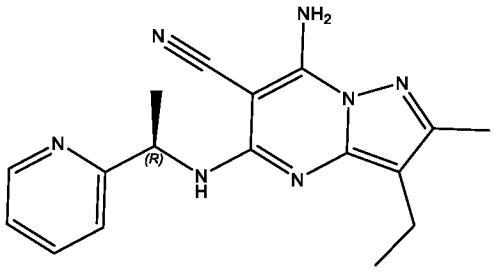
1.7-amino-2,3-dimethyl-5-{[1-(6-methylpyridin-2-yl)ethyl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile;



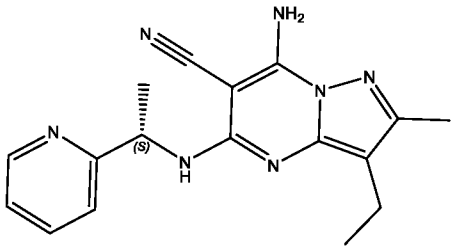
2. 7-amino-2,3-dimethyl-5-{[(1S)-1-(6-methylpyridin-2-yl)ethyl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile;



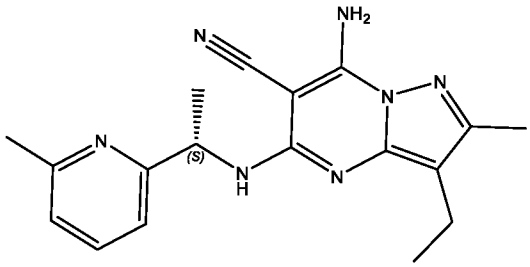
3. (R)-7-Amino-3-ethyl-2-methyl-5-((1-(pyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



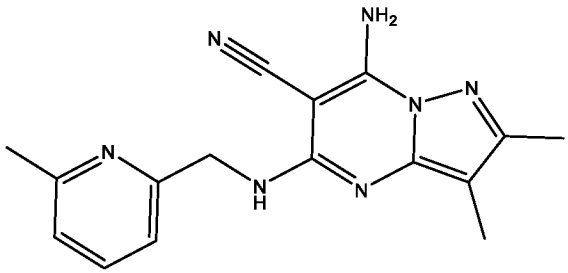
4. (S)-7-Amino-3-ethyl-2-methyl-5-((1-(pyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



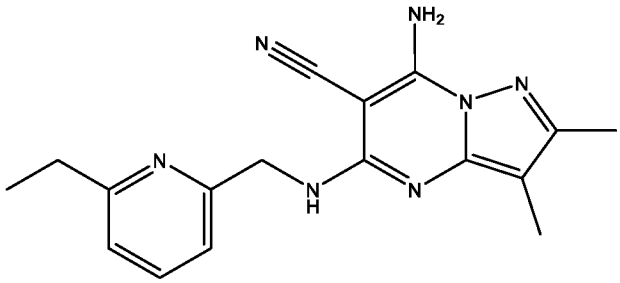
5. (S)-7-Amino-3-ethyl-2-methyl-5-((1-(6-methylpyridin-2-yl) ethyl) amino) pyrazolo [1,5-a] pyrimidine-6-carbonitrile;



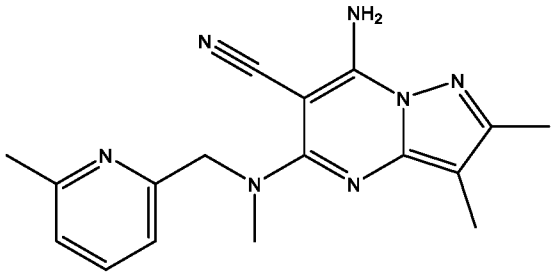
6. 7-amino-2,3-dimethyl-5-{[(6-methylpyridin-2-yl)methyl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile;



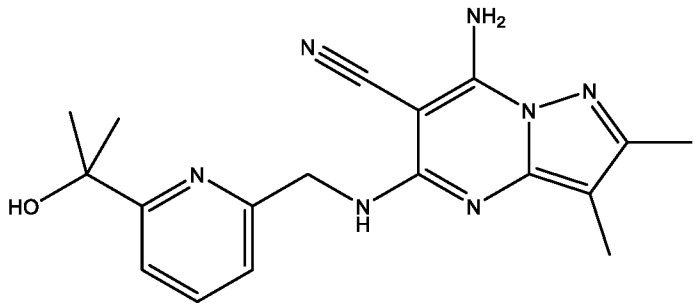
7. 7-amino-5-{[(6-ethylpyridin-2-yl)methyl]amino}-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



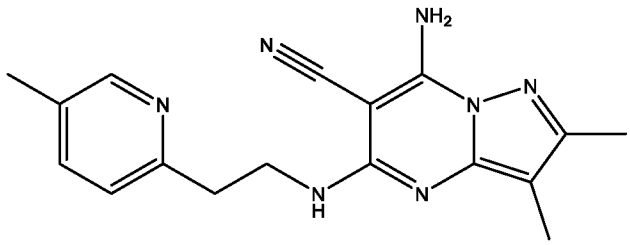
8. 7-amino-2,3-dimethyl-5-{methyl[(6-methylpyridin-2-yl)methyl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile;



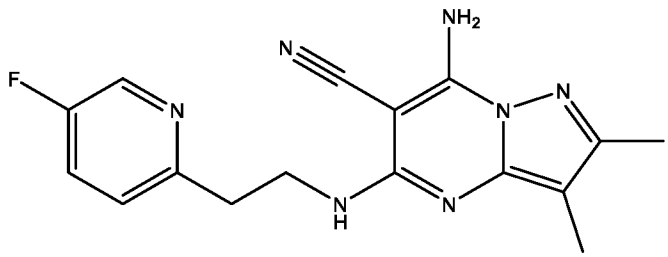
9. 7-amino-5-({[6-(2-hydroxypropan-2-yl)pyridin-2-yl]methyl}amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



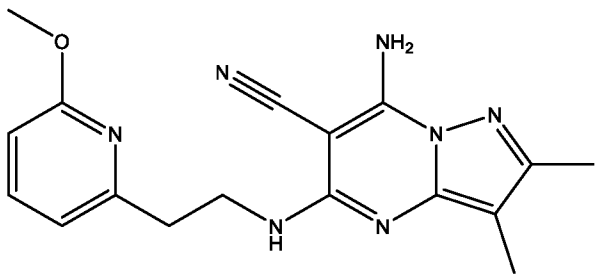
10. 7-Amino-2,3-dimethyl-5-((2-(5-methylpyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



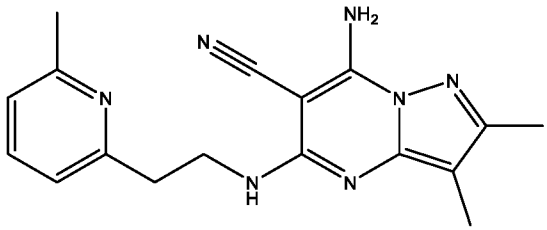
11. 7-amino-5-((2-(5-fluoropyridin-2-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



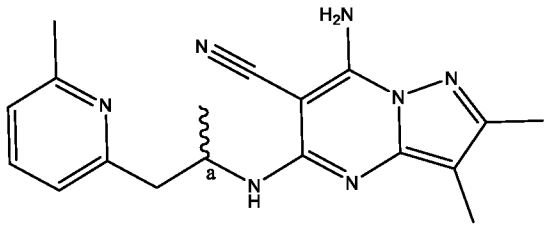
12. 7-amino-5-((2-(6-methoxypyridin-2-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



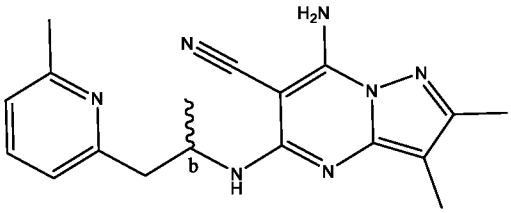
13. 7-amino-5-((2-(6-methylpyridin-2-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



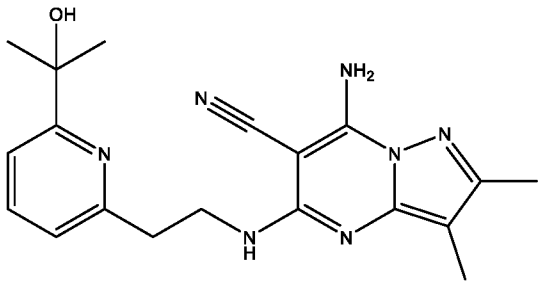
14. Chiral 7-amino-2,3-dimethyl-5-{[1-(6-methylpyridin-2-yl)propan-2-yl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile (Isomer 1);



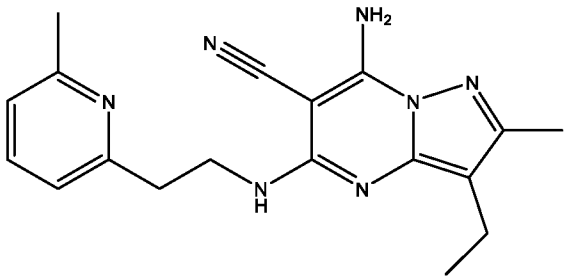
15. Chiral 7-amino-2,3-dimethyl-5-{[1-(6-methylpyridin-2-yl)propan-2-yl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile (Isomer2);



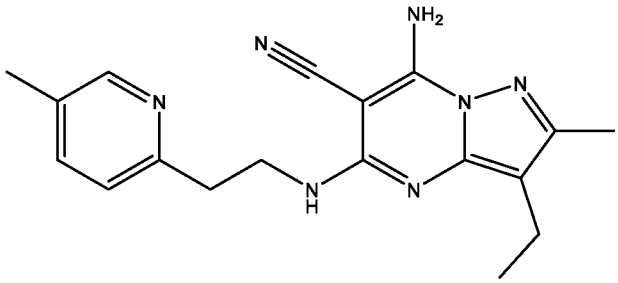
16. 7-amino-5-({2-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]ethyl}amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



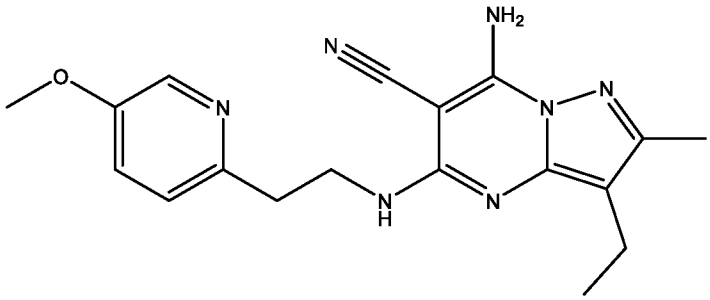
17. 7-Amino-3-ethyl-2-methyl-5-((2-(6-methylpyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



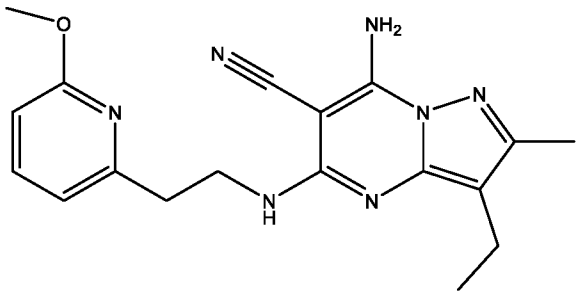
18. 7-Amino-3-ethyl-2-methyl-5-((2-(5-methylpyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



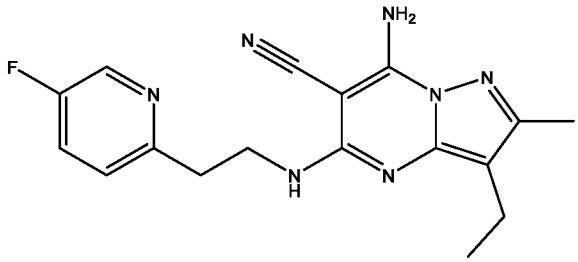
19. 7-Amino-3-ethyl-5-((2-(5-methoxypyridin-2-yl) ethyl) amino)-2-methylpyrazolo [1,5-a] pyrimidine-6-carbonitrile;



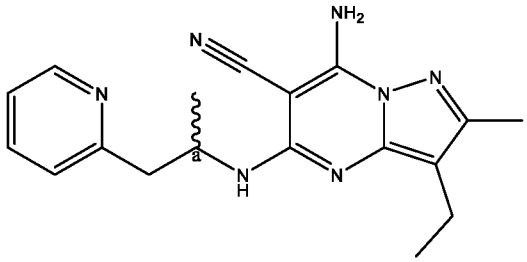
20. 7-Amino-3-ethyl-5-((2-(6-methoxypyridin-2-yl) ethyl) amino)-2-methylpyrazolo [1,5-a] pyrimidine-6-carbonitrile;



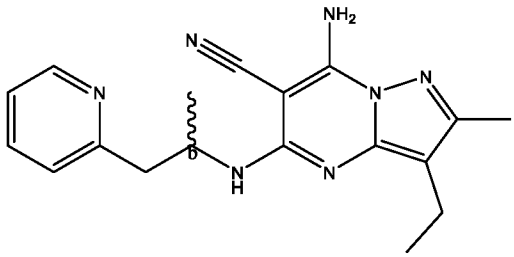
21. 7-Amino-3-ethyl-5-((2-(5-fluoropyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



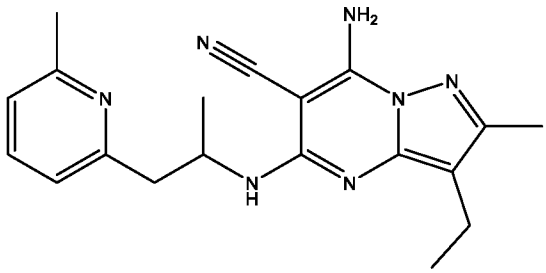
22. Chiral 7-Amino-3-ethyl-2-methyl-5-((1-(pyridin-2-yl) propan-2-yl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (isomer 1);



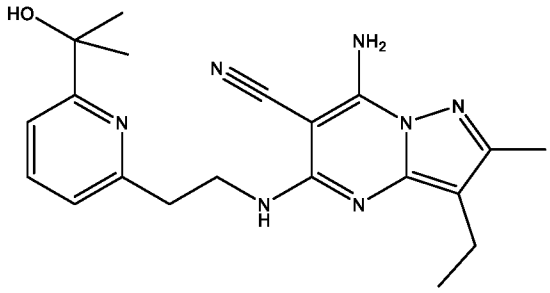
23. Chiral 7-Amino-3-ethyl-2-methyl-5-((1-(pyridin-2-yl) propan-2-yl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile(isomer 2);



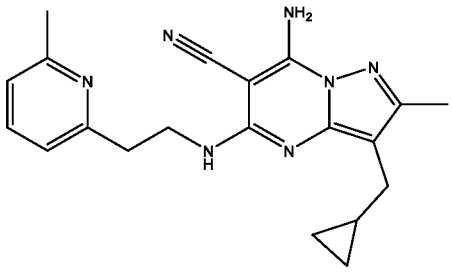
24. 7-Amino-3-ethyl-2-methyl-5-((1-(6-methylpyridin-2-yl) propan-2-yl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



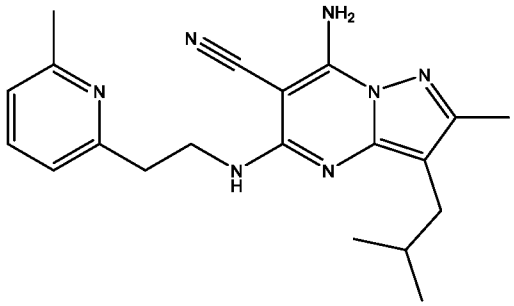
25. 7-amino-3-ethyl-5-({2-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]ethyl}amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



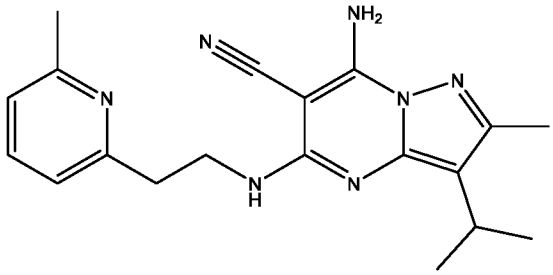
26. 7-amino-3-(cyclopropylmethyl)-2-methyl-5-((2-(6-methylpyridin-2-yl)ethyl) amino) pyrazolo[1,5-a]pyrimidine-6-carbonitrile;



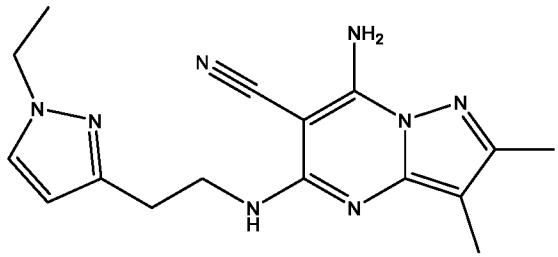
27. 7-amino-3-(isopropylmethyl)-2-methyl-5-((2-(6-methylpyridin-2-yl)ethyl) amino) pyrazolo[1,5-a]pyrimidine-6-carbonitrile;



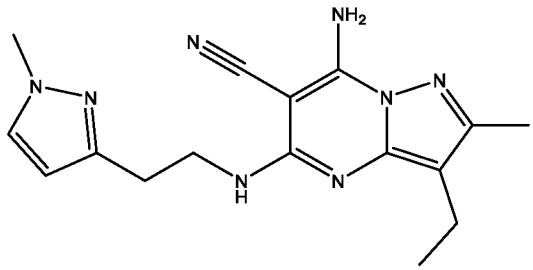
28. 7-amino-3-(isopropyl)-2-methyl-5-((2-(6-methylpyridin-2-yl)ethyl) amino) pyrazolo[1,5-a]pyrimidine-6-carbonitrile;



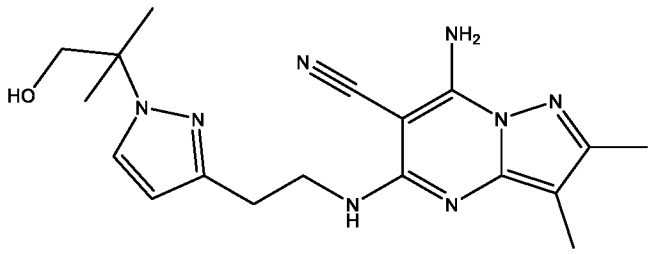
29. 7-amino-5-{[2-(1-ethyl-1H-pyrazol-3-yl)ethyl]amino}-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



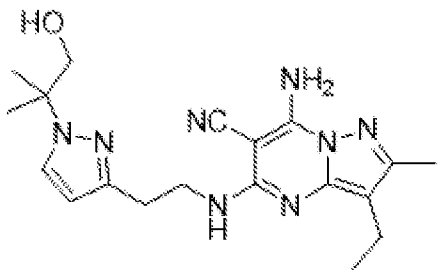
30. 7-amino-3-ethyl-5-{[2-(1-ethyl-1H-pyrazol-3-yl)ethyl]amino}-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



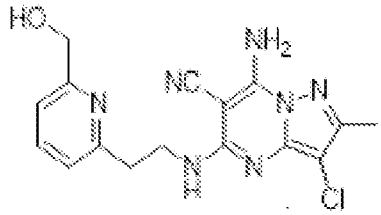
31. 7-amino-5-({2-[1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl]ethyl}amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



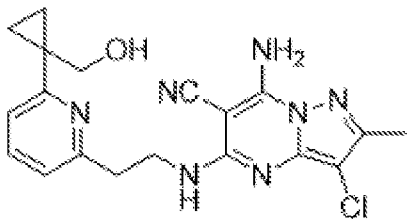
32. 7-amino-3-ethyl-5-((2-(1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



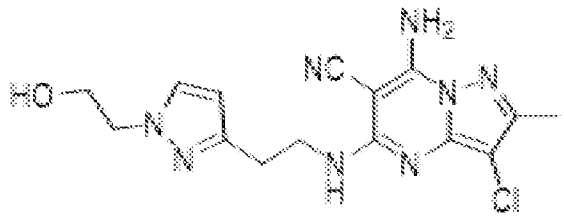
33. 7-amino-3-chloro-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



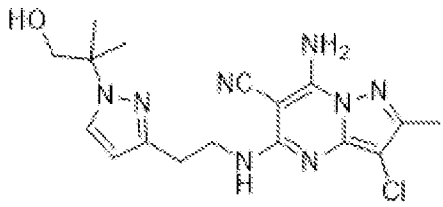
34. 7-amino-3-chloro-5-((2-(6-(1-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



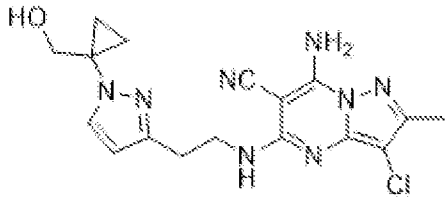
35. 7-amino-3-chloro-5-((2-(1-(2-hydroxyethyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



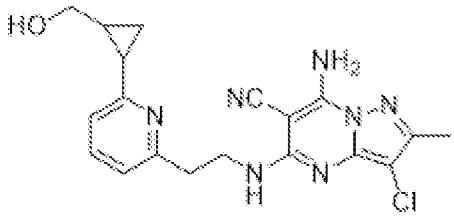
36. 7-amino-3-chloro-5-((2-(1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



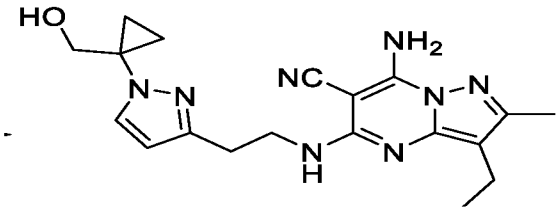
37. 7-amino-3-chloro-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



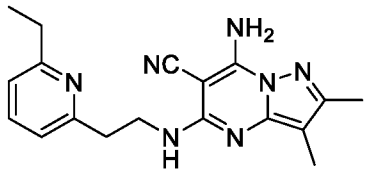
38. 7-amino-3-chloro-5-((2-(6-(2-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



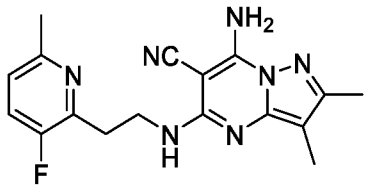
39. 7-amino-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



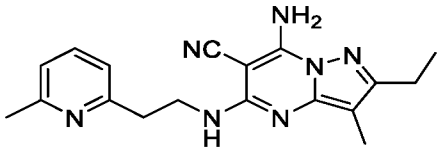
40. amino-5-((2-(6-ethylpyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo [1,5-a] pyrimidine -6-carbonitrile;



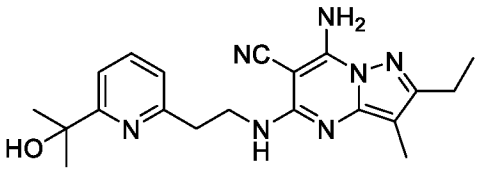
41. 7-amino-5-((2-(3-fluoro-6-methylpyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



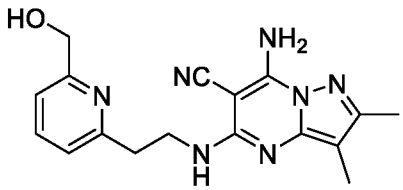
42. 7-amino-2-ethyl-3-methyl-5-((2-(6-methylpyridin-2-yl) ethyl) amino)pyrazolo[1,5-a]pyrimidine-6-carbonitrile;



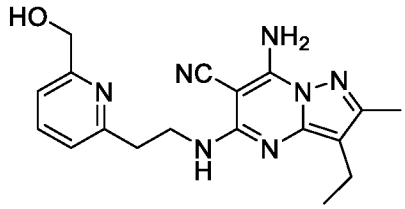
43. 7-amino-2-ethyl-5-((2-(6-(2-hydroxypropan-2-yl) pyridin-2-yl)ethyl)amino)-3-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



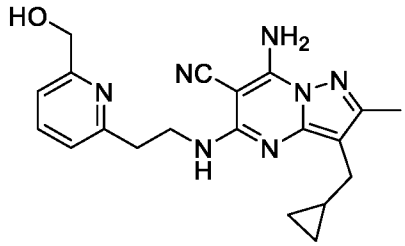
44. 7-amino-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo [1,5-a] pyrimidine-6-carbonitrile;



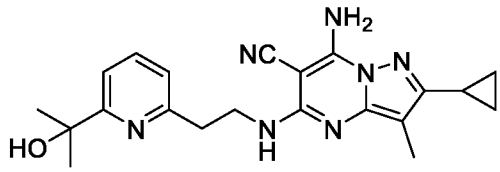
45. 7-amino-3-ethyl-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



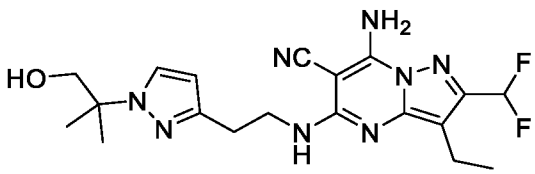
46. 7-amino-3-(cyclopropyl methyl)-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



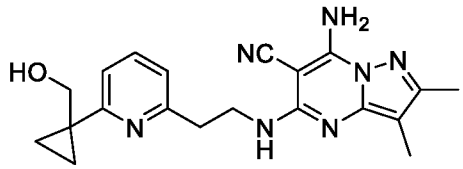
47. 7-amino-2-cyclopropyl-5-((2-(6-(2-hydroxypropan-2-yl) pyridin-2-yl) ethyl)amino)-3-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



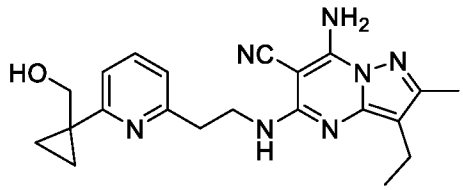
48. 7-amino-2-(difluoromethyl)-3-ethyl-5-((2-(1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl) ethyl) amino)pyrazolo[1,5-a]pyrimidine-6-carbonitrile;



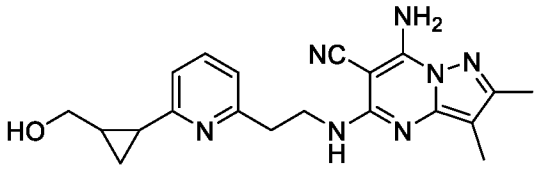
49. 7-amino-5-((2-(6-(1-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl)amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



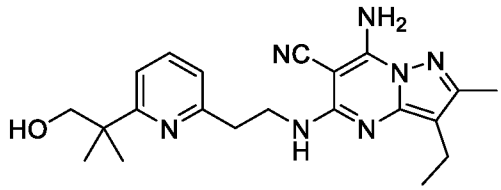
50. 7-amino-3-ethyl-5-((2-(6-(1-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



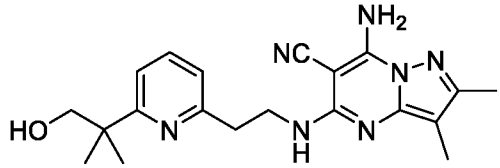
51. 7-amino-5-((2-(6-(2-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl)amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



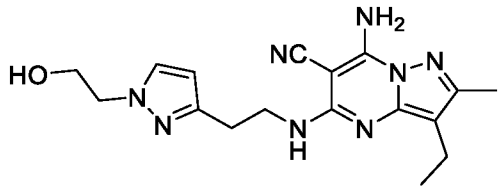
52. 7-amino-3-ethyl-5-((2-(6-(1-hydroxy-2-methylpropan-2-yl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



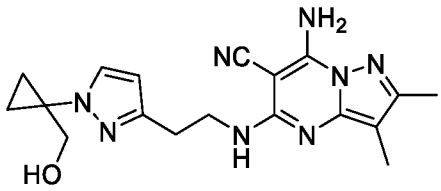
53. 7-amino-5-((2-(6-(1-hydroxy-2-methylpropan-2-yl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



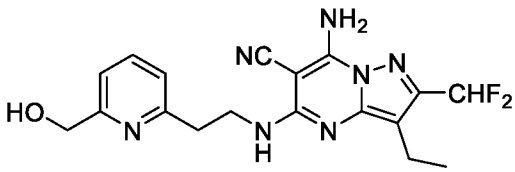
54. 7-amino-3-ethyl-5-((2-(1-(2-hydroxyethyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



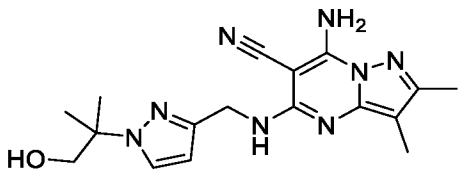
55. 7-amino-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



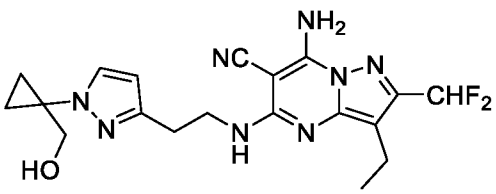
56. 7-amino-2-(difluoro methyl)-3-ethyl-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



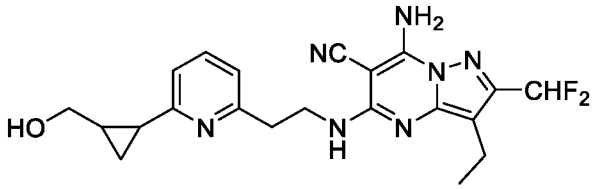
57. 7-amino-5-(((1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl) methyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



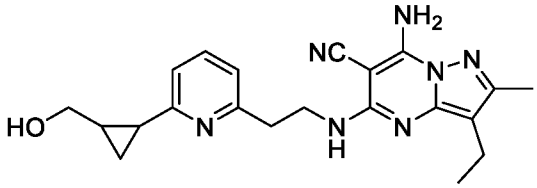
58. 7-amino-2-(difluoro methyl)-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



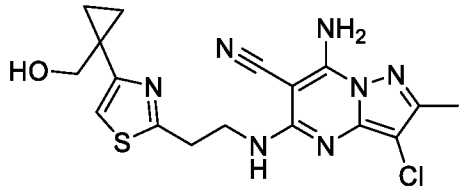
59. 7-amino-2-(difluoro methyl)-3-ethyl-5-((2-(6-(2-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino) pyrazolo[1,5-a]pyrimidine-6-carbonitrile;



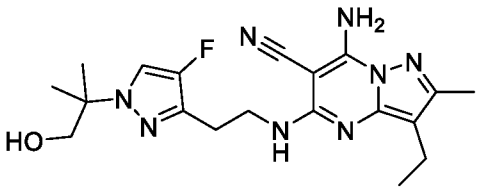
60. 7-amino-3-ethyl-5-((2-(6-(2-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



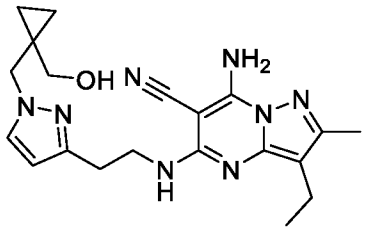
61. 7-amino-3-chloro-5-((2-(4-(1-(hydroxymethyl) cyclopropyl) thiazol-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



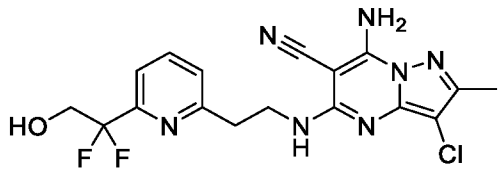
62. 7-amino-3-ethyl-5-((2-(4-fluoro-1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



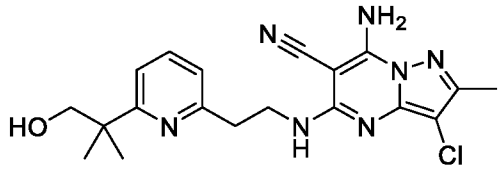
63. 7-amino-3-ethyl-5-((2-(1-((1-(hydroxymethyl) cyclopropyl) methyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



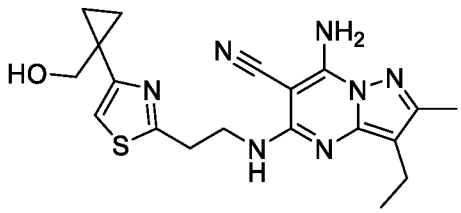
64. 7-amino-3-chloro-5-((2-(6-(1,1-difluoro-2-hydroxyethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



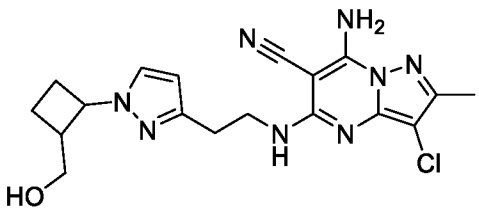
65. 7-amino-3-chloro-5-((2-(6-(1-hydroxy-2-methylpropan-2-yl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



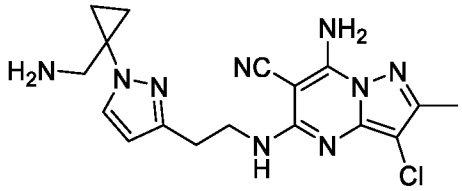
66. 7-amino-3-ethyl-5-((2-(4-(1-(hydroxymethyl) cyclopropyl) thiazol-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



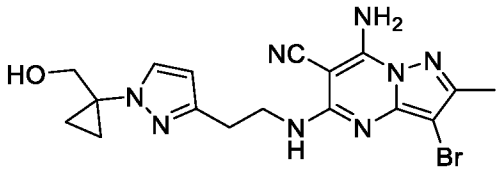
67. 7-amino-3-chloro-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



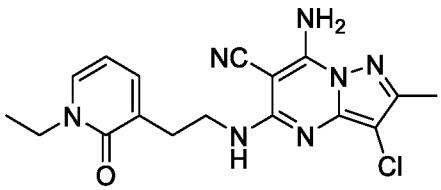
68. 7-amino-5-((2-(1-(1-(amino methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



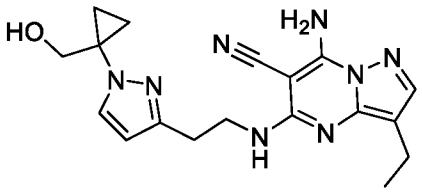
69. 7-amino-3-bromo-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



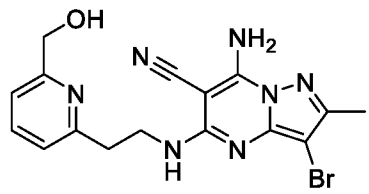
70. 7-amino-3-chloro-5-((2-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



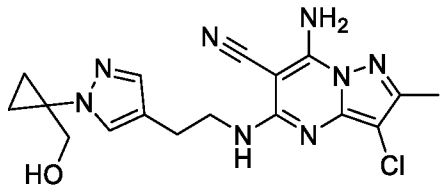
71. 7-amino-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



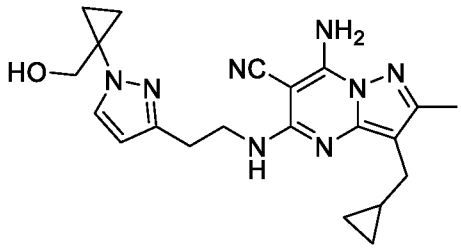
72. 7-amino-3-bromo-5-((2-(6-(hydroxymethyl) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



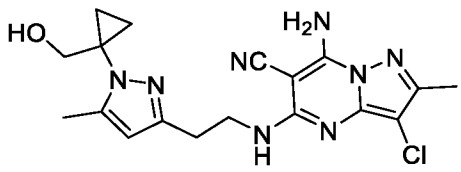
73. 7-amino-3-chloro-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-4-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



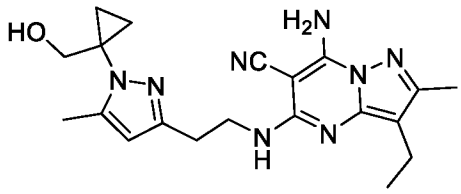
74. 7-amino-3-(cyclopropyl methyl)-5-((2-(1-(1-(hydroxymethyl) cyclopropyl) -1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



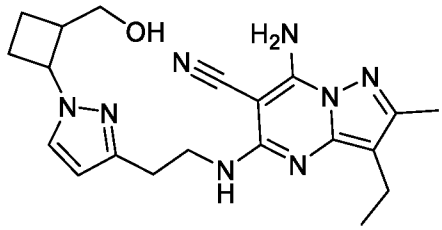
75. 7-amino-3-chloro-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



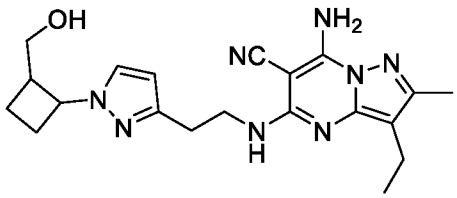
76. 7-amino-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



77. N-((1-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) methyl) acetamide;

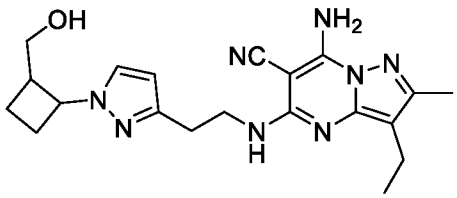


78. (+)- 7-amino-3-ethyl-5-((2-(1-(2-(hydroxymethyl)cyclobutyl)-1H-pyrazol-3-yl)ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



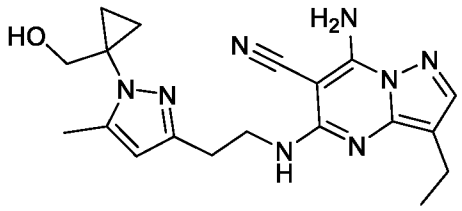
Example 78; dextro(+) rotatory

79. (-) - 7-amino -3-ethyl-5-((2-(1-(2-(hydroxymethyl)cyclobutyl)-1H-pyrazol-3-yl)ethyl) amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

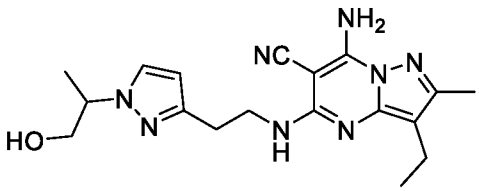


Example 79; leavo(-) rotatory

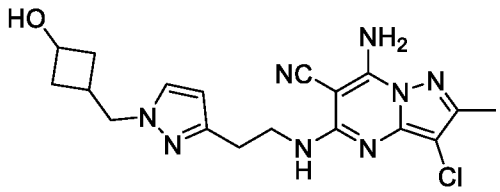
80. 7-amino-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



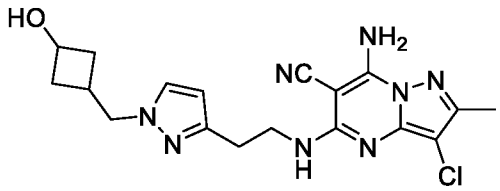
81. 7-amino-3-ethyl-5-((2-(1-(1-hydroxypropan-2-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



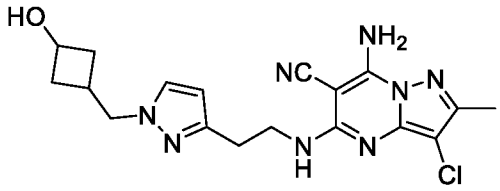
82. (+-) - 7-amino-3-chloro-5-((2-(1-((3-hydroxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



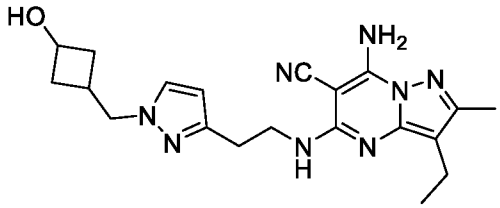
83. (+) - 7-amino-3-chloro-5-((2-(1-((3-hydroxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



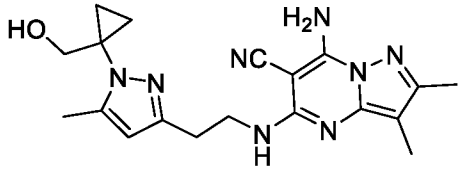
84. (-) - 7-amino-3-chloro-5-((2-(1-((3-hydroxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile(83b);



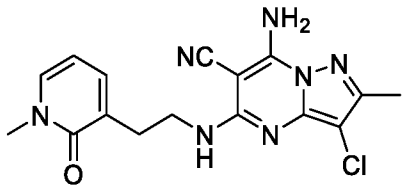
85. 7-amino-3-ethyl-5-((2-(1-((3-hydroxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



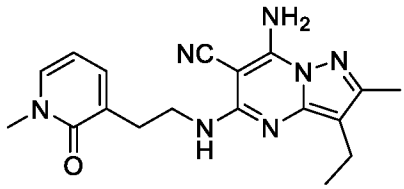
86. 7-amino-5-((2-(1-(1-(hydroxy methyl) cyclopropyl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



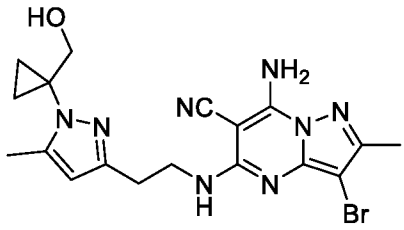
87. 7-amino-3-chloro-2-methyl-5-((2-(1-methyl-2-oxo-1,2-dihydropyridin 3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



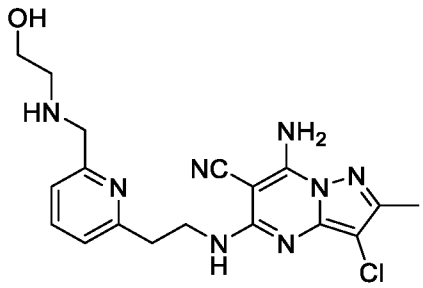
88. 7-amino-3-ethyl-2-methyl-5-((2-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



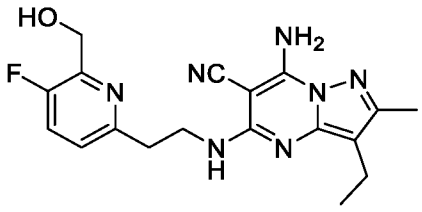
89. 7-amino-3-bromo-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



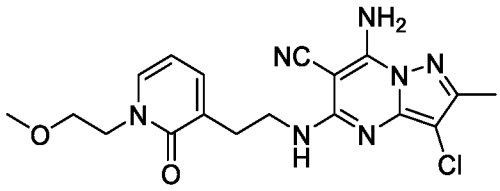
90. 7-amino-3-chloro-5-((2-(6-(((2-hydroxyethyl) amino) methyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



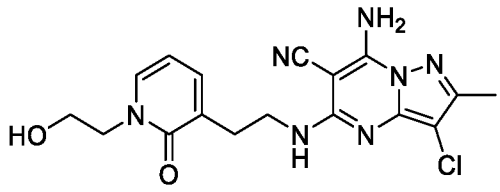
91. 7-amino-3-ethyl-5-((2-(5-fluoro-6-(hydroxymethyl)46yridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



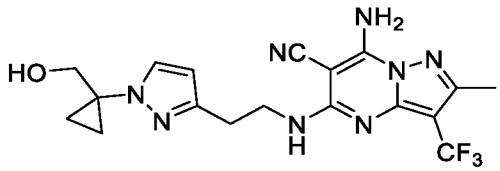
92. 7-amino-3-chloro-5-((2-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



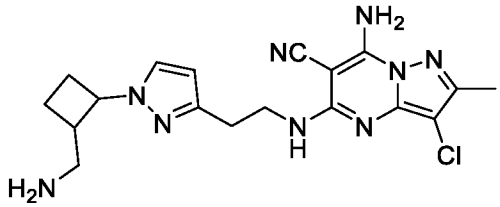
93. 7-amino-3-chloro-5-((2-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



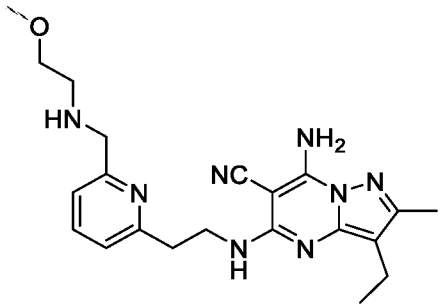
94. 7-amino-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-(trifluoromethyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



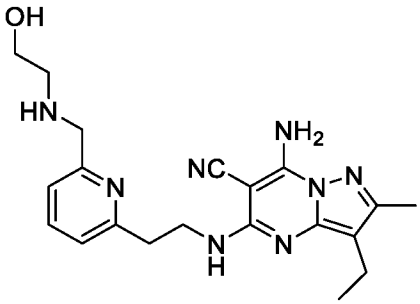
95. 7-amino-5-((2-(1-(2-(amino methyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



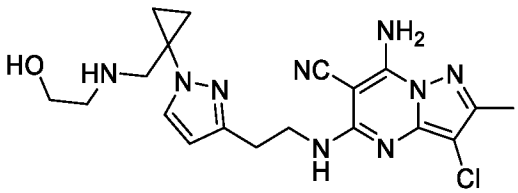
96. 7-amino-3-ethyl-5-((2-(6-(((2-methoxyethyl) amino) methyl)47yridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



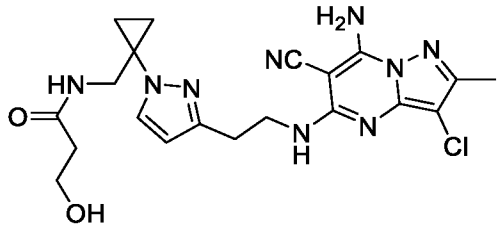
97. 7-amino-3-ethyl-5-((2-(6-(((2-hydroxyethyl) amino) methyl) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



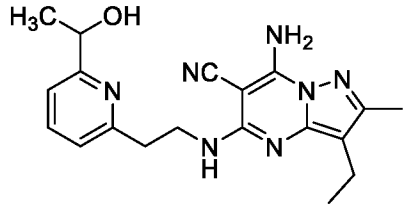
98. 7-amino-3-chloro-5-((2-(1-(1-(((2-hydroxyethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



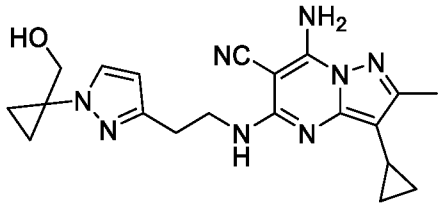
99. N-((1-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) methyl)-3-hydroxypropanamide;



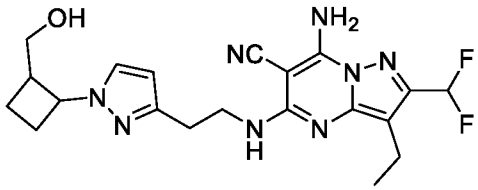
100. 7-amino-3-ethyl-5-((2-(6-(1-hydroxyethyl)49yridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



101. 7-amino-3-cyclopropyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

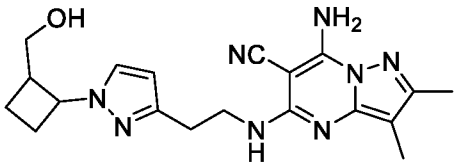


102. 7-amino-2-(difluoro methyl)-3-ethyl-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



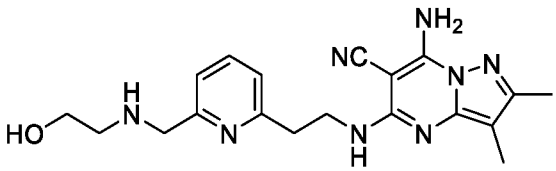
103: 104a, and 104b. (+-)-7-amino-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (103), (+)-7-amino-5-((2-(1-(2-(hydroxymethyl) cyclobutyl) -1H-pyrazol-3-

yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile(104a), (-)-7-amino-5-((2-(1-(2-(hydroxymethyl)cyclobutyl)-1H-pyrazol-3-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile(104b);

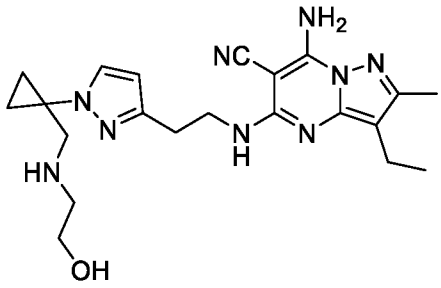


Example 103; racemic(±)
Example 104a; Peak 1;dextro(+) rotatory
Example 104b; Peak 2;leavo(-) rotatory

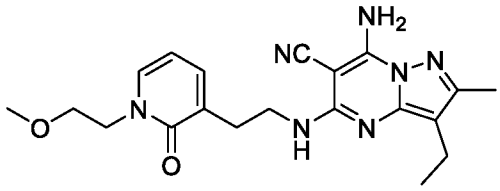
105. 7-amino-5-((2-(6-(((2-hydroxyethyl) amino) methyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



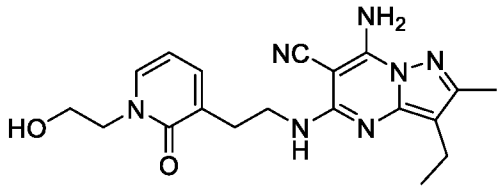
106. 7-amino-3-ethyl-5-((2-(1-(1-(((2-hydroxyethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



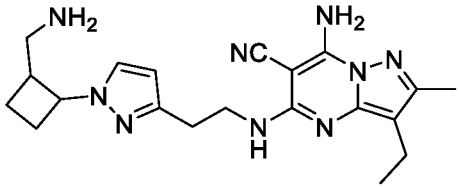
107. 7-amino-3-ethyl-5-((2-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



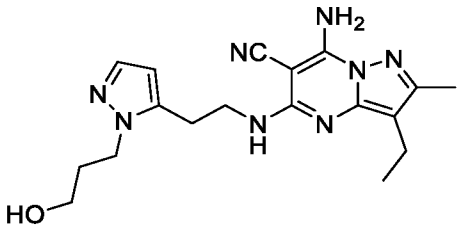
108. 7-amino-3-ethyl-5-((2-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



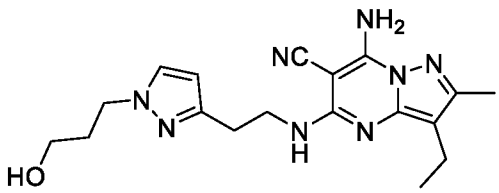
109. 7-amino-5-((2-(1-(2-(amino methyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



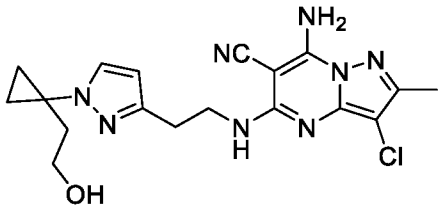
110. 7-amino-3-ethyl-5-((2-(1-(3-hydroxypropyl)-1H-pyrazol-5-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



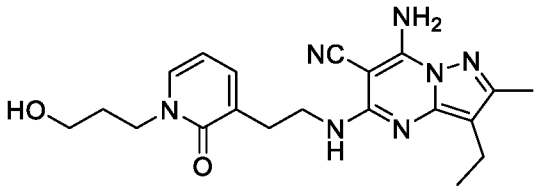
111. 7-amino-3-ethyl-5-((2-(1-(3-hydroxypropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



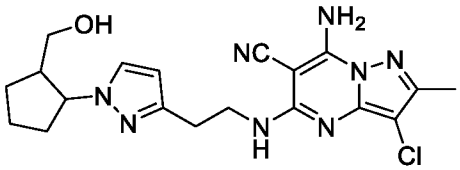
112. 7-amino-3-chloro-5-((2-(1-(1-(2-hydroxyethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



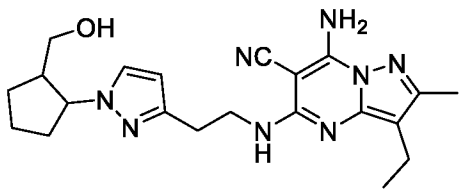
113. 7-amino-3-ethyl-5-((2-(1-(3-hydroxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



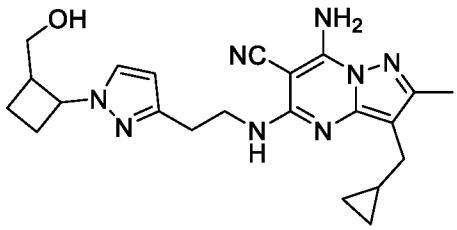
114. 7-amino-3-chloro-5-((2-(1-(2-(hydroxymethyl) cyclopentyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



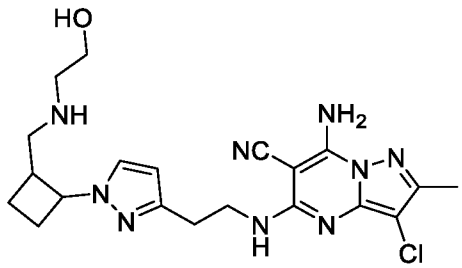
115. 7-amino-3-ethyl-5-((2-(1-(2-(hydroxymethyl) cyclopentyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



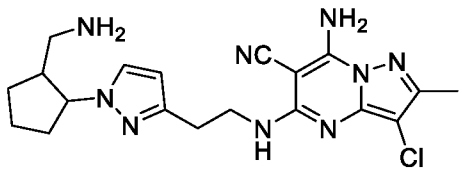
116. 7-amino-3-(cyclopropyl methyl)-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



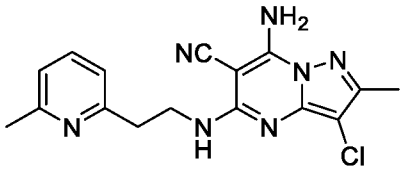
117. 7-amino-3-chloro-5-((2-(1-(2-(((2-hydroxyethyl) amino) methyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



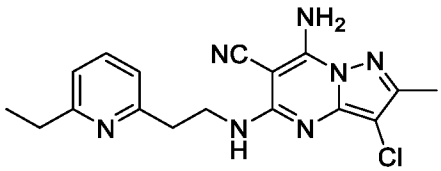
118. 7-amino-5-((2-(1-(2-(amino methyl) cyclopentyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



119. 7-amino-3-chloro-2-methyl-5-((2-(6-methylpyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



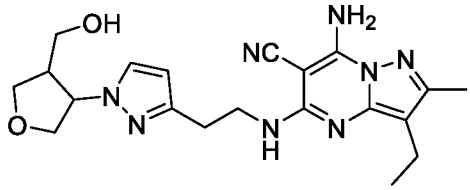
120. 7-amino-3-chloro-5-((2-(6-ethylpyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



121. (+-)-7-amino-3-ethyl-5-((2-(1-(4-(hydroxymethyl)tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)ethyl)amino)-2-methyl pyrazolo[1,5-a]pyrimidine-6-carbonitrile;

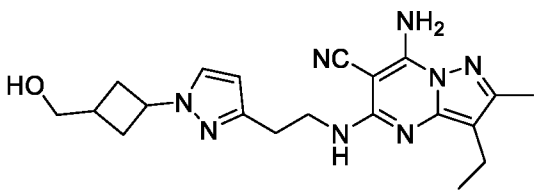
122a. (+)-7-amino-3-ethyl-5-((2-(1-(4-(hydroxy methyl)tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)ethyl)amino)-2-methyl pyrazolo[1,5-a]pyrimidine-6-carbonitrile;

122b. (-)-7-amino-3-ethyl-5-((2-(1-(4-(hydroxy methyl)tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)ethyl)amino)-2-methyl pyrazolo[1,5-a]pyrimidine-6-carbonitrile;

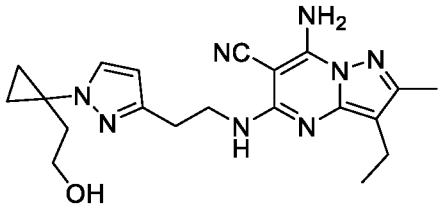


Example 121; racemic(±)
Example 122a; Peak 1;dextro(+) rotatory
Example 122b; Peak 2;leavo(-) rotatory

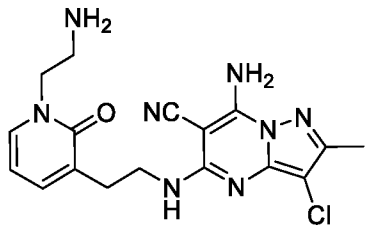
123. 7-amino-3-ethyl-5-((2-(1-(3-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



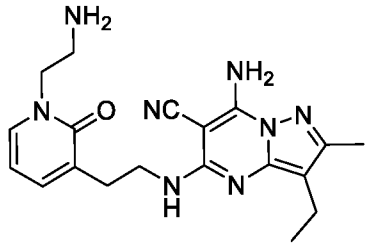
124. 7-amino-3-ethyl-5-((2-(1-(1-(2-hydroxyethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



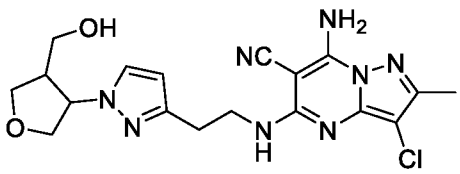
125. 7-amino-5-((2-(1-(2-aminoethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



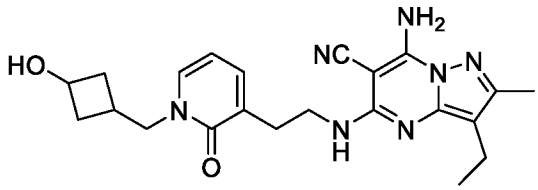
126. 7-amino-5-((2-(1-(2-aminoethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



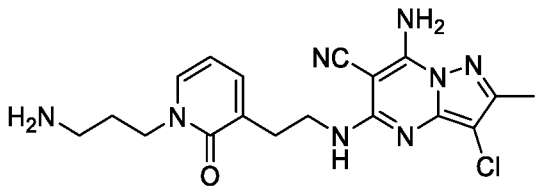
127. 7-amino-3-chloro-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



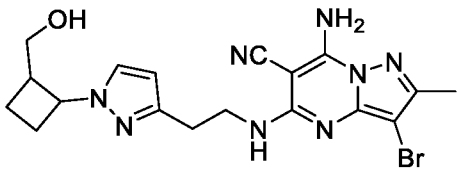
128. 7-amino-3-ethyl-5-((2-(1-((3-hydroxycyclobutyl) methyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;



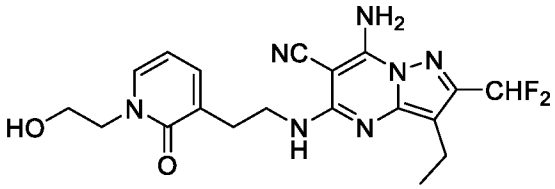
129. 7-amino-5-((2-(1-(3-aminopropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



130. 7-amino-3-bromo-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



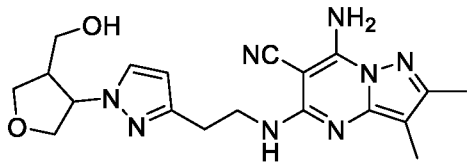
131. 7-amino-2-(difluoromethyl)-3-ethyl-5-((2-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



132. (+-)-7-amino-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

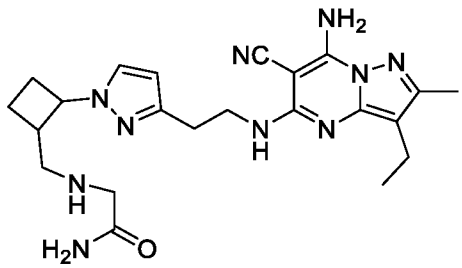
133a. (+)-7-amino-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

133b. (-)-7-amino-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

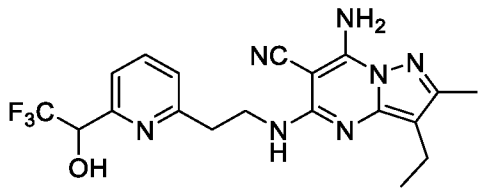


Example 132; racemic(±)
Example 133a; Peak 1;dextro(+) rotatory
Example 133b; Peak 2;leavo(-) rotatory

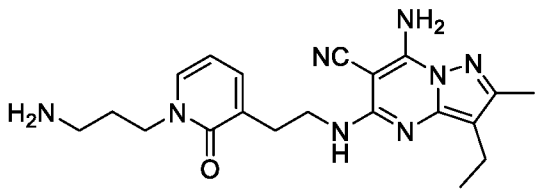
134. 2-(((2-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclobutyl) methyl) amino) acetamide;



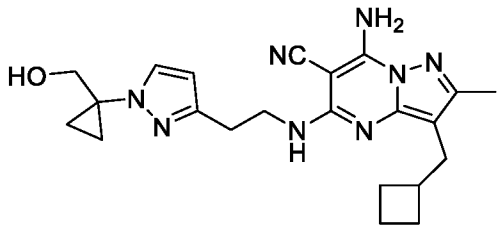
135. 7-amino-3-ethyl-2-methyl-5-((2-(6-(2,2,2-trifluoro-1-hydroxyethyl) pyridine-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6 carbonitrile;



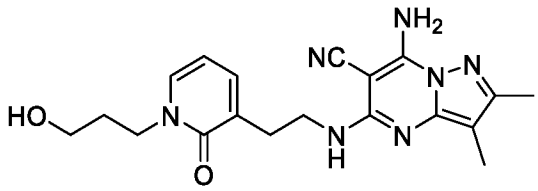
136. 7-amino-5-((2-(1-(3-aminopropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



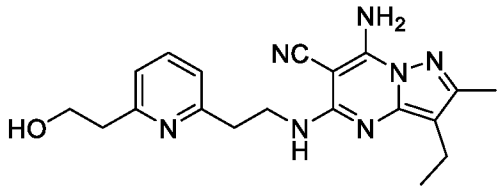
137. 7-amino-3-(cyclo butyl methyl)-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



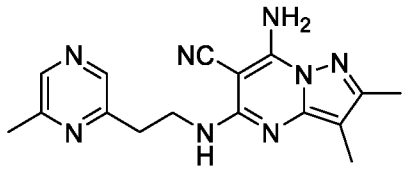
138. 7-amino-5-((2-(1-(3-hydroxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



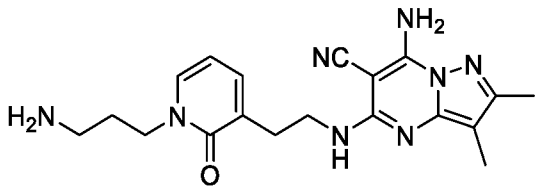
139. 7-amino-3-ethyl-5-((2-(6-(2-hydroxyethyl) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



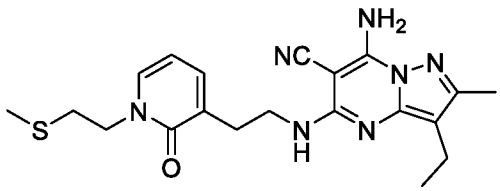
140. 7-amino-2,3-dimethyl-5-((2-(6-methylpyrazin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



141. 7-amino-5-((2-(1-(3-aminopropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



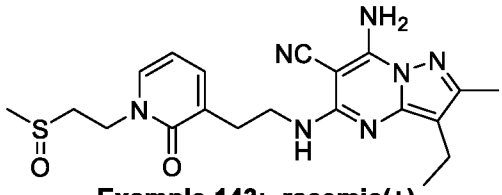
142. 7-amino-3-ethyl-2-methyl-5-((2-(1-(2-(methylthio) ethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a]pyrimidine-6-carbonitrile;



143. Racemic (+-)7-amino-3-ethyl-2-methyl-5-((2-(1-(2-(methyl sulfinyl) ethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

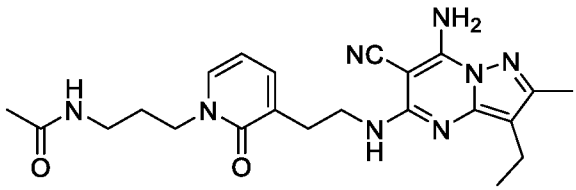
144a. (+)7-amino-3-ethyl-2-methyl-5-((2-(1-(2-(methyl sulfinyl) ethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

144b. (-)7-amino-3-ethyl-2-methyl-5-((2-(1-(2-(methyl sulfinyl) ethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

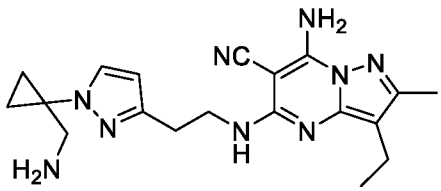


Example 143; racemic(±)
Example 144a; Peak 1;dextro(+) rotatory
Example 144b; Peak 2;leavo(-) rotatory

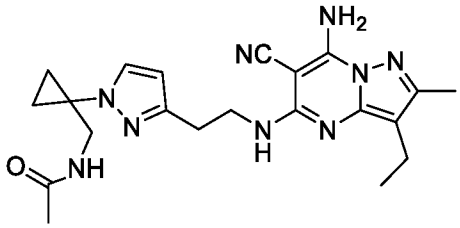
145. N-(3-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-2-oxopyridin-1(2H)-yl) propyl) acetamide;



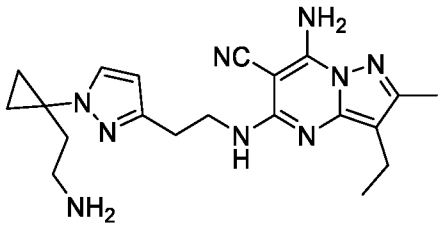
146. 7-amino-5-((2-(1-(1-(amino methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



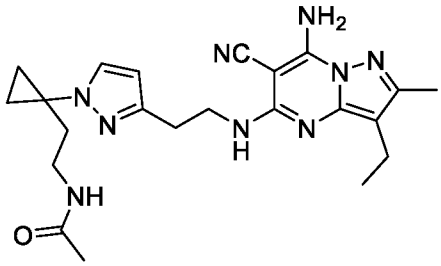
147. N-((1-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) methyl) acetamide;



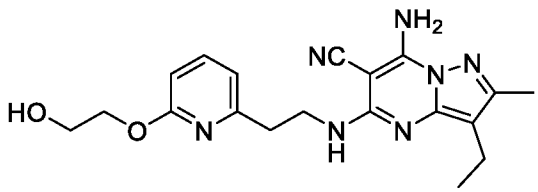
148. 7-amino-5-((2-(1-(1-(2-aminoethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



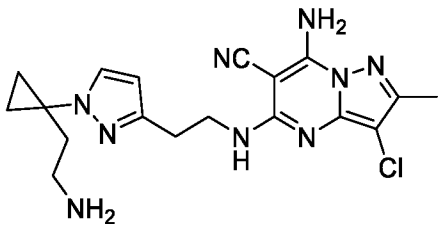
149. N-(2-(1-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) ethyl) acetamide;



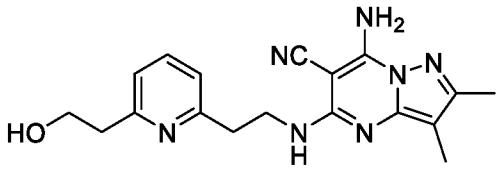
150: 7-amino-3-ethyl-5-((2-(6-(2-hydroxyethoxy)61yridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



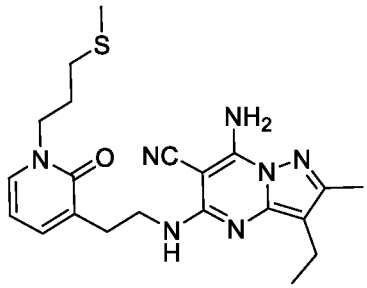
151. 7-amino-5-((2-(1-(1-(2-aminoethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



152. 7-amino-5-((2-(6-(2-hydroxyethyl)61yridine-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

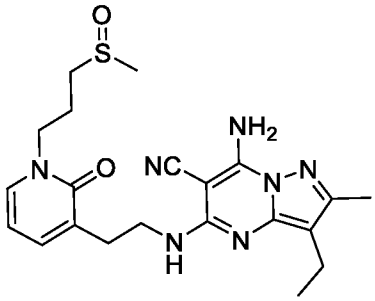


153. 7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methylthio) propyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



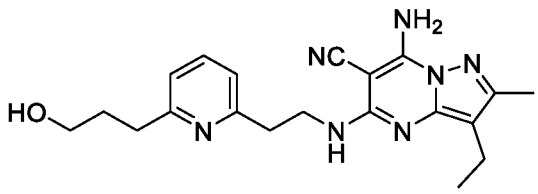
154a (-)-7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methyl sulfinyl) propyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

154b. (+)-7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methyl sulfinyl) propyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

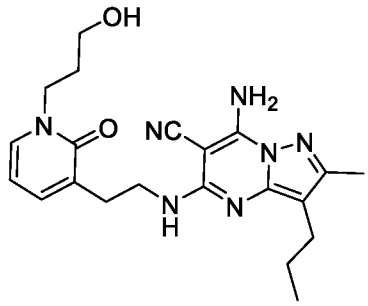


Example 154a; Peak 1; leavo (-) rotatory
Example 154b; Peak 2; dextro (+) rotatory

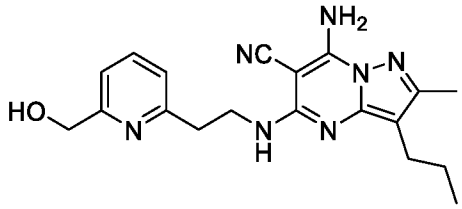
155. 7-amino-3-ethyl-5-((2-(6-(3-hydroxypropyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



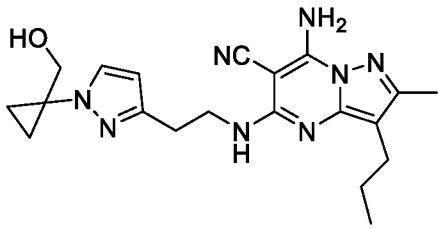
156. 7-amino-5-((2-(1-(3-hydroxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



157. 7-amino-5-((2-(6-(hydroxymethyl)63yridine-2-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

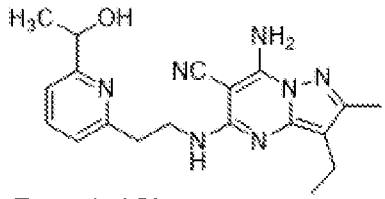


158. 7-amino-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



159a. (+)-7-amino-3-ethyl-5-((2-(6-(1-hydroxyethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

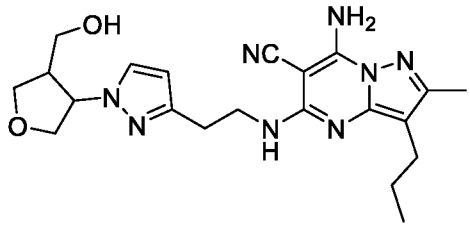
159b.(-)-7-amino-3-ethyl-5-((2-(6-(1-hydroxyethyl) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



Example 159a Peak1: dextro(+) rotatory
Example 159b Peak1: leavo(-) rotatory

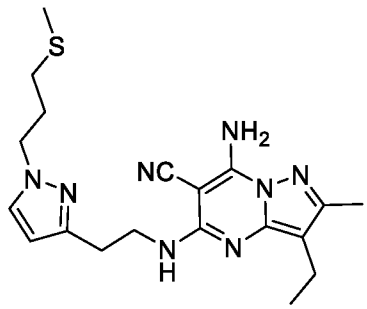
160a. (+) 7-amino-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

160b. (-) 7-amino-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



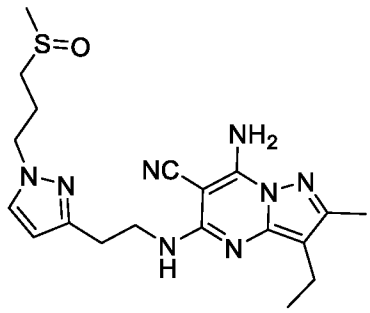
Example 160a; Peak1; Dextro(+) rotatory
Example 160b; Peak2; leavo (-) rotatory

161. 7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methylthio) propyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



162a (-)-7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methyl sulfinyl) propyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a]pyrimidine-6-carbonitrile;

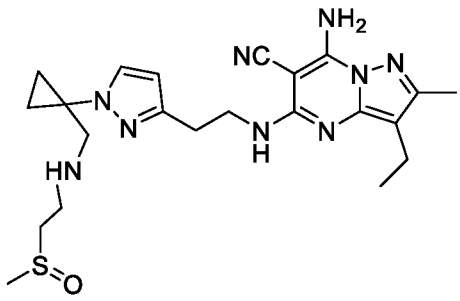
162b. (+)-7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methylsulfinyl)propyl)-1H-pyrazol-3-yl)ethyl)amino)pyrazolo[1,5-a]pyrimidine-6-carbonitrile;



Peak 1; Example 162a; leavo (-) rotatory
Peak 2; Example 162b;dextro (+) rotatory

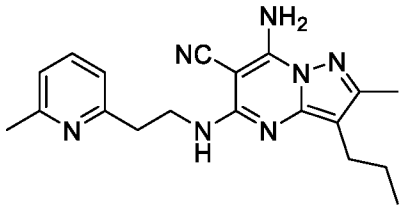
163a.(-)- 7-amino-3-ethyl-2-methyl-5-((2-(1-(1-(((2-(methyl sulfinyl) ethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

163b. (+)-7-amino-3-ethyl-2-methyl-5-((2-(1-(1-(((2-(methyl sulfinyl) ethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;



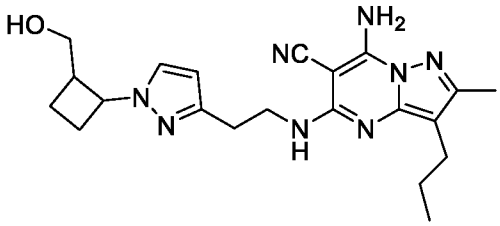
Peak 1; Example 163a; leavo (-) rotatory
Peak 2; Example 163b;dextro (+) rotatory

164. 7-amino-2-methyl-5-((2-(6-methylpyridin-2-yl) ethyl) amino)-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;



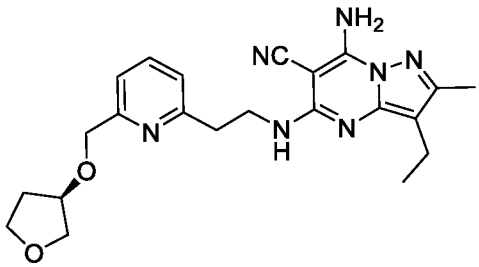
165a (+)-7-amino-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

165b. (-)-7-amino-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

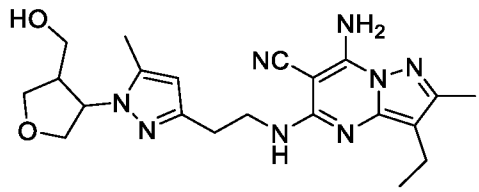


Peak 1; Example 165a;dextro (+) rotatory
Peak 2; Example 165b;leavo (-) rotatory

166. (*R*)-7-amino-3-ethyl-2-methyl-5-((2-(6-(((tetrahydrofuran-3-yl) oxy) methyl) pyridine-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

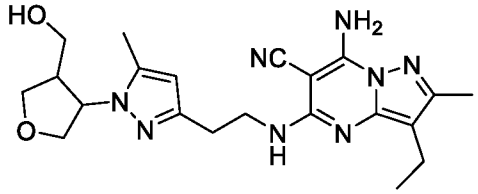


167. (-) - 7-amino-3-ethyl-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile; and



Example 167: Peak 1 : Levo (-) rotatory

168. (+) - 7-amino-3-ethyl-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Example 168: Peak 2 :Dextro (+) rotatory

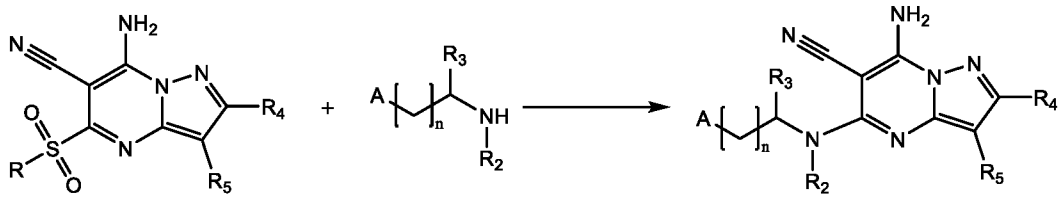
[00058] In an embodiment of the present disclosure, there is provided a compound of Formula I or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof as disclosed herein, for use as a medicament.

[00059] In an embodiment of the present disclosure, there is provided a compound of Formula I or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof, as an antagonist of adenosine 2a receptor ($A_{2a}R$) or adenosine 2b receptor ($A_{2b}R$) or combination of adenosine 2a receptor ($A_{2a}R$) and adenosine 2b receptor ($A_{2b}R$).

[00060] In an embodiment of the present disclosure, there is provided a compound of Formula I or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof as disclosed herein for use in treating of a disease, disorder or condition selected from cancer, parkinson's disease,

asthma, diabetes, and autoimmune disease mediated at least in part by adenosine 2a receptor ($A_{2a}R$) or adenosine 2b receptor ($A_{2b}R$) or combination of $A_{2a}R$ and $A_{2b}R$.

[00061] In an embodiment of the present disclosure, there is provided a process of preparation of compounds of Formula I or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof as disclosed herein, said process comprising: reacting Formula (A), and Formula (B) in the presence of a base to obtain the compounds of Formula I



Formula (A) Formula (B) Formula (I)

wherein R is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-10} aryl, C_{2-10} heteroaryl, or C_{1-10} heterocyclyl; and the substituents are as disclosed herein.

[00062] In an embodiment of the present disclosure, there is provided a process of preparation of compounds of Formula I or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof as disclosed herein, wherein the base is selected from triethylamine, diisopropylethylamine, pyridine, sodium carbonate, potassium carbonate, sodium hydroxide, potassium tertiarybutoxide potassium tertiarybutoxide, sodium hydride, lithium bis(trimethylsilyl)amide (LiHMDS), N-diisopropylethylamine, or combinations thereof.

[00063] In an embodiment of the present disclosure, there is provided a process of preparation of compounds of Formula I or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof as disclosed herein, wherein the process is carried out in the presence of a solvent selected from isopropanol, methanol, n-butanol, dichloromethane, tetrahydrofuran,

dimethylformaide, n-methylpyrrolidone, dimethyl sulfoxide, water, dioxane, acetonitrile, or combinations thereof.

[00064] In an embodiment of the present disclosure, there is provided a pharmaceutical composition comprising compounds of Formula I as disclosed herein and one or more additional therapeutic agent.

[00065] In an embodiment of the present disclosure, there is provided a pharmaceutical composition comprising compounds of Formula I with one or more additional therapeutic agent selected from chemotherapeutic agent, immune checkpoint inhibitors or combinations thereof. In another embodiment of the present disclosure, there is a pharmaceutical composition comprising compounds of Formula I as disclosed herein wherein the one or more additional therapeutic agent is chemotherapeutic agent or immune checkpoint inhibitors.

[00066] In an embodiment of the present disclosure, there is provided a pharmaceutical composition as disclosed herein, wherein the one or more additional therapeutic agent is the chemotherapeutic agent selected from phosphoinositide 3-kinase inhibitor (PI3K) inhibitor, tyrosine kinase inhibitor, signal transducer and activator of transcription 3 (Stat-3) inhibitor, topoisomerase inhibitors, Protein kinase B (AKT) inhibitor, c-Jun N-terminal kinase (JNK1/K2) inhibitors, hypoxia-inducible factor 1 alpha (HIF-1a) inhibitor, extracellular signal-regulated kinase (ERK) inhibitor, poly ADP ribose polymerase -1((PARP-1) inhibitor, cisplatin, or oxaplatin.

[00067] In an embodiment of the present disclosure, there is provided a pharmaceutical composition as disclosed herein, wherein the one or more additional therapeutic agent is the immune checkpoint inhibitor selected from programmed death-1 (PD-1) inhibitor, programmed death-ligand 1 (PD-L1) inhibitor, anti-PD1 antibody, anti-PD-L1 antibody, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, anti-CTLA-4 antibody, T cell immunoglobulin and ITIM domain (TIGIT) inhibitor, ecto-nucleoside triphosphate diphosphohydrolase 1(E-NTPDase, CD39) inhibitor, or ecto-5'-nucleotidase(Ecto5'NTase, CD79) inhibitor.

[00068] In an embodiment of the present disclosure, there is provided a pharmaceutical composition comprising the compounds of Formula I or its

pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, pharmaceutically active derivatives thereof with one or more additional therapeutic agent selected from chemotherapeutic agent or immune checkpoint inhibitors and wherein the one or more additional therapeutic agent selected from phosphoinositide 3-kinase inhibitor (PI3K) inhibitor, tyrosine kinase inhibitor, signal transducer and activator of transcription 3 (Stat-3) inhibitor, topoisomerase inhibitors, Protein kinase B (AKT) inhibitor, c-Jun N-terminal kinase (JNK1/K2) inhibitors, hypoxia-inducible factor 1 alpha (HIF-1a) inhibitor, extracellular signal-regulated kinase (ERK) inhibitor, poly ADP ribose polymerase -1((PARP-1) inhibitor, cisplatin, oxaplatin, programmed death-1 (PD-1) inhibitor, programmed death-ligand 1 (PD-L1) inhibitor, anti-PD1 antibody, anti-PD-L1 antibody, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)inhibitor, anti-CTLA-4 antibody, T cell immunoglobulin and ITIM domain (TIGIT) inhibitor, ecto-nucleoside triphosphate diphosphohydrolase 1(E-NTPDase, CD39) inhibitor, or ecto-5'-nucleotidase(Ecto5'NTase, CD79) inhibitor.

[00069] In an embodiment of the present disclosure, there is provided a method of treatment and/or prevention of a condition mediated by adenosine receptor or a proliferative disorder or a disease or cancer, comprising administering to a subject suffering from a condition mediated by adenosine receptor or a disease or proliferative disorder or a disease or cancer, a therapeutically effective amount of the compounds of Formula I as disclosed herein or the pharmaceutical composition comprising the compounds of Formula I with one or more additional therapeutic agent.

[00070] In an embodiment of the present disclosure, there is provided a method of treatment and/or prevention of a condition mediated by adenosine receptor or a proliferative disorder or a disease or cancer, comprising administering to a subject suffering from a condition mediated by adenosine receptor or proliferative disorder or a disease or cancer, a therapeutically effective amount of the compounds of Formula I as disclosed herein or the pharmaceutical composition comprising the compounds of Formula I with one or more additional therapeutic agent, wherein the condition mediated by adenosine receptor or a proliferative

disorder or a disease or a cancer at least in part by adenosine 2a receptor ($A_{2a}R$), adenosine 2b receptor ($A_{2b}R$), or combinations thereof.

[00071] In an embodiment of the present disclosure, there is provided a method of treatment and/or prevention of a condition mediated by adenosine receptor or a proliferative disorder or cancer, comprising administering to a subject suffering from a condition mediated by adenosine receptor or a disease or proliferative disorder or cancer, a therapeutically effective amount of the compounds of Formula I as disclosed herein or the pharmaceutical composition as disclosed herein, wherein the compounds of Formula (I) administered in an effective amount to reverse or stop the progression of either the adenosine 2a receptor ($A_{2a}R$), or adenosine 2b receptor ($A_{2b}R$), or both mediated immunosuppression.

[00072] In an embodiment of the present disclosure, there is provided a method of treatment and/or prevention of a condition mediated by adenosine receptor or a proliferative disorder or a disease or cancer, comprising administering to a subject suffering from a condition mediated by adenosine receptor or proliferative disorder or a disease or cancer, a therapeutically effective amount of the compounds of Formula I as disclosed herein or the pharmaceutical composition as disclosed herein, wherein the proliferative disorder or disease is cancer or an immune response related disorder or disease or condition.

[00073] In an embodiment of the present disclosure, there is provided a method of treatment and/or prevention of a condition mediated by adenosine receptor or a proliferative disorder or disease or cancer, comprising administering to a subject suffering from a condition mediated by adenosine receptor or a disease or proliferative disorder or cancer, a therapeutically effective amount of the compounds of Formula I as disclosed herein or the pharmaceutical composition as disclosed herein, wherein the cancer is of adrenal gland, brain, bladder, breast, bone, colon, endometrial, oesophagus, head, gastric, kidney, liver, lung, mouth, muscle, neck, pancreas, prostate, retinal, skin, thyroid or white blood cells and said immune related disease, disorder or condition is selected from the group consisting of allergies, alzheimer, asthma, crohn's disease, colitis, chronic obstructive pulmonary

disease, diabetic kidney disorders, glaucoma, lupus, rheumatoid arthritis, multiple sclerosis, pain, panic disorder, pancreatitis, parkinson disease, psoriasis, systemic sclerosis, and ulcerative colitis.

[00074] In an embodiment of the present disclosure, there is provided a use of the compounds of Formula I as disclosed herein or the pharmaceutical composition as disclosed herein for treatment of a condition mediated by adenosine receptor $A_{2a}R$; treatment and/or prevention of a proliferative disorder or disease or cancer or immune related disorder or disease or condition; or treatment of cancer together with other clinically relevant cytotoxic agents or non-cytotoxic agents.

[00075] In an embodiment of the present disclosure, there is provided a use of the compounds of Formula I as disclosed herein or the pharmaceutical composition as disclosed herein for treatment of a condition mediated by adenosine receptor $A_{2b}R$; treatment and/or prevention of a proliferative disorder or disease or cancer or immune related disorder or disease or condition; or treatment of cancer together with other clinically relevant cytotoxic agents or non-cytotoxic agents.

[00076] In an embodiment of the present disclosure, there is provided a use of the compounds of Formula I as disclosed herein or the pharmaceutical composition as disclosed herein for treatment of a condition mediated by adenosine receptors $A_{2a}R$ and $A_{2b}R$; treatment and/or prevention of a proliferative disorder or disease or cancer or immune related disorder or disease or condition; or treatment of cancer together with other clinically relevant cytotoxic agents or non-cytotoxic agents.

EXAMPLES

[00077] As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

Abbreviations

The following abbreviations are employed in the examples and elsewhere herein:

TLC- thin layer chromatography;

HPLC - high pressure liquid chromatography;

MPLC - medium pressure liquid chromatography;

NMR - nuclear magnetic resonance spectroscopy;

DMSO - dimethylsulfoxide;

$CDCl_3$ - deuterated chloroform;

MeOD -deuterated methanol, i.e. D_3COD;

MS - mass spectroscopy; ESP (or ES) - electrospray; EI - electron impact; APCI - atmospheric pressure chemical ionization;

THF - tetrahydrofuran;

DCM - dichloromethane;

MeOH - methanol;

DMF -dimethylformamide;

EtOAc - ethyl acetate;

LC/MS - liquid chromatography/mass spectrometry;

h - hour(s); min is minute(s);

d - day(s);

MTBD - N-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene;

TFA - trifluoroacetic acid; v/v - ratio of volume/volume;

Boc - t-butoxycarbonyl;

Cbz - benzyloxycarbonyl;

Bz - benzoyl;

Atm - atmospheric pressure;

rt -room temperature;

mg - milligram; g denotes gram;

µL - microliter;

mL - milliliter;

L - liter;

µM - micromolar;

nM-Nanomolar

mM - millimolar; M denotes molar;

DMAP- dimethyaminopyridine;

TBDMS -tert-butyldimethylsilyl

N - normal; and

nm - nanometer.

[00078] The following examples provide the details about the synthesis, activities and applications of the compounds of the present disclosure. It should be understood the following is representative only, and that the invention is not limited by the details set forth in these examples.

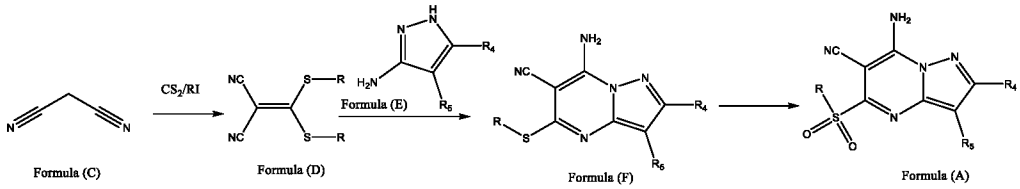
Materials and methods:

[00079] Evaporations were carried out by rotary evaporation in vacuo and work up procedures were carried out after removal of residual solids by filtration; temperatures are quoted as °C; operations were carried out at room temperature, that is typically in the range 18 to 26 °C and without the exclusion of air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere; column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated; in general, the course of reactions was followed by TLC, HPLC, or LC/MS and reaction times are given for illustration only; yields are given for illustration only and are not necessarily the maximum attainable; the structure of the end products of the invention was generally confirmed by NMR and mass spectral techniques. Proton magnetic resonance spectra were generally determined in DMSO d6 unless otherwise stated, using a Bruker DRX 300 spectrometer or a Bruker DRX-400 spectrometer, operating at a field strength of 300 MHz or 400 MHz, respectively. In cases where the NMR spectrum is complex, only diagnostic signals are reported. Chemical shifts are reported in parts per million downfield from tetramethylsilane as an external standard (* scale) and peak multiplicities are shown thus: s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; t, triplet, m, multiplet; br, broad. Fast atom bombardment (FAB) mass spectral data were generally obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive

ion data or negative ion data were collected or using Agilent 1100 series LC/MS equipped with Sedex 75ELSD, and where appropriate, either positive ion data or negative ion data were collected. The lowest mass major ion is reported for molecules where isotope splitting results in multiple mass spectral peaks (for example when chlorine is present). Reverse Phase HPLC was carried out using YMC Pack ODS AQ (100x20 mmID, S 5Å particle size, 12 nm pore size) on Agilent instruments; each intermediate was purified to the standard required for the subsequent stage and was characterized in sufficient detail to confirm that the assigned structure was correct; purity was assessed by HPLC, TLC, or NMR and identity was determined by infrared spectroscopy (IR), mass spectroscopy or NMR spectroscopy as appropriate.

General process for the preparation of the compounds of Formula (A)

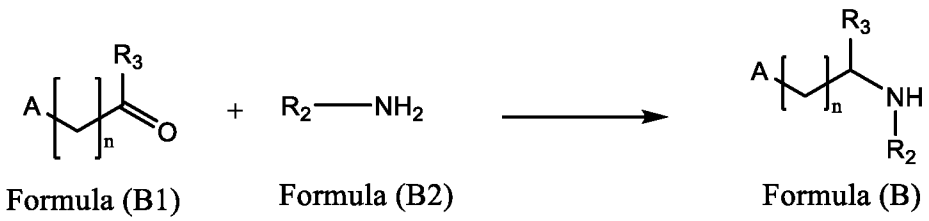
[00080] Compounds of formula (A) was prepared from formula (F) via oxidation using appropriate oxidizing agents (e.g., mCPBA) and the compounds of formula (F) was synthesized by reacting compounds of formula (D) with formula (E) in presence of appropriate base (e.g., pyridine). The formula (D) was obtained by treating formula (C) with carbon disulphide and methyl iodide in presence of appropriate base (e.g., sodium hydride) (Scheme 1).



Scheme 1

General process for the preparation of the compounds of Formula B

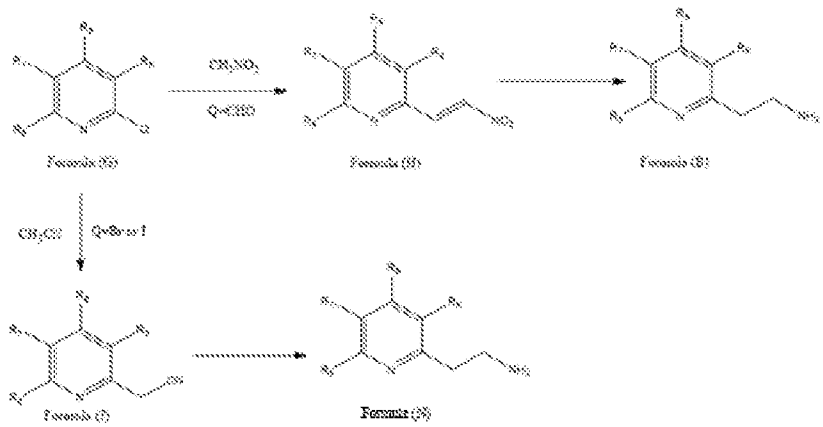
[00081] The preparation of compounds of Formula (B) may be prepared in a variety of ways and many of them are commercially available. The generic route for Formula (B) is given Scheme 2 wherein, the formula (B) was obtained by treating a carbonyl compound of Formula (B1) with an amine of Formula(B2) with suitable reducing reagent.



Formula (B1) Formula (B2) Formula (B)

Scheme 2

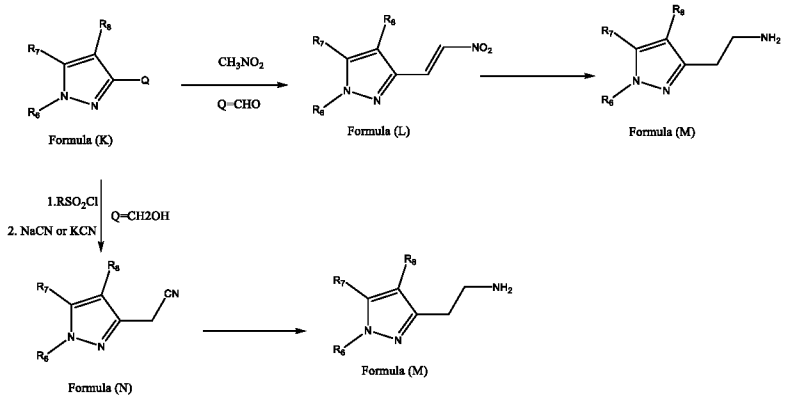
Further, the processes for one of the representative compounds of formula(B) wherein A is six membered rings shown as formula (N) in scheme 3.



Scheme 3

[00082] The compounds of Formula (B) were obtained by reducing either compounds of Formula (H) or (J) with appropriate reducing agents. The compounds of Formula (H) were obtained by treating compounds Formula (G) with nitromethane wherein Q is an aldehyde. The compounds of Formula (J) were obtained by treating compounds of Formula (G) with acetonitrile in presence appropriate alkali metal base (E.g., nBuLi) where in Q is a halogen (E.g., Br or I).

[00083] In similar to the process of making compounds of Formula(I) the

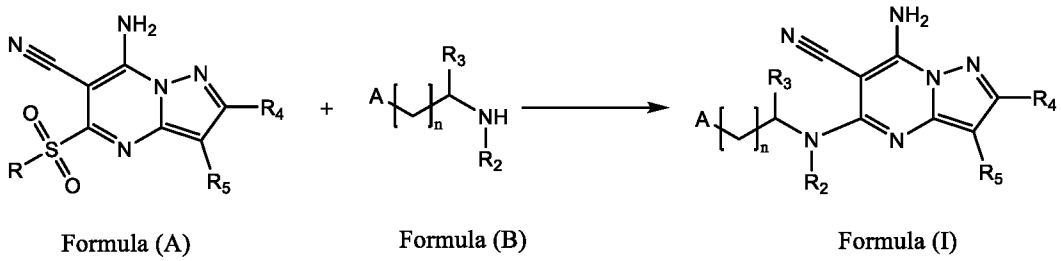


Scheme 4

processes for one of the representative compounds of Formula(B) with five membered rings shown as Formula (M) in scheme 4.

[00084] The examples shown above illustrate some methods useful for the synthesis of compounds of Formula (A) and compound (B) which may be used for the synthesis of compounds of Formula (I). Where a particular solvent or reagent is shown or referred to in the accompanying text, it is to be understood that the chemist of ordinary skill in the art will be able to modify and/or replace that solvent or reagent, as necessary.

[00085] In another embodiment, the compounds of Formula I, can be prepared reacting compounds of Formula (B) with compounds of Formula (A), in the presence of appropriate base and solvents as shown scheme 5.



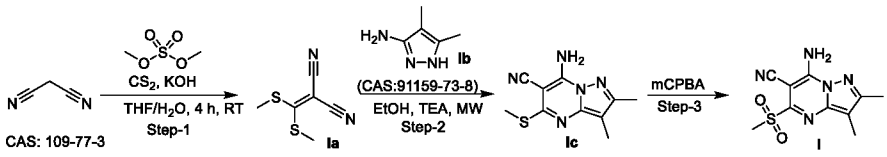
Scheme 5

[00086] The present disclosure provides a process for the preparation of compounds of Formula (I) and the compounds of Formula (I) which may be prepared in a variety of ways. The processes and examples shown below illustrate

some methods useful for the synthesis of compounds of Formula (I) and intermediates which may be used for the synthesis of compounds of Formula (I). Where a particular solvent or reagent is shown or referred to in the accompanying text, it is to be understood that the chemist of ordinary skill in the art will be able to modify and/or replace that solvent or reagent as necessary

Synthesis of Intermediates:

Synthesis of 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile. (I)



Step-1: Synthesis of 2-(bis(methylthio)methylene) malononitrile (Ia)

[00087] A stirred solution of KOH (16.98 g, 302.75 mmol) in water (100 mL) was cooled to 0 °C and was added malononitrile (10 g, 151.37 mmol) in dry THF (20 mL) was added dropwise over a period of 30 min under N_2 atmosphere. The reaction was stirred at room temperature for 1 h and was added CS_2 (17.2 g, 227.06 mmol) at 0 °C. After stirring the reaction mixture at room temperature for about 1 h dimethylsulphate (24.8 g, 196.7 mmol) was added and stirring was continued for another 4h at room temperature. After completion, the reaction mixture was quenched with ice cold water and the solid precipitated was filtered and dried under *vacuo* to afford the compound **Ia** (8 g, 31%) as yellow solid, which was taken forward for further step without purification.

Step-2: Synthesis of 7-amino-2,3-dimethyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (Ic)

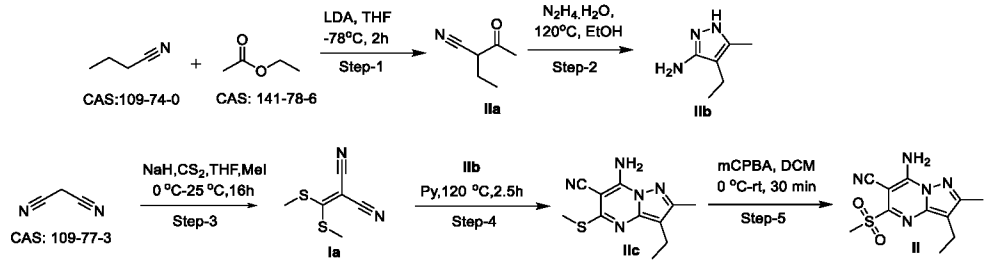
[00088] To a stirred solution of **Ia** (10 g, 58.8 mmol) in ethanol (20 mL) was added **Ib** (4.57 g, 41.17 mmol) at room temperature under N_2 atmosphere. The resulted mixture was heated at 120 °C for 6 h. After that the reaction mixture was cooled to room temperature and the solid precipitated was filtered and washed with

ethanol to give off-white solid, it was purified by column chromatography on silica gel (230-400 mesh, 45% ethyl acetate in pet ether) to obtained **Ic** (3.1 g, 32%); **LC-MS** Calculated. for $C_{10}H_{11}N_5S$: 233.29; Observed.: 234.0; $[M^+ + H]$. **^{1}H NMR (400 MHz, DMSO-D$_6$)**: δ 8.60 (s,2H), 2.68 (s, 3H), 2.37 (s, 3H), 2.13 (s, 3H).

Step-3: Synthesis of 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile. (I)

[00089] A stirred solution of **Ic** (5 g, 21.45 mmol) in dichloromethane (50 mL) was cooled to 0 °C and was added m-CPBA (11.07 g, 64.37 mmol) under N_2 atmosphere. The resulted mixture was stirred at room temperature for 3 h. After that the reaction mixture was quenched with 10% $NaHCO_3$ solution and extracted with DCM (2 x 300 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under *vacuo* to afford the compound **I** (3.1 g, 54%) as an off-white solid which was taken forward for further step without purification. **LC-MS** Calculated. for $C_{10}H_{11}N_5O_2S$: 265.29; Observed.: 266.0; $[M^+ + H]$.**^{1}H NMR (400 MHz, DMSO-D$_6$)**: δ 9.1 (br s, 2H), 3.42 (s, 3H), 2.40 (s, 3H), 2.17 (s, 3H).

<u>Synthesis of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a]pyrimidine-6-carbonitrile. (II)</u>



Step-1: 2-ethyl-3-oxobutanenitrile (IIa)

[00090] To a three neck RB flask, LDA (2M in THF, 36.17 ml, 0.0723 mol) was taken and THF (82.5 ml) was added and cooled to -78 °C. To this solution, butyronitrile (5 g, 0.0723 mol) in THF (10 ml) was added dropwise at -78 °C and the reaction mixture was stirred at -78 °C for 1 h. Then, ethyl acetate (6.42 ml, 0.0657 mol) was added dropwise at -78 °C and the reaction mixture was stirred at -78 °C for 2 h. The progress of the reaction was monitored by TLC. After

completion, the reaction mixture was cooled to 0 °C and quenched with saturated solution of NH_4Cl (25 ml) and extracted with ethyl acetate (50 ml x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to get the title compound **IIa** as yellow viscous oil; Yield: (8 g, 100%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.237-3.205 (q, 1H), 2.499 (s, 3H), 1.153-1.137 (d, J = 6.4 Hz, 3H), 0.973-0.937 (t, J = 7.2 Hz, 3H).

Step-2: 4-ethyl-5-methyl-1H-pyrazol-3-amine (IIb)

[00091] To a stirred solution of 2-ethyl-3-oxobutanenitrile **3** (8 g) in EtOH (80 ml) was added hydrazine hydrate (23.80 ml) and the reaction mixture was heated at 120 °C for 1.5 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to rt and evaporated under reduced pressure. The residue was dissolved in 6N HCl (25 ml) and washed with ethyl acetate (3 x 50 ml). Aq. layer was basified to pH >7 using aqueous ammonia solution and extracted with ethyl acetate (3 x 50 ml). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure to get the title compound **IIa** as light brown viscous liquid was used in the next step without further purification; Yield: (8.1 g, 90%).**^{1}H NMR (400 MHz, CD3OD):** δ 2.354 (q, J = 7.2 Hz, 2H), 2.110 (s, 3H), 1.087-1.049 (t, J = 7.2 Hz, 3H).

Step-3: 2-(Bis(methylthio) methylene) malononitrile (Ia)

[00092] To a stirred solution of malononitrile (5.0 g, 0.075 mol) in DMSO (50 ml) cooled to 0 °C was added K_2CO_3 (11.4 g, 0.0833 mol), CS_2 (5.03 g, 0.0833 mol) and stirred at rt for 3 h. Then the reaction mixture cooled to 0 °C and MeI (9.4 ml, 0.1514 mol) was added and the reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was poured into ice cold water (50 ml) and the precipitate formed was filtered, washed with cold water and dried to get the compound **Ia** as brick red solid which was used in the next step without further purification; Yield: (6.2 g, 51%).

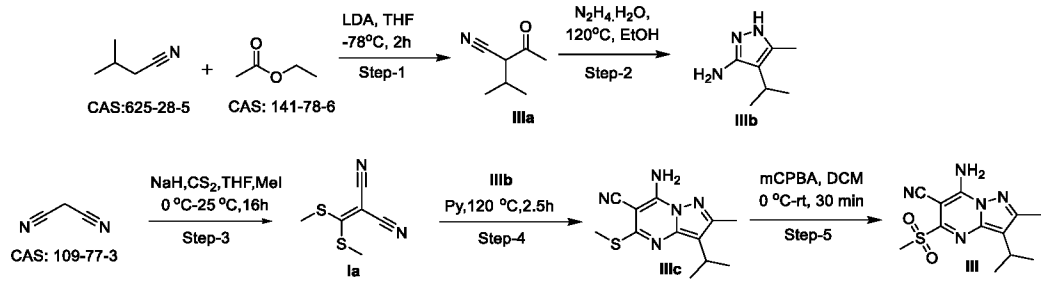
Step-4: 7-amino-3-ethyl-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (IIc)

[00093] To a stirred solution of 2-(bis(methylthio)methylene) malononitrile **Ia** (11.0 g, 0.0647 mol) in pyridine (80 ml) was added 4-ethyl-5-methyl-1H-pyrazol-3-amine (8.1 g, 0.0647 mol) and the reaction mixture was heated at 120°C for 2.5 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated, and the residue was diluted with water (150 ml) and resulting solid was stirred for 2h at 10-15 °C. Filtered the solid and azeotroped with toluene (2 x 50 ml) to get dried title compound **IIc**. Yield: (12.3 g, 78 %). **^{1}H NMR (400 MHz, CD3OD):** δ 2.691-2.634 (q, J = 7.6 Hz, 2H), 2.583 (s, 3H), 2.371 (s, 3H), 1.257-1.205 (t, J = 8 Hz, 3H).

Step-5: 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo [1,5-a] pyrimidine-6-carbonitrile. (II)

[00094] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **IIc** (11.2 g, 0.0481 mol) in DCM (120 ml) cooled to 0 °C, was added *m*-CPBA (33.20 g, 0.19 mol) slowly and the reaction mixture was stirred at rt for 30 min. The progress of the reaction was monitored by TLC (polar spot). After completion, the reaction mixture was quenched with $NaHCO_3$ (150 ml) and extracted with DCM (150 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified using 50% ethyl acetate in hexane to get pure title compound. Yield: (9.5g, 70%). **LC_MS** Calculated for $C_{11}H_{13}N_5O_2S$: 279.10; Observed:280.10 [M^++H].**^{1}H NMR (400 MHz, CD3OD):** δ 3.385 (s, 3H), 2.777-2.721 (q, J = 7.2 Hz, 2H), 2.463 (s, 3H), 1.260-1.230 (t, J = 7.2 Hz, 3H).

Synthesis of 7-amino-3-isopropyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile. (III)



Step-1: 2-acetyl-3-methylbutanenitrile. (IIIa)

[00095] To a three neck RB flask, LDA (2M in THF, 29.8 mL, 0.0595 mol) was taken and THF (100 mL) was added and cooled to -78 °C. To this solution, 3-methylbutanenitrile (CAS:625-28-5, 25 g, 0.0595 mol) in THF (40 mL) was added dropwise at -78 °C and the reaction mixture was stirred at -78 °C for 1 h. Then, ethyl acetate (CAS:141-78-6, 5.2 mL, 0.0536 mol) was added dropwise at -78 °C and the reaction mixture was stirred at -78 °C for 1 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0 °C and quenched with saturated solution of NH_4Cl (50 mL) and extracted with ethyl acetate (80 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to get the title compound **IIIa** as yellow viscous oil; Yield: (6.5 g, 87%). **LC_MS** Calculated for $C_7H_{11}NO$: 125.08; Observed:124.10 [M-H].

Step-2: 4-isopropyl-5-methyl-1H-pyrazol-3-amine. (IIIb)

[00096] To a stirred solution of 2-acetyl-3-methylbutanenitrile **IIIa** (6.5 g, 0.0520 mol) in EtOH (65 mL) was added hydrazine hydrate (19.5 mL, 0.00438 mol) and the reaction mixture was heated at 120 °C for 1.5 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to rt and evaporated under reduced pressure. The residue obtained was diluted with water (100 mL) and extracted with ethyl acetate (80 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to get tittle compound **IIIb** as light brown viscous liquid. This crude product was used as such for the next step without further purification; Yield: (4.5 g, 52%).**^{1}H NMR (400**

MHz, $CDCl_3$): δ 5.18 (bs, 2H), 3.18 (d, *J*=7.6 Hz, 1H), 2.29-2.04 (m, 1H), 1.83 (s, 3H), 1.22 (d, *J*=10.0 Hz, 1H), 1.11 (d, *J*=6.8 Hz, 3H), 1.01 (d, *J*=6.8 Hz, 3H).

Step-3: 2-(Bis(methylthio) methylene) malononitrile. (Ia)

[00097] To a stirred solution of malononitrile (5.0 g, 0.075 mol) in DMSO (50 ml) cooled to 0 °C was added K_2CO_3 (11.4 g, 0.0833 mol), CS_2 (5.03 g, 0.0833 mol) and stirred at rt for 3 h. Then the reaction mixture cooled to 0 °C and MeI (9.4 ml, 0.1514 mol) was added and the reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was poured into ice cold water (50 ml) and the precipitate formed was filtered, washed with cold water and dried to get the compound **Ia** as brick red solid which was used in the next step without further purification; Yield: (6.2 g, 51%).

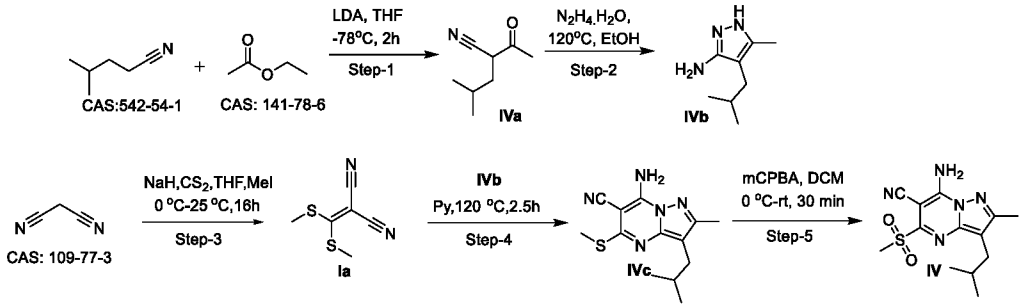
Step-4: 7-amino-3-isopropyl-2-methyl-5-(methylthio) pyrazolo[1,5-*a*]pyrimidine-6-carbonitrile. (IIIc)

[00098] To a stirred solution of 2-(bis(methylthio)methylene) malononitrile **Ia** (6.1 g, 0.0360 mol) in pyridine (50 mL) and 4-isopropyl-5-methyl-1*H*-pyrazol-3-amine **IIIb** (4.5g, 0.0360 mol) and the reaction mixture was heated at 120 °C in for 1.5 h. The progress of the reaction was monitored by TLC. After completion, to the reaction 200 mL water was added and the pale-yellow residue formed was collected by filtration. The solid was washed with fresh water (200 mL) and dried under vacuo to afford the desired compound as a pale-yellow solid. The crude material was used in the next step without further purification; Yield: (6.0 g, 71%). **LC_MS** Calculated for $C_{12}H_{15}N_5S$: 261.10; Observed:262.10 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.20 (bs, 2H), 3.09-3.06 (m, 1H), 2.62 (s, 3H), 2.40 (s, 3H), 1.38 (d, *J*=6.8 Hz, 6H).

Step-5: 7-amino-3-isopropyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile. (III)

[00099] To a stirred solution of 7-amino-3-isopropyl-2-methyl-5-(methylthio) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **IIIc** (6.0 g, 0.023 mol) in DCM (60 mL), cooled to 0 °C, was portion wise added *m*-CPBA (16.0 g, 0.092 mol) and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC (polar spot). After completion, the reaction mixture was quenched with $NaHCO_3$ (100 mL) and extracted with DCM (80 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude material was subjected to silica gel (100-200) column chromatography using ethyl acetate (0-30%) in n-hexane to afford the desired compound **III** as an off-white solid; Yield: (1.5g, 22%). **LC_MS** Calculated for $C_{12}H_{15}N_5O_2S$: 293.09; Observed: 294.05 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D_6):** δ 9.18 (bs, 2H), 3.42 (s, 3H), 3.15-3.12 (m, 1H), 2.45 (s, 3H), 1.34 (d, *J*=6.8 Hz, 6H).

Synthesis of 7-amino-3-isobutyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a]pyrimidine-6-carbonitrile. (1V)



Step-1: 2-Acetyl-4-methylpentanenitrile. (IVa)

[000100] To a three neck RB flask, LDA (2M in THF, 2.5 ml, 0.00514 mol) was taken and THF (10 ml) was added and cooled to -78 °C. To this solution, 4-methylpentanenitrile (CAS:542-54-1, 0.5 g, 0.00514 mol) in THF (4 ml) was added dropwise at -78 °C and the reaction mixture was stirred at -78 °C for 1 h. Then, ethyl acetate (CAS:141-78-6, 0.45 ml, 0.00468 mol) was added dropwise at -78 °C and the reaction mixture was stirred at -78 °C for 2 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0 °C

and quenched with saturated solution of NH_4Cl (5 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to get the title compound **IVa** as yellow viscous oil; Yield: (0.478 g, 66%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.46-3.42 (m, 1H), 2.40 (s, 3H), 1.89-1.76 (m, 2H), 1.70-1.65 (m, 1H), 1.0 (d, J = 6.4 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H).

Step-2: 4-Isobutyl-5-methyl-1*H*-pyrazol-3-amine. (IVb)

[000101] To a stirred solution of 2-acetyl-4-methylpentanenitrile **IVa** (0.470 g, 0.00337 mol) in EtOH (20 ml) was added hydrazine hydrate (0.219 g, 0.00438 mol) and the reaction mixture was heated at 90 °C for 15 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to rt and evaporated under reduced pressure. The residue obtained was diluted with water (10 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure to get crude material **IVb** as light brown viscous liquid. The crude product obtained was taken as such for next step without further purification; Yield: (0.478 g, 92%). **^{1}H NMR (400 MHz, DMSO-D_6):** δ 10.85 (bs, 1H), 4.13 (bs, 2H), 2.04 (d, J = 7.2 Hz, 2H), 1.98 (s, 3H), 1.69-1.62 (m, 1H), 0.83 (d, J = 6.8 Hz, 6H).

Step-3: 2-(Bis(methylthio) methylene) malononitrile. (Ia)

[000102] To a stirred solution of malononitrile (CAS:109-77-3, 5.0 g, 0.075 mol) in DMSO (50 ml) cooled to 0 °C was added K_2CO_3 (11.4 g, 0.0833 mol), CS_2 (5.03 g, 0.0833 mol) and stirred at rt for 3 h. Then the reaction mixture cooled to 0 °C and methyl Iodide (9.4 ml, 0.1514 mol) was added and the reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was poured into ice cold water (50 ml) and the precipitate formed was filtered, washed with cold water and dried to get the compound **Ia** as brick red solid which was used in the next step without further purification; Yield: (6.2 g, 51%).

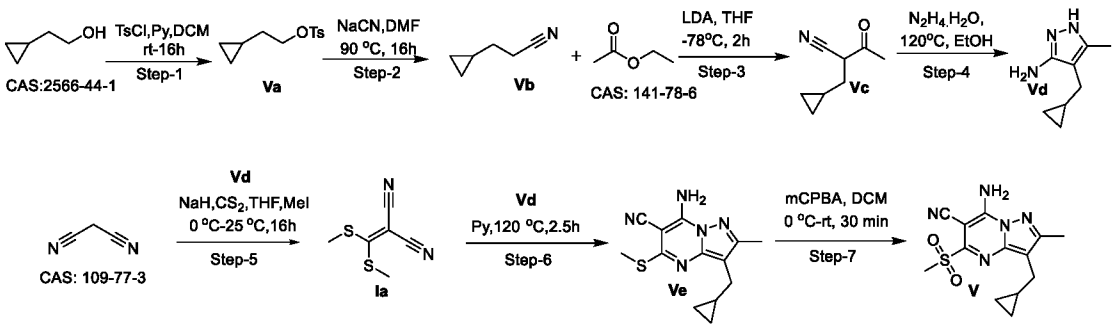
Step-4: 7-Amino-3-isobutyl-2-methyl-5-(methylthio) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile. (IVc)

[000103] To a stirred solution of 2-(bis(methylthio)methylene) malononitrile **Ia** (1.0 g, 0.0065 mol) in EtOH (10 ml) was added TEA (1.81 ml, 0.013 mol) and 4-isobutyl-5-methyl-1*H*-pyrazol-3-amine **IVb** (1.1 g, 0.0065 mol) and the reaction mixture was heated at 100°C in microwave for 1 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated, and the residue was diluted with water (20 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure to get crude compound **IVc**. The crude product obtained was taken for next step without further purification; Yield: (1.64 g, 92 %). **LC_MS** Calculated for $C_{13}H_{17}N_5S$: 275.12; Observed: 276.20 [M^++H]. **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.51 (bs, 2H), 2.53-2.50 (m, 2H), 2.45 (d, J = 7.2 Hz, 2H), 2.37 (t, J = 3.6 Hz, 1H), 2.29 (s, 3H), 1.95-1.88 (m, 1H), 0.88-0.85 (m, 6H).

Step-5: 7-Amino-3-isobutyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (IV)

[000104] To a stirred solution of 7-amino-3-isobutyl-2-methyl-5-(methylthio) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **IVc** (0.65 g, 0.00236 mol) in DCM (10 ml) cooled to 0 °C, was added *m*-CPBA (1.0 g, 0.0059 mol) slowly and the reaction mixture was stirred at rt for 16h. The progress of the reaction was monitored by TLC (polar spot). After completion, the reaction mixture was quenched with $NaHCO_3$ (50 ml) and extracted with DCM (50 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure to get the title compound **IV**. The crude product was used as such for the next step without further purification; Yield: (0.703 g, 97 %). **LC_MS** Calculated for $C_{13}H_{17}N_5O_2S$: 307.11; Observed:308.15 [M^++H]. **^{1}H NMR (400 MHz, DMSO-D_6):** δ 9.19 (bs, 2H), 3.40 (s, 3H), 2.53-2.52 (m, 2H), 2.41 (s, 3H), 1.95-1.92 (m, 1H), 0.96-0.87 (m, 6H).

Synthesis of 7-amino-3-(cyclopropyl methyl)-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile. (V)



Step-1: 2-cyclopropylethyl 4-methylbenzenesulfonate (Va)

[000105] To a stirred solution of 2-cyclopropylethan-1-ol **1** (CAS: 2566-44-1, 5.0 g, 0.0581 mol) in DCM (75 mL) cooled to 0 °C was added pyridine (12.6 mL) followed by an addition of *p*-TsCl (8.9 g, 0.0470 mol) and the reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with diethyl ether (100 ml) and washed sequentially with water (50 mL), 10 % HCl (50 mL), water (10 ml) and dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to get compound **Va** as colorless liquid. The crude product obtained was taken for the next step without further purification; Yield: (8.6 g, 66%). **LC_MS** Calculated for $C_{12}H_{16}O_3S$: 140.32; Observed.141.15 [M^++H]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.81 (d, *J*=8.4 Hz, 2H), 7.35 (d, *J*=8.4 Hz, 2H), 4.9 (t, *J*=6.4 Hz 2H), 2.46 (s, 3H), 1.56-1.51(m, 2H), 0.67-0.65 (m, 1H), 0.40-0.39 (m, 2H), 0.04-0.01 (m, 2H).

Step-2: 3-Cyclopropylpropanenitrile (Vb)

[000106] To a stirred solution of 2-cyclopropylethyl 4-methylbenzenesulfonate **Va** (8.6 g, 0.0357 mol) in DMF (32 mL) was added TBAI (0.526 g) followed by an addition of sodium cyanide (5.2 g, 0.107 mol) and the reaction mixture was heated at 90 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with diethyl ether (150 mL) and washed with water (100 mL x 3), brine (100 mL) and dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to get desired product **Vb** as light brown viscous liquid. This crude product obtained was taken for

the next step without further purification; Yield: (3.3 g, 97%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.74-3.72 (m, 1H), 2.42 (t, *J*=6.8 Hz 2H), 1.59-1.51 (m, 2H), 0.86-0.81 (m, 1H), 0.56-0.53 (m, 2H), 0.16-0.13 (m, 2H).

Step-3: 2-(cyclopropyl methyl)-3-oxobutanenitrile (Vc)

[000107] A three neck RB flask was charged with LDA (2M sol in THF, 15.35 mL, 0.0315 mol) and THF (60 mL) under N_2 atmosphere. The resulting mixture was cooled to -78 °C and a solution of 3-cyclopropylpropanenitrile **Vb** (3.0 g, 0.0315 mol) in THF (24 mL) was dropwise added maintaining temperature to -78 °C. The reaction mixture was stirred at -78 °C for 1 h and ethyl acetate (CAS: 141-78-6, 2.52 g, 0.0287 mol) was dropwise added at -78 °C. The resulting mixture was stirred at -78 °C for 2 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0 °C and quenched with saturated solution of NH_4Cl (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to get the title compound **Vc** as pale-yellow viscous oil; Yield: (3.25 g, 76%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.50-3.47 (m, 1H), 2.41 (s, 3H), 1.92-1.82 (m, 1H), 1.80-1.75 (m, 1H), 0.9-0.86 (m, 1H), 0.61-0.55 (m, 2H), 0.25-0.23 (m, 1H), 0.18-0.14 (m, 1H).

Step-4: 4-(cyclopropyl methyl)-5-methyl-1H-pyrazol-3-amine (Vd)

[000108] To a stirred solution of 2-(cyclopropyl methyl)-3-oxobutanenitrile **Vc** (3.2 g, 0.0233 mol) in EtOH (50 mL) was added hydrazine hydrate (2.19 ml, 0.0349) and the reaction mixture was heated at 90 °C for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to rt and evaporated under reduced pressure. The residue obtained was diluted with $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (50 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to get the title compound **Vd**. The crude product was taken for next step without further purification; Yield: (3.2 g, 91%). **LC_MS** Calculated for $C_8H_{13}N_3$ is 151.11; Observed.152.20 [M^++H]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.80-3.60 (bs, 2H), 2.30

(d, *J*=5.6 Hz 3H), 1.70-1.50 (bs, 1H), 0.90-0.83 (m, 1H), 0.48-0.44 (m, 2H), 0.14-0.10 (m, 2H).

Step-5: 2-(Bis(methylthio) methylene) malononitrile (Ia)

[000109] To a stirred solution of malononitrile (CAS:109-77-3, 5.0 g, 0.075 mol) in DMSO (50 ml) cooled to 0 °C was added K_2CO_3 (11.4 g, 0.0833 mol), CS_2 (5.03 g, 0.0833 mol) and stirred at rt for 3 h. Then the reaction mixture cooled to 0 °C and methyl Iodide (9.4 ml, 0.1514 mol) was added and the reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was poured into ice cold water (50 ml) and the precipitate formed was filtered, washed with cold water and dried to get the compound **Ia** as brick red solid which was used in the next step without further purification; Yield: (6.2 g, 51%).

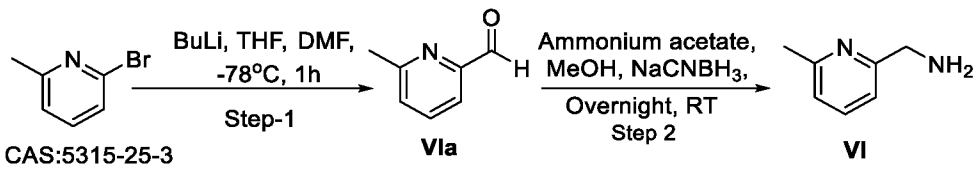
Step-6: **7-amino-3-(cyclopropyl methyl)-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (Ve)**

[000110] To a stirred solution of 2-(bis(methylthio)methylene) malononitrile **Ia** (3.3 g, 0.0198 mol) in pyridine (40 mL) was added 4-(cyclopropyl methyl)-5-methyl-1*H*-pyrazol-3-amine **Vd** (3.0 g, 0.0198 mol) and the reaction mixture was heated at 120 °C for 16 h under N_2 atmosphere. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to rt and poured into ice cold water (50 mL). The precipitate formed was filtered, dried, and washed with cold mixture of ethyl acetate (10%) and *n*-hexane (90%) and dried under vacuo to afford the desired compound as a pale-yellow solid; Yield: (4.3 g, 80%). **LC_MS** Calculated for $C_{13}H_{15}N_5S$:273.10; Observed: 274.10 $[M^+ + H]$.**^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.26 (bs, 2H), 2.61-2.57 (m, 5H), 2.41 (s, 3H), 1.00-0.90 (bs, 1H), 0.45-0.43 (m, 2H), 0.24-0.22 (m, 2H).

Step-7:7-amino-3-(cyclopropyl methyl)-2-methyl-5-(methyl sulfonyl) pyrazolo [1,5-a] pyrimidine-6-carbonitrile. (V)

[000111] To a stirred solution of 7-amino-3-(cyclopropyl methyl)-2-methyl-5-(methylthio) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **Ve** (2.3 g, 0.00842 mol) in DCM (50 mL) cooled to 0 °C, was slowly added *m*-CPBA (5.8 g, 0.0337 mol) and the reaction mixture was stirred at rt for 30 min. The progress of the reaction was monitored by TLC. After completion, the reaction was quenched with $NaHCO_3$ (30 mL) and extracted with DCM (50 mL x 3). The combined organic layer was again given the saturated $NaHCO_3$ (30 mL X 2) wash followed by with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuo to afford the desired compound **V** as a pale-yellow solid; Yield: (2.1 g, 81%). **LC_MS** Calculated for $C_{13}H_{15}N_5O_2S$: 305.09; Observed:306.10 [M^++H]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.00-6.60 (bs, 2H), 3.39 (s, 3H), 2.64 (d, J=6.8, 2H), 2.50 (s, 3H), 0.99-0.97 (bs, 1H), 0.49-0.46 (m, 2H), 0.24-0.22 (m, 2H).

Synthesis of (6-methylpyridin-2-yl) methenamine. (VI)



Step-1: 6-methylpicolinaldehyde. (VIa)

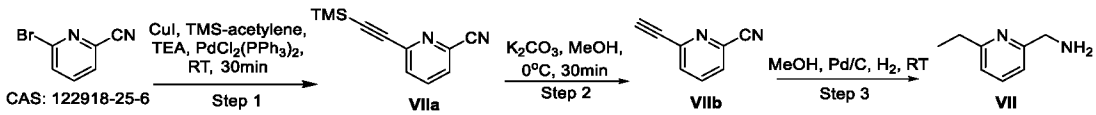
[000112] To a solution of 2-bromo-6-methylpyridine (CAS: 5315-25-3, 5 g, 0.0290 mol) in Toluene (50 ml) was dropwise added n-BuLi (2.5M sol in THF, 11.62 ml, 0.0290 mol) at -78 °C. Reaction mixture was stirred for 1h at -78 °C. To this solution, DMF (2.69 ml, 0.0348 mol) was dropwise added at -78 °C. Reaction mixture was stirred for 1h at -50 °C followed by stirring for 30 min at 5-10 °C and at rt for 40 min. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0 °C and quenched with saturated solution of NH_4Cl (50 ml) and extracted with ethyl acetate (2x75 ml). The organic layer was washed with brine solution (50 ml) and dried with Na_2SO_4, filtered, and evaporated under reduced pressure to get crude material which was column purified using 60-120 silica get. Product was eluted with 5% ethyl acetate in hexane to afford compound **VIa** as pale-

yellow liquid. Yield: (1.4g, 40%). **LC-MS** Calculated for C_7H_7NO: 121.15; Observe.122.15 [M^++1]. **^{1}HNMR (400 MHz, $CDCl_3$):** δ 10.054 (s, 1H), 7.745-7.799 (m, 2H), 7.386-7.404 (d, *J* = 6.8 Hz, 1H), 2.672 (s, 3H).

Step-2: (6-methylpyridin-2-yl) methenamine. (VI)

[000113] To a stirred solution of 6-methylpicolinaldehyde **VIa** (1.4 g, 0.0115 mol) in Methanol (25 ml) was added Ammonium acetate (8.9 g, 0.115 mol) and the reaction mixture was stirred for 30 min at rt. Sodium cyanoborohydride (0.58g, 0.0092 mol) was then portion wise added and continued further stirring at rt for 10h. Progress of the reaction was monitored by TLC. After completion, solvent from reaction mass was removed under reduced pressure. The residue obtained was taken up with water (50 ml) and basified with aq. KOH. product was extracted with 5% MeOH in DCM (3x100 ml). Combined organic layer was dried over Na_2SO_4, filtered, and concentrated at reduced pressure to afford title compound **VI** as brown liquid. Yield: 1.2 g (85%). **LC-MS** Calculated for $C_7H_{10}N_2$: 122.08; Observed.123.08 [M^++1]. **^{1}HNMR (400 MHz, CDCl3):** δ 7.516-7.554 (t, *J* =7.6 Hz, 1H), 7.091-7.072 (d, *J* =7.6 Hz, 1H), 7.025-7.006 (d, *J* =7.6 Hz, 1H), 3.935 (s, 2H), 2.546 (s, 3H).

<u>Synthesis of (6-ethylpyridin-2-yl) methenamine. (VII)</u>



Step-1: 6-((trimethylsilyl)ethynyl) picolinonitrile. (VIIa)

[000114] To a stirred solution of 6-bromopicolinonitrile (CAS: 122918-25-6, 1.5 g, 0.008 mol) in TEA (0.060 mol) was added and it was purged under nitrogen. To this Trimethylsilyl acetylene (1.37 ml, 0.009 mol) followed by copper iodide (0.036 g, 0.0003 mol) was added and purging was continued further for 10 more minutes. After that Pd $(PPh_3)_2Cl_2$ (0.089 g, 0.0001 mol) was added. Then the reaction mixture was stirred at room temperature for 30 minutes. The progress of the reaction was monitored by TLC. After completion, reaction mixture was filtered over celite bed and

concentrated to get desired crude product **VIIa**. Yield: (1.2 g 75 %). **LC_MS** Calculated for $C_{11}H_{12}N_2Si$: 200.08; Observed: 201.15 [M^++1]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.824-7.784 (t, *J* = 8.4 Hz, 1H), 7.652-7.617 (t, *J* = 7.2 Hz, 2H), 0.287 (s, 9H).

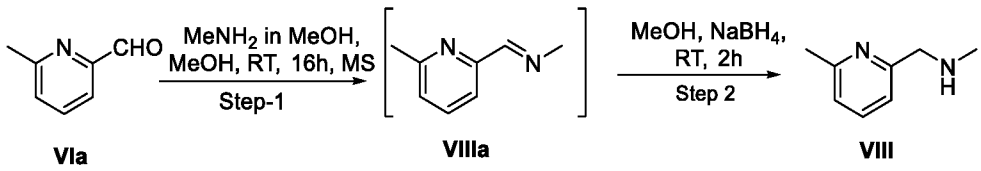
Step-2: 6-ethynylpicolinonitrile. (VIIb)

[000115] To a stirred solution of 6-((trimethylsilyl)ethynyl) picolinonitrile **VIIa** (1.5 g, 0.005 mol) in MeOH (15 ml) cooled to 0 °C, was added K_2CO_3 (0.829 g, 0.005 mol) and the reaction mixture was stirred at 0 °C for 30 min. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with DCM (3x50 ml). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 20% ethyl acetate in hexane to yield the title compound **VIIb** as pale-yellow solid; Yield: (0.260 g, 34 %). **LC_MS** Calculated for $C_8H_4N_2$:128.04; Observed.: Not ionized. **^{1}H NMR (400 MHz, $CDCl_3$):** δ7.857-7.818 (d, *J* = 7.6 Hz, 1H), 7.684-7.7.664 (d, *J* = 8 Hz, 2H), 3.289 (s, H).

Step-3: (6-ethylpyridin-2-yl) methenamine. (VII)

[000116] To a stirred solution of 6-ethynylpicolinonitrile **VIIb** (0.260 g, 0.00203 mol) in MeOH (3 ml) purged with N_2 for 10 min, was added Pd/C (0.100 g) and the reaction mixture was stirred at rt for 24 h under H_2 atmosphere. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was filtered through celite and the filtrate was concentrated. The crude material was purified by column chromatography by eluting with 20% ethyl acetate in hexane to yield the title compound **VII** as pale-yellow liquid; Yield: (0.100 g, 36%). **LC_MS** Calculated for $C_8H_{12}N_2$: 136.10; Observed.: 137 [M^++1]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.583-7.544 (d, *J* = 7.6 Hz, 1H), 7.094-7.075 (d, *J* = 7.6 Hz, 1H), 7.040-7.021 (d, *J* = 7.6 Hz, 1H), 3.959 (s, 2H), 2.840-2.784 (q, *J* = 7.6 Hz, 2H), 1.322-1.255 (t, *J* = 8 Hz, 3H).

Synthesis of N-methyl-1-(6-methylpyridin-2-yl) methenamine. (VIII)



VIa VIIIa VIII

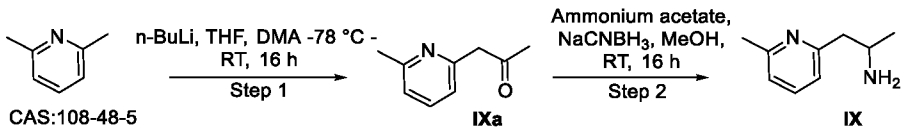
Step-1: (E)-N-methyl-1-(6-methylpyridin-2-yl) methenamine. (VIIIa)

[000117] To a stirred solution of 6-methylpicolinaldehyde **VIa** (0.1 g, 0.000825 mol) in Methanol (5 ml) in molecular sieve was added methylamine (2 ml, 30% solution in methanol) and the resulting reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was filtered through the celite bed and evaporated under reduced pressure to get crude product **VIIIa**. The crude compound obtained was taken directly forward to the next step. Yield: (0.12 g, 100 %).

Step-2: N-methyl-1-(6-methylpyridin-2-yl) methenamine. (VIII)

[000118] To a stirred solution of (E)-N-methyl-1-(6-methylpyridin-2-yl) methenamine **VIIIa** (0.120 g, 0.00089 mol) in methanol (5 ml), was added sodium borohydride (0.051g, 0.00134 mol) at 0°C. Then the temp was allowed to reach room temperature and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure and diluted with 10 ml water and extracted with 10% methanol in DCM (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude purified by manual column by eluted with 10% methanol in DCM product was eluted at 10% methanol in DCM to get the product **VIII.** Yield: (0.123 g, 101%). **LC_MS** Calculated. for $C_8H_{12}N_2$: 136.0; Observed:137 [M^++H]. **^{1}H NMR (400 MHz, CDCl3):** δ 7.647-7.608 (t, J = 8 Hz, 1H), 7.324-7.305 (d, J = 7.6 Hz, 1H), 7.149-7.130 (d, J = 7.6 Hz, 1H), 4.229 (s, 2H), 2.730 (s, 3H), 2.559 (s, 3H).

Synthesis of 1-(6-methylpyridin-2-yl) propan-2-amine. (IX)



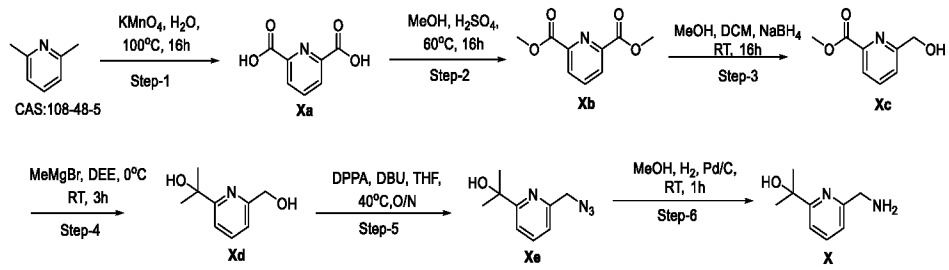
Step-1: 1-(6-Methylpyridin-2-yl) propan-2-one. (IXa)

[000119] To a stirred solution of 2,6-dimethylpyridine (CAS: 108-48-5, 5.0 g, 0.046 mol) in THF (65 ml) at -78°C was added n-BuLi (20.5 ml, 0.0512 mol) dropwise and stirred for 1h. Then *N,N*-Dimethylacetamide (4.1 ml. 0.0443 mol) was added slowly at -78°C and stirred at rt for 16 h. After completion (TLC), the reaction mixture was cooled to rt and quenched with 1.2 M HCl solution (25 ml) and stirred at rt for 30 min. Then, the reaction mixture was extracted with ethyl acetate (200 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by flash column chromatography by eluting with 5% ethyl acetate in hexane to yield the title compound **IXa** as yellow liquid; Yield: (0.713 g, 10.2%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.54 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 7.00 (d, J = 8.0, Hz, 1H), 3.89 (s, 2H), 2.54 (s, 3H), 2.22 (s, 3H).

Step-2: 1-(6-Methylpyridin-2-yl) propan-2-amine. (IX)

[000120] To a stirred solution of 1-(6-methylpyridin-2-yl) propan-2-one **IXa** (0.713 g, 0.00475 mol) in MeOH (20 ml), was added ammonium acetate (3.7 g, 0.04753 mol) and stirred at room temperature for 30 min. Then $NaCNBH_3$ (0.21 g, 0.003327 mol) was added portion-wise and the reaction mixture was stirred at room temperature for 16 h. Then the progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated and diluted with saturated $NaHCO_3$ solution (50 ml) and extracted with diethyl ether (50 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure the desired product **IX** as pale green liquid. This crude product obtained was taken for the next step without further purification; Yield: (0.43 g, 60%). **^{1}H NMR (400 MHz, DMSO-d_6):** δ 7.56 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 7.00 (d, J = 7.6, Hz, 1H), 3.21-3.18 (m, 1H), 2.64 (dd, J = 6.8 Hz, 2.4 Hz, 2H), 2.42 (s, 3H), 0.98 (dd, J = 6.4 Hz, 2.4 Hz, 3H).

Synthesis of 2-(6-(aminomethyl)pyridin-2-yl)propan-2-ol. (X)



Step-1: Pyridine-2,6-dicarboxylic acid. (Xa)

[000121] To a solution of 2,6-dimethylpyridine (CAS:108-48-5, 10 g, 0.17 mol) in 250 ml water, was slowly added 29.49 g of potassium permanganate (0.34 mol) with stirring. The mixture was refluxed until the purple color disappeared. Then, the mixture was cooled down to room temperature and another part of potassium permanganate (29.49 g, 0.34 mol) and water (150 ml) was slowly added. The mixture was refluxed at 100°C over 16 hrs. until the purple color disappeared again. The mixture was cooled down to room temperature. Filtration and removal of solvent until the residual volume down to 100 ml, then sulfuric acid (70%, 17.5 ml) was added slowly. The precipitate was filtered to afford pyridine-2,6-dicarboxylic acid **Xa**. Yield: (8.5 g, 55 %). **LC_MS** Calculated for $C_7H_5NO_4$: 167.02; Observed.:168.02 [M^++1].

Step-2: dimethyl pyridine-2,6-dicarboxylate. (Xb)

[000122] To a stirred solution of Pyridine-2,6-dicarboxylic acid **Xa** (8.5 g, 0.00598 mol) in methanol (1 L), added conc. sulphuric acid (4 ml) dropwise. The reaction mixture was refluxed at 60 °C for 16 hrs. After completion of reaction, removed the solvent by evaporation in vacuo, added water, the solid formed was filtered and dried to get the title compound **Xb**. Yield: (5 g, 51 %). **LC_MS** Calculated for $C_9H_9NO_4$ is 195.05; Observed.: 196.15 [M^++1]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.338-8.314 (m, 2H), 8.055-8.013 (m, 1H), 4.036 (s, 6H).

Step-3: methyl 6-(hydroxymethyl)picolinate. (Xc)

[000123] Into a 500-ml round-bottom flask, was placed a solution of 2,6-dimethyl pyridine-2,6-dicarboxylate **Xb** (5g, 0.00487 mol) in a solvent mixture of methanol (174 ml) and dichloromethane (74 ml). $NaBH_4$ (1.45 g, 0.00502 mol) was added to the reaction mixture in portions at 0°C. The resulting solution was stirred overnight at room temperature, and then it was quenched by the addition of Aq. NH_4Cl

(250 ml). The resulting solution was extracted with dichloromethane (2x200 ml) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1) as eluent to yield methyl 6-(hydroxymethyl) pyridine-2-carboxylate **Xc** as white solid. Yield: (3.9 g, 93 %). **LC_MS** Calculated. for $C_8H_9NO_3$ is 167.16; Observed.: 168.20 [M^++1]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.048-8.029 (d, J=7.6Hz, 1H), 7.875-7.837 (t, J=7.6Hz, 1H), 7.541-7.522 (d, J=7.6Hz, 1H), 4.863 (s, 2H), 4.002 (s, 3H).

Step-4: 2-(6-(hydroxymethyl) pyridin-2-yl) propan-2-ol. (Xd)

[000124] To a stirred solution of methyl 6-(hydroxymethyl) picolinate **Xc** (3 g, 0.0179 mol) in diethyl ether (300 ml), added methyl magnesium bromide (3.4 M, 0.0358 mol, 10.5 ml) dropwise at 0 °C. Then the reaction mixture was stirred at room temperature for 3 hrs. After completion, the reaction mixture was quenched with NH_4Cl and extracted with ethyl acetate (3x200 ml). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 30% ethyl acetate in hexane to yield the title compound as pale-yellow oil; Yield: (2.2 g, 73 %). **LC_MS Calc.** for $C_8H_9NO_3$ is 167.16; Obs.: 168.20 [M^++1]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.735-7.696 (t, *J* = 8 Hz, 1H), 7.333-7.313 (d, *J* = 8Hz, 1H), 7.201-7.182 (d, *J* = 7.6 Hz, 1H), 4.783 (s, 2H), 4.412 (s, 1H), 3.190 (s, 1H), 1.566 (s, 6H).

Step-5: 2-(6-(azidomethyl) pyridin-2-yl) propan-2-ol. (Xe)

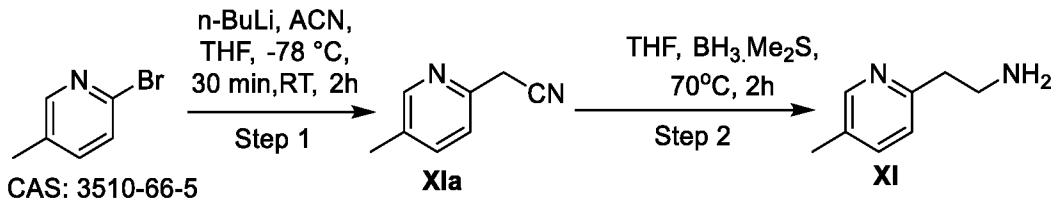
[000125] To a stirred solution of 2-(6-(hydroxymethyl) pyridin-2-yl) propan-2-ol **Xd** (0.4 g, 0.0832mol) in THF (5 ml), DPPA (0.0832 mol) at room temperature. The mixture was cooled to 0 °C and DBU (0.0832 mol) was added at rate such that the internal temperature did not exceed 20 °C. The reaction mixture was then warmed to 40 °C and stirred for 16 hrs. After completion, the reaction mixture was cooled to room temperature, added water (20 ml) and extracted with ethyl acetate (3x20 ml). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 10 % ethyl acetate in hexane to yield the title compound **Xe** as brown liquid; Yield: (0.26 g, 57%). **LC_MS** Calculated for $C_9H_{12}N_4O$ is 192.10; Observed.: 193.10 [M^++1]. **^{1}H NMR**

(400 MHz, $CDCl_3$): δ 7.743-7.724 (t, *J* = 7.6 Hz, 1H), 7.337-7.317 (d, *J* = 8 Hz, 1H), 7.245-7.226 (d, *J* = 7.6 Hz, 1H), 4.905 (s, 1H), 4.465 (s, 2H), 1.550 (s, 6H).

Step-6: 2-(6-(aminomethyl) pyridin-2-yl) propan-2-ol. (X)

[000126] To a stirred solution of 2-(6-(azidomethyl) pyridin-2-yl) propan-2-ol **Xe** (0.26 g) in methanol (10 ml), added Pd/C (100 mg) at room temperature. The reaction was stirred at same temperature for 1 hr under hydrogen. After completion, the reaction mixture was filtered through celite bed, and the bed was washed with methanol. The filtrate was concentrated under reduced pressure to get the title compound **X** as brown liquid; Yield: (0.3 g, crude). The crude product obtained was taken for the next step without further purification.

Synthesis of 2-(5-methylpyridin-2-yl)ethan-1-amine. (XI)



Step-1: 2-(5-Methylpyridin-2-yl) acetonitrile. (XIa)

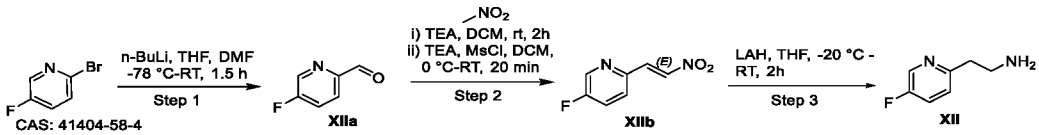
[000127] To a stirred solution of n-BuLi (14 ml, 0.034 mol) in THF (75 ml) was added ACN (1.75 ml, 0.0388 mol) at -78°C and stirred for 1h. Then added 2-bromo-5-methylpyridine (CAS: 3510-66-5, 1.67 g, 0.0097 mol) slowly and stirred at rt for 2 h. After completion (TLC), the reaction mixture was diluted with ice cold water (50 ml) and extracted with ethyl acetate (50 ml x 3). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to get the desired product **Xia** Yield: (0.6 g, crude). The crude product was taken for the next step without further purification.

Step-2: 2-(5-Methylpyridin-2-yl) ethan-1-amine. (XI)

[000128] To a stirred solution of 2-(5-methylpyridin-2-yl) acetonitrile **XIa** (0.6 g, 0.0045 mol) in THF (100 ml) was added BH_3-Me_2S, (10 ml, 0.0020 mol) at room temperature and stirred for 2 h at 70 °C. After completion (TLC), the reaction mixture cooled to room temperature, then added MeOH (5ml) and 10ml 1N HCl and the aqueous layer washed with ethyl acetate separated the layer and the aqueous layer

basified with 1N NaOH and extracted with DCM (100ml x 3). The organic layer was dried with Na_2SO_4, filtered and evaporated under reduced pressure to give title compound **XI**, the crude product was taken for the next step without purification; Yield: (0.2 g, 32%). **LC_MS** Calculated for $C_8H_{12}N_2$ is 136.10; Observed.137.2 [M^++H]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.35 (s, 1H), 7.42 (d, J = 7.6 Hz 1H), 7.06 (d, J = 8.0 Hz 1H), 3.12 (t, J = 6.4 Hz, 2H), 2.91 (d, J = 6.4 Hz, 2H), 2.3 (s, 3H).

Synthesis of 2-(5-fluoropyridin-2-yl)ethan-1-amine. (XII)



Step-1: 5-Fluoropicolinaldehyde. (XIIa)

[000129] To a stirred solution of 2-bromo-5-fluoropyridine (CAS: 41404-58-4, 2.69 g, 0.0147 mol) in toluene (30 ml) at -78°C was added n-BuLi (5.9 ml, 0.0147 mol) dropwise and stirred for 1h. Then DMF (1.36 ml) and added slowly at -50°C and stirred for 30 min. After completion (TLC), the reaction mixture was quenched with MeOH (30 ml) and stirred at 5-10 °C for 30 min. Then, NH_4Cl solution (75 ml) was added and stirred at rt for 40 min and then extracted with ethyl acetate (100 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by flash column chromatography by eluting with 5% ethyl acetate in hexane to yield the title compound **XIIa** as yellow liquid; Yield: (1.01 g, 54.89%). **LC_MS** Calculated for C_6H_4FNO is 125.03; Observed.126.00 [M^++H]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.04 (s,1H), 8.63 (d, J = 2.0 Hz, 1H), 8.05-8.02 (m, 1H), 7.58 (dt, J = 8.4 Hz, 2.8 Hz, 1H).

Step-2: (E)-5-Fluoro-2-(2-nitrovinyl) pyridine. (XIIb)

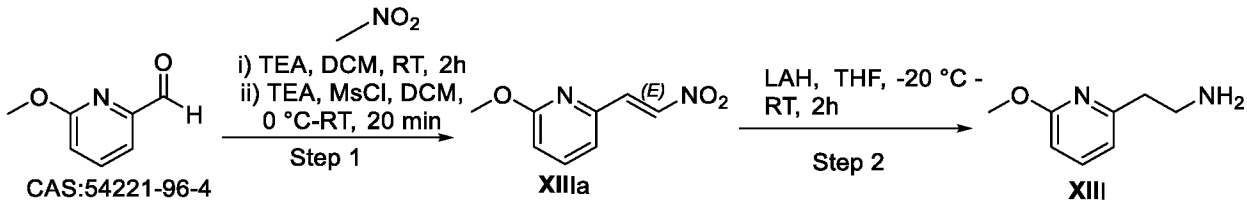
[000130] To a stirred solution of 5-fluoropicolinaldehyde **XIIa** (1.01 g, 0.00807 mol) in DCM (20 ml), was added TEA (2.24 ml, 0.0161 mol) and nitromethane (0.52 ml, 0.00968 mol) and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure. The crude material was dissolved in DCM (20 ml) and treated with TEA (1.77 ml, 0.0242 mol) and MsCl (2.75 ml, 0.0242 mol) at 0 °C

and the reaction mixture was stirred at rt for 20 min. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure. And the crude was purified by column chromatography by eluting with 10% ethyl acetate in hexane to yield the title compound **XIIb** as green solid; Yield: (1.2 g, 88.8%). **LC_MS** Calculated for $C_7H_5FN_2O_2$ is 168.03; Observed.169.00 [M^++H]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.54 (s,1H), 7.93 (q, J = 12.8 Hz, 2H), 7.50-7.49 (m, 2H).

Step-3: 2-(5-Fluoropyridin-2-yl) ethan-1-amine. (XII)

[000131] To a stirred solution of (E)-5-fluoro-2-(2-nitrovinyl) pyridine **XIIb** (1.2 g, 0.0071 mol) in THF (50 ml), was added LAH (1M sol in THF, 21.4 ml, 0.024 mol) at -20 °C dropwise. Then the temp was allowed to reach to rt, and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0 °C and quenched with saturated Na_2SO_4 solution (50 ml) and extracted with ethyl acetate (50 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude was purified by column chromatography by eluting with 10% methanolic NH_3 in DCM to yield the title compound as pale green liquid; Yield: (0.35 g, 35%). **LC_MS** Calculated for $C_7H_9FN_2$ is 140.07; Observed.141.2 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 8.45 (d, J = 3.2 Hz, 1H), 7.62 (dd, J = 8.4 Hz, 2.8 Hz, 1H), 7.34-7.31 (m, 1H), 2.88 (t, J = 6.4 Hz, 2H), 2.81 (d, J = 6.4 Hz, 2H), 2.5 (bs, 2H).

Synthesis of 2-(6-methoxypyridin-2-yl) ethan-1-amine. (XIII)



Step-1: (E)-6-Methoxy-2-(2-nitrovinyl) pyridine. (XIIIa)

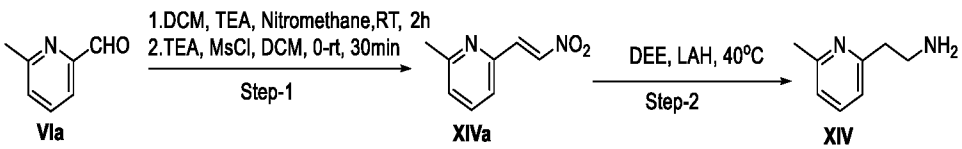
[000132] To a stirred solution of 6-methoxypicolinaldehyde (CAS:54221-96-4, 1.0 g, 0.00724 mol) in DCM (20 ml), was added TEA (2.19 g, 0.0217 mol) and nitromethane (1.32 g, 0.0216 mol) and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure. The crude material was dissolved in

DCM (20 ml) and treated with TEA (2.19 g, 0.0217 mol) and mesyl chloride (2.47 g, 0.0217 mol) at 0 °C and the reaction mixture was stirred at rt for 30 min. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure. And the crude was purified by column chromatography by eluting with 7% ethyl acetate in hexane to yield the title compound **XIIa** as yellow solid; Yield: (0.8 g, 80%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ8.016-7.983 (d, *J* =13.2 Hz, 1H), 7.845-7.812 (d, *J* =13.2 Hz, 1H), 7.652-7.614 (t, *J* = 8Hz, 1H), 7.069-7.052 (d, *J* = 6.8 Hz, 1H), 6.863-6.843 (d, *J* = 8Hz, 1H), 3.969 (s, 3H).

Step-2: 2-(6-Methoxypyridin-2-yl) ethan-1-amine. (XIII)

[000133] To a stirred solution of (E)-6-methoxy-2-(2-nitrovinyl) pyridine **2** (0.8 g, 0.0044 mol) in DEE (16 ml), was added LAH (1M sol in THF, 13.3 ml, 0.0133 mol) at -10 °C dropwise. Then the temp was allowed to reach to rt and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0 °C and quenched with chilled water (10 ml), 15N aq. NaOH (1 ml), and extracted with 10% methanol in DCM (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure to give crude product **XIII** as brown liquid. The crude product was carried forward to next step without purification; Yield: (0.43 g, 63%). **LC_MS** Calculated for $C_8H_{12}N_2O$: 152; Observe.153 [M^++H]. **^{1}H NMR (400 MHz, CDCl3):** *δ* 7.477 (d, 1H), 6.733-6.726 (d, J=2.8Hz, 1H), 6.570-6.560 (m, 2H), 3.918 (s, 3H), 3.108 (t, 2H), 2.820 (t, 2H).

Synthesis of 2-(6-methylpyridin-2-yl) ethan-1-amine. (XIV)



Step-1. (E)-6-Methoxy-2-(2-nitrovinyl) pyridine. (XVa)

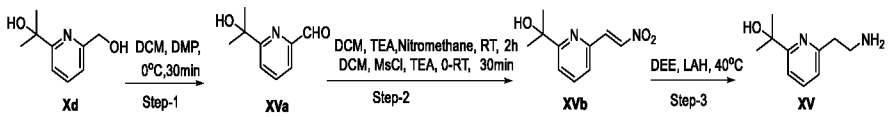
[000134] To a stirred solution of 6-methylpicolinaldehyde **Via** (8.0 g, 0.0660 mol) in DCM (80 ml), was added TEA (13.36 g, 0.132 mol) and nitromethane (5.15 g,

0.079 mol) and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure. The crude material was dissolved in DCM (80 ml) and treated with TEA (20.03 g, 0.198 mol) and mesyl chloride (22.58 g, 0.198 mol) at 0 °C and the reaction mixture was stirred at rt for 30 min. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure. And the crude was purified by column chromatography by eluting with 7-10% ethyl acetate in hexane to yield the title compound **XVa** as brown liquid; Yield: (9 g, 83.33%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ8.076-8.042 (d, J=13.6Hz, 1H), 7.942-7.910 (d, J=12.8Hz, 1H), 7.722-7.605 (t, J=7.2Hz, 1H), 7.331-7.314 (d, J=6.8Hz, 1H), 7.278-7.7.266 (d, J=4.8Hz, 1H), 2.263 (s, 3H).

Step-3: 2-(6-methylpyridin-2-yl) ethan-1-amine (XIV)

[000135] To a stirred solution of (E)-6-methoxy-2-(2-nitrovinyl) pyridine **2** (9.18 g, 0.0559 mol) in DEE (700 ml), was added LAH (1M sol in THF, 224 ml, 0.22 mol) at 0 °C dropwise. Then the temp was raised to 40 °C and continued for 2 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0 °C and quenched with chilled water (50 ml), 15N aq. NaOH (5 ml), and filtered through celite bed. Celite bed was washed with DEE (250 ml). DEE from filtrate was distilled off at reduced pressure to get title compound **XIV** brown liquid which was used for next step without further purification. Yield: (5.09 g, 67%). **LC_MS** Calculated. for $C_8H_{12}N_2$: 136; Observed.137 [M^++H]. **^{1}H NMR (400 MHz, CDCl3):** *δ* 7.577-7.539 (t, *J* = 8 Hz, 1H), 7.050-7.012 (m, 2H), 2.867-2.807 (t, *J* = 6.8 Hz, 2H), 2.771-2.750 (t, *J* = 8.4 Hz, 2H), 2.420 (s, 3H).

Synthesis of 2-(6-(2-aminoethyl) pyridin-2-yl)propan-2-ol.(XV)



Step-1: 6-(2-hydroxypropan-2-yl) picolinaldehyde (XVa)

[000136] To a stirred solution of 2-(6-(hydroxymethyl) pyridin-2-yl) propan-2-ol **Xd** (1.8 g, 0.0107 mol) in DCM (50 ml) , added DMP (6.85 g, 0.0161 mol) portion wise at 0 °C. And the reaction mixture was stirred at same temperature for 30 min. The reaction was monitored by TLC. After completion, the reaction mixture was quenched with aq. Sodium bicarbonate (50 ml) and extracted by DCM (100 ml x 3 times). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. Crude compound was purified by column chromatography, the product was eluted at 10% ethyl acetate/ Hexane to afford title compound **XVa** as pale-yellow oil. Yield: (1.1g, 62%). **^{1}H NMR (400 MHz, CDCl3):** δ 10.094 (s, 1H), 7.929-7.870 (m, 2H), 7.659-7.641 (d, J=7.2Hz, 1H), 4.606 (bs, 1H), 1.607 (s, 6H).

Step-2: (E)-2-(6-(2-nitrovinyl) pyridin-2-yl) propan-2-ol (XVb)

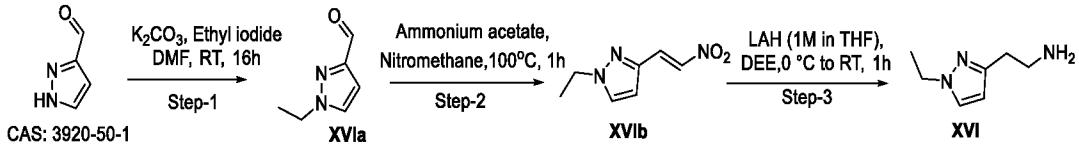
[000137] To a stirred solution of 6-(2-hydroxypropan-2-yl) picolinaldehyde **XVa** (0.5 g, 0.00303 mol) in DCM (5 ml), was added TEA (0.613 g, 0.00606 mol) and nitromethane (0.1 g, 0.0016 mol) and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure. The crude material was dissolved in DCM (20 ml) and treated with TEA (0.67 g, 0.00663 mol) and mesyl chloride (0.756 g, 0.00663 mol) at 0 °C and the reaction mixture was stirred at rt for 30 min. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure. And the crude was purified by column chromatography by eluting with 7% ethyl acetate in hexane to yield the title compound **XVb** as yellow solid; Yield: (0.35 g, 76%). **LC_MS** Calculated for $C_{10}H_{12}N_2O_3$: 208.08; Observed:209.20 [M^++H]. **^{1}H NMR (400 MHz, CDCl3):** δ 8.036-8.003 (d, J=13.2Hz, 1H), 7.951-7.918 (d, J=13.2Hz, 1H), 7.841-7.801 (t, J=8Hz, 1H), 7.531-7.510 (d, J=8.4Hz, 1H), 7.406-7.388 (d, J= 7.2Hz, 1H), 1.577 (s, 6H).

Step-3: 2-(6-(2-aminoethyl) pyridin-2-yl) propan-2-ol (XV)

[000138] To a stirred solution of (E)-1-Methyl-3-(2-nitrovinyl)-1H-pyrazole **3** (0.55 g,0.00264 mol) in diethyl ether (26 ml), was added LAH (1M solution in THF, 0.401g, 0.0106 mol) at 0 °C dropwise. Then the temp was allowed to reach to rt and the reaction mixture was stirred at 40 °C for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0 °C and

quenched with chilled water (3 ml), 15N aq. NaOH (2 ml). Inorganic salts were filtered and washed with DEE (25 ml). Solvent from filtrate were concentrated under reduced pressure to afford crude compound **XV** which was used for next step without further purification. Yield: (0.3g, 63%). **^{1}H NMR (400 MHz, DMSO-d6):** δ 7.666-7.628 (t, J=7.2Hz, 1H), 7.450-7.432 (d, J=7.2Hz, 1H), 7.069-7.050 (d, J=7.6Hz, 1H), 2.886-2.870 (t, J=6.4Hz, 2H), 2.784-2.766 (t, J=7.2Hz, 2H), 1.414 (s, 6H).

Synthesis of 2-(1-ethyl-1H-pyrazol-3-yl) ethan-1-amine. (XVI)



Step-1: 1-ethyl-1H-pyrazole-3-carbaldehyde (XVIa)

[000139] To a stirred solution of 1H-pyrazole-3-carbaldehyde (CAS: 3920-50-1, 3 g, 0.031 mol) in DMF (20 ml) was added Potassium carbonate (10 g, 0.0723 mol) and Ethyl iodide (5.8 g, 0.0374 mol) and the reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC. After completion, water (30 ml) was added and extracted with ethyl acetate (3x30 ml). Combined ethyl acetate layer was washed with 10% brine solution (50 ml). Organic layer was dried over sodium sulphate, filtered, and concentrated to afford crude1-ethyl-1H-pyrazole-3-carbaldehyde which was further purified by column chromatography using 30% ethyl acetate in hexane to afford title compound **XVI** as yellow colored liquid. Yield: (2.4 g, 63 %). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.982 (s, 1H), 7.467-7.462 (d, *J* = 2Hz, 1H), 6.808-6.802 (d, *J* = 2.4 Hz, 1H), 4.307-4.252 (q, *J* = 7.2 Hz, 2H), 1.572-1.536 (t, *J* = 7.2 Hz, 3H).

Step-2: (E)-1-ethyl-3-(2-nitrovinyl)-1H-pyrazole (XVIb)

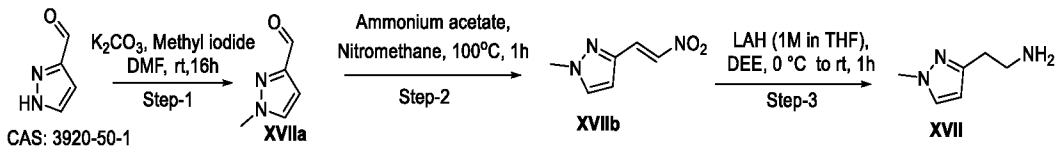
[000140] To a stirred solution of 1-ethyl-1H-pyrazole-3-carbaldehyde **2** (2.4 g, 0.0193 mol) in nitromethane (22 ml) was added Ammonium acetate (2.3 g, 0.029 mol) and the reaction mixture was stirred for 1h at 100 °C. Progress of reaction was monitored by TLC. After completion, solvent from reaction mass was removed under reduced pressure. Residue was taken up with water (50 ml) and extracted with ethyl

acetate (3x35 ml). Combined ethyl acetate layer was washed with 10% brine solution (35 ml). Organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to get the desired product **XVIb**. The crude product was carried forward to next step without further purification. Yield: (1.6 g, 49 %). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.990-7.956 (d, *J* = 13.6 Hz, 1H), 7.637-7.604 (d, *J* = 13.2 Hz, 1H), 7.450-7.446 (d, *J* = 1.6 Hz, 1H), 6.542-6.538 (d, *J* = 1.6 Hz, 1H), 4.253-4.190 (q, *J* = 7.2 Hz, 2H), 1.543-1.506 (t, *J* =7.2 Hz, 3H).

Step-3: 2-(1-ethyl-1H-pyrazol-3-yl) ethan-1-amine (XVI)

[000141] To a stirred solution of (E)-1-ethyl-3-(2-nitrovinyl)-1H-pyrazole **3** (1.5 g, 0.0089 mol) in DEE (60 ml), was added LAH (1M sol in THF, 36 ml, 0.036 mol) at 0 °C dropwise. Then the temp was allowed to reach to rt and the reaction mixture was stirred at 40°C for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0 °C and quenched with chilled water (2 ml), 15N aq. NaOH (1 ml). Inorganic salts were filtered and washed with DEE (25 ml). Solvent from filtrate were concentrated under reduced pressure to afford crude compound **XVI** which was used for next step without further purification. Yield: (1 g, 81 %). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.312 (d, 1H), 6.054-6.050 (d, 1H), 4.150-4.096 (q, *J* = 7.2 Hz, 2H), 3.008-2.974 (t, 2H), 2.787-2.754 (t, 2H), 1.483-1.432 (t, *J* = 7.2 Hz, 3H).

Synthesis of 2-(1-ethyl-1H-pyrazol-3-yl)ethan-1-amine. (XVII)



Step-1: 1-methyl-1H-pyrazole-3-carbaldehyde (XVIIa)

[000142] To a stirred solution of 1H-pyrazole-3-carbaldehyde (CAS: 3920-50-1,5 g,0.052 mol) in DMF (25 ml) was added Potassium carbonate (17.97 g,0.13 mol) and Methyl iodide (8.86 g, 0.0624 mol) and the reaction mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC. After completion, water (50 ml) was added and extracted with ethyl acetate (3x50 ml). Combined ethyl acetate layer was washed with 10% brine solution (50 ml). Organic

layer was dried over sodium sulphate, filtered, and concentrated to afford crude 1-Methyl-1H-pyrazole-3-carbaldehyde, which was further purified by column chromatography using 30% ethyl acetate in hexane to afford title compound **XVIIa** as yellow colored liquid. Yield: (2.6 g, 45%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.960 (s, 1H), 7.431-7.427 (d, *J* = 1.6 Hz, 1H), 6.812-6.805 (d, *J* = 2.8 Hz, 1H), 4.020 (s, 1H).

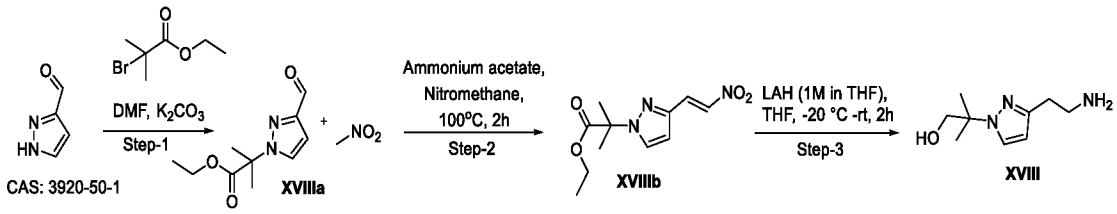
Step-2: (*E*)-1-methyl-3-(2-nitrovinyl)-1H-pyrazole (XVIIb)

[000143] To a stirred solution of 1-Methyl-1H-pyrazole-3-carbaldehyde **XVIIa** (2.4 g, 0.020 mol) in nitromethane (43 ml) was added ammonium acetate (2.5 g, 0.031 mol) and the reaction mixture was stirred for 1h at 100 °C. Then the progress of reaction was monitored by TLC. After completion, solvent from reaction mass was removed under reduced pressure. Residue was taken up with water (50 ml) and extracted with ethyl acetate (3x50 ml). Combined ethyl acetate layer was washed with 10% brine solution (50 ml). Organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude product was purified by column chromatography using 20% ethyl acetate in hexane to afford pure title compound **XVIIb**. Yield: (1.4 g, 49 %). **^{1}H NMR (400 MHz, $CDCl_3$):** δ7.970-7.936 (d, *J* = 13.6 Hz, 1H), 7.631-7.598 (d, *J* = 13.2 Hz, 1H), 7.428-7.422 (d, *J* = 2.4 Hz, 1H), 6.549-6.543 (d, *J* = 2.4 Hz, 1H), 3.971 (s, 3H).

Step-3: 2-(1-Methyl-1H-pyrazol-3-yl) ethan-1-amine (XVII)

[000144] To a stirred solution of (E)-1-Methyl-3-(2-nitrovinyl)-1H-pyrazole **3** (1.4 g, 0.009 mol) in DEE (60 ml), was added LAH (1M solution in THF, 29 ml, 0.029 mol) at 0 °C dropwise. Then the temp was allowed to reach to rt and the reaction mixture was stirred at 40 °C for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0 °C and quenched with chilled water (2 ml), 15N aq. NaOH (1 ml). Inorganic salts were filtered and washed with DEE (25 ml). Solvent from filtrate were concentrated under reduced pressure to afford crude compound **XVII** which was used for next step without further purification. Yield: (1 g, 87%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.278-7.268 (d, *J* = 4Hz, 1H), 6.053-6.050 (d, *J* = 1.2 Hz, H), 3.853 (s, 3H), 3.008-2.969 (t, *J* = 6.8 Hz, 2H), 2.778-2.745 (t, *J* = 6.8 Hz, 2H).

Synthesis of 2-(3-(2-aminoethyl)-1H-pyrazol-1-yl)-2-methylpropan-1-ol. XVIII



Step-1: Ethyl 2-(3-formyl-1H-pyrazol-1-yl)-2-methylpropanoate (XVIIIa)

[000145] To a stirred solution of 1H-pyrazole-3-carbaldehyde (CAS: 3920-50-1, 1 g,0.01 mol) in DMF (5 ml) was added Potassium carbonate (3 g, 0.02 mol) and ethyl 2-bromo-2-methylpropanoate (2 g, 0.01 mol) and the reaction mixture was stirred at room temperature for 16 h. Then the progress of the reaction was monitored by TLC. After completion, water (25 ml) was added and extracted with ethyl acetate (3x25 ml). Combined ethyl acetate layer was washed with 10% brine solution (25 ml). Organic layer was dried over sodium sulphate, filtered, and concentrated to afford crud compound which was further purified by column chromatography using 30% ethyl acetate in hexane to afford title compound **XVIIIa**. Yield: (1.8 g, 82%). **LC_MS** Calculated for $C_{10}H_{14}N_2O_3$ is 210.06; Observed.: 211.20 [M^++1]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.980 (s, 1H), 7.623 (s, 1H), 6.836 (s, 1H), 4.217-4.164 (q, J = 7.2 Hz, 2H), 1.999 (s, 6H), 1.235-1.200 (t, J = 6.8 Hz, 3H).

Step-2: ethyl (E)-2-methyl-2-(3-(2-nitrovinyl)-1H-pyrazol-1-yl) propanoate (XVIIIb)

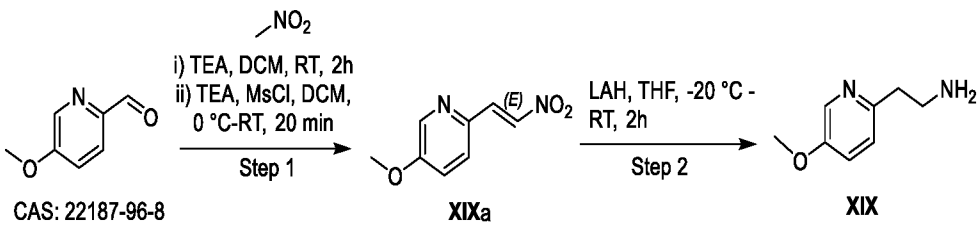
[000146] To a stirred solution of ethyl 2-(3-formyl-1H-pyrazol-1-yl)-2-methylpropanoate **XVIIIa** (1.8 g,0.008 mol) in nitromethane (17 ml) was added Ammonium acetate (0.99 g, 0.0121 mol) and the reaction mixture was stirred for 1h at 100 °C. Progress of reaction was monitored by TLC. After completion, solvent from reaction mass was removed under reduced pressure. Crude product was purified by column chromatography using 20% ethyl acetate in hexane to afford pure title compound **XVIIIb**. Yield: (0.55 g, 25%). **LC_MS** Calculated for $C_{11}H_{15}N_3O_4$ is 253.11; Observed.: 254.20 [M^++1]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.007-7.973 (d, J = 13.6 Hz, 1H),7.629-7.611 (m, 2H), 7.509-7.504 (d, J = 2 Hz, 1H), 6.580-6.574 (d,

J = 2.4 Hz, 1H), 4.210-4.120 (q, J = 7.6 Hz, 2H), 1.187 (s, 6H), 1.237-1.163 (t, J = 7.6 Hz, 3H).

Step-3: 2-(3-(2-aminoethyl)-1H-pyrazol-1-yl)-2-methylpropan-1-ol (XVIII)

[000147] To a stirred solution of ethyl (E)-2-methyl-2-(3-(2-nitrovinyl)-1H-pyrazol-1-yl) propanoate **4** (0.55 g, 0.0021 mol) in DEE (15 ml), was added LAH (1M solution in THF, 8.7 ml, 0.0086 mol) at 0 °C dropwise. Then the temp was allowed to reach to rt and the reaction mixture was stirred at 40 °C for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0 °C and quenched with chilled water (2 ml), 15N aq. NaOH (1 ml). Inorganic salts were filtered and washed with DEE (25 ml). Solvent from filtrate were concentrated under reduced pressure to afford crude compound **XVIII** which was used for next step without further purification. Yield: (0.35 g, 88%). **LC_MS** Calculate for $C_9H_{17}N_3O$ is 183.14; Observe.: 184.30 [M^++1]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.449 (s, 2H), 6.071 (s, 1H), 3.76 (s, 2H), 2.999-2.968 (t, J = 7.6 Hz, 2H), 2.811-2.740 (t, J = 7.6 Hz, 2H), 1.596 (s, 6H).

Synthesis of 2-(5-methoxypyridin-2-yl)ethan-1-amine. XIX



Step-1: (E)-5-Methoxy-2-(2-nitrovinyl) pyridine (XIXa)

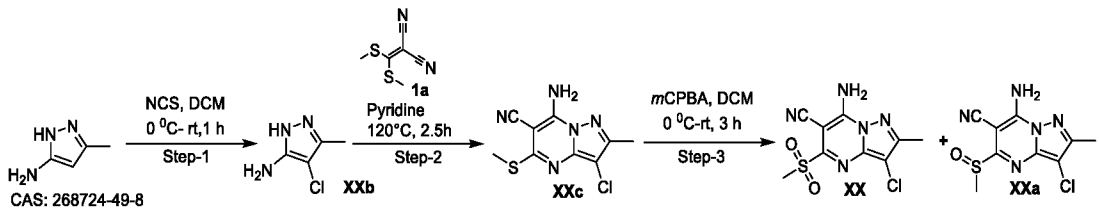
[000148] To a stirred solution of 5-methoxypicolinaldehyde **1** (2.0 g, 0.0145 mol) in DCM (20 ml), was added TEA (4.04 ml, 0.029 mol) and nitromethane **2** (1.06 g, 0.0174 mol) and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure. The crude material was dissolved in DCM (20 ml) and treated with TEA (6.06 ml, 0.0435 mol) and mesyl chloride (3.37 ml, 0.0435 mol) at 0 °C and the reaction mixture was stirred at rt for 30 min. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure. The crude was purified by column

chromatography by eluting with 10% ethyl acetate in hexane to yield the title compound **XIXa** as yellow solid; Yield: (2.47 g, 94%). **LC_MS** Calculated for $C_8H_8N_2O_3$: 180.05; Observe: 181.00 [M++H]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.38 (d, *J* = 3.2 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.26 (s, 1H), 7.22 (dd, *J* = 8.4, 2.8 Hz, 1H), 3.92 (s,3H).

Step-2: 2-(5-Methoxypyridin-2-yl) ethan-1-amine (XIX)

[000149] To a stirred solution of (E)-5-methoxy-2-(2-nitrovinyl) pyridine **3** (2.74 g, 0.0152 mol) in THF (90 ml), was added LAH (1M sol in THF, 45.6 ml, 0.0456 mol) at -10 °C dropwise. Then the temp was allowed to reach to rt and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0 °C and quenched with saturated Na_2SO_4 solution (50 ml) and extracted with ethyl acetate (50 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude was purified by column chromatography by eluting with 10% methanolic NH_3 in DCM to yield the title compound **XIX** as brown liquid; Yield: (0.8 g, 34.78%). **^{1}H NMR (400 MHz, DMSO):** *δ* 8.19 (d, *J* = 2.8 Hz, 1H), 7.3 (dd, *J* = 8.4, 3.2 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 3.79 (s, 3H), 2.88 (t, *J* = 6.0 Hz, 2H), 2.74 (t, *J* = 6.8 Hz, 2H).

[000150] **Synthesis of a mixture of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl)pyrazolo[1,5-a] pyrimidine -6-carbonitrile (XX) and 7-amino-3-chloro-2-methyl-5-(methyl sulfinyl) pyrazolo[1,5-a]pyrimidine-6-carbonitrile. (XXa).**



Step-1: Synthesis of 4-chloro-3-methyl-1H-pyrazol-5-amine (XXb).

[000151] N-Chlorosuccinimide (3.3 g, 0.025 mol) was added portion wise to the stirred solution of 3-methyl-1H-pyrazol-5-amine (CAS: 268724-49-8, 2.0 g, 0.021 mol) in DCM (50 mL) at 0°C, Then the reaction mixture was stirred at rt for 1h. The progress of the reaction was monitored by TLC. Then the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under

reduced pressure to get the crude product. Crude compound obtained was purified by Biotage column chromatography using silica gel (230-400) and 1-5% methanol in DCM as eluent to afford desired product XXb as an off white solid. Yield: 2.0g, 74%. **LCMS** Calculated. for $C_4H_6ClN_3$ is 131.56; Observed.132.0 $[M+H]^+$

Step-2: Synthesis of 7-amino-3-chloro-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine–6- carbonitrile (XXc)

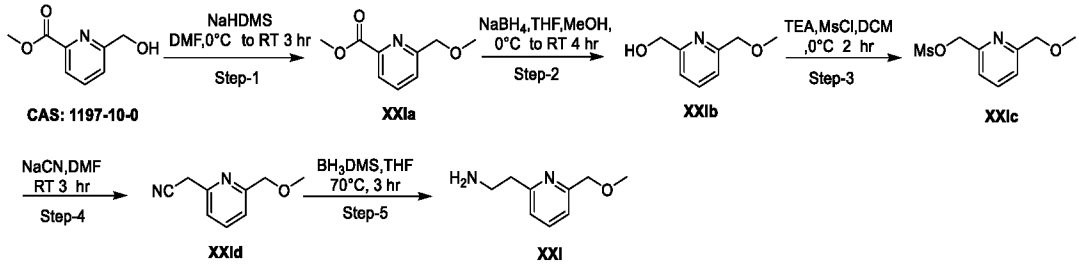
[000152] To a stirred solution of 4-chloro-5-methyl-1H-pyrazol-3-amine **XXb** (1.8 g, 0.0136 mol) in pyridine (5 mL) was added 2-(bis (methylthio) methylene) malononitrile **Ia** (2.8 g, 0.016 mol). The resulting reaction mixture was heated at 120°C for 2.5 h. Then the progress of the reaction was monitored by TLC. Reaction mixture was cooled to room temperature and poured into ice cold water (20 mL). Precipitated compound was filtered and washed with cold water. Then the obtained solid was dried under vacuum and purified by biotage column chromatography using silica gel (230-400) and 5-20 % ethyl acetate in hexane as eluent to afford desired product **XXc** as pale brown colour solid. Yield: 3.5g, 99%. **LCMS** Calculated. for $C_9H_8ClN_5S$ is 253.71; Observed.254.0 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.90 (bs, 2H), 2.57 (S, 3H), 2.37 (S, 3H).

Step-3: Synthesis of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile. (XX) and 7-amino-3-chloro-2-methyl-5- (methyl sulfinyl) pyrazolo [1,5-a] pyrimidine-6-carbonitrile (XXa)

[000153] meta-Chloroperoxybenzoic acid (9.5 g, 0.055 mol) was added portion wise to a stirred solution of 7-amino-3-chloro-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine -6-carbonitrile **XXc** (3.5 g, 0.013 mol) in DCM (50 mL) at 0°C. The reaction mixture was stirred at rt for 3 h. Then the progress of the reaction was monitored by TLC. The reaction mixture was quenched with aqueous $NaHCO_3$ solution (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure and dried under vacuum to get a mixture of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX** and 7-amino-3-

chloro-2-methyl-5- (methyl sulfinyl) pyrazolo [1,5-a] pyrimidine-6-carbonitrile **XXa** as an off white solid. Yield (2.2 g, 56%). This crude material was taken as such for next step without further purification. **LCMS** Calculated. for $C_9H_8ClN_5O_2S$ is 285.71; Observed .286.1 [M+H] **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 9.48 (bs, 2H), 3.42 (S, 3H), 2.45 (S, 3H).

Synthesis of 2-(6-(methoxymethyl) pyridin-2-yl) ethan-1-amine (XXI)



Step-1: Synthesis of methyl 6-methoxy methyl) picolinate. (XXIa)

[000154] A solution of methyl 6-(hydroxymethyl) picolinate (CAS: 1197-10-0, 25 g, 0.15 mol) in DMF (250 mL) was cooled to 0°C, added NaH (7.2 g, 60% wt, 0.18 mol) portion wise and dimethyl sulphate (19 mL, 0.19 mol) dropwise to it and the reaction mixture was stirred at rt for 3 hours. Then the progress of the reaction was monitored by TLC. After completion, the reaction mixture was quenched with ice cold water (200 mL) and extracted with ethyl acetate (3 x 200 mL) and concentrated. Crude product obtained was purified by gravity column used 230-400 silica mesh and the desired product was eluted at 15-20% ethyl acetate in hexane to afford **XXIa** as yellow viscous oil. Yield: 21 g, 78%. **LCMS** Calculated. for $C_9H_{11}NO_3$ is 181.07; Observed 182.20 [M+H]. **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.04 (d, J =7.6 Hz, 1H), 7.86 (t, J =7.6 Hz 1H,), 7.66 (d, J =7.6Hz, 1H,), 4.69(s, 2H), 4.00 (s, 3H), 3.49(s, 3H).

Step-2: Synthesis of (6-(methoxy methyl) pyridin-2-yl) methanol (XXIb)

[000155] A solution of methyl 6-(methoxymethyl) picolinate **XXIa** (21 g, 0.12 mol) in THF (200 mL) was cooled to 0°C, added $NaBH_4$ (13 g, 0.35 mol) portion wise and then reaction mixture was stirred at 25°C for 3 hours. The progress of the reaction was monitored by TLC. Reaction mixture concentrated at low vacuum and added $NaHCO_3$ solution (100 mL) and extracted with DCM (3 x 300 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered,

and evaporated under reduced pressure. Crude compound obtained was purified by gravity column used 230-400 silica mesh and the desired product was eluted at 25-30% ethyl acetate in hexane to afford **XXIb** as yellow viscous oil. Yield: 16.8 g, 93%. **LCMS** Calculated. for $C_8H_{11}NO_2$ is 153.08; Observed 154.25 $[M+H]^+$.**^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.69 (t, J =7.6 Hz, 1H), 7.33 (d, J =7.6 Hz, 1H), 7.14(d, J =7.6Hz, 1H,), 4.74 (d, J = 4.8 Hz, 2H), 4.59(s, 2H), 3.77(t, J = 4.8, 5.2 Hz, 1H) 3.48 (s, 3H).

Step-3: Synthesis of (6-(methoxy methyl) pyridin-2-yl) methyl methane sulfonate (XXIc)

[000156] A solution of (6-(methoxymethyl) pyridin-2-yl) methanol **XXIb** (7 g, 0.05 mol) in DCM (140 mL) was cooled to 0 °C, added TEA (7 g, 0.01 L, 0.07 mol) and MsCl (4 mL, 0.05 mol) dropwise and the reaction mixture was stirred at 0°C for 2 hours. The progress of the reaction was monitored by TLC. Reaction mixture was quenched with $NaHCO_3$ solution (100 mL) and extracted with DCM (3x 200 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to get brown liquid **XXIc** which was used as such for the next step without further purification. Yield: 10 g, 92%. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.79-7.75 (m,1H), 7.42 (d, 1H, J = 8.0 Hz), 7.38 (d, J = 7.6Hz, 1H), 5.32 (s, 2H), 4.57 (s, 2H), 3.48(s, 3H), 3.09(s, 3H).

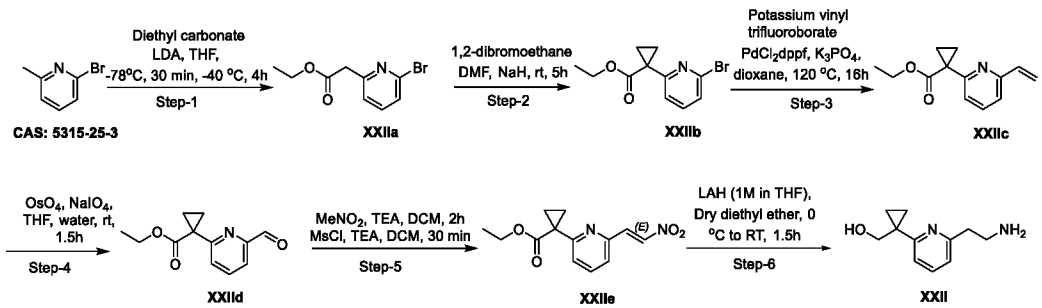
Step-4: Synthesis of 2-(6-(methoxy methyl) pyridin-2-yl) acetonitrile (XXId)

[000157] To a stirred solution of (6-(methoxymethyl) pyridin-2-yl) methyl methane sulfonate **XXIc** (10 g, 0.043 mol) in DMF (100 mL) was added NaCN (2.3 g, 0.048 mol) portion wise and the reaction mixture was stirred at 24°C for 3 hours. The progress of the reaction was monitored by TLC. Reaction Mixture quenched with ice cold water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material obtained was purified by flash Chromatography using silica gel 230-400 mesh, the desired product was eluted with 20 - 25% EtOAc in hexane to afford **XXId** as yellow viscous oil. Yield: 5.1g, 73%. **LCMS** Calculated. for $C_9H_{10}N_2O$ is 162.08; Observed 163.25 $[M+H]^+$.**^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.7-7.7 (m, 1H), 7.40-7.26 (m, 2H), 4.56(s, 2H), 3.92 (s, 2H), 3.48(s, 3H).

Step-5: Synthesis of 2-(6-(methoxy methyl) pyridin-2-yl) ethan-1-amine (XXI)

[000158] A solution of 2-(6-(methoxymethyl) pyridin-2-yl) acetonitrile **XXId** (5.1 g, 0.031 mol) in THF (80 mL) was cooled to 0°C and added BH_3.DMS (15 mL, 0.16 mol) dropwise and the reaction mixture was stirred at 70°C for 3 hours. The progress of the reaction was monitored by TLC. After completion, the reaction was cooled to room temperature and quenched by MeOH (15 mL). The resulting mixture was stirred at room temperature for 30 min. The mixture was acidified using 1 M HCl solution (15 mL) and concentrated under reduced pressure. The residue obtained was taken in water (20 mL) and EtOAc (50 mL) and DCM (50 mL) were added to remove the impurities. The aqueous layer was separated and basified with 2N NaOH solution. The resulting mixture was extracted with DCM (3 x 300 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired compound **XXI** as a brown viscous liquid. The crude compound was used in the next step without further purification. Yield: 3.4 g, 65%. **LCMS** Calculated. for $C_9H_{11}NO_3$ is 166.11; Observed 167.30 $[M+H]^+$. **^{1}H NMR (400 MHz, CDCL3):** δ 7.64-7.60 (m, 1H), 7.26 (d, J = 8 Hz, 1H), 7.07(d, J =7.6Hz, 1H), 4.56(s, 2H), 3.47 (s, 3H), 3.10-3.07(m, 2H), 2.93-2.90(m, 2H).

Synthesis of (1-(6-(2-aminoethyl) pyridin-2-yl) cyclopropyl) methanol (XXII)



Step-1: Synthesis of Ethyl 2-(6-bromopyridin-2-yl) acetate (XXIIa)

[000159] To a solution of lithium diisopropylamide (8 g, 0.04 L, 2M, 2.5 eq, 0.07 mol) in THF (150 mL) at -78 °C under nitrogen atmosphere was added 2-bromo-6-methylpyridine (CAS: 5315-25-3, 5 g, 1 eq, 0.03 mol) dropwise and the resulting mixture was stirred at -78 °C for 30 min. This was followed by an addition

of diethyl carbonate (9 g, 2.5 eq, 0.07 mol). The resulting mixture was stirred at -40 °C for 6 hours. The progress of the reaction was monitored by TLC for the absence of starting material. The reaction was quenched with saturated solution of NH_4Cl (60 mL) and the resulting mixture was extracted with ethyl acetate (70 mL X 2). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford light brown viscous liquid. The crude compound was purified by column chromatography using silica gel (100-200; 250g) and EtOAc (0-10%) in hexane as eluent. The peak eluted with 7% of EtOAc in hexane was concentrated to afford the desired product **XXIIa** as a colorless viscous liquid. Yield: 5.3 g, 70%. **LCMS** Calculated. for $C_9H_{10}BrNO_2$ is 242.99; Observed. 244.10 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.53 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 7.2 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.83 (s, 2H), 1.27 (t, J = 6.8 Hz, 3H).

Step-2: Synthesis of Ethyl 1-(6-bromopyridin-2-yl) cyclopropane-1-carboxylate (XXIIb)

[000160] A stirred solution of ethyl 2-(6-bromopyridin-2-yl) acetate **XXIIa** (4.2 g, 1 eq, 17 mmol) in DMF (25 mL) was cooled to 0° C sodium hydride (1.5 g, 60% Wt. 2.2 eq, 38 mmol) was added. To the resulting mixture 1,2-dibromoethane (7.1 g, 2.2 eq, 38 mmol) was added drop wise and stirred at rt for 4 hr. The reaction was monitored by TLC for the absence of starting material. To the reaction mixture (25 mL) ice cold water was added and the resulting mixture was extracted with ethyl acetate (25 mL x 2). The combined organic layer was given brine wash, dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford a pale brown viscous liquid. The crude compound was purified by silica gel (100-200; 24g) column chromatography using EtOAc (0-20%) in hexane. The peak eluted with 7% EtOAc in hexane was concentrated to afford the desired product **XXIIb** as a pale brown viscous liquid. Yield: 4.1 g, 88%. **LCMS** Calculated. for $C_{11}H_{12}BrNO_2$ is 271.00; Observed. 272.05 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.54 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 7.6

Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 1.67 (t, J = 4.4 Hz, 2H), 1.50 (t, J = 4.4 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H).

Step-3:Synthesis of Ethyl 1-(6-vinylpyridin-2-yl) cyclopropane-1-carboxylate (XXIIc)

[000161] A solution of ethyl 1-(6-bromopyridin-2-yl) cyclopropane-1-carboxylate **XXIIb** (2.8 g, 1 eq, 10 mmol), potassium trifluoro(vinyl)borate (1.7 g, 1.2 eq, 12 mmol) and potassium phosphate, tribasic (3.3 g, 1.3 mL, 1.5 eq, 16 mmol) in 1,4-dioxane (20 mL) was purged with N_2 gas for 15 min with vigorous stirring. To the reaction was added $PdCl_2$(dppf) (0.38 g, 0.05 eq, 0.52 mmol) and heated to 120 °C for 16 hours. The progress of the reaction was monitored by TLC analysis. The reaction was cooled to room temperature and reaction mixture was concentrated under reduced pressure. The residue was added water (70 mL) and the resulting mixture was extracted with ethyl acetate (50 mL x 2). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford a light brown viscous liquid. The crude compound was purified by combi-flash (230-400, 120 g packed) column chromatography using ethyl acetate in hexane and peak eluted with 5% EtOAc in hexane was concentrated to afford **XXIIc** as a light brown viscous liquid; Yield: 1 g, 40%. **LCMS** Calculated. for $C_{13}H_{15}NO_2$ is 217.11; Observed. 218.25 $[M+H]^+$ **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.58 (t, J = 7.6 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 6.78 (q, J = 6.4 Hz, 1H), 6.17 (dd, J = 17.4 & 1.6 Hz, 1H), 5.43 (dd, J = 11.0 & 1.2 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 1.65-1.63 (m, 2H), 1.56-1.53 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H).;

Step-4: Synthesis of Ethyl 1-(6-formylpyridin-2-yl) cyclopropane-1-carboxylate (XXIId)

[000162] To a solution of ethyl 1-(3-vinylphenyl) cyclopropane-1-carboxylate **XXIIc** (1 g, 1 eq, 5 mmol) in THF (18 mL) and water (40 mL) osmium tetra-oxide (4.68 mL, 2.5% Wt. in isobutanol, 0.1 eq, 0.5 mmol) was added and the reaction was stirred at rt for 30 min. Then sodium metaperiodate (1 g, 0.4 mL, 1.5 eq, 7 mmol) was added and the reaction was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. The mixture was diluted with water (50

mL) and extracted with EtOAc (50 mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to afford **XXIId** as brown viscous liquid. The crude was used in the next step without further purification. Yield: 0.95 g, 90 %). %. **LCMS** Calculated. for $C_{13}H_{14}O_3$ is 219.09; Observed. 220.20 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.02 (s, 1H), 7.3 (s, 3H), 4.18 (q, J = 7.2 Hz, 2H), 1.73-1.61 (m, 4H), 1.22 (t, J = 7.2 Hz, 3H).

Step-5: Synthesis of Ethyl (*E*)-1-(6-(2-nitrovinyl) pyridin-2-yl) cyclopropane-1-carboxylate (XXIIe)

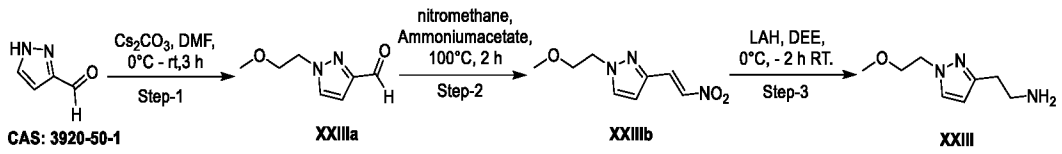
[000163] A stirred solution of ethyl 1-(6-formylpyridin-2-yl) cyclopropane-1-carboxylate **XXIId** (950 mg, 1 eq, 4.33 mmol) in DCM (20 mL) was cooled to 0 °C. To the resulting mixture nitromethane (317 mg, 280 µL, 1.2 eq, 5.20 mmol), triethylamine (2.19 g, 3.02 mL, 5 eq, 21.7 mmol) were added under N_2 gas. The resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure to afford a brown viscous liquid. The mixture was dissolved in fresh DCM (20 mL) and was cooled to 0 °C. Then triethylamine (2.19 g, 3.02 mL, 5 eq, 21.7 mmol) was added to the reaction and this was followed by a drop-wise addition of mesylchloride (1.49 g, 1.01 mL, 3 eq, 13.0 mmol) under N_2 gas. The reaction mixture was stirred at rt for 30 min. The progress of the reaction was monitored by TLC analysis which indicated completion of the reaction. The reaction mixture was concentrated under reduced pressure and water (15mL) was added and extracted with ethyl acetate (15 mL x 2). The combined organic layer was given brine wash, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to afford **XXIIe** as brown viscous liquid. The crude product was taken for next step without further purification. Yield: 1.0 g, 86 %. **LCMS** Calculated. for $C_{13}H_{14}N_2O_4$ is 262.10; Observed.263.20 $[M^+ + H]$

Step-6: Synthesis of (1-(6-(2-Aminoethyl) pyridin-2-yl) cyclopropyl) methanol (XXII)

[000164] To an ice-cold solution of $LiAlH_4$ (20 mL, 1M, 4 eq,) in dry diethyl ether (80 mL) solution was dropwise added a solution of ethyl (*E*)-1-(6-(2-nitrovinyl) pyridin-2-yl) cyclopropane-1-carboxylate **XXIIe** (1 g, 1 eq, 4 mmol) in dry diethyl ether (7 mL). The resulting mixture was stirred at rt for 1 hr. The reaction

was monitored by TLC analysis which indicated the completion of reaction. The reaction mixture was cooled to 0 °C and quenched water (2mL) followed by with 15% KOH solution (3mL). To the mixture was added ethyl acetate (100 mL) and stirred at rt for 20 min. The reaction mixture was filtered, and the residue was washed with 100 mL of ethyl acetate. The combined filtrate was concentrated under reduced pressure to afford a desired compound as pale brown viscous liquid **XXII**. The crude was used in the next step without further purification. Yield: 0.6 g, 80 %. **LCMS** Calculated. for $C_{11}H_{16}N_2O$ is 192.13; Observed. 193.25 $[M+H]^+$.**^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 7.52-7.50 (m, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 3.83 (d, J = 3.6 Hz, 4H), 3.13 (t, J = 6.8 Hz, 2H), 2.90 (t, J = 6.4 Hz, 2H); 1.05-1.01 (m, 2H) 0.90-0.85 (m, 2H).

Synthesis of 2-(1-(2-methoxyethyl)-1H-pyrazol-3-yl) ethan-1-amine (XXIII)



Step-1: Synthesis of 1-(2-methoxyethyl)-1H-pyrazole-3-carbaldehyde) XXIIIa.

[000165] 1-bromo-2-methoxyethane (5.2 g, 0.037mol) was added dropwise to a stirred solution of 1H-pyrazole-3-carbaldehyde (CAS: 3920-50-1: 3.0 g, 0.031mol) and CS_2CO_3 (20.0 g, 0.0624 mol) in DMF (50 mL) at 0°C. Then reaction mixture was stirred at rt for 3h. The progress of the reaction was monitored by TLC. Then the reaction mixture was diluted with water (500 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water (50 mL). the combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude product. Crude product obtained was purified by biotage column chromatography using silica gel (230-400 mesh) and the desired product was eluted at 5-20 % ethyl acetate in hexane to afford **XXIIIa** as colourless liquid Yield: 3.2 g, 66%. **LCMS** Calculated. for $C_7H_{10}N_2O$ is 154.17; Observed.155.2 $[M+H]^+$.**^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 9.97 (S, 1H), 7.54 (d, J = 1.6 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 4.38 (t, J =4.8 Hz, 2H), 3.78 (t, J =5.6 Hz, 2H), 3.34(S, 3H).

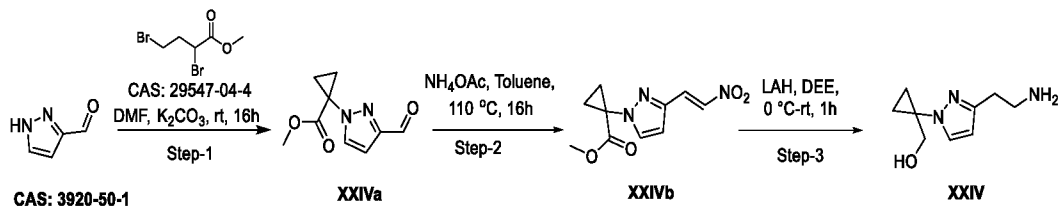
Step-2: Synthesis of (E)-1-(2-methoxyethyl)-3-(2-nitrovinyl)-1H-pyrazole XXIIIb.

[000166] A mixture of 1-(2-methoxyethyl)-1H-pyrazole-3-carbaldehyde **XXIIIa** (3.2 g, 0.019 mol), nitromethane (35 g, 31mL, 0.57 mol) and ammonium acetate (2.2 g, 0.029 mol) were taken in a round bottom flask and the reaction mixture was stirred at 100°C for 2 h. Then the progress of the reaction was monitored by TLC for the absence of staring material. The reaction mixture was evaporated under vacuum to get crude residue which was purified by biotage column chromatography using silica (230-400 mesh). The desired product was eluted at 5-20% ethyl acetate in hexane as eluent to afford desired product as colourless liquid **XXIIIb**. Yield: 2.4 g, 60%. **LCMS** Calculated. for $C_8H_{11}N_3O_3$ is 197.19; Observed.198.2 $[M+H]^+$.

Step-3: Synthesis of 2-(1-(2-methoxyethyl)-1H-pyrazol-3-yl) ethan-1-amine XXIII.

[000167] To a stirred solution of LAH 1.0M in THF (50mL, 0.048 mol) in diethyl ether (125 mL), was added (E)-1-(2-methoxyethyl)-3-(2-nitrovinyl)-1H-pyrazole **XXIIIb** (2.4g, 0.012mol) in THF (5 ml) at 0°C, under argon atmosphere. The reaction mixture was stirred at rt for 2 h. Then the progress of the reaction was monitored by TLC. The reaction mixture was quenched with water (2.4 ml) at 0°C followed by addition of 15% KOH solution (2.4 mL) and water (8 mL). Then the reaction mixture was filtered and washed the solid with ethyl acetate (3 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude **XXIII** as pale-yellow liquid. Yield: 1.5 g, 83% crude.

<u>Synthesis of (1-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclopropyl) methanol. (XXIV)</u>



Step-1: Synthesis of methyl 1-(3-formyl-1H-pyrazol-1-yl) cyclopropane-1-carboxylate (XXIVa)

[000168] Methyl 2,4-dibromobutanoate (CAS: 29547-04-4, 35 g, 0.14 mol) was added to the stirred solution of 1H-pyrazole-3-carbaldehyde (CAS: 3920-50-1, 10 g, 0.1 mol), K_2CO_3 (58 g, 0.42 mol) in DMF (100 mL) at 0°C. Then the reaction mixture was stirred at room temperature for 16 hours. Progress of the reaction was monitored by TLC analysis. Reaction mixture was quenched with cold water and extracted with ethyl acetate (2x 200 mL). The combined organic layer was washed with water (3x 100 mL) and followed by brine solution, dried over anhydrous sodium sulphate, and concentrated. The crude material was purified by combi-flash using 80g column, eluted with 0-25% ethyl acetate: hexane, to afford **XXIVa** as white solid. Yield: 13.5 g, 67%. **LCMS** Calculated. for $C_9H_{10}N_2O_3$ is 194.07; Observed. 195.15 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.97 (s, 1H), 7.58 (s,1H), 6.82 (s, 1H), 3.70 (d, J = 6.8 Hz, 3H), 1.93-1.90 (m, 2H), 1.73-1.70 (m, 2H).

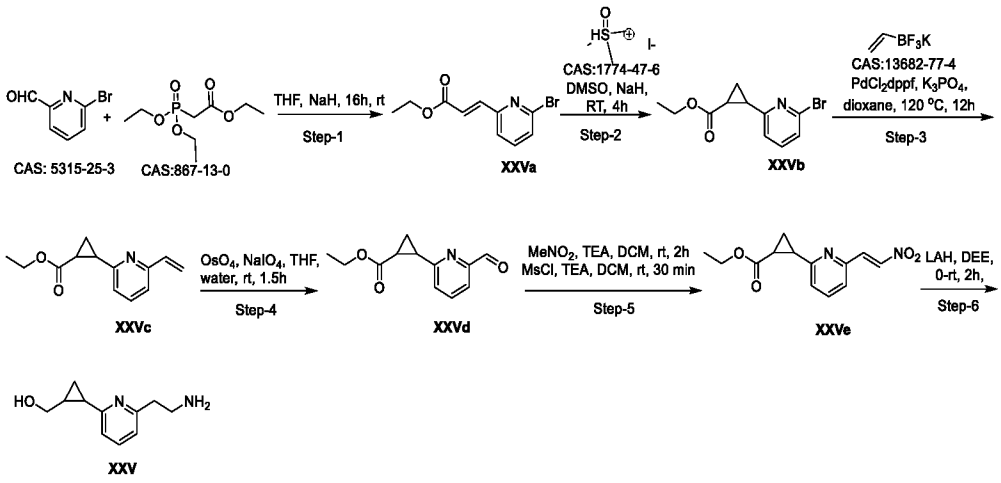
Step-2: Synthesis of methyl (E)-1(3-(2-nitrovinyl)-1H-pyrazol-1-yl) cyclopropane-1-carboxylate (XXIVb)

[000169] To a stirred solution of ethyl 1-(3-formyl-1H-pyrazol-1-yl) cyclopropane-1-carboxylate **XXIVa** (1 g, 0.0051 mol) in toluene (25 mL) was added ammonium acetate (0.6 g, 0.0077 mol) and nitromethane (3.1g, 0.051 mol), and the resulting mixture was stirred at 100 °C for 16 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was quenched with 1N HCl solution (20 mL), extracted with ethyl acetate (2x 20 mL). The combined organic layer was washed with brine solution (15 mL), dried over anhydrous sodium sulphate. Solvent was removed under vacuum. The crude compound was passed through flash column and eluted with 10-20% ethyl acetate in hexane to afford **XXIVb** as white solid. Yield: 1.2 g, 35%. **LCMS** Calculated. for $C_{10}H_{11}N_3O_4$ is 237.07; Observed. 238.15 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.95 (d, J = 13.6 Hz, 1H), 7.61 (d, J = 13.6 Hz, 1H), 7.57 (d, J = 2.4 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 3.7 (s, 3H), 1.91-1.87 (m, 2H), 1.7-1.66 (m, 2H).

Step-3: Synthesis of (1-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclopropyl) methanol (XXIV).

[000170] Methyl (E)-1(3-(2-nitrovinyl)-1H-pyrazol-1-yl) cyclopropane-1-carboxylate **XXIVb** (0.430 g, 0.0018 mol) in THF (5 mL) was added dropwise to a stirred solution of LAH (1M in THF, 7.25 ml, 0.0072 mol) in Et_2O (10 mL) at 0°C and stirred the reaction mixture for 1 hr at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to 0°C and quenched with water (0.4 mL) followed by 15% KOH solution (0.4 mL), water (1.2 mL) and the reaction mixture was stirred for 15-20 min. Reaction mixture was filtered and washed with EtOAc (3 x 20). The combined organic layer was dried over anhydrous sodium sulphate. Concentrated the solvent under reduced pressure to get pale yellow oil **XXIV**. Yield: 0.329 g, 93.8%. **LCMS** Calculated. for $C_9H_{15}N_3O$ is 181.24; Observed. 182.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-d6):** δ 7.40 (d, J = 2.4 Hz, 1H), 6.05 (d, J = 2.0 Hz, 1H), 3.74 (s, 3H), 2.98 (t, J = 6.8 Hz, 2H), 2.76 (t, J = 7.2 Hz, 2H), 1.26-1.23 (m, 2H), 1.09-1.08 (m, 2H).

Synthesis of (2-(6-(2-aminoethyl) pyridin-2-yl) cyclopropyl) methanol (XXV).



Step-1: Synthesis of ethyl (E)-3-(6-bromopyridin-2-yl) acrylate (XXVa)

[000171] To a suspension of sodium hydride (3.2 g, 55% wt, 1.35 eq, 73 mmol) in THF (300 mL) was dropwise added ethyl 2-(diethoxy phosphoryl) acetate (CAS:867-13-0, 15 g, 1.25 eq, 67 mmol) at 0 °C. After 30 min, solution of 6-bromopicolinaldehyde (10 g, 1 eq, 54 mmol) in 30 mL THF was added and the

reaction mixture was stirred at rt for 4h. the progress of reaction was monitored by TLC analysis. After completion of the reaction, the reaction was cooled to 0 °C and water (75 mL) was dropwise added. The resulting mixture was extracted with ethyl acetate (75 mL X 2). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the light brown viscous liquid. The crude compound was purified by silica gel (100-200; 150g) column chromatography using EtOAc (0-20%) in hexane. The peak eluted with 10% of EtOAc in hexane was concentrated to afford **XXVa** as an off white solid. Yield: 10 g, 73%. **LCMS** Calculated. for $C_{10}H_{10}BrNO_2$ is 254.99; Observed. 256.05 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.60-7.54 (m, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 15.2 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H.

Step-2: Synthesis of ethyl 2-(6-bromopyridin-2-yl) cyclopropane-1-carboxylate (XXVb)

[000172] To a solution of Trimethylsulfoxonium Iodide (CAS: 1774-47-6, 19 g, 2.2 eq, 86 mmol) in DMSO (140 mL) was added sodium hydride portion wise (2.2 g, 55% Wt. 1.3 eq, 51 mmol) and the resulting mixture was stirred for one hour at room temperature. A solution of ethyl (*E*)-3-(6-bromopyridin-2-yl) acrylate (10 g, 1 eq, 39 mmol) in mixture of DMSO (60 mL) and THF (60 mL) was slowly added to the reaction. The resulting mixture was stirred for four hours at room temperature. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, 1N HCl (10 mL) was added, and the reaction mixture extracted with diethyl ether (30 mL X 2). The combined organic layer was dried over anhydrous sodium sulphate, the solvent was removed under vacuo. The crude compound was passed through a plug of silica gel (100-200; 120g) in ethyl acetate in hexane (7%) to afford the desired compound **XXVb** as a colourless viscous liquid. Yield: 6.0 g, 60%. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.57-7.39 (m, 1H), 7.27-7.26 (m, 1H), 7.18 (d, J = 7.6 Hz, 1H), 4.25-4.12 (m, 2H), 2.58-2.51 (m, 2H), 2.29-2.25 (m, 2H), 1.34-1.23 (m, 3H)

Step-3: Synthesis of Ethyl 2-(6-vinylpyridin-2-yl) cyclopropane-1-carboxylate (XXVc)

[000173] A solution of ethyl 2-(6-bromopyridin-2-yl) cyclopropane-1-carboxylate (3.9 g, 1 eq, 14 mmol), Potassium Vinyl trifluoroborate (CAS: 13682-77-4, 2.1 g, 1.1 eq, 16 mmol) and potassium phosphate, tribasic (4.6 g, 1.8 mL, 1.5 eq, 22 mmol) in 1,4 dioxane (60 mL) was purged with N_2 gas for 15 min with vigorous stirring. To the reaction was added $PdCl_2$ (dppf) (0.53 g, 0.05 eq, 0.72 mmol) and the seal tube was closed and heated to 120 °C for 16 hours. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, it was cooled to room temperature and reaction mixture was concentrated under reduced pressure. To the residue obtained was added water (80 mL) and the resulting mixture was extracted with ethyl acetate (50 mL x 2). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford a light brown viscous liquid. The crude compound was purified by combi-flash (230-400, 120g packed) column chromatography using ethyl acetate in hexane and peak eluted with 5% EtOAc in hexane was concentrated to afford **XXVc** as a pale-yellow viscous liquid. Yield: 1.8 g, 57%. **LCMS** Calculated. for $C_{13}H_{15}NO_2$ is 217.11; Observed. 218.20 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.51 (t, J = 7.2 Hz, 1H), 7.10-7.07 (m, 2H), 6.78-6.68 (m,1H), 6.78-6.68 (m, 1H), 5.42-5.39 (m, 1H), 4.19-4.14 (m, 1H), 2.63-2.57 (m, 2H), 2.31-2.29 (m, 1H), 1.66-1.56 (m, 2H), 1.34-1.26 (m, 3H).

Step-4: Synthesis of ethyl 2-(6-formylpyridin-2-yl) cyclopropane-1-carboxylate (XXVd)

[000174] To a solution of ethyl 2-(6-vinylpyridin-2-yl) cyclopropane-1-carboxylate **XXVc** (1.6 g, 1 eq, 7.4 mmol) in THF (4.4 mL) and water (10 mL) a solution of osmium tetroxide (7.4 mL g, 2.5% wt% in isobutanol, 0.1 eq, 0.74 mmol) was added and the reaction was stirred at rt for 30 min. Then, sodium metaperiodate (2.4 g, 0.59 mL, 1.5 eq, 11 mmol) was added and the reaction was stirred at rt for 2 h. Then the progress of the reaction was monitored by TLC analysis

which indicated completion of the reaction. The mixture was diluted with water (35 mL) and extracted with EtOAc (30 mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to afford **XXVd** as brown viscous liquid. The crude product obtained was used as such in the next step without further purification. Yield: (1.56 g, 97 %). **LCMS** Calculated. for $C_{12}H_{13}NO_3$ is 219.09; Observed. 220.20 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.95 (s, 1H), 7.76-7.72 (m, 2H), 7.47-7.45 (m, 1H), 4.27-4.16 (m, 2H), 2.70-2.65 (m, 2H), 2.39-2.37 (m, 2H), 1.30-1.27 (m, 3H).

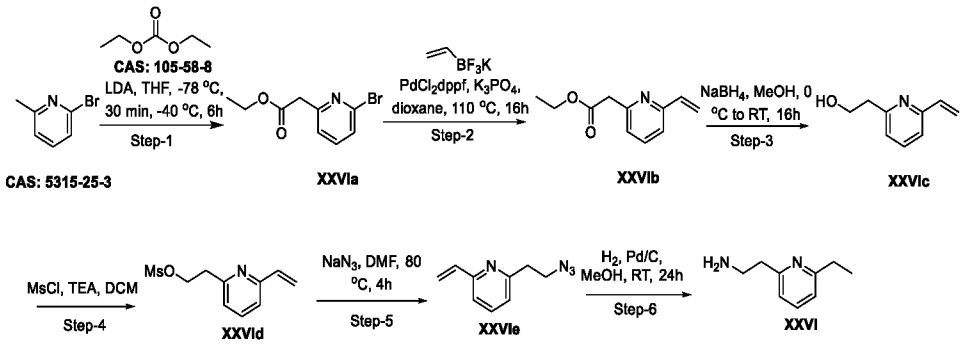
Step-5: Synthesis of ethyl (E)-2-(6-(2-nitrovinyl) pyridin-2-yl) cyclopropane-1-carboxylate (XXVe)

[000175] A stirred solution of ethyl 2-(6-formylpyridin-2-yl) cyclopropane-1-carboxylate **XXVd** (1.72 g, 1 eq, 7.85 mmol) in DCM (15 mL) was cooled to 0 °C. To the resulting mixture nitromethane (575 mg, 1.2 eq, 9.41 mmol) and triethylamine (2.19 mL, 2.0 eq, 15.7 mmol) were added under N_2 gas. The resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure to afford a brown viscous liquid. The mixture was dissolved in fresh DCM (10 mL) and was cooled to 0 °C. Then triethylamine (3.02 mL, 5 eq, 21.7 mmol) was added to the reaction and this was followed by a drop-wise addition of mesyl chloride (1.49 g, 1.01 mL, 3 eq, 13.0 mmol) under N_2 gas. The reaction mixture was stirred at rt for 30 min. The progress of the reaction was monitored by TLC analysis which indicated completion of reaction. The reaction mixture was concentrated under reduced pressure and water (15 mL) was added and extracted with ethyl acetate (15 mL x 2). The combined organic layer was given brine wash, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to afford **XXVe** as a brown viscous liquid. The crude was used in the next step without further purification. Yield: 1.87 g, 100 %.

Step-6: Synthesis of (2-(6-(2-Aminoethyl) pyridin-2-yl) cyclopropyl) methanol (XXV)

[000176] To a cooled $LiAlH_4$ (30 mL, 1M, 4 eq,) in dry diethyl ether (160 mL) using ice bath, was added dropwise a solution of ethyl (*E*)-2-(6-(2-nitrovinyl) pyridin-2-yl) cyclopropane-1-carboxylate (2 g, 1 eq, 8 mmol) in dry diethyl ether (7 mL). The resulting mixture was stirred at rt for 2 h. The reaction was monitored by TLC analysis which indicated the completion of reaction. The reaction mixture was cooled to 0 °C and quenched water (3 mL) followed by with 15% KOH solution (15 mL). To the mixture was added ethyl acetate (75 mL) and stirred at rt for 20 min. The reaction mixture was filtered, and the residue was washed with 100 mL of ethyl acetate. The combined filtrate was concentrated under reduced pressure to afford **XXV** as pale brown viscous liquid. The crude was used as such in the next step without further purification. Yield: 1.03 g, 100%. **LCMS** Calculated. for $C_{11}H_{16}N_2O$ is 192.13; Observed. 193.25 $[M+H]^+$.

Synthesis of 2-(6-ethylpyridin-2-yl) ethan-1-amine (XXVI)



Step-1: Ethyl 2-(6-bromopyridin-2-yl) acetate (XXVIa)

[000177] To a stirred solution of lithium diisopropylamide (110 mL, 2 molar, 220 mmol) in dry THF (500 mL) at -78 °C under inert atmosphere was dropwise added 2-bromo-6-methylpyridine (CAS:5315-25-3,15 g, 87 mmol) and the resulting mixture was stirred at -78 °C for 30 min. This was followed by an addition of diethyl carbonate (CAS: 105-58-8, 26 g, 220 mmol) mixture was stirred at -40 °C for 4 hours. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with saturated solution of NH_4Cl (150 mL), and the resulting mixture was extracted with ethyl acetate (170 mL x 2). The

combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford light brown viscous liquid. The crude compound was purified by silica gel (100-200) column chromatography using ethyl acetate (0-10%) in *n*-hexane. The peak eluted with 7% of ethyl acetate in *n*-hexane was concentrated to afford the desired product **XXVIa** as a colorless viscous liquid. Yield: 12.2g (57%); **LCMS** Calculated. for $C_9H_{11}BrNO_2$ is 246.00, Observed, 246.15; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.53 (t, *J*= 7.6 Hz, 1H), 7.40 (d, *J*= 8.0 Hz, 1H), 7.28 (t, *J*= 7.6 Hz, 1H), 4.19 (q, *J*= 7.2 Hz, 2H), 3.83 (s, 2H), 1.27 (t, *J*= 7.2 Hz, 3H).

Step-2: Ethyl 2-(6-vinylpyridin-2-yl) acetate (XXVIb)

[000178] A solution of ethyl 2-(6-bromopyridin-2-yl) acetate **XXVIa** (3 g, 10.0 mmol), potassium trifluoro(vinyl)borate (2 g, 11.0 mol) and potassium phosphate, tribasic (4 g, 20 mmol) in 1,4 dioxane (40 mL) was purged with N_2 gas for 15 min with vigorous stirring. To the reaction was added $PdCl_2$(dppf) (0.4 g, 0.6 mmol) and the seal tube was closed and heated to 120 °C for 16 hours. The progress of the reaction was monitored by TLC analysis. The reaction was cooled to room temperature and reaction mixture was concentrated under reduced pressure. The residue was added water (70 mL) and the resulting mixture was extracted with ethyl acetate (75 mL x 2). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford a light brown viscous liquid. The crude compound was purified by combi-flash (230-400) column chromatography using ethyl acetate in *n*-hexane and peak eluted with 3% ethyl acetate in hexane was concentrated to afford the desired compound **XXVIb** as a colorless viscous liquid. Yield: 2.0g (90%); **LCMS** Calculated. for $C_{11}H_{14}NO_2$ is 192.10, Observed, 192.25; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.62 (t, *J*= 7.6 Hz, 1H), 7.25 (d, *J*= 7.6 Hz, 1H), 7.17 (d, *J*= 7.6 Hz, 1H), 6.80 (q, *J*= 6.4 Hz, 1H), 6.19 (d, *J*= 17.6 Hz, 1H), 5.47 (d, *J*= 10.8 Hz, 1H), 4.19 (q, *J*= 7.2 Hz, 2H), 1.27 (t, *J*= 7.2 Hz, 3H).

Step-3: 2-(6-Vinylpyridin-2-yl) ethan-1-ol. (XXVIc)

[000179] To a stirred solution of ethyl 2-(6-vinylpyridin-2-yl) acetate **XXVIb** (2 g, 10.0 mmol) in methanol (30 mL) under nitrogen atmosphere was portion wise added at 0 °C sodium borohydride (2 g, 50 mmol). The resulting mixture was stirred

at 0 °C for 30 min and at room temperature for 6 h. The progress of the reaction was monitored by TLC analysis which indicates completion of reaction. To the reaction mixture saturated $NaHCO_3$ solution (50 mL) was added and extracted with ethyl acetate (75 mL x 2). The organic layer was given brine (35 mL) wash, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to afford **XXVIc** as colorless viscous liquid. The crude was taken for next step without further purification. Yield: 1.2 g (80%); **LCMS** Calculated. for $C_9H_{12}NO$ is 150.09, Observed, 150.00; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.59 (t, *J*= 7.6 Hz, 1H), 7.19 (d, *J*= 7.6 Hz, 1H), 7.02 (d, *J*= 8.0 Hz, 1H), 6.81-6.74 (m, 1H), 6.16 (d, *J*= 17.6 Hz, 1H), 5.47 (d, *J*= 10.8 Hz, 1H), 4.03 (t, *J*= 5.6 Hz, 2H), 3.01 (t, *J*= 5.6 Hz, 2H).

Step-4: 2-(6-Vinylpyridin-2-yl) ethyl methane sulfonate (XXVId)

[000180] To a stirred solution of 2-(6-vinylpyridin-2-yl) ethan-1-ol **XXVIc** (1.2 g, 8.0 mmol) in DCM (30 mL) triethylamine (4.5 mL, 32 mmol) was added under nitrogen atmosphere. The resulting mixture was cooled to 0 °C and mesyl-Cl (0.81 mL, 10.0 mmol) was drop wise added. The reaction mixture was stirred at 0 °C for 30 min. The progress of the reaction was monitored by TLC analysis which indicates completion of reaction. To the reaction mixture water (30 mL) was added and extracted with DCM (30 mL X 3). The organic layer was washed with brine (25mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to afford **XXVId** as brown viscous liquid. The crude was taken for next step without further purification. Yield: 1.7 g (93%); **LCMS** Calculated. for $C_{10}H_{14}NO_3S$ is 228.08, Observed, 228.20; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.60 (t, *J*= 7.6 Hz, 1H), 7.22 (d, *J*= 8.0 Hz, 1H), 7.08 (d, *J*= 8.0 Hz, 1H), 6.82-6.75 (m, 1H), 6.22 (d, *J*= 17.6 Hz, 1H), 5.48 (d, *J*= 10.8 Hz, 1H), 4.73-4.66 (m, 2H), 3.21 (t, *J*= 6.4 Hz, 2H), 2.88 (s, 3H).

Step-5: 2-(2-Azidoethyl)-6-vinylpyridine (XXVIe)

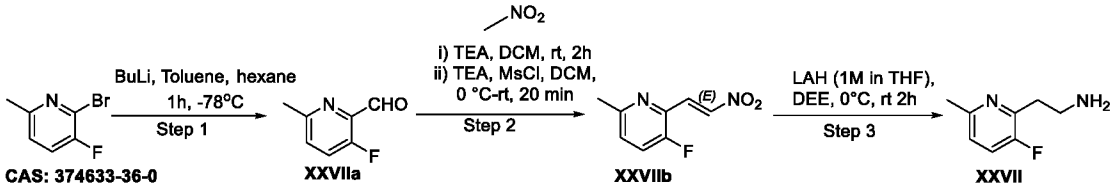
[000181] To a stirred solution of 2-(6-vinylpyridin-2-yl) ethyl methane sulfonate **XXVId** (1.7 g, 7.5 mmol) in DMF (20 mL) sodium azide (1.5 g, 22 mmol) was added under nitrogen atmosphere. The resulting mixture was stirred at 100 °C for 4h. The progress of the reaction was monitored by TLC analysis. After

completion of the reaction water (30 mL) was added and extracted with ethyl acetate (30 mL X 3). The organic layer was washed with brine (25mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to afford brown viscous liquid. The crude product was purified by combi-flash (silica gel 230-400) column chromatography using ethyl acetate (0-40%) in *n*-hexane. The peak eluted with 5% ethyl acetate was concentrated to afford the desired compound **XXVIe** as a colorless viscous liquid. Yield: 0.87 g (67%); **LCMS** Calculated. for $C_9H_{11}N_4$ is 175.10, Observed, 175.25; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.58 (t, *J*= 7.6 Hz, 1H), 7.21 (d, *J*= 7.6 Hz, 1H), 7.06 (d, *J*= 7.6 Hz, 1H), 6.84-6.77 (m, 1H), 6.22 (d, *J*= 17.6 Hz, 1H), 5.47 (d, *J*= 10.8 Hz, 1H), 3.74 (t, *J*= 6.8 Hz, 2H), 3.06 (t, *J*= 6.8 Hz, 2H).

Step-6: 2-(6-Ethylpyridin-2-yl) ethan-1-amine (XXVI)

[000182] In RB flask 2-(2-azidoethyl)-6-vinylpyridine **XXVIe** (0.87 g, 5.0 mmol) was dissolved in methanol (30 mL) and purged with nitrogen for 10 minutes. To this solution palladium on carbon (450 mg, 10%) was added. The reaction was evacuated and refilled with H_2 gas, this procedure was repeated for 3-4 times and the reaction was stirred at room temperature for 16 h maintaining H_2 atmosphere. The progress of reaction was monitored by TLC. After completion, the reaction mixture was filtered through a celite bed and washed with fresh methanol. The combined filtrate was concentrated under vacuo to afford the desired compound **XXVI** as a pale-yellow viscous liquid which was taken for the next step without further purification. Yield: 0.67 g (89%); **LCMS** Calculated for $C_9H_{15}N_2$ is 151.13, Observed, 151.25; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.54-7.46 (m, 1H), 7.01-6.94 (m, 2H), 3.09-2.73 (m, 6H), 1.28 (m, 3H).

Synthesis of 2-(3-fluoro-6-methylpyridin-2-yl) ethan-1-amine (XXVII)



Step-1: 3-Fluoro-6-methylpicolinaldehyde (XXVIIa)

[000183] A two neck RB flask equipped with two way stop-cock, septum and magnetic bar was charged with 2-bromo-3-fluoro-6-methylpyridine (CAS: 374633-36-0; 1.66 g, 8.74 mmol) and dry toluene (10 mL) under N_2 at RT. The resulting mixture was cooled to -78 °C and *n*-butyllithium (3.5 mL, 2M in THF, 8.74 mmol) was added dropwise and stirred the reaction mixture maintaining temperature -78 °C under proper N_2 atmosphere. This was followed by slow addition of dry DMF (1.92 g, 26.2 mmol) at -78°C under N_2 atmosphere. The reaction was stirred at -78 °C under N_2 atmosphere for additional one hour and at -50 °C for 2h. The progress of the reaction was monitored by TLC analysis. The reaction was quenched by slow addition sat. ammonium chloride solution at -78 °C. The resulting mixture was extracted with ethyl acetate (10 mL × 3). The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get the crude brown semi-solid. The crude was subjected to silica gel (230-400 mesh) column chromatography purification using 0-10% ethyl acetate in *n*-hexane to afford the desired compound **XXVIIa** as off-white solid. Yield: 0.175g (14.4%); **LCMS** Calculated. for C_7H_7FNO is 140.05, Observed, 140.25; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.19 (s, 1H), 7.49-7.38 (m, 2H), 2.64 (s, 3H).

Step-2: (E)-3-fluoro-6-methyl-2-(2-nitrovinyl) pyridine (XXVIIb)

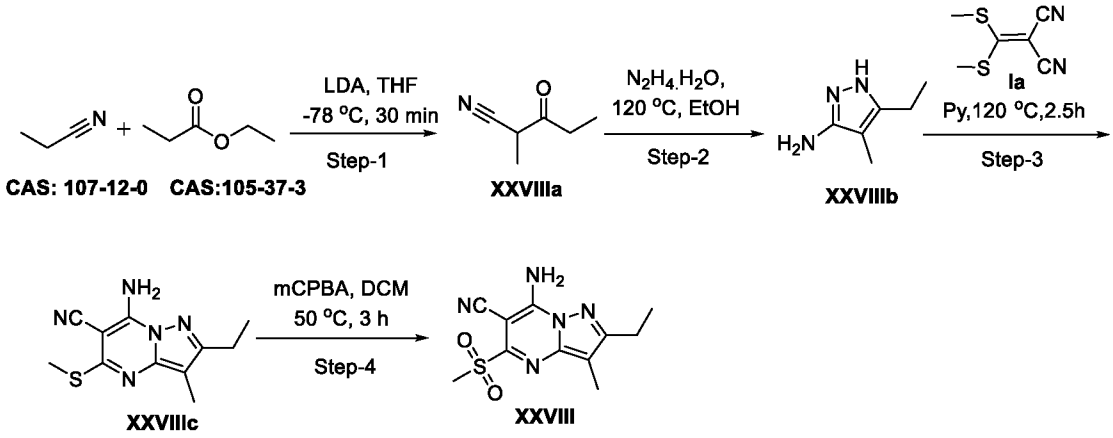
[000184] To a solution of 3-fluoro-6-methylpicolinaldehyde **XXVIIa** (0.4 g, 3 mmol) in DCM (4 mL) under N_2 at room temperature were added triethylamine (0.6 g, 6 mmol) and nitromethane (0.2 mL, 3 mmol) under N_2. The reaction was stirred at RT for 30 min and the progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated to dryness under *vacuo* and the residue was dissolved in fresh dry DCM (4 mL). The mixture was cooled to 0 °C under N_2 atmosphere and TEA (1 mL, 9 mmol) was added. This was followed by slow addition of mesyl chloride (0.7 mL, 9 mmol) at 0 °C under N_2. The reaction was stirred at room temperature for 1h under N_2 at RT. The progress of the reaction was monitored by TLC analysis. After completion, water (10mL) was added, and the resulting mixture was extracted with DCM (5 mL × 3). The combined organic layer was given brine wash, dried over anhydrous sodium

sulphate, and concentrated under reduced pressure to get the brown semisolid. The crude was subjected to silica gel column (230-400) chromatography using 0-10 % ethyl acetate in *n*-hexane to afford the desired compound **XXVIIb** as a colorless viscous liquid. Yield: 93 mg (20%); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.15 (d, *J*= 13.2 Hz, 1H), 8.04 (d, *J*= 13.6 Hz, 1H), 7.39 (t, *J*= 9.2 Hz, 1H), 7.25 (t, *J*= 3.6 Hz, 1H), 2.57 (s, 3H).

Step-3: 2-(3-fluoro-6-methylpyridin-2-yl) ethan-1-amine (XXVII)

[000185] To a two neck 100 mL round bottom flask was charged with dry diethyl ether under N_2 and the solvent was cooled to 0 °C. To this was added LAH (1 mL, 2M in THF, 2.0 mmol) followed by an addition of solution of 1(*E*)-3-fluoro-6-methyl-2-(2-nitrovinyl) pyridine **XXVIIb** (93 mg, 0.51 mmol) in dry diethyl ether: THF (1:1, 2 mL). The resulting mixture was stirred 1 h at RT under N_2. The progress of the reaction was monitored using TLC analysis. After completion, the reaction was cooled to 0°C and quenched with water (0.2 mL) and ethyl acetate (5 mL). The solution was filtered through celite bed. Bed was given wash with ethyl acetate followed by 10% MeOH in DCM. The combined filtrate was dried over anhydrous sodium sulphate and concentrated under *vacuo* to get **XXVII** as brown semisolid crude material. The crude product obtained was taken for the next step without further purification. Yield: 47 mg (60%).

Synthesis of 7-amino-2-ethyl-3-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (XXVIII)



Step-1: 2-methyl-3-oxopentanenitrile (XXVIIIa)

[000186] To a stirred solution of lithium diisopropylamide (110 mL, 2 M, 60 mmol) in dry THF (56 mL) at -78 °C under inert atmosphere was dropwise added propionitrile (CAS: 107-12-0; 4 mL, 60 mmol) and the resulting mixture was stirred at -78 °C for 1 h. This was followed by an addition of ethyl propionate (CAS: 105-37-3; 6 mL, 50 mmol) and the reaction was stirred at -78 °C for additional 1 hour. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with saturated solution of NH_4Cl (20 mL), and the resulting mixture was extracted with ethyl acetate (50 mL x 2). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford as light brown viscous liquid. The crude compound was purified by silica gel (100-200) column chromatography using ethyl acetate (0-10%) in *n*-hexane. The peak eluted with 7% of ethyl acetate in *n*-hexane was concentrated to afford the desired product **XXVIIIa** as a colorless viscous liquid. The crude was taken for next step without further purification. Yield: 4.3g (71%).

Step-2: 5-ethyl-4-methyl-1H-pyrazol-3-amine (XXVIIIb)

[000187] To a stirred solution of 2-methyl-3-oxopentanenitrile **XXVIIIa** (4.3 g, 39 mmol) in ethanol (4 mL) was added hydrazine hydrate (1:1) (2.9 g, 58 mmol) at room temperature and the reaction mixture was stirred at 120 °C for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was cooled to room temperature and concentrated to remove solvent. Obtained residue was dissolved in water (50 mL) and extracted with 10% methanol in DCM (100 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated to afford the desired product **XXVIIIb** as a yellowish viscous liquid. The crude was taken for next step without further purification. Yield: 5.4 g (69 %).

Step-3: 7-amino-2-ethyl-3-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (XXVIIIc).

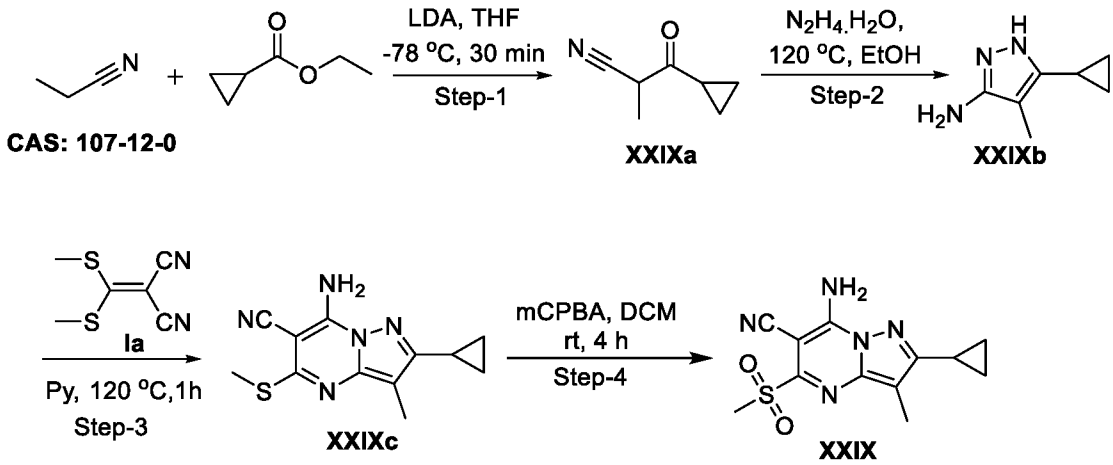
[000188] To a stirred solution of 5-ethyl-4-methyl-1H-pyrazol-3-amine **XXVIIIb** (5.4 g, 32 mmol) in pyridine (30 mL) was added 2-(bis (methylthio) methylene) malononitrile **Ia** (4.0 g 32 mmol). Then reaction mixture was stirred at

120 °C for 3 hours. The progress of the reaction was monitored by TLC. After completion, reaction mixture was cooled to room temperature then poured into ice cold water (100 mL). The formed solid was filtered and washed with ice cold water. solid was dried under vacuum to afford the desired product **XXVIIIc** as an off-white solid. The crude was taken for next step without further purification. Yield: 5.3 g (68 %); **LCMS** Calculated. for $C_{11}H_{14}N_5S$ is 248.32, Observe, 248.20; [M+H] $^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.19 (bs, 2H), 2.75 (q, *J*= 7.6 Hz, 2H), 2.62 (s, 3H), 2.19 (s, 3H), 1.3 (t, *J*= 7.6 Hz, 3H).

Step-4: 7-amino-2-ethyl-3-methyl-5-(methylsulfonyl)-1,2-dihydropyrazolo[1,5-a] pyrimidine-6-carbonitrile (XXVIII).

[000189] To a stirred solution of 7-amino-2-ethyl-3-methyl-5-(methylthio)-1,2-dihydropyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXVIIIc** (5.4 g, 22 mmol) in DCM (60 mL) was portion wise added *m*CPBA (15 g, 87 mmol) at 0 °C under inert atmosphere. The resulting mixture was stirred at room temperature for 4 hours. The progress of reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched with $NaHCO_3$ (50 mL) and extracted with DCM (50 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired product **XXVIII** as an off-white solid. The obtained solid was washed with *n*-hexane (10 mL X 2). The crude solid was taken for next step without further purification. Yield: 1.0 g (18%); **LCMS** Calculated. for $C_{11}H_{16}N_5O_2S$ is 282.33, [M+H] $^+$, Observed, 280.25; $[M+H]^{-2}$

Synthesis of 7-amino-2-cyclopropyl-3-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile. (XXIX)



Step-1: 3-cyclopropyl-2-methyl-3-oxopropanenitrile (XXIXa)

[000190] To a stirred solution of LDA (30 mL, 2 M, 50 mmol) in dry THF (70 mL) at -78 °C under inert atmosphere was added a solution of propenonitrile (CAS:107-12-0; 3 g, 50 mmol) in THF (20 mL) and the resulting mixture was stirred at -78 °C for 1 h. This was followed by an addition of ethyl cyclopropane carboxylate (6 g, 50 mmol) and the mixture was stirred at -70 °C for 1 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with saturated solution of NH_4Cl (50 mL) and the resulting mixture was extracted with ethyl acetate (50 mL x 3) The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford **XXIXa** as light brown viscous liquid. The crude compound was used as such in the next step without further purification. Yield: 4.5g (70%).

Step-2: 5-cyclopropyl-4-methyl-1H-pyrazol-3-amine (XXIXb)

[000191] To a stirred solution of 3-cyclopropyl-2-methyl-3-oxopropanenitrile **XXIXa** (4.2 g, 34 mmol) in ethanol (50 mL) was added hydrazine hydrate (3.3 mL, 50% Wt., 34 mmol) and the reaction mixture was heated at 90 °C for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to rt and evaporated under reduced pressure. The residue obtained was diluted with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material **XXIXb** obtained was used

as such in the next step without further purification. Yield: 4.2 g (90%); **LCMS** Calculated. for $C_7H_{12}N_3$ is 138.20, Observed, 138.25; $[M+H]^+$

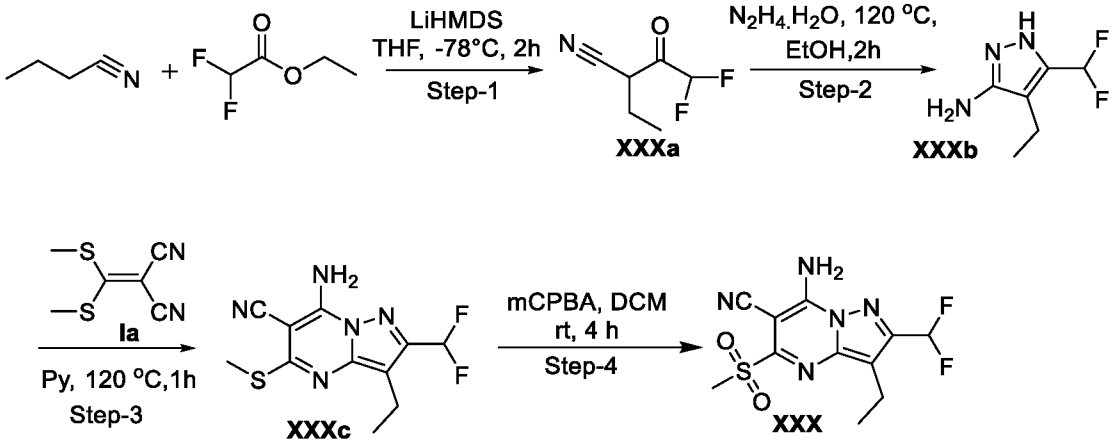
Step-3: 7-amino-2-cyclopropyl-3-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitile (XXIXc)

[000192] To a stirred solution of 2-(bis(methylthio)methylene) malononitrile **Ia** (5.2 g, 31 mmol) in pyridine (35 mL) was added 5-cyclopropyl-4-methyl-1H-pyrazol-3-amine **XXIXb** (4.2 g, 31 mmol) and the reaction mixture was heated at 120 °C for 1 h under N_2 atmosphere. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt and poured into ice cold water (50 mL). The precipitate formed was filtered, dried, and washed with cold mixture of ethyl acetate (10%) and *n*-hexane (90%), dried under *vacuo* to afford the desired compound as a pale-yellow solid. The crude compound **XXIXc** obtained was taken for the next step without further purification. Yield: 4.1g (52%); **LC_MS** Calculated. for $C_{12}H_{14}N_5S$ is 260.34, Observed, 260.20; $[M+H]^+$

Step-4: 7-amino-2-cyclopropyl-3-methyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile (XXIX)

[000193] To a solution of 7-amino-2-cyclopropyl-3-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXIXc** (1 g, 4 mmol) in DCM (20 mL) at 0 °C under N_2 atmosphere was added *m*CPBA (4 g, 60% Wt., 20mmol) and the resulting mixture was stirred at rt for 4 h. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, added sat. $NaHCO_3$ solution (50 ml) and the mixture was stirred vigorously for 15 min. The organic layer was separated and given fresh wash of sat. $NaHCO_3$ solution (50 mL X 3). The organic layers were separated, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under *vacuo* to afford the desired compound as a pale-yellow solid. The compound **XXIX** was used in the next step without further purification. Yield: 0.35g (30%); **LC_MS** Calculated. for $C_{12}H_{14}N_5O_2S$ is 292.34, Observed, 292.20; $[M+H]^+$

Synthesis of 7-amino-2-(difluoro methyl)-3-ethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (XXX)



Step-1: 2-ethyl-4,4-difluoro-3-oxobutanenitrile (XXXa)

[000194] To a solution of LiHMDS (2.4 g, 14 mmol) in THF (200 mL) at -78 °C under inert atmosphere was drop wise added butyronitrile (1.0 g, 14 mmol) in THF (4 mL) and the reaction mixture was stirred at -78 °C for 1 h. This was followed by a dropwise addition of ethyl 2,2-difluoroacetate (1.6 g, 13 mmol) at -78 °C and the reaction mixture was stirred for 2 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was cooled to 0 °C and quenched with saturated solution of ammonium chloride (5 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude was purified by silica gel (230-400 mesh) column chromatography using 0-10% ethyl acetate in *n*-hexane to afford the desired compound **XXXa** as a light brown viscous liquid. Yield: 1.2 g (57%); **LC_MS** Calculated. for $C_6H_6F_2NO$ is 147.11, Observed, 146.12; $[M-H]^-$.

Step-2: 5-(difluoro methyl)-4-ethyl-1H-pyrazol-3-amine (XXXb)

[000195] To a stirred solution of 2-ethyl-4,4-difluoro-3-oxobutanenitrile **XXXa** (1.2 g, 8.2 mmol) in ethanol (40 mL) was added hydrazine hydrate (1:1) (0.49 g, 9.8 mmol) at room temperature and the reaction mixture was stirred at 120 °C for 2 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, reaction mixture was cooled to room temperature and concentrated to remove the solvent. The obtained residue was dissolved in water (30 mL) and extracted with 10% methanol in DCM (50 mL x 2). The combine

organic layer was dried over anhydrous sodium sulphate and concentrated to get crude material **XXXb**. The crude was taken for next step without further purification. **LCMS** Calculated. for $C_6H_9F_2N_3$ is 161.15 Observed. 160.10; $[M-H]^-$.

Step-3: 7-amino-2-(difluoro methyl)-3-ethyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (XXXc)

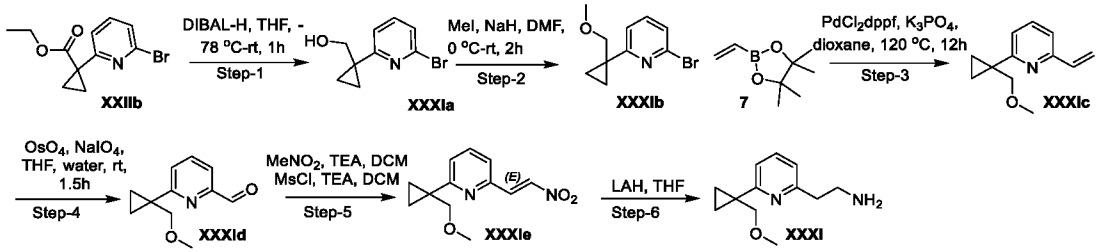
[000196] To a stirred solution of 5-(difluoro methyl)-4-ethyl-1H-pyrazol-3-amine **XXXb** (0.6 g, 4 mmol) in pyridine (2 mL) was added 2-(bis(methylthio)methylene) malononitrile **Ia** (0.8 g, 4 mmol) and the reaction mixture was heated at 120 °C for 2.5 h (using the guard tube). The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt and poured into ice cold water (100 mL). The precipitate formed was filtered and washed with cold water. The solid obtained was dried and azeotrope with toluene to yield the title compound as a pale-yellow solid. The crude was purified by silica gel (230-400) column chromatography by using 0-30 % ethyl acetate in *n*-hexane afford the desired compound **XXXc** as a pale-yellow solid. Yield: 0.5 g (50%); **LCMS** Calculated. for $C_{11}H_{11}F_2N_5S$ is 283.29, Observed, 284.20; $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.77 (s, 1H), 6.30 (s, 2H), 2.87-2.81 (m, 2H), 2.64 (s, 3H), 1.29 (t, *J*=8.0 Hz 3H).

[000197] Step-4: 7-amino-2-(difluoro methyl)-3-ethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (XXX)

[000198] To a stirred solution of 7-amino-2-(difluoro methyl)-3-ethyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXXc** (0.5 g, 2 mmol) in DCM (50 ml) at 0 °C was added mCPBA (1 g, 7 mmol) slowly and the reaction mixture was stirred at rt for 2h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with aq. $NaHCO_3$ (50 ml) and extracted with DCM (50 ml x 3). The organic layer was dried with Na2SO4, filtered, and evaporated under reduced pressure. Crude product **XXX** was taken for next step without further purification. Yield: 0.3 g (50%); LC_MS Calculated. for $C_{11}H_{11}F_2N_5O_2S$ is 315.28, Observed, 316.20; [M+H] +. 1H NMR

(400 **MHz, $CDCl_3$):** δ 9.53 (s, 2H), 7.31 (s, 1H), 3.33 (s, 3H), 2.84-2.78 (m ,2H), 1.23 (t, *J*=8 Hz 3H).

Synthesis of 2-(6-(1-(methoxymethyl) cyclopropyl) pyridin-2-yl) ethan-1-amine (XXXI)



Step-1: (1-(6-bromopyridin-2-yl) cyclopropyl) methanol (XXIIa)

[000199] To a solution of ethyl 1-(6-bromopyridin-2-yl) cyclopropane-1-carboxylate **XXIIb** (2.2 g, 8.1 mmol) in THF (88 mL) at 0 °C was added DIBAL-H (18 mL, 1 M, 18 mmol) under N2 atmosphere and the resulting mixture was stirred at 0°C for 30 min. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was quenched with saturated solution of NH_4Cl (25 mL) and added ethyl acetate (50 ml). The resulting solid was filtered through a celite bed and washed with ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure to afford the desired compound **XXXIa** as a pale-yellow viscous liquid. Yield: 1.68 g (90%); **LCMS** Calculated. for $C_9H_{10}BrNO$ is 228.08, Observed, 230.10; $[M+H]^+$; **^{1}H NMR (400 MHz, dmso-d6):** δ 7.64 (t, *J*= 8 Hz, 1H), 7.53 (d, *J*= 8.0 Hz, 1H), 7.38 (d, *J*= 8 Hz, 1H), 4.82 (t, *J*= 8 Hz, 1H), 3.71(d, *J*= 8 Hz 2H), 1.07-1.04(m, 2H), 0.94-0.91(m,2H).

[000200] **Step-2: 2-bromo-6-(1-(methoxymethyl)cyclopropyl) pyridine (XXXIb)**

[000201] To a stirred solution of (1-(6-bromopyridin-2-yl) cyclopropyl) methanol **XXXIa** (1.68 g, 7.37 mmol) in DMF (10 mL) at 0 °C under inert atmosphere was added sodium hydride (482 mg, 55% Wt., 11.0 mmol) and the resulting mixture was stirred at 0 °C for 5 min. This was followed by an addition of methyl iodide (0.55 mL, 8.84 mmol) and mixture was stirred at rt for 30 min. The progress of the reaction was monitored by TLC analysis. After completion, the

reaction was quenched with ice cold water (20 mL) and the resulting mixture was extracted with ethyl acetate (20 mL x 2). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford **XXXIb** as light brown viscous liquid. The crude was taken for next step without further purification. Yield: 1.79 g (99%); **LCMS** Calculated. for $C_{10}H_{12}BrNO$ is 242.12, Observed, 242.15; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.42 (t, *J*= 8 Hz, 1H), 7.35 (d, *J*= 4 Hz, 1H), 7.23 (t, *J*= 8.0 Hz, 1H), 3.65 (S, 2H), 3.4 (S, 3H), 1.63-1.31 (m, 2H),1.26-0.96 (m,2H)

Step-3: 2-(1-(methoxymethyl) cyclopropyl)-6-vinylpyridine (XXXIc)

[000202] To a solution of 2-bromo-6-(1-(methoxymethyl) cyclopropyl) pyridine **XXXIb** (0.8 g, 3 mmol) in 1,4-Dioxane (15 mL) was added vinyl boronic acid pinacol ester (0.6 mL, 4 mmol) and tri potassium phosphate (1 g, 7 mmol) , purged with N2 gas for 15 min with vigorous stirring. This was followed by an addition of PdCl2(dppf) (0.1 g, 0.2 mmol) and heated to 120 °C for 16 h. The progress of the reaction was monitored by TLC analysis. The reaction was cooled to room temperature and reaction mixture was concentrated under reduced pressure. Then added water (70 mL) and the resulting mixture was extracted with ethyl acetate (50 mL x 2). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford a light brown viscous liquid. The crude compound was purified by combi-flash (230-400, 120g packed) column chromatography using ethyl acetate in hexane and peak eluted with 5% ethyl acetate in hexane was concentrated to afford the desired compound **XXXIc** as an off-white solid. Yield: 0.42 g (70%); **LCMS** Calculated. for $C_{12}H_{15}NO$ is 189.26, Observed, 190.25; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.55-7.51 (m, 2H), 7.06 (d, *J*= 4 Hz, 1H), 6.74 (t, *J*= 8 Hz, 1H), 6.18 (d, *J*=16 Hz 1H), 5.38 (d, *J*=8 Hz 1H), 3.72 (S, 2H),3.40 (S, 3H),1.35(d, *J*= 4 Hz, 2H), 0.93(t, *J*= 4 Hz, 2H),

Step-4: 6-(1-(methoxymethyl) cyclopropyl) picolinaldehyde (XXXId)

[000203] To a solution of 2-(1-(methoxymethyl) cyclopropyl)-6-vinylpyridine **XXXIc** (0.425 g, 2.25 mmol) in THF (9 mL) and water (20 mL), a solution of osmium tetroxide (0.06 mL, 1.12 mmol) was added, and the reaction was stirred at rt for 30 min. This was followed by an addition of sodium periodate

(720 mg, 3.37 mmol) and the reaction was stirred at rt for 1 h. The mixture was diluted with water (20mL) and extracted with ethyl acetate (20mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to afford **XXXId** as brown viscous liquid. The crude was taken for next step without further purification. Yield: 290 mg (67.5%); **LCMS** Calculated. for $C_{11}H_{14}NO_2$ is 191.23, Observed, 192.25; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.97 (S, 1H), 7.76-7.71 (m, 2H), 7.63 (d, *J*= 8.0 Hz, 1H), 3.74 (S, 2H), 3.43(S, 3H), 1.43 (t, *J*= 4 Hz, 2H), 1.02 (t, *J*= 4 Hz, 2H).

Step-5: (E)-2-(1-(methoxymethyl) cyclopropyl)-6-(2-nitrovinyl) pyridine (XXXIe)

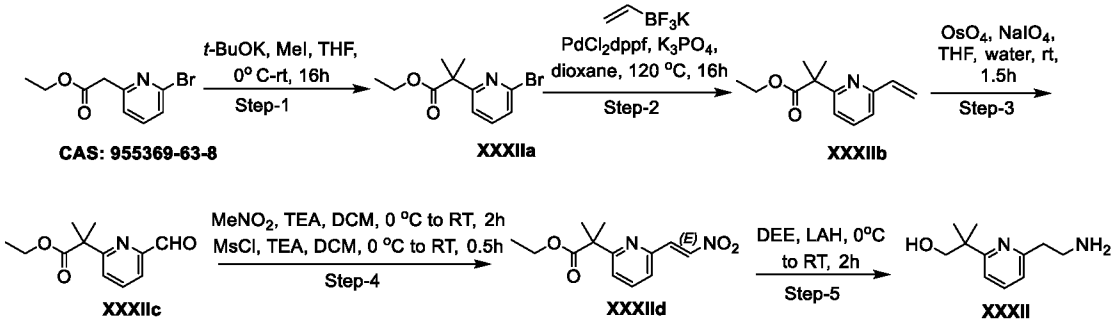
[000204] To a solution of 6-(1-(methoxymethyl) cyclopropyl) picolinaldehyde **XXXId** (0.6 g, 3 mmol) in DCM (12 mL) at 0 °C under inert atmosphere was added nitromethane (0.2 mL, 4 mmol), triethylamine (2 mL, 20mmol) and the resulting mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After the completion of (CHO-OH), DCM was evaporated under reduced pressure to afford a brown viscous liquid. To this added mesyl-Cl (0.7 mL, 9 mmol) and triethylamine (2 mL, 20mmol) drop wise in DCM (10 mL) under N_2 gas at 0 °C. The reaction mixture was stirred at rt for 30 min. The progress of the reaction was monitored by TLC analysis which indicated completion of the reaction. The reaction mixture was concentrated under reduced pressure. Added water (10 mL) and extracted with ethyl acetate (10 mL * 2). The combined organic layer was given brine wash and concentrated under reduced pressure to afford **XXXIe** a brown viscous liquid. The crude was taken for next step without further purification. Yield: 0.7g (99%); **LCMS** Calculated. for $C_{12}H_{15}N_2O_3$ is 234.26, Observed, 235.25; $[M+H]^+$.

Step-6: 2-(6-(1-(methoxymethyl) cyclopropyl) pyridin-2-yl) ethan-1-amine (XXXI)

[000205] To a solution of $LiAlH_4$ (0.06 g, 2 mmol) in dry diethyl ether (20 mL) at 0 °C under inert atmosphere was added (*E*)-2-(1-(methoxymethyl) cyclopropyl)-6-(2-nitrovinyl) pyridine **XXXIe** (0.4 g, 2 mmol) in dry diethyl ether (7 mL) and the resulting mixture was stirred at rt for 1 h. The progress of the

reaction was monitored by TLC analysis. After completion of the reaction, the reaction mixture was cooled to 0°c and quenched with water(1mL). To the resulting mixture 15% KOH solution was added and stirred for 10 min. Added ethyl acetate (25 ml) and stirred at rt for 20 min. The resulting mixture was filtered through a celite bed and the residue was washed with ethyl acetate (50 ml x 4). The combined filtrate was concentrated under reduced pressure to afford a desired compound **XXXI** as a pale brown viscous liquid. The crude was taken for next step without further purification. Yield: 0.34g (99%).

Synthesis of 2-(6-(2-aminoethyl) pyridin-2-yl)-2-methylpropan-1-ol. (XXXII)



Step-1: Ethyl 2-(6-bromopyridin-2-yl)-2-methylpropanoate (XXXIIa)

[000206] A solution of ethyl 2-(6-bromopyridin-2-yl) acetate (CAS: 955369-63-8; 1 g, 4 mmol) in THF (15 mL) was cooled to 0 °C and potassium *tert*-butoxide (1 g, 10 mmol) was added and the resulting mixture was stirred for 30 min under N_2 atmosphere. Then methyl iodide (1 mL, 20 mmol) was drop wise added and reaction mixture was stirred at RT for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated under reduced pressure and water (25 mL) was added. The solution was extracted with ethyl acetate (25 mL x 2). The combined organic layer was dried over anhydrous sodium sulphate and concentrated reduced pressure to afford a light brown viscous liquid. The crude compound was subjected to silica gel (200-300) column chromatography using 0-10% ethyl acetate in *n*-hexane to afford the desired compound **XXXIIa** as colorless viscous liquid. Yield: 1.18g (100%); **LCMS** Calculated. for $C_{11}H_{15}BrNO_2$ is 274.03, Observed, 274.15; $[M+H]^+$.

Step-2: Ethyl 2-methyl-2-(6-vinylpyridin-2-yl) propanoate (XXXIIb)

[000207] A solution of ethyl 2-(6-bromopyridin-2-yl)-2-methylpropanoate **XXXIIa** (1 g, 4 mmol), potassium trifluoro(vinyl)borate (0.5 g, 4 mmol) and potassium phosphate tribasic (1 g, 6 mmol) in 1,4 dioxane (20 mL) was purged with N_2 gas for 15 min with vigorous stirring. To the reaction was added $PdCl_2$(dppf) (0.1 g, 0.2 mmol) and the seal tube was closed and heated to 120 °C for 16 h. The progress of the reaction was monitored by TLC analysis. The reaction was cooled to room temperature and reaction mixture was concentrated under reduced pressure. To the residue was added water (70 mL) and the resulting mixture was extracted with ethyl acetate (50 mL x 2). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford a light brown viscous liquid. The crude compound was purified by combi-flash silica gel (230-400,) column chromatography using ethyl acetate in *n*-hexane and the peak eluted with 5% ethyl acetate in *n*-hexane was concentrated to afford the desired compound **XXXIIb** as an off-white solid. Yield: 0.73g (90%); **LCMS** Calculated. for $C_{13}H_{17}NO_2$ is 220.17, Observed, 220.20; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.59 (t , *J*=7.6 Hz, 1H), 7.15-7.13 (m, 2H), 6.25 (d, *J* = 17.6 Hz, 1H), 5.42 (d , *J*=10.8 Hz, 1H), 4.16 (q, *J*=7.2 Hz, 2H), 1.57 (s, 6H), 1.18 (t , *J*=7.2 Hz, 3H).

Step-3: ethyl 2-(6-formylpyridin-2-yl)-2-methylpropanoate (XXXIIc)

[000208] To a solution of ethyl 2-methyl-2-(6-vinylpyridin-2-yl) propanoate **XXXIIb** (0.73 g, 3.3 mmol) in THF (14 mL) and water (25 mL) and a solution of osmium tetroxide (680 µL, 0.33 mmol) 2.5%wt in isopropanol was added and the reaction was stirred at room temperature for 30 min. Then, Sodium metaperiodate (1.1 g, 5.0 mmol) was added and the reaction was stirred for additional 1 h. The mixture was diluted with water (15 mL) and extracted with ethyl acetate (15 mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to afford **XXXIIc** the brown viscous liquid. The crude was taken for the next step without further purification. Yield: 0.503g (68%); **LCMS** Calculated. for $C_{12}H_{16}NO_3$ is 222.12, Observed, 222.20; $[M+H]^+$; **^{1}H NMR**

(400 MHz, $CDCl_3$): δ 10.03 (s, 1H), 7.83 (d , *J*=3.6 Hz, 2H), 7.53 (t , *J*=4.4 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 1.57 (s, 6H), 1.20 (t , *J*=7.2 Hz, 3H).

Step-4: Ethyl (E)-2-methyl-2-(6-(2-nitrovinyl) pyridin-2-yl) propanoate (XXXIId)

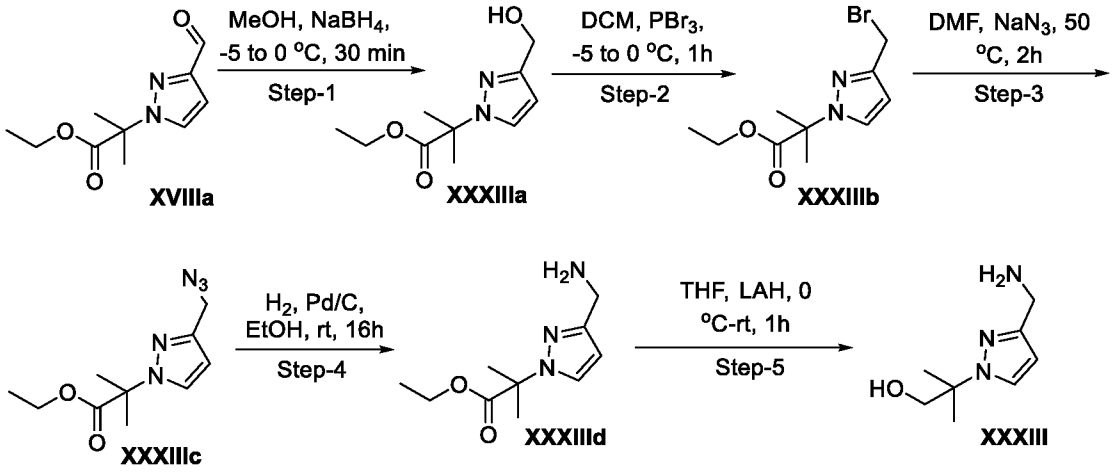
[000209] A stirred solution of ethyl 2-(6-formylpyridin-2-yl)-2-methylpropanoate **XXXIIc** (506 mg, 2.29 mmol) in DCM (15 mL) was cooled to 0 °C and nitromethane (168 mg, 2.74 mmol), triethylamine (1.16 g, 1.59 mL, 11.4 mmol) were added under N_2 atmosphere. The resulting mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After completion of reaction solvent was evaporated under reduced pressure to afford a brown viscous liquid. To the reaction mixture fresh DCM (10 mL) was added and was cooled to 0 °C. This was followed a dropwise addition of methane sulfonyl chloride (786 mg, 6.86 mmol) under N_2 atmosphere. The reaction mixture was stirred at rt for 30 min and the progress of the reaction was monitored by TLC analysis. The reaction mixture was concentrated under reduced pressure and water (20 mL) was added. The mixture was extracted with ethyl acetate (20 mL x 2). The combined organic layer was given brine wash and concentrated under reduced pressure to afford **XXXIId** as brown viscous liquid. The crude was taken for the next step without further purification. Yield: 0.6g (99.3%); **LCMS** Calculated. for $C_{13}H_{17}N_2O_4$ is 265.12, Observed, 265.20; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.03-7.89 (m, 2H), 7.75 (t, *J*=7.6 Hz, 1H), 7.40-7.34 (m , 2H), 4.17 (q, *J* = 6.8 Hz, 2H), 1.58 (s, 6H), 1.20 (t , *J*=7.2 Hz, 3H).

Step-5: 2-(6-(2-aminoethyl) pyridin-2-yl)-2-methylpropan-1-ol (XXXII)

[000210] A solution of aluminum lithium hydride (9 mL, 1 molar, 9 mmol) in dry diethyl ether (50 mL) was cooled to 0 °C. To the resulting mixture a solution of ethyl (*E*)-2-methyl-2-(6-(2-nitrovinyl) pyridin-2-yl) propanoate **XXXIId** (0.6 g, 2 mmol) in dry diethyl ether (10 mL) was added drop wise. The resulting mixture was stirred at rt for 1 h. The progress of the reaction was monitored by TLC analysis which indicated the completion of reaction. The reaction mixture was cooled to 0 °C and dropwise added ice cold water (1mL). To the resulting mixture 15% KOH solution (5mL) was dropwise added followed by dropwise addition of ethyl acetate

(50 mL). The resulting mixture was vigorously stirred at room temperature for 15-20 min. The reaction mixture was filtered through a celite bed, and the residue was washed with fresh ethyl acetate (50 mL X 3). The combined filtrate was concentrated under reduced pressure to afford a desired compound **XXXII** as a light brown viscous liquid. The crude was taken for the next step without further purification. Yield: 0.4g (100%).

Synthesis of 2-(3-(amino methyl)-1H-pyrazol-1-yl)-2-methylpropan-1-ol (XXXIII).



Step-1: Ethyl 2-(3-(hydroxymethyl)-1H-pyrazol-1-yl)-2-methylpropanoate (XXXIIIa).

[000211] A stirred solution of ethyl 2-(3-formyl-1H-pyrazol-1-yl)-2-methylpropanoate **XVIIIa** (1.0 g, 4.8 mmol) in ethanol (10 mL) was cooled to 0 °C, and added sodium borohydride (90 mg, 2.4 mmol) in portions. The reaction mixture was stirred at 0 °C for 30 min and the progress of the reaction was monitored by TLC analysis (polar spot). The reaction mixture was diluted with water 1 mL and removed the solvent under *vacuo*. To the residue was added water (10 mL) and extracted with DCM (10 mL X 3). The combined organic layer was dried anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product **XXXIIIa** was taken for the next step without further purification. Yield: 0.9 g (90%); **LCMS** Calculated. for $C_{10}H_{17}N_2O_3$ is 213.13, Observed,

213.25; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.52 (d, *J*= 2.0 Hz, 1H), 6.28 (d, *J*= 2.0 Hz, 1H), 4.69 (d, *J*= 4.4 Hz, 2H), 4.16 (q, *J*= 6.8 Hz, 2H), 2.09 (s, 1H), 1.84 (s, 6H), 1.21 (t, *J*= 7.2 Hz, 3H).

Step-2: Ethyl 2-(3-(bromomethyl)-1H-pyrazol-1-yl)-2-methyl propanoate (XXXIIIb).

[000212] A stirred solution of ethyl 2-(3-(hydroxymethyl)-1H-pyrazol-1-yl)-2-methylpropanoate **XXXIIIa** (0.2 g, 0.9 mmol) in DCM (5 mL) cooled to 0 °C under inert atmosphere and dropwise added PBr_3 (0.1 mL, 1 mmol). The reaction mixture was stirred at room temperature for 12 h. The progress of the reaction was monitored by TLC analysis (less polar spot). The reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL X 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was subjected to silica gel (230-400 mesh) combi-flash column chromatography using ethyl acetate (0-10%) in *n*-hexane to afford the desired compound **XXXIIIb** as a pale-yellow viscous liquid. Yield: 0.16 g (53%); **LCMS** Calculated. for $C_{10}H_{16}BrN_2O_2$ is 275.04, Observed, 275.15; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.52 (d, *J*= 2.0 Hz, 1H), 6.28 (d, *J*= 2.0 Hz, 1H), 4.69 (d, *J*= 4.4 Hz, 2H), 4.16 (q, *J*= 6.8 Hz, 2H), 2.09 (s, 1H), 1.84 (s, 6H), 1.21 (t, *J*= 7.2 Hz, 3H).

[000213] Step-3: Ethyl 2-(3-(azidomethyl)-1H-pyrazol-1-yl)-2-methyl propanoate (XXXIIIc).

[000214] To a stirred solution of ethyl 2-(3-(bromomethyl)-1H-pyrazol-1-yl)-2-methylpropanoate **XXXIIIb** (400 mg, 1.45 mmol) in DMF (4 mL) was added sodium azide (123 mg, 1.89 mmol) and the reaction mixture was heated at 50°C for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with ice cold water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by combi flash (230-400 mesh) using 0-2% ethyl acetate in *n*-hexane to afford the desired compound **XXXIIIc** as a pale-yellow viscous liquid. Yield: 0.17 g (49.3%); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.55 (d, *J*= 2.4 Hz, 1H),

6.30 (d, *J*= 2.0 Hz, 1H), 4.33(s, 2H), 4.16 (q, *J*= 6.8 Hz, 2H), 1.85 (s, 6H), 1.20 (t, *J*= 6.8 Hz, 3H).

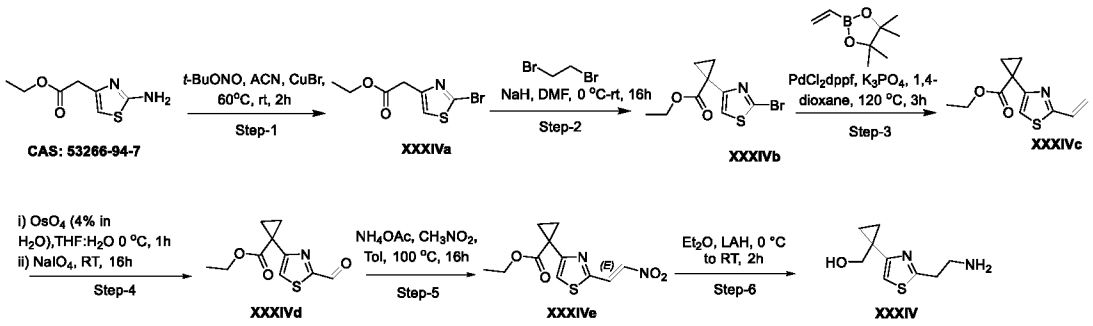
Step-4: Ethyl 2-(3-(amino methyl)-1H-pyrazol-1-yl)-2-methylpropanoate (XXXIIId).

[000215] To a stirred solution of ethyl 2-(3-(azidomethyl)-1H-pyrazol-1-yl)-2-methylpropanoate **XXXIIIc** (170 mg, 0.717 mmol) in ethanol (5 mL), added Pd/C (76.3 mg, 10%, 0.717 mmol) under N_2 atmosphere. hydrogen. The reaction was evacuated and refilled with H_2 gas. The procedure was repeated for 3-4 times and stirred at room temperature under H_2 balloon pressure for 16 h. The progress of the reaction was monitored by TLC analysis (polar spot). After completion, the reaction mixture was filtered through celite bed, and the bed was washed with methanol. The combined filtrate was concentrated under reduced pressure. The crude was purified by silica gel flash (230-400 mesh) column chromatography using 0-5% methanol in DCM to afford the desired compound **XXXIIId** as a pale-yellow liquid. Yield: 0.15 g (99.3%); **LCMS** Calculated. for $C_{10}H_{18}N_3O_2$ is 212.14, Observed, 212.30; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.81 (d, *J*= 2.4 Hz, 1H), 6.27 (d, *J*= 2.4 Hz, 1H), 4.07 (q, *J*= 7.2 Hz, 2H), 3.72 (s, 2H), 1.72 (s, 6H), 1.12 (t, *J*= 6.8 Hz, 3H).

Step-5: 2-(3-(Amino methyl)-1H-pyrazol-1-yl)-2-methylpropan-1-ol (XXXIII).

[000216] To a stirred solution of LAH (2.84 mL, 1 M, 2.84 mmol) in dry diethyl ether (20 mL) solution of ethyl 2-(3-(amino methyl)-1H-pyrazol-1-yl)-2-methylpropanoate **XXXIIId** (150 mg, 0.710 mmol) in diethyl ether (5 ML) was added dropwise at 0 °C. The reaction mixture was stirred at RT for 1 h. The reaction mixture was cooled to 0 °C and quenched with water (0.15 mL), 15% NaOH (0.15 mL) and then with ethyl acetate (10 mL). The residue was filtered through a celite bed and washed with ethyl acetate (50 mL x 3 times). The filtrate was concentrated under reduced pressure to get the compound **XXXIII** as a pale-yellow liquid. The crude was taken for the next step without further purification. Yield: 0.12 g (100%).

[000217] Synthesis of (1-(2-(2-aminoethyl) thiazol-4-yl) cyclopropyl) methanol (XXXIV)



Step-1: Ethyl 2-(2-bromothiazol-4-yl) acetate (XXXIVa)

[000218] To a stirred solution of ethyl 2-(2-aminothiazol-4-yl) acetate (CAS: 53266-94-7, 1.0 g, 5.4 mmol) in ACN (10 mL) was added *tert*-butyl nitrite (0.84 g, 0.97 mL, 8.2 mmol) and the reaction mixture was stirred at 60 °C for 30 min. Then copper(I) bromide (0.77 g, 5.4 mmol) was added, and the reaction was heated at 75 °C for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated, and the residue was subjected silica gel (230-400) column chromatography using 0-10% ethyl acetate in *n*-hexane to afford the desired compound as a pale-yellow viscous liquid. Yield: 0.45 g (34.0%); **LCMS** Calculated. for $C_7H_9BrNO_2S$ is 249.96; Observed. 250.00 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.18 (s, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.81 (s, 2H), 1.28 (t, J = 7.2 Hz, 3H).

Step-2: Ethyl 1-(2-bromothiazol-4-yl) cyclopropane-1-carboxylate (XXXIVb)

[000219] A stirred solution of ethyl 2-(2-bromothiazol-4-yl) acetate **XXXIVa** (200 mg, 0.80 mmol) in DMF (2 mL) was cooled to 0 °C and NaH (42.2 mg, 1.76 mmol) was portion wise added under inert atmosphere. This was followed by dropwise addition of 1,2-dibromoethane (330 mg, 1.76 mmol) over 10 min and the resulting mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC analysis. The reaction mixture quenched with ice cold water and extracted by ethyl acetate (20 mL X 3) and the combined organic layer was dried over anhydrous sodium sulphate. The solvent was concentrated under reduced pressure to afford the desired compound **XXXIVb** as a light brown viscous liquid. Yield: 160 mg (72%); **LCMS** Calculated. for $C_9H_{11}BrNO_2S$ is 277.97; Observed. 278.10 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.47 (s, 1H),

4.17 (q, J = 7.2 Hz, 2H), 1.70-1.68 (m, 2H), 1.50-1.49 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H).

Step-3: Ethyl 1-(2-vinylthiazol-4-yl) cyclopropane-1-carboxylate (XXXIVc)

[000220] To a stirred solution of ethyl 1-(2-bromothiazol-4-yl)cyclopropane-1-carboxylate **XXXIVb** (2.2 g, 8.0 mmol) in 1, 4-dioxane (40 mL) was added trifluoro(vinyl)-l4-borane, potassium salt (1.2 g, 8.8 mmol) and the resulting mixture was purged argon for 10 min. This was followed by an addition of potassium phosphate (2.5 g, 12 mmol) and the mixture was further purged for 5 min before $PdCl_2$(dppf) (0.29 g, 0.40 mmol) was added. The seal tube was closed and heated at 120 °C for 3 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mass was concentrated under *vacuo* the residue was subjected silica gel (230-400 mesh) column chromatography using 0-10% ethyl acetate in *n*-hexane to afford the desired compound **XXXIVc** as a light brown liquid. Yield: 1.1 g (61%); **LCMS** Calculated. for $C_{11}H_{14}NO_2S$ is 224.08; Observed. 224.15 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 (s, 1H), 6.77 (q, J = 6.8 Hz, 1H), 5.98 (d, J = 17.6 Hz, 1H), 5.50 (d, J = 11.2 Hz, 1H), 4.16 (t, J = 7.2 Hz, 2H), 1.69-1.66 (m, 2H), 1.50-1.47 (m, 2H), 1.28-1.22 (m, 3H).

Step-4: Ethyl 1-(2-formylthiazol-4-yl) cyclopropane-1-carboxylate (XXXIVd)

[000221] A stirred solution of ethyl 1-(2-vinylthiazol-4-yl) cyclopropane-1-carboxylate **XXXIVc** (1.1 g, 4.9 mmol) in THF: water (2:1; 16.5 mL) was cooled to 0 °C and added osmium tetroxide (15.75 mL 4% in water, 2.5 mmol) and the reaction mixture was stirred at 0 °C for 1 h. Then sodium periodate (1.6 g, 7.4 mmol) was added, and reaction stirred was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC analysis. The reaction was quenched with water (20 mL) and extracted with ethyl acetate (100 mL X 3). The combined organic layer was concentrated under reduced pressure. The crude residue was subjected to silica gel (230-400) column chromatography using 0-10% ethyl acetate/n-hexane to afford the desired compound **XXXIVd** as a pale-yellow viscous liquid. Yield: 1.0 g (90%); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.92 (s, 1H), 8.04 (s, 1H), 4.20 (q, J = 7.2 Hz, 2H), 1.79 (t, J = 4.0 Hz, 2H), 1.67-1.62 (m, 2H), 1.28-1.22 (m, 3H).

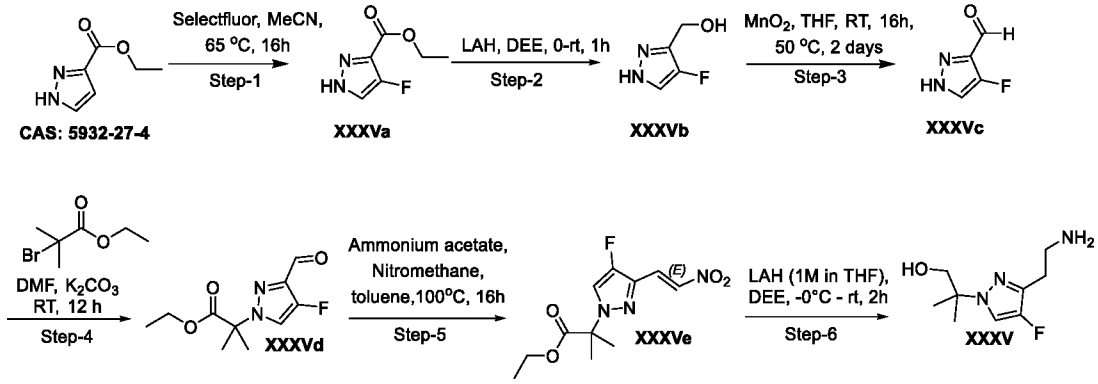
[000222] Step-5: Ethyl (E)-1-(2-(2-nitrovinyl) thiazol-4-yl) cyclopropane-1-carboxylate (XXXIVe)

[000223] To a stirred solution of ethyl 1-(2-formylthiazol-4-yl) cyclopropane-1-carboxylate **XXXIVd** (1.1 g, 4.9 mmol) in DCM (14 mL) were added TEA (2.0 mL, 15 mmol) and nitromethane (0.53 mL, 9.8 mmol) and the reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was concentrated under *vacuo*. The residue was immediately dissolved in fresh DCM (14 mL) and the resulting mixture was cooled to 0 °C. TEA (2.0 mL, 15 mmol) and mesyl-Cl (0.76 mL, 9.8 mmol) were added, and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated solution of $NaHCO_3$ and extracted with DCM (10 mL X 3). The combined organic layer was dried over sodium sulphate and concentrated under reduced pressure. The crude compound **XXXIVe** was taken for the next step without further purification. Yield: 1.2 g (92.3%); **LCMS** Calculated. for $C_{11}H_{13}N_2O_4S$ is 269.06; Observed. 269.15 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.97 (m, 1H), 7.81 (s, J = 13.2 Hz,1H), 4.20 (q, J = 7.2 Hz, 2H), 1.72 (q, J = 3.6 Hz, 2H), 1.61-1.55 (m, 4H), 1.29-1.24 (m, 3H).

Step-6: (1-(2-(2-aminoethyl) thiazol-4-yl) cyclopropyl) methanol (XXXIV)

[000224] A stirred solution of ethyl (*E*)-1-(2-(2-nitrovinyl) thiazol-4-yl) cyclopropane-1-carboxylate **XXXIVe** (1.2 g, 4.5 mmol) in dry diethyl ether (25 mL) was cooled to 0 °C and $LiAlH_4$ solution (18 mL, 1 M, 18 mmol) was dropwise added. The reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC analysis. The reaction was quenched with ice cold water (1 mL), 15% NaOH solution (1 mL). The resulting mixture was stirred at 0 °C for 10 min and ethyl acetate (20 mL) was slowly added. The mixture was stirred for 10 min before it was passed through a celite bed. The bed was washed thoroughly with ethyl acetate (100 mL X 3), and the combined filtrate was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the desired compound **XXXIV** as a pale-yellow viscous liquid. Yield: 0.79 g (78.6%).

Synthesis of 2-(3-(2-aminoethyl)-4-fluoro-1H-pyrazol-1-yl)-2-methylpropan-1-ol (XXXV)



Step-1: Ethyl 4-fluoro-1H-pyrazole-3-carboxylate (XXXVa)

[000225] To a stirred solution of ethyl 1H-pyrazole-3-carboxylate (CAS: 5932-27-4, 1 g, 7.0 mmol) in acetonitrile (15 mL) was added select fluor (4 g, 11.3 mmol) and the reaction mixture was stirred at 65 °C for 16 h under nitrogen atmosphere. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled room temperature, diluted with water (100 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified by combi flash silica gel column chromatography using 0-10% ethyl acetate in *n*-hexane to afford the desired compound **XXXVa** as off-white solid. Yield: 0.5 g (50%); **NMR (400 MHz, $CDCl_3$):** δ 10.95 (bs, 1H), 7.59 (s, 1H), 4.46 - 4.41 (m, 2H) 1.41 (t, *J*= 7.2 Hz, 3H).

Step-2: (4-Fluoro-1H-pyrazol-3-yl) methanol (XXXVb)

[000226] A solution of $LiAlH_4$ (15.2 mL, 1 M in THF, 15.2 mmol) in diethyl ether (20 mL) was cooled to 0 °C and drop wise added a solution of ethyl 4-fluoro-1H-pyrazole-3-carboxylate **XXXVa** (600 mg, 3.79 mmol) in diethyl ether (5 mL) under inert atmosphere. The reaction was stirred at rt for 1 h under and the progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture cooled with ice bath, quenched with drop wise addition of water (3.6 mL) and 15% NaOH (0.6 mL). To the resulting mixture was added ethyl acetate (50 mL) and stirred at rt for 30 min. The mixture was filtered, and the residue was thoroughly washed with fresh ethyl acetate (50 mL x 2). The combined filtrate was

concentrated under reduced pressure to afford the desired compound **XXXVb** as a pale-yellow liquid. The crude was taken for next step without further purification Yield: 0.40 g (90%). **LCMS** Calculated. for $C_4H_5FN_2O$ is 116.10, Observed. 115.00; $[M-H]^+$.

Step-3: 4-Fluoro-1H-pyrazole-3-carbaldehyde (XXXVc)

[000227] To a stirred solution of (4-fluoro-1H-pyrazol-3-yl) methanol **XXXVb** (400 mg, 3.45 mmol) in THF (20 mL) was added MnO_2 (15.0 g, 172 mmol) at 0 °C. The resulting reaction mixture was stirred at 50 °C for 48 h under nitrogen atmosphere. The reaction was cooled to room temperature and filtered through a celite bed. The bed was washed with fresh ethyl acetate (10 mL X 3). The combined filtrate was concentrated under reduced pressure to afford desired product **XXXVc** as a pale-yellow liquid. The crude was taken for next step without further purification. Yield: 0.39 g (99%). **LC_MS** Calculated. for $C_4H_3FN_2O$ is 114.02, Observed.113.10; $[M-H]^+$.

Step-4: Ethyl 2-(4-fluoro-3-formyl-1H-pyrazol-1-yl)-2-methylpropanoate (XXXVd)

[000228] To a stirred solution of 4-fluoro-1H-pyrazole-3-carbaldehyde **XXXVc** (400 mg, 3.51 mmol) in DMF (10 mL) was added cesium carbonate (2.28 g, 7.01 mmol) followed by an addition of ethyl-2-bromo-2-methylpropanoate (821 mg, 4.21 mmol). The resulting reaction mixture was stirred at rt for 12 h under nitrogen atmosphere. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with ice cold water (200 mL) and extracted with ethyl acetate (100 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel (230-400) column chromatography using 0-5% ethyl acetate in *n*-hexane to afford the desired compound **XXXVd** as a colorless liquid. Yield: 0.9 g (100%); **NMR (400 MHz, $CDCl_3$):** δ 9.93 (s, 1H), 7.51- 7.49 (m, 1H), 4.22 - 4.17 (m, 2H) 1.86 (s, 6H), 1.23 (t, J = 7.2 Hz, 3H).

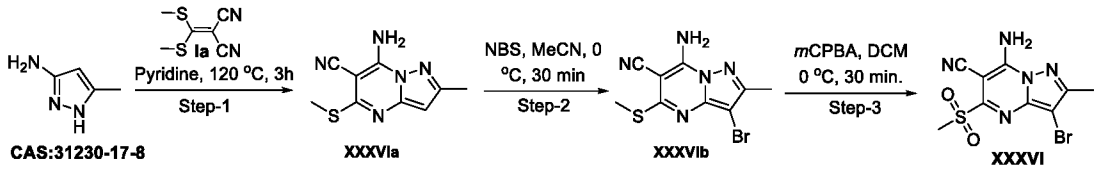
Step-5: Ethyl (E)-2-(4-fluoro-3-(2-nitrovinyl)-1H-pyrazol-1-yl)-2-methylpropanoate (XXXVe)

[000229] To a stirred solution of ethyl 2-(4-fluoro-3-formyl-1H-pyrazol-1-yl)-2-methylpropanoate **XXXVd** (800 mg, 3.51 mmol) in toluene (20 mL) were added nitromethane (2.84 mL, 52.6 mmol) and ammonium acetate (405 mg, 5.26 mmol) under nitrogen atmosphere. The resulting mixture was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature, diluted with 1N HCl (20 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified by combi flash column chromatography using 0-2% ethyl acetate in *n*-hexane to afford the desired compound **XXXVe** as an yellow solid. Yield: 0.5 g (52%); **NMR (400 MHz, $CDCl_3$):** δ 7.94- 7.93 (m, 1H), 7.69-7.64 (m, 1 H), 7.51 (d, J = 5.2 Hz, 1H), 4.21 - 4.16 (m, 2H) 1.83 (s, 6H), 1.23 (t, J = 7.2 Hz, 3H).

Step-6: 2-(3-(2-Aminoethyl)-4-fluoro-1H-pyrazol-1-yl)-2-methylpropan-1-ol (XXXV)

[000230] A stirred solution of $LiAlH_4$ (7.37 mL, 1 M in THF, 7.37 mmol) in diethyl ether (80 mL) cooled to 0 °C and dropwise added solution of ethyl (E)-2-(4-fluoro-3-(2-nitrovinyl)-1H-pyrazol-1-yl)-2-methylpropanoate **XXXVe** (500 mg, 1.84 mmol) in diethyl ether (10 mL) under nitrogen atmosphere. The reaction was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to 0 °C and quenched with water (0.5 mL), 15% NaOH (0.5 mL) and again water (1.5 mL) was added. To the resulting mixture was added ethyl acetate (30 mL) and stirred for 30 min. The mixture was filtered, and the residue was washed with fresh ethyl acetate (100 mL x 3). The combined filtrate was concentrated under reduced pressure to afford the desired compound **XXXV** as pale-yellow liquid. The crude was taken for next step without further purification. Yield: 0.35 g (94%).

Synthesis of 7-amino-3-bromo-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (XXXVI)



Step-1: 7-amino-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (XXXVIa)

[000231] To a solution of 5-methyl-1H-pyrazol-3-amine (CAS: 31230-17-8, 2 g, 20mmol) in pyridine (50 mL) was added 2-(bis(methylthio)methylene) malononitrile **Ia** (4 g, 20 mmol) and stirred at 120 °C for 3 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, added water (500 mL) and filtered the solid to afford the crude compound **XXXVIa** as a pink solid. The crude compound was taken for the next step without further purification. Yield: 3.9 g, (90.0 %); **LCMS** Calculated. for $C_9H_9N_5S$ is 219.06; Observed.: 220.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.68 (s, 2H), 6.25 (s, 1H), 2.52 (d, J = 5.6 Hz, 3H), 2.37 (s, 3H).

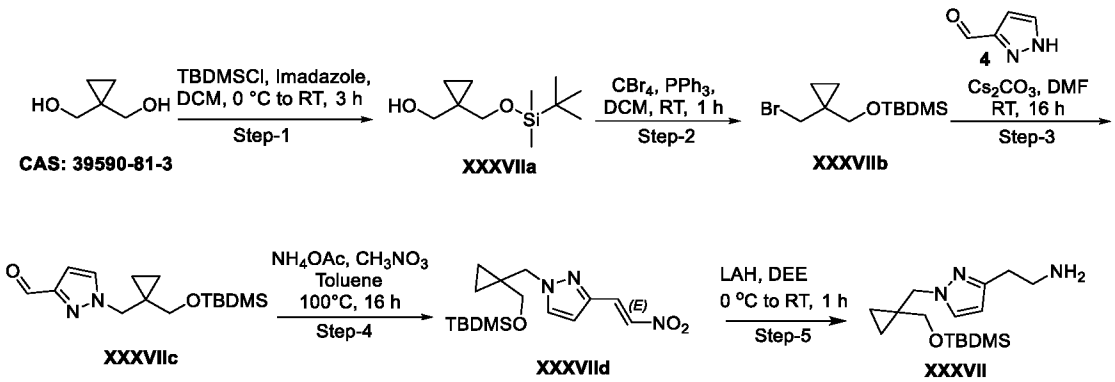
Step-2: 7-amino-3-bromo-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (XXXVIb)

[000232] To a solution of 7-amino-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXXVIa** (1.89 g, 8.62 mmol) in acetonitrile (25 mL) at 0 °C was added N-Bromo succinimide (1.89 g, 10.6 mmol) and stirred at 0 °C for 30 min. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, added water (50 mL) and extracted with ethyl acetate (2 X 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford the desired compound **XXXVIb** as a brown solid. The crude compound was taken for the next step without any further purification. Yield: 1.9 g, (74.0 %); **LCMS** Calculated. for $C_9H_8BrN_5S$ is 296.97; Observed.: 298.15 $[M+H]^+$. **^{1}HNMR (400 MHz, CDCl$_3$):** δ 6.27 (s, 2H), 2.67 (s, 3H), 2.43 (s, 3H).

Step-3: 7-amino-3-bromo-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (XXXVI)

[000233] To a solution of 7-amino-3-bromo-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXXVIb** (0.8 g, 2.68 mmol) in acetonitrile (15 mL) at 0 °C was added *m*CPBA (2.31 g, 13.4 mmol) and stirred at 0 °C for 30 min. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was quenched with sodium bicarbonate (100 mL) and extracted with ethyl acetate (2 X 15 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford the crude compound **XXXVI** as a brown solid. The crude compound was taken for the next step without further purification. Yield: 600 mg, (67.7 %); **LCMS** Calculated. for $C_9H_8BrN_5O_2S$ is 328.96; Observed.: 332 $[M+H]^+$.

Synthesis of 2-(1-((1-(((tert-butyldimethylsilyl) oxy) methyl) cyclopropyl) methyl)-1H-pyrazol-3-yl) ethan-1-amine (XXXVII)



Step-1: (1-(((*tert*-Butyldimethylsilyl) oxy) methyl) cyclopropyl) methanol (XXXVIIa)

[000234] To a stirred solution of cyclopropane-1,1-diyldimethanol (CAS: 39590-81-3, 5 g, 0.05 mol) in DCM (100 mL) was added imidazole (5 g, 0.07 mol) and stirred at room temperature for 10 min, then reaction mixture was cooled to 0 °C followed by drop wise addition of TBDMS-Cl (7 g, 0.05 mol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 h and the reaction was monitored by TLC analysis. After completion, the reaction was quenched with water (50 mL) and extracted with DCM (30 mL X 2). The combined organic layer was dried over anhydrous sodium sulphate. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh)

column chromatography using (0-30%) ethyl acetate in *n*-hexane to afford the desired compound **XXXVIIa** as a colorless liquid. Yield: 5.0 g (50%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.61 (s, 2H), 3.57 (d, J = 5.6 Hz, 2H), 2.74 (t, J = 5.6 Hz, 1H), 0.91 (s, 9H), 0.53-0.50 (m, 2H), 0.47-0.43 (m, 2H). 0.07 (s, 6H).

Step-2: ((1-(Bromomethyl) cyclopropyl) methoxy) (tert-butyl) dimethyl silane (XXXVIIb)

[000235] To a stirred solution of (1-(((tert-butyldimethylsilyl) oxy) methyl) cyclopropyl) methanol **XXXVIIa** (4 g, 20 mmol) in DCM (100 mL) was added triphenylphosphine (7 g, 30 mmol) and stirred at room temperature for 20 min, then reaction mixture was cooled to 0 °C followed by drop wise addition of carbon tetrabromide (9 g, 30 mmol) under nitrogen atmosphere. Then reaction was stirred at room temperature for 1 h and the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (50 mL) and extracted with DCM (25 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using (0-20%) ethyl acetate in *n*-hexane to afford the desired compound **XXXVIIb** as a colorless liquid. Yield: 4.0 g (80%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.56 (s, 2H), 3.49 (s, 2H), 0.93-0.89 (m, 9H), 0.74-0.71 (m, 2H), 0.61-0.57 (m, 2H). 0.07 (s, 6H).

Step-3: 1-((1-(((*tert*-Butyldimethylsilyl) oxy) methyl) cyclopropyl) methyl)-1H-pyrazole-3-carbaldehyde (XXXVIIc)

[000236] To a stirred solution of 1H-pyrazole-3-carbaldehyde (1 g, 10 mmol) in DMF (10 mL) was added cesium carbonate (7 g, 20 mmol) and stirred at room temperature for 20 min, then reaction mixture was cooled to 0 °C followed by drop wise addition of ((1-(bromomethyl) cyclopropyl) methoxy) (tert-butyl) dimethyl silane **XXXVIIb** (3 g, 10 mmol) under nitrogen atmosphere. Then reaction mixture was stirred at room temperature for 16 h and the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (25 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column

chromatography using (0-20%) ethyl acetate in *n*-hexane to afford the desired compound **XXXVIIc** as a colorless liquid. Yield: 1.5 g (50%). **LCMS** Calculated. for $C_{15}H_{26}N_2O_2Si$ is 294.17; Observed. 295.25 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.97 (s, 1H), 7.52 (d, J = 1.6 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H), 4.21 (s, 2H), 3.32 (s, 2H), 0.90 (s, 9H), 0.70-0.68 (m, 2H), 0.58-0.56 (m, 2H). 0.02 (s, 6H).

Step-4: (*E*)-1-((1-(((*tert*-Butyldimethylsilyl) oxy) methyl) cyclopropyl) methyl)-3-(2-nitrovinyl)-1*H*-pyrazole (XXXVIId)

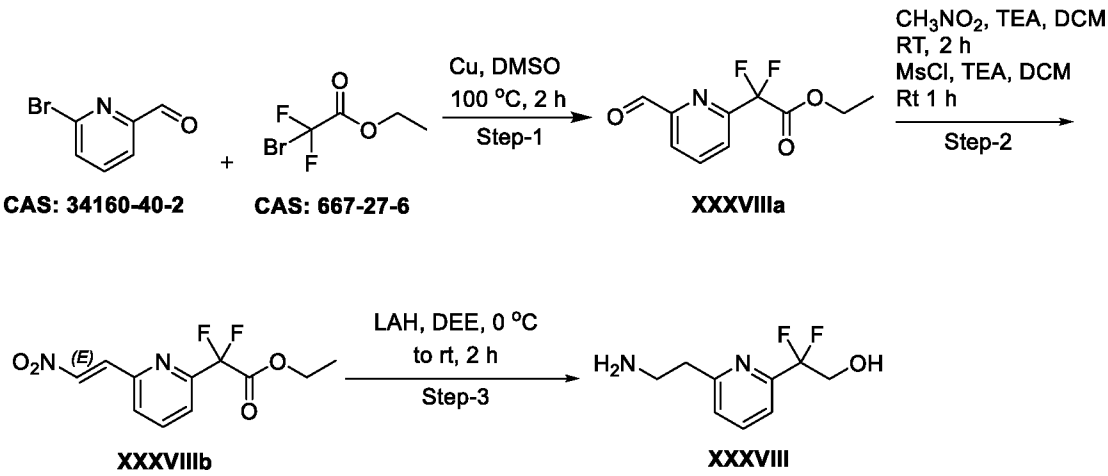
[000237] To a stirred solution of 1-((1-(((*tert*-Butyldimethylsilyl) oxy) methyl) cyclopropyl) methyl)-1*H*-pyrazole-3-carbaldehyde **XXXVIIc** (1.5 g, 5.1 mmol) in toluene (50 mL) was added nitromethane (4.7 g, 4.1 mL, 76 mmol) and stirred at room temperature for 10 min followed by addition of ammonium acetate (0.59 g, 7.6 mmol) then reaction mixture was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was cooled to room temperature, diluted with 1N HCl (50 mL) and extracted with ethyl acetate (25 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using (0-30%) ethyl acetate in *n*-hexane to afford the desired compound **XXXVIId** as a light-yellow solid. Yield: 1.15 g (65%). **LCMS** Calculated. for $C_{16}H_{27}N_3O_3Si$ is 337.18; Observed. 338.20 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.96 (d, J = 13.2 Hz, 1H), 7.61 (d, J = 13.2 Hz, 1H), 7.26 (s, 1H), 6.53 (s, 1H), 4.16 (s, 2H), 3.31 (s, 2H), 0.90 (s, 9H), 0.67 (m, 2H), 0.55 (m, 2H). 0.02 (s, 6H).

Step-5: 2-(1-((1-(((*tert*-Butyldimethylsilyl) oxy) methyl) cyclopropyl) methyl)-1*H*-pyrazol-3-yl) ethan-1-amine (XXXVII)

[000238] To a stirred solution of lithium aluminum hydride (0.01 L, 1.0 molar in THF, 10 mmol) in diethyl ether (70 mL) was added (*E*)-1-((1-(((*tert*-Butyldimethylsilyl) oxy) methyl) cyclopropyl) methyl)-3-(2-nitrovinyl)-1*H*-pyrazole **XXXVIId** (1.15 g, 3.41 mmol) dropwise at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to 0 °C was added 1.2 mL of ice-cold water and 1.2

mL of 15% KOH solution then stirred at room temperature for another 30 min. The resulting reaction mixture was diluted with 100 mL of ethyl acetate filtered through Buchner funnel and the solid was thoroughly washed with 250mL of ethyl acetate. The filtrate was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford a desired compound **XXXVII** as light-yellow liquid. The crude product was taken for the next step without further purification. Yield: 0.81 g (100%). **LCMS** Calculated for $C_{16}H_{31}N_3OSi$ is 309.22; Observed: 310.30 $[M+H]^+$.

Synthesis of 2-(6-(2-aminoethyl) pyridin-2-yl)-2,2-difluoroethan-1-ol (XXXVIII)



Step-1: Ethyl 2,2-difluoro-2-(6-formylpyridin-2-yl) acetate (XXXVIIIa)

[000239] To a solution of 6-bromopicolinaldehyde (CAS: 34160-40-2, 1 g, 5 mmol) in DMSO (5 mL) were added copper (0.8 g, 0.01 mol) and ethyl 2-bromo-2,2-difluoroacetate (CAS: 667-27-6, 1 g, 7 mmol) under N_2 at room temperature in a seal tube with Teflon screw-stopper. Seal tube was closed, and reaction mixture was stirred at 100 °C for 2 h. The reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature was added 50 mL of ethyl acetate and 50mL 1.3 molar potassium dihydrogen phosphate solution. The resulting mixture was stirred at room temperature for 30 min. The solid was filtered off and thoroughly washed with the ethyl acetate (30 mL x 2). The filtrate was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The

residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using 0-6% EtOAc in *n*-hexane to afford the desired compound **XXXVIIIa** as an off-white solid. Yield: 0.93 g (80%). **LCMS** Calculated. for $C_{10}H_9F_2NO_3$ is 229.05; Observed. 230.15 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 9.95 (bs, 1H), 8.35-8.13 (m, 3H), 4.38 (q, J = 7.2 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H).

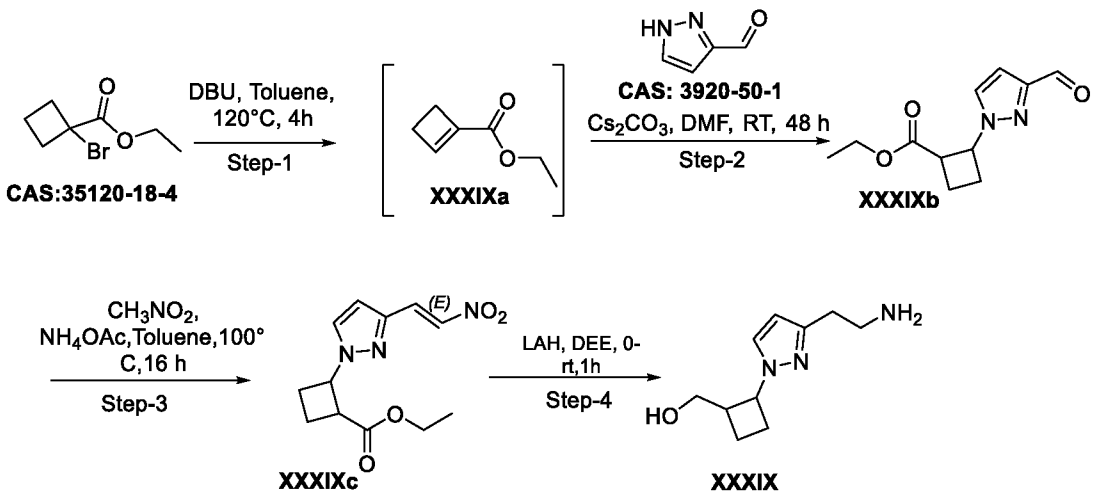
Step-2: Synthesis of ethyl (*E*)-2,2-difluoro-2-(6-(2-nitrovinyl) pyridin-2-yl) acetate (XXXVIIIb)

[000240] To the stirred solution of ethyl 2,2-difluoro-2-(6-formylpyridin-2-yl) acetate **XXXVIIIa** (930 mg, 4.06 mmol) in DCM (20 mL) was added triethylamine (1.13 mL, 8.12 mmol) and nitromethane (263 µL, 4.87 mmol) at room temperature under N_2. The resulting reaction mixture was stirred at room temperature for 2 h and the reaction was monitored by TLC analysis. After completion, DCM was concentrated to dryness and the residue was immediately taken for next in situ step. To a solution of crude ethyl 2,2-difluoro-2-(6-(1-hydroxy-2-nitroethyl) pyridin-2-yl) acetate (1.177 g, 4.06 mmol) in DCM (25 mL) was added triethylamine (1.70 mL, 12.17 mmol) and cooled to 0 °C followed by a dropwise addition of methane sulfonyl chloride (1.394 g, 1.226 mL, 12.17 mmol). The reaction was stirred at room temperature for 1 h. The progress of reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched with water (25 mL) and extracted with DCM (20 X 2). The combined organic layer was washed with 25 mL of brine, passed through anhydrous sodium sulphate, and concentrated under reduced pressure. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using 0-6% ethyl acetate in *n*-hexane to afford the desired compound **XXXVIIIb** as a viscous brown liquid. Yield: 0.77 g (70%). **LCMS** Calculated. for $C_{11}H_{10}F_2N_2O_4$ is 272.06; Observed. 273.15 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.26-7.97 (m, 5H), 4.38 (q, J = 7.2 Hz, 2H), 1.25 (t, J = 4.0 Hz, 3H).

Step-3: Synthesis of 2-(6-(2-Aminoethyl) pyridin-2-yl)-2,2-difluoroethan-1-ol (XXXVIII)

[000241] To a stirred solution of lithium aluminum hydride (11.3 mL, 1.0 molar in THF, 11.3 mmol) in diethyl ether (10 mL) followed by dropwise addition of solution of (*E*)-2,2-difluoro-2-(6-(2-nitrovinyl) pyridin-2-yl) acetate **XXXVIIIb** (0.770 g, 2.83 mmol) in diethyl ether (5 mL) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h and the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to 0 °C was added 0.7 mL of ice-cold water and 0.7 mL of 15% KOH solution then stirred at room temperature for another 30 min. The resulting reaction mixture was diluted with 100 mL of ethyl acetate filtered and the solid was thoroughly washed with 100mL of ethyl acetate. The filtrate was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford a desired compound **XXXVIII** as light brown viscous liquid. The crude was taken for the next step without further purification. Yield: 0.56 g (98%). **LCMS** Calculated. for $C_9H_{12}F_2N_2O$ is 202.09; Observed. 203.25 $[M+H]^+$.

Synthesis of (2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclobutyl) methanol (XXXIX)



Step-1: Ethyl cyclobut-1-ene-1-carboxylate (XXXIXa)

[000242] A stirred solution of DBU (54 mL, 312.3 mmol) in toluene (50 mL) was heated at 150 °C for 20 min and ethyl 1-bromocyclobutane-1-carboxylate (CAS: 35120-18-4, 5.0 g, 52.050 mmol) was added dropwise through septum under inert atmosphere. The reaction mixture was stirred at 110 °C for 3.5 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction

mixture was cooled to room temperature and diluted with ice cold water (200 mL). The mixture was extracted with *n*-hexane (100 mL x 3). The combined organic layer was washed with saturated aq. $NaHSO_4$ (100 mL) solution, followed by with water (100 mL). The organic layer was separated and dried over anhydrous Na_2SO_4, filtered, and concentrated at ambient temperature (20°C, 100 mbar vacuum). (**Note: -** The desired product appeared to be volatile and was passing to the receiver while concentration on rotavapor; the compound). The crude compound **XXXIXa** (compound + some quantity of toluene) was taken for next step by assuming quantitative yield.

Step-2: Ethyl 2-(3-formyl-1H-pyrazol-1-yl) cyclobutane-1-carboxylate (XXXIXb)

[000243] A stirred solution of 1H-pyrazole-3-carbaldehyde (CAS: 3920-50-1, 5.0 g, 52 mmol) in DMF (20 mL), was added K_2CO_3 (14 g, 100 mmol) and the reaction mixture was cooled to 0 °C under inert atmosphere. This was followed by dropwise addition of above mixture of ethyl cyclobut-1-ene-1-carboxylate **XXXIXa** (16 g, 78 mmol) and toluene. The resulting mixture was stirred at rt for 48 h and progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with ice cold water (500 mL) and extracted with ethyl acetate (200 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified by combi flash (230-400 silica) column chromatography using 0-5% ethyl acetate in *n*-hexane to afford the desired compound **XXXIXb** as a colorless viscous liquid. Yield: 1.4 g (10 %); **LCMS** Calculated. for $C_{11}H_{14}N_2O_3$ is 222.10; Observed. 223.05 $[M+1]^+$. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.99 (s, 1H), 7.50 (d, J = 1.6 Hz, 1H), 6.79 (d, J = 2.0 Hz, 1H), 5.00 (t, J = 8.8 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.68-3.66 (m, 1H), 2.75-2.70 (m, 1H), 2.46-2.44 (m, 1H), 2.31-2.26 (m, 1H), 2.10-2.04 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H).

Step-3: Ethyl (E)-2-(3-(2-nitrovinyl)-1H-pyrazol-1-yl) cyclobutane-1-carboxylate (XXXIXc)

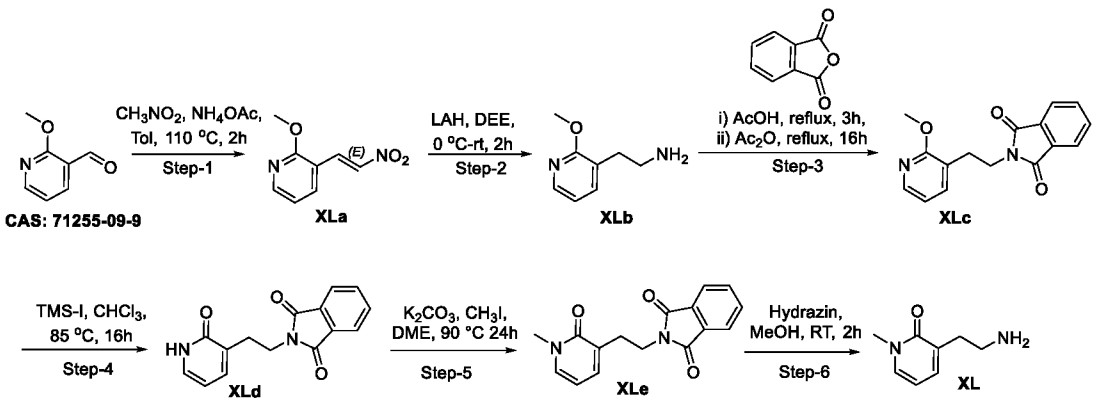
[000244] To a stirred solution of ethyl 2-(3-formyl-1H-pyrazol-1-yl) cyclobutane-1-carboxylate **XXXIXb** (1.4 g, 6.3 mmol) in toluene (20 mL) were

added nitromethane (5.1 mL, 94 mmol) and ammonium acetate (0.73 g, 9.4 mmol) under nitrogen atmosphere. The resulting reaction mixture was stirred at 100 °C for 16 h. The reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt and diluted with 1 N HCl (100 mL). The mixture was extracted with ethyl acetate (300 mL x 3) and combined organic layer was dried with Na_2SO_4. The solution was concentrated under reduced pressure. The crude was purified by combi flash (230-400) column chromatography using 0-5% ethyl acetate in *n*-hexane to afford the desired compound **XXXIXc** as a pale-yellow viscous liquid. **Yield:** 1.2 g (71 %); **LCMS** Calculated. for $C_{12}H_{15}N_3O_4$ is 265.10; Observed.267.30 $[M+1]^+$. **^{1}H NMR (400 MHz, $CDCl_3$): -** δ 7.98 (d, J = 13.6 Hz, 1H), 7.63 (d, J = 13.6 Hz, 1H), 7.48 (s, 1H), 6.52 (d, J = 2.0 Hz, 1H), 4.95 (d, J = 8.4 Hz, 1H), 4.19-4.13 (m, 2H), 3.67-3.60 (m, 1H), 2.45-2.38 (m, 1H), 2.33-2.25 (m, 1H), 2.10-2.00 (m, 1H), 2.09-1.99 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H).

Step-4: (2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclobutyl) methanol (XXXIX)

[000245] To a stirred solution of $LiAlH_4$ (18 mL, 1 molar in THF, 18 mmol) in diethyl ether (100 mL), was dropwise added a solution of ethyl (*E*)-2-(3-(2-nitrovinyl)-1H-pyrazol-1-yl) cyclobutane-1-carboxylate **XXXIXc** (1.2 g, 4.5 mmol) in diethyl ether (50 mL) at 0 °C under inert atmosphere. The resulting mixture was allowed to warm to rt and stirred for 1h. The reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to 0 °C and quenched with water (1.2 mL) and 15% KOH (1.2 mL). The mixture was stirred for 5 min and again added water (2.4 mL). The residue was filtered and washed with ethyl acetate (200 mL x 3). The filtrate was concentrated under reduced pressure to afford the desired compound **XXXIX** as pale-yellow liquid. The crude product was taken for the next step without further purification. **Yield:** 1.1 g (88 %).

Synthesis of 3-(2-aminoethyl)-1-methylpyridin-2(1H)-one (XL)



Step-1: (E)-2-methoxy-3-(2-nitrovinyl) pyridine (XLa)

[000246] To a stirred solution of 2-methoxynicotinaldehyde (CAS: 71255-09-9, 5.50 g, 40.1 mmol) in toluene (60 mL) were added ammonium acetate (4.64 g, 60.2 mmol) and nitromethane (32.4 mL, 602 mmol). The reaction was stirred at 110 °C for 2 h and progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature and diluted with water (100 mL) and the resulting mixture was extracted with ethyl acetate (200 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography using 0-10% ethyl acetate in *n*-hexane to afford the compound as a yellow solid. Yield: 4.5 g (62%). **LCMS** Calculated. for $C_8H_8N_2O_3$ is 180.05, Observed. 181.25 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.28-8.26 (m, 1H), 8.02-7.92 (m, 2H), 7.76-7.73 (m, 1H), 7.02-6.99 (m, 1H). 4.10 (s, 3H).

Step-2: 2-(2-Methoxypyridin-3-yl) ethan-1-amine (XLb)

[000247] To a stirred solution of (*E*)-2-methoxy-3-(2-nitrovinyl) pyridine **XLa** (8.5 g, 47 mmol) in diethyl ether (170 mL) at 0 °C was dropwise added $LiAlH_4$ (141 mL, 1 M in THF, 140 mmol) under inert atmosphere over 20 min. The reaction was stirred at rt for 2 h and progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with water (17 mL) followed by with 15% NaOH solution (8.5 mL) and ethyl acetate (200 mL). The mixture was diluted with ethyl acetate (300 mL) and stirred for 20 min. The white precipitate formed was filtered and washed thoroughly with fresh ethyl acetate (300 mL x 3). The combined organic layer was dried over in sodium sulphate and

concentrated under vacuum to afford the compound **XLb** as brown liquid. Yield: 6.5 g (92%). **^{1}HNMR (400 MHz, $CDCl_3$):** δ 8.04-8.03 (m, 1H), 7.41-7.39 (m, 1H), 6.83-6.80 (m, 1H), 3.97-3.94 (m, 5H), 2.95-2.92 (m, 2H), 2.73-2.69 (m, 2 H).

Step-3: 2-(2-(2-methoxypyridin-3-yl) ethyl) isoindoline-1,3-dione (XLc)

[000248] To a stirred solution of 2-(2-methoxypyridin-3-yl) ethan-1-amine **XLb** (5.2 g, 34 mmol) in acetic acid (60 mL) was added isobenzofuran-1,3-dione (5.1 g, 34 mmol) at room temperature. The resulting reaction mixture was refluxed with vigorous stirring for 3 h. The progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was concentrated under vacuum. The residue was dissolved in acetic anhydride (19 mL, 20 mmol) refluxed with vigorous stirring for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to room temperature and quenched with saturated $NaHCO_3$ solution (200 mL). The mixture was extracted with DCM (300 mL X 3) and combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the crude compound which was subjected to combi flash column chromatography using 0-20% ethyl acetate in *n*-hexane to afford the desired product **XLc** as a yellow solid. Yield: 5.0 g (52%). **LCMS** Calculated. for $C_{16}H_{14}N_2O_3$ is 282.10; Observed. 283.25 $[M+H]^+$.

Step-4: 2-(2-(2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione (XLd)

[000249] To a stirred solution of 2-(2-(2-methoxypyridin-3-yl) ethyl) isoindoline-1,3-dione **XLc** (2.5 g, 8.9 mmol) in chloroform (50 mL) was added TMS-I (6.0 mL, 44 mmol) at room temperature under inert atmosphere. The reaction mixture was stirred at 85 °C for 16 h and progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched by adding methanol (5 mL) and concentrated the reaction mixture. The crude was triturated with ethanol/MTBE (1:3). The solid formed was collected by filtration and dried under vacuum to afford the desired compound **XLd** as a yellow solid. Yield: 1.9 g (79 %). **LCMS** Calculated. for $C_{15}H_{12}N_2O_3$ is 268.08; Observed. 269.05 $[M+H]^+$. **^{1}HNMR (400 MHz, $CDCl_3$):** δ 7.95 (d, J= 6.4 Hz, 1H), 7.80 (t, J= 3.2 Hz, 2H) 7.71-7.69 (m, 3H), 6.67 (bs, 1H), 4.04 (bs, 2H), 3.06 (bs, 2H).

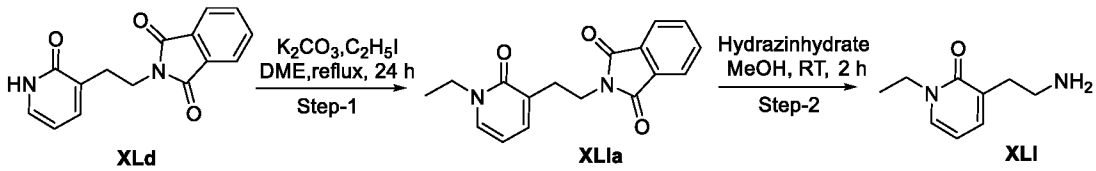
Step-5: 2-(2-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione (XLe)

[000250] To a stirred solution of 2-(2-(2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **XLd** (700 mg, 5.69 mmol) in dimethoxymethane (14 mL) was added K_2CO_3 (1.57 g, 11.4 mmol) followed by an addition of iodomethane (0.7 ml, 11.4 mmol). The resulting reaction mixture was stirred at 90 °C for 24 h under nitrogen atmosphere. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to room temperature and solid was filtered off. The filtrate was concentrated under vacuum and the residue was purified by combi flash silica gel (230-400) column chromatography using 0-20% ethyl acetate in *n*-hexane to afford the desired product **XLe** as a yellow solid. Yield: 0.58 g (74%). **LCMS** Calculated. for $C_{16}H_{14}N_2O_3$ is 282.10; Observed. 283.25 [M^++1]. **^{1}HNMR (400 MHz, $CDCl_3$):** δ 7.82-7.80 (m, 2H), 7.71-7.68 (m, 2H), 7.19-7.17 (m, 1H), 7.11 – 7.10 (m, 1H), 5.99 (t, J = 6.8 Hz, 1H), 4.01 (t, J = 6.8 Hz, 2H), 3.55 (s, 3H), 2.92 (t, J = 6.4 Hz, 2H).

[000251] **Step-6: 3-(2-aminoethyl)-1-methylpyridin-2(1H)-one (XL)**

[000252] To a stirred solution of 2-(2-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione XLe (580 mg, 2.05 mmol) in methanol (5 mL) was added hydrazine hydrate (0.015 mL, 3.08 mmol). The reaction was stirred at rt for 2 h under nitrogen atmosphere. The progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was concentrated under vacuum. Then crude was diluted with water (2 mL) and acidified with conc. HCl (pH=2). The solid formed was filtered and washed with water (2 mL). The aqueous layer was basified with 1N NaOH solution and extracted with 10% methanol in DCM (100 mL X 3). The combined organic layer was dried over sodium sulphate and concentrated under vacuum to afford the desired title compound **XL** as a pale-yellow viscous liquid. The crude was taken for next step without further purification. Yield: 0.3 g (95%). **LC_MS** Calculated. for $C_8H_{12}N_2O$ is 152.09; Observed. 153.00 $[M+H]^+$.

Synthesis of 3-(2-aminoethyl)-1-ethylpyridin-2(1H)-one XLI



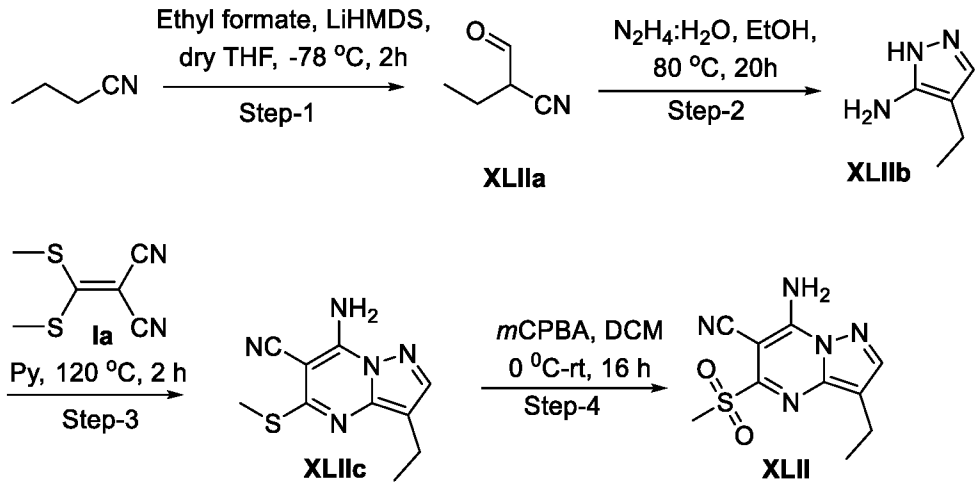
Step-1: Synthesis of 2-(2-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione (XLIa)

[000253] To a solution of (2-(2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **XLd** (0.6 g, 2.24 mmol) in dimethoxy ethane (3 mL) was added K_2CO_3 (0.62 g, 4.47 mmol) and iodoethane (0.7g, 4.47 mmol). The reaction mixture was stirred at 90 °C for 24 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, reaction mixture was filtered and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography with ethyl acetate in hexane (0-50%) to get the desired compound **XLIa** as a yellow solid. Yield: 0.6 g, (90.0 %); **LC_MS** calculated for $C_{17}H_{16}N_2O_3$ is 296.12; Observed: 297.20 $[M+H]^+$.

Step-2: 3-(2-aminoethyl)-1-ethylpyridin-2(1H)-one (XLI)

[000254] To a solution of 2-(2-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **XLIa** (0.6 g, 2.02 mmol) in methanol (6 mL) was added hydrazine hydrate (0.15 mL, 3.04 mmol) and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was concentrated and added water (2 mL), acidified with Conc. HCl to pH~2. Solids were filtered, basified by sodium hydroxide (5 mL) and extracted with ethyl acetate (50 ml X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the crude compound **XLI**. The crude compound was taken for the next step without further purification. Yield: 0.3 g, (89.02 %); **LCMS** Calculated. for $C_9H_{14}N_2O$ is 166.11; Observed. 167.30 $[M+H]^+$.

Synthesis of 7-amino-3-ethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (XLII)



Step-1: 2-formylbutanenitrile (XLIIa)

[000255] To a solution of LiHMDS (20 g, 100 mmol) in THF (200 mL) at -78 °C was added butyronitrile (5 g, 70 mmol) and stirred at the same temperature for 1 h. This was followed by an addition of ethyl formate (6 mL, 70 mmol) and stirred for 1 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was quenched with saturated ammonium chloride (50 mL) and extracted with diethyl ether (200 mL*3). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford the crude compound **XLIIa** as a pale-yellow viscous liquid. The crude compound was directly taken for next step without any further purification. Yield:7.1 g, (89.0 %); **LCMS** Calculated. for C_5H_7NO is 97.05; Observed. 96.00 $[M+H]^+$.

Step-2: 4-Ethyl-1H-pyrazol-5-amine (XLIIb)

[000256] To a solution of 2-formylbutanenitrile **XLIIa** (7.9 g, 81 mmol) and hydrazine hydrate (1:1, 4.8 mL, 98 mmol) in ethanol (80 mL) was added acetic acid (1.6 mL, 28 mmol) and stirred at 80 °C for 20 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was concentrated, added water (100 mL) and extracted with 0.5% methanol in dichloromethane (300 mL*3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to get the crude compound. The crude compound was purified by silica gel (100-200 mesh)

column chromatography with methanol in dichloromethane (0-2%) to afford the desired compound **XLIIb** as a pale-yellow viscous liquid. Yield:5.0 g, (60.0 %).

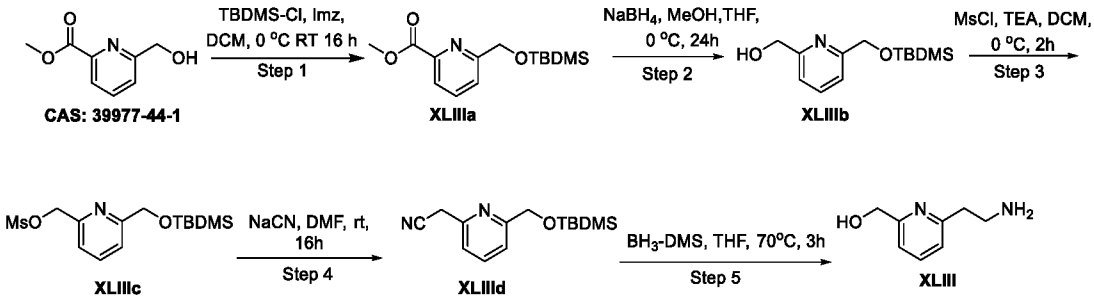
Step-3: 7-amino-3-ethyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (XLIIc)

[000257] To a solution of 4-ethyl-1H-pyrazol-3-amine **XLIIb** (1 g, 9 mmol) in pyridine (10 mL) was added 2-(bis(methylthio)methylene) malononitrile **Ia** (2 g, 10mmol) and stirred the reaction mixture at 120 °C for 2 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was poured into ice-cooled water and filtered the solid. The crude compound was purified by silica gel (100-200 mesh) column chromatography with ethyl acetate in n-hexane (0-10%) to afford the desired compound **XLIIc** as a brownish solid. Yield: 1.5 g, (70.0 %); **LCMS** Calculated. for $C_{10}H_{11}N_5S$ is 233.07; Observed. 232.5 $[M+H]^+$

Step-4: 7-amino-3-ethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (XLII)

[000258] To a solution of 7-amino-3-ethyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (0.7 g, 3.00 mmol) in dichloromethane (20 mL) at 0 °C was added mCPBA (2.59 g, 15.0 mmol) and stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was cooled to 0 °C and quenched with saturated sodium bicarbonate (5 mL) and extracted with ethyl acetate (30 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated to get crude material. The crude compound was washed with pentane and stirred with methanol (2 mL) for 10 min. Solid was filtered and organic layer was concentrated to afford the desired compound **XLII** as an off-white solid. Yield:125 mg, (15.7 %); **LCMS** Calculated. for $C_{10}H_{11}N_5O_2S$ is 265.06; Observed. 266.20 $[M+H]^+$.

[000259] **Synthesis of (6-(2-aminoethyl)164yridine-2-yl) methanol (XLIII)**



Step-1: Methyl 6-(((tert-butyldimethylsilyl) oxy) methyl) picolinate (XLIIIa)

[000260] A stirred solution of methyl 6-(hydroxymethyl) picolinate (CAS: 39977-44-1, 25 g, 0.15 mol) in DCM (500 mL) at 0 °C under inert atmosphere was added imidazole (20 g, 0.30 mol) and the resulting mixture was stirred for 10 min. This was followed by a portion wise addition of TBDMS-Cl (45 g, 0.30 mol) and the was stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with water (500 mL) and the resulting mixture was extracted with ethyl acetate (500 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to get crude compound. The crude compound was purified by silica gel (100-200) column chromatography using 0-10 % ethyl acetate in n-hexane to afford the desired compound **XLIIIa** as an off-white solid. Yield: 33 g (78.0 %); **LCMS** Calculated. $C_{14}H_{23}NO_3Si$ for is 281.14; Observed. 282.35 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** 8.01 (d, J = 7.6 Hz, 1H), 7.86 (t, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 4.93 (s, 2H), 3.99 (s, 3H), 0.96 (s, 9H), 0.12 (s, 6H).

Step-2: (6-(((tert-butyldimethylsilyl) oxy) methyl) pyridin-2-yl) methanol (XLIIIb)

[000261] A stirred solution of methyl 6-(((tert-butyldimethylsilyl) oxy) methyl) picolinate **XLIIIa** (33 g, 0.12 mol) in THF: MeOH (525 mL; 2:1) was cooled to 0 °C and added $NaBH_4$ (13 g, 0.35 mol) in portions under inert atmosphere over 20 min maintaining reaction temperature below 5 °C. The reaction mixture was stirred at rt for 16 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated under reduced pressure and to the residue was added sat. $NaHCO_3$ solution (300 mL). The mixture was extracted with DCM (300 mL X 3) and combined organic layer was dried over

anhydrous sodium sulphate. The solution was filtered and concentrated under reduced pressure. The crude compound was purified by silica gel (100-200) column chromatography using 10-20 % ethyl acetate in *n*-hexane to afford the desired compound **XLIIIb** as a colorless viscous liquid. Yield: 29 g (99.0 %); **LCMS** Calculated. $C_{13}H_{23}NO_2Si$ for is 253.15; Observed. 254.30 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** 7.70 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 4.33 (s, 2H), 4.73 (d, *J* = 4.8 Hz, 2H), 3.78 (t, *J* = 4.8 Hz, 1H), 0.96 (s, 9H), 0.13 (s, 6H).

Step-3: (6-(((tert-butyldimethylsilyl) oxy) methyl) pyridin-2-yl) methyl methane sulfonate (XLIIIc)

[000262] A stirred solution of (6-(((tert-butyldimethylsilyl) oxy) methyl) pyridin-2-yl) methanol **XLIIIb** (29 g, 0.11 mol) and TEA (24 mL, 0.17 mol) in DCM (300 mL) was cooled to 0 °C under inert atmosphere. To the resulting mixture was dropwise added mesyl-Cl (11 mL, 1.2 Eq, 0.14 mol) over 30 min and the reaction mixture was stirred at 0 °C for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was quenched with sat. $NaHCO_3$ solution (300 mL) and extracted with DCM (300 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated over reduced pressure to afford the desired compound **XLIIIc** as a pale-yellow solid. Yield: 40 g (100 %); **LCMS** Calculated. $C_{14}H_{25}NO_4SSi$ for is 331.13; Observed.332.30 $[M+H]^+$.

Step-4: 2-(6-(((tert-butyldimethylsilyl) oxy) methyl) pyridin-2-yl) acetonitrile (XLIIId)

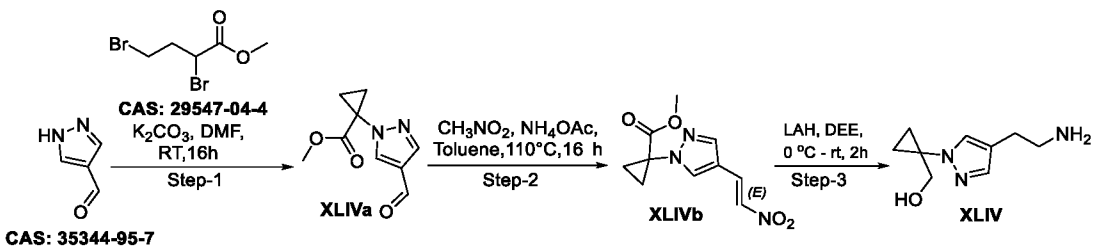
[000263] To a stirred solution of (6-(((tert-butyldimethylsilyl) oxy) methyl) pyridin-2-yl) methyl methane sulfonate **XLIIIc** (40 g, 120 mmol) in DMF (300 mL) was added NaCN (6.49 g, 132 mmol) and the reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with water (500 mL) and the resulting mixture was extracted with ethyl acetate (500 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced

pressure. The crude was purified by silica gel column chromatography using 0-15 % ethyl acetate in *n*-hexane to afford the desired compound **XLIIId** as a yellow viscous liquid. Yield: 21 g (66.7 %); **^{1}H NMR (400 MHz, $CDCl_3$):** 7.75 (t, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 4.80 (s, 2H), 3.89 (s, 2H), 0.96 (s, 9H), 0.12 (s, 6H).

Step-5: Synthesis of (6-(2-aminoethyl) pyridin-2-yl) methanol (XLIII)

[000264] To a stirred solution of 2-(6-(((tert-butyldimethylsilyl) oxy) methyl) pyridin-2-yl) acetonitrile (21 g, 80 mmol) in dry THF (250 mL) at 0 °C was added BH_3.DMS (28.8 mL, 320 mmol) and the reaction mixture was stirred at 70 °C for 3h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to 0 °C and the reaction was quenched with MeOH (15 mL), and stirred for 30 min. Then added water (20 mL) and 1 M HCl solution (15 mL) and the resulting mixture was extracted with ethyl acetate (50 mL) followed by with DCM (50 mL) to get rid of the impurities. The aqueous layer was basified with 2N NaOH solution and extracted with DCM (500 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated to afford the desired compound **XLIII** as a brown viscous liquid. Yield: 9.8 g (81 %); **LCMS** Calculated. $C_8H_{12}N_2O$ for is 152.09; Observed.153.00 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** 7.61 (t, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 2H), 4.73 (s, 2H), 3.11 (q, J = 6.4 Hz, 2H), 2.92 (q, *J* = 6.4 Hz, 2H).

Synthesis of (1-(4-(2-aminoethyl)-1H-pyrazol-1-yl) cyclopropyl) methanol. (XLIV)



Step-1: Methyl 1-(4-formyl-1H-pyrazol-1-yl) cyclopropane-1-carboxylate (XLIVa)

[000265] To a stirred solution of 1H-pyrazole-4-carbaldehyde (CAS: 35344-95-7; 600 mg, 6.24 mmol) in DMF (3 mL) was added K_2CO_3 (3.45 g, 25.0 mmol) at room temperature under inert atmosphere. The reaction mixture was cooled to 0 °C and added methyl 2,4-dibromobutanoate (CAS: 29547-04-4, 2.11 g, 8.12 mmol). The reaction was stirred at rt for16 h. Progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (100 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified by combi flash silica (230-400) column chromatography by using 0-20% ethyl acetate in *n*-hexane to afford the desired product **XLIVa** as a yellow liquid. Yield: 0.9 g (75%). **LCMS** Calculated. for: $C_9H_{10}N_2O_3$ is 194.06; Observed. 195.20 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.88 (s, 1H), 8.06 – 8.01 (m, 1 H), 7.98 (s, 1H), 3.71 (s, 3H) 1.92 – 1.89 (m, 2 H), 1.70 – 1.67 (m, 2H).

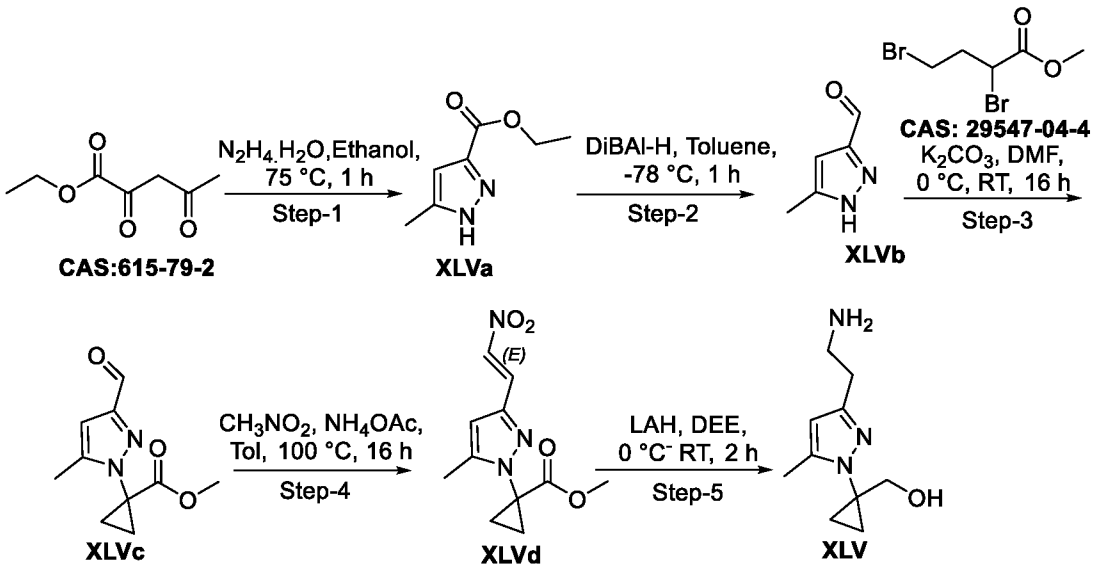
Step-2: Methyl (*E*)-1-(4-(2-nitrovinyl)-1*H*-pyrazol-1-yl) cyclopropane-1-carboxylate (XLIVb)

[000266] To a stirred solution of methyl 1-(4-formyl-1H-pyrazol-1-yl) cyclopropane-1-carboxylate **XLIVa** (800 mg, 4.12 mmol) in toluene (16 mL) were added ammonium acetate (476 mg, 6.18 mmol) and nitromethane (3.77 g, 61.8 mmol) at room temperature. The reaction mixture was stirred at 110 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with 1N HCl (20 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified by flash chromatography (silica gel 230-400 mess) using 0-25 % ethyl acetate in *n*-hexane to afford the compound **XLIVb** as yellow solid. Yield: 0.6 g (62%). **LCMS** Calculated. for $C_{10}H_{11}N_3O_4$ is 237.07; Observed. 238.20 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.92 (d, *J*= 13.6 Hz, 1H), 7.83 (s, 1H), 7.77 (s, 1H), 7.44 (d, *J*= 13.2 Hz, 1H), 3.71 (s, 3H) 1.92 – 1.88 (m, 2 H), 1.68 – 1.58 (m, 2H).

Step-3: (1-(4-(2-aminoethyl)-1H-pyrazol-1-yl) cyclopropyl) methanol (XLIV)

[000267] A solution $LiAlH_4$ (15 mL, 1M in THF, 0.02 mol) in DEE (20 mL) was cooled to 0 °C and dropwise added a solution of methyl(E)-1-(4-(2-nitrovinyl)-1H-pyrazol-1-yl) cyclopropane-1-carboxylate **XLIVb** (0.9 g, 4 mmol) in THF (5 mL). The reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to 0 °C, quenched with water (3 mL), 15% NaOH solution (1 mL) and ethyl acetate (30 mL). The mixture was stirred at RT for 30 min and filtered and the residue was washed with fresh ethyl acetate (50 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the desired compound **XLIV** as a brown liquid. The crude was taken for next step without further purification. Yield: 0.6 g (75%).

Synthesis of (1-(3-(2-aminoethyl)-5-methyl-1H-pyrazol-1-yl) cyclopropyl) methanol. XLV



Step-1: Ethyl 5-methyl-1H-pyrazole-3-carboxylate (XLVa)

[000268] A solution of ethyl 2,4-dioxopentanoate (CAS: 615-79-2, 5 g, 0.03 mol) in ethanol (4 mL) was cooled to 0 °C and hydrazine hydrate (2 mL, 0.03 mol, 1:1) was added dropwise at 0 °C under inert atmosphere. The reaction mixture was refluxed for 1 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in water (50 mL). The mixture was extracted with ethyl

acetate (50 mL X 3) and the combined organic layer was given brine wash, dried over anhydrous sodium sulphate. The solution was concentrated under reduced pressure to obtain the desired product as a pale-yellow solid. The crude was taken for the next step without further purification. Yield: 3.7g (72 %). **LCMS** Calculated. for $C_7H_{10}N_2O_2$ is 154.07; Observed. 155.05 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.60 (s, 1H), 4.38 (q, *J*= 6.8 Hz, 2H), 2.36 (s, 3H), 1.38 (t, *J*= 6.8 Hz, 3H).

Step-2: 5-methyl-1H-pyrazole-3-carbaldehyde (XLVb)

[000269] A solution of ethyl 5-methyl-1H-pyrazole-3-carboxylate **XLVa** (3.6 g, 23 mmol) in dry toluene (54 mL) was cooled to -78 °C under inert atmosphere and DIBAL-H (31 mL, 1.5 molar, 47 mmol) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 1 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with water (10 mL) and methanol (2 mL) at -78 °C. The mixture was stirred at rt for 10-15 min and ethyl acetate (30 mL) was added. The mixture was filtered through celite bed and washed with ethyl acetate thoroughly. The combined organic layer was separated, washed brine solution, and dried over anhydrous sodium sulphate. The solution was concentrated under reduced pressure to afford the desired compound **XLVb** as a pale-yellow solid. The crude product was taken for the next step without further purification. Yield: 1.3g (50 %

Step-3: Methyl 1-(3-formyl-5-methyl-1H-pyrazol-1-yl) cyclopropane-1-carboxylate (XLVc)

[000270] A solution of 5-methyl-1H-pyrazole-3-carbaldehyde **XLVb** (1.3 g, 12 mmol) in DMF (11 mL) was cooled to 0 °C and portion wise added K_2CO_3 (6.5 g, 47 mmol). This was followed by a dropwise addition of methyl 2,4-dibromobutanoate (2.2 mL, 15 mmol) and the reaction mixture was stirred at room temperature for 16 h. The progress of reaction was monitored by TLC analysis. After completion, cold water (50 mL) was added and extracted with ethyl acetate (50 mL X 3). The combined organic layer was given brine wash, dried over anhydrous sodium sulphate, and concentrated to get crude material. The crude material was purified by Combi-flash chromatography (mesh 230-400 silica gel)

column chromatography using 0-10% ethyl acetate in *n*-hexane to afford the desired compound **XLVc** as an off-white solid. Yield: 0.47g, (18.7%). **LCMS** Calculated. for $C_{10}H_{12}N_2O_3$ is 208.08; Observed. 209.10 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.90 (s, 1H), 6.56 (s, 1H), 3.72 (s, 3H), 2.32 (s, 3H), 1.96 (s, 2H), 1.72 (s, 2H).

Step-4: Methyl (E)-1-(5-methyl-3-(2-nitrovinyl)-1H-pyrazol-1-yl) cyclopropane-1-carboxylate (XLVd)

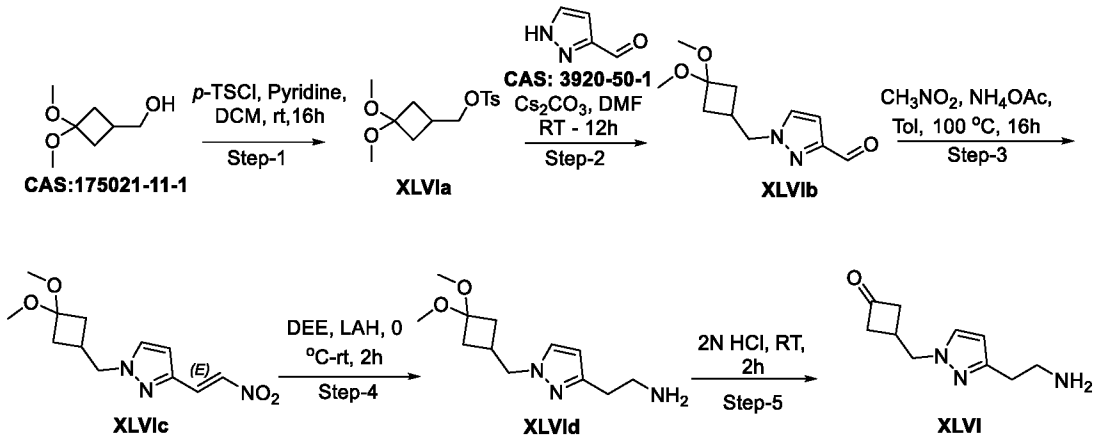
[000271] To a solution of methyl 1-(3-formyl-5-methyl-1H-pyrazol-1-yl) cyclopropane-1-carboxylate **XLVc** (480 mg, 2.31 mmol) in toluene (20 mL) were added ammonium acetate (267 mg, 3.46 mmol) and nitromethane (1.24 mL, 23.1 mmol) under inert atmosphere. The reaction mixture was stirred at 100 °C for 16 h and the progress of the was monitored by TLC analysis. After completion, the reaction was quenched by dropwise addition of 1N HCl solution (20 mL) and the resulting mixture was extracted with ethyl acetate (20 mL X 3). The combined organic phase was washed with 1N HCl solution (20 mL), followed by with brine. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by Combi-flash chromatography silica gel (mesh 230-400) column chromatography using 0-10% ethyl acetate in *n*-hexane to afford the desired product **XLVd** as an off-white solid. Yield:(0. 383g, 66.14%); **LCMS** Calculated. for $C_{11}H_{13}N_3O_4$ is 251.09; Observed. 252.20 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.90 (d, *J*= 13.2 Hz, 1H), 7.55 (d, *J*= 14.0 Hz, 1H), 6.32 (s, 1H), 3.71 (s, 3H), 2.31 (s, 3H), 1.94 (s, 2H), 1.69 (s, 2H).

Step-5: (1-(3-(2-Aminoethyl)-5-methyl-1H-pyrazol-1-yl) cyclopropyl) methanol (XLV)

[000272] A solution of $LiAlH_4$ (6.05 mL, 1 M in THF, 6.05 mmol) in dry diethyl ether (20 mL) was cooled to 0 °C and solution of methyl (*E*)-1-(5-methyl-3-(2-nitrovinyl)-1H-pyrazol-1-yl) cyclopropane-1-carboxylate **XLVd** (380 mg, 1.51 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 2 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to 0 °C and water (0.4 mL) was added slowly. This was followed by slow addition of 15% KOH solution (0.4 mL)

and water (1.2 mL). The mixture was stirred at rt for 10 minutes, ethyl acetate (50 mL) was added and stirring at rt was continued for additional 15 minutes. The mixture was passed through a celite bed and washed thoroughly with fresh ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and concentrated to get desired product **XLV** as pale-yellow oil. The compound was used as such for the next step without further purification. Yield: 0.370g (crude).

Synthesis of 3-((3-(2-aminoethyl)-1H-pyrazol-1-yl) methyl) cyclobutan-1-one. (XLVI)



Step-1: (3,3-dimethoxycyclobutyl) methyl 4-methylbenzenesulfonate (XLVIa)

[000273] To a stirred solution of (3,3-dimethoxycyclobutyl) methanol (CAS:175021-11-1, 5.0 g, 34 mmol) in DCM (100 mL) was added pyridine (8.3 mL, 1.00 mmol) and the reaction mixture was cooled to 0 °C. *p*TSCl (7.2 g, 38 mmol) was added in portions under nitrogen atmosphere. The resulting mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was diluted with saturated $NaHCO_3$ solution (100 mL) and extracted with DCM (100 mL X 3). Combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by combi-flash column chromatography (230-400 silica) using 0-15% ethyl acetate in *n*-hexane to afford the desired compound **XLVIa** as a colorless liquid. Yield: 8.2 g, (82 %); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.79 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H) 4.03 (d, J = 7.2 Hz, 2H), 3.11 (s, 3H), 3.06 (s, 3H), 2.45 (s, 3H), 2.39-2.36 (m, 1H), 2.27-2.23 (m, 2H), 1.83-1.78 (m, 2H).

Step-2: 1-((3,3-dimethoxycyclobutyl) methyl)-1H-pyrazole-3-carbaldehyde (XLVIb)

[000274] To a stirred solution of 1H-pyrazole-3-carbaldehyde (CAS: CAS: 3920-50-1, 2.4 g, 25 mmol) in DMF (20 mL) was added cesium carbonate (16 g, 50 mmol) and the reaction mixture was cooled to 0 °C. (3,3-dimethoxycyclobutyl) methyl 4-methylbenzenesulfonate **XLVIa** (8.3 g, 27 mmol) was added slowly under nitrogen atmosphere. The resulting reaction mixture was stirred at rt for 12 h. Progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (200 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by combi-flash column chromatography using 0-15% ethyl acetate in *n*-hexane to afford the desired compound **XLVIb** as a pale-yellow viscous liquid. Yield: 4.4 g, (78 %); Chemical Formula: $C_{11}H_{16}N_2O_3$, **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.96 (s, 1H), 7.42 (d, *J*= 2.0 Hz, 1H), 6.80 (d, *J*= 2.0 Hz, 1H) 4.29 (d, *J* = 7.6 Hz, 2H), 3.13 (s, 6H), 2.70-2.45 (m, 1H), 2.34-2.32 (m, 2H), 1.96-1.91 (m, 2H).

Step-3: (E)-1-((3,3-dimethoxycyclobutyl) methyl)-3-(2-nitrovinyl)-1H-pyrazole (XLVIc)

[000275] To a stirred solution of 1-((3,3-dimethoxycyclobutyl) methyl)-1H-pyrazole-3-carbaldehyde **XLVIb** (4.4 g, 20 mmol) in toluene (50 mL) was added nitromethane (16 mL, 290 mmol) followed by an addition of ammonium acetate (2.3 g, 29 mmol). The resulting mixture was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was cooled rt, diluted with 1N HCl (50 mL) and extracted with ethyl acetate (100 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by combi-flash column chromatography using 0-10% ethyl acetate in *n*-

hexane to afford the desired compound **XLVIc** as a pale-yellow solid. Yield: 3.3g, (63 %).

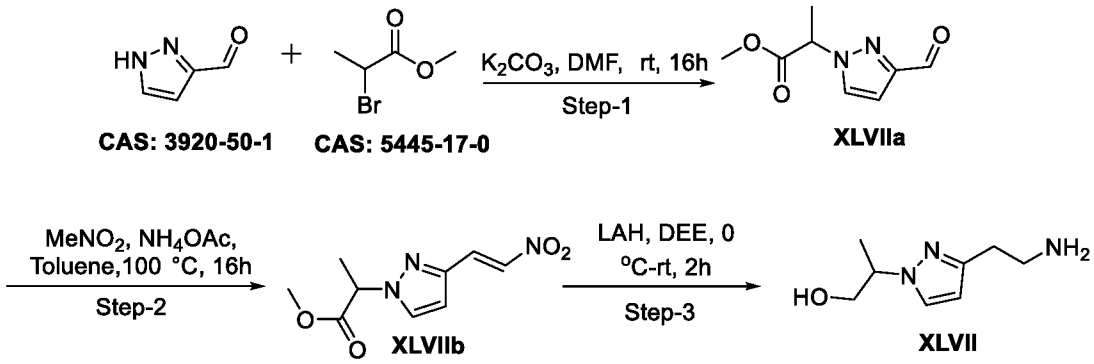
Step-4: 2-(1-((3,3-dimethoxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethan-1-amine (XLVId)

[000276] A stirred solution of $LiAlH_4$ (49 mL, 1 molar in THF, 49 mmol) in diethyl ether (100 mL) was cooled to 0 °C and drop wise added a solution of (E)-1-((3,3-dimethoxycyclobutyl) methyl)-3-(2-nitrovinyl)-1H-pyrazole **XLVIc** (3.3 g, 12 mmol) under inert atmosphere. The resulting mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to 0 °C and quenched with slowly addition of water (3.3 mL), 15% KOH solution (3.3 mL) and again added (10 mL) of water. The resulting reaction mixture was stirred at rt for 20 min and ethyl acetate (100 mL) was added. The mixture was filtered, and the residue was washed fresh ethyl acetate (100 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product **XLVId** was directly taken for next step without purification. Yield: 2.4 g, (crude); **LCMS** Calculated. for $C_{12}H_{21}N_3O_2$ is 239.32; Observed.240.35 $[M+H]^+$.

Step-5: 3-((3-(2-aminoethyl)-1H-pyrazol-1-yl) methyl) cyclobutan-1-one (XLVI)

[000277] To a stirred solution of 2-(1-((3,3-dimethoxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethan-1-amine **XLVId** (2.6 g, 11 mmol) in ethanol (50 mL) was a slowly added 2N HCl (3 mL) at 0 °C under nitrogen atmosphere. The reaction was stirred at rt for 2 h and progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated under vacuum. The crude product **XLVI** was taken directly forward to next step without further purification. Yield:2.4g crude

Synthesis of 2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) propan-1-ol. (XLVII)



Step-1: Methyl 2-(3-formyl-1H-pyrazol-1-yl) propanoate (XLVIIa)

[000278] To a solution of 1H-pyrazole-3-carbaldehyde (CAS: 3920-50-1, 3.0 g, 31 mmol) in DMF (30 mL) was added K_2CO_3 (17 g, 0.12 mol) and the solution was cooled to 0°C under inert atmosphere. Then methyl 2-bromopropanoate (CAS: 5445-17-0, 5.2 mL, 47 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with cold water (50 mL) and extracted with ethyl acetate (100 mL X 3). The combined organic phase was washed with brine and dried over anhydrous sodium sulphate. The solution was concentrated under reduced pressure and the crude material was purified by combi-flash silica gel (230-400) column chromatography using 0-10% ethyl acetate in *n*-hexane to afford the desired compound **XLVIIa** as a colorless oil. Yield: 0.70 g, (13.0%); **LCMS** Calculated. for $C_8H_{10}N_2O_3$ is 182.06; Observed. 183.25 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.98 (s, 1H), 7.59 (s, 1H), 6.86 (s, 1H), 5.19 (q, J = 7.2 Hz, 1H), 3.78 (s, 3H), 1.86 (d, J = 6.8 Hz, 3H).

Step-2: methyl (E)-2-(3-(2-nitrovinyl)-1H-pyrazol-1-yl) propanoate (XLVIIb)

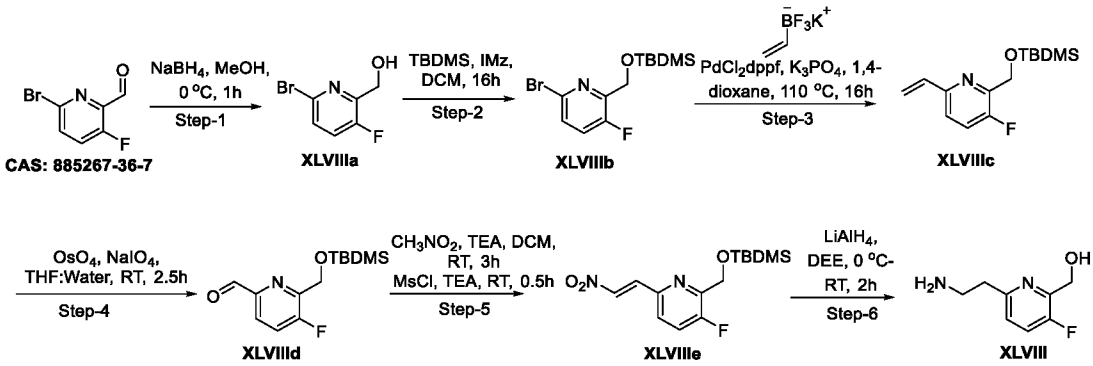
[000279] To a solution of methyl 2-(3-formyl-1H-pyrazol-1-yl) propanoate **XLVIIa** (700 mg, 3.84 mmol) was dissolved in toluene (20 mL) under inert atmosphere were added ammonium acetate (444 mg, 5.76 mmol) and nitromethane (2.07 mL, 38.4 mmol), and the resulting mixture was mixture was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt and quenched with 1N HCl solution (25 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (100 mL X 3). The combined organic layer was washed

with brine, dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude material was purified by combi-flash silica gel (230-4000 column chromatography using 0-20% ethyl acetate in *n*-hexane to afford the desired compound **XLVIIb** as pale-yellow oil. Yield: 560 mg, (65.7%); **LCMS** Calculated. for $C_9H_{11}N_3O_4$ is 225.07; Observed. 226.15 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.97 (d, *J*=13.6 Hz, 1H), δ 7.61, (d, *J*=14.0 Hz, 2H), 6.61 (s, 1H), 5.14 (q, *J* = 7.2 Hz, 1H), 3.77 (s, 3H), 1.83 (d, *J* = 7.2 Hz, 3H).

Step-3: 2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) propan-1-ol (XLVII)

[000280] A solution of $LiAlH_4$ (9.95 mL, 1 M in THF, 9.95 mmol) in diethyl ether (20 mL) was cooled to 0 °C under inert atmosphere and dropwise added a solution of methyl (E)-2-(3-(2-nitrovinyl)-1H-pyrazol-1-yl) propanoate **XLVIIb** (560 mg, 2.49 mmol) in diethyl ether (8 mL). The reaction mixture was stirred at room temperature for 2 h and the progress of reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to 0 °C and quenched with sequential dropwise addition of water (0.6 mL), 15% KOH solution (0.6 mL) and again water (1.8 mL). The reaction mixture was stirred at rt for 10 min and ethyl acetate (50 mL) was added and stirred for additional 15 min. The mixture was filtered and thoroughly washed with ethyl acetate (50 mL X 3). The combined organic layer was concentrated under reduced pressure to afford the desired product **XLVII** as pale-yellow oil. Yield: 0.47 g, (100%); **LCMS** Calculated. for $C_8H_{15}N_3O$ is 169.12; Observed. 170.35 $[M+H]^+$.

Synthesis of (6-(2-aminoethyl)-3-fluoropyridin-2-yl) methanol (XLVIII)



Step-1: (6-bromo-3-fluoropyridin-2-yl) methanol (XLVIIIa)

[000281] To a solution of 6-bromo-3-fluoropicolinaldehyde (CAS: 885267-36-7, 2 g, 10mmol) in Methanol (20 mL) at 0^0C was added NaBH4 (0.4 g, 10mmol) and stirred at the same temperature for 30 min. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, added NaHCO3 (50mL) and extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine (25mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to afford the desired product **XLVIIIa** as off-white solid. The crude was taken for the next step without any further purification. Yield: 1.96 g, (100.0 %); **LCMS** calculated for C_6H_5BrFNO is 204.95; Observed: 206.20 [M+H] $^+$.**^{1}HNMR (400 MHz, $CDCl_3$,):** δ 7.74-7.63 (m, 2H), 5.47 (t, *J* = 6.4Hz, 1H), 4.55-4.54 (m, 2H).

Step-2: 6-bromo-2-(((tert-butyldimethylsilyl) oxy) methyl)-3-fluoropyridine (XLVIIIb)

[000282] To a solution of (6-bromo-3-fluoropyridin-2-yl) methanol **XLVIIIa** (1.96 g, 9.51 mmol) in DCM (50 mL) was added imidazole (0.972 g, 14.3 mmol). The reaction mixture was stirred at rt for 30 min This was followed by an addition of TBDMS-Cl (1.72 g, 11.4 mmol) at 0 ºC and stirred at rt for 16h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, water (50 mL) was added and extracted with dichloromethane (50 mL x 2). The combined organic layer was washed with brine (25mL) dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography using ethyl acetate in *n*-hexane (0-15%) to afford the desired compound **XLVIIIb** as a colorless viscous liquid. Yield: 2.8 g, (98.0 %); **LCMS** calculated for $C_{12}H_{19}BrFNOSi$ is 319.04; Observed. 321.95 [M+H] $^+$.**^{1}HNMR (400 MHz, $cdcl_3$,):** δ 7.41-7.38 (m, 1H), 7.28-7.24 (m, 1H), 4.82 (d, *J* = 6.0 Hz, 2H), 0.91 (s, 9H), 0.12 (s, 6H).

Step-3: 2-(((tert-butyldimethylsilyl) oxy) methyl)-3-fluoro-6-vinylpyridine (XLVIIIc)

[000283] To a solution of 6-bromo-2-(((tert-butyldimethylsilyl) oxy) methyl)-3-fluoropyridine **XLVIIIb** (1.8 g, 5.6 mmol) and potassium trifluoro(vinyl)borate (1-) (0.90 g, 6.7 mmol) in 1,4-dioxane (20 mL) was added potassium phosphate,

tribasic (1.8 g, 8.4 mmol) and purged with N_2 for 10 min. This was followed by an addition of $PdCl_2$(dppf) (0.21 g, 0.28 mmol) and stirred at 110 °C for 16h.The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was cooled to room temperature and added water (50 mL), extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography using ethyl acetate in *n*-hexane (0-10%) to afford the desired product **XLVIIIc** as a colorless viscous liquid. Yield: 2.67 g, (93.0 %); **LCMS** calculated for $C_{14}H_{22}FNOSi$ is 267.15; Observed. 268.35 $[M+H]^+$.**^{1}HNMR (400 MHz, $CDCl_3$,):** δ 7.34-7.24 (m, 2H), 6.82-6.75 (m, 1H), 6.13 (d, *J*=17.6 Hz, 1H), 5.43 (d, *J* = 10.8 Hz, 1H), 4.87 (s, 2H), 0.92 (s, 9H), 0.12 (s, 6H).

Step-4: 6-(((tert-butyldimethylsilyl) oxy) methyl)-5-fluoropicolinaldehyde (XLVIIId)

[000284] To a solution of 2-((tert-butyldimethylsilyl) oxy)-3-fluoro-6-vinylpyridine **XLVIIIc** (2.67 g, 10.5 mmol) in THF (25 mL) at 0 °C was added osmium (VIII) oxide (6.67 mL, 4% in water, 1.05 mmol) and the stirred at rt for 30 min. This was followed by an addition of sodium periodate (2.25 g, 10.5 mmol) and stirred at rt for 2 h. The reaction was monitored by TLC analysis. After the completion of the reaction, added water (35 mL) and extracted with ethyl acetate (35 mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford the crude as a brown viscous liquid. The crude compound was purified by silica gel (230-400 mesh) column chromatography using ethyl acetate in *n*-hexane (0-5%) to afford the desired compound **XLVIIId** as a colorless viscous liquid. Yield: 1.3 g, (48.0 %); **LCMS** calculated for $C_{12}H_{20}FNO_2Si$ is 269.12; Obs. 270.30 $[M+H]^+$.**^{1}HNMR (400 MHz, $CDCl_3$,):** δ 10.04 (s, 1H), 7.96 (q, *J*= 4.8 Hz, 1H), 7.53 (t, *J*= 8.4 Hz, 1H), 4.96 (s, 2H), 0.93 (s, 9H), 0.14 (s, 6H).

Step-5: (E)-2-(((tert-butyldimethylsilyl) oxy) methyl)-3-fluoro-6-(2-nitrovinyl) pyridine (XLVIIIe)

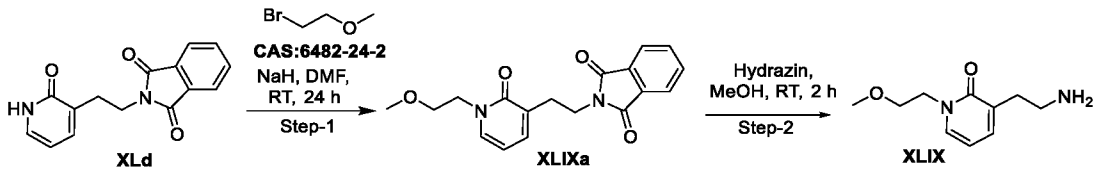
[000285] To a solution of 6-(((tert-butyldimethylsilyl) oxy) methyl)-5-fluoropicolinaldehyde **XLVIIId** (1.3 g, 4.8 mmol) in dichloromethane (15 mL) at 0 °C were added nitromethane (0.31 mL, 5.8 mmol) and triethylamine (3.4 mL, 24 mmol). The resulting mixture was stirred at rt for 3 h. The progress of the reaction was monitored by TLC analysis. After the complete consumption of the starting material, the reaction mixture was concentrated, and the residue was dissolved in fresh DCM (10 mL). The resulting mixture was cooled to 0 °C and triethyl amine (3.4 mL, 34 mmol) was added followed by a dropwise addition of solution of mesyl-Cl (1.1 mL, 14 mmol) under inert atmosphere. The reaction mixture was stirred at rt for 30 min. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was concentrated, added water (25mL) and extracted with ethyl acetate (25 mL x 2). The combined organic layer was washed with brine (50 mL) and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography using ethyl acetate in *n*-hexane (0-5%) to afford the desired product **XLVIIIe** as a colorless viscous liquid. Yield: 0.78 g, (52.0 %); **LCMS** calculated for $C_{14}H_{21}FN_2O_3Si$ is 312.13; Observed. 313.30 $[M+H]^+$ **^{1}HNMR (400 MHz, cdcl$_3$,):** δ 7.97-7.90 (m, 2H), 7.44 (t, *J* =5.2 Hz, 2H), 4.89 (s, 2H), 0.93 (s, 9H), 0.13 (s, 6H).

Step-6: (6-(2-aminoethyl)-3-fluoropyridin-2-yl) methanol (XLVIII)

[000286] To a solution of lithium aluminum (III) hydride (10 mL, 1 M, 10 mmol) in dry diethyl ether (60 mL) at 0 °C was added a solution of (E)-2-((tert-butyldimethylsilyl) oxy)-3-fluoro-6-(2-nitrovinyl) pyridine **XLVIIIe** (0.78 g, 2.6 mmol) in dry diethyl ether (10 mL). The resulting mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was cooled to 0 °C and added ice cold water (0.7 mL). This was followed by an addition of 15% KOH (0.7 mL) and stirred for 20 min. Added ethyl acetate (75 mL) and stirred at rt for 30 min. The reaction mixture was filtered, and the residue was washed with ethyl acetate (100 mL). Filtrate was concentrated under reduced pressure to afford the desired compound **XLVIII** as a pale-yellow viscous liquid. The crude was taken for the next step

without any further purification. Yield: 0.4 g, (90.0 %); **LCMS** calculated for $C_8H_{11}FN_2O$ is 170.09; Observed: 171.30 $[M+H]^+$.

Synthesis of 3-(2-aminoethyl)-1-(2-methoxyethyl) pyridine-2(1H)-one (XLIX)



Step-1 2-(2-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione (XLIXa)

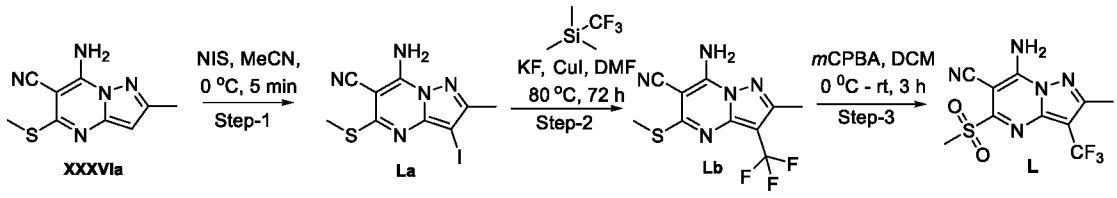
[000287] To a stirred solution of 2-(2-(2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **XLd** (1.2 g, 4.5 mmol) in DMF (10 mL) was cooled 0 °C and added NaH (0.13 g, 5.4 mmol). This was followed by dropwise addition of 1-bromo-2-methoxyethane (CAS:6482-24-2, 0.93 g, 6.7 mmol) and the resulting reaction mixture was stirred at room temperature for 24 hours. The progress of the reaction was monitored by TLC. The reaction was quenched with water (100 mL) and the resulting mixture was extracted with ethyl acetate (200 ml x 3) and the combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude residue was subjected silica gel (230-400 mesh) column chromatography using 10-70% ethyl acetate in *n*-hexane to afford the desired compound **XLIXa** as a yellow liquid. Yield: 400 mg (27%); **LCMS** Calculated. for $C_{18}H_{18}N_2O_4$ is 326.13; Observed. 327.00 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.811-7.791 (m, 2H), 7.696-7.674 (m, 2H), 7.244-7.222 (m, 1H), 7.121-7.104 (m, 1H), 5.973 (t, J = 6.8 Hz, 1H), 4.099 (t, J = 5.2 Hz, 2H), 4.016 (t, J = 6.4 Hz, 2H), 3.663 (t, J = 5.2 Hz, 2H), 3.329 (s, 3H), 2.959-2.931 (m, 2H).

Step-2: 3-(2-aminoethyl)-1-(2-methoxyethyl) pyridin-2(1H)-one (XLIX)

[000288] To a stirred solution of 2-(2-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **XLIXa** (400 mg, 1.23 mmol) in MeOH (4 mL) was added hydrazine hydrate (61.4 mg, 1.23 mmol) and the reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated and was added 2 mL of water then acidified with conc. HCl (pH = 2). Filtered the

precipitated solids and washed with water. The filtrate was basified with 4M. NaOH solution and extracted with ethyl acetate (50 ml X 3), the combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the desired compound a **XLIX** s a yellow liquid. Yield: 200 mg (91%); **LCMS** Calculated. for $C_{10}H_{16}N_2O_4$ is 196.12; Observed. 197.30 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.257-7.212 (m, 2H), 6.110 (t, J = 6.8 Hz, 1H), 4.980 (bs, 2H), 4.124 (t, J = 4.8 Hz, 2H), 3.678 (t, J = 4.8 Hz, 2H), 3.326 (s, 3H), 2.959 (t, J = 6.8 Hz, 2H), 2.689 (t, J = 6.8 Hz, 2H).

Synthesis of 7-amino-2-methyl-5-(methyl sulfonyl)-3-(trifluoromethyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (L)



Step-1: 7-amino-3-iodo-2-methyl-5-(methylthio) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile (La)

[000289] To a stirred solution of 7-amino-2-methyl-5-(methylthio) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **XXXVIa** (2.0 g, 9.00 mmol) in acetonitrile (20 mL) was added *N*-iodosuccinimide (2.0 g, 9.00 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 5 min. The progress of the reaction was monitored by TLC analysis. After completion, precipitated solid was filtered and collected solid was washed with excess of acetonitrile (50 mL) dried under high *vacuo* to afford desired pure product **La** as a brown solid. Yield: 2.8 g (90%); **LCMS** Calculated. for $C_9H_8IN_5S$ is 344.95; Observed. 346.10 $[M+H]^+$; **^{1}HNMR (400 MHz, DMSO-D_6):** δ 8.84 (bs, 2H), 2.59 (s, 3H), 2.37 (s, 3H).

Step-2: 7-amino-2-methyl-5-(methylthio)-3-(trifluoromethyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile (Lb)

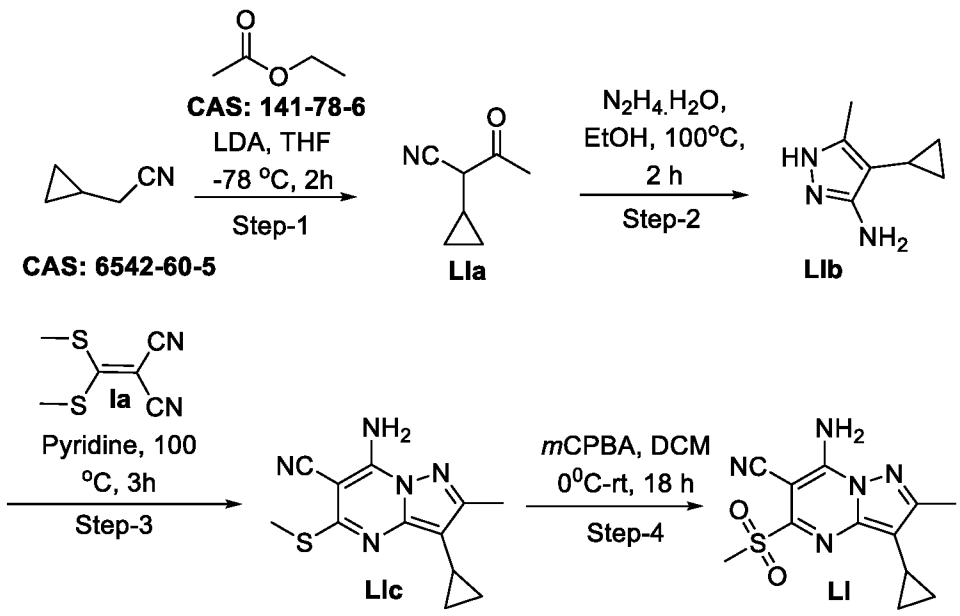
[000290] To a stirred solution of 7-amino-3-iodo-2-methyl-5-(methylthio) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **La** (1.0 g, 2.897 mmol) in DMF (10 mL) were added CuI (2.43 g, 12.75 mmol), trifluoro methyl trimethyl silane (1.483 g, 10.43 mmol) and potassium fluoride (0.606 g, 10.43 mmol) at room temperature

under N_2 atmosphere. The resulting mixture was stirred at 80 °C for 72 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with 35 mL of DCM and filtered. The filtrate was concentrated under reduced pressure to afford black crude semi-solid. The crude compound **Lb** was taken for the next step without further purification. Yield: 0.32 g (40.4%); **LC-MS** Calculated. for $C_{10}H_8F3N_5S$ is 287.05; Observed. 286.15 [M-H] $^+$; **^{1}HNMR (400 MHz, $CDCl_3$):** δ 6.34 (bs, 2H), 2.96 (s, 3H), 2.89 (s, 3H).

Step-3: 7-amino-2-methyl-5-(methyl sulfonyl)-3-(trifluoromethyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile (L)

[000291] To a stirred solution of 7-amino-2-methyl-5-(methylthio)-3-(trifluoromethyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **Lb** (0.23 g, 0.801 mmol) in acetonitrile (10 mL) was added mCPBA (0.691 g, 4.00 mmol) at 0 °C under N_2 atmosphere. The resulting mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC analysis. After completion, to the reaction mixture was added sat. sodium bicarbonate solution (10 mL) and filtered the precipitated solid and dried under *vacuo* to afford desired product **L** as an off- white solid. The crude compound was taken for the next step without further purification. Yield: 0.17 g (66.5%); **LCMS** Calculated. for $C_{10}H_8F_3N_5O_2S$ is 319.04; Observed. 318.10 [M-H] $^+$; **^{1}HNMR (400 MHz, $CDCl_3$):** δ 2.77 (s, 3H), 2.23 (s, 3H).

Synthesis of 7-amino-3-cyclopropyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (LI)



Step-1: 2-cyclopropyl-3-oxobutanenitrile (LIa)

[000292] To a stirred solution of LDA (9.2 mL, 2 molar, 8 mmol) in THF (30 mL) at -78 °C was drop wise added solution of 2-cyclopropylacetonitrile (CAS: 6542-60-5, 1.5 g, 18 mmol) in THF (10 mL) over 10-15 min. The resulting mixture was stirred for 1 h at the same temperature. This was followed by a dropwise addition of dry ethyl acetate (CAS: 141-78-6, 1.6 mL, 17 mmol) at -78 °C. The resulting mixture was stirred at same temperature for additional 1 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched with sat. NH_4Cl solution (50 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford the desired compound **LIa** as brown liquid. Yield: 2.0 g (86%). **LCMS** Calculated. for C_7H_9NO is 123.06; Observed: 122.25 $[M-1]^+$.

Step-2: 4-cyclopropyl-5-methyl-1H-pyrazol-3-amine (LIb)

[000293] To a stirred solution of 2-cyclopropyl-3-oxobutanenitrile **LIa** (2.4 g, 19 mmol) in ethanol (20 mL) was added hydrazine hydrate (1:1, 1.4 mL, 29 mmol) under inert atmosphere and the reaction mixture was heated at 100 °C for 2 h. The progress of the reaction was monitored by TLC analysis. After completion,

the reaction mixture was cooled to rt and concentrated under reduced pressure. The obtained residue was dissolved in water (50 mL) and extracted with 10% MeOH in DCM (50 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired compound **LIb** as a pale-yellow viscous liquid. Yield: 1.65 g (61%). **LCMS** Calculated. for $C_7H_{11}N_3$ is 137.09; Observed. 138.30 $[M+H]^+$.

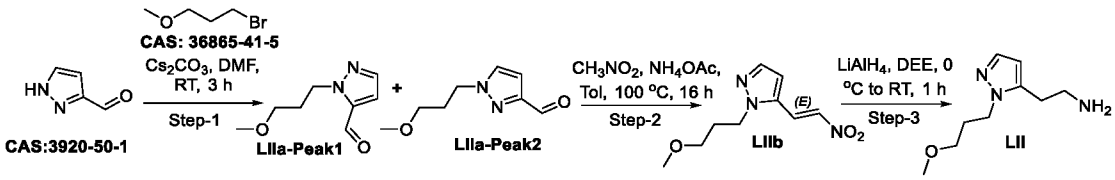
Step-3: 7-amino-3-cyclopropyl-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (LIc)

[000294] To a stirred solution of 4-cyclopropyl-5-methyl-4H-pyrazol-3-amine **LIb** (2.0 g, 15 mmol) in pyridine (10 mL) was added 2-(bis(methylthio)methylene) malononitrile **Ia** (2.5 g, 15 mmol). The resulting mixture was stirred at 100 °C for 3 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt and poured into ice cold water (500 mL). The precipitate formed was filtered and washed with cold water (100 mL). The obtained solid was dried and under vacuum to get the title compound **LIc** as pale-yellow solid. Yield: 2.2 g (52%). **LCMS** Calculated. for $C_{12}H_{13}N_5S$ is 259.09; Observed. 260.25 $[M+1]^+$.

Step-4:7-amino-3-cyclopropyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (LI)

[000295] A stirred solution of 7-amino-3-cyclopropyl-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **LIc** (2.2 g, 8.5 mmol) in DCM (50 mL) at 0°C was portion-wise added mCPBA (7.3 g, 42 mmol). The resulting reaction mixture was stirred at RT for 18 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated under vacuum. The crude was diluted with saturated sodium bicarbonate solution (100 mL) and stirred for 30 min. The solid formed was filtered and washed with water (100 mL X 3) followed by with *n*-pentane (100 mL x 3). The solid was dried under vacuum to afford the compound **LI** as an off-white solid. Yield: 2.2 g (52%). **^{1}HNMR (400 MHz, DMSO-D$_6$,):** δ 9.06 (bs, 2H), 3.38 (s, 3H), 2.46 (s, 3H), 1.81-1.77 (m, 1H), 1.06-1.01 (m, 2H), 0.19- 0.89 (m, 2H).

Synthesis of 2-(1-(3-methoxypropyl)-1H-pyrazol-5-yl) ethan-1-amine. (LII)



Step-1: 1-(3-methoxypropyl)-1H-pyrazole-5-carbaldehyde (LIIa-Peak1) and 1-(3-methoxypropyl)-1H-pyrazole-3-carbaldehyde (LIIa-Peak2)

[000296] To a solution of 1H-pyrazole-3-carbaldehyde (CAS:3920-50-1, 3 g, 30 mmol) in DMF (15 mL) was added cesium carbonate (30 g, 90 mmol) and stirred at rt for 10 min. This was followed by an addition of 1-bromo-3-methoxypropane (CAS: 36865-41-5, 6 g, 40 mmol) and stirred at rt for 3 h. The progress of the reaction was monitored by TLC analysis. The TLC and LC-MS analyses indicated formation of less polar close two spots with same molecular ion peaks (*m/z*= 169.15) indicated formation of the regio-isomers. After the completion of the reaction, water (25 mL) was added and extracted with ethyl acetate (3x25 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to afford the crude compound as a pale-yellow solid. The crude compound was purified by silica gel (230-400 mesh) column chromatography using ethyl acetate in *n*-hexane (0-20%) to afford the desired products as off-white solids. The structures of the desired products (**LIIa- Peak 1** and **LIIa- Peak II**) were confirmed by ^{1}H NOESY study, the fraction-1 was corresponding to **LIIa-Peak 1** whereas the fraction 2 was corresponds to **LIIa-Peak II**.

[000297] **LIIa-Peak I:** Yield: 0.6 g (11.4%); **LCMS** Calculated. for $C_8H_{12}N_2O_2$ is 168.08; Observed. 169.30 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$,):** δ 9.88 (s, 1H), 7.56 (s, 1H), 6.91 (d, *J* = 4.0 Hz 1H), 4.64 (t, *J* = 7.2 Hz, 2H), 3.36 (t, *J* = 6.0 Hz, 2H), 3.31 (s, 3H), 2.10 (t, *J* = 6.8 Hz, 2H).

[000298] **LIIa-Peak II:** Yield: 3.0 g, (57.0 %); **LCMS** Calculated. for $C_8H_{12}N_2O_2$ is 168.08; Observed. 169.15 $[M+H]^+$ **^{1}H NMR (400 MHz, $CDCl_3$,):** δ 9.96 (s, 2H), 7.45 (d, *J* = 2.0 Hz 1H), 6.79 (d, *J* = 2.8 Hz 1H), 4.33 (t, *J* = 6.8 Hz, 2H), 3.33 (t, *J* = 5.2 Hz, 5H), 2.16 (t, *J* = 6.0 Hz, 2H).

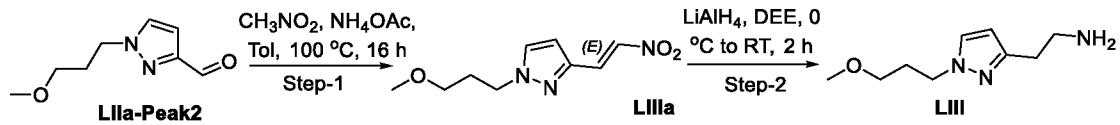
Step-2: (E)-1-(3-methoxypropyl)-5-(2-nitrovinyl)-1H-pyrazole (LIIb):

[000299] To a solution of 1-(3-methoxypropyl)-1H-pyrazole-5-carbaldehyde (**LIIa-Peak 1**) (0.79 g, 4.67 mmol) in toluene (25 mL) were added ammonium acetate (0.54 g, 7.00 mmol) and nitromethane (2.52 mL, 46.7 mmol). The reaction mixture was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was quenched with 1N HCl (25 mL) and extracted with ethyl acetate (3x25 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to get the crude material. The crude compound was purified by silica gel (230-400 mesh) column chromatography with ethyl acetate in *n*-hexane (0-20%) to afford the desired product **LIIb** as a pale-yellow solid. Yield: 0.51 g, (51.6 %); **LCMS** Calculated. for $C_9H_{13}N_3O_3$ is 211.09; Observed. 212.30 $[M+H]^+$.

Step-3: 2-(1-(3-methoxypropyl)-1H-pyrazol-5-yl) ethan-1-amine (LII)

[000300] To a solution of lithium aluminum hydride (9 mL, 1 M in THF, 9 mmol) in diethyl ether (20 mL) at 0 °C was added a solution of (E)-1-(3-methoxypropyl)-5-(2-nitrovinyl)-1H-pyrazole **LIIb** (0.5 g, 2 mmol) in diethyl ether (20 mL) and stirred at rt for 1 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was cooled to 0 °C, added water (0.5 mL), 15% KOH (0.5 mL), water (1.5 mL) and stirred for 10 min. Added ethyl acetate (50 mL) and stirred for 15 min. The solids were filtered and washed with ethyl acetate (20 mL*3). The combined organic layer was concentrated and washed with hexane to afford the desired product **LII** as a colorless oil. Yield:0.29 g, (70 %); **LCMS** Calculated. for $C_9H_{17}N_3O$ is 183.14; Observed. 183.00 $[M+H]^+$.

Synthesis of 2-(1-(3-methoxypropyl)-1H-pyrazol-3-yl) ethan-1-amine. (LIII)



Step-1: (E)-1-(3-methoxypropyl)-3-(2-nitrovinyl)-1H-pyrazole (LIIIa)

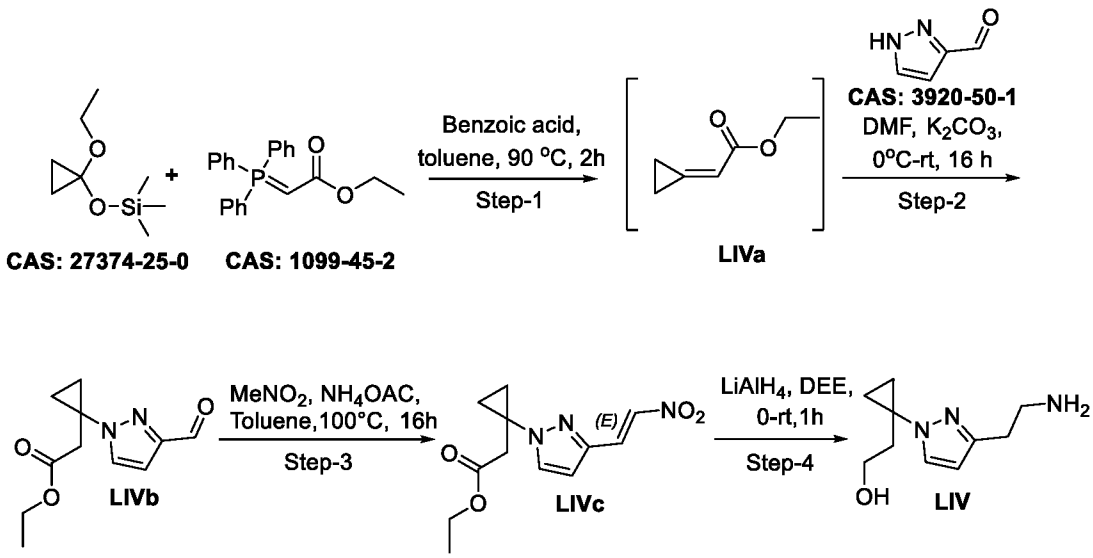
[000301] To a solution of 1-(3-methoxypropyl)-1H-pyrazole-3-carbaldehyde. **LIIa-Peak 2** (3.5 g, 21 mmol) in toluene (100 mL) were added ammonium acetate

(2.4 g, 31 mmol) and nitromethane (11.0 mL, 210 mmol) and the reaction mixture was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was quenched with 1N HCl (100 mL) and extracted with ethyl acetate (100 mL*3). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to get the crude material. The crude compound was purified by silica gel (230-400 mesh) column chromatography with ethyl acetate in *n*-hexane (0-20%) to afford desired product **LIIIa** as a pale-yellow solid. Yield: 2.72 g, (62.0 %); **LCMS** Calc. for $C_9H_{13}N_3O_3$ is 211.09; Obs. 212.30 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$,):** δ 7.97 (d, *J* =13.6 Hz, 1H), 7.61 (d, *J* =13.6 Hz, 1H), 7.43 (d, *J* =2 Hz, 1H), 7.26-7.23 (m, 1H), 4.28 (q, *J* =15.6 Hz, 2H), 3.33-3.31 (m, 5H), 2.17 (q, *J* =4 Hz, 2H)

Step-2: 2-(1-(3-methoxypropyl)-1H-pyrazol-3-yl) ethan-1-amine (LIII)

[000302] To a solution of lithium aluminum hydride (51 mL, 1 M in THF, 51 mmol) in diethyl ether (100 mL) at 0 °C was added a solution of (E)-1-(3-methoxypropyl)-3-(2-nitrovinyl)-1H-pyrazole **LIIIa** (2.7 g, 13 mmol) in diethyl ether (100 mL). The reaction mixture was stirred at rt for 1 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was cooled to 0 °C, added of water (2.7 mL) followed by of 15% KOH (2.7 mL) and water (8.1mL). The reaction mixture was stirred for 10 min. Then added ethyl acetate (150 mL) and stirred for 15 min. The solid was filtered and washed with ethyl acetate (3x 50 mL). The combined organic layer was concentrated and washed with *n*-hexane to afford the desired product **LIII** as a yellow solid. Yield: 2.15 g, (92 %); **LCMS** Calculated. for $C_9H_{17}N_3O$ is 183.13. Observed. 183.65 $[M+H]^+$.**^{1}H NMR (400 MHz, $CDCl_3$,):** δ 7.32-7.25 (m, 2H), 6.04 (d, *J* =2.0 Hz, 1H), 4.16 (t, *J* =4.0 Hz, 2H), 3.32-3.29 (m, 5H), 2.99-2.96 (m, 2H), 2.76 (t, *J* =8.0 Hz, 1H), 2.12-2.05 (m, 2H)

Synthesis of 2-(1-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclopropyl) ethan-1-ol. (LIV)



Step-1: ethyl 2-cyclopropylideneacetate (LIVa)

[000303] To a solution of (1-ethoxycyclopropoxy) trimethyl silane (CAS: 27374-25-0, 10.0 g, 11.5 mL, 57.37 mmol) in toluene (100 mL) were added ethyl 2-(triphenyl-l5-phosphaneylidene) acetate (CAS: 1099-45-2, 21.98 g, 63.10 mmol) and benzoic acid (7.36 g, 60.23 mmol). The reaction mixture was stirred at 90 °C for 2 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was cooled to rt, diluted with *n*-pentane, and poured onto the silica gel (100-200) bed and eluted with 0-1% Et_2O in *n*-pentane to afford the desired compound as a colorless liquid. Yield: 5.3 g (73.6%).

Step-2: Ethyl 2-(1-(3-formyl-1H-pyrazol-1-yl) cyclopropyl) acetate (LIVb)

[000304] To a solution of 1H-pyrazole-3-carbaldehyde (CAS: 3920-50-1, 2.0 g, 21 mmol) in *N*, *N*-dimethyl formamide (20 mL) was added potassium carbonate (4.3 g, 31 mmol) and the reaction mixture was stirred at rt for 20 min. This was followed by an addition of ethyl 2-cyclopropylideneacetate **LIVa** (5.3 g, 42 mmol) at 0 °C and the reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (100 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography using ethyl acetate in *n*-hexane (0-30%) to afford the desired product **LIVb** as a light-yellow

color liquid. Yield: 1.46 g, (32.0 %); **LCMS** Calculated. for $C_{11}H_{14}N_2O_3$ is 222.1; Observed: 223.2 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$,):** δ 9.95 (s, 1H), 7.65 (d, *J* = 2 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 2.87 (s, 2H), 1.422-1.35 (m, 2H), 1.26-1.18 (m, 5H).

Step-3: Ethyl (E)-2-(1-(3-(2-nitrovinyl)-1H-pyrazol-1-yl) cyclopropyl) acetate (LIVc)

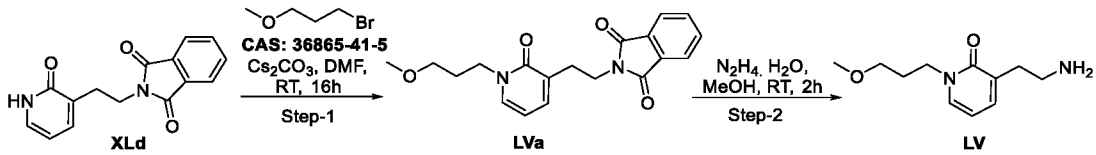
[000305] To a solution of ethyl 2-(1-(3-formyl-1H-pyrazol-1-yl) cyclopropyl) acetate **LIVb** (1.46 g, 6.57 mmol) in toluene (50 mL) was added nitromethane (6.02 g, 98.5 mmol) and the reaction mixture was stirred at rt for 10 min. This was followed by an addition of ammonium acetate (0.76 g, 9.85 mmol) and the reaction mixture was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was cooled rt, diluted with 1N HCl (50 mL) and extracted with ethyl acetate (100 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography using 0-10% ethyl acetate in *n*-hexane to afford the desired product **LIVc** as a light-yellow color liquid. Yield:1.2 g, (69 %). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.95 (d, *J* = 13.2 Hz, 2H), 7.64-7.27 (m, 2H), 6.45 (d, *J* = 2.4 Hz, 1H), 4.12-4.07 (m, 2H), 2.84 (s, 2H), 1.42-1.31 (m, 2H), 1.29-1.15 (m, 4H).

Step-4: 7-amino-3-ethyl-5-((2-(1-(3-hydroxypropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (LIV)

[000306] To a solution of $LiAlH_4$ (0.69 g, 18 mmol) in diethyl ether (100 mL) at 0 °C was added a solution of ethyl (E)-2-(1-(3-(2-nitrovinyl)-1H-pyrazol-1-yl) cyclopropyl) acetate (1.2 g, 4.5 mmol) in diethyl ether (50 mL) and the reaction mixture was stirred at rt for 1 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was cooled to 0 °C and quenched with water (1.2 mL), 15% KOH (1.2 mL) followed by water (3.6 mL). The mixture was filtered, and the white residue was thoroughly washed with ethyl acetate (150 mL x 3). The combined filtrate was concentrated under reduced pressure to afford the desired product **LIV** as a pale-yellow viscous liquid. Yield:

0.6g, (67.7 %); **LCMS** Calculated. for $C_{10}H_{17}N_3O$ is 195.14; Observed. 196.50 $[M+H]^+$.

Synthesis of 3-(2-aminoethyl)-1-(3-methoxypropyl) pyridin-2(1H)-one. (LV)



Step-1: 2-(2-(1-(3-methoxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione (LVa)

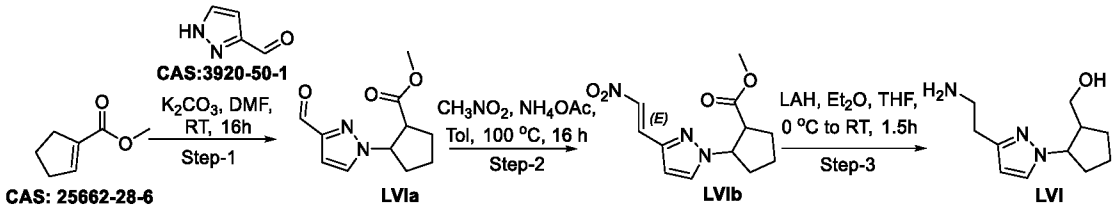
[000307] To a stirred solution of 2-(2-(2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **XLd** (1.2 g, 4.5 mmol) in DMF (10 mL) was added Cs_2CO_3 (2.2 g, 6.7 mmol) at room temperature under N_2 atmosphere. The reaction mixture was cooled to 0° C, drop wise added 1-bromo-3-methoxypropane (CAS: 36865-41-5, 0.60 mL, 5.4 mmol. The resulting reaction mixture was stirred at 25 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 50 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulphate, and concentrated under vacuum. The crude compound was purified by combi flash column chromatography using ethyl acetate in *n*-hexane (0-30%) to afford the desired compound **LVa** as colorless viscous liquid. Yield: 0.6 g, (40%); **LCMS** Calculated. for $C_{19}H_{20}N_2O_4$ is 340.14; Observed.: 341.30 $[M+H]^+$.

Step-2: 3-(2-aminoethyl)-1-(3-methoxypropyl) pyridin-2(1H)-one (LV)

[000308] To a stirred solution of 2-(2-(1-(3-methoxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **LVa** (600 mg, 1.76 mmol) in MeOH (6 mL) was added hydrazine hydrate (1:1, 107 µL, 2.12 mmol). The reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated, and crude was diluted with water (2 mL). The mixture was acidified with conc. HCl (pH=2). Solid formed was filtered and washed by water. The aqueous layer was basified (pH=9). with 1N NaOH solution and extracted with ethyl acetate (3 x 50 mL). Combined organic layer was dried over anhydrous sodium sulphate and concentrated under vacuum to afford the desired compound **LV** as a colorless viscous liquid. The crude

was as such taken for next step without further purification. Yield: 350 mg, (94.4 %); **LCMS** Calculated. for $C_{11}H_{18}N_2O_2$ is 210.14; Observed.: 211.30 $[M+H]^+$.

Synthesis of (2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclopentyl) methanol. (LVI)



Step-1: methyl 2-(3-formyl-1H-pyrazol-1-yl) cyclopentane-1-carboxylate (LVIa)

[000309] To stirred solution of 1H-pyrazole-3-carbaldehyde (CAS: 3920-50-1, 2 g, 20 mmol) in DMF (15 mL) was added potassium carbonate (6 g, 40 mmol) under N_2 and stirred at rt for 10 min under inert atmosphere. To the resulting mixture was added methyl cyclopent-1-ene-1-carboxylate (CAS: 25662-28-6, 3 g, 20 mmol) and stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (30 mL×3). The combine organic layer was washed with brine (50 mL), dried over anhydrous sodium sulphate, and concentrated under vacuum to afford pale-yellow solid. The crude was purified by combi flash silica gel (230-400) column chromatography using 0-15% ethyl acetate in *n*-hexane to afford the desired compound **LVIa** as a colorless viscous oil. Yield: 2.32g (50%); **LCMS** Calculated. for $C_{11}H_{14}N_2O$ is 222.10; Observed. 223.25 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.95 (s, 1H), 7.51 (d, J= 2 Hz, 1H), 6.77-6.76 (m, 1H), 5.00 (q, J = 8.0 Hz, 1H), 3.68 (s, 3H), 3.42-3.32 (m, 1H), 2.35-2.08 (m, 3H), 2.06-1.26 (m, 3H).

Step-2: Methyl (*E*)-2-(3-(2-nitrovinyl)-1*H*-pyrazol-1-yl) cyclopentane-1-carboxylate (LVIb)

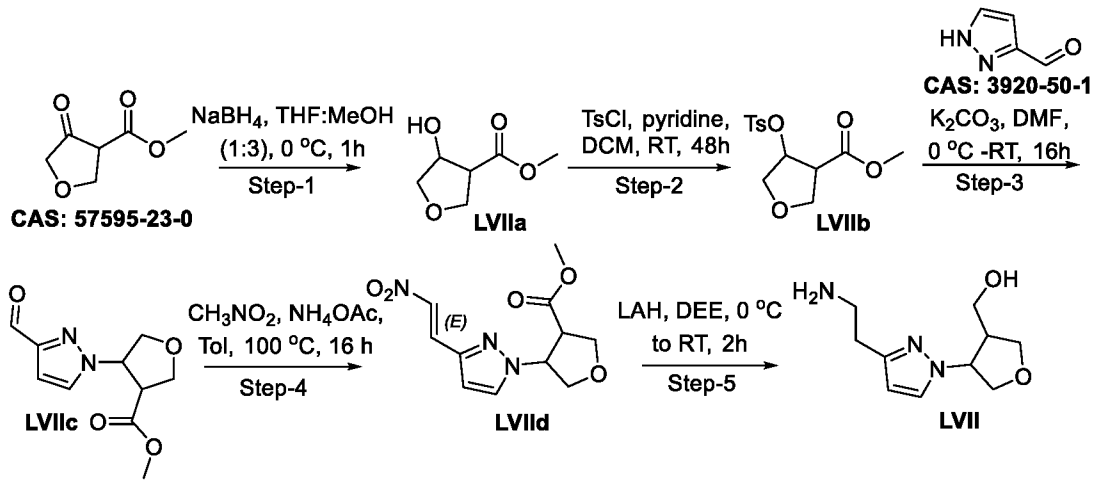
[000310] To a stirred solution of methyl 2-(3-formyl-1*H*-pyrazol-1-yl) cyclopentane-1-carboxylate **LVIa** (2.32 g, 10.4 mmol) in toluene (75 mL) were added ammonium acetate (1.21 g, 15.7 mmol) and nitromethane (5.63 mL, 104 mmol) under inert atmosphere. The resulting mixture was stirred at 100 °C for 16

h. The progress of reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with 1N HCl solution (75 mL) and extracted with ethyl acetate (50 mL × 3). The combine organic layer was washed with brine (100 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to get crude material. The crude was purified by Combi-flash chromatography (230-400 silica gel) column chromatography using 0-15% ethyl acetate in *n*-hexane to afford the desired compound **LVIb** as a pale-yellow solid. Yield: 1.6g (58%); **LCMS** Calculated. for $C_{12}H_{15}N_3O_4$ is 265.10; Observed.: 266.25 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.96 (d, J = 13.2, Hz 1H), 7.60 (d, J = 13.6 Hz, 1 H), 7.50 (d, J = 1.6 Hz, 1 H), 6.50 (d, J = 2.0 Hz, 1 H), 4.95-4.93 (m, 1H), 3.69 (s, 3H), 3.30-3.28 (m, 1H), 2.30-2.21 (m, 3H), 2.03-1.85 (m, 3H).

Step-3: (2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclopentyl) methanol (LVI)

[000311] A stirred solution of $LiAlH_4$ (30 mL, 1 M in THF, 30 mmol) in diethyl ether (80 mL) was cooled to 0 °C and drop wise added a solution of methyl (E)-2-(3-(2-nitrovinyl)-1H-pyrazol-1-yl) cyclopentane-1-carboxylate **LVIb** (1.6 g, 6.0 mmol) in THF (10 mL) under inert atmosphere. The resulting mixture was stirred at room temperature for 1.5 h. The progress of reaction was monitored by TLC analysis. After completion, reaction mixture was cooled to 0 °C, quenched by dropwise addition of water (1.6 mL). This was followed by addition of 15% KOH solution (1.6 mL) and again water (4.8 mL). Then ethyl acetate (50 mL) was added to the resulting mixture and stirred for 20 minutes at rt. The mixture was filtered and solid was washed with fresh ethyl acetate (100 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated to afford the desired compound **LVI** as a pale-yellow thick oil. The crude material was washed with *n*-hexane, dried under *vacuo,* and used for next step without purification. Yield: 1.25g (99%); **LCMS** Calculated. for $C_{11}H_{19}N_3O$ is 209.15; Observed.: 210.30 $[M+H]^+$.

Synthesis of (4-(3-(2-aminoethyl)-1H-pyrazol-1-yl) tetrahydrofuran-3-yl)methanol. LVII



Step-1: methyl 4-hydroxytetrahydrofuran-3-carboxylate (LVIIa)

[000312] To a solution of methyl 4-oxotetrahydrofuran-3-carboxylate (CAS: 57595-23-0, 25 g, 0.173 mol) in THF: MeOH (2.5L; 1:3) and the solution was cooled to 0 °C under inert atmosphere. To this solution, sodium borohydride (3.25 g, 0.087 mol) was added portion wise. The reaction mixture was stirred at 0 °C for 1 h and the progress of reaction was monitored by TLC analysis. After completion, the reaction was quenched by slow addition of water (400 mL). The resulting mixture was extracted with chloroform (700 mL × 3). The combined organic layer dried over anhydrous sodium sulphate, filtered, and concentrated under *vacuo* to afford the desired compound **LVIIa** as a colorless oil. The crude was taken for the next step without purification (product is active for $KMnO_4$ stain). Yield: 21 g (83.3%).

Step-2: methyl 4-(tosyloxy) tetrahydrofuran-3-carboxylate (LVIIb)

[000313] To a stirred solution of methyl 4-hydroxytetrahydrofuran-3-carboxylate **LVIIa** (43 g, 0.294 mmol) in DCM (800 mL) were added pyridine (71 mL, 0.882 mol) and 4-methylbenzenesulfonyl chloride (168.15 g, 0.882 mol) under N_2 atmosphere. The reaction mixture was stirred at rt for 48 h and the progress of the reaction was monitored by TLC analysis. After completion, water (250 mL) was added, and the resulting mixture was extracted with DCM (300 mL × 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under vacuum to get the light brown oil. The crude was subjected to silica gel (60-120) column chromatography using 0-15% ethyl acetate in *n*-hexane

to afford the desired compound **LVIIb** as a pale-yellow oil. Yield: 80 g (90.6%); **Note:** *Tosyl elimination product also forms along with the expected product. The mixture was taken as such for the next step as both leads to the formation of desired product.* **LCMS** Calculated for $C_{13}H_{16}O_6S$ is 300.06; Observe: 301.25 $[M+H]^+$.

Step-3: Methyl 4-(3-formyl-1H-pyrazol-1-yl) tetrahydrofuran-3-carboxylate (LVIIc)

[000314] To a solution of 1H-pyrazole-3-carbaldehyde (26 g, 0.270 mol) in DMF (1.2 L) under N_2 was added potassium carbonate (74 g, 0.535 mmol) and the resulting mixture was stirred at rt for 10 min. Methyl 4-(tosyloxy) tetrahydrofuran-3-carboxylate **LVIIb** (83 g, 0.276 mol) was added drop wise, and the reaction was stirred at rt for 16 hours under N_2 atmosphere. The progress of the reaction was monitored by TLC analysis. After completion, water (1.5 L) was added, and the mixture was extracted with ethyl acetate (700 mL × 3). The combined organic layer washed with brine, dried over anhydrous sodium sulphate, and concentrated under *vacuo* to afford the crude as brown viscous liquid. The crude was subjected to silica gel column chromatography (60-120 mesh) using 0-15 % ethyl acetate in *n*-hexane to afford the desired compound LVIIc as a pale-yellow viscous liquid. Yield: 35 g (50.7%). **LCMS** Calculated. for $C_{10}H_{12}N_2O_4$ is 224.07; Observed.: 225.25 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.97 (s, 1H), 7.57 (d, J = 2.0 Hz, 1H), 6.82 (d, J = 2.4 Hz, 1H), 5.37-5.33 (m, 1H), 4.44 (t, J = 8.4 Hz, 1H), 4.28-4.17 (m, 2H), 4.12-4.08 (m, 1H), 3.86-3.77 (m, 3H), 3.65-3.60 (m, 1H).

Step-4: Methyl (E)-4-(3-(2-nitrovinyl)-1H-pyrazol-1-yl) tetrahydrofuran-3-carboxylate (LVIId)

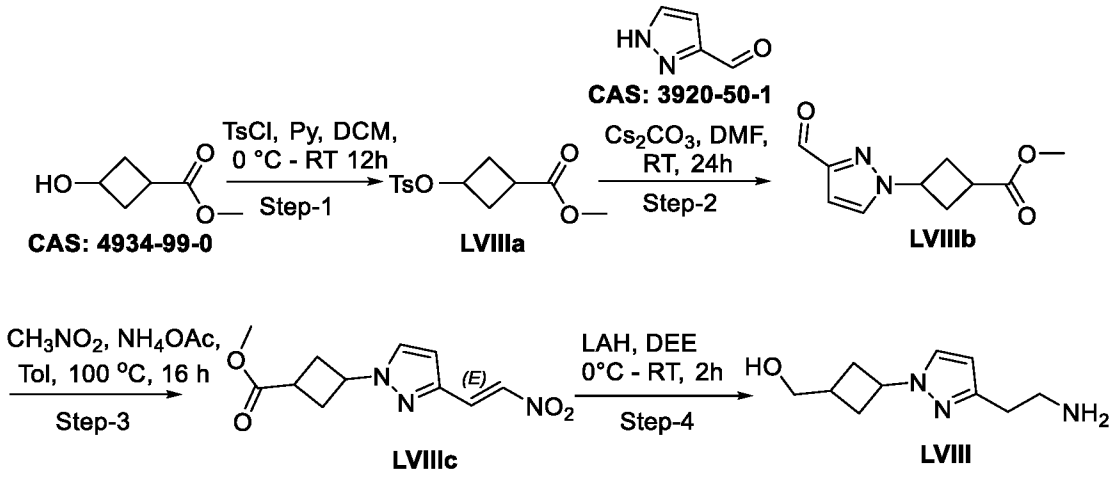
[000315] To a solution of methyl 4-(3-formyl-1H-pyrazol-1-yl) tetrahydrofuran-3-carboxylate **LVIIc** (28 g, 0.127 mol) toluene (750 mL) were added ammonium acetate (14.7 g, 0.191 mol) and nitromethane (68.4 mL, 1.27 mol). The reaction mixture was stirred at 100 °C for 16 h under inert atmosphere. The progress of the reaction was monitored by TLC analysis and complete consumption of the starting material was confirmed by using 2,4 DNP stain. After completion, the reaction mixture was cooled to rt and quenched with 1N HCl (750 mL) and the organic layer was separated. The aqueous layer was extracted with

ethyl acetate (500 mL × 3). The combined organic layer was given brine wash, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crude material was purified by silica gel (mesh 60-120) column chromatography using 0-15 % ethyl acetate in *n*-hexane to afford the desired compound **LVIId** as a pale-yellow oil. Yield: 19.6 g (57.8%). **LCMS** Calculated. for $C_{11}H_{13}N_3O_5$ is 267.08; Observed.; 268.25 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.96 (t, J = 6.4 Hz, 1H), 7.63-7.55 (m, 2H), 6.55 (d, J = 2.4 Hz, 1H), 5.31-5.27 (m, 1H), 4.48-4.39 (m, 1H), 4.27-4.22 (m, 1H), 4.16-4.06 (m, 2H), 3.75 (s, 3H), 3.61-3.56 (m, 1H).

Step-5: (4-(3-(2-aminoethyl)-1H-pyrazol-1-yl) tetrahydrofuran-3-yl) methanol (LVII).

[000316] A solution of $LiAlH_4$ (365 mL, 1 M in THF, 0.365 mol) in diethyl ether (1000 mL) was cooled to 0 °C under inert atmosphere. To resulting mixture was drop wise added a solution methyl (E)-4-(3-(2-nitrovinyl)-1H-pyrazol-1-yl) tetrahydrofuran-3-carboxylate **LVIId** (19.5 g, 0.073 mol) in diethyl ether (200 mL) over period of 15 min. The reaction mixture was stirred at room temperature for 1.5 h. The progress of the reaction was monitored by TLC analysis (ninhydrin stain). After completion, the reaction mixture was cooled to 0 °C and water (19.5 mL) was added slowly. This was followed a slow addition of (19.5 mL) of 15% KOH solution. Again water (58.5 mL) was added slowly the mixture was stirred at rt for 10 min. To this was added ethyl acetate (500 mL) and stirred for additional 30 min. The mixture was filtered, and the residue was washed thoroughly with ethyl acetate (500 mL). The residue was transferred back to reaction flask and stirred with fresh ethyl acetate (500 mL) for 10 min and filtered. The procedure was repeated for 3-4 times and the combined filtrate was dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford the desired product **LVII** a light brown viscous liquid. Yield: 13.9 g (90.2% crude). **LCMS** Calculated for $C_{10}H_{17}N_3O_2$ is 211.13; Observe 212.30 $[M+H]^+$.

Synthesis of (3-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclobutyl) methanol. (LVIII)



[000317] **Step-1: Methyl 3-(tosyloxy) cyclobutane-1-carboxylate (LVIIIa)**

[000318] To a stirred solution of methyl 3-hydroxycyclobutane-1-carboxylate (CAS: 4934-99-0, 5 g, 40 mmol) in DCM (30 mL) was added pyridine (9 mL, 100 mmol) under inert atmosphere. The reaction mixture was cooled to 0 °C and portion wise added 4-methylbenzenesulfonyl chloride (10 g, 60 mol). The resulting mixture was stirred at rt for 12 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (30 mL) and extracted with DCM (35 mL x 2). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulphated and concentrated under reduced pressure. The crude product was purified by combi-flash column chromatography by eluting with ethyl acetate in *n*-hexane (0-15%). The peak was eluted at 10% ethyl acetate in *n*-hexane was concentrated to afford the desired compound **LVIIIa** as colorless viscous liquid. Yield: 8 g (70%). **LCMS** Calculated. for $C_{13}H_{16}O_5S$ is 284.07; Observed: 285 $[M+H]^+$. δ 7.78 (d, J = 8.0 2H), 7.34 (d, J = 8.0 2H), 4.75-4.71 (m, 1H), 3.66 (s, 3H), 2.62-2.60 (m, 1H), 2.51-2.39 (m, 7H).

Step-2: Methyl 3-(3-formyl-1H-pyrazol-1-yl) cyclobutane-1-carboxylate (LVIIIb).

[000319] To a stirred solution of 1H-pyrazole-3-carbaldehyde (CAS: 3920-50-1, 1.5 g, 16 mmol) in DMF (30 mL) were added cesium carbonate (10 g, 31 mmol) and methyl 3-(tosyloxy) cyclobutane-1-carboxylate **LVIIIa** (5.8 g, 20 mmol) under nitrogen. The resulting reaction mixture was stirred at rt for 24 h. The

progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (75 mL x 2). The combined organic layer was washed with brine (35 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crude product was purified by combi-flash silica gel (100-200) column chromatography using 0-20% ethyl acetate in *n*-hexane to afford the desired compound **LVIIIb** as a colorless viscous liquid. Yield: 1.7 g (52%). **LCMS** Calculated. for $C_{10}H_{12}N_2O_3$ is 208.08; Observed. 209.25 $[M+H]^+$.

Step-3: Methyl (E)-3-(3-(2-nitrovinyl)-1H-pyrazol-1-yl) cyclobutane-1-carboxylate (LVIIIc)

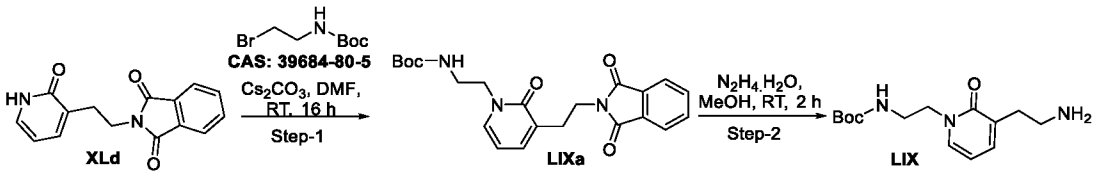
[000320] To a stirred solution of methyl 3-(3-formyl-1H-pyrazol-1-yl) cyclobutane-1-carboxylate **LVIIIb** (1.4 g, 6.7 mmol) in toluene (15 mL) were added ammonium acetate (0.78 g, 10 mmol) and nitromethane (5.4 mL, 10 mmol) under nitrogen. The resulting mixture was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was cooled to room temperature diluted with water (15 mL). The resultant mixture was extracted with ethyl acetate (20 mL x 2) and combined organic layer was washed with brine. The organic layer was dried over anhydrous sodium sulphate, concentrated under reduced pressure. The crude compound was purified by silica gel (100-200; 250g) combi flash column chromatography using methanol in DCM (0-0.5%) to afford the desired compound **LVIIIc** as a colorless viscous liquid. Yield: 0.35 g (21%). **LCMS** Calculated. for $C_{11}H_{13}N_3O_4$ is 251.09; Observed.: 252.25 $[M+H]^+$.

Step-4: (3-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclobutyl) methanol (LVIII)

[000321] A stirred solution of $LiAlH_4$ (5.6 mL, 1 M in THF, 5.6 mmol) in diethyl ether (100 mL), was cooled to 0 °C and dropwise added a solution of methyl (E)-3-(3-(2-nitrovinyl)-1H-pyrazol-1-yl) cyclobutane-1-carboxylate (0.35 g, 1.4 mmol) under nitrogen atmosphere. The reaction mixture was stirred at rt for 2h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to 0 °C, quenched with water (0.35 mL), 15% KOH (0.35 mL) and again with water (1.2 mL). The resulting reaction

mixture was filtered and washed with ethyl acetate (50 mL x 3). The combined filtrate was concentrated under reduced pressure to afford the compound **LVIII** as colorless viscous liquid. The crude was directly taken for next step without purification. **Yield**: 0.2 g (70%). **LCMS** Calculated. for $C_{10}H_{17}N_3O$ is 195.13; Observed. 196.45 $[M+H]^+$.

Synthesis of tert-butyl (2-(3-(2-aminoethyl)-2-oxopyridin-1(2H)-yl) ethyl) carbamate (LIX)



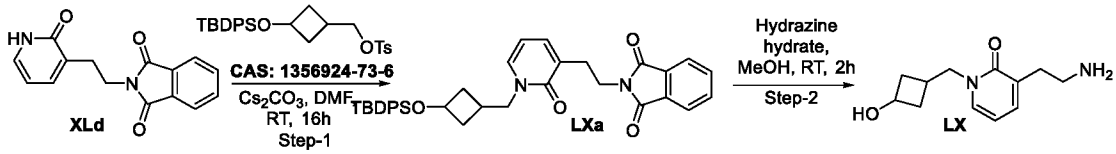
Step-1: tert-butyl (2-(3-(2-(1,3-dioxoisoindolin-2-yl) ethyl)-2-oxopyridin-1(2H)-yl) ethyl) carbamate (LIXa)

[000322] To a stirred solution of 2-(2-(2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **XLd** (0.8 g, 3 mmol) in DMF (7 mL) was added cesium carbonate (1.0 g, 4.00 mmol) and tert-butyl (2-bromoethyl) carbamate (CAS: 39684-80-5, 0.8 g, 4.00 mmol) and the reaction mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with water (10 mL) and the resulting mixture was extracted with ethyl acetate (50 mL X 3). The combined organic layer was dried over sodium sulphate and concentrated under reduced pressure. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using (10-50%) ethyl acetate in *n*-hexane to afford the desired compound **LIXa** as a yellow liquid. Yield: 0.520 g (50%). **LCMS** Calculated. for $C_{22}H_{25}N_3O_5$ is 411.17; Obs. 412.30 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.01-8.00 (m, 1H), 7.84-7.82 (m, 2H), 7.72-7.70 (m, 2H), 7.40 (d, J = 6.4 Hz, 1H), 6.79-6.76 (m, 1H), 4.38 (s, 2H), 3.96 (t, J = 7.6 Hz, 2H), 3.57 (s, 2H), 2.95 (t, J = 9.2 Hz, 2H), 1.54-1.39 (m, 9H).

Step-2: tert-butyl (2-(3-(2-aminoethyl)-2-oxopyridin-1(2H)-yl) ethyl) carbamate (LIX)

[000323] To a stirred solution of tert-butyl (2-(3-(2-(1,3-dioxoisoindolin-2-yl) ethyl)-2-oxopyridin-1(2H)-yl) ethyl) carbamate **LIXa** (0.52 g, 1.3 mmol) in MeOH (4 mL) was added hydrazine hydrate (1:1; 0.15 mL, 1.5 mmol) and the reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, MeOH was concentrated and was added 2 mL of water then acidified with conc. HCl (pH = 2). Filtered the precipitated solid and washed with water. The filtrate was basified with 4M. NaOH solution and extracted with 10% MeOH/DCM (100 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the desired compound **LIX** as a yellow liquid. Yield: 0.260 g (72.22%). **LCMS** Calculated. for $C_{14}H_{23}N_3O_3$ is 281.17; Observed. 282.30 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.24 (d, J = 6.4 Hz, 1H), 7.16 (d, J = 6.4 Hz, 1H), 6.85 (bs, 1H), 6.13 (t, J = 6.4 Hz, 1H), 5.14 (bs, 1H), 4.02 (t, J = 5.2 Hz, 2H), 3.48-3.45 (m, 2H), 2.97 (t, J = 6.8 Hz, 2H), 2.69 (t, J = 6.8 Hz, 2H), 1.42 (s, 9H).

Synthesis of 3-(2-aminoethyl)-1-((3-hydroxycyclobutyl) methyl) pyridine-2(1H)-one. (LX)



Step-1: 2-(2-(1-((3-((tert-butyl diphenyl silyl) oxy) cyclobutyl) methyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione (LXa)

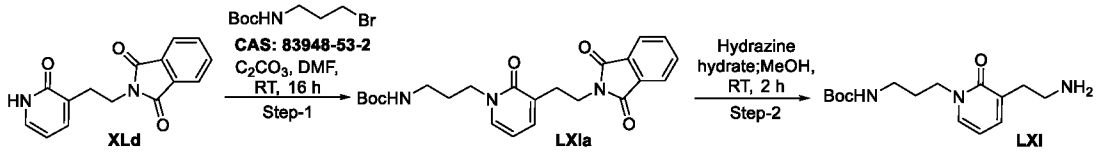
[000324] A stirred solution of 2-(2-(2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **XLd** (1.2 g, 4.5 mmol) in DMF (15 mL) was cooled to 0 °C and added Cs_2CO_3 (1.7 g, 5.4 mmol) followed by an addition of (3-((tert-butyldiphenylsilyl) oxy) cyclobutyl) methyl 4-methylbenzenesulfonate (CAS: 1356924-73-6, 3.1 g, 6.3 mmol). The reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched with water (25 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate

and concentrated under reduced pressure. The crude was purified by combi flash column chromatography (silica gel 230-400) eluted with 0-50 % ethyl acetate in *n*-hexane to afford the desired compound **LXa** as a brown liquid. Yield: 1.1 g (42%). **LCMS** Calculated. for $C_{36}H_{38}N_2O_4Si$ is 590.26; Observed.: 591.40 $[M+H]^+$.

Step-2: 3-(2-aminoethyl)-1-((3-hydroxycyclobutyl) methyl) pyridin-2(1H)-one (LX)

[000325] To a stirred solution of 2-(2-(1-((3-((tert-butyldiphenylsilyl) oxy) cyclobutyl) methyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **LXa** (1.1 g, 1.9 mmol) in MeOH (25 mL) was added hydrazine hydrate (1:1, 0.2 mL, 2.8 mmol) drop wise under N_2 atmosphere. The resulting reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was concentrated under vacuum. The crude was diluted with water (2 mL), acidified with conc. HCl (pH= 2). The solid formed was filtered and washed with water. The combined filtrate was basified with 10% NaOH solution, extracted with 10% methanol in DCM (200 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford the desired compound **LX** as light brown viscous liquid. Yield: 0.380 g (92%). **LCMS** Calculated. for $C_{12}H_{18}N_2O_2$ is 222.29; Observed. 223.30 $[M+H]^+$.

Synthesis of tert-butyl (3-(3-(2-aminoethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate. (LXI)



Step-1: tert-butyl (3-(3-(2-(1,3-dioxoisoindolin-2-yl) ethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate (LXIa)

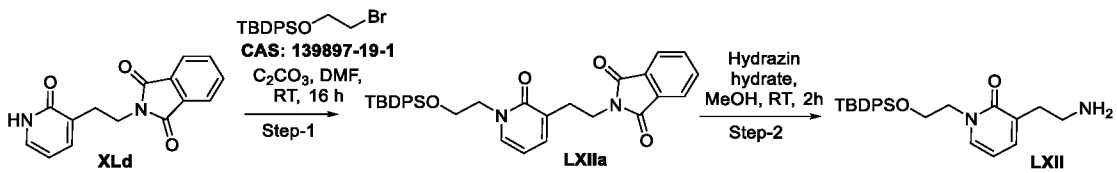
[000326] To a solution of 2-(2-(2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **XLd** (0.6 g, 2.24 mmol) in DMF (6 mL) at rt was added Cs_2CO_3 (0.874 g, 2.68 mmol) followed by tert-butyl (3-bromopropyl) carbamate (CAS: 83948-53-2, 0.639 g, 2.68 mmol) and the reaction mixture was stirred

at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion, added water (20 mL) and extracted with ethyl acetate (25 mL X 2). The combined organic layer was washed with brine (10 mL X 2), dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crude compound was purified by silica gel (100-200 mesh) with ethyl acetate in *n*-hexane (0-50%) to afford the desired product **LXIa** as a colorless liquid. Yield: 0.7 g, (74.0 %); **LCMS** Calculated. for $C_{23}H_{27}N_3O_5$ is 425.19; Observed: 426.35 $[M+H]^+$.

Step-2: tert-butyl (3-(3-(2-aminoethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate (LXI)

[000327] To a solution of tert-butyl (3-(3-(2-(1,3-dioxoisoindolin-2-yl) ethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate **LXIa** (0.7 g, 2 mmol) in methanol (10 mL) at rt was added hydrazine hydrate (0.2 mL, 3 mmol) and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was concentrated, added water (2 mL) and acidified with conc. HCl to pH~2. The solids were filtered, basified by 2N sodium hydroxide, and extracted with dichloromethane (200 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the desired product as a colorless viscous liquid. The crude compound **LXI** was taken for the next step without any further purification. Yield: 0.38 g, (80 %); **LCMS** Calculated. for $C_{15}H_{25}N_3O_3$ is 295.18; Observed: 296.35 $[M+H]^+$.

Synthesis of 3-(2-aminoethyl)-1-(2-((tert-butyl diphenyl silyl) oxy) ethyl) pyridine-2(1H)-one. (LXII)



Step-1: tert-butyl (3-(3-(2-(1,3-dioxoisoindolin-2-yl) ethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate (LXIIa)

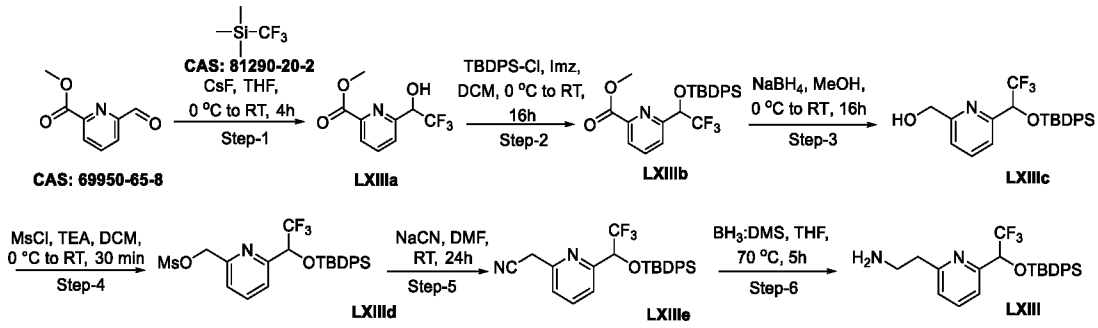
[000328] To a solution of 2-(2-(2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **XLd** (1.2 g, 4.5 mmol) in DMF (10 mL) were added (2-

bromoethoxy) (tert-butyl) diphenyl silane (CAS: 139897-19-1, 2.0 g, 5.4 mmol) and cesium carbonate (2.2 g, 6.7 mmol). The reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, added water (50 mL) and extracted with ethyl acetate (200 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by silica gel (60-120 mesh) column chromatography with ethyl acetate in hexane (0-50%) to afford the desired product **LXIIa** as a pale-yellow solid. Yield:1.2 g, (48%); **LCMS** Calculated. for $C_{33}H_{34}N_2O_4Si$ is 550.22; Observed: 551.40 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.79 (q, *J* = 2.8 Hz, 2H), 7.68-7.67 (m, 2H), 7.53 (d, *J* = 7.2 Hz, 4H), 7.42-7.26 (m, 7H), 7.14 (d, *J* = 6.4 Hz, 1H), 5.97 (t, *J* = 7.2 Hz, 1H), 4.08-3.93 (m, 6H), 2.90 (t, *J* = 8.0 Hz, 2H), 1.01 (s, 9H).

Step-2: tert-butyl (3-(3-(2-aminoethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate (LXII)

[000329] To a solution of 2-(2-(1-(2-((tert-butyl diphenyl silyl) oxy) ethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **LXIIa** (1.2 g, 2.2 mmol) in methanol (4 mL) was added hydrazine hydrate (0.13 g, 2.6 mmol) and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was concentrated, added water (2 mL) and acidified with conc. HCl to pH~ 2. The solids were filtered, basified by 2N NaOH and extracted with 10% methanol in dichloromethane (200 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated to afford the desired product **LXII** as a pale-yellow viscous liquid. The crude compound was taken for the next step without any further purification. Yield: 7g; **LCMS** Calculated. for $C_{25}H_{32}N_2O_2Si$ is 420.22; Observed: 421.35 $[M+H]^+$.

[000330] Synthesis of 2-(6-(1-((tert-butyl diphenyl silyl) oxy)-2,2,2-trifluoroethyl) pyridin-2-yl) ethan-1-amine. (LXIII)



Step-1: Synthesis of methyl 6-(2,2,2-trifluoro-1-hydroxyethyl) picolinate (LXIIIa)

[000331] A stirred solution of methyl 6-formylpicolinate (CAS: 69950-65-8, 2.5 g, 15 mmol) in THF (10 mL) was cooled to 0 °C under inert atmosphere and were added CsF (4.6 g, 30 mmol) and trimethyl(trifluoromethyl)silane (CAS: 81290-20-2, 3.2 g, 23 mmol). The reaction mixture was stirred at rt for 4 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with water (30 mL) and extracted with ethyl acetate (100 mL X 3). The combined organic layer was concentrated under reduced pressure. The crude was triturated with *n*-pentane (20 mL x 3) and dried to afford the desired compound **LXIIIa** as a pale-yellow solid. Yield: 3.0g (83.0 %); **LCMS** Calculated. for $C_9H_8F_3NO_3$ is 235.05; Observed: 236.20 $[M+H]^+$.**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.18 (d, *J*=7.6 Hz, 1H), 7.96 (t, *J*=7.6 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 5.17-5.14 (q, *J* = 6.4 Hz, 1H), 4.01 (s, 3H)

Step-2: methyl 6-(1-((tert-butyl diphenyl silyl) oxy)-2,2,2-trifluoroethyl) picolinate (LXIIIb)

[000332] A stirred solution of methyl 6-(2,2,2-trifluoro-1-hydroxyethyl) picolinate **LXIIIa** (3 g, 0.01 mol) in DCM (500 mL) was cooled to 0 °C and added imidazole (2 g, 0.03 mol). This was followed by drop wise addition of tert-butyl choro diphenyl silane (7 g, 0.03 mol). The reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with water (50 mL) and the resulting mixture was extracted with ethyl acetate (200 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified by silica gel (230-400) column chromatography

using 10-20 % ethyl acetate /*n*-hexane to afford the desired compound **LXIIIb** as a pale-yellow liquid. Yield: 6.0 g, (100 %); **LCMS** Calculated. for $C_{25}H_{26}F_3NO_3Si$ is 473.16; Observed: 474.25 $[M+H]^+$.

Step-3: (6-(1-((tert-butyl diphenyl silyl) oxy)-2,2,2-trifluoroethyl)pyridin-2-yl)methanol (LXIIIc)

[000333] A stirred solution of methyl 6-(1-((tert-butyl diphenyl silyl) oxy)-2,2,2-trifluoroethyl) picolinate **LXIIIb** (6 g, 0.01 mol) in MeOH (60 mL) was cooled to 0 °C and $NaBH_4$ (2 g, 0.05 mol) was added in portions. The reaction mixture was stirred at rt for 16 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated and added sat. $NaHCO_3$ solution (500 mL). The resulting mixture was extracted with DCM (600 mL X 3) and concentrated under reduced pressure. The crude was purified by silica gel (230-400 mesh) column chromatography using 10-50 % ethyl acetate in *n*-hexane to afford the desired compound **LXIIIc** as a pale-yellow viscous liquid. Yield: 4.5 g (75%); **LCMS** Calculated. for $C_{24}H_{26}F_3NO_2Si$ is 445.17; Observed. 446.30 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.64 (q, *J*=7.6 Hz, 3H), 7.51 (d, *J*= 7.6 Hz,1H), 7.44 (d, *J* = 6.8 Hz, 3H), 7.38-7.32 (m, 3H), 7.26-7.20 (m, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 5.07 (q, *J*=6.4 Hz, 1H), 4.61 (d, *J*=4.8 Hz, 2H), 3.41(t, *J* = 4.8 Hz, 1H), 1.55 (s, 1H), 1.08 (s, 9H).

Step-4: (6-(1-((tert-butyl diphenyl silyl) oxy)-2,2,2-trifluoroethyl) pyridin-2-yl) methyl methane sulfonate (LXIIId)

[000334] A stirred solution of (6-(1-((tert-butyl diphenyl silyl) oxy)-2,2,2-trifluoroethyl) pyridin-2-yl) methanol **LXIIIc** (4.5 g, 10 mmol) in DCM (100 mL) was cooled to 0 °C and added TEA (6.1 g, 8.4 mL, 61 mmol). The resulting mixture was stirred for 5 min and mesyl-Cl (1.2 mL, 15 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and the progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with sat. $NaHCO_3$ solution (100 mL) and extracted with DCM (300 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford desired compound **LXIIId** as a

brown liquid. The crude compound was taken for next step without further purification. Yield: 5 g (96%).

Step-5: 2-(6-(1-((tert-butyl diphenyl silyl) oxy)-2,2,2-trifluoroethyl) pyridin-2-yl) acetonitrile (LXIIIe)

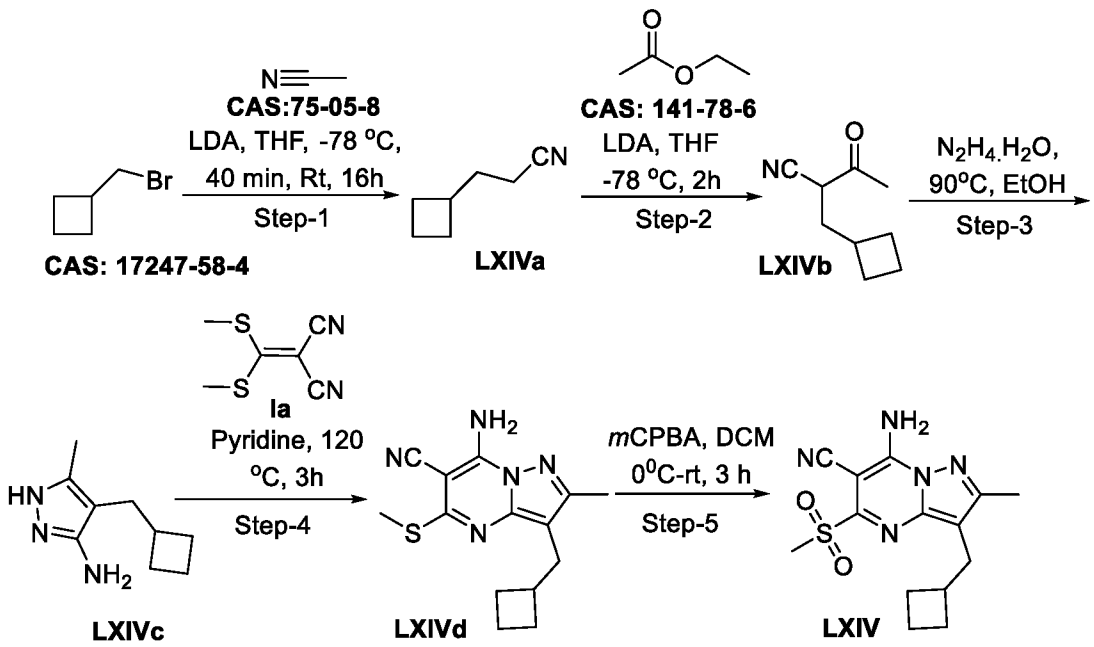
[000335] To a stirred solution of (6-(1-((tert-butyl diphenyl silyl) oxy)-2,2,2-trifluoroethyl) pyridin-2-yl) methyl methane sulfonate **LXIIId** (6 g, 11.4 mmol) in DMF (60 mL) was added NaCN (1.34 g, 22.9 mmol) and the reaction mixture was stirred at rt for 24 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with water (50 mL) and the resulting mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified by silica gel (230-400 mesh) column chromatography using 10-30% ethyl acetate in *n*-hexane to afford the desired compound **LXIIIe** a pale-yellow viscous liquid. Yield: 2.5 g (83.0%); **LCMS** Calculated. for $C_{25}H_{25}F_3N_2OSi$ is 454.17; Observed.: 455.30 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.72-7.67 (m, 2H), 7.59 (t, *J* = 8.0 Hz, 2H), 7.46-7.32 (m, 6H), 7.25-7.21 (m, 2H), 5.06 (q, *J*= 6.4 Hz, 1H), 3.73 (d, *J* = 8.0 Hz, 2H) 1.07 (bs, 9H)

Step-6: 2-(6-(1-((tert-butyl diphenyl silyl) oxy)-2,2,2-trifluoroethyl) pyridin-2-yl) ethan-1-amine (LXIII)

[000336] To a stirred solution of 2-(6-(1-((tert-butyl diphenyl silyl) oxy)-2,2,2-trifluoroethyl) pyridin-2-yl) acetonitrile **LXIIIe** (2.5 g, 5.5 mmol) in THF (40 mL) at 0 °C was dropwise added BH_3.DMS (11 mL, 2 M in THF, 22.0 mmol). The reaction mixture was stirred at 70 °C for 5 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to 0 °C before it was quenched with MeOH (7 mL). The mixture was stirred for 30 min and added 1 M HCl solution (10 mL). The mixture was concentrated to half under reduced pressure and extracted with ethyl acetate (50 mL) followed by with DCM (50 mL) to get rid of impurities. The aqueous layer was basified (pH 8-9) with 2N NaOH and extracted with DCM (500 mL X 3), dried over sodium sulphate, and concentrated under reduced pressure to afford the desire compound **LXIII** as a

brown liquid. The crude compound taken for next step without further purification. Yield: 1.6 g (64%); **LCMS** Calculated. for $C_{25}H_{29}F_3N_2OSi$ is 458.20; Observed.: 459.35 [M+H]

Synthesis of 7-amino-3-(cyclo butyl methyl)-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile. (LXIV)



Step-1: 3-cyclobutylpropanenitrile (LXIVa)

[000337] In a 3 neck RB flask, acetonitrile (CAS:75-05-8, 1.4 g, 1.8 mL, 34 mmol) was taken in dry THF (74.2 mL) and the solution was cooled to -78 °C. To this was dropwise added LDA (17 mL, 2.0 M in THF/heptane/ethylbenzene, 34 mmol) under inert atmosphere. The reaction mixture was stirred at -78 °C for 40 min and a solution of (bromomethyl)cyclo butane (CAS: 17247-58-4, 3.8 mL, 34 mmol) in dry THF (15 mL) was added drop wise at -78 °C. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was cooled to 0 °C and quenched with saturated ammonium chloride solution (65 mL). The resulting mixture was extracted with DCM (50 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified by flash column chromatography using 0-10% ethyl acetate in *n*-hexane to afford the desired compound **LXIVa** as a pale-yellow liquid. **Yield**: 1.65g, (37.2%).

Step-2: 2-(cyclo butyl methyl)-3-oxobutanenitrile (LXIVb)

[000338] In a 3 neck RB flask, LDA (5.0 mL, 2.0 M in THF/heptane/ethylbenzene, 10 mmol) was diluted with dry THF (11.5 mL) under inert atmosphere and cooled to -78 °C. To this was dropwise added a solution 3-cyclobutylpropanenitrile **LXIVa** (1.1 g, 10 mmol) in dry THF (6.0 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 1 h. Then dry ethyl acetate (CAS: 141-78-6, 0.81 g, 0.90 mL, 9.2 mmol) was drop wise added at -78 °C and stirring was continued for additional 1 h maintaining reaction temperature at -78 °C. The reaction mixture was quenched with saturated ammonium chloride solution (6.0 mL) and extracted with diethyl ether (20 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the desired product **LXIVb** as a brown liquid. The crude product was taken for the next step without further purification. **Yield:** (1.65g, 37.24%).

Step-3: 4-(cyclobutylmethyl)-5-methyl-1H-pyrazol-3-amine (LXIVc)

[000339] To a solution of 2-(cyclobutylmethyl)-3-oxobutanenitrile **LXIVb** (1.5 g, 9.9 mmol) in ethanol (16 mL) was added hydrazine hydrate (4.5 mL, 92 mmol) and the reaction mixture was stirred at 120 °C for 1.5 h. The progress of reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was washed with *n*-hexane (20 mL X 2) and dried under *vacuo*. To the residue was added water (10 mL) and extracted with 40% isopropanol in chloroform (15 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the desired product LXIVc as a brown oil. The crude was taken for the next step without further purification. **Yield:** (0.711 g, 44.43%); **LCMS** Calculated for $C_9H_{15}N_3$ is 165.13; Observed:166.30 $[M+H]^+$.

Step-4: 7-amino-3-(cyclobutylmethyl)-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (LXIVd)

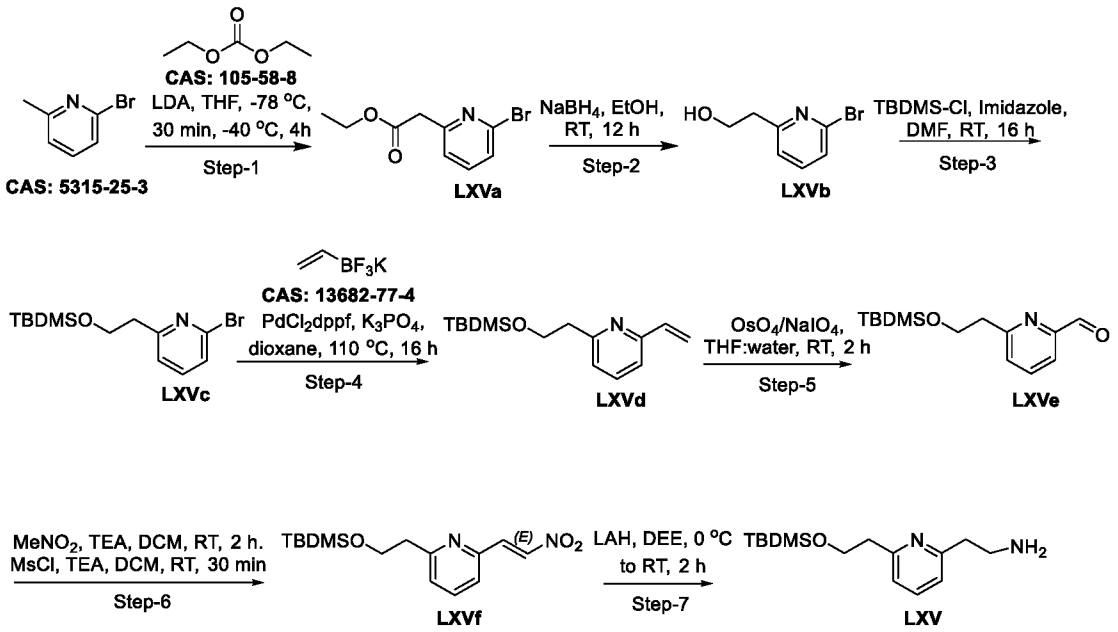
[000340] To a solution of 4-(cyclobutylmethyl)-5-methyl-1H-pyrazol-3-amine (707 mg, 4.28 mmol) in pyridine (7 mL) was added 2-(bis (methylthio) methylene) malononitrile **LXIVc** (728 mg, 4.28 mmol) under inert atmosphere. The

reaction mixture was stirred at 120 °C for 3 h and progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to room temperature and quenched with ice cold water. The mixture was extracted with ethyl acetate (10 mL X 3). The combined organic layer was washed with brine, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to get crude material. The crude material was purified by silica gel (100-200) column chromatography using 0-20% ethyl acetate in *n*-hexane to afford the desired **LXIVd** as an off-white solid. **Yield:** 0.40 g (32.5%); **LCMS** Calculated. for $C_{14}H_{17}N_5S$ is 287.12; Observed: 288.25 $[M+H]^+$.

Step-5: 7-amino-3-(cyclobutylmethyl)-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyridine-6carbonotrile (LXIV)

[000341] A solution of 7-amino-3-(cyclobutylmethyl)-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **LXIVd** (400 mg, 1.39 mmol) in DCM (10 mL) was cooled to 0 °C and *m*-CPBA (961 mg, 5.57 mmol) was added in portions. The reaction mixture was stirred at room temperature for 3 h. Progress of reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched by slow addition of saturated sodium bicarbonate solution (50 mL). The resulting mixture was extracted with DCM (20 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to get crude material. The crude material was purified by flash column chromatography (combi-flash) using 0-30% ethyl acetate in *n*-hexane to afford the desired product **LXIV** as an off white-solid. Yield:(203 mg (45.61%); **LCMS** Calculated. for $C_{14}H_{17}N_5O_2S$ is 319.11, Observed. 320.25 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 9.19 (bs, 2H), 3.42 (s, 3H), 2.73 (d, J =7.6 Hz, 2H), 2.61-2.58 (m,1H), 2.41 (s, 3H), 1.93 (d, J =4.4 Hz, 1H), 1.80-1.67 (m, 4H).

Synthesis of 2-(6-(2-((tert-butyl dimethyl silyl) oxy) ethyl) pyridin-2-yl) ethan-1-amine. (LXV)



Step-1: ethyl 2-(6-bromopyridin-2-yl) acetate (LXVa)

[000342] A stirred solution of lithium diisopropylamide (110 mL, 2.0 M in THF/heptane/ethylbenzene, 0.22 mol) in THF (500 mL) was cooled to -78 °C and added 2-bromo-6-methylpyridine (CAS: 5315-25-3, 15 g, 87 mmol) under N_2 atmosphere. The mixture was stirred at -78 °C for 30 min followed by a dropwise addition of diethyl carbonate (CAS: 105-58-8, 26 g, 0.22 mol) and the reaction mixture was stirred at -40 °C for 4 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with saturated ammonium chloride solution (150 mL) and extracted with ethyl acetate (100 mL X 3). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was subjected to silica gel (230-400) column chromatography using 0-10% ethyl acetate in *n*-hexane to afford the desired compound **LXVa** as a colorless liquid. Yield: (12.2 g, 57%); **LCMS** Calculated. for $C_9H_{10}BrNO_2$ is 242.98; Observed. 244.15 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.53 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.30-7.27 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.83 (s, 2H), 1.27 (t, J = 7.2 Hz, 3H).

Step-2: 2-(6-bromopyridin-2-yl) ethan-1-ol. (LXVb)

[000343] To a stirred solution of ethyl 2-(6-methylpyrazin-2-yl) acetate **LXVa** (3 g, 10 mmol) in ethanol (30 mL) was added sodium borohydride (2.32 g,

61.47 mmol) at 0 °C in portions under N_2 atmosphere and the reaction mixture was stirred at room temperature for 12 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with water (50 mL) and the resulting mixture was extracted with ethyl acetate (30 mL X 3). The combined organic layer was dried over sodium sulphate and concentrated under reduced pressure to afford the pure compound **LXVb** as colorless viscous liquid. Yield: (1.7 g, 70%); **LCMS** Calculated. for C_7H_8BrNO is 200.97; Observed. 202.00 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.48 (t, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 4.02 (q, J = 5.2 Hz, 2H), 3.03-3.00 (m, 3H).

Step-3: 2-bromo-6-(2-((tert-butyldimethylsilyl) oxy) ethyl) pyridine (LXVc)

[000344] To a stirred solution of 2-(6-bromopyridin-2-yl) ethan-1-ol **LXVb** (1.7 g, 8.4 mmol) in DCM (25 mL) was added 1*H*-imidazole (1.1 g, 17 mmol) and the reaction mixture stirred at room temperature for 30 min under nitrogen followed by drop wise addition of tert-butyl choro dimethyl silane (2.5 g, 17 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 16 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched with water (50 mL) and extracted with DCM (20 mL X 2). The combined organic layer was dried over anhydrous sodium sulphate. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using (0-6%) ethyl acetate in *n*-hexane to afford the desired compound **LXVc** as a colorless viscous liquid. Yield: 2.3 g (86%); **LCMS** Calculated. for $C_{13}H_{22}BrNOSi$ is 315.06; Observed. 316.25 $[M+H]^+$; **^{1}HNMR (400 MHz, $CDCl_3$):** δ 7.44 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 3.96 (t, J = 6.0 Hz, 2H), 2.95 (t, J = 6.0 Hz, 2H), 0.82 (s, 9H), 0.06 (s, 6H).

Step-4: 2-(2-((tert-butyldimethylsilyl) oxy) ethyl)-6-vinylpyridine (LXVd)

[000345] To a stirred solution of 2-bromo-6-(2-((tert-butyldimethylsilyl) oxy) ethyl) pyridine **LXVc** (2.3 g, 7.3 mmol) was added potassium trifluoro(vinyl)borate (1.1 g, 8.0 mmol) and potassium phosphate tribasic (2.3 g, 11 mmol) in 1,4 dioxane (30 mL) and purged with N_2 gas for 15 min with vigorous stirring. To the reaction was added $PdCl_2$(dppf) (0.27 g, 0.36 mmol) and the seal tube with Teflon screw-stopper was closed and heated to 110 °C for 16 h. The progress of the reaction was

monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. To the residue was added 70 mL of water and extracted with ethyl acetate (50 mL X 2). The combined organic layer was dried over anhydrous sodium sulphate and concentrated to obtain crude product. The crude product was subjected to silica gel (230-400 mesh) column chromatography using 0-6% ethyl acetate in *n*-hexane to afford the desired compound **LXVd** as a colorless viscous liquid. Yield: 1.6 g (84%); **LCMS** Calculated. for $C_{15}H_{25}NOSi$ is 263.17; Observed. 264.30 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.54 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.81 (dd, J = 17.6, 10.8 Hz, 1H), 6.17 (d, J = 17.6 Hz, 1H), 5.44 (d, J = 10.8 Hz, 1H), 4.00 (t, J = 6.4 Hz, 2H), 2.99 (t, J = 6.4 Hz, 2H), 0.83 (s, 9H), 0.05 (s, 6H).

Step-5: 6-(2-((tert-butyldimethylsilyl) oxy) ethyl) picolinaldehyde (LXVe)

[000346] To a stirred solution of 2-(2-((tert-butyldimethylsilyl) oxy) ethyl)-6-vinylpyridine **LXVd** (1.6 g, 6.1 mmol) in THF (1.1 mL) and water (2.5 mL) was added osmium (VIII) oxide (3.8 mL, 4% in H_2O, 0.61 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 30 min. This was followed by portion wise addition of sodium metaperiodate (1.9 g, 9.1 mmol) and the reaction was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (15 mL) and the resulting mixture was extracted with ethyl acetate (20 mL X 2). The combined organic layer was dried over anhydrous sodium sulphate. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using 0-6% ethyl acetate in *n*-hexane to afford the desired compound **LXVe** as a colorless viscous liquid. Yield: 0.7 g (40%); **LCMS** Calculated. for $C_{14}H_{23}NO_2Si$ is 265.14; Observed. 266.30 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.06 (s, 1H), 7.82-7.75 (m, 2H), 7.44 (d, J = 7.2 Hz, 1H), 4.03 (t, J = 6.4 Hz, 2H), 3.09 (t, J = 6.4 Hz, 2H), 0.82 (s, 9H), 0.06 (s, 6H).

Step-6: (E)-2-(2-((tert-butyldimethylsilyl) oxy) ethyl)-6-(2-nitrovinyl) pyridine (LXVf)

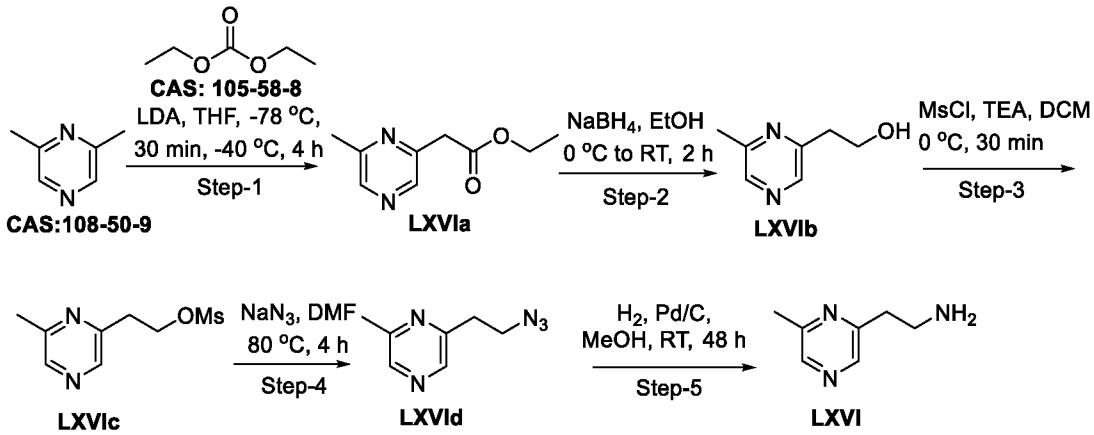
[000347] To a stirred solution of 6-(2-((tert-butyldimethylsilyl) oxy) ethyl) picolinaldehyde **LXVe** (0.7 g, 3 mmol) in DCM (20 mL) was added triethylamine (2.78 mL, 20 mmol) and nitromethane (0.3 mL, 8 mmol) under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h and the progress of the reaction was monitored by TLC analysis. After completion of reaction, DCM was concentrated under reduced pressure. The resulting residue was taken in DCM (20 mL) was added triethylamine (2.78 mL, 20 mmol) and cooled to 0 °C followed by drop wise addition of methane sulfonyl chloride (0.6 mL, 8 mmol). The resulting mixture was stirred at 0 °C for 30 min and the progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (40 mL) and extracted with DCM (20 mL X 2). The combined organic layer was dried over anhydrous sodium sulphate. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using 0-6% ethyl acetate in *n*-hexane to afford the desired compound **LXVf** as a yellow viscous liquid. Yield: 0.7 g, (90%); **LCMS** Calculated. for $C_{15}H_{24}N_2O_3Si$ is 308.15; Observed. 309.30 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.02 (d, J = 13.2 Hz, 1H), 7.89 (d, J = 13.2 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.31-7.29 (m, 2H), 4.00 (t, J = 6.4 Hz, 2H), 3.07-2.99 (m, 2H), 0.80 (s, 9H), 0.06 (s, 6H).

Step-7: 2-(6-(2-((tert-butyldimethylsilyl) oxy) ethyl) pyridin-2-yl) ethan-1-amine (LXV)

[000348] To a stirred solution of aluminum (III) lithium hydride (10 mL, 1.0 M in THF, 10 mmol) in diethyl ether (70 mL) was dropwise added (*E*)-2-(2-((tert-butyldimethylsilyl) oxy) ethyl)-6-(2-nitrovinyl) pyridine **LXVf** (0.7 g, 3 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h and the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to 0 °C was added 1 mL of ice-cold water and 1 mL of 15% KOH solution then stirred at room temperature for another 30 min. The resulting reaction mixture was diluted with 250 mL of ethyl acetate filtered through Buchner funnel and the solid was thoroughly washed with 250mL of ethyl acetate. The filtrate was dried over anhydrous sodium sulphate and

concentrated under reduced pressure to afford a desired compound **LXV** as light brown viscous liquid. Yield: 0.54 g (85%); **LCMS** Calculated. for $C_{15}H_{28}N_2OSi$ is 280.20; Observed. 281.35 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.50 (t, J = 7.6 Hz, 1H), 7.31-7.29 (m, 1H), 7.05-6.98 (m, 2H), 6.89 (d, J = 8.4 Hz, 1H), 3.96 (t, J = 6.4 Hz, 2H), 3.10-2.88 (m, 6H), 0.80 (s, 9H), 0.06 (s, 6H).

Synthesis of 2-(6-methylpyrazin-2-yl) ethan-1-amine (LXVI)



Step-1: Synthesis of ethyl 2-(6-methylpyrazin-2-yl) acetate (LXVIa)

[000349] To a stirred solution of 1.0 M lithium diisopropylamide (7 g, 0.07 L, 70 mmol) in THF (80 mL) was cooled to -78 °C was added 2,6-dimethylpyrazine (CAS:108-50-9, 3 g, 30 mol) under N_2 atmosphere and stirred at -78° C for 30 min followed by dropwise addition of diethyl carbonate (CAS: 105-58-8, 4 g, 4 mL, 30 mol) and then the reaction mixture was stirred at -40° C for 4 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with saturated ammonium chloride solution (50 mL) and extracted with ethyl acetate (30 mL X 3). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was subjected to silica gel (230-400) column chromatography using 0-30% ethyl acetate in *n*-hexane to afford the desired compound **LXVIa** as a colorless liquid. Yield: 4.5 g (90 %); **LCMS** Calculated. for $C_9H_{12}N_2O_2$ is 180.08; Observed. 181.30 $[M+H]^+$; **^{1}HNMR (400 MHz, $CDCl_3$,):** δ 8.39-8.36 (m, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.83 (s, 2H), 2.55 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H).

Step-2: 2-(6-methylpyrazin-2-yl) ethan-1-ol (LXVIb)

[000350] To a stirred solution of ethyl 2-(6-methylpyrazin-2-yl) acetate **LXVIa** (4.5 g, 25 mmol) in ethanol (100 mL) was added sodium borohydride (3.8 g, 100 mmol) at 0 °C in portions under N_2 atmosphere and the reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with water (50 mL) and the resulting mixture was extracted with ethyl acetate (30 mL X 3). The combined organic layer was dried over sodium sulphate and concentrated under reduced pressure to afford the pure compound **LXVIb** as colorless viscous liquid. Yield: (3.5 g, 100 %); **LCMS** Calculated. for $C_7H_{10}N_2O$ is 138.07; Observed. 139.30 $[M+H]^+$; **^{1}HNMR (400 MHz, $CDCl_3$):** δ 8.33-8.29 (m, 2H), 5.31 (t, 1H), 4.03 (t, J = 5.6 Hz, 2H), 3.02 (t, J = 5.6 Hz, 2H) 2.55 (s, 3H).

Step-3: 2-(6-methylpyrazin-2-yl) ethyl methane sulfonate (LXVIc)

[000351] To a stirred solution of 2-(6-methylpyrazin-2-yl) ethan-1-ol LXVIb (3.5 g, 25 mmol) in DCM (100 mL) was added triethylamine (6.4 g, 8.8 mL, 63 mmol) followed by dropwise addition of mesyl chloride (3.8 g, 2.6 mL, 33 mmol) at 0 °C and stirred the reaction mixture at 0 °C for 30 min. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with water (20 mL) and the resulting mixture was extracted with DCM (20 mL X 3). The combined organic layer was dried over sodium sulphate and concentrated under reduced pressure to afford the pure compound **LXVIc** as a brown liquid. Yield: 5.0 g (90 %); **LCMS** Calculated. for $C_8H_{12}N_2O_3S$ is 216.05; Observed. 217.25 $[M+H]^+$; **^{1}HNMR (400 MHz, $CDCl_3$):** δ 8.35-8.31 (m, 2H), 4.65 (t, J = 6.0 Hz, 2H), 3.21 (t, J = 6.4 Hz, 2H), 3.01 (s, 3H) 2.55 (s, 3H).

Step-4: 2-(2-azidoethyl)-6-methylpyrazine (LXVId)

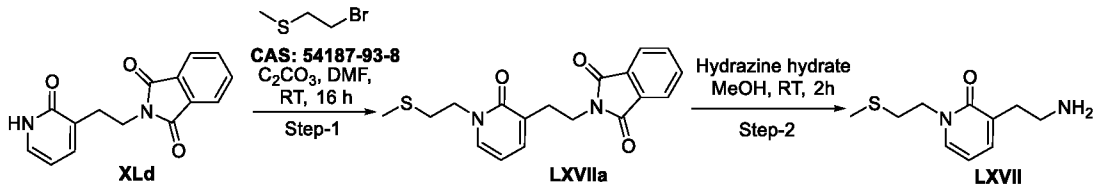
[000352] To a solution of 2-(6-methylpyrazin-2-yl) ethyl methane sulfonate **LXVIc** (5 g, 20 mmol) in DMF (50 mL) was added sodium azide (6 g, 90 mmol) and the resulting mixture was stirred at 80 °C for 4 h under N_2 atmosphere. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with ice cold water (20 mL) and the resulting mixture was extracted with ethyl acetate (20 mL X 3). The combined organic layer was dried over sodium sulphate and concentrated under reduced

pressure to afford the pure compound **LXVId** as a brown viscous liquid. Yield: 3.9 g (97.5%); **LCMS** Calculated. for $C_7H_9N_5$ is 163.08; Observed. 164.05 $[M+H]^+$; **^{1}HNMR (400 MHz, $CDCl_3$):** δ 8.38-8.31 (m, 2H), 3.73 (t, J = 6.4 Hz, 2H), 3.04 (t, J = 6.8 Hz, 2H), 2.56 (s, 3H).

Step-5: 2-(6-methylpyrazin-2-yl) ethan-1-amine (LXVI)

[000353] To a stirred solution of 2-(2-azidoethyl)-6-methylpyrazine **LXVId** (3.9 g, 24 mmol) in methanol (80 mL) was added Pd/C (10%, 1.3 g, 12 mmol) under N_2 atmosphere and stirred at room temperature for 48 h under H_2 bladder. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was filtered through celite bed, washed with methanol (25ml X 2) and concentrated under reduced pressure to afford the desired compound **LXVI** as a colorless viscous liquid. Yield: 2.2 g (67%); **LCMS** Calculated. for $C_7H_{11}N_3$ is 137.09; Observed. 138.30 $[M+H]^+$; **^{1}HNMR (400 MHz, $CDCl_3$):** δ 8.29 (d, J = 8.8 Hz, 2H), 3.10 (t, J = 6.8 Hz, 2H), 2.96-2.89 (m, 4H), 2.55 (s, 3H).

Synthesis of 3-(2-aminoethyl)-1-(2-(methylthio) ethyl) pyridine-2(1H)-one (LXVII)



Step-1: 2-(2-(1-(2-(methylthio) ethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione (LXVIIa)

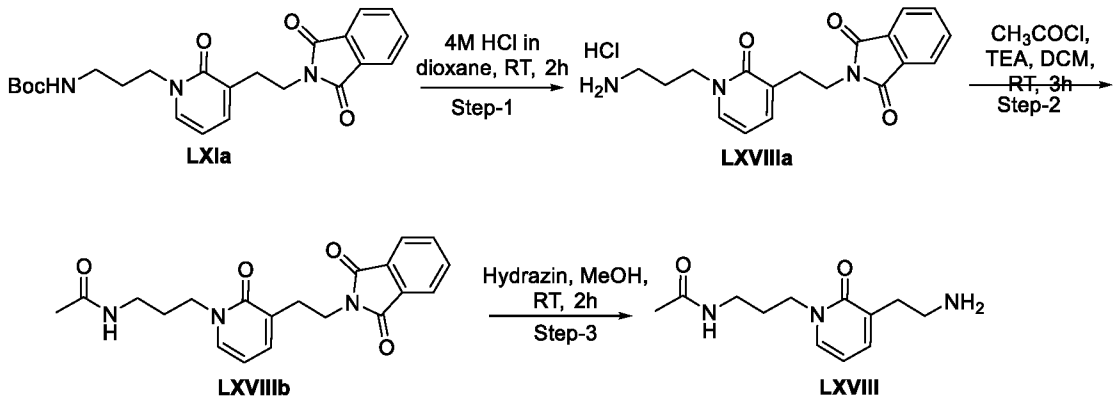
[000354] To a stirred solution of 2-(2-(2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **XLd** (8 g, 0.03 mol) in DMF (80 mL) was added Cs_2CO_3 (10 g, 0.04 mol) at rt under N_2 atmosphere. This was followed by a drop wise addition of (2-chloroethyl) (methyl) sulfane (CAS: 54187-93-8, 4 g, 0.04 mol) and the reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis which indicated the formation of less polar spot corresponds to O-alkylated product and polar spot corresponds to N-alkylated product. After completion of the reaction, water (100 ml) was added, and the

mixture was extracted with ethyl acetate (150 mL X 2). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated over reduced pressure. The crude compound was purified by flash column chromatography (silica gel, 230-400) using ethyl acetate in *n*-hexane (0-40%) to afford the desired compound **LXVIIa** as a colorless viscous liquid. Yield: 6.0 g (60%); **LCMS** Calculated. for $C_{18}H_{18}N_2O_3S$ is 342.10; Observed. 343.25. $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80 (q, J = 2.8 Hz, 2H), 7.69 (q, J = 3.2 Hz, 2H), 7.22 (t, J = 6.4 Hz, 1H), 7.12 (d, J = 6.0 Hz, 1H), 6.02 (t, J = 6.4 Hz, 1H), 4.10-4.00 (m, 4H), 3.31-2.70 (m, 4H), 2.07 (s, 3H).

Step-2: 3-(2-aminoethyl)-1-(2-(methylthio) ethyl) pyridin-2(1H)-one (LXVII)

[000355] To a stirred solution of 2-(2-(1-(2-(methylthio) ethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **LXVIIa** (6.0 g, 17.52 mmol) in MeOH (60 mL) was added hydrazine hydrate (1.316 g, 26.28 mmol) and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated, and the residue was dissolved in water (10 mL). The resulting mixture was acidified (pH=2) with conc. HCl and the solid formed was removed by filtration. The filtrate was basified with 4N NaOH solution (pH=8-9) and extracted with methanol: DCM (0.5:9.5 v/v) (300 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the desired compound **LXVII** as a sticky solid. The crude compound was taken for next step without further purification. Yield: 4.0 g (100%); **LCMS** Calculated. for $C_{10}H_{16}N_2OS$ is 212.10; Observed. 213.25 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.02 (s, 4H), 7.24 (t, J = 13.6 Hz, 2H), 6.14 (t, J = 6.8 Hz, 1H), 4.11 (d, J = 6.8 Hz, 2H), 3.47 (s, 2H), 2.94 (m, 2H), 2.68 (t, J = 6.8 Hz, 2H), 2.11 (s, 3H).

Synthesis of N-(3-(3-(2-aminoethyl)-2-oxopyridin-1(2H)-yl) propyl) acetamide (LXVIII)



Step-1: 2-(2-(1-(3-aminopropyl)-2-oxo-1,2-dihydropyridin-3-yl)ethyl)isoindoline-1,3-dione (LXVIIIa):

[000356] To a stirred solution of tert-butyl (3-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-oxopyridin-1(2H)-yl)propyl)carbamate **LXIa** (700 mg, 1.65 mmol) in 1,4-dioxane (4 mL) was added HCl in dioxane (0.412 mL, 4 molar, 1.65 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at rt for 2 h and progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated under reduced pressure, the residue was triturated with diethyl ether and dried under *vacuo* to afford the desired compound **LXVIIIa** as an off-white solid. Yield: 430 mg (80%); **LCMS** Calculated. for $C_{18}H_{19}N_3O_3$ is 325.14; Observed.: 326.25 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D_6):** 8.06 (s, 3H), 7.83 (d, *J* = 1.6 Hz, 4H), 7.63 (d, *J* = 5.2 Hz, 1H), 7.19 (d, *J* = 5.6 Hz, 1H), 6.10 (t, *J* = 6.4 Hz, 1H), 3.98 (t, *J* = 6.4 Hz, 2H), 3.85 (t, *J* = 6.0 Hz, 2H), 2.79-2.72 (m, 3H), 1.99-1.92 (m , 2H).

Step-2: N-(3-(3-(2-(1,3-dioxoisoindolin-2-yl) ethyl)-2-oxopyridin-1(2H)-yl) propyl) acetamide (LXVIIIb):

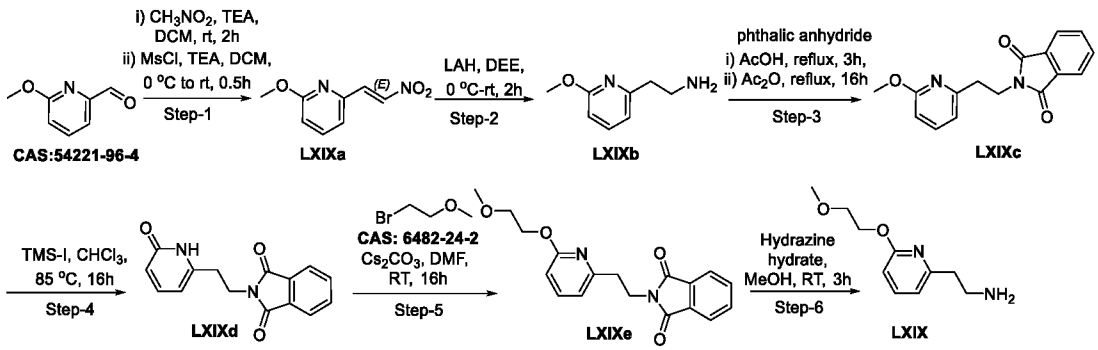
[000357] To a stirred solution of 2-(2-(1-(3-aminopropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **LXVIIIa** (400 mg, 1.23 mmol) in THF (10 mL) were added TEA (171 µL, 1.23 mmol) and DMAP (15.0 mg, 123 µmol) at rt under N_2 atmosphere. This was followed by a drop wise addition of acetic anhydride (139 µL, 1.48 mmol) and the resulting reaction mixture was stirred at rt for 3 h. The progress of the reaction was monitored by TLC analysis. After completion, sat. $NaHCO_3$ solution (10 mL) was added, and the resulting mixture

was extracted with DCM (50 ml X 2). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the desired compound **LXVIIIb** as an off-white solid. Yield: 350 mg (78%); **LCMS** Calculated. for $C_{20}H_{21}N_3O_4$ is 367.15; Observed.:368.30 $[M+H]^+$.

Step-3: N-(3-(3-(2-aminoethyl)-2-oxopyridin-1(2H)-yl) propyl) acetamide (LXVIII)

[000358] To a stirred solution of N-(3-(3-(2-(1,3-dioxoisoindolin-2-yl) ethyl)-2-oxopyridin-1(2H)-yl) propyl) acetamide **LXVIIIb** (350 mg, 953 µmol) in MeOH (5 mL) was added hydrazine hydrate (71.5 mg, 1.43 mmol) and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated, and the residue was dissolve in water (2 mL). The mixture was acidified (pH=2) using conc. HCl, the solid formed was filtered and washed with water. The filtrate was basified with 4N NaOH solution (pH=8-9) and extracted with DCM (50 ml X 3). The combined organic layer was dried over anhydrous sodium sulfate and concentrated over reduced pressure. The crude compound **LXVIII** was taken for next step without further purification. Yield: 210 mg (93%); **LCMS** Calculated. for $C_{12}H_{19}N_3O_2$ is 237.14; Observed. 238.30 $[M+H]^+$.

Synthesis of 2-(6-(2-methoxyethoxy) pyridin-2-yl) ethan-1-amine (LXIX)



Step-1: (*E*)-2-methoxy-6-(2-nitrovinyl) pyridine (LXIXa)

[000359] To a stirred solution of 6-methoxypicolinaldehyde (CAS:54221-96-4, 3 g, 0.02 mol) in DCM (30 mL) under inert atmosphere were added TEA (6 mL, 0.04 mol) and nitromethane (2 g, 0.03 mol) at room temperature. The reaction mixture was stirred at rt for 2 h and the progress of the reaction was monitored by

TLC analysis. The reaction mixture was concentrated to dryness under reduced pressure and the residue was dissolved in fresh DCM (40 mL). The solution was cooled to 0 °C under inert atmosphere and was added TEA (9 mL, 0.07 mol). This was followed by a dropwise addition of mesyl-Cl (3 mL, 0.03 mol) over 10 min. The resultant mixture was stirred at 0 °C for 30 min and quenched with saturated solution of $NaHCO_3$. The mixture was extracted with DCM (100 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated over reduced pressure. The crude was purified by silica-gel (230-400) column chromatography using 10-30 % ethyl acetate in *n*-hexane to afford the desired compound **LXIXa** as a pale-yellow solid. Yield: 1.8 g (45%). **LCMS** Calculated. for $C_8H_8N_2O_3$ is 180.05; Observed. 181.25; $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.00 (d, J = 12.8 Hz, 1H), 7.83 (d, J = 12.8 Hz, 1H), 7.64 (t, J = 7.2 Hz, 1H), 7.06 (d, J = 7.2 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 3.97 (s, 3H).

Step-2: 2-(6-methoxypyridin-2-yl) ethan-1-amine (LXIXb)

[000360] A stirred solution of $LiAlH_4$ (120 mL, 1 M in THF, 0.12 mol) in diethyl ether (300mL) was cooled to 0 °C under inert atmosphere and dropwise added a solution of (*E*)-2-methoxy-6-(2-nitrovinyl) pyridine **LXIXa** (7.3 g, 41 mmol) in THF (30 mL) over 15 min. The resulting mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to 0 °C and quenched with ice cold water (24 mL). Then added 15% NaOH solution (8 ml) and ethyl acetate (200 mL). The mixture was stirred at rt for 15 min and filtered. The residue was washed thoroughly with ethyl acetate (500 mL X 3). The combined filtrate was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the desired compound **LXIXb** as a pale-yellow viscous liquid. Yield: 5.0 g (80.6%). **LCMS** Calculated. for $C_8H_{12}N_2O$ is 152.09; Observed. 153.30; $[M+H]^+$.

Step-3: 2-(2-(6-methoxypyridin-2-yl) ethyl) isoindoline-1,3-dione (LXIXc)

[000361] To a stirred solution of 2-(6-methoxypyridin-2-yl) ethan-1-amine **LXIXb** (5 g, 0.03 mol) in acetic acid (50 mL) was added in isobenzofuran-1,3-dione (6 g, 0.04 mol) under inert atmosphere. The resulting mixture was stirred at 140 °C for 3 h. Then reaction mixture was concentrated under reduced pressure to

dryness. To the residue was added acetic anhydride (20 mL, 0.2 mol) and stirring at140 °C was continued for additional 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to rt and quenched with sat. $NaHCO_3$ solution (200 mL). The resulting mixture was extracted with DCM (300 mL X 3) and the combined organic layer was dried over anhydrous sodium sulphate. The organic layer was filtered and concentrated under reduced pressure. The crude was purified by silica-gel (230-400) column chromatography using 0-10 % ethyl acetate in *n*-hexane to afford the desired compound **LXIXc** as off-white solid. Yield: 5.0 g (55%). **LCMS** Calculated. for $C_{16}H_{14}N_2O_3$ is 282.10; Obs. 283.20; $[M+H]^+$.

Step-4: 2-(2-(6-oxo-1,6-dihydropyridin-2-yl) ethyl) isoindoline-1,3-dione (LXIXd)

[000362] To a stirred solution of 2-(2-(6-methoxypyridin-2-yl) ethyl) isoindoline-1,3-dione **LXIXc** (5.0 g, 18 mmol) in $CHCl_3$ (80 mL) was added TMS-I (4.8 mL, 35 mmol) and the reaction mixture was stirred at 85 °C for16 h. The progress of the reaction was monitored by TLC analysis. After completion, reaction was cooled to rt and quenched with MeOH (20 mL). The resulting mixture was concentrated under reduced pressure and the residue was triturated in MTBE/EtOH (5:1). The solid formed was collected by filtration and dried to afford the desired compound **LXIXd** as an off-white solid. Yield: 2.8 g (58%). **LCMS** Calculated. for $C_{15}H_{12}N_2O_3$ is 268.09; Observed. 269.25; $[M+H]^+$; **^{1}H NMR (400 MHz, CD_3OD):** δ 7.84 (bs, 4H), 7.54 (t, J = 7.2 Hz, 1H), 6.44 (d, J = 8.8 Hz, 1H), 6.33 (d, J = 6.8 Hz, 1H), 3.90 (bs, 2H), 2.88 (bs, 2H).

Step-5: 2-(2-(6-(2-methoxyethoxy) pyridin-2-yl) ethyl) isoindoline-1,3-dione (LXIXe)

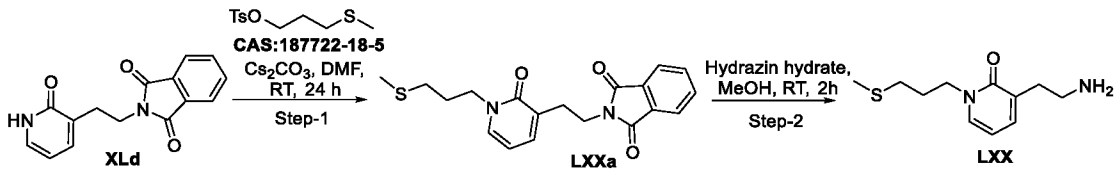
[000363] To a stirred solution of 2-(2-(6-oxo-1,6-dihydropyridin-2-yl) ethyl) isoindoline-1,3-dione **LXIXd** (0.70 g, 2.61 mmol) in DMF (10 mL) was added Cs_2CO_3 (1.70 g, 5.22 mmol) and stirred for 20 min at rt. The mixture was cooled to 0 °C and added 1-chloro-2-methoxyethane (370 mg, 3.91 mmol) slowly under nitrogen atmosphere. The reaction was stirred at rt for 16 h and the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted

with water (100 mL) and extracted with ethyl acetate (50 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by combi flash column silica gel (230-400) column chromatography using 0-20% ethyl acetate in *n*-hexane to afford the desired compound **LXIXe** as a pale-yellow viscous liquid. The crude compound was taken for the next step without further purification; Yield: 0.35 g (39%).

Step-6: 2-(6-(2-methoxyethoxy) pyridin-2-yl) ethan-1-amine (LXIX)

[000364] To a stirred solution of 2-(2-(6-(2-methoxyethoxy)-1,6-dihydropyridin-2-yl) ethyl) isoindoline-1,3-dione **LXIXe** (0.65 g, 2.0 mmol) in methanol (10 mL) was added hydrazine hydrate (0.14 mL, 3.0 mmol) and the reaction was stirred for at rt for 3 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated, and the crude was diluted with 10% NaOH solution (50 mL). The mixture was extracted with ethyl acetate (20 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired compound **LXIX** as a pale-yellow viscous liquid. The crude taken for the next step without further purification. Yield: 0.5 g (80 %)

Synthesis of 3-(2-aminoethyl)-1-(3-(methylthio) propyl) pyridin-2(1H)-one. (LXX)



Step-1: 2-(2-(1-(3-(methylthio) propyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione (LXXa)

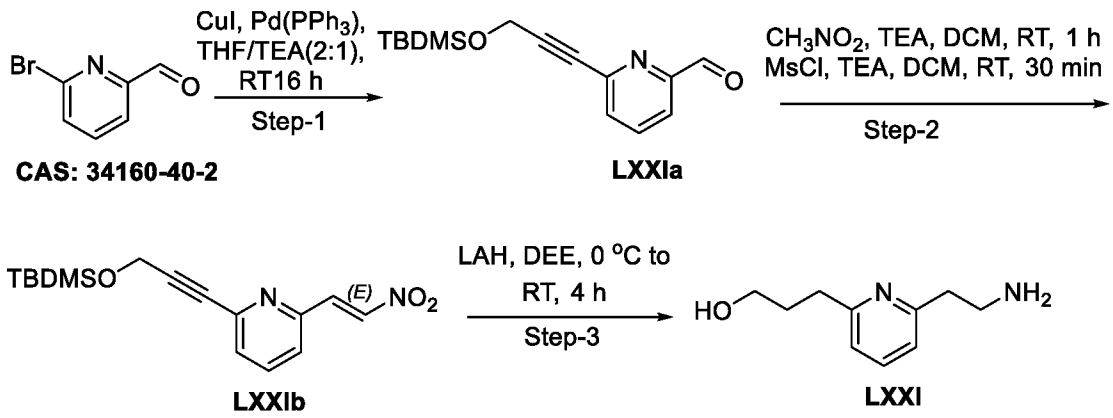
[000365] To a solution of 2-(2-(2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **XLd** (5.0 g, 18.64 mmol) in N, N-dimethyl formamide (15 mL) were added cesium carbonate (12.15 g, 37.28 mmol) and 3-(methylthio) propyl 4-methylbenzenesulfonate (CAS:187722-18-5 , 5.82 g, 22.37 mmol). The reaction mixture was stirred at rt for 24 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, added water (300 mL) and

extracted with ethyl acetate (500 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography with ethyl acetate in *n*-hexane (0-50%) to afford the desired product **LXXa** as a pale-yellow viscous liquid. Yield: 3.9 g, (59.0 %); **LCMS** Calculated. for $C_{19}H_{20}N_2O_3S$ is 356.12; Observed 357 [M+H] +.**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.02 (s, 3H), 7.80 (q, J = 2.4 Hz, 2H), 7.68 (q, J = 2.4 Hz, 2H), 4.02 (q, J =8 Hz, 4H), 2.91 (d, J = 4 Hz, 4H), 2.52 (t, J = 8 Hz, 2H), 2.11 (s, 1H), 2.04 (t, J =8 Hz, 2 H).

Step-2: 3-(2-aminoethyl)-1-(3-(methylthio) propyl) pyridin-2(1H)-one (LXX)

[000366] To a solution of 2-(2-(1-(3-(methylthio) propyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) isoindoline-1,3-dione **LXXa** (1.90 g, 5.330 mmol) in methanol (4 mL) was added hydrazine hydrate (0.32 g, 6.397 mmol) and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was concentrated, added water (5 mL) and acidified with conc. HCl to pH~1. The solids were filtered, basified by sodium hydroxide (1 N) and extracted with 10 % methanol in dichloromethane (500 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate to afford the desired compound **LXX** as a pale-yellow viscous liquid. The crude compound was taken for the next step without any further purification. Yield: 0.9 g, (75.0 %); **LCMS** Calculated. for $C_{11}H_{18}N_2OS$ is 226.11; Observed: 227.25 [M+H] +. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.22 (d, J = 6.4 Hz, 2H), 6.13 (d, J = 6.8 Hz, 1H), 4.05 (t, J = 6.8 Hz, 2H), 2.95 (t, J = 6.4 Hz, 3H), 2.68 (t, J = 6.8 Hz, 2H), 2.53 (t, J = 7.2 Hz, 2H), 2.11-2.01(m, 6H).

Synthesis of 3-(6-(2-aminoethyl)222yridine-2-yl) propan-1-ol (LXXI)



Step-1: 6-(3-((tert-butyldimethylsilyl) oxy) prop-1-yn-1-yl) picolinaldehyde (LXXIa)

[000367] To a stirred solution of 6-bromopicolinaldehyde (CAS: 34160-40-2, 1.0 g, 5.38 mmol) was added CuI (0.372 g, 1.61 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.932 g, 0.81 mmol) in 2: 1 THF/triethylamine (10 mL) and purged with N_2 gas for 15 min with vigorous stirring. To the reaction was added tert-butyl dimethyl(prop-2-yn-1-yloxy) silane (1.10 g, 6.45 mmol) and the seal tube with Teflon screw-stopper was closed and stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with 100 mL of water and extracted with ethyl acetate (50 mL X 2). The combined organic layer was dried over anhydrous sodium sulphate and concentrated to obtain crude product. The crude product was subjected to silica gel (230-400 mesh) column chromatography using 0-6% ethyl acetate in *n*-hexane to afford the desired compound **LXXIa** as a colorless viscous liquid. Yield: (1.4 g, 95%); **LCMS** Calculate. for $C_{15}H_{21}NO_2Si$ is 275.13; Observed. 276.00 $[M+H]^+$; **^{1}HNMR (400 MHz, $CDCl_3$):** δ 10.05 (s, 1H), 7.91 (dd, J = 7.6, 1.2 Hz, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.64 (dd, J = 7.6, 1.2 Hz, 1H), 4.60 (s, 2H), 0.85 (s, 9H), 0.18 (s, 6H).

Step-2: (*E*)-2-(3-((tert-butyldimethylsilyl) oxy) prop-1-yn-1-yl)-6-(2-nitrovinyl) pyridine (LXXIb)

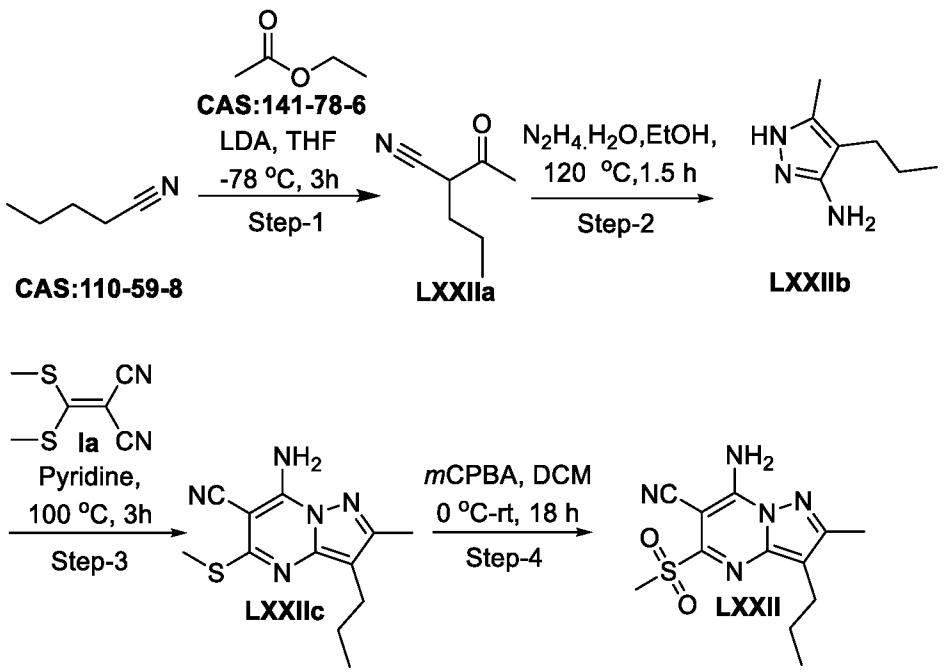
[000368] To a stirred solution of 6-(3-((tert-butyldimethylsilyl) oxy) prop-1-yn-1-yl) picolinaldehyde **LXXIa** (1.4 g, 5.1 mmol) in DCM (20 mL) was added triethylamine (1.5 g, 2.1 mL, 15 mmol) and nitromethane (4.7 g, 4.1 mL, 76 mmol)

under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 1 h and the progress of the reaction was monitored by TLC analysis. After completion of reaction, DCM was concentrated under reduced pressure. The resulting residue was taken in DCM (20 mL) was added triethylamine (1.5 g, 2.1 mL, 15 mmol) and cooled to 0 °C followed by drop wise addition of methane sulfonyl chloride (1.7 g, 1.2 mL, 7.6 mmol). The mixture was stirred at 0 °C for 30 min and the progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (40 mL) and extracted with DCM (20 mL X 2). The combined organic layer was dried over anhydrous sodium sulphate. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using 0-6% ethyl acetate in *n*-hexane to afford the desired compound **LXXIb** as a yellow viscous liquid. Yield: 1.1 g (68%); **LCMS** Calculate. for $C_{16}H_{22}N_2O_3Si$ is 318.14; Observed. 319.30 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.03 (d, J = 13.2 Hz, 1H), 7.87 (d, J = 13.2 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 4.49 (s, 2H), 0.94 (s, 9H), 0.18 (s, 6H).

Step-3: 3-(6-(2-aminoethyl) pyridin-2-yl) propan-1-ol. (LXXI)

[000369] To a stirred solution of lithium aluminum hydride (13.8 mL, 1.0 M in THF, 14 mmol) in diethyl ether (70 mL) was added (*E*)-2-(2-((tert-butyldimethylsilyl) oxy) ethyl)-6-(2-nitrovinyl) pyridine **LXXIb** (1.1 g, 3.5 mmol) dropwise at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4 h and the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to 0 °C was added 1 mL of ice-cold water and 1 mL of 15% KOH solution then stirred at room temperature for another 30 min. The resulting reaction mixture was diluted with 100 mL of ethyl acetate filtered through Buchner funnel and the solid was thoroughly washed with 100mL of ethyl acetate. The filtrate was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford a desired compound **LXXI** as light brown viscous liquid. Yield: (0.7 g, 85%).

Synthesis of 7-amino-2-methyl-5-(methyl sulfonyl)-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile. (LXXII)



Step-1: 2-acetylpentanenitrile (LXXIIa)

[000370] A stirred solution of lithium diisopropylamide (30 mL, 2.0 M in THF/heptane/ethylbenzene, 0.06 mol) in dry THF (300 mL) was cooled to -78 °C under inert atmosphere and dropwise added a solution of pentane nitrile (CAS:110-59-8, 5 g, 6.48 mL, 1 Eq, 0.06 mol) in THF (20 mL). The resulting mixture was stirred -78 °C for 1 h. To the reaction was dropwise added dry ethyl acetate (6 mL, 0.06 mol) over 10 min and the mixture was stirred at -78 °C for additional 2 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched with saturated solution of NH_4Cl (100 mL) and extracted with ethyl acetate (200 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired compound **LXXIIa** as a pale-yellow viscous liquid. Yield: 10.0 g.

Step-2: 5-methyl-4-propyl-1H-pyrazol-3-amine (LXXIIb)

[000371] To a stirred solution of 2-acetylpentanenitrile **LXXIIa** (10 g, 80 mmol) in ethanol (100 mL) was added hydrazine hydrate (5.8 mL, 0.12 mol) and the reaction mixture was stirred under inert atmosphere at 120 °C for 1.5 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt and concentrated under reduced pressure. The

residue obtained was diluted with water (100 mL) and extracted with 10% MeOH in DCM (200 mL x 5). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired compound **LXXIIb** as a pale-yellow viscous liquid. The crude material was used in the next step without further purification. Yield: 9.3 g. (83.6%); **LCMS** Calculated. for $C_7H_{13}N_3$ is 139.11; Observed.140.30 $[M+H]^+$.

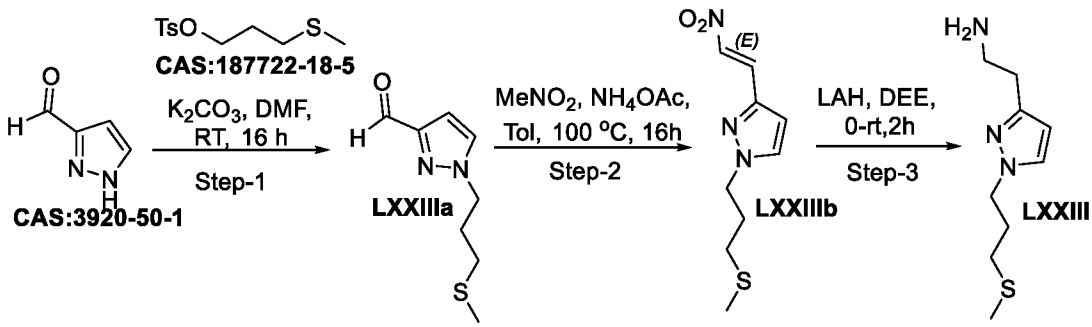
Step-3: 7-amino-2-methyl-5-(methylthio)-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (LXXIIc)

[000372] A mixture of 5-methyl-4-propyl-1H-pyrazol-3-amine (9.3 g, 67 mmol), 2-(bis(methylthio)methyl) malononitrile **LXXIIb** (13 g, 73 mmol) and pyridine (50 mL) was stirred at 100 °C under inert atmosphere for 3 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt and poured into ice cold water (1000 mL). The precipitate formed was filtered and washed with cold water. The solid obtained was dried under vacuum to afford the title compound **LXXIIc** as a pale- yellow solid. Yield: 15 g (88%). **LCMS** Calculated. for $C_{12}H_{15}N_5S$ is 261.10; Observed.262.20 $[M+H]^+$.

Step-4: 7-amino-2-methyl-5-(methylsulfonyl)-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (LXXII)

[000373] To a stirred solution of 7-amino-2-methyl-5-(methylthio)-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **LXXIIc** (15 g, 57 mmol) in solvent DCM (1000 mL) at 0 °C was added *m*CPBA (50 g, 0.29 mol) in portions under inert atmosphere. The resulting mixture was stirred at room temperature for 18 h and progress of the reaction was monitored by TLC analysis. After completion, the solvent was removed under vacuum and to the yellow precipitate was added saturated sodium bicarbonate solution (250 mL). The resulting mixture was stirred at rt for 30 min, the solid was collected by filtration and dried under reduced pressure to afford the desired compound **LXXII** as a pale-yellow solid. Yield: 7.5 g (44 %); **LCMS:** Calculated. for $C_{12}H_{15}N_5O_2S$ is 293.09; Observed. 294.20 [M+H]

Synthesis of 2-(1-(3-(methylthio) propyl)-1H-pyrazol-3-yl) ethan-1-amine (LXXIII)



Step-1: 1-(3-(methylthio) propyl)-1H-pyrazole-3-carbaldehyde (LXXIIIa)

[000374] To a stirred solution of 1H-pyrazole-3-carbaldehyde (CAS:3920-50-1, 3 g, 0.0312 mol) in DMF (50 mL) was added Cs_2CO_3 (15.27 g, 0.0469 mol) and the resulting reaction mixture was cooled to 0° C. To this was dropwise added of 3-(methylthio) propyl 4-methylbenzenesulfonate (CAS:187722-18-5, 9.75 g, 0.037 mol) under nitrogen. The resulting mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford the crude yellow liquid. The crude material was purified by column chromatography (silica 230-400) eluted with 0-10% ethyl acetate in *n*-hexane to afford the compound **LXXIIIa** as a pale-yellow liquid. Yield: 2.5 g (40%). **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 9.87 (s, 1H), 7.96 (s, 1H), 6.78 (d, J= 1.6 Hz, 1H), 4.33 (t, J = 6.8 Hz, 2H), 2.44 (t, J = 7.2 Hz, 2H), 2.11-2.08 (m, 2H), 2.05 (s, 3H).

Step-2: (*E*)-1-(3-(methylthio) propyl)-3-(2-nitrovinyl)-1H-pyrazole (LXXIIIb)

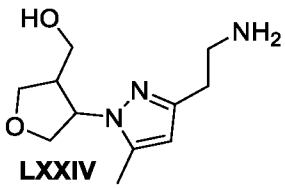
[000375] To a stirred solution of 1-(3-(methylthio) propyl)-1H-pyrazole-3-carbaldehyde **LXXIIIa** (1.1 g, 6.0 mmol) in toluene (20 mL) were added nitromethane (5.5 g, 90 mmol) and ammonium acetate (0.69 g, 9.0 mmol) under nitrogen atmosphere. The resulting mixture was stirred at 100 °C for 16 h and progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was cooled to room temperature, diluted with cold 1N HCl solution (15 mL) and extracted with ethyl acetate (100 mL X 3). The combined organic layer was washed with water (100 mL). The organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford the

crude brown semi-solid. The crude material was purified by silica gel (100-200) column chromatography using 0-10% ethyl acetate in *n*-hexane to afford the desired compound **LXXIIIb** as a pale-yellow liquid. Yield: 0.9 g (66%); δ 7.96 (d, J = 13.6 Hz, 1H), 7.61 (d, J = 13.6 Hz, 1H), 7.47 (d, J = 1.6 Hz, 1H), 6.53 (d, J = 1.6 Hz, 1H), 4.30 (t, J = 6.4 Hz, 2H), 2.46 (t, J = 6.8 Hz, 2H), 2.22-2.15 (m, 2H), 2.10 (s, 3H).

Step-3: 2-(1-(3-(methylthio) propyl)-1H-pyrazol-3-yl) ethan-1-amine (LXXIII)

[000376] A stirred solution of $LiAlH_4$ (15.8 mL, 1 M in THF, 15.8 mmol) in diethyl ether (50 mL) was cooled to 0 °C. and dropwise added solution of (E)-1-(3-(methylthio) propyl)-3-(2-nitrovinyl)-1H-pyrazole **LXXIIIb** (900 mg, 3.96 mmol) in diethyl ether (5 mL). The reaction mixture was stirred at rt for 2 h and progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was cooled to 0 °C and quenched with water (0.9 mL), followed by with 15% KOH ((0.9 mL). Then water (1.8 mL) and ethyl acetate (50 mL) were added. The resulting reaction mixture was stirred at rt for 30 min. The mixture was filtered, and solid residue was washed with fresh ethyl acetate (250 mL x 3). The combined filtrate was concentrated under reduced pressure to afford the desired compound **LXXIII** as a light brown viscous liquid. Yield: 700 mg (88.7%); **LCMS** Calculated. for $C_9H_{17}N_3S$ is 199.11; Observed. 200.25 $[M+H]^+$.

Synthesis of (4-(3-(2-aminoethyl)-5-methyl-1H-pyrazol-1-yl) tetrahydrofuran-3-yl) methanol (LXXIV)

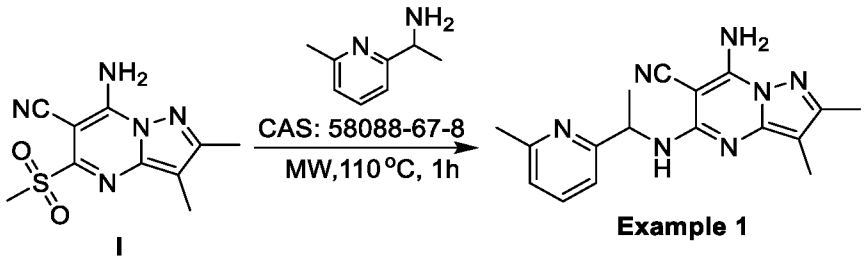


LXXIV

[000377] The title compound **LXXIV** was prepared in analogus to **LVII** by using 5-methyl-1H-pyrazole-3-carbaldehyde (CAS: 3273-44-7) instead of 1H-pyrazole-3-carbaldehyde (CAS: 3920-50-1). **LXXIV** was obtained as an off white

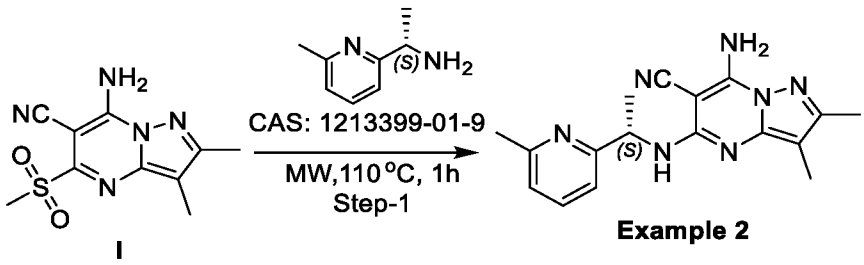
solid. The crude product obtained is taken for the next step without further purification. **LCMS** Calculated. for C11H19N3O2 is 225.29; Observed. 226.40 $[M+H]^+$.

Example 1: 7-amino-2,3-dimethyl-5-{[1-(6-methylpyridin-2-yl) ethyl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile



[000378] To a mixture of **1** (80 mg, 0.30 mmol) and racemic 1-(6-methylpyridin-2-yl) ethan-1-amine (CAS: 58088-67-8) (65 mg, 0.45 mmol) in DMF (3 mL) was added Et_3N (0.1 mL). The resulted mixture was irradiated under constant microwave for about 1 h at 120 °C. After completion, the reaction mixture was concentrated in *vacuo* to get the crude. The crude was purified by reverse phase preparative HPLC to afford the title compound **(Example1)** as white solid. Yield: 15 mg, 15.62%; **LC-MS** Calculated for $C_{17}H_{19}N_7$: 321.39; Observed.:322.1; $[M^+ + H]$. **^{1}H NMR (400 MHz, DMSO-D$_6$)**: δ 8.21 (s, 2H), 7.69-7.64 (m, 1H), 7.27 (d, *J* = 8.00 Hz, 1H), 7.14 (dd, *J* = 1.60, 7.60 Hz, 1H), 6.97 (d, *J* = 4.40 Hz, 1H), 5.28-5.25 (m, 1H), 2.50 (s, 3H) 2.22 (s, 3H), 1.95 (s, 3H), 1.51-1.48 (m, 3H). **HPLC:** 2.39 min; 98.85 %; HPLC Column: Atlantis dC18 (250*4.6) mm 5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

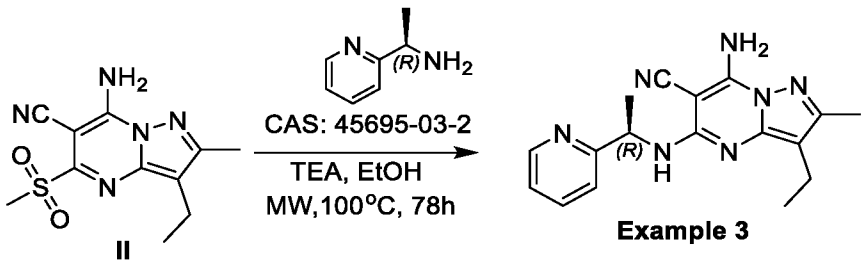
Example 2: 7-amino-2,3-dimethyl-5-{[(1S)-1-(6-methylpyridin-2-yl)ethyl] amino}pyrazolo [1,5-a]pyrimidine-6-carbonitrile



Example 2 was synthesized similar to example **1** using intermediate **I** and charily pure (S)-1-(6-methylpyridin-2-yl) ethan-1-amine (CAS:1213399-01-9)

[000379] **LC-MS** Calculated for $C_{17}H_{19}N_7$: 321.39; Observe.: 322.0; [M^++H]. **^{1}H NMR (400 MHz, DMSO-D$_6$)**: δ 8.19 (br s, 1H), 7.66 (t, *J* = 7.60 Hz, 1H), 7.27 (d, *J* = 7.60 Hz, 1H), 7.14 (d, *J* = 7.60 Hz, 1H), 6.97 (d, *J* = 7.20 Hz, 1H), 5.27 (t, *J* = 7.20 Hz, 1H), 2.23 (s, 3H), 1.94 (s, 3H), 1.50 (d, *J* = 6.80 Hz, 3H). **HPLC:** 2.39 min; 95.99 %; Column: X-Bridge C8(50X4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile. **Chiral HPLC:** 4.23 min; 100 % ee; Column: Lux C4, Mobile Phase A: 0.5% Isopropyl amine in methanol, Mobile phase B: Methanol (30%), Flowrate: 3 mL/min, Injected Volume: 15 µl.

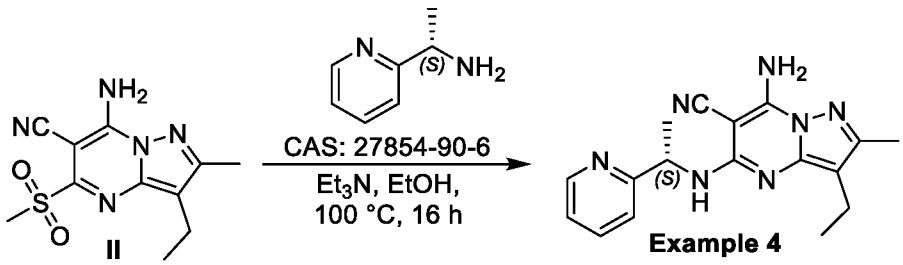
Example 3: (R)-7-Amino-3-ethyl-2-methyl-5-((1-(pyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000380] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.15 g, 0.0005376 mol) and (R)-1-(pyridin-2-yl) ethan-1-amine (CAS: 45695-03-2, 0.2627 g, 0.00215 mol) in EtOH (15 ml) in a sealed tube, was added TEA (0.6 ml, 0.0043 mol) and the reaction mixture was stirred at 100 °C for 78 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure and the crude material was purified by column chromatography by eluting with 20% EtOAc in hexane to yield the title compound **(Example 3)** as off-white solid; Yield: (0.038 g, 22%). **LC-MS** Calculated for $C_{17}H_{19}N_7$ is 321.17;

Observe:322.15 [M$^+$+1].**^{1}HNMR (400 MHz, DMSO-d$_6$,):** δ 8.530-8.541 (d, *J* = 4.4 Hz, 1H), 8.165 (bs, 2H), 7.730-7.773 (m, 1H), 7.449-7.469 (d, *J* = 8Hz, 1H), 7.241-7.272 (m, 1H), 6.869-6.852 (d, *J* = 6.8 Hz, 1H), 5.229-5.298 (m, 1H), 2.387-2.406 (q, *J* = 7.6 Hz, 2H), 2.229 (s, 3H), 1.496-1.513 (d, *J* = 6.8 Hz, 3H), 1.002-1.040 (t, *J* = 7.2 Hz, 3H). **HPLC**: 10.35 min; 97.80 %, XBridge C18 (4.6*150) mm, 5µ, Mobile Phase A: 10mM ammonium bicarbonate in water, Mobile Phase B: Acetonitrile: **Chiral HPLC:** 4.56 min; >97 % ee; Column: Chiral Pak IC (250*4.6) mm,5µ; Mobile Phase A: 0.1% diethylamine in hexane, Mobile phase B: Ethanol (90:10), Flowrate: 1 mL/min, Injected Volume: 5 µl

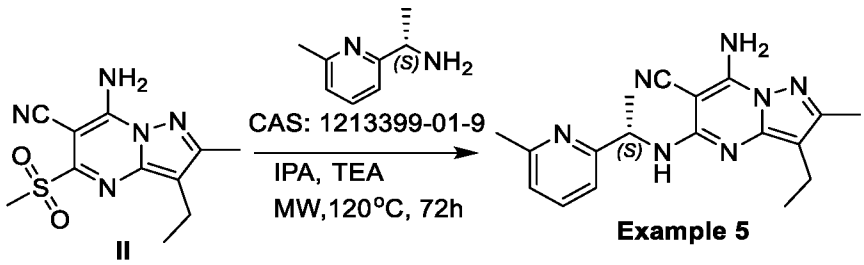
Example 4: (S)-7-Amino-3-ethyl-2-methyl-5-((1-(pyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000381] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.15 g, 0.0005376 mol) and (S)-1-(pyridin-2-yl) ethan-1-amine (CAS:27854-90-6; 0.262 g, 0.00215 mol) in EtOH (12 ml) in a sealed tube, was added TEA (0.21 ml, 0.0016 mol) and the reaction mixture was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with EtOAc (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 30% EtOAc in hexane to yield the title compound **(Example 4)** as off-white solid; Yield: (0.040 g, 23%). **LC-MS:** Calculated for $C_{17}H_{19}N_7$ is 321.17; Observe:322.15 [M$^+$+1].**^{1}HNMR (400 MHz, DMSO-d$_6$,):** δ 8.533-8.5444 (d, *J* = 4.4 Hz, 1H), 8.190 (bs, 2H), 7.734-7.772 (t, *J* = 7.2 Hz, 1H), 7.452-7.471 (d, *J* = 7.6 Hz, 1H), 7.242-7.273 (m, 1H), 6.872-6.855 (d, *J* = 6.8 Hz, 1H), 5.249-5.283 (m, 1H), 2.370-2.426 (q, *J* = 8 Hz, 2H), 2.231 (s, 3H), 1.514-1.497 (d, *J*

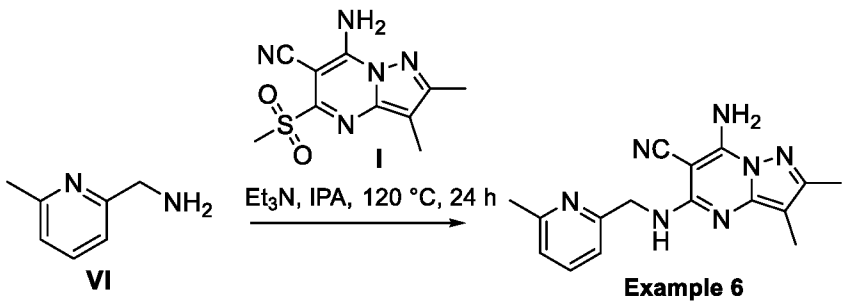
= 6.8 Hz, 3H), 1.004-1.041 (t, *J* = 6.8 Hz, 3H). **HPLC**: 10.34 min; 96.02 %, Column: X Bridge C18 (4.6*150) mm,5µ, Mobile Phase A: 10mM Ammonium bicarbonate in water, Mobile Phase B: Acetonitrile. **Chiral HPLC**: 4.72 min; >97 % ee; Column: Chiral Pak IC (250*4.6) mm, 5µ Mobile Phase A: 0.1% Diethylamine in hexane, Mobile phase B: EtOH (90:10). Flowrate: 1 mL/min, Injected Volume: 5 µl

Example 5: (S)-7-Amino-3-ethyl-2-methyl-5-((1-(6-methylpyridin-2-yl) ethyl) amino) pyrazolo [1,5-a] pyrimidine-6-carbonitrile



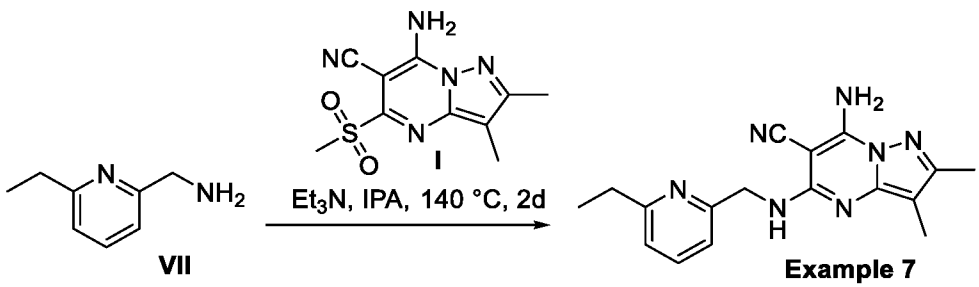
[000382] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.205 g, 0.000735 mol) and (S)-1-(6-methylpyridin-2-yl) ethan-1-amine (CAS: 1213399-01-9, 0.2 g, 0.00147 mol) in IPA (4 ml) in a sealed tube was added TEA (0.32 ml, 0.00172 mol) and the reaction mixture was stirred at 120 °C for 72 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with EtOAc (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 20% EtOAc in hexane to yield the title compound as off-white solid; Yield: (0.0358 g, 17.4%). **LC_MS Calc**. for $C_{18}H_{21}N_7$ is 335.17; Obs.336.20 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 8.18 (bs, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.6 (d, *J* = 7.6 Hz, 1H), 6.98(d, *J* = 7.2 Hz, 1H), 5.19 (t, *J* = 6.8 Hz, 1H), 2.42 (q, *J* = 7.2, Hz, 2H), 2.23 (s,3H), 1.49 (d, *J* = 6.8 Hz, 3H), 1.04 (t, *J* = 7.6 Hz, 3H). **HPLC:** 11.02 min; 95.75 %, Column: X -Bridge C18 (50X4.6) mm, mm,5µm, Mobile Phase A: 10mM ammonium bicarbonate in water, B: Acetonitrile

Example 6: 7-amino-2,3-dimethyl-5-{[(6-methylpyridin-2-yl) methyl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile



[000383] To a stirred solution of 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (0.25 g, 0.00094 mol) and (6-methylpyridin-2-yl)methanamine **VI** (0.46 g, 0.00377 mol) in IPA (10 ml) in a sealed tube, was added TEA (1.3ml g, 0.00377 mol) and the reaction mixture was stirred at 120 °C for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure and the crude material was purified by column chromatography by eluting with 20% ethyl acetate in hexane to yield the title compound **(Example 6)** as off-white solid; Yield: (0.1 g, 38%). **LC-MS** Calculated for $C_{16}H_{17}N_7$ is 307.15; Observe. 308.20 [M^++1]. **^{1}HNMR (400 MHz, DMSO-d_6,):** δ 8.177 (bs, 2H), 7.633-7.594 (t, *J* = 8 Hz, 1H), 7.232-7.206 (t, *J* = 4.8 Hz, 1H), 7.141-7.096 (m, 2H), 4.616-4.604 (d, *J* = 4.8 Hz, 2H), 2.465 (s, 3H), 2.215 (s, 3H), 1.896 (s, 3H). **HPLC**: 9.34min, 97.80 %, Column: X Bridge C18 (4.6x150) mm,5µ, Mobile Phase A: 10mM Ammonium bicarbonate in water, Mobile Phase B: Acetonitrile.

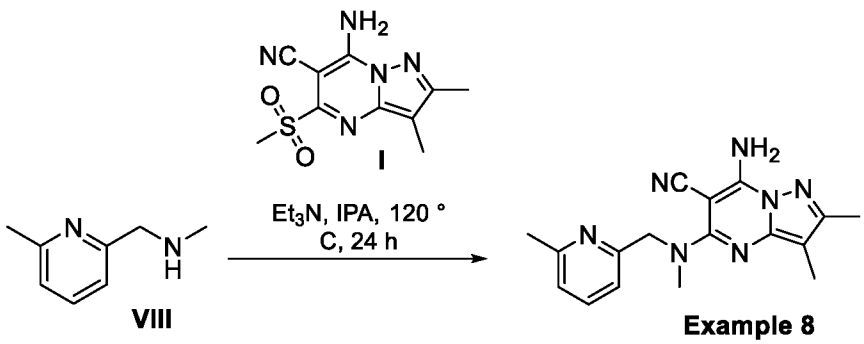
Example 7: 7-amino-5-{[(6-ethylpyridin-2-yl) methyl] amino} -2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000384] To a stirred solution of 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile I (0.100 g, 0.000377 mol) and (6-

ethylpyridin-2-yl) methenamine **VII** (0.102 g, 0.000754 mol) in IPA (10 ml), was added TEA (0.2 ml, 0.00150 mol) and the reaction mixture was heated at 140 °C for 2 days. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (3x20 ml). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 20% ethyl acetate in hexane to yield the title compound **(Example 7)** as off- white solid; Yield: (0.1 g, 12 %). **LC-MS** Calculated for $C_{17}H_{19}N_7$ is 324.18; Observe: 321.17 [M^++1]. **^{1}HNMR (400 MHz, DMSO-d_6,):** δ8.213 (bs, 2H), 7.665-7.628 (t, *J* = 7.6 Hz, 1H), 7.247 (bs, 1H), 7.169-7.150 (d, *J* = 7.6 Hz, 1H), 7.136-7.117 (d, *J* = 7.6 Hz, 1H), 4.630-4.619 (d, *J* = 4.4 Hz, 2H), 2.777-2.721 (q, *J* = 7.6 Hz, 2H), 2.217 (s, 3H), 1.905 (s, 3H), 1.268-1.233 (t, *J* = 7.6 Hz, 3H). **HPLC**:10.18 min, 99.44 %, Column: X Bridge C18 (4.6x150) mm,5µ, Mobile Phase A: Ammonium bicarbonate in water, Mobile Phase B: Acetonitrile.

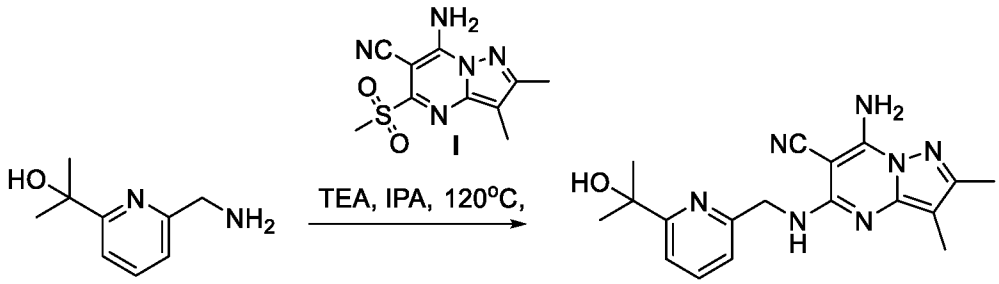
Example 8: 7-amino-2,3-dimethyl-5- {methyl [(6-methylpyridin-2-yl) methyl] amino} pyrazolo [1,5-a] pyrimidine-6-carbonitrile



[000385] To a stirred solution of 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (0.2 g, 0.000754 mol) and N-methyl-1-(6-methylpyridin-2-yl) methanamine **VIII** (0.123 g, 0.9056 mmol) in IPA (4 ml), was added TEA (0.2 ml, 0.0015 mol) and the reaction mixture was heated at 150 °C for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with DCM (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure to give the desired product **(Example 8).** The crude material was purified by Prep

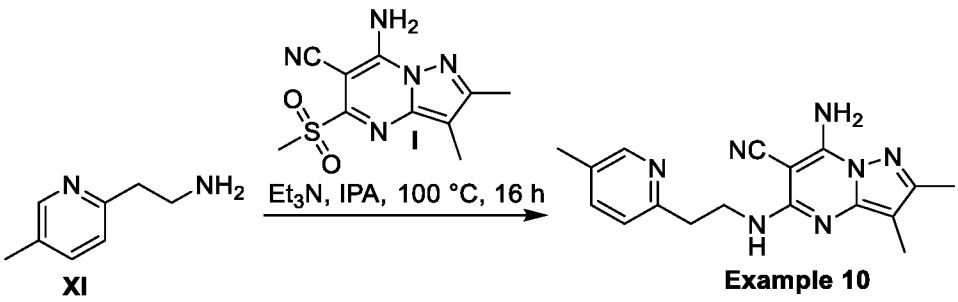
HPLC. Yield: 25 mg. **LC_MS** Calculated for $C_{17}H_{19}N_7$: 321.17; Observe: 322.17 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.187 (bs, 2H), 7.656-7.617 (d, J=8Hz, 1H), 7.128-7.086 (d, J=8.4Hz, 2H), 4.831 (s, 2H), 3.153 (s, 3H), 2.447 (s, 3H), 2.250 (s, 3H), 1.0 (s, 3H). **HPLC**: 9.73 min, 98.52 %, Column: X -Bridge C18 (50X4.6) mm, mm,5µm, Mobile Phase A: 10mM Ammonium bicarbonate in water, B: ACN.

Example 9: 7-amino-5-({[6-(2-hydroxypropan-2-yl) pyridin-2-yl] methyl}amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile



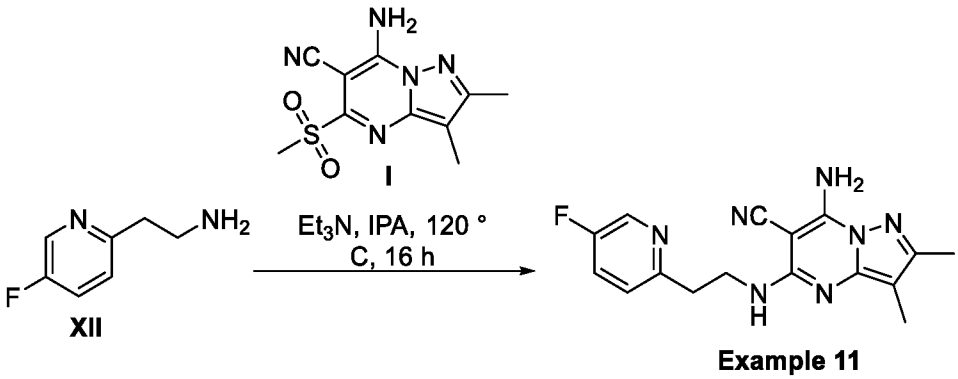
[000386] To a stirred solution 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (0.15g, 0.00039 mol) and 2-(6-(aminomethyl) pyridin-2-yl) propan-2-ol **X** (0.3 g, 0.00180 mol) in IPA (5 ml), was added TEA (0.6 ml, 0.0043 mol) and the reaction mixture was heated at 120 °C for 16 hrs. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (3x20 ml). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by prep HPLC to yield the title compound as off-white solid; Yield: (0.03 g, 15 %). **LC-MS** Calculated for $C_{18}H_{21}N_7O$: 351.18; Observe: 352.25 [M^++1]. **^{1}HNMR (400 MHz, DMSO-d$_6$,):** δ 8.202 (bs, 2H), 7.744-7.706 (t, *J* = 7.6 Hz, 1H), 7.529-7.511 (d, *J* = 7.2 Hz, 1H), 7.218-7.199 (d, *J* = 7.6 Hz, 2H), 5.215 (bs, 1H), 4.649-4.637 (d, *J* = 4.8 Hz, 2H), 2.221 (s, 3H), 1.920 (s, 3H), 1.461 (s, 6H). **HPLC**: 9.42 min, 97.56 %, X Bridge C18 (4.6x150) mm,5µ, Mobile Phase A: 10mM Ammonium bicarbonate in water, Mobile Phase B: Acetonitrile.

Example 10: 7-Amino-2,3-dimethyl-5-((2-(5-methylpyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



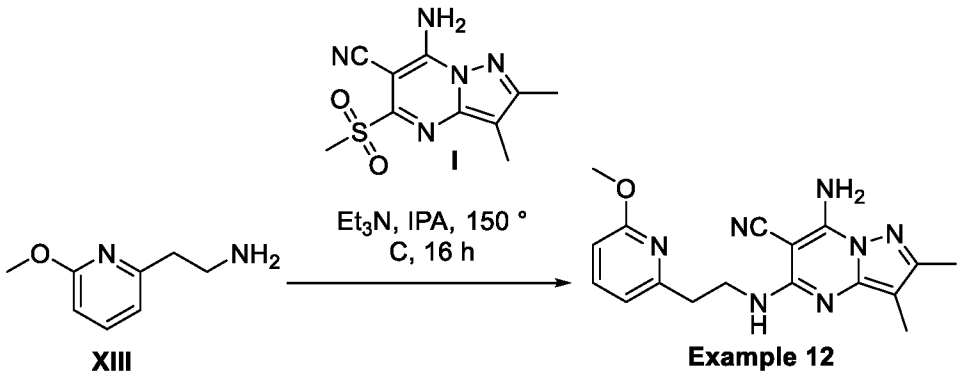
[000387] To a stirred solution of 7-amino-2,3-dimethyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (0.25 g, 0.000943 mol) and 2-(5-methylpyridin-2-yl) ethan-1-amine **XI** (0.192 g, 0.00141 mol) in IPA (5 ml), was added TEA (0.5 ml, 0.00377 mol) and the reaction mixture was heated at 100 °C for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 40% ethyl acetate in hexane to yield the title compound **(Example 10)** as off-white solid; Yield: (0.050 g, 20%). **LC_MS** Calculated for $C_{17}H_{19}N_7$: 321.39; Observe: 322.20 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.32 (bs, 1H), 8.09 (bs, 2H),7.52 (d, J = 6.8 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.80-6.78 (m, 1H), 3.67-3.64 (m, 2H), 2.99 (d, J = 6.8, Hz, 2H), 2.23 (d, J = 12, Hz, 3H),1.96 (s,1H). **HPLC**: 9.55min, 96.36 %, Column: X -Bridge C^{18} (50X4.6) mm, mm,5µm, Mobile Phase A: 10mM ammonium bicarbonate in water, B: Acetonitrile.

Example 11: 7-amino-5-((2-(5-fluoropyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000388] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (0.2 g, 0.000754 mol) and 2-(5-fluoropyridin-2-yl) ethan-1-amine **XII** (0.35 g, 0.0025 mol) in IPA (10 ml), was added TEA (0.63 ml, 0.0045 mol) and the reaction mixture was heated at 120 °C for 3 days. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 50% ethyl acetate in hexane to yield the title compound **(Example 11)** as off-white solid; Yield: (0.070 g, 28%). **LC_MS** Calculated for $C_{16}H_{16}FN_7$: 325.155; Observe:326.15 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.45 (d, J = 2.40 Hz, 1H), 8.09 (bs, 2H), 7.64 (dt, J = 8.8 Hz, 3.2 Hz, 1H), 7.36-7.33 (m, 1H), 6.78-6.67 (m, 1H), 3.67 (q, J = 6.8, Hz, 2H), 3.05 (t, J = 7.2, Hz, 2H), 2.24 (s, 3H), 1.95 (s, 3H). **HPLC**: 97.34 %, Column: X -Bridge C18 (50X4.6) mm, 5µm, Mobile Phase A: 10mM ammonium bicarbonate in water, B: Acetonitrile

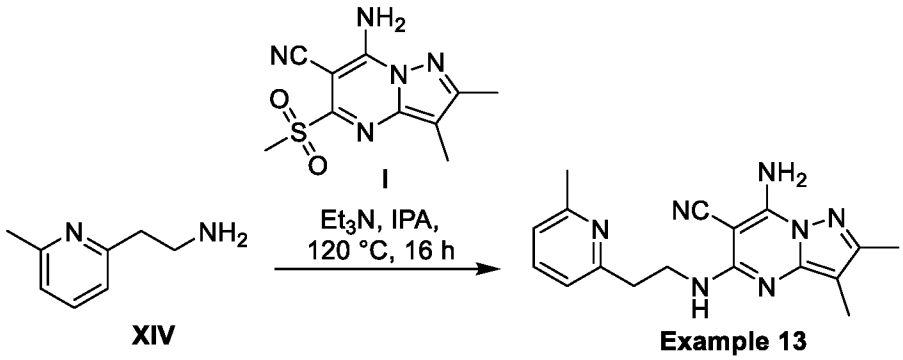
Example 12: 7-amino-5-((2-(6-methoxypyridin-2-yl) ethyl)amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000389] To a stirred solution of 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (0.2 g, 0.000754 mol) and 2-(6-methoxypyridin-2-yl) ethan-1-amine **XIII** (0.353 g, 0.00226 mol) in IPA (4 ml), was added TEA (0.229 g, 0.00226 mol) and the reaction mixture was heated at 150 °C for

16h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 20% ethyl acetate in hexane to yield the title compound **(Example 12)** as off-white solid; Yield: (0.10 g, 40%). **LC_MS** Calculated for $C_{17}H_{19}N_7O$: 337.17; Observe:338.15 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.1 (bs, 2H), 7.624-7.585 (t, J = 7.6 Hz, 1H), 6.862-6.844 (d, J = 7.2 Hz, 1H), 6.640-6.598 (m, 2H), 3.870 (s, 3H), 3.718-3.703 (m, 2H), 2.982-2.965 (t, J =6.8 Hz, 2H), 2.227 (s, 3H), 1.965 (s, 3H). **HPLC**: 10.83 min, 98.823 %, Column: X -Bridge C^{18} (50X4.6) mm, 5µm, Mobile Phase A: 10mM Ammonium bicarbonate in water, B: Acetonitrile.

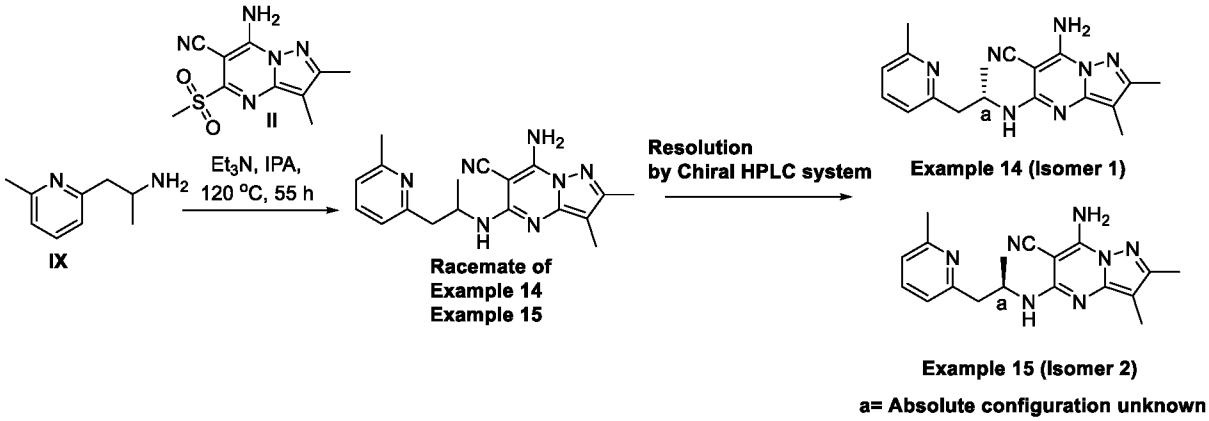
Example 13: 7-amino-5-((2-(6-methylpyridin-2-yl) ethyl)amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000390] To a stirred solution of 7-amino-2,3-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (0.2 g, 0.0007547 mol) and 2-(6-methylpyridin-2-yl) ethan-1-amine **XIV** (0.411 g, 0.00301 mol) in IPA (10 ml) in a sealed tube, was added TEA (0.6 ml, 0.0045 mol) and the reaction mixture was stirred at 120 °C for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure and the crude material was purified by combi flash by eluting with 15% ethyl acetate in hexane to yield the title compound **(Example 13)** as off-white solid; Yield: (0.105 g, 43%). **LC_MS** Calculated for $C_{17}H_{19}N_7$ is 321.17; Observe: 322.25 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.11 (bs, 2H), 7.60 (t, J = 7.2 Hz, 1H), 7.08 (d, J = 8.0 Hz, 2H), 6.93-6.90 (m, 1H), 3.67 (q, J = 6.4, Hz, 2H), 2.99 (d, J = 6.8, Hz, 2H), 2.22 (s, 3H),

2.48 (s, 3H), 1.96 (s, 3H). **HPLC**: 98.96 %, Column: X -Bridge C18 (50X4.6) mm, mm,5µm, Mobile Phase A: 10mM ammonium bicarbonate in water, B: Acetonitrile.

Example 14 and 15 (Racemic): 7-Amino-3-ethyl-2-methyl-5-((1-(pyridin-2-yl) propan-2-yl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000391] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.150 g, 0.000537 mol) and 1-(pyridin-2-yl) propan-2-amine **IX** (0.220 g, 0.00484 mol) in IPA (3 ml), was added TEA (0.6 ml, 0.0032 mol) and the reaction mixture was heated in a sealed tube at 120 °C for 60 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 50% ethyl acetate in hexane to yield the title compound **(Example 14 and 15 Racemate)** as off-white solid; Yield: (0.071 g, 39%). The crude racemic compound obtained (220 mg) was resolved into its two enantiomers by chiral preparative HPLC system.

Example 14: Chiral 7-amino-2,3-dimethyl-5-{[1-(6-methylpyridin-2-yl)propan-2-yl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile. (Isomer 1)

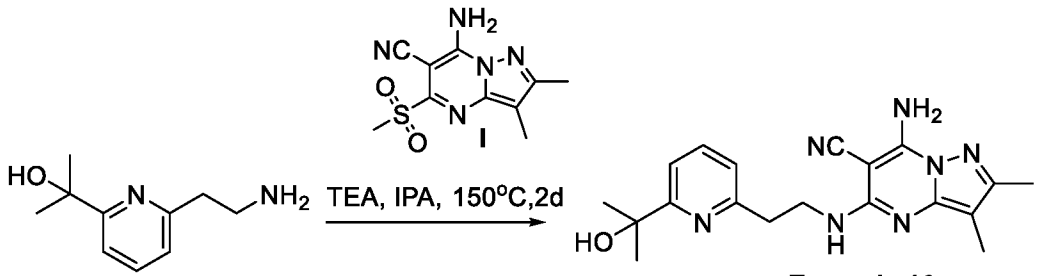
[000392] Yield: 64.1 gm: **LC-MS** Calculated **for** $C_{18}H_{21}N_7$: 335.19; Observe: 336.20 $[M+1]^+$. **^{1}HNMR (400 MHz, DMSO-d_6,):** δ 8.10 (bs, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 6.8 Hz, 1H), 4.51-4.48 (m, 1H), 3.00-2.96 (m, 2H), 2.50 (s, 3H), 2.22 (s, 3H), 1.96 (s, 3H), 1.14 (d, *J* = 5.6 Hz, 3H); **HPLC**: 10.31 min, 99.38 %, 10.307 min; X Bridge C18 (4.6x150) mm,5µ, Mobile Phase A:

10mM Ammonium bicarbonate in water, Mobile Phase B: Acetonitrile. **Chiral HPLC:** Purity = 98.91%, Rt = 17.205 min, Chiral Pak IC (250*4.6) mm,5µ, Mobile Phase A: 0.1% diethyl amine in n-hexane, Mobile Phase B: Isopropanol: dichloromethane (90:5:5); Flow rate: 0.8 mL/min

Example 15: Chiral 7-amino-2,3-dimethyl-5-{[1-(6-methylpyridin-2-yl)propan-2-yl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile. (Isomer 2)

[000393] Yield: 55.6 gm; **LC-MS** Calculated for $C_{18}H_{21}N_7$: 335.19; Observe: 336.20 $[M+1]^+$. **^{1}HNMR (400 MHz, DMSO-d_6,):** δ 8.10 (bs, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 6.8 Hz, 1H), 4.51-4.48 (m, 1H), 3.00-2.96 (m, 2H), 2.50 (s, 3H), 2.22 (s, 3H), 1.96 (s, 3H), 1.14 (d, *J* = 5.6 Hz, 3H); **HPLC** Purity = 99.52 %, Rt = 10.312 min; X Bridge C18 (4.6x150) mm,5µ, Mobile Phase A: 10mM Ammonium bicarbonate in water, Mobile Phase B: Acetonitrile. **Chiral HPLC:** Purity = 100%, Rt = 20.769 min, Chiral Pak IC (250*4.6) mm,5µ, Mobile Phase A: 0.1% diethyl amine in n-hexane, Mobile Phase B: Isopropanol: dichloromethane (90:5:5); Flow rate: 0.8 mL/min

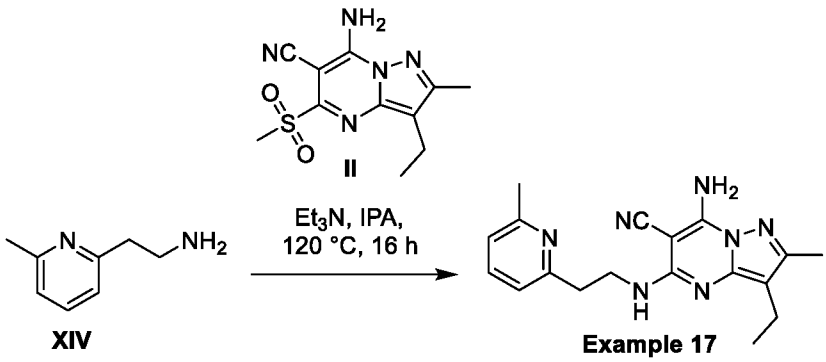
Example 16: 7-amino-5-({2-[6-(2-hydroxypropan-2-yl) pyridin-2-yl]ethyl}amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.



[000394] To a stirred solution of 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (0.15 g, 0.00056 mol) and 2-(6-(2-aminoethyl) pyridin-2-yl) propan-2-ol **XV** (0.153 g, 0.00084 mol) in IPA (10 ml), was added TEA (0.343 g, 0.00339 mol) and the reaction mixture was heated at 150 °C for 2 days. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with DCM (20 ml x 3).

The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by Prep HPLC to get off white title compound **(Example 16)**. Yield: (0.025 g, 12%). **LC_MS** Calculated for $C_{19}H_{23}N_7O$: 365.20; Observe: 388.1 [M+Na$^+$]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.086 (bs, 2H), 7.677 (t, 1H), 7.477-7.458 (d, J = 7.6 Hz, 1H), 7.124-7.105 (d, J = 7.6 Hz, 1H), 6.609 (t, 1H), 5.163 (s, 1H), 3.726-3.711 (t, J = 6 Hz, 2H), 3.046-3.012 (t, J = 6.8 Hz, 2H), 2.227 (s, 3H), 1.964 (s, 3H), 1.435 (s, 6H). **HPLC**: 9.69 min, 98.95 %, X -Bridge C18 (50X4.6) mm, mm,5µm, Mobile Phase A: 10mM Ammonium bicarbonate in water, B: Acetonitrile.

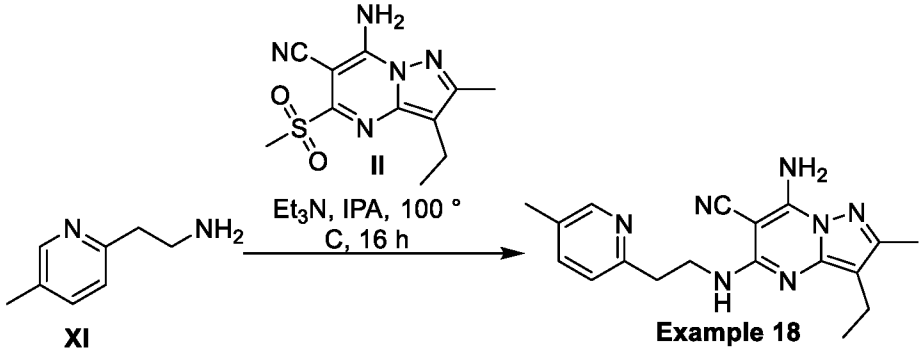
[000395] Example 17: 7-Amino-3-ethyl-2-methyl-5-((2-(6-methylpyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000396] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methylation) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.15 g, 0.0005376 mol) and 2-(6-methylpyridin-2-yl) ethan-1-amine **XIV** (0.292 g, 0.00215 mol) in IPA (5 ml) in a sealed tube, was added TEA (0.23 ml, 0.0016 mol) and the reaction mixture was stirred at 120 °C for 16 h. The progress of the reaction was monitored by TLC (non-polar spot). After completion, the reaction mixture was evaporated under reduced pressure and the crude material was purified by column chromatography by eluting with 40% ethyl acetate in hexane to yield the title compound **(Example 17)** as off-white solid; Yield: (0.056 g, 31%). **LC_MS** Calculated for $C_{18}H_{21}N_7$: 335.17; Obs.336.15 [M$^+$+H]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.10 (bs, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.08 (dd, J = 8.0, 3.6 Hz, 2H), 6.92 (t, J = 4.8 Hz, 1H), 3.66 (q, J = 6.0, Hz, 2H), 2.99 (t, J = 6.8, Hz, 2H), 2.50-2.43 (m, 5H), 2.24 (s, 3H), 1.24 (t, J = 7.6 Hz,

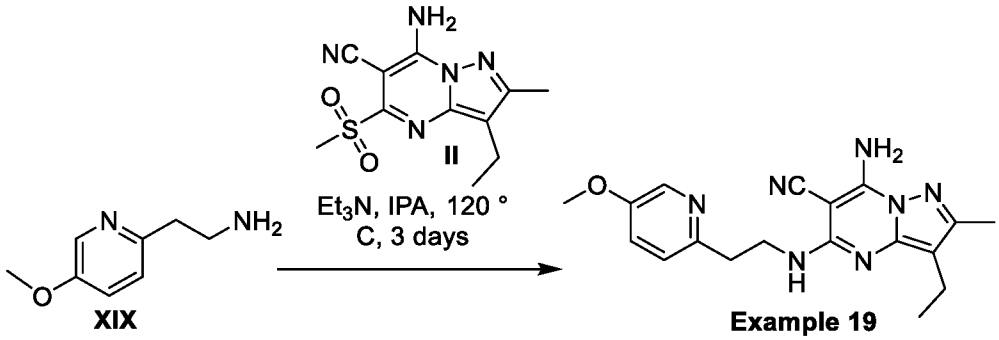
3H). **_HPLC**: 99.57 %, X -Bridge C18 (50X4.6) mm, mm,5µm, Mobile Phase A: 10mM ammonium bicarbonate in water, B: Acetonitrile.

Example 18: 7-Amino-3-ethyl-2-methyl-5-((2-(5-methylpyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



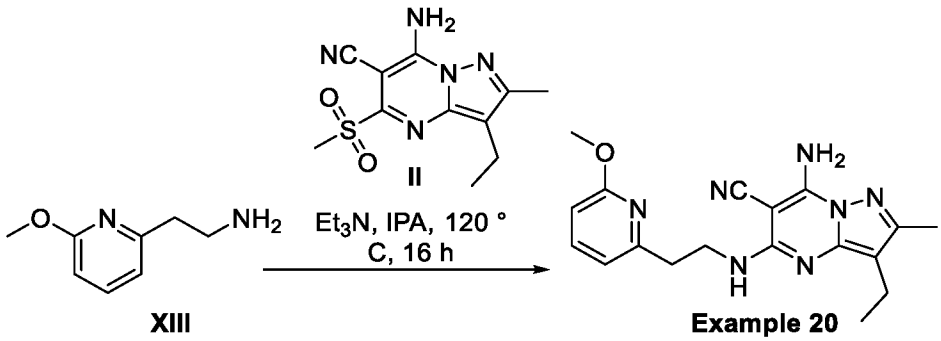
[000397] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.15 g, 0.00049 mol) and 2-(5-methylpyridin-2-yl) ethan-1-amine **XI** (0.166 g, 0.00122 mol) in IPA (10 ml), was added TEA (0.342 ml, 0.000725 mol) and the reaction mixture was heated at 100 °C for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 40% ethyl acetate in hexane to yield the title compound **(Example 18)** as off-white solid; Yield: (0.050 g, 31%). **LC_MS** Calculated. for $C_{18}H_{21}N_7$: 335.17; Obs.336.15 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.32 (s, 1H), 8.09 (bs, 2H), 7.52 (d, J = 6.4 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.80 (t, J = 5.2 Hz, 1H), 3.67-3.62 (m, 2H), 2.99 (t, J = 7.2, Hz, 2H), 2.43 (d, J = 7.6, Hz, 2H), 2.25 (d, J = 4.0 Hz, 6H), 1.11 (t, J = 7.6 Hz, 3H). **HPLC**: 98.81 %, Zorbax SB-C8 (4.6*75) mm,3.5µ, Mobile Phase A: 10mM ammonium bicarbonate in water, B: Acetonitrile.

Example 19: 7-Amino-3-ethyl-5-((2-(5-methoxypyridin-2-yl) ethyl) amino)-2-methylpyrazolo [1,5-a] pyrimidine-6-carbonitrile.



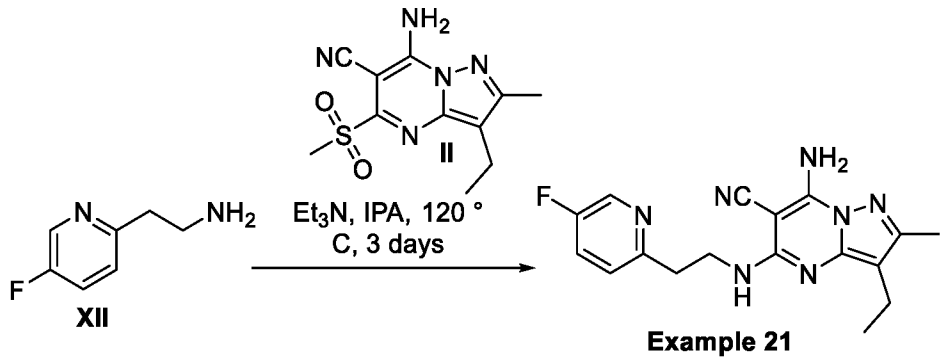
[000398] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.2 g, 0.000716 mol) and 2-(5-methoxypyridin-2-yl) ethan-1-amine **XIX** (0.435 g, 0.00286 mol) in IPA (5 ml), was added TEA (0.6 ml, 0.0043 mol) and the reaction mixture was heated at 120 °C for 3 days. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 50% ethyl acetate in hexane to yield the title compound **(Example 19)** as off-white solid; Yield: (0.080 g, 31.8%). **LC_MS** Calculated for $C_{18}H_{21}N_7O$: 351.18; Observe: 352.20 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.20 (d, J = 2.8 Hz, 1H), 8.08 (bs, 2H), 7.33 (dd, J = 8.4, 2.8 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.75 (t, J = 5.6 Hz, 1H), 3.79 (s, 3H), 3.64 (q, J = 6.8, Hz, 2H), 2.98 (t, J = 7.2, Hz, 2H), 2.5-2.40 (m, 2H), 2.24 (s, 3H), 1.12 (t, J = 7.6 Hz, 3H). **HPLC**: 99.23 %, X -Bridge C18 (50X4.6) mm, mm,5µm, Mobile Phase A: 10mM ammonium bicarbonate in water, B: Acetonitrile

Example 20: 7-Amino-3-ethyl-5-((2-(6-methoxypyridin-2-yl) ethyl) amino)-2-methylpyrazolo [1,5-a] pyrimidine-6-carbonitrile.



[000399] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.2 g, 0.000716 mol) and 2-(6-methoxypyridin-2-yl) ethan-1-amine **XIII** (0.230 g, 0.00151 mol) in IPA (5 ml), was added TEA (0.6 ml, 0.0043 mol) and the reaction mixture was heated at 120 °C for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by flash column chromatography by eluting with 50% ethyl acetate in hexane to yield the title compound **(Example 20)** as off-white solid; Yield: (0.097 g, 38.6%). **LC_MS** Calculated. for $C_{18}H_{21}N_7O$ is 351.18; Observe:352.25 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.09 (bs, 2H), 7.60 (t, J = 8.0 Hz, 1H), 6.84 (d, J = 7.20 Hz, 1H), 6.64-6.61 (m, 2H), 3.86 (s, 3H), 3.69 (q, J = 6.0, Hz, 2H), 2.96 (t, J = 7.2, Hz, 2H), 2.46 (q, J = 7.2 Hz, 2H), 2.24 (s, 3H), 1.12 (t, J = 7.6 Hz, 3H). **HPLC**: 98.52 %, X -Bridge C18 (50X4.6) mm, mm,5µm, Mobile Phase A: 10mM ammonium bicarbonate in water, B: Acetonitrile.

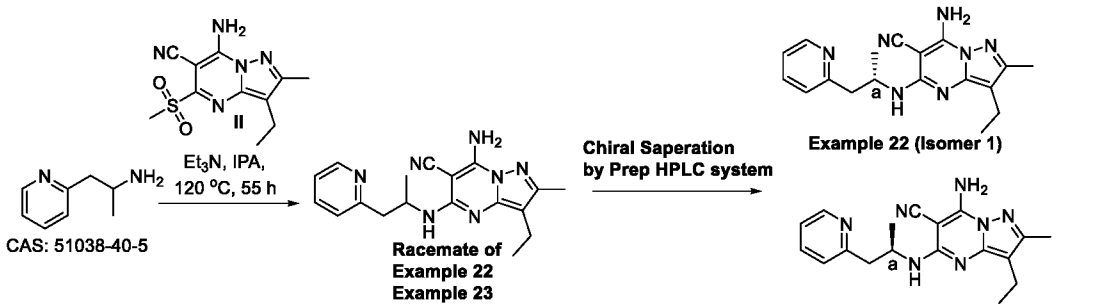
Example 21: 7-Amino-3-ethyl-5-((2-(5-fluoropyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000400] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.2 g, 0.000716 mol) and 2-(5-fluoropyridin-2-yl) ethan-1-amine **XII** (0.4 g, 0.00286 mol) in IPA (5 ml), was added TEA (0.6 ml, 0.0043 mol) and the reaction mixture was heated at 120 °C for 3 days. The progress of the reaction was monitored by TLC (non-polar spot). After completion, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and

evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 50% ethyl acetate in hexane to yield the title compound **(Example 21)** as off-white solid; Yield: (0.050 g, 20.5%). **LC_MS** Calculated for $C_{17}H_{18}FN_7$: 339.16; Observe.340.20 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.45 (d, J = 2.40 Hz, 1H), 8.10 (bs, 2H), 7.64 (dt, J = 8.4, 2.8 Hz, 1H), 7.35-7.31 (m, 1H), 6.75 (d, J = 5.2 Hz, 1H), 3.67 (q, J = 6.8, Hz, 2H), 3.05 (t, J = 7.2, Hz, 2H), 2.44 (q, J = 7.2 Hz, 2H), 2.24 (s, 3H), 1.11 (t, J = 7.6 Hz, 3H), **HPLC**: 98.34 %, X -Bridge C18 (50X4.6) mm, mm,5µm, Mobile Phase A: 10mM ammonium bicarbonate in water, B: Acetonitrile.

Example 22 and 23 (Racemate) : 7-Amino-3-ethyl-2-methyl-5-((1-(pyridin-2-yl) propan-2-yl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (Racemic)



[000401] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.150 g, 0.000537 mol) and 1-(pyridin-2-yl) propan-2-amine (CAS: 51038-40-5, 0.220 g, 0.00484 mol) in IPA (3 ml), was added TEA (0.6 ml, 0.0032 mol) and the reaction mixture was heated in a sealed tube at 120 °C for 60 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 50% ethyl acetate in hexane to yield the title compound as off-white solid; Yield: (0.071 g, 39%). Then the racemic compound of (**Example 22 and 23**) (71 mg) was resolved into its two enantiomers by chiral preparative HPLC system

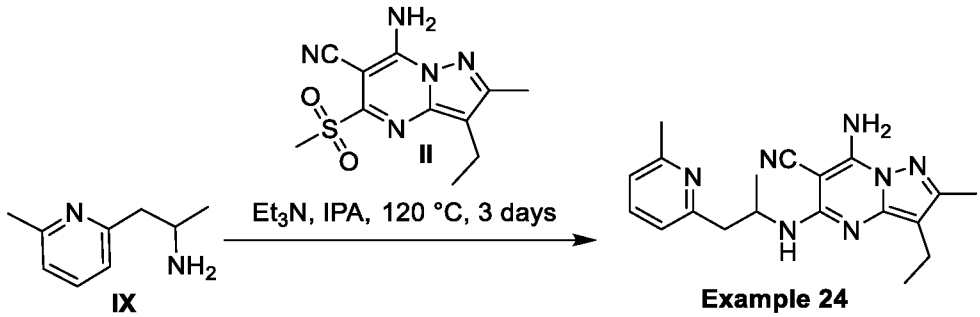
Example 22. Chiral 7-Amino-3-ethyl-2-methyl-5-((1-(pyridin-2-yl) propan-2-yl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile. (Isomer 1)

[000402] Yield: 0.0154 g: **LC_MS** Calculated for $C_{18}H_{21}N_7$: 335.19; Observe:336.20 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.48 (d, J = 4.4 Hz, 1H), 8.07 (bs, 2H), 7.70 (dt, J = 7.6 Hz, 1.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 6.71(d, J = 7.6 Hz, 1H), 4.51-4.48 (m, 1H), 3.11-3.06 (m, 1H), 2.96-2.91 (m, 1H), 2.45 (q, J = 7.6 Hz, 2H), 2.23 (s, 3H) 1.16 (d, J = 6.4, Hz, 3H), 1.10 (t, J = 7.6 Hz, 3H). **HPLC**: 97.85 %, Column: X -Bridge C8 (50X4.6) mm, mm,5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

Example 23. Chiral 7-Amino-3-ethyl-2-methyl-5-((1-(pyridin-2-yl) propan-2-yl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile. (Isomer 2)

[000403] Yield: 0.0164 g: **LC_MS** Calculated for $C_{18}H_{21}N_7$: 335.19; Observe: 336.20 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.48 (d, J = 4.0 Hz, 1H), 8.07 (bs, 2H), 7.69 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.20 (t, J = 6.8 Hz, 1H), 6.71(d, J = 7.6 Hz, 1H), 4.51-4.48 (m, 1H), 3.11-3.06 (m, 1H), 2.96-2.91 (m, 1H), 2.45 (q, J = 7.6 Hz, 2H), 2.23 (s, 3H) 1.16 (d, J = 6.4, Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H). **HPLC**: 98.38 %, X -Bridge C8 (50X4.6) mm, mm,5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

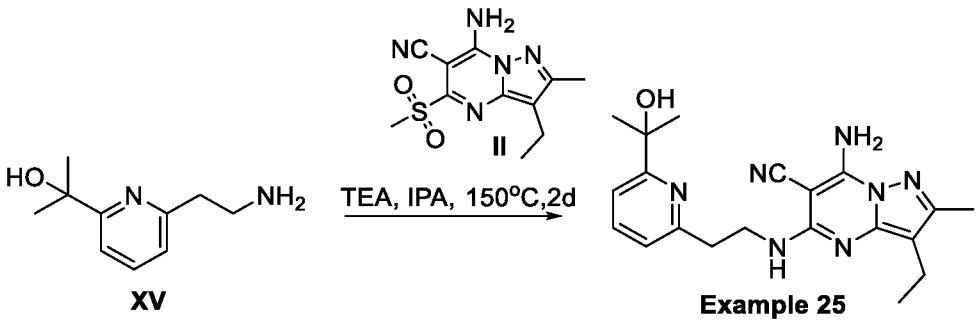
Example 24: 7-Amino-3-ethyl-2-methyl-5-((1-(6-methylpyridin-2-yl) propan-2-yl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000404] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methylthio) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.5 g, 0.00179 mol) and 1-(6-methylpyridin-2-yl) propan-2-amine **IX** (0.430 g, 0.00284 mol) in IPA (10 ml), was

added TEA (1.49 ml, 0.01075 mol) and the reaction mixture was heated at 120 °C for 3 days. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by flash column chromatography by eluting with 10% ethyl acetate in hexane to yield the title compound **(Example 24)** as racemic off-white solid; Yield: (0.350 g, 56%).). **LC_MS** Calculated for $C_{19}H_{23}N_7$ is 349.2; Observe: 350.20 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.11 (brs, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 8.80 Hz, 2H), 6.93 (d, *J* = 7.2, Hz, 1H), 4.5-4.4 (m, 1H), 2.9-2.93 (m, 2H), 2.49 (s, 3H), 2.43 (q, *J* = 7.60 Hz, 2H), 2.23 (s, 3H), 1.15 (d, *J* = 6.8, Hz, 3H), 1.10 (t, *J* = 7.6, Hz, 3H **HPLC**: 95.52 %, X -Bridge C18 (50X4.6) mm, mm,5µm, Mobile Phase A: 10mM ammonium bicarbonate in water B: Acetonitrile.

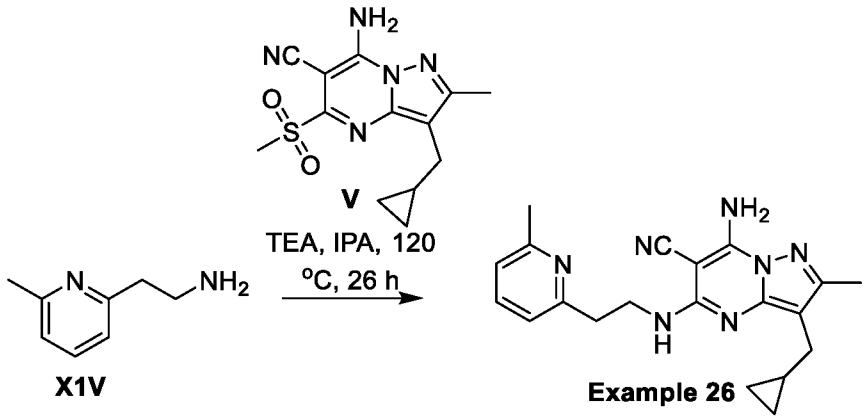
Example 25: 7-amino-3-ethyl-5-({2-[6-(2-hydroxypropan-2-yl) pyridin-2-yl] ethyl} amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.



[000405] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.15 g, 0.000537 mol) and 2-(6-(2-aminoethyl) pyridin-2-yl) propan-2-ol **XV** (0.145 g, 0.000804 mol) in IPA (10 ml), was added TEA (0.326 g, 0.00322 mol) and the reaction mixture was heated at 150 °C for 2days. The progress of the reaction was monitored by TLC. After completion, reaction mixture was concentrated to dryness under reduced pressure. the reaction mixture was diluted with water (20 ml) and extracted with Ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under

reduced pressure to get the desired product **(Example 25).** The crude material was purified by Prep HPLC. Yield: (0.03 g, 14.7 %). **LC_MS** Calculated for $C_{20}H_{25}N_7O$ is 379.21; Observe: 380.25 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.104 (bs, 2H), 7.695-7.657 (t, J = 7.2 Hz, 1H), 7.478-7.459 (d, J = 7.6 Hz, 1H), 7.113-7.094 (d, J = 7.6 Hz, 1H), 6.659 (t, 1H), 5.170 (s, 1H), 3.709-3.694 (t, J = 6 Hz, 2H), 3.044-3.011 (t, J = 6.8 Hz, 2H), 2.455 (t, 2H), 2.247 (s, 3H), 1.434 (s, 6H), 1.145-1.108 (t, J = 7.2 Hz, 3H). **HPLC**: 98.77 %, X -Bridge C18 (50X4.6) mm, mm,5µm, Mobile Phase A: 10mM Ammonium bicarbonate in water, B: Acetonitrile.

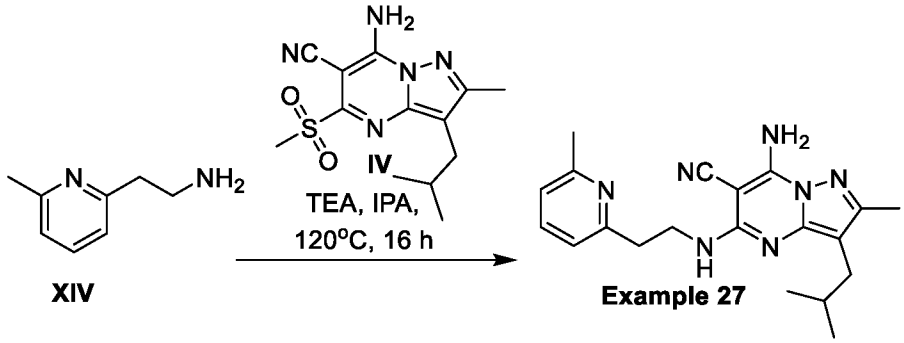
Example 26: 7-amino-3-(cyclopropylmethyl)-2-methyl-5-((2-(6-methylpyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000406] A solution of 7-amino-3-(cyclopropyl methyl)-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **V** (0.212 g, 0.000697 mol) and 2-(6-methylpyridin-2-yl) ethan-1-amine **XIV** (0.190 g, 0.00139 mol) in IPA (5 mL) was purged with N_2 gas for 10 min and TEA (0.58 ml, 0.00418 mol) was added. The reaction mixture was heated at 120 °C for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (50 mL). The resulting was extracted with water (20 mL x 3). The organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude material was purified by silica gel (combi flash) column chromatography by eluting with 40% ethyl acetate in *n*-hexane to yield the title compound **(Example 26)** as an off-white solid; Yield: (0.140 g, 56%). **LC_MS Calculated** for $C_{20}H_{23}N_7$ is 361.20; Observe: 362.20 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.12 (bs, 2H),

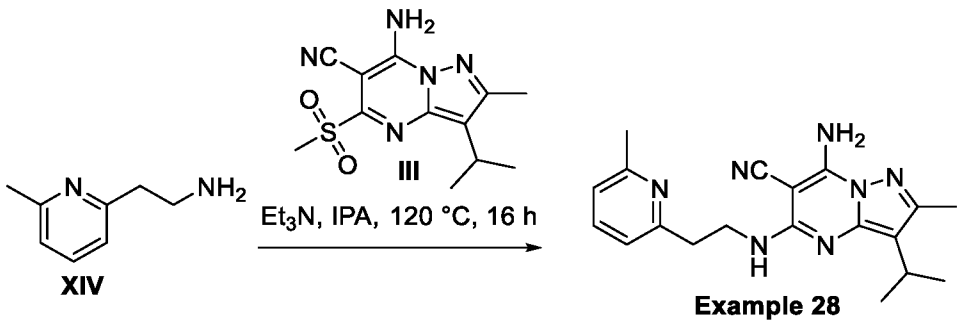
7.6 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 2H), 6.98-6.92 (m, 1H), 3.65 (q, *J* = 6.0, Hz, 2H), 2.98 (t, *J* = 6.8, Hz, 2H), 2.4 (d, *J* = 6.8 Hz, 2H), 2.2 (s, 3H), 1.0-0.95 (m, 1H), 0.35 (d, *J* = 7.6 Hz, 2H), 0.18 (d, *J* = 4.4 Hz, 2H). **HPLC**: 11.10 min, 95.83 %, X -Bridge C18 (50X4.6) mm, mm,5µm, Mobile Phase A: 10mM ammonium bicarbonate in water, B: Acetonitrile.

Example 27: 7-amino-3-(isopropylmethyl)-2-methyl-5-((2-(6-methylpyridin-2-yl)ethyl) amino) pyrazolo[1,5-a]pyrimidine-6-carbonitrile.



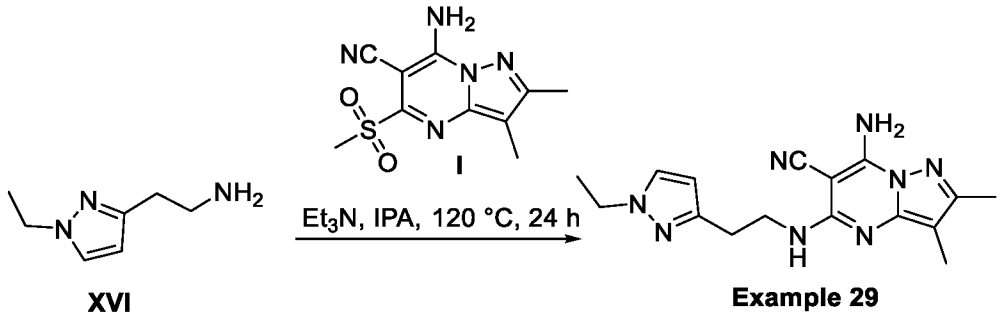
[000407] To a stirred solution of 7-amino-3-isobutyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **IV** (0.150 g, 0.00049 mol) and 2-(6-methylpyridin-2-yl)ethan-1-amine **XIV** (0.2 g, 0.00146 mol) in isopropanol (15 ml) in a sealed tube, was added TEA (0.41 ml, 0.0029 mol) and the reaction mixture was stirred at 120 °C for 16 h. The progress of the reaction was monitored by TLC (less-polar spot). After completion, the reaction mixture was evaporated under reduced pressure and the crude material was purified by column chromatography by eluting with 0-25% ethyl acetate in *n*-hexane to yield the title compound **(Example 27)** as an off-white solid; Yield: (0.125 g, 71 %). **LC_MS** Calculated for $C_{20}H_{25}N_7$ is 363.22; Observe.364.20 [M^++H]. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (bs, 2H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 2H), 6.92 (s, 1H), 3.64-3.61 (m, 2H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 2.32 (d, *J* = 7.2 Hz, 2H), 2.23 (s, 3H), 1.81-1.95 (m, 1H) 0.87 (d, *J* = 6.8 Hz, 6H); **HPLC**: 11.66 min, 97.26 %, X -Bridge C18 (50X4.6) mm, mm,5µm, Mobile Phase A: 10mM Ammonium bicarbonate in water, B: Acetonitrile.

Example 28: 7-amino-3-(isopropyl)-2-methyl-5-((2-(6-methylpyridin-2-yl)ethyl) amino) pyrazolo[1,5-a]pyrimidine-6-carbonitrile.



[000408] To a stirred solution of 7-amino-3-isopropyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **III** (0.2 g, 0.00068 mol) and 2-(6-methylpyridin-2-yl)ethan-1-amine **XIV** (0.278 g, 0.00204 mol) in IPA (2 ml) in a sealed tube, was added TEA (0.278 g, 0.00274 mol) and the reaction mixture was stirred at 120 °C for 16 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure and the crude material was purified by column chromatography by eluting with 20% ethyl acetate in hexane to yield the title compound **(Example 28)** as off-white solid; Yield: (0.068g, 29%). **LC-MS** Calculated for $C_{19}H_{23}N_7$: 349.20; Observe: 350.20 [M^++1]. **^{1}HNMR (400 MHz, DMSO-d$_6$,):** δ 8.063 (bs, 2H), 7.612-7.574 (t, *J* =7.6 Hz, 1H),7.088-7.047 (t, *J* = 8.4Hz, 2H), 6.893 (bs, 1H), 3.657-3.644 (m 2H), 2.995-2.979 (t, *J* =6.4 Hz, 2H), 2.942-2.908 (m, 1H), 2.460 (s, 3H), 2.257 (s, 3H), 1.303-1.286 (d, *J* = 6.8 Hz, 6H). **HPLC**: 11.28 min, 98.85 %, Column: X Bridge C18 (4.6x150) mm,5µ, Mobile Phase A: 10mM Ammonium bicarbonate in water, Mobile Phase B: Acetonitrile.

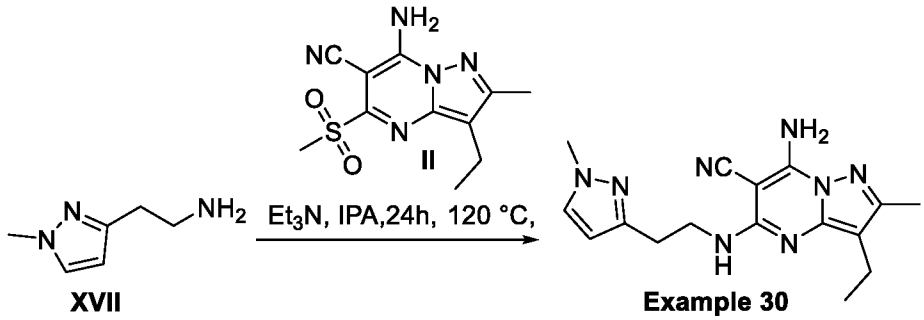
Example 29: 7-amino-5-{[2-(1-ethyl-1H-pyrazol-3-yl) ethyl]amino}-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.



[000409] To a stirred solution of 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (0.2 g, 0.000943 mol) and 2-(1-ethyl-1H-

pyrazol-3-yl) ethan-1-amine **XVI** (0.387 g, 0.00282 mol) in IPA (3 ml), was added TEA (0.381 g, 0.00377 mol) and the reaction mixture was heated at 120 °C for 16h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 20% ethyl acetate in hexane to yield the title compound **(Example 29)** as off-white solid; Yield: (0.057 g, 18 %). **LC-MS** Calculated for $C_{17}H_{19}N_7$: 324.39; Observe: 3325.2 [M^++1]. **^{1}HNMR (400 MHz, DMSO-d_6,):** δ 8.11 (bs, 2H), 7.611-7.608 (d, *J* = 1.2 Hz, 1H), 6.642 (m, 1H), 6.071-6.067 (d, *J* = 1.6 Hz, 1H), 4.092-4.037 (q, *J* = 7.6 Hz, 2H), 3.590-3.575 (t, *J* = 6 Hz, 2H), 2.840-2.804 (t, *J* = 7.2 Hz, 2H), 2.229 (s, 3H), 1.966 (s, 3H), 1.369-1.332 (t, *J* = 7.6 Hz, 3H). **HPLC**: 9.28 min, 99.42 %, X Bridge C18 (4.6x150) mm,5µ, Mobile Phase A: 10mM Ammonium bicarbonate in water, Mobile Phase B: Acetonitrile.

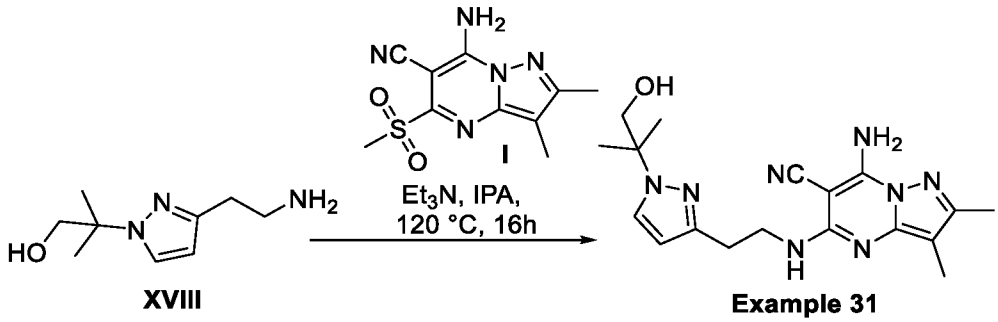
Example 30: 7-amino-3-ethyl-5-{[2-(1-ethyl-1H-pyrazol-3-yl)ethyl]amino}-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.



[000410] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.25 g, 0.000925 mol) and 2-(1-Methyl-1H-pyrazol-3-yl) ethan-1-amine **XVII** (0.343 g, 0.00278 mol) in IPA (5 ml), was added TEA (0.374 g, 0.00370 mol) and the reaction mixture was heated at 120 °C for 24 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by

eluting with 20% ethyl acetate in hexane to yield the title compound **(Example 30)** as off-white solid; Yield: (0.037 g, 12 %). **LC-MS** Calculated for $C_{16}H_{20}N_8$: 324.18; Observe: 325.18 [M^++1]. **^{1}HNMR (400 MHz, DMSO-d$_6$,):** δ 8.094 (bs, 2H), 7.560-7.556 (d, *J* = 1.6 Hz, 1H), 6.685-6.658 (t, *J* = 5.2 Hz, 1H), 6.054-6.049 (d, *J* = 2 Hz, 1H), 3.772 (s, 3H), 3.582-3.533 (t, *J* = 6.8 Hz, 2H), 2.830-2.794 (t, *J* = 7.2 Hz, 2H), 2.446-2.428 (q, 2H), 2.247 (s, 3H), 1.136-1.099 (t, *J* = 7.2 Hz, 3H). **HPLC**: 9.49 min, 97.43 %, X Bridge C18 (4.6x150) mm,5µ, Mobile Phase A: 10mM Ammonium bicarbonate in water, Mobile Phase B: Acetonitrile.

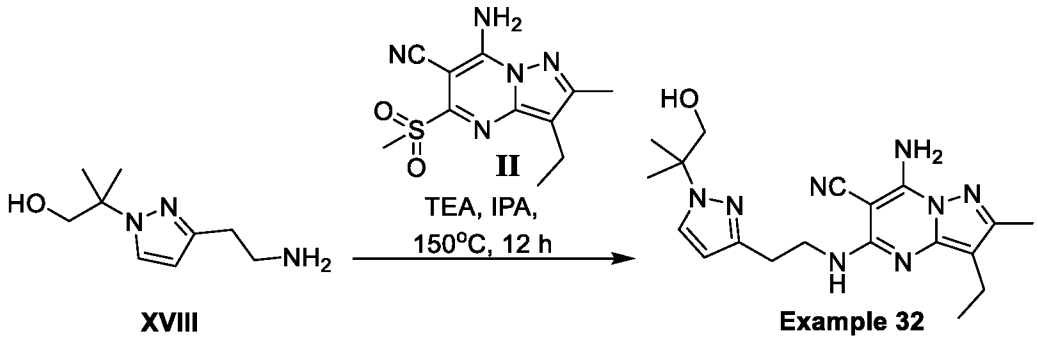
Example 31: 7-amino-5-({2-[1-(1-hydroxy-2-methylpropan-2-yl) -1H-pyrazol-3-yl] ethyl}amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.



[000411] To a stirred solution of 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (0.2 g, 0.00075 mol) and 2-(3-(2-aminoethyl)-1H-pyrazol-1-yl)-2-methylpropan-1-ol **XVIII** (0.345 g, 0.00188 mol) in IPA (5 ml), was added TEA (0.229 g, 0.00226 mol) and the reaction mixture was heated at 120 °C for 16h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (20 ml x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 20-50% ethyl acetate in hexane to yield the title compound **(Example 31)** as off-white solid; Yield: (0.1 g, 36 %). **LC-MS** Calculated for $C_{18}H_{24}N_8O$: 368.21; Observe: 369.21 [M^++1]. **^{1}HNMR (400 MHz, DMSO-d$_6$,):** δ 8.105 (bs, 1H), 7.650 (s, 1H), 6.593-6.581 (t, 1H), 6.062 (s, 1H), 4.901-4.874 (t, *J* = 5.6 Hz, 1H), 3.616-3.548 (m, 4H), 2.840-2.805 (t, *J* = 6.8 Hz, 2H), 2.229 (s, 3H), 1.968 (s, 3H), 1.439 (s, 6H). **HPLC**: 8.93 min, 97.57 %,

Column: X Bridge C18 (4.6x150) mm,5µ, Mobile Phase A: 10mM Ammonium bicarbonate in water, Mobile Phase B: Acetonitrile.

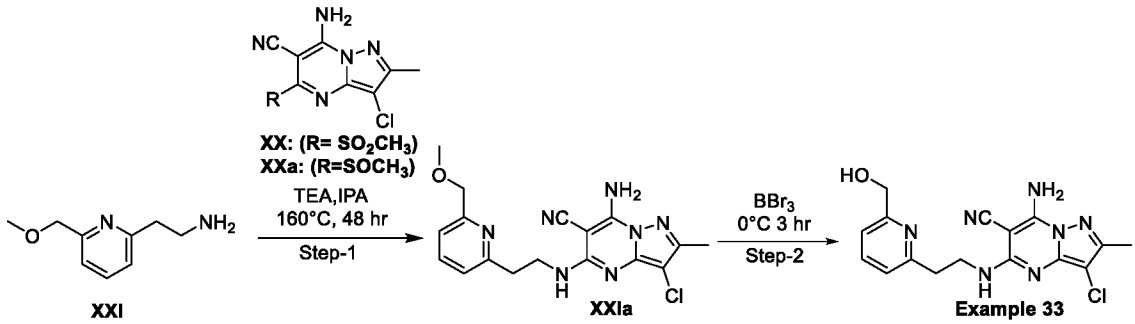
Example 32. 7-amino-3-ethyl-5-((2-(1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



XVIII **Example 32**

[000412] 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (2.0 g, 0.0071 mol), 2-(3-(2-aminoethyl)-1H-pyrazol-1-yl)-2-methylpropan-1-ol **XXIV** (3.2 g, 0.017 mol), IPA (5 mL) and triethylamine (6.0 mL, 0.043 mol) were taken in a seal tube and the reaction mixture was stirred at 150°C for 12h. The reaction was monitored by TLC. The reaction mixture was diluted with water (20 mL) and extract with ethyl acetate (3x 20 mL). The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get crude product. Crude product was purified by biotage column chromatography using silica gel (230-400) and 10-30% ethyl acetate in hexane as eluent to afford the title compound **Example 32** as an off white solid. Yield: 1.048g, 38.8%. **LCMS** Calculated. for $C_{19}H_{26}N_8O$ is 382.47; Observed.383.1 $[M+H]^+$.**^{1}H NMR (400 MHz, DMSO-*d*6):** δ 8.09 (bs, 2H), 7.64 (d, J = 2.0 Hz, 1H), 6.59 (t, J = 5.2 Hz, 1H), 6.05 (d, J = 2.4 Hz, 2H), 4.88 (m, 1H), 3.59-3.54 (m, 4H),2.82 (t, J = 6.8 Hz, 2H), 2.5-2.4 (m, 2H), 2.47 (s, 3H), 1.437 (s, 6H), 1.12 (t, J = 7.2 Hz, 3H). **HPLC**: 99.11 %, X-Bridge C18 (50X4.6) mm, 5µm, Mobile Phase A: 10mM ammonium bicarbonate in water, B: Acetonitrile

Example 33. 7-amino-3-chloro-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



Synthesis of 7-amino-3-ethyl-5-((2-(6-(methoxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo [1,5-a] pyrimidine-6-carbonitrile. XXIa

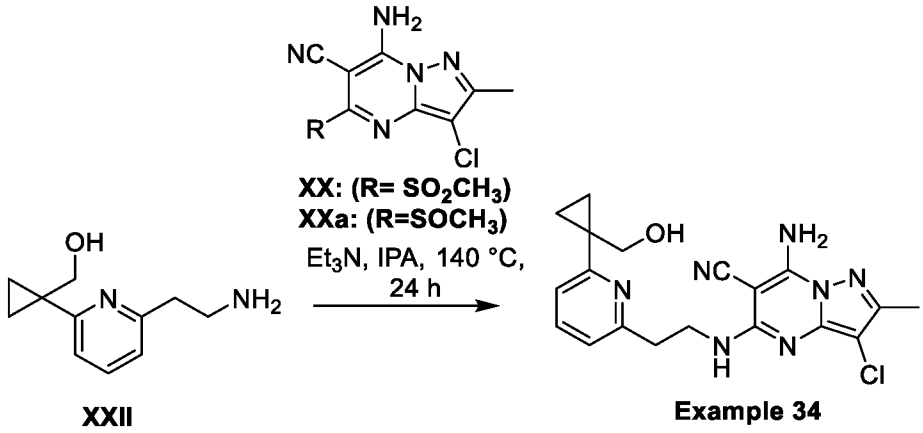
[000413] A stirred solution of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl)pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX** and 7-amino-3-chloro-2-methyl-5- (methyl sulfinyl) pyrazolo [1,5-a] pyrimidine-6-carbonitrile **XXa** (1.6g, 0.056 mol) in IPA (60 mL) was added 2-(6-(methoxy methyl) pyridin-2-yl) ethan-1-amine **XXI** (3.7 g, 0.022 mol) and TEA (4.7 mL, 0.034 mol) in a sealed tube under argon atmosphere and the reaction mixture was stirred at 160°C for 48 hours. The progress of the reaction was monitored by TLC. After completion of the reaction mixture was evaporated under reduced pressure and the crude material was purified by gravity column and compound eluted in 25-30 % Ethyl acetate in DCM. To yield the desired compound **XXIa** as off-white solid; Yield: 1.2 g, 57%. **LCMS** Calculated for $C_{17}H_{18}ClN_7O$ is 371.13; Observed.372.15 $[M+H]^+$.**^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.42 (bs, 2H), 7.74 (t, *J*=8.0 Hz,1H), 7.26-7.19 (m, 3H), 4.51 (s, 2H), 3.69 (t, *J*=5.6 Hz,2H), 3.36 (s, 3H), 3.03 (t, *J* = 5.6 Hz, 2H), 2.27 (s, 3H).

Synthesis of 7-amino-3-ethyl-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000414] A stirred solution of 7-amino-3-ethyl-5-((2-(6-(methoxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXIa** (1.2 g, 0.0032 mol) in DCM (3ml) was cool to 0 °C added BBr_3 (0.46 mL, 0.0048 mol) dropwise and the reaction mixture was stirred at 0 °C for 3 hours. The progress of the reaction was monitored by TLC. The reaction mixture quenched with $NaHCO_3$ solution (100 mL) and extracted with DCM (3x 200 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered, and

concentrated to afford crude product. Crude compound obtained was purified by gravity column using 230-400 mesh silica gel. The desired product eluted at 35-40% ethyl acetate in hexane to afford title compound **(Example 33)** as off-white solid. Yield: 0.631g, 53 %. **LCMS** Calculated for $C_{16}H_{16}ClN_7O$ is 357.11; Observed.358.15 $[M+H]^+$.**^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.40 (bs, 2H), 7.72 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.20-7.15(m ,2H), 5.36(t, J = 5.6 Hz, 1H), 4.58 (d, J =5.6Hz, 2H), 3.70-3.68 (m, 2H), 3.02 (t, J = 7.2 Hz, 2H), 2.27 (s, 3H). **HPLC:** 97.91 %, INT ODS 3V- C18 (4.6X250) mm,5µm, Mobile phase A: 0.1% Formic acid in water, B: Acetonitrile

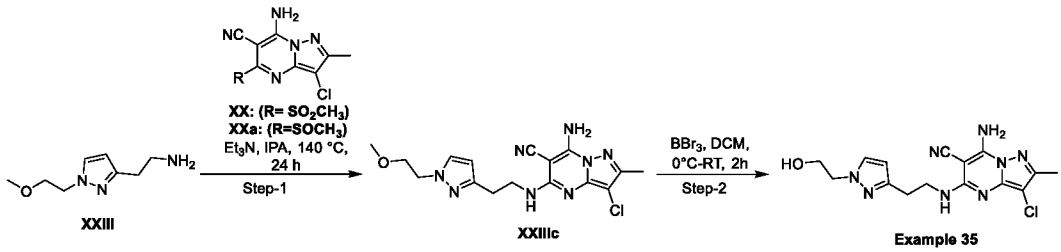
Example 34: 7-amino-3-chloro-5-((2-(6-(1-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000415] To a mixture of 7-amino-3-chloro-2-methyl-5-(methylsulfonyl)pyrazolo[1,5-*a*]pyrimidine-6-carbonitrile **XX** and 7-amino-3-chloro-2-methyl-5- (methyl sulfinyl) pyrazolo [1,5-a] pyrimidine-6-carbonitrile **XXa** (0.25 g, 1 eq, 0.88 mmol) in isopropanol (10 mL) was added (1-(6-(2-aminoethyl) pyridin-2-yl)cyclopropyl)methanol **XXII** (0.34 g, 2 eq, 1.8 mmol) followed by triethylamine (0.27 g, 0.37 mL, 3 eq, 2.6 mmol) in a sealed tube and the resulting mixture was purged with N_2 for 10 min and caped. Then the reaction mixture was heated at 140 °C for 24 hours. Then the progress of the reaction was monitored by TLC for the absence of starting material. The reaction was cooled to RT and concentrated under vacuo. The residue obtained was added

ethyl acetate (20mL) and water (20 mL). The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, concentrated under vacuo to afford light brown viscous liquid. The crude compound was subjected to silica gel (230-400) column chromatography using ethyl acetate (0-80%) in n- hexane. The peak eluted with 45% Ethyl acetate in hexane was concentrated to afford the title compound **(Example 34)** as an off white solid. Yield: 0.04 g, 11 %. **LCMS** Calculated. for $C_{19}H_{20}ClN_7O$ is 397.14; Observed.398.20 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.38 (bs, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.94 (t, J = 6.0 Hz, 1H), 4.71 (t, J = 6.0 Hz, 1H), 3.75-3.67 (m, 4H), 2.97 (t, J = 7.2 Hz, 2H), 2.28 (s, 3H), 1.13-1.10 (m, 2H), 0.87-0.85 (m, 2H), **HPLC** : 99.63 %, X -Bridge C18 (50X4.6) mm, 5µm, Mobile Phase A: 10mM Ammonium bicarbonate in water, B: Acetonitrile.

Example 35: 7-amino-3-chloro-5-((2-(1-(2-hydroxyethyl)-4,5-dihydro-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



Synthesis of 7-amino-3-chloro-5-((2-(1-(2-methoxyethyl)-4,5-dihydro-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (XXIIIc)

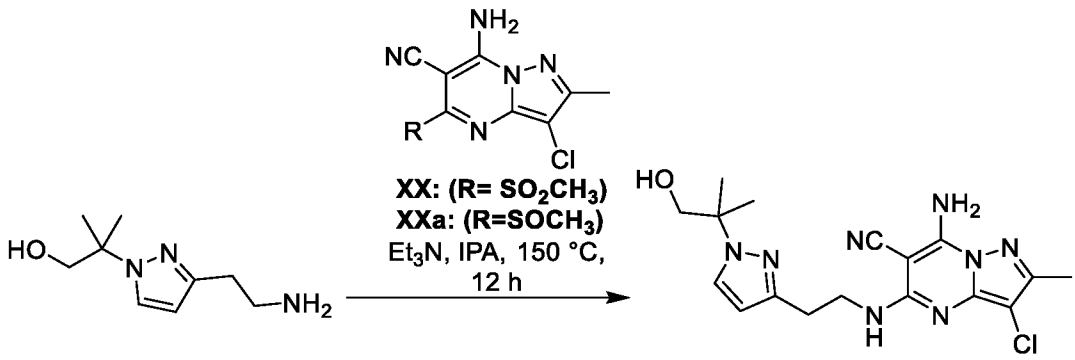
[000416] To a mixture of 7-amino-3-chloro-2-methyl-5-(methylsulfonyl)pyrazolo[1,5-*a*]pyrimidine-6-carbonitrile **XX** and 7-amino-3-chloro-2-methyl-5- (methyl sulfinyl) pyrazolo [1,5-a] pyrimidine-6-carbonitrile **XXa** (0.25 g, 1 eq, 0.88 mmol) in isopropanol (5 mL) was added 2-(1-(2-methoxyethyl)-1H-pyrazol-3-yl) ethan-1-amine **XXIII** (0.296 g, 0.0014 mol) and triethylamine (0.3mL, 0.0021mol) was taken in the seal tube and the resulting reaction mixture was stirred at 150°C for 12 h. The reaction was monitored by TLC. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over anhydrous

Na_2SO_4 and evaporated under reduced pressure to get crude product. Crude product obtained was purified by biotage column chromatography using silica gel (230-400) and 1% methanol in DCM as eluent to afford **XXIIIc** as an off white solid. Yield: 0.160 g, 61%, **LCMS** Calculated. for $C_{16}H_{21}ClN_8O$ is 374.85; Observed.375.25 $[M+H]^+$.

7-amino-3-chloro-5-((2-(1-(2-hydroxyethyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl pyrazolo [1,5-a] pyrimidine-6-carbonitrile

[000417] To a stirred solution of 7-amino-3-chloro-5-((2-(1-(2-methoxyethyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXIIIc** (0.160 g, 4.268 mol) in DCM (15 mL), slowly added BBr_3 (0.06mL, 6.4 mol) at 0°C, and then reaction mixture was stirred at RT for 1h. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). the combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude product. The crude product obtained was purified by biotage column chromatography (12g silica gel column) and by eluting with methanol in DCM (0-2%). to afford title compound **(Example 35)** as an off white solid. Yield: 0.066g, 43%. **LCMS** Calculated. for $C_{15}H_{19}ClN_8O$ is 360.81; Observed. 361.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.39 (bs, 2H), 7.58 (S, 1H), 7.02 (m, 1H), 6.07 (s, 1H), 4.83 (t, J = 10.8 Hz, 1H), 4.07 (t, J = 11.2 Hz, 2H), 3.73-3.70 (m, 2H) 3.62-3.57 (M, 2H), 2.82 (t, J = 7.2 Hz, 2H), 2.27 (s, 3H). **HPLC**: 98.51 %, YMC-Pack ODS-AQ (4.6X250) mm,5µm, Mobile Phase A: 10mM ammonium acetate in water, B: Acetonitrile

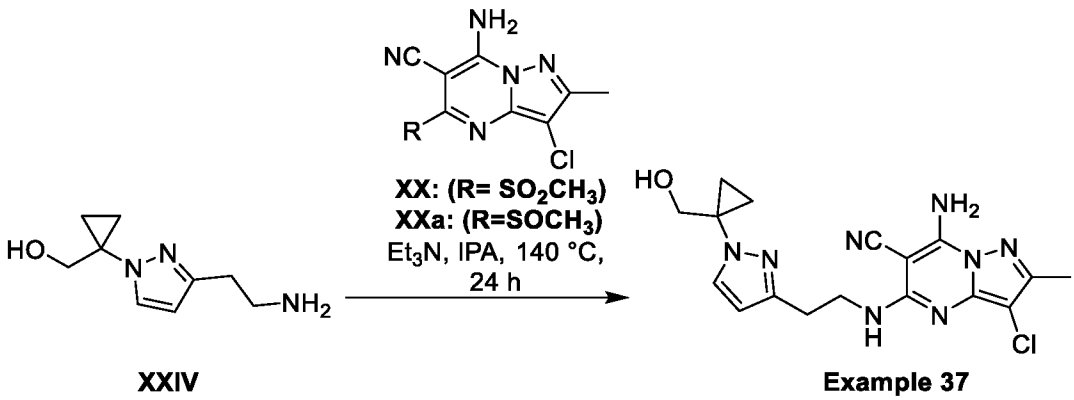
Example 36: 7-amino-3-chloro-5-((2-(1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



XVIII **Example 36**

[000418] To a mixture of 7-amino-3-chloro-2-methyl-5-(methylsulfonyl)pyrazolo[1,5-*a*]pyrimidine-6-carbonitrile **XX** and 7-amino-3-chloro-2-methyl-5- (methyl sulfinyl) pyrazolo [1,5-a] pyrimidine-6-carbonitrile **XXa** (0.25 g, 1 eq, 0.88 mmol) in isopropanol (10 mL) was added 2-(3-(2-aminoethyl)-1H-pyrazol-1-yl)-2-methylpropan-1-ol **XVIII** (0.096g, 5.25 mol), triethylamine (0.1mL, 0.0011mol) were taken in a seal tube and the resulting reaction mixture was stirred at 150°C for 12 h. Then the progress of the reaction was monitored by TLC. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude product. Then the obtained crude product was purified by biotage column chromatography using silica gel (230-400) and 1% methanol in DCM as eluent to afford title compound **(Example 36)** as an off white solid. Yield: 0.055 g, 40%. **LCMS** Calculated. for $C_{16}H_{21}ClN_8O$ is 388.86; Observed.389.2 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.46 (d, J = 2.4 Hz,1H), 6.11 (d, J = 2.0 Hz,1H), 6.04 (bs, 2H), 5.78 (bs, 1H), 3.88 – 3.83 (m, 4H), 3.49 - 3.47 (m, 1H), 2.95 (d, J = 6.4 Hz, 2H) 2.3(s, 3H), 1.55 (s, 6H). **HPLC**: 97.5 %, INT ODS 3V- C18 (4.6X250) mm,5µm, Mobile Phase A: 0.1% Formic acid in water B: Acetonitrile

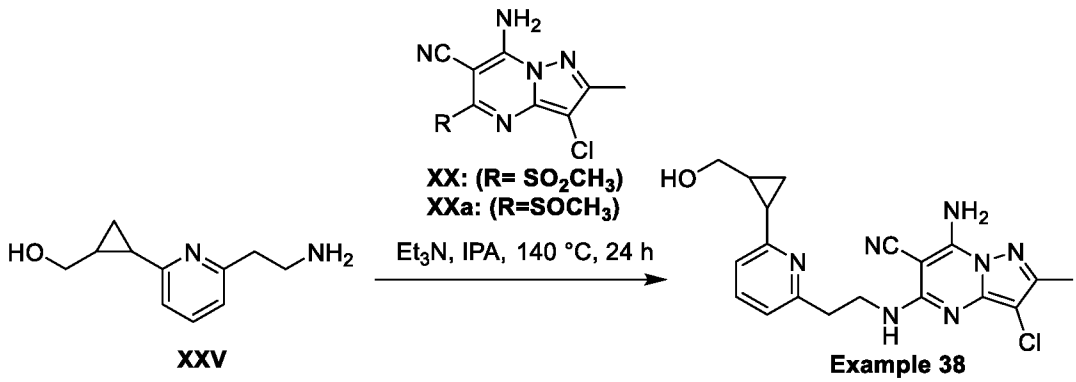
Example 37: 7-amino-3-chloro-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



XXIV **Example 37**

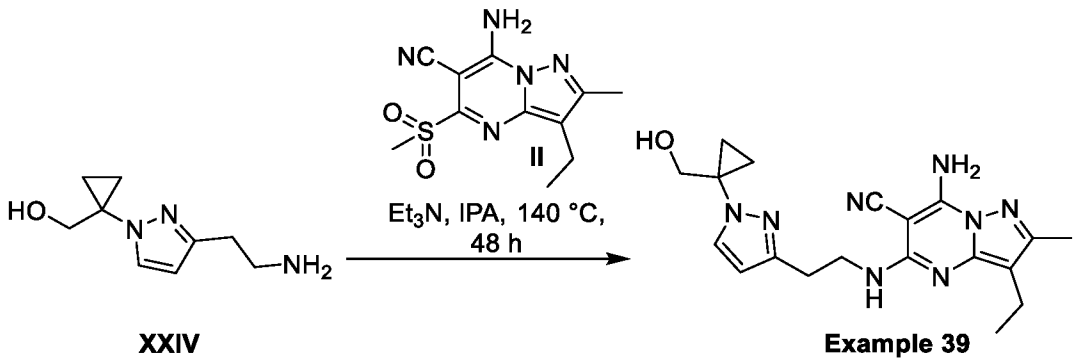
[000419] To a mixture of 7-amino-3-chloro-2-methyl-5-(methylsulfonyl)pyrazolo[1,5-*a*]pyrimidine-6-carbonitrile **XX** and 7-amino-3-chloro-2-methyl-5- (methyl sulfinyl) pyrazolo [1,5-a] pyrimidine-6-carbonitrile **XXa** (0.25 g, 1 eq, 0.88 mmol) in isopropanol (10 mL) was added a mixture of (1-(3-(2-aminoethyl)-1*H*-pyrazol-1-yl) cyclopropyl)methanol (0.30 g, 0.0017 mol), **XXIV** (0.3 g, 0.0007 mol), triethylamine (0.425 g, 0.0042 mol) were taken in a seal tube and purged with N_2 for 10 min. Then the resulting reaction mixture was heated at 140 °C for 24 hours. The progress of the reaction was monitored by TLC. The reaction was cooled to rt and concentrated under *vacuo*. To the residue add ethyl acetate (20 mL) and water (20 mL). The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate. The organic layer was concentrated under vacuo and the crude compound was purified by combi-flash (230-400; 40 g column) using 80% ethyl acetate and hexane to afford the title compound (**Example 37**) as an off white solid. Yield: 0.1 g, 36.9 %. **LCMS** Calculated. for $C_{17}H_{19}ClN_8O$ is 386.14; Observed. 387.15 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.40 (bs, 2H), 7.62 (d, J = 2.0 Hz, 1H), 6.94 (t, J = 5.6 Hz, 1H), 6.06 (d, J = 2.0 Hz, 1H), 4.88 (t, J = 5.6 Hz, 1H), 3.63-3.58 (m, 4H), 2.82 (t, J = 7.6 Hz, 2H), 2.28 (s, 3H), 1.09-1.07 (m, 2H), 0.97-0.95 (m, 2H). **HPLC**: 99.14 %, X -Bridge C18 (50X4.6) mm, 5µm, Mobile Phase A: 10mM Ammonium bicarbonate in water, B: Acetonitrile.

Example 38: 7-amino-3-chloro-5-((2-(6-(2-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000420] To a mixture of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*]pyrimidine-6-carbonitrile **XX** and 7-amino-3-chloro-2-methyl-5-(methyl sulfinyl) pyrazolo [1,5-a] pyrimidine-6-carbonitrile **XXa** (0.25g, 0.88 mmol) in isopropanol (10 mL) was added triethylamine (0.27 g, 2.6 mmol) and (2-(6-(2-aminoethyl) pyridin-2-yl)cyclopropyl)methanol **XXV** (0.3 g, 2 mmol) in a seal tube. The resulting reaction mixture was purged with N_2 for 10 min and heated at 140 °C for 24 hours. Then the progress of the reaction was monitored by TLC analysis. The reaction was cooled to room temperature and concentrated under vacuo. To the residue was added ethyl acetate (20 mL) and water (20 mL). The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under vacuo to afford light brown viscous liquid. The crude compound was purified by prep-HPLC to get the title compound **(Example 38)** as white solid using X-bridge Prep C18 (250X19) mm, 5.0µm, mobile phase A:10mm ammonium bi-carbonate in water; B: acetonitrile. Yield: 0.04 g, 11 %. **LCMS** Calculated. for $C_{19}H_{20}ClN_7O$ is 397.14; Observed.398.15 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.39 (bs, 2H), 7.54 (t, J = 7.2 Hz, 1H), 7.06-7.00 (m, 3H), 4.56 (t, J = 5.2 Hz, 1H), 3.70-3.65 (m, 2H), 3.50-3.44 (m, 1H), 3.40-3.33 (m, 1H), 2.96 (t, J = 6.8 Hz, 2H), 2.28 (s, 3H), 1.99-1.95 (m, 1H), 1.58-1.55 (m, 1H), 1.10-1.06 (m, 1H), 0.89-0.84 (m, 1H). **HPLC**: 97.87 %, INT ODS 3V-C18 (4.6X250) mm,5µm. Mobile Phase A: 0.1% formic acid in water, B: Acetonitrile.

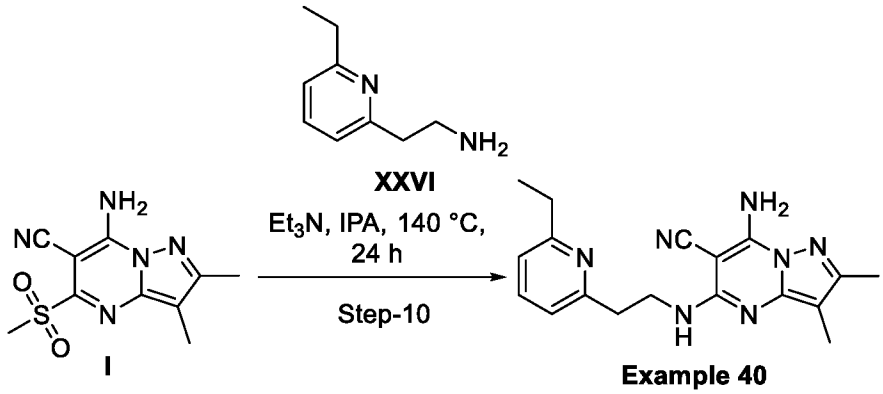
Example 39 :7-amino-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



XXIV **Example 39**

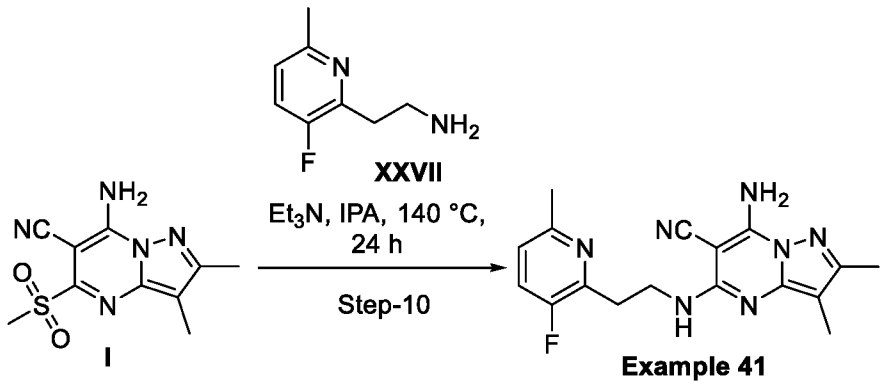
[000421] In a seal tube, a solution of (1-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclopropyl) methanol **XXIV** (260 mg, 0.0009 mol) and 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (420 mg, 0.0023 mol) in isopropanol (15 mL) was taken and added triethylamine (0.7mL, 0.0055 mol). The resulting reaction mixture was purged with N2 for 10 min. The seal tube was heated at 140°C for 48 hours. The progress of the reaction was monitored by TLC. The reaction was cooled to room temperature and concentrated under vacuo. To the residue was added ethyl acetate and water. The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under vacuum. The crude compound was purified by preparative HPLC to obtain the title compound **(Example 39)** as yellow solid. Yield: (0.025 g, 7.1 %). **LCMS** Calculated. for $C_{19}H_{24}N_8O$ is 380.21; Observed. 381.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D6):** δ 8.10 (bs, 1H), 7.61 (d, *J* = 1.6 Hz, 1H), 6.59 (s, 1H), 6.04 (d, *J* = 1.6 Hz, 1H), 4.87 (t, *J* = 5.6 Hz, 1H), 3.59 -3.54 (m, 3H), 2.80 (t, *J* = 6.8 Hz, 2H), 2.5 (m, 2H), 2.47 (s, 3H), 1.13-1.07 (m, 5H), 0.97 -0.94 (m, 2H). **HPLC**: 97.16 %, X -Bridge C18 (50X4.6) mm, 5µm, Mobile Phase A: 10mM Ammonium bicarbonate in water, B: Acetonitrile.

Example 40: 7-amino-5-((2-(6-ethylpyridin-2-yl) ethyl) amino)-2,3-dimethyl pyrazolo [1,5-*a*] pyrimidine-6-carbonitrile



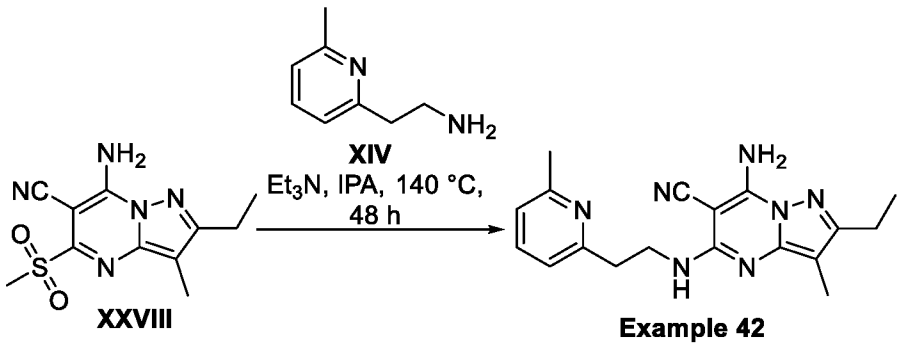
[000422] To a solution of 2-(6-ethylpyridin-2-yl) ethan-1-amine **XXVI** (0.74 g, 4.9 mmol) and 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile I (0.65 g, 2.5 mmol) in isopropanol (10 mL) was added triethylamine (2.0 mL, 15 mmol). The resulting mixture was purged with N_2 for 10 min. The seal tube was closed tightly and heated at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. The reaction was cooled to room temperature and the reaction mixture was concentrated under *vacuo*. To the residue were added ethyl acetate (50 mL) and water (50 mL) and mixed well. The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under vacuo to afford light brown viscous liquid. The crude compound was purified by combi-flash (230-400) silica gel column chromatography using ethyl acetate in *n*-hexane and peak eluted with 15% ethyl acetate in *n*-hexane was concentrated to afford the desired title compound (**Example 40**) as an off-white solid. Yield: 0.3 g (34%); **LC_MS** Calculated. for $C_{18}H_{22}N_7$ is 336.20, Observed, 336.30; $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (s, 2H), 7.63 (t, *J*= 7.6 Hz, 1H), 7.11 (d, *J*= 7.6 Hz, 2H), 6.86 (t, *J*= 5.2 Hz, 1H), 3.71-3.67 (m, 2H), 3.01 (t, *J*= 6.8 Hz, 2H), 5.47 (d, *J*= 10.8 Hz, 1H), 3.74 (t, *J*= 6.8 Hz, 2H), 2.75 (q, *J*= 7.6 Hz, 2H), 2.23 (s, 1H), 1.97 (s, 3H), 1.23 (t, *J*=7.6 Hz, 2H); **HPLC** Purity = 98.00 %, INT ODS 3V-C18 (4.6x250)mm, 5µ; Mobile Phase A: 0.1% Formic acid in water: Mobile Phase B: Acetonitrile; Retention time = 7.721 min.

Example 41: 7-amino-5-((2-(3-fluoro-6-methylpyridin-2-yl) ethyl)amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.



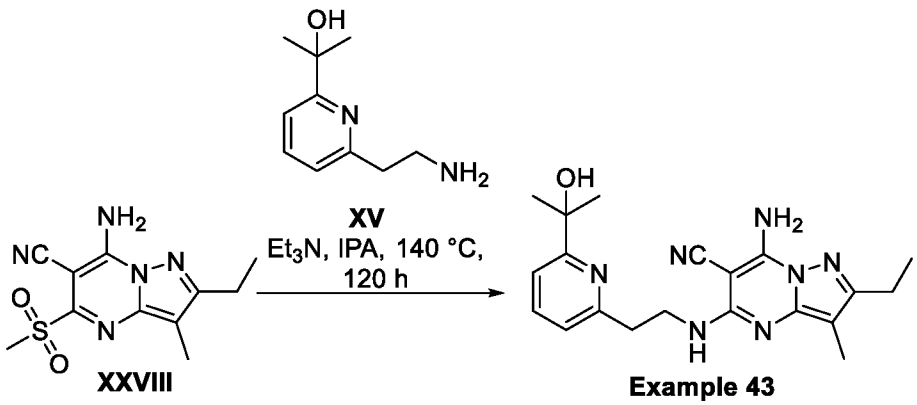
[000423] To a solution of 2-(3-fluoro-6-methylpyridin-2-yl) ethan-1-amine **XXVII** (203 mg, 1.32 mmol) and 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile I (175 mg, 0.66 mmol) in isopropanol (10 mL) was added TEA (0.55 mL, 3.96 mmol). The resulting mixture was purged with N_2, sealed the tube, and heated at 150 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated under reduced pressure. To the residue water (15 mL) was added and the resulting mixture was extracted with ethyl acetate (15 mL X 2). The combined organic layer was given brine wash, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crude obtained subjected to silica gel (230-400) column chromatography using 5-35% ethyl acetate in *n*-hexane to afford the desired compound as an off-white solid. Yield: 10.2 g (5%); **LC_MS** Calculated. for $C_{17}H_{19}FN_7$ is 340.17, Observed: 340.25; $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.10 (s, 2H), 7.51 (t, *J*= 84 Hz, 1H), 7.15 (q, *J*= 4.4 Hz, 1H), 6.85 (t, *J*= 5.2 Hz, 1H), 3.70 (q, *J*= 6.0 Hz, 1H), 3.05 (t, *J*= 4.8 Hz, 2H), 2.45 (s, 3H), 2.22 (s, 3H), 1.95 (s, 3H); **HPLC** Purity = 95.27 %, XBridge C18 (4.6 x 150)mm, 5µ; Mobile Phase A: 10mM ammonium bicarbonate in H_2O: Mobile Phase B: Acetonitrile; Retention time = 10.10 min.

Example 42: 7-amino-2-ethyl-3-methyl-5-((2-(6-methylpyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile .



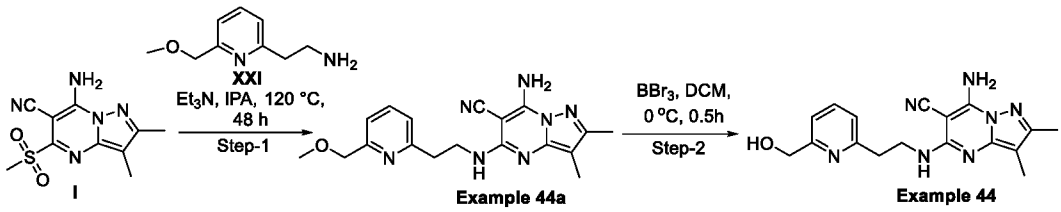
[000424] To a mixture of 7-amino-2-ethyl-3-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (0.200 g, 0.716 mmol) **XXVIII** and 2-(6-methylpyridin-2-yl) ethan-1-amine **XIV** (0.300 g, 2.20 mmol) in isopropanol (5 mL) was added triethylamine (0.6mL, 4.0 mmol). The resulting mixture was purged with N_2 for 10 min. The seal tube was closed tightly and heated at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. The reaction mixture was cooled to room temperature and the reaction mixture was concentrated under *vacuo*. To the residue were added ethyl acetate (50 mL) and water (50 mL) and mixed well. The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under vacuo to afford light brown viscous liquid. The crude compound was purified by combi-flash (230-400) silica gel column chromatography using ethyl acetate in *n*-hexane and peak eluted with 70% ethyl acetate in *n*-hexane fraction solvent was concentrated to afford the desired compound as an off-white solid. Yield: 0.088 g (44%); **LC_MS** Calculated. for $C_{18}H_{22}N_7$ is 336.42, Observed: 336.30; $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.07 (bs, 2H), 7.60 (t, *J*= 8.0 Hz, 1H), 7.08 (d, *J*= 8.0 Hz, 2H), 6.91 (t, *J*= 5.2 Hz, 1H), 3.69-3.64 (m, 2H), 2.99 (t, *J*= 6.8 Hz, 2H), 2.67-2.58 (m, 2H), 2.47 (s, 3H), 1.98 (s, 3H), 1.19 (t, *J*=7.2 Hz, 3H); **HPLC** Purity = 97.67 %, XBridge C18 (4.6 x150)mm, 5µ, Mobile phase A: 10mM ammonium bicarbonate in H_2O: Mobile Phase B: Acetonitrile; Retention time = 10.406 min.

Example 43: 7-amino-2-ethyl-5-((2-(6-(2-hydroxypropan-2-yl) pyridin-2-yl) ethyl) amino)-3-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000425] To a stirred solution of 7-amino-2-ethyl-3-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXVIII** (150 mg, 0.537 mmol) in isopropanol (5 mL) were added triethylamine (0.3 mL, 2.68 mmol) followed by 2-(6-(2-aminoethyl) pyridin-2-yl) propan-2-ol **XV** (0.145 g, 0.80 mmol). The resulting mixture was purged with N_2 for 10 min. The seal tube was closed tightly and heated at 140 °C for 120 h. The progress of the reaction was monitored by TLC analysis. Then reaction was cooled to room temperature and added water (50 mL). The aqueous layer was extracted with ethyl acetate (50 mL). The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under vacuum to afford light brown viscous liquid. The crude material was purified by prep HPLC method using YMC AQUA ODS (250 X 20) mm, 5.0 microns column; Mobile phase A:10mM Ammonium bicarbonate in water. Mobile phase B: ACN: MeOH (1:1) to afford the desired title compound **Example 43** as an off-white solid. Yield: 0.014 g (7%); **LC_MS** Calculated. for $C_{20}H_{25}N_7O$ is 379.21, Observed, 380.30; $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.06 (bs, 2H), 7.67 (t, *J*= 7.6 Hz, 1H), 7.46 (d, *J*= 7.6 Hz, 1H), 7.11 (d, *J*= 7.6 Hz, 1H), 6.61(bs, 1H), 5.16 (s, 1H), 3.72-3.71 (m, 2H), 3.03 (t, *J*= 6.4 Hz, 2H), 2.67-2.59 (m, 2H), 1.98 (s, 3H), 1.43 (s, 6H), 1.19-1.17 (m, 3H); **HPLC Purity** = 97.65 %, XBridge C18 (4.6 X 150) mm, 5µ; Mobile Phase A: 10mM ammonium bicarbonate in H_2O: Mobile Phase B: Acetonitrile; Retention time =10.42 min.

Example 44: 7-amino-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



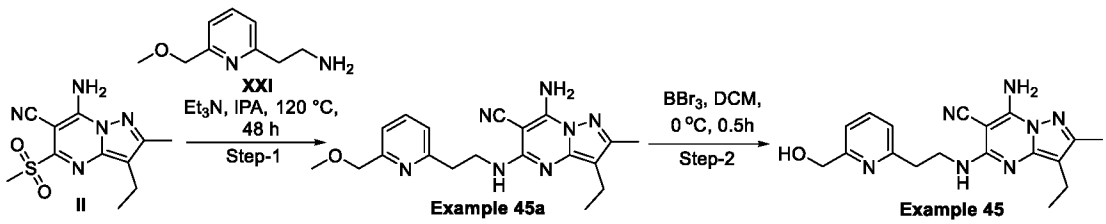
Step-1: 2-amino-5-((2-(6-(methoxymethyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (44a)

[000426] A stirred solution of 2-(6-(methoxymethyl) pyridin-2-yl) ethan-1-amine **XXI** (0.414 g, 2.49 mmol) and 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (0.300 g, 1.13 mmol) in isopropanol (7 mL) was added triethylamine (0.8 mL, 5.65 mmol) and the resulting mixture was purged with N_2 for 10 min. The seal tube was closed tightly and heated at 120 °C for 48 h. The progress of the reaction was monitored by TLC analysis. The reaction was cooled to room temperature and the reaction mixture was concentrated under *vacuo*. To the residue were added ethyl acetate (50 mL) and water (50 mL) and mixed well. The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under vacuo to afford light brown viscous liquid. The crude compound was purified by combi-flash (230-400) silica gel column chromatography using ethyl acetate in *n*-hexane and peak eluted with 20% ethyl acetate in *n*-hexane. Product fractions solvent was concentrated to afford the desired title compound **Example 44a** as off-white solid. Yield: 0.230 g (58%); **LC_MS** Calculated. for $C_{18}H_{21}N_7O$ is 351.18, Observed, 352.25; $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (bs, 2H), 7.73 (d, J = 7.6 Hz, 1H) 7.22 (m, 2H), 6.84 (m, 1H) 4.51 (S, 2H), 3.68- 3.67 (m, 2H), 3.36 (s, 3H), 3.02 (t, J= 6.8 Hz, 2H), 2.27 (s, 3H), 1.96 (s, 3H), **HPLC** Purity = 98.27 %, INT ODS 3V-C18 (4.6x250)mm, 5µ; Mobile Phase A: 0.1% Formic acid in water: Mobile Phase B: Acetonitrile; Retention time =8.70 min.

Step-2: 7-amino-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (44)

[000427] A stirred solution of 7-amino-5-((2-(6-(methoxymethyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 44a** (120 mg, 0.341 mmol) in DCM (5 mL) was cool to 0 °C then added BBr_3 (0.03 mL, 0.341 mmol) and the reaction mixture was stirred at 0°C for 30 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with $NaHCO_3$ solution 2 ml and extracted with DCM (10 ml X 3) and dried over anhydrous sodium sulphate and concentrated at low vacuum. Crude solid was washed with 2 ml acetonitrile to get the pure title compound **Example 44** as off- white solid. Yield: 0.230 g (58%); **LC_MS** Calculated for $C_{17}H_{19}N_7O$ is 338.4, $[M+H]^+$; Observed 337.17; $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.05 (bs, 2H), 7.72 (d, J = 7.6 Hz, 1H) 7.31 (d, J = 7.2 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H) 6.78 (bs, 1H) 5.36 (bs, 1H), 4.58 (S, 2H), 3.68-3.67 (m, 2H), 3.01 (t, J= 6.4 Hz, 2H), 2.22 (s, 3H), 1.96 (s, 3H), **HPLC Purity** = 98.19 %, XBridge C18 (4.6 X150) mm, 5µ, Mobile Phase A: 10mM ammonium bicarbonate in water: Mobile Phase B: Acetonitrile; Retention time = 8.30 min.

Example 45: 7-amino-3-ethyl-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



Step-1: Synthesis of 7-amino-3-ethyl-5-((2-(6-(methoxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrilev (Example 45a)

[000428] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **II** (2.0 g, 7.2 mmol) in isopropanol (40 mL) were added TEA (5.9 mL, 43 mmol) and 2-(6-(methoxymethyl) pyridin-2-yl) ethan-1-amine **XXI** (3.0 g, 18 mmol). The resulting mixture was purged with N_2 for 10 min. The seal tube was closed tightly and heated

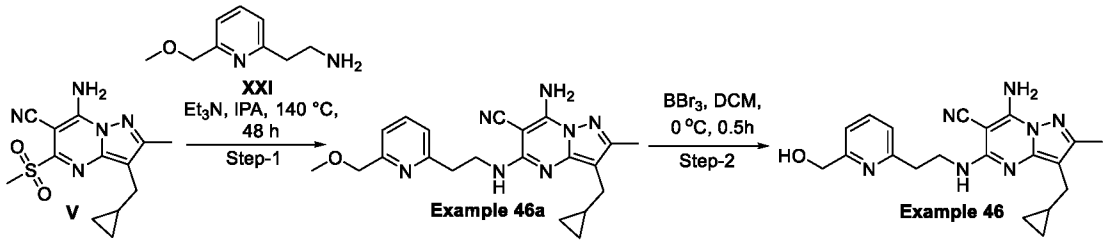
at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. The reaction was cooled to room temperature and the reaction mixture was concentrated under *vacuo*. To the residue were added ethyl acetate (50 mL) and water (50 mL) and mixed well. The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under *vacuo* to afford light brown viscous liquid. The crude compound was purified by combi-flash silica gel (230-400) column chromatography using 10-70% ethyl acetate in *n*-hexane to afford the desired compound **Example 45a** as off-white solid. Yield: 1.3 g (50 %); **LC_MS** Calculated for $C_{19}H_{23}N_7O$ is 365.20; Observed. 366.25 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.112 (bs, 2H), 7.751-7.713 (t, J = 7.2 Hz, 1H), 7.256-7.185 (m, 2H), 6.854 (bs, 1H), 4.507 (s, 2H), 3.693-3.647 (m, 2H), 3.361 (s, 3H), 3.044-3.010 (t, J = 6.8 Hz, 2H), 2.469-2.431 (m, 2H), 2.247 (s, 3H), 1.139-1.101 (t, J =7.6Hz, 3H).

Step-2:7-amino-3-ethyl-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl)amino)-2-methylpyrazolo[1,5-*a*]pyrimidine-6-carbonitrile

[000429] A stirred solution of 7-amino-3-ethyl-5-((2-(6-(methoxymethyl) pyridin-2-yl)ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile (75 mg, 0.205 mmol) in DCM (5 mL) was cooled to 0 °C and added BBr_3 (0.0 19 mL, 0.205 mmol). The resulting mixture was stirred at 0 °C for 1h. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, reaction mixture was quenched with sat. $NaHCO_3$ solution (2 mL) and extracted with DCM (10 mL X 3). Combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under *vacuo*. The crude solid was washed with *n*-pentane (2 mL) to get the pure compound as an off- white solid. Yield: 30 mg (42%); **LCMS** Calculated. for $C_{18}H_{21}N_7O$ is 351.18, $[M+H]^+$; Observed, 352.30; $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.085 (bs, 2H), 7.739-7.700 (t, J= 8.0 Hz, 1H) 7.326-7.306 (d, J= 8.0 Hz, 1H), 7.149-7.130 (d, J= 7.6 Hz, 1H), 6.873-6.846 (t, J= 5.2 Hz, 1H), 5.371-5.342 (d, J= 5.6 Hz, 1H), 4.588-4.574 (d, J= 5.6 Hz, 2H), 3.687-3.639 (m, 2H), 3.030-2.996 (d, J= 6.8 Hz, 2H), 2.449-2.434 (m, 2H), 2.248 (s, 3H), 1.175-1.105 (t, J=7.2 Hz, 3H), HPLC Purity = 99.09 %, Retention time =

8.228 min. INT ODS 3V-C18 (4.6 x 250) mm, 5µ; 0.1% Formic acid in water: Mobile Phase B: Acetonitrile; Flow rate: 1.0 mL/min.

Example 46: 7-amino-3-(cyclopropyl methyl)-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



Step-1: Synthesis of 7-amino-3-(cyclopropyl methyl)-5-((2-(6-(methoxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (46a)

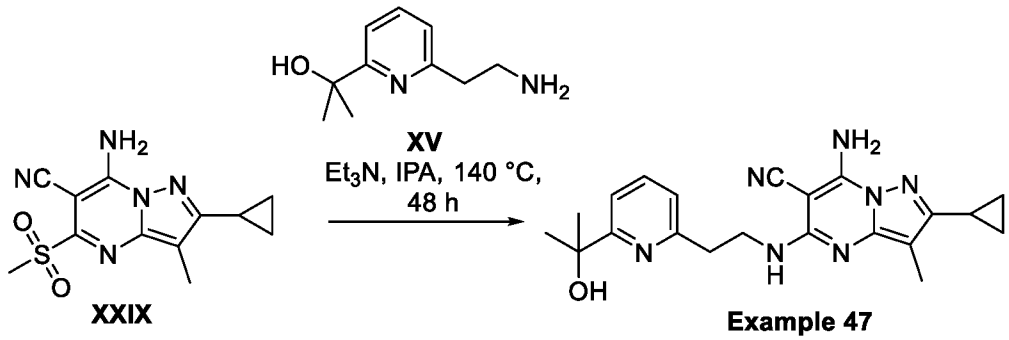
[000430] A stirred solution of 7-amino-3-(cyclopropyl methyl)-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **V** (220 mg, 0.720 mmol) in isopropanol (10 mL) were added 2-(6-(methoxymethyl) pyridin-2-yl) ethan-1-amine **XXI** (299 mg, 1.80 mmol) and TEA (0.703 mL, 5.04 mmol). The resulting mixture was purged with nitrogen for 10 min. The seal tube was closed tightly and heated at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. The reaction was cooled to room temperature and the reaction mixture was concentrated under *vacuo*. To the residue were added ethyl acetate (50 mL) and water (50 mL) and mixed well. The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under vacuum to afford light brown viscous liquid. The crude compound was purified by combi-flash (230-400) silica gel column chromatography using ethyl acetate in DCM and peak eluted with 25% ethyl acetate in DCM, fraction solvent was concentrated to afford the desired compound **Example 46a** as off-white solid. Yield: 0.160 g (57 %); **LC_MS** Calculated. for $C_{21}H_{25}N_7O$ is 391.47 Observed. 392.30 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.12 (bs, 2H) , 7.73 (t, J = 7.2 Hz, 1H), 7.25-7.17 (m, 2H), 6.86 (bs, 1H), 4.50 (s, 2H), 3.68-3.65 (m, 2H), 3.36 (s, 3H), 3.04-3.00 (t, J = 6.4 Hz, 2H), 2.38-2.33 (m, 2H), 2.26 (s, 3H), 0.95-0.94 (m, 1H), 0.36-0.34 (m, 2H), 0.17-0.16(m, 2H). **HPLC Purity** = 96.56 %, INT ODS 3V-C18 (4.6 x 250)

mm, 5µ; Mobile Phase A: 0.1% Formic acid in water: Mobile Phase B: Acetonitrile; Retention time = 9.49 min.

Step-2: 7-amino-3-(cyclopropyl methyl)-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

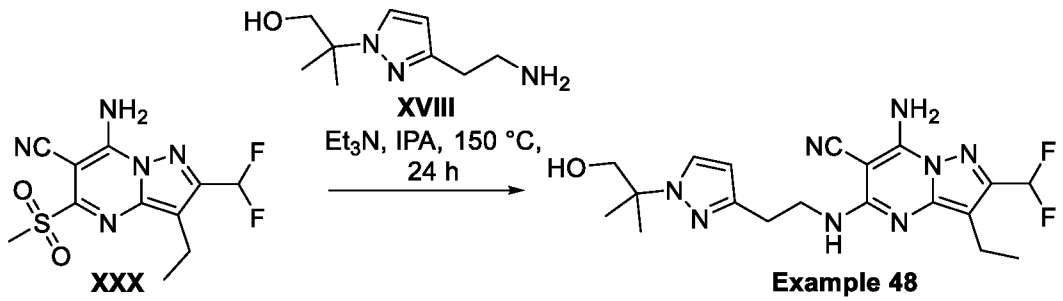
[000431] A stirred solution of 7-amino-3-(cyclopropyl methyl)-5-((2-(6-(methoxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (70 mg, 0.18 mmol) in DCM (5 mL) was added BBr_3 (0.017 mL, 0.18 mmol) at 0°C. The resulting mixture was stirred for 30 min at 0°C. The progress of the reaction was monitored by TLC analysis. After completion of the reaction mixture was quenched with $NaHCO_3$ solution (2 ml) and extracted with dichloromethane (10 ml X 3) and dried over sodium sulphate and concentrated at low vacuum. Crude was purified by prep-HPLC. Method: Xbridge C18, 19x250mm, 5mic. 10mm ammonium bicarbonate in water and acetonitrile. Prep fractions was evaporated to get pure title compound **Example 46** as off- white solid. Yield: 6.8 mg (10%). **LCMS** Calculated. for $C_{20}H_{23}N_7O$ is 377.20 $[M+H]^+$; Observed. 378.3 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (bs, 2H), 7.73-7.96 (m, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.87 (bs, 1H), 5.35 (*t*, J = 5.6 Hz, 1H), 4.58-4.57 (m, 2H), 3.66-3.64 (m, 2H), 3.00 (t, J = 6.8 Hz, 3H), 2.39-2.32 (m, 2H), 2.26 (s, 3H), 0.85-0.83 (m, 1H), 0.36-0.34 (m, 2H), 0.17-0.16(m, 2H). **HPLC Purity** = 92.88 %, INT ODS 3V-C18 (4.6x250) mm, 5µ; Mobile Phase A: 0.1% Formic acid in water: Mobile Phase B: Acetonitrile; Retention time = 9.58 min.

[000432] Example 47: 7-amino-2-cyclopropyl-5-((2-(6-(2-hydroxypropan-2-yl) pyridin-2-yl) ethyl)amino)-3-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.



[000433] To a solution of 7-amino-2-cyclopropyl-3-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX1X** (0.13 g, 0.45 mmol) in IPA (4 mL) at rt under N_2 atmosphere were added 2-(6-(2-aminoethyl) pyridin-2-yl) propan-2-ol **XV** (0.24 g, 1.3 mmol) and triethylamine (0.31 mL, 2.2 mmol) and the seal tube was heated at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, the reaction mixture was cooled to rt, and 20 mL water was added. The resulting mixture was extracted with ethyl acetate (20 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuo to afford light brown semi solid. The compound was purified by reverse phase HPLC using Mobile phase A: 10 mM ammonium bicarbonate in water: Mobile phase B: acetonitrile (column: YMC pack ODS-Aq; 250X20 mm; 50 um) and the peak eluted at retention time 17min with 50% acetonitrile and flow rate 17 mL/min was concentrated to afford the desired compound **Example 47** as off-white solid. Yield: 3.4 mg (2%); **LC_MS** Calculated. for $C_{21}H_{26}N_7O$ is 392.49, Observed, 392.30; $[M+H]^+$ HPLC Purity = 97.04 %, Column: INT ODS 3V-C18 (4.6 x 250) mm, 5µ Mobile phase A: 0.1% TFA in water Mobile phase B: Acetonitrile

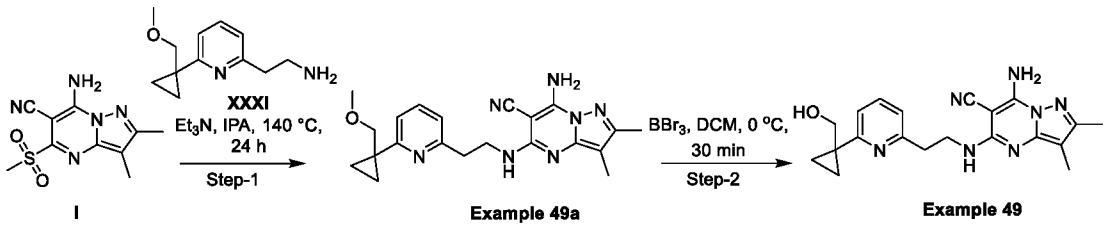
Example 48: 7-amino-2-(difluoromethyl)-3-ethyl-5-((2-(1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile .



[000434] To a stirred solution of 7-amino-2-(difluoro methyl)-3-ethyl-5-(methyl sulfonyl) pyrazolo[1,5-a]pyrimidine-6-carbonitrile **XXX** (0.3 g, 0.951mmol) and 2-(3-(2-aminoethyl)-1H-pyrazol-1-yl)-2-methylpropan-1-ol **XVIII** (0.523 g, 2.85mmol) in IPA (5 mL) was added TEA (0.8 mL, 5.71 mmol) and the reaction mixture was heated at 150 °C for 24 h. The progress of the reaction was monitored by TLC. After

completion, after completion, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by column chromatography by eluting with 50% ethyl acetate in hexane to yield the title compound as off-white solid. Yield: 0.098 g (25%); **LC_MS** Calculated. for $C_{19}H_{24}F_2N_8O$ is 418.20, Observed. 419.30; [M+H] +. **1H NMR (400 MHz, dmso-d6):** δ 8.42 (s, 2H), 7.64 (d, *J*=4 Hz, 1H), 7.04-6.90 (m, 2H), 6.05 (d, *J*=2 Hz, 1H), 4.88 (s, 1H), 3.61-3.32 (m, 4H), 2.83 (t, *J*=4 Hz, 2H), 2.62-2.50 (m, 2H), 1.43 (s, 6H), 1.16(t, *J*=4 Hz,3H). **HPLC** Purity = 99.09 %, Column: XBridge C18 (4.6 x150) mm, 5µ Mobile phase A: 10mM ammonium bicarbonate in H_2O Mobile phase B: acetonitrile; Retention time = 10.250 min.

Example 49: 7-amino-5-((2-(6-(1-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Step-1: 7-amino-5-((2-(6-(1-(methoxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (49a)

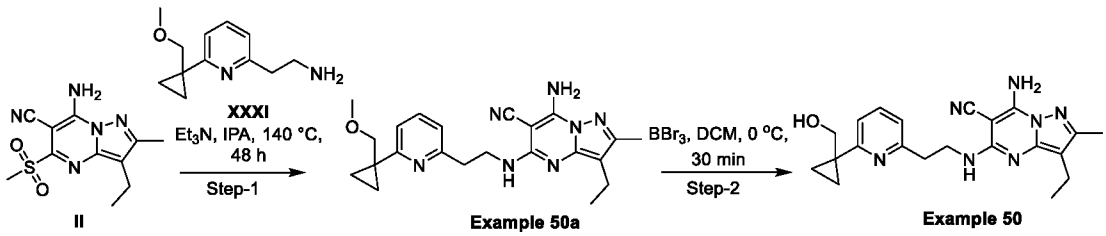
[000435] To a solution of 2-(6-(1-(methoxymethyl) cyclopropyl) pyridin-2-yl) ethan-1-amine (0.53 g, 2.6 mmol) **XXXI** and 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (0.34 g, 1.3 mmol) in isopropanol (10 mL) was added triethylamine (0.54 mL, 3.8 mmol) and the resulting mixture was purged with N_2 for 10 min. The seal tube was closed tightly and heated at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under *vacuo*. To this, added ethyl acetate (20 mL) and water (20 mL). The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under *vacuo* to afford light brown viscous liquid. The crude compound was subjected to silica gel (230-400; packed 40g) column chromatography using ethyl acetate (0-25%) in n- hexane. The

peak eluted with 22% ethyl acetate in hexane was concentrated to afford the desired compound **Example 49a** as off-white solid. Yield: 100 mg (20%); **LC_MS** Calculated. for $C_{21}H_{25}N_7O$ is 391.48, Observed 392.25; $[M+H]^+$; HPLC Purity = 95.12 %, INT_9010_AA_22.lcm; **^{1}H NMR (400 MHz, DMSO-D6):** δ 8.08 (S, 2H), 7.58 (d, *j*=8 Hz 1H), 7.24 (d, *J*= 8.0 Hz, 1H), 7.02 (d, j=8 Hz ,1H), 6.57(S, 1H), 3.68 (t, *J*= 8 Hz, 4H), 3.30 (d, *J*= 20 Hz, 3H), 2.96 (t, *J*= 8 Hz, 2H), 2.23(S, 3H), 1.97(S, 3H), 1.19(S, 2H), 0.87 (d, *J*= 4 Hz, 2H).

Step-2: 7-amino-5-((2-(6-(1-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile

[000436] To a solution of 7-amino-5-((2-(6-(1-(methoxymethyl)cyclopropyl)pyridin-2-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile **Example 49a** (70 mg, 0.18 mmol) in DCM (7 mL) at 0 °C was added BBr_3 (0.02 mL, 0.18 mmol) drop wise and stirred for 30 min.The reaction mixture was monitored by TLC analysis in which both bromo analogue and desired product was observed. Then to the resulting mixture, sodium formate (0.007 mL, 0.18 mmol) and catalytic amount of TBAB was added and stirred for 48 h. The reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl solution. To this, water(2mL) was added and extracted with DCM (2 mL x 2). The combined organic layer was washed with brine and concentrated under reduced pressure to afford a light brown viscous liquid. The crude compound was purified by reverse phase HPLC; YMC AQUA ODS (250 X 20) mm. 5.0 microns. Mobile phase A:10 mm Ammonium bicarbonate in H_2O; Mobile phase B: ACN: MeOH (1:1) to afford the desired title compound **Example 49** as a light brown solid. Yield: 67 mg (43 %); **LCMS** Calculated. for $C_{20}H_{23}N_7O$ is 377.47, Observed, 378.25; $[M+H]^+$; HPLC Purity = 98.27 %, Column: Symmetry-C18 (4.6*75) mm,3.5µ Mobile phase A: 10mM ammonium bicarbonate in water. Mobile phase B: ACN. **^{1}H NMR (400 MHz, dmso-d6):** δ 8.08 (S, 2H), 7.59 (t, *j*=8 Hz 1H), 7.29 (t, *J*= 8.0 Hz, 1H), 7.02 (d, j=8 Hz ,1H), 6.57(t, *j*=8 Hz 1H), 4.72 (t, *J*= 4 Hz, 1H),

3.75-3.66 (m, 4H), 2.96 (t, *J*= 8 Hz, 2H), 2.23(S, 3H), 1.97(S, 3H), 1.19(S, 2H), 0.87 (d, *J*= 4 Hz, 2H).



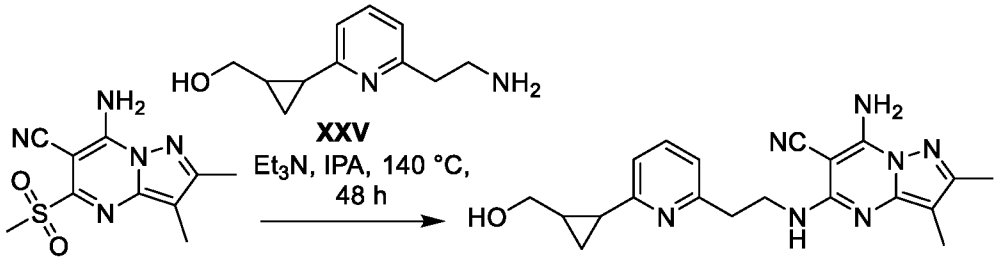
Step-1: 7-amino-3-ethyl-5-((2-(6-(1-(methoxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile(50a)

[000437] To a solution of 2-(6-(1-(methoxymethyl) cyclopropyl) pyridin-2-yl) ethan-1-amine **XXXI** (0.24 g, 1.1 mmol) and 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.16 g, 0.57 mmol) in isopropanol (10 mL) was added triethylamine (0.24 mL, 1.7 mmol) and the resulting mixture was purged with N_2 for 10 min. The seal tube was closed tightly and heated at 140 °C for 48 h. the progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under *vacuo*. Added ethyl acetate (20 mL) and water (20 mL). The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under *vacuo* to afford light brown viscous liquid. The crude compound was subjected to silica gel (230-400; packed 40g) column chromatography using ethyl acetate (0-25%) in *n*-hexane. The peak eluted with 22% ethyl acetate in *n*-hexane was concentrated to afford the desired compound **Example 50a** as an off-white solid. Yield: 0.095g (41%). **LCMS** Calculated. for $C_{22}H_{27}N_7O$ is 405.51; Observed.406.35 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.08 (s, 2H), 7.59 (t, *J* = 8 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.01 (d , *J*=8 Hz, 1H), 6.60 (t, *J*=4 Hz 1H), 3.65 (t, *J*=12 Hz 4H), 3.30 (d , *J*=16 Hz, 3H), 2.96 (t, *J* = 8 Hz, 2H), 2.50-2.43(m, 2H), 2.25 (s, 3H), 1.23-1.19 (m, 2H), 1.15 (t, *J*=8 Hz 3H), 0.89-0.86 (m, 2H); **HPLC** Purity = 98.45 %, Column : XBridge C18 (4.6 x150)mm, 5µ Mobile phase A : 10mM ammonium bicarbonate in H_2O. Mobile phase B : acetonitrile

Step-2: 7-amino-3-ethyl-5-((2-(6-(1-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000438] To a solution of 7-amino-3-ethyl-5-((2-(6-(1-(methoxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 50a** (70 mg, 0.17 mmol) in DCM (7 mL) at 0 °C was added BBr_3 (0.02 mL, 0.17 mmol) in dropwise and stirred for 30 min. The reaction mixture was monitored by TLC analysis in which both bromo analogue and desired product was observed. Then added sodium formate (0.007 mL, 0.17 mmol) and catalytic amount of TBAB, stirred for 48 h. The reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl solution. Added water(2mL) and extracted with DCM (2mLx2). The combined organic layer was washed with brine and concentrated under reduced pressure to afford a light brown viscous liquid. The crude compound was purified by Reverse phase HPLC: YMC AQUA ODS (250X20) mm, 5.0 microns; Mobile phase A:10mm Ammonium bicarbonate in H_2O; Mobile phase B: ACN: MeOH (1:1) to afford the desired title compound **Example 50** as an off-white solid. Yield: 0.015g (22%). **LCMS** Calculated. for $C_{21}H_{25}N_7O$ is 391.47; Observed.392.25 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.08 (s, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.01 (d , J=8.0 Hz, 1H), 6.60 (t, J=4.0 Hz 1H), 4.71(d, J=4.0 Hz, 1H) 3.74-3.65 (m, 4H), 2.96 (t, J = 8.0 Hz, 2H), 2.50-2.43(m, 2H), 2.25 (s, 3H), 1.23-1.19 (m, 2H), 1.15 (t, J=8.0 Hz 3H), 0.89-0.86 (m, 2H); **HPLC** Purity = 98.78 %, Column : Symmetry-C18 (4.6 x 75)mm, 3.5µ; Mobile phase A : 10mM ammonium acetate in H_2O Mobile phase B : Acetonitrile.

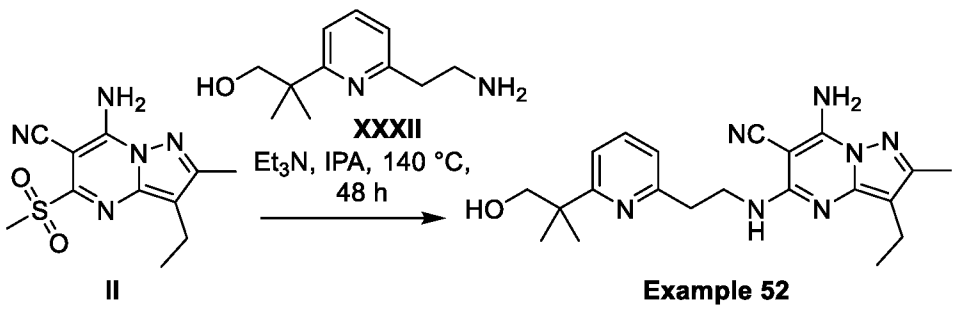
Example 51: 7-amino-5-((2-(6-(2-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



I **Example 51**

[000439] To a solution of (2-(6-(2-aminoethyl) pyridin-2-yl) cyclopropyl) methanol XXV (0.36 g, 1.9 mmol) and 7-amino-2,3-dimethyl-5-(methylsulfonyl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile **I** (0.25 g, 0.94 mmol) in IPA (10 mL) was added triethylamine (0.39 mL, 2.8 mmol) and purged with N_2 for 10 min. The seal tube was closed tightly and heated at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was cooled to rt and concentrated under *vacuo*. Added water (20 mL) and extracted with ethyl acetate (20 mL x 2). The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under *vacuo* to afford light brown viscous liquid. The crude compound was purified by silica gel (230-400 mesh) column chromatography using ethyl acetate in *n*- hexane (0-80%) to afford the desired title compound **Example 51** as an off-white solid. Yield: (30 mg, 8.4 %); **LC_MS** Calculated. for $C_{20}H_{23}N_7O$ is 377.45; Observed.378.25 $[M+H]^+$. **HPLC** Purity = 99.36 %, Column : YMC-Pack ODS-AQ (4.6 x 150)mm, 5µ Mobile phase A : 10mM ammonium acetate in H_2O; Mobile phase B : ACN ; Rt=11.620 min. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.09 (s, 2H), 7.53 (t, J = 8 Hz, 1H), 7.06-6.98 (m, 2H), 6.65 (t, J = 4 Hz, 1H), 4.56 (t, J = 6.8 Hz, 1H), 3.68-3.35 (m, 4H), 2.95 (t, J = 8 Hz, 2H), 2.23 (s, 3H), 1.95 (t, J = 4 Hz, 4H), 1.59-1.54 (m, 1H), 1.10-1.06 (m, 1H), 1.06-0.85 (m, 1H).

Example 52: 7-amino-3-ethyl-5-((2-(6-(1-hydroxy-2-methylpropan-2-yl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

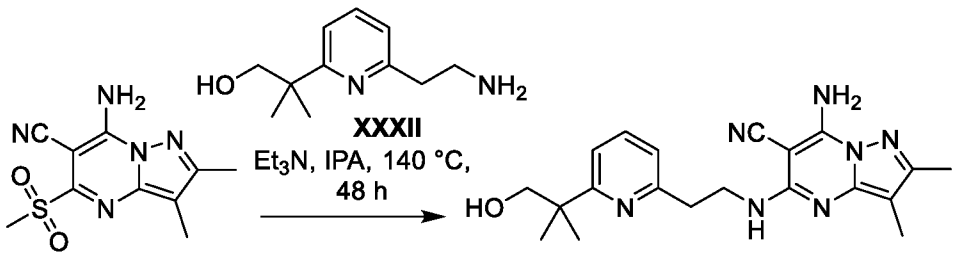


II **Example 52**

[000440] To a solution of 2-(6-(2-aminoethyl) pyridin-2-yl)-2-methylpropan-1-ol **XXXII** (0.2 g, 1 mmol) and 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a]pyrimidine-6-carbonitrile **II** (0.2 g, 0.7 mmol) in isopropanol (10 mL) was added triethylamine (0.4 mL, 3 mmol) and the resulting mixture was purged

with N_2 for 10 min. The seal tube was closed tightly and heated at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. The reaction was cooled to RT and the reaction mixture was concentrated under *vacuo*. To the residue was added ethyl acetate (20 mL) and water (20 mL). The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under vacuo to afford light brown viscous liquid. The crude compound was purified by reverse phase HPLC, Column: Xbridge Prep C18 (250 x19) mm, 5.0 µ; Mobile phase A:10mm Ammonium bi carbonate in water; Mobile phase B: Acetonitrile to afford the desired title compound **Example 52** as an off-white solid. Yield: 32 mg (10 %); **LC_MS** Calculated. for $C_{21}H_{28}N_7O$ is 394.24; Observed. 394.30 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.09 (bs, 2H), 7.63 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.07 (d , J=7.2 Hz, 1H), 6.65 (bs, 1H), 4.64 (t, J=5.6 Hz, 1H), 3.73-3.68 (m , 2H), 3.55 (d, J = 5.6 Hz, 2H), 3.02 (t, J = 6.8 Hz, 2H), 2.46-2.41 (m, 2H), 2.25 (s, 3H), 1.26 (s, 6H), 1.13 (t, J = 7.2 Hz, 3H); **HPLC Purity** = 98.27 %, YMC-Pack ODS-AQ(4.6 X 150)mm, 5µ, Mobile phase A : 10mM ammonium acetate in water Mobile phase B: Acetonitrile.

Example 53: 7-amino-5-((2-(6-(1-hydroxy-2-methylpropan-2-yl) pyridine-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

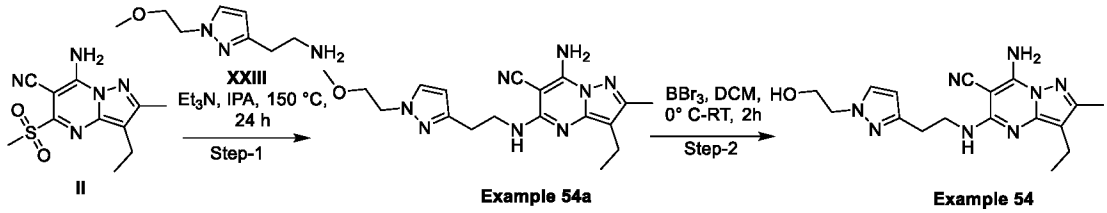


I Example 53

[000441] To a solution of 2-(6-(2-aminoethyl) pyridin-2-yl)-2-methylpropan-1-ol (0.2 g, 1 mmol) and 7-amino-2,3-dimethyl-5-(methylsulfonyl) pyrazolo[1,5-a]pyrimidine-6-carbonitrile (0.2 g, 0.8 mmol) in isopropanol (10 mL) was added triethylamine (0.4 mL, 3 mmol) and the resulting mixture was purged with N_2 for 10 min. The seal tube was closed tightly and heated at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. The reaction was cooled to RT and the reaction mass was concentrated under *vacuo*. To the residue were added

ethyl acetate (20 mL) and water (20 mL). The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under vacuo to afford light brown viscous liquid. The crude compound was purified by reverse phase HPLC, Column: Xbridge Prep C18 (250 x19) mm, 5.0 µ; Mobile phase A:10mm Ammonium bicarbonate in water; Mobile phase B: Acetonitrile to afford the desired compound **Example 53** as off-white solid. Yield: 32 mg (10 %); **LC_MS** Calculated. for $C_{20}H_{26}N_7O$ is 380.22; Observed. 380.25 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.09 (bs, 2H), 7.63 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.09 (d , J=7.6 Hz, 1H), 6.62 (bs, 1H), 4.65 (t, J=5.6 Hz, 1H), 3.74-3.69 (m , 2H), 3.55 (d, J = 5.6 Hz, 2H), 3.02 (t, J = 7.2 Hz, 2H), 2.23 (s, 3H), 1.97 (s, 3H), 1.24 (s, 6H); **HPLC Purity** = 98.27 %, YMC-Pack ODS-AQ(4.6 X 150)mm, 5µ, Mobile phase A : 10mM ammonium acetate in H_2O B: Acetonitrile.

Example 54: 7-amino-3-ethyl-5-((2-(1-(2-hydroxyethyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



Step-1: 7-amino-3-ethyl-5-((2-(1-(2-methoxyethyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 54a).

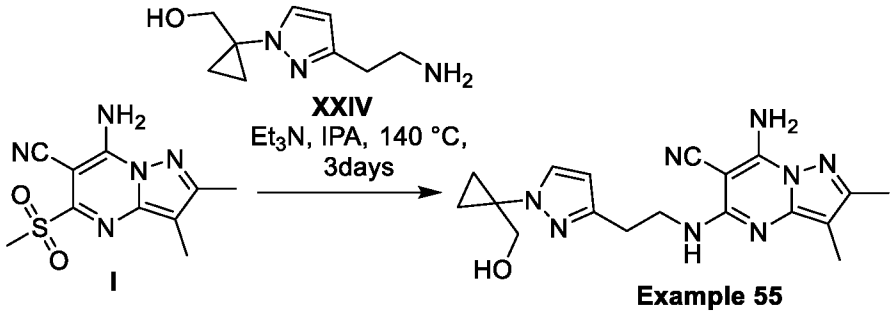
[000442] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*]pyrimidine-6-carbonitrile **II** (0.700 g, 2.51 mmol) and 2-(1-(2-methoxyethyl)-1*H*-pyrazol-3-yl)ethan-1-amine **XXIII** (0.85 g, 5.02 mmol) in isopropanol (2.5 mL) in a sealed tube was added triethylamine (2.10 mL, 15.0 mmol) and the reaction mixture was stirred at 150 °C for 24 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel (100-200) column chromatography by eluting with 50% ethyl acetate in *n*-hexane to yield the title compound **Example 54a** as an off-white solid. Yield: 0.3g (32.5%); **LC_MS**

Calculate. for $C_{18}H_{25}N_8O$ is 369.22; Observed. 369.25 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.10 (bs, 2H), 7.58 (d, J = 2.0 Hz, 1H), 6.66 (t, J = 5.2 Hz, 1H), 6.06 (d, J = 2.0 Hz, 1H), 4.18 (q, J = 5.2 Hz, 2H), 3.66 (t, J = 5.2 Hz, 2H), 3.59-3.55 (m, 2H), 2.21 (s, 3H), 2.82 (t, J = 7.2 Hz, 2H), 2.47-2.43 (m, 2H), 2.25 (s, 3H), 1.12 (t, J = 7.6 Hz, 3H); **HPLC Purity** = 99.78 %, YMC-Pack ODS-AQ (4.6 X 150)mm, 5µ, Mobile phase A : 10mM ammonium acetate in water. Mobile phase B: Acetonitrile.

Step-2: 7-amino-3-ethyl-5-((2-(1-(2-hydroxyethyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

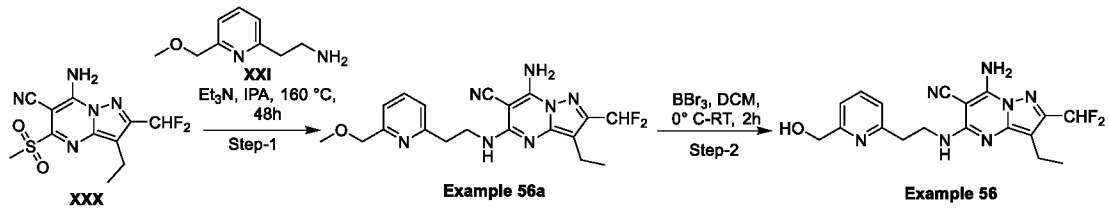
[000443] A stirred solution of 7-amino-3-ethyl-5-((2-(1-(2-methoxyethyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 54a** (0.3 g, 0.8 mmol) in DCM (50ml) was cooled to 0 °C, and BBr_3 (0.09 mL, 1 mmol) was added slowly. After completion, the reaction mixture was quenched with methanol (0.5 mL) and diluted with water (20 mL). The resulting mixture was extracted with DCM (20 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel (100-200) column chromatography by eluting with 1-5% methanol in DCM to afford the desired title compound **Example 54** as off-white solid. Yield: 50 mg (33%); **LC_MS** Calculated for $C_{17}H_{23}N_8O$ is 355.20; Observed. 355.25 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.29 (bs, 2H), 7.65 (s, 1H), 6.89 (bs, 1H), 6.12 (s, 1H), 4.09 (t, J = 5.6 Hz, 2H), 3.71 (t, J = 5.6 Hz, 2H), 3.62 (t, J = 7.2 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H), 2.55-2.50 (m, 3H), 2.26 (s, 3H), 1.11 (t, J = 7.6 Hz, 3H); **HPLC Purity** = 99.78 %, YMC-Pack ODS-AQ (4.6 X 150)mm, 5µ, Mobile phase A : 10mM ammonium acetate in water. Mobile phase B: Acetonitrile.

Example 55: 7-amino-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000444] In a seal tube was charged with 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **I** (2.1 g, 7.9 mmol), (1-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclopropyl) methanol **XXIV** (2 g, 11 mmol) and isopropanol (60 mL). The resulting mixture was purged with N_2 gas for 5 min and TEA (6.6 mL, 47 mmol) was added. The seal tube was stirred at 140 °C for 3 days. The progress of reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated to remove the solvent. The residue was dissolved in water (40 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine and dried over anhydrous sodium sulphate. The crude material obtained upon removal of the solvent was purified by flash chromatography (combi-flash) using 50-100 % ethyl acetate in *n*-hexane to afford the desired compound as an off-white solid. Yield: 1.0 g (34.4%); **LC_MS** Calculated. for $C_{18}H_{23}N_8O$ is 367.20; Observed. 367.25 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.12 (bs, 2H), 7.62 (d, J = 2.0 Hz, 1H), 6.58 (t, J = 5.6 Hz, 1H), 6.05 (d, J = 2.0 Hz, 1H), 4.89 (d, J = 5.6 Hz, 1H), 3.61-3.56 (m, 4H), 2.81 (t, J = 7.2 Hz, 2H), 2.50 (s, 3H), 1.97 (s, 3H), 1.10-1.07 (m, 2H), 0.98-0.95 (m, 2H); **HPLC Purity** = 99.01 %.

[000445] Example 56: 7-amino-2-(difluoro methyl)-3-ethyl-5-((2-(6-(hydroxymethyl) pyridine-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile



Step-1: 7-amino-2-(difluoro methyl)-3-ethyl-5-((2-(6-(methoxymethyl) pyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 56a)

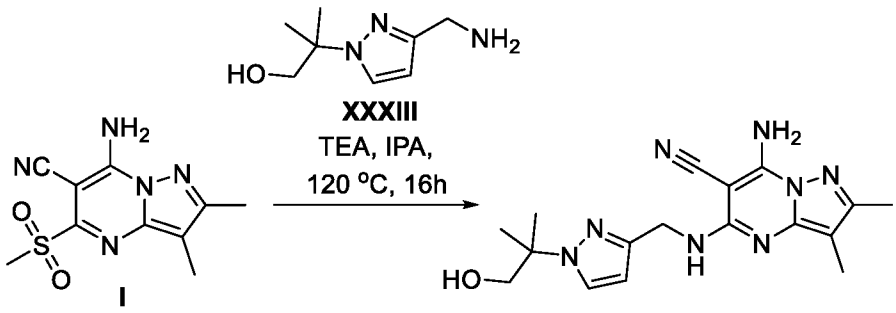
[000446] To a stirred solution of 7-amino-2-(difluoro methyl)-3-ethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXX** (200 mg, 0.634 mmol) in isopropanol (6 mL) were added TEA (0.53 mL, 3.81 mmol) and 2-(6-(methoxymethyl) pyridin-2-yl) ethan-1-amine **XXI** (264 mg, 1.59 mmol). The resulting mixture was purged with N_2 gas for 5 min and the seal tube was heated at

160 °C with vigorous stirring for 48 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated under reduced pressure. The crude was subjected to silica gel (230-400) combi-flash column chromatography using 0-25% ethyl acetate/*n*-hexane to afford the desired compound **Example 56a** as an off-white solid. Yield: 140 mg (55 %); **LC_MS** Calculated. for $C_{19}H_{22}F_2N_7O$ is 402.19; Observed. 402.20 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.43 (bs, 2H), 7.73 (t, J = 7.6 Hz, 1H), 7.26-7.21 (m, 2H), 7.13-6.91 (m, 2H), 4.50 (s, 2H), 3.69 (bs, 1H), 3.36 (s, 3H), 3.04 (t, J=6.4 Hz, 2H), 2.67-2.61 (m, 3H), 1.16 (t, J = 7.6 Hz, 3H).

Step-2: 7-amino-2-(difluoro methyl)-3-ethyl-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000447] A stirred solution of 7-amino-2-(difluoro methyl)-3-ethyl-5((2-(6-(methoxymethyl) pyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 56a** (140 mg, 0.349 mmol) in dry DCM (5 mL) was cooled to 0 °C under N_2 atmosphere and BBr_3 (49.5 µL, 0.523 mmol) in dry DCM (0.5 mL) was slowly added. The reaction mixture was stirred at 0 °C for 2 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction cooled to 0 °C and was quenched with MeOH (0.5 mL). The reaction mixture was concentrated under reduced pressure and the crude was stirred in sat. $NaHCO_3$ solution for 30 min. The solid was collected by filtration and was purified by silica gel (230-400 mesh) column chromatography using 30-80 % ethyl acetate in *n*-hexane to afford the desired title compound **Example 56** as off-white solid. Yield: 72.2 mg (53 %); **LC_MS** Calculated. for $C_{17}H_{22}N_8O$ is 355.20; Observed. 355.25 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.14 (bs, 2H), 7.65 (d, J = 1.6 Hz, 1H), 6.79 (bs, 1H), 6.16 (t, J = 2.0 Hz, 1H), 4.92 (d, J = 5.6 Hz, 1H), 4.38 (d, J = 5.2 Hz, 2H), 3.55 (d, J = 5.6 Hz, 2H), 2.23 (s, 3H), 1.97 (s, 3H), 1.44 (s, 6H). **HPLC purity**= 98.22%; XBridge C18 (4.6*150) mm, 5µ; Mobile Phase A: 10mM ammonium bicarbonate in water; Mobile Phase B: Acetonitrile.

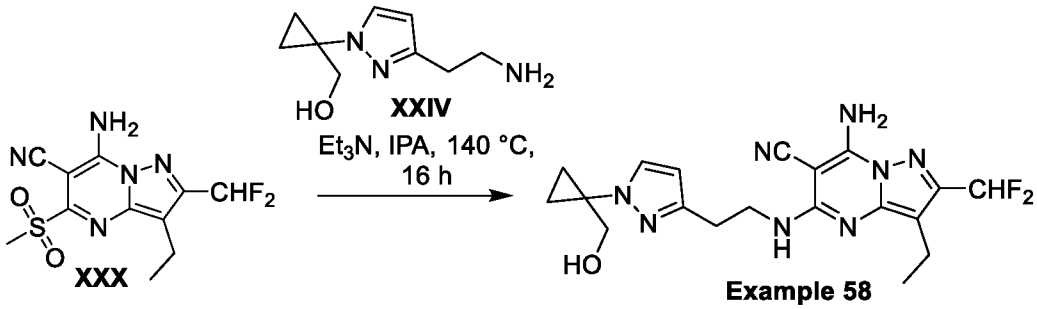
Example 57: 7-amino-5-(((1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl) methyl) amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile



Example 57

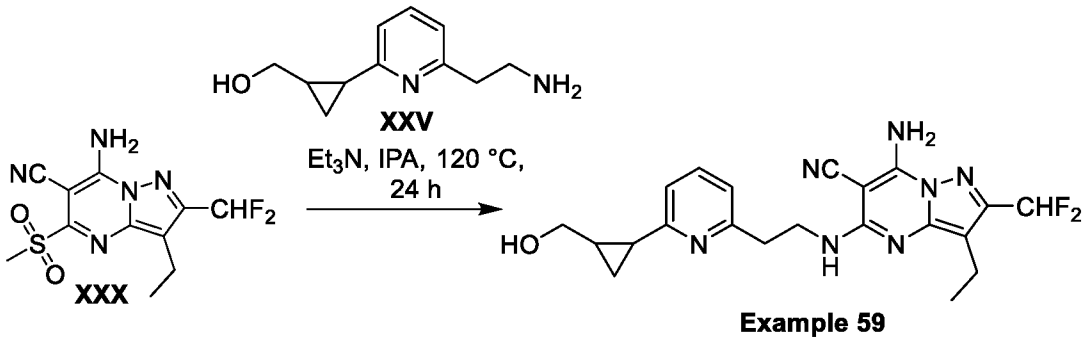
[000448] To a stirred solution of 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (0.15 g, 0.57 mmol) and 2-(3-(aminomethyl)-1H-pyrazol-1-yl)-2-methylpropan-1-ol (0.12 g, 0.71 mmol) in 2-propanol **XXXIII** (5 mL), was added triethylamine (0.47 mL, 3.4 mmol) and the reaction mixture was heated at 120 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (100 ml) and extracted with ethyl acetate (100 mL x 3). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude was purified by flash silica gel (230-400 mesh) using 0-2% methanol in DCM to afford the desired title compound **Example 57** as an off-white solid. Yield: 45.0 mg (20 %); **LC_MS** Calculated. for $C_{17}H_{22}N_8O$ is 355.20; Observed. 355.25 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.14 (bs, 2H), 7.65 (d, J = 1.6 Hz, 1H), 6.79 (bs, 1H), 6.16 (t, J = 2.0 Hz, 1H), 4.92 (d, J = 5.6 Hz, 1H), 4.38 (d, J = 5.2 Hz, 2H), 3.55 (d, J = 5.6 Hz, 2H), 2.23 (s, 3H), 1.97 (s, 3H), 1.44 (s, 6H); **HPLC purity**= 98.22%; XBridge C18 (4.6 X 150) mm, 5µ; Mobile Phase A: 10mM ammonium bicarbonate in H_2O; Mobile Phase B: Acetonitrile.

Example 58: 7-amino-2-(difluoro methyl)-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a]pyrimidine-6-carbonitrile



[000449] A seal tube was charged with 7-amino-2-(difluoro methyl)-3-ethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (146 mg, 0.463 mmol), (1-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclopropyl)methanol (150 mg, 0.828 mmol) and 2-propanol (6 mL). The resulting mixture was purged with N_2 gas for 5 min and TEA (0.387 mL, 2.78 mmol) was added. The reaction was stirred at 140 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture concentrated, and the residue was dissolved in water (10 mL). The resulting mixture was extracted with ethyl acetate (15 mL X 2). The combined organic layer was washed with brine and dried over anhydrous sodium sulphate. The solvent was removed, and the crude material was purified by flash chromatography (combi-flash) using 20-80 % ethyl acetate in *n*-hexane to afford the desired compound as an off-white solid. Yield: 18 mg (9.3 %); **LC_MS** Calculated. for $C_{19}H_{23}F_2N_8O$ is 417.20; Observed. 417.20 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.45 (bs, 2H), 7.62 (s, 1H), 7.12-6.87 (m, 2H), 6.08 (s, 1H), 4.96 (bs, 1H), 3.61-3.58 (m, 4H), 2.84 (bs, 2H), 2.71-2.60 (m, 2H), 1.23-1.16 (m, 3H), 1.14-0.98 (m, 4H); HPLC purity= 95.15%; XBridge C18 (4.6 X 150) mm, 5µ; Mobile Phase A: 10mM NH_4HCO_3 in water; Mobile Phase B: Acetonitrile; Retention time: 11.678 min.

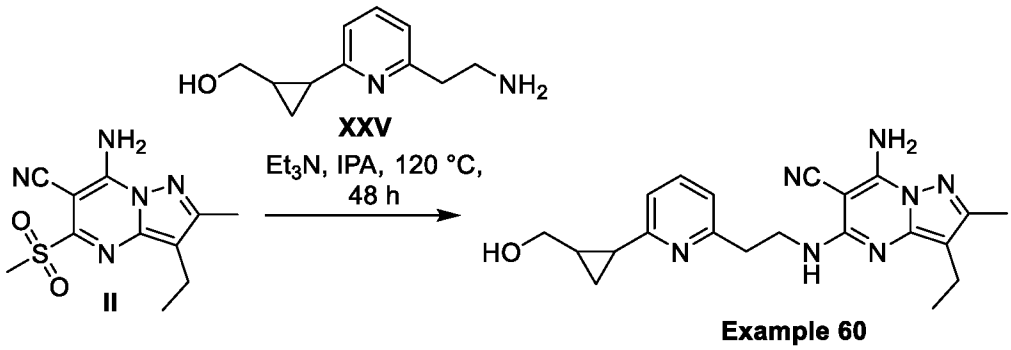
Example 59: 7-amino-2-(difluoro methyl)-3-ethyl-5-((2-(6-(2-(hydroxymethyl) cyclopropyl)pyridin-2-yl)ethyl)amino)pyrazolo[1,5-a]pyrimidine-6-carbonitrile



Example 59

[000450] To a solution of (2-(6-(2-aminoethyl) pyridin-2-yl) cyclopropyl) methanol **XXV** (0.3 g, 2 mmol) and 7-amino-2-(difluoro methyl)-3-ethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXX** (0.2 g, 0.8 mmol) in isopropanol (10 mL) was added triethylamine (0.7 mL, 5 mmol) and the resulting mixture was purged with N_2 for 10 min. The seal tube was closed tightly and heated at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. The reaction was cooled to RT and the reaction mixture was concentrated under *vacuo*. To the residue was added ethyl acetate (20 mL) and water (20 mL). The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under *vacuo* to afford light brown viscous liquid. The crude compound was purified by reverse phase prep-HPLC using YMC AQUA ODS (250X20) mm.5µ; Mobile phase A:10mm Ammonium bicarbonate in H_2O, Mobile phase B: ACN: MeOH (1:1). Yield: (50 mg, 4 %). **LC_MS** Calculated. for $C_{21}H_{24}F_2N_7O$ is 428.20; Observed.428.20 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.42 (bs, 2H), 7.53 (t, J = 7.6 Hz, 1H), 7.18-6.91 (m, 4H), 4.57 (t, J = 6.0 Hz, 1H), 3.66 (bs, 2H), 3.68-3.36 (m, 2H), 2.97 (t, J = 6.8 Hz, 2H), 2.68-2.55 (m, 2H), 1.96 (bs, 1H), 1.58 (bs, 1H), 1.19 (t, J = 7.2 Hz, 2H), 1.09 (bs, 1H), 1.07 (bs); **HPLC** Purity = 96.58 %, XB_9010ABC Rt=10.262 min; Chiral **HPLC** (two peaks); Chiral Pak IG (250 X 4.6) mm, 5µ; Mobile phase: A:0.1%DEA in Hex, B:EtOH (90:10); **P1**= 51.29 %, Rt=19.022 min; **P2**= 48.71 %, Rt=21.731 min.

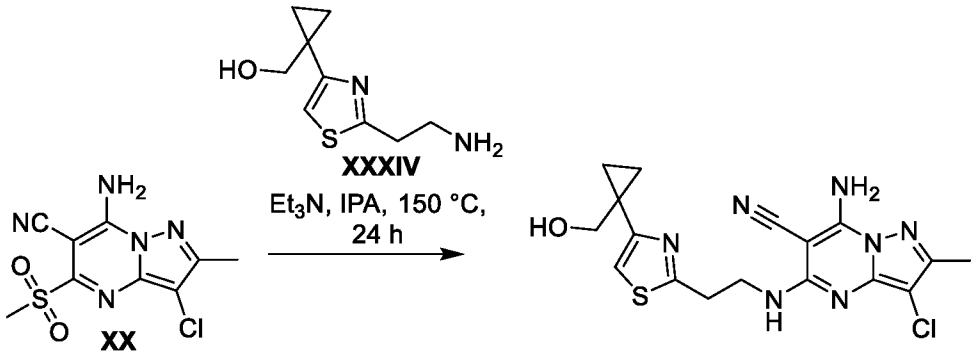
Example 60: 7-amino-3-ethyl-5-((2-(6-(2-(hydroxymethyl) cyclopropyl)284**yridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.**



Example 60

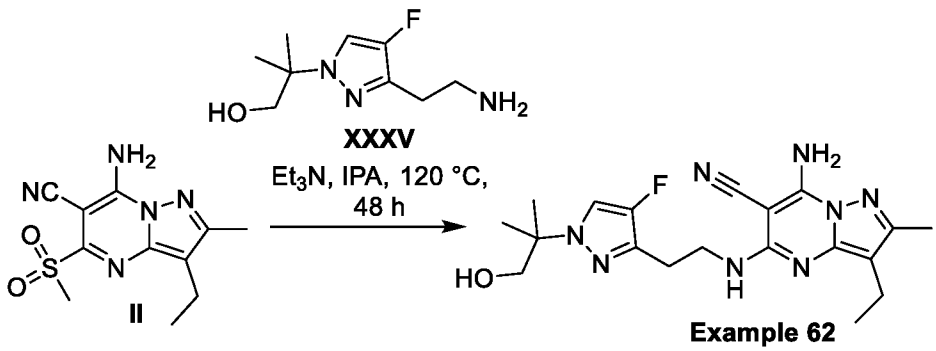
[000451] To a solution of (2-(6-(2-aminoethyl) pyridin-2-yl) cyclopropyl) methanol **XXV** (344 mg, 1.79 mmol) and 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (250 mg, 0.89 mmol) in isopropanol (10 mL) was added triethylamine (0.750 mL, 5.37 mmol) and the resulting mixture was purged with N_2 for 10 min. The seal tube was closed tightly and heated at 120 °C for 48 h. The progress of the reaction was monitored by TLC analysis. The reaction was cooled to RT and the reaction mixture was concentrated under *vacuo*. To the residue was added ethyl acetate (30 mL) and water (20 mL). The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under *vacuo* to afford light brown viscous liquid. The crude was purified by combi flash (230-400 mesh) column chromatography by using 0-20% ethyl acetate in *n*-hexane to afford the desired title compound **Example 60** as an off-white solid. Yield: (45 mg, 20 %). **LC_MS** Calculated. for $C_{21}H_{26}N_7O$ is 392.22; Observed. 392.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.09 (bs, 2H), 7.53 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.68 (bs, 1H), 4.56 (t, J = 5.6 Hz, 1H), 3.67-3.62 (m, 2H), 3.51-3.47 (m, 1H), 3.39-3.32 (m, 1H), 2.95 (t, J = 7.2 Hz, 2H), 2.48-2.40 (m, 2H), 2.25 (s, 3H), 1.98-1.94 (m, 1H), 1.59-1.56 (m, 1H), 1.20-1.06 (m, 4H), 0.89-0.85 (m, 1H); **HPLC** Purity = 96.79 %, Rt=10.262 min; Chiral **HPLC** (two peaks); Chiral Pak IG (250 X 4.6) mm, 5µ; Mobile phase: A: 0.1%DEA In Hex, B:EtOH (90:10); **P1**= 49.98 %, Rt=26.408 min; **P2**= 50.02 %, Rt=32.475 min.

Example 61: 7-amino-3-chloro-5-((2-(4-(1-(hydroxymethyl) cyclopropyl) thiazol-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



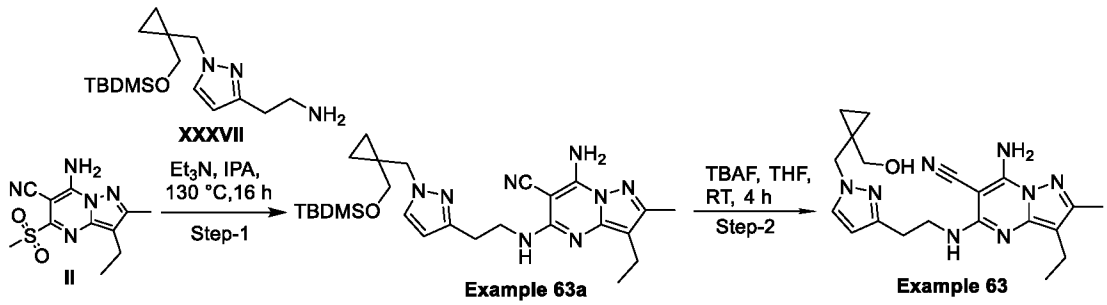
[000452] To a stirred solution of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX** (0.15 g, 0.53 mmol) in isopropanol (5 mL) were added (1-(2-(2-aminoethyl) thiazol-4-yl)cyclopropyl)methanol **XXXIV** (0.31 g, 1.6 mmol) and TEA (0.37 mL, 2.6 mmol). The reaction mixture was stirred at 150 °C for 24 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated and to the residue was added water (15 mL). The resulting mixture was extracted with ethyl acetate (20 mL X 2) and the combined organic layer was dried over anhydrous sodium sulphate. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using (10-60%) ethyl acetate in *n*-hexane to afford the desired title compound **Example 61** as a light brown solid. Yield: 11.3 mg (5%); **LC_MS** Calculated. for $C_{17}H_{18}ClN_7OS$ is 403.10; Observed. 404.15 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.43 (bs, 2H), 7.16 (s, 1H), 7.10 (t, J = 5.2 Hz, 1H), 4.69 (t, J = 5.6 Hz, 1H), 3.71-3.65 (m, 4H), 3.22 (t, J = 6.8 Hz, 2H), 2.28 (s, 3H), 0.99-0.96 (m, 2H), 0.84-0.81 (m, 2H). HPLC Purity = 99.01 %; INT ODS 3V-C18 (4.6 x 250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile; Rt= 11.614 min.

Example 62: 7-amino-3-ethyl-5-((2-(4-fluoro-1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000453] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (250 mg, 0.895 mmol) and 2-(3-(2-aminoethyl)-4-fluoro-1H-pyrazol-1-yl)-2-methylpropan-1-ol. **XXXV** (350 mg, 1.74 mmol) in 2-propanol (10 mL) was added triethylamine (0.748 mL, 5.37 mmol). The resulting mixture was heated at 120 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to room temperature and crude was diluted with ethyl acetate (20 mL) and water (20 mL) and mixed well. The combined organic layer was washed with brine, dried over anhydrous sodium sulphate, and concentrated under vacuum to afford light brown viscous liquid. The crude compound was purified by combi-flash silica (230-400) column chromatography by eluting with 10-50% ethyl acetate in *n*-hexane to afford the desired compound **Example 62** as an off-white solid. Yield: 0.11 g (30%). **LC_MS** Calculated. for $C_{19}H_{25}FN_8O$ is 400.21; Observed.401.25 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.10 (bs, 2H), 7.79 (d J = 4.8 Hz, 1H), 6.65 (bs, 1H), 4.91- 4.90 (m, 1H), 3.58 - 3.55 (m, 2H), 3.51 - 3.49 (m, 2H), 2.84 - 2.80 (m, 2H), 2.46 – 2.42 (m, 2H), 2.25 (m, 3H), 1.39 (s, 6H), 1.11 (t, J = 7.60 Hz, 3H); **HPLC** Purity = 99.09 %; Rt= 10.08 min;

Example 63: 7-amino-3-ethyl-5-((2-(1-((1-(hydroxymethyl) cyclopropyl)methyl)-1H-pyrazol-3-yl)ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile



[000454] Step-1: 7-Amino-5-((2-(1-((1-(((*tert*-butyl dimethyl silyl) oxy) methyl) cyclopropyl) methyl)-1*H*-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-*a*] pyrimidine -6-carbonitrile (Example 63a)

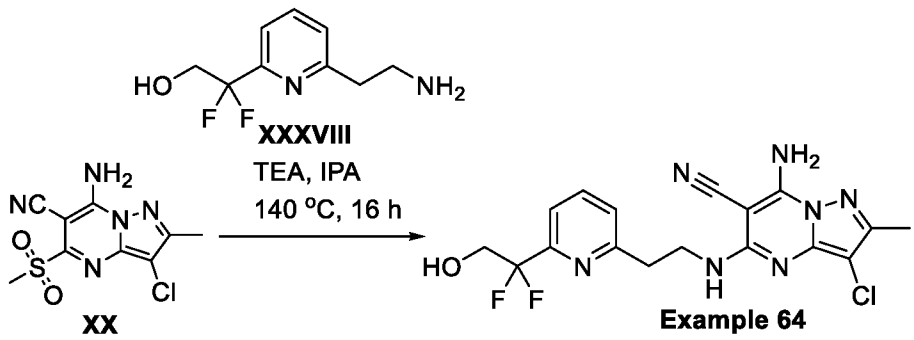
[000455] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **II** (250 mg, 0.895 mmol) in 2-propanol (20 mL) was added 2-(1-((1-(((tert-butyl dimethyl silyl) oxy) methyl)cyclopropyl)methyl)-1H-pyrazol-3-yl)ethan-1-amine **XXXVII** (416 mg, 1.34 mmol) and triethylamine (624 µL, 4.48 mmol) under nitrogen. The resulting mixture was stirred at 130 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature and diluted with water (30 mL) then extracted with ethyl acetate (20 mL X 3). The combined organic layer was washed with 25 mL of brine and passed through anhydrous sodium sulphate then concentrated under reduced pressure. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using 0-5% MeOH in DCM to afford the desired compound **Example 63a** as a light-yellow solid. Yield: 0.15 g (33%). **LC-MS** Calculated. for $C_{26}H_{40}N_8OSi$ is 508.30; Observed. 509.35 $[M+H]^+$.

Step-2: 7-amino-3-ethyl-5-((2-(1-((1-(hydroxymethyl) cyclopropyl) methyl)-1*H*-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-*a*]pyrimidine-6-carbonitrile

[000456] To a stirred solution of 7-amino-5-((2-(1-((1-(((tert-butyldimethylsilyl)oxy)methyl)cyclopropyl)methyl)-1*H*-pyrazol-3-yl)ethyl)amino)-3-ethyl-2-methylpyrazolo[1,5-*a*]pyrimidine-6-carbonitrile **Example 63a** (0.150 g, 0.295 mmol) in THF (5 mL) was added TBAF (154 mg,

1.0 M in THF, 0.590 mmol) and the reaction mixture was stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (50 mL) and extracted with ethyl DCM (30 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under vacuo to afford a desired crude compound. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using 0-6% MeOH in DCM to afford the desired compound **Example 63** as an Off-white solid. Yield: 66 mg (57%). **LC-MS** Calculated for $C_{20}H_{26}N_8O$ is 394.22; Observed: 395.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (bs, 2H), 7.59 (d, J = 2.0 Hz, 1H), 6.67 (t, J = 5.6 Hz, 1H), 6.07 (d, J = 2.0 Hz, 1H), 4.62 (t, J = 5.6 Hz, 1H), 4.02 (s, 2H), 3.57 (q, J = 5.6 Hz, 2H), 3.17 (d, J = 5.6 Hz, 2H), 2.82 (t, J = 7.6 Hz, 2H), 2.56-2.43 (m, 2H), 2.25 (s, 3H), 1.12 (t, J = 7.6 Hz, 3H), 0.54-0.51 (m, 2H), 0.43-0.41 (m, 2H). **HPLC**: Rt = 11.567 min; Purity = 99.39%, INT ODS 3V-C18 (4.6 X 250) mm, 5µ, Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile.

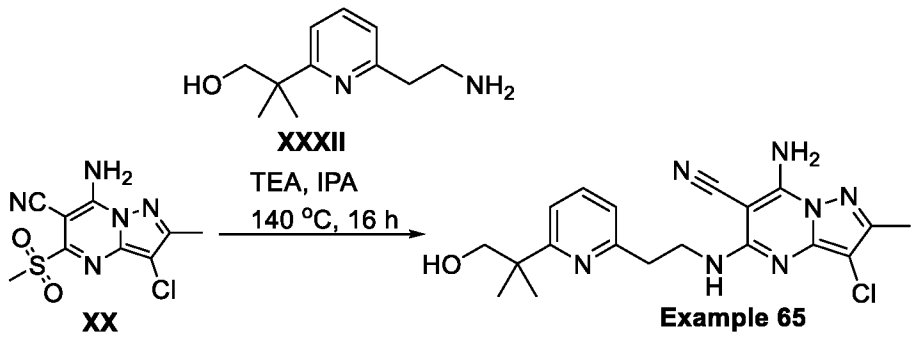
Example 64: 7-amino-3-chloro-5-((2-(6-(1,1-difluoro-2-hydroxyethyl) pyridin-2-yl) ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile



[000457] To a stirred solution of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX** (0.2 g, 0.7 mmol) in 2-propanol was added 2-(6-(2-Aminoethyl)pyridin-2-yl)-2,2-difluoroethan-1-ol **XXXVIII** (0.3 g, 1 mmol) and triethylamine (0.8 g, 7 mmol) under N_2 and the reaction mixture was stirred at 140 °C for 16 h. The progress of reaction was monitored by TLC analysis. After completion, reaction mixture was cooled to room

temperature, diluted with water (25mL) and extracted with ethyl acetate (20 mL × 3). The combined organic phase was dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain crude product. The obtained crude material was purified by reverse phase preparative HPLC (Column: Phenomenex, Kinetic C18 (250× 20) mm, 5µm. A:10mm Ammonium bicarbonate in water. B: Acetonitrile) to obtain the pure desired off-white solid material. Yield: 0.05 g (8.0%). **LC-MS** Calculated. for $C_{17}H_{16}ClF_2N_7O$ is 407.10; Observed. 408.15 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.41 (bs, 2H), 7.89 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.07 (t, J = 5.6 Hz, 1H), 5.49 (t, J = 6.4 Hz, 1H), 4.00 (td, J = 14.4, 6.8 Hz, 2H), 3.73 (q, J = 6.8 Hz, 2H), 3.10 (t, J = 6.8 Hz, 2H), 2.28 (s, 3H). **HPLC**: 97.65%,

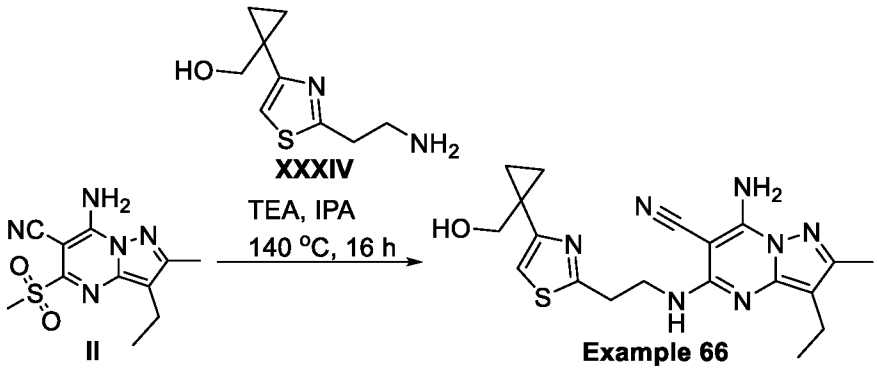
Example 65: 7-amino-3-chloro-5-((2-(6-(1-hydroxy-2-methylpropan-2-yl)pyridin-2-yl)ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile



[000458] To a stirred solution of 2-(6-(2-aminoethyl) pyridin-2-yl)-2-methylpropan-1-ol **XXXII** (0.4 g, 2 mmol) in 2-propanol (20 mL) were added 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **XX** (0.3 g, 1 mmol) and triethylamine (0.4 mL, 3 mmol) under nitrogen. The resulting mixture was stirred at 120 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature and diluted with water (30 mL) then extracted with ethyl acetate (25 mL X 2). The combined organic layer was washed with 25 mL of brine and passed through anhydrous sodium sulphate then concentrated under reduced pressure. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using 0-35% ethyl acetate in *n*-hexane

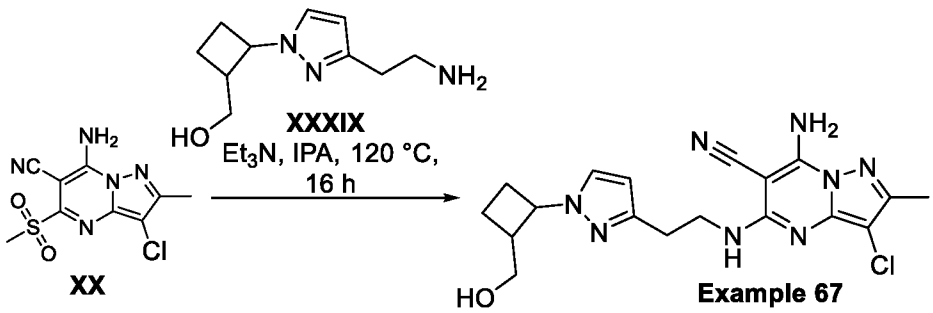
to afford the desired title compound **Example 65** as off-white solid. Yield: 127 mg (30%). **LC-MS:** calculated. for $C_{19}H_{22}ClN_7O$ is 399.15; Observed. 400.20 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.39 (bs, 2H), 7.63 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.10 (d , J = 8.0 Hz, 1H), 6.97 (t, J = 5.2 Hz, 1H), 4.64 (t, J = 5.2 Hz, 1H), 3.73 (q , J = 6.0 Hz, 2H), 3.55 (d, J = 5.6 Hz, 2H), 3.03 (t, J = 6.4 Hz, 2H), 2.28 (s, 3H), 1.24 (s, 6H). **HPLC** Purity = 97.50%,

Example 66: 7-amino-3-ethyl-5-((2-(4-(1-(hydroxymethyl) cyclopropyl)thiazol-2-yl)ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile)



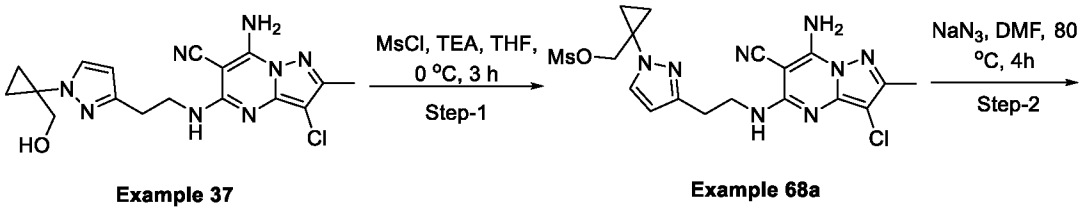
[000459] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.15 g, 0.54 mmol) in isopropanol (5 mL) were added (1-(2-(2-aminoethyl) thiazol-4-yl) cyclopropyl) methanol **XXXIV** (0.32 g, 1.6 mmol) and TEA (0.37 mL, 2.7 mmol) in sealed tube. The reaction mixture was stirred at 120 °C for 48 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated under reduced pressure and crude was purified by flash silica gel (230-400) column chromatography using 0-35 % ethyl acetate in *n*-hexane to afford the title compound **Example 66** as a yellow sticky solid. Yield: 7.2 mg (3%). **LC-MS** Calculated. for $C_{19}H_{23}N_7OS$ is 397.16; Observed. 398.20 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.13 (bs, 2H), 7.15 (s, 1H), 6.79 (bs, 1H), 4.68 (bs, 1H) 3.66-3.64 (m, 4H), 3.20 (t, J = 7.2 Hz, 2H), 2.45-2.43 (m, 2H), 2.25 (s, 3H), 1.12 (t, J = 7.6 Hz, 4H), 0.99-0.97 (m, 3H). **HPLC:** 12.104 min; 98.45%, INT ODS 3V-C18 (4.6*250) mm, 5µ, Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 67: Synthesis of 7-amino-3-chloro-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

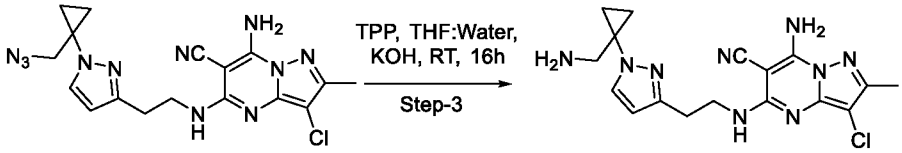


[000460] To a stirred solution of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX** (2.2 g, 7.7 mmol) and (2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclobutyl) methanol **XXXIX** (1.5 g, 7.7 mmol) in 2-propanol (50 mL) was added triethylamine (6.4 mL, 46 mmol). The resulting mixture was heated at 120 °C for 16 h in seal tube. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt and concentrated in vacuum. The residue was dissolved in water (20 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over sodium sulphate, filtered, and concentrated under reduced pressure. The crude was purified by Biotage flash silica gel (230-400) column chromatography using 0-50% ethyl acetate in *n*-hexane to afford the desired title compound **Example 67** as an off-white solid. Yield: 2.3 g, (74 %); **LC_MS** Calculated. for $C_{18}H_{21}ClN_8O$ is 400.15; Observed. 401.30 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.40 (bs, 2H), 7.66 (d, J = 1.6 Hz, 1H), 7.00 (t, J = 4.8 Hz, 1H), 6.08 (d, J = 2.0 Hz, 1H), 4.60 (t, J = 5.2 Hz, 1H), 4.52-4.50 (m, 1H), 3.63-3.58 (m, 2H), 3.41-3.39 (m, 2H), 2.85-2.78 (m, 3H), 2.34-2.20 (m, 5H), 1.80-1.78 (m, 1H), 1.60-1.55 (m, 1H). **HPLC**: 10.082 min; 99.13%, Column: INT ODS 3V-C18 (4.6*250) mm,5µ Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile, Flow: 1.0 mL/min.

Example 68: 7-amino-5-((2-(1-(1-(amino methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Example 37 Example 68a



Example 68b Example 68

Step-1: Synthesis of (1-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) methyl methane sulfonate. (Example 68a)

[000461] To a solution of 7-amino-3-chloro-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 37** (2.69 g, 6.95 mmol) in THF (20 mL) at 0 °C was added triethylamine (4.85 mL, 34.8 mmol) and methane sulfonyl chloride (0.6mL, 7.65 mmol). The reaction mixture was stirred at 0 °C 3 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was warmed to rt and diluted with $NaHCO_3$ solution (100 mL). The mixture was extracted with DCM (100 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography using ethyl acetate in hexane (0-100%) to afford the desired compound **Example 68a**as a light-yellow liquid. Yield: 1.8 g, (56.0 %); **LC_MS** Calculated. for $C_{18}H_{21}ClN_8O_3S$ is 464.11; Observed: 465.25 $[M+H]^+$.

Step-2: Synthesis of 7-amino-5-((2-(1-(1-(azidomethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 68b)

[000462] To a solution of (1-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl)

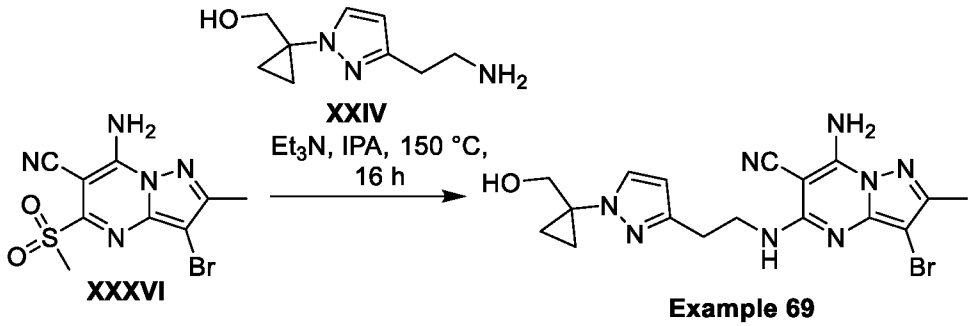
cyclopropyl) methyl methane sulfonate **Example 68a** (1.8 g, 3.9 mmol) in N, N-dimethyl formamide (10 mL) was added sodium azide (1.0 g, 15 mmol) and heated at 80 °C for 4 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, reaction mixture was cooled to rt, diluted with water (30 mL), and extracted with ethyl acetate (50 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography eluted with ethyl acetate in n-hexane (0-30%) to afford the desired product **Example 68b** as a light-yellow solid. Yield: 1.24 g, (77.0 %); **LCMS** Calculated. for $C_{17}H_{18}ClN_{11}$ is 411.14; Observed: 412.3 $[M+H]^+$ **^{1}HNMR (400 MHz, $CDCl_3$,):** δ 7.47 (d, *J* = 2 Hz, 1H), 6.11-6.06 (m, 4H), 3.88-3.84 (m, 2H), 3.60 (s, 2H), 2.95 (t, *J* = 6 Hz, 2H), 2.35 (s, 3H), 1.36 (t, *J* = 6.4 Hz, 2H), 1.10 (t, *J* = 7.2 Hz, 2H).

Step-3: 7-amino-5-((2-(1-(1-(amino methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000463] To a solution of 7-amino-5-((2-(1-(1-(azidomethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 68b**(0.3 g, 0.7 mmol) in THF (10 mL) and water (3 mL) was added triphenylphosphine (0.3 g, 1 mmol). The reaction mixture was stirred at for 10 min. This was followed by an addition of potassium hydroxide (0.04 g, 0.7 mmol) and stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, diluted with water (20 ml) and extracted with ethyl acetate (20 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel (60-120 mesh) column chromatography eluted with methanol in dichloromethane (0-10%) to afford the desired title product **Example 68** as an off-white solid. Yield: 0.25 g, (83.0 %); **LCMS** Calculated. for $C_{17}H_{20}ClN_9$ is 385.15; Observed: 386.3 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D_6):** δ 7.69 (d, *J* = 2 Hz, 2H), 6.95-6.93 (m, 4H), 6.14 (d, *J* = 2 Hz, 1H), 3.88-3.84 (m, 2H), 3.60 (s, 2H), 2.95 (t, *J* = 6 Hz, 2H), 2.35 (s, 3H), 1.19-1.14 (m, 4H).

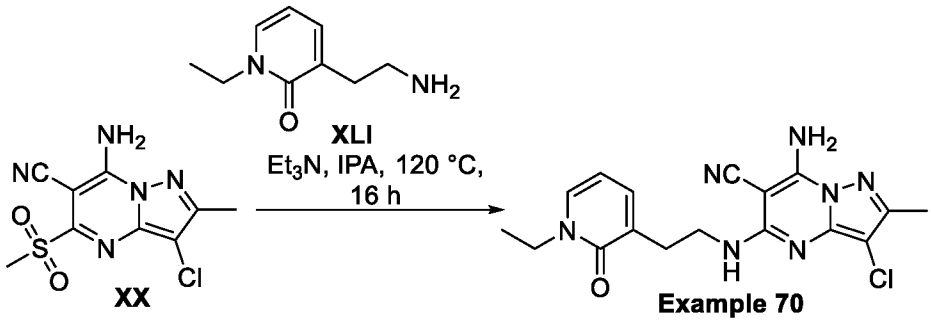
HPLC: 7.963 min; 99.08 %, INT ODS 3V-C18 (4.6*250) mm, 5µ, Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile

Example 69: 7-amino-3-bromo-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



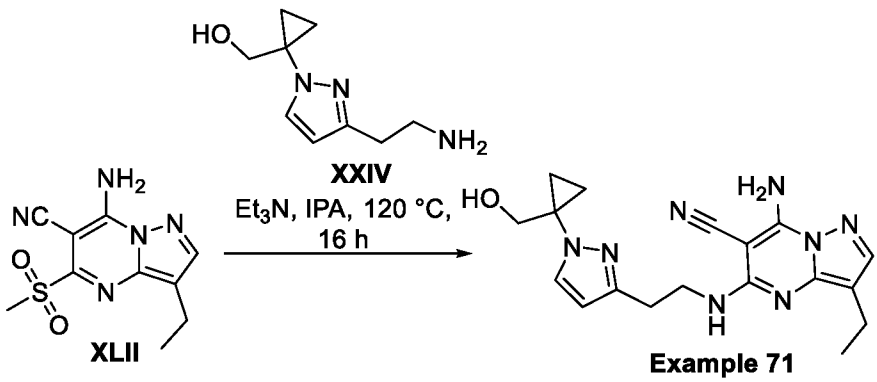
[000464] To a solution of 7-amino-3-bromo-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXXVI** (0.3 g, 0.91mmol) in isopropyl alcohol (15 mL) were added (1-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclopropyl) methanol (0.33 g, 1.82 mmol) and triethylamine (0.76 mL, 5.45 mmol) and stirred at 150 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, added water (50 mL) and extracted with ethyl acetate (2 X 25 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford the crude compound as a brown semi-solid. The crude compound was purified by silica gel (230-400 mesh) column chromatography with methanol in dichloromethane (0-5%) to afford the desired compound **Example 69** as a brown solid. Yield: 0.1 g, (25.5 %); **LC_MS** Calculated. for $C_{17}H_{19}BrN_8O$ is 430.08; Observed.: 431.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.39 (bs, 2H), 7.62 (d, J = 2.4 Hz, 1H), 6.95 (t, J = 5.2 Hz, 1H), 6.06 (d, J = 2.64 Hz, 1H), 4.88 (t, J = 5.6 Hz, 1H), 3.63-3.58 (m, 4H), 2.82 (t, J = 8 Hz, 2H), 2.29 (d, J = 21 Hz, 3H), 1.07-0.94 (m, 4H); **HPLC Purity** : 10.993 min; 96.42 %, INT ODS 3V-C18 (4.6*250)mm, 5µ; Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile; Flow rate: 1.0 mL/min

Example 70: 7-amino-3-chloro-5-((2-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000465] To a solution of 3-(2-aminoethyl)-1-ethylpyridin-2(1H)-one **XLI** (0.2 g, 0.7 mmol) in isopropyl alcohol (5 mL) were added 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX** (0.12g, 0.7mmol) and triethylamine (0.5 mL, 3.50 mmol). The reaction mixture was stirred at 160 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, solids were filtered, washed with ethyl acetate (50 mL) and triturated with acetonitrile to afford the desired product as an off-white solid. Yield:0.15 g, (58.0 %); **LC_MS** Calculated. for $C_{17}H_{18}ClN_7O$ is 371.13; Observed. 372.20 [M+H] +. **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.35 (s, 2H), 7.58-7.57 (m, 1H), 7.29 (d, *J*=4.4 Hz, 1H), 7.08 (t, *J*=5.2 Hz, 1H), 6.17 (t, *J*=4 Hz, 1H), 3.95-3.89 (m, 2H), 3.56-3.51 (m, 2H), 2.74 (t, *J*=6.4 Hz, 2H), 2.27 (s, 3H), 1.22(t, *J*=8 Hz, 3H); **HPLC**: 95.69 %.

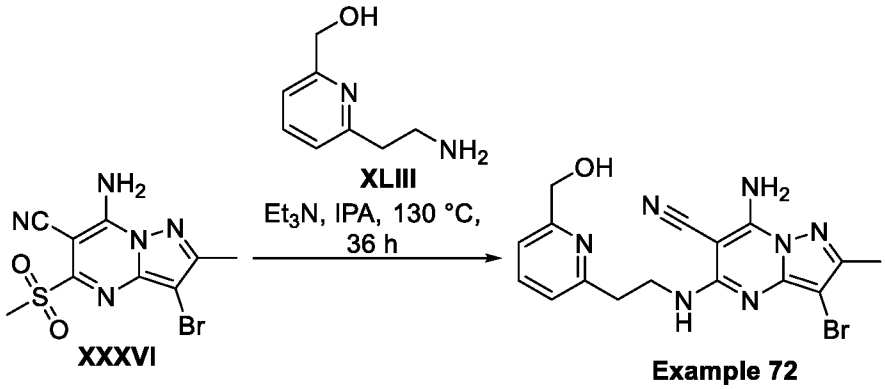
Example 71: 7-amino-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000466] To a solution of **7**-amino-3-ethyl-5-(methyl sulfonyl) pyrazolo[1,5-a]pyrimidine-6-carbonitrile **XLII** (0.12 g, 0.452 mmol) in isopropyl alcohol (15 mL) were added (1-(3-(2-aminoethyl)-1H-pyrazol-1-yl)cyclopropyl)methanol

XXIV (0.18 g, 0.993 mmol) and triethylamine (0.378 mL, 2.71 mmol) and the reaction mixture was stirred at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, concentrated and added water (10 mL), extracted with ethyl acetate (20 mL X 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulphate, and concentrated to get the crude material. The crude compound was purified by silica gel (60-120 mesh) column chromatography with ethyl acetate in *n*-hexane (0-60%) to afford the desired compound **Example 71** as an off-white solid. Yield: 48.3 mg, (29.2 %); **LC_MS** Calculated. for $C_{18}H_{22}N_8O$ is 366.19; Observed. 367.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.23 (s, 2H), 7.82 (s, 1H), 7.62 (s, 1H), 6.66 (s, 1H), 6.04 (s, 1H), 4.87 (t, *J* =5.6 Hz, 1H), 3.59 (t, *J* =5.6 Hz, 3H), 2.82 (t, *J* =7.2 Hz, 2H), 1.20-1.17 (m, 2H), 1.08 (d, *J* =6.4 Hz, 2H), 0.97-0.94 (m, 2H). **HPLC**: 98.98 %,

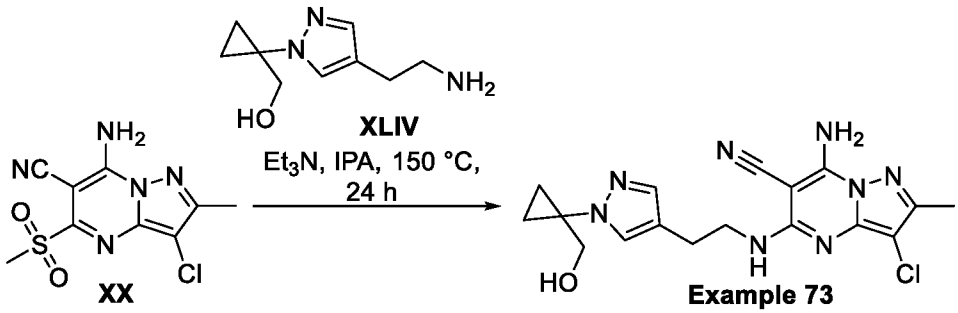
Example 72: 7-amino-3-bromo-5-((2-(6-(hydroxymethyl) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000467] To a solution of 7-amino-3-bromo-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXXVI** (0.3 g, 0.9 mmol) and (6-(2-aminoethyl) pyridin-2-yl) methanol **XLIII** (0.2 g, 1 mmol) in isopropyl alcohol (10 mL) was added triethylamine (0.6 mL, 5 mmol) and the reaction mixture was stirred at 130 °C for 36 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was cooled to rt, diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated

under reduced pressure. The crude compound purified by silica gel (230-400 mesh) column chromatography using ethyl acetate in *n*-hexane (0-50%) to afford the desired compound **Example 72** as an off-white solid. Yield: 21.6 mg, (5.0 %); **LCMS** Calculated. for $C_{16}H_{16}BrN_7O$ is 401.06; Observed. 402.1 $[M+H]^+$.**^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.39 (s, 2H), 7.73 (t, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz,, 1H), 7.21-7.17 (m, 2H), 5.36 (t, *J* = 4.0 Hz, 1H), 4.58 (d, *J* = 4.0 Hz, 2H), 3.69 (d, *J* = 4.0 Hz, 2H), 3.02 (t, *J* = 6.4 Hz, 2H), 2.27 (s, 3H). **HPLC**: 95.94 %.

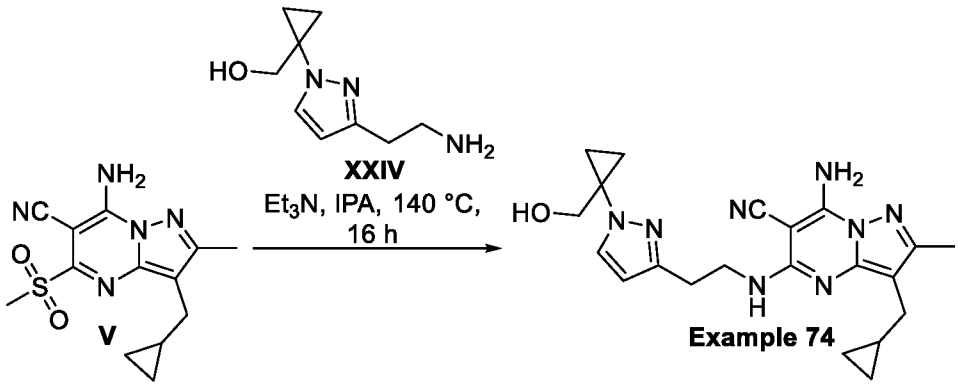
Example 73: 7-amino-3-chloro-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-4-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000468] To a solution of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX** (0.2 g, 0.7 mmol) in isopropanol (5 mL) was added (1-(4-(2-aminoethyl)-1H-pyrazol-1-yl)cyclopropyl)methanol **XLIV** (0.4 g, 2 mmol). The mixture was purged with N_2 gas for 5 min and triethylamine (0.5 mL, 4 mmol) was added. The reaction mixture in seal tube was heated at 150 °C for 24 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to room temperature and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in water (20 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic layer was given brine wash, dried over anhydrous sodium sulphate, and concentrated under vacuum to afford a light brown viscous liquid. The crude compound was purified by combi-flash silica gel (230-400) column chromatography using 10-60% ethyl acetate in *n*-hexane to afford the desired compound **Example 73** as an off-white solid. Yield: 33 mg (11%). **LC_MS** Calc. for $C_{17}H_{19}ClN_8O$ is 386.13; Obs. 387.20 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$,):** 8.38 (bs, 2H), 7.57 (s, 1H), 7.29 (s, 1H), 7.01 (bs, 1H), 4.89 (bs, 1H), 3.59 (d,

J=5.6 Hz, 2H), 3.51 – 3.45 (m, 2H), 2.69 (bs, 2H), 2.28 (s, 3H), 1.04 (bs, 2H), 0.97 (bs, 2H). **HPLC**: 99.30 %, 8.430 min; XBridge C18 (4.6*150) mm, 5µ, Mobile Phase A: 10mM ammonium bicarbonate in water, Mobile Phase B: Acetonitrile.

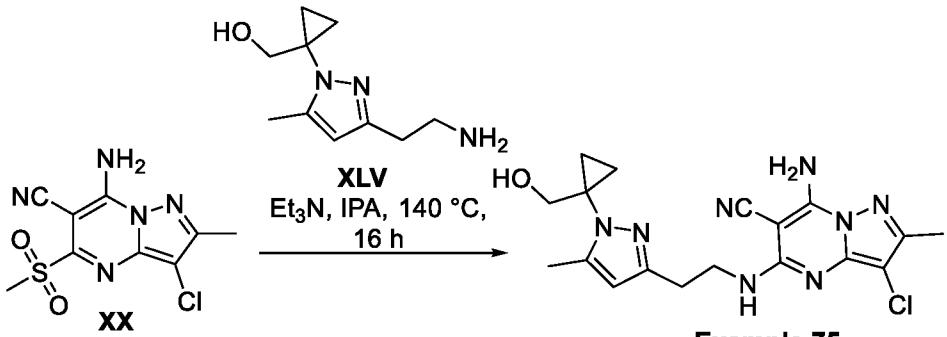
Example 74: 7-amino-3-(cyclopropyl methyl)-5-((2-(1-(1-(hydroxymethyl) cyclopropyl) -1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000469] To a solution of 7-amino-3-(cyclopropyl methyl)-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **V** (0.2 g, 0.7 mmol) and (1-(3-(2-aminoethyl)-1H-pyrazol-1-yl)cyclopropyl)methanol **XXIV** (0.2 g, 1 mmol) in isopropyl alcohol (10 mL) was added triethylamine (0.5 mL, 4 mmol) and the reaction mixture was stirred at 140 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was concentrated, added water (20 mL) and extracted with ethyl acetate (25 mL × 3). The combined organic layer was washed with brine (25 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to get the crude material. The crude compound was purified by reverse phase preparative HPLC method by using Column: Inertsil (20×250mm), 5mic. Channel A: 0.1% Formic acid in H_2O. Channel B: Acetonitrile: Methanol: 1:1 to afford the desired compound **Example 74** as an off-white solid. Yield:0.063 g, (20.0 %); **LC_MS** Calculated. for $C_{21}H_{26}N_8O$ is 406.22; Observed: 407.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (s, 2H), 7.62 (s, 1H), 6.63 (bs, 1H), 6.03 (s, 1H), 4.88 (t, *J*= 5.6 Hz, 1H), 3.6-3.53 (m, 4H), 2.81 (t, *J*= 7.2 Hz, 2H), 2.39 (d, *J*= 6.4 Hz, 2H), 2.27 (s, 3H), 1.08 (s, 2H), 0.96 (s,3H), 0.35 (d, *J*= 7.6 Hz, 2H), 0.17 (d, *J*= 4.4 Hz, 2H). **HPLC**: 98.50 %, 11.831 min; Column: INT ODS 3V-C18 (4.6*250)

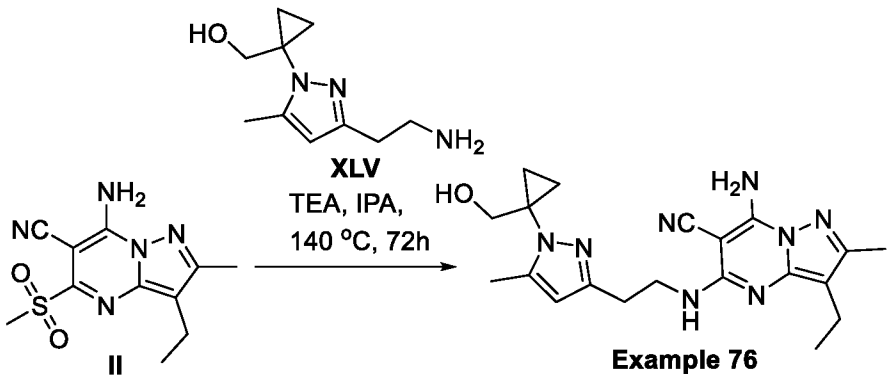
mm, 5µ; Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile; Flow: 1.0 mL/min

Example 75: 7-amino-3-chloro-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000470] A seal tube was charged with 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX** (160 mg, 0.560 mmol), (1-(3-(2-aminoethyl)-5-methyl-1H-pyrazol-1-yl) cyclopropyl) methanol **XLV** (186 mg, 0.952 mmol) and 2-propanol (25 mL). The resulting mixture was purged with N_2 gas for 5 min and triethyl amine (0.47 mL, 3.36 mmol) was added. The reaction mixture was stirred at 140 °C for 16 h. The progress of reaction was monitored by TLC analysis. After completion, water (20 mL) was added, and the resulting mixture was extracted with ethyl acetate (20 mL X 3). The combined organic layer was given brine wash, dried over anhydrous sodium sulphate, and concentrated to get crude material. The crude was purified by Combi-flash silica gel (230-400 mesh) column chromatography using 10-60% ethyl acetate in *n*-hexane to afford the desired compound **Example 75** as an off-white solid. Yield: (30 mg, 13.39 %); **LC-MS** Calculated. for $C_{18}H_{21}ClN_8O$ is 400.15; Observed: 401.20 $[M+H]^+$.**^{1}H NMR (400 MHz, DMSO-d$_6$,):** δ 8.39 (s, 2H), 6.91 (bs, 1H), 5.84 (s, 1H), 4.90 (bs, 1H), 3.58-3.53 (m, 4H), 2.74 (t, J = 7.2 Hz, 2H), 2.30-2.26 (m, 6H), 1.03 (d, J = 9.2 Hz, 4H); **HPLC**: 10.892 min; 97.34 %, INT ODS 3V-C18 (4.6*250)mm, 5µ, Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile: Flow : 1.0 mL/min

Example 76: 7-amino-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.

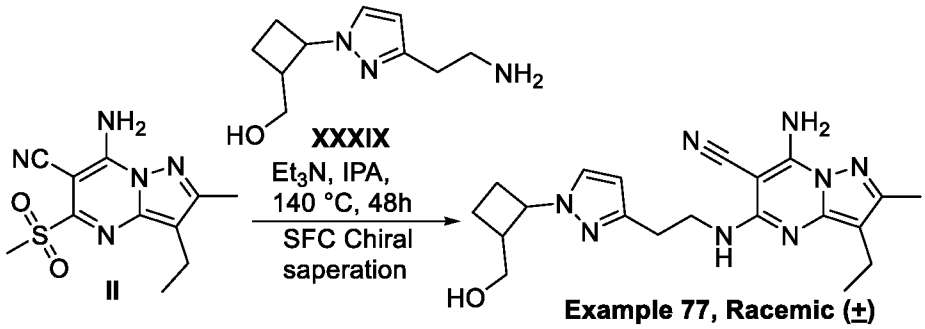


[000471] A seal tube was charged with 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (170 mg, 0.609 mmol), (1-(3-(2-aminoethyl)-5-methyl-1H-pyrazol-1-yl) cyclopropyl) methanol **XLV** (185 mg, 0.947 mmol) and 2-propanol (20 mL). The resulting mixture was purged with N_2 gas with vigorous stirring and triethyl amine (0.51 mL, 3.65 mmol) was added. The reaction mixture was stirred at 140 °C for 3 days and progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to rt, and water (20 mL) was added. The mixture was extracted with ethyl acetate (15 mL X 3). The combined organic layer was given brine wash and dried over anhydrous sodium sulphate. The crude material obtained upon removal of the solvent under *vacuo* was subjected to flash chromatography using Biotage system and 0-4% methanol in DCM as elluent to afford the desired compound **Example 76** as an off-white solid. Yield: (70 mg, 29%); **LC-MS** Calculated for $C_{20}H_{26}N_8O$ is 394.22; Observed: 395.25 [M^++1].**^{1}HNMR (400 MHz, DMSO-d_6,):** δ 8.09 (bs, 2H), 6.56 (bs, 1H), 5.82 (s, 1H), 4.89 (t, *J* = 5.6 Hz, 1H), 3.54-3.51 (m, 4H), 2.73 (d, *J*= 6.4, 2H), 2.33-2.25 (m, 6H), 1.13-1.02 (m, 7H). **HPLC** purity: 11.193 min; 98.87 %, INT ODS 3V-C18 (4.6*250) mm, 5µ, Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile.

Example 77: Racemic (+-) -7-amino-3-ethyl-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

Example 78. (+)- 7-amino-3-ethyl-5-((2-(1-(2-(hydroxymethyl)cyclobutyl)-1H-pyrazol-3-yl)ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.

Example 79 (-) - 7-amino -3-ethyl-5-((2-(1-(2-(hydroxymethyl)cyclobutyl)-1H-pyrazol-3-yl)ethyl) amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.



Peak-1; Example 78; dextro(+) rotatory
Peak-1; Example 79; leavo(-) rotatory

[000472] A stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (20.0 g, 71.6 mmol) and (2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclobutyl) methanol **XXXIX** (28.0 g, 143 mmol) in 2-propanol (50 mL), was added triethylamine (60.0 mL, 430 mmol). The resulting reaction mixture was heated in seal tube at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt and diluted with water (200 mL) and extracted with ethyl acetate (200 mL x 3). The combined organic layer was washed with saturated brine solution (200 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude compound was purified by combi-flash column chromatography (silica 230-400) by eluting with 0-50% ethyl acetate in *n*-hexane to afford the desired compound **Example 77** as off-white solid. **Yield:** 13.9 g, (49%). **LC-MS** Calculated. for $C_{20}H_{26}N_8O$ is 394.22; Observed. 395.35 $[M+H]^+$. **^{1}HNMR (400 MHz, DMSO-D$_6$,):** δ 8.11 (bs, 2H), 7.65 (m, 1H), 6.66 (bs, 1H), 6.07 (m, 1H), 4.60 (t, J =5.2 Hz, 1H), 4.54-4.47 (m, 1H), 3.58-3.57 (m, 2H), 3.42-3.39 (m, 2H), 2.84-2.81(m, 3H), 2.47-2.41 (m, 2H), 2.34-2.18 (m, 5H), 1.83-1.76 (m, 1), 1.61-1.56 (m, 1H), 1.12 (t, J =7.6 Hz, 3H). **HPLC**: 11.728 min; 96.66 %, Column:

Column: INT ODS 3V-C18 (4.6*250) mm,5µ Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile Flow: 1.0 mL/min.

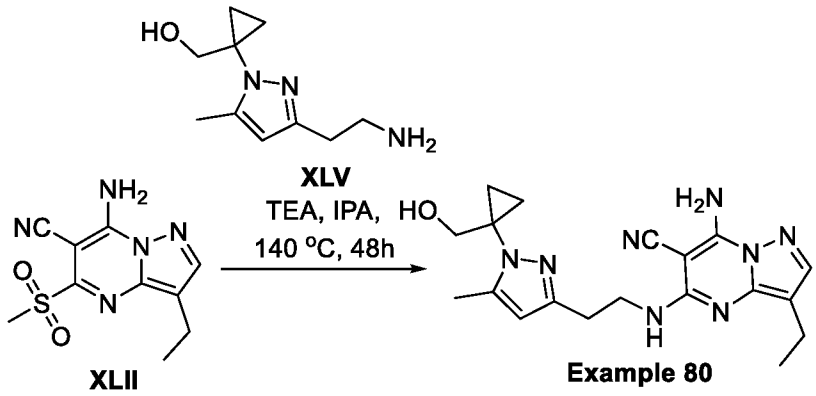
[000473] The above racemic compound was subjected to chiral separation by SFC {The sample was dissolved in ~165 mL of Tetrahydrofuran: Methanol (1:1)}, Column Chiral Pak IG (250 * 21) mm, 5.0 µm; Mobile phase 75:25 (A: B). A=Liquid CO_2, B= 0.1% Isopropyl amine in Isopropyl alcohol: Acetonitrile (1:1), Flow rate: 25mL/min; Wavelength 254 nm to yield 6.2 g of peak 1, Example 78, $[\alpha]_{D=}$ +43.15 °, c=0.103, MeOH) and 3.9 g of peak 2, Example 79, $[\alpha]_{D=}$ -33.63 °, c=0.101, MeOH) as off-white solids, respectively.

Peak-1; Example 78: (+)- 7-amino-3-ethyl-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile, LCMS: Calculated. for $C_{20}H_{26}N_8O$ is 394.22; Observed.: 395.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.10 (bs, 2H), 7.65-7.64 (m, 1H), 6.66-6.63 (m, 1H), 6.06 (m, 1H), 4.59 (m, 1H), 4.53-4.47 (m, 1H), 3.60-3.55 (m, 2H), 3.40 (m, 2H), 2.84-2.81(m, 3H), 2.46-2.43 (m, 2H), 2.34-2.18 (m, 5H), 1.82-1.75 (m, 1H), 1.63-1.56 (m, 1H), 1.12 (t, *J* =7.6 Hz, 3H). **HPLC**: 11.711 min; 99.76 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile; Flow: 1.0 mL/min. **Chiral HPLC;** Column Name: Chiral Pak IG (4.6 * 250mm), 5 µm; Co-Solvent Name: IPA: MeCN (1:1) + 0.1% TEA; Total flow rate: 3g /mL; % of Co-Solvent: 30; Temperature: 25 °C, Back Pressure: 1500 psi.

Peak-2; Example 79 ; (-)- 7-amino-3-ethyl-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile, LC-MS Calculated: for $C_{20}H_{26}N_8O$ is 394.22; Observed: 395.35 $[M+1]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.10 (bs, 2H), 7.64 (m, 1H), 6.65-6.64 (bs, 1H), 6.06 (m, 1H), 4.60-4.58 (m, 1H), 4.53-4.47 (m, 1H), 3.60-3.55 (m, 2H), 3.41-3.37 (m, 2H), 2.84-2.79(m, 3H), 2.47-2.43 (m, 2H), 2.34-2.18 (m, 5H), 1.80-1.76 (m, 1), 1.60-1.56 (m, 1H), 1.12 (t, *J* =7.6 Hz, 3H). **HPLC**: 11.721 min; 98.87 %, Column: Column: INT ODS 3V-C18 (4.6*250) mm,5µ Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile Flow: 1.0 mL/min; **Chiral HPLC;** Method information: Column Name: chiral Pak IG (4.6*250mm), 5µm; Co-Solvent Name:

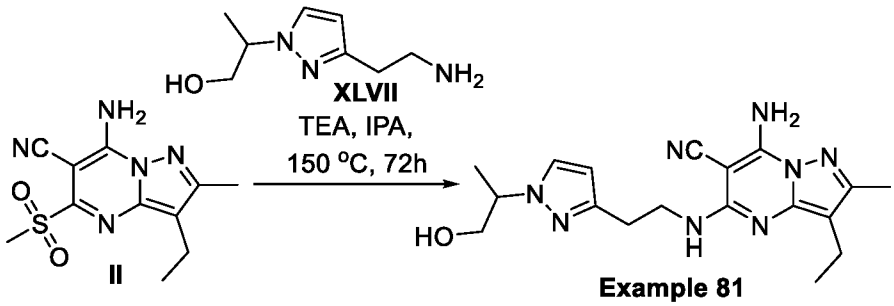
IPA: MeCN (1:1)+ 0.1% TEA; Total flow rate : 3g/mL % of Co-Solvent : 30% Temperature :25°C, ABPR Pressure :1500psi.

Example 80: 7-amino-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000474] To a stirred solution of 7-amino-3-ethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XLII** (150 mg, 0.565 mmol) and (1-(3-(2-aminoethyl)-5-methyl-1H-pyrazol-1-yl) cyclopropyl) methanol **XLV** (221 mg, 1.13 mmol) in 2-propanol (5 mL) was added triethylamine (0.474 mL, 3.39 mmol). The resulting mixture was purged with N_2 gas, and heated at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (100 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure**.** The crude was purified by combi flash silica gel (230-400 mesh) column chromatography using 0-3% MeOH in DCM to afford the desired compound **Example 80** as off-white solid. Yield: (38 mg, 17.67 %); **LCMS** Calculated. for $C_{19}H_{24}N_8O$ is 380.21; Observed: 381.35 $[M^+ +1]$.**^{1}HNMR (400 MHz, DMSO-d$_6$,):** δ 8.23 (bs, 2H), 7.82 (s, 1H), 6.64 (t, *J* = 5.2 Hz, 1H), 5.82 (s, 1H), 4.90 (t, *J* = 6.0 Hz, 1H), 3.58-3.51 (m, 4H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.30 (s, 3H), 1.19 (t, *J* = 7.6 Hz, 3H), 1.03 (d, *J* = 8.8 Hz, 4H). **HPLC**: 8.84 min; 98.79 %, INT ODS 3V-C18 (4.6*250) mm, 5µ, Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile

Example 81: 7-amino-3-ethyl-5-((2-(1-(1-hydroxypropan-2-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

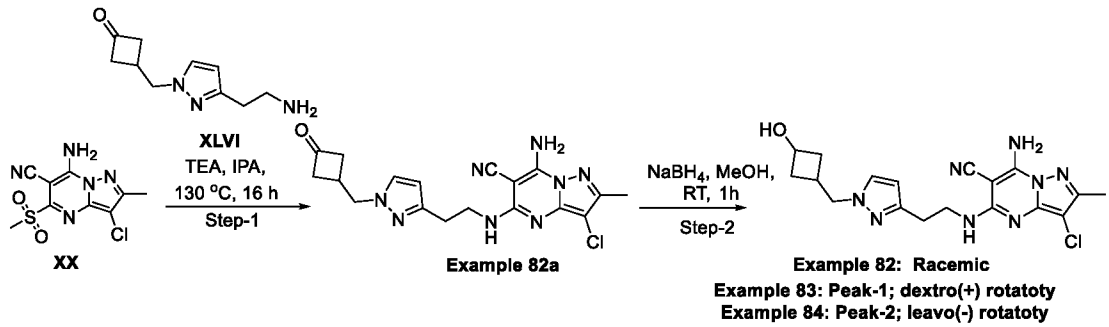


[000475] In a seal tube 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (120 mg, 430 µmol) and 2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) propan-1-ol **XLVII** (109 mg, 644 µmol) were dissolved in isopropanol (15 mL) under inert atmosphere. To the reaction was added TEA (0.36 mL, 2.58 mmol) was added and the reaction mixture was stirred at 150 °C for 72 h. The progress of reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt and concentrated under reduced pressure. The crude material subjected to silica gel (230-400) flash column chromatography (Biotage) using 0-3 % methanol in DCM to afford the desired compound **Example 81** as off-white solid. Yield: 30 mg (18.9%). **LC-MS** Calculated. for $C_{18}H_{24}N_8O$ is 368.20; Observed.: 369.40 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.10 (bs, 2H), 7.60 (bs, 1H), 6.65 (bs, 1H), 6.05 (d, J = 1.6 Hz, 1H), 4.84 (t, J = 5.2 Hz, 1H), 4.26 (q, J = 6.0 Hz, 1H), 3.67-3.55 (m, 4H), 2.82 (t, J = 7.2 Hz, 2H), 2.47-2.45 (m, 2H), 2.25 (s, 3H), 1.36 (d, J = 7.2 Hz, 3H) 1.12 (t, J = 7.6 Hz, 3H). **HPLC**: 11.091 min; 97.12%, INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile; Racemic compound: **Chiral HPLC**: Peak-1: 18.077 min; 50.27 %, Peak-2: 20.226 min; 49.73%; Column: Chiral Pak IA (250 * 4.6) mm, 5µ; Mobile phase: 0.1%TFA in Hex, B: IPA (90:10) Flow:1.0 mL/min.

Example 82: (+-) - 7-amino-3-chloro-5-((2-(1-((3-hydroxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

Example 83: (+) - 7-amino-3-chloro-5-((2-(1-((3-hydroxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

Example 84: (-) - 7-amino-3-chloro-5-((2-(1-((3-hydroxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Step-1: 7-amino-3-chloro-2-methyl-5-((2-(1-((3-oxocyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 82a)

[000476] To a stirred solution of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX** (0.5 g, 2 mmol) and 3-((3-(2-aminoethyl)-1H-pyrazol-1-yl) methyl) cyclobutan-1-one **XLVI** (0.8 g, 4 mmol) in IPA (10 mL), in sealed tube, was added TEA (1.4 mL, 10 mmol). The reaction was stirred at 130 °C for 16 h and progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt and diluted with water (20 mL). The resulting mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was subjected to silica gel (230-400) combi-flash column chromatography using 0-3% methanol in DCM to afford the desired compound **Example 82a** as a pale-yellow solid. Yield: 0.3g crude (43%).

Step-2: 7-amino-3-chloro-5-((2-(1-((3-hydroxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (82)

[000477] To a stirred solution of 7-amino-3-chloro-2-methyl-5-((2-(1-((3-oxocyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a]

pyrimidine-6-carbonitrile **Example 82a** (0.3 g, 0.8 mmol) in methanol (5 mL) was added sodium borohydride (0.01 g, 0.4 mmol) in portions at 0 °C. The resulting reaction mixture was stirred at rt for 1 h. The reaction was monitored by TLC analysis. After completion, the reaction mixture concentrated under *vacuo* and the residue was dissolved in water (15 mL). The mixture was extracted with DCM (10 mL x 3). Combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by combi-flash column chromatography (230-400) using 0-10% methanol in DCM to afford the racemic compound **Example 82** as off-white solid. Yield: 21 mg, (29 %).

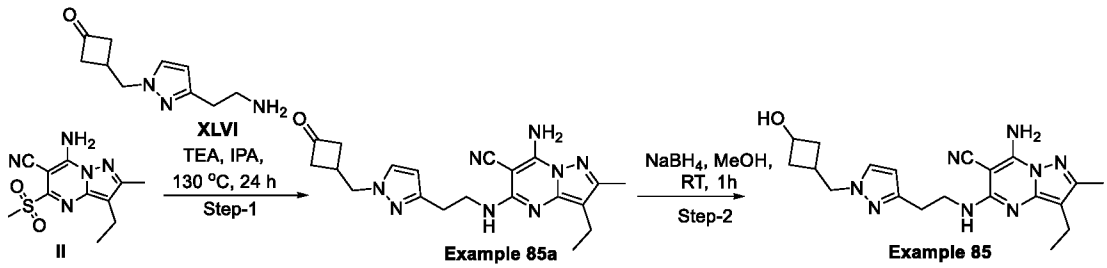
[000478] The above racemic compound was subjected to chiral separation by chiral HPLC separation (Chiral Pak IC (250*21) mm, 5µ Mobile phase A: 0.1%DEA In Hex, B: EtOH (90:10) Flow :1.0 mL/min) to yield 6.2 g of peak 1 $[\alpha]_D$ = +43.15 °, c=0.103, MeOH) and 3.9 g of peak 2 $[\alpha]_D$ = -33.63 °, c=0.101, MeOH) as off-white solids, respectively.

[000479] **Example 83a: Peak-1** Yield: 51 mg, (40 %); **LCMS** Calculated. for $C_{18}H_{21}ClN_8O$ is 400.87; Observed. 401.30 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.39 (bs, 2H), 7.56 (d, *J*= 2.0 Hz, 1H), 7.01-6.99 (bs, 1H), 6.06 (d, *J*= 2.0 Hz, 1H), 4.98 (d, *J* = 6.4 Hz, 1H), 4.02 (d, *J* = 6.8 Hz, 2H), 3.93-3.88 (m, 1H), 3.62-3.57 (m, 2H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.28 (s, 3H), 2.20-2.10 (m, 3H), 1.58-1.54 (m, 2H). **HPLC**: 10.906 min; 99.15 %, Column: Column: INT ODS 3V-C18 (4.6*250) mm,5µ Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile Flow: 1.0 ml/min. **Chiral HPLC;** 19.597 min; 100 %, Column: Chiral Pak IC (250*4.6) mm, 5µ, Mobile phase: A: 0.1% DEA in Hex, B: EtOH (90:10) Flow :1.0 mL/min.

[000480] **Example 84: Peak-2;** Yield: 16 mg, (20 %); **LC_MS** Calculated. for $C_{18}H_{21}ClN_8O$ is 400.87; Observed.401.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.39 (bs, 2H), 7.62 (d, *J*= 2.0 Hz, 1H), 7.01 (t, *J*= 5.2 Hz, 1H), 6.07 (d, *J*= 1.6 Hz, 1H), 4.97 (d, *J* = 6.0 Hz, 1H), 4.21-4.16 (m, 1H), 4.06 (d, *J*= 7.6 Hz, 2H), 3.62-3.57 (m, 2H), 2.82 (t, *J* = 7.2 Hz, 2H), 2.28 (s, 3H), 2.01-1.99 (m, 2H), 1.91-1.84 (m, 2H). **HPLC**: 10.912 min; 98.65 %, INT ODS 3V-C18 (4.6*250) mm, 5µ Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile; Flow:

1.0 mL/min. **Chiral HPLC;** 22.356 min; 95.90 %; Chiral Pak IC (250*4.6) mm, 5µ; Mobile phase: A: 0.1% DEA In Hex, B: EtOH (90:10) Flow :1.0 mL/min.

Example 85: 7-amino-3-ethyl-5-((2-(1-((3-hydroxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



Step-1: 7-amino-3-ethyl-2-methyl-5-((2-(1-((3-oxocyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 85a)

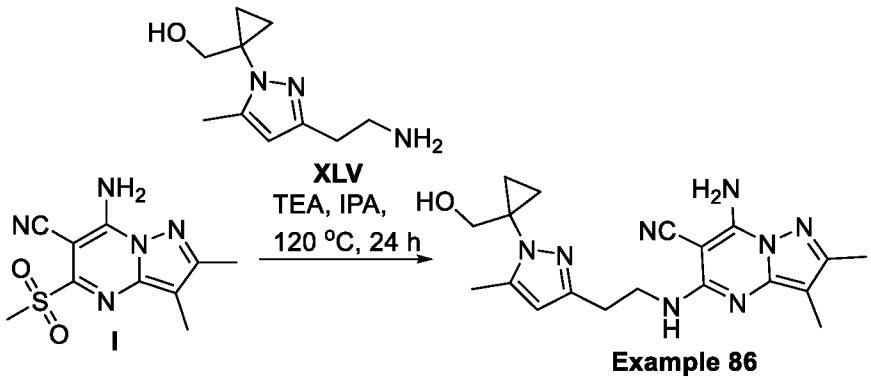
[000481] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.5 g, 2 mmol) and 3-((3-(2-aminoethyl)-1H-pyrazol-1-yl) methyl) cyclobutan-1-one **XLVI** (0.8 g, 4 mmol) in IPA (10 mL), in sealed tube, was added TEA (1.4 mL, 10 mmol). The reaction mixture was stirred at 130 °C for 24 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt and diluted with water (20 mL). The mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by combi-flash column chromatography (230-400) using 0-10% methanol in DCM to afford the desired compound **Example 85a** as an off-white solid. Yield: 273 mg, (39 %); **LC_MS** Calculated. for $C_{20}H_{24}N_8O$ is 392.20; Obs. 393.35 $[M+H]^+$.

[000482] Step-2: 7-amino-3-ethyl-5-((2-(1-((3-hydroxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.

[000483] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-((2-(1-((3-oxocyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl)amino)pyrazolo[1,5-a]pyrimidine-6-carbonitrile **Example 85a** (0.270 g, 0.688 mmol) in methanol (5 mL) was

portion wise added sodium borohydride (13.0 mg, 0.344 mmol) at 0 °C under inert atmosphere. The reaction was stirred at rt for 1 h and progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated under vacuum and the residue was diluted with water (15 mL). The mixture was extracted with DCM (10 mL x 3) and the combined organic layer was dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure. The crude compound was purified by combi-flash column chromatography (230-400) using 0-10% methanol in DCM to afford the desired title compound **Example 85** as off-white solid. Yield: 23 mg, (19 %).. **LC_MS** Calculated. for $C_{20}H_{26}N_8O$ is 394.22; Observed. 395.40 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.10 (bs, 2H), 7.61-7.55 (m 1H), 6.66-6.62 (m, 1H), 6.05 (s, 1H), 4.98 (t, J = 6.4 Hz, 1H), 4.07-4.00 (m, 2H), 3.91-3.88 (m, 1H), 3.59-3.54 (m, 2H), 2.81 (t, J = 7.2 Hz, 2H), 2.46-2.43 (m, 2H), 2.24 (s, 3H), 2.20-2.10 (m, 3H), 1.92-1.88 (m, 1H), 1.58-1.54 (m, 1H), 1.12 (t, J = 7.2 Hz, 3H). **HPLC**: 11.054 min; 96.42 %; INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

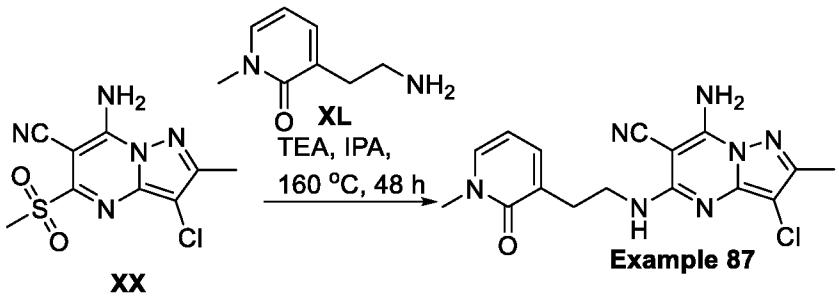
[000484] Example 86: 7-amino-5-((2-(1-(1-(hydroxy methyl) cyclopropyl)-5-methyl-1H-pyrazol-3-yl) ethyl)amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.



[000485] To a stirred solution of 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (136 mg, 0.512 mmol) and (1-(3-(2-aminoethyl)-5-methyl-1H-pyrazol-1-yl) cyclopropyl) methanol **XLV** (200 mg, 1.02 mmol) in 2-propanol (5 mL) was added triethylamine (0.429 mL, 3.07 mmol) under inert atmosphere. The reaction mixture in seal tube was heated at 120 °C for

24 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to room temperature and diluted with water (50 ml). The resulting mixture was extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified by flash column chromatography using 0-3% methanol in DCM to afford the compound **Example 86** as off-white solid. Yield: 25 mg, (12.8 %); **LCMS** Calculated. for $C_{19}H_{24}N_8O$ is 380.20; Observed. 381.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.10 (bs, 2H), 6.55 (t, J= 5.2, 1H), 5.83 (s, 1H), 4.90 (t, J = 6.0 Hz, 1H), 3.58-3.51 (m, 4H), 2.73 (t, J = 7.2 Hz, 2H), 2.29 (s, 3H), 2.22 (s, 3H), 1.96 (s, 3H), 1.07- 0.99 (m, 4H). **HPLC**: 10.03 min; 98.06 %, Column: INT ODS 3V-C18 (4.6x250) mm, 5µ; 0.1% Formic acid in water: Mobile Phase B: Acetonitrile.

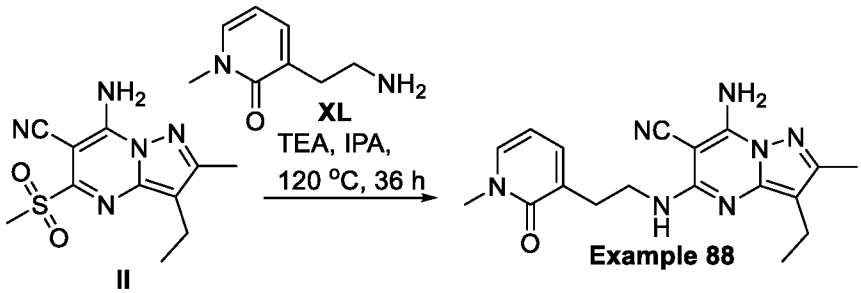
Example 87: 7-amino-3-chloro-2-methyl-5-((2-(1-methyl-2-oxo-1,2-dihydropyridin 3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000486] To a stirred solution of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX** (150 mg, 0.525 mmol) in isopropanol (5 mL) were added 3-(2-aminoethyl)-1-methylpyridin-2(1H)-one **XL** (160 mg, 1.05 mmol) and TEA (0.366 mL, 2.63 mmol) in a sealed tube. The resulting reaction mixture was stirred at 160 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion the reaction mixture was cooled room temperature and precipitated solid was filtered. The solid was washed with DCM (2 mL) and diethyl ether (2 mL) to afford pure title compound **Example 87** as off-white solid. Yield: 60 mg, (30 %); **LCMS** Calculated. for $C_{16}H_{16}ClN_7O$ is 357.11; Observed. 358.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.33 (bs, 2H), 7.57-7.55 (m, 1H), 7.29-7.28 (m, 1H), 7.07 (t, J = 5.2 Hz, 1H),

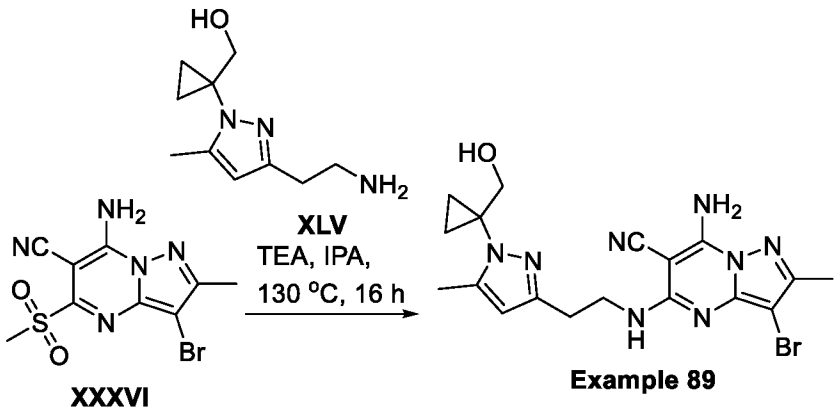
6.14 (t, *J* = 6.8 Hz, 1H), 3.56-3.52 (m, 2H), 3.44 (s, 3H), 2.74-2.73 (m, 2H), 2.27 (s, 3H). **HPLC**:10.896 min; 98.54 %, INT ODS 3V-C18 (4.6x250) mm, 5µ; 0.1% Formic acid in water: Mobile Phase B: Acetonitrile; Flow rate: 1.0 mL/min.

Example 88: 7-amino-3-ethyl-2-methyl-5-((2-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



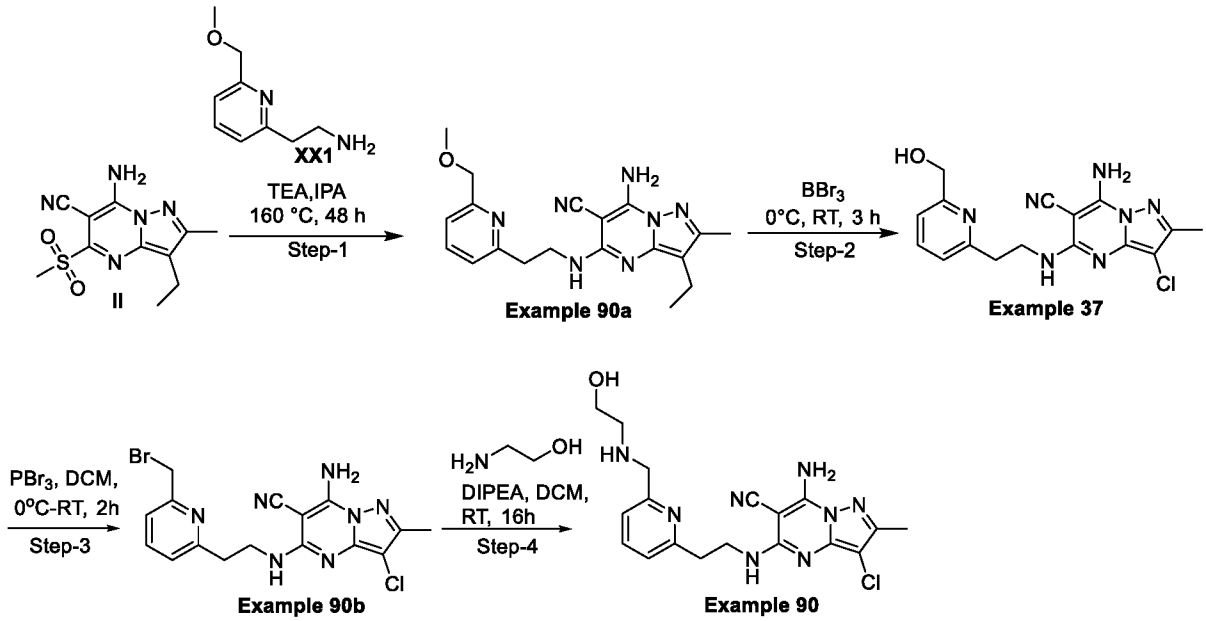
[000487] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (150 mg, 0.537 mmol) in IPA (5 mL) were added 3-(2-aminoethyl)-1-methylpyridin-2(1H)-one **XL** (163 mg, 1.07 mmol) and TEA (0.374 ml, 2.69 mmol) in a sealed tube. The resulting reaction mixture was stirred at 160°C for 48 hours. The progress of the reaction was monitored by TLC analysis. After completion reaction was cooled to room temperature and diluted with ethyl acetate (20 mL) and water (20 mL) and mixed well. The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under vacuo to afford light brown viscous liquid. The crude compound was purified by combi-flash (230-400) silica gel column chromatography using ethyl acetate in *n*-hexane and peak was eluted with 30% ethyl acetate in *n*-hexane, fraction solvent was concentrated to afford the desired compound **Example 88** as an off-white solid. Yield: (84 mg, 42 %); **LCMS** Calculated for $C_{18}H_{21}N_7O$ is 351.18; Observed. 352.30 $[M+1]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.049 (s, 2H), 7.567 – 7.546 (m, 1H), 7.271- 7.255 (m, 1H), 6.705 (t, *J* = 5.2 Hz, 1H), 6.134 (t, *J* = 6.8 Hz, 1H), 3.541 – 3.494 (m, 2 H), 3.437 (s, 3H), 2.737 (t, *J* = 6.4 Hz, 2H), 2.470 – 2.433 (m, 2H), 2.239 (s, 3H), 1.106 (t, *J* = 7.2 Hz, 3H). **HPLC**: 10.312 min; 97.38 %. INT ODS 3V-C18 (4.6x250) mm, 5µ; 0.1% Formic acid in water: Mobile Phase B: Acetonitrile.

Example 89: 7-amino-3-bromo-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000488] To a solution of 7-amino-3-bromo-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXXVI** (0.5 g, 2 mmol) and (1-(3-(2-aminoethyl)-5-methyl-1H-pyrazol-1-yl) cyclopropyl) methanol **XLV** (0.6 g, 3 mmol) in 2-propanol (10 mL) was added triethylamine (1 mL, 9.0 mmol) and the reaction mixture was stirred at 130 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was cooled to rt and diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography using ethyl acetate in *n*-hexane (0-70%) to afford the desired compound **Example 89** as off-white solid. Yield: 40 mg, (5.0 %); **LCMS** Calculated for $C_{17}H_{19}BrN_8O$ is 430.09; Observed: 431.15 $[M+H]^+$. **^{1}HNMR (400 MHz, DMSO-d$_6$,):** δ 8.48 (s, 2H), 8.04 (s, 1H), 6.99 (t, J = 5.2 Hz, 1H), 5.85 (s, 1H), 4.90 (t, J = 6.0 Hz, 1H), 3.61-3.51 (m, 4H), 2.763-2.670 (m, 2H), 2.31 (d, J = 10 Hz, 3H), 1.03 (d, J = 8.8 Hz, 4H). **HPLC:** 10.46 min; 98.55 %, INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile; Flow: 1.0 mL/min

Example 90: 7-amino-3-chloro-5-((2-(6-(((2-hydroxyethyl) amino) methyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



Step-1: 7-amino-3-ethyl-5-((2-(6-(methoxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 90a)

[000489] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **II** (2.0 g, 7.2 mmol) in isopropanol (40 mL) were added TEA (6.0 mL, 43 mmol) and 2-(6-(methoxymethyl) pyridin-2-yl) ethan-1-amine **XXI** (3.0 g, 18 mmol) and the reaction mixture was stirred at 160 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated under reduced pressure and the crude material was purified by silica gel (230-400) column chromatography by eluting with 0-40 % ethyl acetate in *n*-hexane to afford the title compound **Example 90a** as an off-white solid. Yield: 1.3 g (50.0 %); **LCMS** Calculated. for $C_{19}H_{23}N_7O$ is 365.20; Observed.366.25 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (bs, 2H), 7.75-7.71 (t, J = 8.0 Hz, 1H), 7.26-7.19 (m, 2H), 6.95 (s, 1H), 4.51 (s, 2H), 3.69-3.65 (q, J = 6.4 Hz, 2H), 3.36 (s, 3H), 3.04-3.01 (t, J = 6.8 Hz, 2H), 2.50-2.43 (q, J=7.6 Hz, 2H), 2.25 (s, 3H) ,1.14-1.10 (t, J =7.6Hz, 3H).

Step-2: 7-amino-3-ethyl-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 37)

[000490] A stirred solution of 7-amino-3-ethyl-5-((2-(6-(methoxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **Example 90a** (1.3 g, 3.6 mmol) in DCM (5 mL) was cooled to 0 °C and dropwise added a solution of BBr_3 (0.50 mL, 5.3 mmol) in DCM (3 mL). The reaction was stirred at 0 °C for 3 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched by saturated $NaHCO_3$ solution (100 mL). The resulting mixture was extracted with DCM (200 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under *vacuo*. The crude compound was purified by silica gel (230-400 mesh) column chromatography using 0-4 % MeOH in dichloromethane to afford the desired compound **Example 37** as an off-white solid. Yield: 0.53g (41.0 %); **LCMS** Calculated. for $C_{18}H_{21}N_7O$ is 351.18; Obsderved.352.15 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.11 (bs, 2H), 7.72-7.70 (d, J = 7.2 Hz, 1H), 7.33-7.31 (d, J = 8.0 Hz, 1H), 7.15-7.13 (d , J=7.6 Hz, 1H), 6.85 (s, 1H), 5.37 (bs, 1H), 4.58-4.57 (d , J=4 Hz, 2H), 3.67-3.63 (t, J = 5.6 Hz, 2H), 3.03-2.99 (t, 2H), 2.50-2.43 (q, J=7.6 Hz, 2H), 2.25 (s, 3H), 1.14-1.10 (t , J=7.6 Hz, 3H); **HPLC Purity** = 99.32 %, XBridge C18 (4.6 * 150) mm, 5µ; Mobile phase A : 0.1% formic acid in H_2O, B: acetonitrile; Flow: 1.0 mL/min.

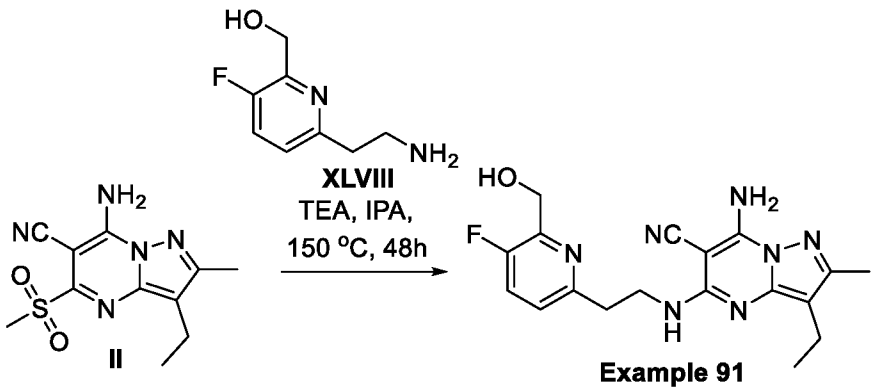
Step-3: 7-amino-5-((2-(6-(bromomethyl) pyridin-2-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 90b)

[000491] To a solution of 7-amino-3-chloro-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 90a** (100 mg, 0.3 mmol) in DCM (2 mL) at 0 °C was added PBr_3 (0.03 mL, 0.33 mmol). The reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was quenched with sat. $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product **Example 90b** was taken for the next step without any further purification. Yield: 0.1g, (84.74 %); **LCMS** Calculated. for $C_{16}H_{15}BrClN_7$ is 419.03; Observed. 420.10 $[M+H]^+$.

Step-4: 7-amino-3-chloro-5-((2-(6-(((2-hydroxyethyl) amino) methyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000492] To a solution of 7-amino-5-((2-(6-(bromomethyl) pyridin-2-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 90b** (0.1g, 0.24 mmol) and 2-aminoethan-1-ol (0.03 g, 0.5 mmol) in DCM (4 mL) was added DIPEA (0.12 mL, 0.71mmol). The reaction mixture was stirred at rt for 16 hours. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by PREP-HPLC (0.1%TFA in water: Acetonitrile: methanol (1:1); Inertsil ODS 3V 250*20mm, 5.0µm) to afford the desired product **Example 90** as a yellow-solid. Yield: 23.1 mg, (24.0 %); **LC-MS** Calculated. for $C_{18}H_{21}ClN_8O$ is 400.15; Observed. 401.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.60-8.00 (bs, 2H), 7.70-7.66 (t, J = 8.0 Hz, 1H), 7.28-7.15 (m, 3H), 4.473 (s, 1H), 3.82 (s, 2H), 3.73-3.68 (m, 2H), 3.48-3.38 (d, J = 4.8 Hz, 2H), 3.04-3.01 (t, J = 6.5 Hz, 2H), 2.62-2.59 (t, J = 5.6 Hz, 2H), 2.28 (s, 3H). 1.10-1.06 (m, 1H), 1.06-0.85 (m, 1H). **HPLC**: 7.944 min; 99.51 %, INT ODS 3V-C18 (4.6*250) mm, 5µ, Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile; Flow: 1.0 mL/min

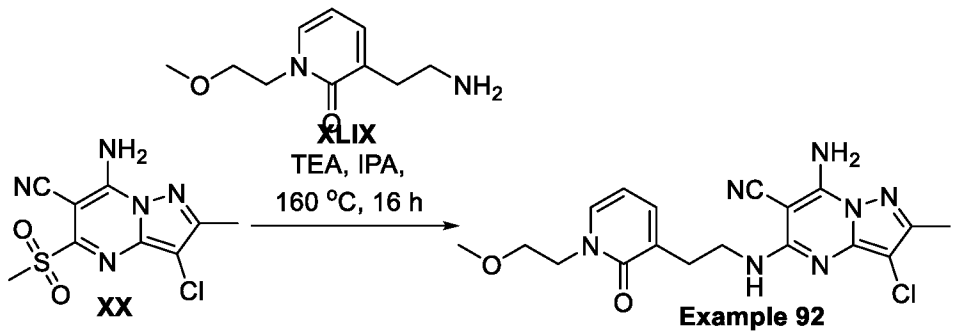
Example 91: 7-amino-3-ethyl-5-((2-(5-fluoro-6-(hydroxymethyl)315yridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000493] To a solution of (6-(2-aminoethyl)-3-fluoropyridin-2-yl) methanol **XLVIII** (0.2 g, 1 mmol) and 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl)

pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.2 g, 0.7 mmol) in isopropanol (10 mL) triethylamine (0.3 mL, 2 mmol) was added. The resulting mixture was purged with N_2 for 10 min and heated at 150 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was cooled to rt and concentrated under reduced pressure. Added water (10 mL) and extracted with ethyl acetate (10 mL*3). The combined organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to afford the crude as a light brown viscous liquid. The crude compound **Example 91** was purified by revered phase prep-HPLC; YMC AQUA ODS (250X20) mm.5.0 microns. Mobile phase A:10mm Ammonium bicarbonate in H_2O; Mobile phase B: Acetonitrile: Methanol (1:1). Yield: 18.0 g, (7.0 %); **LCMS** calculated for $C_{18}H_{20}FN_7O$ is 369.17; Observed. 370.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 7.88 (bs, 1H), 7.60 (t, *J*=9.6 Hz, 1H), 7.27 (q, *J*=4.8 Hz, 1H), 6.53 (bs, 1H), 5.22 (bs, 1H), 4.56 (s, 2H), 3.68-3.63 (m, 2H), 3.03 (t, *J* = 6.8 Hz, 2H), 2.47-2.41 (m, 2H), 2.22 (s, 3H), 1.11 (t, *J* =7.6 Hz, 3H). **HPLC**: 11.64 min; 96.49 %, INT ODS 3V-C18 (4.6*250) mm, 5µ, Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile; Flow: 1.0 mL/min

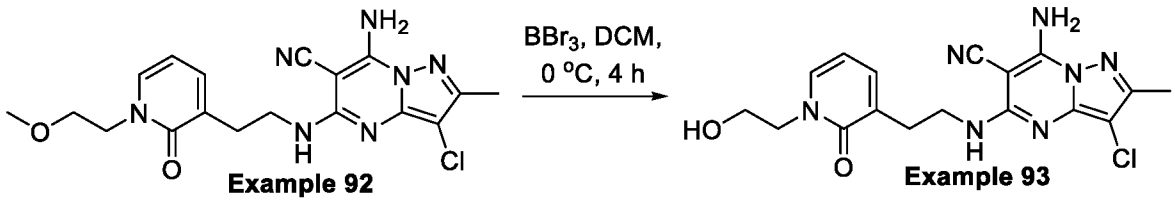
Example 92: 7-amino-3-chloro-5-((2-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000494] To a stirred solution of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile XX (2 g, 7 mmol) in IPA (10 mL) was added 3-(2-aminoethyl)-1-(2-methoxyethyl) pyridin-2(1H)-one (3 g, 0.01 mol) and TEA (4 g, 6 mL, 0.04 mol) in a sealed tube. The reaction mixture was stirred at 160 °C for 16 hours and the progress of the reaction was monitored by TLC analysis.

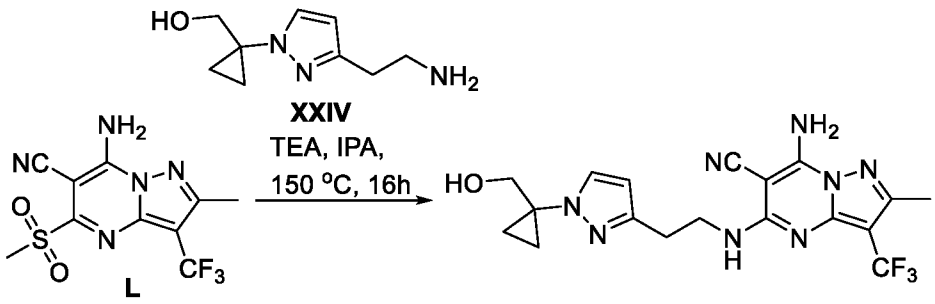
After completion, reaction mixture was allowed to room temperature and filtered the precipitated solids and then solids were washed with MeOH, diethyl ether and acetonitrile to afford the desired compound as a white solid. Yield: 1.3 g (40%); **LCMS** Calculated. for $C_{18}H_{20}ClN_7O_2$ is 401.14; Observed. 402.25 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.347 (bs, 2H), 7.479 (d, J = 6.0 Hz, 1H), 7.293 (d, J = 6.0 Hz, 1H), 7.080 (s, 1H), 6.151 (t, J = 6.8 Hz, 1H), 4.076-4.052 (m, 2H), 3.602-3.538 (m, 4H), 3.227 (s, 3H), 2.765-2.734 (m, 2H) 2.270 (s, 3H). HPLC Purity = 92.97%, Rt = 11.332.

Example 93: 7-amino-3-chloro-5-((2-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.



[000495] To a stirred solution of 7-amino-3-chloro-5-((2-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 92** (1.3 g, 3.2 mmol) in DCM (20 mL) was cooled to 0 °C and was added dropwise addition of BBr3 (1.2 g, 0.46 mL, 4.9 mmol). The reaction mixture was stirred at 0 °C for 4 hours. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with water (50 mL) and extracted with ethyl acetate (50 ml x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude residue was subjected silica gel (230-400 mesh) column chromatography using 0-10% MeOH in DCM to afford the desired compound **Example 93** as a bluish solid. Yield: (850 mg, 65%); **LCMS** Calculated for $C_{17}H_{18}ClN_7O_2$ is 387.12; Observe:388.25 $[M^+ +1]$.**^{1}HNMR (400 MHz, DMSO-d$_6$,):** δ 8.354 (bs, 2H), 7.490 (d, J = 6.4 Hz, 1H), 7.318 (d, J = 6.4 Hz, 1H), 7.116-7.093 (m, 1H), 6.153 (t, J = 6.4 Hz, 1H), 4.856 (J = 5.6 Hz, 1H), 3.972-3.945 (m, 2H), 3.663-3.624 (m, 2H), 3.561-3.517 (m, 2H), 2.751 (t, J = 6.4 Hz, 2H), 2.271 (s, 3H). HPLC Purity = 99.67%, Rt = 10.122.

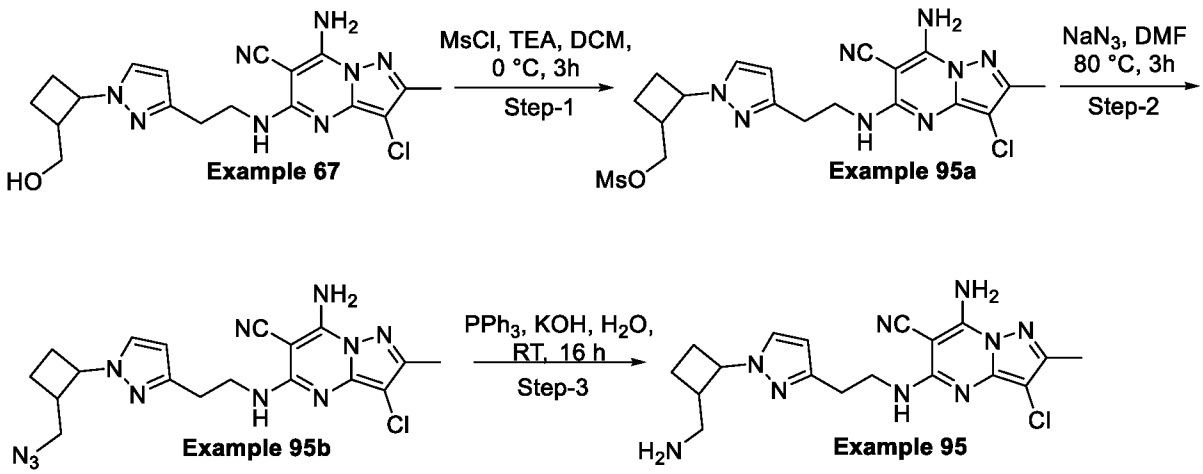
Example 94: 7-amino-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-(trifluoromethyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile



Example 94

[000496] To a stirred solution of 7-amino-2-methyl-5-(methyl sulfonyl)-3-(trifluoromethyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **L** (0.17 g, 0.564 mmol) in 2-propanol (10 mL) were added (1-(3-(2-aminoethyl)-1H-pyrazol-1-yl)cyclopropyl)methanol (0.205 g, 1.13 mmol) and triethylamine (0.343 g, 3.39 mmol) at room temperature under N_2 atmosphere. The resulting mixture was stirred at 150 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with water (50 mL) and extracted with ethyl acetate (25 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude residue was subjected silica gel (230-400 mesh) column chromatography using 0-3% MeOH in DCM to afford the desired compound **Example 94** as a brown solid. Yield: 0.035 g (16%); **LCMS** Calculated. for $C_{18}H_{19}F_3N_8O$ is 420.16; Observed. 421.30 $[M+H]^+$; **^{1}HNMR (400 MHz, DMSO-D$_6$,):** δ 8.50 (bs, 2H), 7.61 (d, J = 2.0 Hz, 1H), 7.21 (t, J = 5.2 Hz, 1H), 6.02 (d, J = 2.0 Hz, 1H), 4.89 (t, J = 6.0 Hz, 1H), 3.58-3.56 (m, 4H), 2.82-2.79 (m, 2H), 2.36 (s, 3H), 1.28-1.23 (m, 2H), 1.08-1.05 (m, 2H). **HPLC** Purity = 94.37%; INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile; Rt = 11.738.

Example 95: 7-amino-5-((2-(1-(2-(amino methyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000497] Step-1: (2-(5-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclobutyl) methyl methane sulfonate (Example 95a)

[000498] To a stirred solution of 7-amino-3-chloro-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 67** (0.9 g, 2 mmol) in DCM (100 mL) was added triethylamine (2 mL, 10 mmol) under inert atmosphere. The resulting mixture was cooled to 0 °C and drop wise added methane sulfonyl chloride (0.2 mL, 2 mmol). The reaction mixture was stirred at 0 °C for 3h and progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with sat. Na_2HCO_3 solution (100 mL) and extracted with DCM (100 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by silica gel (mess 230-400) column chromatography using 0-50 % ethyl acetate in *n*-hexane to afford the desired compound **Example 95a** as a pale-yellow solid. Yield: 0.770 g (77%). **LCMS** Calculated. for $C_{19}H_{23}ClN_8O_3S$ is 478.13; Observed. 479.30 $[M+H]^+$.

Step-2: 7-amino-5-((2-(1-(2-(azidomethyl) cyclobutyl)-1H-pyrazol-5-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 95b)

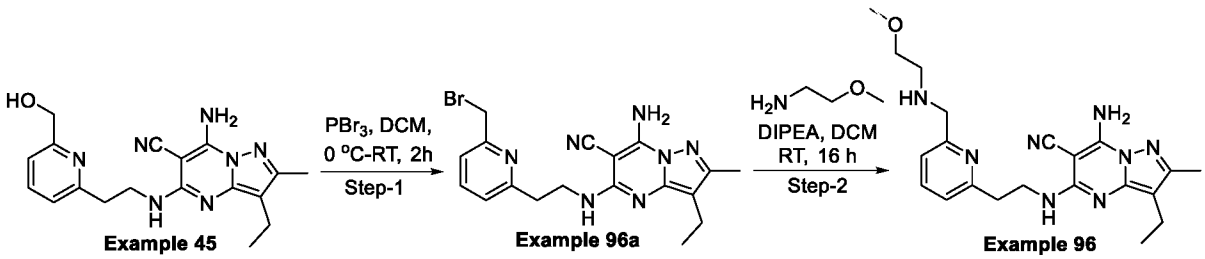
[000499] To a stirred solution of (2-(5-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclobutyl)

methyl methane sulfonate **Example 95a** (0.9 g, 1.88 mmol) in DMF (10 mL) was added sodium azide (489 mg, 7.52 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 3 h under nitrogen atmosphere. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to RT and diluted with water (50 mL). The mixture was extracted with ethyl acetate (50 mL X 3) and the combined organic layer was dried over anhydrous Na_2SO_4 before it was concentrated under reduced pressure. The crude was purified by combi flash silica gel (mess 230-400) column chromatography by using 10-40% ethyl acetate in *n*-hexane to afford the desired compound **Example 95b** as a pale-yellow solid. Yield:0.56 g (70%). **LC-MS** Calc. for $C_{18}H_{20}ClN_{11}$ is 425.15; Obs. 426.30 $[M+H]^+$.

[000500] Step-3: 7-amino-5-((2-(1-(2-(amino methyl) cyclobutyl)-1H-pyrazol-5-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000501] To a stirred solution of 7-amino-5-((2-(1-(2-(azidomethyl) cyclobutyl)-1H-pyrazol-5-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 95b** (0.56 g, 1.3 mmol) in THF: H_2O (12 mL; 3:1) were added triphenylphosphine (0.52 g, 2.0 mmol) and potassium hydroxide (74 mg, 1.3 mmol). The resulting mixture was stirred at RT for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was diluted with water (10 mL) and extracted with DCM (50 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by combi flash chromatography eluted with 0-5 % methanol in DCM to afford the desired title compound **Example 95** as an off-white solid. Yield: 50 mg, (10 %). **LCMS** Calculated. for $C_{18}H_{22}ClN_9$ is 399.16; Obs. 400.30 $[M+H]^+$; **^{1}HNMR (400 MHz, DMSO-d_6,):** δ 7.92 (bs, 4H), 7.69 (d, *J*= 2.0 Hz, 1H), 7.01 (t, *J* = 5.2 Hz, 1H), 6.14 (d, *J*= 1.6 Hz, 1H), 4.56 (q, *J*= 8.0 Hz, 1H), 3.63 (q, *J*= 6.0 Hz, 2H), 2.96- 2.86 (m, 5H), 2.44-2.28 (m, 5H), 2.01-1.91 (m, 1H), 1.59 (m, 1H). **HPLC**: 8.144 min; 99.58%, INT ODS 3V-C18 (4.6x250) mm, 5µ; 0.1% Formic acid in water: Mobile Phase B: Acetonitrile.

Example 96: 7-amino-3-ethyl-5-((2-(6-(((2-methoxyethyl) amino) methyl)321yridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.



[000502] Step-1: 7-amino-5-((2-(6-(bromomethyl) pyridin-2-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 96a)

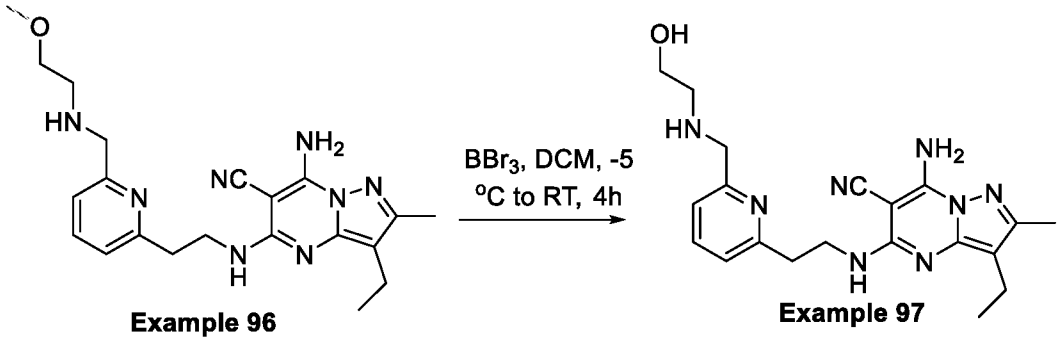
[000503] A solution of 7-amino-3-ethyl-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 45** (200 mg, 0.569 mol) in DCM (4 mL) was cooled to 0 °C and a solution of PBr_3 (0.161 mL, 1.71 mmol) in DCM (1 mL) was dropwise added under inert atmosphere. The reaction mixture was stirred at rt for 2 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with sat. $NaHCO_3$ solution (10 mL) and the resulting mixture was extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified by silica gel (230-400 mesh) column chromatography using 0-20% ethyl acetate in *n*-hexane to afford the desired compound **Example 96a** as an off-white solid. Yield: 120 mg (50%); **LCMS** Calculated. for $C_{18}H_{20}BrN_7$ is 415.09; Observed. 416.30 $[M+H]^+$. **^{1}HNMR (400 MHz, $CDCl_3$,):** δ 7.65-7.61 (m, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.41 (bs, 1H), 6.01 (bs, 2H), 4.64 (s, 2H), 3.91-3.87 (m, 2H), 3.11 (t, J = 6.0 Hz, 2H), 2.59-2.32 (m, 2H), 2.05 (s, 3H), 0.89-0.83 (m, 3H).

Step-2: 7-amino-3-ethyl-5-((2-(6-(((2-methoxyethyl) amino) methyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000504] To a solution of 2-methoxyethan-1-amine (26.1 mg, 0.348 mmol) in DCM (4 mL) was added DIPEA (112 mg, 0.869 mmol) and the resulting mixture

was stirred at rt for 10 min. To this was added a solution of 7-amino-5-((2-(6-(bromomethyl) pyridin-2-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 96** (120 mg, 0.29 mmol) in DCM (1 mL). The reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. The reaction was quenched with water (20 mL) and the resulting mixture was extracted with DCM (50 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified by silica gel (230-400 mesh) column chromatography using 0-5% MeOH in DCM to afford the desired compound **Example 96** as an off-white solid. Yield: 80 mg, (77 %); **LCMS** Calculated. for $C_{21}H_{28}N_8O$ is 408.24; Observed.: 409.40 [M^++1]. **^{1}HNMR (400 MHz, DMSO-D_6,):** δ 8.12 (bs, 2H), 7.76 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 6.78 (bs, 1H), 4.10 (bs, 2H), 3.72-3.69 (m, 2H), 3.53 (t, J = 5.6 Hz, 2H), 3.27 (s, 3H), 3.08 (t, J = 6.8 Hz, 2H), 2.97 (t, J = 5.2 Hz, 2H), 2.50-2.44 (m, 2H), 2.25 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H); **HPLC**: 8.235 min; 96.75 %, INT ODS 3V-C18 (4.6*250)mm, 5µ, Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile.

Example 97: 7-amino-3-ethyl-5-((2-(6-(((2-hydroxyethyl) amino) methyl) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

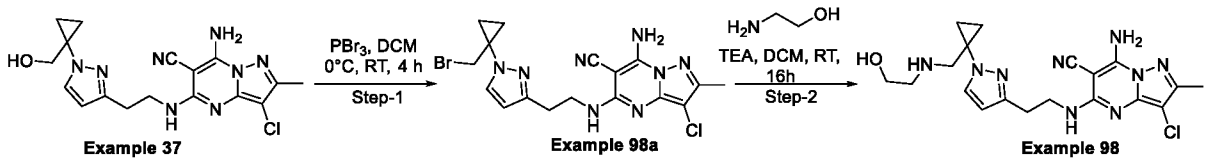


Example 96 Example 97

[000505] A solution of 7-amino-3-ethyl-5-((2-(6-(((2-methoxyethyl) amino) methyl) pyridin-2-yl) ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile **Example 96** (60 mg, 0.15 mmol) in DCM (4 mL) was cooled to -5 °C and dropwise added solution of BBr_3 (21 µL, 0.22 mmol) in DCM (0.5 mL). The

reaction mixture was stirred at rt for 4 h. The progress of the reaction was monitored by TLC analysis. The reaction was quenched with sat. $NaHCO_3$ solution (20 mL) and the resulting mixture was extracted with DCM (50 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified by silica gel (230-400 mesh) column chromatography using 0-10% MeOH in DCM to afford the desired compound **Example 97** as an off-white solid. Yield: 20.2 mg (29%); **LC-MS** Calc. for $C_{20}H_{26}N_8O$ is 394.22; Obs.: 395.40 [M^++1]. **^{1}HNMR (400 MHz, DMSO-D$_6$,):** δ 8.12 (bs, 2H), 7.75 (t, J = 7.6 Hz, 1H), 7.34-7.23 (m, 3H), 6.79 (bs, 1H), 4.91 (bs, 1H), 4.09 (s, 2H), 3.73-3.69 (m, 2H), 3.60 (bs, 2H), 3.07 (t, J = 6.8 Hz, 2H), 2.87 (t, J = 5.2 Hz, 2H), 2.47-2.44 (m, 2H), 2.25 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H); **HPLC**: 7.998 min; 96.80 %, INT ODS 3V-C18 (4.6*250)mm, 5µ, Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile.

Example 98: 7-amino-3-chloro-5-((2-(1-(1-(((2-hydroxyethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



Step-1: 7-amino-5-((2-(1-(1-(bromomethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

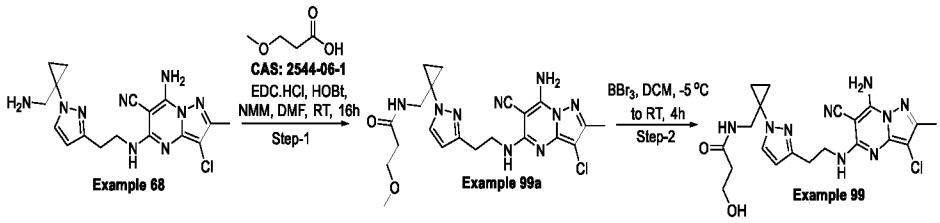
[000506] A solution of 7-amino-3-chloro-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 37** (300 mg, 0.776 mmol) in DCM (10 mL) was cooled to 0 °C under inert atmosphere and PBr_3 (110 µL, 1.16 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 4 h and the progress of reaction was monitored by TLC analysis. After completion, the reaction was cooled to 0 °C and quenched slowly with saturated sodium bicarbonate solution. The resulting mixture was extracted with DCM (10 mL X 3), the combined organic layer was given brine wash, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crude material was purified by combi flash chromatography

using 10-50% ethyl acetate in *n*-hexane to afford the desired compound **Example 98a** as off-white solid. Yield: (90 mg, 25.78%); **LCMS** Calculated for $C_{17}H_{18}BrClN_8$.05 is 450.01; Observed: 451.20 [M^++H].

Step-2: 7-amino-3-chloro-5-((2-(1-(1-(((2-hydroxyethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl)amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000507] To a solution of 7-amino-5-((2-(1-(1-(bromomethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 98a** (90 mg, 0.20 mmol) in DCM (3 mL) were dropwise added DIPEA (0.10 mL, 0.60 mmol) and 2-aminoethan-1-ol (18 µL, 0.30 mmol) under inert atmosphere at rt. The reaction mixture was stirred for 16 h and the progress of the reaction was monitored by TLC analysis. Then additional 2-aminoethan-1-ol (18 µL, 0.30 mmol) was added stirring was continued for 3 days. After completion, the reaction was quenched with 10% NaOH solution (10 mL) and extracted with DCM (10 mL X 3). The combined organic layer was washed brine solution, dried over anhydrous sodium sulphate, and concentrated under reduced pressure**.** The crude material was purified by flash chromatography (Biotage) using 0-10% methanolic ammonia (7M) in DCM to afford **Example 98** as off-white solid. Yield: 25 mg (30.12%). **LCMS** Calculated for $C_{19}H_{24}ClN_9O$ is 429.18; Observed: 430.35 [M^++1]. **^{1}HNMR (400 MHz, DMSO-D_6,):** δ 8.42 (bs, 2H), 7.74 (d, J = 2.0 Hz, 1H), 6.94 (t, J = 5.2 Hz, 1H), 6.15 (d, J = 2.0 Hz, 2H), 5.07 (bs, 1H), 3.66-3.57 (m, 4H), 3.41-3.38 (m, 2H), 2.87-2.83 (m, 4H), 2.28 (s, 3H), 1.24-1.20 (m, 4H). **HPLC**: 7.992 min; 99.59|%, INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile.

Example 99: N-((1-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) methyl)-3-hydroxypropanamide.



Step-1: N-((1-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) methyl)-3-methoxypropanamide

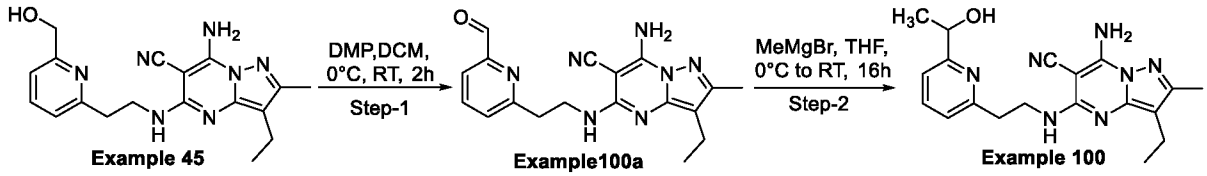
[000508] To a stirred solution of 7-amino-5-((2-(1-(1-(aminomethyl)cyclopropyl)-1H-pyrazol-3-yl)ethyl)amino)-3-chloro-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile **Example 68** (0.2 g, 0.5 mmol) in DMF (5 mL) were added 3-methoxypropanoic acid (0.08 g, 0.8 mmol), *N*, *N*-diisopropylethylamine (0.2 mL, 1 mmol), 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimideHydrochloride (0.1 g, 10.8 mmol) and HOBt (0.1 g, 0.8 mmol) at 0 °C under inert atmosphere. The reaction was stirred for 16 h at room temperature. Then the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (20 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by combi flash (230-400) column chromatography using 0-1% methanol in DCM to afford the desired compound **Example 99a** as off-white solid. Yield: (180 mg, 90%); **LCMS** Calculated for $C_{21}H_{26}ClN_9O_2$ is 471.19; Observed: 472.35 [M^++1]. **^{1}HNMR (400 MHz, DMSO-D$_6$):** δ 8.40 (bs, 2H), 7.90 (t, *J* = 5.6 Hz, 1H), 7.59 (s, 1H), 6.95 (t, *J* = 5.2 Hz, 1H), 6.07 (d, *J* = 2.0 Hz, 1H), 3.63-3.49 (m, 2H), 3.47-3.39 (m, 4H), 3.18 (t, *J* = 5.6 Hz, 3H), 2.82 (t, *J* = 7.2 Hz, 2H), 2.33-2.28 (m, 5H), 1.09-1.00 (m, 4H).

Step-2: *N*-((1-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) methyl)-3-hydroxypropanamide

[000509] To a stirred solution of *N*-((1-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) methyl)-3-methoxypropanamide **Example 99a** (0.180 g, 0.381 mmol) in DCM (20 mL) was added BBr_3 (54.1 µL, 0.572 mmol) at 0 °C over a

period of 5 min. The reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with methanol 1 mL and diluted with saturated sodium bicarbonate solution (20 mL). The mixture was extracted with DCM (20 mL X 3) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by combi-flash (230-400) column chromatography using 0-5% methanol in DCM to afford the desired compound **Example 99** as off-white solid. Yield: (175 mg, 37.0%); **LCMS** Calculated. for $C_{20}H_{24}ClN_9O_2$ is 457.17; Observed: 458.35 [M^++1]. **^{1}HNMR (400 MHz, DMSO-D$_6$):** δ 8.41 (bs, 2H), 7.86 (t, *J* = 5.6 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 6.95 (t, *J* = 5.2 Hz, 1H), 6.06 (d, *J* = 2.0 Hz, 1H), 4.55 (t, *J* = 5.2 Hz, 1H), 3.63-3.54 (m, 4H), 3.43 (d, *J* = 5.6 Hz, 2H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.28 (s, 3H), 2.21 t, *J* = 6.4 Hz, 2H), 1.09-1.00 (m, 4H); **HPLC**: 9.98 min; 97.70 %, INT ODS 3V-C18 (4.6*250)mm, 5µ, Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile.

Example 100: 7-amino-3-ethyl-5-((2-(6-(1-hydroxyethyl)326yridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



Step-1: 7-amino-3-ethyl-5-((2-(6-formylpyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

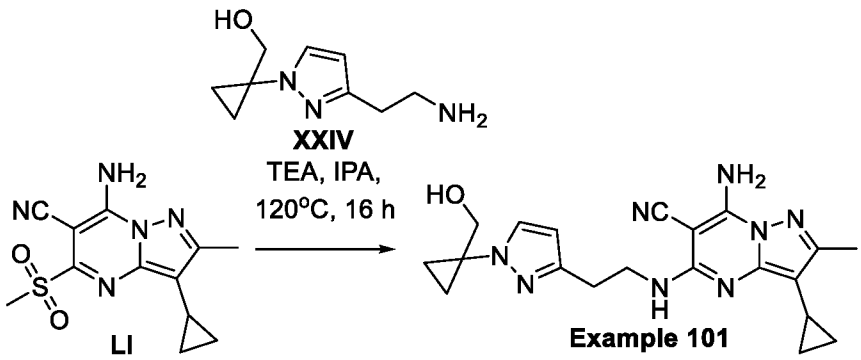
[000510] A solution of 7-amino-3-ethyl-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 45** (200 mg, 0.57 mmol) in DCM (5 mL) was added Dess-martin periodinane (290 mg, 0.683 mmol). The reaction mixture was stirred at 0 °C for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was filtered through a celite bed and washed with ethyl acetate (50 mL x 2). The combined filtrates were dried over anhydrous sodium sulphate and concentrated

under reduced pressure. The crude was purified by silica gel (230-400 mesh) column chromatography using 20% ethyl acetate in *n*-hexane to afford the desired compound **Example 100a** as an off-white solid. Yield: (135mg, 67.8%); **LCMS** Calculated for $C_{18}H_{19}N_7O$ is 349.17; Observe: 350.35 [M^++1]; **^{1}HNMR (400 MHz, $CDCl_3$):** δ 10.176 (s, 1H), 7.862-7.790 (m, 2H), 7.790-7.746 (m, 1H), 6.166 (s, 1H), 6.035 (s, 2H), 3.986-3.941 (m, 2H), 3.245-3.214 (t, *J* = 6.0 Hz, 1H), 2.592-2.535 (q, *J* = 7.6 Hz, 1H), 2.324 (s, 3H), 2.174 (s, 1H), 1.213-1.175 (t, *J* = 7.6 Hz, 3H).

Step-2: 7-amino-3-ethyl-5-((2-(6-(1-hydroxyethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

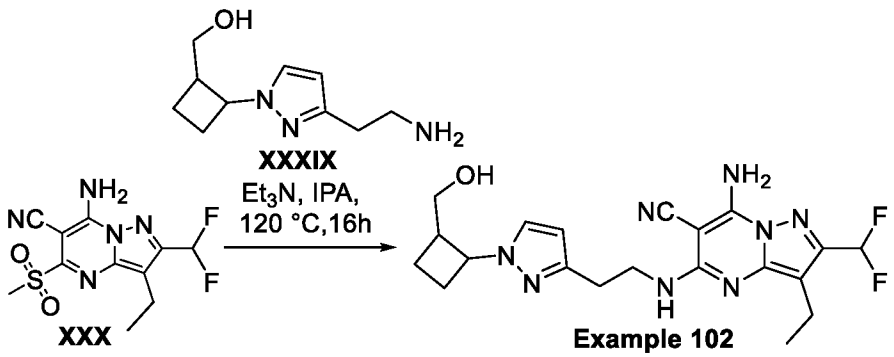
[000511] A solution of 7-amino-3-ethyl-5-((2-(6-formylpyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 100a** (130 mg, 0.372 mmol) in THF (3mL) was cooled to 0 °C and added methyl magnesium bromide (0.446 mL, 1 M, 0.446 mmol). The reaction mixture was stirred at rt for 3 h. The progress of the reaction was monitored by TLC analysis**.** After completion, the reaction was quenched with saturated NH_4Cl solution (20 mL) and extracted with ethyl acetate (50 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified by flash silica gel chromatography using 10-50% ethyl acetate in *n*-hexane to afford the desired compound **Example 100** as an off-white solid. Yield: (18 mg, 7%); **LCMS** Calculated for $C_{19}H_{23}N_7O7$ is 365.20 ; Observe: 366.40 [M^++1].**^{1}HNMR (400 MHz, DMSO-d_6,):** δ 8.10 (s, 2H), 7.72-7.68 (t, *J* = 7.6 Hz, 1H), 7.36-7.34 (d, *J* = 7.6 Hz, 1H), 7.14-7.12 (d, *J* = 7.2 Hz, 1H), 6.83 (s, H), 5.29-5.28 (t, *J* = 4.4 Hz, 1H), 4.75 (bs, 1H), 3.67 (bs, 2H), 3.04-3.00 (m, 2H), 3.51-2.44 (m, 2H), 2.25 (s, 3H), 1.37-1.35 (d, *J* = 6.4 Hz, 3H), 1.15-1.11 (t, *J* = 7.6 Hz, 3H). **HPLC**: 8.49 min; 98.85 %, INT ODS 3V-C18 (4.6*250) mm, 5µ, Mobile Phase A: 0.1% formic acid in water, Mobile Phase B: Acetonitrile:

Example 101: 7-amino-3-cyclopropyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000512] To a stirred solution of 7-amino-3-cyclopropyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **LI** (0.2 g, 0.7 mmol) and (1-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclopropyl) methanol **XXIV** (0.2 g, 1 mmol) in isopropanol (5 mL) in a sealed tube, was added TEA (0.3 mL, 2 mmol). The resulting reaction mixture was stirred at 120 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to RT and diluted with water (20 mL). The resulting mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by combi-flash column chromatography using eluted with 0-70% ethyl acetate in *n*-hexane to afford the desired title compound **Example 101** as off-white solid. Yield 100 mg (33%). **LCMS** Calculated. for $C_{20}H_{24}N_8O$ is 392.20; Observed. 393.35 $[M+1]^+$. **^{1}HNMR (400 MHz, DMSO-D$_6$,):** δ 8.09 (bs, 2H), 7.62-7.62 (m, 1H), 6.65 (t, J = 5.2 Hz, 1H), 6.06 – 6.05 (m, 1H), 4.88 (q, J = 5.6 Hz, 1H), 3.59 (d, J = 5.2 Hz, 2H) 3.55-3.50 (m, 2H), 2.80 (d, J = 7.6 Hz, 2H), 2.30 (s, 3H), 1.62-1.55 (m, 1H), 1.10-1.07 (m, 2H), 1.00 – 0.95 (m, 4H), 0.76-0.72 (m, 2H). **HPLC:** 11.217 min; 99.74%, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ, Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile.

Example 102: 7-amino-2-(difluoro methyl)-3-ethyl-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile

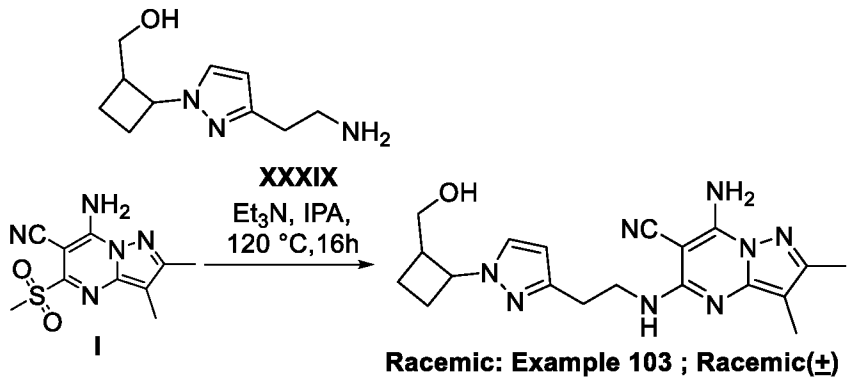


[000513] To a stirred solution of 7-amino-2-(difluoro methyl)-3-ethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXX** (0.2 g, 0.6 mmol) and (2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclobutyl) methanol (0.2 g, 1 mmol) in isopropanol (5 mL) in a sealed tube, was added TEA (0.3 mL, 2 mmol). The reaction mixture was stirred at 120 °C for 16 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to RT, diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by combi-flash column chromatography using 0-50% ethyl acetate in *n*-hexane to afford the desired compound **Example 102** as off-white solid. Yield: 0.12 g (40%). **LCMS** Calculated. for $C_{20}H_{24}F_2N_8O$ is 430.20; Observed. 431.35 $[M+1]^+$. **^{1}HNMR (400 MHz, DMSO-D$_6$,):** δ 8.43 (bs, 2H), 7.65 (d, J = 2.0 Hz, 1H), 7.18-6.91 (m, 2H), 6.07 (d, J = 2.0 Hz, 1H), 4.60 (t, J = 5.2 Hz, 1H), 4.51 (q, J = 8.8 Hz, 1H), 3.63-3.58 (m, 2H), 3.41-3.36 (m, 2H), 2.86-2.77 (m, 3H), 2.63-2.58 (m, 2H), 2.33-2.20 (m, 2H), 1.83-1.76 (m, 1H), 1.61-1.56 (m, 1H), 1.16 (t, J = 7.6 Hz, 3H). **HPLC**: 12.298 min; 98.94 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile

Example 103: Racemic (+-)-7-amino-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

Example 104a: (+)-7-amino-5-((2-(1-(2-(hydroxymethyl) cyclobutyl) -1H-pyrazol-3-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.

[000514] Example 104b: (-)-7-amino-5-((2-(1-(2-(hydroxymethyl)cyclobutyl)-1H-pyrazol-3-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.



[000515] To a stirred solution of 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (200 mg, 0.754 mmol) and (2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclobutyl) methanol **XXXIX** (294 mg, 1.51 mmol) in 2-propanol (10 mL) was added triethylamine (0.631 mL, 4.52 mmol). The reaction mixture was heated at 120 °C for 16 h. The progress of the reaction was monitored by TLC analysis. The reaction mixture was cooled to rt and diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over in anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude was purified by combi flash silica gel (230-400) column chromatography using 0-1% methanol in DCM to afford the desired racemic compound **Example 103** as off-white solid. Yield: 0.1 g (35%). **LC-MS** Calculated. for $C_{19}H_{24}N_8O$ is 380.20; Observed: 381.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.10 (bs, 2H), 7.65 (d, J=2.0 Hz, 1H), 6.63 (t, J = 5.2 Hz, 1H), 6.07 (s, 1H), 4.59 (t, J =5.2 Hz, 1H), 4.54-4.47 (m, 1H), 3.61-3.56 (m, 2H), 3.41-3.37 (m, 2H), 2.84-2.77 (m, 3H), 2.34-2.27 (m, 1H), 2.22-2.18 (m, 4H), 1.96 (s, 3H), 1.83-1.76 (m, 1H), 1.63-1.53 (m, 1H). **HPLC**: 10.864 min; 98.31 %, Column: INT ODS 3V-C18 (4.6*250) mm,5µ Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile.

[000516] The racemic compound **Example 103** (7g) was subjected to chiral separation by SFC {The sample was dissolved in ~115 mL of Tetrahydrofuran:

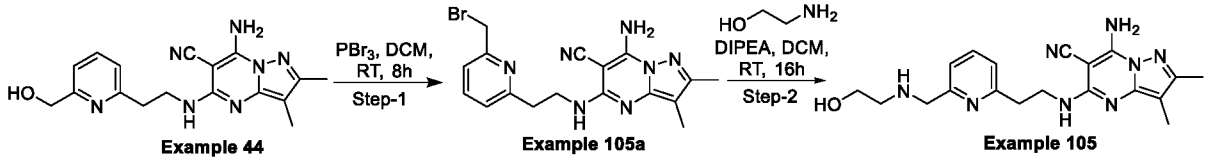
Methanol (1:1)}, Column: Chiral Pak IG (250 * 21) mm, 5.0 µm; Mobile phase 72:28 (A: B). A=Liquid CO_2, B= 0.1% Isopropyl amine in Isopropyl alcohol: Acetonitrile (1:1), Flow rate: 25.2mL/min; Wavelength 254 nm to yield 2.89 g of **peak 1; Example 104a;** $[\alpha]_D$ = +42.97 °, c=0.101, MeOH) and 2.28 g of **peak 2, Example 104a;** $[\alpha]_D$ = -35.41 °, c=0.101, MeOH) as off-white solids, respectively. Absolute stereochemistry of the chiral center is unknown.

Peak-1; Example 104a ;(+)-7-amino-5-((2-(1-(2-(hydroxymethyl) cyclobutyl) -1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile,

[000517] **LC-MS** Calculated. for $C_{19}H_{24}N_8O$ is 380.20; Observed.: 381.35 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.10 (bs, 2H), 7.65 (bs, 1H), 6.63 (m, 1H), 6.07 (bs, 1H), 4.59 (t, J =5.2 Hz, 1H), 4.52-4.98 (m, 1H), 3.60-3.58 (m, 2H), 3.41-3.39 (m, 2H), 2.84-2.81(m, 3H), 2.32-2.22 (m, 5H), 1.96 (s, 3H), 1.80-1.78 (m, 1H), 1.60-1.55 (m, 1H). **HPLC**: 10.864 min; 98.31 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile; **Chiral HPLC**: 99.37%; Rt=14.476 min; Chiral Pak IG (250*4.6) mm, 5µ Mobile phase: A: 0.1%DEA In Hex, B: IPA: MeOH (1:1) Isocratic mode: 80:20 Flow :1.0 ml/min.

Peak-2; Example 104b; (-)-7-amino-5-((2-(1-(2-(hydroxymethyl) cyclobutyl) -1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile. LCMS Calculated. for $C_{19}H_{24}N_8O$ is 380.20; Observed. 381.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.10 (bs, 2H), 7.65 (bs, 1H), 6.63 (m, 1H), 6.07 (bs, 1H), 4.59 (t, J =5.2 Hz, 1H), 4.52-4.98 (m, 1H), 3.60-3.58 (m, 2H), 3.41-3.39 (m, 2H), 2.84-2.81(m, 3H), 2.32-2.22 (m, 5H), 1.96 (s, 3H), 1.80-1.78 (m, 1H), 1.60-1.55 (m, 1H). **HPLC**: 10.813 min; 99.40 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile. **Chiral HPLC:** 99.35%; Rt=16.114 min; Column: Chiral Pak IG (250*4.6) mm, 5µ, Mobile phase: A:0.1%DEA In Hex, B: IPA: MeOH (1:1), Isocratic mode :80:20, Flow :1.0 ml/min.

Example 105: 7-amino-5-((2-(6-(((2-hydroxyethyl) amino) methyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



Example 44 Example 105a Example 105

Step-1. 7-amino-5-((2-(6-(bromomethyl) pyridin-2-yl) ethyl) amino)-2,3-dimethyl pyrazolo[1,5-a] pyrimidine-6-carbonitrile.

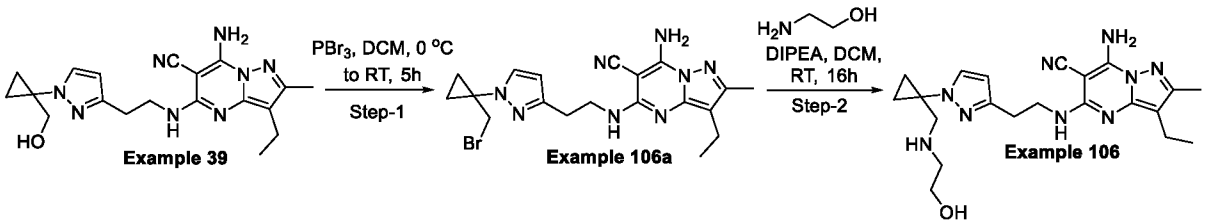
[000518] A solution of 7-amino-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 44** (210 mg, 0.622 mmol) in DCM (6 mL) was added PBr_3 (0.176 mL, 1.87 mmol) at 0 °C. The reaction mixture was stirred at rt for 8 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with sat. $NaHCO_3$ solution (30 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the title compound **Example 105a** as off-white solid. Yield: 0.16 g (64.25%). **LCMS** Calculated. for $C_{17}H_{18}BrN_7$ is 399.08; Obs. 402.30 [M^++3].

Step-2: 7-amino-5-((2-(6-(((2-hydroxyethyl) amino) methyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000519] To a stirred solution of 2-aminoethan-1-ol (29.3 mg, 0.480 mmol) in DCM (4 mL) were added DIPEA (0.280 mL, 1.20 mmol) and 7-amino-5-((2-(6-(bromomethyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 105a** (160 mg 0.40 mmol) under inert atmosphere. The resulting mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, reaction was quenched with water (20 mL) and extracted with DCM (50 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified by reverse phase prep HPLC: YMC Triat C18 (250*20) mm, 5.0µm; Mobile phase A: 10mm Ammonium bicarbonate in water, B: Acetonitrile: Methanol (1:1) to afford the desired compound **Example 105** as off-white solid. Yield: 61 mg (40%); **LCMS** Calculated. for $C_{19}H_{24}N_8O$ is 380.20;

Observed. 381.35 $[M+H]^+$. **^{1}HNMR (400 MHz, DMSO-d$_6$,):** δ 8.09 (bs, 2H), 7.67 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.84 (t, J = 5.2 Hz, 1H), 4.48-4.46 (m, 1H), 3.81 (s, 2H), 3.70- 3.66 (m, 2H), 3.49-3.45 (m, 3H), 3.03-2.97 (m, 2H), 2.62-2.59 (m, 2H), 2.22 (s, 3H), 1.96 (s, 3H). **HPLC**: 7.799 min; 98.16 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile.

Example 106: 7-amino-3-ethyl-5-((2-(1-(1-(((2-hydroxyethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



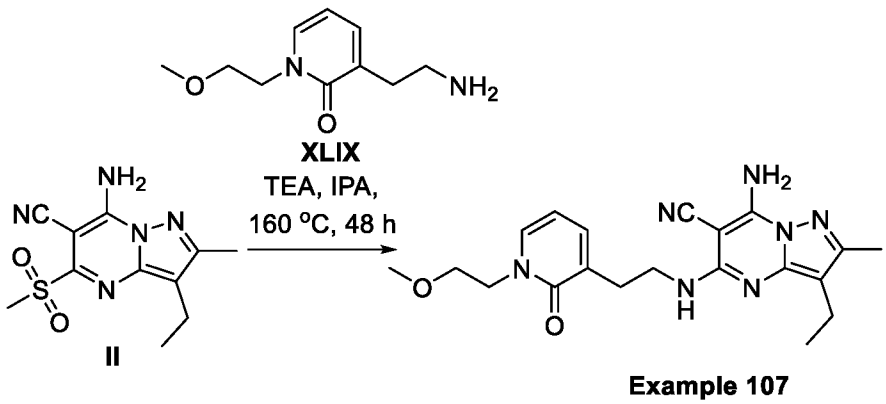
Step-1: 7-amino-5-((2-(1-(1-(bromomethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 106a)

[000520] To a solution of 7-amino-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 39** (500 mg, 1.31 mmol) in DCM (13 mL) was dropwise added PBr_3 (0. 248 mL, 2.63 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 5 h. The progress of reaction was monitored by TLC analysis. After completion reaction mixture was cooled to 0 °C and quenched slowly with saturated sodium bicarbonate solution. The mixture was extracted with DCM (30 mL X 3) and the combined organic layer was washed with brine, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. Obtained solid was washed with *n*-pentane to afford the pure compound **Example 106a** as off-white solid. Yield: 390 mg (66.9%). **LCMS** Calculated. for $C_{19}H_{23}BrN_8$ is 442.12; Observed. 443.25 $[M+H]^+$.

Step-2: 7-amino-3-ethyl-5-((2-(1-(1-(((2-hydroxyethyl) amino) methyl) cyclopropyl) -1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

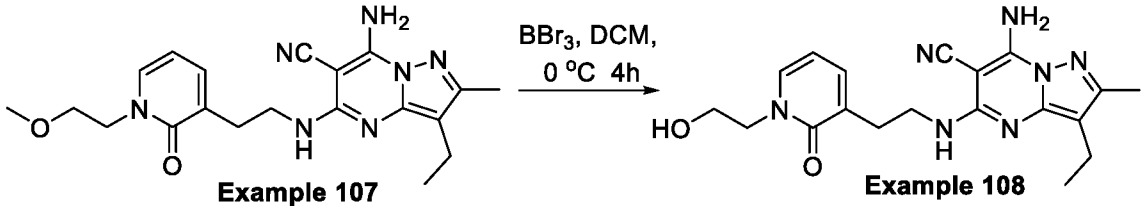
[000521] To a solution of 7-amino-5-((2-(1-(1-(bromomethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 106a** (200 mg, 0.451 mmol) in DCM (8 mL) were added DIPEA (0.236 mL, 1.35 mmol) and 2-aminoethan-1-ol (55.1 mg, 0.902 mmol) at RT. The resulting reaction mixture was stirred for 16h. The progress of reaction was monitored by TLC analysis. After completion, the reaction was quenched with 10% NaOH solution (20 mL) and extracted with DCM (20 mL X 3). The combined organic layer was washed with 10% NaOH solution (20 mL X 6) followed by with brine. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by flash chromatography by eluting with 0-5% methanolic ammonia (7M) in DCM to afford the desired compound **Example 106** as off-white solid. Yield: 50 mg (27%). **LCMS** Calculated. for $C_{21}H_{29}N_9O$ is 423.25; Observed. 424.40 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.08 (bs, 2H), 7.63 (m, 1H), 6.57-6.55 (m, 1H), 6.03 (m, 1H), 4.37 (t, J = 4.8 Hz, 1H), 3.59-3.54 (m, 2H), 2.83-2.78 (m, 4H), 2.46-2.43 (m, 4H), 2.24 (s, 3H), 1.58 (bs, 1H), 1.13-1.07 (m, 6H), 0.94-0.91 (m, 2H). **HPLC**: 8.087 min; 98.52%, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile Flow: 1.0 mL/min.

Example 107: 7-amino-3-ethyl-5-((2-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000522] To a solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.12 g, 430 mmol) and 3-(2-aminoethyl)-1-(2-methoxyethyl) pyridin-2(1H)-one **XLIX** (0.253 g, 1.29 mmol) in isopropyl alcohol (4 mL) was added triethylamine (0.359 mL, 2.58 mmol) and the reaction mixture was stirred at 160 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was quenched with water (50 mL) extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography using 0-10% methanol in dichloromethane to afford the desired compound **Example 107** as a yellow solid. Yield: 0.09 g, (53.0 %); **LCMS** Calculated. for $C_{20}H_{25}N_7O_2$ is 395.21; Observed. 396.35 $[M+H]^+$. **^{1}HNMR (400 MHz, DMSO-D$_6$):** δ 8.05 (bs, 2H), 7.48 (q, *J* = 1.6 Hz, 1H), 7.29 (d, *J* = 5.2 Hz, 1H), 6.71 (t, *J* = 5.2 Hz, 1H), 6.14 (t, *J* = 6.4 Hz, 1H), 4.06 (t, *J* = 5.6 Hz, 2H), 3.60-3.50 (m, 4H), 3.22 (s, 3H), 2.75 (t, *J* = 6.4 Hz, 2H), 2.47 (m, 2H), 2.24 (s, 3H), 1.11 (t, *J* = 7.6 Hz, 3H). **HPLC**: 10.54 min; 97.67 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ, Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile; Flow: 1.0 mL/min

Example 108: 7-amino-3-ethyl-5-((2-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

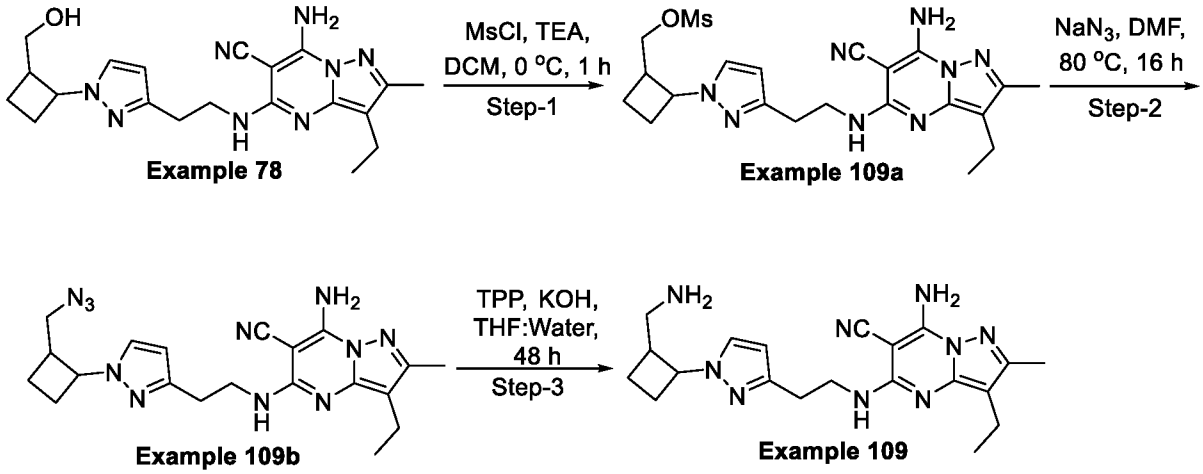


Example 107 Example 108

[000523] To a solution of 7-amino-3-ethyl-5-((2-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 107** (0.07 g, 0.18 mmol) in dichloromethane (4 mL) at 0 °C was added BBr_3 (0.025 mL, 0.27 mmol) and the reaction mixture was stirred at 0 °C for 4 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched with $NaHCO_3$ (50 mL) and

extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography with 0-10 % methanol in dichloromethane to afford the desired title product **Example 108** as off-white solid. Yield: 0.05 g, (73.0 %); **LCMS** Calculated. for $C_{19}H_{23}N_7O_2$ is 381.19; Observed: 382.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D_6,):** δ 8.05 (s, 2H), 7.48 (d, *J* = 6.4 Hz, 1H), 7.29 (d, *J* = 6.4 Hz, 1H), 6.73 (t, *J* = 4.8 Hz, 1H), 6.14 (t, *J* = 6.8 Hz, 1H), 4.85 (t, *J* = 5.6 Hz, 1H), 3.95 (t, *J* = 5.2 Hz, 1H), 3.66-3.62 (q, *J* = 10.8 Hz, 2H), 3.54-3.49 (q, *J* = 6.4 Hz, 2H), 2.75 (t, *J* = 6.4 Hz, 2H), 2.48-2.42 (m, 3H), 2.24 (s, 3H), 1.11 (t, *J* = 7.6 Hz, 3H). **HPLC**:98.68 %.

Example 109: 7-amino-5-((2-(1-(2-(amino methyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000524] Step-1: (2-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclobutyl) methyl methane sulfonate (Example 109a)

[000525] To a solution of 7-amino-3-ethyl-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 78** (2.0 g, 5.07 mmol) in dichloromethane (50 mL) at 0 °C were added triethylamine (3.53 mL, 25.3 mmol) and mesyl-Cl (0.474 mL, 6.08 mmol). The reaction mixture was stirred at 0 °C for 1 h. After the completion, the reaction was quenched with water (50 mL) and extracted with dichloromethane (50 mL*3). The combined organic layer was dried over Na_2SO_4, filtered, and

concentrated under reduced pressure. The crude compound was purified by silica gel (60-120 mesh) column chromatography with ethyl acetate in *n*-hexane (0-10%) to afford the desired product **Example 109a** as a pale-yellow viscous liquid. Yield: 2.3 g, (95.83 %).

Step-2: 7-amino-5-((2-(1-(2-(azidomethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 109b)

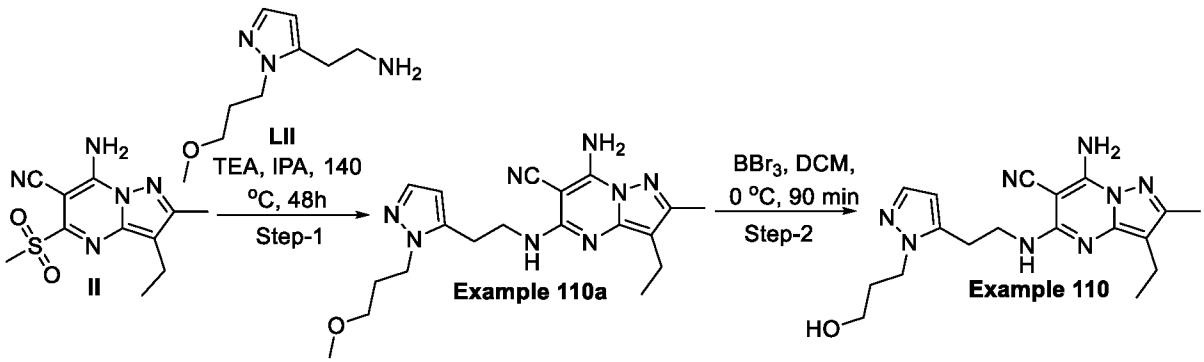
[000526] To a solution of (2-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclobutyl) methyl methane sulfonate **Example 109a** (2.30 g, 4.87 mmol) in DMF (20 mL) was added sodium azide (1.27 g, 19.5 mmol) and the reaction mixture was stirred at 80 °C for 16 h. After the completion of the reaction, the reaction mixture was cooled to rt, quenched with water (100 mL) and extracted with ethyl acetate (3x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography with ethyl acetate in hexane (0-20%) to afford the desired product **Example 109b** as a pale-yellow viscous liquid. Yield:2 g, (98.0 %). **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.10 (s, 2H), 7.95 (s, 1H), 7.68 (d, *J* = 2Hz, 1H), 6.64 (t, *J* = 5.2Hz, 1H), 6.09 (d, *J* = 2Hz, 1H), 4.53 (d, *J* = 8.4 Hz, 1H), 3.61-3.56 (q, *J* = 6.8 Hz, 2H), 3.45-3.43 (q, *J* = 42 Hz, 2H), 2.99 (m, 1H), 2.83 (t, *J* = 6.8 Hz, 2H), 2.47-2.43 (m, 2H), 2.39-2.24 (m, 5H), 1.98-1.91(m, 1H), 1.58-1.53 (m, 1H), 1.18-1.10 (m, 3H).

Step-3: 7-amino-5-((2-(1-(2-(amino methyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000527] To a solution of 7-amino-5-((2-(1-(2-(azidomethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 109b** (2.0 g, 4.8 mmol) in tetrahydrofuran (2.5 mL) and H2O (0.5 mL) were added Ph_3P (1.9 g, 7.2 mmol) and potassium hydroxide (0.27 g, 4.8 mmol) . The reaction mixture was stirred at rt for 48 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was quenched with water (100 mL) and extracted with ethyl acetate (3x

100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel (60-120 mesh) column chromatography with methanol in dichloromethane (0-10%) to afford the desired product **Example 109** as off-white solid. Yield:1.1 g, (57.89 %); **LCMS** calculated for $C_{20}H_{27}N_9$ is 393.24; Observed: 394.40 [M+H]+.**^{1}HNMR (400 MHz, DMSO-d$_6$,):** δ 7.68 (d, *J* = 1.6 Hz, 1H), 6.64 (t, *J* = 5.2Hz, 1H), 6.06 (d, *J* = 2Hz, 1H), 4.45 (q, *J* = 8Hz, 5H), 3.58 (q, *J* = 6Hz, 2H), 2.81 (t, *J* = 14 Hz, 2H), 2.66-2.55 (m, 3H), 2.47-2.43 (m, 2H), 2.33-2.25 (m, 5H), 1.83-1.73 (m, 1H), 1.52-1.48 (m, 1H), 1.12 (t, *J* = 7.6 Hz, 3H). **HPLC**: 99.69 %.

Example 110: 7-amino-3-ethyl-5-((2-(1-(3-hydroxypropyl)-1H-pyrazol-5-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Step-1: 7-amino-3-ethyl-5-((2-(1-(3-methoxypropyl)-1H-pyrazol-5-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

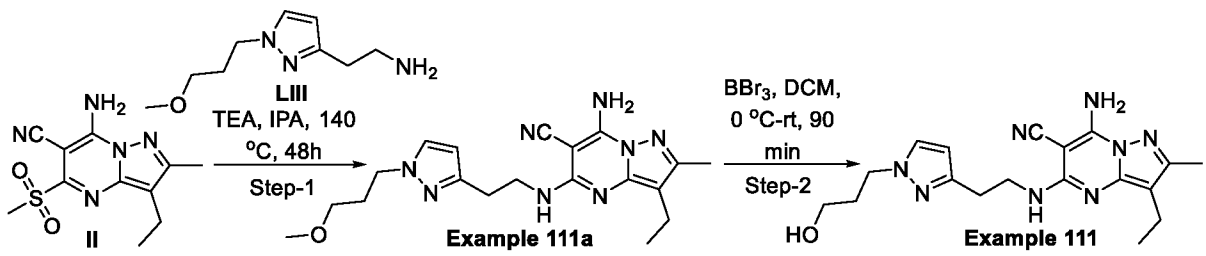
[000528] To a solution of 2-(1-(3-methoxypropyl)-1H-pyrazol-5-yl) ethan-1-amine **LII** (0.25 g, 0.90 mmol) and 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.33 g, 1.8 mmol) in isopropyl alcohol (20 mL) was added triethylamine (0.75 mL, 5.4 mmol) and the reaction mixture was stirred at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, added water (25 mL) and extracted with ethyl acetate (25 mL X 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to get crude material. The crude compound was purified by silica gel (230-400 mesh) column chromatography with methanol in dichloromethane (0-

5%) to afford the desired product **Example 110a** as off-white solid. Yield:0.14 g, (41.0 %); **LCMS** Calculated. for $C_{19}H_{26}N_8O$ is 382.22; Observed. 383.35 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.12 (s, 2H), 7.34 (d, *J* = 1.6 Hz 1H), 6.86 (t, *J* = 5.6 Hz 1H), 6.06 (s, 1H), 4.10 (t, *J* = 6.8 Hz. 3H), 3.58-3.53 (m, 2H), 3.16 (s, 3H), 2.93 (t, *J* = 7.2 Hz, 2H), 2.50-2.44 (m, 2H), 2.25 (s, 3H), 2.25-1.94 (m, 3H), 1.12 (t, *J* = 8.0 Hz, 3H).

Step 2: 7-amino-3-ethyl-5-((2-(1-(3-hydroxypropyl)-1H-pyrazol-5-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000529] To a solution of 7-amino-3-ethyl-5-((2-(1-(3-methoxypropyl)-1H-pyrazol-5-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 110a** (0.140 g, 0.37 mmol) in dichloromethane (4 mL) at 0 °C was added boron tribromide (0.668 mL, 0.55 mmol). The reaction mixture was stirred at rt for 90 min. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, added water (5 mL) and extracted with dichloromethane (10 mL*3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulphate, and concentrated to afford the crude compound. The crude compound was purified by (230-400 mesh) column chromatography with methanol in dichloromethane (0-5%) to afford the desired product **Example 110** as off-white solid. Yield:0.035 g, (26.0 %); **LCMS** Calculated. for $C_{18}H_{24}N_8O$ is 368.21; Observed: 369.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.12 (s, 2H), 7.32 (d, *J* = 1.2 Hz 1H), 6.84 (s, 1H), 6.06 (d, *J* = 1.6 Hz, 1H), 4.53 (t, *J* = 4.8 Hz, 1H), 4.12 (t, *J* = 7.2 Hz, 2H), 3.56 (m, 2H), 3.38-3.36 (m, 2H), 2.94 (d, *J* = 7.6 Hz, 2H), 2.47-2.45 (m, 2H), 2.25 (s, 3H), 1.875 (m, 2H), 1.12 (t, *J* = 7.2 Hz, 3H): **HPLC**: 99.05 %.

Example 111: 7-amino-3-ethyl-5-((2-(1-(3-hydroxypropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



Step-1: 7-amino-3-ethyl-5-((2-(1-(3-methoxypropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 111a)

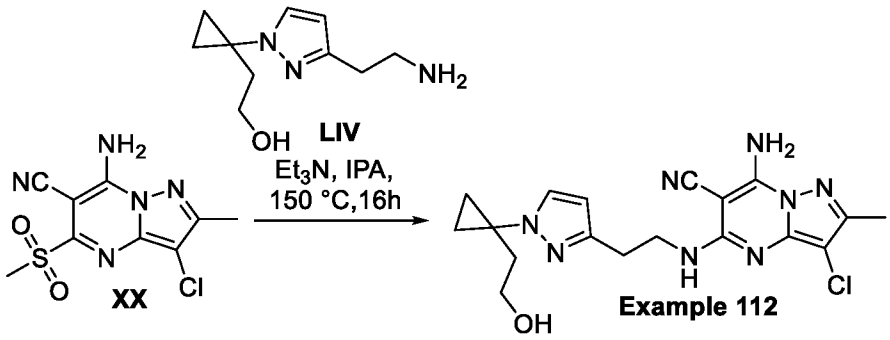
[000530] To a solution of 2-(1-(3-methoxypropyl)-1H-pyrazol-3-yl) ethan-1-amine **LIII** (0.275 g, 0.985 mmol) and 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.36 g, 1.97 mmol) in isopropyl alcohol (25 mL) was added triethylamine (0.823 mL, 5.91 mmol) and the reaction mixture was stirred at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. Reaction mixture was cooled to rt, added water (30 mL) and extracted with ethyl acetate (30 mL * 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to get the crude material. The crude compound was purified by preparative HPLC using column: YMC, Triart, C18 (20×250) mm 5mic. Channel A: 0.1% formic acid in water and channel B: acetonitrile to afford the desired product **Example 111a** as an off-white solid. Yield: 0.25 g, (66.0 %); **LCMS** calculated for $C_{19}H_{26}N_8O$ is 382.22; Observed: 383.35 [M+H] +.**^{1}HNMR (400 MHz, DMSO-d$_6$,):** δ 8.09 (s, 2H), 7.58 (s, 1H), 6.63 (d, *J* = 4.0 Hz, 1H), 6.06 (s, 1H), 4.07 (t, *J* = 8.0 Hz, 2H), 3.58 (q, *J* = 4.0 Hz, 2H), 3.33-3.21 (m, 5H), 2.82 (t, *J* = 8.0 Hz, 2H), 2.50-2.25 (m, 5H), 1.97 (q, *J* = 8.0 Hz, 2H), 1.12 (t, *J* = 8.8 Hz, 3H). **HPLC**: 12.384 min; 99.71 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ, Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile.

Step-2: 7-amino-3-ethyl-5-((2-(1-(3-hydroxypropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000531] To a solution of 7-amino-3-ethyl-5-((2-(1-(3-methoxypropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 111a** (0.11 g, 0.29 mmol) in dichloromethane (4 mL) at 0 °C was added boron tribromide (0.052 mL, 0.43 mmol) and stirred at rt for 90 min. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulphate, and concentrated to afford the crude compound. The crude compound was purified by silica gel (230-400

mesh) column chromatography with methanol in dichloromethane (0-3%) to afford the desired product **Example 111** as off-white solid. Yield: 0.05 g, (47.0 %); **LCMS** Calculated. for $C_{18}H_{24}N_8O$ is 368.21 Observed. 369.35 $[M+1]^+$.**^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.10 (s, 2H), 7.58 (s, 1H), 6.64 (s, 1H), 6.05 (s, 1H), 4.54 (t, *J* = 5.2 Hz, 1H), 4.08 (t, *J* = 6.8 Hz, 2H), 3.57 (d, *J* = 6 Hz, 2H), 3.37 (m, 2H), 2.82 (t, *J* = 6.8 Hz, 2H), 2.47-2.43 (m, 2H), 2.25 (s, 3H), 1.89 (t, *J* = 8.0 Hz, 2H), 1.12 (t, *J* = 7.6 Hz, 3H). **HPLC**:98.29 %.

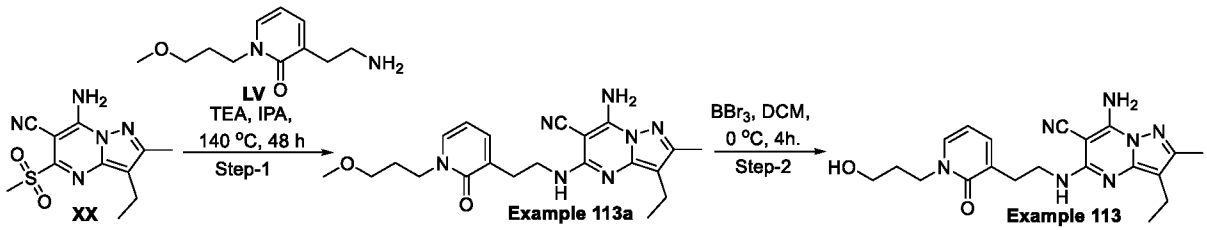
Example 112: 7-amino-3-chloro-5-((2-(1-(1-(2-hydroxyethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000532] To a solution of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX** (0.3 g, 1.05 mmol) and 2-(1-(3-(2-aminoethyl)-1H-pyrazol-1-yl)cyclopropyl)ethan-1-ol **LIV** (0.41 g, 2.10 mmol) in isopropyl alcohol (10 mL) was added triethylamine (0.878 mL, 6.30 mmol) and the reaction mixture was stirred at 150 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was cooled to rt, diluted with water (50 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography using ethyl acetate in *n*-hexane (0-70%) to afford the desired product **Example 112** as an off-white solid. Yield: 0.16 g, (38.0 %); **LCMS** Calculated. for $C_{18}H_{21}ClN_8O$ is 400.15; Observed. 401.30 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.39 (s, 2H), 7.62 (s, 1H), 6.92 (bs, 1H), 6.05 (s, 1H), 4.37 (t, *J* = 4.8 Hz, 1H), 3.61-3.58 (m, 2H), 3.28-3.26 (m, 2H), 2.81 (t, *J* = 6.8 Hz, 2H), 2.28 (s, 3H), 1.87 (t, *J* = 7.2 Hz, 2H), 1.1 (s, 2H), 1.0 (s, 2H). **HPLC**: 11.102 min; 99.36 %, Column: INT ODS 3V-C18

(4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 113: 7-amino-3-ethyl-5-((2-(1-(3-hydroxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



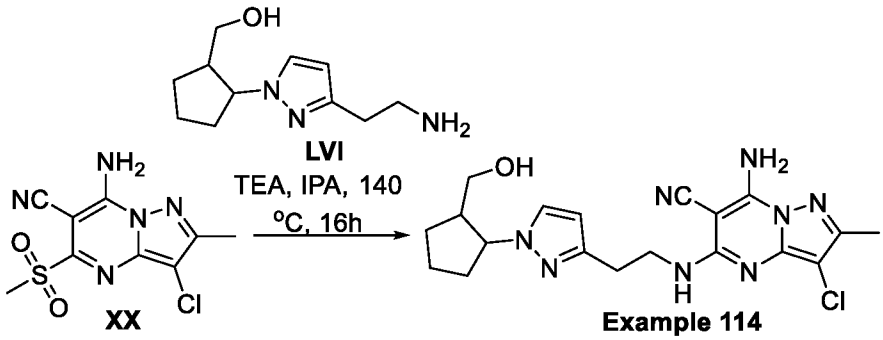
Step-1: 7-amino-3-ethyl-5-((2-(1-(3-methoxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000533] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX** (300 mg, 1.07 mmol) in IPA (6 mL) were added TEA (0.898 mL, 6.44 mmol) and 3-(2-aminoethyl)-1-(3-methoxypropyl) pyridin-2(1H)-one **LV** (339 mg, 1.61 mmol) in a sealed tube. The reaction mixture was stirred at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was diluted with water (50 mL) and the resulting mixture was extracted with ethyl acetate (3 X 50 mL). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by flash column chromatography (silica gel, 230-400) using 0-2% methanol in DCM to afford the desired product **Example 113a** as an off-white solid. Yield: 170 mg (38.7%); **LCMS** Calculated. for $C_{21}H_{27}N_7O_2$ is 409.22; Observed.: 410.35 $[M+H]^+$.**^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.05 (bs, 2H), 7.49 (d, J= 6.4 Hz, 1H), 7.28 (d, J= 6.4 Hz, 1H), 6.69 (bs, 1H), 6.15 (t, J= 6.4 Hz, 1H), 3.92 (d, J= 6.8 Hz, 2H), 3.52 (d, J= 5.2 Hz, 2H), 3.29 (s, 2H), 3.21 (s, 3H), 2.74 (bs, 2H), 2.45-2.33 (m, 2H), 2.24 (s, 3H), 1.88 (d, J= 6.0 Hz, 2H), 1.10 (t, J= 7.2 Hz, 3H). **HPLC**: 10.741 min; 97.134%, Column: INT ODS 3V-C18 (4.6*250) mm,5µ Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile, Flow: 1.0 ml/min:

Step-2: 7-amino-3-ethyl-5-((2-(1-(3-hydroxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

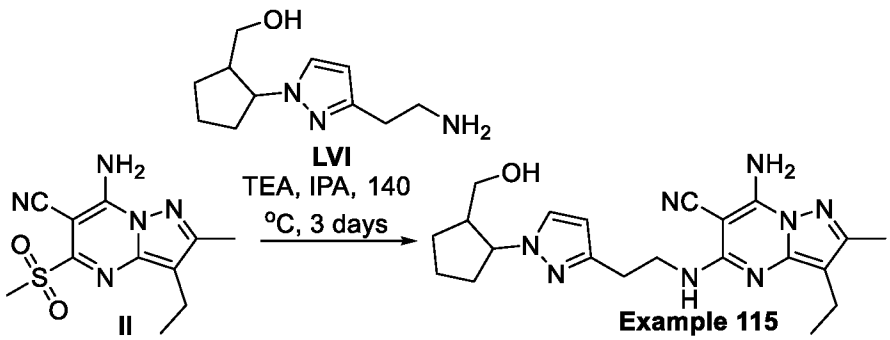
[000534] A stirred solution of 7-amino-3-ethyl-5-((2-(1-(3-methoxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile **Example 113a** (120 mg, 0.293 mmol) in DCM (10 mL) was cooled to 0 °C and dropwise added BBr_3 (55.4 µL, 0.586 mmol) under N_2 atmosphere. The resulting reaction mixture was stirred at 0 °C for 4 h. Progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched with water (50 mL) and the resulting mixture was extracted with DCM (50 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The compound was purified by flash column chromatography (silica gel, 230-400) using 0-5% methanol in DCM to afford the desired compound **Example 113** as an off-white solid. Yield: 21mg (30%); **LCMS** Calculated. for $C_{20}H_{25}N_7O_2$ is 395.21; Observed.: 396.30 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D_6,):** δ 8.05 (bs, 2H), 7.51 (d, *J*= 6.0 Hz, 1H), 7.28 (d, *J*= 6.4 Hz, 1H), 6.71 (d, *J*= 5.2 Hz, 1H), 4.58 (d, *J*= 5.2 Hz, 1H), 3.94 (d, *J*= 6.8 Hz, 2H), 3.52 (q, *J*= 5.6 Hz, 2H), 3.41-3.36 (m, 2H), 2.74 (d, *J*= 6.4 Hz, 2H), 2.47-2.42 (m, 2H), 2.24 (s, 3H), 1.81-1.75 (m, 2H), 1.11 (t, *J*= 7.2 Hz, 3H). **HPLC**: 9.708 min; 99.24%, Column: INT ODS 3V-C18 (4.6*250) mm,5µ Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile, Flow: 1.0 mL/min.

Example 114: 7-amino-3-chloro-5-((2-(1-(2-(hydroxymethyl) cyclopentyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



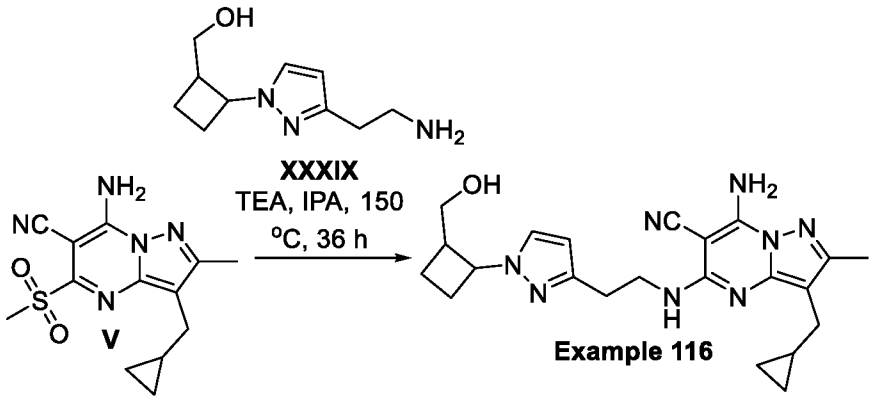
[000535] In a seal tube 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (0.675 g, 2.36 mmol) and (2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclopentyl) methanol (0.89 g, 4.3 mmol) were dissolved in IPA (75 mL) at rt under inert atmosphere. To this solution TEA (1.98 mL, 14.2 mmol) was added and the resulting reaction mixture was stirred at 140 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was cooled to room temperature, diluted with water (75 mL), and extracted with ethyl acetate (50 mL X 3). The combined organic layer was washed with brine, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to get crude material. The crude material was subjected to silica gel (230-400) column chromatography purification (Biotage) using 0-10 % methanol in DCM to afford the desired compound as an off-white solid. Yield: 0.64g (64.8 %); **LCMS** Calculated. for $C_{19}H_{23}ClN_8O$ is 414.17; Observed.: 415.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.39 (bs, 2H), 7.62 (d, J = 2.0 Hz, 1H), 6.95 (t, J = 5.2 Hz, 1H), 6.07 (d, J = 2.0 Hz, 1H), 4.56 (t, J = 5.2 Hz, 1H), 4.35 (q, J = 7.6 Hz, 1H), 3.63-3.58 (m, 2H), 3.39-3.34 (m, 1H), 3.32-3.25 (m, 1H), 2.84 (t, J = 7.2 Hz, 2H), 2.31-2.25 (m, 4H), 2.05-1.93 (m, 2H), 1.91-1.82 (m, 1H), 1.80-1.72 (m, 1H), 1.65-1.55 (m, 1H), 1.51-1.42 (m, 1H). **HPLC**: 11.807 min; 98.02 %, INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min: **Chiral HPLC:** Peak-1: 26.237 min, (48.94%); Peak-2: 28.814 min (51.06%); Chiral Pak IA (250*4.6) mm, 5µ Mobile phase: A: 0.1%DEA In n-Hex, B: EtOH (90:10) Flow:1.0 mL/min.

Example 115: 7-amino-3-ethyl-5-((2-(1-(2-(hydroxymethyl) cyclopentyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000536] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (275 mg, 0.985 mmol) in isopropanol (25 mL) were added (2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclopentyl) methanol **LVI** (412 mg, 1.97 mmol) and TEA (0.823 mL, 5.91 mmol) under inert atmosphere. The resulting reaction mixture was stirred at 140 °C for 3 days and the progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was cooled to room temperature, diluted with water (30 mL), and extracted with ethyl acetate (30 mL × 3). The combined organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered, and concentrated under vacuum to get the crude. The crude was purified by combi flash silica gel (230-400) column chromatography using 0-3% methanol in DCM to afford the desired compound **Example 115** as off -white solid. Yield: 0.18g (44.8%); **LCMS** Calculated. for $C_{21}H_{28}N_8O$ is 408.24; Observed.: 409.40 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.09 (bs, 2H), 7.61 (bs, 1H), 6.61 (bs, 1H), 6.05 (s, 1H), 4.58 (t, J = 5.2 Hz, 1H), 4.34 (q, J = 7.6 Hz, 1H), 3.58-3.56 (m, 2H), 3.38-3.36 (m, 2H), 2.81 (t, J = 7.2 Hz, 2H), 2.45-2.43 (m, 2H), 2.33-2.28 (m, 4H), 2.02-1.95 (m, 2H), 1.92-1.83 (m, 1H), 1.80-1.74 (m, 1H), 1.63-1.57 (m, 1H), 1.51-1.42 (m, 1H), 1.12 (t, J = 7.2 Hz, 3H). **HPLC**: 12.204 min; 98.51 %, INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

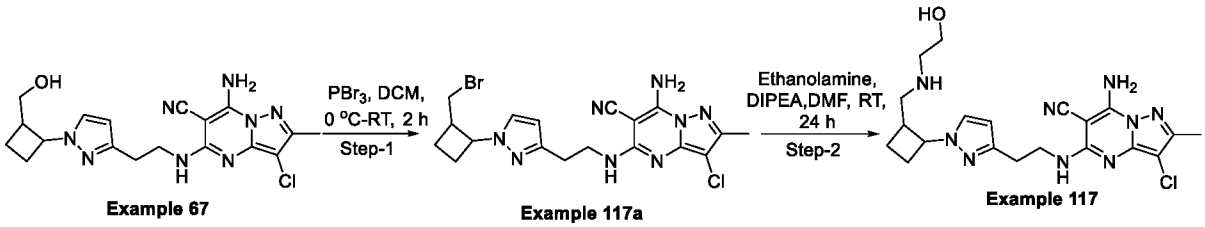
Example 116: 7-amino-3-(cyclopropyl methyl)-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000537] To a stirred solution of 7-amino-3-(cyclopropyl methyl)-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **V** (0.3 g, 1 mmol), (2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclobutyl) methanol **XXXIX** (0.5 g, 2 mmol) in isopropanol (10 mL) was added triethylamine (0.8 mL, 6 mmol) at rt under inert atmosphere. The resulting mixture was stirred at 150 °C for 36 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to rt, diluted with water (20 mL), and extracted with ethyl acetate (20 mL X 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulphate, and concentrated under vacuum. Crude compound was purified by reverse phase prep-HPLC (YMC AQUA ODS (250X20) mm. 5.0 µ; Mobile phase A: 10 mm ammonium bicarbonate in H_2O, Mobile phase B: ACN: MeOH (1:1)) to afford desired compound **Example 116** as off -white solid. Yield: 110 mg (30%); **LCMS** Calculated. for $C_{22}H_{28}N_8O$ is 420.23; Observed.: 421.40 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (bs, 2H), 7.64 (bs, 1H), 6.69 (t, J = 5.2 Hz, 1H), 6.05 (bs, 1H), 4.59 (t, J = 4.8 Hz, 1H), 4.50 (q, J = 8.4 Hz, 1H), 3.60-3.54 (m, 2H), 3.42-3.34 (m, 2H), 2.84-2.80 (m, 3H), 2.40-2.18 (m, 7H), 1.79 (q, J = 9.2 Hz, 1H), 1.63-1.56 (m, 1H), 0.95 (bs, 1H), 0.35 (d, J = 7.6 Hz, 2H), 0.18-0.17 (m, 2H); **HPLC**: 12.449 min; 95.40 %, INT ODS 3V-C18 (4.6 * 250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min: Racemic compound: **Chiral HPLC:** Peak-1: 19.970 min; 49.75 %, Peak-2: 23.164 min; 50.25 %; Column: Chiral Pak IA

(250*4.6) mm, 5µ; Mobile phase: A: 0.1%DEA In Hex, B: EtOH (90:10) Flow:1.0 mL/min.

Example 117: 7-amino-3-chloro-5-((2-(1-(2-(((2-hydroxyethyl) amino) methyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Example 67 Example 117a Example 117

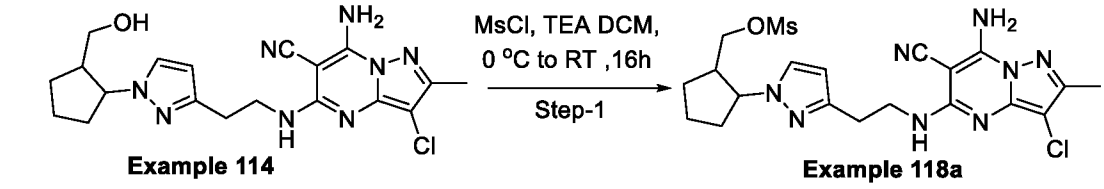
Step-1: 7-amino-5-((2-(1-(2-(bromomethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 117a)

[000538] To a solution of 7-amino-3-chloro-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 67** (0.2 g, 0.5 mmol) in dichloromethane (5 mL) at 0 °C was added PBr_3 (0.07 mL, 0.7 mmol) and the reaction mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was diluted with $NaHCO_3$ (20 ml) and extracted with dichloromethane (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography using ethyl acetate in *n*-hexane (0-70%) to afford the desired compound **Example 117a** as off-white solid. Yield: (0.08 g, 40%); **LC-MS** Calculated. for $C_{18}H_{20}BrClN_8$ is 462.07; Observed: 465.00 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37 (d, *J* = 4 Hz, 1H), 6.33 (s, 1H), 4.47 (d, *J* = 8.8 Hz, 3H), 3.86 (q, *J* = 4.0 Hz, 2H), 3.58-3.50 (m, 2H), 3.26 (d, *J* = 8.0 Hz, 1H), 2.94 (t, *J* = 4.0 Hz, 1H), 2.56 (t, *J* = 12.0 Hz, 1H), 2.36 (d, *J* = 10.8 Hz, 4H), 2.11 (d, *J* = 12.0 Hz, 1H), 1.67-1.56 (m, *J* = 8.0 Hz, 1H), 1.26 (s, 2H).

Step-2: 7-amino-3-chloro-5-((2-(1-(2-(((2-hydroxyethyl) amino) methyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000539] To a solution of 7-amino-5-((2-(1-(2-(bromomethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (0.08 g, 0.17 mmol) in N,N-dimethylformamide (5 mL) were added diisopropylethylamine (0.075 mL, 0.43 mmol) and 2-aminoethan-1-ol (16 mg, 0.26 mmol). The reaction mixture was stirred at rt for 24 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography using ethyl acetate in *n*-hexane (0-70%) to afford the desired product **Example 117** as off-white solid. Yield: (0.02 g, 26%); **LCMS** Calculated. for $C_{20}H_{26}ClN_9O$ is 443.19; Observed: 444.35 $[M+H]^+$.**^{1}HNMR (400 MHz, DMSO-d$_6$,):** δ 8.60-8.30 (bs, 2H), 7.68 (s, 1H), 6.99 (s, 1H), 6.09 (s, 1H), 4.42 (s, 2H), 3.61 (s, 2H), 3.39-3.32 (d, *J* = 8.0 Hz, 3H), 2.83 (s, 3H), 2.66 (d, *J* = 8.0 Hz, 3H), 2.34-2.28 (m, 5H), 1.89 (d, *J* = 12.0 Hz, 1H), 1.47 (d, *J* = 8.0 Hz, 1H). **HPLC**: 8.168 min; 99.28 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ, Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 118: 7-amino-5-((2-(1-(2-(amino methyl) cyclopentyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



Step-1: (2-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopentyl) methyl methane sulfonate (Example 118a)

[000540] To a solution of 7-amino-3-chloro-5-((2-(1-(2-(hydroxymethyl) cyclopentyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 114** (0.45 g, 1.1 mmol) in dichloromethane (5 mL) was added triethylamine (0.68 mL, 4.9 mmol) and cooled to 0 °C. This was followed by an addition of methane sulfonyl chloride (0.19 mL, 1.8 mmol) at 0 °C and the reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction was quenched with water (10 mL) and extracted with dichloromethane (10 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulphate, and concentrated to afford the crude compound **Example 118a** as a light brown thick liquid. The crude compound was taken for the next step without any further purification. Yield: 0.51 g, (95 %); **LCMS** Calculated. for $C_{20}H_{25}ClN_8O_3S$ is 492.15; Observed: 493.30 $[M+H]^+$. **^{1}H NMR (400 MHz, $CDCl_3$,):** δ 7.37 (d, *J* = 8.0 Hz, 1H), 6.09 (s, 1H), 4.39 (d, *J* = 4.0 Hz, 1H), 4.29-4.21 (m, 1H), 3.84 (d, *J* = 8.0 Hz, 1H), 3.32-3.23 (m, 3H), 2.80 (s, 3H), 2.35-2.30 (m, 2H), 2.21-1.74 (m, 4H), 1.35-1.25 (m, 5H).

Step-2: 7-amino-5-((2-(1-(2-(azidomethyl) cyclopentyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 118b)

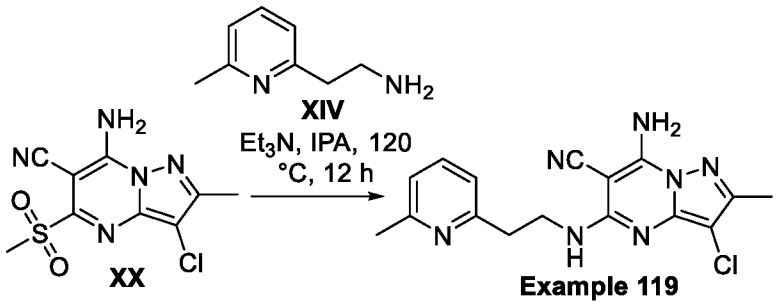
[000541] To a solution of (2-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopentyl) methyl methane sulfonate **Example 118a** (0.68 g, 1.4 mmol) in *N, N*-dimethyl formamide (3 mL) was added sodium azide (0.45 g, 6.9 mmol) and the reaction mixture was stirred at 80 °C for 2 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated to afford the crude compound as brown liquid. The crude

compound was purified by silica gel (230-400 mesh) column chromatography using 0-30% ethyl acetate in *n*-hexane to afford the desired product **Example 118b** as a pale-yellow oil. Yield: (0.10 g, 17 %); **LCMS** Calculated. for $C_{19}H_{22}ClN_{11}$ is 439.17; Observed: 440.35 $[M+H]^+$.

Step-3: 7-amino-5-((2-(1-(2-(amino methyl) cyclopentyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

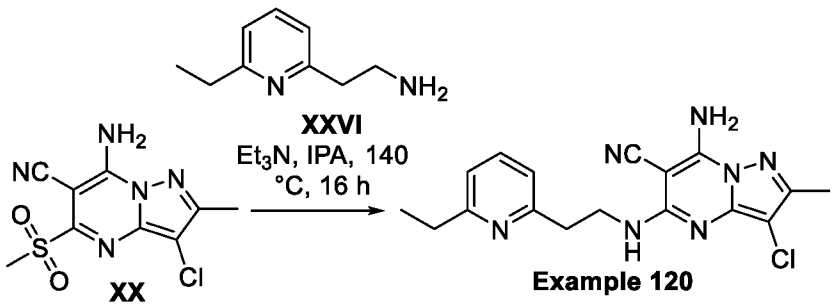
[000542] To a solution of 7-amino-5-((2-(1-(2-(azidomethyl) cyclopentyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 118b** (0.1 g, 0.2 mmol) in THF (3.6 mL) and water (1.2 mL) was added triphenylphosphine (0.09 g, 0.3 mmol) and the reaction mixture was stirred at rt for 10 min. This was followed by an addition of potassium hydroxide (0.034 g, 0.607 mmol) and the reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (20 mL X 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude material. The crude compound was purified by silica gel (60-120 mesh) column chromatography with methanolic ammonia in dichloromethane (0-5%) to afford the desired product **Example 118** as an off-white solid. Yield: (0.05g, 50%); **LCMS** Calculated. for $C_{19}H_{24}ClN_9$ **is** 413.18; Observed: 414.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D_6,):** δ 7.71 (d, *J* = 4.0 Hz, 5H), 6.97 (d, *J* = 4.0 Hz, 1H), 6.12 (d, *J* = 4.0 Hz, 1H), 4.36 (d, *J* = 8.0 Hz, 1H), 3.62 (d, *J* = 8.0 Hz, 2H), 2.86-2.74 (m, 4H), 2.42 (t, *J* = 4.0 Hz, 2H), 2.28 (s, 3H), 2.07-1.98 (m, 2H), 1.80 (d, *J* = 8.0 Hz, 1H), 1.69 (m, 1H), 1.43 (s,1H). **HPLC**: 98.32 %.

Example 119: 7-amino-3-chloro-2-methyl-5-((2-(6-methylpyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000543] To a solution of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX** (0.2 g, 0.7 mmol) and 2-(6-methylpyridin-2-yl) ethan-1-amine (0.2 g, 2 mmol) in isopropyl alcohol (10 mL) was added triethylamine **XIV** (0.6 mL, 4 mmol) and the reaction mixture was stirred at 120 °C for 12 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt, added water (20 mL) and extracted with ethyl acetate (25 mL x 2). The combined organic layer was washed with brine (15mL), dried over anhydrous sodium sulphate, and concentrated under pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography using 0-70% ethyl acetate in *n*-hexane to afford the desired product **Example 119** as off-white solid. Yield: 0.121g (50%); **LCMS** Calculated. for $C_{16}H_{16}ClN_7$ is 341.11; Observed: 342.30 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.41 (bs, 2H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.27 (bs, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 4.0-3.67 (m, 2H), 3.00 (t, *J* = 8.0 Hz, 2H), 2.49 (d, *J* = 8.0 Hz, 3H), 2.28 (s, 3H). **HPLC**: 7.756 min; 99.21 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ, Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min

Example 120: 7-amino-3-chloro-5-((2-(6-ethylpyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

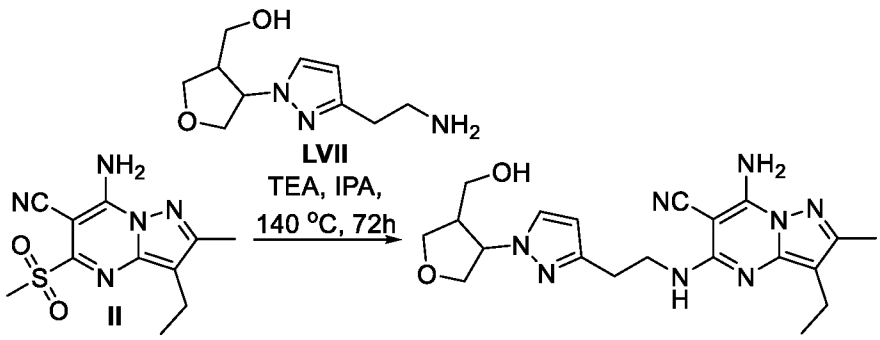


[000544] To a solution of 2-(6-ethylpyridin-2-yl) ethan-1-amine **XXVI** (0.2 g, 0.7 mmol) and 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a]pyrimidine-6-carbonitrile **XX** (0.21 g, 1.40 mmol) in isopropyl alcohol (10 mL) was added triethylamine (0.585 mL, 4.20 mmol) and the reaction mixture was stirred at 140 °C for 16 h. The progress of reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was cooled to rt and concentrated under reduced pressure. Added water (10 mL) and extracted with ethyl acetate (20 mL X 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to get the crude material. The crude compound was purified by silica gel (60-120, mesh) column chromatography using 0-30% ethyl acetate in *n*-hexane to afford the desired product **Example 120** as an off-white solid. Yield: 0.16 g, (63.9%); **LCMS** Calculated. for $C_{17}H_{18}ClN_7$ is 355.13; Observed. 356.05 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.39 (bs, 2H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.19 (bs, 1H), 7.09 (q, *J* = 4.0 Hz, 2H), 3.71 (q, *J* = 4.0 Hz, 2H), 3.01 (t, *J* = 8.0 Hz, 2H), 2.74 (q, *J* = 8.0 Hz, 2H), 2.28 (s, 3H), 1.22 (t, *J* = 8.0 Hz, 3H). **HPLC**: 7.991 min; 99.61 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ, Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 121. (+-)-7-amino-3-ethyl-5-((2-(1-(4-(hydroxymethyl)tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)ethyl)amino)-2-methyl pyrazolo[1,5-a]pyrimidine-6-carbonitrile.

Example 122a. (+)-7-amino-3-ethyl-5-((2-(1-(4-(hydroxy methyl)tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)ethyl)amino)-2-methyl pyrazolo[1,5-a]pyrimidine-6-carbonitrile.

Example 122b. (-)-7-amino-3-ethyl-5-((2-(1-(4-(hydroxy methyl)tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)ethyl)amino)-2-methyl pyrazolo[1,5-a]pyrimidine-6-carbonitrile.



[000545] To a solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (150 mg, 0.537 mol) and (4-(3-(2-aminoethyl)-1H-pyrazol-1-yl) tetrahydrofuran-3-yl) methanol **LVII** (227 mg, 1.07 mmol) in isopropanol (5 mL) was added triethylamine (449 mL, 3.22 mmol). The resulting mixture was purged with N_2 gas for 5 min and stirred at 140 °C for 72 h. The progress of the reaction was monitored by TLC analysis. The reaction mixture was cooled to room temperature and added water (15 mL). The resulting mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with brine, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crude material was subjected to silica gel flash column chromatography using 0-3% methanol in DCM to afford the desired compound **Example 121** as an off-white solid. Yield: 0.09 g (41 %); **LC-MS** Calculated. for $C_{20}H_{26}N_8O_2$ is 410.21; Observed. 411.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.10 (bs, 2H), 7.66 (d, J = 1.6 Hz, 1H), 6.60 (t, J = 5.2 Hz, 1H), 6.36 (d, J = 1.6 Hz, 1H), 4.85 (t, J = 5.2 Hz, 1H), 4.68-4.67 (m, 1H), 4.08-3.98 (m, 2H), 3.85-3.83 (m, 1H), 3.62-3.57 (m, 3H), 3.45 (bs, 2H), 2.83 (t, J = 6.8 Hz, 1H) 2.66 (bs, 1H), 2.47-2.43 (m, 2H), 2.25 (s, 3H), 1.12 (t, J = 7.6 Hz, 3H); **HPLC**: 10.899 min; 97.82 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile Flow: 1.0 mL/min.

[000546] Further the racemic compound **Example 121** was subjected to chiral SFC (Column Name: IG (21*250mm), 5µm; Co-Solvent Name: MeCN:MeOH 1:1 (0.1% TEA); Total flow rate: 100 mL; % of Co-Solvent: 27; Back Pressure :100 bar) and separated in to peak-1 and peak-2.

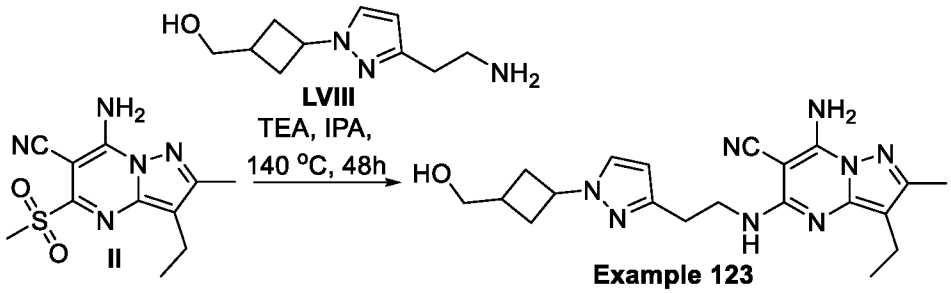
Peak-1; Example 122a ;(38 mg)

[000547] **LC-MS** Calc. for $C_{20}H_{26}N_8O_2$ is 410.21; Obs. 411.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.12 (bs, 2H), 7.67 (bs, 1H), 6.62 (bs, 1H), 6.10 (bs, 1H), 4.85 (t, J = 5.2 Hz, 1H), 4.68-4.67 (m, 1H), 4.08-3.98 (m, 2H), 3.86-3.84 (m, 1H), 3.62-3.57 (m, 3H), 3.45 (bs, 2H), 2.83 (t, J = 6.8 Hz, 2H), 2.66 (bs, 1H), 2.47-2.43 (m, 2H), 2.25 (s, 3H), 1.12 (t, J = 7.6 Hz, 3H); **HPLC**: 10.899 min; 99.30 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile Flow: 1.0 mL/min; **Chiral HPLC:** 7.725; 95.05%; Column Name: IG (4.6*250mm), 5µm; Co-Solvent Name: ACN MEOH 1:1 (0.1% TEA); Total flow rate: 3g/mL; % of Co-Solvent: 30; Temperature: 30 °C; ABPR Pressure :1500psi); Specific optical rotation ($[\alpha]_D$); (c 0.1 in MeOH)= 47.00.

Peak-2; Example 122a ;(39 mg)

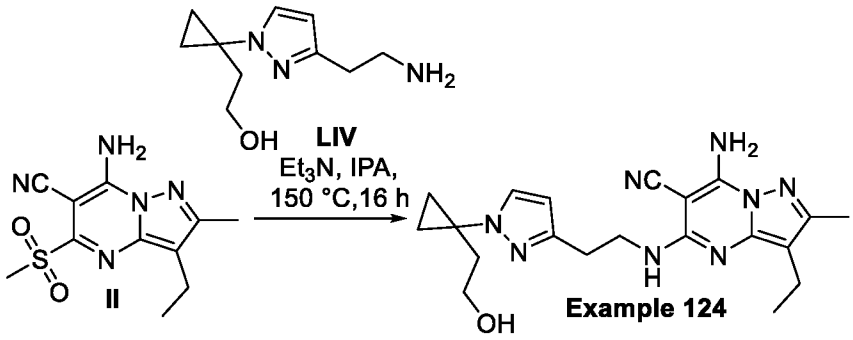
[000548] **LC-MS** Calc. for $C_{20}H_{26}N_8O_2$ is 410.21; Obs. 411.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (bs, 2H), 7.67 (bs, 1H), 6.61 (bs, 1H), 6.10 (bs, 1H), 4.85 (bs, 1H), 4.68-4.67 (m, 1H), 4.08-3.99 (m, 2H), 3.86-3.84 (m, 1H), 3.62-3.59 (m, 3H), 3.45 (bs, 2H), 2.83 (t, J = 6.8 Hz, 2H), 2.66 (bs, 1H), 2.47-2.43 (m, 2H), 2.25 (s, 3H), 1.12 (t, J = 7.6 Hz, 3H); ; **HPLC**: 10.847 min; 98.88 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile Flow: 1.0 mL/min; **Chiral HPLC:** 11.052 min; 98.61%; Column Name: IG (4.6*250mm), 5µm; Co-Solvent Name: ACN MEOH 1:1 (0.1% TEA); Total flow rate: 3g/mL; % of Co-Solvent: 30; Temperature: 30 °C; ABPR Pressure :1500psi); Specific optical rotation ($[\alpha]_D$); (c 0.1 in MeOH)= -38.80.

Example 123: 7-amino-3-ethyl-5-((2-(1-(3-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



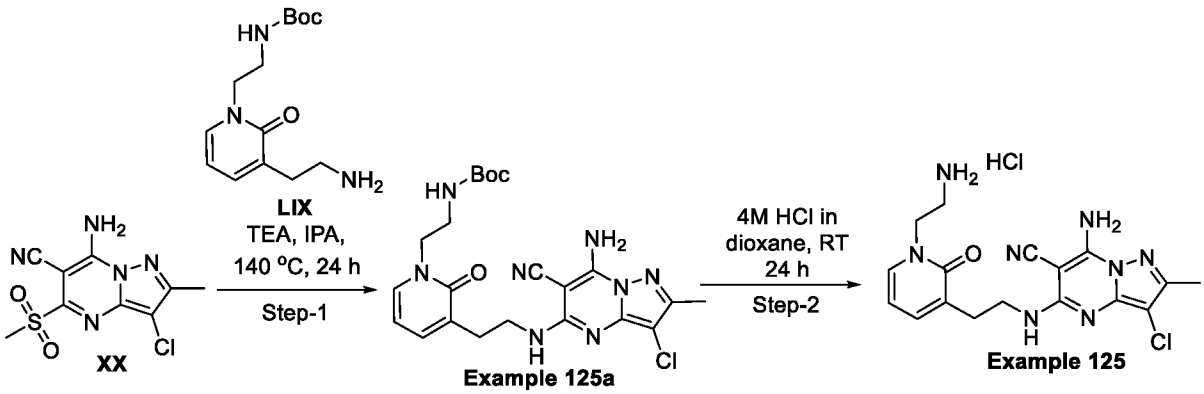
[000549] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.2 g, 0.716 mmol) in isopropanol (10 mL) was added (3-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclobutyl) methanol **LVIII** (0.3 g, 1 mmol). The mixture was purged with N_2 gas and triethylamine (0.5 mL, 4 mmol) was added. The resulting mixture was stirred at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature, diluted with water (20 mL), extracted with ethyl acetate (25 mL x 2). The combined organic layer was washed with brine (15 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crude product was purified by combi-flash (silica gel 230-400) column chromatography using ethyl acetate in *n*-hexane (0-50%) to afford the desired compound **Example 123** as pale-yellow solid. Yield: 45 mg (20 %); **LCMS** Calculated. for $C_{20}H_{26}N_8O$ is 394.22; Observed. 395.35 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.10 (bs, 2H), 7.69-7.66 (m, 1H), 6.64 (bs, 1H), 6.09-6.06 (m, 1H), 4.82 (t, J = 8.0 Hz, 1H), 4.67 (bs, 1H), 3.59-3.49 (m, 5H), 2.84 (t, J = 6.8 Hz, 2H), 2.45 (bs, 2H), 2.33 (bs, 2H), 2.24 (s, 3H), 2.21-2.19 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H). **HPLC**: 11.415 min; 97.65|%, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile, Flow: 1.0 mL/min.

Example 124: 7-amino-3-ethyl-5-((2-(1-(1-(2-hydroxyethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile



[000550] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methylsulfonyl)pyrazolo[1,5-*a*]pyrimidine-6-carbonitrile **II** (0.3 g, 1 mmol) and 2-(1-(3-(2-aminoethyl)-1H-pyrazol-1-yl)cyclopropyl)ethan-1-ol **LIV** (0.4 g, 2 mmol) in isopropanol (5 mL) in a sealed tube was added triethylamine (0.3g, 3 mmol) and the reaction mixture was stirred at 150 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature and diluted with water (50 mL) and extracted with ethyl acetate (20 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was subjected to silica gel (230-400 mesh) column chromatography using 0-70% ethyl acetate in *n*-hexane to afford the desired compound **Example 124** as off-white solid. Yield: 0.12 g (30%); **LCMS** Calculated. for $C_{20}H_{26}N_8O$ is 394.22; Observed. 395.35 [M^++1]. **^{1}HNMR (400 MHz, DMSO-D$_6$,):** δ 8.09 (bs, 2H), 7.61 (s, 1H), 6.57 (s, 1H), 6.03 (s, 1H), 4.37 (t, J = 6.4 Hz, 1H), 3.57 (q, J = 6.4 Hz, 2H), 3.33-3.28 (m, 2H), 2.81 (t, J = 6.4 Hz, 2H), 2.46-2.43 (m, 2H), 2.24 (s, 3H), 1.86 (t, J = 6.4 Hz, 2H), 1.13-1.07 (m, 5H), 0.90 (s, 2H). **HPLC**: 11.38 min; 99.24|%, INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile.

Example 125: 7-amino-5-((2-(1-(2-aminoethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



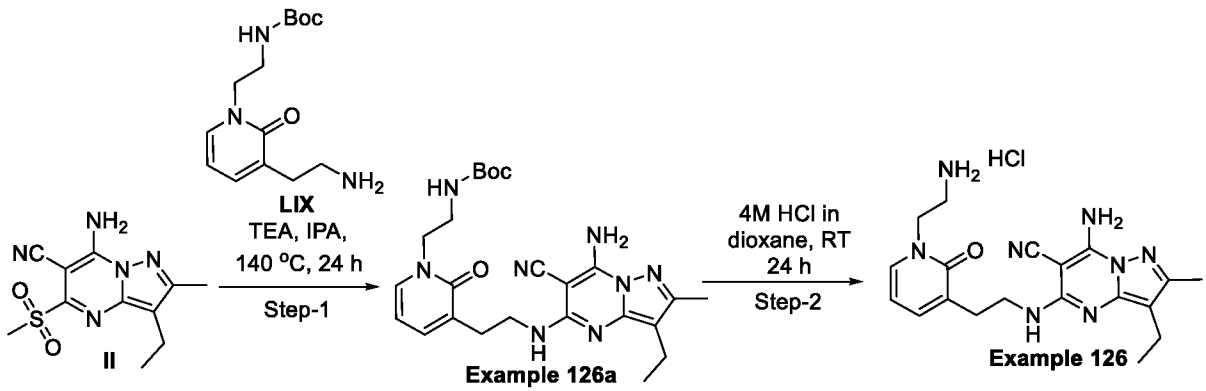
[000551] Step-1: tert-butyl (2-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-2-oxopyridin-1(2H)-yl) ethyl) carbamate (Example 125a). To a stirred solution of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX** (150 mg, 0.525 mmol) in 2-propanol (5 mL) was added triethylamine (319 mg, 439 µL, 3.15 mmol) and tert-butyl (2-(3-(2-aminoethyl)-2-oxopyridin-1(2H)-yl)ethyl)carbamate **LIX** and the reaction mixture was stirred at 140 °C for 24 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature and precipitated solid was filtered washed with MeOH and diethyl ether to afford desired pure product **Example 125a** as an off-white solid. Yield: 150 mg (59%). **LCMS** Calculated. for $C_{22}H_{27}ClN_8O_3$ is 486.18; Observed. 487.35 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.31 (bs, 2H), 7.36-7.29 (m, 2H), 7.07 (s, 1H), 6.88 (s, 1H), 6.15 (t, J = 6.4 Hz, 1H), 5.14 (bs, 1H), 3.92 (s, 2H), 3.54-3.53 (m, 2H), 3.24-3.23 (m, 2H), 2.74 (t, J = 6.0 Hz, 2H), 2.27 (s, 3H), 1.33 (s, 9H).

[000552] Step-2: 7-amino-5-((2-(1-(2-aminoethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile hydrochloride salt

[000553] To a stirred solution of tert-butyl (2-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-2-oxopyridin-1(2H)-yl) ethyl) carbamate **Example 125a** (150 mg, 0.308 mmol) in dioxane (5 mL) was cooled to 0 °C and was added 4.0 M hydrogen chloride in dioxane (112 mg, 770 µL, 3.08 mmol). The reaction mixture was stirred at room temperature for 24 hours. The progress of the reaction was monitored by TLC analysis. After

completion, the reaction mixture was concentrated under reduced pressure and obtained solid was washed with diethyl ether (2 mL X 2) to afford the title compound **Example 125** as off-white solid as a HCl salt. Yield: 100 mg, (84.03 %); **LCMS** Calculated. for $C_{17}H_{19}ClN_8O$ is 386.13; Observed: 387.35 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.38 (bs, 2H), 8.09 (bs, 2H), 7.57 (bs, 1H), 7.37 (bs, 1H), 7.06 (bs, 1H), 6.25 (bs, 1H), 4.60 (bs, 2H), 4.17 (s, 2H), 3.16 (s, 2H), 2.76 (s, 2H), 2.27 (s, 3H). **HPLC** Purity = 99.18 %; Rt= 7.827 min; INT ODS 3V-C18 (4.6 x 250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile.

Example 126: 7-amino-5-((2-(1-(2-aminoethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000554] Step-1: *tert*-Butyl (2-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-2-oxopyridin-1(2H)-yl) ethyl) carbamate (Example 126a)

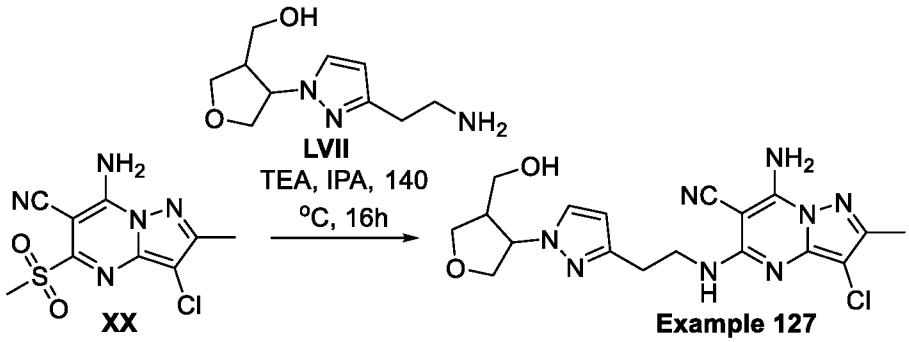
[000555] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methylsulfonyl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile **II** (200 mg, 0.716 mmol) in 2-propanol (5 mL) were added triethylamine (435 mg, 599 µL, 4.30 mmol) and tert-butyl (2-(3-(2-aminoethyl)-2-oxopyridin-1(2H)-yl)ethyl)carbamate **LIX** (423 mg, 1.50 mmol) and the reaction mixture was stirred at 140 °C for 24 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using 1-5% MeOH in DCM to afford the desired compound **Example 126a** as off-white solid. Yield: 180 mg

(52%). **LCMS** Calculated. for $C_{24}H_{32}N_8O_3$ is 480.25; Observed. 481.35 $[M+H]^+$; **^{1}HNMR (400 MHz, DMSO-D$_6$):** δ 8.05 (s, 2H), 7.36-7.270 (m, 2H), 6.87 (s, 1H), 6.71 (s, 1H), 6.15 (t, J = 6.4 Hz, 1H), 3.92 (s, 2H), 3.51 (t, J = 4.8 Hz, 2H), 3.23 (d, J = 4.8 Hz, 2H), 2.73 (s, 2H), 2.45 (d, J = 7.6 Hz, 2H), 2.24 (s, 3H), 1.33-1.23 (m, 9H), 1.10 (t, J = 7.2 Hz, 3H).

Step-2: 7-amino-5-((2-(1-(2-aminoethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile hydrochloride salt

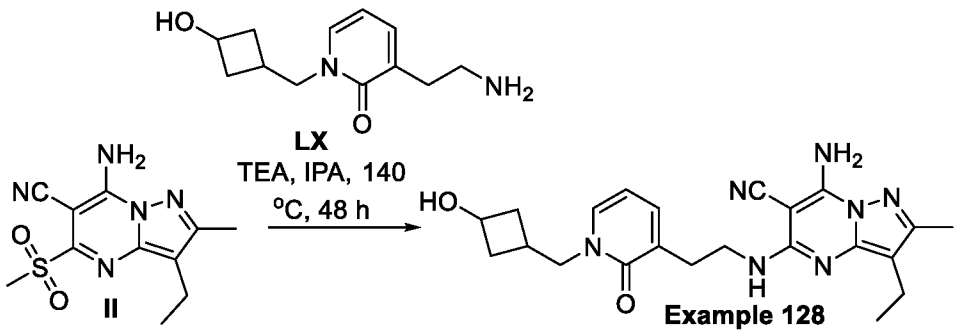
[000556] To a stirred solution of tert-butyl (2-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-2-oxopyridin-1(2H)-yl) ethyl) carbamate **Example 126a** (180 mg, 0.375 mmol) in dioxane (5 mL) was cooled to 0 °C and was added 4.0 M hydrogen chloride in dioxane (137 mg, 936 µL, 3.75 mmol). The reaction mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was concentrated under reduced pressure and obtained solid was washed with diethyl ether (2 mL X 2) to afford the title compound **Example 126** as off-white solid as a HCl salt. Yield: (120 mg, 84 %); **LCMS** Calculated. for $C_{19}H_{24}N_8O$ is 380.20; Observed. 381.35 $[M+H]^+$; **^{1}HNMR (400 MHz, DMSO-D$_6$):** δ 8.23 (s, 2H), 8.06 (s, 2H), 7.58 (d, J = 6.0 Hz, 1H), 7.38 (d, J = 6.0 Hz, 1H), 6.94 (s, 1H), 6.27 (t, J = 6.0 Hz, 1H), 4.16 (s, 2H), 3.56 (m, 4H), 3.17 (d, J = 4.8 Hz, 2H), 2.77 (s, 2H), 2.25 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H). **HPLC:** 97.69 %.

Example 127: 7-amino-3-chloro-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000557] To a stirred solution of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo [1,5-a] pyrimidine-6-carbonitrile **XX** (0.15 g, 0.53 mmol) in 2-propanol (20 mL) was added (4-(3-(2-aminoethyl)-1H-pyrazol-1-yl) tetrahydrofuran-3-yl) methanol **LVII** (0.20 g, 0.95 mmol). The mixture was purged with N_2 gas for 5 min and TEA (0.44 mL, 3.2 mmol) was added. The resulting mixture in a sela tube was stirred at 140 °C for 16 h. The progress of reaction was monitored by TLC analysis. After completion, the reaction was cooled to room temperature and the reaction mixture was diluted with water (20 mL). The mixture was extracted with ethyl acetate (25 mL X 3). The combined organic layer was given brine wash, dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude material was purified by Biotage (230-400 silica gel) using 0- 3% methanol in DCM to afford the desired compound **Example 127** as an off-white solid. Yield: 78 mg, (36 %); **LCMS** Calculated. for $C_{18}H_{21}ClN_8O_2$ is 416.14; Observed.: 417.30 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.40 (bs, 2H), 7.67 (s, 1H), 6.95 (bs, 1H), 6.12 (bs, 1H), 4.86 (bs, 1H), 4.69-4.68 (m, 1H), 4.08-3.99 (m, 2H), 3.86-3.83 (m, 1H), 3.62-3.59 (m, 3H), 3.45 (bs, 2H), 2.84 (t, J = 7.2 Hz, 2H), 2.68 (bs, 1H), 2.28 (s, 3H). **HPLC**: 10.616 min; 99.62%, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile, Flow: 1.0 mL/min:

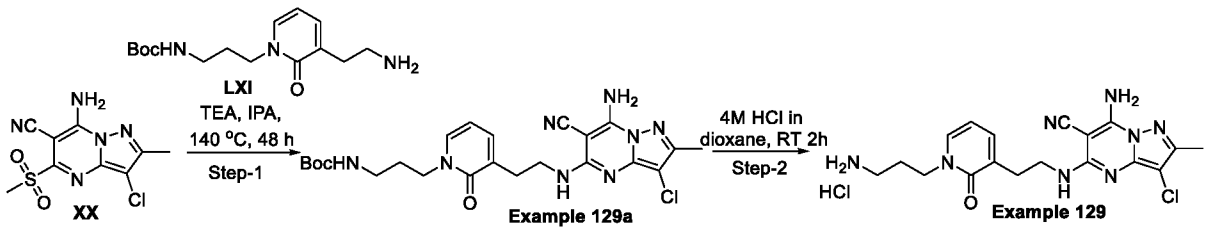
Example 128: 7-amino-3-ethyl-5-((2-(1-((3-hydroxycyclobutyl) methyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile.



[000558] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (200 mg, 0.716 mmol) in isopropanol (6 mL) were added TEA (0.599 mL, 4.30 mmol) and 3-(2-

aminoethyl)-1-((3-hydroxycyclobutyl) methyl) pyridin-2(1H)-one **LX** (350 mg, 1.58 mmol) in a sealed tube. The resulting mixture was stirred at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was diluted with water (25 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The compound was purified by flash column chromatography (silica gel 230-400) by eluting with methanol in DCM (0-5%) to afford the desired compound **LX** as off-white solid. Yield: 15 mg (5 %); **LCMS** Calculated. for $C_{22}H_{27}N_7O_2$ is 421.22; Observed. 422.35 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.05 (bs, 2H), 7.50 (bs, 1H), 7.26 (bs, 1H), 6.69 (bs, 1H),6.13 (bs, 1H), 5.00 (bs, 1H), 3.89 (bs, 3H), 3.51 (bs, 2H), 2.73-2.67 (m, 2H), 2.24-2.15 (m, 7H), 1.57 (bs, 2H), 1.24 (bs, 1H), 1.10 (bs, 3H). **HPLC**: 9.608 min; 96.45%, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 129: 7-amino-5-((2-(1-(3-aminopropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Step-1: tert-butyl (3-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate (Example 129a)

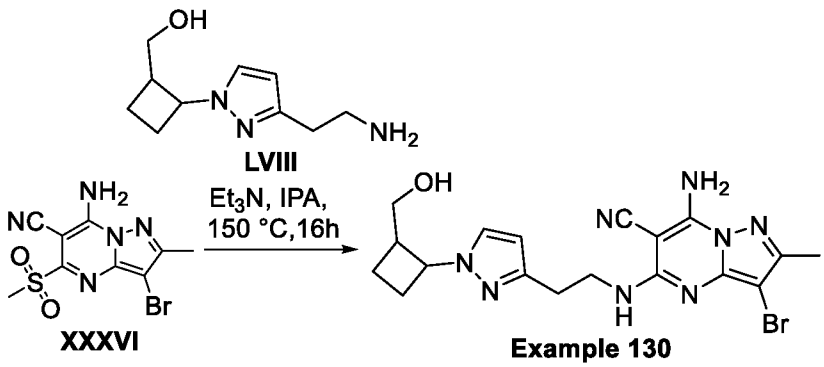
[000559] To a solution of 7-amino-3-chloro-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XX** (0.3 g, 1.05 mmol) in isopropyl alcohol (10 mL) were added triethylamine (0.878 mL, 6.30 mmol) and tert-butyl (3-(3-(2-aminoethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate **LXI** (0.682 g, 2.31 mmol). The reaction mixture was stirred at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to rt and added water (10 mL). The mixture was extracted with ethyl acetate (50 mL X 2). The combined organic layer was dried over anhydrous sodium

sulphate and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) with methanol in dichloromethane (0-10%) to afford the desired product **Example 129a** as an off-white solid. Yield: 0.3 g, (50.0 %); **LCMS** Calculated. for $C_{23}H_{29}ClN_8O_3$ is 500.99; Observed. 501.40 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.35 (s, 2H), 7.56 (d, *J*=6.4 Hz, 1H), 7.28 (d, *J*=6.4 Hz, 1H), 7.07 (t, *J*=4.8 Hz, 1H), 6.85 (s, 1H), 6.17 (t, *J*= 6.8 Hz, 1H), 3.88 (t, *J*=6.8 Hz, 2H), 3.55 (t, *J*= 6.4 Hz, 2H), 2.92 (d, *J*= 6Hz, 2H), 2.74 (t, *J*=6.8 Hz, 2H), 2.27 (s, 3H), 1.74 (t, *J*=6.8 Hz, 2H), 1.34 (m, 9H)..

Step-2: 7-amino-5-((2-(1-(3-aminopropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

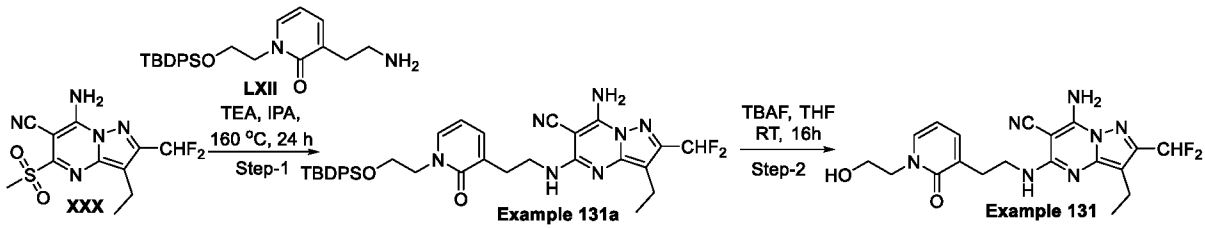
[000560] To a solution of tert-butyl (3-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate **Example 129a** (0.3 g, 0.599 mmol) in 1,4-dioxane (4 mL) was added 4 M HCl in dioxane (0.30 mL, 1.20 mmol) and stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was concentrated, triturated with diethyl ether and *n*-pentane, dried to afford the desired product **Example 129** as an off-white solid. Yield: 0.125 g, (52.1 %); **LCMS** Calculated. for $C_{18}H_{21}ClN_8O$ is 400.15; Observed: 401.3 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.38 (s, 2H), 8.16 (bs, 3H), 7.67 (s, 1H), 7.33 (s,1H), 7.11 (s, 1H), 6.23 (s, 1H), 4.03 (s, 2H), 3.57 (s, 2H), 2.76 (s, 3H), 2.27 (s, 3H), 2.00 (s, 2H). **HPLC**: 7.796 min; 99.01 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 130: 7-amino-3-bromo-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000561] To a solution of 7-amino-3-bromo-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXXVI** (0.17 g, 0.515 mmol) in isopropyl alcohol (10 mL) were added (2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclobutyl) methanol **LVIII** (0.201 g, 1.03 mmol) and triethylamine (0.431 mL, 3.09 mmol) and the reaction mixture was stirred at 150 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction was cooled to rt, added water (50 mL) and extracted with ethyl acetate (25 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford the crude compound. The crude compound was purified by silica gel (60-120 mesh) column chromatography with methanol in dichloromethane (0-5%) to afford the desired product **Example 130** as an off-white. Yield: 50 mg, (22 %); **LCMS** Calculated. for $C_{18}H_{21}BrN_8O$ is 444.10; Observed. 445.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.39 (s, 2H), 7.66 (s, 1H), 7.00 (s, 1H), 6.09 (s, 1H), 4.60 (t, *J* = 5.2 Hz, 1H), 4.51 (q, *J* = 8.8 Hz, 1H), 3.61 (q, *J* = 6.0 Hz, 2H), 3.40 (t, *J* = 4.8 Hz, 2H), 2.83 (q, *J* = 7.2 Hz, 3H), 2.37-2.29 (m, 2H), 2.27-2.18 (m, 1H), 1.79 (q, *J* = 9.6 Hz, 2H), 1.58(m, 2H). **HPLC**: 11.722 min; 95.47 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 131: 7-amino-2-(difluoromethyl)-3-ethyl-5-((2-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Step-1: tert-butyl (3-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate (Example 131a)

[000562] To a solution of 7-amino-2-(difluoro methyl)-3-ethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **XXX** (0.3 g, 0.951mmol) in isopropyl alcohol (4 mL) were added 3-(2-aminoethyl)-1-(2-((tert-butyl diphenyl silyl) oxy) ethyl) pyridin-2(1H)-one **LXII** (0.8 g, 1.90 mmol) and triethylamine (0.796 mL, 5.71 mmol). The reaction mixture was stirred at 160 °C for 24 h. The progress of the reaction was monitored by TLC analysis. After the completion, added water (50 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the desired compound **Example 131a** as a pale-yellow solid. The crude compound was taken for the next step without any further purification. Yield: 0.4 g, (64 %); **LCMS** Calculated. for $C_{35}H_{39}F_2N_7O_2Si$ is 655.29; Observed: 656.45 $[M+H]^+$.

Step-2: 7-amino-5-((2-(1-(3-aminopropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

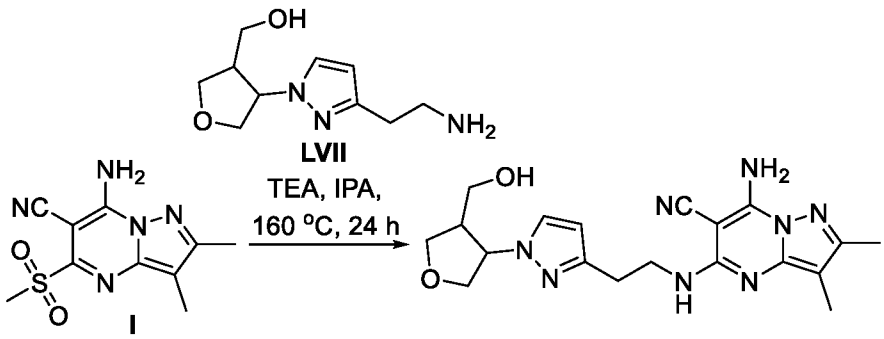
[000563] To a solution of 7-amino-5-((2-(1-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2-oxo-1,2-dihydropyridin-3-yl)ethyl)amino)-2-(difluoromethyl)-3-ethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile **Example 131a** (0.4 g, 0.61mmol) in tetrahydrofuran (10 mL) was added TBAF (1.22 mL, 1M in THF, 1.22 mmol) and the reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, added sat. $NaHCO_3$ (20 mL) and filtered the solid to afford the desired title product **Example 131** as an off-white solid. Yield: 0.19 g, (75 %); **LCMS** Calculated. for $C_{19}H_{21}F_2N_7O_2$ is 417.17; Observed: 418.30 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-d_6,):** δ 8.38 (bs, 2H), 7.48-6.90 (m, 4H), 6.14 (s, 1H), 4.85 (s, 1H),

3.95 (s, 2H), 3.63-3.54 (m, 4H), 2.76 (s, 3H), 1.15 (s, 3H). **HPLC**: 10.959 min; 99.46 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 132. (+-)-7-amino-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile .

Example 133a. (+)-7-amino-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

Example 133b. (-)-7-amino-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile .



[000564] To a solution of (4-(3-(2-aminoethyl)-1H-pyrazol-1-yl) tetrahydrofuran-3-yl) methanol **LVII** (0.2 g, 0.8 mmol) and 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (0.3 g, 2 mmol) in isopropyl alcohol (20 mL) was added triethylamine (0.8 mL, 6 mmol) and the reaction mixture was stirred at 140 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was cooled to rt, added water (20 mL) and extracted with ethyl acetate (25 mL X 3). The combined organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude material. The

crude compound was purified by silica gel (230-400 mesh) column chromatography using methanol dichloromethane (0-3%) to afford the desired product **Example 132** as off-white solid. Yield: 0.3 g, (46.0%); **LCMS** Calculated. for $C_{19}H_{24}N_8O_2$ is 396.20; Observed: 397.35 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (bs, 2H), 7.67 (d, *J* = 2.0 Hz, 1H), 6.58 (t, *J* = 5.2 Hz, 1H), 6.11 (d, *J* = 2.0 Hz, 1H), 4.85 (t, *J* = 5.2 Hz, 1H), 4.67 (m, 1H), 4.08-3.99 (m, 2H), 3.87-3.83 (m, 1H), 3.62-3.59 (m, 3H), 3.57-3.42 (m, 2H), 2.83 (t, *J* = 8.0 Hz, 2H), 2.69-2.65 (m, 1H), 2.23 (s, 3H), 1.97 (s, 3H). **HPLC**: 10.060 min; 95.02 %; INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water; Mobile phase B : Acetonitrile.

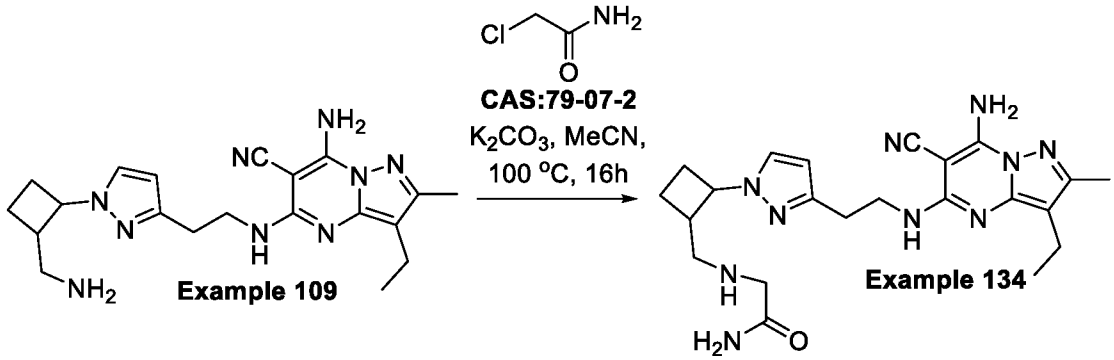
[000565] Further the racemic compound **Example 132** was subjected to chiral SFC (Column Name: Chiral Pak IG (250*21) mm, 5µ; Mobile phase: A: 0.1%DEA In Hex, B: EtOH (70:30); Flow :1.0 mL/min and separated into peak-1, **Example 133a** (and peak-2, **Example 133b,**

[000566] **Peak-1: Example 133a** Yield: 37 mg. **LC-MS** Calculated. for $C_{19}H_{24}N_8O_2$ is 396.20; Observed: 397.35 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** *δ* 8.11 (bs, 2H), 7.67 (bs, 1H), 6.58 (t, *J* = 5.2 Hz, 1H), 6.12 (bs, 1H), 4.85 (t, *J* = 5.2 Hz, 1H), 4.69-4.67 (m, 1H), 4.08-3.99 (m, 2H), 3.87-3.83 (m, 1H), 3.62-3.56 (m, 3H), 3.46-3.42 (m, 2H), 2.83 (t, *J* = 8.0 Hz, 2H), 2.69-2.65 (m, 1H), 2.23 (s, 3H), 1.97 (s, 3H). **HPLC**: 9.942 min; 99.40 %, INT ODS 3V-C18 (4.6 * 250) mm, 5µ; Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile.; **Chiral HPLC:** 15.018 min; 100%; Column Name- Chiral Pak IG (250*4.6) mm, 5µ; Mobile phase: A:0.1% DEA In Hex, B: EtOH (70:30) Flow :1.0 mL/min; % of Co-Solvent: 30; Temperature: 30 °C; ABPR pressure :1500psi); Flow :1.0 mL/min.

[000567] **Peak-2: Example 133b);** Yield: 31.6 mg. **LCMS** Calculated. for $C_{19}H_{24}N_8O_2$ is 396.2; Observed : 397.35 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** *δ* 8.10 (bs, 2H), 7.67 (s, 1H), 6.58 (bs, 1H), 6.12 (s, 1H), 4.85 (t, *J* = 5.2 Hz, 1H), 4.68 (d , *J* = 6.0 Hz, 1H), 4.08-3.99 (m, 2H), 3.87-3.83 (m, 1H), 3.62-3.58 (m, 3H), 3.46 (bs, 2H), 2.83 (t, *J* = 6.8 Hz, 2H), 2.67 (bs, 1H), 2.23 (s, 3H), 1.97 (s, 3H). **HPLC**: 9.947 min; 96.76 %, INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile; Flow: 1.0 mL/min;

Chiral HPLC: 19.618 min; 97.13%; Column Name- Chiral Pak IG (250*4.6) mm, 5µ; Mobile phase: A:0.1% DEA In Hex, B: EtOH (70:30); Flow :1.0 mL/min; % of Co-Solvent: 30; Temperature: 30 °C; ABPR pressure :1500 psi).

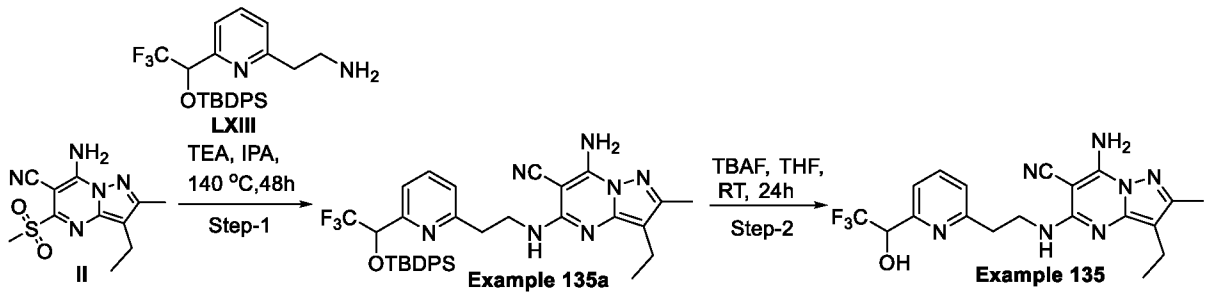
Example 134: 2-(((2-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclobutyl) methyl) amino) acetamide



[000568] To a stirred solution of 7-amino-5-((2-(1-(2-(amino methyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 109** (150 mg, 0.381 mmol) in acetonitrile (5 mL) was added K_2CO_3 (79.0 mg, 0.572 mmol) and the resulting mixture was stirred at rt for 5 min. This was followed by an addition of 2-chloroacetamide (CAS: CAS:79-07-2, 39.2 mg, 0.419 mmol) at 0 °C and the reaction mixture was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt, diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was subjected to silica gel (230-400) flash column chromatography using methanol in DCM (0-10%) to afford the desired compound **Example 134** as an off-white solid. Yield: 25 mg (14.5%); **LCMS** Calculated. for $C_{23}H_{31}N_9O$ is 450.26; Observed: 449.30 $[M-H]^+$. **^{1}H NMR (400 MHz, DMSO-D_6,):** δ 8.10 (s, 2H), 7.68 (s, 1H), 7.21 (s, 1H), 7.01 (s, 1H), 6.66 (s, 1H), 6.07 (s, 1H), 4.45 (d, *J*=7.6 Hz,1H), 3.48 (s, 3H), 2.96 (s, 2H), 2.83 (s, 4H), 2.38-2.24 (m, 7H), 1.89 (s, 1H), 1.48 (s, 2H), 1.12 (bs, 4H). **HPLC**: 8.133 min;

95.40%, INT ODS 3V-C18 (4.6*250) mm, 5µ, Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile.

Example 135: 7-amino-3-ethyl-2-methyl-5-((2-(6-(2,2,2-trifluoro-1-hydroxyethyl) pyridine-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6 carbonitrile



Step-1: 7-amino-5-((2-(6-(1-((tert-butyl diphenyl silyl) oxy)-2,2,2-trifluoroethyl) pyridin-2-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 135a)

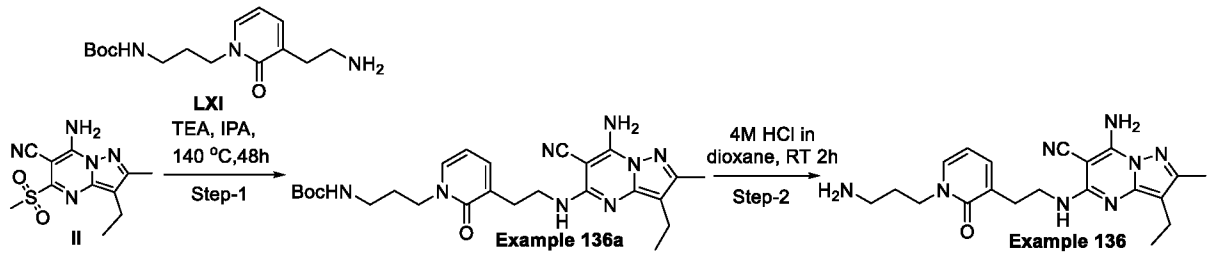
[000569] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.48 g, 1.7 mmol) in isopropanol (10 mL) was added triethylamine (1.4 mL, 10 mmol) and the resulting mixture was purged with N_2 gas in seal tube for 5 min. This was followed by an addition of 2-(6-(1-((tert-butyl diphenyl silyl) oxy)-2,2,2-trifluoroethyl) pyridin-2-yl) ethan-1-amine **LXIII** (1.6 g, 3.4 mmol) and reaction mixture was stirred at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to rt and quenched with water (50 mL). The resulting mixture was extracted with (100 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the desired compound **Example 135a** as a pale-yellow viscous liquid. The crude was taken for next step without further purification. Yield: 1.0g, (90.9%); **LCMS** Calculated. for $C_{35}H_{38}F_3N_7OSi$ Is 657.29; Observed: 656.40 $[M-H]^+$.

Step-2: 7-amino-3-ethyl-2-methyl-5-((2-(6-(2,2,2-trifluoro-1-hydroxyethyl) pyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000570] To a stirred solution of 7-amino-5-((2-(6-(1-((tert-butyl diphenyl silyl) oxy)-2,2,2-trifluoroethyl) pyridin-2-yl) ethyl) amino)-3-ethyl-2-

methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 135a** (1 g, 2 mmol) in THF (70 mL) was added TBAF (4 mL, 1M in THF, 4 mmol). The reaction mixture was stirred at rt for 24 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with sat. $NaHCO_3$ (50 mL) and extracted with DCM (100 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified silica gel (230-400) column chromatography using 1-5 % MeOH in DCM to afford the desired compound **Example 135** as an off-white solid. Yield: 400mg (66.0%); **LCMS** Calculated. for $C_{19}H_{20}F_3N_7O$ is 419.17; Observed.: 420.10 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.12 (bs, 2H), 7.83 (t, *J*=7.6 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 6.96 (d, 5.6 Hz,1H), 6.92 (bs, 1H), 5.16 (t, *J*=7.2 Hz, 1H), 3.68 (t, *J*= 4.8 Hz, 2H), 3.06 (t, *J*= 6.4 Hz, 2H), 2.50-2.43 (m, 2H), 2.25 (s, 3H), 1.12 (t, *J*=7.6 Hz, 3H); **HPLC Purity** = 98.69%, INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile Phase A: 0.1% Formic acid in water: Mobile Phase B: Acetonitrile; Retention time = 12.84 min

Example 136: 7-amino-5-((2-(1-(3-aminopropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Step-1: tert-butyl (3-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate (Example 136a)

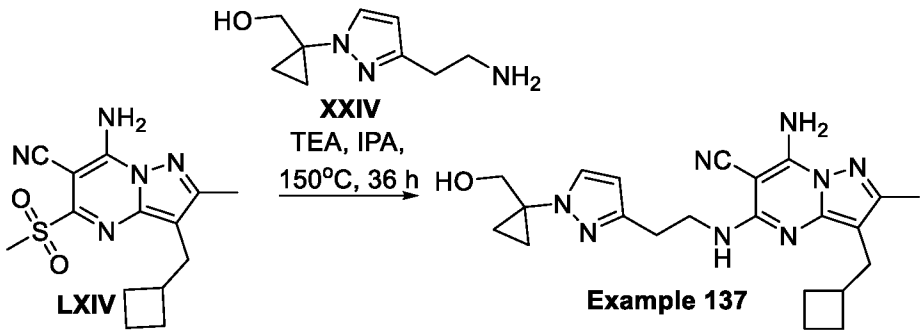
[000571] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (180 mg, 0.644 mmol) in isopropanol (6 mL) were added triethylamine (391 mg, 539 µL, 3.87 mmol) and tert-butyl (3-(3-(2-aminoethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate **LXI** (381 mg, 1.29 mmol) in a sealed tube. The reaction mixture was stirred at 140 °C for 48 h and the progress of the reaction was monitored by TLC

analysis. After completion, water (15 mL) was added and extracted with ethyl acetate (25 mL X 2). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The compound was purified by flash column chromatography (silica gel, 230-400) using methanol in DCM (0-10%) to afford the desired compound **Example 136a** as an off-white solid. Yield**:** 95 mg (30 %) **LCMS** Calculated. for $C_{25}H_{34}N_8O_3$ is 494.28 Observed. 495.20 $[M+H]^+$: **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.05 (bs, 2H), 7.55 (d, *J*= 6.4 Hz, 1H), 7.27 (d, *J* = 6.4 Hz, 1H), 6.84 (bs, 1H), 6.16 (*t*, *J* = 6.8 Hz, 1H), 3.90-3.87 (m, 3H), 3.52-3.50 (m, 2H), 2.92 (d, *J* = 6.0 Hz, 2H), 2.73 (t, *J*= 6.4 Hz, 2H) 2.45-2.41 (m, 2H), 2.24 (s, 3H) 1.74 (t, *J*= 6.4 Hz, 2H), 1.38 (bs, 9H), 1.10 (t, *J*=7.2 Hz, 3H).

Step-2: 7-amino-5-((2-(1-(3-aminopropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

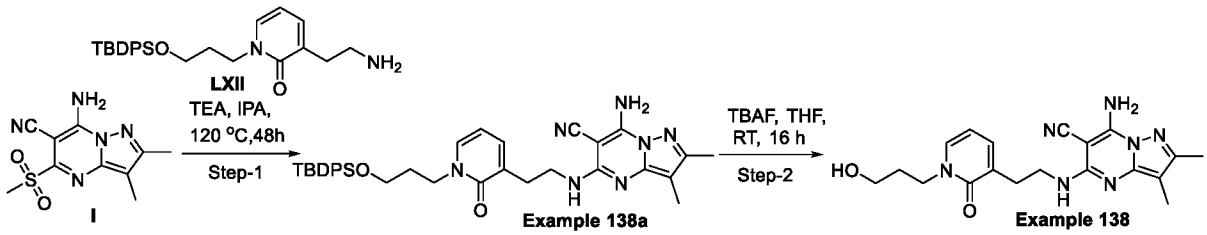
[000572] To a stirred solution of tert-butyl (3-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate) **Example 136a** (95 mg, 0.19 mmol) in 1,4-dioxane (3 mL) at 0 °C was drop wise added 4M HCl in dioxane (9.4 µL, 0.38 mmol) under inert atmosphere. The mixture was stirred at rt for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, sat. sodium bicarbonate solution (5 mL) was added and extracted with DCM (25 mL X 2). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to afford the desired compound **Example 136** as an off-white solid. Yield: 35 mg (46%) **LCMS** Calculated. for $C_{20}H_{26}N_8O$ is 394.22 $[M+H]^+$; Observed. 395.40 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.03 (bs, 4H), 7.63 (d, *J*=6.0 Hz, 1H), 7.31 (d, *J* = 6.8 Hz, 1H), 6.71 (t, *J* = 5.2 Hz, 1H), 6.22 (t, *J*=6.8 Hz, 1H), 4.01 (t, *J* = 6.8 Hz, 2H), 3.55-3.50 (m, 2H), 3.66-3.64 (m, 2H), 2.77 (t, *J* = 6.8 Hz, 4H), 2.44-2.42 (m, 2H), 2.25 (s, 3H), 1.98 (t, *J*=6.8 Hz, 1H), 1.11(t, *J*= 7.6 Hz, 2H); **HPLC** Purity = 98.23%, INT ODS 3V-C18 (4.6*250)mm,5µ; Mobile Phase A: 0.1% Formic acid in water: Mobile Phase B: Acetonitrile; Retention time = 7.972 min; Flow : 1.0 mL/min.

Example 137: 7-amino-3-(cyclobutylmethyl)-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000573] In a seal tube 7-amino-3-(cyclobutylmethyl)-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyridine-6carbonotrile **LXIV** (130 mg, 0.407 mmol) and (1-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclopropyl) methanol **XXIV** (184 mg, 1.02 mmol) were dissolved in isopropanol (10 mL). To this solution TEA (0.340 mL, 2.44 mmol) was added and the reaction mixture was stirred at 150 °C for 36 h. The progress of reaction was monitored by TLC analysis. After completion, reaction was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in water (10 mL) and extracted with ethyl acetate (10 mL X 3). The combined organic layer was washed with brine and dried over anhydrous sodium sulphate. The solution was concentrated under reduced pressure and crude material was purified by flash chromatography (Biotage) column using 0-5% methanol in DCM to afford the desired compound **Example 137** as an off-white solid. **Yield:** 60 mg (35%); **LCMS** Calculated. for $C_{22}H_{28}N_8O$ is 420.24; Observed: 421.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.09 (bs, 2H), 7.62 (s, 1H), 6.64 (t, *J* = 5.2 Hz, 1H), 6.04 (s, 1H), 4.88 (t, *J*=6.0 Hz, 1H), 3.60-3.54 (m , 4H), 2.81 (t, *J*=7.2 Hz, 2H), 2.59-2.50 (m, 3H), 2.23 (s, 3H), 1.92 (bs, 2H), 1.78-1.67 (m, 4H), 1.09(d, *J*= 6.8 Hz, 2H) 0.96 (t, *J*=4.8 Hz, 2H); **HPLC** Purity = 97.23%, INT ODS 3V-C18 (4.6 x 250) mm, 5µ; Mobile Phase A: 0.1% Formic acid in water: Mobile Phase B: Acetonitrile; Retention time =12.68 min.

Example 138: 7-amino-5-((2-(1-(3-hydroxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



Step-1: 7-amino-5-((2-(1-(3-((tert-butyl diphenyl silyl) oxy) propyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 138a)

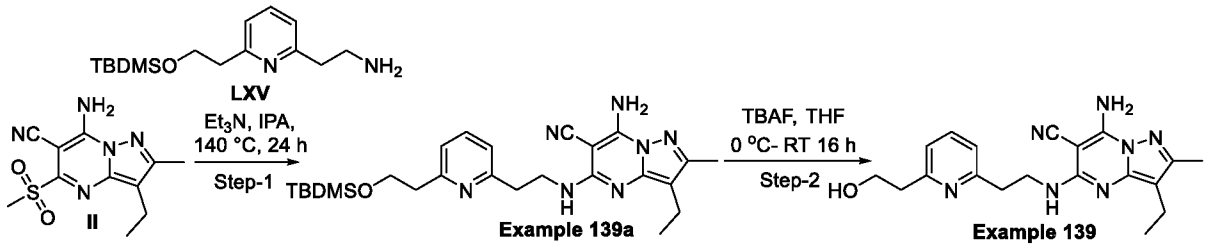
[000574] To a stirred solution of 7-amino-2,3-dimethyl-5-(methylsulfonyl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile **I** (0.25 g, 0.94 mmol) in isopropanol (5 mL) were added triethylamine (0.57 g, 0.79 mL, 5.7 mmol) and 3-(2-aminoethyl)-1-(3-((tert-butyldiphenylsilyl)oxy)propyl)pyridin-2(1H)-one **LXII** (1.2 g, 2.8 mmol) and the reaction mixture was stirred at 120 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature and quenched with water (50 mL). The resulting mixture was extracted with ethyl acetate (25 mL X 3), and the combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the desired compound **Example 138a** as yellow liquid. Yield: (0.25 g, 43.1%); **LCMS** Calculated. for $C_{35}H_{41}N_7O_2Si$ is 619.31; Observed. 620.30 $[M+H]^+$; **^{1}HNMR (400 MHz, $CDCl_3$):** δ 7.80-7.71 (m, 2H), 7.65-7.64 (d, 2H), 7.44-7.38 (m, 8H), 7.24-7.20 (m, 2H), 6.96 (d, J = 8.8 Hz, 1H), 6.10 (t, J = 7.6 Hz, 1H), 4.15-4.09 (m, 2H), 3.87-3.85 (m, 2H), 3.68 (t, J = 5.2 Hz, 2H), 3.08 (s, 2H), 2.79-2.76 (m, 2H), 2.05 (s, 3H), 1.97 (s, 3H), 1.08 (s, 9H).

Step-2: 7-amino-5-((2-(1-(3-hydroxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000575] To a stirred solution of 7-amino-5-((2-(1-(3-((tert-butyldiphenylsilyl)oxy)propyl)-2-oxo-1,2-dihydropyridin-3-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile **Example 138a** (0.25 g, 0.40 mmol) in THF (10 mL) was added TBAF (0.8 mL, 1 M in THF, 0.81 mmol) and the reaction mixture was stirred at room temperature for 16 h. The

progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched with saturated $NaHCO_3$ (200 mL) and extracted with DCM (300 mL X 3), and the combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using (1-5%) MeOH in DCM to afford the desired compound **Example 138** as off-white solid. Yield: 0.080 g, (52 %); **LCMS** Calculated. for $C_{19}H_{23}N_7O_2$ is 381.19; Observed. 382.30 $[M+H]^+$; **^{1}HNMR (400 MHz, DMSO-d_6,):** δ 8.05 (s, 2H), 8.51 (d, *J* = 6.0 Hz, 1H), 7.28 (d, *J* = 6.0 Hz, 1H), 6.69 (s, 1H), 6.16 (t, *J* = 6.8 Hz, 1H), 4.58 (t, *J* = 4.8 Hz, 1H), 3.94 (t, *J* = 6.8 Hz, 2H), 3.53 (d, *J* = 5.6 Hz, 2H), 3.38 (s, *J* = 5.6 Hz, 2H), 2.74 (t, *J* = 6.4 Hz, 2H), 2.22 (s, 3H), 1.95 (s, 3H), 1.78 (t, *J* = 6.4 Hz, 2H). **HPLC**: Rt = 9.176 min; purity = 95.99%; INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile.

Example 139: 7-amino-3-ethyl-5-((2-(6-(2-hydroxyethyl) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Step-1: 7-amino-5-((2-(6-(2-((tert-butyldimethylsilyl) oxy) ethyl) pyridin-2-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 139a)

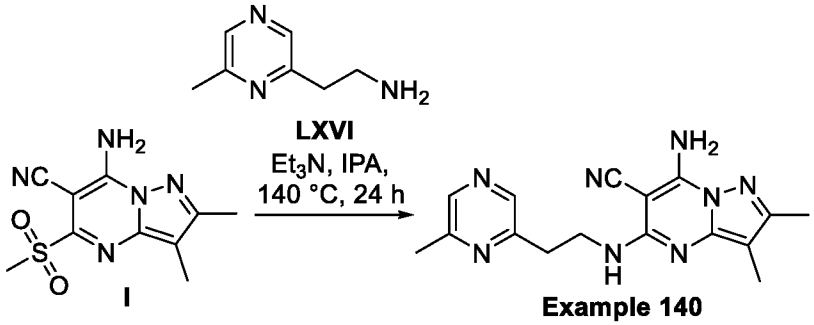
[000576] To a stirred solution of 2-(6-(2-((tert-butyldimethylsilyl) oxy) ethyl) pyridin-2-yl) ethan-1-amine **LXV** (0.26 g, 0.93 mmol) in 2-propanol (20 mL) was added 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **II** (0.52 g, 1.9 mmol) and triethylamine (0.28 g, 0.39 mL, 2.8 mmol) under nitrogen. The resulting mixture was stirred at 140 °C for 24 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature and diluted with water (30 mL) then

extracted with ethyl acetate (45 mL X 2). The combined organic layer was washed with 25 mL of brine and passed through anhydrous sodium sulphate then concentrated under reduced pressure. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using 0-15% ethyl acetate in *n*-hexane to afford the desired compound **Example 139a** as a pale-yellow viscous liquid. Yield: 0.2 g, 40%); **LCMS** Calculated. for $C_{25}H_{37}N_7OSi$ is 479.28; Observed. 480.45 $[M+H]^+$; **^{1}HNMR (400 MHz, $CDCl_3$):** δ 7.51 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 6.44 (bs, 1H), 5.94 (bs, 2H), 4.01 (t, J = 6.0 Hz, 2H), 3.87 (q, J = 6.0 Hz, 2H), 3.08-3.02 (m, 4H), 2.56 (q, J = 7.2 Hz, 2H), 2.32 (s, 3H), 1.19 (t, J = 6.0 Hz, 3H), 0.86 (s, 9H), 0.08 (s, 6H).

Step-2: 7-amino-3-ethyl-5-((2-(6-(2-hydroxyethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-*a*] pyrimidine-6-carbonitrile

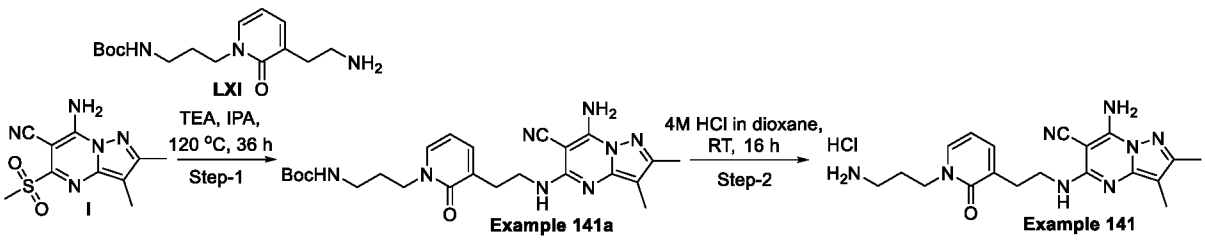
[000577] To a stirred solution of 7-amino-5-((2-(6-(2-((tert-butyldimethylsilyl) oxy) ethyl) pyridin-2-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **Example 139a** (0.20 g, 0.42 mmol) in THF (10 mL) was added TBAF (0.84 mL, 1M in THF, 0.84 mmol) and reaction mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under *vacuo* to afford a desired compound. The crude compound was washed with *n*-pentane (5 mL). to afford pure desired product **Example 139** as an off-white solid. Yield: 0.11 g (72%); **LCMS** Calculated. for $C_{19}H_{23}N_7O$ is 365.19; Observed. 366.35 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.10 (bs, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.11-7.10 (m, 2H), 6.85 (t, J = 4.8 Hz, 1H), 4.61 (bs, 1H), 3.74 (q, J = 6.4 Hz, 2H), 3.66 (q, J = 6.4 Hz, 2H), 3.01 (t, J = 6.4 Hz, 2H), 2.88 (t, J = 6.4 Hz, 2H), 2.47-2.44 (m, 2H), 2.25 (s, 3H), 1.13 (t, J = 7.6 Hz, 3H). **HPLC**: 7.892 min; 96.98 %, INT ODS 3V-C18 (4.6 x 150) mm, 5µ, Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile.

Example 140: 7-amino-2,3-dimethyl-5-((2-(6-methylpyrazin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000578] To a stirred solution of 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **I** (300 mg, 1.13 mmol) in 2-propanol (6 mL) was added triethylamine (687 mg, 946 µL, 6.79 mmol) and 2-(6-methylpyrazin-2-yl) ethan-1-amine **LXVI** (341 mg, 2.49 mmol) and the reaction mixture was stirred at 140 °C for 24 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched with water (25 mL) and the resulting mixture was extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was subjected to silica gel (230-400) column chromatography using 0-5% methanol in DCM to afford the desired compound **Example 140** as an off-white solid. Yield: (100 mg, 27%); **LCMS** Calculated. for $C_{16}H_{18}N_8$ is 322.16; Observed. 323.30 $[M+H]^+$; **^{1}HNMR (400 MHz, DMSO-D$_6$):** δ 8.35 (d, J = 6.4 Hz, 2H), 8.11 (bs, 2H), 6.82 (s, 1H), 3.70 (d, J = 6.4 Hz, 2H), 3.04 (t, J = 6.4 Hz, 2H), 2.48 (s, 3H), 2.23 (s, 3H), 1.95 (s, 3H). **HPLC**: Rt = 10.813 min; Purity = 97.81%, INT ODS 3V-C18 (4.6 x 250) mm, 5µ; Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile.

Example 141: 7-amino-5-((2-(1-(3-aminopropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Step-1: tert-butyl (3-(3-(2-((7-amino-6-cyano-2,3-dimethylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate (Example 141a)

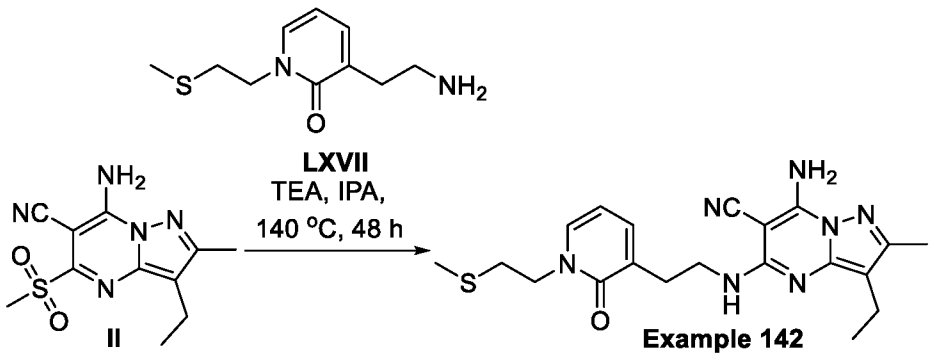
[000579] To a stirred solution of 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **I** (170 mg, 64 µmol) in isopropanol (5 mL) were added TEA (536µL, 3.84 mmol) and tert-butyl (3-(3-(2-aminoethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate **LXI** (284 mg, 961 µmol), in a sealed tube under N_2 atmosphere. The reaction mixture was stirred at 120 °C for 36 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to rt and the reaction mixture was concentrated under reduced pressure. The residue compound was purified by column chromatography (silica gel; 230-400 mesh) using 0-3 % MeOH/DCM to afford the desired product **Example 141a** as an off-white solid. Yield: 150 mg (49 %); **LCMS** Calculated. for $C_{24}H_{32}N_8O_3$ is 480.50; Observed. 481.40 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D_6):** 8.05 (bs, 2H), 7.55 (d, *J* = 6.0 Hz, 1H), 7.27 (d, *J* = 5.6 Hz, 1H), 6.85 (s, 1H), 6.69 (t, *J* = 5.2 Hz, 1H), 6.16 (t, *J* = 6.8 Hz, 1H), 3.88 (t, *J* = 6.8 Hz, 2H), 3.52 (q, *J* = 6.4 Hz, 2H), 2.92 (d, *J* = 6.0 Hz, 2H), 2.73 (t, *J* =6.8 Hz, 2H), 2.28 (s, 3H)), 1.98 (s, 3H), 1.73 (t, *J* = 6.8 Hz, 2H) ,1.37(s, 9H).

Step-2: 7-amino-5-((2-(1-(3-aminopropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile: hydrochloride salt

[000580] A solution of tert-butyl (3-(3-(2-((7-amino-6-cyano-2,3-dimethylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-2-oxopyridin-1(2H)-yl) propyl) carbamate **Example 141a** (150 mg, 312 µmol) in 1-4-dioxane (5 mL) was cooled to 0 °C and added hydrogen chloride in dioxane (780 µL, 4 molar, 3.12 mmol). The reaction mixture was stirred at rt for 16 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture concentrated under reduced pressure and solid obtained was washed with diethyl ether (2 mL X 2) to afford the desire product **Example 141** as an off-white solid. Yield: 74.1 mg (57 %); **LCMS** Calculated. for $C_{17}H_{19}N_7$ is 380.20; Observed. 381.35 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D_6,):** 8.35 (bs, 2H), 7.96 (bs, 3H),

7.67 (d, *J* = 6.0 Hz, 1H), 7.39 (d, *J* = 6.0 Hz, 1H), 6.28 (t, *J* = 6.8 Hz,1H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.54 (d, *J* = 6.4 Hz, 2H), 2.76 (t, *J* = 6.8 Hz, 4H), 2.24 (s, 3H), 2.03-1.96 (m, 5H); **HPLC**: 7.617 min; 95.87 %; INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow : 1.0 mL/min.

Example 142: 7-amino-3-ethyl-2-methyl-5-((2-(1-(2-(methylthio)ethyl)-2-oxo-1,2-dihydropyridin-3-yl)ethyl)amino)pyrazolo[1,5-a]pyrimidine-6-carbonitrile.



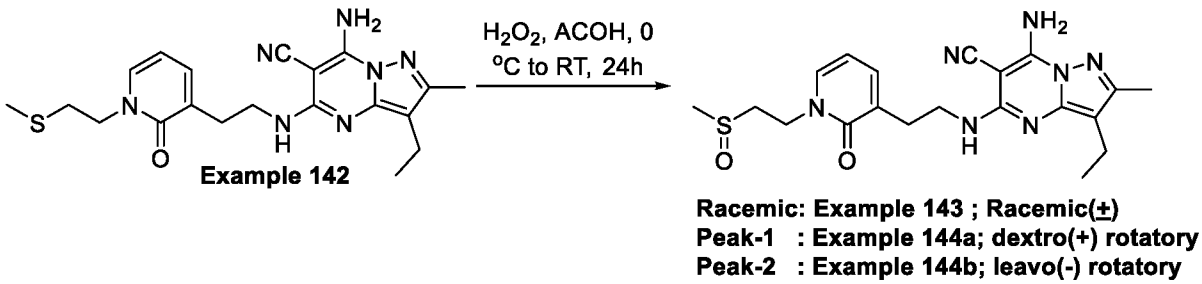
[000581] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (4 g, 0.01 mol) in IPA (50 mL) were added TEA (12.5 mL, 0.09 mol) and 3-(2-aminoethyl)-1-(2-(methylthio) ethyl) pyridin-2(1H)-one **LXVII** (7 g, 0.03 mol), in a sealed tube. The reaction mixture was stirred at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to RT and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to obtained crude compound. The crude compound was purified by flash column chromatography (silica gel, 230-400) using 0-5% methanol in DCM to afford the desired compound as a yellow solid. Yield: 2.0 g (30%); **LCMS** Calculated. for $C_{20}H_{25}N_7OS$ is 411.18; Observed. 412.25 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.04 (bs, 2H), 7.58 (d, *J* = 5.2 Hz, 1H), 7.31 (s, *J* = 4.8 Hz, 1H), 6.70 (s, 1H), 6.17 (s, 1H), 4.07 (s, 2H), 3.52 (s, 2H), 2.75-2.67 (m, 4H), 2.44 (d, *J* =7.2 Hz, 2H), 2.23 (s, 3H), 2.06 (s, 3H), 1.67 (d, *J* =6.4 Hz, 3H). **HPLC**: 11.96 min; 99.40|%, INT ODS 3V-C18 (4.6*250) mm, 5µ;

Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 143. Racemic (+-)7-amino-3-ethyl-2-methyl-5-((2-(1-(2-(methyl sulfinyl) ethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.

Example 144a. (+)7-amino-3-ethyl-2-methyl-5-((2-(1-(2-(methyl sulfinyl) ethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.

Example 144b. (-)7-amino-3-ethyl-2-methyl-5-((2-(1-(2-(methyl sulfinyl) ethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Example 142

Racemic: Example 143 ; Racemic(±)
Peak-1 : Example 144a; dextro(+) rotatory
Peak-2 : Example 144b; leavo(-) rotatory

[000582] A solution of 7-amino-3-ethyl-2-methyl-5-((2-(1-(2-(methylthio) ethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 142** (0.230 g, 0.559 mmol) and in acetic acid (5 mL) was cooled to 0 °C and added H_2O_2 (205 µL, 6.71 mmol). The reaction mixture was stirred at rt for 24 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with sat. $NaHCO_3$ solution (20 mL) and extracted with ethyl acetate (100 mL X 3). The combined organic layer was concentrated under reduced pressure. The crude compound was purified by column chromatography (silica gel 230-400 mesh) using 0-3% MeOH/DCM to afford the desired compound **Example 143** as an off-white solid. Yield: 180 mg (75%); **LCMS** Calculated. for $C_{20}H_{25}N_7O_2S$ is 427.18; Observed. 428.30 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.04 (bs, 2H), 7.56 (d, J = 6.0 Hz, 1H), 7.31 (d, J = 5.6 Hz, 1H), 6.67 (s, 1H), 6.21 (d, J = 6.4 Hz, 1H), 4.33 (t, J = 6.0 Hz, 1H), 4.15

(t, J = 6.4 Hz, 1H), 3.51 (d, J = 4.4 Hz, 2H), 3.22 (m, 2H), 3.06-3.02 (m, 1H), 2.75 (s, 2H), 2.60 (s, 2H), 2.49-2.41 (m, 2H), 2.23 (s, 3H), 1.10 (t, J = 6.8 Hz, 3H); **HPLC**: 9.537 min; 99.04 %, INT ODS 3V-C18 (4.6 * 250) mm, 5µ; Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile; Flow: 1.0 mL/min.

[000583] Further the racemic compound **Example 143** was subjected to chiral SFC (column IC (21 * 250 mm), 5µm; Co-Solvent Name: MeOH, % of Co-Solvent: 40; ABPR Pressure :1500 psi) and separated into peak-1 **Example 144a** and peak-2 **Example 144b** Absolute stereochemistry of the chiral center is unknown

Peak1: Example 144a

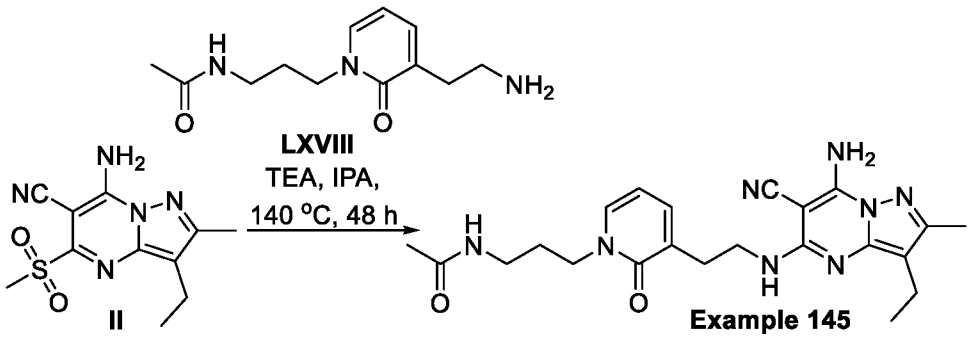
[000584] Yield:16.2 mg; **LCMS** Calculated. for $C_{20}H_{25}N_7O_2S$ is 427.18; Observed. 428.30 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.07 (bs, 2H), 7.56 (q, J = 1.6 Hz, 1H), 7.32 (q, J = 1.6 Hz, 1H), 6.70 (t, J = 5.2 Hz, 1H), 6.21 (t, J = 6.8 Hz, 1H), 4.36-4.30 (m, 1H), 4.15-4.14 (m, 1H), 3.52 (q, J = 6.4 Hz, 2H), 3.26-3.16 (m, 1H), 3.07-2.99 (m, 1H), 2.75 (t, J = 6.8 Hz, 2H), 2.60 (s, 3H), 2.45-2.42 (m, 2H), 2.24 (s, 3H), 1.10 (t, J = 7.6 Hz, 3H); **HPLC**: 9.468 min; 99.20%, INT ODS 3V-C18 (4.6 * 250) mm, 5µ; Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile.; **Chiral HPLC:** 8.582 min; 100%; Column Name-IC (4.6*250mm), 5µm; Co-Solvent Name: MeOH; Total flow rate: 3g/mL; % of Co-Solvent: 40; Temperature: 30 °C; ABPR pressure :1500 psi); Specific optical rotation ($[\alpha]_D$); (c 0.1 in MeOH) =75.62.

Peak-2: Example 144b

[000585] Yield:16.2 mg. **LCMS** Calculated. for $C_{20}H_{25}N_7O_2S$ is 427.18; Observed. 428.30 $[M+H]^+$. **^{1}HNMR (400 MHz, DMSO-D$_6$,):** δ 8.06 (bs, 2H), 7.57 (d, J = 6.0 Hz, 1H), 7.32 (d, J = 6.0 Hz, 1H), 6.69 (bs, 1H), 6.21 (t, J = 6.8 Hz, 1H), 4.34-4.32 (m, 1H), 4.18-4.16 (m, 1H), 3.53-3.52 (m, 2H), 3.26-3.21 (m, 1H), 3.06-3.10 (m, 1H), 2.77 (bs, 2H), 2.60 (s, 3H), 2.45-2.42 (m, 2H), 2.24 (s, 3H), 1.11 (t, J = 7.6 Hz, 3H); **HPLC**: 9.436 min; 97.05%, INT ODS 3V-C18 (4.6 * 250) mm, 5µ; Mobile Phase A: 0.1% Formic acid in water, Mobile Phase B: Acetonitrile; **Chiral HPLC:** 9.293 min; 97.46 %; Column Name-IC (4.6*250mm), 5µm; Co-Solvent Name: MeOH; Total flow rate: 3g/mL; % of Co-Solvent: 40; Temperature: 30 °C;

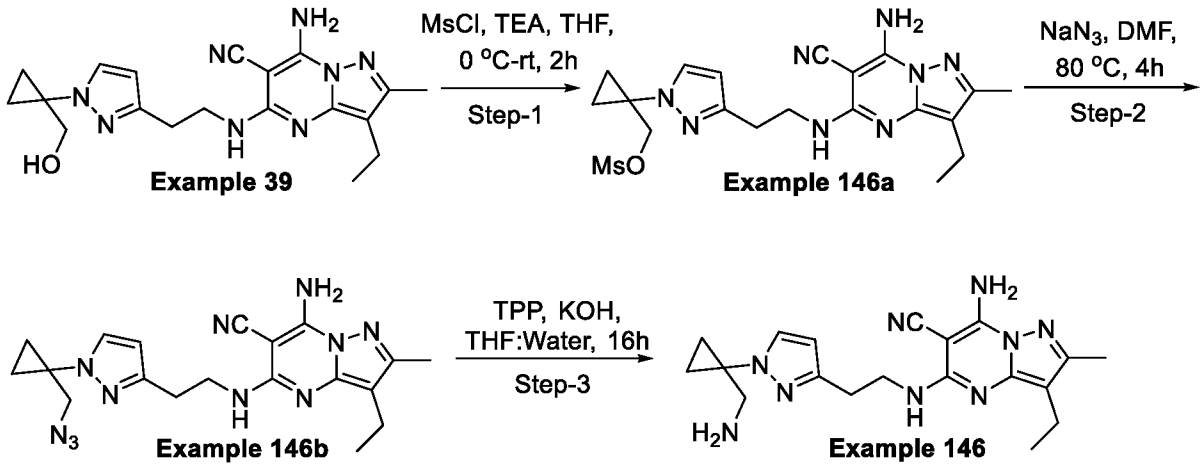
ABPR pressure :1500 psi); Specific optical rotation ([α]$_D$); (c 0.1 in MeOH) = -48.96.

Example 145: N-(3-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-2-oxopyridin-1(2H)-yl) propyl) acetamide.



[000586] To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (100 mg, 358 µmol) in IPA (6 mL) were added TEA (299 µL, 2.15 mmol) and N-(3-(3-(2-aminoethyl)-2-oxopyridin-1(2H)-yl) propyl) acetamide **LXVIII** (212 mg, 895 µmol) in a sealed tube under N_2 atmosphere. The reaction mixture was stirred at 140 °C for 48 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to rt and quenched with water (50 mL). The resulting mixture was extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude compound was purified by flash column chromatography (silica gel, 230-400) using methanol in DCM (0-5%) to afford the desired compound **Example 145** as an off-white solid. Yield: 120 mg (77%); **LCMS** Calculated. for $C_{22}H_{28}N_8O_2$ is 436.23 Observed. 437.40 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 8.05 (bs, 2H), 7.85 (s, 1H), 7.56 (d, *J* = 6.4 Hz, 1H), 7.27 (d, *J* = 6.4 Hz, 1H), 6.72 (s, 1H), 6.17 (t, , *J* = 6.8 Hz, 1H), 3.89 (t, *J* = 6.4 Hz, 2H), 3.52 (d, *J* = 5.2 Hz, 2H), 3.03 (q, *J* = 6.4 Hz, 2H), 2.74 (t, *J* = 6.0 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.24 (s, 3H), 1.80-1.74 (m, 5H), 1.11 (t, *J* = 7.2 Hz, 3H); **HPLC**: 9.668 min; 98.89%; INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 146: 7-amino-5-((2-(1-(1-(amino methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Step-1: (1-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) methyl methane sulfonate (Example 146a)

[000587] To a solution of 7-amino-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 39** (1.0 g, 2.6 mmol) in THF (20 mL) triethylamine (1.1 mL, 7.9 mmol) was added and the reaction mixture was cooled to 0 °C under N_2 atmosphere. Then methane sulfonyl chloride (0.53 mL, 5.3 mmol) was added dropwise, and the reaction mixture was stirred at rt for 2 h. The progress of reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched with water (30 mL) and extracted with DCM (30 mL X 3). The combined organic was given brine wash, dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get crude material. The crude product obtained was purified by combi-flash chromatography (230-400) using 0-50 % ethyl acetate in *n*-hexane to afford the desired compound **Example 146a** as a pale-yellow semi-solid. **Yield:** 0.459 g (38.3%); **LCMS** Calculated. for $C_{20}H_{26}N_8O_3S$ is 458.18; Observed. 459.30 $[M+H]^+$.

Step-2: 7-amino-5-((2-(1-(1-(azidomethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 146b)

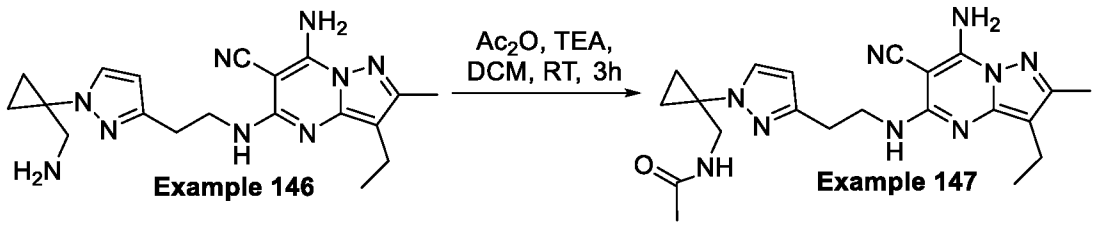
[000588] To a solution of (1-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl)amino)ethyl)-1H-pyrazol-1-yl)cyclopropyl)methyl methane sulfonate **Example 146a** (450 mg, 0.98 mmol) in DMF (2 mL) sodium azide (319 mg, 4.91 mmol) was added and the reaction mixture was stirred at 80 °C for 4 h. Progress of reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (30 mL X 3). The combined organic layer was washed with brine and dried over anhydrous sodium sulphate. The solution was concentrated under reduced pressure to afford the desired compound **Example 146b** as a light brown viscous liquid. The crude product was taken for the next step without further purification. Yield: 477 mg (Crude); **LCMS** Calculated. for $C_{19}H_{23}N_{11}$ is 405.21; Observed. 406.35 $[M+H]^+$.

Step-3: 7-amino-5-((2-(1-(1-(amino methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000589] To a solution of 7-amino-5-((2-(1-(1-(azidomethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 146b** (390 mg, 0.96 mmol) in THF: H2O (8.0 mL; 3:1) Ph_3P (378 mg, 1.44 mmol) was added, and the reaction mixture was stirred for 10 minutes at RT under inert atmosphere. Then potassium hydroxide (54.0 mg, 0.96 mmol) was added, and the reaction mixture was stirred at RT for 16 h. Progress of reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (30 mL X 3). The combined organic layer was washed with brine and dried over anhydrous sodium sulphate. The mixture was concentrated under reduced pressure to get crude material. The crude was purified by flash silica gel column chromatography (Biotage) using 0-5% methanolic ammonia (7M) in DCM afford the desired compound **Example 146** as a light green semi solid. **Yield:** 280 mg (76.71%); **LCMS** Calculated. for $C_{19}H_{25}N_9$ is 379.22; Observed. 380.40 $[M+H]^+$. **^{1}H NMR**

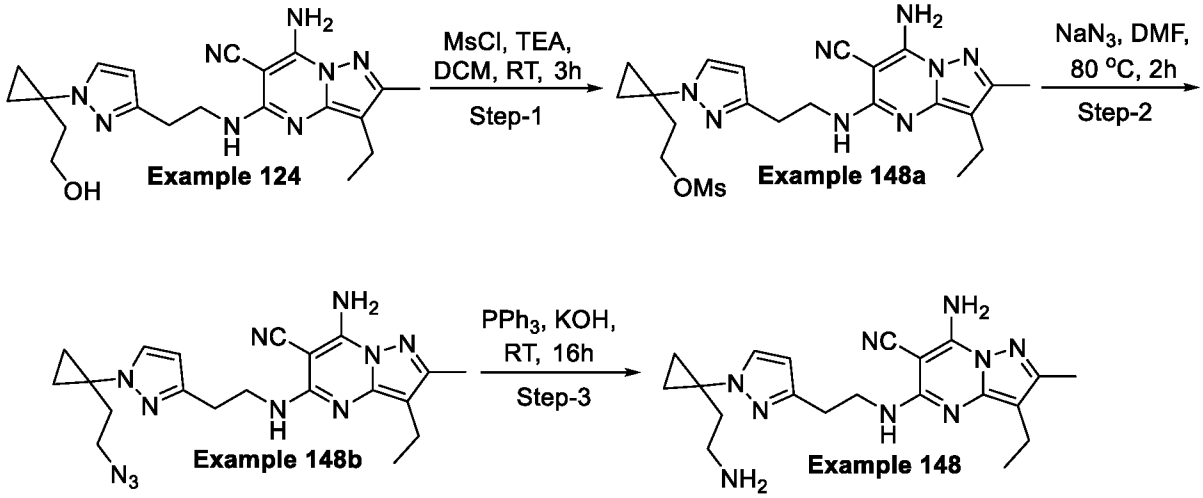
(400 MHz, DMSO-D6): δ 8.15 (bs, 2H), 7.64 (d, J = 2.0 Hz, 1H), 6.57 (t, J = 5.2 Hz, 1H), 6.05 (d, J = 2.4 Hz, 1H), 3.56 (q, J = 5.6 Hz, 2H), 2.83-2.80 (m, 5H), 2.55-2.50 (m, 2H), 2.49-2.43 (m, 2H), 2.25 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H), 1.05-1.02 (m, 2H), 0.98-0.93 (m, 2H); **HPLC**: 7.967 min; 99.45 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile Flow: 1.0 mL/min.

Example 147: N-((1-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) methyl) acetamide



[000590] To a solution of 7-amino-5-((2-(1-(1-(amino methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 146** (50 mg, 0.13 mmol) in DCM (1 mL), TEA (46 µL, 0.33 mmol) was added. This was followed by an addition of solution of acetic anhydride (12 µL, 0.13 mmol) in DCM (0.5 mL). The resulting mixture was stirred at room temperature for 3 h and progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with cold water (10 mL) and extracted with DCM (10 mL X 3). The combined organic layer was washed with brine and dried over anhydrous sodium sulphate. The solution was concentrated, and the residue was washed with diethyl ether to afford the desired product **Example 147** as an off-white solid. Yield: 30 mg (53.57%); **LCMS** Calculated. for $C_{21}H_{27}N_9O$ is 421.23; Observed. 422.40 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D6):** δ 8.10 (bs, 2H), 7.87 (bs, 1H), 7.60 (d, J = 1.6 Hz, 1H), 6.59 (t, J = 5.6 Hz, 1H), 6.05 (d, J = 2.0 Hz, 1H), 3.60-3.55 (m, 2H), 3.42-3.33 (m, 2H), 2.81 (t, J = 7.2 Hz, 2H), 2.47-2.43 (m, 2H), 2.25 (s, 3H), 1.77 (s, 3H), 1.37-1.08 (m, 5H), 1.02 (bs, 2H); **HPLC**: 10.766 min; 95.29 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 148: 7-amino-5-((2-(1-(1-(2-aminoethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Step-1: 2-(1-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) ethyl methane sulfonate (148a)

[000591] To a stirred solution of 7-amino-3-ethyl-5-((2-(1-(1-(2-hydroxyethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 124** (860 mg, 2.18 mmol) in DCM (100 mL) was added triethylamine (1.52 mL, 10.9 mmol) under N_2 atmosphere. The resulting mixture was cooled to 0 °C and methane sulfonyl chloride (0.187 mL, 2.40 mmol) was added dropwise over the period of 10 min. The reaction was stirred at 0 °C for 3 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with sat. $NaHCO_3$ solution (50 mL) and extracted with DCM (50 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was subjected to silica gel (230-400) combi-flash column chromatography using 0-50 % ethyl acetate in *n*-hexane to afford the desired compound **Example 148a** as a pale-yellow solid. Yield: 197 mg (19 %); **LCMS** Calculated. for $C_{21}H_{28}N_8O_3S$ is 472.20; Observed. 473.30 $[M+H]^{+}$.

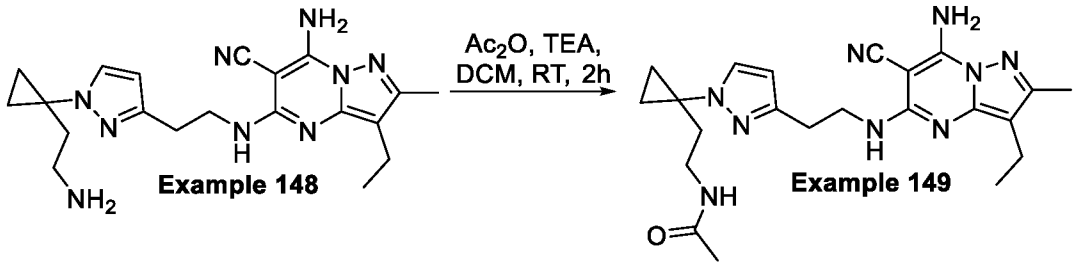
Step-2: 7-amino-5-((2-(1-(1-(2-azidoethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 148b)

[000592] To a stirred solution of 2-(1-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) ethyl methane sulfonate **Example 148a** (197 mg, 0.417 mmol) in DMF (5 mL) was added sodium azide (108 mg, 1.67 mmol). The reaction was stirred at 80 °C for 2 h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was subjected to silica gel (230-400) combi-flash column chromatography using 0-40% ethyl acetate in *n*-hexane to afford the desired compound **Example 148b** as an off-white solid. Yield: 90 mg (51 %); **LCMS** Calculated. for $C_{20}H_{25}N_{11}$ is 419.23; Observed. 420.30 $[M+H]^+$.

Step-3: 7-amino-5-((2-(1-(1-(2-aminoethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

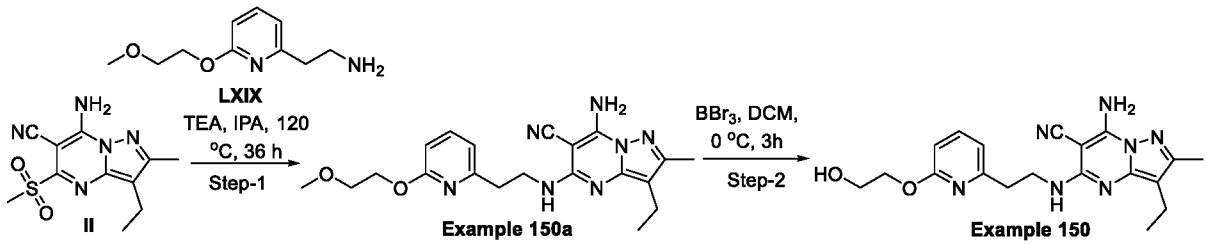
[000593] To a stirred solution of 7-amino-5-((2-(1-(1-(2-azidoethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 148b** (90 mg, 0.21 mmol) in THF: H_2O (8 mL; 3:1) was added triphenylphosphine (84 mg, 0.32 mmol) and stirred for 10 min at rt. This was followed by an addition of KOH (12 mg, 0.21 mmol) under nitrogen atmosphere. The reaction was stirred at rt for 16 h. After completion, the reaction mixture was diluted with water (10 mL) and extracted with DCM (50 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by combi-flash column chromatography using 0-5% methanol in DCM to afford the desired compound **Example 148** as an off-white solid. Yield: 70 mg (83 %); **LCMS** Calculated. for $C_{20}H_{27}N_9$ is 393.23; Observed. 394.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 7.65 (bs, 1H), 6.55 (bs, 1H), 6.04 (s, 1H), 3.58-3.57 (m, 3H), 2.81 (t, J = 6.8 Hz, 2H), 2.47-2.40 (m, 4H), 2.25 (s, 3H), 1.82-1.76 (m, 3H), 1.14-1.08 (m, 5H), 0.98 (s, 1H), 0.93 (s, 2H); **HPLC**: 8.143 min; 98.92 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 149: N-(2-(1-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) ethyl) acetamide (Example 149)



[000594] To a stirred solution of 7-amino-5-((2-(1-(1-(2-aminoethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 148** (50 mg, 0.13 mmol) in DCM (10 mL) were added triethylamine (35 µL, 0.25 mmol) and acetic anhydride (18 µL, 0.19 mmol) under inert atmosphere. The reaction mixture was stirred at rt for 2h and the progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (20 mL) and extracted with DCM (20 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was subjected to silica gel (230-400) combi-flash column chromatography using 0-10% methanol in DCM to afford the desired compound **Example 149** as an off-white solid. Yield: 10 mg (18 %); **LCMS** Calculated. for $C_{22}H_{29}N_9O$ is 435.25; Observed. 436.40 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.10 (bs, 2H), 7.68 (bs, 2H), 6.59 (bs, 1H), 6.05 (bs, 1H), 3.58-3.57 (m, 2H), 2.94-2.92 (m, 2H), 2.82 (bs, 2H), 2.25 (s, 3H), 1.83 (bs, 2H), 1.74 (s, 3H), 1.14-1.09 (m, 5H), 2.01 (s, 2H); **HPLC**: 11.045 min; 99.30 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile Flow: 1.0 mL/min.

Example 150: 7-amino-3-ethyl-5-((2-(6-(2-hydroxyethoxy)386yridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000595] Step-1: 7-amino-3-ethyl-5-((2-(6-(2-methoxyethoxy) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 150a)

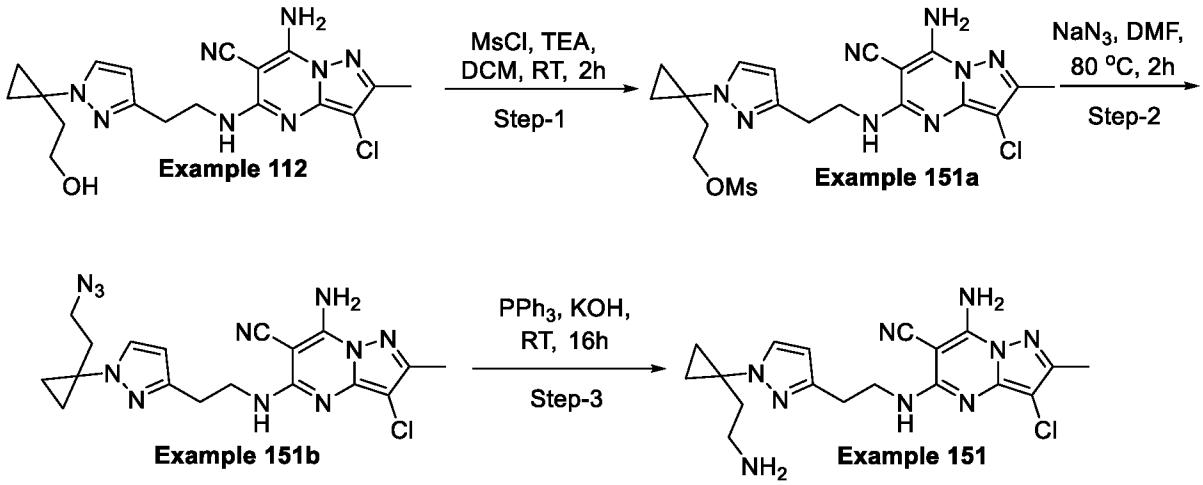
[000596] To a stirred solution of 2-(6-(2-methoxyethoxy)-1,6-dihydropyridin-2-yl) ethan-1-amine **LXIX** (0.3 g, 2 mmol) in isopropanol (10 mL) were added 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.5 g, 2 mmol) and triethylamine (0.4 mL, 3 mmol). The reaction was stirred at 120 °C for 16 h. After completion, the reaction mixture was cooled to rt and diluted with water (50 mL). The mixture was extracted with ethyl acetate (100 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by combi flash silica gel (230-400) column chromatography using 0-50 % ethyl acetate in *n*-hexane to afford the desired compound **Example 150a** as an off-white solid. Yield: 0.35 g (58 %); **LCMS** Calculated. for $C_{20}H_{25}N_7O_2$ is 395.21; Observed. $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 7.49 (t, J = 7.6 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 5.98 (s, 2H), 5.73 (s, 1H), 4.56 (t, J = 4.8 Hz, 2H), 3.87 (q, J = 6.0 Hz, 2H), 3.45 (s, 3H), 3.02 (t, J = 6.4 Hz, 2H) 2.56 (q, J = 7.2 Hz, 2H), 2.32 (s, 3H), 1.19 (t, J = 7.6 Hz, 3H).

Step-2: 7-amino-3-ethyl-5-((2-(6-(2-hydroxyethoxy) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000597] To a stirred solution of 7-amino-3-ethyl-5-((2-(6-(2-methoxyethoxy) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 150a** (250 mg, 0.632 mmol) in DCM (20 mL) was added BBr_3 (65.7 µL, 0.695 mmol). The reaction was stirred at 0 °C for 3h and the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with saturated $NaHCO_3$ solution (10 mL) and extracted with DCM (20

mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by combi flash silica gel (230-400) column chromatography using 0-5 % methanol in DCM to afford the desired compound **Example 150** as an off-white solid. Yield: 150 mg (62 %); **LCMS** Calculated. for $C_{19}H_{23}N_7O_2$ is 381.19; Observed. 382.30 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.09 (bs, 2H), 7.61 (t, J = 7.6 Hz, 1H), 6.83 (t, J = 7.6 Hz, 1H), 6.63 (t, J = 8.0 Hz, 2H), 4.79 (t, J = 5.6 Hz, 1H), 4.29 (t, J = 8.0 Hz, 1H), 3.73-3.65 (m, 4H), 2.95 (t, J = 7.2 Hz, 2H) 2.47-2.43 (m, 2H), 2.25 (s, 3H), 1.13 (t, J = 7.6 Hz, 3H); **HPLC**: 11.872 min; 98.65 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile Flow: 1.0 mL/min.

Example 151: 7-amino-5-((2-(1-(1-(2-aminoethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



Step-1: 2-(1-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) ethyl methane sulfonate (Example 151a)

[000598] To a stirred solution of 7-amino-3-chloro-5-((2-(1-(1-(2-hydroxyethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 112** (460 mg, 1.15 mmol) in DCM (50 mL) was slowly added triethylamine (0.800 mL, 5.74 mmol) and the resulting mixture was cooled to 0 °C under inert atmosphere. This was followed by a dropwise addition of solution of methane sulfonyl chloride (0.098 mL, 1.26

mmol) in DCM (1 mL) over 10 min. The progress of the reaction was monitored by TLC analysis. After completion, to the reaction was diluted with $NaHCO_3$ solution (50 mL) and extracted with DCM (50 ml X 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired compound **Example 151a** as a pale-yellow viscous liquid. The crude compound was taken for the next step without purification. Yield: 0.5 g (90 %); **LCMS** Calculated. for $C_{19}H_{23}ClN_8O_3S$ is 478.13; Observed. 479.25 $[M+H]^+$.

Step-2: 7-amino-5-((2-(1-(1-(2-azidoethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (151b)

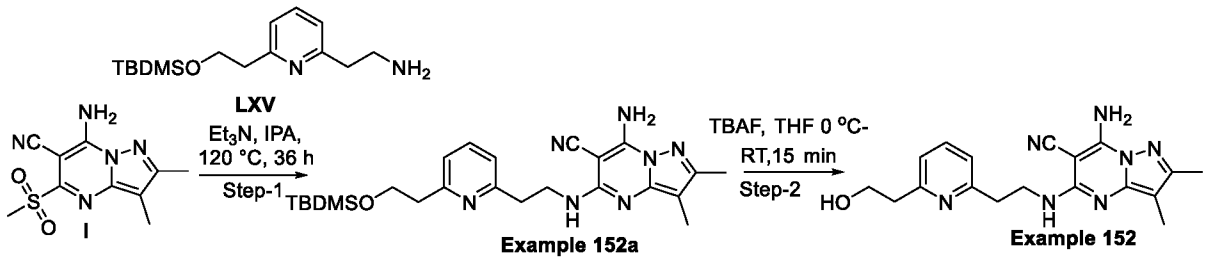
[000599] To a stirred solution of 2-(1-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) ethyl methane sulfonate **Example 151a** (500 mg, mmol) in DMF (5 mL) was added sodium azide (271 mg, 4.18 mmol) and the reaction mixture was stirred at 80 °C for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt and diluted with water (20 mL). The mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by combi-flash silica gel (230-400) column chromatography using 0-30 % ethyl acetate in *n*-hexane to afford the desired compound **Example 151b** as a pale-yellow viscous liquid. **Yield**: 0.135 g (30 %); **LCMS** Calculated. for $C_{18}H_{20}ClN_{11}$ is 425.16; Observed. 426.25 $[M+H]^+$.

Step-3: 7-amino-5-((2-(1-(1-(2-aminoethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000600] To a stirred solution of 7-amino-5-((2-(1-(1-(2-azidoethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 151b** (135 mg, 0.317 mmol) in THF: water (8 mL; 3:1) was added triphenylphosphine (83.1 mg, 0.317 mmol) and stirred at rt for 10 min. This was followed by addition of KOH (26.7 mg, 0.475 mmol) under nitrogen atmosphere. The reaction mixture was stirred at rt for 16 h and progress of

the reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (10 mL) and extracted with DCM (50 mL X 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by silica-gel (230-400) Biotage column chromatography using methanol in DCM (0-15%) to afford the desired compound **Example 151** as an off-white solid. **Yield:** 35 mg (27%); **LCMS** Calculated. for $C_{18}H_{22}ClN_9$ is 399.16; Observed. 400.15 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 7.98 (bs, 4H), 7.74 (d, J = 2.0 Hz, 1H), 6.96 (t, J = 5.2 Hz, 1H), 6.11 (d, J = 2.4 Hz, 1H), 3.64-3.59 (m, 2H), 2.83 (t, J = 7.2 Hz, 2H), 2.72-2.68 (m, 2H), 2.28 (s, 3H), 2.01-1.97 (m, 2H), 1.16-1.14 (m, 2H), 0.98-0.95 (m, 2H); **HPLC**: 8.050 min; 99.35 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 152: 7-amino-5-((2-(6-(2-hydroxyethyl)390yridine-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



[000601] Step-1: 7-amino-5-((2-(6-(2-((tert-butyl dimethyl silyl) oxy) ethyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 152a)

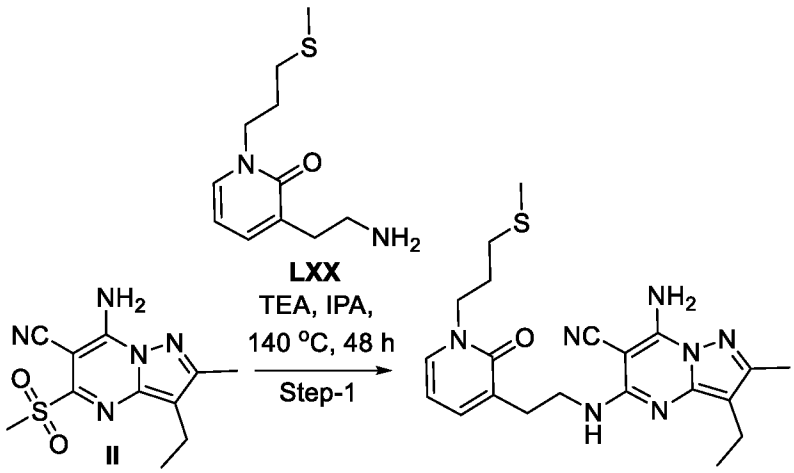
[000602] To stirred solution of 7-amino-2,3-dimethyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (0.2 g, 0.7 mmol) and 2-(6-(2-((tert-butyl dimethyl silyl) oxy) ethyl) pyridin-2-yl) ethan-1-amine **LXV** in isopropanol (5 mL) was added TEA (0.6 mL, 4 mmol) at room temperature under inert atmosphere. The resulting reaction mixture was stirred at 120 °C for 36 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to room temperature diluted with water (100 mL). The resulting mixture was extracted with ethyl acetate (20 mL x 2). The combined organic layers

were dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford **Example 152a** as a light-yellow viscous liquid. The crude compound was taken for the next step without further purification. **Yield:** 0.120g (crude).

Step-2: 7-amino-5-((2-(6-(2-hydroxyethyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000603] To a stirred solution of 7-amino-5-((2-(6-(2-((tert-butyldimethylsilyl) oxy) ethyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 152a** (0.09 g, 0.2 mmol) in THF (10 mL) was added TBAF (0.3 mL, 1M in THF, 0.3 mmol) at 0 °C under N_2 and stirred it at room temperature for 15 min. The progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was diluted with water (20 mL) and extracted with DCM (15 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford a brown viscous liquid. The crude compound was purified by combi flash chromatography by eluted with 0-4% methanol in DCM to get the desired compound **Example 152** as an off-white solid. **Yield:** 30 mg (42%); **LCMS** Calculated. for $C_{18}H_{21}N_7O$ is 351.18; Observed. 352.30 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.12 (bs, 3H), 7.43 (bs, 2H), 6.86 (bs, 1H), 5.12-4.50 (bs, 1H), 3.75-3.73 (m, 4H), 3.16-3.00 (m, 4H), 2.22 (s, 3H), 1.93 (m, 3H); **HPLC**: 7.50 min; 98.09 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

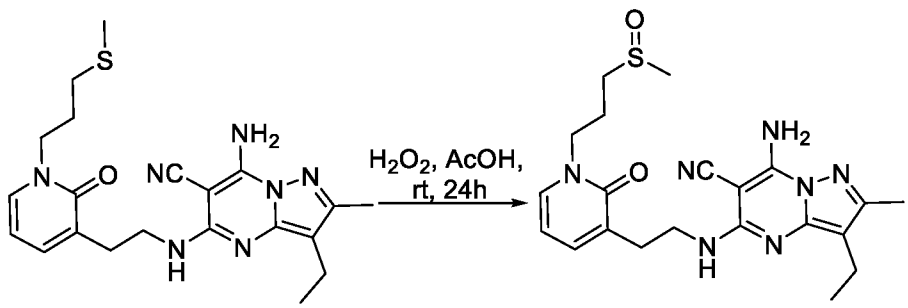
Example 153: 7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methylthio) propyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)pyrazolo[1,5-a]pyrimidine-6-carbonitrile.



[000604] To a solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **II** (0.5 g, 1.79 mmol) in isopropyl alcohol (10 mL) were added triethylamine (1.50 mL, 10.7 mmol) and 3-(2-aminoethyl)-1-(3-(methylthio) propyl) pyridin-2(1H)-one **LXX** (0.891 g, 3.94 mmol). The reaction mixture was stirred at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was concentrated under reduced pressure to get the crude material. The crude compound was purified by silica gel (230-400 mesh) column chromatography with ethyl acetate in dichloromethane (0-50%) to afford the desired product **Example 153** as an off-white solid. Yield: 0.4 g, (52.0%); **LCMS** Calculated. for $C_{21}H_{27}N_7OS$ is 425.19; Observed: 426 $[M+H]^+$.**^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.05 (bs, 2H), 7.54-7.52 (m, 1H), 7.28 (d, J = 4.8 Hz, 1H), 6.70 (s, 1H), 6.16 (t, J = 6.8 Hz, 1H), 3.95 (t, J = 6.8 Hz, 2H), 3.51 (t, J = 5.6 Hz, 2H), 2.74 (t, J = 6.8 Hz, 2H), 2.47-2.413 (m, 4H), 2.24 (s, 3H), 2.04 (s, 3H), 1.91 (m, 2H), 1.10 (t, J = 7.6 Hz, 3H); **HPLC**: 11.682 min; 97.14 %, Column :INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A : 0.1% Formic acid in water; Mobile phase B : Acetonitrile; Flow: 1.0 mL/min.

Example 154a (-)-7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methyl sulfinyl) propyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.

Example 154b. (+)-7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methyl sulfinyl) propyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Example 153

Peak-1 : Example 154a; leavo(-) rotator
Peak-2 : Example 154b;dextro(+) rotatory

[000605] To a solution of 7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methylthio) propyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 153** (0.490 g, 1.15 mmol) in acetic acid (5 mL) at 0 °C was added H_2O_2 (0.635 mL, 20.7 mmol). The reaction mixture was stirred at rt for 24 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, added $NaHCO_3$ (50 mL) and extracted with ethyl acetate (200 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated. The crude compound was purified by silica gel (230-400 mesh) column chromatography with methanol in dichloromethane (0-10%) to afford the desired racemic product as an off-white solid. Yield:0.4 g, (78.0 %); **LCMS** Calculated. for $C_{21}H_{27}N_7O_2S$ is 441.19; Observed: 442 [M+H] +.**^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.05 (s, 2H), 7.57 (d, , J=6.0 Hz, 1H), 7.29 (d, J = 5.6 Hz, 1H), 6.71 (s, 1H), 6.18 (t, J =6.4 Hz, 1H), 4.01 (s, 2H), 3.52 (d, J =4.8 Hz, 2H), 2.75-2.65 (m, 3H), 2.45-2.43 (m, 6H), 2.24 (s, 3H), 2.04-2.01 (m, 2H), 1.11 (t, J =7.2 Hz, 3H); **HPLC**: 9.406 min; 99.57 %, Column : INT ODS 3V-C18 (4.6*250)mm, 5µ, Mobile phase A : 0.1% Formic acid in water; Mobile phase B : Acetonitrile; Flow: 1.0 mL/min.

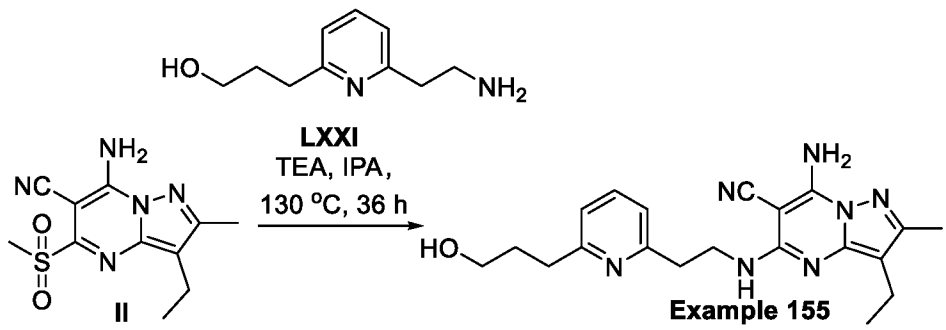
[000606] Further the above racemic compound was subjected to chiral SFC (Column Name: Chiral Pak IC (21*250mm), 5µm; Co-Solvent Name: MeOH: n-hexane (1:1) + 0.1%TEA; Total flow rate: 3g/mL; % of Co-Solvent: 35; Back Pressure: 1500psi; and separated into peak-1 **Example 154a** and peak-2 **Example 154b Peak-1; Example 154a:** (39 mg) **LCMS** Calculated. for $C_{21}H_{27}N_7O_2S$ is 441.19; Observed. 442.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.06 (bs, 2H), 7.57 (bs, 1H), 7.28 (bs, 1H), 6.72 (bs, 1H), 6.18 (bs, 1H), 4.01

(bs, 2H), 3.52 (bs, 2H), 2.75 (bs, 3H), 2.66 (bs, 4H), 2.33 (bs, 2H), 2.24 (s, 3H), 2.02 (bs, 2H), 1.11 (bs, 3H); **HPLC**: 9.410 min; 99.56 %, Column :INT ODS 3V-C18 (4.6*250)mm, 5µ; Mobile phase A : 0.1% Formic acid in water; Mobile phase B : Acetonitrile; Flow : 1.0 mL/min; **Chiral HPLC:** 34.165 min; 98.46%; Column Name : IG (4.6*250mm),5µm; Co-Solvent Name : EtOH:MeOH 1:1 (0.1% DEA); Total flow rate : 3g/mL; % of Co-Solvent :40; Temperature :30 °C ABPR Pressure : 1500psi; Specific optical rotation ($[\alpha]_D$); (c 0.1 in MeOH) = -20.59

Peak-2; Example 154b; (39 mg)

[000607] **LCMS** Calculated. for $C_{21}H_{27}N_7O_2S$ is 441.19; Observed. 442.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.04 (bs, 2H), 7.58-7.56 (m, 1H), 7.29 (d, J = 5.2 Hz, 1H), 6.69 (bs, 1H), 6.18 (t, J = 6.4 Hz, 1H), 4.03-3.99 (m, 2H), 3.52 (q, J = 6.4 Hz, 2H), 2.78-2.73 (m, 2H), 2.68-2.63 (m, 1H), 2.52-2.5 (m, 4H), 2.47-2.41 (m, 2H), 2.24 (s, 3H), 2.02 (m, 2H), 1.1(t, J = 7.6 Hz, 3H); **HPLC**: 9.408 min; 99.12 %, Column :INT ODS 3V-C18 (4.6*250)mm,5µ; Mobile phase A : 0.1% Formic acid in water; Mobile phase B : Acetonitrile; Flow : 1.0 ml/min; **Chiral HPLC:** 44.033 min; 95.30%; Column Name : IG (4.6*250mm), 5µm; Co-Solvent Name : EtOH:MeOH (0.1% DEA); Total flow rate: 3g/mL; % of Co-Solvent :40; Temperature :30 °C; ABPR Pressure :1500psi; Specific optical rotation ($[\alpha]_D$); (c 0.1 in MeOH)= +23.05.

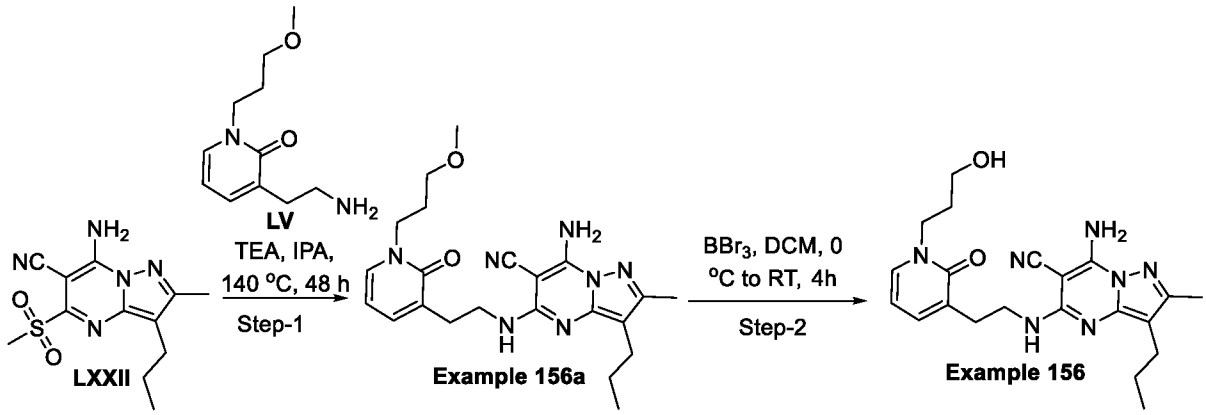
Example 155: 7-amino-3-ethyl-5-((2-(6-(3-hydroxypropyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000608] To a stirred solution of **7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile** II **(0.3 g, 1 mmol)** in 2-propanol (20 mL) was added **3-(6-(2-aminoethyl) pyridin-2-yl) propan-1-ol** LXXI **(0.7 g, 4 mmol)** and triethylamine **(0.7 g, 0.9 mL, 6 mmol)** under nitrogen.

The resulting mixture was stirred at 130 °C for 36 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature and diluted with water (30 mL) then extracted with ethyl acetate (45 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue obtained upon removal of the solvent was subjected to silica gel (230-400 mesh) column chromatography using 0-5% MeOH in DCM to afford the desired compound **Example 155** as an off-white solid. Yield: (0.028 g, 7%); **LCMS** Calculated. for $C_{20}H_{25}N_7O$ is 379.21; Observed. 380.35 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.10 (bs, 2H), 7.61 (t, J = 7.6 Hz, 1H), 7.07 (d, J = 7.6 Hz, 2H), 6.86 (t, J = 5.2 Hz, 1H), 4.46 (t, J = 5.2 Hz, 1H), 3.67 (q, J = 6.8 Hz, 2H), 3.44 (q, J = 6.8 Hz, 2H), 3.00 (t, J = 6.8 Hz, 2H), 2.75 (t, J = 6.8 Hz, 2H), 2.47-2.43 (m, 2H), 2.25 (s, 3H), 1.81 (quint, J = 6.8 Hz, 2H), 1.12 (t, J = 6.8 Hz, 3H). **HPLC**: Rt = 7.837 min; Purity = 99.59 %, INT ODS 3V-C18 (4.6 x 250) mm, 5µ, Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile.

Example 156: 7-amino-5-((2-(1-(3-hydroxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile



Step-1: 7-amino-5-((2-(1-(3-methoxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 156a)

[000609] To a stirred solution of 7-amino-2-methyl-5-(methyl sulfonyl)-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **LXXII** (250 mg, 852 µmol) and 3-

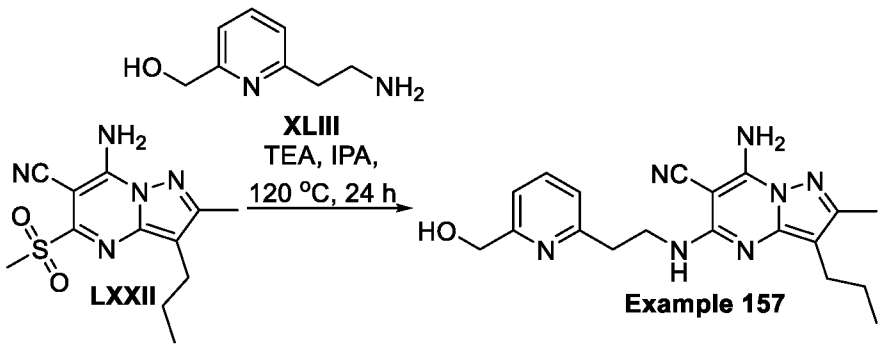
(2-aminoethyl)-1-(3-methoxypropyl) pyridin-2(1H)-one **LV** (394 mg, 1.87 mmol) in isopropanol (5 mL) was added TEA (0.713 mL, 5.11 mmol) under inert atmosphere in a sealed tube. The reaction mixture was stirred at 140 °C for 48 h and progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to rt and the reaction mixture was diluted with water (10 mL). The resulting mixture was extracted with ethyl acetate (50 mL x 3) and the combined organic layer was dried over anhydrous sodium sulfate. The solution was concentrated under reduced pressure. The crude compound was purified by flash column chromatography (silica gel, 230-400; 10g) using 0-5% methanol in DCM to afford the desired compound **Example 156a** as an off-white solid. Yield: 136 mg (36.0 %); **LCMS** Calculated. for $C_{22}H_{29}N_7O_2$ is 423.52; Observed. 424.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.06 (bs, 2H), 7.66 (d, J = 6.4 Hz, 1H), 7.27 (d, J = 6.4 Hz, 1H), 6.71 (s, 1H), 6.15 (t, J = 6.4 Hz, 1H), 3.92 (t, J = 6.4 Hz, 2H), 3.50 (d, J = 5.2 Hz, 2H), 3.30 (t, J = 12.4 Hz, 2H), 3.21 (s, 3H), 2.70 (d, J = 26.8 Hz, 2H), 2.40-2.23 (m, 5H), 1.87 (t, J = 6.8 Hz, 2H), 1.53 (q, J = 6.8 Hz, 2H), 0.86 (t, J = 7.2 Hz, 3H).

Step-4: 7-amino-3-ethyl-5-((2-(6-(3-hydroxypropyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000610] To a solution of 7-amino-5-((2-(1-(3-methoxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 156a** (130 mg, 307 µmol) in DCM (15 mL) at 0 °C was dropwise added BBr_3 (43.5 µL, 460 µmol) under N_2 atmosphere. The reaction mixture was stirred at 0 °C for 4 h and progress of the reaction was monitored by TLC analysis. After completion, the reaction was quenched with sat. $NaHCO_3$ solution (20 mL), and the resulting mixture was extracted with DCM (100 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by flash silica gel column chromatography using 0-5% methanol in DCM to afford the desired compound **Example 156** as an off-white solid. Yield: 20 mg (16.0 %); **LCMS** Calculated. for $C_{21}H_{27}N_7O_2$ is 409.22; Observed. 410.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.05 (bs, 2H), 7.51 (d, J = 5.2 Hz, 1H), 7.27 (d, J = 5.6

Hz, 1H), 6.72 (s, 1H), 6.16 (t, *J* = 6.8 Hz, 1H), 4.58 (s, 1H), 3.94 (t, *J* = 6.4 Hz, 2H), 3.48 (q, *J* = 6.8 Hz, 2H), 3.38 (t, *J* = 5.2 Hz, 2H), 2.74 (t, *J* =6.8 Hz, 2H), 2.41 (d, *J* = 7.2 Hz, 2HH), 2.23 (s, 3H), 1.78 (p, *J* = 6.4 Hz, 2H), 1.58-1.49 (m, 2H), 0.86 (t, *J* = 7.6 Hz, 3H). **HPLC**: 10.555 min; 98.04 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

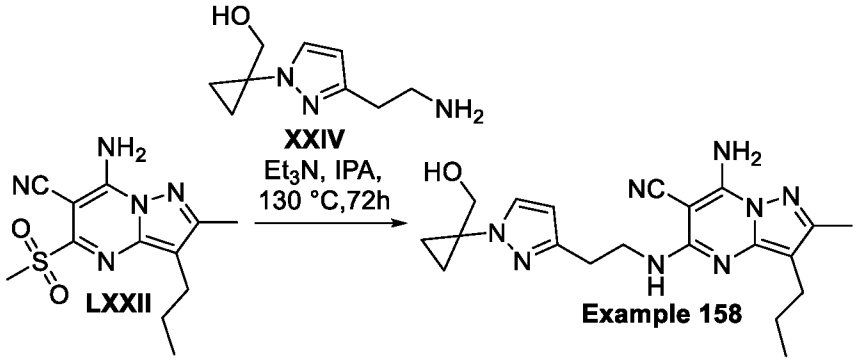
Example 157: 7-amino-5-((2-(6-(hydroxymethyl)397yridine-2-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000611] To a stirred solution of 7-amino-2-methyl-5-(methyl sulfonyl)-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **LXXII** (0.2 g, 682 µmol) and (6-(2-aminoethyl) pyridin-2-yl) methanol **XLIII** (311 mg, 2.05 mmol) in isopropanol (10 mL) was added triethyl amine (570 µL, 4.09 mmol) under inert atmosphere. The resulting mixture in a sealed tube was stirred at 140 °C for 24 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to rt and water (100 mL) was added. The resulting mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified by silica gel (230-400) column chromatography using 0-5 % MeOH in DCM to afford the desired compound **Example 157** as an off-white solid. Yield: 120 mg (48 %); **LCMS** Calculated. for $C_{19}H_{23}N_7O$ is 365.20; Observed. 366.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (bs, 2H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 6.87 (bs, 1H), 5.37 (t, *J* = 5.6 Hz, 1H), 4.58 (d, *J* = 5.2 Hz, 2H), 3.65 (d, *J* = 7.6 Hz, 2H), 3.01 (t, *J* = 6.4 Hz, 2H), 2.43 (t, *J* = 6.8 Hz, 2H), 2.24 (s, 3H), 1.56 (q, *J* = 6.8 Hz, 2H) 0.87 (t, *J* = 6.8

Hz, 3H); **HPLC**: 8.609 min; 99.43 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile Flow: 1.0 mL/min.

Example 158: 7-amino-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

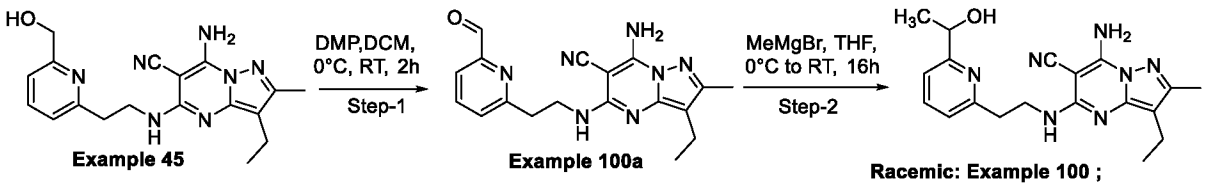


[000612] To a stirred solution of (1-(3-(2-aminoethyl)-1H-pyrazol-1-yl)cyclopropyl)methanol **XXIV** (232 mg, 1.28 mmol) and 7-amino-2-methyl-5-(methylsulfonyl)-3-propylpyrazolo[1,5-a]pyrimidine-6-carbonitrile **LXXII** (150 mg, 511 µmol) in isopropanol (10 mL), in a sealed tube, was added triethylamine (214 µL, 1.53 mmol) and the reaction mixture was stirred at 140 °C for 3 days. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to rt and diluted with water (50 mL). The resulting mixture was extracted with ethyl acetate (20 mL x 3) and the combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude compound was subjected to silica gel (230-400) combi-flash column chromatography using 0-3 % methanol in DCM to afford the desired compound **Example 158** as an off-white solid. Yield: 130 mg (64.0 %); **LCMS** Calculated. for $C_{20}H_{26}N_8O$ is 394.22; Observed. 395.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$)**: δ 8.10 (bs, 2H), 7.61 (s, 1H), 6.61 (s, 1H), 6.03 (s, 1H), 4.88 (s, 1H), 3.57 (q, , J = 5.2 Hz, 4H), 2.80 (s, 2H), 2.42 (s, 2H), 2.23 (s, 3H), 1.56 (t, , J = 6.8 Hz, 2H), 1.07 (s, 2H) ,0.96 (s, 2H), 0.86 (t, J = 6.8 Hz, 3H); **HPLC:** 11.706 min; 99.15 %, Column: INT ODS 3V-C18 (4.6 * 250) mm, 5µ; Mobile

phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 159a. (+)-7-amino-3-ethyl-5-((2-(6-(1-hydroxyethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

Example 159b.(-)-7-amino-3-ethyl-5-((2-(6-(1-hydroxyethyl) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Racemic: Example 100 ;
Racemic(±)
Peak-1 : Example 159a; dextro(+) rotatory
Peak-2 : Example 159b; leavo(-) rotatory

Step-1: 7-amino-3-ethyl-5-((2-(6-formylpyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 100a)

[000613] To a stirred solution of 7-amino-3-ethyl-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 45** (200 mg, 0.57 mmol) in DCM (5 mL) under inert atmosphere was added dess-martin periodinane (290 mg, 0.683 mmol). The reaction mixture was stirred at 0 °C for 2 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was filtered through a celite bed and washed with ethyl acetate (50 mL x 2). The combined filtrates were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified by silica gel (230-400 mesh) column chromatography using 20% ethyl acetate in *n*-hexane to afford the desired compound **Example 100a** as an off-white solid. Yield: 135 mg (67.8%); **LCMS** Calculated. for $C_{18}H_{19}N_7O$ is 349.17; Observed.: 350.35 $[M+H]^+$; **^{1}H NMR (400 MHz, $CDCl_3$):** 10.17 (s, 1H), 7.86-7.79 (m, 2H), 7.42 (q, J = 0.8 Hz, 1H), 6.17 (s, 1H), 6.03 (s, 2H), 3.96 (q, J = 6.0 Hz, 2H), 3.23 (t, J = 6.0 Hz, 2H), 2.56 (q, J = 7.6 Hz, 2H), 2.32 (s, 3H), 1.19 (t, J = 8.0 Hz, 3H).

Step-2: 7-amino-3-ethyl-5-((2-(6-(1-hydroxyethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 100)

[000614] A solution of 7-amino-3-ethyl-5-((2-(6-formylpyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 100a** (130 mg, 0.372 mmol) in THF (3mL) was cooled to 0 °C and added methyl magnesium bromide (0.446 mL, 1 M in THF, 0.446 mmol). The reaction mixture was stirred at rt for 3 h. The progress of the reaction was monitored by TLC analysis**.** After completion, the reaction was quenched with saturated NH_4Cl solution (20 mL) and extracted with ethyl acetate (50 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified by flash silica gel chromatography using 10-50%ethyl acetate in *n*-hexane to afford the desired compound **Example 100** as an off-white solid. Yield: (18 mg, 7%); **LCMS** Calculated. for $C_{19}H_{23}N_7O7$ is 365.20; Observed. 366.40 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D_6,):**. δ 8.10 (bs, 2H), 7.70 (t, *J*= 7.2 Hz, 1H), 7.34 (d, *J*= 7.6 Hz, 1H), 7.13 (d, *J*= 7.2 Hz, 1H), 6.82 (bs, 1H), 5.29 (d, *J*= 3.2 Hz, 1H), 4.75 (t, *J*= 5.6 Hz, 1H), 3.68 (d, *J*= 5.6 Hz, 2H), 3.02 (t, *J*= 6.0 Hz, 2H), 2.45 (t, *J*= 7.6 Hz, 2H), 2.25 (s, 3H), 1.36 (d, *J*= 6.0 Hz, 3H), 1.13 (t, *J*= 7.2 Hz, 3H). **HPLC**: 8.497 min; 98.85 %, INT ODS 3V-C18 (4.6*250) mm, 5µ, Mobile Phase A: 0.1% formic acid in water, Mobile Phase B: Acetonitrile; Flow :1.0 mL/min.

[000615] Further the racemic compound (example100)- 2.50 g was subjected to chiral SFC purification (Column Name: Chiralpak IC (21*250mm), 5µm; Co-Solvent Name: Methanol: IPA (1:1) + 0.1% TEA; % of Co-Solvent: 25%; Temperature :25 °C; Flow :1.0 mL/min to separate the diastereomers named as Peak-1 **Example 159a;** and Peak-2; **Example 159b;**

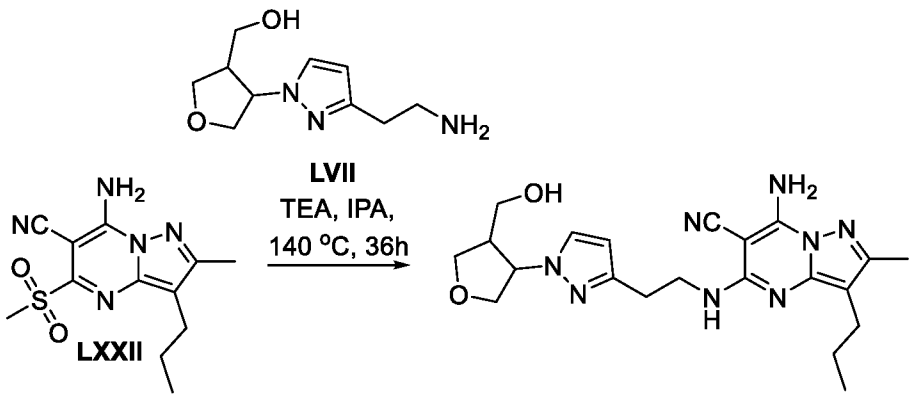
[000616] **Peak-1; Example 159a; (Yield:** 708 mg, **LC-MS** Calc. for $C_{19}H_{23}N_7O$ is 365.20; Obs. 366.30 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D_6,):** δ 8.10 (bs, 2H), 7.70 (t, *J*= 7.2 Hz, 1H), 7.34 (d, *J*= 7.6 Hz, 1H), 7.13 (d, *J*= 7.2 Hz, 1H), 6.82 (bs, 1H), 5.29 (d, *J*= 3.2 Hz, 1H), 4.75 (t, *J*= 5.6 Hz, 1H), 3.68 (d, *J*= 5.6 Hz, 2H), 3.02 (t, *J*= 6.0 Hz, 2H), 2.45 (t, *J*= 7.6 Hz, 2H), 2.24 (s, 3H), 1.36 (d, *J*= 6.0 Hz, 3H), 1.13 (t, *J*= 7.2 Hz, 3H). **HPLC**: 8.354 min; 99.38

%, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile; **Chiral HPLC**: 100%; Rt=5.692 min Column Name: Chiralpak IC (4.6*250 mm), 5µm; Co-Solvent Name: Methanol: IPA (1:1) + 0.1%TEA; Total flow rate: 3g/mL, % of Co-Solvent: 25 %; Temperature :25 °C; ABPR Pressure :1500psi; Specific optical rotation: +36.63.

[000617] Peak-2; Example 159b; Yield: 711 mg, **LCMS** Calculated. for $C_{19}H_{23}N_7O$ is 365.20; Observed. 366.30 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.10 (bs, 2H), 7.70 (t, *J*= 7.2 Hz, 1H), 7.34 (d, *J*= 7.6 Hz, 1H), 7.13 (d, *J*= 7.2 Hz, 1H), 6.82 (bs, 1H), 5.29 (d, *J*= 3.2 Hz, 1H), 4.75 (t, *J*= 5.6 Hz, 1H), 3.68 (d, *J*= 5.6 Hz, 2H), 3.02 (t, *J*= 6.0 Hz, 2H), 2.45 (t, *J*= 7.6 Hz, 2H), 2.24 (s, 3H), 1.36 (d, *J*= 6.0 Hz, 3H), 1.13 (t, *J*= 7.2 Hz, 3H). **HPLC**: 8.360 min; 99.10 %; Column: INT ODS 3V-C18 (4.6 * 250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; **Chiral HPLC**: 96.20%; Rt=6.173 min Column Name: Chiralpak IC (4.6 * 250mm), 5µm; Co-Solvent Name : Methanol: IPA (1:1)+0.1%TEA, Total flow rate: 3g/mL, % of Co-Solvent : 25%; Temperature :25° C, ABPR Pressure :1500psi; Specific optical rotation: -16.070.

Example 160a. (+) 7-amino-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

Example 160b. (-) 7-amino-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Peak-1 : Example 160a; dextro(+) rotatory
Peak-2 : Example 160b; leavo(-) rotatory

[000618] In a 50 mL seal tube, 7-amino-2-methyl-5-(methyl sulfonyl)-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **LXXII** (230 mg, 0.784 mmol) and (4-(3-(2-aminoethyl)-1H-pyrazol-1-yl) tetrahydrofuran-3-yl) methanol **LVII** (199 mg, 0.941 mmol) were dissolved in isopropanol (15 mL). The mixture was purged with N_2 gas for 5 min. To this was added TEA (0.656 mL, 4.70 mmol) was added and the reaction mixture was stirred at 140 °C for 3 days. The progress of reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature and added water (20 mL). The resulting mixture was extracted with ethyl acetate (25 mL × 3). The combined organic layer was washed with brine and dried over anhydrous sodium sulphate. The solution was concentrated under reduced pressure to get crude material. The crude material was subjected to silica gel column chromatography purification using 0-3% methanol in DCM to afford the desired compound as an off-white solid. Yield: 0.12g (36.0%).

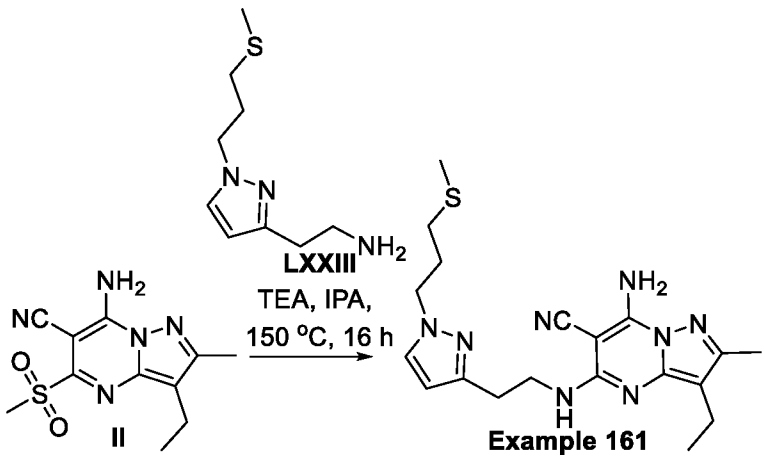
[000619] Further the racemic compound was subjected to chiral SFC purification (Column: Chiral Pak IG (250 * 21) mm, 5µ; Co-Solvent Name: MeCN: MeOH (1:1) + 0.1 %TEA; Total flow rate: 3g/mL; % of Co-Solvent: 30; Temperature :30 °C; ABPR Pressure :1500psi and isolated the diastereomers as peak-1; **Example 160a** ; and peak-2 ; **Example 160b;**

[000620] **Peak-1; Example 160a; Yield:** 22 mg. **LCMS** Calculated. for $C_{21}H_{28}N_8O_2$ is 424.51; Observed.: 425.35 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.08 (bs , 2H), 7.66 (d , J = 1.6 Hz, 1H), 6.61 (bs , 1H), 6.08 (d , J = 1.6 Hz, 1H), 4.84 (t , J = 4.8 Hz, 1H), 4.67 (q , J = 4.8 Hz, 1H), 4.07-3.98 (m ,

2H), 3.85 (q , *J* =4.0 Hz, 1H), 3.62-3.53 (m , 3H), 3.46 (q , *J* =6.8 Hz, 2H), 2.83 (t , *J* =7.2 Hz, 2H), 2.66 (q , *J* = 6.0 Hz, 1H), 2.42 (t , *J* = 7.2 Hz, 2H), 2.23 (s , 3H), 1.55 (q , *J* = 7.2 Hz, 2H), 0.86 (t , *J* = 7.2 Hz, 3H). **HPLC**: 11.559 min; 99.57 %, Column: INT ODS 3V-C18 (4.6 * 250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water Mobile phase B: Acetonitrile; **Chiral HPLC**: 98.37%; Rt=6.704 min; Chiral Pak IG (250 * 4.6) mm, 5µ; Mobile phase MeCN: MeOH (1:1) + 0.1% TEA, Total flow rate: 3g/mL, % of Co-Solvent: 30, Temperature :30 °C, ABPR Pressure :1500psi**.**

[000621] Peak-2; Example 160b; Yield: 19.5 mg. **LCMS** Calculated. for $C_{21}H_{28}N_8O_2$ is 424.51; Observed.: 425.35 $[M+H]^+$; **^{1}H NMR (400 MHz, DMSO-D$_6$,):** δ 8.08 (bs, 2H), 7.66 (d, *J* = 2.0 Hz, 1H), 6.61 (bs, 1H), 6.07 (d, *J* = 2.0 Hz, 1H), 4.83 (t, *J* = 5.2 Hz, 1H), 4.67 (q, *J* = 6.4 Hz, 1H), 4.07-3.98 (m , 2H), 3.84 (q, *J* =4.0 Hz, 1H), 3.62-3.53 (m , 2H), 3.45 (q, *J* = 2.4 Hz, 2H), 2.83 (t, *J* =7.2 Hz, 2H), 2.67 (s, 1H), 2.42 (t, *J* = 7.2 Hz, 2H), 2.24 (s, 3H), 1.56 (q, *J* = 7.2 Hz, 2H), 0.86 (t, *J* = 7.2 Hz, 3H). **HPLC**: 11.561 min; 99.45 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; **Chiral HPLC**: 98.84%; Rt=8.492 min; Chiral Pak IG (250 * 4.6) mm, 5µ, Mobile phase: MeCN: MeOH (1:1) +0.1%TEA; Total flow rate: 3g/mL; % of Co-Solvent: 30; Temperature :30 °C; ABPR Pressure :1500psi**.**

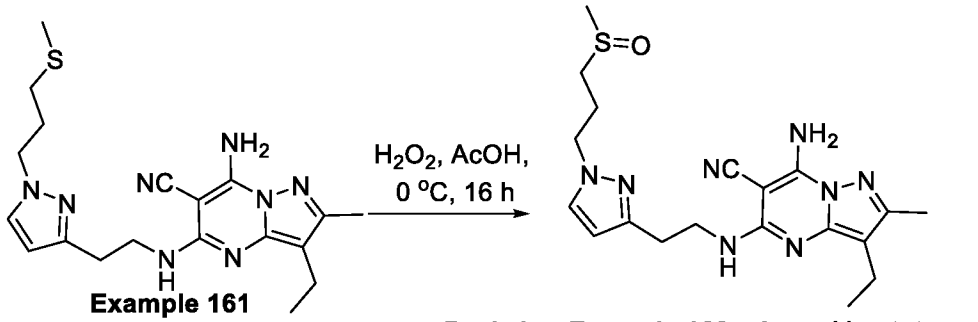
Example 161: 7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methylthio) propyl)-1H-pyrazol-3-yl)ethyl)amino)pyrazolo[1,5-a]pyrimidine-6-carbonitrile



[000622] In a seal tube, to a solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile II (500 mg, 1.79 mmol) and 2-(1-(3-(methylthio) propyl)-1H-pyrazol-3-yl) ethan-1-amine **LXXIII** (892 mg, 4.48 mmol) in isopropanol (10 mL) was added triethylamine (1.50 mL, 10.7 mmol) at rt under nitrogen. The resulting reaction mixture was stirred at 150 °C for 16 h and progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to rt and diluted with water (50 mL). The mixture was extracted with ethyl acetate (2 X 25 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude material was purified by combi flash (silica gel 230-400) column chromatography using 0-1% methanol in DCM to afford the desired compound **Example 161** as an off-white solid. Yield: 350 mg (44.9%); **LCMS** Calculated. for $C_{19}H_{26}N_8S$ is 398.20; Observed. 399.35; $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D_6):** δ 8.10 (bs, 2H), 7.61 (d, J = 1.6 Hz, 1H), 6.64 (t, J = 5.2 Hz, 1H), 6.07 (bs, 1H), 4.11 (t, J = 6.8 Hz, 2H), 3.57 (q, J = 6.4 Hz, 2H), 2.82 (t, J = 6.8 Hz, 2H), 2.46-2.43 (m, 2H), 2.38 (t, J = 6.8 Hz, 2H), 2.25 (s, 3H), 2.03-2.00 (m, 5H), 1.12 (t, J = 7.2 Hz, 3H); **HPLC**: 13.280 min; 99.11%, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 162a: (-)-7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methyl sulfinyl) propyl)-1H-pyrazol-3-yl) ethyl) amino)pyrazolo[1,5-a]pyrimidine-6-carbonitrile.

Example 162b: (+)-7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methylsulfinyl)propyl)-1H-pyrazol-3-yl)ethyl)amino)pyrazolo[1,5-a]pyrimidine-6-carbonitrile.



[000623] To a solution of 7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methylthio) propyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 161** (310 mg, 0.778 mmol) in acetic acid (5 mL) was dropwise added H_2O_2 (9.53 mL, 3% Wt, 9.33 mmol) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at rt for 16 h and the progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was cooled to rt and added water (50 mL). The mixture was extracted with ethyl acetate (25 mL X 2). The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude material was triturated with diethyl ether and dried to afford the desired compound as an off-white solid. Yield: 0.35 g (95.9%).

[000624] Further, the racemic compound was subjected to chiral SFC purification using Chiral pack IA (21*250mm), 5µm. Co-Solvent Name: EtOH: MeOH 1:1 (TEA 0.1%);

[000625] Total flow rate: 3g/mL; % of Co-Solvent: 30, and resolved the enantiomers identified as peak-1 **Example 162a**; (and peak-2; **Example 162b**.

Peak-1; Example 162a: (39 mg)

[000626] **LC-MS** Calc. for $C_{19}H_{26}N_8OS$ is 414.19; Obs. 415.30 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (bs, 2H), 7.65 (s, 1H), 6.65 (bs, 1H), 6.09 (s, 1H), 4.16 (t, J = 6.4 Hz, 2H), 3.57 (q, J = 6.4 Hz, 2H), 2.83 (t, J = 7.2 Hz, 2H), 2.73-2.56 (m, 3H), 2.50-2.43 (m, 4H), 2.25 (s, 3H), 2.12 (t, J = 7.2 Hz, 2H), 1.12 (t, J = 7.2 Hz, 3H); **HPLC**: 10.354 min; 99.50%, Column: INT ODS 3V-C18 (4.6 * 250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile

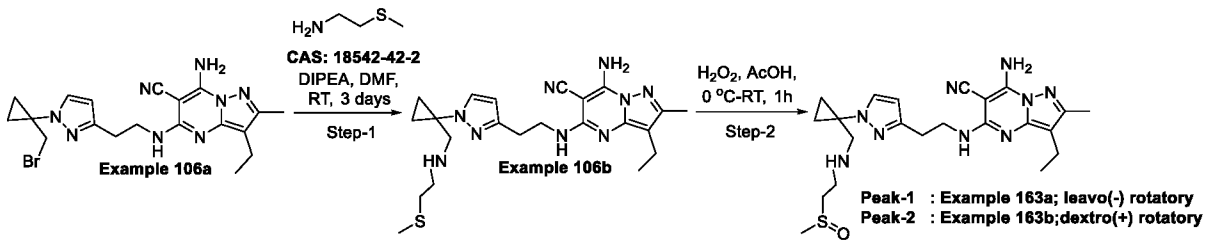
phase B: Acetonitrile Flow: 1.0 mL/min; **Chiral HPLC:** 12.297 min; 100%; Column Name: IA (4.6*250mm),5µm; Co-Solvent Name: MeOH; Total flow rate: 3g/mL; % of Co-Solvent: 30; Temperature: 30 °C; ABPR Pressure :1500psi); Specific optical rotation ([α]$_D$); (c 0.1 in MeOH)= -21.359.

Peak-2; Example 162b : (39 mg)

[000627] **LC-MS** Calc. for $C_{19}H_{26}N_8OS$ is 414.19; Obs. 415.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (bs, 2H), 7.64 (d, J = 2.0 Hz, 1H), 6.65 (m, 1H), 6.08 (d, J = 2.0 Hz, 1H), 4.16 (t, J = 6.4 Hz, 2H), 3.57 (d, J = 5.6 Hz, 2H), 2.83 (t, J = 6.8 Hz, 2H), 2.68-2.56 (m, 3H), 2.50-2.43 (m, 4H), 2.25 (s, 3H), 2.14-2.10 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H); **HPLC**: 10.343 min; 99.03%, Column: INT ODS 3V-C18 (4.6*250)mm,5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min; **Chiral HPLC:** 18.799 min; 100%; Column Name: IA (4.6*250mm), 5µm; Co-Solvent Name: MeOH; Total flow rate: 3g/mL; % of Co-Solvent: 30; Temperature: 30 °C; ABPR Pressure :1500psi); Specific optical rotation ([α]$_D$); (c 0.1 in MeOH)= 26.47.

Example 163a: (-)- 7-amino-3-ethyl-2-methyl-5-((2-(1-(1-(((2-(methyl sulfinyl) ethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile

Example 163b: (+)-7-amino-3-ethyl-2-methyl-5-((2-(1-(1-(((2-(methyl sulfinyl) ethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile



Step-1: 7-amino-3-ethyl-2-methyl-5-((2-(1-(1-(((2-(methylthio) ethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (Example 106b)

[000628] To a solution of 7-amino-5-((2-(1-(1-(bromomethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-

carbonitrile **Example 106a** (426 mg, 0.961 mmol) in DMF (5 mL) under inert atmosphere were added DIPEA (0.502 mL, 2.88 mmol) and 2-(methylthio) ethan-1-amine (0.180 mL, 1.92 mmol). The resulting reaction mixture was stirred at rt for 3 days and progress of reaction was monitored by TLC analysis. After completion, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL X 3). The combine organic layer was washed with brine, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crude material was purified by flash silica gel column chromatography (Biotage) using 0-5% methanol in DCM to afford the desired compound **Example 106b** as an off- white solid. Yield: 390 mg (89.9%) **LCMS** Calculated. for $C_{22}H_{31}N_9S$ is 453.24; Observed. 454.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 7.45 (bs, 1H), 6.06 (bs, 1H), 5.97 (bs, 2H), 5.61 (bs, 1H), 3.80-3.78 (m, 2H), 2.98-2.94 (m, 4H), 2.78-2.76 (m, 2H), 2.57-2.54 (m, 4H), 2.32 (s, 3H), 2.04 (s, 3H), 1.27 (bs, 3H), 1.18 (t, J = 7.2 Hz, 3H), 1.02 (bs, 2H).

Step-2: 7-amino-3-ethyl-2-methyl-5-((2-(1-(1-(((2-(methyl sulfinyl) ethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile

[000629] A solution of 7-amino-3-ethyl-2-methyl-5-((2-(1-(1-(((2-(methylthio) ethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile **Example 106b** (392 mg, 0.864 mmol) in acetic acid (8 mL) was cooled to 0 °C and dropwise added H_2O_2 (11.8 mL, 3% wt, 10.4 mmol). The resultant mixture was stirred at rt for 1 h and progress of the reaction was monitored by TLC analysis. After completion, reaction mixture was cooled to 0 °C and quenched with saturated sodium bicarbonate solution (till effervescence stops). The mixture was extracted with DCM (50 mL X 6) and combine organic layer was washed with water (20 mL) followed by with brine. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by flash silica gel column chromatography (Biotage) using 0-5 % methanol in DCM to afford the desired compound as an off-white solid. Yield: 0.27g (66.6%). Further the racemic compound was subjected to chiral SFC purification (Column Name: Column Name

: Chiralpak IC (21*250mm), 5µm; Co-Solvent Name : MeOH; Total flow rate : 3g/mL; % of Co-Solvent : 30; Temperature : 30 °C, ABPR Pressure :1500psi, and separated in to peak-1; **Example 163a**; and peak-2; **Example 163b**.

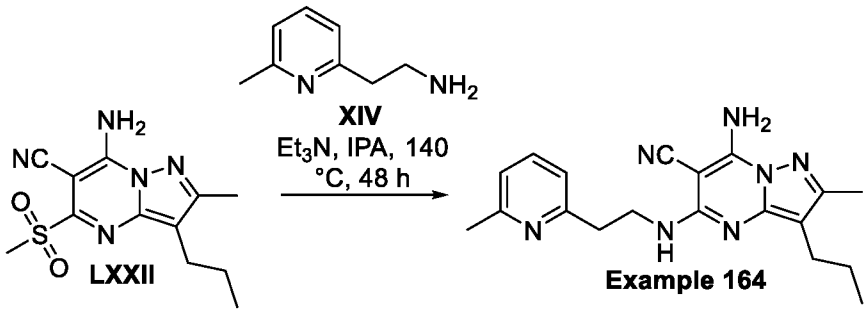
Peak-1; Example 163a; (39 mg)

[000630] **LCMS:** Calculated. for $C_{22}H_{31}N_9OS$ is 469.23; Observed. 470.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.08 (bs, 2H), 7.65 (bs, 1H), 6.55 (bs, 1H), 6.04 (bs, 1H), 3.58-3.56 (m, 2H), 2.88-2.60 (m, 8H), 2.47-2.42 (m, 5H), 2.25 (s, 3H), 1.87 (bs, 1H), 1.14-1.08 (m, 5H), 0.94 (bs, 2H). **HPLC**: 7.945 min; 98.91 %, Column: INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min; **Chiral HPLC:** 13.070 min; 100%; Column Name: Chiral Pak IC (4.6 * 250mm), 5µm; Co-Solvent Name: MeOH; Total flow rate: 3g/mL; % of Co-Solvent: 30; Temperature: 30 °C; ABPR Pressure :1500psi); Specific optical rotation ($[\alpha]_D$); (c 0.1 in MeOH)= -37.00.

Peak-2; Example 163b; (39 mg)

[000631] **LC-MS:** Calculated. for $C_{22}H_{31}N_9OS$ is 469.23; Observed. 470.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.08 (bs, 2H), 7.65 (bs, 1H), 6.55 (bs, 1H), 6.04 (bs, 1H), 3.57 (bs, 2H), 2.99-2.67 (m, 8H), 2.49-2.79 (m, 5H), 2.25 (s, 3H), 1.86 (bs, 1H), 1.13-1.08 (m, 5H), 0.94 (bs, 2H). **HPLC**: 7.950 min; 99.28%, Column: INT ODS 3V-C18 (4.6 * 250)mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile Flow: 1.0 mL/min; **Chiral HPLC:** 14.490 min; 95.87%; Column Name: Chiral Pak IC (4.6 * 250mm), 5µm; Co-Solvent Name: MeOH; Total flow rate: 3g/mL; % of Co-Solvent: 30; Temperature: 30 °C; ABPR Pressure :1500psi); Specific optical rotation ($[\alpha]_D$); (c 0.1 in MeOH)= +36.40.

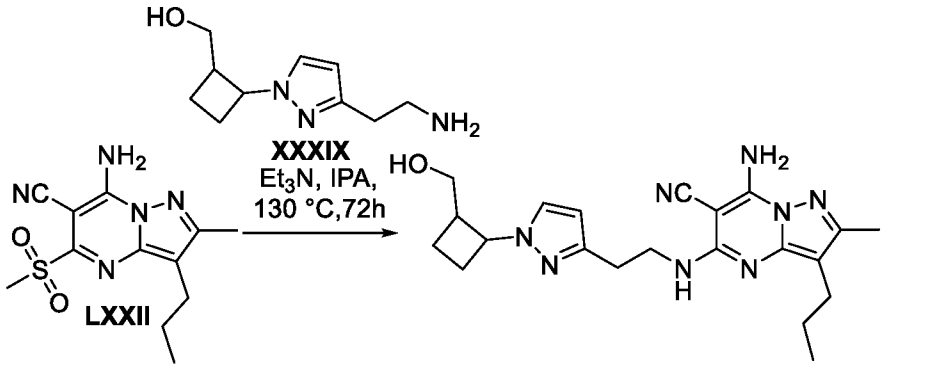
Example 164: 7-amino-2-methyl-5-((2-(6-methylpyridin-2-yl) ethyl) amino)-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000632] To a stirred solution of 2-(6-methylpyridin-2-yl) ethan-1-amine **XIV** (279 mg, 2.05 mmol) and 7-amino-2-methyl-5-(methyl sulfonyl)-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **LXXII** (300 mg, 1.02 mmol) in IPA (15 mL) was added triethylamine (0.855 mL, 6.14 mmol). The resulting mixture was stirred at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After completion, the reaction was cooled to rt and diluted with water (50 mL). The resulting mixture was extracted with ethyl acetate (150 mL X 3). The combined organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford the crude brown semi-solid. The crude material was purified by flash silica gel (Biotage) column chromatography using 0-3% MeOH in DCM to afford the desired compound **Example 164** as a light brown solid. Yield: 230 mg (64.4%); **LCMS** Calculated, for $C_{19}H_{23}N_7$ is 349.20; Observed. 350.35 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (bs, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.08 (t, J = 6.4 Hz, 2H), 6.94 (d, J = 5.2 Hz, 1H), 3.65 (q, J = 6.8 Hz, 2H), 2.99 (t, J = 7.2, 2H), 2.47 (s, 3H), 2.43 (t, J = 6.8, 2H), 2.24 (s, 3H), 1.55 (q, J = 6.8 Hz, 2H), 0.87 (t, J = 7.2 Hz, 3H); **HPLC**: 8.220 min; 98.88%, Column: INT ODS 3V-C18 (4.6 * 250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water, Mobile phase B: Acetonitrile; Flow: 1.0 mL/min.

Example 165a: (+)-7-amino-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile

Example 165a: (-)-7-amino-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Peak-1 : Example 165a; dextro(+) rotatory
Peak-2 : Example 165b; leavo(-) rotatory

[000633] To a solution of 7-amino-2-methyl-5-(methyl sulfonyl)-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile **LXXII** (0.5 g, 1.70 mmol) and (2-(3-(2-aminoethyl)-1H-pyrazol-1-yl) cyclobutyl) methanol **XXXIX** (0.67 g, 3.41 mmol) in isopropyl alcohol (15 mL) was added triethylamine (0713 mL, 5.11mmol) and the reaction mixture was stirred at 130 °C for 72 h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography with ethyl acetate in hexane (0-70%) to afford the desired product as an off-white solid. Yield: 0.172 g, (25.0 %).

[000634] Further the racemic compound was subjected to chiral SFC purification (Column Name: IG (21 * 250mm), 5µm; Co-Solvent Name: EtOH: IPA+0.1%TEA; Total flow rate: 3g/mL; % of Co-Solvent :30; Temperature: 30 °C; ABPR Pressure :1500psiand) to separate into peak-1; **Example 165a** and peak-2; **Peak-2; Example 165b;** (39 mg)

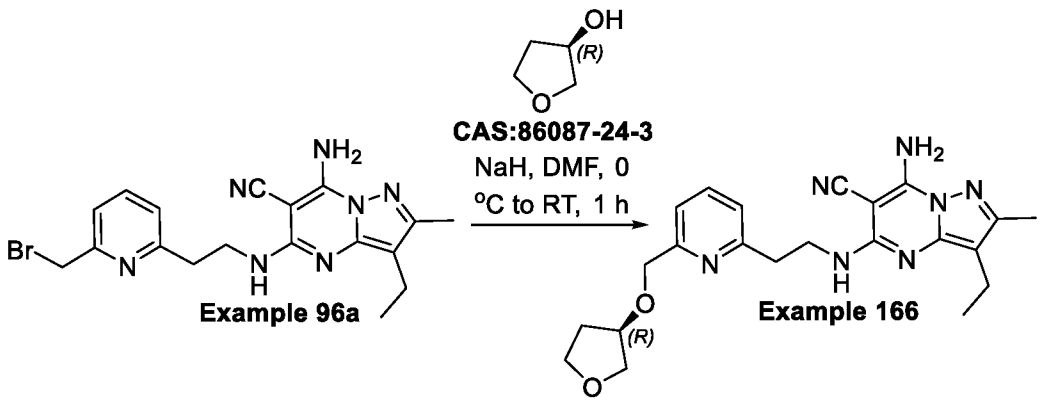
Peak-1; Example 165a; (39 mg)

LCMS Calculated. for $C_{21}H_{28}N_8O$ is 408.24; Observed. 409.4 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (bs, 2H), 7.65 (bs, 1H), 6.69 (bs, 1H), 6.10 (bs, 1H), 4.61-4.59 (m, 1H), 4.50 (d, J = 8.4 Hz, 1H), 3.56 (d, J = 5.6 Hz, 2H), 3.41-3.90 (m, 2H), 2.82 (t, J = 6.8 Hz, 3H), 2.42 (t, J = 7.2 Hz, 2H), 2.32-2.21 (m, 5H), 1.79 (d, J = 9.6 Hz, 1H), 1.56 (m, 3H), 0.86 (t, J = 7.2 Hz, 3H); **HPLC**: 12.404 min; 99.46 %, Column :INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile; Flow: 1.0 mL/min; **Chiral HPLC:** 5.319 min; 100 %; Column Name : IG (4.6 * 250mm), 5µm; Co-Solvent Name : EtOH:IPA+0.1%TEA; Total flow rate : 3g/mL; % of Co-Solvent: 30; Temperature :30 °C; ABPR Pressure :1500psi; Specific optical rotation ($[\alpha]_D$); (c 0.1 in MeOH)= +43.98

Peak-2; Example 165b; (39 mg)

LC-MS Calculated. for $C_{21}H_{28}N_8O$ is 408.24; Observed. 409.4 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (bs, 2H), 7.65 (bs, 1H), 6.69 (bs, 1H), 6.10 (bs, 1H), 4.61 (bs, 1H), 4.54-4.48 (q, J = 8.8 Hz, 1H), 3.5 (d, J = 6.0 Hz, 2H), 3.4 (s, 2H), 2.82 (t, J = 6.4 Hz, 3H), 2.42 (t, J = 7.2 Hz, 2H), 2.32-2.18 (m, 5H), 1.79 (q, J = 8.4 Hz, 1H), 1.57 (m, 3H), 0.86 (t, J = 7.2 Hz, 3H) ; **HPLC** : 12.407 min; 99.32 %, Column : INT ODS 3V-C18 (4.6 * 250)mm, 5µ ; Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile; Flow: 1.0 mL/min; **Chiral HPLC:** 5.712 min; 96.58%; Column Name : IG (4.6 * 250mm), 5 µ; Co-Solvent Name : EtOH:IPA+0.1%TEA; Total flow rate : 3g/mL; % of Co-Solvent :30; Temperature :30 °C; ABPR Pressure :1500psi; Specific optical rotation ($[\alpha]_D$); (c 0.1 in MeOH)=.-27.72.

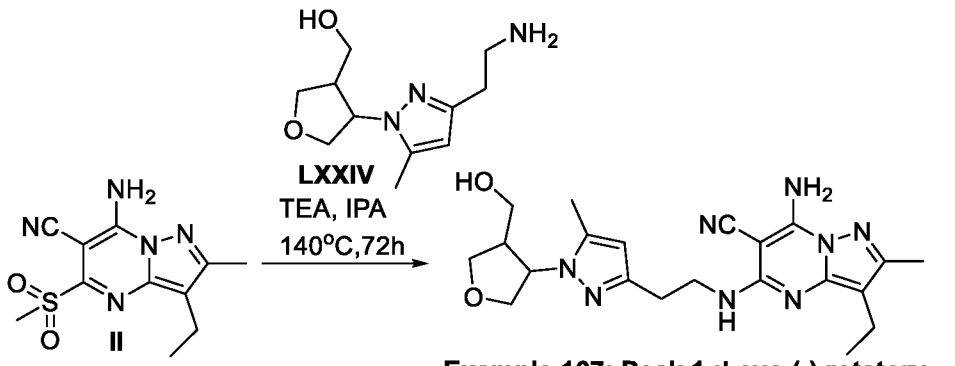
Example 166: (*R*)-7-amino-3-ethyl-2-methyl-5-((2-(6-(((tetrahydrofuran-3-yl) oxy) methyl) pyridine-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



[000635] To a solution of (*R*)-tetrahydrofuran-3-ol (CAS:86087-24-3, 0.038 mg, 0.434 mmol) in DMF (10 mL) at 0 °C was added sodium hydride (10 mg, 0.434 mmol) and the mixture was stirred under inert atmosphere for 5 min. This was followed by dropwise addition of solution of 7-amino-5-((2-(6-(bromomethyl) pyridin-2-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile. **Example 96a** (0.18 g, 434 mmol) in DMF (1 mL). The reaction mixture was stirred at rt for 1 h and progress of the reaction was monitored by TLC analysis. After completion, the reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography using ethyl acetate in n-hexane (0-30%) to afford the desired product **Example 166** as off-white solid. Yield: 0.045 g, (24.0 %); **LCMS** Calculated. for $C_{22}H_{27}N_7O_2$ is 421.22; Observed: 422 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.12 (bs, 2H), 7.73 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 6.87 (bs, 1H), 4.57 (t, J = 14.8 Hz, 2H), 4.26 (bs, 1H), 3.79-3.75 (m, 2H), 3.68 (t, J = 7.2 Hz, 4H), 3.026 (t, J = 6 Hz, 2H), 2.48-2.45 (m, 2H), 2.33-2.25 (m, 3H), 1.97 (d, J = 4.0 Hz, 2H), 1.14-1.06 (m, 3H); **HPLC**: 10.260 min; 98.27 %, Mobile phase A : 0.1% Formic acid in water; Mobile phase B : Acetonitrile; Flow : 1.0 mL/min; **Chiral HPLC:** 5.602 min; 100.00%; Column Name : IC (4.6 * 250mm), 5µm; Co-Solvent Name : EtOH; Total flow rate : 3g/mL; % of Co-Solvent :30; Temperature :30 °C; ABPR Pressure :1500psi; Specific optical rotation ($[\alpha]_D$): (c 0.1 in MeOH)= -0.784.

[000636] Example 167: (-)-7-amino-3-ethyl-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile.

[000637] Example 168: (+)-7-amino-3-ethyl-5-((2-(1-(4-(hydroxy methyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl pyrazolo[1,5-a] pyrimidine-6-carbonitrile.



Example 167: Peak 1 :Levo (-) rotatory
Example 168: Peak 2 :Dextro (+) rotatory

To a stirred solution of 7-amino-3-ethyl-2-methyl-5-(methyl sulfonyl) pyrazolo[1,5-*a*] pyrimidine-6-carbonitrile **II** (0.5 g, 1.18 mmol) in 2-propanol (5 mL) were added (4-(3-(2-aminoethyl)-5-methyl-1H-pyrazol-1-yl) tetrahydrofuran-3-yl) methanol **LXXIV** (0.6 g, 2.66 mmol) and triethylamine (1.5 mL, 10.76 mmol). The reaction mixture in seal tube was stirred at 140 °C for 48 h. The progress of the reaction was monitored by TLC analysis. After the completion, the reaction mixture was cooled and diluted with water (20 mL). The mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel (230-400 mesh) column chromatography with ethyl acetate in *n*-hexane (10-50%) to afford the desired product as an off-white solid. Yield: 0.3 g, (59.7 %). The racemic compound (0.3 g) was subjected to chiral separation by SFC {The sample was dissolved in 4.5 mL of tetrahydrofuran: methanol (1:1)}, column : chiral Pak IG (250 * 21) mm, 5.0 µm;

mobile phase 82:18 (A:B).A=Liquid CO_2, B= 0.1% triethyl amine in acetonitrile: methanol (1:1), Flow rate:18 mL/min ; Wavelength 254 nm; to yield 56 mg of **peak 1; Example 167**: $[\alpha]_{D=}$ -27.00 °, c=0.1, MeOH) and 58 mg of **peak 2**; **Example 168** $[\alpha]_{D=}$ +33.00 °, c=0.1, MeOH) as off-white solids, respectively.

Peak-1; Example 167: **LCMS** Calculated. for $C_{21}H_{28}N_8O_2$ is 425.23; Observed. 425.40 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.11 (bs, 2H), 6.56 (t, *J*= 4.8 Hz, 1H), 5.88 (s, 1H), 6.12 (s, 1H), 4.83 (t, *J*= 5.2 Hz, 1H), 4.65-4.61 (m, 1H), 4.05 (q, *J*= 8.0 Hz, 2H), 3.81 (t, *J*= 8.4 Hz, 1H), 3.64 (t, *J*= 5.2 Hz, 1H), 3.55-3.52 (m, 2H), 3.41 (t, *J*= 5.6 Hz, 2H), 2.76 (t, *J*= 7.2 Hz, 2H), 2.72-2.67 (m, 1H), 2.47-2.43 (m, 1H), 2.25 (s, 3H), 2.23 (s, 3H), 1.12 (t, *J*= 7.6 Hz, 3H); **HPLC**: 11.220 min; 97.97 %, Column :INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile; Flow: 1.0 mL/min; **Chiral HPLC:** 18.698 min; 100 %; Column Name : IG (4.6 * 250 mm), 5µm; Co-Solvent Name : MeCN:MeOH+0.1%DEA; Total flow rate : 3g/mL; % of Co-Solvent: 20; Temperature :30 °C; ABPR Pressure :1500 psi.

Peak-2; Example 168: **LCMS** Calculated. for $C_{21}H_{28}N_8O_2$ is 425.23; Observed. 425.40 $[M+H]^+$. **^{1}H NMR (400 MHz, DMSO-D$_6$):** δ 8.12 (bs, 2H), 6.55 (bs, 1H), 5.89 (s, 1H), 6.12 (s, 1H), 4.83 (bs, 1H), 4.64-4.62 (m, 1H), 4.05 (q, *J*= 8.0 Hz, 2H), 3.82 (t, *J*= 6.4 Hz, 1H), 3.65-3.62 (m, 1H), 3.55-3.52 (m, 2H), 3.41 (bs, 2H), 2.76 (t, *J*= 6.8 Hz, 2H), 2.75-2.69 (m, 1H), 2.47-2.43 (m, 1H), 2.25 (s, 3H), 2.23 (s, 3H), 1.12 (t, *J*= 7.6 Hz, 3H); **HPLC**: 11.218 min; 98.62 %, Column :INT ODS 3V-C18 (4.6*250) mm, 5µ; Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile; Flow: 1.0 mL/min; **Chiral HPLC:** 22.260 min; 99.13 %; Column Name : IG (4.6 * 250 mm), 5µm; Co-Solvent Name : MeCN:MeOH+0.1%DEA; Total flow rate : 3g/mL; % of Co-Solvent: 20; Temperature :30 °C; ABPR Pressure :1500 psi.

Biological Activity

Inhibition of cAMP in HEK

[000638] Adenosine A2A receptors and Adenosine A2B receptors induce the production of cAMP when activated/stimulated by an agonist like adenosine or 5′-(N-Ethylcarboxamido) adenosine (NECA). A Time-Resolved Fluorescence Energy Transfer (TR-FRET) assay was used to show the inhibition of this cAMP production in HEK cells upon treatment with compounds of the Formula I of the present disclosure.

Determination of Adenosine 2a receptor(A2aR) and Adenosine 2b (A2bR) receptor antagonism IC50 using 5′-(N-Ethylcarboxamido) adenosine (NECA) as agonist

[000639] HEK-293 cells expressing A2A receptor (#ES-011-C) or A2B receptor (#ES 013-C) were obtained from PerkinElmer. Cells were maintained in DMEM medium supplemented with 10% FBS and 200 µg/mL of G418 at 37 °C and 5% CO_2. The cells were cultured in antibiotic free medium for a period of 16-20 hours prior to the assay. All subsequent steps of the assay are performed at room temperature (22-24 °C). The cells were harvested at about 80% confluency by gentle flushing with PBS, recovered by centrifugation and resuspended in stimulation buffer at the concentration of 5.0 x 10^6 cells/mL. About 800-1000 cells per well were pre-incubated for 10 minutes with the compounds of the present invention before adding the agonist NECA at 5 nM for A_2A and 30 nM for A_2B corresponding to their respective EC_{90} for a total stimulation time of 30 minutes.

[000640] The IC_{50}s of compounds of Formula I were determined by assessing the cAMP levels using the Lance Ultra cAMP Kit (PerkinElmer, TRF0263) on white 384 well plates (Corning 3572). The assays were conducted in a stimulation buffer containing 1X DMEM, 5mM HEPES, 0.1% BSA stabilizer and 20-30 µM Rolipram. Serial dilutions of compounds were made in stimulation buffer to achieve a final concentration of high micromolar (10 µM to 0.08 nM) in the reaction volume of 10 µL. The total reaction volume was 10 µL (5 µL of cells, 2.5 µL of antagonist and 2.5 µL of agonist). The stimulation was ended, and the reaction completed by adding 5 µL of 4X Eu-cAMP tracer working solution and 5 µL of 4X ULight-anti-cAMP working solution. The TR-FRET signal was measured after 1-hour incubation using a Tecan M1000 reader.

Determination of Adenosine 2a receptor($A_{2a}R$) and Adenosine 2b ($A_{2b}R$) receptor antagonism IC_{50} using high concentration of adenosine (30 µm) to mimic the pathological conditions

[000641] HEK-293 cells expressing A_{2A} receptor (#ES-011-C) or A_{2B} receptor (#ES 013-C) were obtained from PerkinElmer. Cells were maintained in DMEM medium supplemented with 10% FBS and 200 µg/mL of G418 at 37 °C and 5% CO2. The cells were cultured in antibiotic free medium for a period of 16-20 hours prior to the assay. All subsequent steps of the assay are performed at room temperature (22-24 °C). The cells were harvested at about 80% confluency by gentle flushing with PBS, recovered by centrifugation and resuspended in stimulation buffer at the concentration of 5.0 x 106 cells/mL. About 1500 cells per well were pre-incubated for 10 minutes with the compounds of the present invention before adding the agonist Adenosine at a high concentration (30 µM) for a total stimulation time of 30 minutes.The IC50s of compounds of formula (I) were determined by assessing the cAMP levels using the Lance Ultra cAMP Kit (PerkinElmer, TRF0263) on white 384 well plates (Corning 3572). The assays were conducted in a stimulation buffer containing 1X DMEM, 5mM HEPES, 2 % Human serum albumin (HSA), 100 µM Rolipram and 30 µM erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA). Serial dilutions of compounds were made in stimulation buffer to achieve a final concentration of high micromolar in a reaction volume of 10 µL. The total reaction volume was 10 µL (5 µL of cells, 2.5 µL of antagonist and 2.5 µL of agonist). ZM241385 and AB928 were used as reference compounds. The stimulation was ended, and the reaction completed by adding 5 µL of 4X Eu-cAMP tracer working solution and 5 µL of 4X ULight-anti-cAMP working solution. The TR FRET signal was measured after 1-hour incubation using a Tecan M1000 or a PerkinElmer Victor Nivo plate reader.

Results:

[000642] IC_{50}s of the antagonists of Formula (I) against A_{2a} and A_{2b} receptor expressing HEK-293 cells are presented in Table 1

Table 1

Example	$A_{2A}R$ IC_{50} (nM) (@5 nM NECA)	$A_{2B}R$ IC_{50} (nM) (@30 nM NECA)	$A_{2A}R$ IC_{50} (nM) (@30 µM Adenosine)	$A_{2B}R$ IC_{50} (nM) (@30 µM Adenosine)
1	10	1326	ND	ND
2	2.0	547	ND	ND
3	1014	> 3000	ND	ND
4	25	1374	ND	ND
5	0.15	0.87	ND	ND
6	6.6	> 3000	ND	ND
7	0.59	> 3000	ND	ND
8	46	1683	ND	ND
9	ND	1131	ND	ND
10	2.3	41	ND	ND
11	6.8	43	ND	ND
12	0.9	3.7	ND	ND
13	0.25	3.4	300	2319
14	1	7	ND	ND
15	ND	102	ND	ND
16	2	53	ND	ND
17	0.15	0.87	260	2378
18	5.5	9.5	ND	ND
19	2.1	36	ND	ND
20	ND	4	ND	ND

21	3.9	13	ND	ND
22	2.5	2.2	ND	ND
23	11	130	ND	ND
24	ND	2.5	ND	ND
25	0.2	14	ND	ND
26	2.9	0.83	ND	ND
27	ND	654	ND	ND
28	31	17	ND	ND
29	1	18	ND	ND
30	ND	4.5	ND	ND
31	0.73	51	ND	ND
32	0.5	7.3	452	2126
33	0.38	0.97	206	1423
34	0.4	6	160	ND
35	0.92	16	ND	ND
36	0.8	22	250	ND
37	0.12	7	78	1767
38	0.1	4.4	178	ND
39	0.23	0.94	120	1833
40	<0.1	3.6	260	2378
41	0.88	73	ND	ND
42	0.88	76	ND	ND
43	2.3	123	ND	ND
44	1.3	2.3	ND	ND

45	0.58	2.9	935	650
46	1.9	ND	ND	ND
47	7.2	ND	ND	ND
48	2.2	51	7659	ND
49	0.3	6	635	4260
50	0.2	3.6	2161	2367
51	0.17	2.1	348	1287
52	0.54	29.3	ND	ND
53	0.3	27	ND	ND
54	0.74	5	ND	ND
55	0.74	8.6	250	3789
56	3.3	11	ND	ND
57	13	100	ND	ND
58	0.22	4.7	756	12208
59	ND	9	1083	ND
60	ND	0.94	211	ND
61	<1	24	574	ND
62	5	42	ND	ND
63	ND	7.3	810	2798
64	ND	11	284	9075
65	<1	27	227	15000
66	5	21	ND	ND
67	0.1	ND	50	1881
68	ND	ND	161	9382

69	ND	ND	68	2053
70	ND	ND	125	>15000
71	ND	ND	158	2820
72	ND	ND	362	3116
73	ND	ND	>15000	>15000
74	ND	ND	398	1076
75	ND	ND	43	7147
76	ND	ND	50	1593
77	0.1	2	81	700
78	ND	ND	200	798
79	<0.1	2	88	586
80	ND	12	83	3804
81	ND	3.6	63	1054
82	ND	7	110	2338
83	ND	ND	109	2646
84	ND	ND	102	4245
85	ND	3	211	1070
86	0.2	19	43	2554
87	ND	ND	80	1764
88	ND	ND	286	1298
89	ND	ND	66	2371
90	ND	ND	77	1830
91	ND	ND	628	1617
92	ND	ND	79	5645

93	ND	ND	50	1227
94	ND	ND	104	10000
95	1.2	53	112	1060
96	ND	ND	456	ND
97	ND	ND	451	1428
98	ND	ND	100	>15000
99	ND	ND	69	20000
100	ND	ND	139	1007
101	ND	ND	2100	>15000
102	ND	ND	804	8301
103	ND	ND	100	2592
104a	ND	ND	88	2262
104b	ND	ND	102	2607
105	ND	ND	ND	3869
106	ND	ND	75	4388
107	ND	ND	224	1548
108	ND	ND	392	1074
109	ND	ND	402	723
110	ND	ND	>15000	>15000
111	ND	ND	666	2383
112	ND	ND	84	10829
113	ND	ND	187	1051
114	ND	ND	96	4384
115	0.3	9	117	829

116	ND	ND	427	2100
117	ND	ND	66	3061
118	ND	ND	78	7849
119	ND	ND	260	3412
120	ND	ND	529	8630
121	ND	ND	245	895
122a	ND	ND	289	707
122b	ND	ND	130	521
123	ND	ND	405	1580
124	ND	ND	126	2219
125	ND	ND	767	>15000
126	ND	ND	1885	3551
127	ND	ND	161	2171
128	ND	ND	368	1110
129	ND	ND	237	5664
130	ND	ND	280	5880
131	ND	ND	1457	>15000
132	ND	ND	248	ND
133a	ND	ND	554	6685
133b	ND	ND	136	6073
134	ND	ND	475	2509
135	ND	ND	1312	2216
136	ND	ND	506	2613
137	ND	ND	820	>15000

138	ND	ND	88	2048
139	ND	ND	165	482
140	ND	ND	6019	>15000
141	ND	ND	679	4749
142	ND	ND	141	1665
143	ND	ND	667	1340
144a	ND	ND	327	821
144b	ND	ND	254	815
145	ND	ND	294	1125
146	ND	ND	255	2469
147	ND	ND	363	9076
148	ND	ND	161	2736
149	ND	ND	43	988
150	ND	ND	1153	1626
151	ND	ND	95	4614
152	ND	ND	209	1788
153	ND	ND	195	1193
154a	ND	ND	1055	1544
154b	ND	ND	1010	1411
155	ND	ND	181	429
156	ND	ND	750	2954
157	ND	ND	1669	2934
158	ND	ND	805	3347
159a	ND	ND	139	911

159b	ND	ND	457	1022
160a	ND	ND	579	1931
160b	ND	ND	341	1252
161	ND	ND	2768	3965
162a	ND	ND	1881	5793
162b	ND	ND	1233	2725
163a	ND	ND	72	11129
163b	ND	ND	82	12177
164	ND	ND	8258	>15000
165a	ND	ND	2164	>15000
165b	ND	ND	1535	9157
166	ND	ND	1424	466
167	ND	ND	100	700
168	ND	ND	90	650
ZM241385	3.5	ND	27296	16745

ND- not determined.

From Table 1, it can be observed that the compounds of the present disclosure exhibit very potent antagonism against both adenosine 2aR and 2bR with sub nanomolar to nanomolar potency under the physiological condition of adenosine agonist(NECA). It also evident from Table-1 is that the compound of the present invention also demonstrates very potent functional antagonism against adenosine 2aR and 2bR with nanomolar to micromolar potency under high adenosine concentrations (30μM) which mimics the pathological disease conditions. Hence the compounds present

disclosure demonstrates superior dual antagonism compared to reference adenosine antagonist(ZM241385)

CYTOKINE RESTORATION IN HUMAN PBMCS

[000643] The representative compounds of Formula (I) are of interest due to their potent dual functional antagonism of adenosine 2a and 2b receptors through inhibition of cyclic AMP in HEK 293 cells. The ability of the invention compounds disclosed herein to restore the cytokines (IL-2 and TNF-α) release under adenosine agonist (NECA) environment evaluated using human Peripheral blood mononuclear cells (PBMCs).

PBMC ISOLATION

[000644] Peripheral blood was collected from healthy adult individuals in vacutainer tube. Peripheral blood mononuclear cells (PBMCs) were isolated via density gradient centrifugation, which uses Ficoll (Histopaque buffer) combined with short, low-speed centrifugation, to separate different cell populations. Diluted defibrinated blood was layered on a Ficoll and centrifuged at 1800 rpm for 20 minutes at 22 ºC. Differential migration of cells during centrifugation results in the formation of layers containing different cell types. The bottom layer contains erythrocytes. Remaining cells (i.e., lymphocytes, monocytes, and platelets) that are not dense enough to penetrate the Ficoll media layers (densities of 1.0770 g/ml), forms a buffy coat at the interface between the upper plasma layer and the Ficoll media layer. After carefully collected the buffy coat excess of platelets, Ficoll and plasma were removed by washing it with isotonic sterile phosphate buffered saline (PBS) and resulting cell pellet was resuspended in RPMI media with 5 % FBS an P/S. The isolated PBMCs were allowed to be conditioned for an hour at 37 ºC in a CO_2 incubator. These cells were subsequently used for specific downstream assay.

CYTOKINE RESTORATION ASSAY IN HUMAN PBMCs

[000645] Isolated PBMC (3 x 10^5 cells /200 µl) were plated in in 96 well microtiter plate in RPMI media with 5%FBS in presence of 100 units of penicillin

plus 100 µg/ml streptomycin. NECA was added at a final concentration of 5 µM, control wells were maintained without NECA suppression (i.e., no NECA control). The assay plates were incubated at 37° C for 4 hours in a CO_2 incubator. Various concentrations of test compounds were added into respective wells in triplicates. Pre-washed anti CD3/28 Dynabeads (2.5 µL) was added for CD4 and CD8+ T-cell stimulation (to obtain a bead-to-cell ratio of 1:1). The assay plate was incubated at 37°C in 5% CO_2 and 20% ambient O_2 maximum for 48 hours. At the end of 48 hours, the activated PBMC were harvested, and culture supernatants were used directly for further analysis.

[000646] Forty-eight hours post treatment, 15 µL of cell-free supernatant was collected and assayed for secreted IL2 using the human Interleukin 2 (hIL2) – LANCE Ultra Detection Kit (Perkin Elmer). Similarly, level of soluble Tumor Necrosis Factor alpha (TNFα) was determined using human TNFα LANCE Ultra Detection Kit (Perkin Elmer). T-FRET signal was measured with Tecan spark multimode plate reader. Data was analyzed by graph-pad prism9. EC_{50}s of the compounds of Formula (I) in restoration of cytokine release under adenosine agonist from the human PBMCS are presented in Table 2

Table 2

Example	IL-2 restoration EC_{50} (nM)	TNF-α restoration EC_{50} (nM)
13	5.5	5.2
39	4.2	2.3
79	2.2	1.4
122b	1.4	1.2
155	3.6	3.2
ZM241385	200	60.5

hERG inhibition assay

[000647] To test if the compounds of Formula I has any safety risk by inhibiting cardiac ion channel, particularly the potassium channel (Ikr, hERG), compounds were tested using electrophysiological assays to evaluate its potential activity on hERG ion channel. The representative compounds of formula I were tested for inhibition of the human ether a go-go related gene (hERG) K+ channel

using Qpatch HTX automated electrophysiology. 6-Point concentration-response curves were generated using three-fold serial dilutions from a maximum final test concentration of 300µM and the results are presented in Table 3.

[000648] Compounds were solubilised to 100mM in DMSO before dilution in HBPS to 100 µM. 6-Point concentration-response curves were generated using 3.16-fold serial dilutions from the top test concentration. Electrophysiological recordings were made from a Chinese Hamster Ovary cell line stably expressing the full-length hERG potassium channel. Single cell ionic currents were measured in whole-cell patch clamp configuration at room temperature (21-23°C) using the Qpatch HTX platform (Sophion). Intracellular solution contained (mM): 120 KF, 20 KCl, 10 EGTA, 10 HEPES and was buffered to pH 7.3. The extracellular solution (HEPES-buffered physiological saline, HBPS) contained (mM): 145 NaCl, 4 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 10 HEPES, 10 glucose, buffered to pH7.4. Cells were clamped at a holding potential of -80mV. Cells were stepped to +20mV for 2s then -40mV for 3s before returning to the holding potential. This sweep was repeated 10 times at 10s intervals. hERG currents were measured from the tail step and referenced to the holding current. Compounds were then incubated for 2 minutes prior to a second measurement of ion channel current using an identical pulse train.

Table 3: hERG IC_{50} values

Example	hERG IC_{50} (µM)
13	>100
39	>100
79	>100
122b	>100
155	>100
Cisapride	0.14

Plasma Protein Binding Assay:

[000649] Protein binding is measured using the equilibrium dialysis technique. Compound is added to 10% plasma giving a concentration of 10 µM and dialysed with isotonic buffer for 18 hours at 37° C. The plasma and buffer solutions are analysed using generic LC UV/MS and the first apparent binding constant for the compound derived. The binding constant is then used to determine the % free in 100% plasma

The percentage of plasma bound/unbound fraction preparation was calculated as follows

$$\%Unbound = 100 * \frac{F_C}{T_C}$$

$$\%Recovery = 100 * \frac{(F_C + T_C)}{T_O}$$

where,

T_c = Total plasma concentration was determined by the calculated concentration on the plasma side of the chamber

F_c = Total plasma concentration was determined by the calculated concentration on the buffer side of the chamber

T_o = Total compound concentration determined before analysis.

Table 4 Multi Species (Mice; Rat; Dog & Human) Plasma Protein binding of Example 13, Example 122b, Example 39

Species	**Example 13**	**Example 122b**	**Example 39**
mouse, CD-1	90.67	ND	87.52

rat, Sprague-Dawley	90.36	86.07	75.14
dog, Beagle	91.00	84.99	84.44
human	95.00	88.33	90.87

ND: Not determined

***In vitro In vivo* Extrapolation (IVIVE) of Clearance in multiple species (Rat/Dog & Human) & Prediction of Human Pharmacokinetic (PK) Parameters**

[000650] Well stirred model was used for predicting human CL using human hepatocyte Clint and free fraction (fu) in human plasma. Liver blood flow rates, liver weights, hepatocellularity and *in vitro in vivo* correlation / extrapolation (IVIVC / E) templates routinely employed (Smith et al., Pharmacokinetics and Metabolism in Drug Design, Methods and Principles in Medicinal Chemistry Volume 13, 2004 Wiley – VCH, Weinheim, Germany) were used for prediction.

[000651] Briefly, thawed cryopreserved hepatocytes was transferred into the pre-warmed (maintained at 37°C) buffer medium, and hepatocytes was mixed by gently inverting the tube 3 times. The cell suspension was centrifuged at 50xg room temperature for 5 min. The supernatant was discarded, and cell pellet was loosened by gently swirling the centrifuge tube. The hepatocytes were resuspended in 2 mL pre-warmed buffer. The total cell count was determined and the number of viable cells by trypan blue dye exclusion method. The acceptable cell viability at the beginning of the assay was ~85%. The hepatocyte suspension was diluted with the buffer to attain a final concentration of 1 million cells/mL ($1*10^6$ cells/mL).

[000652] The stock (10 mM) solution of test compounds and positive controls was prepared in dimethyl sulfoxide (DMSO). Subsequently, sub stock (1 mM) solutions were prepared by diluting 10 µL of 10 mM stock solution with 90 mL of DMSO. The final working stock (1µM) solutions were prepared by diluting 2 µL

of sub stock solution with 1998 µL of incubation media. For the assay, working stock solution (1µM) was spiked into hepatocyte incubation mixture to obtain a final concentration of 0.5 µM. Final organic content in the assay was <0.1%.

[000653] The stability assay was conducted in duplicate (n=2). Manually 200 µL of diluted hepatocyte suspension ($1*10^6$ cells/mL) was added to each well of a 48 well plate. 200 µL of test compound (1 µM) prepared was added in the incubation medium to each of the wells containing hepatocytes. Final concentration of hepatocytes and test compound in the assay were $0.5*10^6$ cells/mL (0.5 million cells/mL) and 0.5 µM, respectively. The 48 well plate was placed in an incubator maintained at 37°C, 5% CO_2 atmosphere and 95% relative humidity. The hepatocyte mixture was incubated for 120 mins with constant shaking at 250 rpm. At each time point (0, 5, 10, 15, 30, 60, 90 and 120 mins), 50 µL aliquot of hepatocyte mixture was added into 96 deep well plate and precipitated with 200 µL of acetonitrile containing internal standard. The samples were vortex mixed and centrifuged for 10 mins at 4000 rpm. Post centrifugation, the supernatant (100 µL) was separated and transfer to a fresh 96 well plate and diluted with 100 µL of water. The samples were analyzed using LCMS/MS method.

[000654] The metabolic stability was expressed as the percentage of parent remaining is calculated from the peak area ratio of NCE remaining after incubation (tx) compared to the time zero (t_0) incubation. The percentage of parent test compound remaining at each time point was calculated by comparing the peak area ratio of test compound after incubation (tx) with peak area of time zero (t_0) incubation. Similarly, half-life (t1⁄2) was calculated using following equation:

$$In - vitro\ T_{1/2} = \frac{0.693}{K_{el}}$$

The intrinsic clearance (Clint) was calculated using the following equations:

$$CL_{int} = \frac{0.693}{K_{el}} x \frac{\mu L\ of\ incubation}{K_{el} x\ Number\ of\ cells/incubation} x\ no\ of \frac{cells}{gram} liver$$

Scaling factors to represent hypocellularity million cells/ gm liver and liver/kg body wt.

Table 5 Metabolic stability and Intrinsic Clearance of Example 122b, Example 13 and Example 39 determined from Rat; Dog and Human in-vitro hepatocytes assay

Compounds	Rat		Dog		Human	
	CLint (µl/min/10^6)	CLint T1/2	CLint (µl/min/10^6)	CLint T1/2	CLint (µl/min/10^6)	CLint T1/2
Example 122b	4.7	216	<4.1	>240	<4.1	>240
Example 13	34	29	9.5	107	<8.2	>120
Example 39	<8.2	>120	10.8	92	<8.2	>120

Table 6: *Invitro- In vivo Extrapolation* (IVIVE) of intrinsic clearance (CL_{int}) of Example 122b, Example 13 and Example 39 determined using Rat, Dog and Human hepatocytes

Compound	Species	Hepatocyte Clint (µl/min/10^6)	Predicted CL_h (mL/min/kg)	Total $CL_{Systemic}$ in plasma (mL/min/kg)	Vss (L/kg)	T1/2 (hr) (IV bolus)	% F
Example 122b	Rat	4.7	16	78	1.6	0.33	21
	Dog	<4.1	10	ND	ND	ND	ND

	Human	<4.1	8.6	ND	ND	ND	ND
Example 13	Rat	34	41	69	1.4	0.41	<1
	Dog	9.5	17	33	1.8	0.77	25
	Human	<8.2	12	ND	ND	ND	ND
Example 39	Rat	<8.2	23	90	2.4	1.2	27
	Dog	10.8	18	52	2.0	0.45	25
	Human	<8.2	12	ND	ND	ND	ND

ND: Not determined

Cell based permeability/efflux Caco-2 assay:

[000655] The intestinal permeability of the compounds is critical for good oral absorption and hence it was determined using Caco-2 assay.

[000656] Briefly, Permeability in a Caco-2 monolayer was determined at 10 µM. High density Caco-2 cells were obtained with fluent monolayer with trans epithelial electrical resistance (TEER) values greater than 350 ohm.cm^2 in the assay at 21 days of culture in 24 or 96 well insert plates. TEER was measured both before and after performing all the transport experiments. P_{app} was measured in apical A to basolateral B direction. Transport buffer, 800 µL Hanks balanced salt sodium (HBSS) (pH 7.4) consisting of 10 mM HEPES without proteins was first dispensed to the basal side of the monolayer. The assay was then initiated by adding 200 µL of compound solution to the apical side (all test compounds were diluted in HBSS, pH 6.5, with 1% DMSO as co-solvent). Two µL and 200 µL of samples were withdrawn before and at 45- and 120-min post addition of test compound, from the

apical donor compartment and the base lateral receiver compartment, respectively. The transwell plates were kept for 120 min of incubation time at 37°C, 5% CO2, 95% relative humidity. At the end of incubation, sample solutions from both donor and receiver wells were mixed with acetonitrile containing internal standard (IS) immediately. Samples were analyzed including starting dosing solution, donor solution, and receiver solution by LC/MS/MS (API-4500). Concentrations of test compound was expressed as area ratio of analytes versus internal standard (IS).

[000657] A passive permeability was determined by complete chemical inhibition of the three major efflux transporters, ABCB1 (P - gp), ABCG2 (BCRP) and ABCC2 (MRP2) in Caco-2 cells using a cocktail of chemical inhibitors quinidine (P-gp), sulfasalazine (BCRP) and benzbromarone (MRP2)

The mean apparent permeability (P_{app}, X 10^{-6} nm/sec) is calculated as follows

$$\text{Papp} = \frac{dq}{dt} \text{X} \frac{1}{\text{Co}} \text{X} \frac{1}{\text{A}}$$

Where dq/dt = rate of transport (rate of transport of compound in the receiver compartment), Co = initial concentration in the donor compartment, A = surface area of the effective filter membrane. Plot the cumulative amount of transported drug against time to obtain rate transport.

The percent recovery was calculated using the following equation

$$\%Recovery = \frac{Total\ compound\ in\ donor\ and\ receiver\ chamber\ at\ the\ end\ of\ experiment}{Initial\ amount\ of\ compound\ loaded\ in\ donor\ chamber} x\ 100$$

$$Efflux\ ratio = \frac{P_{app} values\ in\ B \rightarrow A}{P_{app} values\ in\ A \rightarrow B}$$

Efflux ratio >2.0 suggest that the compound is subjected to apical efflux and provides evidence for involvement of one or more transport pathways in the transport of test compound.

Table 7 Bi-directional permeability of *Example 122b, Example 13 and Example 39* measured in the CaCo-2 assay

Properties	Example 122b	Example 13	Example 39
A-B permeability X 10^{-6} cm/s	14.4	58.0	18.4
B-A permeability X 10^{-6} cm/s	15.9	19.5	18.5

Pharmacokinetic studies of Example 13, Example 122b and Example 39 in mice, rats, and dogs:

[000658] Intravenous (i.v) and Oral formulations for pharmacokinetic (PK) studies was formulated in different vehicles and excipients to achieve the desirable solubility for intravenous and Oral routes of administration.

[000659] Appropriate amount of the test compound was weighed and dissolved in required volume of the vehicles, followed by vertexing for a few seconds to dissolve the compound. Then the solution (or) suspension was sonicated at room temperature for 5 minutes to obtain a visually clear solution and or homogenous suspension. All the formulations were prepared freshly at room temperature before dosing. All these formulations were observed to be stable at room temperature for more than 24 hours. The formulation details of each of the compound tested was given in the Table 8.

Rodent (Mice & Rat) Pharmacokinetic (PK) Studies

[000660] The rodent pharmacokinetic studies were carried out in male Sprague-Dawley (SD) rats (8-12 weeks of age, weighing 280 ± 20 g at the time of dosing) and CD1 mice (8-12 weeks of age, weighing 30-35 g body weight at the time of dosing) to estimate the plasma clearance, volume of distribution and terminal half-life, area under curve (AUC) and peak plasma concentration (C_{max}) and time of peak plasma concentration (T_{max}) following intravenous and oral routes of administration. The detailed experimental design is described in the Table 8 below.

[000661] Rats were anaesthetized by Isoflurane anaesthesia. The jugular and femoral veins of rat were cannulated, and the study was performed 48 h post cannulation. At each time point about 100 µL of rat blood was collected from the jugular vein into a labelled microfuge tube containing 200 mM K_2EDTA solution (20 µL per mL of blood) and equivalent volume of heparinized saline was replaced following sample collection. Similarly, 25 µL of mice blood was collected from the saphenous vein into a labelled microfuge tube containing 200 mM K_2EDTA solution

[000662] Serial blood sampling method was used for blood collection. Blood samples were collected at pre-dose, 0.25 h, 0.5, 1, 2, 4, 6, 8 and 24-hours post dose. The blood samples were processed to obtain the plasma samples within 30 min of scheduled sampling time. All plasma samples were stored -70 °C until bioanalysis.

Non-Rodent (Dog) PK Study:

[000663] The dog PK study was carried out in male Beagle dogs of minimum 10 Kg body weight to estimate the plasma clearance, volume of distribution and terminal half-life, area under curve (AUC) and peak plasma concentration (C_{max}), time of peak plasma concentration (T_{max}) and absolute bioavailability (%F) following intravenous and oral routes of administration**.** The detailed experimental design is provided in Table-8.

Table 8: Pharmacokinetic Study design of Example 13, Example 122b and Example 39 *in* Mice, Rats and Dogs

Test item	Species/Strain/Gender	Route /condition	Dose (mg/kg)	Dose volume (mL/kg)	Formulation details
Example 13	Rat/SD/Male	IV bolus /Fed	3	2	5% w/v ascorbic

					acid in water, pH adjusted to~ 4.1 using 8.4% NaHCO3
	Rat/SD/Male	Oral/ Fasted	100	10	5% Ascorbic acid: 10%TPGS: 6%Solutol: 5%Poloxamer: water q.s
	Mice/CD1/Male	Subcutaneous /Fed	5	5	5% w/v ascorbic acid in water +15%TPGS
	Mice/CD1/Male	Oral/ Fasted	30	10	10%v/v DMSO: 5%v/v Ethanol: 15%v/v TPGS in water: Saline q. s

	Dog/Beagle/Male	IV bolus /Fed	3	2	5% w/v L-Ascorbic Acid in water, pH adjusted to 4 using 8.4% w/v sodium bicarbonate (NaHCO3)
	Dog/Beagle/Male	Oral/ Fasted	10	5	10%v/v Dimethyl sulfoxide (DMSO): 5%v/v Ethanol: 15%v/v TPGS in water: 70%v/v sterile Saline.
Example 39	Mice/CD1/Male	IV bolus /Fed	15	5	15%v/v DMSO: 25%v/v PEG400: 10%v/v Ethanol:

					50%v/v Normal saline
	Mice/CD1/Male	Oral/ Fasted	30	10	10%v/v DMSO: 30% v/v PEG400: 10%v/v Ethanol: 5%v/v tween80: 45%v/v Saline
	Mice/CD1/Male	Oral/ Fasted	30	10	10%v/v DMSO: 5%v/v Ethanol: 15%v/v TPGS in water: 70%v/v normal saline
	Rat/SD/Male	IV bolus /Fed	15	5	15%v/v DMSO + 25%v/v PEG400 +10%v/v Ethanol +

					50%v/v Normal saline
	Rat/SD/Male	Oral/ Fasted	100	10	10%v/v DMSO: 30%v/v PEG400: 10% v/v Ethanol: 5% v/v tween80: 45% v/v Saline
	Dog/Beagle/Male	IV bolus /Fed	3	2	20%v/v N, N-Dimethyl acetamide (DMA): 10%v/v PEG400: 70% v/v sterile saline.
	Dog/Beagle/Male	Oral/ Fasted	10	5	10%v/v DMSO: 5%v/v Ethanol: 15%v/v TPGS in

					water: 70%v/v Saline.
Example 122b	Mice/CD1/Male	Oral/ Fasted	100	10	10%v/v DMSO: 5%v/v Ethanol: 15% v/v TPGS in water: Saline q.s
	Rat/SD/Male	IV bolus /Fed	5	2	10%v/v DMSO: 5%v/v Solutol HS: 20%v/v PEG400: Saline q.s
	Rat/SD/Male	Oral/ Fasted	30	10	10%v/v DMSO: 5%v/v Ethanol: 15%v/v TPGS in water: Saline q.s

[000664] Briefly, Example 13 and Example 39 was administered to a group of 3 non-naïve male dogs. The first set of 3 animals received an intravenous administration and following a washout period of 7 days, received an oral administration of Example 13. Following a further 7-day washout the animals will then repeat the intravenous and oral dosing regimen with an administration of Example 39. Blood samples (1 mL) was collected from the jugular vein by venepuncture into tubes containing K2EDTA anticoagulant at the following sampling times:

IV: Predose, 0.083 (5 min), 0.25, 0.5, 1, 2, 4, 8 and 24 hrs post-dose.

PO: Predose, 0.25, 0.5, 1, 2, 4, 8 and 24 hrs post-dose.

[000665] Immediately following collection blood samples was inverted to ensure mixing with anticoagulant and placed on wet ice. As soon as practically possible samples were centrifuged (3000 rpm, 10 min, at 4°C) and the resultant plasma decanted into appropriately labelled polypropylene tubes in 96-well plate format and stored in a freezer set to maintain a temperature of ≤-65°C, until analysis.

[000666] Plasma samples were analysed for a fit-for purpose LC-MS/MS method with a lower limit of quantification. The pharmacokinetic parameters were calculated using the non-compartmental analysis tool of validated Phoenix® WinNonlin® software (Certara, USA version 8.4) with linear up and log down method for estimating AUC.

[000667] All animals in intravenous (IV bolus) group were under fed state and animals in oral groups were fasted overnight (min 12hr) before dose administration and food was provided 4 h post dose administration. All animals were received water *ad libitum* during the study period. The mean (±SD) pharmacokinetic parameters of Example 13, Example 122b & Example 39 following IV bolus and Oral dose administration in Mice/Rat and Dog is provided in Table-9.

Table 9: Mean (±SD) Pharmacokinetic Parameters of Example 12, Example 122b and Example 39 following IV bolus and Oral dose administration in Mice, Rat and Dog

Compound	Species	Route	Dose mg/k	Co*/ ng/m	T_{ma} h	AUC_{0-t} h*ng/m	AUC_{0-} h*ng/m	CL mL/min/	V_{ss} L/K	$t_{1/2}$ h	% F
Example 13	Mice	p.o	30	236 ±	0.2	138 ±	148 ±	ND			
		s.c	10	1346	0.5	1504 ±	1539 ±	ND			
	Rat	i.v	3	2242	-	728 ±	730 ±	69 ± 9.0	1.4	0.4	
		p.o	10	4.2 ±	0.2	3.7 ±	-	ND			<1
	Dog	i.v	3	2899	NA	1497 ±	1526 ±	33 ± 3.6	1.75	0.7	
		p.o	10	839 ±	0.5	1253 ±	1319 ±	ND			25 ± 11
Example 39	Mice	i.v	15	2236	NA	4498 ±	4503	58 ± 14	1.0	0.9	
		p.o	30	3300	0.2	1360 ±	1364 ±	ND			15
	Rat	i.v	15	8676	NA	2831 ±	2835 ±	90 ± 15	2.4	1.2	
		p.o	100	4103	0.2	5152 ±	5344 ±	ND			27 ± 13
	Dog	i.v	3	1352	NA	929 ±	975 ±	52 ± 8.7	2.0	0.4	
		p.o	10	618	0.5	756	827	ND			25
		p.o	30	201 ±	0.5	382 ±	ND	ND			
Example 122b	Mice	p.o	100	1378	0.2	10504	10524	ND			
	Rat	i.v	5	4169	NA	1098 ±	1104 ±	78 ± 17	1.58	0.3	
		p.o	30	983 ±	0.5	1415 ±	1440 ±	ND			21

*C_0 is reported only for IV parameters; NA: Not applicable; ND: Not determined; #Median

[000668] Good bioavailability of 25% observed in dogs for example 13 and 39. Total systemic clearance of Example 13 is equivalent to that of hepatic clearance and High volume of distribution, 3x of total body water (TBW). Whereas Example 39 had 1.7x higher clearance than hepatic clearance and high volume of distribution (3.3x TBW). Rapid absorption post administration with T_{max} of 0.5 h and similar C_{max} at 10 mg/kg dose level for both the compounds

[000669] In rats & mice, total CL is similar to hepatic clearance for Example 13 and 1.6x high for Example 39. Highly distributed (2x than TBW). 27% bioavailability for Example 39 and <5% for Example 13 in rats was observed. High oral exposure in mice was observed for Example 39 than Example 13.

[000670] Following subcutaneous (SC) dose administration of example 13 in mice, the exposure was 32x higher than the oral route. It indicates that absorption from subcutaneous route results in significantly higher exposures than oral route of administration for example 13 in mice. Overall, the pharmacokinetic studies of representative compounds of Formula I indicates the compounds amenable for both parenteral and peroral route of administration for treating disease conditions.

[000671] In mice at 100 mg/kg post oral dose administration, **Example122b** have demonstrated very good exposure ($AUC_{0-t,}$10504 ng.h/mL) and C_{max} (13787 ng/mL) with T_{max} of 0.25 hr.

[000672] In rats at 30 mg/kg post oral administration Example 122b had achieved good exposure and with an absolute bioavailability of 21% . Total plasma systemic clearance (CL) following IV bolus administration for **Example 122b** was 1.3x higher than hepatic blood flow, similarly Volume of distribution (V_{ss}) was 2.5 higher than total body water indicating that the compound was e highly distributed.

***In vivo* efficacy of example13 on CT-26 syngeneic colon cancer mice model**

[000673] CT-26 syngeneic model of colon cancer in BALB/c is an established model and has been reported widely in literature for screening of compounds in efficacy studies for immune-oncology therapeutics.

CT-26 Cell line expansion and sub-culturing: CT26 (CT26.WT, ATCC® CRL-2638) is an N-nitroso-N-methylurethane- (NNMU) induced, undifferentiated colon carcinoma cell line derived from Mus musculus, mouse colon tissue. Cells were cultured using standard techniques in RPMI 1640 with 10% FBS and 1x penicillin–streptomycin solution at 37 °C with 5% CO2 in a suitable incubator. Cell density was determined using a hemocytometer upon harvest and the cells were prepared in 100 µL of cold PBS in a microfuge tube and kept on ice until use for inoculations.

[000674] Mice: All animal studies were conducted in accordance with an Institutional Animal Care and Use Committee. 6- to 8-week-old Balb/c mice were typically housed in sterilized suspended standard, polysulfone cages, with stainless steel top grills having facilities for holding pelleted food and drinking water in polycarbonate bottles with stainless steel sipper tubes and environment enrichment objects in the vivarium for two weeks prior to tumor cell injection. The same conditions were maintained throughout the subsequent tumor engraftment and treatment evaluation.

[000675] Tumor engraftment: All animals were inoculated with $5x10^5$/mouse in 100µL subcutaneously in the lower right flank. Tumor growth was monitored twice a week from Day 4 onwards using a calibrated digital vernier caliper and the tumor volume calculated using the formula, tumor volume (mm3) = length X (width) 2/2. Once tumor volume reaches 100±50 mm^3 on Day 12, all animals were randomized into respective treatment groups as per study plan. See Table 1 for details regarding the setup and dosing of animals. Tumor volume at the time of randomization was 90 mm^3. There was no statistical significance in tumor volume at the time of treatment initiation. Post randomization, animals were treated with the test substance for 21 days. The average tumor volume/size in the treatment group allowed to reach up to 2500mm^3, beyond this tumor size the animals to be sacrificed humanely as per general guidelines. The efficacy experimental design summarized in Table 10.

[000676] Formulation and administration: Formulations were prepared with the components listed in Table 11 every day and mixed well before dosing each time and administered orally. The anti PD-1antibody was administered via the intraperitoneal route.

Table10: **Efficacy experimental design**

Group	Treatment	n	dose (mg/kg)	Route	Regimen	Duration
1	Vehicle	10	10ml/kg	PO	BID	Day 1 to Day 21
3	PD-1 Antibody	8	5	IP	Every 3 days	Day 1 to Day 21
4	Example 13	10	1	PO	TID	Day 1 to Day 21
5	Example 13	10	3	PO	TID	Day 1 to Day 21
6	Example 13	10	10	PO	TID	Day 1 to Day 21
7	Example 13	10	30	PO	TID	Day 1 to Day 21

- TID: Dosed three times in a day at 4 h interval (ex 9.00 am, 01.00 pm and 05.00 pm)
- BID: Dosed two times in a day at ~8 h interval (ex 9.00 am and 05.00 pm)
- Example 13 and vehicle were dosed by oral route every day from Day 1 to Day 21.
- Anti-mouse PD-1 antibody was dosed by IP route every three days

Table 11: **Formulations used for the efficacy studies**

Treatment	Vehicle
Example 13	30% Gelucire 44/14+10% Solutol HS-15+ 30% Propylene Glycol in saline

Anti-mouse PD-1 Antibody (Bioxcel , USA)	PBS pH 7.4
Vehicle	30% Gelucire 44/14+10% Solutol HS-15+ 30% Propylene Glycol in saline

The in vivo efficacy effect of **Example-13** on Tumor volume is summarized in Figure 1. Data is represented as Mean ± SEM n=4-10, *p<0.05 Vs Vehicle, One-Way ANOVA followed by Dunnett's multiple comparison test. All animals injected with CT-26 increased tumor volume, vehicle treatment group from Day 11 onwards showed increased tumor volume compared to other treatment groups. EXAMPLE-13 treatment showed trend towards decrease in tumor volume from Day 11 onwards till the end of study period that is till Day 22. While the 1 mg/kg, PO, TID did not show significant change in tumor volume the 3 mg/kg, 10 mg/kg, and 30 mg/kg, PO, TID groups showed 35 %, 35 %, and 48 % respective decrease in tumor volume by day 22. Significant decrease in tumor volume was observed on Day 18 and Day 22 compared to vehicle treatment. PD-1 antibody dosed at 5mg/kg; IP (every 3 days) control treatment group showed trend towards decrease in tumor volume, 29 % and 25 % respectively, however not statistically significant compared to vehicle treatment.

Biomarker (Granzyme-B) analysis in tumour samples from the efficacy studies

[000673] On Day 22, the animals from the efficacy study above were euthanized by overdose of gaseous anaesthesia and tumor samples were collected and their weights were recorded before evaluating for Granzyme-B by FACs analysis.

[000674] Approximately 100 mg of tissue samples were homogenized, and the single cell suspensions were fixed and permeabilized using Miltenyi Biotec and BD kit-based reagents before staining with anti-Granzyme-B antibodies. Cells were subjected to FACS analysis while using isotype controls to ensure the specific binding of antibody

and unstained cells as a negative control. The result obtained were analyzed using Flow Jo software and represented in Figure 2.

[000675] Example-13, 30 mg/kg TID treatment group showed significant increase in tumor Granzyme B expression as compared to vehicle treatment and anti-PD1 antibody treatment groups. Granzyme B is expressed in the granules of cytotoxic T lymphocytes and NK cells and is an important protein that is implicated in its ability to bring about apoptosis. Significant increase in Granzyme B expression in tumor tissue indicates the probable mechanism that inhibits tumor growth on treatment with the test compounds belonging to compounds of Formula (I) having dual adenosine 2a and 2b receptor functional antagonism

ADVANTAGES OF THE PRESENT INVENTION:

[000676] The present disclosure provides a new class of heterocyclic compounds of Formula I its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof. The present disclosure provides a new class of heterocyclic compounds of Formula I for use as a medicament. The compounds of Formula I act as antagonists for adenosine receptors and particularly adenosine $A_{2a}R$ and $A_{2b}R$ receptors. The compounds of Formula I can be widely used in the treatment of proliferative disorders, diseases, condition, cancer or immune related diseases mediated by the adenosine receptors.

[000677] The compounds of the present disclosure also shown to restore the cytokine release (IL-2 and TNF-a) under adenosine agonist background in human PBMC indicates the confirmation of immune activation via adenosine $A_{2a}R$ and $A_{2b}R$ receptors functional antagonism.

[000678] The compounds of the present disclosure exhibit high degree of selectivity against hERG channel and may be devoid of cardio toxicity in animal and human.

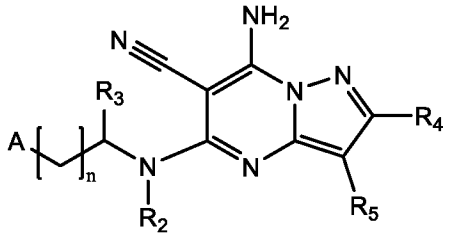
[000679] The compounds of the present disclosure demonstrates desirable pharmacokinetic profile in rat and efficacious in CT-26 syngeneic colon cancer mice

model thus confirming *in vivo* proof of principle in animal through adenosine $A_{2a}R$ and $A_{2b}R$ receptors functional antagonism.

[000680] The present disclosure also provides a pharmaceutical composition comprising the compounds of Formula I with additional therapeutic agents. The present disclosure further provides a schematic synthetic preparation process for the compounds of Formula I.

I/We claim:

1. A compound of Formula I



Formula I

or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof,

wherein A is selected from C_{5-10} aryl, C_{2-10} heteroaryl, C_{3-6} cycloalkyl, or C_{1-10} heterocyclyl; wherein C_{5-10} aryl, C_{2-10} heteroaryl, C_{3-6} cycloalkyl, or C_{1-10} heterocyclyl is optionally substituted with one or more substituents selected from R_6, R_7, R_8, R_9, R_{9a}, or oxo;

R_2 is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl;

R_3 is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl; wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy;

R_4 and R_5 are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, -CO-N(R_{10} R_{11}), C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl are optionally substituted with one or more groups selected from C_{3-6} cycloalkyl, C_{1-6} alkoxy, or C_{1-10} heterocyclyl; or R_4 and R_5 are joined together to form C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{4-10} carbocyclyl or C_{1-10} heterocyclyl is optionally substituted with 1 to 3 groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

R_{10} and R_{11} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{3-6} halocycloalkyl, C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl;

R_6 is selected from hydrogen, halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, C_{3-6} halocycloalkyl, -Y-O-C_{1-6} alkyl, -Y-O-C_{3-6} cycloalkyl, -Y-CO-NH-R_{13}, -Y-Z, C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{1-6} alkylhydroxy, or C_{1-10} heterocyclyl is optionally substituted with one or more groups selected from halogen, hydroxyl, amine, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, C_{1-6} haloalkoxy, C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{3-6} cycloalkyl, or C_{1-6} aminoalkyl, is optionally further substituted with one or more groups independently selected from halogen, hydroxyl, C_{1-6} alkylhydroxy, -C(O)C_{1-6} alkyl, -C(O)NH_2, -C(O)-C_{1-6}alkylhydroxy, or C_{1-10} heterocyclyl, and C_{1-10} heterocyclyl is optionally substituted with 1 to 3 groups independently selected from halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

Y is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, or C_{3-6} cycloalkenyl; and C_{1-6} alkyl is optionally substituted with C_{3-6} cycloalkyl;

Z is selected from -OH, -NH_2, -COOH, -SO_2NH_2, -SO_2CH_3, -$SOCH_3$, -SCH_3, CH_2-NH-(C_{1-6} alkyl)-$SOCH_3$, -O-P(=O)$(OH)_2$, -$CONH_2$, -CONH(C_{1-6} alkyl), -SO_2NH(C_{1-6} alkyl), CON(C_{1-6} alkyl)$_2$, -NHCO(C_{1-6} alkyl), C_{4-10} carbocyclyl, or C_{1-10} heterocyclyl, wherein C_{1-10} heterocyclyl has 1 to 4 heteroatoms independently selected from O, N or S, and optionally substituted with 1 to 3 groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

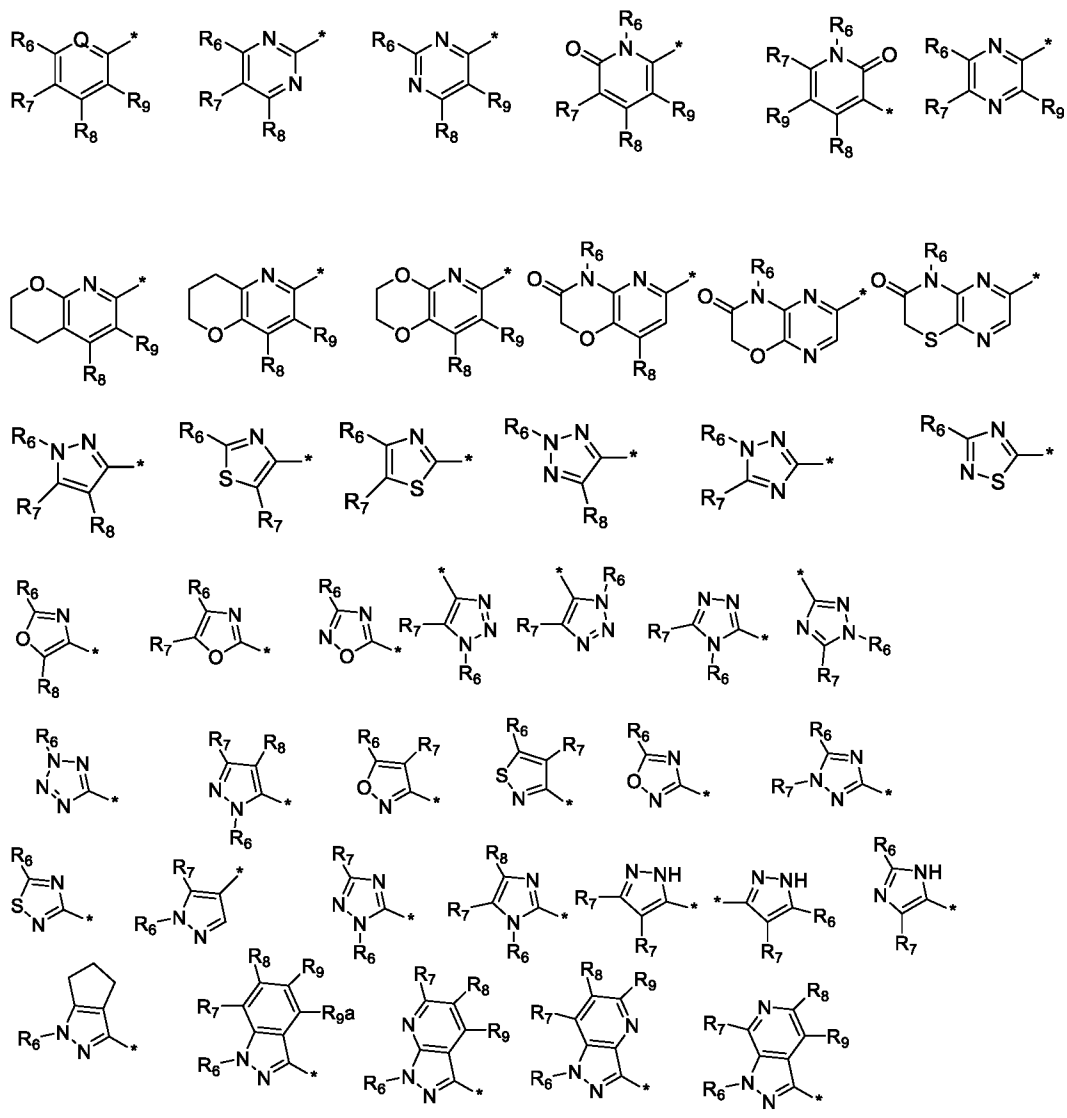
R_{13} is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or C_{3-6} halocycloalkyl;

R_7, R_8, R_9, and R_{9a} are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or C_{3-6} halocycloalkyl;

and

n is 0, 1, or 2.

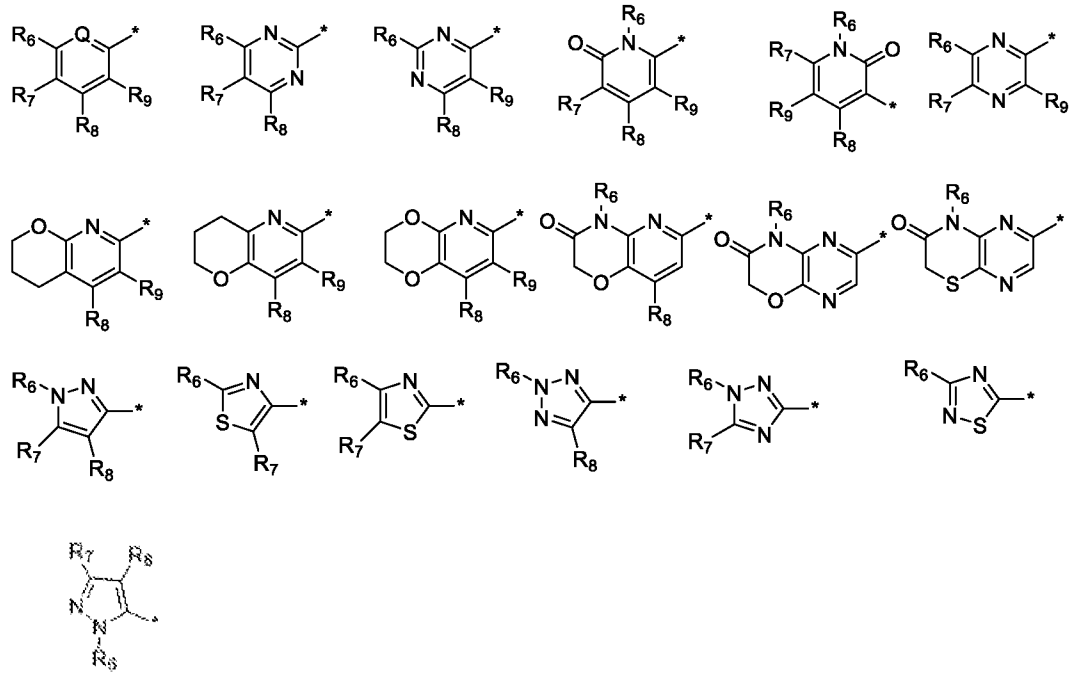
2. The compound as claimed in claim 1, or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, and pharmaceutically active derivatives thereof, wherein A is selected from



* is the point of attachment.

wherein Q is N or CR_1, wherein R_1 is selected from cyano, hydrogen, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy; and C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl is optionally substituted with C_{1-6}alkoxy.

3. The compound as claimed in claim 1, or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof, wherein A is selected from



Q is N or CR_1;

R_1 is selected from cyano, hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} alkoxy;

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

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

R_4 and R_5 are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy; wherein C_{1-6} alkyl optionally substituted with one or more groups selected from C_{3-6} cycloalkyl, or C_{1-6} alkoxy;

R_6 is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, -Y-CO-NH-R_{13}, -Y-Z, or C_{1-10} heterocyclyl, wherein C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} alkylhydroxy, or C_{1-10} heterocyclyl is optionally substituted with one or more groups selected from halogen, hydroxyl, amine, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylhydroxy, C_{1-6} aminoalkyl, C_{1-6} haloalkoxy, or C_{1-10} heterocyclyl, wherein C_{3-6} cycloalkyl, or C_{1-6} aminoalkyl is optionally further substituted with one or more groups independently selected from halogen, hydroxyl, C_{1-6} alkylhydroxy, -C(O)C_{1-6} alkyl, -C(O)NH_2, or -C(O)-C_{1-6}alkylhydroxy;

Y is C_{1-6} alkyl or C_{3-6} cycloalkyl; Z is selected from -SO_2NH_2, -SO_2CH_3, -$SOCH_3$, -SCH_3, CH_2-NH-(C_{1-6} alkyl)-$SOCH_3$, -$CONH_2$, -CONH(C_{1-6} alkyl), -SO_2NH(C_{1-6} alkyl), CON(C_{1-6} alkyl)$_2$, or -NHCO(C_{1-6} alkyl);

R_{13} is selected from hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl;

R_7, R_8, R_9, and R_{9a} are independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, or C_{1-6} alkoxy;

and

n is 0, 1 or 2.

4.The compound as claimed in any one of the claims 1 to 3, or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof, is selected from a group consisting of:

1. 7-amino-2,3-dimethyl-5-{[1-(6-methylpyridin-2-yl)ethyl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile;
2. 7-amino-2,3-dimethyl-5-{[(1S)-1-(6-methylpyridin-2-yl)ethyl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile;
3. (R)-7-Amino-3-ethyl-2-methyl-5-((1-(pyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;
4. (S)-7-Amino-3-ethyl-2-methyl-5-((1-(pyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

5. (S)-7-Amino-3-ethyl-2-methyl-5-((1-(6-methylpyridin-2-yl) ethyl) amino) pyrazolo [1,5-a] pyrimidine-6-carbonitrile;
6. 7-amino-2,3-dimethyl-5-{[(6-methylpyridin-2-yl)methyl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile;
7. 7-amino-5-{[(6-ethylpyridin-2-yl)methyl]amino}-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;
8. 7-amino-2,3-dimethyl-5-{methyl[(6-methylpyridin-2-yl)methyl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile;
9. 7-amino-5-({[6-(2-hydroxypropan-2-yl)pyridin-2-yl]methyl}amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;
10. 7-Amino-2,3-dimethyl-5-((2-(5-methylpyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;
11. 7-amino-5-((2-(5-fluoropyridin-2-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;
12. 7-amino-5-((2-(6-methoxypyridin-2-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;
13. 7-amino-5-((2-(6-methylpyridin-2-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;
14. 7-amino-2,3-dimethyl-5-{[1-(6-methylpyridin-2-yl)propan-2-yl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile;
15. 7-amino-2,3-dimethyl-5-{[1-(6-methylpyridin-2-yl)propan-2-yl]amino}pyrazolo[1,5-a]pyrimidine-6-carbonitrile;
16. 7-amino-5-({2-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]ethyl}amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;
17. 7-Amino-3-ethyl-2-methyl-5-((2-(6-methylpyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;
18. 7-Amino-3-ethyl-2-methyl-5-((2-(5-methylpyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

19. : 7-Amino-3-ethyl-5-((2-(5-methoxypyridin-2-yl) ethyl) amino)-2-methylpyrazolo [1,5-a] pyrimidine-6-carbonitrile;

20. 7-Amino-3-ethyl-5-((2-(6-methoxypyridin-2-yl) ethyl) amino)-2-methylpyrazolo [1,5-a] pyrimidine-6-carbonitrile;

21. 7-Amino-3-ethyl-5-((2-(5-fluoropyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

22. 7-Amino-3-ethyl-2-methyl-5-((1-(pyridin-2-yl) propan-2-yl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

23. 7-Amino-3-ethyl-2-methyl-5-((1-(pyridin-2-yl) propan-2-yl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

24. 7-Amino-3-ethyl-2-methyl-5-((1-(6-methylpyridin-2-yl) propan-2-yl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

25. 7-amino-3-ethyl-5-({2-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]ethyl}amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

26. 7-amino-3-(cyclopropylmethyl)-2-methyl-5-((2-(6-methylpyridin-2-yl)ethyl) amino) pyrazolo[1,5-a]pyrimidine-6-carbonitrile;

27. 7-amino-3-(isopropylmethyl)-2-methyl-5-((2-(6-methylpyridin-2-yl)ethyl) amino) pyrazolo[1,5-a]pyrimidine-6-carbonitrile;

28. 7-amino-3-(isopropyl)-2-methyl-5-((2-(6-methylpyridin-2-yl)ethyl) amino) pyrazolo[1,5-a]pyrimidine-6-carbonitrile;

29. 7-amino-5-{[2-(1-ethyl-1H-pyrazol-3-yl)ethyl]amino}-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

30. 7-amino-3-ethyl-5-{[2-(1-ethyl-1H-pyrazol-3-yl)ethyl]amino}-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

31. 7-amino-5-({2-[1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl]ethyl}amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

32. 7-amino-3-ethyl-5-((2-(1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

33. 7-amino-3-chloro-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

34. 7-amino-3-chloro-5-((2-(6-(1-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

35. 7-amino-3-chloro-5-((2-(1-(2-hydroxyethyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

36. 7-amino-3-chloro-5-((2-(1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

37. 7-amino-3-chloro-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

38. 7-amino-3-chloro-5-((2-(6-(2-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

39. 7-amino-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

40. amino-5-((2-(6-ethylpyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo [1,5-a] pyrimidine -6-carbonitrile;

41. 7-amino-5-((2-(3-fluoro-6-methylpyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

42. 7-amino-2-ethyl-3-methyl-5-((2-(6-methylpyridin-2-yl) ethyl) amino)pyrazolo[1,5-a]pyrimidine-6-carbonitrile;

43. 7-amino-2-ethyl-5-((2-(6-(2-hydroxypropan-2-yl) pyridin-2-yl)ethyl)amino)-3-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

44. 7-amino-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo [1,5-a] pyrimidine-6-carbonitrile;

45. 7-amino-3-ethyl-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

46. 7-amino-3-(cyclopropyl methyl)-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

47. 7-amino-2-cyclopropyl-5-((2-(6-(2-hydroxypropan-2-yl) pyridin-2-yl) ethyl)amino)-3-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

48. 7-amino-2-(difluoromethyl)-3-ethyl-5-((2-(1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl) ethyl) amino)pyrazolo[1,5-a]pyrimidine-6-carbonitrile;

49. 7-amino-5-((2-(6-(1-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl)amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

50. 7-amino-3-ethyl-5-((2-(6-(1-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

51. 7-amino-5-((2-(6-(2-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl)amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

52. 7-amino-3-ethyl-5-((2-(6-(1-hydroxy-2-methylpropan-2-yl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

53. 7-amino-5-((2-(6-(1-hydroxy-2-methylpropan-2-yl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

54. 7-amino-3-ethyl-5-((2-(1-(2-hydroxyethyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

55. 7-amino-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

56. 7-amino-2-(difluoro methyl)-3-ethyl-5-((2-(6-(hydroxymethyl) pyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

57. 7-amino-5-(((1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl) methyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

58. 7-amino-2-(difluoro methyl)-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

59. 7-amino-2-(difluoro methyl)-3-ethyl-5-((2-(6-(2-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino) pyrazolo[1,5-a]pyrimidine-6-carbonitrile;

60. 7-amino-3-ethyl-5-((2-(6-(2-(hydroxymethyl) cyclopropyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

61. 7-amino-3-chloro-5-((2-(4-(1-(hydroxymethyl) cyclopropyl) thiazol-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

62. 7-amino-3-ethyl-5-((2-(4-fluoro-1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

63. 7-amino-3-ethyl-5-((2-(1-((1-(hydroxymethyl) cyclopropyl) methyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

64. 7-amino-3-chloro-5-((2-(6-(1,1-difluoro-2-hydroxyethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

65. 7-amino-3-chloro-5-((2-(6-(1-hydroxy-2-methylpropan-2-yl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

66. 7-amino-3-ethyl-5-((2-(4-(1-(hydroxymethyl) cyclopropyl) thiazol-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

67. 7-amino-3-chloro-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

68. 7-amino-5-((2-(1-(1-(amino methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

69. 7-amino-3-bromo-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

70. 7-amino-3-chloro-5-((2-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

71. 7-amino-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

72. 7-amino-3-bromo-5-((2-(6-(hydroxymethyl) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

73. 7-amino-3-chloro-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-4-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

74. 7-amino-3-(cyclopropyl methyl)-5-((2-(1-(1-(hydroxymethyl) cyclopropyl) -1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

75. 7-amino-3-chloro-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

76. 7-amino-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

77. N-((1-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) methyl) acetamide;

78. (+)- 7-amino-3-ethyl-5-((2-(1-(2-(hydroxymethyl)cyclobutyl)-1H-pyrazol-3-yl)ethyl)amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

79. (-) - 7-amino -3-ethyl-5-((2-(1-(2-(hydroxymethyl)cyclobutyl)-1H-pyrazol-3-yl)ethyl) amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

80. 7-amino-3-ethyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

81. 7-amino-3-ethyl-5-((2-(1-(1-hydroxypropan-2-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

82. (+-) - 7-amino-3-chloro-5-((2-(1-((3-hydroxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

83. (+) - 7-amino-3-chloro-5-((2-(1-((3-hydroxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

84. (-) - 7-amino-3-chloro-5-((2-(1-((3-hydroxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile(83b);

85. 7-amino-3-ethyl-5-((2-(1-((3-hydroxycyclobutyl) methyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

86. 7-amino-5-((2-(1-(1-(hydroxy methyl) cyclopropyl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

87. 7-amino-3-chloro-2-methyl-5-((2-(1-methyl-2-oxo-1,2-dihydropyridin 3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

88. 7-amino-3-ethyl-2-methyl-5-((2-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

89. 7-amino-3-bromo-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

90. 7-amino-3-chloro-5-((2-(6-(((2-hydroxyethyl) amino) methyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

91. 7-amino-3-ethyl-5-((2-(5-fluoro-6-(hydroxymethyl) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

92. 7-amino-3-chloro-5-((2-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

93. 7-amino-3-chloro-5-((2-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

94. 7-amino-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-(trifluoromethyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

95. 7-amino-5-((2-(1-(2-(amino methyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

96. 7-amino-3-ethyl-5-((2-(6-(((2-methoxyethyl) amino) methyl) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

97. 7-amino-3-ethyl-5-((2-(6-(((2-hydroxyethyl) amino) methyl) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

98. 7-amino-3-chloro-5-((2-(1-(1-(((2-hydroxyethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

99. N-((1-(3-(2-((7-amino-3-chloro-6-cyano-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) methyl)-3-hydroxypropanamide;

100. 7-amino-3-ethyl-5-((2-(6-(1-hydroxyethyl) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

101. 7-amino-3-cyclopropyl-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

102. 7-amino-2-(difluoro methyl)-3-ethyl-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

103. (+-)-7-amino-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

104. (+)-7-amino-5-((2-(1-(2-(hydroxymethyl) cyclobutyl) -1H-pyrazol-3-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile (104a);

104b. (-)-7-amino-5-((2-(1-(2-(hydroxymethyl)cyclobutyl)-1H-pyrazol-3-yl)ethyl)amino)-2,3-dimethylpyrazolo[1,5-a]pyrimidine-6-carbonitrile (104b);

105. 7-amino-5-((2-(6-(((2-hydroxyethyl) amino) methyl) pyridin-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

106. 7-amino-3-ethyl-5-((2-(1-(1-(((2-hydroxyethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

107. 7-amino-3-ethyl-5-((2-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

108. 7-amino-3-ethyl-5-((2-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

109. 7-amino-5-((2-(1-(2-(amino methyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

110. 7-amino-3-ethyl-5-((2-(1-(3-hydroxypropyl)-1H-pyrazol-5-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

111. 7-amino-3-ethyl-5-((2-(1-(3-hydroxypropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

112. 7-amino-3-chloro-5-((2-(1-(1-(2-hydroxyethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

113. 7-amino-3-ethyl-5-((2-(1-(3-hydroxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

114. 7-amino-3-chloro-5-((2-(1-(2-(hydroxymethyl) cyclopentyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

115. 7-amino-3-ethyl-5-((2-(1-(2-(hydroxymethyl) cyclopentyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

116. 7-amino-3-(cyclopropyl methyl)-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

117. 7-amino-3-chloro-5-((2-(1-(2-(((2-hydroxyethyl) amino) methyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

118. 7-amino-5-((2-(1-(2-(amino methyl) cyclopentyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

119. 7-amino-3-chloro-2-methyl-5-((2-(6-methylpyridin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

120. 7-amino-3-chloro-5-((2-(6-ethylpyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

121. (+-)-7-amino-3-ethyl-5-((2-(1-(4-(hydroxymethyl)tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)ethyl)amino)-2-methyl pyrazolo[1,5-a]pyrimidine-6-carbonitrile;

122. (+)-7-amino-3-ethyl-5-((2-(1-(4-(hydroxy methyl)tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)ethyl)amino)-2-methyl pyrazolo[1,5-a]pyrimidine-6-carbonitrile (122a);

122b. (-)-7-amino-3-ethyl-5-((2-(1-(4-(hydroxy methyl)tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)ethyl)amino)-2-methyl pyrazolo[1,5-a]pyrimidine-6-carbonitrile;

123. (-)-7-amino-3-ethyl-5-((2-(1-(4-(hydroxy methyl)tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)ethyl)amino)-2-methyl pyrazolo[1,5-a]pyrimidine-6-carbonitrile;

124. 7-amino-3-ethyl-5-((2-(1-(3-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

125. 7-amino-3-ethyl-5-((2-(1-(1-(2-hydroxyethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

126. 7-amino-5-((2-(1-(2-aminoethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

127. 7-amino-3-chloro-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

128. 7-amino-3-ethyl-5-((2-(1-((3-hydroxycyclobutyl) methyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a]pyrimidine-6-carbonitrile;

129. 7-amino-5-((2-(1-(3-aminopropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile; ;

130. 7-amino-3-bromo-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

131. 7-amino-2-(difluoromethyl)-3-ethyl-5-((2-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

132. (+-)-7-amino-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

133. (+)-7-amino-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (133a);

133b. (-)-7-amino-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

134. 2-(((2-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclobutyl) methyl) amino) acetamide;

135. 7-amino-3-ethyl-2-methyl-5-((2-(6-(2,2,2-trifluoro-1-hydroxyethyl) pyridine-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6 carbonitrile;

136. 7-amino-5-((2-(1-(3-aminopropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

137. 7-amino-3-(cyclo butyl methyl)-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

138. 7-amino-5-((2-(1-(3-hydroxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

139. 7-amino-3-ethyl-5-((2-(6-(2-hydroxyethyl) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

140. 7-amino-2,3-dimethyl-5-((2-(6-methylpyrazin-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

141. 7-amino-5-((2-(1-(3-aminopropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

142. 7-amino-3-ethyl-2-methyl-5-((2-(1-(2-(methylthio) ethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a]pyrimidine-6-carbonitrile;

143. (+-)7-amino-3-ethyl-2-methyl-5-((2-(1-(2-(methyl sulfinyl) ethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

144a. (+)7-amino-3-ethyl-2-methyl-5-((2-(1-(2-(methyl sulfinyl) ethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

144b. (-)7-amino-3-ethyl-2-methyl-5-((2-(1-(2-(methyl sulfinyl) ethyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

145. N-(3-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-2-oxopyridin-1(2H)-yl) propyl) acetamide;

146. 7-amino-5-((2-(1-(1-(amino methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

147. N-((1-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) methyl) acetamide;

148. 7-amino-5-((2-(1-(1-(2-aminoethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

149. N-(2-(1-(3-(2-((7-amino-6-cyano-3-ethyl-2-methylpyrazolo[1,5-a] pyrimidin-5-yl) amino) ethyl)-1H-pyrazol-1-yl) cyclopropyl) ethyl) acetamide;

150. 7-amino-3-ethyl-5-((2-(6-(2-hydroxyethoxy) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

151. 7-amino-5-((2-(1-(1-(2-aminoethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-3-chloro-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

152. 7-amino-5-((2-(6-(2-hydroxyethyl) pyridine-2-yl) ethyl) amino)-2,3-dimethylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

153. 7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methylthio) propyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

154. (-)-7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methyl sulfinyl) propyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (154a);

154b. (+)-7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methyl sulfinyl) propyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

155. 7-amino-3-ethyl-5-((2-(6-(3-hydroxypropyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

156. 7-amino-5-((2-(1-(3-hydroxypropyl)-2-oxo-1,2-dihydropyridin-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

157. 7-amino-5-((2-(6-(hydroxymethyl) pyridine-2-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

158. 7-amino-5-((2-(1-(1-(hydroxymethyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

159. (+)-7-amino-3-ethyl-5-((2-(6-(1-hydroxyethyl) pyridin-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (159a);

159b. (-)-7-amino-3-ethyl-5-((2-(6-(1-hydroxyethyl) pyridine-2-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

160. (+) 7-amino-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (160a);

160a. (-) 7-amino-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

161. 7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methylthio) propyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

162. (-)-7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methyl sulfinyl) propyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a]pyrimidine-6-carbonitrile (162a);

162b. (+)-7-amino-3-ethyl-2-methyl-5-((2-(1-(3-(methylsulfinyl)propyl)-1H-pyrazol-3-yl)ethyl)amino)pyrazolo[1,5-a]pyrimidine-6-carbonitrile;

163. (-)- 7-amino-3-ethyl-2-methyl-5-((2-(1-(1-(((2-(methyl sulfinyl) ethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (163a);

163b. (+)-7-amino-3-ethyl-2-methyl-5-((2-(1-(1-(((2-(methyl sulfinyl) ethyl) amino) methyl) cyclopropyl)-1H-pyrazol-3-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

164. 7-amino-2-methyl-5-((2-(6-methylpyridin-2-yl) ethyl) amino)-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

165. (+)-7-amino-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile (165a);

165b. (-)-7-amino-5-((2-(1-(2-(hydroxymethyl) cyclobutyl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl-3-propylpyrazolo[1,5-a] pyrimidine-6-carbonitrile;

166. (R)-7-amino-3-ethyl-2-methyl-5-((2-(6-(((tetrahydrofuran-3-yl) oxy) methyl) pyridine-2-yl) ethyl) amino) pyrazolo[1,5-a] pyrimidine-6-carbonitrile;

167. (-)-7-amino-3-ethyl-5-((2-(1-(4-(hydroxymethyl) tetrahydrofuran-3-yl)-5-methyl-1H-pyrazol-3-yl) ethyl) amino)-2-methylpyrazolo[1,5-a] pyrimidine-6-carbonitrile; and

168. (+)-7-amino-3-ethyl-5-((2-(1-(4-(hydroxy methyl) tetrahydrofuran-3-yl)-1H-pyrazol-3-yl) ethyl) amino)-2-methyl pyrazolo[1,5-a] pyrimidine-6-carbonitrile.

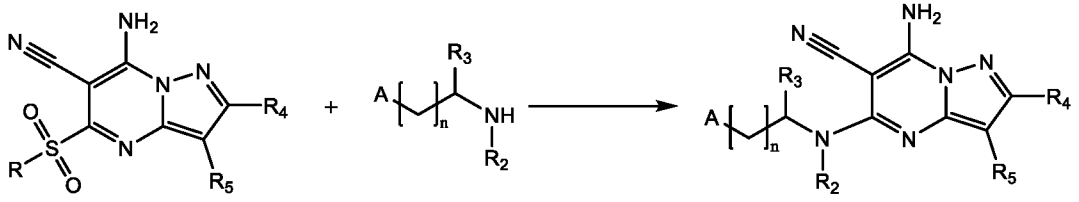
5. The compound as claimed in any one of the claims 1 to 4 or its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, pharmaceutically active derivatives thereof, for use as a medicament.

6. The compound as claimed in any one of the claims 1 to 4, its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, and pharmaceutically active derivatives thereof acts as antagonist of

adenosine 2a receptor ($A_{2a}R$) or adenosine 2b receptor ($A_{2b}R$) or combination of adenosine 2a receptor ($A_{2a}R$) and adenosine 2b receptor ($A_{2b}R$).

7. The compound as claimed in any one of the claims 1 to 4, its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, and pharmaceutically active derivatives thereof, for use in treating of a disease, disorder or condition selected from cancer, parkinson's disease, asthma, diabetes, and autoimmune disease mediated at least in part by adenosine 2a receptor ($A_{2a}R$), or adenosine 2b receptor ($A_{2b}R$), or combination of $A_{2a}R$ and $A_{2b}R$.

8. A process of preparation of compounds of Formula I as claimed in any one of the claims 1 to 4, its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, stereoisomers, racemates, and pharmaceutically active derivatives thereof, said process comprising: reacting Formula (A), and Formula (B) in the presence of a base to obtain the compounds of Formula I,



Formula (A) Formula (B) Formula I

wherein R is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-10} aryl, C_{2-10} heteroaryl, or C_{1-10} heterocyclyl; and the substituents are as defined in claim 1.

9. The process as claimed in claim 8, wherein the base is selected from triethylamine, diisopropylethylamine, pyridine, sodium carbonate, potassium carbonate, sodium hydroxide, potassium tertiarybutoxide potassium tertiarybutoxide, sodium hydride, lithium bis(trimethylsilyl)amide (LiHMDS), N-diisopropylethylamine, or combinations thereof.

10. The process as claimed in claim 8, wherein the process is carried out in the presence of a solvent selected from isopropanol, methanol, n-butanol,

dichloromethane, tetrahydrofuran, dimethylformaide, n-methylpyrrolidone, Dimethyl sulfoxide, water, dioxane, acetonitrile, or combinations thereof.

11. A pharmaceutical composition comprising compounds of Formula I as claimed in any one of the claims 1 to 4 and one or more additional therapeutic agent.

12. The composition as claimed in claim 11, wherein the one or more additional therapeutic agent is chemotherapeutic agent or immune checkpoint inhibitors; the chemotherapeutic agent is selected from phosphoinositide 3-kinase inhibitor (PI3K) inhibitor, tyrosine kinase inhibitor, signal transducer and activator of transcription 3 (Stat-3) inhibitor, topoisomerase inhibitors, Protein kinase B (AKT) inhibitor, c-Jun N-terminal kinase (JNK1/K2) inhibitors, hypoxia-inducible factor 1 alpha (HIF-1a) inhibitor, extracellular signal-regulated kinase (ERK) inhibitor, poly ADP ribose polymerase -1((PARP-1) inhibitor, cisplatin, or oxaplatin; and the immune checkpoint inhibitor is selected from programmed death-1 (PD-1) inhibitor, programmed death-ligand 1 (PD-L1) inhibitor, anti-PD1 antibody, anti-PD-L1 antibody, cytotoxic T-lymphocyte-associated protein 4 (CTLA4)inhibitor, anti-CTLA4 antibody, T cell immunoglobulin and ITIM domain (TIGIT) inhibitor, ecto-nucleoside triphosphate diphosphohydrolase 1(E-NTPDase, CD39) inhibitor, or ecto-5'-nucleotidase(Ecto5'NTase, CD79) inhibitor.

13. A method of treatment and/or prevention of a condition mediated by adenosine receptor or a proliferative disorder or cancer, comprising administering to a subject suffering from a condition mediated by adenosine receptor or a disease or proliferative disorder or cancer, a therapeutically effective amount of the compounds of Formula I as claimed in claims 1 to 4 or the pharmaceutical composition as claimed in claims 11 to 12.

14. The method as claimed in claim 13, wherein the disease or disorder or condition mediated at least in part by adenosine 2a receptor ($A_{2a}R$), adenosine 2b receptor ($A_{2b}R$), or combinations thereof.

15. The method as claimed in claim 13, wherein the compounds of Formula (I) administered in an effective amount to reverse or stop the progression of either the

adenosine 2a receptor ($A_{2a}R$) or adenosine 2b receptor ($A_{2a}R$) or both mediated immunosuppression.

16. The method as claimed in claim 13, wherein said disease, disorder or condition is cancer or an immune response related disease, disorder, or condition.

17. The method as claimed in claim 16, wherein said cancer is of adrenal gland, brain, bladder, breast, bone, colon, endometrial, oesophagus, head, gastric, kidney, liver, lung, mouth, muscle, neck, pancreas, prostate, retinal, skin, thyroid or white blood cells and said immune related disease, disorder or condition is selected from the group consisting of allergies, alzheimer, asthma, crohn's disease, colitis, chronic obstructive pulmonary disease, diabetic kidney disorders, glaucoma, lupus, rheumatoid arthritis, multiple sclerosis, pain, panic disorder, pancreatitis, parkinson disease, psoriasis, systemic sclerosis, and ulcerative colitis.

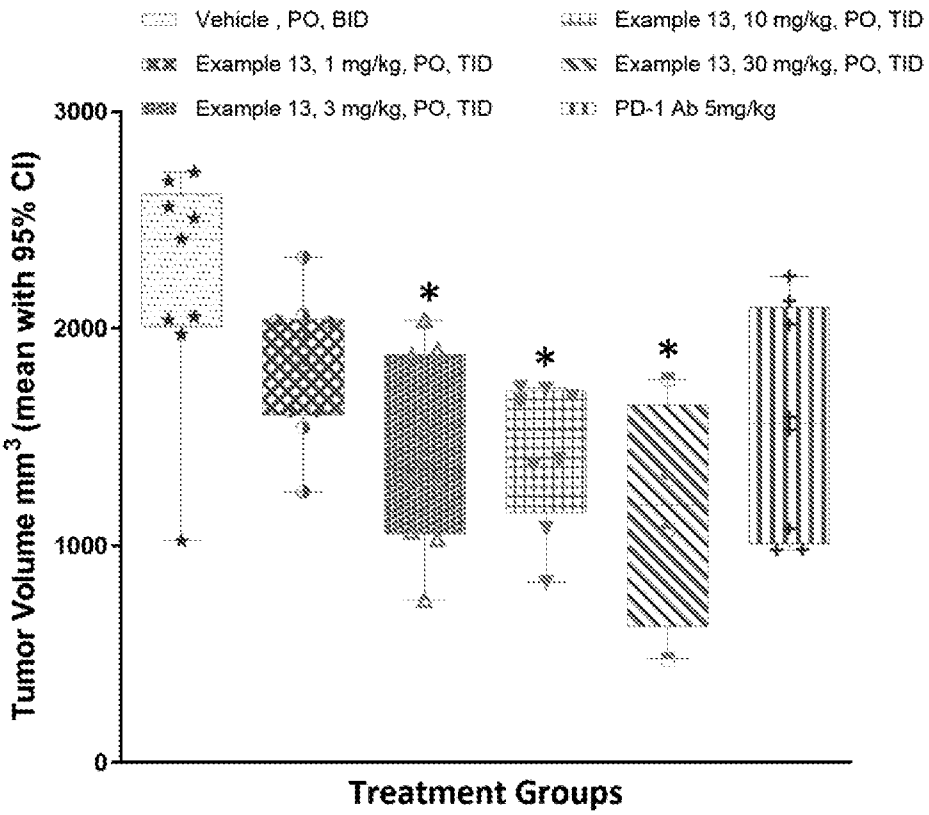


Figure 1

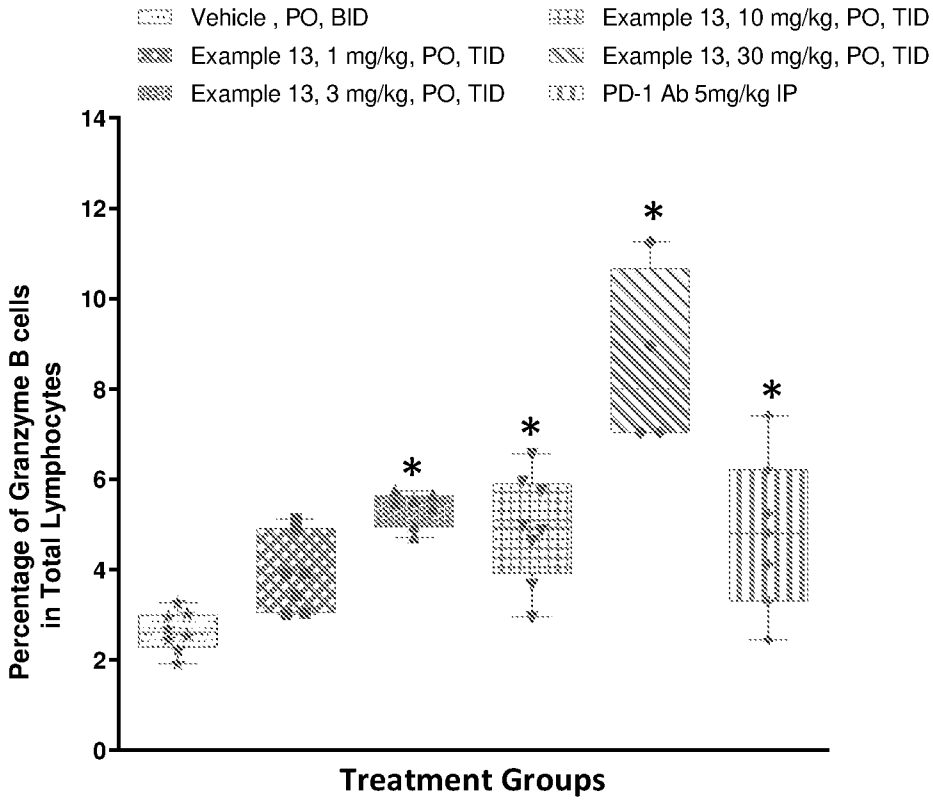


Figure 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2022/050018

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61P35/00 A61K31/519
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 977 144 A (FUJIMOTO ROGER A [US] ET AL) 11 December 1990 (1990-12-11) claim 1	1-17
A	WO 01/17999 A2 (HOFFMANN LA ROCHE [CH]) 15 March 2001 (2001-03-15) claims 1, 22 page 67; example 247	1-17

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 March 2022	28/03/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gutke, Hans-Jürgen

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2022/050018

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HASSAN AISHA Y. ET AL: "Synthesis and Anticancer Evaluation of Some Novel 5-Amino[1,2,4]Triazole Derivatives", JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 55, no. 6, 1 June 2018 (2018-06-01), pages 1450-1478, XP055894581, US ISSN: 0022-152X, DOI: 10.1002/jhet.3184 Retrieved from the Internet: URL:https://api.wiley.com/onlinelibrary/tdm/v1/articles/10.1002%2Fjhet.3184> compound 5 -----	1-17

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INTERNATIONAL SEARCH REPORT

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International application No
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