TRIAMINO PYRIMIDINE COMPOUNDS AS CDK7 INHIBITORS AND METHODS THEREOF

FIELD OF INVENTION

[0001] The present disclosure relates to the field of medicinal chemistry and therapeutic agents. Particularly, the present disclosure provides compounds which could be used for therapeutic applications for treatment of cancer.

BACKGROUND OF THE INVENTION

[0002] Cyclin-dependent kinase 7 (CDK7) plays an important role in two cellular processes that are often dysregulated during oncogenesis which are (a) regulation of RNA polymerase II-mediated transcription and (b) cell cycle progression as the CDK activating kinase (*Fisher, R. P. (2019) doi: 10.1080/21541264.2018.1553483*). Traditionally, CDKs are classified into two exclusive sets: the cell-cycle CDKs (CDK1, 2, 4 and 6) and the transcriptional CDKs (CDK8, 9, 12 and 13). However, CDK7 functions in both of the above-mentioned cellular processes (Fisher, 2005. doi: 10.1242/jcs.02718.) with stringent modes of substrate recognition (*Larochelle, S. et al., doi: 10.1038/nsmb1028*). The transcription associated CDKs are emerging as important targets and biomarkers in oncology. In contrast to the cell cycle associated CDKs, this family of CDKs play critical roles in regulating gene expression at multiple levels, including transcription, splicing, intronic polyadenylation, and epigenetics. Certain cancer types can also become addicted to dysregulated transcriptional programs of specific genes, whose high expression is facilitated by super enhancers (SEs) (*Chipumuro, E. et al., doi: 10.1016/j.cell.2014.10.024; Bradner, J. E., Hnisz, D. and Young, R. A., doi: 10.1016/j.cell.2016.12.013; Fisher, R. P., doi: 10.1080/21541264.2018.1553483*). CDK7 is enriched at SEs, including those that drive expression of oncogenes, and it seems to mediate this transcriptional addiction (*Wang, Y. et al. (2015) doi: 10.1016/j.cell.2015.08.063; Bradner, J. E., Hnisz, D. and Young, R. A. et. al., doi: 10.1016/j.cell.2016.12.013; Fisher, R. P. et. al., (2019)*

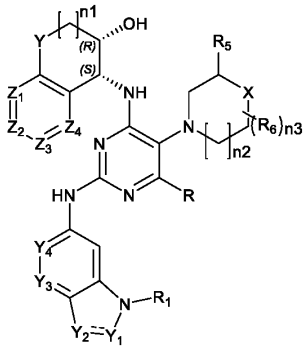
doi: 10.1080/21541264.2018.1553483). It is closely coupled to the cellular metabolism in tumour cells by influencing glucose consumption and glycolysis (*Ghezzi C, Wong A, et. al., doi: 10.1038/s41467-019-13334-8; Yao Y, Ng JF, Park WD, et al. doi: 10.1182/blood.2022018885*). This indicates that CDK7 has larger global effects beyond cell cycle and transcription.

[0003] There were initial concerns about the toxicity of targeting CDK7 due to its role in normal cells (*Fisher, R. P. et.al., doi: 10.1242/jcs.02718; Lolli, G. and Johnson, L. N. (2005) 'CAK-Cyclin-Dependent Activating Kinase: A key kinase in cell cycle control and a target for Drugs?', Cell Cycle. PMID: 15876871*). However, the development of highly specific inhibitors has resulted in effective reduction of tumor growth in vivo especially in combination with CDK4/6 inhibitors (*Hazel, P. et al., doi: 10.1002/cmdc.201600535; Patel, H. et al., doi: 10.1158/1535-7163*). There is further evidence that transcription is dysregulated in cancer cells and that the transcription of certain genes is disproportionately sensitive to inhibition of transcription (*Wang, Y. et al., doi: 10.1016/j.cell.2015.08.063; Patel, H. et al., doi: 10.1158/1535-7163*). Overexpression of components of the CDK7 complex has also been observed in various types of tumors, including various types of breast cancer (*Patel, H. et al., doi: 10.1158/1535-7163; Teng, Y. et al., doi: 10.1016/j.ejmech.2019.111641*). This makes CDK7 an attractive target of anti-cancer drugs, and interest in the potential therapeutic use of CDK7 inhibitors in cancer is rapidly growing (*Hazel, P. et al., doi: 10.1002/cmdc.201600535; Teng, Y. et al., doi: 10.1016/j.ejmech.2019.111641; Chou J, Quigley DA, Robinson TM, Feng FY, Ashworth A. et. al., doi: 10.1158/2159-8290.CD-19-0528*).

[0004] Therefore, there is a need in the art to develop therapeutic agents that selectively and efficiently inhibit CDK7 to enhance the efficacy of cancer therapies. Furthermore, there is a dire requirement for the development of therapeutic drugs that overcome the limitations of the conventional drugs that inhibit CDK4/6 and thereby offer a new approach for treating drug-resistant tumors, ultimately improving the benefit-risk profile of cancer patients.

SUMMARY OF THE INVENTION

[0005] In a first aspect of the present disclosure, there is provided a compound of Formula I, its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, or pharmaceutically active derivatives thereof,



Formula I

wherein R_1 is selected from 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, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl;

Y_1 is N or C(=O);

Y_2 is selected from N, O, CR_2, or NR_3, wherein R_2 and R_3 are independently selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

--- refers to single bond or double bond between Y_1 and Y_2;

Y_3 and Y_4 are independently N or CR_4, wherein R_4 is selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl; wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

R is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy;

R_5 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl, wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

X is selected from CR_7, O, S, S=O, SO_2, or NR_7; R_7 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $NH(CO)_pR_8$, or $C(=O)R_8$; R_8 is selected from C_{1-6} alkyl, C_{1-

$_6$ aminoalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl or C_{3-8} heterocyclyl is optionally substituted with hydroxy, amino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{3-8} heteroaryl or C_{3-8} heterocyclyl; wherein C_{3-8} heterocyclyl is optionally substituted with one or more groups selected from oxo or C_{1-6} alkyl;

p is 0 or 1;

R_6 is selected from hydrogen, amino, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} aminoalkyl, $C(=O)NR_{9a}R_{9b}$, -NH-C(=O) R_9 or $-NHCH_2R_9$; wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy or cyano;

R_9, R_{9a} and R_{9b} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, C_{3-12} heteroaryl, wherein C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from cyano, oxo, hydroxy, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, -S-C_{1-6} alkyl, -S(O)-C_{1-6} alkyl, -$S(O)_2$-C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{3-12} heteroaryl or C_{3-8} heterocyclyl, wherein C_{3-8} heterocyclyl or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from C_{1-6} alkyl; or R_{9a} and R_{9b} are combined together to form a C_{3-8} heterocyclyl optionally substituted with one or more substituents selected from oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} aminoalkyl;

Z_1, Z_2, Z_3, and Z_4 are independently selected from N or CR_{10}:

R_{10} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

Y is selected from O, S, S=O, SO_2, N-CH3, N-C(=O)CH_3 or CR_{11};

R_{11} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

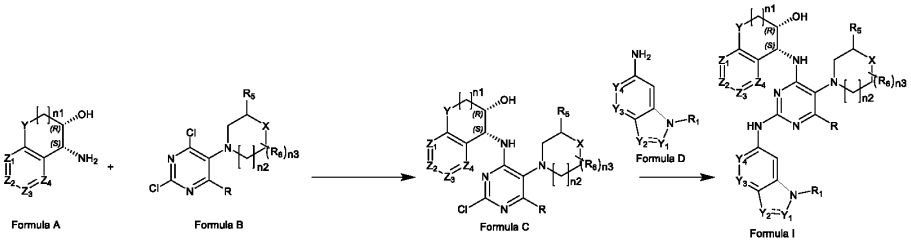
n1 is 0, 1 or 2;

n2 is 0, 1 or 2; and

n3 is selected from 0 to 3.

[0006] In a second aspect of the present disclosure, there is provided there is provided a process of preparation of compounds of Formula I as disclosed herein,

the process comprising: reacting Formula (A) and Formula (B) followed by reacting with Formula (D) in the presence of a base to obtain the compound of Formula I,



wherein, R_1 is selected from 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} alkoxy, C_{1-6} haloalkoxy, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl;

Y_1 is N or C(=O);

Y_2 is selected from N, O, CR_2 or NR_3, wherein R_2 and R_3 are independently selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

--- refers to single bond or double bond between Y_1 and Y_2;

Y_3 and Y_4 are independently N or CR_4, wherein R_4 is selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl; wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

R is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy;

R_5 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl, wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

n1 is 0, 1 or 2;

X is selected from CR_7, O, S, S=O, SO_2, or NR_7; R_7 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $NH(CO)_pR_8$, or $C(=O)R_8$; R_8 is selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl or C_{3-8} heterocyclyl is optionally substituted with hydroxy, amino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{3-8} heteroaryl; wherein C_{3-8} heterocyclyl is optionally substituted with one or more groups selected from oxo or C_{1-6} alkyl; p is 0 or 1;

R_6 is selected from hydrogen, amino, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} aminoalkyl, $C(=O)NR_{9a}R_{9b}$, -NH-C(=O) R_9 or $-NHCH_2R_9$; wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy, or cyano;

R_9, R_{9a} and R_{9b} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, C_{3-12} heteroaryl, wherein C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from cyano, oxo, hydroxy, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, -S-C_{1-6} alkyl, -S(O)-C_{1-6} alkyl, -$S(O)_2$-C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{3-12} heteroaryl or C_{3-8} heterocyclyl, wherein C_{3-8} heterocyclyl or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from C_{1-6} alkyl; or R_{9a} and R_{9b} are combined together to form a C_{3-8} heterocyclyl optionally substituted with one or more substituents selected from oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} aminoalkyl;

Z_1, Z_2, Z_3, and Z_4 are independently selected from N or CR_{10};

R_{10} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

Y is selected from O, S, S=O, SO_2, N-CH3, $N-C(=O)CH_3$ or CR_{11};

R_{11} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl , C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

n2 is 0, 1 or 2; and

n3 is selected from 0 to 3.

[0007] In a third aspect of the present disclosure, there is provided a compound of Formula I as disclosed herein, for use in the manufacture of a medicament.

[0008] In a fourth aspect of the present disclosure, there is provided a combination comprising of compounds of Formula I as disclosed herein, with at least one additional therapeutic agent.

[0009] In a fifth aspect of the present disclosure, there is provided a combination comprising of compounds of Formula Ia and Ib as disclosed herein, with at least one additional therapeutic agent.

[00010] In a sixth aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound of Formula I as disclosed herein, with at least one pharmaceutically acceptable excipient.

[00011] In a seventh aspect of the present disclosure, there is provided a method of treating cancer in a subject, the method comprising administering the compound as disclosed herein or the combination as disclosed herein, or the pharmaceutical composition as disclosed herein to the subject in need thereof.

[00012] In an eighth aspect of the present disclosure, there is provided a method of treating a disease or condition mediated by cyclin dependent kinase 7 or cyclin dependent kinase 7 with cyclin H and MAT1 or CDK-activating kinase (CAK) or combinations thereof to a subject in need thereof, the method comprising administering the compound as disclosed herein or the combination as disclosed herein or the pharmaceutical composition as disclosed herein to the subject in need thereof.

[00013] These and other features, aspects, and advantages of the present subject matter will become better understood with reference to the following appended claims and detailed 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 claimed subject matter, nor is it intended to be used to limit the scope of the claimed subject matter.

BRIEF DESCRIPTION OF THE DRAWINGS

[00014] Figure 1 depicts Mean tumor growth kinetics test compounds in athymic nude mice bearing subcutaneous HCT116 tumor. Values are represented as Mean ± SEM of 8 animals in each group, Statistical analysis carried out by two-way ANOVA followed by Bonferroni post-test. ****P<0.0001, in accordance with an embodiment of the present disclosure.

[00015] Figure 2 depicts Mean tumor weight (mg) of test compounds in athymic nude mice bearing subcutaneous HCT116 tumor at termination after treatment. Values are represented as Mean ± SEM of 8 animals in each group,

Statistical analysis was carried out by one way ANOVA followed by the Dunnett test. ***P<0.001 in accordance with an embodiment of the present disclosure.

[00016] Figure 3 depicts Percentage (%) change in body weight of athymic nude mice-bearing subcutaneous HCT-116 tumor, values are represented as Mean ± SEM of 8 animals in each group, in accordance with an embodiment of the present disclosure.

[00017] Figure 4 depicts Mean tumor growth kinetics test compounds in athymic nude mice bearing subcutaneous MDA-MB-468 tumor, values are represented as Mean ± SEM of 8 animals in each group. Statistical analysis carried out by two-way ANOVA followed by Bonferroni post-test. ****P<0.0001, in accordance with an embodiment of the present disclosure.

[00018] Figure 5 depicts Mean tumor weight (mg) of test compounds in athymic nude mice bearing subcutaneous MDA-MB-468 tumor at termination after treatment, values are represented as Mean ± SEM of 8 animals in each group. Statistical analysis was carried out by one way ANOVA followed by the Dunnett test. ***P<0.001, in accordance with an embodiment of the present disclosure.

[00019] Figure 6 depicts Percentage (%) change in body weight of athymic nude mice-bearing subcutaneous MDA-MB-468 tumor, values are represented as Mean ± SEM of 8 animals in each group, in accordance with an embodiment of the present disclosure

DESCRIPTION OF THE INVENTION

[00020] Those skilled in the art will be aware that the present disclosure is subject to variations and modifications other than those specifically described. It is to be understood that the present disclosure includes all such variations and modifications. The disclosure also includes all such steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any or more of such steps or features.

Definitions

[00021] 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.

[00022] 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.

[00023] 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.

[00024] The term “including” is used to mean “including but not limited to”, “including” and “including but not limited to” are used interchangeably.

[00025] In the structural formulae given herein and throughout the present disclosure, the following terms have been indicated meaning, unless specifically stated otherwise.

[00026] 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.

[00027] 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.

[00028] The term "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, methane sulphonic, ethane sulphonic, benzene sulphonic 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.

[00029] The term "intermediates" refers to compounds that are useful in generating the target compounds. The intermediates are compounds that are involved in the synthetic mechanism and are further ingested or consumed in the reaction to obtain the target compound. The intermediates may have structural similarities with respect to the target compound. In an aspect of the present disclosure, the compounds of Formula Ia and Formula Ib are two forms of the compound of Formula I.

[00030] The term "pharmaceutically active derivatives" refers to compounds of Formula I, its derived or related compounds which are biologically active possess therapeutic effect, and are useful in treating, preventing, curing or diagnosing a disease, disorder, or condition.

[00031] The compounds discussed herein in many instances may have been named and/or checked with ACD/Name by ACD/Labs® and/or Chemdraw by CambridgeSoft®.

[00032] The term "tautomer" refers to two or more isomers of a compound which exist together in equilibrium, and are readily interchanged by migration of an atom or group within the molecule.

[00033] The term "polymorphs" refers to crystal forms of the same molecule, and different polymorphs may have different physical properties, such as 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.

[00034] 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 a compound of Formula I, and salts thereof. Compounds according to Formula I contain a basic functional group and are therefore capable of forming pharmaceutically acceptable acid addition salts by treatment with a suitable acid. Suitable acids include pharmaceutically acceptable inorganic acids and pharmaceutically acceptable organic acids. Representative pharmaceutically acceptable acid addition salts include hydrochloride, hydrobromide, nitrate, methylnitrate, sulfate, bisulfate, sulfamate, phosphate, acetate, 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.

[00035] The term "solvate", as used herein, refers to a crystal form of a substance which contains solvent.

[00036] The term "hydrate" refers to a solvate form of a substance wherein the solvent is water.

[00037] 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).

[00038] The compounds provided herein include the corresponding enantiomers and stereoisomers, that is, the pure form of the stereoisomers, in terms of geometrical isomer, enantiomer, or diastereomer, and the mixture of enantiomeric and stereoisomeric form of said compounds. Further, the mixture of enantiomeric and stereoisomeric forms can be resolved into their pure component by the methods known in the art, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallization, using chiral derivatizing agents, etc. Also, pure enantiomers and stereoisomers can be obtained from intermediates or metabolites and reagents that are in the form of pure enantiomers and stereoisomers by known asymmetric synthetic methods.

[00039] The term “alkyl” refers to a saturated hydrocarbon chain having the specified number of carbon atoms. For example, which are not limited, $C_{1\text{-}6}$ alkyl refers to an alkyl group having from 1–6 carbon atoms. Alkyl groups may be straight or branched chained groups which may be optionally substituted. Representative branched alkyl groups have one, two, or three branches. Preferred alkyl groups include, without limitation, methyl, ethyl, n-propyl, and isopropyl. One or more hydrogens of the alkyl groups may be optionally replaced with deuterium such as CD_3, CHD_2, CDH_2, CH_2CD_3, CD_2CH_3 and the like.

[00040] The term “alkenyl” refers to an unsaturated hydrocarbon chain having a specific number of carbon atoms and at least one double bond between carbon

atoms. For example, which are not limited, C_{1-6} alkenyl refers to an alkenyl group having from 1–6 carbon atoms. Alkenyl groups may be straight or branched chained groups. Representative branched alkenyl groups have one or two, branches. Preferred alkenyl groups include, without limitation, ethenyl, n-propenyl, and isopropenyl.

[00041] The term "alkynyl" refers to an unsaturated hydrocarbon chain having a specific number of carbon atoms and at least one triple bond between carbon atoms. For example, C_{2-6} alkynyl refers to an alkynyl group having from 2–6 carbon atoms. Alkynyl groups may be straight or branched chained groups which may be optionally substituted. Representative branched alkyl groups have one, two, or three branches. Preferred alkynyl groups include, without limitation, ethynyl, n-propynyl, or butynyl.

[00042] The term "alkoxy" refers to an alkyl group attached via an oxygen linkage to the rest of the molecule. For example, C_{1-6} alkoxy refers to an alkyl group having from 1 – 6 carbon atoms attached via an oxygen linkage to the rest of the molecule. Preferred alkoxy groups include, without limitation, $–OCH_3$ (methoxy), $–OC_2H_5$ (ethoxy) and the like.

[00043] The term "amino" refers to $-NH_2$ group.

[00044] The term "hydroxy" refers to -OH group.

[00045] The term "cyano" refers to -CN group.

[00046] The term "oxo" refers to =O group.

[00047] The term "haloalkyl" as used herein, refers to an alkyl group as defined herein, wherein one or more hydrogen of alky group is substituted with halogen atoms. Examples of haloalkyl include, but are not limited to trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, dichloromethyl, chloromethyl, and the like.

[00048] The term "haloalkoxy" refers to a haloalkyl group attached via an oxygen linkage to the rest of the molecule. Examples of haloalkoxy include, but are not limited to trifluoromethoxy, difluoromethoxy, fluoromethoxy, trichloromethoxy, dichloromethoxy, chloromethoxy, and the like.

[00049] The term “heterocyclic” and “heterocyclyl” refer to saturated or unsaturated rings containing specific number of carbon atoms with one or more heteroatoms and the heterocyclic group may be monocyclic, bicyclic, or polycyclic. The heterocyclic group may be fused, bridged, or spiral structures and may be optionally substituted. In certain embodiments, 'heterocyclyl' groups are saturated. In other embodiments, 'heterocyclyl' groups are unsaturated. In few embodiments, 'heterocyclyl' groups are partially unsaturated. 'Heterocyclyl' groups containing more than one heteroatom may contain different heteroatoms selected from N, S, and O. 'Heterocyclyl' groups may be substituted with one or more substituents as defined herein. 'Heterocyclyl' includes oxetanyl, morpholinyl, pyrrolidinyl, piperazinyl, piperidinyl, tetrahydropyranyl, azepinyl, oxazepinyl, azabicyclo[3.1.0]hexanyl.

[00050] The term “heteroaryl” refers to an aromatic heterocyclic ring radical as defined above. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom resulting in the creation of a stable structure. The heteroaryl refers to an aromatic ring with one or more hetero atoms selected from N, O or S with carbon ranging between 2 to 10.

[00051] The term “cycloalkyl” refers to a saturated hydrocarbon ring having a specified number of carbon atoms. Examples of cycloalkyl include but are not limited to C_{3-6} cycloalkyl refers to a cycloalkyl group having from 3 to 6 member atoms. Preferred cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, groups and the like. The cycloalkyl group can be optionally substituted.

[00052] The term “aminoalkyl” or “alkylamino” refers to an alkyl group as defined above attached via amino linkage to the rest of the molecule. For example, C_{1-6} aminoalkyl refers to an alkyl group having from 1 to 6 carbon atoms attached via amino linkage to the rest of the molecule. Preferred aminoalkyl groups include, without limitation, $-NHCH_3$, $-N(CH_3)_2$, and the like. The aminoalkyl group may be optionally substituted.

[00053] The term " CDK7 inhibitor" or "inhibitor of CDK7" as used herein, refers to compounds of Formula I which can effectively inhibit CDK7 enzymes. The

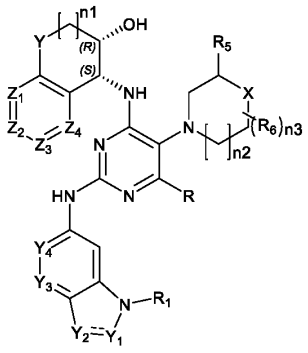
compounds of Formula I also capable of inhibiting cyclin dependent kinase 7 with cyclin H and MAT1 or CDK-activating kinase (CAK) or combinations thereof.

[00054] A term once described, the same meaning applies for it, throughout the patent.

[00055] As discussed in the background, the existing therapeutic compositions treat the tumor growth by the inhibition of CDK4/6 enzyme and there is a need for therapeutic agents that selectively and efficiently inhibit CDK7 to enhance the efficacy of cancer therapies. Further the present disclosure aims to overcome the limitations of the current CDK4/6 inhibitor class of drugs and offer a new approach for treating drug-resistant tumors, ultimately improving the therapeutic effect of the drug and enhance the benefit-risk profile of cancer patients.

[00056] Accordingly, the present disclosure provides compound of Formula I, its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, or pharmaceutically active derivatives thereof for the inhibition of CDK7.

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



Formula I

wherein R_1 is selected from 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, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl;

Y_1 is N or C(=O);

Y_2 is selected from N, O, CR_2, or NR_3, wherein R_2 and R_3 are independently selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

--- refers to single bond or double bond between Y_1 and Y_2;

Y_3 and Y_4 are independently N or CR_4, wherein R_4 is selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl; wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

R is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy;

R_5 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl, wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

X is selected from CR_7, O, S, S=O, SO_2, or NR_7; R_7 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $NH(CO)_pR_8$, or $C(=O)R_8$; R_8 is selected from C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl or C_{3-8} heterocyclyl is optionally substituted with hydroxy, amino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{3-8} heteroaryl or C_{3-8} heterocyclyl; wherein C_{3-8} heterocyclyl is optionally substituted with one or more groups selected from oxo or C_{1-6} alkyl;

p is 0 or 1;

R_6 is selected from hydrogen, amino, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} aminoalkyl, $C(=O)NR_{9a}R_{9b}$, -NH-C(=O)R_9 or -$NHCH_2R_9$; wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy or cyano;

R_9, R_{9a} and R_{9b} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, C_{3-12} heteroaryl, wherein C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from cyano, oxo, hydroxy, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, -S-C_{1-6} alkyl, -S(O)-C_{1-6} alkyl, -$S(O)_2$-C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{3-12} heteroaryl or C_{3-8} heterocyclyl, wherein C_{3-8} heterocyclyl or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from C_{1-6} alkyl; or R_{9a} and R_{9b} are combined together to form a C_{3-8} heterocyclyl optionally substituted

with one or more substituents selected from oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} aminoalkyl;

Z_1, Z_2, Z_3, and Z_4 are independently selected from N or CR_{10};

R_{10} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

Y is selected from O, S, S=O, SO_2, N-CH3, N-C(=O)CH_3 or CR_{11};

R_{11} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

n1 is 0, 1 or 2;

n2 is 0, 1 or 2; and

n3 is selected from 0 to 3.

[00058] In another embodiment of the present disclosure, there is provided a compound of Formula I as disclosed herein, wherein R_1 is selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or C_{1-6} alkoxy, wherein C_{1-4} alkyl is optionally substituted with hydroxy, C_{1-4} alkoxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl;

Y_1 is N or C(=O);

Y_2 is selected from N, O, or CR_2; wherein R_2 is selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

--- refers to single bond or double bond between Y_1 and Y_2;

Y_3 and Y_4 are independently CR_4, wherein R_4 is selected from hydrogen, halogen, C_{1-4} alkyl, or C_{1-6} haloalkyl; wherein C_{1-4} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

R is selected from hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy;

R_5 is selected from hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{3-4} cycloalkyl, wherein C_{1-4} alkyl is optionally substituted with C_{1-4} alkoxy or hydroxy;

X is selected from CR_7, O, S, S=O, SO_2, or NR_7; R_7 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $NH(CO)_pR_8$, or $C(=O)R_8$; R_8 is selected from C_{1-4} alkyl, C_{1-4} aminoalkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl, wherein C_{1-4} alkyl or C_{3-8} heterocyclyl is optionally substituted with hydroxy, amino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} aminoalkyl, C_{3-8} heteroaryl or C_{3-8} heterocyclyl; wherein C_{3-8}

heterocyclyl is optionally substituted with one or more groups selected from oxo or C_{1-4} alkyl;

p is 0 or 1;

R_6 is selected from hydrogen, amino, C_{1-6} alkyl, C_{1-6} aminoalkyl, $C(=O)NR_{9a}R_{9b}$, -NH-$C(=O)R_9$ or $-NHCH_2R_9$; wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy or cyano;

R_9, R_{9a} and R_{9b} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, C_{3-12} heteroaryl, wherein C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from cyano, oxo, hydroxy, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, -S-C_{1-6} alkyl, -S(O)-C_{1-6} alkyl, -$S(O)_2$-C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{3-12} heteroaryl or C_{3-8} heterocyclyl, wherein C_{3-8} heterocyclyl or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from C_{1-6} alkyl; or R_{9a} and R_{9b} are combined together to form a C_{3-8} heterocyclyl optionally substituted with one or more substituents selected from oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} aminoalkyl;

Z_1, Z_2, Z_3, and Z_4 are independently selected from N or CR_{10}:

R_{10} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

Y is selected from O, N-CH_3, N-$C(=O)CH_3$ or CR_{11};

R_{11} is hydrogen, cyano, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, or C_{1-4} haloalkoxy;

n1 is 0, or 1;

n2 is 0 or 1; and

n3 is selected from 1 to 3.

[00059] In yet another embodiment of the present disclosure, there is provided a compound of Formula I, as disclosed herein, wherein R_1 is selected from C_{1-3} alkyl, C_{2-3} alkenyl, or C_{2-3} alkynyl, wherein C_{2-3} alkyl is optionally substituted with C_1 alkoxy;

Y_1 is N or C(=O);

Y_2 is O or CR_2; wherein R_2 is selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

when Y_1 is N, Y_2 is CR_2; and when Y_1 is C(=O), Y_2 is O;

--- refers to single bond or double bond between Y_1 and Y_2;

Y_3 and Y_4 are independently CR_4, wherein R_4 is selected from hydrogen, halogen, or C_1 alkyl;

R is hydrogen;

R_5 is selected from hydrogen, or C_1 alkyl;

X is CR_7 or NR_7; R_7 is selected from hydrogen, C_{1-6} alkyl, $NH(CO)_pR_8$, or $C(=O)R_8$;

R_8 is selected from C_{1-4} alkyl, C_{1-4} aminoalkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl, wherein C_{1-4} alkyl or C_{3-8} heterocyclyl is optionally substituted with hydroxy, amino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} aminoalkyl, C_{3-8} heteroaryl or C_{3-8} heterocyclyl; wherein C_{3-8} heterocyclyl is optionally substituted with one or more groups selected from oxo or C_{1-6} alkyl;

p is 1;

R_6 is selected from hydrogen, C_{1-6} alkyl, $C(=O)NR_{9a}R_{9b}$, -NH-C(=O)R_9 or -$NHCH_2R_9$; wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy or cyano;

R_9, R_{9a} and R_{9b} are independently selected from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, C_{1-4} aminoalkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, C_{3-12} heteroaryl, wherein C_{1-4} alkyl, C_{1-4} aminoalkyl, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from cyano, oxo, hydroxy, halogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} aminoalkyl, C_{3-12} heteroaryl or C_{3-8} heterocyclyl, wherein C_{3-8} heterocyclyl or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from C_{1-4} alkyl;

or R_{9a} and R_{9b} are combined together to form a C_{3-8} heterocyclyl optionally substituted with one or more substituents selected from oxo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} aminoalkyl;

Z_1, Z_2, Z_3, and Z_4 are independently CR_{10}; R_{10} is hydrogen;

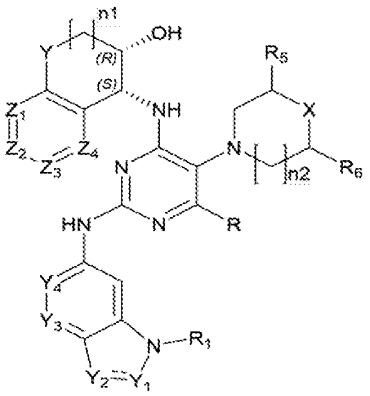
Y is $CR_{11;}$ R_{11} is hydrogen;

n1 is 0;

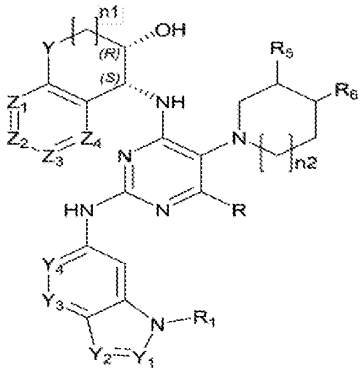
n2 is 1; and

n3 is 1.

[00060] In an embodiment of the present disclosure there is provided a compound of Formula I as disclosed herein, wherein the compound of Formula I is selected from,



Formula Ia



Formula Ib

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

wherein R_1 is selected from 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} alkoxy, C_{1-6} haloalkoxy, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl;

Y_1 is N or C(=O);

Y_2 is N, O, CR_2 or NR_3, wherein R_2 and R_3 are independently selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

--- refers to single bond or double bond between Y_1 and Y_2;

Y_3 and Y_4 are independently N or CR_4, wherein R_4 is selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl; C_{1-6} wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

R is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy;

R_5 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl, wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

n1 is 0, 1 or 2;

X is selected from CR_7, O, S, S=O, SO_2, or NR_7; R_7 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $NH(CO)_pR_8$, or $C(=O)R_8$; R_8 is selected from C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl or C_{3-8} heterocyclyl is optionally substituted with hydroxy, amino, C_{1-6} alkyl, C1-6 alkoxy, C_{1-6} aminoalkyl, C_{3-8} heteroaryl or C_{3-8} heterocyclyl; wherein C_{3-8} heterocyclyl is optionally substituted with one or more groups selected from oxo or C_{1-6} alkyl;

R_6 is selected from hydrogen, amino, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} aminoalkyl, $C(=O)NR_{9a}R_{9b}$, -NH-C(=O)R_9 or -$NHCH_2R_9$; wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy or cyano;

p is 0 or 1;

R_9, R_{9a} and R_{9b} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, C_{3-12} heteroaryl, wherein C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from cyano, oxo, hydroxy, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, -S-C_{1-6} alkyl, -S(O)-C_{1-6} alkyl, -$S(O)_2$-C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{3-12} heteroaryl or C_{3-8} heterocyclyl, wherein C_{3-8} heterocyclyl, or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from C_{1-6} alkyl; or R_{9a} and R_{9b} are combined together to form a C_{3-8} heterocyclyl optionally substituted with one or more substituents selected from oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} aminoalkyl;

Z_1, Z_2, Z_3, and Z_4 are independently selected from N or CR_{10}:

R_{10} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

Y is selected from O, S, S=O, SO_2, N-CH_3, N-C(=O)CH_3 or CR_{11};

R_{11} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy; and
n2 is 0, 1 or 2.

[00061] In another embodiment of the present disclosure there is provided a compound of Formula I as disclosed herein, wherein R_1 is selected from C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, or C_{3-8} heterocyclyl, wherein C_{1-3} alkyl is optionally substituted with hydroxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl;

Y_1 is N or C(=O);
Y_2 is N, O, CR_2 or NR_3, wherein R_2 and R_3 are independently selected from hydrogen, halogen, C_{1-3} alkyl, or C_{1-3} haloalkyl;

--- refers to single bond or double bond between Y_1 and Y_2;

Y_3 and Y_4 are independently N or CR_4, wherein R_4 is selected from hydrogen, halogen, C_{1-3} alkyl, or C_{1-3} haloalkyl; wherein C_{1-3} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;
R is selected from hydrogen, C_{1-3} alkyl, C_{1-3} haloalkyl, or C_{1-3} alkoxy;
R_5 is selected from hydrogen, C_{1-3} alkyl, C_{1-3} haloalkyl, or C_{3-6} cycloalkyl, wherein C_{1-3} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;
n1 is 0, 1 or 2;
X is selected from CR_7, O, S, S=O, SO_2, or NR_7; R_7 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $NH(CO)_pR_8$, or $C(=O)R_8$; R_8 is selected from C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl or C_{3-8} heterocyclyl is optionally substituted with hydroxy, amino, C_{1-6} alkyl, C1-6 alkoxy, C_{1-6} aminoalkyl, C_{3-8} heteroaryl or C_{3-8} heterocyclyl; wherein C_{3-8} heterocyclyl is optionally substituted with one or more groups selected from oxo or C_{1-6} alkyl;
R_6 is selected from hydrogen, amino, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} aminoalkyl, $C(=O)NR_{9a}R_{9b}$, -NH-C(=O)R_9 or -$NHCH_2R_9$; wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy or cyano;
p is 0 or 1;

R_9, R_{9a} and R_{9b} are independently selected from hydrogen, C_{1-3} alkyl, C_{2-4} alkenyl, C_{1-3} haloalkyl, C_{1-3} aminoalkyl, C_{1-3} alkoxy, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, C_{3-12} heteroaryl, wherein C_{1-3} alkyl, C_{1-3} aminoalkyl, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from cyano, oxo, hydroxy, halogen, C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy, -S-C_{1-6} alkyl, -S(O)-C_{1-6} alkyl, -S(O)$_2$-C_{1-6} alkyl, C_{1-3} haloalkyl, C_{1-3} aminoalkyl, C_{3-12} heteroaryl or C_{3-8} heterocyclyl, wherein C_{3-8} heterocyclyl or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from C_{1-3} alkyl; or R_{9a} and R_{9b} are combined together to form a C_{3-8} heterocyclyl optionally substituted with one or more substituents selected from oxo, C_{1-3} alkyl, C_{1-3} haloalkyl, or C_{1-3} aminoalkyl;

Z_1, Z_2, Z_3, and Z_4 are independently selected from N or CR_{10}:

R_{10} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

Y is selected from O, N-CH_3, N-C(=O)CH_3 or CR_{11};

R_{11} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy; and

n2 is 0, 1 or 2.

[00062] In an embodiment of the present disclosure there is provided a compound of Formula I as disclosed herein, wherein R_1 is selected from 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} alkoxy, C_{1-6} haloalkoxy;

Y_1 is N when --- is a double bond and Y_2 is N or CR_2 wherein R_2 is selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

Y_1 is C(=O) when --- is a single bond and Y_2 is O or NR_3 wherein R_3 is selected from hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

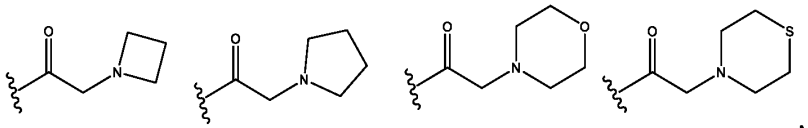
Y_3 and Y_4 are independently N or CR_4, wherein R_4 is selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl; C_{1-6} wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

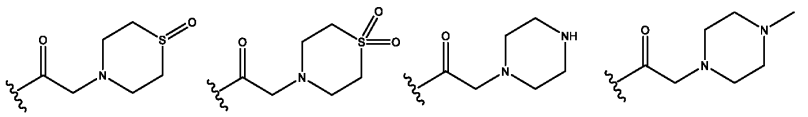
R is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl or C_{1-6} alkoxy;

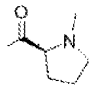
R_5 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl, wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

n1 is 0, 1 or 2;

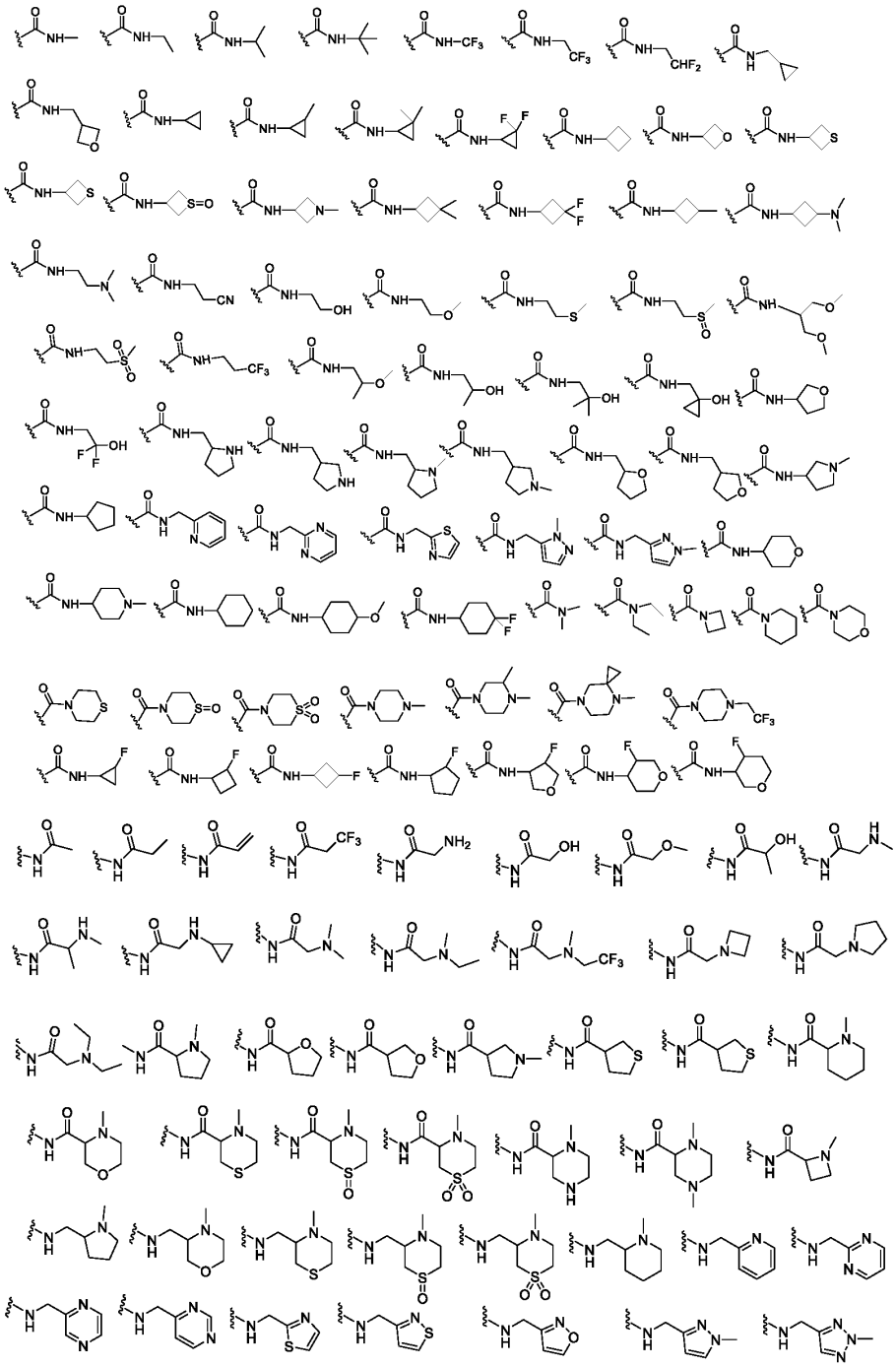
X is CR_7, O, S, S=O, SO_2, or NR_7; R_7 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(=O)C_{1-6}$ alkyl, $C(=O)C_{3-6}$ cycloalkyl, $C(=O)CH_2OH$, $C(=O)CH_2OCH_3$, $C(=O)CH_2NH_2$, $C(=O)CH_2NHCH_3$, $C(=O)CH_2N(CH_3)_2$,

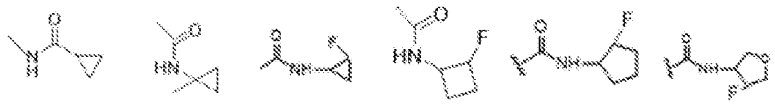

,




;

R_6 is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy; C_{1-6} haloalkoxy, CH_2OH, CH_2OCH_3, NH_2, $N(CH_3)_2$,





Z_1, Z_2, Z_3, and Z_4 are independently selected from N or CR_{10}:

R_{10} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

Y is selected from O or CR_{11};

R_{11} is hydrogen, cyano, fluoro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

n2 is 0 or 1.

[00063] In an embodiment of the present disclosure there is provided a compound of Formula I as disclosed herein, wherein

R_1 is selected from CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2CH_2CH_3$, CH_2CHF_2, $CH_2CH_2CHF_2$, $CH_2CH_2OCH_3$, $CH_2CH_2OCF_3$, $CH_2CH_2OCF_3$, $CH_2CH_2OCHF_2$, CH_2CH_2CHOH, $CH(CH_3)CH_2CH_3$,



Y_1 is N when --- is a double bond and Y_2 is N or CR_2, wherein R_2 is selected from hydrogen, fluoro, or CH_3;

Y_1 is C(=O) when --- is a single bond and Y_2 is O or NR_3, wherein R_3 is selected from hydrogen, CH_3, or CF_3;

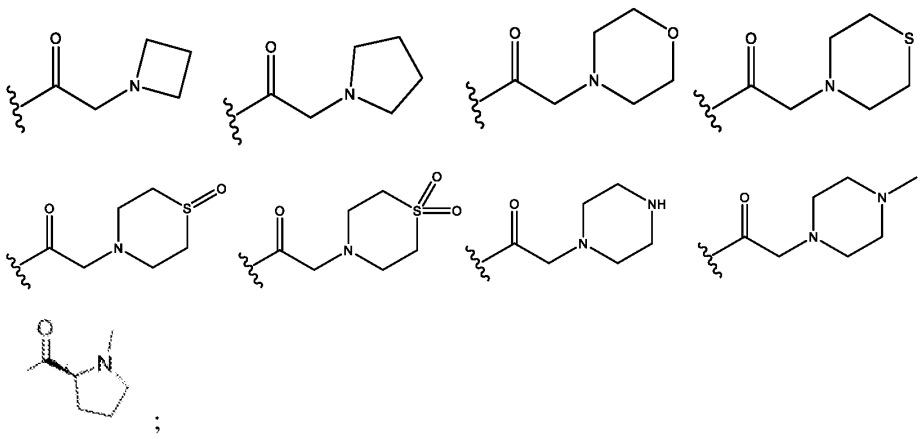
Y_3 and Y_4 are independently N or CR_4, wherein R_4 is selected from hydrogen, fluoro, or CH_3;

R is selected from hydrogen, CH_3, OCH_3, or CF_3;

R_5 is selected from hydrogen, CH_3, CH_2CH_3, CF_3, or ;

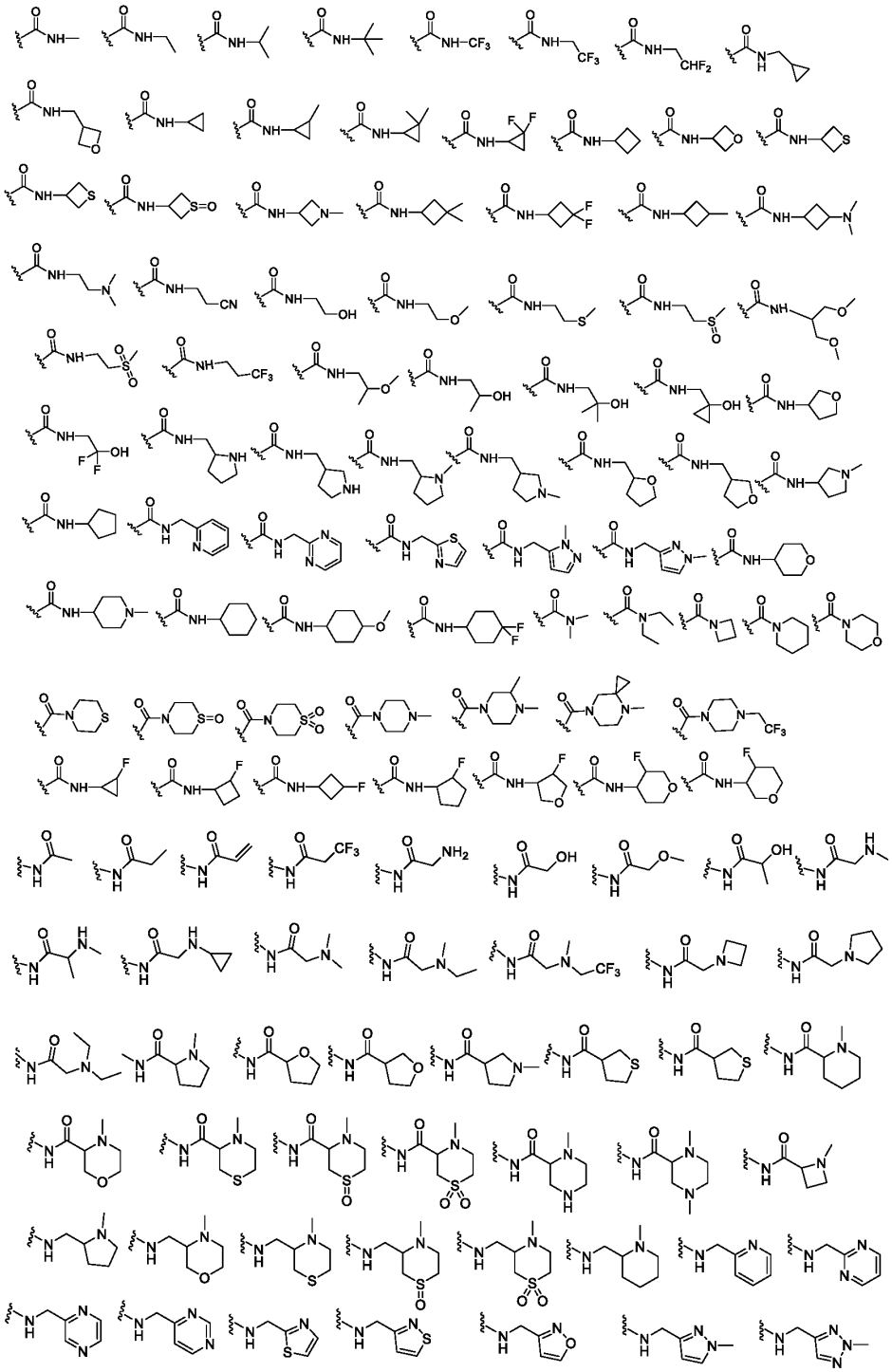
n1 is 0, 1 or 2;

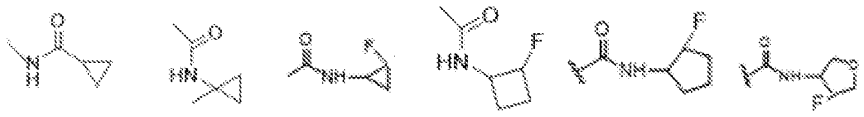
X is selected from CR_7, O, S, S=O, SO_2, or NR_7; R_7 is independently selected from hydrogen, CH_3, CH_2CH_3, $C(=O)CH_3$, $C(=O)CH_2CH_3$, C(=O)cyclopropyl, $C(=O)CH_2OH$, $C(=O)CH_2OCH_3$, $C(=O)CH_2NH_2$, $C(=O)CH_2NHCH_3$, $C(=O)CH_2N(CH_3)_2$,



;

R_6 is selected from hydrogen, CH_3, CH_2CH_3, CF_3, CH_2CH_3, OCH_3, OCF_3, CH_2OH, CH_2OCH_3, NH_2, $N(CH_3)_2$,





Z_1, Z_2, Z_3, and Z_4 are independently selected from N or CR_{10};

R_{10} is hydrogen, cyano, fluoro, chloro, CH_3, CF_3, OCH_3, or OCF_3;

Y is selected from O or CR_{11};

R_{11} is hydrogen, or CH_3;

n2 is 0 or 1.

[00064] In an embodiment of the present disclosure there is provided a compound of Formula I as disclosed herein, wherein R_1 is selected from CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2CH_2CH_3$, CH_2CHF_2, $CH_2CH_2CHF_2$, $CH_2CH\ OCH_3$, or -CH_2-CH=CH_2;

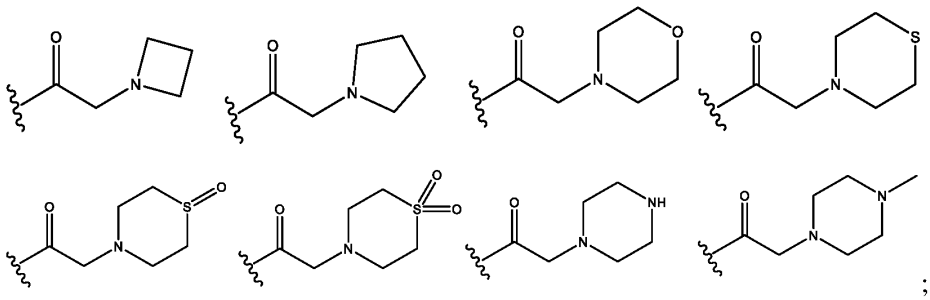
Y_1 is N when --- is a double bond and Y_2 is CH;

Y_1 is C(=O) when --- is a single bond and Y_2 is O;

R is hydrogen;

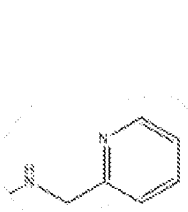
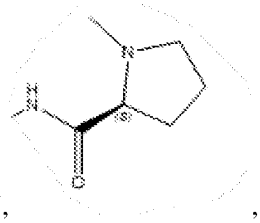
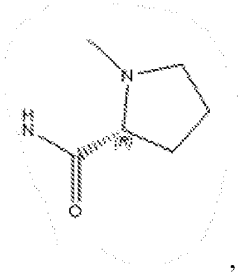
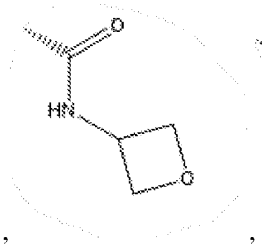
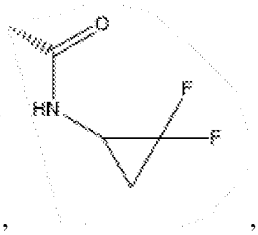
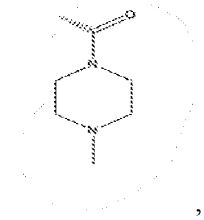
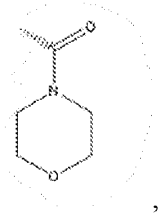
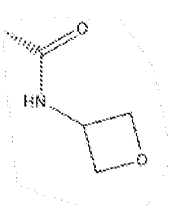
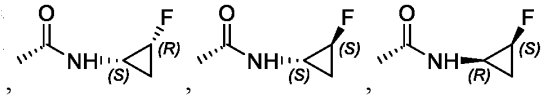
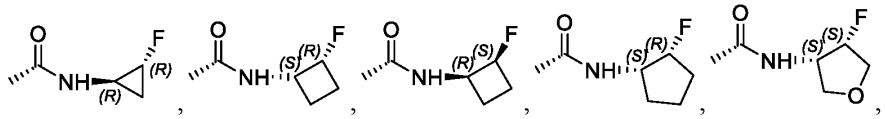
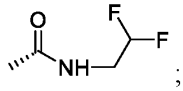
R_5 is hydrogen, or CH_3;

X is CR_7, or NR_7; R_7 is independently selected from hydrogen, CH_3, CH_2CH_3, C(=O)CH_3, C(=O)CH_2CH_3, C(=O)cyclopropyl, C(=O)CH_2OH, C(=O)CH_2OCH_3, C(=O)CH_2NH_2, C(=O)CH_2NHCH_3, C(=O)$CH_2N(CH_3)_2$,



;

R_6 is independently selected from hydrogen, CH_3, CH_2CH_3, CF_3, CH_2CH_3, OCH_3, OCF_3, CH_2OH, CH_2OCH_3, NH_2, $N(CH_3)_2$, -C(O)-NH-CH_2-CH_3, -C(O)-NH-$CH(CH_3)_2$, -NH-C(O)- CH_2-CH_3, -NH-C(O)-CH_2-$N(CH_3)_2$, -C(=O)-NH-

cyclopropyl, -NH-C(=O)-cyclopropyl, , , , , , , , , , , ;

Z_1, Z_2, Z_3, and Z_4 are independently CH;

Y is CH; and

n2 is 0 or 1.

[00065] In an embodiment of the present disclosure there is provided a compound of Formula I as disclosed herein, wherein the compound is selected from a group consisting of:

i. (S)-N-ethyl-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-isopropyl-1H-indazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide (Example 1);

ii.(S)-1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-ethylpiperidine-3-carboxamide (Example 3);

iii. (S)-N-ethyl-1-(2-((5-fluoro-1-propyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide (Example 4);

iv. (1S,2R)-1-((2-((1-allyl-5-fluoro-1H-indazol-6-yl)amino)-5-((S)-3-(hydroxymethyl)piperidin-1-yl)pyrimidin-4-yl)amino)-2,3-dihydro-1H-inden-2-ol (Example 5);

v. (S)-1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-isopropylpiperidine-3-carboxamide (Example 6);

vi. 1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-ethylpiperidine-4-carboxamide (Example 7);

vii. 1-((S)-4-(2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino)ethan-1-one (Example 8);

viii. 1-((S)-4-(2-((5-fluoro-1-(prop-2-yn-1-yl)-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino)ethan-1-one (Example 9);

ix. 1-((S)-4-(2-((5-fluoro-1-isopropyl-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino)ethan-1-one (Example 10);

x. 1-((S)-4-(2-((5-fluoro-1-(2-methoxyethyl)-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino)ethan-1-one (Example 11);

xi. N-(1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-4-yl) propionamide (Example 12);

xii. 1-((S)-4-(2-((1-allyl-5-methyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino) ethan-1-one (Example 13);

xiii. 2-(dimethylamino)-N-(1-(2-((1-ethyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-4-yl) acetamide (Example 14);

xiv. (S)-1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 15);

xv. N-(1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-4-yl)-2-(dimethylamino) acetamide (Example 16);

xvi. 2-(dimethylamino)-N-(1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl)amino)pyrimidin-5-yl)piperidin-4-yl)acetamide (Example 17);

xvii. 1-((S)-4-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino) ethan-1-one (Example 18);

xviii. (S)-1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 19);

xix. 1-((S)-4-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-morpholinoethan-1-one (Example 20);

xx. (1S,2R)-1-((2-((1-allyl-1H-indazol-6-yl) amino)-5-(4-((pyridin-2-ylmethyl) amino) piperidin-1-yl) pyrimidin-4-yl) amino)-2,3-dihydro-1H-inden-2-ol (Example 21);

xxi. (S)-N-(1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-4-yl)-1-methylpyrrolidine-2-carboxamide (Example 22);

xxii. (R)-N-(1-(2-((1-allyl-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidin-4-yl)-1-methylpyrrolidine-2-carboxamide (Example 23);

xxiii. (S)-N-cyclopropyl-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 24);

xxiv. (S)-1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-(oxetan-3-yl) piperidine-3-carboxamide (Example 25);

xxv. (3S)-1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-(2,2-difluorocyclopropyl)piperidine-3-carboxamide (Example 26);

xxvi. (R)-1-(2-((1-allyl-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 27);

xxvii. N-((S)-1-(2-((1-allyl-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidin-3-yl)cyclopropanecarboxamide (Example 28);

xxviii. (S)-1-(2-((1-allyl-5-methyl-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 29);

xxix. (S)-1-(2-((1-allyl-4-fluoro-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 30);

xxx. ((S)-1-(2-((1-allyl-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidin-3-yl)(4-methylpiperazin-1-yl)methanone (Example 31);

xxxi. (S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl)amino)pyrimidin-5-yl)-N-isopropylpiperidine-3-carboxamide (Example 32);

xxxii. (S)-N-cyclopropyl-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((5-methyl-1-(prop-2-yn-1-yl)-1H-indazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide (Example 33);

xxxiii. ((S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl)amino)pyrimidin-5-yl)piperidin-3-yl)(morpholino)methanone (Example 34);

xxxiv. (S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl)amino)pyrimidin-5-yl)-N-(oxetan-3-yl)piperidine-3-carboxamide (Example 35);

xxxv. (S)-N-cyclopropyl-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((2-oxo-3-(prop-2-yn-1-yl)-2,3-dihydrobenzo[d]oxazol-5-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide (Example 36);

xxxvi. (S)-1-(2-(1-(R)-but-3-yn-2-yl)-1H-indazol-6-yl) amino)-4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 37);

xxxvii. (S)-1-(2-((1-(S)-but-3-yn-2-yl)-1H-indazol-6-yl) amino)-4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 38);

xxxviii. (S)-N-cyclopropyl-1-(4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-(1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3] triazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide ((Example 39);

xxxix. (S)-N-(2,2-difluoroethyl)-1-(4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 40);

xl. (S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl)-N-(1-methyl cyclopropyl) piperidine-3-carboxamide (Example 41);

xli. (S)-1-(2-(1-(R)-but-3-yn-2-yl)-1H-benzo[d][1,2,3] triazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-cyclopropyl piperidine-3-carboxamide (Example 42);

xlii. (S)-N-cyclopropyl-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-(1-isopropyl-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 43);

xliii. (S)-1-(2-((1-allyl-1H-benzo[d] [1,2,3] triazol-6-yl) amino)-4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 44);

xliv. (S)-1-(2-((1-((R)-but-3-yn-2-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-(2,2-difluoroethyl)piperidine-3-carboxamide (Example 45);

xlv. (S)-1-(2-(1-(S)-but-3-yn-2-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino)-4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropyl piperidine-3-carboxamide (Example 46);

xlvi. (3S)-N-(2,2-difluorocyclopropyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 47);

xlvii. (S)-N-(2,2-difluoroethyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-(1-isopropyl-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 48);

xlviii. S)-1-(2-((1-((S)-but-3-yn-2-yl)-1H-benzo[d][1,2,3] triazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-(2,2-difluoro ethyl) piperidine-3-carboxamide (Example 49);

xlix. (S)-1-(2-((1-((R)-but-3-yn-2-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-((R)-2,2-difluorocyclopropyl)piperidine-3-carboxamide (Example 50);

l. (S)-N-((1S,2R)-2-fluorocyclopropyl)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino) pyrimidin-5-yl)piperidine-3-carboxamide (Example 51);

li. (S)-N-((1R,2R)-2-fluorocyclopropyl)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-

benzo[d][1,2,3]triazol-6-yl)amino) pyrimidin-5-yl)piperidine-3-carboxamide (Example 52);

lii. (S)-N-((1S,2S)-2-fluorocyclopropyl)-1-(4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3] triazol-6-yl)amino) pyrimidin-5-yl)piperidine-3-carboxamide (Example 53);

liii. (S)-N-((1R,2S)-2-fluorocyclopropyl)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 54);

liv. (S)-N-((1S,2R)-2-fluorocyclopropyl)-1-(4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 55);

lv. (S)-N-((1S,2R)-2-fluorocyclopropyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-isopropyl-1H-benzo[d][1,2,3] triazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide (Example 56);

lvi. (R)-N-((1S,2R)-2-fluorocyclopropyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 57);

lvii. (R)-N-cyclopropyl-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-(1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 58);

lviii. (3S)-N-(2-fluorocyclobutyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 59);

lix. (S)-N-((1R,2S)-2-fluorocyclobutyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 60);

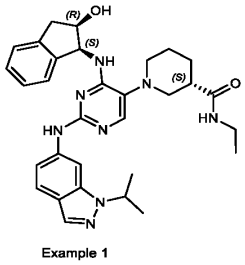
lx. (S)-N-((1S,2R)-2-fluorocyclobutyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 61);

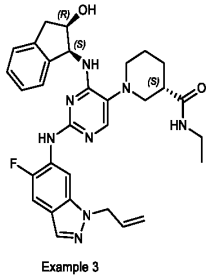
lxi. (S)-N-((1S,2R)-2-fluorocyclopropyl)-4-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino)pyrimidin-5-yl)morpholine-2-carboxamide (Example 62);

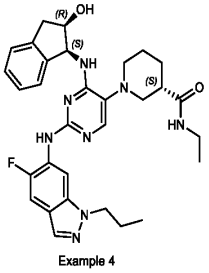
lxii. (S)-N-((1S,2R)-2-fluorocyclopropyl)-4-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino)pyrimidin-5-yl)piperazine-2-carboxamide (Example 63);

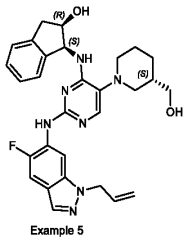
lxiii. (S)-N-((1S,2R)-2-fluorocyclopentyl)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide (Example 64);

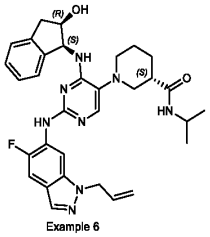
lxiv. (S)-N-((3S,4S)-4-fluorotetrahydrofuran-3-yl)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide (Example 65).

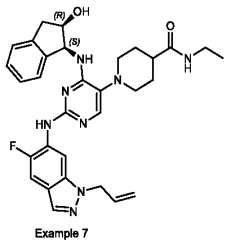

Example 1

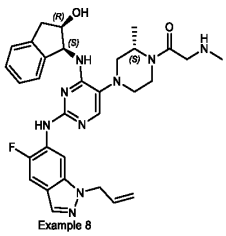

Example 3

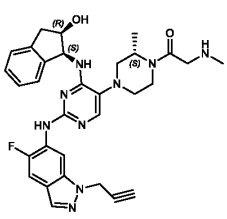

Example 4


Example 5

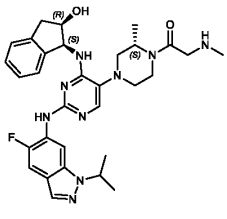

Example 6


Example 7

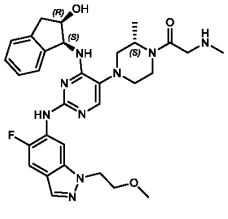

Example 8



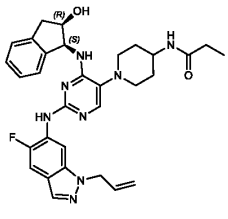
Example 9



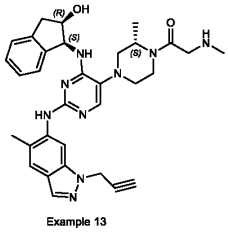
Example 10



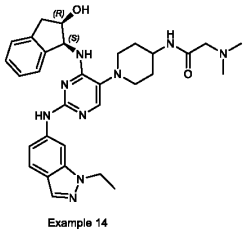
Example 11



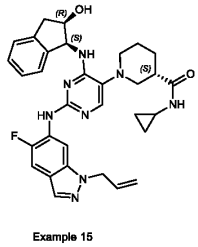
Example 12



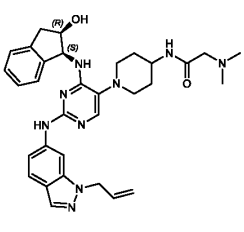
Example 13



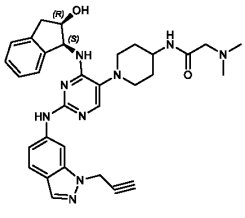
Example 14



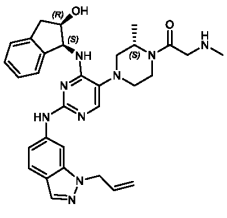
Example 15



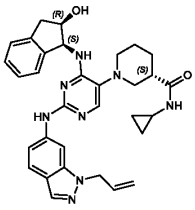
Example 16



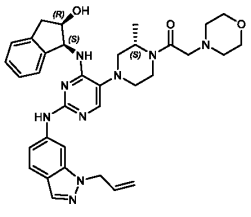
Example 17



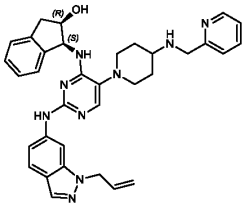
Example 18



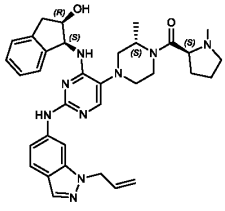
Example 19



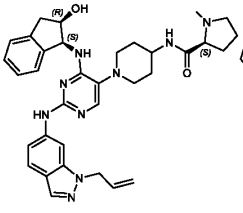
Example 20



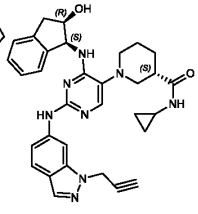
Example 21



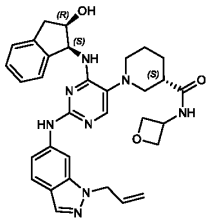
Example 22



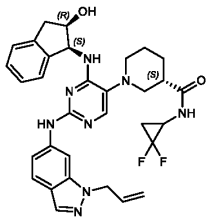
Example 23



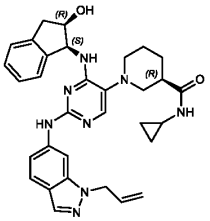
Example 24



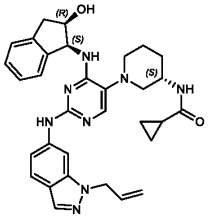
Example 25



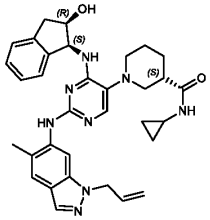
Example 26



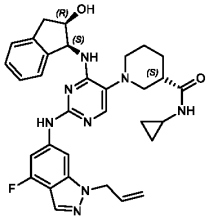
Example 27



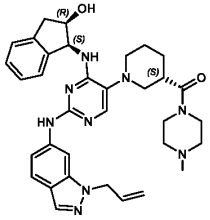
Example 28



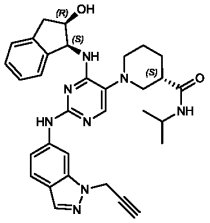
Example 29



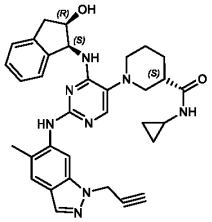
Example 30



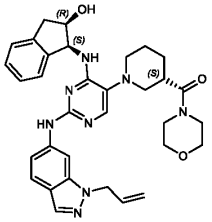
Example 31



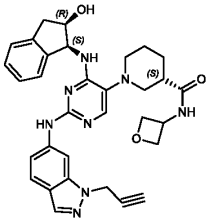
Example 32



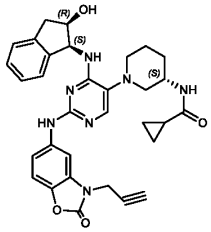
Example 33



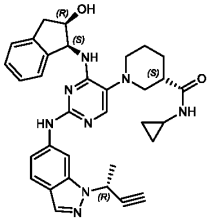
Example 34



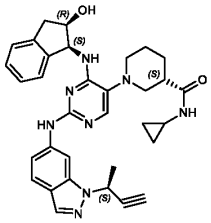
Example 35



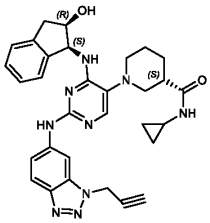
Example 36



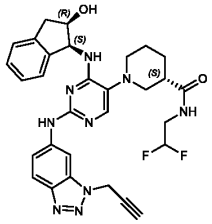
Example 37



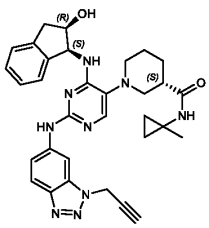
Example 38



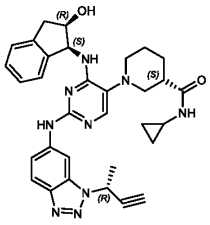
Example 39



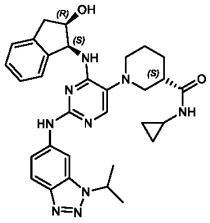
Example 40



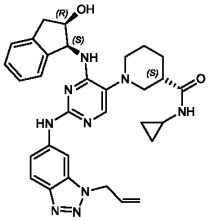
Example 41



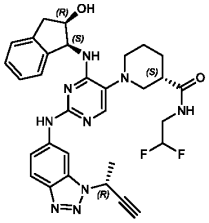
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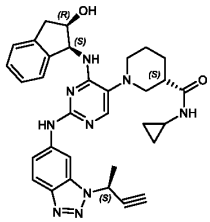
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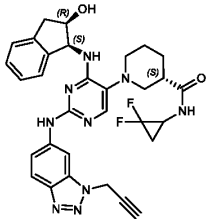
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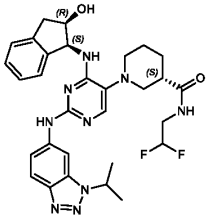
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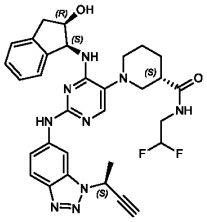
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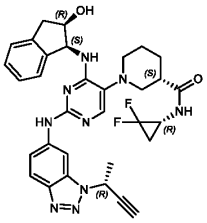
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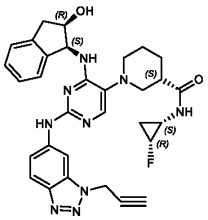
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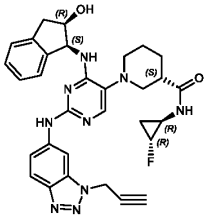
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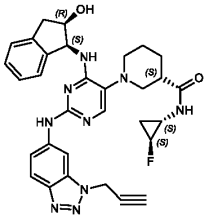
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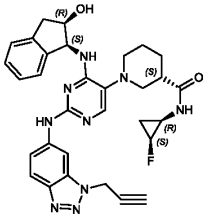
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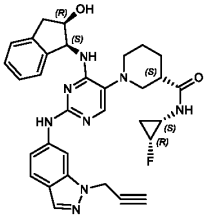
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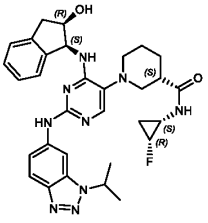
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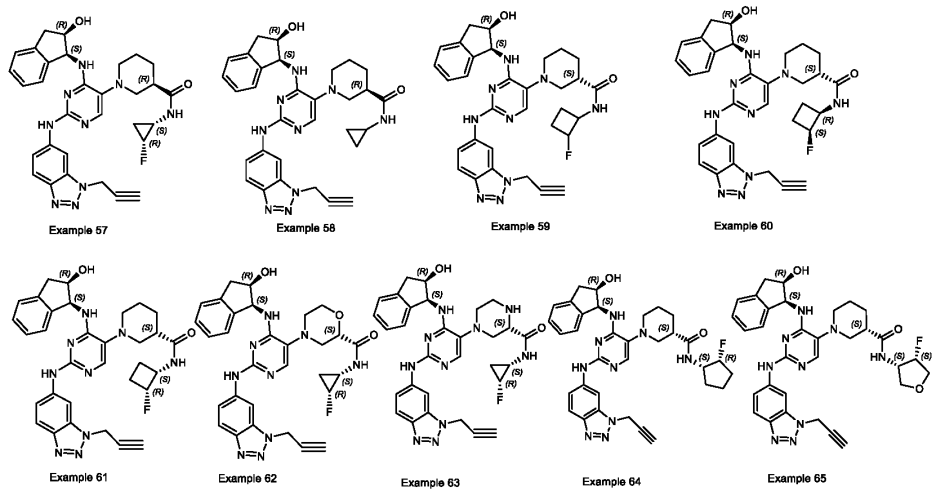
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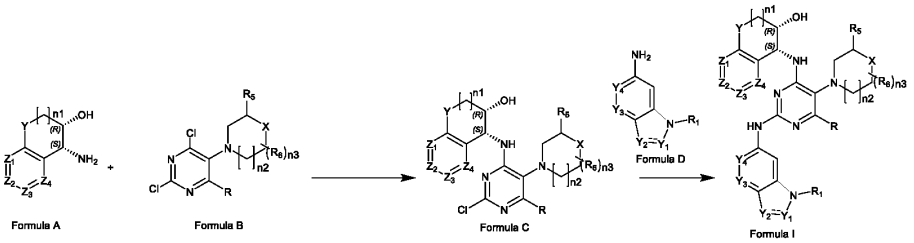
Example 55



Example 56



[00066] In an embodiment of the present disclosure, there is provided a process of preparation of compounds of Formula I as disclosed herein, the process comprising: reacting Formula (A) and Formula (B) followed by reacting with Formula (D) in the presence of a base to obtain the compound of Formula I,



R_1 is selected from 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} alkoxy, C_{1-6} haloalkoxy, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl;

Y_1 is N or C(=O);

Y_2 is selected from N, O, CR_2 or NR_3, wherein R_2 and R_3 are independently selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

--- refers to single bond or double bond between Y_1 and Y_2;

Y_3 and Y_4 are independently N or CR_4, wherein R_4 is selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl; wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

R is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy;

R_5 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl, wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

n1 is 0, 1 or 2;

X is selected from CR_7, O, S, S=O, SO_2, or NR_7; R_7 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $NH(CO)_pR_8$, or $C(=O)R_8$; R_8 is selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl or C_{3-8} heterocyclyl is optionally substituted with hydroxy, amino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{3-8} heteroaryl; wherein C_{3-8} heterocyclyl is optionally substituted with one or more groups selected from oxo or C_{1-6} alkyl; p is 0 or 1;

R_6 is selected from hydrogen, amino, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} aminoalkyl, $C(=O)NR_{9a}R_{9b}$, -NH-C(=O) R_9 or $-NHCH_2R_9$; wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy, or cyano;

R_9, R_{9a} and R_{9b} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, C_{3-12} heteroaryl, wherein C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from cyano, oxo, hydroxy, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, -S-C_{1-6} alkyl, -S(O)-C_{1-6} alkyl, -$S(O)_2$-C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{3-12} heteroaryl or C_{3-8} heterocyclyl, wherein C_{3-8} heterocyclyl or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from C_{1-6} alkyl; or R_{9a} and R_{9b} are combined together to form a C_{3-8} heterocyclyl optionally substituted with one or more substituents selected from oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} aminoalkyl;

Z_1, Z_2, Z_3, and Z_4 are independently selected from N or CR_{10};

R_{10} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

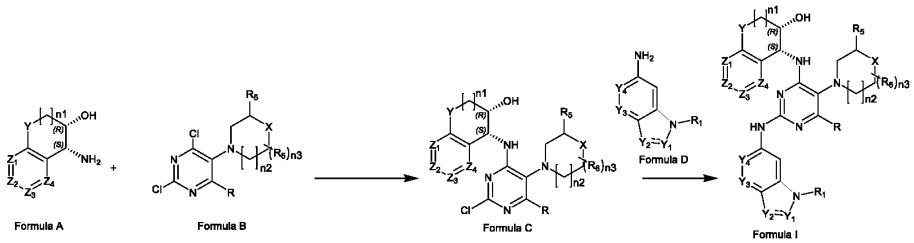
Y is selected from O, S, S=O, SO_2, N-CH_3, N-C(=O)CH_3, or CR_{11};

R_{11} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl , C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

n2 is 0 or 1; and

n3 is selected from 0 to 3.

[00067] In another embodiment of the present disclosure, there is provided a process of preparation of compounds of Formula I as disclosed herein, the process comprising: reacting Formula (A) and Formula (B) to obtain Formula (C), followed by reacting Formula (C) with Formula (D) in the presence of a base to obtain the compound of Formula I.

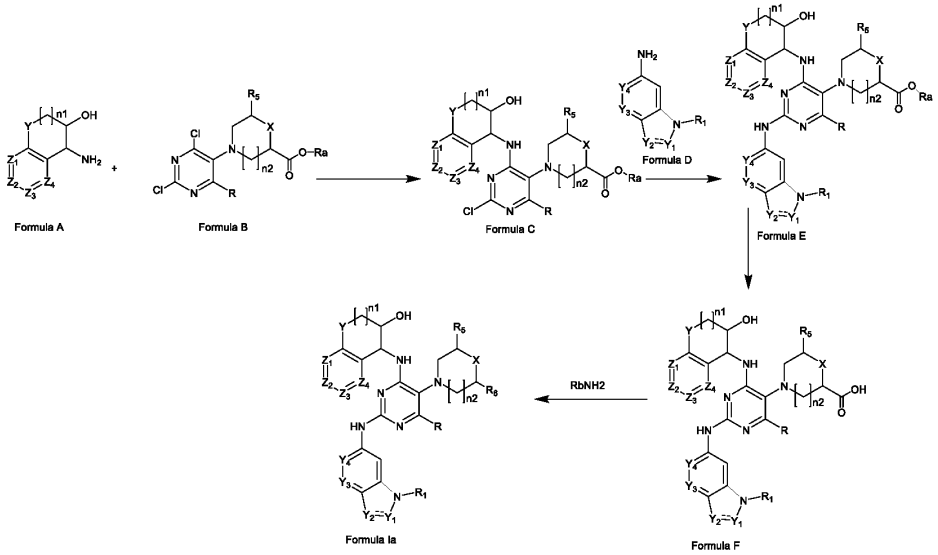


[00068] In an embodiment of the present disclosure there is provided a process of preparation of compounds of Formula I as disclosed herein, wherein the base is selected from the group consisting of triethylamine, diisopropylethylamine, pyridine, sodium hydride, potassium tertiary butoxide, sodium carbonate, potassium carbonate, and combinations thereof.

[00069] In an embodiment of the present disclosure there is provided a process of preparation of compounds of Formula I as disclosed herein, wherein the process is carried out in the presence of a coupling reagent selected from HATU((Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium), CDI (Carbonyldiimidazole), EDCI(1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide), or combinations thereof.

[00070] In an embodiment of the present disclosure there is provided a process of preparation of compounds of Formula Ia as disclosed herein, the process comprising: a. reacting Formula (A) and Formula (B'), followed by reacting with Formula (D) in the presence of a base to obtain a compound of Formula (E); b.

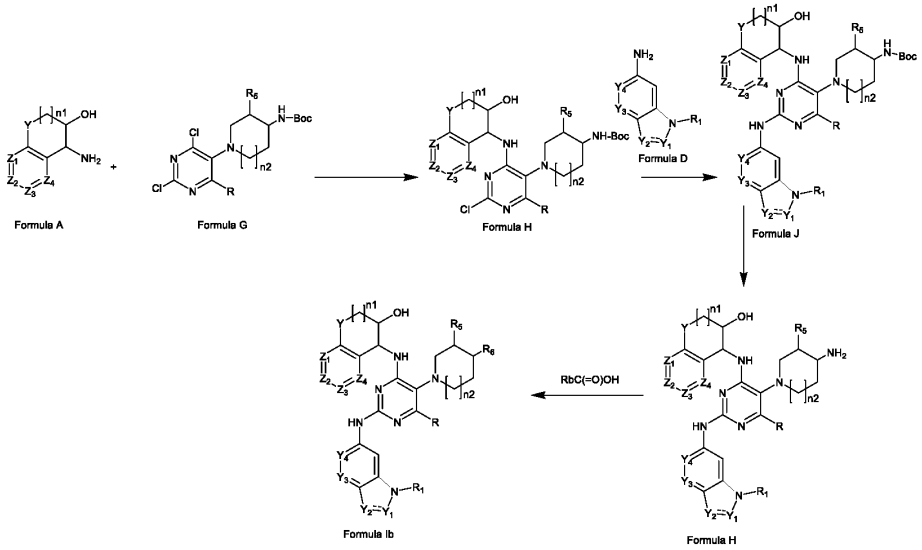
hydrolyzing the compound of Formula (E), followed by reacting with an amine (R_bNH_2) to obtain the compound of Formula Ia, wherein R_6 is -$NHCOR_b$.



Scheme1

[00071] In another embodiment of the present disclosure there is provided a process of preparation of compounds of Formula Ia as disclosed herein, the process comprising: a. reacting Formula (A) and Formula (B') to obtain Formula (C), followed by reacting Formula (C) with Formula (D) in the presence of a base to obtain a compound of Formula (E); b. hydrolyzing the compound of Formula (E) to obtain Formula (F), followed by reacting Formula (F) with an amine (R_bNH_2) to obtain the compound of Formula Ia, wherein R_6 is -$NHCOR_b$.

[00072] In an embodiment of the present disclosure there is provided a process of preparation of compounds of Formula Ib as disclosed herein, the process comprising: a. reacting Formula (A) and Formula (G) to obtain Formula (H), followed by reacting Formula (H) with Formula (D) in the presence of a base to obtain a compound of Formula (J); and b. treating of the compound of Formula (J) with a first acid to obtain Formula (K), followed by treating Formula (K) with a second acid (R_bCOOH) to obtain the compound of Formula Ib, wherein R_6 is -$NHC(O)R_b$.



Scheme 2

[00073] In another embodiment of the present disclosure there is provided a process of preparation of compounds of Formula Ib as disclosed herein, the process comprising: a. reacting Formula (A) and Formula (G), followed by reacting with Formula (D) in the presence of a base to obtain a compound of Formula (J); and b. treating of the compound of Formula (J) with an acid (R_bCOOH) to obtain the compound of Formula Ib, wherein R_6 is $-NHC(O)R_b$.

[00074] In an embodiment of the present disclosure, there is provided a process of preparation of compound of Formula Ia as disclosed herein, wherein the base is selected from the group consisting of triethylamine, diisopropylethylamine, pyridine, sodium hydride, potassium tertiary butoxide, sodium carbonate, potassium carbonate, and combinations thereof.

In an embodiment of the present disclosure there is provided a process of preparation of compounds of Formula Ia as disclosed herein, wherein the process is carried out in the presence of a coupling reagent selected from HATU((Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium), CDI (Carbonyldiimidazole), EDCI(1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide), or combinations thereof.

[00075] In an embodiment of the present disclosure there is provided a compound of Formula I as disclosed herein, for use in the manufacture of a medicament.

[00076] In an embodiment of the present disclosure there is provided a compound of Formula I as disclosed herein, wherein the compound is an inhibitor of cyclin dependent kinase 7 or cyclin dependent kinase 7 with cyclin H and MAT1 or CDK-activating kinase (CAK) or combinations thereof.

[00077] In an embodiment of the present disclosure there is provided a compound of Formula I as disclosed herein, for use in treating of cancer mediated at least in part by cyclin dependent kinase 7 or cyclin dependent kinase 7 with cyclin H and MAT1 or CDK-activating kinase (CAK) or combinations thereof.

[00078] In an embodiment of the present disclosure there is provided a compound of Formula I as disclosed herein, for the manufacture of a medicament for treating cancer mediated at least in part by cyclin dependent kinase 7 or cyclin dependent kinase 7 with cyclin H and MAT1 or CDK-activating kinase (CAK) or combinations thereof.

[00079] In an embodiment of the present disclosure there is provided a compound of Formula I as disclosed herein, wherein said cancer is selected from cancer of adrenal gland, brain, bladder, breast, bone, colon, oesophagus, head, gastric, kidney, liver, lung, muscle, neck, pancreas, prostate, skin, thyroid or white blood cells.

[00080] In an embodiment of the present disclosure there is provided a combination comprising of compounds of Formula I as disclosed herein, with at least one additional therapeutic agent.

[00081] In an embodiment of the present disclosure there is provided a combination comprising of compounds of Formula Ia and Ib as disclosed herein, with at least one additional therapeutic agent.

[00082] In an embodiment of the present disclosure there is provided a combination as disclosed herein, wherein the additional therapeutic agent is selected from chemotherapeutic agent or immune checkpoint inhibitors.

[00083] In an embodiment of the present disclosure there is provided a combination as disclosed herein, wherein chemotherapeutic agent is selected from CDK4/6 inhibitor, BCl2 (B-cell lymphoma-2) inhibitor, Bcl-XL (B-cell lymphoma-extra-large) inhibitor, anti-estrogen, anti-progesterone, KRas inhibitor, Braf inhibitor, EGFR inhibitor, angiogenesis inhibitor, 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 (PARP) inhibitor, cisplatin, oxaplatin or combinations thereof.

[00084] In an embodiment of the present disclosure there is provided a combination as disclosed herein, wherein the immune checkpoint inhibitors 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 (CTL4), inhibitor, anti-CTL4 antibody, T cell immunoglobulin and ITIM domain (TIGIT) inhibitor, ecto-nucleoside triphosphate diphosphohydrolase 1(E-NTPDase, CD39) inhibitor, ecto-5'-nucleotidase(Ecto5'NTase, CD79) inhibitor, protein tyrosine phosphatases non-receptor type 1/2 (PTPN1/2) inhibitors, or combinations thereof.

[00085] In an embodiment of the present disclosure there is provided a pharmaceutical composition comprising the compound of Formula I as disclosed herein, with at least one pharmaceutically acceptable excipient.

[00086] In an embodiment of the present disclosure there is provided a pharmaceutical composition as disclosed herein, wherein the composition is in the form of powder, tablet, liquid, or emulsion.

[00087] In an embodiment of the present disclosure there is provided a method of treating cancer in a subject, the method comprising administering the compound as disclosed herein or the combination as disclosed herein, or the pharmaceutical composition as disclosed herein to the subject in need thereof.

[00088] In an embodiment of the present disclosure there is provided a method of treating cancer in a subject, the method comprising administering an effective amount the compound as disclosed herein or the combination as disclosed herein, or the pharmaceutical composition as disclosed herein to the subject in need thereof.

[00089] In an embodiment of the present disclosure there is provided a method of treating cancer as disclosed herein, wherein the cancer is selected from cancer of adrenal gland, brain, bladder, breast, bone, colon, oesophagus, head, gastric, kidney, liver, lung, muscle, neck, pancreas, prostate, skin, thyroid or white blood cells.

[00090] In an embodiment of the present disclosure there is provided a method of treating a disease or condition mediated by cyclin dependent kinase 7 or cyclin dependent kinase 7 with cyclin H and MAT1 or CDK-activating kinase (CAK) or combinations thereof to a subject in need thereof, the method comprising administering the compound as disclosed herein or the combination as disclosed herein or the pharmaceutical composition as disclosed herein to the subject.

[00091] In an embodiment of the present disclosure there is provided a method of treating a disease or condition as disclosed herein, wherein the disease or condition is selected from cancer of adrenal gland, brain, bladder, breast, bone, colon, oesophagus, head, gastric, kidney, liver, lung, muscle, neck, pancreas, prostate, skin, thyroid or white blood cells.

[00092] Although the subject matter has been described in considerable detail with reference to certain examples and implementations thereof, other implementations are possible.

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;

UPLC - Ultra Performance 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;

DIPEA - N,N-Diisopropylethylamine

HATU - Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium

EtOAc - ethyl acetate;

LC/MS - liquid chromatography/mass spectrometry;

h - hour(s);

min - 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.

EXAMPLES

[00093] 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:

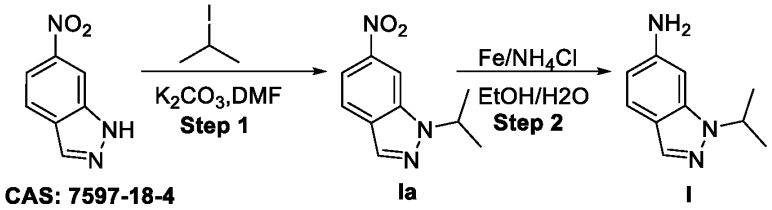
[00094] Evaporations were carried out by rotary evaporation in vacuo and work up procedures were carried out after removal of residual solids by filtration; temperatures are quoted as °C; operations were carried out at room temperature, that is typically in the range 18 to 26 °C and without the exclusion 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)

Synthesis of Intermediates:

Synthesis of 1-isopropyl-1H-indazol-6-amine. (I)



Step-1: Synthesis of 1-isopropyl-6-nitro-1*H*-indazole (Ia):

[00095] To a stirred solution of 6-nitro-1H-indazole (CAS: 7597-18-4, 10.0 g, 61.297 mmol) in DMF (100 mL) under nitrogen atmosphere was added potassium carbonate (K_2CO_3, 25.414 g, 183.89 mmol) followed by 2-Iodopropane (9.2 mL,91.946 mmol) at room temperature. The resulting reaction mixture was heated at 80 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room

temperature, diluted with water (100 mL), and extracted with ethyl acetate (2 x 100 mL). The combined organic phase was dried over Na_2SO_4(sodium sulphate). The solvent was filtered and evaporated in *vacuo* to get the crude product. The obtained crude product was purified by silica gel (230-400 mesh, 100 g packed, flow rate 40 mL/minutes & 254-280 nm wavelength) Biotage column chromatography using ethyl acetate (0-30 %) in petroleum ether and the peak was eluted with 13 % of ethyl acetate in petroleum ether concentrated to afford the desired compound **Ia** as a pale-yellow color solid. Yield: (6.1 g, 52 %).

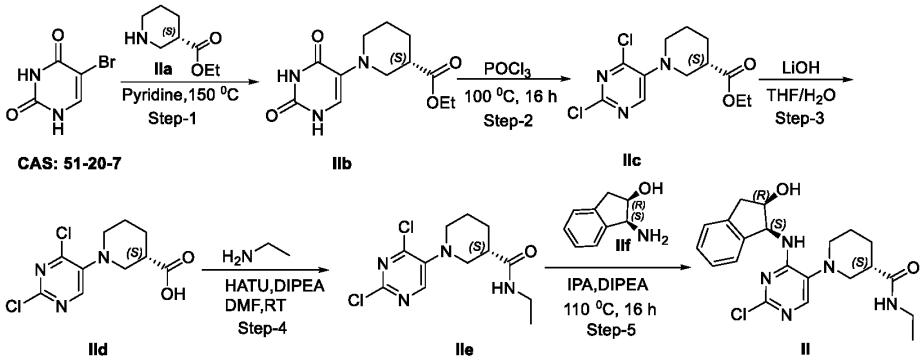
[00096] **LC_MS:** Calc. for $C_{10}H_{11}N_3O_2$: 205.22; Obs.: 206.1 [M^++H]. **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ 8.78 (s, 1H), 8.34 (s, 1H), 8.03-8.00 (m, 1H), 7.97-7.94 (m, 1H), 5.31-5.24 (m, 1H), 1.52-1.50 (m, 6H).

Step-2: Synthesis of 1-isopropyl-1*H*-indazol-6-amine (I)

[00097] To a stirred solution of 1-isopropyl-6-nitro-1H-indazole **Ia** (6.1 g, 29.75 mmol) in ethanol (60 mL) under nitrogen atmosphere was added ammonium chloride (NH_4Cl, 7.91 g, 148.78 mmol) in 40 mL of water followed by iron (8.30 g, 148.78 mmol). The reaction mixture was heated at 80°C for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a celite bed and washed with ethyl acetate (70 mL). The filtrate was concentrated in *vacuo* to get a brown color residue. The residue was diluted with water (70 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product. The crude product was triturated with petroleum ether to get the pure compound **I** as brown color solid. Yield: (4.1 g, 78.84%).

[00098] **LC_MS:** Calc. for $C_{10}H_{13}N_3$: 175.24; Obs.: 176.1 [M^++H]. **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ 7.70 (s, 1H), 7.35 (d, J = 8.80 Hz, 1H), 6.52-6.48 (m, 3H), 5.26 (s, 1H), 4.67-4.60 (m, 1H), 1.42 (d, J = 6.80 Hz, 6H).

Synthesis of (S)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-ethylpiperidine-3-carboxamide (II)



Step-1: Ethyl (*S*)-1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) piperidine-3-carboxylate (IIb)

[00099] A solution of 5-Bromouracil (CAS: 51-20-7, 6.00 g, 31.42 mmol) and ethyl (S)-piperidine-3-carboxylate (**IIa**, 5.927 g, 37.70 mmol) in pyridine (30 mL) was irradiated at 150 °C for 1.5 hours in the microwave. The progress of the reaction was monitored by UPLC. After completion of the reaction, acetonitrile (50 mL) was added and stirred for 15 minutes, filtered, and dried under a vacuum that affords the crude product. The crude product was triturated with methyl tert-butyl ether (20 mL) to get the pure desired product (**IIb)** as an off-white solid. Yield: (5.1 g, 60.78%).

[000100] **LCMS**: Calc. for $C_{12}H_{17}N_3O_4$: 267.28; Obs.:267.9 [M^++H].

Step-2: Synthesis of ethyl (*S*)-1-(2,4-dichloropyrimidin-5-yl) piperidine-3-carboxylate (IIc)

[000101] A solution of ethyl (S)-1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) piperidine-3-carboxylate **IIb** (5.10 g, 19.08 mmol) in $POCl_3$ (phosphoryl chloride, 75 mL, 0.80 mol) was heated at 100 °C for 16 hours under a nitrogen atmosphere. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and the reaction mixture was concentrated under reduced pressure and the residue was basified using 10 % sodium bicarbonate solution (100 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 3). The organic layer was dried over sodium sulfate and concentrated under a *vacuum* to get the crude product. The obtained

crude product was purified by silica gel (230-400 mesh, 25 g packed, flow rate 30 mL/minutes & 254-280 nm wavelength) Biotage column chromatography using ethyl acetate (0-30 %) in petroleum ether and the peak was eluted with 15 % of ethyl acetate in petroleum ether concentrated to afford the desired product **IIc** as a pale-yellow color liquid. Yield: (3.30 g, 56.89%). **LC_MS**: Calc. for $C_{12}H_{15}Cl_2N_3O_2$: 304.17; Obs.: 304.1 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 8.54 (s, 1H), 4.05-4.11 (m, 2H), 3.48 (dd, *J* = 3.60, Hz, 1H), 3.46-3.45 (m, 1H), 3.05-3.02 (m, 1H), 2.99 (m, 1H), 2.71-2.68 (m, 1H), 1.99 (m, 1H), 1.82 (m, 1H), 1.18-1.16 (m, 3H), 1.58-1.58 (m, 2H).

Step-3: Synthesis of (*S*)-1-(2,4-dichloropyrimidin-5-yl) piperidine-3-carboxylic acid (IId)

[000102] To a stirred solution of ethyl (*S*)-1-(2,4-dichloropyrimidin-5-yl) piperidine-3-carboxylate **IIc** (3.30 g, 10.85 mmol) in a mixture of THF (30 mL) and water (30 mL) was added LiOH.H_2O (0.68 g, 16.27 mmol) at room temperature under nitrogen atmosphere, and the resulting reaction mixture was allowed to stir at room temperature for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (30 mL), neutralized with 1.5N HCl, a product extracted with ethyl acetate, (2 x 50 mL), the organic layer dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude product **IId** as off white solid. The crude product was taken to the next step without further purification. Yield: (2.7g, 90.30%). **LC_MS**: Calc. for $C_{10}H_{11}Cl_2N_3O_2$: 276.12; Obs.: 274.0 [M^+-H].

Step-4: Synthesis of (*S*)-1-(2,4-dichloropyrimidin-5-yl)-*N*-ethylpiperidine-3-carboxamide (IIe):

[000103] To a solution of (*S*)-1-(2,4-dichloropyrimidin-5-yl) piperidine-3-carboxylic acid **(IId)** (1.000 g, 3.622 mmol) and ethane amine (2.716 mL, 5.432 mmol, 2M) in THF (10 mL), were added DIPEA (1.58 mL, 9.054 mmol) followed by HATU (1.652 g, 4.346 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 16 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with 10% aq. $NaHCO_3$, stirred for 30 minutes, and the

precipitated solid was filtered and dried under vacuum to afford the crude product as an off-white solid. The crude product was triturated with methyl tert-butyl ether (10 mL) to get the pure compound **IIe** as an off-white solid; Yield: (0.51 g, 42.48%).

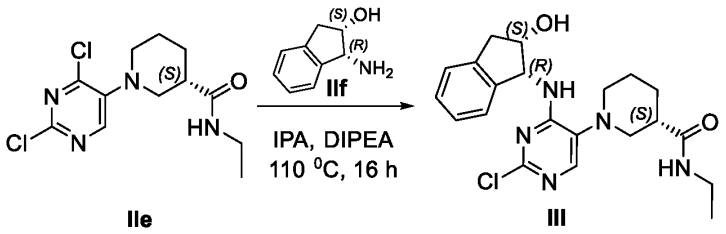
LC_MS: Calc. for $C_{12}H_{16}Cl_2N_4O$: 303.13; Obs.: 304.8 [M^++H].

Step-5: Synthesis of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino) pyrimidin-5-yl)-*N*-ethylpiperidine-3-carboxamide (II):

[000104] To a solution of (*S*)-1-(2,4-dichloropyrimidin-5-yl)-*N*-ethylpiperidine-3-carboxamide **(IIe)** (0.500 g, 1.65 mmol) and (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol **(IIf)** (0.295 g, 1.98 mmol) in 2-propanol (20 mL), was added DIPEA (0.639 g, 4.95 mmol) at room temperature, under nitrogen atmosphere and the resulting reaction mixture was heated at 110 °C for 16 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and concentrated under reduced pressure to afford the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 60% ethyl acetate in petroleum ether to yield the title compound **II** as an off-white liquid; Yield: (0.380 g, 53.81%).

[000105] **LC_MS:** Calc. for $C_{21}H_{26}ClN_5O_2$:415.81; Obs.: 416.1 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 7.83 (br s, 2H), 7.28-7.23 (m, 4H), 5.44-5.39 (m, 2H), 4.57 (br s, 1H), 3.18-3.02 (m, 5H), 3.01-2.61 (m, 5H), 1.76 (m, 1H), 1.65-1.56 (m, 2H), 1.01 , (m, 1H), 0.96 (t, J = 7.20 Hz, 3H).

Synthesis of (S)-1-(2-chloro-4-(((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-ethylpiperidine-3-carboxamide (III)

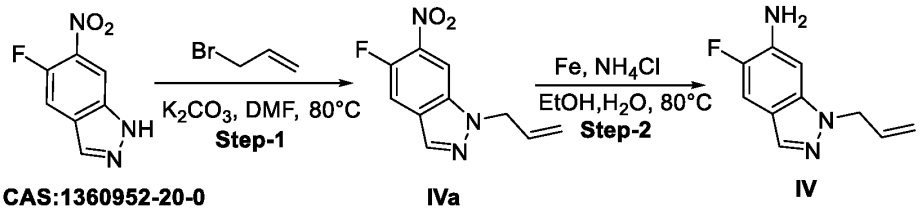


[000106] To a stirred solution (*S*)-1-(2,4-dichloropyrimidin-5-yl)-*N*-ethylpiperidine-3-carboxamide **(IIe)** (0.3 g, 0.989 mmol) in isopropyl alcohol (IPA) (15 mL) was added DIPEA (1.03 mL, 5.93 mmol) followed by (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol **(IIf)** (0.177 g, 1.18 mmol) at room temperature,

under nitrogen atmosphere. The resulting reaction mixture was heated at 110 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and concentrated under reduced pressure to afford the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 80-85% ethyl acetate in petroleum ether to yield the title compound **III** as an off-white solid; Yield: (0.120 g, 29.26%).

[000107] **LC_MS**: Calc. for: $C_{21}H_{26}ClN_5O_2$:415.92; Obs.: 416.2 [M^++H].

Synthesis of 1-allyl-5-fluoro-1H-indazol-6-amine (IV)



CAS:1360952-20-0 **IVa** **IV**

Step-1: Synthesis of 1-allyl-5-fluoro-6-nitro-1H-indazole (IVa):

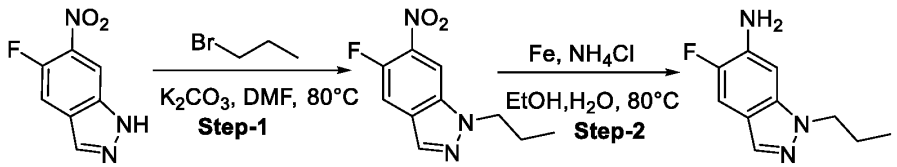
[000108] To a stirred solution of 5-fluoro-6-nitro-1*H*-indazole (CAS: 1360952-20-0, 2.0 g, 11.04 mmol) in DMF (20 mL) under nitrogen atmosphere was added potassium carbonate (3.05 g, 22.08 mmol) followed by allyl bromide (CAS: 106-95-6; 1.60 g, 13.25 mmol) at room temperature. The resulting reaction mixture was heated at 80 °C for an hour. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (40 mL), and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 9% ethyl acetate in petroleum ether to yield the title compound **IVa** as a white solid; Yield: (0.95 g, 38.93%). **LC_MS:** Calc. for $C_{10}H_8FN_3O_2$: 221.19; Obs.: 222.1 [M^+-H]. **^{1}H NMR (300 MHz, DMSO-d_6):** δ 8.69 (s, 1H), 8.31 (s, 1H), 7.98 (d, J = 11.10 Hz, 1H), 6.07-6.02 (m, 1H), 5.23 (m, 2H), 5.17 (d, J = 15.90 Hz, 2H).

Step-2: Synthesis of 1-allyl-5-fluoro-1H-indazol-6-amine (IV)

[000109] To a stirred solution of 1-allyl-5-fluoro-6-nitro-1H-indazole **(IVa)** (0.95 g, 4.29 mmol) in ethanol (15 mL) under nitrogen atmosphere was added NH_4Cl (1.15 g, 21.47 mmol) in 25 mL of water followed by iron (1.20 g, 21.47 mmol). The reaction mixture was heated at 80 °C for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a celite bed and washed with ethyl acetate (100 mL). The filtrate was concentrated in *vacuo* to get brown residue. The residue was diluted with water (50 mL) and extracted with ethyl acetate (2 x 80 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product. The crude product was dried to get the title compound **IV** as a pale-yellow liquid; Yield: (0.8 g, 94.72%).

[000110] **LC_MS:** Calc. for $C_{10}H_{10}FN_3$: 191.21; Obs.:192.1 $[M^+ + H]$. **^{1}H NMR (300 MHz, DMSO-d_6):** δ 7.76 (s, 1H), 7.33 (d, J = 11.40 Hz, 1H), 6.67 (m, 1H), 6.01-5.96 (m, 1H), 5.42 (br s, 2H), 5.17 (m, 1H), 4.99 (d, J = 12.00 Hz, 1H), 4.86 (s, 2H).

Synthesis of 5-fluoro-1-propyl-1H-indazol-6-amine (V)



CAS: 1360952-20-0 **Va** **V**

Step-1: Synthesis of 5-fluoro-6-nitro-1-propyl-1*H*-indazole (Va):

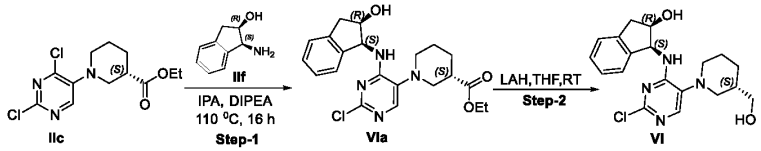
[000111] To a stirred solution of 5-fluoro-6-nitro-1*H*-indazole (CAS: 1360952-20-0, 0.6 g, 3.31 mmol) in DMF (10 mL) under nitrogen atmosphere was added potassium carbonate (0.916 g, 6.63 mmol) followed by 1-bromopropane (CAS: 106-94-5; 0.53 g, 4.31 mmol) at room temperature. The resulting reaction mixture was heated at 80 °C for an hour. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (40 mL), and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered

and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 9% ethyl acetate in petroleum ether to yield the title compound **Va** as a white solid; Yield: (0.29 g, 32.3%). **LC_MS:** Calc. for $C_{10}H_{10}FN_3O_2$: 223.21; Obs.: 223.1 [M^+-H].

Step-2:Synthesis of 5-fluoro-1-propyl-1*H*-indazol-6-amine (V)

[000112] To a stirred solution of 5-fluoro-6-nitro-1-propyl-1*H*-indazole **(Va)** (0.29 g, 1.30 mmol) in ethanol (10 mL) under nitrogen atmosphere was added NH_4Cl (0.347 g, 6.50 mmol) in 15 mL of water followed by iron (0.363 g, 6.50 mmol). The reaction mixture was heated at 80 °C for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a celite bed and washed with ethyl acetate (100 mL). The filtrate was concentrated in *vacuo* to get brown residue. The residue was diluted with water (50 mL) and extracted with ethyl acetate (2 x 80 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product. The crude product was dried to get the title compound **V** as a pale-yellow liquid; Yield: (0.2 g, 79.68%). **LC_MS:** Calc. for $C_{10}H_{12}FN_3$: 193.23; Obs.: 194.1 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 7.74 (s, 1H), 7.31 (d, J = 11.20 Hz, 1H), 6.72 (d, J = 7.20 Hz, 1H), 5.38 (br s, 2H), 4.09 (t, J = 6.80 Hz, 2H), 1.83-1.76 (m, 2H), 0.87 (t, J = 3.60 Hz, 3H).

Synthesis of (1S,2R)-1-((2-chloro-5-((S)-3-(hydroxymethyl) piperidin-1-yl) pyrimidin-4-yl) amino)-2,3-dihydro-1H-inden-2-ol (VI)



Step-1: Synthesis of ethyl (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylate (VIa)

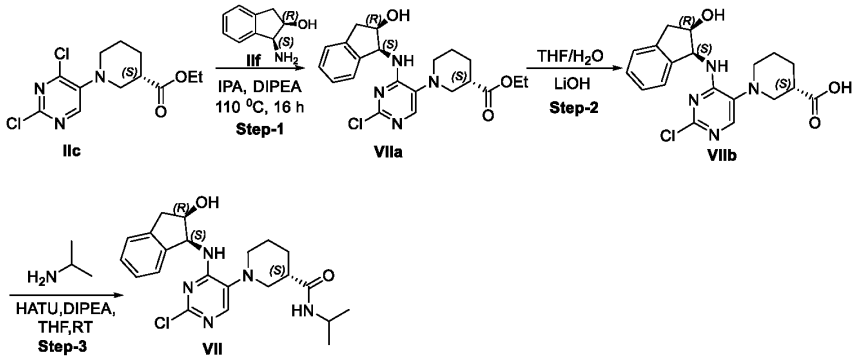
[000113] To a stirred solution of ethyl (*S*)-1-(2,4-dichloropyrimidin-5-yl) piperidine-3-carboxylate **(IIc)** (1.0 g, 3.288 mmol) in IPA (30 mL) was added DIPEA (3.44 mL, 19.73 mmol), followed by (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol **(IIf)** (0.588 g, 3.945 mmol) at room temperature, under nitrogen

atmosphere. The resulting reaction mixture was heated at 110 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and concentrated under reduced pressure to afford the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 80-85% ethyl acetate in petroleum ether to yield the title compound **VIa** as a pale-brown liquid; Yield: (0.90 g, 65.69%). **LC_MS:** Calc. for $C_{21}H_{25}ClN_4O_3$: 416.91; Obs.: 417.2[M^++H].

Step-2: Synthesis of (1S,2R)-1-((2-chloro-5-((S)-3-(hydroxymethyl) piperidin-1-yl) pyrimidin-4-yl) amino)-2,3-dihydro-1H-inden-2-ol (VI)

[000114] To a solution of ethyl (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)pyrimidin-5-yl)piperidine-3-carboxylate **(VIa)** (0.700 g, 1.679 mmol) in THF (15 mL), were added Lithium aluminum hydride 2.0M solution in tetrahydrofuran (1.679 mL, 3.358 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 1 hour. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with sodium sulphate at 0 °C and stirred for 15 minutes. The residue was basified using 10% $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated under a *vacuum* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 80% ethyl acetate in petroleum ether to yield the title compound **VI** as an off-white solid; Yield: (0.500 g, 66 %). **LC_MS:** Calc. for $C_{19}H_{23}ClN_4O_2$:374.87; Obs.: 375.2 [M^++H].

Synthesis of (S)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-isopropylpiperidine-3-carboxamide (VII)



Step-1: Synthesis of ethyl (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylate (VIIa)

[000115] To a stirred solution of ethyl (*S*)-1-(2,4-dichloropyrimidin-5-yl) piperidine-3-carboxylate **(IIc)** (1.0 g, 3.288 mmol) in IPA (30 mL) was added DIPEA (3.44 mL, 19.73 mmol), followed by (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol **(IIf)** (0.588 g, 3.945 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated at 110 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and concentrated under reduced pressure to afford the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 80-85% ethyl acetate in petroleum ether to yield the title compound **VIIa** as a pale-brown liquid; Yield: (0.90 g, 65.69%). **LC_MS:** Calc. for $C_{21}H_{25}ClN_4O_3$: 416.91; Obs.: 417.2[M^++H].

Step-2: Synthesis of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylic acid (VIIb):

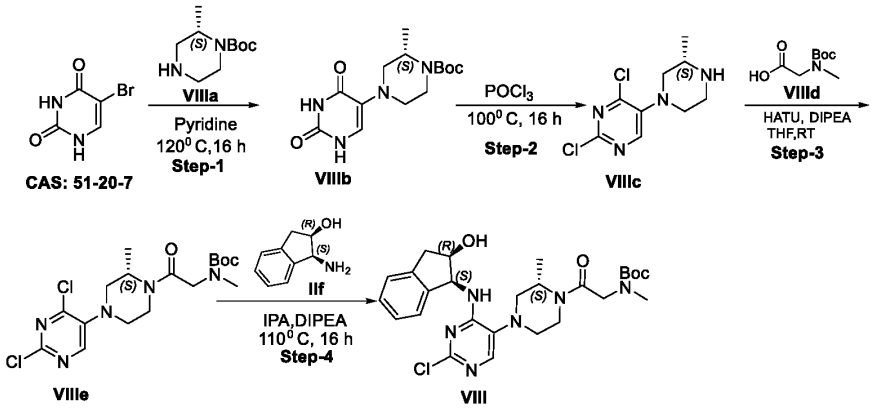
[000116] To a stirred solution of ethyl (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylate **(VIIa)** (0.900 g, 2.16 mmol) in a mixture of THF (15 mL) and water (15 mL) was added $LiOH.H_2O$ (0.300 g, 9.23mmol) at room temperature under nitrogen atmosphere. The resulting reaction mixture was allowed to stir at room temperature for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (50 mL), neutralized with 1.5N HCl, and the product was extracted with ethyl acetate (2 x 100 mL). The

organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product **VIIb** as an off-white solid. The crude product was taken to the next step without further purification; Yield: (0.600 g, 66.6%). **LC_MS**: Calc. for $C_{19}H_{21}ClN_4O_3$: 388.85; Obs.: 389.1[M^++H].

Step-3: Synthesis of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-isopropylpiperidine-3-carboxamide (VII):

[000117] To a solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)** (0.200 g, 0.514 mmol) and propan-2-amine (CAS: 75-31-0, 0.030 g, 0.514 mmol, 2M) in THF (10 mL), were added DIPEA (0.269 mL, 1.543 mmol) followed by HATU (0.234 g, 0.617 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was basified using 10% $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated under a *vacuum* to get the crude product **VII** as pale-yellow solid. Yield: (0.15 g, 33 %). **LC_MS:** Calc. for $C_{22}H_{28}ClN_5O_2$:429.95; Obs.: 430.2 [M^++H].

Synthesis of tert-butyl (2-((S)-4-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-oxoethyl) (methyl)carbamate (VIII)



Step-1: Synthesis of tert-butyl (*S*)-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-methylpiperazine-1-carboxylate (VIIIb):

[000118] To a suspension of 5-Bromouracil (CAS: 51-20-7, 20.0 g, 104.72 mmol) and **VIIIa** (31.46 g, 157.08 mmol) in pyridine (300 mL) was heated to 110° C for 16 hours. After completion of the reaction, the reaction mixture was cooled to room temperature and a (1:1) mixture of methyl tert-butyl ether and acetonitrile (200 mL) was charged. The reaction mixture was stirred, filtered, washed thoroughly with acetonitrile, and dried under *vacuum* to get pure product **VIIIb** as a white solid. Yield: (19 g 58.0%). **^{1}H NMR (300 MHz, DMSO-d_6):** δ 11.07 (s, 1H), 10.49 (s, 1H), 6.73 (d, J = 4.00 Hz, 1H), 4.13 (s, 1H), 3.72 (d, J = 17.20 Hz, 1H), 3.17-3.02 (m, 3H), 2.44 (dd, J = 4.80, 15.20 Hz, 1H), 2.36-2.28 (m, 1H), 1.41 (s, 9H), 1.20 (d, J = 8.80 Hz, 3H). **LC_MS** Calc. for $C_{14}H_{22}N_4O_4$: 310.35; Obs.: 211.0 (De Boc) [M^++H].

Step-2: Synthesis of (*S*)-2,4-dichloro-5-(3-methylpiperazin-1-yl) pyrimidine (VIIIc)

[000119] To a suspension of **VIIIb** (16.0 g, 51.55 mmol) in POCl3 (240 mL) under nitrogen atmosphere and the resulting reaction mixture was stirred at 100 °C for 16 hours (clear solution). After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the residue was basified using aq. sodium bicarbonate solution. The aqueous layer was extracted with 10% methanol in dichloromethane (3 X 500 mL). The organic layer was passed through sodium sulfate and concentrated under a vacuum to get a crude solid. The crude was washed with MTBE and dried under vacuum *to* get the crude product **VIIIc** as a pale brown solid. Yield: (12 g, 78%).**LC_MS**: Calc. for $C_9H_{12}Cl_2N_4$: 247.12; Obs.: 249.1 [M^++H].

Step-3: Synthesis of tert-butyl (*S*)-(2-(4-(2,4-dichloropyrimidin-5-yl)-2-methyl piperazine-1-yl)-2-oxoethyl) (methyl)carbamate (VIIIe):

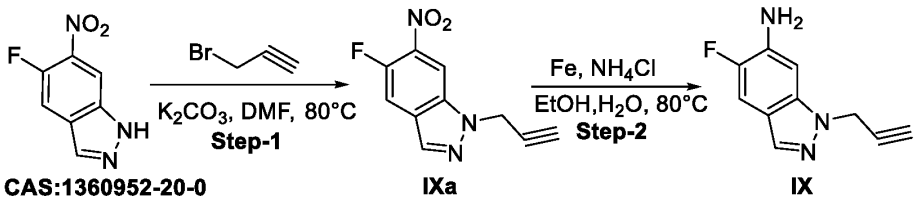
[000120] To a stirred solution of **VIIIc** (2.48 g, 10.042 mmol) and **VIIId** (2.0 g, 10.570 mmol) in THF (40 mL) were added DIPEA (5.52 mL, 31.711 mmol) followed by HATU (4.8231 g, 12.684 mmol) at 0°C under nitrogen

atmosphere and the resulting reaction mixture was allowed to stir at room temperature for 3 h. The reaction progress is monitored by TLC. After completion of the reaction, the reaction mixture was quenched with 10% aq. $NaHCO_3$ was diluted with water and extracted with ethyl acetate (2 X 50 mL). The organic phase was washed with water, and brine and dried under Na_2SO_4. The solvent was filtered and evaporated under a *vacuum* to get the crude product as a brown liquid. The crude compound was purified by silica gel (230-400 mesh,50 g packed, flow rate 35 mL/minutes & 254-280 nm wavelength) Biotage flash column chromatography using ethyl acetate (0-100%) in petroleum ether and the peak was eluted with 60% ethyl acetate was concentrated to afford the desired compound **(VIIIe)** as a pale brown liquid. Yield: (1.3 g, 29%). **LC_MS**: Calc. for $C_{17}H_{25}Cl_2N_5O_3$: 418.32; Obs.: 318.1 [M^+-Boc].

Step-4: Synthesis of tert-butyl (2-((*S*)-4-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-oxoethyl) (methyl)carbamate (VIII)

[000121] To a stirred solution of **VIIIe** (1.3 g, 3.10 mmol) and **IIf** (0.51 mg, 3.418 mmol) in IPA (52 mL) under nitrogen atmosphere was added DIPEA (3.25 mL, 18.646 mmol). The resulting reaction mixture was then stirred at 110 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mass was concentrated under a vacuum to get the crude. The crude compound was purified by silica gel (230-400, 50 g, packed) Biotage flash column chromatography using methanol (0-10%) in ethyl acetate and the peak was eluted with 8% methanol in ethyl acetate was concentrated to afford the desired compound **(VIII)** as an off-white solid. Yield: (1.25g, 75.7%). **LCMS:** Calc. for $C_{26}H_{35}ClN_6O_4$**:** 531.05; Obs.: 531.2 [M^++H].

Synthesis of 5-fluoro-1-(prop-2-yn-1-yl)-1H-indazol-6-amine (IX)



CAS:1360952-20-0 **IXa** **IX**

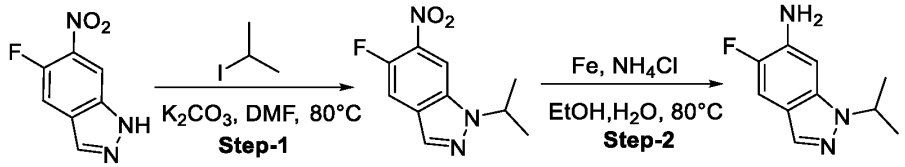
Step-1: Synthesis of 5-fluoro-6-nitro-1-(prop-2-yn-1-yl)-1H-indazole (IXa):

[000122] To a stirred solution of 5-fluoro-6-nitro-1*H*-indazole (CAS: 1360952-20-0, 1.0 g, 5.52 mmol) in DMF (10 mL) under nitrogen atmosphere was added potassium carbonate (1.52 g, 11.04 mmol) followed by 3-bromoprop-1-yne (CAS:106-96-7; 0.675 g, 11.04 mmol) at room temperature. The resulting reaction mixture was heated at 80 °C for an hour. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (30 mL), and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 10% ethyl acetate in petroleum ether to yield the title compound **IXa** as a white solid; Yield: (0.8 g, 66.11%). **LC_MS:** Calc. for $C_{10}H_6FN_3O_2$: 219.18; Obs.: 219.2 [M^+-H].

Step-2: Synthesis of 5-fluoro-1-(prop-2-yn-1-yl)-1H-indazol-6-amine (IX)

[000123] To a stirred solution of 5-fluoro-6-nitro-1-(prop-2-yn-1-yl)-1H-indazole **(IXa)** (0.8 g, 3.65 mmol) in ethanol (15 mL) under nitrogen atmosphere was added NH_4Cl (0.975 g, 18.2 mmol) in 25 mL of water followed by iron (1.02 g, 18.2 mmol). The reaction mixture was heated at 80 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a celite bed and washed with ethyl acetate (100 mL). The filtrate was concentrated in *vacuo* to get brown residue. The residue was diluted with water (50 mL) and extracted with ethyl acetate (2 x 80 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product. The crude product was dried to get the title compound **IX** as a pale-yellow liquid; Yield: (0.41 g, 59.42%). **LC_MS:** Calc. for $C_{10}H_8FN_3$: 189.19; Obs.:190.3 [M^++H].

Synthesis of 5-fluoro-1-isopropyl-1H-indazol-6-amine (X)



CAS:1360952-20-0 **Xa** **X**

Step-1: Synthesis of 5-fluoro-1-isopropyl-6-nitro-1H-indazole (Xa):

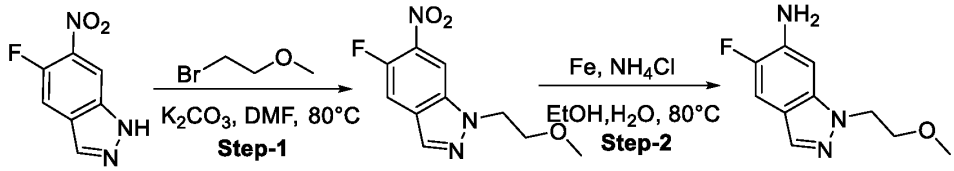
[000124] To a stirred solution of 5-fluoro-6-nitro-1*H*-indazole (CAS: 1360952-20-0, 1 g, 5.5 mmol) in DMF (10 mL) under nitrogen atmosphere was added potassium carbonate (1.45 g, 10.47 mmol) followed by 1-bromopropane (CAS: 75-30-9, 1.33 g, 7.85 mmol) at room temperature. The resulting reaction mixture was heated at 80 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (40 mL), and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 9% ethyl acetate in petroleum ether to yield the title compound **Xa** as a white solid; Yield: (0.6 g, 48.78%).**LC_MS:** Calc. for $C_{10}H_{10}FN_3O_2$: 223.21; Obs.: 224.1[M^++H]. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)**: δ 8.74 (m, 1H), 8.29 (s, 1H), 7.95 (d, J = 11.40 Hz, 1H), 5.28-5.15 (m, 1H), 1.49 (s, 6H).

Step-2: Synthesis of 5-fluoro-1-isopropyl-1H-indazol-6-amine (X)

[000125] To a stirred solution of 5-fluoro-1-isopropyl-6-nitro-1H-indazole **Xa** (0.6 g, 2.68 mmol) in ethanol (10 mL) under nitrogen atmosphere was added NH_4Cl (0.71 g, 13.44 mmol) in 15 mL of water followed by iron (0.73 g, 13.44 mmol). The reaction mixture was heated at 90 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a celite bed and washed with ethyl acetate (100 mL). The filtrate was concentrated in *vacuo* to get brown residue. The residue was diluted with water (50 mL) and extracted with ethyl acetate (2 x 80 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product. The crude product was dried to get the title compound **X** as a pale-yellow

liquid; Yield: (0.42 g, 82.35%). **LC_MS:** Calc. for $C_{10}H_{12}FN_3$: 193.23; Obs.: 194.2 [M^++H]. **^{1}H NMR (300 MHz, DMSO-d_6):** δ 7.74 (s, 1H), 7.31 (d, J = 11.10 Hz, 1H), 6.75 (d, J = 7.80 Hz, 1H), 5.37 (br s, 2H), 4.70-4.62 (m, 1H), 1.42 (d, J = 6.60 Hz, 6H).

Synthesis of 5-fluoro-1-(2-methoxyethyl)-1H-indazol-6-amine (XI)



CAS:1360952-20-0 **XIa** **XI**

Step-1: Synthesis of 5-fluoro-1-(2-methoxyethyl)-6-nitro-1H-indazole (XIa):

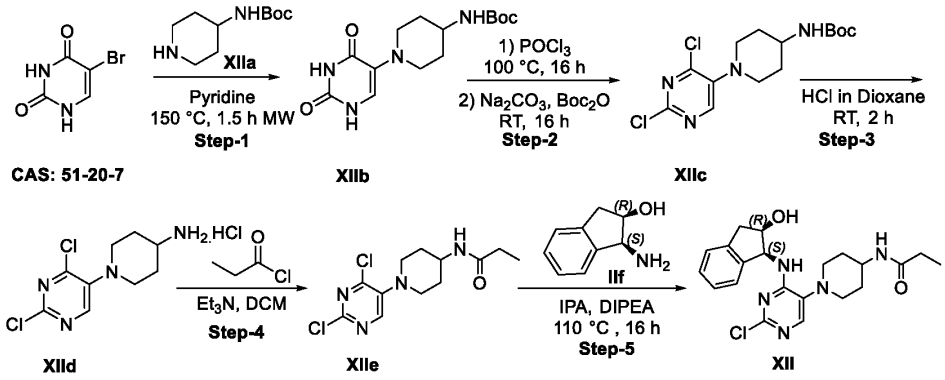
[000126] To a stirred solution of 5-fluoro-6-nitro-1H-indazole (CAS: 1360952-20-0, 2.00 g, 11.04 mmol) in DMF (20 mL) under nitrogen atmosphere was added potassium carbonate (4.58 g, 33.13 mmol) followed by 1-bromo-2-methoxyethane (2.30 g, 16.56 mmol) at room temperature. The resulting reaction mixture was heated at 80 °C for 1 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (50 mL), and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 13% ethyl acetate in petroleum ether to yield the title compound **XIa** as a pale-yellow solid; Yield: (1.0 g, 33.8 %). **LC_MS:** Calc. for $C_{10}H_{10}FN_3O_3$: 239.21; Obs.: 239.1 [M-H]$^+$.

Step-2: Synthesis of 5-fluoro-1-(2-methoxyethyl)-1H-indazol-6-amine (XI)

[000127] To a stirred solution of 5-fluoro-1-(2-methoxyethyl)-6-nitro-1H-indazole **(XIa)** (1.00 g, 4.180 mmol) in ethanol (10 mL) under nitrogen atmosphere was added NH_4Cl (1.12 g, 20.90 mmol) in 10 mL of water followed by iron (1.16 g, 20.90 mmol). The reaction mixture was heated at 80 °C for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the

reaction mixture was filtered through a celite bed and washed with ethyl acetate (70 mL). The filtrate was concentrated in *vacuo* to get brown residue. The residue was diluted with water (70 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product. The crude product was triturated with petroleum ether to get the title compound **XI** as Pale-yellow solid; Yield: (0.9 g, 94.97 %). **LC_MS:** Calc. for $C_{10}H_{12}FN_3O$: 209.22; Obs.: 210.1$[M+H]^+$.

Synthesis of N-(1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-4-yl) propionamide (XII)



Step-1: Synthesis of *tert*-butyl (1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) piperidin-4-yl) carbamate (XIIb)

[000128] A 100 mL round bottom flask was charged with 5-bromouracil (CAS: 51-20-7, 2.00 g, 10.47 mmol), *tert*-butyl piperidin-4-ylcarbamate **(XIIa)** (2.51 g, 12.57 mmol) and pyridine (10.00 mL). The resulting reaction mixture was stirred at 100 °C for 16 hours. The reaction progress was monitored by UPLC. The reaction mixture was cooled to room temperature, diluted with acetonitrile, stirred for 15 minutes, filtered, and dried under vacuum to afford the desired product **(XIIb)** as an off-white solid; Yield: (1.82 g, 52.1 %). **LC_MS:** Calc. for $C_{14}H_{22}N_4O_4$: 310.35; Obs.: 309.6$[M-H]^+$ and 311.0 $[M^+ + H]$; **^{1}H-NMR (400 MHz, DMSO-*d6*):** δ 11.02 (s, 1H), 10.43 (d, J = 6.80 Hz, 1H), 6.82 (d, J = 9.60 Hz, 1H), 6.71 (s, 1H), 3.21 (t, J = 15.20 Hz, 2H), 2.36 (t, J = 14.80 Hz, 2H), 1.72 (d, J = 14.80 Hz, 2H), 1.46 (t, J = 16.00 Hz, 2H), 1.39 (s,9H).

Step-2: Synthesis of *tert*-butyl (1-(2,4-dichloropyrimidin-5-yl) piperidin-4-yl) carbamate (XIIc)

[000129] To *tert*-butyl (1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) piperidin-4-yl) carbamate **(XIIb)** (1.82 g, 5.864 mmol) was added $POCl_3$ (46 g, 0.30 mmol) at room temperature under nitrogen atmosphere. The resulting reaction mixture was heated to 100 °C for 16 hours. The reaction mixture was cooled to room temperature, and $POCl_3$ was removed under reduced pressure. The residue was dissolved in THF (50mL) and poured into crushed ice water (50 mL), basified with Na_2CO_3 (by adjusting pH~8) then, was added Boc_2O (1.28 g, 5.864 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with water and ethyl acetate and separated into two layers. The aqueous layer was extracted with ethyl acetate (2 x 200mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product as a brown gummy solid. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 20% ethyl acetate in petroleum ether to yield the title compound **XIIc** as a white solid; Yield: (0.83 g, 31 %). **UPLC_MS:** Calc. for $C_{14}H_{20}Cl_2N_4O_2$: 347.24; Obs.: 290.6[M-56]+ and 346.8 [M^++H]; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.21 (s, 1H), 4.53 (s, 1H), 3.67 (s, 1H), 3.42 (d, J = 12.40 Hz, 2H), 2.94-2.87 (m, 2H), 2.10 (q, J = 12.80 Hz, 1H), 1.61-1.66 (m, 3H), 1.47 (m, 9H).

Step-3: Synthesis of 1-(2,4-dichloropyrimidin-5-yl) piperidin-4-amine hydrochloride (XIId)

[000130] To a solution of *tert*-butyl (1-(2,4-dichloropyrimidin-5-yl) piperidin-4-yl) carbamate **(XIIc)** (0.82 g, 2.36 mmol) in DCM (10 mL), was added HCl in Dioxane (13 g, 0.37 mol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 1 hour. The reaction progress was monitored by TLC. The reaction mixture was concentrated under reduced pressure to afford the crude product as an off-white solid. The obtained crude was triturated with MTBE, decanted and the solid was dried under vacuum to afford the desired compound **XIId** as a white solid; Yield: (0.71 g, 78%). **UPLC_MS** Calc. for $C_9H_{13}Cl_3N_4$: 247.200; Obs.: 246.9 [M^++H].

Step-4: Synthesis of *N*-(1-(2,4-dichloropyrimidin-5-yl) piperidin-4-yl) propionamide (XIIe)

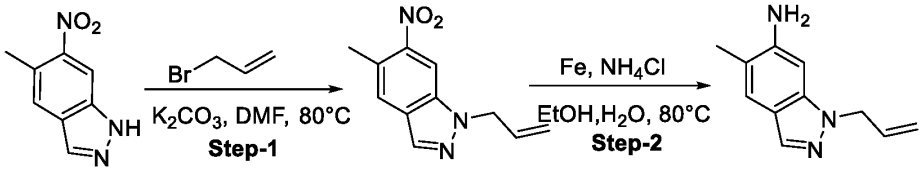
[000131] To a solution of 1-(2,4-dichloropyrimidin-5-yl) piperidin-4-amine hydrochloride **(XIId)** (0.35 g, 1.23 mmol) in DCM (10 mL), were added TEA (0.375 g, 3.70 mmol) and propionyl chloride (0.126 g, 1.36 mmol) at 0 °C under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 1 hour. The reaction progress monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to remove the solvent and afford the crude product as a brown solid. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 80% ethyl acetate in petroleum ether to yield the title compound **XIIe** as a white solid. Yield: 0.2 g, 46.6%).

[000132] **UPLC_MS** Calc. for $C_{12}H_{16}Cl_2N_4O$: 303.19; Obs.: 302.19 [M^++H]; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.22 (s, 1H), 5.38 (s, 1H), 4.00-4.04 (m, 1H), 3.44 (d, *J* = 12.40 Hz, 2H), 2.97-2.90 (m, 2H), 2.24 (q, *J* = 7.60 Hz, 2H), 2.12 (m, 2H), 1.68 (t, *J* = 7.60 Hz, 2H), 1.20 (t, *J* = 7.60 Hz, 3H).

Step-5: Synthesis of *N*-(1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino)pyrimidin-5-yl)piperidin-4-yl)propionamide (XII)

[000133] To a solution of *N*-(1-(2,4-dichloropyrimidin-5-yl) piperidin-4-yl) propionamide **(XIIe)** (0.20 g, 0.660 mmol) and (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol **(IIf)** (0.118 g, 0.792 mmol) in 2-propanol (10 mL), was added DIPEA (0.25 g, 1.98 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 110 °C for 24 hours. The reaction progress was monitored by UPLC and LCMS. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure to afford the crude product as a brown gummy solid. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 4% methanol in DCM to yield the title compound **XII** as an off-white solid; Yield: (0.11 g, 35.1%). **UPLC_MS**: Calc. for $C_{21}H_{26}ClN_5O_2$: 415.92; Obs.: 415.9 [M^++H] and 413.9 [M^+-H].

Synthesis of 1-allyl-5-methyl-1H-indazol-6-amine (XIII)



CAS:72521-00-7 XIIIa XIII

Step-1: Synthesis of 1-allyl-5-methyl-6-nitro-1H-indazole (XIIIa):

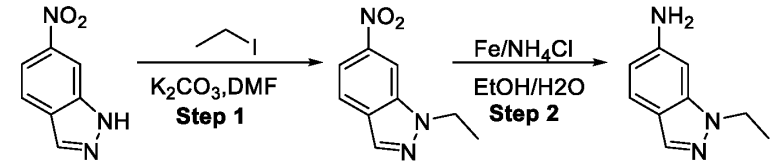
[000134] To a stirred solution of 5-methyl-6-nitro-1H-indazole (CAS: 72521-00-7, 1.50 g, 8.46 mmol) in DMF (30 mL) under nitrogen atmosphere was added Potassium carbonate (2.34 g, 16.93 mmol) followed by allyl bromide (CAS: 106-95-6; 1.53 g, 12.70 mmol) at room temperature. The resulting reaction mixture was heated at 80 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (50 mL), and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 13% ethyl acetate in petroleum ether to yield the title compound **XIIIa** as a pale-brown solid; Yield: (0.83 g, 45.3%). **LC_MS:** Calc. for $C_{11}H_{11}N_3O_2$: 217.23; Obs.: 218.0 [M^++H]. **^{1}H NMR (300 MHz, DMSO-d_6):** δ 8.44 (s, 1H), 8.23 (s, 1H), 8.23 (s, 1H), 6.08-6.04 (m, 1H), 5.19 (br s, 1H), 5.20 (br s, 1H), 5.06 (d, J = 11.40 Hz, 2H), 2.55 (br s, 3H).

Step-2: Synthesis of 1-allyl-5-methyl-1H-indazol-6-amine (XIII)

[000135] To a stirred solution of 1-allyl-5-methyl-6-nitro-1H-indazole **(XIIIa)** (0.82 g, 3.77 mmol) in ethanol (20 mL) under nitrogen atmosphere was added NH4Cl (0.20 g, 3.77 mmol) in 20 mL of water followed by iron (1.054 g, 18.87 mmol). The reaction mixture was heated at 80 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a celite bed and washed with ethyl acetate (70 mL). The filtrate was concentrated in *vacuo* to get brown residue. The residue was diluted with water (70 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layer was dried over Na2SO4, filtered, and evaporated under a vacuum to get the crude product. The crude product was triturated with petroleum

ether to get the title compound **XIII** as a pale brown solid; Yield: (0.3 g, 43.90%). **LC_MS:** Calc. for $C_{11}H_{13}N_3$:187.25; Obs.:188.1 [M++H]. **1H NMR** (400 MHz, DMSO-d6): δ 7.68 (s, 1H), 7.28 (s, 1H), 6.55 (s, 1H), 6.00-5.97 (m, 1H), 5.14-5.11 (m, 3H), 4.95 (d, J = 1.60 Hz, 1H), 4.83-4.81 (m, 2H), 2.14 (s, 3H).

Synthesis of 1-ethyl-1H-indazol-6-amine (XIV)



CAS: 7597-18-4 **XIVa** **XIV**

Step-1: Synthesis of 1-ethyl-6-nitro-1*H*-indazole (XIVa):

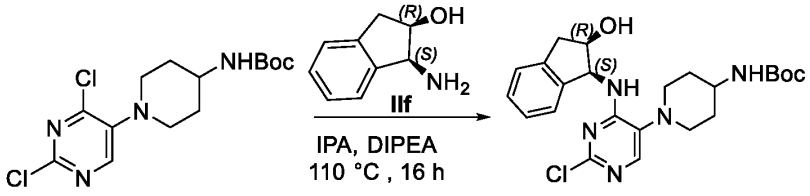
[000136] To a stirred solution of 6-nitro-1*H*-indazole (CAS: 7597-18-4, 3.0 g, 18 mmol) in DMF (30 mL) under nitrogen atmosphere was added sodium hydride (0.88 g, 28 mmol) at 0 °C, stirred for 30 min, then added iodoethane (4.3 g,28 mmol) at 0 °C, resulting reaction mixture allowed to stir at 27 °C for 1 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (40 mL), and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 10% ethyl acetate in petroleum ether to yield the title compound **XIVa** as an off-white solid; Yield: (1.91 g, 54%). LC_MS: Calc. for $C_9H_9N_3O_2$: 191.19; Obs: 192.1 [M++H]. 1H NMR (400 MHz, DMSO-d6): *δ* 8.43 (s, 1H), 8.14 (s, 1H), 8.04 (d, *J* = 2 Hz,1H), 7.87-7.85 (m, 1H), 4.56 (qt, *J* = 7.20 Hz, 2H), 1.60 (t, *J* = 7.60 Hz, 3H).

Step-2: Synthesis of 1-ethyl-1*H*-indazol-6-amine (XIV)

[000137] To a stirred solution of 1-ethyl-6-nitro-1*H*-indazole **(XIVa)** (1.800 g, 9.415 mmol) in ethanol (40 mL) under nitrogen atmosphere was added NH_4Cl (3.022g, 56.49 mmol) in 20 mL of water followed by iron (1.577 g, 28.24 mmol). The reaction mixture was heated at 80 °C for 3 hours. The progress of the reaction

was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a celite bed and washed with ethyl acetate (100 mL). The filtrate was concentrated in *vacuo* to get brown residue. The residue was diluted with water (50 mL) and extracted with ethyl acetate (2 x 80 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 50% ethyl acetate in petroleum ether to yield the title compound **XIV** as off-white solid. Yield: (1.41 g, 84%). **LC_MS:** Calc. for $C_9H_{11}N_3$: 161.21; Obs.:162 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 7.70 (s, 1H), 7.35 (d, J = 1.60, 1H), 6.52-6.49 (m, 2H), 5.30 (s, 2H), 4.19 (q, J = 9.60, 2H), 1.32 (t, J = 9.60, 3H).

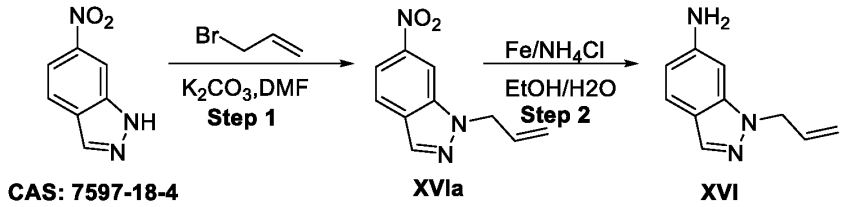
Synthesis of tert-butyl (1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-4-yl) carbamate (XV)



XIIc **XV**

[000138] To a solution tert-butyl (1-(2,4-dichloropyrimidin-5-yl) piperidin-4-yl)carbamate **(XIIc)** (0.500 g, 1.440 mmol) and (1*S*,2*R*)-1-amino-2,3-dihydro-1H-inden-2-ol **IIf** (0.214 g, 1.440 mmol) in 2-Propanol (10 mL), was added DIPEA (0.465 g, 3.600 mmol) at room temperature, under nitrogen atmosphere and the resulting reaction mixture was heated at 110 °C for 1 hour. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and concentrated under reduced pressure to afford the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 70% ethyl acetate in petroleum ether to yield the title compound **(XV)** as an off-white solid; Yield: (0.200 g, 30%). **LC_MS:** Calc. for $C_{23}H_{30}ClN_5O_3$:459.98; Obs.: 460.2 [M^++H].

Synthesis of 1-allyl-1H-indazol-6-amine (XVI)



CAS: 7597-18-4 XVIa XVI

Step-1: Synthesis of 1-allyl-6-nitro-1*H*-indazole (XVIa):

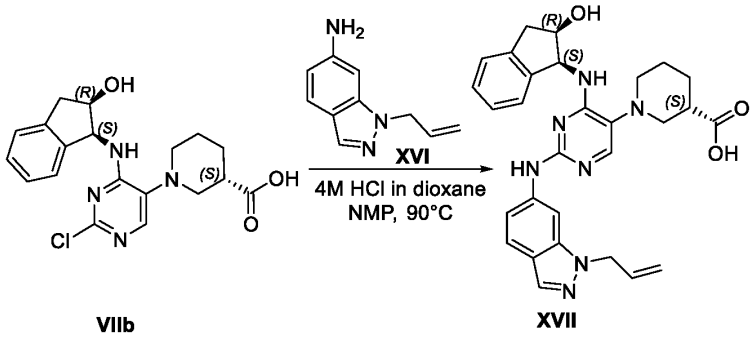
[000139] To a stirred solution of 6-nitro-1*H*-indazole (CAS: 7597-18-4, 5.0 g, 30.65 mmol) in DMF (50 mL) under nitrogen atmosphere was added potassium carbonate (8.47 g, 61.30 mmol) followed by allyl bromide (CAS: 106-95-6; 3.70 g, 30.65 mmol) at room temperature. The resulting reaction mixture was heated at 80 °C for an hour. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (40 mL), and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 9% ethyl acetate in petroleum ether to yield the title compound **XVIa** as a brown solid; Yield: (2.5 g, 32.99%). **LC_MS:** Calc. for $C_{10}H_9N_3O_2$: 203.20; Obs: 204.1 [M^++H]. **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ 8.74-8.73 (m, 1H), 8.35 (d, J = 1.20 Hz, 1H), 8.05-8.03 (m, 1H), 7.99-7.96 (m, 1H), 6.05-6.08 (m, 1H), 5.21 (d, J = 1.60 Hz, 2H), 5.19-5.18 (m, 1H), 5.11-5.05 (m, 1H).

Step-2: Synthesis of 1-allyl-1*H*-indazol-6-amine (XVI)

[000140] To a stirred solution of 1-allyl-6-nitro-1*H*-indazole **(XVIa)** (2.1 g, 10.33 mmol) in ethanol (15 mL) under nitrogen atmosphere was added NH_4Cl (2.76 g, 51.67 mmol) in 25 mL of water followed by iron (2.88 g, 51.67 mmol). The reaction mixture was heated at 80 °C for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a celite bed and washed with ethyl acetate (100 mL). The filtrate was concentrated in *vacuo* to get brown residue. The residue was diluted with water (50 mL) and extracted with ethyl acetate (2 x 80 mL). The combined organic layer

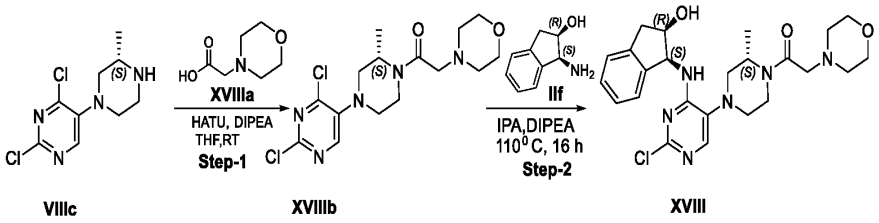
was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product. The crude product was dried to get the title compound **XVI** as a brown solid; Yield: (1.3 g, 70.49%). **LC_MS:** Calc. for $C_{10}H_{11}N_3$: 173.22; Obs.:174.1 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 7.73 (d, J = 0.80 Hz, 1H), 7.38-7.36 (m, 1H), 6.52-6.49 (m, 1H), 6.45-6.44 (m, 1H), 5.94-5.93 (m, 1H), 5.32 (s, 2H), 5.16-5.12 (m, 1H), 5.00-4.95 (m, 1H), 4.83-4.81 (m, 2H).

Synthesis of (S)-1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylic acid (XVII)



[000141] To a stirred solution (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylic acid **(VIIb)** (0.14 g, 0.360 mmol), 1-allyl-1*H*-indazol-6-amine **(XVI)** (0.063 g, 0.360 mmol) in NMP (2 mL) was added 4M HCl in dioxane (0.2 mL, 0.8 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (1 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product as brown liquid. The obtained crude product **XVII** was as such taken for next step without purification. Yield: (0.42 g, crude). **LC_MS**: Calc. for $C_{29}H_{31}N_7O_3$: 525.61; Obs.: 526.2 [M^++H].

Synthesis of 1-((S)-4-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-morpholinoethan-1-one (XVIII)



Step-1: Synthesis of (*S*)-1-(4-(2,4-dichloropyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-morpholinoethan-1-one (XVIIIb)

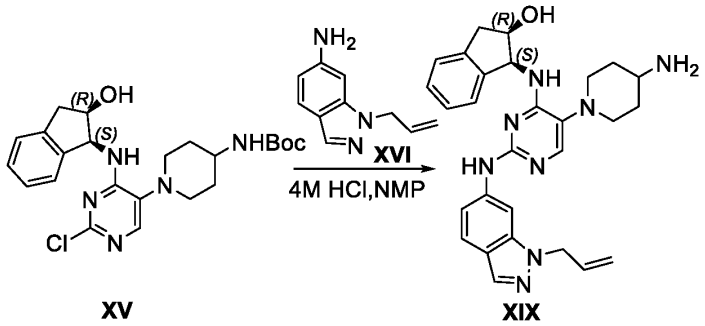
[000142] To a solution of (*S*)-2,4-dichloro-5-(3-methylpiperazin-1-yl) pyrimidine **(VIIIc)** (0.300 g, 1.24 mmol) in THF (10 mL), were added TEA (0.338 mL, 2.428 mmol) and 2-morpholinoacetic acid **(XVIIIa)** (0.328 g, 1.578 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 16 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with water (20 mL). The aqueous layer was extracted with ethyl acetate (30 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated under a *vacuum* to get the crude product as yellow gummy mass. The obtained crude product was taken to next step without purification to afford the title compound **(XVIIIb)** as a yellow gummy mass; Crude Yield: (0.50 g, crude) **LC_MS**: Calc. for $C_{15}H_{21}Cl_2N_5O_2$: 374.27; Obs.: 374.1 $[M^+ + H]$.

Step-2: Synthesis of 1-((*S*)-4-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-morpholinoethan-1-one (XVIII):

[000143] To a solution (*S*)-1-(4-XVIIIb) (oropyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-morpholinoethan-1-one **(XVIIIb)** (0.500 g, 1.34 mmol) and (1*S*,2*R*)-1-amino-2,3-dihydro-1H-inden-2-ol (**IIf**) (0.239 g, 1.60 mmol) in 2-Propanol (10 mL), was added DIPEA (0.931 g, 5.34 mmol) at room temperature, under nitrogen atmosphere and the resulting reaction mixture was

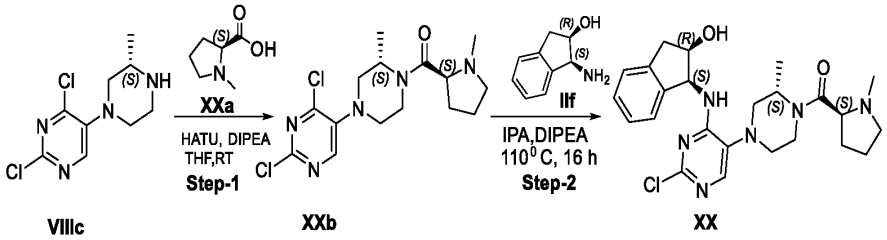
heated at 100 °C for 2 hour. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and concentrated under reduced pressure to afford the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 70% ethyl acetate in petroleum ether to yield the title compound **(XVIII)** as a pale-yellow gummy liquid; Yield: (0.3 g, 34.3%). **LC_MS:** Calc. for $C_{24}H_{31}ClN_6O_3$: 487.00; Obs.: 487.2[M^++H].

Synthesis of (1S,2R)-1-((2-((1-allyl-1H-indazol-6-yl) amino)-5-(4-aminopiperidin-1-yl) pyrimidin-4-yl) amino)-2,3-dihydro-1H-inden-2-ol (XIX)



[000144] To a stirred solution tert-butyl (1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-4-yl) carbamate **(XV)** (0.150 g, 0.326 mmol), 1-allyl-1H-indazol-6-amine **(XVI)** (0.056 g, 0.326 mmol) in NMP (3 mL) was added 4M HCl in dioxane (0.5 mL, 0.652 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 7 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (10 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product **XIX** as a yellow gummy liquid; Yield: (0.210 g, 82%). **LC_MS:** Calc. for $C_{28}H_{32}N_8O$:496.62; Obs.: 497.2 [M^++H].

Synthesis of 2-chloro-4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-5-((S)-3-methyl-4-(methyl-L-prolyl) piperazin-1-yl) pyrimidine. (XX)



Step-1: Synthesis of 2,4-dichloro-5-((*S*)-3-methyl-4-(methyl-L-prolyl) piperazin-1-yl) pyrimidine (XXb):

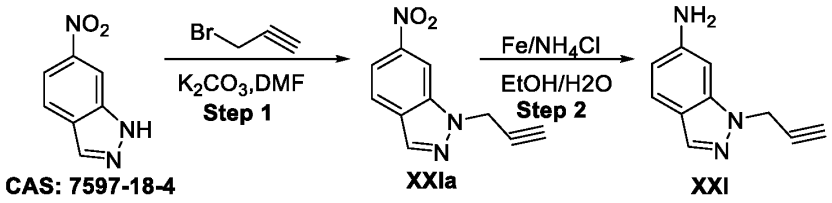
[000145] To a solution of (*S*)-2,4-dichloro-5-(3-methylpiperazin-1-yl) pyrimidine **(VIIIc)** (0.200 g, 0.809 mmol) in THF (10 mL), were added DIPEA (0.352 mL, 2.02 mmol) followed by HATU (0.369 g, 0.971 mmol) and methyl-L-proline **(XXa)** (0.125 g, 0.971 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with water (20 mL). The aqueous layer was extracted with ethyl acetate (30 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated under a *vacuum* to get the crude product as yellow gummy mass. The obtained crude product was taken to next step without purification to afford the title compound **(XXb)** as brown liquid; Crude Yield: (0.200 g, 16.1%). **LC_MS**: Calc. for $C_{15}H_{21}C_{l2}N_5O$: 358.27; Obs.: 358.2 [M^++H].

Step-2: Synthesis of 2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)-5-((*S*)-3-methyl-4-(methyl-L-prolyl)piperazin-1-yl)pyrimidine (XX):

[000146] To a solution 2,4-dichloro-5-((*S*)-3-methyl-4-(methyl-L-prolyl)piperazin-1-yl)pyrimidine (**XXb**) (0.350 g, 0.977 mmol) and (1S,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (**IIf**) (0.146 g, 0.977 mmol) in 2-Propanol (10 mL), was added DIPEA (0.68 mL, 3.91 mmol) at room temperature, under nitrogen atmosphere and the resulting reaction mixture was heated at 100 °C for 2 hours. The reaction progress was monitored by TLC. After completion of the reaction, the

reaction mixture was cooled to room temperature, and concentrated under reduced pressure to afford the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 70% ethyl acetate in petroleum ether to yield the title compound **(XX)** as an off-white solid; Yield: (0.200 g, 10%). **LC_MS:** Calc. for $C_{24}H_{31}ClN_6O_2$: 471.00; Obs.: 471.2 [M^++H].

Synthesis of 1-(prop-2-yn-1-yl)-1H-indazol-6-amine (XXI)



Step-1: Synthesis of 6-nitro-1-(prop-2-yn-1-yl)-1*H*-indazole (XXIa):

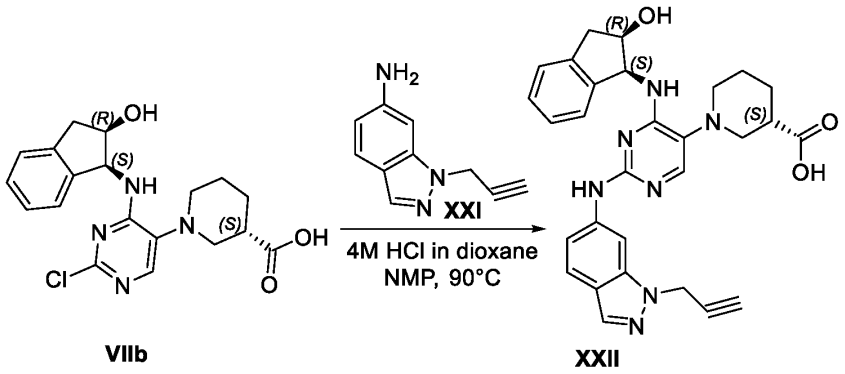
[000147] To a stirred solution of 6-nitro-1*H*-indazole (CAS 70315-70-7, 2.00 g, 12.26 mmol) in DMF (20 mL) under nitrogen atmosphere was added potassium carbonate (3.39 g, 24.52 mmol) followed by 3-bromoprop-1-yne (CAS:106-96-7; 1.06 mL, 12.26 mmol) at room temperature. The resulting reaction mixture was heated at 80 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (100 mL), and extracted with ethyl acetate (2 x 100 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 13% ethyl acetate in petroleum ether to yield the title compound **XXIa** as an off-white solid; Yield: (1.00 g, 38.92%). **LC_MS:** Calc. for $C_{10}H_7N_3O_2$: 201.18; Obs.: 202.1 [M^++H]. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 8.83 (s, 1H), 8.38 (s, 1H), 8.08-8.00 (m, 2H), 5.56 (s, 2H), 3.47 (m, 1H).

Step-2: Synthesis of 1-(prop-2-yn-1-yl)-1*H*-indazol-6-amine (XXI)

[000148] To a stirred solution of 6-nitro-1-(prop-2-yn-1-yl)-1*H*-indazole **(XXIa)** (1.00 g, 4.97 mmol) in ethanol (10 mL) under nitrogen atmosphere was added NH_4Cl (1.32 g, 24.85 mmol) in 15 mL of water followed by iron (1.38 g,

24.85 mmol). The reaction mixture was heated at 80 °C for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a Celite bed and washed with ethyl acetate (70 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The residue was diluted with water (70 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product. The crude product was triturated with petroleum ether to get the title compound **XXI** as a brown liquid; Yield: (0.8 g, 90.9 %). **LC_MS:** Calc. for $C_{10}H_9N_3$: 171.20; Obs.: 172.1 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 7.74 (s, 1H), 7.38-7.36 (m, 1H), 6.55-6.52 (m, 2H), 5.41 (s, 2H), 5.06(d, J = 2.40 Hz,), 3.32 (s, 1H).

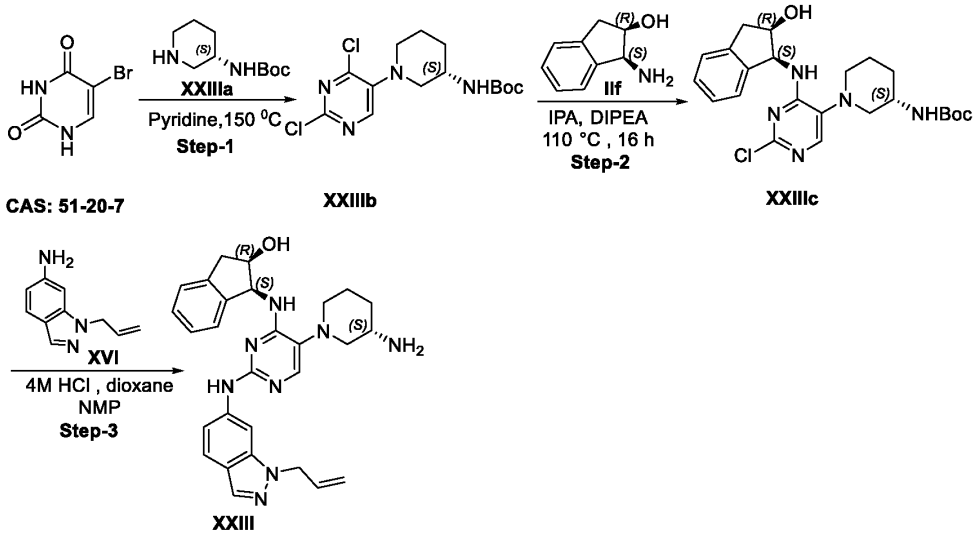
Synthesis of (S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylic acid (XXII)



[000149] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)** (0.25 g, 0.64 mmol) and 1-(prop-2-yn-1-yl)-1*H*-indazol-6-amine **(XXI)** (0.11g, 0.64 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.3 mL, 1.29 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 2 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mass was cooled to room temperature, diluted with water (5 mL), neutralized by triethylamine, and extracted with ethyl

acetate (2 x 10 mL). The organic phase was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product (**XXII**) as a brown liquid; Yield: (0.35 g, crude). **LC_MS: Calc**. for $C_{29}H_{29}N_7O_3$: 523.60; Obs.: 524.2.2 [M^++H].

Synthesis of N-((S)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-3-yl) propionamide (XXIII)



Step-1: Synthesis of *tert*-butyl (*S*)-(1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) piperidin-3-yl) carbamate (XXIIIb)

[000150] A solution of 5-bromopyrimidine-2,4(1*H*,3*H*)-dione (CAS: 51-20-7, 10.00 g, 52.36 mmol) and *tert*-butyl (*S*)-piperidin-3-ylcarbamate **(XXIIIa)** (12.58 g, 62.83 mmol) in pyridine (50 mL) was irradiated at 150 °C for 1.5 hours in the microwave. The progress of the reaction was monitored by UPLC. After completion of the reaction, acetonitrile (100 mL) was added, stirred for 15 minutes, filtered, and dried under vacuum to afford the crude product. The crude product was triturated with methyl tert-butyl ether (50 mL) to get the pure compound **XXIIIb** as a brown solid. The crude product was taken to the next step without further purification; Yield: (7.0 g, crude). **LCMS**: Calc. for $C_{14}H_{22}N_4O_4$: 310.35; Obs.: 309.2 [M^+-H].

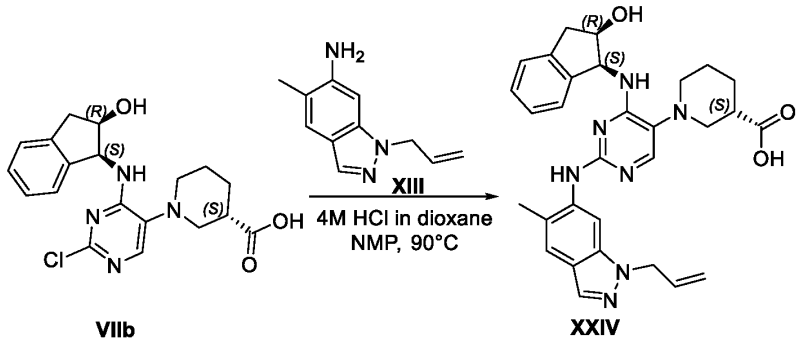
Step-2: Synthesis of tert-butyl ((*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-3-yl) carbamate (XXIIIc):

[000151] To a solution tert-butyl (*S*)-(1-(2,4-dichloropyrimidin-5-yl) piperidin-3-yl) carbamate **(XXIIIb)** (0.650 g, 1.872 mmol) and (1*S*,2*R*)-1-amino-2,3-dihydro-1H-inden-2-ol **(IIf)** (0.335 g, 2.24 mmol) in 2-Propanol (10 mL), was added DIPEA (0.725 g, 5.616 mmol) at room temperature, under nitrogen atmosphere and the resulting reaction mixture was heated at 100 °C for 2 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and concentrated under reduced pressure to afford the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 70% ethyl acetate in petroleum ether to yield the title compound **(XXIIIc)** as an off-white solid; Yield: (0.4 g, 40%). **LC_MS:** Calc. for $C_{23}H_{30}ClN_5O_3$: 459.98; Obs.: 460.2 [M^++H].

Step-3: Synthesis of (1*S*,2*R*)-1-((2-((1-allyl-1H-indazol-6-yl) amino)-5-((*S*)-3-aminopiperidin-1-yl) pyrimidin-4-yl) amino)-2,3-dihydro-1H-inden-2-ol (XXIII)

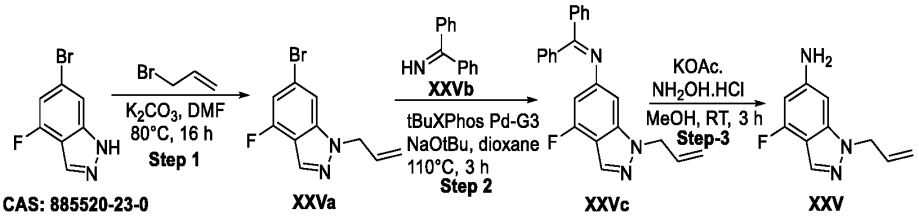
[000152] To a stirred solution tert-butyl ((*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidin-3-yl)carbamate **(XXIIIc)** (0.20 g, 0.43 mmol) and 1-allyl-1H-indazol-6-amine **(XVI)** (0.075 g, 0.43 mmol) in NMP (4 mL) was added 4M HCl in dioxane (0.217 mL, 0.869 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 6 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product. The obtained crude product was taken to next step without purification to afford the title compound **(XXIII)** as a pale-yellow gummy liquid; Crude Yield: (0.200 g). **LC_MS**: Calc. for $C_{28}H_{32}N_8O$: 496.62; Obs.: 495.2 [M^+-H].

Synthesis of (S)-1-(2-((1-allyl-5-methyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylic acid. (XXIV)



[000153] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)** (0.20 g, 0.51 mmol) and 1-allyl-5-methyl-1H-indazol-6-amine **(XIII)** (0.096g, 0.51 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.2 mL, 1.03 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 2 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mass was cooled to room temperature, diluted with water (5 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 10 mL). The organic phase was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product (**XXIV**) as a brown liquid; Yield: (0.20 g, 30.0%). **LC_MS: Calc**. for $C_{30}H_{33}N_7O_3$: 539.64; Obs.: 540.2 [M^++H].

Synthesis of 1-allyl-4-fluoro-1H-indazol-6-amine (XXV)



Step-1: Synthesis of 1-allyl-6-bromo-4-fluoro-1*H*-indazole (XXVa):

[000154] To a stirred solution of 6-bromo-4-fluoro-1H-indazole (CAS: 885520-23-0, 3.0 g, 13.951 mmol) in DMF (20 mL) under nitrogen atmosphere was added potassium carbonate (2.89 g, 20.911 mmol) followed by 3-bromoprop-1-ene (1.68 g, 13.886 mmol) at room temperature. The resulting reaction mixture was heated at 80 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (2 x 100 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 7% ethyl acetate in petroleum ether to yield the title compound **XXVa** as a pale brown solid; Yield: (0.85 g, 23.88%). **LC_MS:** Calc. for $C_{10}H_8BrFN_2$: 255.09; Obs.: 257.0 [M^+-H]. **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ 8.25 (s, 1H), 7.89 (s, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.04-6.00 (m, 1H), 5.19 (d, J = 6.00 Hz, 1H), 5.19-5.14 (m, 2H), 5.08 (s, 1H).

Step-2: Synthesis of N-(1-allyl-4-fluoro-1*H*-indazol-6-yl)-1,1-diphenylmethanimine (XXVc)

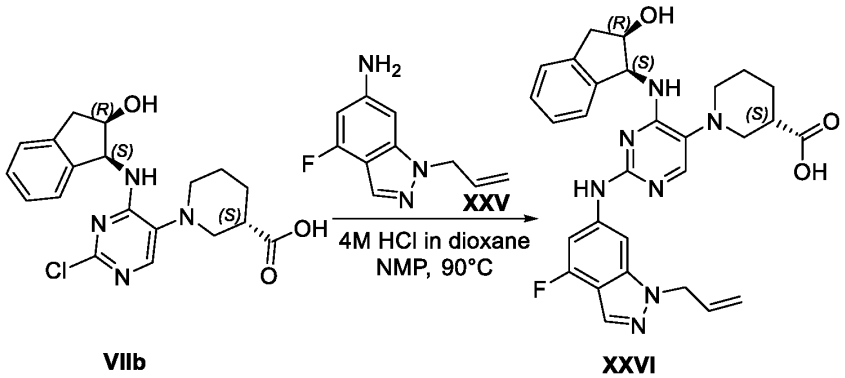
[000155] To a stirred solution of 1-allyl-6-bromo-4-fluoro-1H-indazole **(XXVa)** (0.6 g, 2.352 mmol) in 1,4-dioxane (30 mL), Benzophenone imine **(XXVb)** (0.47 g, 2.593 mmol) and sodium tert-butoxide (0.34 g, 3.537 mmol) were added under nitrogen atmosphere. The reaction mixture was degassed for 3 minutes followed by tBuXPhos Pd-G3 (0.2 g, 0.236 mmol) was added. The reaction mixture was heated at 110 °C for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a celite bed and washed with ethyl acetate (100 mL). The filtrate was diluted with water (20 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 20% ethyl acetate in petroleum ether to yield the title compound **XXVc** as a pale-yellow liquid; Yield: (1.3 g, crude). **LC_MS:** Calc. for $C_{23}H_{18}FN_3$: 355.42; Obs.:356.1 [M^++H]. **^{1}H NMR (300 MHz, DMSO-d$_6$):** δ 8.01 (s, 1H), 7.76-7.73 (m, 3H), 7.62-7. 51 (m, 3H), 7.32-7.30 (m, 2H), 7.20 (d, J

= 4.40 Hz, 2H), 6.72 (s, 1H), 6.44-6.40 (m, 1H), 5.90 (m, 1H), 5.1-5.0 (m, 2H), 4.93-4.88 (m, 2H),

Step-3: Synthesis of 1-allyl-4-fluoro-1*H*-indazol-6-amine (XXV)

[000156] To a stirred solution of N-(1-allyl-4-fluoro-1*H*-indazol-6-yl)-1,1-diphenylmethanimine **(XXVc)** (1.2 g, 3.376 mmol) in methanol (20 mL), potassium acetate (0.83 g, 8.457 mmol) followed by Hydroxylamine hydrochloride (0.47 g, 6.763 mmol) were added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic layer was further washed with brine (50 mL), dried over Na_2SO_4, filtered, and evaporated under vacuo to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 18% ethyl acetate in petroleum ether to yield the title compound **XXV** as a pale brown solid; Yield: (0.41 g, 63.56%). **LC_MS:** Calc. for $C_{10}H_{10}FN_3$: 191.21; Obs.:192.1 [M^++H]. **^{1}H NMR (300 MHz, DMSO-d$_6$):** δ 7.82 (s, 1H), 6.27-6.26 (m, 2H), 6.00-5.93 (m, 1H), 5.58 (br s, 2H), 5.16-5.13 (m, 1H), 4.97-4.92 (m, 1H), 4.82 (br s, 2H).

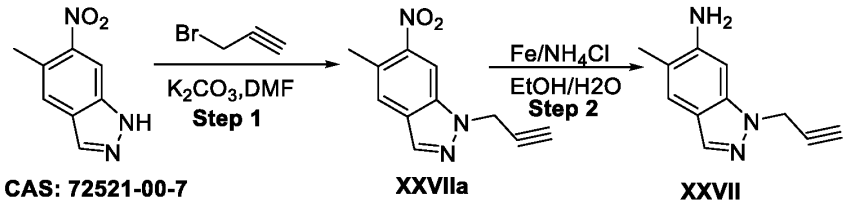
<u>Synthesis of (S)-1-(2-((1-allyl-4-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylic acid (XXVI)</u>



[000157] To a stirred solution (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)**

(0.15 g, 0.385 mmol), 1-allyl-4-fluoro-1*H*-indazol-6-amine (**XXV**) (0.074 g, 0.385 mmol) in NMP (2 mL) was added 4M HCl in dioxane (0.2 mL, 0.8 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (1 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product **XXVI** as brown liquid. The obtained crude product was as such taken for next step without purification. Yield: (0.18 g, crude). **LC_MS**: Calc. for $C_{29}H_{30}FN_7O_3$: 543.60; Obs.: 544.3 [M^++H].

Synthesis of 5-methyl-1-(prop-2-yn-1-yl)-1H-indazol-6-amine (XXVII)



CAS: 72521-00-7 **XXVIIa** **XXVII**

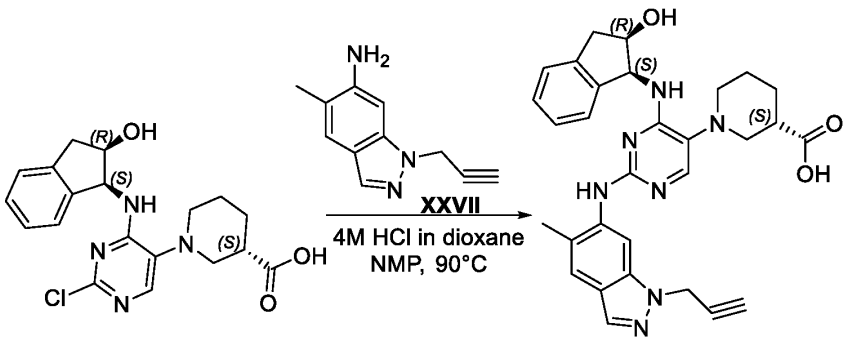
Step-1: Synthesis of 5-methyl-6-nitro-1-(prop-2-yn-1-yl)-1H-indazole (XXVIIa):

[000158] To a stirred solution of 5-methyl-6-nitro-1*H*-indazole (CAS 72521-00-7, 1.00 g, 5.644 mmol) in DMF (10 mL) under nitrogen atmosphere was added potassium carbonate (1.56 g, 11.28 mmol) followed by 3-bromoprop-1-yne (0.671 g, 5.644 mmol) at room temperature. The resulting reaction mixture was heated at 80 °C for 4 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (100 mL), and extracted with ethyl acetate (2 x 100 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 30 % ethyl acetate in petroleum ether to yield the title compound **XXVIIa** as a pale-yellow solid; Yield: (0.6 g, 50%). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 8.54 (s, 1H), 8.26 (s, 1H), 7.89 (s, 1H), 5.46 (s, 2H), 3.45-3.44 (m, 1H), 2.56 (s, 3H

Step-2: Synthesis of 5-methyl-1-(prop-2-yn-1-yl)-1H-indazol-6-amine (XXVII)

[000159] To a stirred solution of 5-methyl-6-nitro-1-(prop-2-yn-1-yl)-1H-indazole **(XXVIIa)** (0.600 g, 2.78 mmol) in ethanol (20 mL) under nitrogen atmosphere was added NH_4Cl (0.894 g, 16.73 mmol) in 6.7 mL of water followed by iron (0.467 g, 8.364 mmol). The reaction mixture was heated at 80 °C for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a Celite bed and washed with ethyl acetate (70 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The residue was diluted with water (70 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product. The crude product was triturated with petroleum ether to get the title compound **XXVII** as a pale brown solid; Yield: (0.4 g, 76%). **LC_MS:** Calc. for $C_{11}H_{11}N_3$: 185.23; Obs.: 186.2 [M^++H].

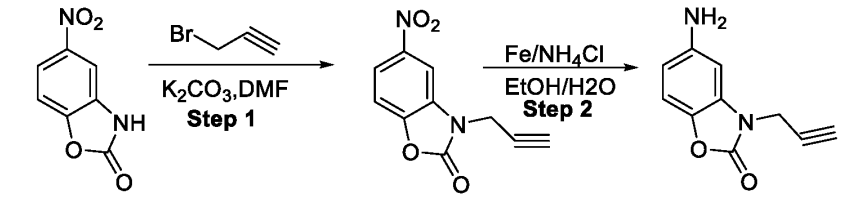
Synthesis of (S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((5-methyl-1-(prop-2-yn-1-yl)-1H-indazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylic acid (XXVIII)



[000160] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)** (0.25 g, 0.64 mmol) and 5-methyl-1-(prop-2-yn-1-yl)-1*H*-indazol-6-amine **(XXVII)** (0.12g, 0.64 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.3 mL, 1.29 mmol) at room temperature, under nitrogen atmosphere. The resulting

reaction mixture was heated to 90 °C for 16 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mass was cooled to room temperature, diluted with water (5 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 10 mL). The organic phase was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product **(XXVIII)** as a brown liquid; Yield: (0.16 g, crude). **LC_MS: Calc**. for $C_{30}H_{31}N_7O_3$: 537.62; Obs.: 538.3 [M^++H].

Synthesis of 5-amino-3-(prop-2-yn-1-yl) benzo[d]oxazol-2(3H)-one (XXIX)



CAS:3889-13-2 **XXIXa** **XXIX**

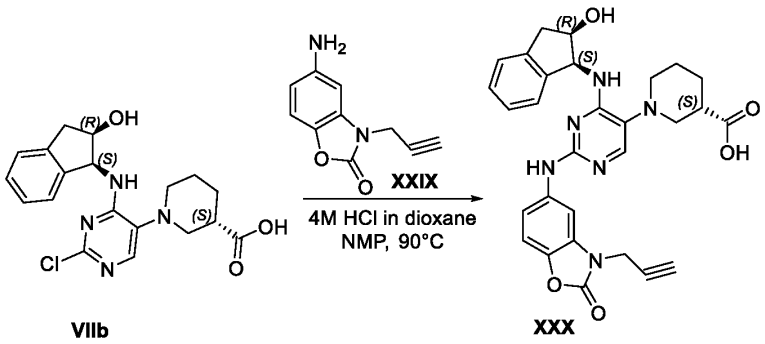
[000161] Step-1: Synthesis of 5-nitro-3-(prop-2-yn-1-yl) benzo[d]oxazol-2(3*H*)-one (XXIXa):

[000162] To a stirred solution of 5-nitrobenzo[d]oxazol-2(3*H*)-one (CAS 3889-13-2, 2.00 g, 11.10 mmol) in DMF (20 mL) under nitrogen atmosphere was added potassium carbonate (3.04 g, 22.09 mmol) followed by 3-bromoprop-1-yne (1.48 mL, 16.65 mmol) at room temperature. The resulting reaction mixture was heated at 80 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (100 mL), and extracted with ethyl acetate (2 x 100 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 13% ethyl acetate in petroleum ether to yield the title compound **XXIXa** as an off-white solid; Yield: (1.00 g, 38.92%). **LC_MS:** Calc. for $C_{10}H_6N_2O_4$: 218.17; Obs.: 218.9 [M^++H].

Step-2: Synthesis of 5-amino-3-(prop-2-yn-1-yl) benzo[d]oxazol-2(3*H*)-one (XXIX):

[000163] To a stirred solution of 5-nitro-3-(prop-2-yn-1-yl) benzo[d]oxazol-2(3*H*)-one **(XXIXa)** (2.00 g, 9.17mmol) in ethanol (10 mL) under nitrogen atmosphere was added NH_4Cl (2.45 g, 45.84 mmol) in 15 mL of water followed by iron (2.56 g, 45.84 mmol). The reaction mixture was heated at 80 °C for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a Celite bed and washed with ethyl acetate (70 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The residue was diluted with water (70 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product. The crude product was triturated with petroleum ether to get the title compound **XXIX** as a brown liquid; Yield: (1.00 g, 43%). **LC_MS:** Calc. for $C_{10}H_9N_3$: 171.20; Obs.: 172.1 [M^++H]. **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ 7.00 (d, J = 8.40 Hz, 1H), 6.50 (s, 1H), 6.32 (s, 1H), 5.16 (s, 2H), 4.60 (s, 2H), 3.43 (s, 1H).

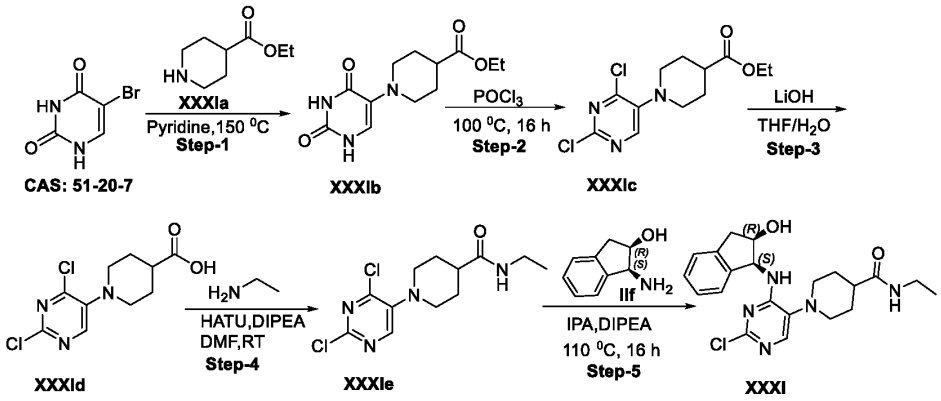
Synthesis of (S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((2-oxo-3-(prop-2-yn-1-yl)-2,3-dihydrobenzo[d]oxazol-5-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylic acid (XXX)



[000164] To a stirred solution of benzo1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)** (0.25 g, 0.64 mmol) and 5-amino-3-(prop-2-yn-1-yl)benzo[d]oxazol-2(3H)-one **(XXIX)** (0.12g, 0.64 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.3 mL, 1.29 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 2 hours. The reaction progress

was monitored by UPLC. After completion of the reaction, the reaction mass was cooled to room temperature, diluted with water (5 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 10 mL). The organic phase was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product **(XXX)** as a brown liquid; Yield: (0.30 g, crude). **LC_MS: Calc**. for $C_{29}H_{28}N_6O_5$: 540.58; Obs.: 541.2 [M^++H].

Synthesis of 1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-ethylpiperidine-4-carboxamide (XXXI)



Step-1: Synthesis of ethyl 1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) piperidine-4-carboxylate (XXXIb)

[000165] A 20 mL Biotage vial was charged with 5-bromopyrimidine-2,4(1*H*,3*H*)-dione (CAS: 51-20-7, 3.00 g, 15.71 mmol), ethyl piperidine-4-carboxylate **XXXIa** (2.96 g, 18.85 mmol) and pyridine (10 mL) were added. The resulting reaction mixture was irradiated under the microwave at 150 °C for 1.5 hours. The reaction progress was monitored by UPLC. The reaction mixture was cooled to room temperature, diluted with acetonitrile, and stirred for 15 minutes, filtered, and dried under vacuum to afford **XXXIb** as an off-white solid; Yield: (2.55 g, 57.6%). **LC_MS:** Calc. for $C_{12}H_{17}N_3O_4$: 267.28; Obs.: 266.1[M-H]$^+$ and 268.0 [M^++H]; **^{1}H-NMR (400 MHz, DMSO-*d6*):** δ 11.02 (s, 1H), 10.43 (d, *J* = 6.80 Hz, 1H), 6.82 (d, *J* = 9.60 Hz, 1H), 6.71 (s, 1H), 3.21 (t, *J* = 15.20 Hz, 2H),

2.36 (t, *J* = 14.80 Hz, 2H), 1.72 (d, *J* = 14.80 Hz, 2H), 1.46 (t, *J* = 16.00 Hz, 2H), 1.39 (s, 9H).

Step-2: Synthesis of ethyl 1-(2,4-dichloro-1,2-dihydropyrimidin-5-yl) piperidine-4-carboxylate (XXXIc)

[000166] To ethyl 1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) piperidine-4-carboxylate **(XXXIb)** (1.00 g, 3.741 mmol) was added $POCl_3$ (16 g, 0.11 mol) at room temperature under nitrogen atmosphere. The resulting reaction mixture was heated to 100 °C for 16 hours. The reaction mixture was diluted with water and ethyl acetate, separated into two layers, and the aqueous layer was extracted with ethyl acetate (2 x 50mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product as a brown gummy solid. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 20% ethyl acetate in petroleum ether to yield the title compound **XXXIc** as a white solid; Yield: (0.25 g, 21%); **UPLC_MS:** Calc. for $C_{10}H_{15}Cl_2N_3O_2$: 304.17; Obs.: 303.9 [M^++H]; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.21 (s, 1H), 4.53 (s, 1H), 3.67 (s, 1H), 3.42 (d, *J* = 12.40 Hz, 2H), 2.94-2.87 (m, 2H), 2.10 (q, *J* = 12.80 Hz, 1H), 1.61-1.66 (m, 3H), 1.47 (m, 9H).

Step-3: Synthesis of 1-(2,4-dichloro-1,2-dihydropyrimidin-5-yl) piperidine-4-carboxylic acid (XXXId)

[000167] To a solution of ethyl 1-(2,4-dichloro-1,2-dihydropyrimidin-5-yl) piperidine-4-carboxylate **(XXXIc)** (0.250 g, 0.822 mmol) in mixture of THF (2 mL) and water (2 mL) was added $LiOH.H_2O$ (0.052 g, 1.23 mmol) at room temperature under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC and UPLC. The reaction mixture was diluted with water, neutralized with 1.5N HCl, and the product was extracted with ethyl acetate (2 x 20mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude desired compound **XXXId** as a white solid; Yield: (0.21 g, 62%). **UPLC_MS** Calc. for $C_{10}H_{13}Cl_2N_3O_2$: 276.12; Obs.: 275.9 [M^++H] and 273.9 [M^+-H].

Step-4: Synthesis of 1-(2,4-dichloro-1,2-dihydropyrimidin-5-yl)-*N*-ethylpiperidine-4-carboxamide (XXXIe)

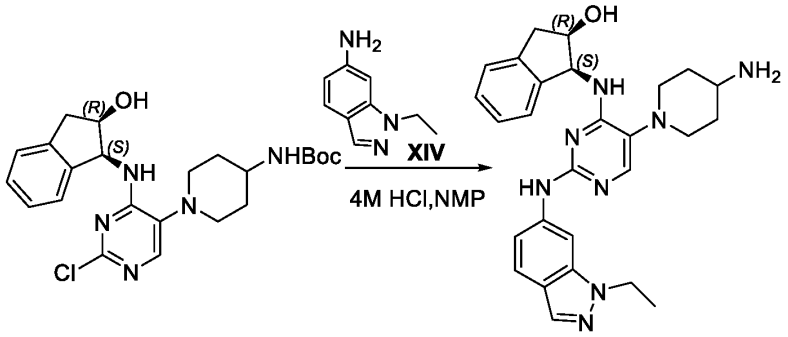
[000168] To a solution of 1-(2,4-dichloro-1,2-dihydropyrimidin-5-yl) piperidine-4-carboxylic acid **(XXXId)** (0.200 g, 0.724 mmol) and ethane amine (0.049 g, 1.09 mmol) in THF (5 mL), were added DIPEA (0.234 g, 1.81 mmol) followed by HATU (0.330 g, 0.869 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 16 hours. The reaction progress monitored by TLC and UPLC. The reaction mixture was quenched with 10% aq. $NaHCO_3$, stirred for 30 minutes, and the precipitated solid was filtered, and dried under vacuum to afford the crude compound **XXXIe** as an off-white solid; Yield: (0.105 g, 46.6%). **UPLC_MS** Calc. for $C_{12}H_{16}Cl_2N_4O$: 303.19; Obs.: 303.0 [M^++H] and 305.0 [M^++2]; **^{1}H-NMR (400 MHz, DMSO-*d6*):** δ 8.52 (s, 1H), 7.84 (t, *J* = 5.20 Hz, 1H), 3.40 (d, *J* = 12.00 Hz, 2H), 3.11-3.04 (m, 2H), 2.82-2.79 (m, 2H), 2.27-2.22 (m, 1H), 1.69-1.77 (m, 4H), 1.01 (t, *J* = 7.20 Hz, 3H).

Step-5: Synthesis of 1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino) pyrimidin-5-yl)-*N*-ethylpiperidine-4-carboxamide (XXXI)

[000169] To a solution 1-(2,4-dichloro-1,2-dihydropyrimidin-5-yl)-*N*-ethylpiperidine-4-carboxamide **(XXXIe)** (0.20 g, 0.660 mmol) and (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol **(IIf)** (0.118 g, 0.792 mmol) in 2-propanol (10 mL), was added DIPEA (0.256 g, 1.98 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 110 °C for 24 hours. The reaction progress was monitored by UPLC. The reaction mixture was concentrated under reduced pressure to afford the crude product as a brown gummy solid. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 100% ethyl acetate to yield the title compound **XXXI** as an off-white solid; Yield: (0.2 g, 66%). **UPLC_MS**: Calc. for $C_{21}H_{26}ClN_5O_2$: 415.92; Obs.: 416.0 [M^++H] and 413.9 [M^+-H]; **^{1}H-NMR (400 MHz, DMSO-*d6*):** δ 7.87 (s, 1H), 7.80 (t, J = 5.20 Hz, 1H), 7.18-7.26 (m, 4H), 6.75 (d, *J* = 8.40 Hz, 1H), 5.54 (d, *J* = 5.20 Hz, 1H), 5.42 (q, *J* = 5.20 Hz, 1H), 4.54 (d, *J* = 4.40 Hz, 1H), 3.04-3.12 (m,

5H), 2.86 (d, *J* = 16.40 Hz, 1H), 2.67-2.62 (m, 2H), 2.21-2.17 (m, 1H), 1.72-1.62 (m, 4H), 0.99 (t, *J* = 7.20 Hz, 3H).

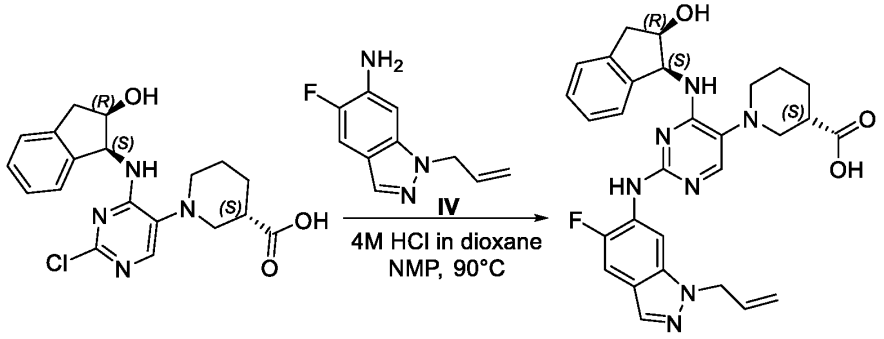
Synthesis of (1S,2R)-1-((5-(4-aminopiperidin-1-yl)-2-((1-ethyl-1H-indazol-6-yl) amino) pyrimidin-4-yl) amino)-2,3-dihydro-1H-inden-2-ol (XXXII)



XV **XXXII**

[000170] To a stirred solution tert-butyl (1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidin-4-yl)carbamate **(XV)** (0.150 g, 0.326 mmol), 1-ethyl-1H-indazol-6-amine **(XIV)** (0.052 g, 0.326 mmol) in NMP (5 mL) was added 4M HCl in dioxane (0.163 mL, 0.652 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to afford the desired product (**XXXII**) as brown gummy solid; Yield: (0.15 g, 49%). **LC_MS**: Calc. for $C_{27}H_{32}N_8O$: 484.61; Obs.: 485.3 [M^++H];

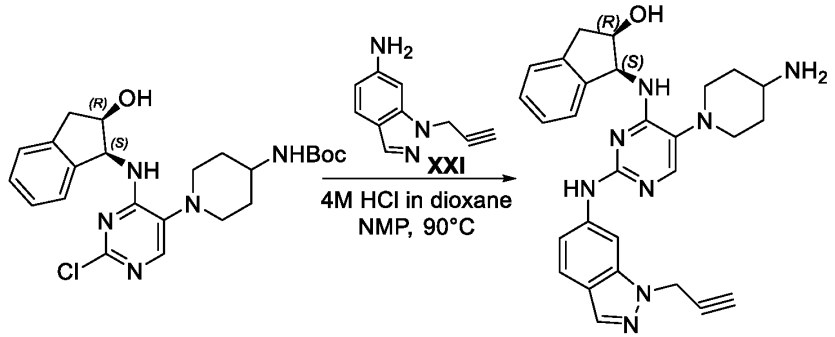
Synthesis of (S)-1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylic acid (XXXIII)



VIIb XXXIII

[000171] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)** (0.600 g, 1.543 mmol) and 1-allyl-5-fluoro-1H-indazol-6-amine **(IV)** (0.295 g, 1.543 mmol) in NMP (3 mL) was added 4M HCl in dioxane (0.174 mL, 0.697 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 5 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product **XXXIII** as pale-yellow liquid. Yield: (0.8 g, 95 %). **LC_MS:** Calc. for $C_{29}H_{30}FN_7O_3$:543.60; Obs.: 544.3 [M^++H].

<u>Synthesis of (1S,2R)-1-((5-(4-aminopiperidin-1-yl)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl) amino) pyrimidin-4-yl) amino)-2,3-dihydro-1H-inden-2-ol (XXXIV)</u>

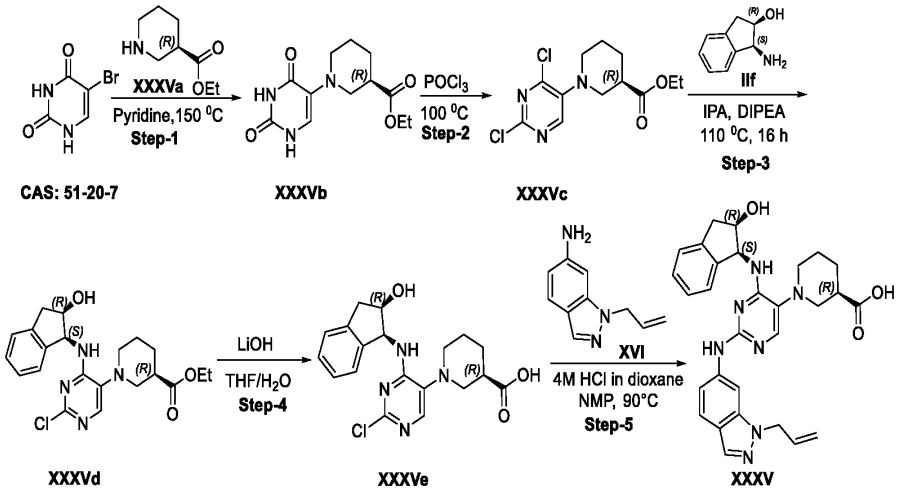


XV XXXIV

[000172] To a stirred solution tert-butyl (1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino)pyrimidin-5-yl)piperidin-4-yl)carbamate **(XV)**

(0.15 g, 0.32 mmol), 1-(prop-2-yn-1-yl)-1*H*-indazol-6-amine **(XXI)** (0.05 g, 0.32 mmol) in NMP (3 mL) was added 4M HCl in dioxane (0.3 mL) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (10 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 40 mL). The combined organic layer was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product (**XXXIV**). Yield: (0.18 g, crude). Note: The crude product was as such taken for next step without purification. **LC_MS**: Calc. for $C_{28}H_{30}N_8O$: 494.60; Obs.: 495.1[M^++H].

Synthesis of (R)-1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylic acid (XXXV)



Step-1: Synthesis of ethyl (*R*)-1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) piperidine-3-carboxylate (XXXVb):

[000173] To a solution of 5-bromopyrimidine-2,4(1*H*,3*H*)-dione (CAS: 51-20-7, 4.00 g, 20.94 mmol) and ethyl (*R*)-piperidine-3-carboxylate **(XXXVa)** (3.30 g, 20.96 mmol) in pyridine (50 mL) was irradiated at 150 °C for 1.5 hours in the microwave. The progress of the reaction was monitored by UPLC. After completion of the reaction, acetonitrile (100 mL) was added, stirred for 15 minutes,

filtered, and dried under a vacuum that affords the crude product. The crude product was triturated with methyl tert-butyl ether (50 mL) to get the pure compound **XXXVb** as an off-white solid; Yield: (3.00 g, 70.3%). **LCMS**: Calc. for $C_{12}H_{17}N_3O_4$: 267.28; Obs.:268.2 [M^++H].

Step-2: Synthesis of ethyl (*R*)-1-(2,4-dichloropyrimidin-5-yl) piperidine-3-carboxylate (XXXVc):

[000174] A solution of ethyl (*R*)-1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) piperidine-3-carboxylate **(XXXVb)** (3.00 g, 11.22 mmol) in $POCl_3$ (45 mL,482.6 mmol) was heated at 100 °C for 16 hours under a nitrogen atmosphere. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was basified using 10% $NaHCO_3$ solution (200 mL). The aqueous layer was extracted with ethyl acetate (120 mL x 3). The organic layer was dried over Na_2SO_4 and concentrated under a *vacuum* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 20% ethyl acetate in petroleum ether to yield the title compound **XXXVc** as a pale-yellow liquid; Yield: (2.00 g, 58.5%). **LC_MS**: Calc. for $C_{12}H_{15}Cl_2N_3O_2$: 304.17; Obs.: 304.1 [M^++H].

Step-3: Synthesis of ethyl (*R*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylate (XXXVd);

[000175] To a stirred solution of Ethyl (*S*)-1-(2,4-dichloropyrimidin-5-yl) piperidine-3-carboxylate **(XXXVc)** (2.0 g, 6.58 mmol) in IPA (30 mL) was added DIPEA (3.0 mL, 16.44 mmol), followed by (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol **(IIf)** (0.98 g, 6.58 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated at 110 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and concentrated under reduced pressure to afford the crude product **(XXXVd).** The crude material was purified by silica gel (Biotage) column chromatography by eluting with 80-85% ethyl acetate in petroleum ether to yield the title compound as a pale-brown liquid;

Yield: (1.80 g, 62.02%). **LC_MS:** Calc. for $C_{21}H_{25}ClN_4O_3$: 416.91; Obs.: 417.2[M^++H].

Step-4: Synthesis of (*R*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylic acid (XXXVe):

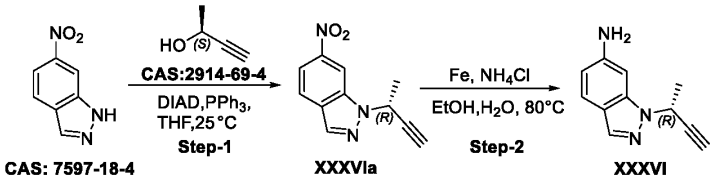
[000176] To a stirred solution of ethyl (*R*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylate **(XXXVd)** (4.32 g, 4.32 mmol) in a mixture of THF (15 mL) and water (15 mL) was added LiOH.H_2O (0.300 g, 6.62 mmol) at room temperature under nitrogen atmosphere. The resulting reaction mixture was allowed to stir at room temperature for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (50 mL), neutralized with 1.5N HCl, and the product was extracted with ethyl acetate (2 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product **XXXVe** as an off-white solid. The crude product was taken to the next step without further purification; Yield: (1.200 g, 57.30%). **LC_MS**: Calc. for $C_{19}H_{21}ClN_4O_3$: 388.85; Obs.: 389.1[M^++H].

Step-5: Synthesis of (*R*)-1-(2-((1-allyl-1*H*-indazol-6-yl) amino)-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide) (XXXV):

[000177] To a stirred solution of (*R*)-1-(2-((1-allyl-1*H*-indazol-6-yl)amino)-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(XXXVe)** (0.30 g, 0.77 mmol) and 1-allyl-1H-indazol-6-amine **(XVI)** (0.13g, 0.77 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.3 mL, 1.54 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 2 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mass was cooled to room temperature, diluted with water (5 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 10 mL). The organic phase was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude

product (**XXXV**) as a brown liquid; Yield: (0.31 g, crude). **LC_MS: Calc**. for $C_{29}H_{31}N_7O_3$: 525.61; Obs.: 526.3 [M^++H].

Synthesis of (*R*)-1-(but-3-yn-2-yl)-1*H*-indazol-6-amine (XXXVI)



Step-1: Synthesis of (*R*)-1-(but-3-yn-2-yl)-6-nitro-1*H*-indazole (XXXVIa):

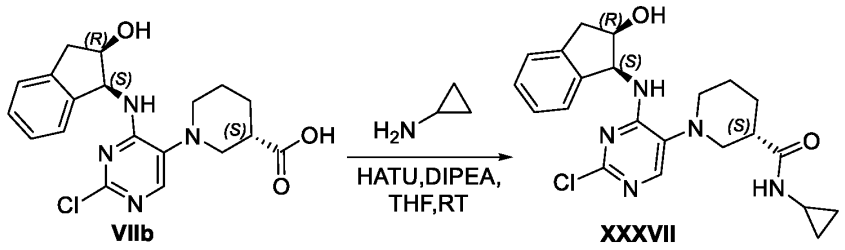
[000178] To a stirred solution of 6-nitro-1*H*-indazole (CAS: 7597-18-4; 3.0 g, 18 mmol) and (*S*)-but-3-yn-2-ol (CAS: 2914-69-4; 1.54g, 22mmol) in THF (30 mL) under nitrogen atmosphere, was added Triphenylphosphine (5.78 g, 22 mmol) at 0 °C, then added DIAD (4.46 g, 28 mmol). The resulting reaction mixture was allowed to stir at 25 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (40 mL), and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 40% ethyl acetate in petroleum ether to yield the title compound **XXXVIa** as a yellow solid; Yield: (2.3 g, 58%). LC_MS: Calc. for $C_{11}H_9N_3O_2$: 215.21; Obs: 216.1 [M^++H]. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 8.87-8.87 (m, 1H), 8.40-8.40 (m, 1H), 8.07-7.99 (m, 2H), 6.18-6.12 (m, 1H), 3.54 (d, J = 2.40 Hz, 1H), 1.78 (d, J = 7.20 Hz, 3H).

Step-2: Synthesis of (*R*)-1-(but-3-yn-2-yl)-1*H*-indazol-6-amine (XXXVI)

[000179] To a stirred solution of (*R*)-1-(but-3-yn-2-yl)-6-nitro-1*H*-indazole **(XXXVIa)** (2.30 g, 10.69 mmol) in ethanol (25 mL) under nitrogen atmosphere, was added NH_4Cl (2.85 g, 53.44 mmol) in 25 mL of water followed by iron (2.98 g, 53.44 mmol). The reaction mixture was heated at 80 °C for 1 hour. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a celite bed and washed with ethyl acetate (100 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The

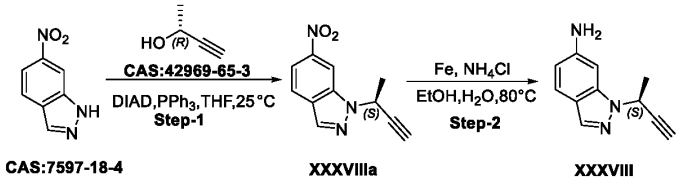
residue was diluted with water (50 mL) and extracted with ethyl acetate (2 x 80 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product **(XXXVI)** as brown solid. Yield: (1.8 g, 89%). **LC_MS:** Calc. for $C_{11}H_{11}N_3$: 185.2; Obs.:186.2 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 7.74 (d, *J* = 0.80 Hz, 1H), 7.38 (d, *J* = 8.80 Hz, 1H), 6.64-6.63 (m, 1H), 6.54-6.52 (m, 1H), 5.51-5.46 (m, 1H), 5.40 (s, 2H), 3.41 (d, *J* = 2.40 Hz, 2H), 1.69 (d, *J* = 6.80 Hz, 2H).

Synthesis of (S)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (XXXVII)



[000180] To a solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)** (0.800 g, 2.06 mmol) and Cyclopropanamine (CAS: **765-30-0**: 0.141 g, 2.47 mmol,) in DMF (10 mL), were added DIPEA (1.08 mL, 6.17 mmol) followed by HATU (0.939 g, 2.47 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. The reaction mixture was quenched with water, DMF was concentrated under reduced pressure and 10% aq $NaHCO_3$ solution was added and extracted with ethyl acetate (2 times). The organic phase was dried under Na_2SO_4 and the solvent was filtered and evaporated in *vacuo* to get the crude desired product **(XXXVII)** as a brown gummy liquid; Yield: (0.85 g, 43%). **LC_MS**: Calc. for $C_{22}H_{26}ClN_5O_2$: 427.93; Obs.: 428.2 [M^++H].

Synthesis of (S)-1-(but-3-yn-2-yl)-1H-indazol-6-amine (XXXVIII)



CAS:7597-18-4 XXXVIIIa XXXVIII

Step-1: Synthesis of (*S*)-1-(but-3-yn-2-yl)-6-nitro-1*H*-indazole (XXXVIIIa):

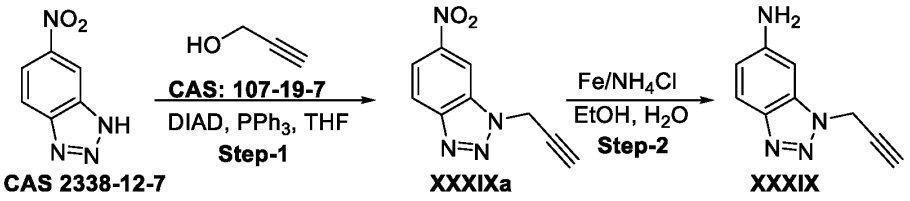
[000181] To a stirred solution of 6-nitro-1*H*-indazole (CAS: 7597-18-4, 3.00 g, 18.39 mmol) and (*R*)-but-3-yn-2-ol) (CAS: 42969-65-3,1.54g, 22.07 mmol) in THF (30 mL) under nitrogen atmosphere was added Triphenylphosphine (5.78 g, 22 mmol) at 0 °C, then added DIAD (4.46 g,28 mmol), resulting reaction mixture was allowed to stir at 25 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (40 mL), and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 40% ethyl acetate in petroleum ether to yield the title compound **XXXVIIIa** as a yellow solid; Yield: (2.4 g, 59%). **LC_MS:** Calc. for $C_{11}H_9N_3O_2$: 215.21; Obs: 216.1 [M^++H]. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 8.87-8.87 (m, 1H), 8.40 (d, *J* = 0.80 Hz, 1H), 8.07-7.99 (m, 2H), 6.18-6.12 (m, 1H), 3.55 (d, *J* = 2.40 Hz, 1H), 1.78 (d, *J* = 7.20 Hz, 3H).

Step-2: Synthesis of (*S*)-1-(but-3-yn-2-yl)-1*H*-indazol-6-amine (XXXVIII)

[000182] To a stirred solution of (*S*)-1-(but-3-yn-2-yl)-6-nitro-1*H*-indazole **(XXXVIIIa)** (2.40 g, 11.15 mmol) in ethanol (25 mL) under nitrogen atmosphere was added NH_4Cl (2.98 g, 55.76 mmol) in 25 mL of water followed by iron (3.11 g, 55.76 mmol). The reaction mixture was heated at 80 °C for 1 hour. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a celite bed and washed with ethyl acetate (100 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The residue was diluted with water (50 mL) and extracted with ethyl acetate (2 x 80 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product **(XXXVIII)** as a brown solid. Yield: (2.0 g, 99%). **LC_MS:** Calc. for $C_{11}H_{11}N_3$: 185.2; Obs.:186.2 [M^++H]. **^{1}H NMR (400**

MHz, DMSO-d_6): δ 7.74 (d, *J* = 0.80 Hz, 1H), 7.38 (d, *J* = 8.40 Hz, 1H), 6.64 (s, 1H), 6.54-6.52 (m, 1H), 5.49-5.47 (m, 1H), 5.38 (s, 2H), 3.40 (d, *J* = 2.00 Hz, 1H), 1.69 (d, *J* = 6.80 Hz, 3H).

Synthesis of 1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-amine (XXXIX)



Step-1: Synthesis of 6-nitro-1-(prop-2-yn-1-yl)-1*H*-benzo[d] [1,2,3]triazole (XXXIXa):

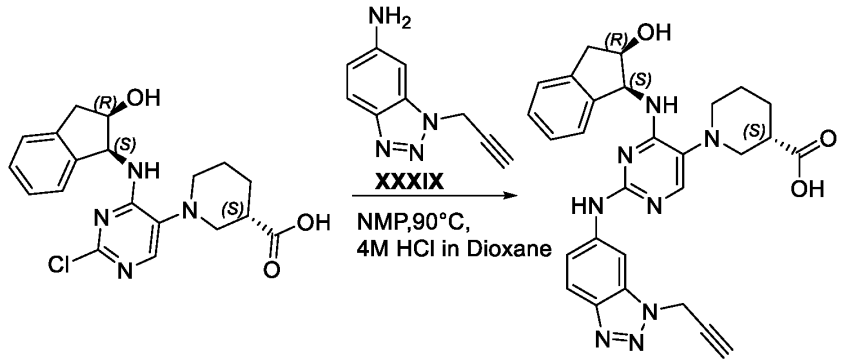
[000183] To a stirred solution of 5-Nitro benzotriazole (CAS 2338-12-7, 6.00 g, 36.56 mmol) in THF (60 mL) under nitrogen atmosphere, were added propargyl alcohol (CAS: 107-19-7: 2.459 g, 2.57 mL, 1.2 eq, 43.87 mmol) followed by triphenylphosphine (11.51 g, 1.2 eq, 43.87 mmol), followed by DIAD (8.871 g, 8.530 mL, 1.2 eq, 43.87 mmol) at 0°C. The resulting reaction mixture was allowed to stir continuously at RT for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (80 mL) and was extracted with ethyl acetate (2 x 80 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 30 % ethyl acetate in petroleum ether to yield the title compound **XXXIXa** as an off-white solid; Yield: (1.6 g, 21%). **LC_MS:** Calc. for $C_9H_6N_4O_2$: 202.17; Obs.: 203.2 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: *δ* 8.76 (s, 1H), 8.75-8.76 (m, 1H), 8.32-8.35 (m, 1H), 5.60-5.61 (m, 2H), 2.64-2.66 (m, 1H), 8.32-8.35 (m, 1H), 5.60-5.61 (m, 2H), 2.64-2.66 (m,1H), (m,1H).

Step-2: 1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine (XXXIX)

[000184] To a stirred solution of 6-nitro-1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazole **(XXXIXa)** (1.6 g, 1 eq, 7.91 mmol) in ethanol (20 mL)

under nitrogen atmosphere, was added NH_4Cl (2.12 g, 5eq, 39.57 mmol) in 20 mL of water followed by iron (2.21 g,5 eq, 39.57 mmol). The reaction mixture was heated at 80 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a Celite bed and was washed with ethyl acetate (70 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The residue was diluted with water (70 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product. The crude product was triturated with petroleum-ether to get the title compound **XXXIX** as a yellow solid; Yield: (1.3 g, 95.5%). **LC_MS:** Calc. for $C_9H_8N_4$: 172.19; Obs.: 173.2 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 7.84 (d, J = 8.40 Hz, 1H), 6.81-6.80 (m, 1H), 6.79 (s, 1H), 5.34-5.30 (m, 2H), 4.07 (brs, 2H), 2.48 (t, J = 2.80 Hz, 1H).

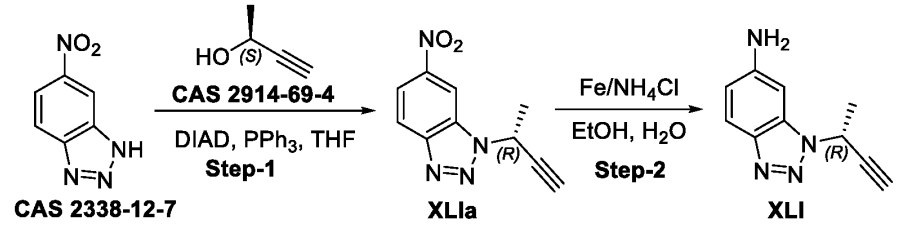
Synthesis of (S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3] triazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid (XL)



[000185] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)** (4.00 g, 1 Eq, 10.3 mmol) and 1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine **(XXXIX)** (2.13 g, 1.2 Eq, 12.3 mmol) in NMP (10 mL), was added 4M HCl in dioxane (1.50 g, 10.3 mL, 4 molar, 4 Eq, 41.1 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 3

hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mass was cooled to room temperature. The reaction mass was then evaporated in *vacuo* to get the crude product **(XL)** as a brown liquid; Yield: (4 g, crude). **LC_MS:** Calc. for $C_{28}H_{28}N_8O_3$: 524.58; Obs.: 525.2 [M^++H].

Synthesis of (R)-1-(but-3-yn-2-yl)-1H-benzo[d][1,2,3]triazol-6-amine (XLI)



Step-1: Synthesis of (*R*)-1-(but-3-yn-2-yl)-6-nitro-1*H*-benzo[d][1,2,3]triazole (XLIa):

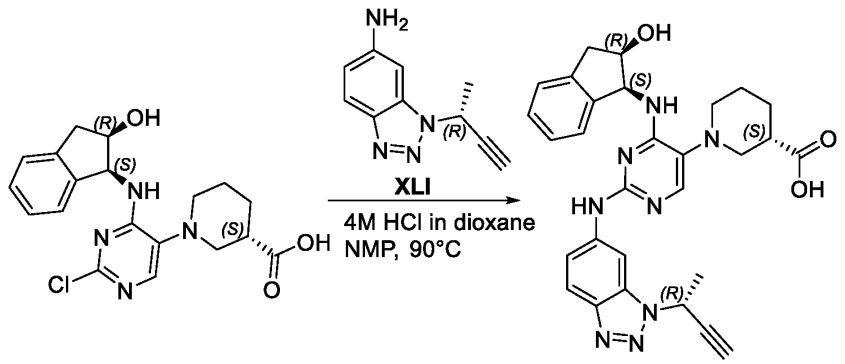
[000186] To a stirred solution of 6-nitro-1*H*-benzo[d][1,2,3]triazole (CAS 2338-12-7, 8.000 g, 1 eq, 48.74 mmol) in THF (60 mL) under nitrogen atmosphere, were added (*S*)-but-3-yn-2-ol (CAS 2914-69-4, 4.100 g, 4.6 mL, 1.2 eq, 58.49 mmol) followed by triphenylphosphine (15.34 g, 1.2 eq, 58.49 mmol) followed by DIAD (11.83 g, 11.37 mL, 1.2 eq, 58.49 mmol) at 0°C. The resulting reaction mixture was allowed to stir continuously at RT for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (80 mL) and was extracted with ethyl acetate (2 x 80 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *a vacuum* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 30 % ethyl acetate in petroleum ether to yield the title compound **(XLIa)** as a pale brown solid; Yield: (2 g, 18.3%). **LC_MS:** Calc. for $C_{10}H_8N_4O_2$: 216.20; Obs.: 217.1 [M^++H]. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 8.84 (s, 1H), 8.32 (d, J = 6.80 Hz, 1H), 8.24 (d, J = 8.80 Hz, 1H), 6.06-6.00 (m, 1H), 2.75 (s, 1H), 2.05 (s, 3H).

Step-2: (*R*)-1-(but-3-yn-2-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine (XLI)

[000187] To a stirred solution of (*R*)-1-(but-3-yn-2-yl)-6-nitro-1*H*-benzo[d][1,2,3]triazole **(XLIa)** (2 g, 1 eq, 9.25 mmol) in ethanol (20 mL) under

nitrogen atmosphere, was added NH_4Cl (2.47 g, 5 eq, 46.25 mmol) in 20 mL of water followed by iron (2.58 g, 5 eq, 46.25 mmol). The reaction mixture was heated at 80 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a Celite bed and washed with ethyl acetate (70 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The residue was diluted with water (70 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product. The crude product was triturated with petroleum ether to get the title compound **(XLI)** as a yellow solid; Yield: (1.3 g, 75.5%). **LC_MS:** Calc. for $C_{10}H_{10}N_4$: 186.22; Obs.: 187.2 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 7.83 (d, J = 8.00 Hz, 1H), 6.89 (s, 1H), 6.78 (d, J = 6.80 Hz, 1H), 5.84-5.78 (m, 1H), 4.05 (m, 2H), 2.58 (s, 1H), 1.91 (s, 3H).

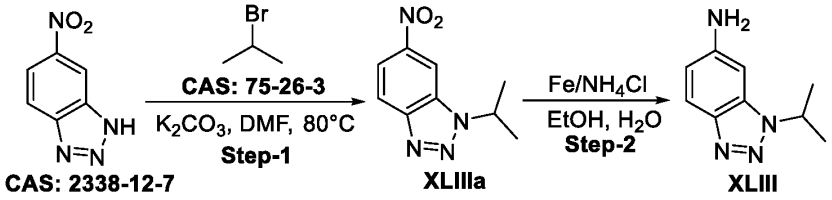
Synthesis of (S)-1-(2-((1-((R)-but-3-yn-2-yl)-1H-benzo[d][1,2,3] triazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid (XLII)



[000188] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)** (3.000 g, 1 Eq, 7.715 mmol) and (*R*)-1-(but-3-yn-2-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine **(XLI)** (2.13 g, 1.2 Eq, 12.3 mmol) in NMP (20 mL), was added 4M HCl in dioxane (562.6 mg, 3.858 mL, 4 molar, 2 Eq, 15.43 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for

3 hours. The reaction progress was monitored by UPLC. After completion of the reaction mass was cooled to room temperature, reaction mass was evaporated in *vacuo* to get the crude product (**XLII**) as a brown liquid; Yield: (3 g, crude). **LC_MS:** Calc. for $C_{29}H_{30}N_8O_3$: 538.61; Obs.: 539.2 [M^++H].

Synthesis of 1-isopropyl-1H-benzo[d][1,2,3]triazol-6-amine (XLIII)



Step-1: 1-isopropyl-6-nitro-1*H*-benzo[d] [1,2,3] triazole (XLIIIa):

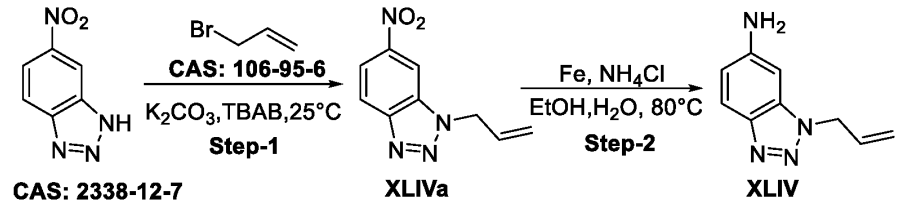
[000189] To a stirred solution of 6-nitro-1*H*-benzo[d][1,2,3]triazole (CAS 2338-12-7, 2.000 g, 1 eq, 12.19 mmol) in DMF (20 mL) under nitrogen atmosphere, were added 2-bromopropane (CAS 75-26-3, 1.799 g, 1.373 mL, 1.2 eq, 14.62 mmol) followed by K_2CO_3 (5.052 g, 3 eq, 36.56 mmol). The resulting reaction mixture continued stirring for 3 hours at 80 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (2 x 40 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 30 % ethyl acetate in petroleum ether to yield the title compound **XLIIIa** as a pale yellow solid; Yield: (0.35 g, 13.9%). **LC_MS:** Calc. for $C_9H_{10}N_4O_2$: 206.21; Obs.: 207.2 [M^++H]. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 8.59-8.58 (m, 1H), 8.30-8.27 (m, 1H), 8.23-8.20 (m, 1H), 5.24-5.17 (m, 1H), 1.83 (d, *J* = 6.80 Hz, 6H)

Step-2: 1-isopropyl-1*H*-benzo[d][1,2,3]triazol-6-amine (XLIII)

[000190] To a stirred solution of 1-isopropyl-6-nitro-1*H*-benzo[d][1,2,3]triazole **(XLIIIa)** (0.350 g, 1 eq, 1.70 mmol) in ethanol (5 mL) under nitrogen atmosphere, were added NH_4Cl (454 mg, 5 eq, 8.49 mmol) in 5 mL of water, followed by iron (474 mg, 5 eq, 8.49 mmol) .The reaction mixture was

heated at 80 °C for 1 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a Celite bed and washed with ethyl acetate (30 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The residue was diluted with water (30 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product. The crude product was triturated with petroleum ether to get the title compound **XLIII** as a brown gum; Yield: (0.28 g, 91%). **LC_MS:** Calc. for $C_9H_{12}N_4$: 176.22; Obs.: 177.2 [M^++H]. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.83-7.81 (m, 1H), 6.78-6.75 (m, 1H), 6.65-6.64 (m, 1H), 4.96-4.89 (m, 1H), 4.02 (s, 2H), 1.73-1.68 (m, 6H).

Synthesis of 1-allyl-1H-benzo[d][1,2,3]triazol-6-amine (XLIV)



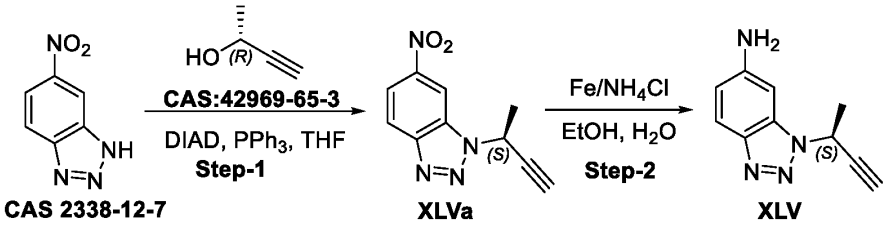
Step-1: Synthesis of 1-allyl-6-nitro-1*H*-benzo[d][1,2,3]triazole (XLIVa)

[000191] To a stirred solution of 6-nitro-1*H*-benzo[d][1,2,3]triazole (CAS: 2338-12-7, 1.5 g, 9.14 mmol) and 3-bromoprop-1-ene (CAS No: 106-95-6, 1.12g, 9.23 mmol) in DMF (20 mL) under nitrogen atmosphere was added Potassium carbonate (1.27 g, 9.23 mmol) at 0 °C, then added Tetra butyl ammonium bromide (0.29 g, 0.91mmol), resulting reaction mixture allowed to stir at 25 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (40 mL), and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 10% ethyl acetate in petroleum ether to yield the title compound (**XLIVa)** as a Brown solid; Yield: (0.20 g, 2.6%). **LC_MS:** Calc. for $C_9H_8N_4O_2$: 204.19; Obs: 204.8 [M+H].

Step-2: Synthesis of 1-allyl-1*H*-benzo[d][1,2,3]triazol-6-amine (XLIV)

[000192] To a stirred solution of 1-allyl-6-nitro-1*H*-benzo[d][1,2,3]triazole **(XLIVa)** (0.20g, 0.97 mmol) in ethanol (20 mL) under nitrogen atmosphere was added NH_4Cl (0.26 g, 4.90 mmol) in 15 mL of water followed by iron (0.26 g, 4.90 mmol). The reaction mixture was heated at 80 °C for 1 hour. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a celite bed and washed with ethyl acetate (25 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The residue was diluted with water (25 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under *vacuum* to get the crude product **(XLIV)** as brown solid. Yield: (0.110 g, 64.0%). **LC_MS:** Calc. for $C_9H_{10}N_4$: 174.2; Obs.:175.2 [M^++H].

Synthesis of (S)-1-(but-3-yn-2-yl)-1H-benzo[d][1,2,3]triazol-6-amine (XLV)



Step-1: Synthesis of (*S*)-1-(but-3-yn-2-yl)-6-nitro-1*H*-benzo[d] [1,2,3] triazole (XLVa):

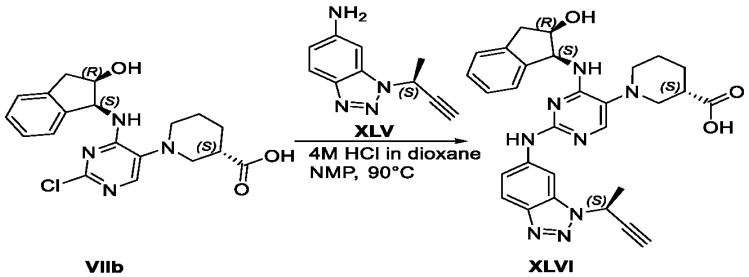
[000193] To a stirred solution of 6-nitro-1*H*-benzo[d][1,2,3]triazole (CAS 2338-12-7, 8.000 g, 1 eq, 48.74 mmol) in THF (60 mL) under nitrogen atmosphere, were added (*S*)-but-3-yn-2-ol (CAS 42969-65-3, 4.100 g, 4.6 mL, 1.2 eq, 58.49 mmol) followed by triphenylphosphine (15.34 g, 1.2 eq, 58.49 mmol) followed by DIAD (11.83 g, 11.37 mL, 1.2 eq, 58.49 mmol) at 0°C. The resulting reaction mixture was allowed to stir continuously at RT for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (80 mL) and was extracted with ethyl acetate (2 x 80 mL). The combined organic phase was dried over Na_2SO_4. The solvent was filtered and evaporated in *a vacuum* to get the crude product. The crude material

was purified by silica gel (Biotage) column chromatography by eluting with 30 % ethyl acetate in petroleum ether to yield the title compound **(XLVa)** as a pale brown solid; Yield: (2 g, 18.3%). **LC_MS:** Calc. for $C_{10}H_8N_4O_2$: 216.20; Obs.: 217.1 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 8.84 (s, 1H), 8.32 (d, J = 6.80 Hz, 1H), 8.24 (d, J = 8.80 Hz, 1H), 6.06-6.00 (m, 1H), 2.75 (s, 1H), 2.05 (s, 3H).

Step-2: (*S*)-1-(but-3-yn-2-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine (XLV)

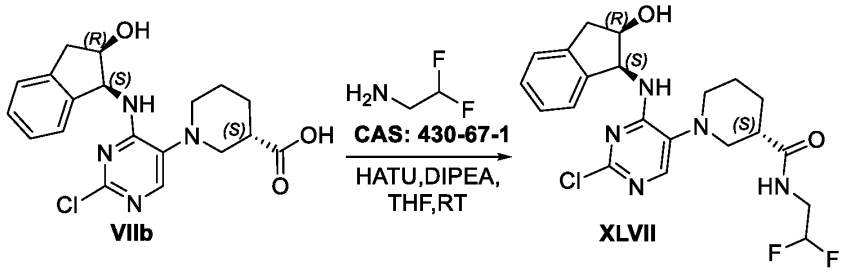
[000194] To a stirred solution of (*S*)-1-(but-3-yn-2-yl)-6-nitro-1*H*-benzo[d][1,2,3]triazole **(XLVa)** (2 g, 1 eq, 9.25 mmol) in ethanol (20 mL) under nitrogen atmosphere, was added NH_4Cl (2.47 g, 5 eq, 46.25 mmol) in 20 mL of water followed by iron (2.58 g, 5 eq, 46.25 mmol). The reaction mixture was heated at 80 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a Celite bed and washed with ethyl acetate (70 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The residue was diluted with water (70 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude product. The crude product was triturated with petroleum ether to get the title compound **(XLV)** as a yellow solid; Yield: (1.3 g, 75.5%). **LC_MS:** Calc. for $C_{10}H_{10}N_4$: 186.22; Obs.: 187.2 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 7.83 (d, J = 8.00 Hz, 1H), 6.89 (s, 1H), 6.78 (d, J = 6.80 Hz, 1H), 5.84-5.78 (m, 1H), 4.05 (m, 2H), 2.58 (s, 1H), 1.91 (s, 3H).

Synthesis of (S)-1-(2-((1-((S)-but-3-yn-2-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid (XLVI)



[000195] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylic acid **(VIIb)** (0.200 g, 0.51 mmol) and (*S*)-1-(but-3-yn-2-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine **(XLV)** (0.095 g, 0.51 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.2 mL, 1.03 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 16 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude desired product (**XLVI**) as brown gummy liquid. Yield: (0.20 g, 19.8 %). **LC_MS**: Calc. for $C_{29}H_{30}N_8O_3$: 538.61; Obs.: 539.2 [M^++H].

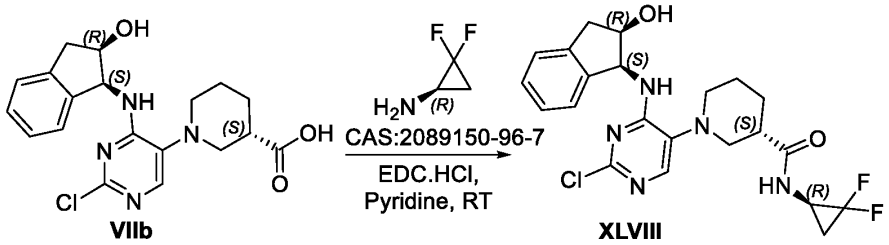
Synthesis of (S)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-(2,2-difluoroethyl) piperidine-3-carboxamide (XLVII)



[000196] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb,** 0.3 g, 1 eq, 0.7715 mmol) and 2,2-difluoroethan-1-amine hydrochloride (CAS: 430-67-1, 87.56 mg, 1.4 eq, 1.08 mmol) were added DIPEA (598 mg, 806 µL, 3 eq, 2.31 mmol) followed by T3P 50% in ethyl acetate (0.91 ml g, 2 eq, 1.545 mmol) at 0°C, under nitrogen atmosphere. The resulting reaction mixture was stirred at RT for 16 hours, under nitrogen atmosphere. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mass was diluted with water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude

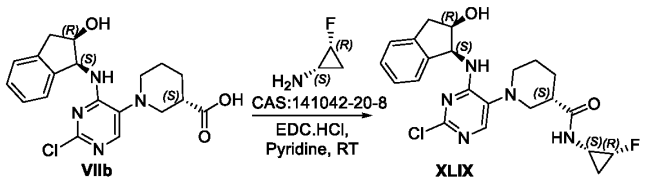
product (**XLVII**) as color less gummy solid; Yield: (0.35 g, crude). **LC_MS: Calc**. for $C_{21}H_{24}ClF_2N_5O_2$: 451.90; Obs.: 452.1 [M^++H].

Synthesis of (S)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-((R)-2,2-difluorocyclopropyl) piperidine-3-carboxamide (XLVIII)



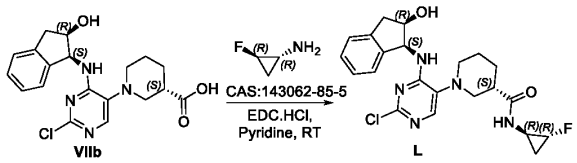
[000197] To a solution of (*S*)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid (**VIIb**) (0.500 g, 1.3 mmol) and (*R*)-2,2-difluorocyclopropan-1-amine (CAS: 2089150-96-7, 0.718 g, 7.72 mmol,) in Pyridine (2 mL), were added EDC.HCl (0.499 g, 3.21 mmol) at RT, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 16 hours. The reaction progress was monitored by TLC. The reaction mixture was quenched with 10% aq $NaHCO_3$ solution. Added water and extracted with ethyl acetate (2 times). The organic phase was dried under Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product as a yellow solid. The obtained crude product was purified by isolera column chromatography (silica gel 100-200 mesh; 100 g snap, flow rate 60 mL/min; absorbance - 254 nm, 100% ethyl acetate in petroleum ether), The product fractions were concentrated to get the product (**XLVIII**) as white solid; Yield: (0.25 g, 34%). **LC_MS**: Calc. for $C_{22}H_{24}ClF_2N_5O_2$: 463.91; Obs.: 464.2 [M^++H].

Synthesis of (S)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-((1S,2R)-2-fluorocyclopropyl) piperidine-3-carboxamide (XLIX)



[000198] To a solution of (*S*)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)** (2.00 g, 5.14 mmol) and (1S,2R)-2-fluorocyclopropan-1-amine (CAS: 141042-20-8, 2.32 g, 30.9 mmol,) in Pyridine (2 mL), were added EDC.HCl (2.46 g, 12.9 mmol) at RT, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 2 hours. The reaction progress was monitored by TLC. The reaction mixture was quenched with 10% aq NaHCO3 solution, added water and extracted with ethyl acetate (2 times). The organic phase was dried under Na_2SO_4. The solvent was filtered and evaporated in *vacuo* to get the crude product as a brown solid. The obtained crude product was purified by isolera column chromatography (silica gel 100-200 mesh; 100 g snap, flow rate 60 mL/min; absorbance - 254 nm, 100% ethyl acetate in petroleum ether). The product fractions were concentrated to get the product (**XLIX**) as an off white solid; Yield: (2.00 g, 66.7%). **LC_MS**: Calc. for $C_{22}H_{25}ClFN_5O_2$: 445.3; Obs.: 446.2 [M^++H].

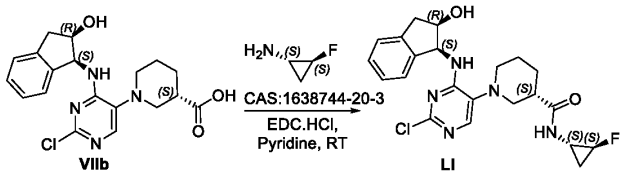
Synthesis of (S)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-((1R,2R)-2-fluorocyclopropyl) piperidine-3-carboxamide (L)



[000199] To a solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)** (0.150 g, 0.38 mmol) and (1*R*,2*R*)-2-fluorocyclopropan-1-amine (CAS: 143062-85-5, 0.17 g, 2.31 mmol,) in Pyridine (1mL), were added EDC.HCl (0.15g, 0.96 mmol) at room temperature, under a nitrogen atmosphere. The resulting reaction mixture

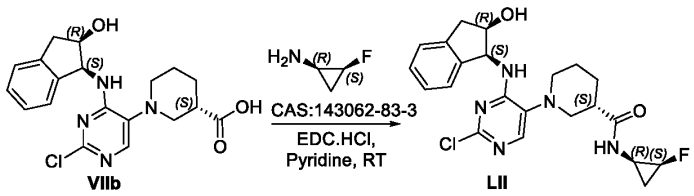
was stirred at room temperature for 2 hours. The progress of the reaction was monitored by TLC, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (2 X 50 ml). The combined organic layer was washed with 1.5 N HCl solution to remove excess pyridine. The solvent was filtered and evaporated in *vacuo* to get the crude product (**L**) as a brown solid; Yield: (0.12 g, 60 %). **LC_MS**: Calc. for $C_{22}H_{25}ClFN_5O_2$: 445.92; Obs.: 446.2 [M^++H].

Synthesis of (S)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-((1S,2S)-2-fluorocyclopropyl) piperidine-3-carboxamide (LI)



[000200] To a solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)** (0.150 g, 0.38 mmol) and (1*S*,2*S*)-2-fluorocyclopropan-1-amine (CAS:1638744-20-3, 0.17 g, 2.31 mmol,) in Pyridine (1 mL), were added EDC.HCl (0.15g, 0.96 mmol) at room temperature, under a nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 2 hours. The reaction progress was monitored by TLC. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (2 x 25 mL). The combined organic layer was washed with a diluted solution of 1.5 N HCl (20 mL) to remove excess pyridine. The solvent was filtered and evaporated in *vacuo* to get the crude product (**LI**) as a brown solid; Yield: (0.10 g, 54%). **LC_MS**: Calc. for $C_{22}H_{25}ClFN_5O_2$: 445.92; Obs.: 446.2 [M^++H].

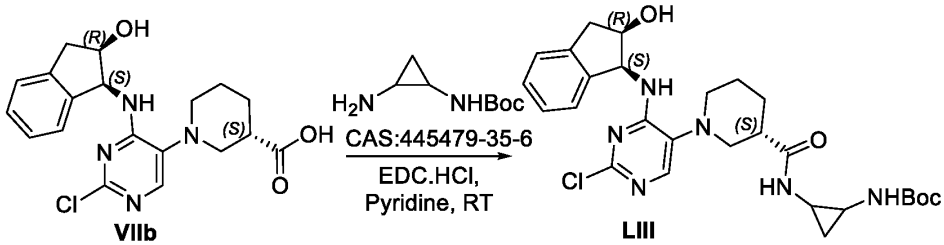
Synthesis of (S)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-((1R,2S)-2-fluorocyclopropyl) piperidine-3-carboxamide (LII)



VIIb LII

[000201] To a solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)** (0.150 g, 0.38 mmol) and (1*R*,2*S*)-2-fluorocyclopropan-1-amine (CAS Number: 143062-83-3, 0.17 g, 2.31 mmol,) in Pyridine (1 mL), were added EDC.HCl (0.15g, 0.96 mmol) at room temperature, under a nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 2 hours. The reaction progress was monitored by TLC. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (2x 25 mL). The combined organic layer was washed with 1.5 N HCl solution (10 mL) to remove excess pyridine. The solvent was filtered and evaporated in *vacuo* to get the crude product (**LII**) as a brown solid; Yield: (0.12 g, 65 %). **LC_MS**: Calc. for $C_{22}H_{25}ClFN_5O_2$: 445.92; Obs.: 446.2 [M^++H].

Synthesis of tert-butyl (2-((S)-1-(2-chloro-4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamido) cyclopropyl) carbamate (LIII)

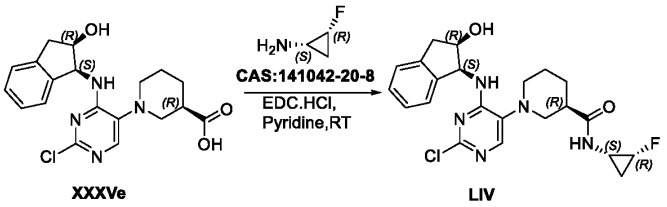


VIIb LIII

[000202] To a solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIIb)** (0.200 g, 0.51 mmol) and tert-butyl (2-aminocyclopropyl)carbamate (CAS Number: 445479-35-6, 0.106 g, 0.61 mmol,) in Pyridine (1mL), were added EDC.HCl (0.246 g, 0.96 mmol) at room temperature, under a nitrogen atmosphere.

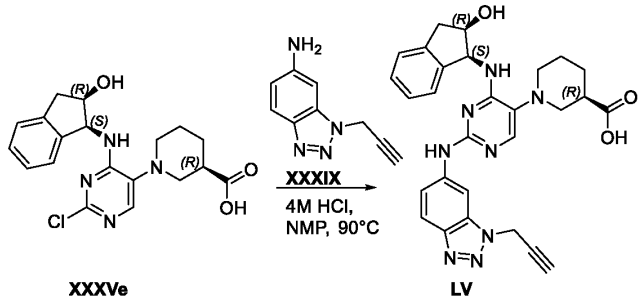
The resulting reaction mixture was stirred at room temperature for 1 hour. The progress of the reaction was monitored by TLC. The reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (2x 20 mL). The combined organic layer was washed with 1.5 N HCl solution (20 mL) to remove excess pyridine. The solvent was filtered and evaporated in *vacuo* to get the crude product (**LIII**) as a brown solid; Yield: (0.2 g, 52.5 %). **LC_MS**: Calc. for $C_{27}H_{35}ClN_6O_4$: 543.06.; Obs.: 543.2 [M^++H].

Synthesis of (R)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-((1S,2R)-2-fluorocyclopropyl) piperidine-3-carboxamide (LIV)



[000203] To a solution of (*R*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid (**XXXVe**) (0.39 g, 1.00 mmol) and (1*S*,2*R*)-2-fluorocyclopropan-1-amine (CAS: 141042-20-8, 0.45 g, 6.02 mmol,) in Pyridine (2 mL), were added EDC.HCl (0.39g, 2.5 mmol) at room temperature, under a nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 2 hours. The reaction progress was monitored by TLC. The reaction mixture was quenched with water (20 mL) and was extracted with ethyl acetate twice (2 X 20 mL). The combined organic layer was washed with 1M HCl solution to remove the excess of pyridine. The solvent was filtered and evaporated in *vacuo* to get the crude product (**LIV**) as a brown solid; Yield: (0.3 g, 46.7%). **LC_MS**: Calc. for $C_{22}H_{25}ClFN_5O_2$: 445.3; Obs.: 446.2 [M^++H]. **1H-NMR (400 MHz, DMSO-*d*$_6$):** δ 8.58(q, *J* = 1.20 Hz, 1H), 8.03-8.00 (m, 1H), 7.85-7.82 (m, 1H), 7.39-7.37 (m, 1H), 7.18-7.25 (m, 3H), 5.43-5.40 (m, 3H), 4.57-4.54 (m, 2H), 3.17 (dd, *J* = 4.80, 16.20 Hz, 2H), 3.00-2.87 (m, 3H), 2.60-2.55 (m, 2H), 1.80 (t, *J* = 8.80 Hz, 2H), 1.53-1.51 (m, 2H), 1.00-0.98 (m, 1H), 0.97-0.83 (m, 1H).

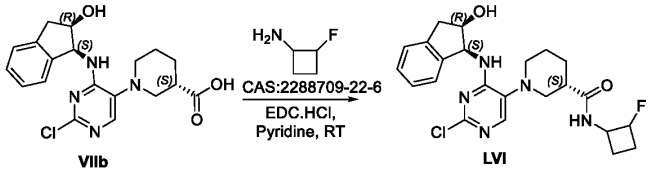
Synthesis of (R)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[1,2,3]triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxylic acid (LV)



XXXVe LV

[000204] To a stirred solution of (*R*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(XXXVe)** (0.15 g, 0.38 mmol) and 1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine **(XXXIX)** (0.079 g, 0.46 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.2 mL, 1.54 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated at 90 °C for 4 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude desired product (**LV**) as a brown gummy liquid. Yield: (0.15 g, 31.6%). **LC_MS**: Calc. for $C_{28}H_{28}N_8O_3$: 524.58; Obs.: 525.2[M^++H].

Synthesis of (3S)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-(2-fluorocyclobutyl) piperidine-3-carboxamide (LVI)

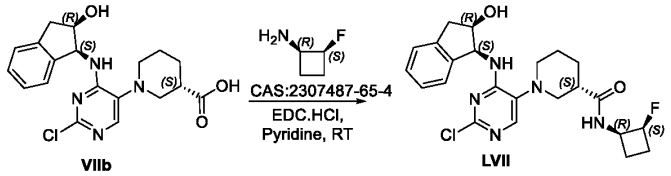


VIIb LVI

[000205] To a solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)** (0.20 g, 0.51 mmol) and 2-fluorocyclobutan-1-amine (CAS Number: 2288709-22-

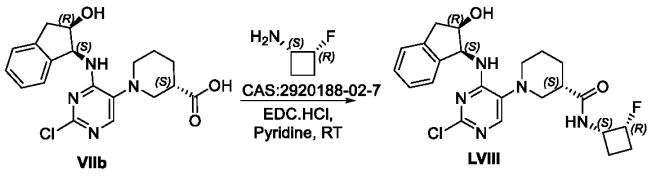
6, 0.27g, 3.09 mmol,) in pyridine (2 mL), were added EDC.HCl (0.25g, 1.29 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 1 hour. The reaction progress was monitored by TLC. The reaction mixture was quenched with water (20 mL) and was extracted with ethyl acetate twice (2 X 20 mL). The combined organic layer was washed with 1M HCl to remove the excess of pyridine. The solvent was filtered and evaporated in *vacuo* to get the crude product (**LVI**) as a brown solid; Yield: (0.20 g, 83.9%). **LC_MS**: Calc. for $C_{23}H_{27}ClFN_5O_2$: 459.95; Obs.: 460.2 [M^++H].

Synthesis of (S)-1-(2-chloro-4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-((1R,2S)-2-fluorocyclobutyl) piperidine-3-carboxamide (LVII)



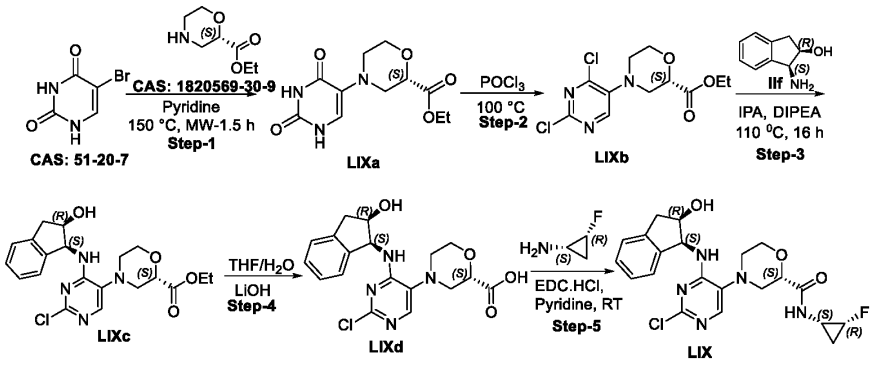
[000206] To a solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(VIIb)** (0.20 g, 0.51 mmol) and 2-fluorocyclobutan-1-amine (CAS:2307487-65-4, 0.27g, 3.09 mmol,) in pyridine (2 mL), were added EDC.HCl (0.25g, 1.29 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 1 hour. The reaction progress was monitored by TLC. The reaction mixture was quenched with water (20 mL) and was extracted with ethyl acetate twice (2 X 20 mL). The combined organic layer was washed with 1M HCl to remove the excess of pyridine. The solvent was filtered and evaporated in *vacuo* to get the crude product (**LVII**) as a brown solid; Yield: (0.20 g, 83.9%). **LC_MS**: Calc. for $C_{23}H_{27}ClFN_5O_2$: 459.95; Obs.: 460.2 [M^++H].

Synthesis of (S)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-((1S,2R)-2-fluorocyclobutyl) piperidine-3-carboxamide (LVIII)



[000207] To a solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid (**VIIb**) (0.20 g, 0.51 mmol) and 2-fluorocyclobutan-1-amine (CAS: 2920188-02-7, 0.27g, 3.09 mmol,) in pyridine (2 mL), were added EDC.HCl (0.25g, 1.29 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 1 hour. The reaction progress was monitored by TLC. The reaction mixture was quenched with water (20 mL) and was extracted with ethyl acetate twice (2 X 20 mL). The combined organic layer was washed with 1M HCl to remove the excess of pyridine. The solvent was filtered and evaporated in *vacuo* to get the crude product (**LVIII**) as a brown solid; Yield: (0.20 g, 83.9%). **LC_MS**: Calc. for $C_{23}H_{27}ClFN_5O_2$: 459.95; Obs.: 460.2 [M^++H].

<u>Synthesis of (S)-4-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-((1S,2R)-2-fluorocyclopropyl) morpholine fluorocyclopropyl) morpholine-2-carboxamide (LIX)</u>



Step-1: Synthesis of ethyl 4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) morpholine-2-carboxylate (LIXa)

[000208] A solution of 5-bromopyrimidine-2,4(1*H*,3*H*)-dione (CAS: 51-20-7, 10.00 g, 52.36 mmol) and ethyl (S)-morpholine-2-carboxylate **(CAS: 1820569-30-9)** (13.31 g, 68.07 mmol) in pyridine (50 mL) was irradiated at 150 °C for 1.5 hours in the microwave. The progress of the reaction was monitored by UPLC. After completion of the reaction, acetonitrile (100 mL) was added, stirred for 15 minutes, filtered, and dried under a vacuum that affords the crude product. The crude product was triturated with methyl tert-butyl ether (50 mL) to get the pure compound **LIXa** as an off-white solid; Yield: (7.7 g, 54.64). **LCMS**: Calc. for $C_{11}H_{15}N_3O_5$: 269.26; Obs.: 270.1 [M^++H].

Step-2: Synthesis of ethyl (S)-4-(2,4-dichloropyrimidin-5-yl) morpholine-2-carboxylate (LIXb)

[000209] A solution of ethyl (S)-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) morpholine-2-carboxylate **(LIXa)** (6.0 g, 22.28 mmol) in $POCl_3$ (60 mL, 0.64 mmol) was heated at 100 °C for 16 hours, under a nitrogen atmosphere. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and the reaction mixture was concentrated under reduced pressure. The residue was basified using 10% $NaHCO_3$ solution (400 mL). The aqueous layer was extracted with ethyl acetate (3 x 120 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under a *vacuum* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting 20% ethyl acetate in petroleum ether to yield the title compound **LIXb** as a brown liquid; Yield: (2.30 g, 33.72%). **LCMS**: Calc. for $C_{11}H_{13}Cl_2N_3O_3$: 306.14; Obs.:305.9 [M^++H].

Step-3: Synthesis of ethyl (S)-4-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) morpholine-2-carboxylate (LIXc)

[000210] To a stirred solution of ethyl (S)-4-(2,4-dichloropyrimidin-5-yl)morpholine-2-carboxylate **(LIXb)** (0.400 g, 1.30 mmol) in IPA (20 mL), was added DIPEA (0.680 mL, 3.91 mmol), followed by (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol **(IIf)** (0.233 g, 1.56 mmol), under a nitrogen atmosphere. The resulting reaction mixture was heated at 110 °C for 16 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction

mixture was cooled to room temperature and concentrated under reduced pressure to afford the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 90% ethyl acetate in petroleum ether to yield the title compound **LIXc** as off-white solid; Yield: (0.20 g, 36.56%). **LC_MS:** Calc. for $C_{20}H_{23}ClN_4O_4$: 418.88; Obs.: 419.1 [M^++H].

Step-4:Synthesis of (S)-4-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) morpholine-2-carboxylic acid (LIXd)

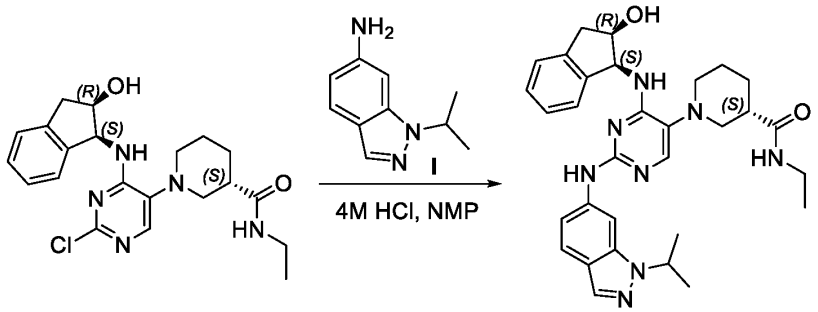
[000211] To a stirred solution of ethyl (S)-4-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)morpholine-2-carboxylate **(LIXc)** (1.80 g, 5.88 mmol) in a mixture of THF (20 mL) and water (20 mL) was added $LiOH.H_2O$ (0.370 g, 8.81 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (30 mL), neutralized with 1.5N HCl, and then extracted with ethyl acetate (2 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product **LIXd** as a brown gummy liquid. The crude product was taken to the next step without further purification; Yield: (1.42 g, 87.11%). **LC_MS:** Calc. for $C_{18}H_{19}ClN_4O_4$: 390.82; Obs.: 391.8. [M^+-H].

Step-5: Synthesis of (S)-4-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-((1S,2R)-2-fluorocyclopropyl) morpholine-2-carboxamide (LIX)

[000212] To a solution of (S)-4-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)morpholine-2-carboxylic acid **(LIXd)** (0.30 g, 0.76 mmol) and (1*S*,2*R*)-2-fluorocyclopropan-1-amine HCl (CAS Number: 141042-20-8, 0.35 g, 4.61 mmol,) in Pyridine (2 mL), were added EDC hydrochloride (0.29 g, 1.92 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 1 hour. The reaction progress was monitored by TLC, reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (2x20 mL),

Combined organic layer was washed with 1M of HCl to remove excess of pyridine. The solvent was filtered and evaporated in *vacuo* to get the crude product (**LIX**) as a brown solid; Yield: (0.3 g, 79.6%). **LC_MS**: Calc. for $C_{21}H_{23}ClFN_5O_3$: 447.9; Obs.: 448.2 [M^++H].

Example 1: (S)-N-ethyl-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-isopropyl-1H-indazol-6-yl) amino)pyrimidin-5-yl)piperidine-3-carboxamide

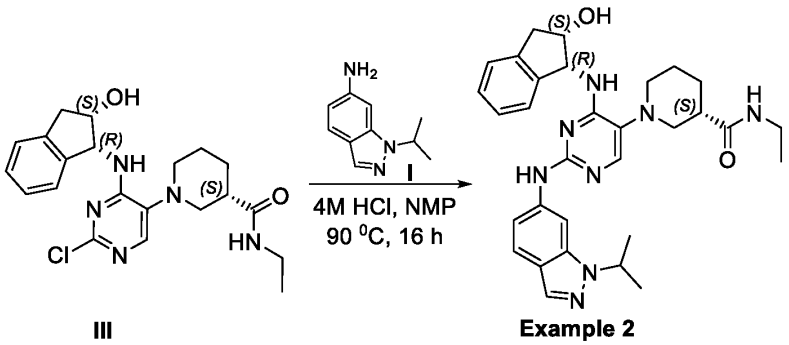


II **Example 1**

[000213] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-ethylpiperidine-3-carboxamide **(II)** (**Formula C**, 0.120 g, 0.289 mmol) and 1-isopropyl-1*H*-indazol-6-amine **(I)** (**Formula D**, 0.06 g, 0.346 mmol) in NMP (5 mL), was added 4M HCl in dioxane (0.11 mL, 0.433 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 2 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mass was cooled to room temperature, diluted with water (5 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 10 mL). The organic phase was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product. The crude material was purified by silica gel (Biotage) column chromatography by eluting with 5% methanol in DCM to yield the title compound **Example 1** as an off-white solid; Yield: (0.105 g, 64.5%).

[000214] **LC_MS: Calc**. for $C_{31}H_{38}N_8O_2$: 554.60; Obs.: 555.2 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 9.46 (br s, 1H), 8.44 (br s, 1H), 7.84 (t, J = 16.00 Hz, 3H), 7.51 (d, J = 8.40 Hz, 1H), 7.33 (d, J = 7.60 Hz, 1H), 7.26 (t, J = 7.20 Hz, 1H), 7.18 (t, J = 7.60 Hz, 1H), 7.04 (m, 1H), 5.64-5.60 (m, 2H), 4.65-4.62 (m, 1H), 3.78 (s, 1H), 3.16 (d, J = 4.00 Hz, 1H), 3.06-2.99 (m, 6H), 2.35 (m, 2H), 1.76 (m, 2H), 1.51 (m, 4H), 1.24 (m, 3H), 1.13 (d, J = 12.00 Hz, 6H); **HPLC:** Purity = 98.00%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

Example 2:(S)-N-ethyl-1-(4-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-isopropyl-1H-indazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide

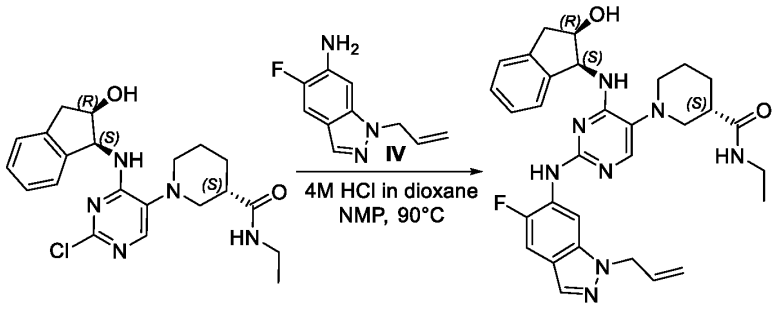


[000215] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-ethylpiperidine-3-carboxamide **(III)** (Formula C, 0.120 g, 0.289 mmol) 1-isopropyl-1*H*-indazol-6-amine **(I)** (Formula D, 0.055 g, 0.317 mmol) in NMP (2 mL) was added 4M HCl in dioxane (0.14 mL, 0.577 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (10 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product. The obtained crude product was purified by Prep-HPLC purification using TFA in water and

acetonitrile to afford the desired compound **Example 2** as an off-white solid; Yield: (0.062 g, 38.75%).

[000216] **LC_MS**: Calc. for $C_{31}H_{38}N_8O_2$: 554.70; Obs.: 555.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 9.32 (s, 1H), 8.49 (s, 1H), 7.89-7.88 (m, 1H), 7.82-7.78 (m, 2H), 7.47 (d, J = 8.80 Hz, 1H), 7.35-7.32 (m, 2H), 7.28-7.25 (m, 1H), 7.21-7.17 (m, 1H), 7.03 (m, 1H), 6.80 (s, 1H), 5.65-5.63 (m, 1H), 5.53 (d, J = 4.00 Hz, 1H), 4.63-4.60 (m, 1H), 3.75 (m, 1H), 3.19-3.15 (m, 2H), 2.99-2.95 (m, 6H), 2.42-2.41 (m, 1H), 1.72 (m, 2H), 1.50 (m, 2H), 1.11-1.08 (m, 3H), 1.01-0.95 (m, 6H); **HPLC** Purity = 99.80%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

Example 3: (S)-1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-ethylpiperidine-3-carboxamide

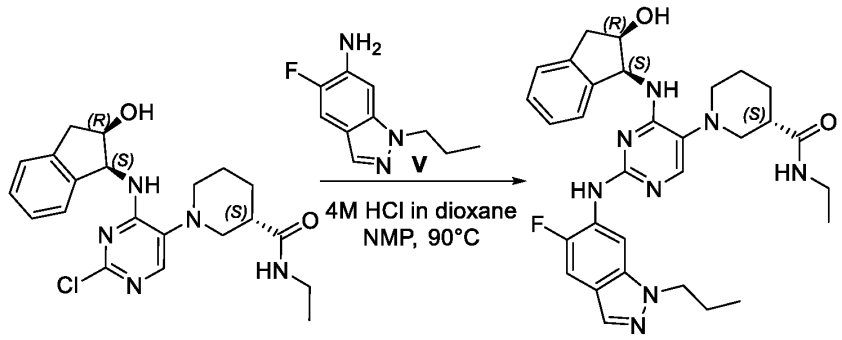


[000217] To a stirred solution (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino) pyrimidin-5-yl)-N-ethylpiperidine-3-carboxamide **(II)** (Formula C, 0.20 g, 0.48 mmol) and 1-allyl-5-fluoro-1*H*-indazol-6-amine **(IV)** (Formula D, 0.091 g, 0.48 mmol) in NMP (3 mL) was added 4M HCl in dioxane (0.24 mL, 0.961 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 6 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product. The obtained crude product was

purified by Prep-HPLC purification using ammonium bicarbonate in water and acetonitrile to afford the desired compound **Example 3** as an off-white solid; Yield: (0.030 g, 10.9%).

[000218] **LC_MS**: Calc. for $C_{31}H_{35}FN_8O_2$: 570.67; Obs.: 571.3 [M^++H]. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 8.48 (d, *J* = 6.80 Hz, 1H), 8.15 (d, *J* = 2.80 Hz, 1H), 7.89-7.83 (m, 3H), 7.54-7.51 (m, 1H), 7.32-7.30 (m, 1H), 7.25-7.22 (m, 2H), 7.16-7.13 (m, 1H), 6.85 (s, 1H), 5.60-5.51 (m, 3H), 4.95-4.92 (m, 1H), 4.65-4.61 (m, 2H), 4.48-4.43 (m, 1H), 4.31-4.27 (m, 1H), 3.18-3.13 (m, 1H), 3.06-2.91 (m, 6H), 2.68 (s, 1H), 2.39-2.33 (m, 1H), 1.79-1.72 (m, 2H), 1.55 (s, 2H), 0.99-0.95 (m, 3H); **HPLC** Purity = 99.70%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

Example 4: (S)-N-ethyl-1-(2-((5-fluoro-1-propyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide



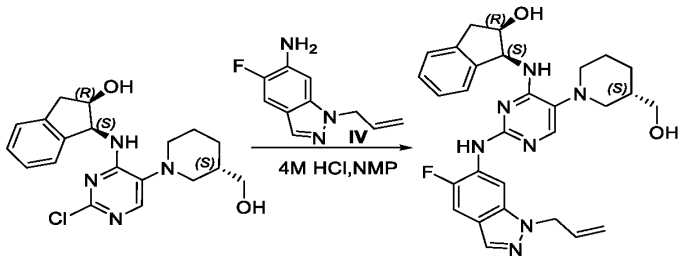
II **Example 4**

[000219] To a stirred solution (*S*)-1-(2 chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-*N*-ethylpiperidine-3-carboxamide **(II)** (Formula C, 0.15 g, 0.360 mmol), 5-fluoro-1-propyl-1*H*-indazol-6-amine **(V)** (Formula D, 70 mg, 0.362 mmol) in NMP (2 mL) was added 4M HCl in dioxane (0.2 mL, 0.8 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (10 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x

20 mL). The combined organic layer was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product. The obtained crude product was purified by Prep-HPLC purification using 10 mM NH_4CO_3 in water and acetonitrile to afford the desired compound. The compound was further triturated with diethyl ether, the white solid thrown out was allowed to settle and the supernatant was decanted. The solid obtained was dried under high *vacuo*, to get free base of Example 4 as an off-white solid; Yield: (0.079 g, 38%).

[000220] **LC_MS**: Calc. for $C_{31}H_{37}FN_8O_2$: 572.69; Obs.: 573.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 8.50 (d, J = 6.80 Hz, 1H), 8.11 (s, 1H), 7.85 (dd, J = 5.20, 12.80 Hz, 3H), 7.50 (d, J = 11.20 Hz, 1H), 7.32-7.26 (m, 3H), 7.24 (d, J = 7.20 Hz, 1H), 7.13 (br s, 1H), 5.58 (d, J = 2.80 Hz, 2H), 3.68-3.35 (m, 3H), 3.31-3.01 (m, 7H), 2.51 (br s, 1H), 1.53-1.48 (m, 6H), 1.12-0.95 (m, 4H), 0.53 (t, J = 7.60 Hz, 3H); **HPLC** Purity = 99.51%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 5 mM Ammonium bicarbonate in water, Mobile Phase B: Acetonitrile.

Example 5: (1S,2R)-1-((2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-5-((S)-3-(hydroxymethyl) piperidin-1-yl) pyrimidin-4-yl) amino)-2,3-dihydro-1H-inden-2-ol.

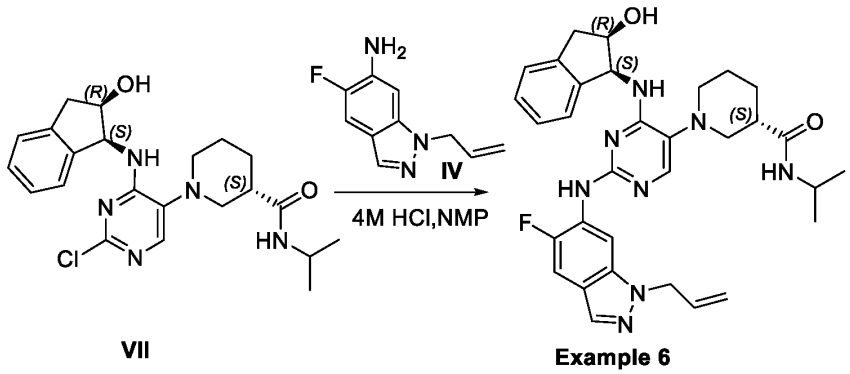


[000221] To a stirred solution (1*S*,2*R*)-1-((2-chloro-5-((*S*)-3-(hydroxymethyl) piperidin-1-yl)pyrimidin-4-yl)amino)-2,3-dihydro-1H-inden-2-ol **(VI)** (Formula C, 0.150 g, 0.400 mmol), and 1-allyl-5-fluoro-1H-indazol-6-amine **(IV)** (Formula D, 0.076 g, 0.348 mmol) in NMP (4 mL) was added 4M HCl in dioxane (0.2 mL, 0.800 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (10

mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product. The obtained crude product was purified by Prep-HPLC purification using Ammonium bicarbonate in water and acetonitrile to afford the desired compound **Example 5** as an off-white solid; Yield: (0.050 g, 23 %).

[000222] **LC_MS**: Calc. for $C_{29}H_{32}FN_7O_2$: 529.62; Obs.: 530.2 [M^++H]; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**:: δ 8.47 (d, J = 6.80 Hz, 1H), 8.21 (s, 1H), 7.89-7.85 (m, 2H), 7.55-7.52 (m, 1H), 7.32-7.22 (m, 4H), 7.17-7.10 (m, 1H), 6.77 (d, J = 5.20 Hz, 1H), 5.62-5.53 (m, 3H), 4.95-4.92 (m, 1H), 4.46-4.61 (m, 5H), 2.93-3.07 (m, 5H), 2.53 (s, 3H), 1.71 (s, 3H), 1.12-1.08 (m, 1H) ; **HPLC** Purity = 97.86%, X - Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

Example 6: (S)-1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-isopropylpiperidine-3-carboxamide

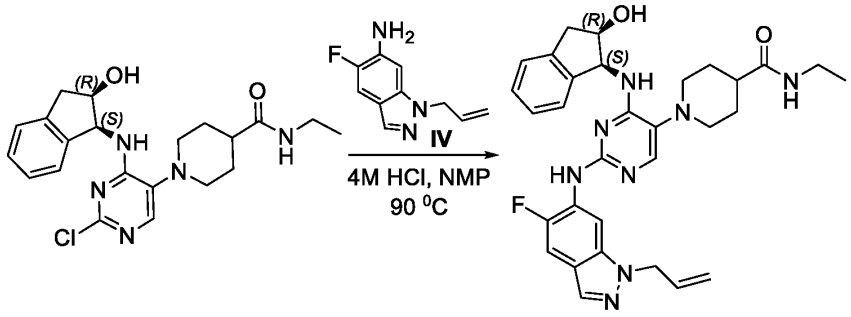


[000223] To a stirred solution (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-isopropylpiperidine-3-carboxamide **(VII)** (Formula C, 0.150 g, 0.348 mmol), 1-allyl-5-fluoro-1H-indazol-6-amine **(IV)** (Formula D, 0.066 g, 0.348 mmol) in NMP (3 mL) was added 4M HCl in dioxane (0.174 mL, 0.697 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 3 hours. The progress of

the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (10 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product. The obtained crude product was purified by Prep-HPLC purification using Ammonium bicarbonate in water and acetonitrile to afford free base of the desired compound **Example 6** as an off-white solid; Yield: (0.048 g, 23%).

[000224] **LC_MS**: Calc. for $C_{32}H_{37}FN_8O_2$: 584.70; Obs.: 585.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 8.47 (br s, 1H), 8.13 (br s, 1H), 7.88 (s, 2H), 7.66 (s, 1H), 7.52 (d, *J* = 11.20 Hz, 1H), 7.25-7.22 (m, 3H), 7.15 (d, *J* = 6.80 Hz, 1H), 5.55-5.52 (m, 3H), 4.94 (d, *J* = 9.60 Hz, 1H), 4.66-4.31 (m, 4H), 3.79 (d, *J* = 7.20 Hz, 1H), 3.13-3.01 (m, 4H), 1.62 (m, 4H), 1.11 (s, 4H), 1.00 (d, *J* = 6.80 Hz, 6H); **HPLC** Purity = 98.33%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

Example 7: 1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-ethylpiperidine-4-carboxamide



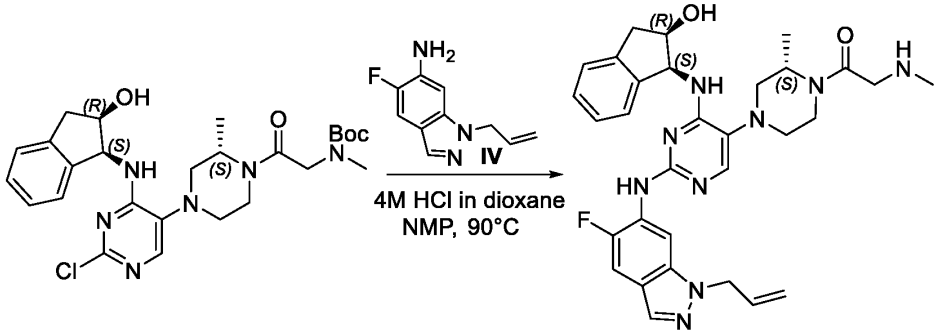
XXXI **Example 7**

[000225] To a stirred solution 1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino) pyrimidin-5-yl)-N-ethylpiperidine-4-carboxamide **(XXXI)** (Formula C, 0.15 g, 0.36 mmol) and 1-allyl-5-fluoro-1*H*-indazol-6-amine **(IV)** (0.068 g, 0.36 mmol) in NMP (3 mL) was added 4M HCl in dioxane (Formula D, 0.18 mL, 0.721 mmol) at room temperature, under nitrogen atmosphere. The

reaction mixture was heated at 90°C for 6 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product. The obtained crude product was purified by Prep-HPLC purification using ammonium bicarbonate in water and acetonitrile to afford the desired compound **Example 7** as an off-white solid; Yield: (0.098 g, 48%).

[000226] **LC_MS**: Calc. for $C_{31}H_{35}FN8O_2$: 570.67; Obs.: 571.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 8.47 (d, J = 6.80 Hz, 1H), 8.20 (s, 1H), 7.89-7.87 (m, 2H), 7.81-7.78 (m, 1H), 7.54-7.52 (m, 1H), 7.31 (d, J = 7.20 Hz, 1H), 7.27-7.23 (m, 2H), 7.18-7.14 (m, 1H), 6.79-6.77 (m, 1H), 5.54-5.56 (m, 3H), 4.95-4.92 (m, 1H), 4.65-4.57 (m, 2H), 4.46-4.45 (m, 1H), 4.30-4.29 (m, 1H), 3.18-3.15 (m, 1H), 3.09-3.02 (m, 4H), 2.93-2.89 (m, 1H), 2.70-2.66 (m, 2H), 2.25-2.15 (m, 1H), 1.74-1.71 (m, 4H), 1.02-0.98 (m, 3H). **HPLC** Purity = 98.35%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

Example 8: 1-(S)-4-(2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino) ethan-1-one



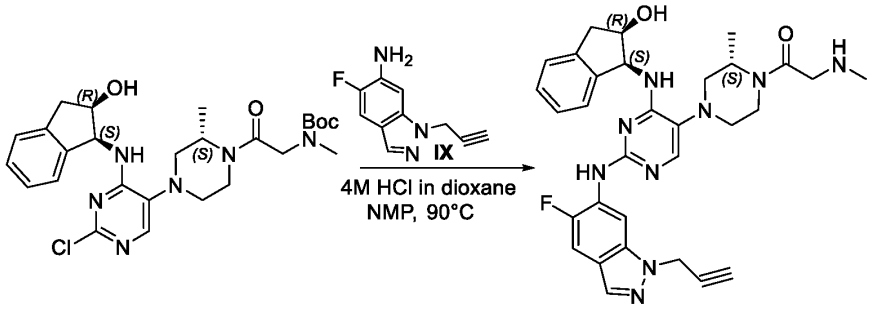
VIII **Example 8**

[000227] To a stirred solution *t*ert-butyl (2-((*S*)-4-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-oxoethyl)(methyl)carbamate **(VIII)** (Formula C, 0.15 g, 0.282 mmol), 1-allyl-5-fluoro-1*H*-indazol-6-amine **(IV)** (Formula D, 0.054 g, 0.282 mmol) in NMP (2

mL) was added 4M HCl in dioxane (0.14 mL, 0.565 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (10 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product. The obtained crude product was purified by Prep-HPLC purification using 10mM Ammonium bicarbonate in water and acetonitrile to afford the gummy mass. The compound was further triturated with diethyl ether, the white solid thrown out was allowed to settle and the supernatant were decanted. The solid obtained was dried under high *vacuo*, to get free base of **Example 8** as an off-white solid; Yield: (0.022 g, 12%).

[000228] **LC_MS**: Calc. for $C_{31}H_{36}FN_9O_2$: 585.69; Obs.: 586.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 8.44 (d, J = 6.80 Hz, 1H), 8.19 (s, 1H), 7.89 (d, J = 6.00 Hz, 2H), 7.53 (d, J = 11.20 Hz, 1H), 7.27-7.22 (m, 4H), 6.77 (d, J = 8.00 Hz, 1H), 5.53 (d, J = 4.40 Hz, 3H), 4.94 (m, 1H), 4.67-4.58 (m, 7H), 3.12 (s, 3H), 2.87-2.53 (m, 6H), 2.27 (s, 3H), 1.14 (m Hz, 3H); **HPLC** Purity = 93.52%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 5mM Ammonium bicarbonate in water, Mobile phase B: Acetonitrile.

Example 9: 1-((S)-4-(2-((5-fluoro-1-(prop-2-yn-1-yl)-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino)ethan-1-one

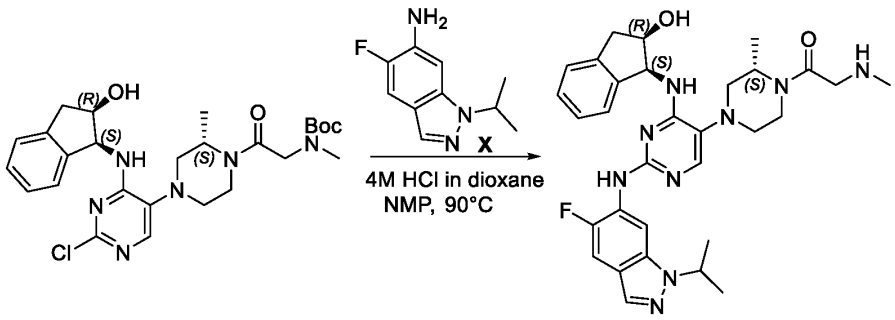


VIII Example 9

[000229] To a stirred solution *t*ert-butyl (2-((*S*)-4-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-oxoethyl)(methyl)carbamate **(VIII)** (Formula C, 0.15 g, 0.282 mmol), 5-fluoro-1-(prop-2-yn-1-yl)-1H-indazol-6-amine **(IX)** (Formula D, 0.053 g, 0.282 mmol) in NMP (2 mL) was added 4M HCl in dioxane (0.14 mL, 0.565 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (10 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product. The obtained crude product was purified by Prep-HPLC purification using 0.1 % TFA in water and acetonitrile to afford the gummy mass. The compound was further triturated with diethyl ether, the white solid thrown out was allowed to settle and the supernatant was decanted. The solid obtained was dried under high *vacuo*, to get TFA salt of **Example 9** as an off-white solid; Yield: (0.020 g, 12.5%).

[000230] **LC_MS**: Calc. for $C_{31}H_{34}FN_9O_2$: 583.67; Obs.: 584.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 8.71 (br s, 1H), 8.45 (d, J = 6.80 Hz, 1H), 8.01 (s, 1H), 7.96 (br s, 1H), 7.71 (d, J = 10.80 Hz, 2H), 7.34 (d, J = 7.60 Hz, 2H), 7.30-7.26 (m, 1H), 7.18-7.10 (m, 1H), 5.57 (br s, 1H), 4.80-4.75 (m, 1H), 4.65 (br s, 1H), 4.33-3.84 (m, 4H), 3.29-2.97 (m, 8H), 2.68-2.51 (m, 6H), 1.27-1.20 (m, 3H); **HPLC** Purity = 98.479%, Atlantis T3 (150 X 4.6) mm, 3µm, Mobile Phase A: 0.1% TFA in water, Mobile phase B: Acetonitrile.

Example 10: 1-((S)-4-(2-((5-fluoro-1-isopropyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino) ethan-1-one

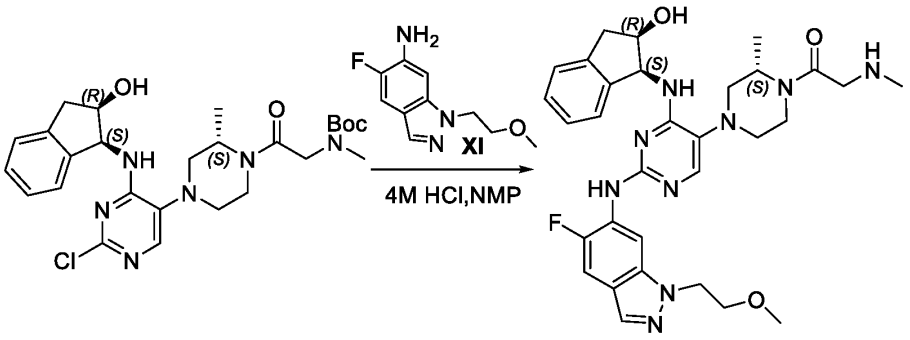


VIII **Example 10**

[000231] To a stirred solution tert-butyl (2-((*S*)-4-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-oxoethyl)(methyl)carbamate **(VIII)** (Formula C, 0.10 g, 0.188 mmol) 5-fluoro-1-isopropyl-1H-indazol-6-amine **(X)** (Formula D, 0.043 g, 0.226 mmol) in NMP (2 mL) was added 4M HCl in dioxane (0.94 mL, 0.377 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (10 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product. The obtained crude product was purified by Prep-HPLC purification using 0.1% Ammonium bicarbonate in water in water and acetonitrile to afford the desired compound **Example 10** as an off-white solid; Yield: (0.023 g, 21.75%).

[000232] **LC_MS**: Calc. for $C_{31}H_{38}FN_9O_2$: 587.70; Obs.: 588.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 8.52 (d, *J* = 6.40 Hz, 1H), 8.20 (m, 1H), 7.88 (d, *J* = 11.80 Hz, 2H), 7.49 (d, *J* = 5.20 Hz, 1H), 7.34 (t, *J* = 8.40 Hz, 2H), 7.28 (t, *J* = 6.80 Hz, 1H), 7.20 (t, *J* = 7.60 Hz, 1H), 6.83 (d, *J* = 8.40 Hz, 1H), 5.59 (s, 1H), 4.60 (s, 2H), 4.33 (m, 2H), 3.83 (m, 3H), 3.14 (s, 2H), 2.94-2.90 (m, 3H), 2.68 (m, 3H), 2.32 (s, 3H), 1.20-1.18 (m, 6H), 1.07 (d, *J* = 6.40 Hz, 3H). **HPLC** Purity = 91.12%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

Example 11: 1-((S)-4-(2-((5-fluoro-1-(2-methoxyethyl)-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino) ethan-1-one

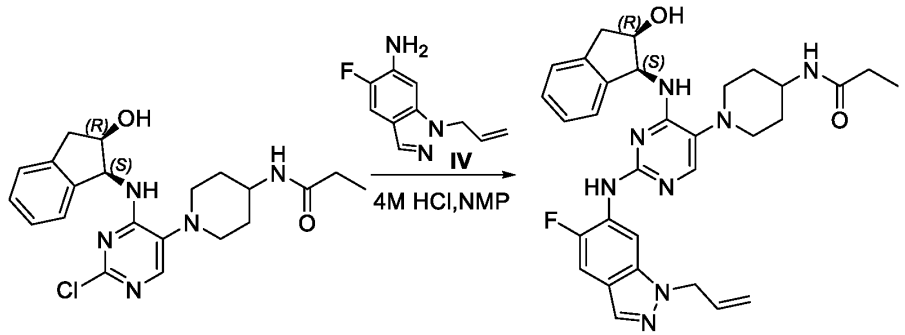


[000233] To a solution of *tert*-butyl (2-((*S*)-4-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-oxoethyl)(methyl)carbamate **(VIII)** (Formula C, 0.10 g, 0.18 mmol) and 5-fluoro-1-(2-methoxyethyl)-1H-indazol-6-amine **(XI)** (Formula D, 0.039 g, 0.18 mmol) in NMP (3 mL), was added 4M HCl in Dioxane (0.027 g, 0.75 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 2 hours. The reaction progress was monitored by UPLC. After the completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water, and neutralized with 10% aq. $NaHCO_3$, and extracted with ethyl acetate (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product as a brown gummy solid. The obtained crude was purified by Preparative HPLC reverse phase (Ammonium bicarbonate in water and acetonitrile) to afford desired product **Example 11** as an Off-white solid; Yield: (0.006 g, 5%).

[000234] **LC_MS:** Calc. for: $C_{31}H_{38}FN_9O3$: 603.70; Obs.: 604.3 $[M+H]^+$ and **1H-NMR (400 MHz, DMSO-*d6*):** δ 8.53 (d, J = 6.80 Hz, 1H), 8.28 (s, 1H), 7.92 (s, 1H), 7.89 (s, 1H), 7.51 (s, 1H), 7.31 (t, J = 8.00 Hz, 2H), 7.24 (t, J = 7.20 Hz, 1H), 7.16 (t, J = 7.20 Hz, 1H), 6.78 (d, J = 8.40 Hz, 1H), 5.62-5.56 (m, 2H), 4.60 (d, J = 4.80 Hz, 2H), 3.92-3.87 (m, 1H), 3.75-3.65 (m, 2H), 3.75-3.65 (m, 2H),

3.20-3.15 (m, 2H), 3.02 (s, 4H), 2.99-2.85 (m, 5H), 2.31 (s, 4H), 1.36-1.18 (m, 4H), **HPLC** Purity = 94.13%, Column: X-Bridge C8(50 X 4.6)mm,3.5µm, Mobile phase: A:5mM Ammonium bicarbonate in water: B:ACN, Flow:1.0mL/min.

Example 12: N-(1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-4-yl) propionamide

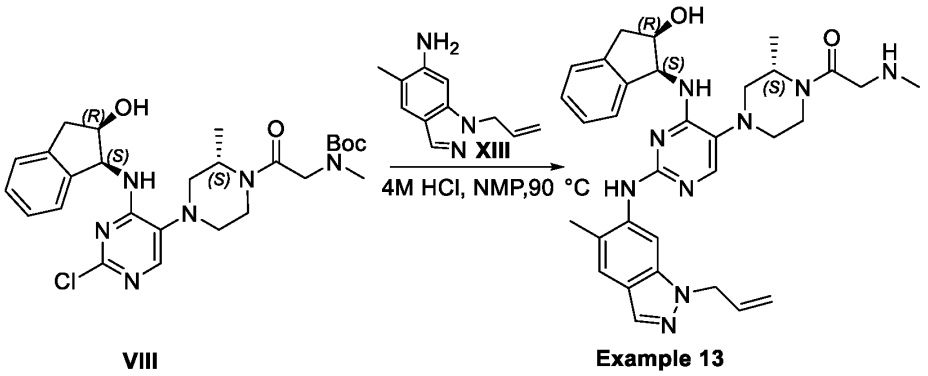


XII **Example 12**

[000235] To a stirred solution of N-(1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)piperidin-4-yl)propionamide **(XII)** (Formula C, 0.100 g, 0.240 mmol), 1-allyl-5-fluoro-1H-indazol-6-amine **(IV)** (Formula D, 0.045 g, 0.240 mmol) in NMP (4 mL) was added 4M HCl in dioxane (0.12 mL, 0.480 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (10 mL), neutralized by triethylamine, and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, the solvent was filtered and evaporated in *vacuo* to get the crude product. The obtained crude product was purified by Prep-HPLC purification using Ammonium bicarbonate in water and acetonitrile to afford the desired compound **Example 12** as a pale-yellow solid; Yield: (0.005 g, 3%).

[000236] **LC_MS**: Calc. for $C_{31}H_{35}FN_8O_2$: 570.67; Obs.: 571.4 $[M^+ + H]$; **HPLC** Purity = 93.75%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

Example 13: 1-((S)-4-(2-((1-allyl-5-methyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino) ethan-1-one

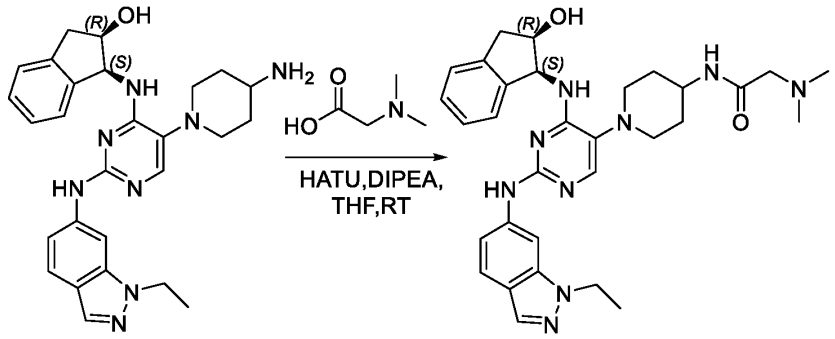


[000237] To a solution of *tert*-butyl (2-((*S*)-4-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-oxoethyl)(methyl)carbamate **(VIII)** (Formula C, 0.13 g, 0.24 mmol) and 1-allyl-5-methyl-1H-indazol-6-amine **(XIII)** (Formula D, 0.045 g, 0.24 mmol) in NMP (3 mL), was added 4M HCl in Dioxane (0.017 g, 0.49 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 2 hours. The reaction progress was monitored by UPLC. After the completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water, and neutralized with 10% aq. $NaHCO_3$, and extracted with ethyl acetate (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product as a brown gummy liquid. The obtained crude was purified by Preparative HPLC reverse phase (ammonium bicarbonate in water + ACN) to afford desired product **Example 13** as an off-white solid; Yield: (0.016 g, 10%).

[000238] **LC_MS:** Calc. for $C_{32}H_{39}N_9O_2$: 5:81.73; Obs.: 582.3 [M^++H] ; **1H-NMR (400 MHz, DMSO-*d6*):** δ 8.25 (s, 1H), 8.17 (s, 1H), 7.83 (s, 3H), 7.49 (s, 1H), 7.30-7.21 (m, 1H), 7.30-7.23 (m, 2H), 7.16-7.06 (m, 1H), 6.69 (d, J = 8.40 Hz, 1H), 5.64-5.61 (m, 1H), 5.48 (t, J = 8.00 Hz, 2H), 4.94 (m, 1H), 4.69 (s, 1H), 4.65 (s, 1H), 4.49-4.44 (m, 3H), 4.50 (s, 1H), 3.18 (m, 2H), 3.12-3.10 (m, 2H), 2.97-2.82

(m, 5H), 2.45 (d, *J* = 5.60 Hz, 6H), 1.24 (br s, 3H). **HPLC** Purity; 90.52%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A:0.1% TFA in water Mobile phase: B: ACN, Flow:2.0mL/min.

Example 14: 2-(dimethyl amino)-N-(1-(2-((1-ethyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-4-yl) acetamide



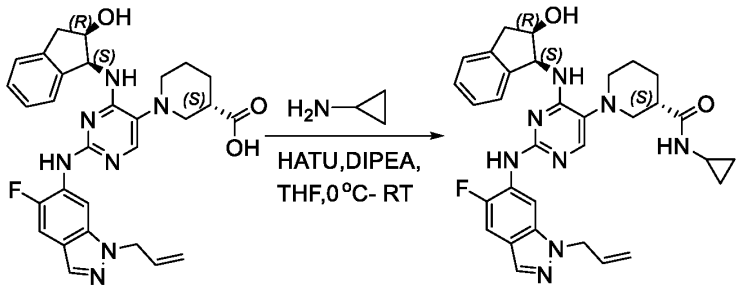
XXXII **Example14**

[000239] To a solution of (1*S*,2*R*)-1-((5-(4-aminopiperidin-1-yl)-2-((1-ethyl-1H-indazol-6-yl)amino)pyrimidin-4-yl)amino)-2,3-dihydro-1H-inden-2-ol **(XXXII)** (0.150 g, 0.161 mmol) and dimethylglycine (0.016 g, 0.514 mmol, 2M) in THF (10 mL), were added DIPEA (0.084 mL, 0.482 mmol) followed by HATU (0.073 g, 0.193 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The obtained crude product was purified by Prep-HPLC purification using formic acid in water and acetonitrile to afford the desired compound **Example 14** as off-white solid; Yield: (0.060 g, 65%).

[000240] **LC_MS**: Calc. for $C_{31}H_{39}N_9O_2$: 569.71; Obs.:570.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 9.31 (s, 1H), 8.48 (s, 1H), 8.16 (s, 2H), 7.90 (s, 1H), 7.77-7.77 (m, 1H), 7.72 (d, *J* = 8.00 Hz, 1H), 7.48 (d, *J* = 8.80 Hz, 1H), 7.35-7.30 (m, 2H), 7.26-7.23 (m, 1H), 7.19-7.15 (m, 1H), 7.09-7.06 (m, 1H), 6.68 (d, *J* = 8.40 Hz, 1H), 5.66-5.63 (m, 2H), 4.64-4.62 (m, 1H), 3.64-3.51 (m, 1H), 3.04 (d, *J* = 11.20 Hz, 3H), 2.92-2.89 (m, 3H), 2.81-2.75 (m, 2H), 2.22 (s, 6H), 1.81-1.78

(m, 2H), 1.56 (s, 2H), 0.97-0.93 (m, 3H). **HPLC** Purity = 99.18%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

Example 15: (S)-1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide



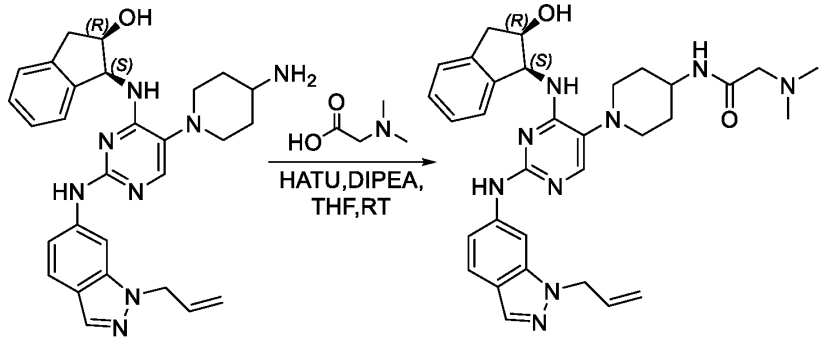
XXXIII **Example 15**

[000241] To a solution of (*S*)-1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl)amino)-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(XXXIII)** (0.150 g, 0.275 mmol) and cyclopropane amine (Formula D, 0.015 g, 0.275 mmol) in THF (10 mL), were added DIPEA (0.144 mL, 0.827 mmol) followed by HATU (0.125 g, 0.331 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 2 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was basified using 10% $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated under a *vacuum* to get the crude product. The obtained crude product was purified by Prep-HPLC purification using Ammonium bicarbonate in water and acetonitrile to afford the desired compound **Example 15** as an off-white solid; Yield: (0.030 g, 20 %).

[000242] **LC_MS**: Calc. for $C_{32}H_{35}FN_8O_2$: 582.68.70; Obs.: 583.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** : δ 8.47 (d, *J* = 6.80 Hz, 1H), 8.19 (s, 1H), 7.89-7.87 (m, 3H), 7.53 (d, *J* = 11.20 Hz, 1H), 7.31 (d, *J* = 7.60 Hz, 1H), 7.25-7.22 (m,

2H), 7.16-7.13 (m, 1H), 6.86 (m, 1H), 5.51-5.54 (m, 2H), 4.92-4.95 (m, 1H), 4.55-4.70 (m, 2H), 4.40-4.50 (m, 1H), 4.25-4.35 (m, 1H), 3.14-3.32 (m, 1H), 3.08-3.13 (m, 1H), 2.91-2.95 (m, 3H), 2.67-2.68 (m, 2H), 1.65-1.85 (m, 2H), 1.40-1.60 (m, 2H), 1.05-1.15 (m, 5H), 0.50-0.60 (m, 1H).; **HPLC** Purity = 99.59%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

Example 16: N-(1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-4-yl)-2-(dimethyl amino) acetamide

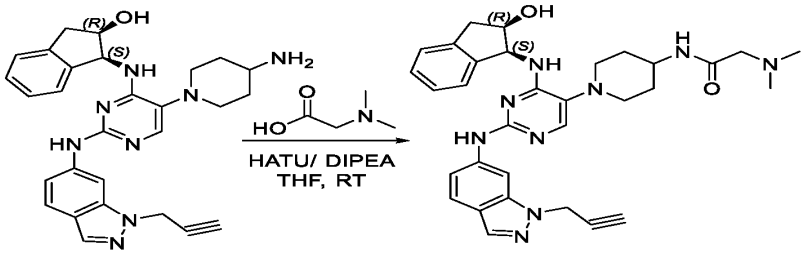


[000243] To a solution of (1*S*,2*R*)-1-((2-((1-allyl-1H-indazol-6-yl)amino)-5-(4-aminopiperidin-1-yl)pyrimidin-4-yl)amino)-2,3-dihydro-1H-inden-2-ol (**XIX**) (0.210 g, 0.422 mmol) and dimethylglycine (0.043 g, 0.422 mmol) in THF (10 mL), were added DIPEA (0.368 mL, 2.114 mmol) followed by HATU (0.209 g, 0.549 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 2 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was basified using 10% $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated under a *vacuum* to get the crude product as pale-yellow solid. The obtained crude product was purified by Prep-HPLC purification using Ammonium bicarbonate in water and acetonitrile to afford free

base of the desired compound **Example 16** as an off-white solid; Yield: (0.097 g, 38 %).

[000244] **LC_MS**: Calc. for $C_{32}H_{39}N_9O_2$; 581.73; Obs.: 582.3 [M^++H]. **HPLC** Purity = 95.75%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile. 1H-NMR (**400 MHz**, **DMSO-*d*$_6$**): δ 9.30 (s, 1H), 8.42 (s, 1H), 7.89 (s, 1H), 7.82 (s, 1H), 7.67 (d, *J* = 8.40 Hz, 1H), 7.50 (d, *J* = 8.80 Hz, 1H), 7.33-7.23 (m, 3H), 7.18-7.11 (m, 2H), 6.66 (d, *J* = 8.40 Hz, 1H), 5.60-5.53 (m, 3H), 4.92 (d, *J* = 10.40 Hz, 1H), 4.63-4.58 (m, 2H), 4.36 (d, *J* = 4.40 Hz, 1H), 4.23 (d, *J* = 8.00 Hz, 1H), 3.78 (s, 1H), 3.20-3.16 (m, 1H), 3.02-2.95 (m, 3H), 2.91-2.80 (m, 2H), 2.77-2.75 (m, 2H), 2.19 (s, 6H), 1.80 (t, *J* = 10.00 Hz, 2H), 1.58 (m, 2H), 1.11 (s, 1H).

Example 17: 2-(dimethylamino)-N-(1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl) amino) pyrimidin-5-yl) piperidin-4-yl) acetamide



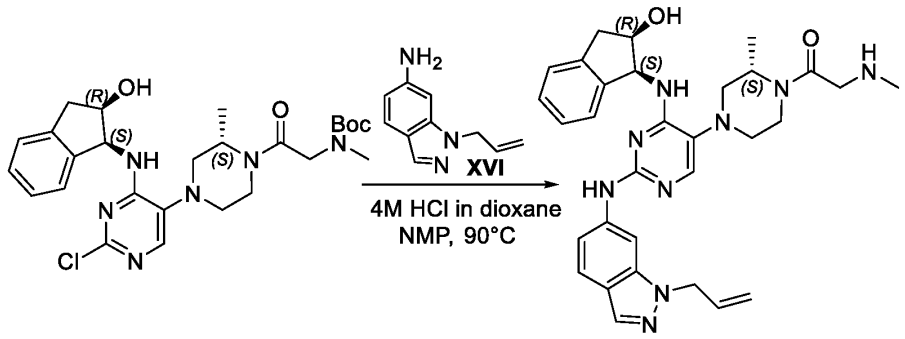
XXXIV Example 17

[000245] To a solution of (1*S*,2*R*)-1-((5-(4-aminopiperidin-1-yl)-2-((1-(prop-2-yn-1-yl)-1*H*-indazol-6-yl)amino)pyrimidin-4-yl)amino)-2,3-dihydro-1*H*-inden-2-ol (**XXXIV**) (0.18 g, 0.36 mmol) and dimethylglycine (0.03 mL, 0.36 mmol) in THF (10 mL), were added DIPEA (0.2 mL, 1.14 mmol) followed by HATU (0.17 g, 0.44 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was basified using 10% $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated under a *vacuum* to get the crude

product as an off white solid. The obtained crude product was purified by Prep-HPLC purification using 10mM Ammonium bicarbonate in water and acetonitrile to afford the desired compound as gummy mass. The compound was further triturated with diethyl ether, the off-white solid thrown out was allowed to settle and the supernatant was decanted. The solid obtained was dried under high *vacuo*, to afford free base of desired product **Example 17** as an off-white solid. Yield: (0.22 g, 10.0 %),

[000246] **LC_MS:** Calc. for $C_{32}H_{37}N_9O_2$: 579.71; Obs.: 580.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6):** δ 9.39 (s, 1H), 8.61 (s, 1H), 7.91 (s, 1H), 7.81 (s, 1H), 7.68 (d, J = 8.00 Hz, 1H), 7.51 (d, J = 8.80 Hz, 1H), 7.33 (t, J = 6.40 Hz, 2H), 7.24 (t, J = 7.20 Hz, 1H), 7.17-7.15 (m, 2H), 6.70 (d, J = 8.00 Hz, 1H), 5.69-5.67 (m, 1H), 5.55 (d, J = 4.40 Hz, 1H), 4.67-4.62 (m, 2H), 3.27-3.24 (m, 4H), 3.02-2.76 (m, 7H), 2.19 (s, 6H), 1.79 (t, J = 11.20 Hz, 2H), 1.61-1.57 (m, 2H); **HPLC** Purity: 97.78%, Column: X-Bridge C8(50 X 4.6) mm, 3.5µm, Mobile phase: A: Ammonium bicarbonate in water, Mobile phase: B: Acetonitrile.

Example 18: 1-(S)-4-(2-((1-allyl-1H-indazol-6-yl) amino)-4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino) ethan-1-one

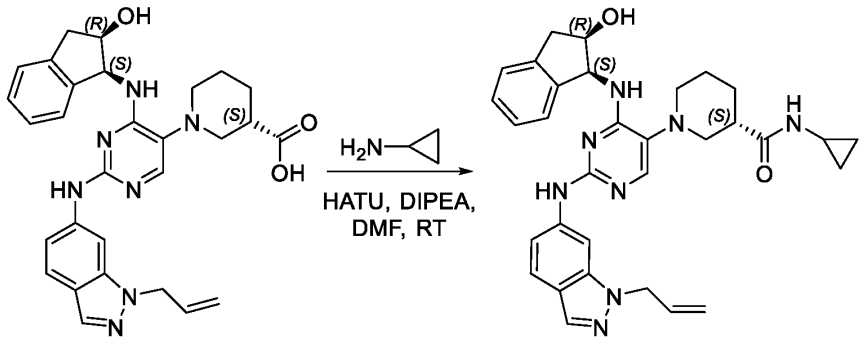


VIII **Example 18**

[000247] To a stirred solution tert-butyl (2-((*S*)-4-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-oxoethyl)(methyl)carbamate **(VIII)** (Formula C, 0.2 g, 0.376 mmol), 1-allyl-1*H*-indazol-6-amine **(XVI)** (Formula D, 0.065 g, 0.376 mmol) in NMP (3 mL) was

added 4M HCl in dioxane (0.37 mL, 1.50 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90°C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product. The obtained crude product was purified by Prep-HPLC purification using 10mm TFA in water and acetonitrile to afford to get of **Example 18** as an off-white solid; Yield: (0.080 g, 37%). **LC_MS**: Calc. for $C_{31}H_{37}N_9O_2$: 567.70; Obs.: 568.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 9.33 (s, 1H), 8.48-8.41 (m, 1H), 8.00-7.82 (m, 2H), 7.55-7.50 (m, 1H), 7.33-7.31 (m, 2H), 7.27-7.23 (m, 1H), 7.19-7.13 (m, 2H), 6.79-6.75 (m, 1H), 5.62-5.55 (m, 3H), 4.94-4.91 (m, 1H), 4.63-4.59 (m, 3H), 4.43-4.18 (m, 3H), 3.40 (m, 1H), 3.28-3.16 (m, 2H), 3.00-2.78 (m, 6H), 2.31 (s, 3H), 2.28-1.11 (m, 4H). **HPLC** Purity = 95.02%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile phase B: Acetonitrile.

Example 19: (S)-1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide



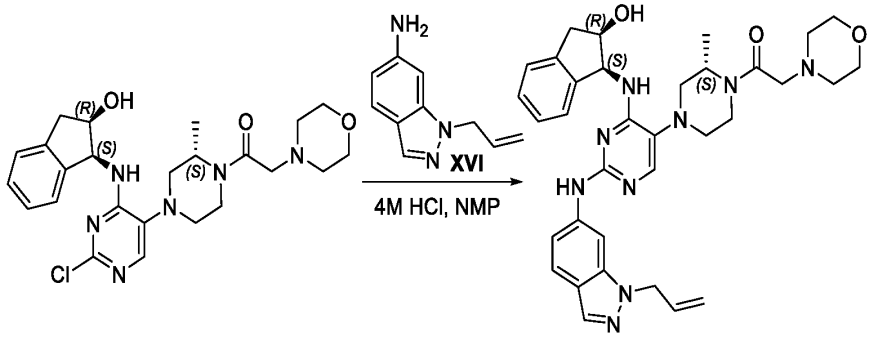
XVII **Example 19**

[000248] To a solution of (*S*)-1-(2-((1-allyl-1*H*-indazol-6-yl)amino)-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(XVII)** (0.20 g, 0.38 mmol) and cyclopropane amine (0.03 mL, 0.457 mmol) in THF (10 mL), were added DIPEA (0.17 mL, 0.95 mmol) followed by HATU (0.17 g, 0.46 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress

was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was basified using 10% $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated under a *vacuum* to get the crude product as off-white solid. The obtained crude product was purified by Prep-HPLC purification using Ammonium bicarbonate in water and acetonitrile to afford free base of the desired compound **Example 19** as an Off-white solid; Yield: (0.045 g, 21 %).

[000249] **LC_MS**: Calc. for $C_{32}H_{36}N_8O_2$: 564.69; Obs.: 565.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 9.30 (s, 1H), 8.42 (s, 1H), 7.83-7.80 (m, 3H), 7.50 (d, J = 8.40 Hz, 1H), 7.28-7.13 (m, 5H), 5.58-5.51 (m, 3H), 4.93-4.91 (m, 1H), 4.63-4.61 (m, 2H), 4.10-4.09 (m, 3H), 3.18 (s, 2H), 2.96-2.53 (m, 5H), 2.51-2.50 (m, 1H), 1.75-1.53 (m, 4H), 0.58-0.55 (m, 2H), 0.36-0.33 (m, 2H); **HPLC** Purity = 99.07%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A : Ammonium bicarbonate in water, Mobile Phase B: Acetonitrile.

Example 20: 1-((S)-4-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-morpholinoethan-1-one



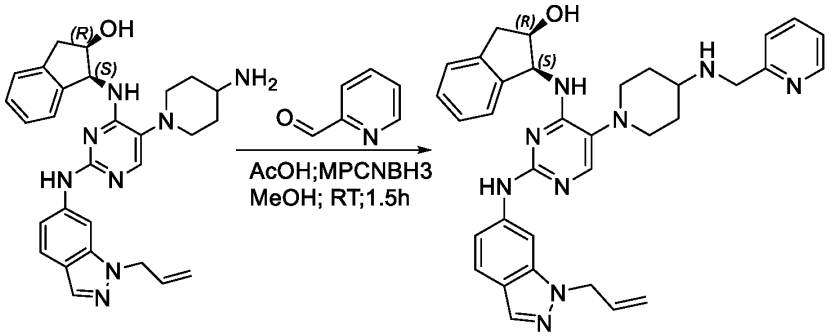
XVIII Example 20

[000250] To a stirred solution 1-((*S*)-4-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-morpholinoethan-1-one **(XVIII)** (Formula C, 0.100 g, 0.205 mmol) and 1-allyl-1H-indazol-6-amine **(XVI)** (Formula D, 0.035 g, 0.205 mmol) in NMP (4 mL) was

added 4M HCl in dioxane (0.103 mL, 0.411 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to get the crude product as yellow gummy mass. The obtained crude product was purified by Prep-HPLC purification using 10mM Ammonium bicarbonate in water and acetonitrile, the product fractions were concentrated under *vacuo* to afford the desired compound as off-white solid. The product was further triturated with diethyl ether, the white solid thrown out was allowed to settle and the supernatant was decanted. The solid was dried under high *vacuo*, to get free base desired compound **Example 20** as an off-white solid; Yield: (0.050 g, 39%).

[000251] **LC_MS**: Calc. for $C_{34}H_{41}N_9O_3$: 623.76; Obs.:624.3 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: 9.33 (br s, 1H), 8.41 (s, 1H), 7.88 (s, 1H), 7.82 (s, 1H), 7.51 (dd, J = 8.80, Hz, 1H), 7.33-7.31 (m, 2H), 7.27-7.23 (m, 1H), 7.19-7.13 (m, 2H), 6.76 (d, J = 7.60 Hz, 1H), 5.60-5.55 (m, 3H), 4.92-4.94 (m, 1H), 4.59-4.63 (m, 2H), 3.95-4.39 (m, 4H), 3.45-3.58 (m, 4H).; **HPLC** Purity = 99.86%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1 % TFA in water, Mobile Phase B: Acetonitrile.

Example 21: (1S,2R)-1-((2-((1-allyl-1H-indazol-6-yl) amino)-5-(4-((pyridin-2-ylmethyl) amino) piperidin-1-yl) pyrimidin-4-yl) amino)-2,3-dihydro-1H-inden-2-ol (BWC5070)

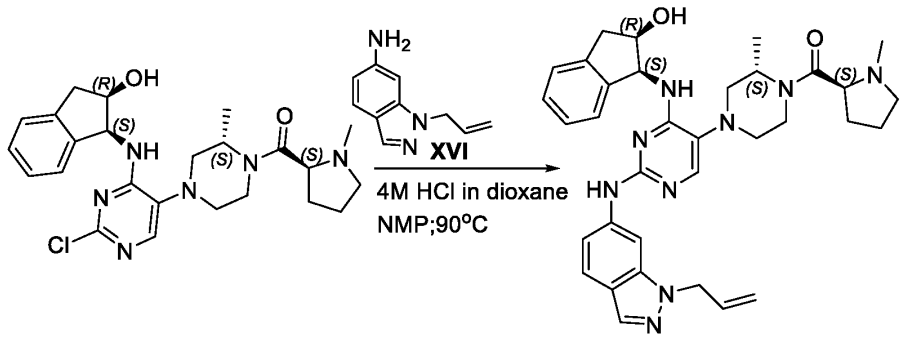


XIX Example 21

[000252] To a mixture of (1*S*,2*R*)-1-((2-((1-allyl-1H-indazol-6-yl)amino)-5-(4-aminopiperidin-1-yl)pyrimidin-4-yl)amino)-2,3-dihydro-1H-inden-2-ol **(XIX)** (0.1 g, 0.201 mmol) and picolinaldehyde (25.88 mg, 0.241 mmol) in a dry MeOH (10 mL)/DCE (10 mL) were added acetic acid (0.2 mL), sodium acetate (82.59 mg, 1.007 mmol) and MPCNBH$_3$ resin (0.1 g) at room temperature under nitrogen atmosphere. The resulting mixture continued to stir at room temperature for 1.5 hours. After completion of the reaction mixture, the reaction mixture was filtered, quenched with water (1 mL) and concentrated in *vacuo* to get crude. The obtained crude product was purified by Prep-HPLC purification using 10mM Ammonium bicarbonate in water and acetonitrile, the product fraction was concentrated under vacuo to get gummy mass. The product was further triturated with diethyl ether, the off-white solid thrown out was allowed to settle and the supernatant was decanted. The solid was dried under high *vacuo*, to afford free base of desired compound **Example 21** as an off-white solid; Yield: (0.012 g, 10.17%).

[000253] **LC_MS**: Calc. for $C_{34}H_{37}N_9O$: 587.73; Obs.: 588.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 9.27 (br s, 1H), 8.49 (br s, 1H), 8.42 (s, 1H), 7.84-7.81 (m, 2H), 7.75-7.74 (m, 1H), 7.51-7.45 (m, 2H), 7.31-7.13 (m, 6H), 6.70 (d, *J* = 8.40 Hz, 1H), 5.55 (br s, 3H), 4.93-4.90 (m, 1H), 4.62-4.58 (m, 2H), 4.35 (d, *J* = 4.80 Hz, 2H), 3.84 (s, 2H), 3.08-2.56 (m, 6H), 1.92 (m, 2H), 1.24 (m, 2H), 1.11 (m, 2H); **HPLC** Purity = 97.62%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

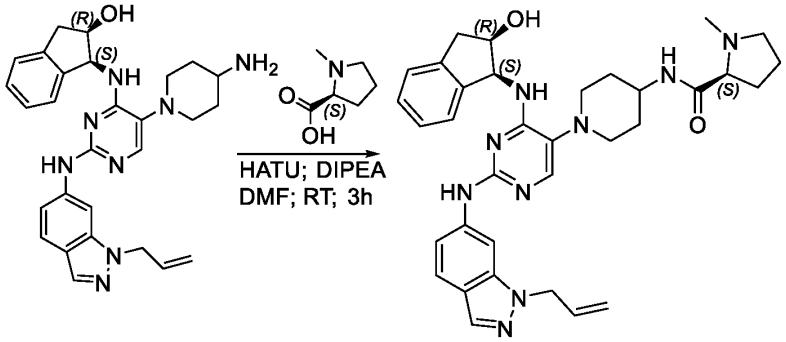
Example 22: ((S)-4-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl) ((S)-1-methylpyrrolidin-2-yl) methanone



[000254] To a stirred solution 2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)-5-((*S*)-3-methyl-4-(methyl-L-prolyl)piperazin-1-yl)pyrimidine **(XX)** (Formula C, 0.100 g, 0.212 mmol) and 1-allyl-1H-indazol-6-amine **(XVI)** (Formula D, 0.036 g, 0.212 mmol) in NMP (3 mL) was added 4M HCl in dioxane (0.212 mL, 0.849 mmol) at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 90 °C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to get the crude product as yellow gummy mass. The obtained crude product was purified by Prep-HPLC purification using 10 mM Ammonium bicarbonate in water and acetonitrile, the product fractions were concentrated under *vacuo* to afford the desired compound as off-white solid. The product was further triturated with diethyl ether, the white solid thrown out was allowed to settle and the supernatant was decanted. The solid was dried under high *vacuo*, to get free base of the desired compound **Example 22** as an off-white solid; Yield: (0.020 g, 15%).

[000255] **LC_MS**: Calc. for $C_{34}H_{41}N_9O_2$: 607.76; Obs.:608.3 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 9.34 (br s, 1H), 8.42 (s, 1H), 7.89 (s, 1H), 7.82 (s, 1H), 7.50-7.52 (m, 1H), 7.31-7.33 (m, 2H), 7.25-7.27 (m, 1H), 7.12-7.23 (m, 2H), 6.76 (d, J = -8.00 Hz, 1H), 5.54-5.59 (m, 3H), 4.93-4.90 (m, 1H), 4.59-4.63 (m, 3H), 4.37-4.41 (m, 2H), 4.11-4.21 (m, 1H).; **HPLC** Purity = 97.54%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1 % TFA in water, Mobile Phase B: Acetonitrile.

Example 23: (S)-N-(1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-4-yl)-1-methylpyrrolidine-2 carboxamide

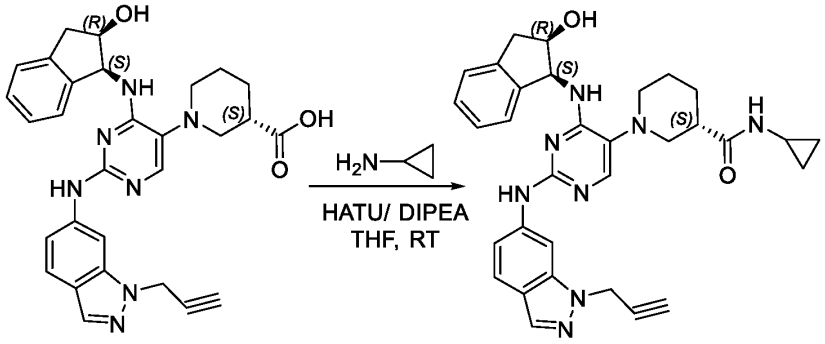


XIX Example 23

[000256] To a solution of (1*S*,2*R*)-1-((2-((1-allyl-1H-indazol-6-yl)amino)-5-(4-aminopiperidin-1-yl)pyrimidin-4-yl)amino)-2,3-dihydro-1H-inden-2-ol **(XIX)** (0.100 g, 0.201 mmol) and methyl-L-proline (0.026 g, 0.201 mmol) in DMF (10 mL), were added DIPEA (0.105 mL, 0.604 mmol) followed by HATU (0.091 g, 0.241 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The obtained crude product was purified by Prep-HPLC purification using ammonium bicarbonate in water and acetonitrile to afford the desired compound **Example 23** as a pale-yellow solid; Yield: (0.015 g, 11%).

[000257] **LC_MS**: Calc. for $C_{34}H_{41}N_9O_2$: 607.76; Obs.:608.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**:): δ 9.29 (s, 1H), 8.71 (d, J = 2 Hz, 1H), 8.63 (d, J = 1.6 Hz, 1H), 8.41-8.37 (m, 1H), 7.91-7.87 (m, 2H), 7.82-7.82 (m, 1H), 7.67-7.64 (m, 1H), 7.52-7.49 (m, 2H), 7.33-7.23 (m, 3H), 7.18-7.12 (m, 2H), 6.68-6.66 (m, 1H), 5.57-5.52 (m, 3H), 4.92 (t, J = 1.6 Hz 2H), 4.64-4.60 (m, 2H), 4.45-4.36 (m, 1H), 4.22-4.08 (m, 1H), 3.75 (s, 1H), 3.20 (m, 2H), 3.03-3.00 (m, 2H), 2.82-2.77 (m, 2H), 2.60 (m, 2H), 2.00-1.70 (m, 5H), 1.60-1.50 (m, 2H). **HPLC** Purity = 93.32%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

Example 24: (S)-N-cyclopropyl-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl) amino) pyrimidin-5-yl)piperidine-3-carboxamide



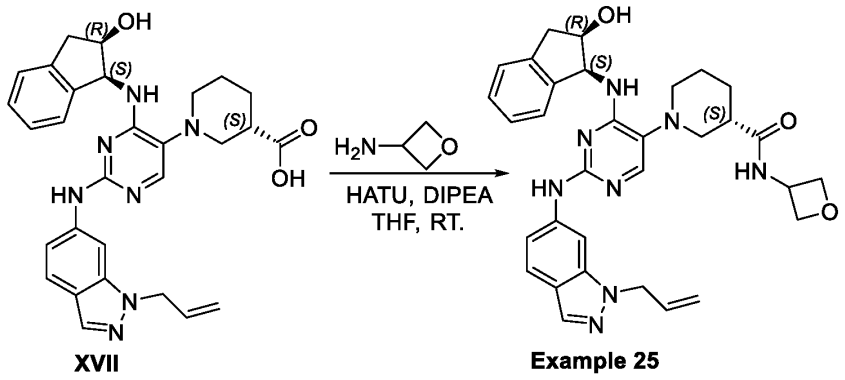
XXII **Example 24**

[000258] To a solution of (*S*)-1-(4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1*H*-indazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(XXII)** (0.3 g, 0.57 mmol) and cyclopropane amine (0.039 mL, 0.57 mmol) in THF (10 mL), were added DIPEA (0.25 mL, 1.43 mmol) followed by HATU (0.26 g, 0.68 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was washed with ethyl acetate (20 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The residue was diluted with water (20 mL) and extracted with ethyl acetate (2 x 40 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude. The obtained crude product was purified by Prep-HPLC purification using 10mM Ammonium bicarbonate in water and acetonitrile to afford the desired compound as gummy mass. The compound was further triturated with diethyl ether, the off-white solid thrown out was allowed to settle and the supernatant was decanted. The solid obtained was dried under high *vacuo*, to afford desired product **Example 24** as an off-white solid. Yield: (0.14 g, 43.3%).

[000259] **LC_MS:** Calc. for $C_{32}H_{34}N_8O_2$: 562.68; Obs.: 563.2 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6):** δ 9.39 (br s, 1H), 8.61 (s, 1H), 7.88 (d, J = 4.40 Hz,

2H), 7.81 (s, 1H), 7.51 (d, *J* = 8.80 Hz, 1H), 7.31 (t, *J* = 7.60 Hz, 2H), 7.23 (t, *J* = 7.20 Hz, 1H), 7.13 (d, *J* = 7.60, Hz, 2H), 6.81 (d, *J* = 4.00, 1H), 5.54 (m, 2H), 4.65 (d, *J* = 4.40 Hz, 2H), 3.18-3.32 (m, 3H), 2.96-2.92 (m, 4H), 2.59-2.57 (m, 3H), 1.12-1.08 (m, 4H), 0.58-0.56 (m, 2H), 0.35-0.34 (m, 2H); **HPLC** Purity: 99.79%, Column: X-Bridge C8(50 X 4.6) mm, 3.5µm, Mobile phase: A: Ammonium bicarbonate in water, Mobile phase: B: Acetonitrile.

Example 25: (S)-1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-(oxetan-3-yl) piperidine-3-carboxamide

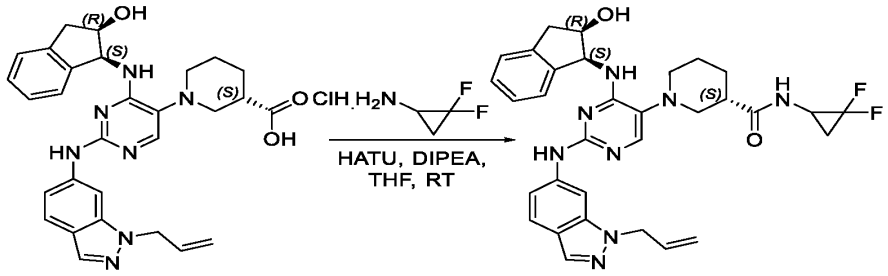


[000260] To a solution of (*S*)-1-(2-((1-allyl-1*H*-indazol-6-yl)amino)-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(XVII)** (0.25 g, 0.475 mmol) in THF (10 mL), were added DIPEA (0.5 mL, 3 mmol) followed by HATU (0.235 g, 0.618 mmol) and oxetan-3-amine (0.045 g, 0.619 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was basified using 10% $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated under a *vacuum* to get the crude product as yellow gummy mass. The obtained crude product was purified by Prep-HPLC purification using 0.1% TFA in water and acetonitrile, the product fractions were concentrated under *vacuo* to afford the desired compound as

colorless gummy mass. The product was further triturated with diethyl ether, the white solid thrown out was allowed to settle and the supernatant was decanted. The solid was dried under high *vacuo*, to get TFA salt of **Example 25** as an off-white solid; Yield: (0.055 g, 19.92%).

[000261] **LC_MS**: Calc. for $C_{32}H_{36}N_8O_3$: 580.69 Obs.: 581.3 [M^++H]. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 9.41 (br s, 1H), 8.59 (d, *J* = 6.40 Hz, 1H), 8.40 (s, 1H), 7.87-7.83 (m, 2H), 7.53 (d, *J* = 8.80 Hz, 1H), 7.33-7.23 (m, 3H), 7.18-7.11 (m, 2H), 6.91-6.88 (m, 1H), 5.60-5.52 (m, 3H), 4.93-4.90 (m, 1H), 4.59-4.75 (m, 6H), 4.35-4.45 (m, 3H), 4.15-4.25 (m, 1H), 3.18-3.10 (m, Hz, 1H), 2.93-3.01 (m, 4H), 2.50-2.56 (m, 1H), 2.45-2.50 (m, 2H), 1.73-1.90 (m, 2H), 1.50-1.56 (m, 2H).; **HPLC** Purity = 98.62%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

Example 26: (3S)-1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-(2,2-difluorocyclopropyl) piperidine-3-carboxamide



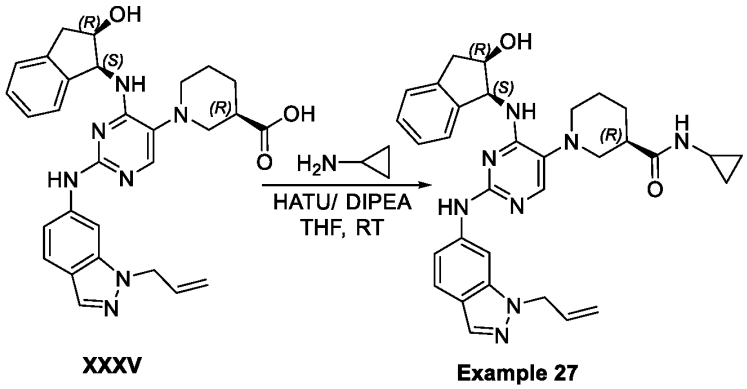
XVII **Example 26**

[000262] To a solution of (*S*)-1-(2-((1-allyl-1*H*-indazol-6-yl)amino)-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(XVII)** (0.20 g, 0.381 mmol) in THF (10 mL), were added DIPEA (0.166 mL, 0.951 mmol) followed by HATU (0.174 g, 0.457 mmol) and 2,2-difluorocyclopropan-1-amine hydrochloride (0.046 g, 0.495 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced

pressure. The residue was basified using 10% $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated under a *vacuum* to get the crude product as yellow gummy mass. The obtained crude product was purified by Prep-HPLC purification using 10 mM Ammonium bicarbonate in water and acetonitrile, the product fractions were concentrated under *vacuo* to afford the desired compound as colorless gummy mass. The product was further triturated with diethyl ether, the white solid thrown out was allowed to settle and the supernatant was decanted. The solid was dried under high *vacuo*, to get free base desired compound **Example 26** as an off-white solid; Yield: (0.018 g, 7.5%).

[000263] **LC_MS**: Calc. for $C_{32}H_{34}F_2N_8O_2$: 600.67; Obs.: 601.3 [M^++H]. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 9.31 (br s, 1H), 8.42 (s, 1H), 8.28 (d, J = 3.60 Hz, 1H), 8.18 (s, 1H), 7.89 (s, 1H), 7.82 (s, 1H), 7.52-7.49 (m, 1H), 7.22-7.32 (m, 3H), 7.11-7.18 (m, 2H), 6.80-6.77 (m, 1H), 5.52-5.59 (m, 2H), 4.92 (d, J = 10.40, Hz, 1H), 4.61 (d, J = 16.00 Hz, 2H), 4.36 (m, 1H); **HPLC** Purity = 95.74%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1 % TFA in water, Mobile Phase B: Acetonitrile.

Example 27: (R)-1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide



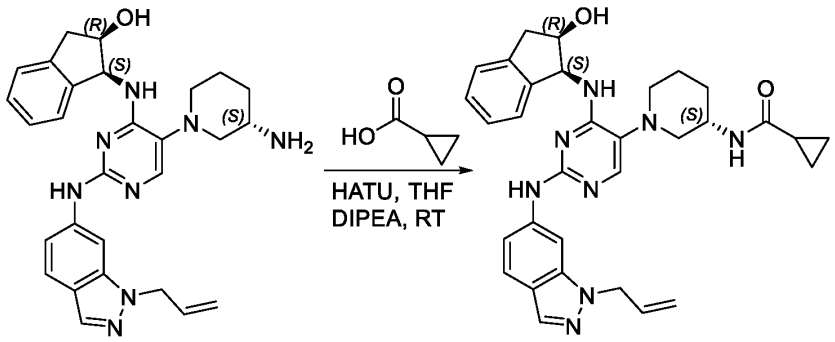
XXXV **Example 27**

[000264] To a solution of (R)-1-(2-((1-allyl-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-

yl)piperidine-3-carboxylic acid **(XXXV)** (0.15 g, 0.28 mmol) and cyclopropane amine (0.02 mL, 0.38 mmol) in THF (10 mL), were added DIPEA (0.20 mL, 0.86 mmol) followed by HATU (0.13 g, 0.34 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was washed with ethyl acetate (20 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The residue was diluted with water (20 mL) and extracted with ethyl acetate (2 x 40 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude. The obtained crude product was purified by Prep-HPLC purification using 10mM Ammonium bicarbonate in water and acetonitrile to afford the desired compound as gummy mass. The compound was further triturated with diethyl ether, the off-white solid thrown out was allowed to settle and the supernatant was decanted. The solid obtained was dried under high *vacuo*, to afford desired product **Example 27** (**BWC5207**) as an off-white solid. Yield: (0.100 g, 61.9%).

[000265] **LC_MS:** Calc. for $C_{32}H_{36}N_8O_2$: 565.20; Obs.: 564.69 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6):** δ 9.30 (br s, 1H), 8.41 (s, 1H), 7.88-7.81 (m, 3H), 7.50 (d, J = 8.80 Hz, 1H), 7.33-7.23 (m, 3H), 7.18-7.11 (m, 2H), 6.74 (m, 1H), 5.59-5.47 (m, 3H), 4.92 (d, J = 1.20 Hz, 1H), 4.63-4.59 (m, 2H), 4.36-4.35 (m, 1H), 4.10-4.20 (m, 1H), 3.17-3.19 (m, 1H), 3.15-2.92 (m, 4H), 2.62-2.58 (m, 2H), 2.52-2.37 (m, 1H), 1.78-1.71 (m, 2H), 1.38-1.55 (m, 2H), 0.60-0.56 (m, 2H), 0.38-0.35 (m, 2H).; **HPLC** Purity: 99.79%, Column: X-Bridge C8(50 X 4.6) mm, 3.5µm, Mobile phase: A: Ammonium bicarbonate in water, Mobile phase: B: Acetonitrile.

Example 28: N-((S)-1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-3-yl) cyclopropane carboxamide

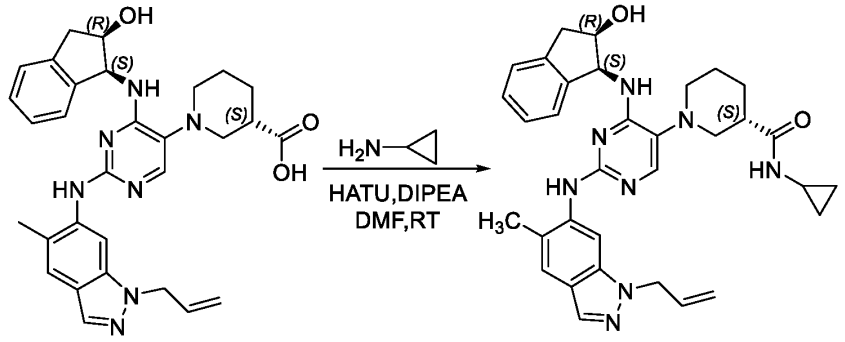


XXIII **Example 28**

[000266] To a solution of (1*S*,2*R*)-1-((2-((1-allyl-1H-indazol-6-yl)amino)-5-((*S*)-3-aminopiperidin-1-yl)pyrimidin-4-yl)amino)-2,3-dihydro-1H-inden-2-ol **(XXIII)** (0.2 g, 0.402 mmol) in THF (10 mL), were added DIPEA (0.2 mL, 1.208 mmol) followed by HATU (0.183 g, 0.483 mmol) and cyclopropane carboxylic acid (0.045 g, 0.523 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to get the crude product as yellow gummy mass. The obtained crude product was purified by Prep-HPLC purification using 10 mM Ammonium bicarbonate in water and acetonitrile, the product fractions were concentrated under *vacuo* to afford the desired compound as colorless gummy mass. The product was further triturated with diethyl ether, the white solid thrown out was allowed to settle and the supernatant was decanted. The solid was dried under high *vacuo*, to get free base desired compound **Example 28** as an off-white solid; Yield: (0.096 g, 42%).

[000267] **LC_MS**: Calc. for $C_{32}H_{36}N_8O_2$: 564.69; Obs.: 565.3 [M^++H]. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: 9.29 (br s, 1H), 8.41 (s, 1H), 8.00 (d, *J* = 7.60 Hz, 1H), 7.86-7.82 (m, 2H), 7.52-7.50 (m, 1H), 7.32-7.31 (m, 2H), 7.30-7.22 (m, 1H), 7.16-7.12 (m, 1H), 6.67 (d, *J* = 8.40 Hz, 1H), 5.45-5.60 (m, 3H), 4.91-4.94 (m, 2H), 4.60-4.64 (m, 2H), 4.40 (m, 1H), 4.20-4.30 (m, 1H).; **HPLC** Purity = 99.71%, X - Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile.

Example 29: (S)-1-(2-((1-allyl-5-methyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide



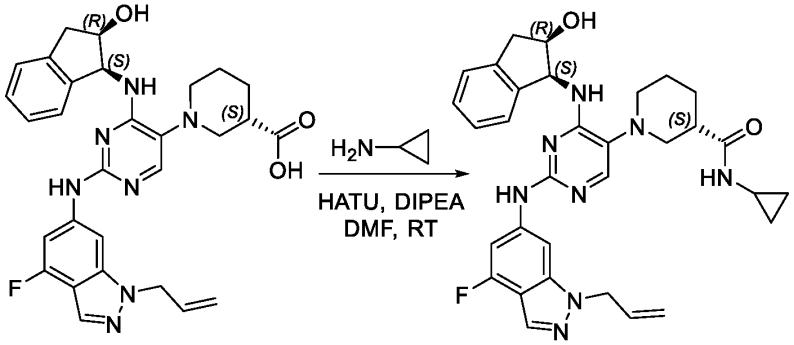
XXIV **Example 29**

[000268] To a solution of ((*S*)-1-(2-((1-allyl-5-methyl-1*H*-indazol-6-yl)amino)-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(XXIV)** (0.2 g, 0.37 mmol) and cyclopropane amine (0.025 mL, 0.45 mmol) in DMF (10 mL), were added DIPEA (0.20 mL, 1.11 mmol) followed by HATU (0.17 g, 0.45 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was washed with ethyl acetate (20 mL). The filtrate was concentrated in *vacuo* to get brown residue. The residue was diluted with water (20 mL) and extracted with ethyl acetate (2 x 40 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude. The obtained crude product was purified by Prep-HPLC purification using 10 mM Ammonium bicarbonate in water and acetonitrile to afford the desired compound as gummy mass. The compound was further triturated with diethyl ether, the off-white solid thrown out was allowed to settle and the supernatant was decanted. The solid obtained was dried under high *vacuo*, to afford desired product **Example 29** as an off-white solid. Yield: (0.090 g, 41.0%).

[000269] **LC_MS:** Calc. for $C_{33}H_{38}N_8O_2$: 578.72; Obs.: 579.4 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6):** δ 8.23 (br s, 1H), 7.87-7.83 (m, 3H), 7.77 (br s, 1H),

7.48 (s, 1H), 7.30-7.14 (m, 4H), 5.49-5.46 (m, 3H), 4.93-4.55 (m, 5H), 3.14-2.51 (m, 9H), 2.36-2.33 (m, 3H), 1.76-1.51 (m, 4H), 0.57-0.54 (m, 4H); **HPLC** Purity: 99.79%, Column: X-Bridge C8(50 X 4.6) mm, 3.5µm, Mobile phase: A: Ammonium bicarbonate in water, Mobile phase: B: Acetonitrile.

Example 30: (S)-1-(2-((1-allyl-4-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide

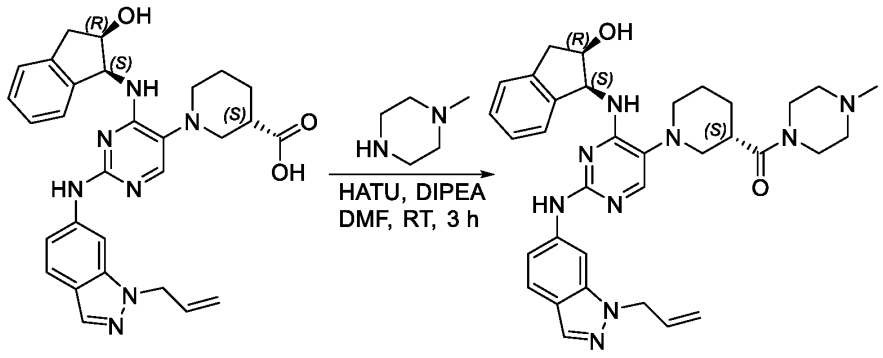


[000270] To a solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(XXVI)** (0.15 g, 0.275 mmol) and cyclopropane amine (0.019 g, 0.332 mmol) in DMF (10 mL), were added DIPEA (0.5 mL, 3 mmol) followed by HATU (0.136 g, 0.357 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was basified using 10% $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated under a *vacuum* to get the crude product as yellow gummy mass. The obtained crude product was purified by Prep-HPLC purification using 10 mM Ammonium bicarbonate in water and acetonitrile, the product fractions were concentrated under *vacuo* to afford the desired compound as colorless gummy mass. The product was further triturated with

diethyl ether, the white solid thrown out was allowed to settle and the supernatant was decanted. The solid was dried under high *vacuo*, to get free base desired compound **Example 30** as an off-white solid; Yield: (0.064 g, 39.8%).

[000271] **LC_MS: Calc.** for $C_{32}H_{35}FN_8O_2$: 582.68; Obs.: 583.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 9.43 (br s, 1H), 8.22 (br s, 1H), 7.89 (d, J = 4.80 Hz, 3H), 7.30 (d, J = 9.20, 12.20 Hz, 3H), 7.24 (d, J = 7.20, Hz, 1H), 7.08 (d, J = 12.40, 1H), 6.83-6.76 (m, 1H), 5.57-5.52 (m, 3H), 4.95 (d, J = 1.20 Hz, 1H), 4.64 (d, J = 4.00 Hz, 2H), 4.40 (m, 4H), 3.15 (d, J = 4.40 Hz, 1H), 3.01-2.92 (m, 3H), 2.59-2.56 (m, 1H), 2.50-2.34 (m, 3H), 1.53 (m, 2H), 0.59-0.55 (m, 2H), 0.36-0.34 (m, 2H); **HPLC** Purity = 98.54%, X-Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 5mM Ammonium bicarbonate in water, Mobile Phase B: Acetonitrile.

Example 31: ((S)-1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-3-yl)(4-methylpiperazin-1-yl)methanone



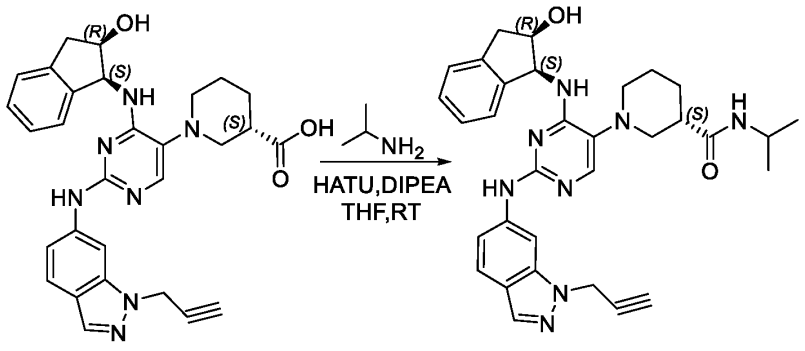
XVII **Example 31**

[000272] To a solution of (*S*)-1-(2-((1-allyl-1*H*-indazol-6-yl)amino)-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(XVII)** (0.25 g, 0.475 mmol) in DMF (10 mL), were added DIPEA (0.5 mL, 3 mmol) followed by HATU (0.235 g, 0.618 mmol) and 1-methylpiperazine (0.062 g, 0.619 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was basified using

10% $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated under a *vacuum* to get the crude product as yellow gummy mass. The obtained crude product was purified by Prep-HPLC purification using 10 mM Ammonium bicarbonate in water and acetonitrile, the product fractions were concentrated under *vacuo* to afford the desired compound as colorless gummy mass. The product was further triturated with diethyl ether, the white solid thrown out was allowed to settle and the supernatant was decanted. The solid was dried under high *vacuo*, to get free base desired compound **Example 31** as an off-white solid; Yield: (0.023 g, 7.95%).

[000273] **LC_MS**: Calc. for $C_{34}H_{41}N_9O_2$: 607.76; Obs.: 608.3 [M^++H]. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)**: δ 9.30 (br s, 1H), 8.44 (s, 1H), 7.82 (m, 2H), 7.49 (m, Hz, 1H), 7.34-7.22 (m, 5H), 6.78 (br s, 1H), 5.63-5.55 (m, 3H), 4.93-4.90 (m, 1H), 4.65-4.57 (m, 4H), 3.21-3.08 (m, 4H), 3.02-2.76 (m,6H), 2.01-.215 (m, 4H), 1.81-1.73 (m, 5H), 1.12 (s, 3H); **HPLC** Purity = 95.50%, X -Bridge C8 (50 X 4.6) mm, 3.5µm, Mobile Phase A: 5mM Ammonium bicarbonate in water, Mobile Phase B: Acetonitrile.

Example 32: (S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl) amino) pyrimidin-5-yl)-N-isopropylpiperidine-3-carboxamide



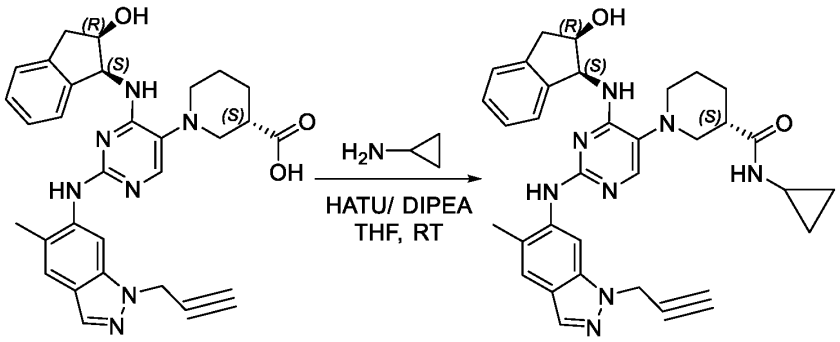
XXII **Example 32**

[000274] To a solution of (*S*)-1-(4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1*H*-indazol-6-yl)amino)pyrimidin-5-

yl)piperidine-3-carboxylic acid **(XXII)** (0.15g, 0.28 mmol) and Propane-2-amine (0.016 mL, 0.29 mmol) in THF (10 mL), were added DIPEA (0.13 mL, 0.72 mmol) followed by HATU (0.13 g, 0.34 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was washed with ethyl acetate (20 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The residue was diluted with water (20 mL) and extracted with ethyl acetate (2 x 40 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude. The obtained crude product was purified by Prep-HPLC purification using 10 mM Formic acid in water and acetonitrile to afford the desired compound as gummy mass. The compound was further triturated with diethyl ether, the off-white solid thrown out was allowed to settle and the supernatant was decanted. The solid obtained was dried under high *vacuo*, to afford desired product **Example 32** as an off-white solid. Yield: (0.010 g, 6.0 %).

[000275] **LC_MS:** Calc. for $C_{32}H_{36}N_8O_2$: 564.69; Obs.: 565.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ 9.37 (s, 1H), 8.60 (s, 1H), 7.89 (br s, 1H), 7.81 (s, 1H), 7.68-7.66 (m, 1H), 7.51 (d, J = 8.40 Hz, 1H), 7.32 (t, J = 6.80 Hz, 2H), 7.24 (t, J = 3.60 Hz, 1H), 7.25-7.23 (m, 2H), 6.85 (br s, 1H), 5.69-5.50 (m, 2H), 4.66-4.61 (m, 2H), 4.01-3.76 (m, 2H), 3.18-2.92 (m, 6H), 2.41-2.39 (m, 1H), 1.80-1.60 (m, 4H), 1.11-1.00 (m, 7H); **HPLC** Purity: 96.69%, Column: X-Bridge C8(50 X 4.6) mm, 3.5µm, Mobile phase: A: 0.1% Formic acid in water, Mobile phase: B: Acetonitrile.

Example 33: (S)-N-cyclopropyl-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((5-methyl-1-(prop-2-yn-1-yl)-1H-indazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide



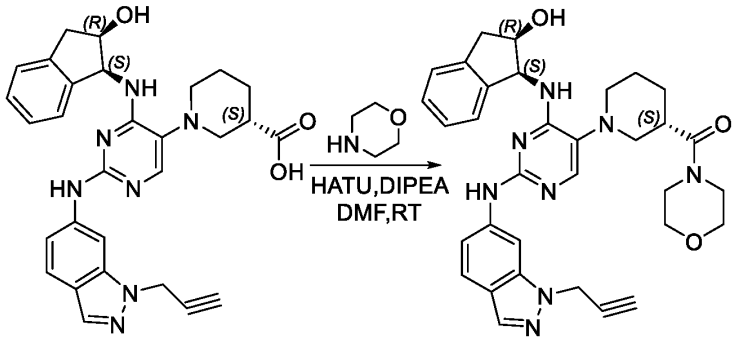
XXVIII **Example 33**

[000276] To a solution (*S*)-1-(4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)-2-((5-methyl-1-(prop-2-yn-1-yl)-1*H*-indazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid (**XXVIII**) (0.15 g, 0.27 mmol) and cyclopropane amine (0.02 mL, 0.27 mmol) in THF (10 mL), were added DIPEA (0.12 mL, 0.69 mmol) followed by HATU (0.13 g, 0.34 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 16 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was washed with ethyl acetate (20 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The residue was diluted with water (20 mL) and extracted with ethyl acetate (2 x 40 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude. The obtained crude product was purified by Prep-HPLC purification using 10mM Ammonium bicarbonate in water and acetonitrile to afford the desired compound as gummy mass. The compound was further triturated with diethyl ether, the off-white solid thrown out was allowed to settle and the supernatant was decanted. The solid obtained was dried under high *vacuo*, to afford desired product **Example 33** as an off-white solid. Yield: (0.030 g, 18%).

[000277] **LC_MS:** Calc. for $C_{33}H_{36}N_8O_2$: 576.71; Obs.: 577.30 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6):** δ 8.43 (d, J = 5.60 Hz, 1H), 7.88-7.82 (m, 3H), 7.77 (d, J = 3.20 Hz, 1H), 7.49 (s, 1H), 7.31-7.20 (m, 3H), 7.15-7.11 (m, 1H), 5.60-5.48 (m, 2H), 4.71-4.66 (m, 1H), 4.60-4.59 (m, 1H), 4.31 (d, J = 2.00 Hz, 1H), 3.23-3.17 (m, 3H), 2.98 (s, 1H), 2.93-2.89 (m, 3H), 2.60-2.56 (m, 2H), 2.37 (s, 4H), 1.75 (m,

2H), 1.55 (m, 2H), 1.11 (s, 1H), 0.58-0.55 (m, 2H), 0.36-0.34 (m, 2H).**HPLC** Purity: 97.76%, Column: X-Bridge C8(50 X 4.6) mm, 3.5µm, Mobile phase: A: Ammonium bicarbonate in water, Mobile phase: B: Acetonitrile.

Example 34: ((S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl) amino)pyrimidin-5-yl)piperidin-3-yl)(morpholino) methanone



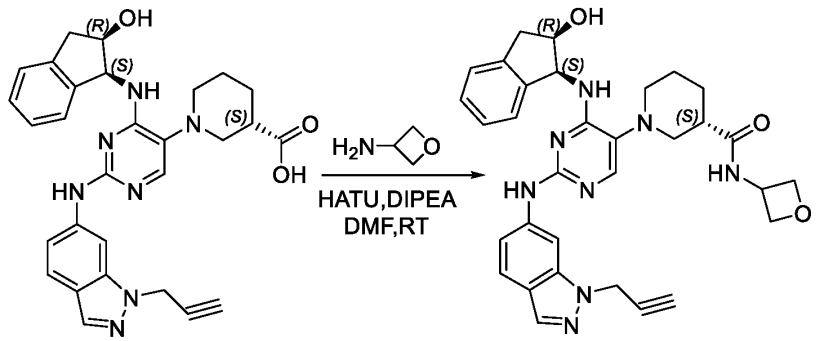
XXII **Example 34**

[000278] To a solution of ((*S*)-1-(4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1*H*-indazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid(**I**) (0.2 g, 0.38 mmol) and morpholine **(II)** (0.03mL, 0.38 mmol) in DMF (10 mL), were added DIPEA (0.16 mL, 0.95 mmol) followed by HATU (0.174 g, 0.46 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was washed with ethyl acetate (20 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The residue was diluted with water (20 mL) and extracted with ethyl acetate (2 x 40 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude. The obtained crude product was purified by Prep-HPLC purification using 10mM Ammonium bicarbonate in water and acetonitrile to afford the desired compound as gummy mass. The compound was further triturated with diethyl ether, the off-white solid thrown out was allowed to settle and the supernatant was decanted. The solid obtained was dried under

high *vacuo*, to afford desired product **Example 34** as an off-white solid. Yield: (0.060 g, 26.0%).

[000279] **LC_MS:** Calc. for $C_{33}H_{36}N_8O_3$: 592.70; Obs.: 593.2 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6):** δ 9.38 (s, 1H), 8.61 (br s, 1H), 7.86 (s, 1H), 7.81 (br s, 1H), 7.51 (d, J = 8.80 Hz, 1H), 7.33 (t, J = 6.80 Hz, 2H), 7.24 (t, J = 7.20 Hz, 1H), 7.16-7.13 (m, 2H), 6.77 (br s, 1H), 5.69-5.62 (m, 2H), 4.67-4.59 (m, 2H), 4.09-3.98 (m, 1H), 3.45-3.37 (m, 3H), 3.31-3.24 (m, 6H), 3.17-2.93 (m, 7H), 1.82-1.11 (m, 4H); **HPLC** Purity: 98.02%, Column: X-Bridge C8(50 X 4.6) mm, 3.5µm, Mobile phase: A: Formic acid in water, Mobile phase: B: Acetonitrile.

Example 35: (S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl)amino)pyrimidin-5-yl)-N-(oxetan-3-yl)piperidine-3-carboxamide



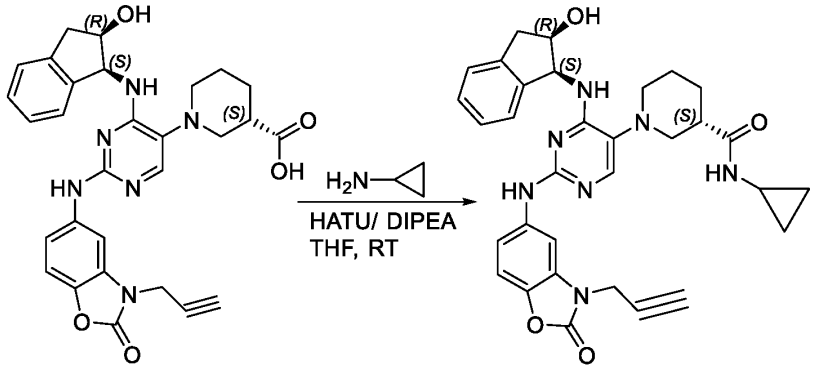
XXII **Example 35**

[000280] To a solution of (*S*)-1-(4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1*H*-indazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid (**XXII**) (0.2 g, 0.38 mmol) and oxetan-3-amine (0.03mL, 0.38 mmol) in DMF (10 mL), were added DIPEA (0.16 mL, 0.96 mmol) followed by HATU (0.17 g, 0.45 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was washed with ethyl acetate (20 mL). The filtrate was concentrated in *vacuo* to get a brown residue. The residue was diluted with water (20 mL) and extracted with ethyl acetate (2 x 40 mL). The combined organic layer was dried

over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude. The obtained crude product was purified by Prep-HPLC purification using 10mM Ammonium bicarbonate in water and acetonitrile to afford the desired compound as gummy mass. The compound was further triturated with diethyl ether, the off-white solid thrown out was allowed to settle and the supernatant was decanted. The solid obtained was dried under high *vacuo*, to afford desired product **Example 35** as an off-white solid. Yield: (0.035 g, 16.0%).

[000281] **LC_MS:** Calc. for $C_{32}H_{34}N_8O_3$: 578.68; Obs.: 579.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6):** δ 9.38 (s, 1H), 8.61-8.57 (m, 2H), 7.89 (br s, 1H), 7.82 (s, 1H), 7.51 (d, J = 8.80 Hz, 1H), 7.32 (t, J = 6.80 Hz, 2H), 7.24 (t, J = 7.20 Hz, 1H), 7.16-7.12 (m, 2H), 6.83 (br s, 1H), 5.68 (t, J = 5.60 Hz, 1H), 5.51 (br s, 1H), 4.74-4.64 (m, 5H), 4.39-4.35 (m, 2H), 3.26-3.24 (m, 3H), 3.03-2.93 (m, 4H), 2.68-2.58 (m, 2H), 1.84-1.54 (m, 4H); **HPLC** Purity: 98.00%, Column: X-Bridge C8(50 X 4.6) mm, 3.5µm, Mobile phase: A: TFA in water, Mobile phase: B: Acetonitrile.

Example 36: (S)-N-cyclopropyl-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((2-oxo-3-(prop-2-yn-1-yl)-2,3-dihydrobenzo[d]oxazol-5-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide



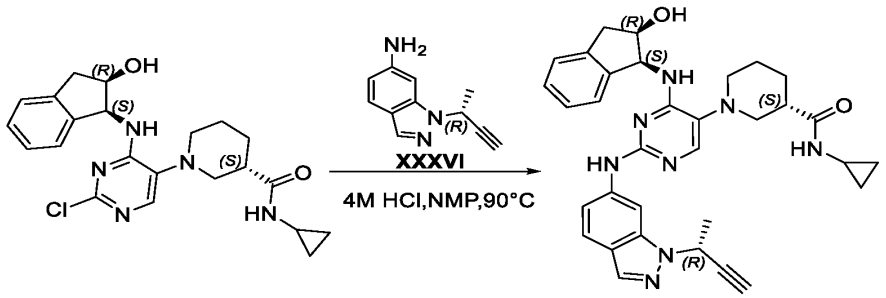
XXX **Example 36**

[000282] To a solution (*S*)-1-(4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)-2-((2-oxo-3-(prop-2-yn-1-yl)-2,3-dihydrobenzo[d]oxazol-5-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid (**XXX**) (0.3 g, 0.55 mmol) and cyclopropane amine (0.03 mL, 0.55 mmol) in THF (10 mL), were added

DIPEA (0.20 mL, 1.39 mmol) followed by HATU (0.26 g, 0.66 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was washed with ethyl acetate (20 mL). The filtrate was concentrated in *vacuo* to get brown residue. The residue was diluted with water (20 mL) and extracted with ethyl acetate (2 x 40 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under a *vacuum* to get the crude. The obtained crude product was purified by Prep-HPLC purification using 10mM Ammonium bicarbonate in water and acetonitrile to afford the desired compound as gummy mass. The compound was further triturated with diethyl ether, the off-white solid thrown out was allowed to settle and the supernatant were decanted. The solid obtained was dried under high *vacuo*, to afford desired product **Example 36** as an off-white solid. Yield: (0.080 g, 25%),

[000283] **LC_MS:** Calc. for $C_{32}H_{34}N_7O_4$: 579.68; Obs.: 580.20 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6):** δ 9.25 (s, 1H), 8.28 (d, J = 6.80 Hz, 1H), 7.87-7.83 (m, 2H), 7.31-7.16 (m, 6H), 6.75 (br s, 1H), 5.59-5.49 (m, 2H), 4.62-4.60 (m, 1H), 4.29 (s, 2H), 3.24-2.90 (m, 6H), 2.60-2.56 (m, 2H), 2.50 (m, 1H), 1.75-1.52 (m, 4H), 0.58-0.55 (m, 2H), 0.36-0.32 (m, 2H); **HPLC** Purity: 98.62%, Column: X-Bridge C8(50 X 4.6) mm, 3.5µm, Mobile phase: A: Ammonium bicarbonate in water, Mobile phase: B: Acetonitrile.

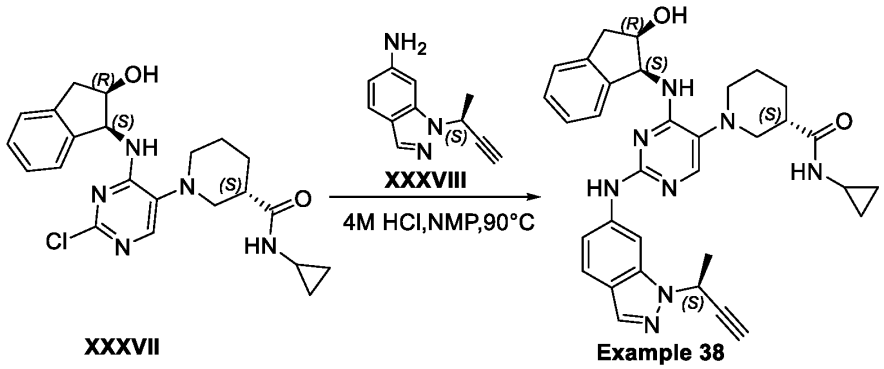
Example 37: (S)-1-(2-(1-(R)-but-3-yn-2-yl)-1H-indazol-6-yl) amino)-4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide



XXXVII **Example 37**

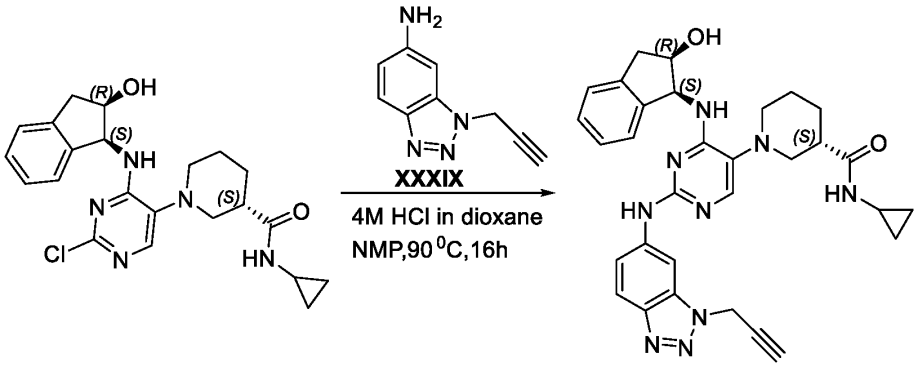
[000284] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-cyclopropylpiperidine-3-carboxamide **(XXXVII)** (0.400 g, 0.93 mmol) and (*R*)-1-(but-3-yn-2-yl)-1*H*-indazol-6-amine **(XXXVI)** (0.173 g, 0.93 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.2 mL, 3.74 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 16 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The obtained crude was purified by preparative HPLC reverse phase in ammonium bicarbonate in water and acetonitrile to afford the desired product **Example 37** as an Off-white solid. Yield: (0.122 g, 22.6 %), **LC_MS:** Calc. $C_{33}H_{36}N_8O_2$:576.71.; Obs.: 577.3 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 9.42 (s, 1H), 8.65 (s, 1H), 7.89 (d, J = 5.60 Hz, 2H), 7.83 (s, 1H), 7.50 (d, J = 8.40 Hz, 1H), 7.38-7.31 (m, 2H), 7.28-7.24 (m, 1H), 7.19-7.14 (m, 1H), 7.11-7.09 (m, 1H), 6.88 (s, 1H), 5.68-5.57 (m, 1H), 4.65-4.60 (m, 1H), 4.11 (s, 1H), 3.27 (d, J = 2.00 Hz, 2H), 3.08 (s, 2H), 3.02-2.92 (m, 4H), 2.59-2.56 (m, 2H), 1.76-1.73 (m, 2H), 1.54-1.48 (m, 2H), 1.34-1.24 (m, 3H), 0.59-0.54 (m, 2H), 0.38 (s, 2H). **HPLC** Purity:99.73%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A:0.1% TFA in water Mobile phase: B: ACN.

Example 38: (S)-1-(2-((1-(S)-but-3-yn-2-yl)-1H-indazol-6-yl) amino)-4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide



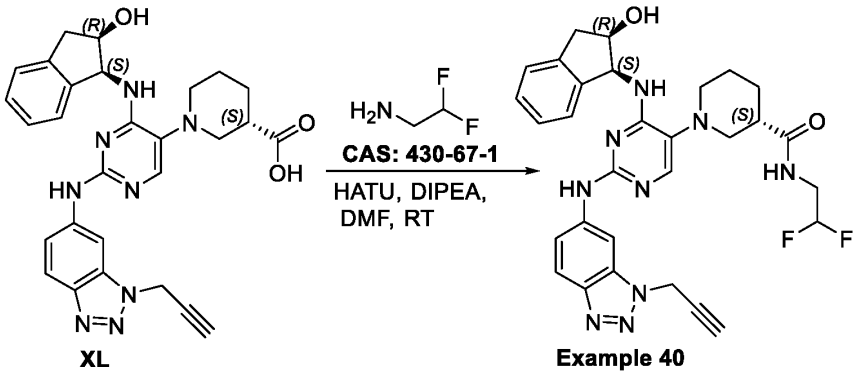
[000285] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-cyclopropylpiperidine-3-carboxamide **(XXXVII)** (0.400 g, 1.05 mmol) and (*S*)-1-(but-3-yn-2-yl)-1*H*-indazol-6-amine **(XXXVIII)** (0.195 g, 1.05 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.2 mL, 4.21 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 16 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The obtained crude was purified by Preparative HPLC reverse phase in ammonium bicarbonate in water and acetonitrile to afford desired product **Example 38** as an Off-white solid. Yield: (0.110 g,18.0 %), **LC_MS:** Calc. $C_{33}H_{36}N_8O_2$:576.71.; Obs.: 577.3 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 9.33 (s, 1H), 8.55 (s, 1H), 7.88 (d, J = 4.00 Hz, 2H), 7.82 (s, 1H), 7.51 (d, J = 8.40 Hz, 1H), 7.31 (d, J = 7.20 Hz, 1H), 7.26-7.16 (m, 2H), 7.14-7.12 (m, 2H), 6.81 (s, 1H), 5.76-5.73 (m, 1H), 5.52 (s, 1H), 4.98 (d, J = 5.60 Hz, 1H), 4.64 (d, J = 4.00 Hz, 1H), 3.39 (d, J = 2.40 Hz, 2H), 3.24-3.22 (m, 1H), 3.01-2.91 (m, 4H), 1.78-1.72 (m, 2H), 1.53 (s, 2H), 1.20 (d, J = 6.80 Hz, 3H), 1.11 (s, 2H), 0.58-0.54 (m, 2H), 0.40-0.30 (m, 2H). **HPLC** Purity;99.18%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A: Ammonium bicarbonate in water: B: ACN.

Example 39: (S)-N-cyclopropyl-1-(4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-(1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3] triazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide



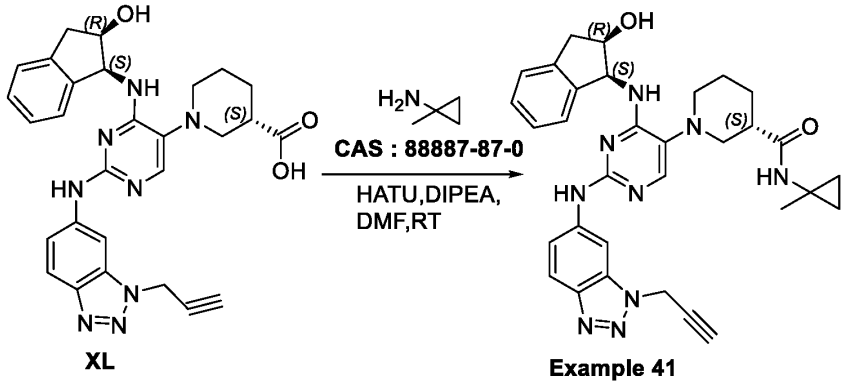
[000286] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-cyclopropylpiperidine-3-carboxamide **(XXXVII)** (0.300 g, 0.7 mmol) and 1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine **(XXXIX)** (0.121g, 0.70 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.2 mL, 0.93 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 16 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The obtained crude was purified by Preparative HPLC reverse phase in ammonium bicarbonate in water and acetonitrile to afford desired product **Example 39** as an off-white solid. Yield: (0.070 g, 17 %), **LC_MS:** Calc. $C_{31}H_{33}N_9O_2$:563.67; Obs.: 564.3 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 9.61 (s, 1H), 8.78 (d, J = 1.60 Hz, 1H), 7.91-7.86 (m, 2H), 7.81 (d, J = 8.80 Hz, 1H), 7.40-7.38 (m, 1H), 7.34-7.22 (m, 3H), 7.14-7.11 (m, 1H), 6.86-6.84 (m, 1H), 5.65 (d, J = 2.40 Hz, 1H), 5.54 (d, J = 4.40 Hz, 1H), 5.19-5.14 (m, 1H), 4.65 (d, J = 4.80 Hz, 1H), 4.36-4.20 (m, 1H), 3.41-3.40 (m, 1H), 3.31 (s, 1H), 3.00-2.92 (m, 4H), 2.60-2.56 (m, 2H), 2.34-2.33 (m, 1H), 1.90-1.76 (m, 2H), 1.55-1.45 (m, 2H), 0.58-0.55 (m, 2H), 0.36-0.34 (m, 2H). **HPLC** Purity; 97.36%, Column: X-Bridge C8(50 X 4.6) mm,5µm, Mobile phase: A:0.1% TFA in water Mobile phase: B: ACN.

Example 40: (S)-N-(2,2-difluoroethyl)-1-(4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide



[000287] To a solution (*S*)-1-(4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid (**XL**) (2.000 g, 1 eq, 3.813 mmol) and 2,2-difluoroethan-1-amine (CAS: 430-67-1: 463.6 mg, 414 µL, 1.5 eq, 5.719 mmol) in DMF (20 mL), were added DIPEA (1.478 g, 1.99 mL, 3 eq, 11.44 mmol) followed by HATU (2.175 g, 1.5 eq, 5.719 mmol) at 0°C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 16 hours. The reaction progress was monitored by TLC. After completion of the reaction, ice water was added to the reaction mixture, solid precipitated out. This was kept for stirring for 30min in ice water and then filtered off and washed thoroughly with ice water and dried under vacuum to get crude as pale brown solid. The obtained crude product was purified by Prep-HPLC purification using 10mM Ammonium bicarbonate in water and acetonitrile to afford the desired compound as a gummy mass. The compound was further triturated with diethyl ether, the off-white solid thrown out was allowed to settle down and the supernatant was decanted. The solid obtained was dried under a high *vacuum*, to afford the desired product **Example 40** as an off-white solid. Yield: (0.55 g, 24.5%), **LC_MS:** Calc. for $C_{30}H_{31}F_2N_9O_2$: 587.64; Obs.: 588.30 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6):** δ 9.61 (s, 1H), 8.78 (s, 1H), 8.28-8.25 (m, 1H), 7.92 (s, 1H), 7.82 (d, J = 8.80 Hz, 1H), 7.40 (d, J = 10.00 Hz, 1H), 7.32-7.29 (m, 2H), 7.24 (t, J = 7.20 Hz, 1H), 7.14 (t, J = 7.20 Hz, 1H), 6.85 (brs, 1H), 6.09-5.94 (m, 1H), 5.81-5.80 (m, 1H), 5.51 (brs, 1H), 5.17 (d, J = 8.00 Hz, 1H), 4.68-4.64 (m, 1H), 4.36-4.30 (m, 1H), 3.47-3.43 (m, 2H), 3.40-3.39 (m, 2H), 3.33-3.27 (m, 1H), 3.02-2.92 (m, 4H), 2.51-2.48 (m, 1H), 1.82-1.74 (m, 2H), 1.74-1.56 (m, 2H). **HPLC** Purity: 99.94%, Column: X-Bridge C18(150 X 4.6) mm, 3.5µm, Mobile phase: A: Ammonium bicarbonate in water, Mobile phase: B: Acetonitrile

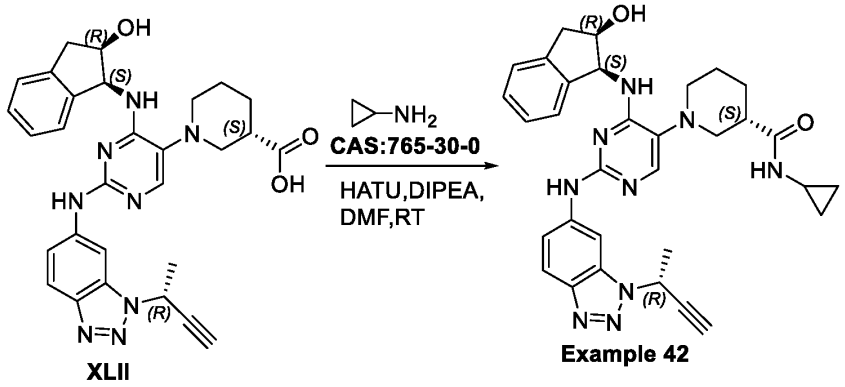
Example 41: (S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl)-N-(1-methyl cyclopropyl) piperidine-3-carboxamide



XL Example 41

[000288] To a solution of (*S*)-1-(4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(XL)** (0.200 g, 0.38 mmol) and 1-methylcyclopropan-1-amine (CAS : 88887-87-0, 0.027 mL, 0.38 mmol,) in DMF (10 mL), were added DIPEA (0.21 mL, 1.14 mmol) followed by HATU (0.174 g, 0.45 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 4 hours. The reaction progress was monitored by UPLC, reaction mixture was quenched with water, and DMF was concentrated under reduced pressure. 10% aq $NaHCO_3$ solution was added and extracted with ethyl acetate (2 times) the organic phase was dried under Na_2SO_4, and the solvent was filtered and evaporated in *vacuo* to get the crude product. The obtained crude was purified by Preparative HPLC reverse phase in ammonium bicarbonate in water and acetonitrile to afford desired product **Example 41** as an Off-white solid. Yield: (0.112 g, 50.6 %), **LC_MS:** Calc. $C_{32}H_{35}N_9O_2$:577.69.; Obs.: 578.2 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 9.60 (s, 1H), 8.78 (d, J = 1.60 Hz, 1H), 8.04 (s, 1H), 7.90 (d, J = 3.20 Hz, 1H), 7.82 (d, J = 9.20 Hz, 1H), 7.41-7.38 (m, 1H), 7.34-7.29 (m, 2H), 7.25-7.22 (m, 1H), 7.15-7.11 (m, 1H), 6.85 (s, 1H), 5.67-5.64 (m, 1H), 5.52 (d, J = 4.40 Hz, 1H), 5.20-5.15 (m, 1H), 4.66 (d, J = 5.20 Hz, 1H), 4.35-4.25 (m, 1H), 3.40 (s, 1H), 3.29-3.24 (m, 2H), 3.02-2.89 (m, 3H), 1.74-1.70 (m, 2H), 1.53 (s, 2H), 1.24-1.22 (m, 3H), 1.11 (s, 1H), 0.55-0.47 (m, 3H). **HPLC** Purity: 99.06%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A: Ammonium bicarbonate in water, Mobile phase: B: ACN.

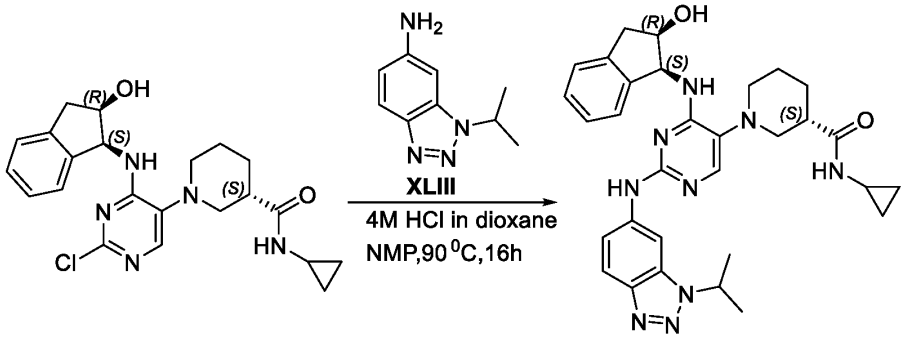
Example 42: (S)-1-(2-(1-(R)-but-3-yn-2-yl)-1H-benzo[d][1,2,3] triazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-cyclopropyl piperidine-3-carboxamide



[000289] To a solution of (*S*)-1-(2-((1-((*R*)-but-3-yn-2-yl)-1*H*-benzo[d][1,2,3]triazol-6-yl)amino)-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(XLII)** (1.00 g, 1.85 mmol) and cyclopropane amine (CAS:765-30-0, 0.02 mL, 2.22 mmol,) in DMF (10 mL), were added DIPEA (1.0 mL, 5.57 mmol) followed by HATU (0.847 g, 2.22 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 4 hours. The reaction progress was monitored by UPLC, reaction mixture was quenched with water and DMF was concentrated under reduced pressure. 10% aqueous $NaHCO_3$ solution was added and extracted with ethyl acetate (2 times). The organic phase was dried under Na_2SO_4, and the solvent was filtered and evaporated in *vacuo* to get the crude product. The obtained crude was purified by Preparative HPLC reverse phase in ammonium bicarbonate in water and acetonitrile to afford desired product **Example 42** as an Off-white solid. Yield: (0.57 g, 52.9 %), **LC_MS:** Calc. $C_{32}H_{35}N_9O_2$:577.69.; Obs.: 578.2 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6)**: δ 9.63 (s, 1H), 8.78 (s, 1H), 7.92-7.87 (m, 2H), 7.83-7.80 (m, 1H), 7.38-7.36 (m, 2H), 7.33-7.24 (m, 2H), 7.19-7.13 (m, 1H), 6.85-6.80 (m, 1H), 5.66-5.57 (m, 2H), 4.64-4.63 (m, 2H), 3.42-3.38 (m, 1H), 3.24 (s, 1H), 3.03-2.94 (m, 4H), 2.94-2.56 (m, 2H), 2.34 (d, J = 1.60 Hz, 1H), 1.56-1.55 (m, 7H), 0.59-0.56 (m, 2H), 0.36-0.34 (m, 2H). **HPLC** Purity: 99.61%,

Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A: 0.1% TFA in H_2O, Mobile phase: B: ACN.

Example 43: (S)-N-cyclopropyl-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-(1-isopropyl-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide

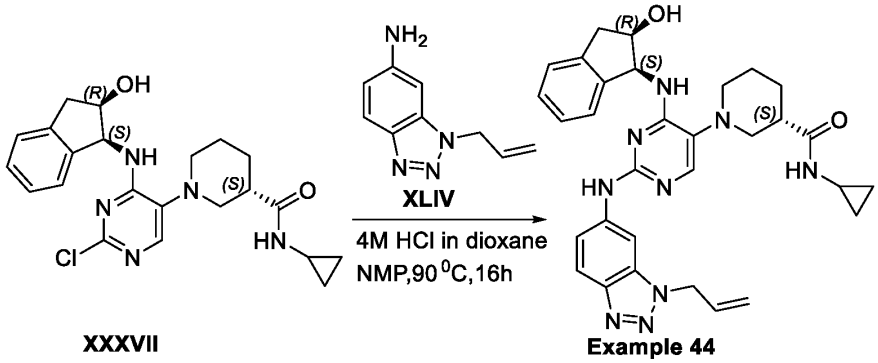


XXXVII **Example 43**

[000290] To a stirred solution (S)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide **(XXXVII)** (0.200 g, 0.46 mmol) and 1-isopropyl-1H-benzo[d][1,2,3]triazol-6-amine **(XLIII)** (0.082g, 0.46 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.2 mL, 1.40 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 16 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The obtained crude was purified by Preparative HPLC reverse phase in ammonium bicarbonate in water and acetonitrile to afford desired product **Example 43** as an Off-white solid. Yield: (0.012 g, 4.3%), **LC_MS:** Calc. $C_{31}H_{37}N_9O_2$:567.70; Obs.: 568.3 [M^++H]:1H-NMR (300 MHz, DMSO-d6): δ 9.54 (s, 1H), 8.61 (s, 1H), 7.91-7.87 (m, 2H), 7.77 (d, J = 8.00 Hz, 1H), 7.36-7.31 (m, 5H), 6.84 (s, 1H), 5.63-5.60 (m, 1H), 5.57-5.56 (m, 1H), 4.65-4.61 (m, 1H), 3.98-3.95 (m, 1H), 3.33-3.18 (m, 2H), 3.01-2.94 (m, 4H), 2.60-2.59 (m, 2H), 1.79-1.73 (m, 2H), 1.56-1.53 (m, 2H), 1.24-1.18 (m, 6H), 0.58-0.55 (m, 2H), 0.36-0.34 (m, 2H). **HPLC** Purity;95.23%,

Column: X-Bridge C8(50 X 4.6) mm,5µm, Mobile phase: A:0.1% TFA in water Mobile phase: B: ACN.

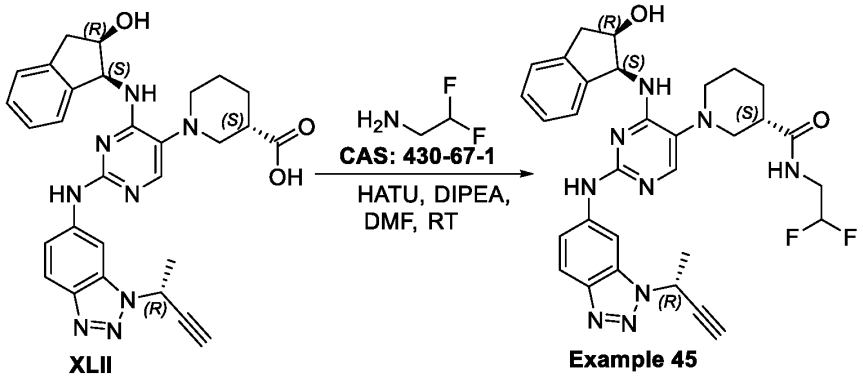
Example 44: (S)-1-(2-((1-allyl-1H-benzo[d] [1,2,3] triazol-6-yl) amino)-4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide



[000291] To a stirred solution (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-cyclopropylpiperidine-3-carboxamide **(XXXVII)** (0.200 g, 0.46 mmol) and 1-allyl-1*H*-benzo[d][1,2,3]triazol-6-amine **(XLIV)** (0.082g, 0.46 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.2 mL, 0.93 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 16 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The obtained crude was purified by Preparative HPLC reverse phase in 0.1% TFA in water and acetonitrile to afford desired product **Example 44** as an Off-white solid. Yield: (0.012 g, 4.1%), **LC_MS:** Calc. $C_{31}H_{35}N_9O_2$:565.68; Obs.: 566.2 [M^++H]:1H-NMR (400 MHz, DMSO-d6): δ 10.36 (s, 1H), 8.30 (s, 1H), 7.99 (d, J = 8.80 Hz, 1H), 7.98-7.82 (m, 2H), 7.37-7.33 (m, 3H), 7.30-7.26 (m, 1H), 7.19-7.09 (m, 1H), 5.68 (s, 1H), 5.58-5.55 (m, 1H), 4.98 (d, J = 10.80 Hz, 2H), 4.69-4.64 (m, 3H), 3.68-3.42 (m, 1H), 3.42-3.38 (m, 1H), 3.17-2.98 (m, 3H), 2.61-2.61 (m, 1H), 2.50-2.38 (m, 2H), 1.76-1.74 (m, 2H) 1.56-1.50 (m, 2H), 1.12-1.08 (m, 1H), 0.58-0.56 (m, 2H), 0.34-0.33 (m, 2H). **HPLC** Purity; 90.07%, Column: X-Bridge C8(50

X 4.6) mm,3.5µm, Mobile phase: A: ammonium bicarbonate in water Mobile phase: B: ACN.

Example 45: (S)-1-(2-((1-((R)-but-3-yn-2-yl)-1H-benzo[d][1,2,3] triazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-(2,2-difluoroethyl)piperidine-3-carboxamide

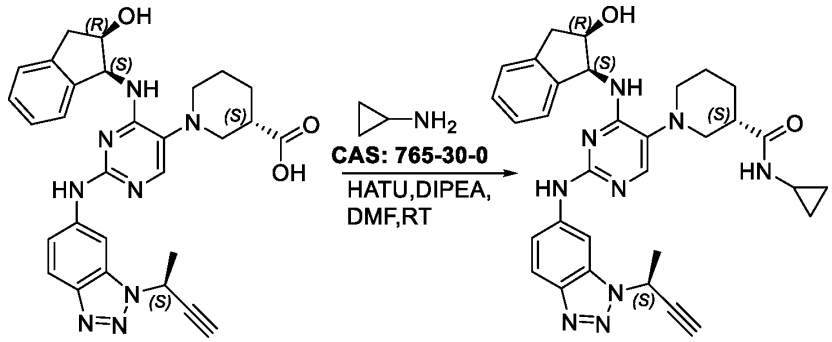


XLII Example 45

[000292] To a solution (*S*)-1-(2-((1-((*R*)-but-3-yn-2-yl)-1*H*-benzo[d][1,2,3]triazol-6-yl)amino)-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(XLII)** (1.500 g, 1 eq, 2.785 mmol) and 2,2-difluoroethan-1-amine (CAS 430-67-1, 338.7 mg, 302 µL, 1.5 eq, 4.177 mmol) in DMF (20 mL), were added DIPEA (1.080 g, 1.46 mL, 3 eq, 8.355 mmol) followed by HATU (1.588 g, 1.5 Eq, 4.177 mmol) at 0°C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 16 hours. The reaction progress was monitored by TLC. After completion of the reaction, to the reaction mixture ice water was added, solid was precipitated out. This was kept stirring for 30 min with ice water and then filtered off and washed thoroughly with ice water and dried under vacuum to get crude as pale brown solid. The obtained crude product was purified by Prep-HPLC purification using 10mM Ammonium bicarbonate in water and acetonitrile to afford the desired compound as a gummy mass. The compound was further triturated with diethyl ether, the off-white solid thrown out was allowed to settle and the supernatant was decanted. The solid obtained was dried under high *vacuum*, to afford the desired product **Example 45** as an off-white solid. Yield: (0.55 g, 24.5%),

LC_MS: Calc. for $C_{31}H_{33}F_2N_9O_2$: 601.66; Obs.: 602.30 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6):** δ 10.65 (brs, 1H), 8.58 (s, 1H), 8.32-8.31 (m, 1H), 7.99 (d, J = 4.80 Hz, 1H), 7.91-7.89 (m, 1H), 7.40-7.35 (m, 3H), 7.31-7.29 (m, 1H), 7.25 (s, 1H), 7.20-7.18 (m, 1H), 7.12 (s, 1H), 7.00 (s, 1H), 6.91 (s, 1H), 5.68-5.64 (m, 2H), 4.68-4.65 (m, 1H), 3.46-3.44 (m, 4H), 3.39-3.36 (m, 2H), 3.01-2.97 (m, 3H), 1.81-1.71 (m, 2H), 1.55-1.57 (m, 5H).**HPLC** Purity: 98.1%, Column: Sunfire C18 (50 x 4.6) mm 5µm, Mobile phase: A: TFA in water, Mobile phase: B: Acetonitrile.

Example 46: (S)-1-(2-(1-(S)-but-3-yn-2-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino)-4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropyl piperidine-3-carboxamide

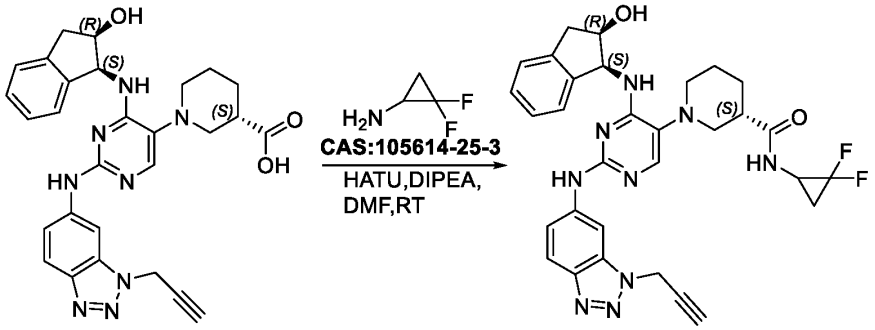


XLVI Example 46

[000293] To a solution of (S)-1-(2-((1-((S)-but-3-yn-2-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(XLVI)** (0.200 g, 0.37 mmol) and cyclopropane amine (CAS: 765-30-0) (0.021 g, 0.37 mmol,) in DMF (10 mL), were added DIPEA (0.2 mL, 1.11 mmol) followed by HATU (0.169 g, 0.45 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 2 hours. The reaction progress was monitored by TLC. The reaction mixture was quenched with water. DMF was concentrated under reduced pressure. 10% aqueous $NaHCO_3$, solution was added and extracted with ethyl acetate (2 times). The organic phase was dried under Na_2SO_4, and the solvent was filtered and evaporated in *vacuo* to get the crude desired product as brown liquid. The obtained crude was purified by Preparative HPLC reverse phase in

ammonium bicarbonate in water and acetonitrile to afford desired product **Example 46** as an Off-white solid. Yield: (0.013 g, 6.00 %), **LC_MS:** Calc. $C_{32}H_{35}N_9O_2$:577.69.; Obs.: 577.3 [M^++H]:1H-NMR (400 MHz, DMSO-d6): δ 9.62 (s, 1H), 8.80 (s, 1H), 7.92-7.86 (m, 2H), 7.82 (d, *J* = 8.80 Hz, 1H), 7.38 (d, *J* = 2.00 Hz, 1H), 7.31 (d, *J* = 7.60 Hz, 1H), 7.21-7.18 (m, 2H), 7.13-7.09 (m, 1H), 6.88 (s, 1H), 5.81-5.77 (m, 1H), 5.60-5.56 (m, 2H), 4.68-4.67 (m, 1H), 3.72-3.71 (m, 1H), 3.34-3.24 (m, 1H), 3.02-2.93 (m, 4H), 2.60-2.52 (m, 3H), 1.76-1.73 (m, 2H), 1.53 (m, 2H), 1.10 (t, *J* = 7.20 Hz, 3H), 0.58-0.55 (m, 2H), 0.34-0.32 (m, 2H). **HPLC** Purity; 98.31%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A: Ammonium bicarbonate in H_2O Mobile phase: B: ACN.

Example 47: (3S)-N-(2,2-difluorocyclopropyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide

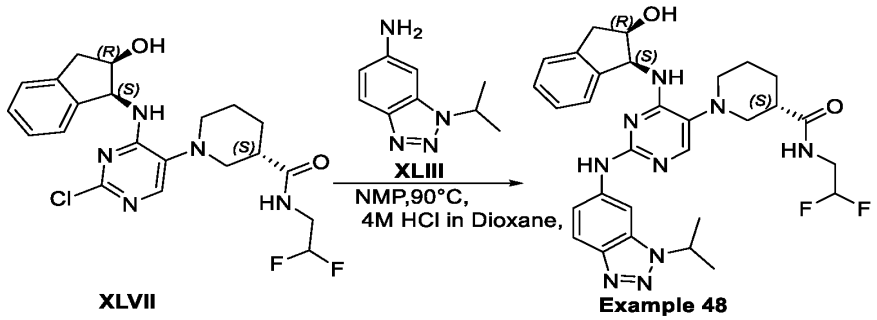


XL **Example 47**

[000294] To a solution of (*S*)-1-(4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3] triazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(XL)** (0.200 g, 0.38 mmol) and 2,2-difluorocyclopropan-1-amine HCl (CAS: 105614-25-3, 0.042 g, 0.45 mmol,) in DMF (10 mL), were added DIPEA (0.2 mL, 1.14 mmol) followed by HATU (0.174 g, 0.45 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 16 hours. The reaction progress was monitored by TLC. The reaction mixture was quenched with water and DMF was concentrated under reduced pressure. 10% aq $NaHCO_3$ solution was

added and extracted with ethyl acetate (2 times) the organic phase was dried under Na_2SO_4, and the solvent was filtered and evaporated in *vacuo* to get the crude desired product as brown liquid. The obtained crude was purified by Preparative HPLC reverse phase in 0.1% TFA in water and acetonitrile to afford desired product **Example 47** as an Off-white solid. Yield: (0.014 g, 6.01 %), **LC_MS:** Calc. $C_{31}H_{31}F_2N_9O_2$: 599.65.; Obs.: 600.2 [M^++H]:1H-NMR (400 MHz, DMSO-d6): δ 10.19 (s, 1H), 8.55 (s, 1H), 8.30-8.32 (m, 2H), 7.98-7.96 (m, 1H), 7.82-7.86 (m, 1H), 7.42-7.37 (m, 4H), 7.36-7.33 (m, 2H), 7.29-7.21 (m, 2H), 5.65 (s, 2H), 5.28-5.24 (m, 1H), 4.68 (s, 1H), 3.23-2.96 (m, 4H), 3.01-2.96 (m, 3H), 1.91-1.86 (m, 3H), 1.83-1.81 (m, 1H), 1.76-1.58 (m, 2H), 1.58-1.42 (m, 1H). **HPLC** Purity;98.87%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A:0.1% TFA in H_2O: Mobile phase: B: ACN.

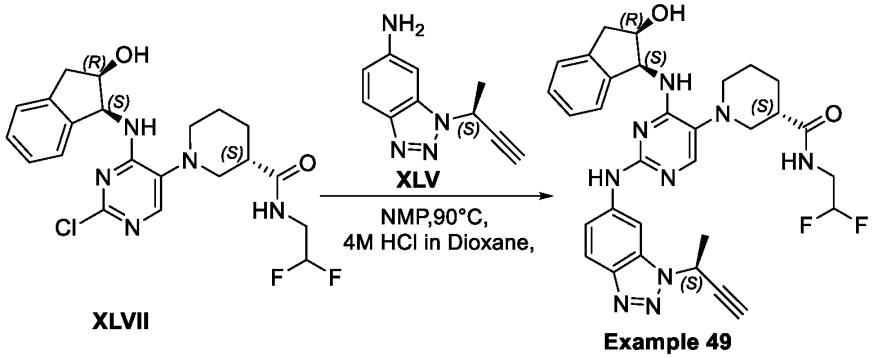
Example 48: (S)-N-(2,2-difluoroethyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-(1-isopropyl-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide



[000295] To a solution (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-(2,2-difluoroethyl)piperidine-3-carboxamide **(XLVII)** (0.350 g, 1 eq, 0.775 mmol) and 1-isopropyl-1*H*-benzo[d][1,2,3]triazol-6-amine (**XLIII**) (164 mg, 1.2 eq, 0.929 mmol) in NMP (3 mL), was added 4M HCl in dioxane (56.5 mg, 0.387 mL, 4 molar, 2 eq, 1.55 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 3 hours. The reaction progress was monitored by LCMS. After completion of the reaction, the reaction mass was cooled to room temperature,

reaction mass evaporated in *vacuo* to get the crude product. The obtained crude product was purified by Prep-HPLC purification using 10mM Ammonium bicarbonate in water and acetonitrile to afford the desired compound as gummy mass. The compound was further triturated with diethyl ether, the off-white solid thrown out was allowed to settle and the supernatant was decanted. The solid obtained was dried under high *vacuo*, to afford desired product **Example 48** as an off-white solid. Yield: (20 mg, 5.4%), **LC_MS:** Calc. for $C_{30}H_{35}F_2N_9O_2$: 591.67; Obs.: 592.4 [M^++H]. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 9.54 (s, 1H), 8.62 (d, *J* = 1.20 Hz, 1H), 8.28-8.25 (m, 1H), 7.91 (d, *J* = 4.80 Hz, 1H), 7.78 (d, *J* = 9.20 Hz, 1H), 7.28-7.35 (m, 4H), 7.20-7.15 (m, 1H), 6.85 (bs, 1H), 6.10-5.94 (m, 1H), 5.76 (s, 1H), 5.70-5.60 (m, 2H), 4.65-4.60 (m, 1H), 4.00 (bs, 1H), 3.41-3.45 (m, 2H), 3.20-3.15 (m, 1H), 3.02-2.94 (m, 4H), 2.59-2.56 (m, 1H), 1.85-1.75 (m, 2H), 1.59-1.54 (m, 2H), 1.22-1.19 (m, 6H). **HPLC** Purity: 96.8%, Column: X-Bridge C8(50X4.6) mm,3.5µm, Mobile phase: A: ammonium bicarbonate in water, Mobile phase: B: Acetonitrile.

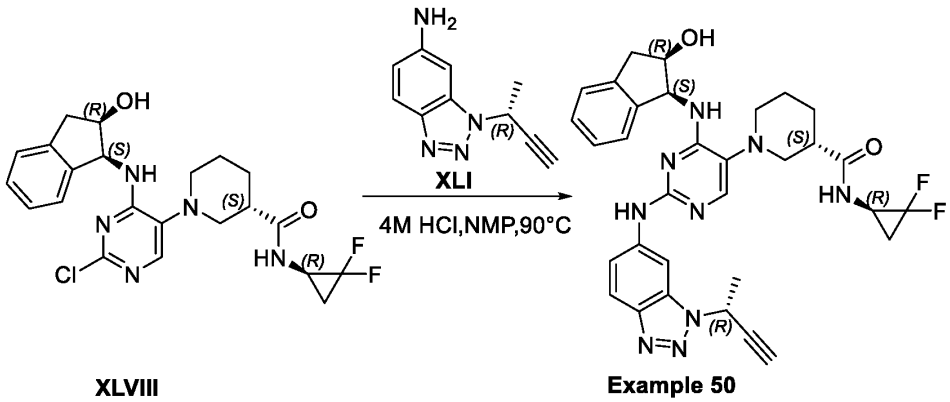
Example 49: (S)-1-(2-((1-((S)-but-3-yn-2-yl)-1H-benzo[d][1,2,3] triazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-(2,2-difluoro ethyl) piperidine-3-carboxamide



[000296] To a solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-(2,2-difluoroethyl)piperidine-3-carboxamide (**XLVII**) (0.100 g, 1 eq, 0.221 mmol) and (*S*)-1-(but-3-yn-2-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine (**XLV**) (41.2 mg, 1 eq, 0.221 mmol) in NMP (1 mL), was added 4M HCl in dioxane (24.2 mg, 0.166 mL, 3 eq, 0.664 mmol) at

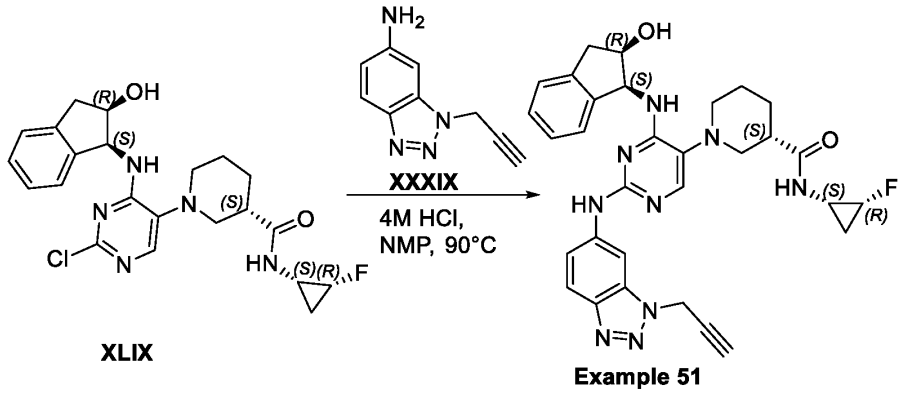
room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 16 hours. The reaction progress was monitored by LCMS. After completion of the reaction, the reaction mass was cooled to room temperature, reaction mass evaporated in *vacuo* to get the crude product. The obtained crude product was purified by Prep-HPLC purification using 10mM Ammonium bicarbonate in water and acetonitrile to afford the desired compound as gummy mass. The compound was further triturated with diethyl ether, the off-white solid thrown out was allowed to settle and the supernatant was decanted. The solid obtained was dried under high *vacuo*, to afford desired product **Example 49** as an off-white solid. Yield: (20 mg, 15%), **LC_MS:** Calc. for $C_{31}H_{33}F_2N_9O_2$: 601.66; Obs.: 602.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6):** δ 9.63 (s, 1H), 8.80 (d, *J* = 1.20 Hz, 1H), 8.30-8.27 (m, 1H), 7.92 (d, *J* = 2.80 Hz, 1H), 7.82 (d, *J* = 8.80 Hz, 1H), 7.39-7.36 (m, 1H), 7.31 (d, *J* = 7.60 Hz, 1H), 7.22-7.18 (m, 2H), 7.13-7.10 (m, 1H), 6.87 (bs, 1H), 5.96-5.95 (m, 1H), 5.81-5.77 (m, 2H), 5.62-5.57 (m, 2H), 4.68-4.65 (m, 1H), 3.72-3.71 (m, 1H), 3.71-3.43 (m, 2H), 3.28-3.23 (m, 2H), 3.02-2.93 (m, 4H), 1.75 (m, 2H), 1.55-1.54 (m, 2H), 1.11-1.09 (m, 3H). **HPLC** Purity: 99.06%, Column: X-Bridge C8 (50X4.6) mm,3.5µm, Mobile phase: A: TFA in water, Mobile phase: B: Acetonitrile.

Example 50: (S)-1-(2-((1-((R)-but-3-yn-2-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-((R)-2,2-difluorocyclopropyl)piperidine-3-carboxamide



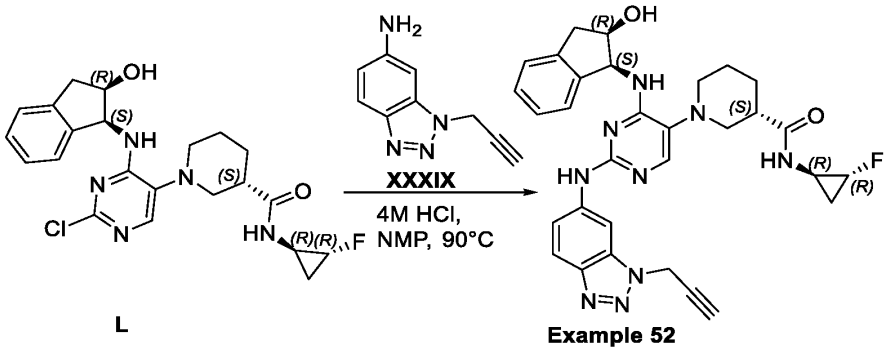
[000297] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-((R)-2,2-difluorocyclopropyl)piperidine-3-carboxamide **(XLVIII)** (0.250 g, 0.54 mmol) and (*R*)-1-(but-3-yn-2-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine **(XLI)** (0.100 g, 0.53 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.2 mL, 2.16 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 16 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The obtained crude was purified by Preparative HPLC reverse phase in ammonium bicarbonate in water and acetonitrile to afford desired product **Example 50** as an Off-white solid. Yield: (0.008g, 2%), **LC_MS:** Calc. $C_{32}H_{33}F_2N_9O_2$:613.67.; Obs.: 614.2 [M^++H]. **1H-NMR (300 MHz, DMSO-*d6*)**: δ 9.62 (s, 1H), 8.79 (d, *J* = 1.20 Hz, 1H), 8.28 (s, 1H), 7.93 (s, 1H), 7.82 (d, *J* = 9.20 Hz, 1H), 7.39-7.35 (m, 2H), 7.30-7.24 (m, 2H), 7.17-7.14 (m, 1H), 6.85 (bs, 1H), 5.66-5.63 (m, 1H), 5.55 (s, 1H), 4.65-4.57 (m, 2H), 3.40 (s, 1H), 3.28-3.23 (m, 3H), 2.98-2.92 (m, 4H), 2.68-2.67 (m, 1H), 1.84-1.78 (m, 3H), 1.57-1.55 (m, 5H), 1.42-1.41 (m, 1H). **HPLC** Purity; 97.55%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A:0.1% TFA in water Mobile phase: B: ACN.

Example 51: (S)-N-((1S,2R)-2-fluorocyclopropyl)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino) pyrimidin-5-yl)piperidine-3-carboxamide



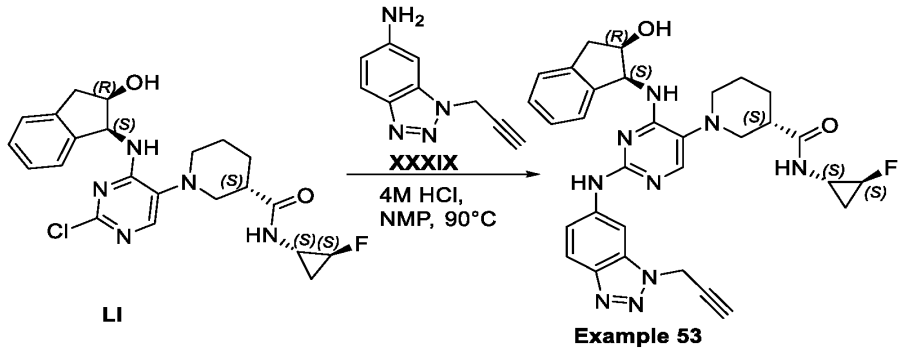
[000298] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-((1*S*,2*R*)-2-fluorocyclopropyl)piperidine-3-carboxamide **(XLIX)** (0.1.50g, 3.36 mmol) and 1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine **(XXXIX)** (0.69 g, 4.03 mmol) in NMP (3 mL), was added 4M HCl in dioxane (3.36 mL, 13.46 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 16 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The obtained crude was purified by Preparative HPLC reverse phase in ammonium bicarbonate in water and acetonitrile to afford desired product **Example 51** as an Off-white solid. Yield: (1.00g, 5.081%), **LC_MS:** Calc. $C_{31}H_{32}FN_9O_2$:581.66.; Obs.: 582.2 [M^++H]. 1H-NMR (400 MHz, DMSO-d_6): δ 9.62 (s, 1H), 8.78 (d, *J* = 1.20 Hz, 1H), 8.03 (d, *J* = 4.00 Hz, 1H), 7.92 (s, 1H), 7.82 (d, *J* = 8.80 Hz, 1H), 7.41-7.38 (m, 1H), 7.34-7.28 (m, 2H), 7.25-7.21 (m, 1H), 7.14-7.11 (m, 1H), 6.84 (bs, 1H), 5.67-5.64 (m, 1H), 5.53 (d, J = 4.40 Hz, 1H), 5.20-5.15 (m, 1H), 4.73-4.56 (m, 2H), 4.35-4.25 (m, 1H), 3.41-3.39 (m, 1H), 3.29-3.24 (m, 2H), 3.04-3.01 (m, 1H), 2.96-2.92 (m, 3H), 2.63-2.61 (m, 2H), 1.84-1.75 (m, 2H), 1.56 (bs, 2H), 1.03-0.97 (m, 1H), 0.86-0.80 (m, 1H). **HPLC** Purity;99.41%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A:0.1% TFA in water Mobile phase: B: ACN.

Example 52: (S)-N-((1R,2R)-2-fluorocyclopropyl)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino) pyrimidin-5-yl)piperidine-3-carboxamide



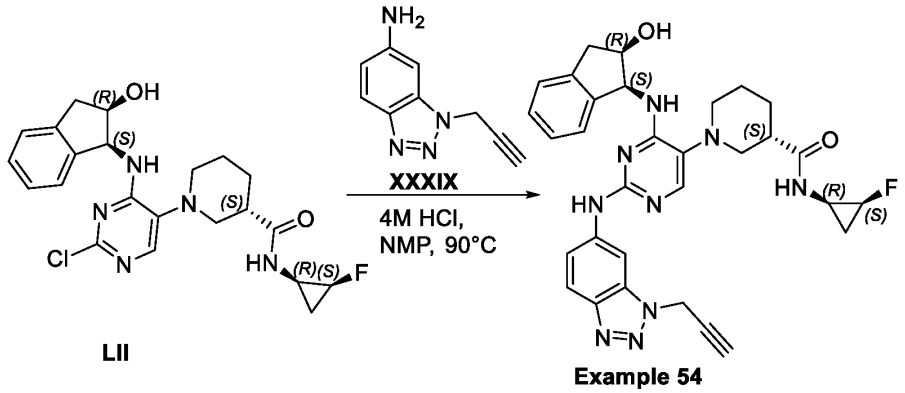
[000299] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-((1*R*,2*R*)-2-fluorocyclopropyl)piperidine-3-carboxamide **(L)** (0.12 g, 0.26 mmol) and 1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine **(XXXIX)** (0.046 g, 0.27 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.1 mL, 1.01 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 16 hours. The progress of the reaction was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The crude was purified by Preparative HPLC reverse phase using ammonium bicarbonate in water and acetonitrile to afford the desired product **Example 52** as an off-white solid. Yield: (0.050 g, 32%), **LC_MS:** Calc. $C_{31}H_{32}FN_9O_2$:581.66; Obs.: 582.3 [M^++H]:1H-NMR (400 MHz, DMSO-d6): δ 9.61 (s, 1H), 8.78 -8.72 (m, 1H), 7.91 (d, J = 3.60 Hz, 2H), 7.82 (d, J = 8.80 Hz, 1H), 7.41-7.39 (m, 1H), 7.31 (dd, J = 7.20, 12.40 Hz, 2H), 7.24 (t, J = 7.20 Hz, 1H), 7.14 (q, J = 7.20 Hz, 1H), 5.67-5.64 (m, 1H), 5.52 (d, J = 4.00 Hz, 1H), 5.17 (dd, J = 2.40, 18.00 Hz, 1H), 4.66-4.64 (m, 2H), 4.29 (m, 1H), 3.40 (t, J = 2.40 Hz, 1H), 3.29-3.24 (m, 1H), 2.98-2.91 (m, 5H), 2.61-2.51 (m, 1H), 2.34-2.34 (m, 1H), 1.82-1.71 (m, 2H), 1.51-1.46 (m, 2H), 1.31-0.81 (m, 1H), 0.84-0.82 (m, 1H). **HPLC** Purity; 99.20%, Column: X-Bridge C8 (50 X 4.6) mm,3.5µm, Mobile phase: A: Ammonium bicarbonate in water Mobile phase: B: ACN

Example 53: (S)-N-((1S,2S)-2-fluorocyclopropyl)-1-(4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3] triazol-6-yl)amino) pyrimidin-5-yl)piperidine-3-carboxamide



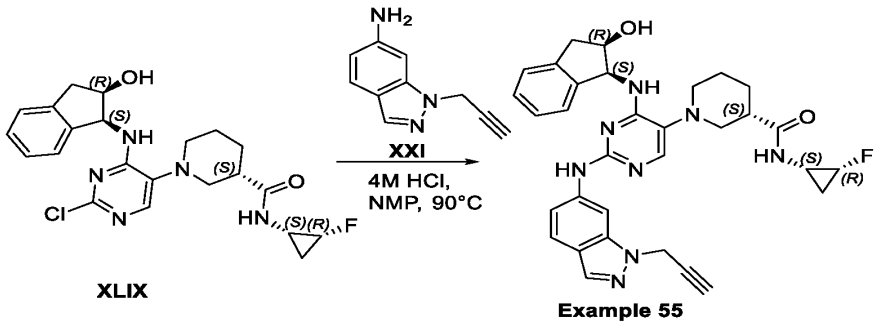
[000300] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-N-((1*S*,2*S*)-2-fluorocyclopropyl)piperidine-3-carboxamide **(LI)** (0.12 g, 0.26 mmol) and 1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine **(XXXIX)** (0.046 g, 0.27 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.1 mL, 1.01 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 16 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The crude product was purified by Preparative HPLC reverse phase using 0.1% TFA in water and acetonitrile to afford the desired product **Example 53** as an off-white solid. Yield: (0.011 g, 4%), **LC_MS:** Calc. $C_{31}H_{32}FN_9O_2$:581.66; Obs.: 582.3 [M^++H]:1H-NMR (400 MHz, DMSO-d6): δ 8.53 (s, 1H), 8.00-7.84 (m, 3H), 7.41-7.33 (m, 4H), 7.27 (t, J = 6.80 Hz, 1H), 7.16 (t, J = 8.00 Hz, 1H), 5.65 (t, J = 6.40 Hz, 2H), 5.31-5.22 (m, 1H), 4.68-4.49 (m, 2H), 3.71-3.68 (m, 1H), 3.41 (q, J = 2.40 Hz, 2H), 3.38-3.23 (m, 2H), 3.02-2.90 (m, 3H), 2.39-2.34 (m, 2H), 1.81-1.70 (m, 2H), 1.63-1.36 (m, 2H), 1.24-1.08 (m, 2H), 0.85-0.81 (m, 1H). **HPLC** Purity; 94.71%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A: 0.1% TFA in water Mobile phase: B: ACN.

Example 54: (S)-N-((1R,2S)-2-fluorocyclopropyl)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino) pyrimidin-5-yl) piperidine-3-carboxamide



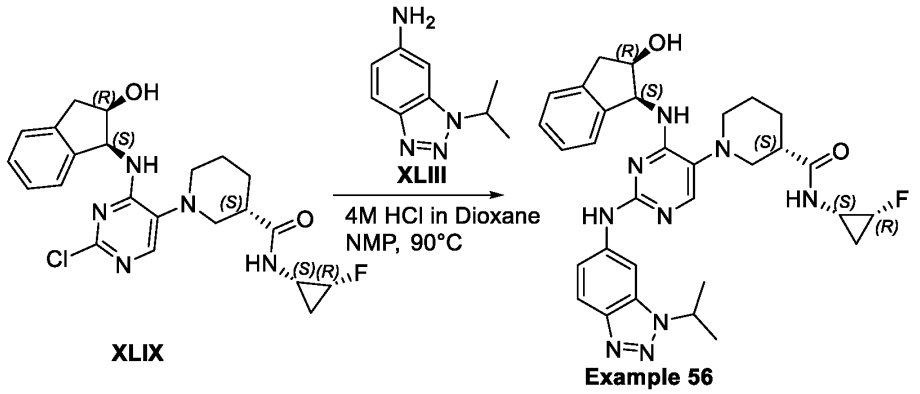
[000301] To a stirred solution of (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-((1*R*,2*S*)-2-fluorocyclopropyl)piperidine-3-carboxamide **(LII)** (0.12 g, 0.26 mmol) and 1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine **(XXXIX)** (0.046 g, 0.27 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.1 mL, 1.01 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 16 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The crude product was purified by Preparative HPLC reverse phase using ammonium bicarbonate in water and acetonitrile to afford the desired product **Example 54** as an Off-white solid. Yield: (0.020 g, 7.6%), **LC_MS:** Calc. $C_{31}H_{32}FN_9O_2$:581.66; Obs.: 582.3 [M^++H]:1H-NMR (400 MHz, DMSO-d6): δ 9.61 (s, 1H), 8.78 (d, J = 1.20 Hz, 1H), 8.02 (d, J = 4.00 Hz, 1H), 7.91 (d, J = 7.20 Hz, 1H), 7.82 (d, J = 9.20 Hz, 1H), 7.16 (t, J = 8.00 Hz, 1H), 7.40 (dd, J = 1.60, 9.00 Hz, 1H), 7.32 (t, J = 10.00 Hz, 2H), 7.24 (t, J = 7.20 Hz, 1H), 7.13 (t, J = 7.60 Hz, 1H), 5.66 (q, J = 5.20 Hz, 1H), 5.53 (d, J = 4.40 Hz, 1H), 5.17 (dd, J = 2.80, 17.80 Hz, 1H), 4.66-4.65 (m, 2H), 4.31-4.26 (m, 1H), 3.41-3.40 (m, 1H), 3.38-3.30 (m, 1H), 3.01-2.93 (m, 4H), 2.60 (t, J = 4.40 Hz, 2H), 1.81-1.71 (m, 2H), 1.60-1.48 (m, 2H), 1.00-0.98 (m, 1H), 0.96-0.81 (m, 2H), **HPLC** Purity; 99.72%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A: 0.1% TFA in water Mobile phase: B: ACN

Example 55: (S)-N-((1S,2R)-2-fluorocyclopropyl)-1-(4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide



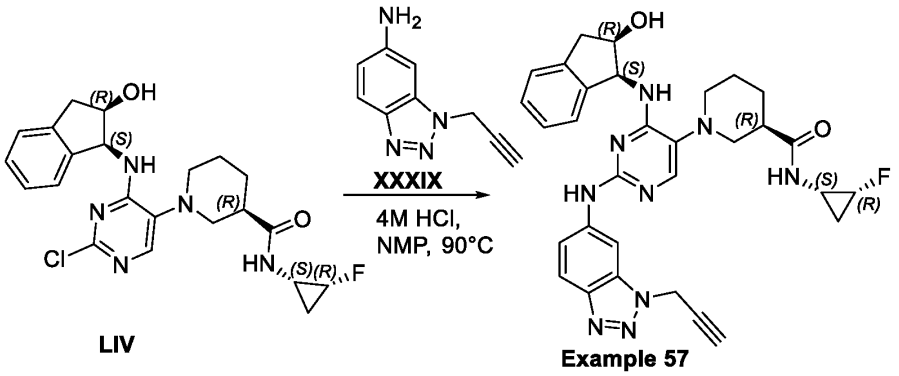
[000302] To a solution (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-((1*S*,2*R*)-2-fluorocyclopropyl)piperidine-3-carboxamide **(XLIX)** (0.100 g, 1 eq, 0.224 mmol) and 1-(prop-2-yn-1-yl)-1*H*-indazol-6-amine **(XXI)** (38.4 mg, 1 eq, 0.224 mmol) in DMF (20 mL), was added 4M HCl in dioxane (16.4 mg, 2 eq, 0.449 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 3 hours. The reaction progress was monitored by LCMS. After completion of the reaction mass was cooled to room temperature, reaction mass was concentrated under *vacuo* to get the crude product. The crude product was purified by Prep-HPLC purification using 10mM Ammonium bicarbonate in water and acetonitrile to afford the desired compound as a gummy mass. The compound was further triturated with diethyl ether, the off-white solid thrown out was allowed to settle and the supernatant was decanted. The solid obtained was dried under high *vacuum*, to afford the desired product **Example 55** as an off-white solid. Yield: (37 mg, 28%), **LC_MS:** Calc. for $C_{32}H_{33}FN_8O_2$: 580.67; Obs.: 581.3 [M^++H]; **^{1}H NMR (400 MHz, DMSO-d_6):** δ 9.39 (s, 1H), 8.61 (s, 1H), 8.03 (d, J = 4.00 Hz, 1H), 7.90 (s, 1H), 7.81 (s, 1H), 7.51 (d, J = 8.80 Hz, 1H), 7.31 (t, J = 7.60 Hz, 1H), 7.23 (t, J = 7.60 Hz, 1H), 7.14 (t, J = 8.40 Hz, 1H), 6.82 (s, 1H), 5.68 (t, J = 5.20 Hz, 1H), 5.54 (d, J = 4.00 Hz, 1H), 4.72-4.62 (m, 3H), 4.02-3.98 (m, 1H), 3.30-3.24 (m, 2H), 3.17 (d, J = 5.20 Hz, 1H), 3.08 (s, 1H), 3.02 (d, J = 11.20 Hz, 1H), 2.96-2.92 (m, 2H), 2.62-2.56 (m, 2H), 1.84-1.82 (m, 2H), 1.75-1.56 (m, 2H), 1.56-1.01 (m, 2H), 0.91-0.99 (m, 2H). **HPLC** Purity: 99.3%, Column: X-Bridge C8 (50 x 4.6) mm 3.5µm, Mobile phase: A: TFA in water, Mobile phase: B: Acetonitrile.

Example 56: (S)-N-((1S,2R)-2-2-fluorocyclopropyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-(1-isopropyl-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl)piperidine-3-carboxamide



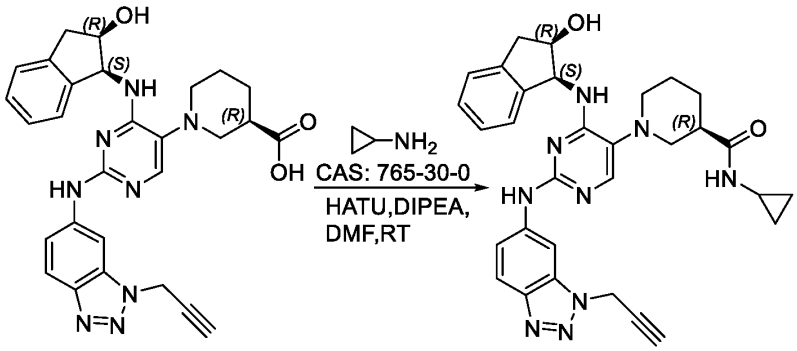
[000303] To a stirred solution (*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-((1*S*,2*R*)-2-fluorocyclopropyl)piperidine-3-carboxamide **(XLIX)** (0.200 g, 0.45 mmol) and 1-isopropyl-1*H*-benzo[d][1,2,3]triazol-6-amine **(XLIII)** (0.094g, 0.53 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.2 mL, 1.79 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 16 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The obtained crude was purified by Preparative HPLC reverse phase in ammonium bicarbonate in water and acetonitrile to afford desired product **Example 56** as an Off-white solid. Yield: (0.112 g, 41.2%), **LC_MS:** Calc. $C_{31}H_{36}FN_9O_2$:585.69; Obs.: 586.4[M^++H]. **1H-NMR (400 MHz, DMSO-*d6*):** δ 9.56 (s, 1H), 8.62 (d, *J* = 1.20 Hz, 1H), 8.04 (d, *J* = 4.00 Hz, 1H), 7.92 (s, 1H), 7.77 (d, *J* = 8.80 Hz, 1H), 7.25-7.25 (m, 4H), 7.16 (q, *J* = 7.60 Hz, 1H), 6.84 (s, 1H), 5.58 (t, *J* = 4.00 Hz, 2H), 4.73-4.56 (m, 2H), 3.97 (s, 1H), 3.17 (d, *J* = 4.00 Hz, 2H), 3.02-2.93 (m, 4H), 2.63 (d, *J* = Hz, 2H), 1.80 (m, 2H), 1.55 (d, *J* = 8.00 Hz, 2H), 1.20 (q, *J* = 6.40 Hz, 6H), 1.01 (m, 1H), 0.80 (m, 1H). **HPLC** Purity;96.62%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A: Ammonium bicarbonate in water Mobile phase: B: ACN.

Example 57: (R)-N-((1S,2R)-2-fluorocyclopropyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide



[000304] To a stirred solution of (*R*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-((1*S*,2*R*)-2-fluorocyclopropyl)piperidine-3-carboxamide **(LIV)** (0.15 g, 0.33 mmol) and 1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine **(XXXIX)** (0.69 g, 4.04 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.2 mL, 1.35 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated at 90 °C for 4 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The obtained crude was purified by Preparative HPLC reverse phase using ammonium bicarbonate in water and acetonitrile to afford the desired product **Example 57** as an Off-white solid. Yield: (0.035g, 17%), **LC_MS:** Calc. $C_{31}H_{32}FN_9O_2$:581.66.; Obs.: 582.2 [M^++H]: 1H-NMR (400 MHz, DMSO-d_6):δ 9.62 (s, 1H), 8.78 (s, 1H), 8.02 (d, J = 4.40 Hz, 1H), 7.91 (s, 1H), 7.82 (d, J = 9.20 Hz, 1H), 7.40 (d, J = 1.60 Hz, 1H), 7.36 (q, J = 7.60 Hz, 2H), 7.25 (t, J = 7.20 Hz, 1H), 7.15 (t, J = 7.20 Hz, 1H), 6.79 (s, 1H), 5.72 (d, J = 37.60 Hz, 1H), 5.65 (d, J = 7.60 Hz, 1H), 5.17 (dd, J = -20.40, Hz, 1H), 4.74-4.63 (m, 2H), 4.57 (t, J = 2.80 Hz, 2H), 4.40-4.30 (m, 1H)3.29 (t, J = 12.00 Hz, 2H), 3.05 (d, J = 8.40 Hz, 1H), 2.95 (t, J = 9.20 Hz, 3H), 2.68-2.63 (m, 1H), 1.82-1.73 (m, 2H), 1.58-1.43 (m, 2H), 1.00 (d, J = 8.40 Hz, 1H), 0.86-0.82 (m, 1H), **HPLC** Purity; 97.44%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A:0.1% TFA in water Mobile phase: B: ACN.

Example 58: (R)-N-cyclopropyl-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-(1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide

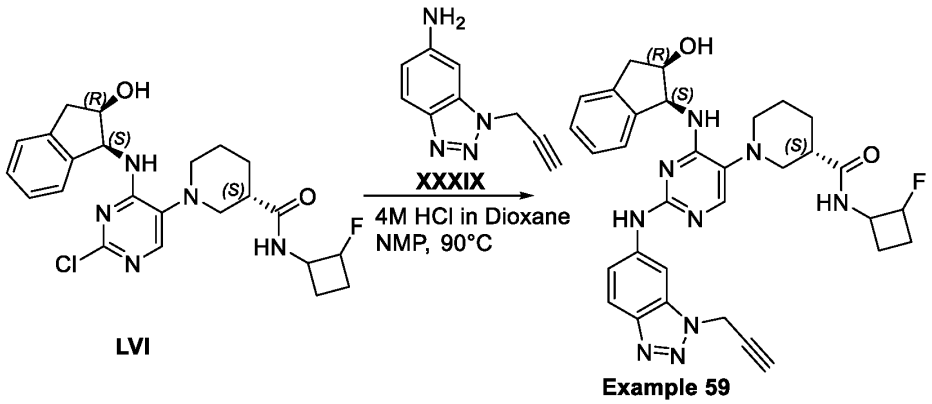


LV **Example 58**

[000305] To a solution of (*R*)-1-(4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxylic acid **(LV)** (0.15 g, 0.34 mmol) and cyclopropane amine (CAS: 765-30-0, 0.02 mL, 0.34 mmol,) in DMF (10 mL), were added DIPEA (0.1 mL, 0.71 mmol) followed by HATU (0.13 g, 0.34 mmol) at 0 °C, under nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 4 hours. The reaction progress was monitored by UPLC. The reaction mixture was quenched with water (10 mL). DMF was concentrated under reduced pressure. 10% aq. $NaHCO_3$ solution was added and extracted with ethyl acetate (2 X 20 mL). The organic phase was dried under Na_2SO_4, and the solvent was filtered and evaporated in *vacuo* to get the crude product. The obtained crude was purified by Preparative HPLC reverse phase using ammonium bicarbonate in water and acetonitrile to afford the desired product **Example 58** as an Off-white solid. Yield: (0.060 g, 36.0 %), **LC_MS:** Calc. $C_{31}H_{33}N_9O_2$:563.67.; Obs.: 564.4 [M^++H]:1H-NMR (400 MHz, DMSO-d_6): δ 9.62 (s, 1H), 8.78 (s, 1H), 7.91-7.87 (m, 2H), 7.82 (d, J = 8.80 Hz, 1H), 7.40 (d, J = 1.60 Hz, 1H), 7.38-7.31 (m, 2H), 7.26 (t, J = 6.80 Hz, 1H), 7.15 (t, J = 7.20 Hz, 1H), 5.65 (t, J = 6.40 Hz, 1H), 5.51 (t, J = 4.00 Hz, 1H), 5.17 (d, J = 18.40 Hz, 1H), 4.64

(t, J = 4.40 Hz, 1H), 4.32 (dd, J = 19.20, Hz, 1H), 3.41-3.40 (m, 1H), 3.30-3.24 (m, 1H), 3.03-2.81 (m, 4H), 1.78-1.72 (m, 2H), 2.52-2.49 (m, 2H), 1.55-1.46 (m, 2H), 0.58 (t, J = 2.40 Hz, 2H), 0.36 (t, J = 7.20 Hz, 2H), **HPLC** Purity; 96.77%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A: Ammonium bicarbonate in water, Mobile phase: B: ACN.

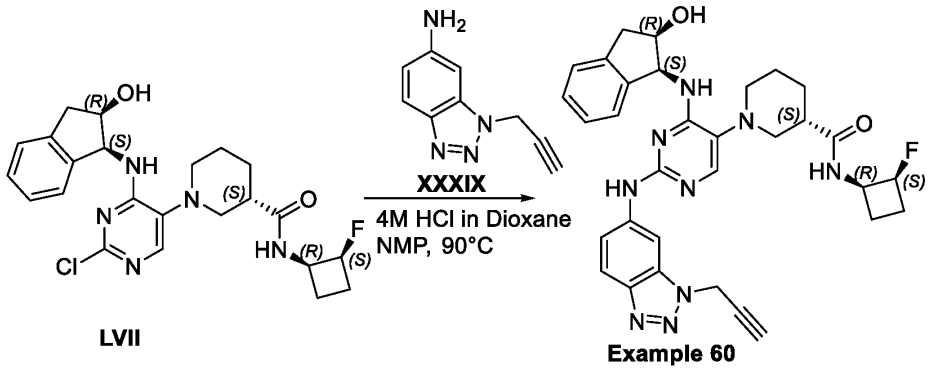
Example 59: (3S)-N-(2-fluorocyclobutyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide



[000306] To a stirred solution of (3*S*)-1-(2-chloro-4-(((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)pyrimidin-5-yl)-*N*-(2-fluorocyclobutyl)piperidine-3-carboxamide **(LVI)** (0.20 g, 0.43 mmol) and 1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine **(XXXIX)** (0.089 g, 0.522 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.2 mL, 1.74mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated at 90 °C for 4 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The obtained crude was purified by Preparative HPLC reverse phase using ammonium bicarbonate in water and acetonitrile to afford desired racemic product **Example 59** as an Off-white solid. Yield: (0.120g, 46.2%), **LC_MS:** Calc. $C_{32}H_{34}FN_9O_2$:595.68.; Obs.: 596.2[M^++H]. **1H-NMR (400 MHz, DMSO-*d6*):** δ 9.63 (s, 1H), 8.79 (s, 1H), 8.28-8.18 (m, 1H), 7.93-7.91 (m, 1H), 7.82 (d, J = 9.20 Hz, 1H), 7.15-7.38 (m, 5H), 6.85 (d, J = 4.80 Hz, 1H), 5.68-5.64 (m, 1H), 5.54 (s,

1H), 5.18 (m, 1H), 5.00 (m, 1H), 4.68-4.64 (m, 1H), 4.36-4.31 (m, 2H), 3.41 (s, 1H), 3.28-3.24 (m, 2H), 3.04-2.93 (m, 5H), 2.02-2.07 (m, 4H), 1.83-1.74 (m, 2H), 1.56 (bs, 2H). **HPLC** Purity: 99.82%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A: ammonium bicarbonate in water Mobile phase: B: ACN.

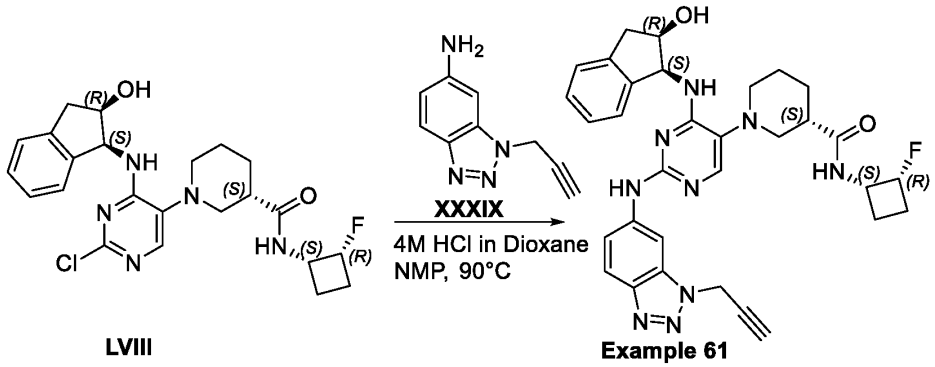
Example 60: (S)-N-((1R,2S)-2-fluorocyclobutyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide



[000307] To a stirred solution of (S)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-((1R,2S)-2-fluorocyclobutyl)piperidine-3-carboxamide **(LVII)** (0.20 g, 0.43 mmol) and 1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine **(XXXIX)** (0.089 g, 0.522 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.2 mL, 1.74mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated at 90 °C for 4 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The obtained crude was purified by Preparative HPLC reverse phase using ammonium bicarbonate in water and acetonitrile to afford desired racemic product **Example 60** as an Off-white solid. Yield: (0.09g, 9%), **LC_MS:** Calc. $C_{32}H_{34}FN_9O_2$:595.68.; Obs.: 596.2[M^++H]. **1H-NMR (400 MHz, DMSO-*d6*):** δ 9.63 (s, 1H), 8.79 (s, 1H), 8.27 (d, J = 8.40 Hz, 1H), 7.92 (d, J = 3.60 Hz, 1H), 7.82 (d, J = 9.20 Hz, 1H), 7.39 (dd, J = 1.60, 9.20 Hz, 1H), 7.34-7.30 (m, 2H), 7.24 (t, J = 7.60 Hz, 1H), 7.13 (t, J = 7.60 Hz, 1H), 6.89-6.82 (m,

1H), 5.68-5.65 (m, 1H), 5.53 (s, 1H), 5.18 (m, 1H), 4.68-4.64 (m, 2H), 4.22-4.17 (m, 2H), 3.42-3.40 (m, 1H), 3.29-3.24 (m, 1H), 3.03-2.93 (m, 4H), 2.40 (s, 1H), 2.09-2.05 (m, 1H), 1.96-1.93 (m, 1H), 1.84-1.82 (m, 1H), 1.76 (s, 1H), 1.73-1.69 (m, 2H), 1.57 (d, J = 10.80 Hz, 2H), 1.24-1.20 (m, 1H). **HPLC** Purity: 99.36%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A: ammonium bicarbonate in water Mobile phase: B: ACN.

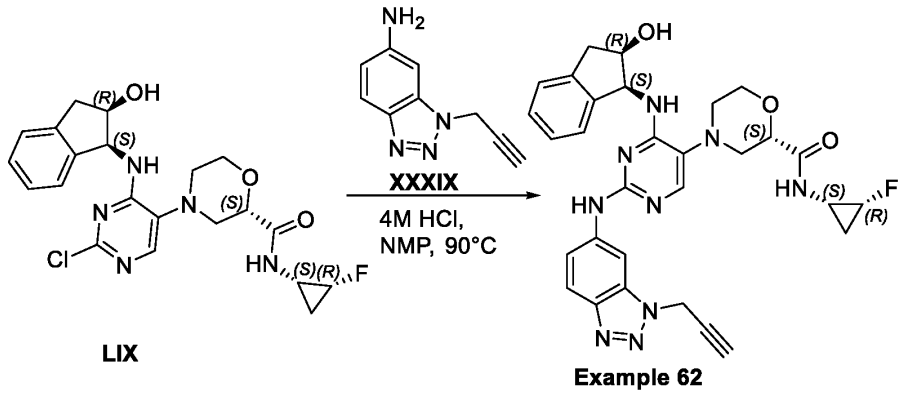
Example 61: (S)-N-((1S,2R)-2-fluorocyclobutyl)-1-(4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino) pyrimidin-5-yl)piperidine-3-carboxamide



[000308] To a stirred solution of (S)-1-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-((1S,2R)-2-fluorocyclobutyl)piperidine-3-carboxamide **(LVIII)** (0.20 g, 0.43 mmol) and 1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine **(XXXIX)** (0.089 g, 0.522 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.2 mL, 1.74mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated at 90 °C for 4 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The obtained crude was purified by Preparative HPLC reverse phase using ammonium bicarbonate in water and acetonitrile to afford desired racemic product **Example 61** as an Off-white solid. Yield: (0.035, 35%), **LC_MS:** Calc. $C_{32}H_{34}FN_9O_2$:595.68.; Obs.: 596.2[M^++H]. **1H-NMR (400 MHz, DMSO-*d6*):** δ 9.63 (d, J = 2.00 Hz, 1H), 8.79 (d, J = 1.60 Hz, 1H), 8.20 (dd, J = 8.00, 12.80 Hz, 1H), 7.92 (d, J = 2.40 Hz, 1H), 7.82 (d, J = 8.80 Hz, 1H), 7.39

(dd, *J* = 1.60, 9.20 Hz, 1H), 7.32 (dd, *J* = 7.60, 11.20 Hz, 2H), 7.24 (t, *J* = 7.20 Hz, 1H), 7.13 (t, *J* = 7.20 Hz, 1H), 6.86 (s, 1H), 5.68-5.65 (m, 1H), 5.55 (s, 1H), 5.20-5.15 (m, 1H), 5.00-4.90 (m, 1H), 4.66 (d, *J* = 4.00 Hz, 1H), 4.34-4.33 (m, 2H), 3.41-3.41 (m, 1H), 3.29-3.17 (m, 2H), 3.04-2.93 (m, 5H), 2.00-2.06 (m, 4H), 1.75 (m, 2H), 1.56 (m, 2H). **HPLC** Purity: 99.76%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A: ammonium bicarbonate in water Mobile phase: B: ACN.

Example 62: (S)-N-((1S,2R)-2-fluorocyclopropyl)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) -2-(1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) morpholine-2-carboxamide



[000309] To a stirred solution of (S)-4-(2-chloro-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-((1S,2R)-2-fluorocyclopropyl)morpholine-2-carboxamide **(LIX)** (0.30 g, 0.67 mmol) and 1-(prop-2-yn-1-yl)-1*H*-benzo[d][1,2,3]triazol-6-amine **(XXXIX)** (0.13 g, 0.80 mmol) in NMP (3 mL), was added 4M HCl in dioxane (0.2 mL, 2.68 mmol) at room temperature, under nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 4 hours. The reaction progress was monitored by UPLC. After completion of the reaction, the reaction mixture was evaporated in *vacuo* to get the crude product as a brown liquid. The obtained crude was purified by Preparative HPLC reverse phase using ammonium bicarbonate in water and

acetonitrile to afford desired product **Example 62** as an off-white solid. Yield: (0.045g, 11%), **LC_MS:** Calc. $C_{30}H_{30}FN_9O_3$:583.63.; Obs.: 584.2 [M^++H]: 1H-NMR (400 MHz, DMSO-d6): δ 9.65 (s, 1H), 8.77 (s, 1H), 7.98 (s, 1H), 7.90 (d, *J* = 4.00 Hz, 1H), 7.84-7.82 (m, 1H), 7.43-7.40 (m, 1H), 7.34-7.32 (m, 1H), 7.24 (t, J = 7.60 Hz, 1H), 7.15 (t, *J* = 7.60 Hz, 1H), 6.87-6.85 (m, 1H), 5.68 (t, *J* = 5.20 Hz, 1H), 5.51 (s, 1H), 5.22-5.22 (m, 1H), 4.67-4.66 (m, 2H), 4.60 (m, 1H), 4.12-4.09 (m, 1H), 4.01-3.98 (m, 1H), 3.65 (m, 1H), 3.40-3.39 (m, 1H), 3.33 (m, 1H), 3.16 (d, *J* = 10.40 Hz, 2H), 2.97-2.71 (m, 4H), 2.70-2.68 (m, 1H), 1.03 (m, 1H), 1.01-0.99 (m, 1H). **HPLC** Purity;99.79%, Column: X-Bridge C8(50 X 4.6) mm,3.5µm, Mobile phase: A: Ammonium bicarbonate in water Mobile phase: B: ACN.

Biological Activity

Biochemical inhibition of CDK7 by radiometric assay using a scintillation counter

[000310] Radiometric protein kinase assay was used to measure kinase activity of CDK7 enzyme. The experiment was performed as below:

[000311] CDK7/cyclin H/MAT1 (h) was incubated with 8 mM MOPS buffer pH 7.0, 0.2 mM EDTA, 500 µM peptide, 10 mM magnesium acetate and [gamma-^{33}P]-ATP along with test compound (specific activity and concentration as required). The reaction was initiated by the addition of the Mg/ATP mix. After incubation for 40 min at room temperature, the reaction was stopped by the addition of phosphoric acid to a concentration of 0.5%. An aliquot of the reaction was then spotted onto a filter and washed four times for 4 min in 0.425% phosphoric acid and once in methanol prior to drying and scintillation counting.

Assay Conditions:

Substrate: 500 µM peptides

Tracer: ^{33}P

ATP Concentration:10 µM

Incubation: 40 min at room temperature

Cellular inhibition CDK7, CDK2,CDK4,CDK6,CDK9 enzymes in HEK293 cells by Nano BRET assays

[000312] Nano BRET assay was used to measure kinase activity of different CDK's (7,2,4,6 and 9) enzyme in a HEK293 cell, and the protocol is given below.

[000313] Protocol: Nano BRET (Promega NanoLuc Technology) assays were performed as per the manufacturer's instructions. In brief, HEK293 cells were transfected using Lipofectamine 3000 in Opti-MEM containing ratios of 9.0 µg/ml of Transfection Carrier DNA, 1.0 µg/ml of NanoLuc fusion vector DNA and 1ml of Opti-MEM. After incubation for 20 minutes at room temperature, 1 part lipid/DNA complex was added to 20 parts HEK293 cells in suspension. Cells (4x10^5) were then plated and incubated for 36h. Respective compounds (indicated concentration) and appropriate NanoBRET tracer was added (as per manufacturer instructions) to cells at a ratio of 1 part tracer to 20 parts cell suspension and incubated for 1h. Plates were removed and incubated at room temperature for 15 minutes to equilibrate before 3x complete substrate plus inhibitor was added. Following 2-3 minutes of incubation at room temperature, donor and acceptor emissions were captured at 460 nm and 600 nm respectively using a Tecan Spark plate reader.

[000314] Analysis: NanoBRET assay quantifying the intracellular displacement of tracer from the ATP pocket of the CDK's.

[000315] IC_{50} of the compounds Formula (I) against CDK7 enzyme from the radiometric and Nano BRET assay are presented in Table 1, and IC_{50} of the selected compounds Formula (I) against CDK2,CDK4,CDK6 and CDK9 from Nano BRET assay are presented in Table 2.

Table-1: CDK7 IC_{50} of compounds of Formula I by radiometric and Nano BRET assays

Example Number	**CDK7 IC_{50} (nM) by Radiometric assay**	**CDK7 IC_{50} (nM) by NanoBRET**
1	29	ND
2	10000	ND

Example Number	CDK7 IC_{50} (nM) by Radiometric assay	CDK7 IC_{50} (nM) by NanoBRET
3	36	ND
4	77	ND
5	39	ND
6	25	ND
7	18	ND
8	15	ND
9	46	1019
10	21	ND
11	60	ND
12	28	ND
13	120	ND
14	50	ND
15	20	151
16	39	162
17	35	ND
18	26	1173
19	27	75
20	20	100
21	30	ND
22	27	440
23	40	319
24	28	59
25	34	ND
26	36	ND
27	39	559
28	29	179
29	170	2100
30	93	1400
31	31	ND
32	25	73
33	ND	796
34	ND	241
35	ND	239
36	ND	55
37	ND	10
38	ND	15
39	ND	3
40	ND	5
41	ND	15

Example Number	CDK7 IC_{50} (nM) by Radiometric assay	CDK7 IC_{50} (nM) by NanoBRET
42	ND	5
43	ND	4
44	ND	5
45	ND	1
46	ND	7
47	ND	3
48	ND	4
49	ND	5
50	ND	3
51	ND	1
52	ND	11
53	ND	10
54	ND	6
55	ND	26
56	ND	1.6
57	ND	50
58	ND	25
59	ND	16
60	ND	5
61	ND	1
Samuraciclib	15	75

ND- not determined.

Table-2: CDK2, CDK4,CDK6 and CDK9 IC_{50} of selected compounds of formula I by Nano BRET assays

Example Number	CDK2 IC_{50} (nM) by NanoBRET	CDK4 IC_{50} (nM) by NanoBRETT	CDK6 IC_{50} (nM) by NanoBRETT	CDK9 IC_{50} (nM) by NanoBRETT
24	92	1607	1604	925
37	88	1105	486	634
39	250	887	587	213
44	256	2301	1467	284
45	126	628	1159	147
51	43	289	297	49
55	56	732	2011	281
56	114	362	421	59
60	94	345	629	165
61	62	472	260	109
Samuraciclib	521	1273	>3000	>3000

ND- not determined.

Growth inhibitory concentration determination against different cancer types: Cell Lines: A549, HCT116 , MDA-MB-231, MDA-MB-468

[000316] The representative compounds of Formula (I) are of interest due to their potent inhibition of CDK7 enzymes and their ability to inhibit the growth of proliferating afore mentioned cancer cell lines.

[000317] Cells were cultured in respective culture medium (as per ATCC instructions). The cells were maintained at 37 °C in a humidified atmosphere with 5% CO2 to achieve exponential growth. Upon reaching 80% confluency, cells were dissociated using 0.5% trypsin/EDTA for subsequent experiments. Cell viability was determined using CellTiter-Glo as a readout method. Cells, adjusted to a density of 10,000 cells and seeded in a 96-well plate with 150 µL of medium per well and incubated overnight at 37 °C in a CO_2 incubator. The following day, cells were exposed to varying concentrations of test compounds dissolved in 1% dimethyl sulfoxide (DMSO), alongside appropriate assay controls. Incubation continued for an additional 48 hours at 37 °C in a CO_2 incubator. Cell viability assays were conducted according to the manufacturer's specifications for CellTiter-Glo Luminescent Cell Viability Assay (Promega).CC50 (50% cytotoxic concentration) is considered as the lowest concentration at which 50% cell viability is observed.

[000318] GI_{50} (growth inhibitory concentration) of the compounds of Formula I against cancer cell-linesare presented in Table-3.

Table-3: Growth inhibitory concentration determination (GI_{50})

Example Number	**HCT116_GI_{50} (µM)**	**MDA-MB_231_GI_{50} (µM)**	**MDA-MB_468_GI_{50} (µM**
1	2.5	ND	ND
2	>40	ND	ND
3	5	ND	ND
4	5	ND	ND
5	10	ND	ND
6	2.5	ND	ND

Example Number	HCT116_GI_{50} (µM)	MDA-MB_231_GI_{50} (µM)	MDA-MB_468_GI_{50} (µM
7	10	ND	ND
8	5	ND	ND
9	5	ND	ND
10	5	ND	ND
11	5	ND	ND
12	5	ND	ND
13	20	ND	ND
14	1.25	ND	ND
15	2.5	ND	ND
16	1.25	ND	ND
17	1.25	ND	ND
18	5	ND	ND
19	0.625	ND	ND
20	1.25	ND	ND
21	1.25	ND	ND
22	2.5	ND	ND
23	1.25	ND	ND
24	0.625	0.12	0.37
25	2.5	ND	ND
26	2.5	0.12	ND
27	2.5	2.5	ND
28	1.25	0.6	ND
29	5	ND	ND
30	10	ND	ND
31	2.5	ND	ND
32	0.625	0.6	ND
33	5	ND	ND
34	1.25	ND	ND
35	1.25	ND	ND
36	5	ND	ND
37	0.12	0.12	ND
38	0.30	0.30	ND
39	0.1	0.10	0.10
40	0.12	0.12	0.37
41	0.08	0.12	ND
42	0.04	0.12	ND
43	0.04	0.12	ND
44	0.04	0.08	ND
45	0.02	0.18	0.18

Example Number	HCT116_GI_{50} (µM)	MDA-MB_231_GI_{50} (µM)	MDA-MB_468_GI_{50} (µM
46	0.12	0.30	ND
47	0.04	0.10	0.10
48	0.12	0.30	ND
49	0.10	0.30	0.30
50	0.06	0.18	0.18
51	0.02	0.04	0.04
52	0.37	0.12	0.37
53	0.37	0.37	1.1
54	0.04	0.08	0.12
55	0.37	0.37	0.37
56	0.04	0.10	0.10
57	1.25	1.25	1.25
58	1.25	1.25	1.25
59	0.37	0.37	0.12
60	0.37	0.3	0.3
61	0.18	0.04	0.04
Samuraciclib	0.315	0.625	0.625

Rodent pharmacokinetics(PK) study of selected compounds of formula I:

[000319] The PK study was carried out in male CD1 mice and SD rats to estimate the plasma clearance, volume of distribution and terminal half-life, area under curve (AUC_{0-t}) 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-4.

Table-4: Pharmacokinetic Study design of Examples 24, 39, and 45 in Mice and Rats

Test item	Species/Strain /Gender	Route /condition	Dose (mg/kg)	Dose volume (mL/kg)	Formulation details
Example 24	Mice/CD1/Male	Oral/Fasted	15	10	2%v/v Gelucire: 1%v/v TPGS: 0.5% v/v

					Solutol HS: Water q.s
	Mice/CD1/Male	Oral/Fasted	30	10	10%v/v DMA : 2%v/v Tween80 : 2%v/v Gelucire 44/14 : water q.s
	Rat/SD/Male	i.v inf 60min/Fed	10	5	10%w/v Captsol in water (q.s): 0.4% Lactic acid (pH needs to adjust to 4.5 using 10%NaHCO3 solution)
	Rat/SD/Male	Oral/Fasted	30	10	10%v/v DMA : 2%v/v Tween80 : 2%v/v Gelucire 44/14 : Water q.s
Example 39	Rat/SD/Male	i.v bolus/Fed	5	5	5%w/v L-Ascorbic acid in water
	Rat/SD/Male	Oral/Fasted	30	10	10%v/v Labrasol: 5%w/v Ascorbic acid + 1%v/v TPGS + Water
Example 45	Rat/SD/Male	i.v inf 60 min/Fed	10	5	10%w/v Captsol in water (q.s):

					0.4% Lactic acid (pH adjusted to adjust to 4.5 using 10%NaHCO3 solution)
	Rat/SD/Male	Oral/Fasted	30	10	2%v/v Gelucire 44/14: 1%v/v TPGS: 0.5%v/v Solutol HS15: Water q.s

[000320] Briefly, all animals in the intravenous (i.v infusion & bolus) group were in the fed state, and animals in oral groups were fasted overnight (6 hr) before dose administration, and food was provided 4 h post-dose administration. All animals received water *ad-libitum* during the study period. Example 24 was experimented on mice and rats, whereas example 39 and example 45 were in Rats. The pharmacokinetic study design in Mice and Rats is provided in Table-4.
Blood samples (0.2 mL for Rats & 0.025 mL for Mice)) were collected from the jugular vein (Rats) and Saphenous vein (mice) into tubes containing K_2EDTA anticoagulant at the following sampling times:
IV infusion: 0.25 h, 0.5, 0.58, 0.75, 1, 2, 4, 6, 8 and 24 hours
IV bolus: Predose, 0.083 (5 min), 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hrs post-dose.
PO: Predose, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hrs post-dose.

[000321] Immediately following collection, blood samples were 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 was decanted into appropriately labelled polypropylene tubes in 96-well

plate format and stored in a freezer set to maintain a temperature of ≤-70°C, until analysis.

[000322] 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 a linear up and log down method for estimating AUC.

[000323] The mean (±SD) pharmacokinetic parameters of Example 24, Example 39 and Example 45 following IV bolus/Infusion and Oral dose administration in Mice and Rats are provided in the Table-5.

Table-5: Mean (±SD) Pharmacokinetic Parameters of Example 24, Example 39, and Example 45 following IV bolus and Oral dose administration in Mice and Rat

Compound	**Species**	**Route**	**Dose**	**C_{max}/Co***	**T_{max} #**	**AUC_{0-t}**	**AUC_{0-inf}**	**CL**	**V_{ss}**	**$t_{1/2}$**	**%F**
			mg/kg	**ng/mL**	**h**	**h*ng/mL**	**h*ng/mL**	**mL/min/kg**	**L/Kg**	**h**	
Example 24	Mice	p.o	15	459 ± 209	0.5 (0.5-1.0)	811 ± 292	814 ± 292	ND			
		p.o	30	1692 ± 631	1.0 (1.0-1.0)	4094 ± 2031	4102 ± 2030	ND			
	Rat	i.v infusion	10	2876 ± 223	0.5	5820 ± 853	6877 ± 814	25 ± 3.1	16 ± 4.4	10.5 ± 2.0	32 ± 8.5
		p.o	30	1241 ± 250	4.0 (1.0-4.0)	5689 ± 2204	ND				
Example 45	Rat	i.v infusion	10	2651 ± 752	0.5 (0.25-0.5)	2413 ± 255	2418 ± 255	69 ± 7.6	3.6 ± 0.78	1.1 ± 0.08	3.4 ± 0.5
		p.o	30	59 ± 14	0.5 (0.5-0.5)	244 ± 48	ND				
Example 39	Rat	i.v bolus	5	2142 ± 335	ND	1188 ± 156	1192 ± 153	71 ± 9.7	4.7 ± 1.5	1.6 ± 0.6	33 ± 5.2
		p.o	30	426 ± 182	4.0 (1.0-6.0)	2369 ± 453	ND				

* For i.v groups; # median (min-max); ND-not determined; i.v infusion for 60min

Results were expressed in mean ± SD; n=3 animals/group.

[000324] Example 24 and example 39 achieved good oral bioavailability (%F) of 32-33, and Example 45 low bioavailability of 3.4%. The total systemic clearance of Example 24 was moderate to that of hepatic clearance and high volume of distribution >2x total body water (TBW). Whereas Example 45 had 1.2x higher

clearance than hepatic clearance and a moderate volume of distribution. Example 39 had 1.3x higher clearance than hepatic clearance and a moderate volume of distribution.

[000325] Example 24 achieved good systemic exposure (AUC_{0-t} 5689 h*ng/mL) at a 30 mg/kg dose level in rats. Whereas Example 45 and Example 39 achieved relatively less systemic exposure ($AUC_{0-t,}$ 244 & 2369 h*ng/mL) compared to Example 24 in rats after oral administration at a dose level of 30 mg/kg.

[000326] In mice at 15 and 30 mg/kg post oral dose administration, Example 24 has demonstrated good systemic exposure ($AUC_{0-t,}$ 811 to 4102 ng.h/mL) and C_{max} (459 to 1692 ng/mL) with T_{max} of 0.5 to 1.0 hour.

Abbreviations:

i.v	intravenous
p.o	per oral
Vdss	Volume of distribution steady state
CL	Total Systemic Clearance
$t_{1/2}$	Half-life
ND	Not Determined
%F	Percent bioavailability
C_0	initial concentration at 0 time point post IV bolus/infusion administration
AUC_{0-t}	area under curve from o to last quantifiable time point
T_{max}	Time for maximum concentration

In vivo efficacy of Example 24 on HCT116 colon cancer xenograft model

[000327] This experimental system relies on immunodeficient mice to provide a host for the establishment of human xenografts. Crl:NU-*Foxn1*^{nu} (Athymic Nude Mice) implanted with human HCT116 tumor cells serve as a suitable model for evaluating anti-tumor activity of new chemical entities.

[000328] The HCT116 cell line is a commonly used human colorectal cancer cell line as a model system in drug discovery, and in identifying therapeutic interventions. Cells were cultured using standard techniques in McCoy's 5a complete growth medium (with 10% FBS) and 1X Antibiotic-antimycotic solution at 37 °C

with 5% CO_2 in a suitable incubator. Harvested cells are resuspended in serum-free media containing 50% Matrigel and kept on ice until inoculation.

[000329] Mice: All animal studies were conducted in accordance with the guidelines of the Committee for Control and Supervision of Experiments on Animals, India. 6- to 8-week-old (age at the time of engraftment) Crl:NU-*Foxn1*^{nu} mice were typically housed in sterilized, individually vented, polysulfone cages with stainless steel top grills having facilities for holding pelleted food and drinking water in polycarbonate bottles with stainless steel sipper tubes. Throughout the tumor engraftment and treatment evaluation period, the environmental conditions were maintained with adequate fresh air supply of 13.0 air changes/hour, temperature of 21-23 ^{0}C, relative humidity 57-64%, and the photoperiod was 12 hours light and 12 hours dark cycle.

[000330] Tumor engraftment: Female athymic nude mice were inoculated with 5x10^{6} (in 200µL) HCT116 cells per mouse 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 the tumor volume reached 90±10 mm^{3}, animals were randomized into respective treatment groups as per study plan. See Table 6 for details regarding the setup and dosing of animals. Post randomization, animals were treated with the test substance for 21 days. The efficacy experimental design is summarized in Table-6.

Table-6: Efficacy experimental design

Group	Treatment	n	dose (mg/kg)	Route	Regimen	Duration
1	Vehicle	8	10ml/kg	PO	TID	Day 1 to Day 21
2	Example 24	8	5	PO	TID	Day 1 to Day 21
3	Example 24	8	15	PO	TID	Day 1 to Day 21
4	Example 24 + Olaparib	8	5 50	PO PO	TID UID	Day 1 to Day 21 Day 1 to Day 21
5	Olaparib	8	50	PO	UID	Day 1 to Day 21
6	Paclitaxel	8	15	IP	On day 0, 3, 6, 9 and 12	

- *Paclitaxel was dosed by IP route every three days*

[000331] Tumor Growth Inhibition (TGI) was calculated using the following formula: TGI = (1 - T/C) x 100, where T = (Mean TV of the test group on Day X - Mean TV of the test group on Day 1); C = (Mean TV of the control group on Day X - Mean TV of the control group on Day 1).

[000332] Formulation and administration: Formulations were prepared with the components listed in Table-7 every day and mixed well before dosing each time, and administered orally.

Table-7: Formulations used for the efficacy studies

Treatment	Vehicle
Example 24	10 % v/v DMA (N, N Dimethyl acetamide) + 2 % v/v Tween80 + Water + 2 % v/v Gelucire 44/14
Vehicle	10 % v/v DMA (N, N Dimethyl acetamide) + 2 % v/v Tween80 + Water + 2 % v/v Gelucire 44/14
Olaparib	10 % v/v DMSO 10 % w/v, hydroxypropyl-β-cyclodextrin in PBS pH 7.4 quantity sufficient (q.s).
Paclitaxel	100 mg/16.7mL stock solution diluted with PBS (pH7.4)

[000333] The in vivo efficacy effect of Example 24 on Tumor volume had been summarized in Figures 1 and 2.

[000334] Example 24 alone, and its combination with Olaparib exhibited significant anti-tumor activity compared to vehicle control group against HCT116 xenograft tumor model. observed as early as day 7 and persisted till study termination at day 21 (Figures 1 and Figure 2- shows tumor weight). Significant and dose dependent tumor growth inhibition was observed when treated with a low dose of Example 24 at 5mg/kg (TID), resulting in a TGI of 66%, and a high dose of 15mg/kg (TID) with a TGI of 71%. The TGI further improved to 76% when low dose 5mg/kg (TID) Example 24 was combined with Olaparib (50mg/kg, UID), and was significantly better than Olaparib alone treatment that had a TGI of only 45%. The treatment groups at tested dose levels were well tolerated with no mortality and mild to moderate body weight loss of about 5% (Figure 3) was observed in Example 24 treatment groups during the experimental period.

In vivo efficacy of Example 24 on MDA-MB-468 Triple Negative Breast Cancer xenograft model

[000335] This experimental system relies on immunodeficient mice to provide a host for the establishment of human xenografts. Crl:NU-*Foxn1*^{nu} (Athymic Nude Mice) implanted with human MDA-MB-468 Triple Negative Breast Cancer (TNBC) tumor cells are found to be a suitable model for evaluating antitumor activity of new chemical entities.

[000336] MDA-MB-468 cells are characterized by their triple-negative status, lacking the expression of the estrogen receptor (ER), progesterone receptor (PR) and HER2. They have been reported widely in literature for screening compounds in efficacy studies for antitumor activity. Cells were cultured using standard techniques in L-15 complete growth medium (with 10% FBS) and 1X Antibiotic-antimycotic solution at 37 °C with 5% CO2 in a suitable incubator. Cells upon harvest were re-suspended in serum-free media containing 50% Matrigel and kept on ice until use for inoculations.

[000337] Mice: All animal studies were conducted in accordance with the guidelines of the Committee for Control and Supervision of Experiments on Animals,

India. 7- to 9-week-old (at the time of engraftment) Crl:NU-*Foxn1*^{nu} mice were typically housed in sterilized, individually vented, polysulfone cages, with stainless steel top grills having facilities for holding pelleted food and drinking water in polycarbonate bottles with stainless steel sipper tubes. Throughout the tumor engraftment and treatment evaluation period, the environmental conditions were constant with adequate fresh air supply of 13.0 air changes/hour, temperature of 21-23°C, relative humidity 57-64%, and the photoperiod was 12 hours light and 12 hours dark cycle.

Table-8: Efficacy experimental design

Grou	Treatment	n	dose (mg/kg)	Route	Regimer	Duration
1	Vehicle	8	10ml/kg	PO	TID	Day 1 to Day 21
2	Example 24	8	5 30	PO	TID	Day 1 to Day 21 Day21 to Day 42
3	Example 24	8	15	PO	TID	Day 1 to Day 21

[000338] Tumor engraftment: Female athymic nude mice were inoculated with $5x10^6$ (in 200µL) MDA-MB-468 cells per mouse 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 reached 80±15 mm^3, all animals were randomized into respective treatment groups as per study plan. See Table 8 for details regarding the setup and dosing of animals. Tumor volume at the time of randomization was ~80 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 42 days. The efficacy experimental design is summarized in Table-8. Tumor Growth Inhibition (TGI) was calculated using the following formula: TGI = (1 - T/C) x 100, where T = (Mean TV of the test group on

Day X - Mean TV of the test group on Day 1); C = (Mean TV of the control group on Day X - Mean TV of the control group on Day 1).Formulation and

[000339] administration: Formulations were prepared with the components listed in Table-7 every day and mixed well before dosing each time, and administered orally.

[000340] The in vivo efficacy effect of Example 24 on Tumor volume had been summarized in Figures 4 and 5.

[000341] Example 24 exhibited significant anti-tumor activity compared to vehicle control group against MDA-MB-468 xenograft tumor model. This notable difference was observed as early as day 21 and persisted till study termination at day 42 (Figures 4, & Figure 5- shows tumor weight). Significant tumor growth inhibition was observed when treated with a low dose of Example 24 at 15mg/kg (TID), resulting in a TGI of 55%, and a 5mg/kg for 20 days followed by a high dose of 30mg/kg (TID, day 21-42) that lead to a TGI of 81%. The treatment groups at tested dose levels were well tolerated with no mortality and mild to moderate body weight loss of less than 10% (Figure 6) was observed in Example 24 treatment groups during the long experimental period of 42 days.

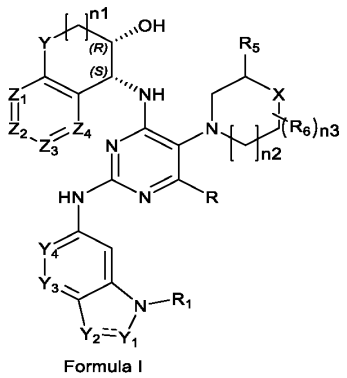
ADVANTAGES OF THE PRESENT DISCLOSURE

[000342] The present disclosure provide compounds of Formula I, that exhibit enhanced and selective therapeutic effect for cancer treatment. Inhibiting CDK7 is a promising therapeutic strategy in cancer as CDK7 regulates the transcription of cancer-causing genes, promotes uncontrolled cell cycle progression and resistance to anti-hormone therapy. Compounds of Formula (I) exhibits better selectivity over other key CDK isoforms(CDK2,CDK4,CDK6 and CDK9), demonstrates excellent antiproliferative with apoptotic activity in different cancer cell types and also efficacious in reducing tumour growth in mice xenograft models inoculated with metastatic cell lines like MDA-MB-468 (TNBC) and HCT-116 (CRC). The present disclosure also provides simple and facile process for preparing the compounds of Formula I. A combination of compounds of Formula I optionally together with other chemotherapeutic agents or immune checkpoint inhibitors are also useful in

treating conditions or diseases mediated by cyclin dependent kinase 7 or cyclin dependent kinase 7 with cyclin H and MAT1 or CDK-activating kinase (CAK) or combinations thereof.

I/We claim:

1. A compound of Formula I, its pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, or pharmaceutically active derivatives thereof,



Formula I

Formula I

wherein R_1 is selected from 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, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl;

Y_1 is N or C(=O);

Y_2 is selected from N, O, CR_2, or NR_3, wherein R_2 and R_3 are independently selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

--- refers to single bond or double bond between Y_1 and Y_2;

Y_3 and Y_4 are independently N or CR_4, wherein R_4 is selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl; wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

R is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy;

R_5 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl, wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

X is selected from CR_7, O, S, S=O, SO_2, or NR_7; R_7 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $NH(CO)_pR_8$, or $C(=O)R_8$; R_8 is selected from C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl

or C_{3-8} heterocyclyl is optionally substituted with hydroxy, amino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{3-8} heteroaryl or C_{3-8} heterocyclyl; wherein C_{3-8} heterocyclyl is optionally substituted with one or more groups selected from oxo or C_{1-6} alkyl;

p is 0 or 1;

R_6 is selected from hydrogen, amino, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} aminoalkyl, $C(=O)NR_{9a}R_{9b}$, -NH-C(=O)R_9 or -NHCH$_2R_9$; wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy or cyano;

R_9, R_{9a} and R_{9b} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, C_{3-12} heteroaryl, wherein C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from cyano, oxo, hydroxy, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, -S-C_{1-6} alkyl, -S(O)-C_{1-6} alkyl, -S(O)$_2$-C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{3-12} heteroaryl or C_{3-8} heterocyclyl, wherein C_{3-8} heterocyclyl or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from C_{1-6} alkyl; or R_{9a} and R_{9b} are combined together to form a C_{3-8} heterocyclyl optionally substituted with one or more substituents selected from oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} aminoalkyl;

Z_1, Z_2, Z_3, and Z_4 are independently selected from N or CR_{10};

R_{10} is selected from hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

Y is selected from O, S, S=O, SO_2, N-CH_3, N-C(=O)CH_3, or CR_{11};

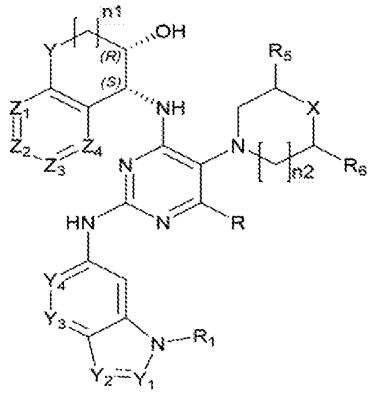
R_{11} is selected from hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

n1 is 0, 1 or 2;

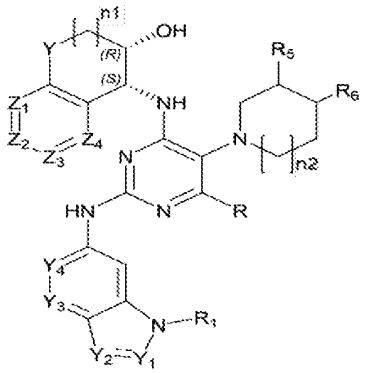
n2 is 0, 1 or 2; and

n3 is selected from 0 to 3.

2. The compound of Formula I as claimed in claim 1, wherein the compound of Formula I is selected from,



Formula Ia



Formula Ib

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

wherein R_1 is selected from 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} alkoxy, C_{1-6} haloalkoxy, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl;

Y_1 is N or C(=O);

Y_2 is selected from N, O, CR_2 or NR_3, wherein R_2 and R_3 are independently selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

--- refers to single bond or double bond between Y_1 and Y_2;

Y_3 and Y_4 are independently N or CR_4, wherein R_4 is selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl; C_{1-6} wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

R is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy;

R_5 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl, wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

n1 is 0, 1 or 2;

X is selected from CR_7, O, S, S=O, SO_2, or NR_7; R_7 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $NH(CO)_pR_8$, or $C(=O)R_8$; R_8 is selected from C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl or C_{3-8} heterocyclyl is optionally substituted with hydroxy, amino, C_{1-6} alkyl, C1-6

alkoxy, C_{1-6} aminoalkyl, C_{3-8} heteroaryl or C_{3-8} heterocyclyl; wherein C_{3-8} heterocyclyl is optionally substituted with one or more groups selected from oxo or C_{1-6} alkyl;

R_6 is selected from hydrogen, amino, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} aminoalkyl, $C(=O)NR_{9a}R_{9b}$, -NH-C(=O) R_9 or $-NHCH_2R_9$; wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy or cyano; p is 0 or 1;

R_9, R_{9a} and R_{9b} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, C_{3-12} heteroaryl, wherein C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from cyano, oxo, hydroxy, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, -S-C_{1-6} alkyl, -S(O)-C_{1-6} alkyl, -$S(O)_2$-C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{3-12} heteroaryl or C_{3-8} heterocyclyl, wherein C_{3-8} heterocyclyl or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from C_{1-6} alkyl; or R_{9a} and R_{9b} are combined together to form a C_{3-8} heterocyclyl optionally substituted with one or more substituents selected from oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} aminoalkyl;

Z_1, Z_2, Z_3, and Z_4 are independently selected from N or CR_{10}:

R_{10} is selected from hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl , C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

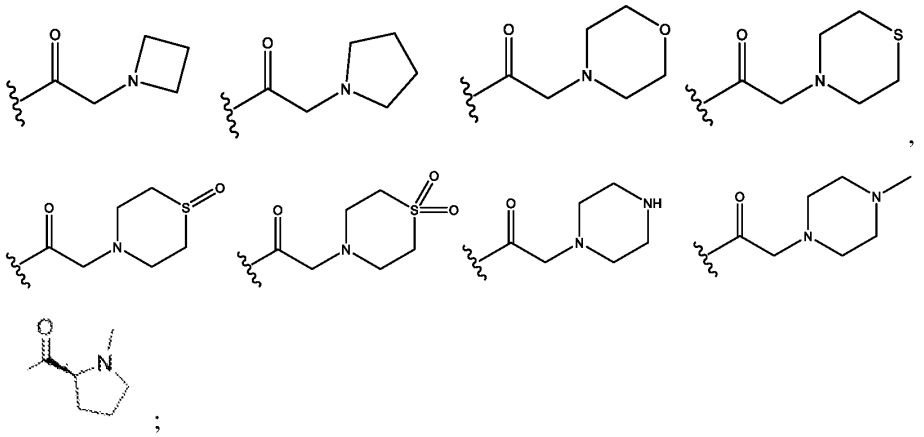
Y is selected from O, S, S=O, SO_2, N-CH_3, N-C(=O)CH_3 or CR_{11};

R_{11} is selected from hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy; and

n2 is 0, 1 or 2.

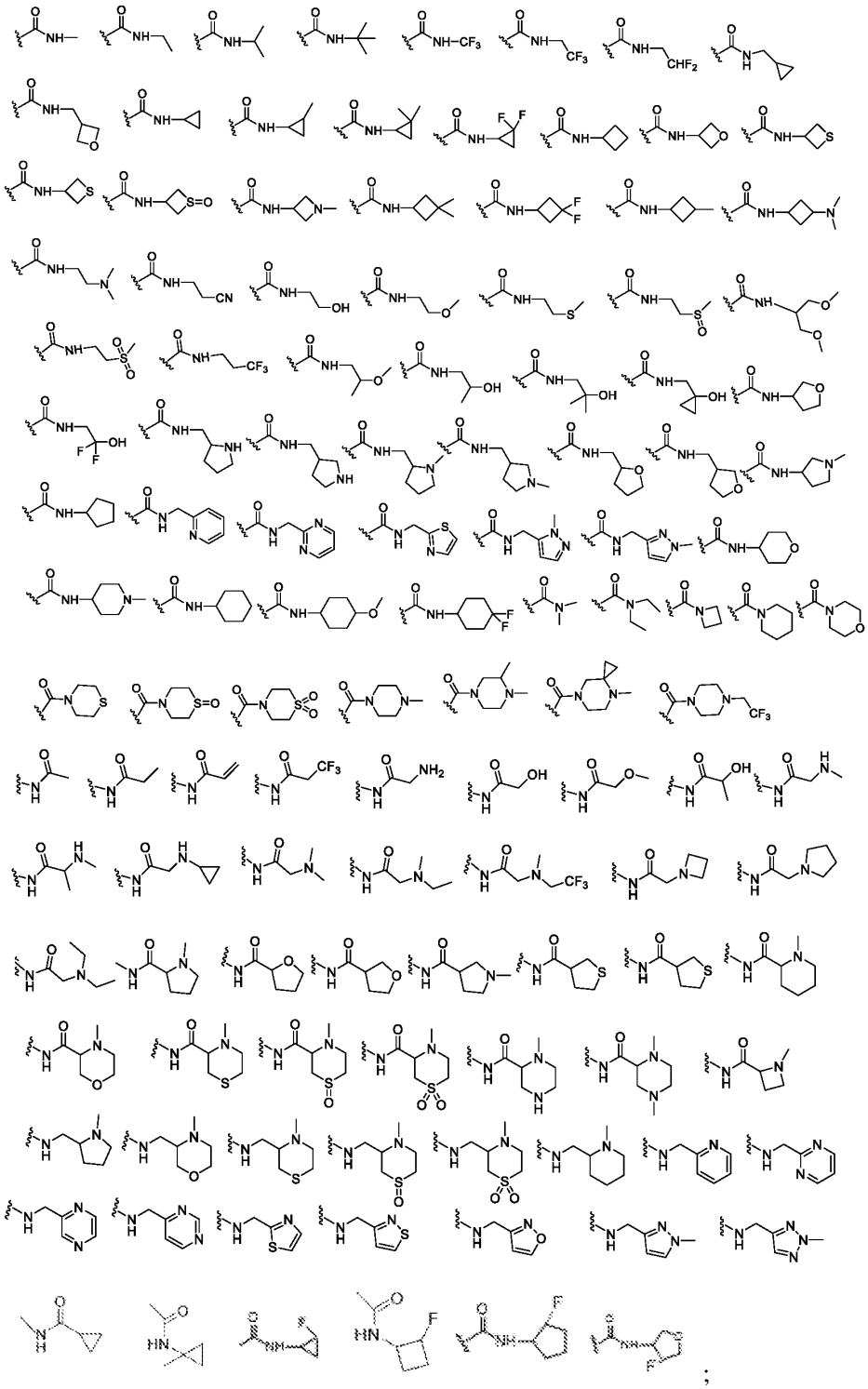
3. The compound as claimed in claim 1 or 2, wherein R_1 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy; Y_1 is N when --- is a double bond and Y_2 is N or CR_2, wherein R_2 is selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;Y_1 is C(=O) when --- is a single bond and Y_2 is O or NR_3, wherein R_3 is selected from hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl; Y_3 and Y_4 are independently N or CR_4,

wherein R_4 is selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl; C_{1-6} wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy; R is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl or C_{1-6} alkoxy; R_5 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl, wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy; n1 is 0, 1 or 2; X is selected from CR_7, O, S, S=O, SO_2, or NR_7; R_7 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(=O)C_{1-6}$ alkyl, $C(=O)C_{3-6}$ cycloalkyl, $C(=O)CH_2OH$, $C(=O)CH_2OCH_3$; $C(=O)CH_2NH_2$, $C(=O)CH_2NHCH_3$, $C(=O)CH_2N(CH_3)_2$,



;

R_6 is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy; C_{1-6} haloalkoxy, CH_2OH, CH_2OCH_3, NH_2, $N(CH_3)_2$,



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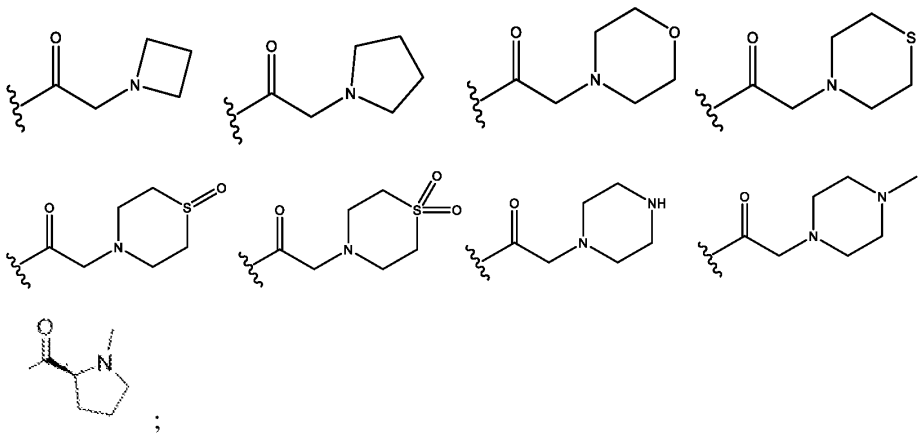
Z_1, Z_2, Z_3, and Z_4 are independently selected from N or CR_{10}; R_{10} is selected from hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy; Y is selected from O or CR_{11}; R_{11} is selected from hydrogen, cyano, fluoro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy; n1 is 0, 1 or 2; and n2 is 0 or 1.

4. The compound as claimed in claim 1 or 2, wherein R_1 is selected from CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2CH_2CH_3$, CH_2CHF_2, $CH_2CH_2CHF_2$, $CH_2CH_2OCH_3$, $CH_2CH_2OCF_3$, $CH_2CH_2OCF_3$, $CH_2CH_2OCHF_2$, $CH_2CH_2CH_2OH$, $CH(CH_3)CH_2CH_3$,



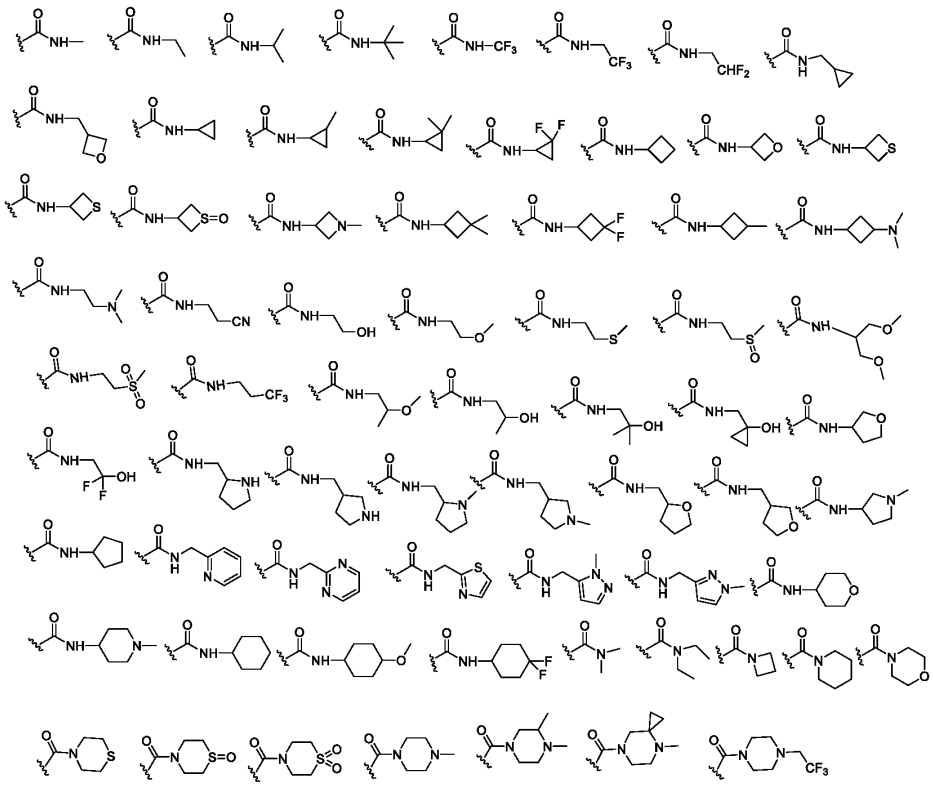
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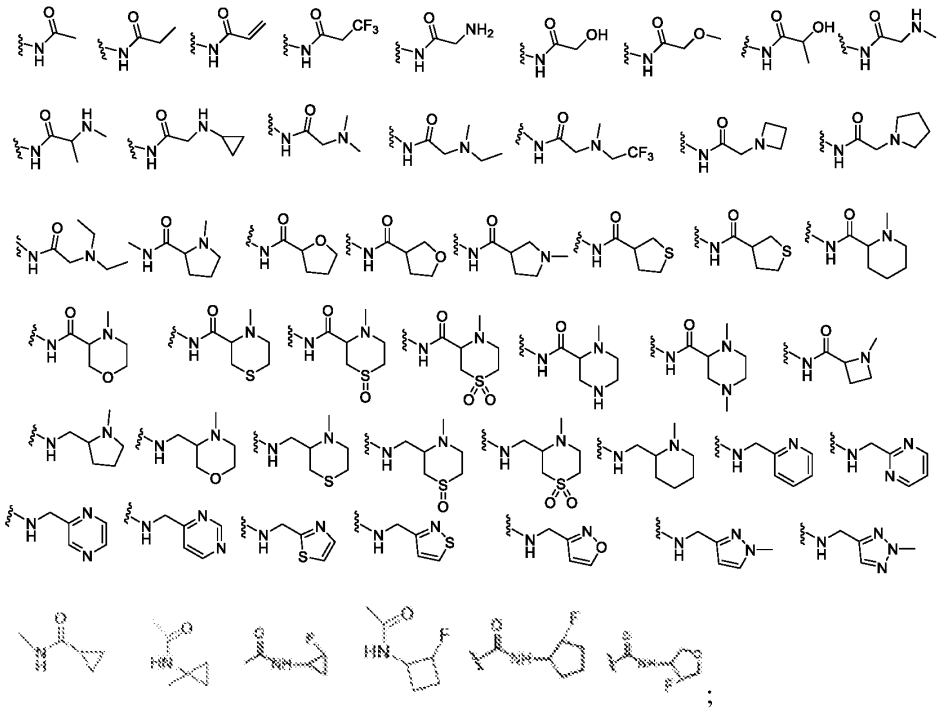
Y_1 is N when --- is a double bond and Y_2 is N or CR_2, wherein R_2 is selected from hydrogen, fluoro, or CH_3;Y_1 is C(=O) when --- is a single bond and Y_2 is O or NR_3, wherein R_3 is selected from hydrogen, CH_3, or CF_3;Y_3 and Y_4 are independently N or CR_4, wherein R_4 is selected from hydrogen, fluoro, or CH_3; R is selected from hydrogen, CH_3, OCH_3, or CF_3; R_5 is selected from hydrogen, CH_3, CH_2CH_3, CF_3, or  ; n1 is 0, 1 or 2; X is selected from CR_7, O, S, S=O, SO_2, or NR_7; R_7 is independently selected from hydrogen, CH_3, CH_2CH_3, $C(=O)CH_3$, $C(=O)CH_2CH_3$, C(=O)cyclopropyl, $C(=O)CH_2OH$, $C(=O)CH_2OCH_3$, $C(=O)CH_2NH_2$, $C(=O)CH_2NHCH_3$, $C(=O)CH_2N(CH_3)_2$,



;

R_6 is selected from hydrogen, CH_3, CH_2CH_3, CF_3, CH_2CH_3, OCH_3, OCF_3, CH_2OH, CH_2OCH_3, NH_2, $N(CH_3)_2$,





;

Z_1, Z_2, Z_3, and Z_4 are independently selected from N or CR_{10};

R_{10} is hydrogen, cyano, fluoro, chloro, CH_3, CF_3, OCH_3, or OCF_3;

Y is selected from O or CR_{11};

R_{11} is hydrogen, or CH_3; and

n2 is 0 or 1.

5. The compound as claimed in claims 1 to 4, wherein the compound is selected from a group consisting of:

i.(S)-N-ethyl-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-isopropyl-1H-indazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide (Example 1);

ii.(S)-1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-ethylpiperidine-3-carboxamide (Example 3);

iii.(S)-N-ethyl-1-(2-((5-fluoro-1-propyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide (Example 4);

iv.(1S,2R)-1-((2-((1-allyl-5-fluoro-1H-indazol-6-yl)amino)-5-((S)-3-(hydroxymethyl)piperidin-1-yl)pyrimidin-4-yl)amino)-2,3-dihydro-1H-inden-2-ol (Example 5);

v.(S)-1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-isopropylpiperidine-3-carboxamide (Example 6);

vi.1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-ethylpiperidine-4-carboxamide (Example 7);

vii.1-((S)-4-(2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino)ethan-1-one (Example 8);

viii.1-((S)-4-(2-((5-fluoro-1-(prop-2-yn-1-yl)-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino)ethan-1-one (Example 9);

ix.1-((S)-4-(2-((5-fluoro-1-isopropyl-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino)ethan-1-one (Example 10);

x.1-((S)-4-(2-((5-fluoro-1-(2-methoxyethyl)-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino)ethan-1-one (Example 11);

xi.N-(1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-4-yl) propionamide (Example 12);

xii.1-((S)-4-(2-((1-allyl-5-methyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino) ethan-1-one (Example 13);

xiii.2-(dimethylamino)-N-(1-(2-((1-ethyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-4-yl) acetamide (Example 14);

xiv.(S)-1-(2-((1-allyl-5-fluoro-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 15);

xv.N-(1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl) piperidin-4-yl)-2-(dimethylamino) acetamide (Example 16);

xvi.2-(dimethylamino)-N-(1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl)amino)pyrimidin-5-yl)piperidin-4-yl)acetamide (Example 17);

xvii.1-((S)-4-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-(methylamino) ethan-1-one (Example 18);

xviii.(S)-1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 19);

xix.1-((S)-4-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl)-2-morpholinoethan-1-one (Example 20);

xx.(1S,2R)-1-((2-((1-allyl-1H-indazol-6-yl) amino)-5-(4-((pyridin-2-ylmethyl) amino) piperidin-1-yl) pyrimidin-4-yl) amino)-2,3-dihydro-1H-inden-2-ol (Example 21);

xxi.((S)-4-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-2-methylpiperazin-1-yl) ((S)-1-methylpyrrolidin-2-yl) methanone (Example 22);

xxii.(R)-N-(1-(2-((1-allyl-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidin-4-yl)-1-methylpyrrolidine-2-carboxamide (Example 23);

xxiii.(S)-N-cyclopropyl-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 24);

xxiv.(S)-1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-(oxetan-3-yl) piperidine-3-carboxamide (Example 25);

xxv.(3S)-1-(2-((1-allyl-1H-indazol-6-yl) amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-(2,2-difluorocyclopropyl)piperidine-3-carboxamide (Example 26);

xxvi.(R)-1-(2-((1-allyl-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 27);

xxvii.N-((S)-1-(2-((1-allyl-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidin-3-yl)cyclopropanecarboxamide (Example 28);

xxviii.(S)-1-(2-((1-allyl-5-methyl-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 29);

xxix.(S)-1-(2-((1-allyl-4-fluoro-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 30);

xxx.((S)-1-(2-((1-allyl-1H-indazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)piperidin-3-yl)(4-methylpiperazin-1-yl)methanone (Example 31);

xxxi.(S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl)amino)pyrimidin-5-yl)-N-isopropylpiperidine-3-carboxamide (Example 32);

xxxii.(S)-N-cyclopropyl-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((5-methyl-1-(prop-2-yn-1-yl)-1H-indazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide (Example 33);

xxxiii.((S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl)amino)pyrimidin-5-yl)piperidin-3-yl)(morpholino)methanone (Example 34);

xxxiv.(S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl)amino)pyrimidin-5-yl)-N-(oxetan-3-yl)piperidine-3-carboxamide (Example 35);

xxxv.(S)-N-cyclopropyl-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((2-oxo-3-(prop-2-yn-1-yl)-2,3-dihydrobenzo[d]oxazol-5-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide (Example 36);

xxxvi.(S)-1-(2-(1-(R)-but-3-yn-2-yl)-1H-indazol-6-yl) amino)-4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 37);

xxxvii.(S)-1-(2-((1-(S)-but-3-yn-2-yl)-1H-indazol-6-yl) amino)-4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 38);

xxxviii.(S)-N-cyclopropyl-1-(4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-(1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3] triazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide ((Example 39);

xxxix.(S)-N-(2,2-difluoroethyl)-1-(4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 40);

xl.(S)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl)-N-(1-methyl cyclopropyl) piperidine-3-carboxamide (Example 41);

xli.(S)-1-(2-(1-(R)-but-3-yn-2-yl)-1H-benzo[d][1,2,3] triazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-cyclopropyl piperidine-3-carboxamide (Example 42);

xlii.(S)-N-cyclopropyl-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-(1-isopropyl-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 43);

xliii.(S)-1-(2-((1-allyl-1H-benzo[d] [1,2,3] triazol-6-yl) amino)-4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropylpiperidine-3-carboxamide (Example 44);

xliv.(S)-1-(2-((1-((R)-but-3-yn-2-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-(2,2-difluoroethyl)piperidine-3-carboxamide (Example 45);

xlv.(S)-1-(2-(1-(S)-but-3-yn-2-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino)-4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino) pyrimidin-5-yl)-N-cyclopropyl piperidine-3-carboxamide (Example 46);

xlvi.(3S)-N-(2,2-difluorocyclopropyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 47);

xlvii.(S)-N-(2,2-difluoroethyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-(1-isopropyl-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 48);

xlviii.S)-1-(2-((1-((S)-but-3-yn-2-yl)-1H-benzo[d][1,2,3] triazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-(2,2-difluoro ethyl) piperidine-3-carboxamide (Example 49);

xlix.(S)-1-(2-((1-((R)-but-3-yn-2-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino)-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)pyrimidin-5-yl)-N-((R)-2,2-difluorocyclopropyl)piperidine-3-carboxamide (Example 50);

l.(S)-N-((1S,2R)-2-fluorocyclopropyl)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino) pyrimidin-5-yl)piperidine-3-carboxamide (Example 51);

li.(S)-N-((1R,2R)-2-fluorocyclopropyl)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino) pyrimidin-5-yl)piperidine-3-carboxamide (Example 52);

lii.(S)-N-((1S,2S)-2-fluorocyclopropyl)-1-(4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3] triazol-6-yl)amino) pyrimidin-5-yl)piperidine-3-carboxamide (Example 53);

liii.(S)-N-((1R,2S)-2-fluorocyclopropyl)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 54);

liv. (S)-N-((1S,2R)-2-fluorocyclopropyl)-1-(4-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-indazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 55);

lv.(S)-N-((1S,2R)-2-fluorocyclopropyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-isopropyl-1H-benzo[d][1,2,3] triazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide (Example 56);

lvi.(R)-N-((1S,2R)-2-fluorocyclopropyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 57);

lvii.(R)-N-cyclopropyl-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-(1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 58);

lviii.(3S)-N-(2-fluorocyclobutyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 59);

lix.(S)-N-((1R,2S)-2-fluorocyclobutyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 60);

lx.(S)-N-((1S,2R)-2-fluorocyclobutyl)-1-(4-(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl) amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d] [1,2,3] triazol-6-yl) amino) pyrimidin-5-yl) piperidine-3-carboxamide (Example 61);

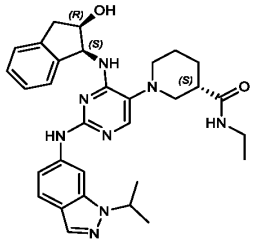
lxi.(S)-N-((1S,2R)-2-fluorocyclopropyl)-4-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-

benzo[d][1,2,3]triazol-6-yl)amino)pyrimidin-5-yl)morpholine-2-carboxamide (Example 62);

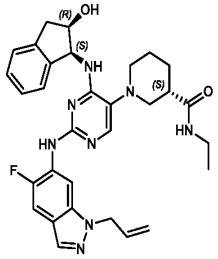
lxii. (S)-N-((1S,2R)-2-fluorocyclopropyl)-4-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino)pyrimidin-5-yl)piperazine-2-carboxamide (Example 63);

lxiii. (S)-N-((1S,2R)-2-fluorocyclopentyl)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide (Example 64);

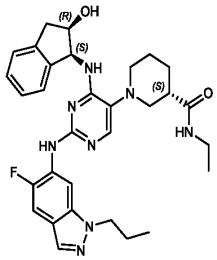
lxiv. (S)-N-((3S,4S)-4-fluorotetrahydrofuran-3-yl)-1-(4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)-2-((1-(prop-2-yn-1-yl)-1H-benzo[d][1,2,3]triazol-6-yl)amino)pyrimidin-5-yl)piperidine-3-carboxamide (Example 65).



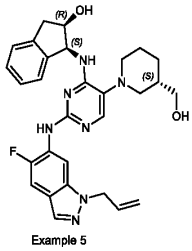
Example 1



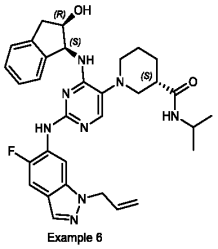
Example 3



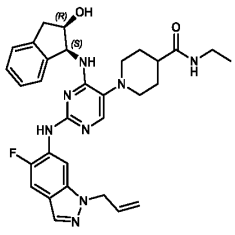
Example 4



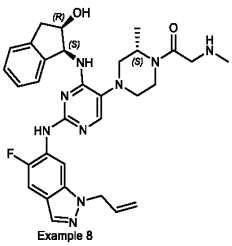
Example 5



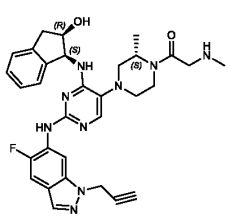
Example 6



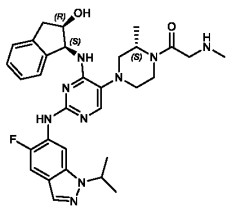
Example 7



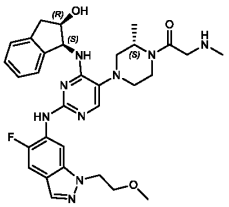
Example 8



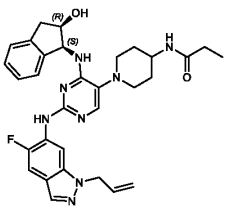
Example 9



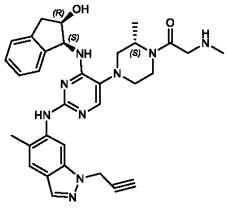
Example 10



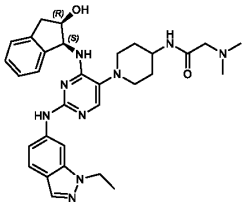
Example 11



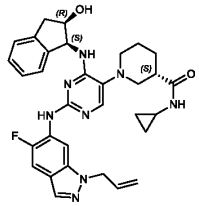
Example 12



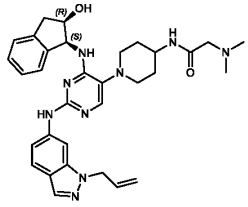
Example 13



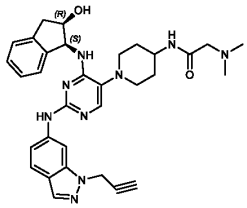
Example 14



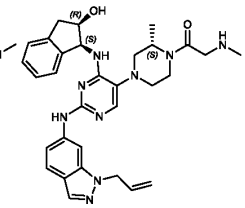
Example 15



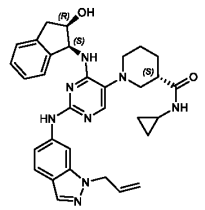
Example 16



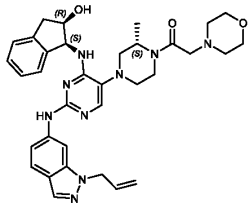
Example 17



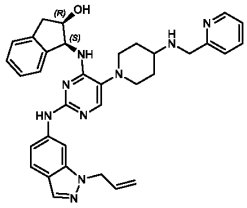
Example 18



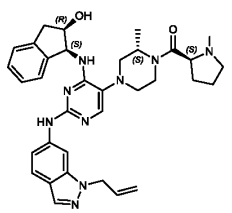
Example 19



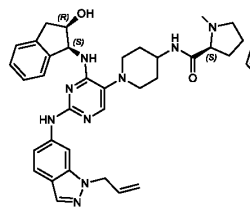
Example 20



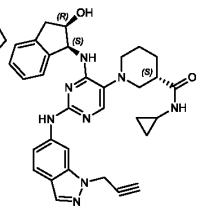
Example 21



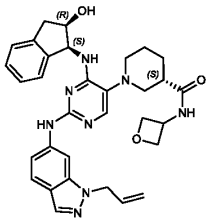
Example 22



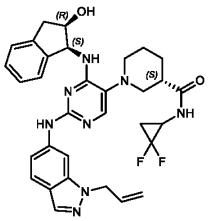
Example 23



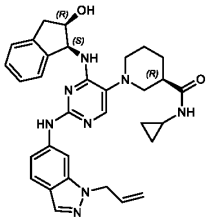
Example 24



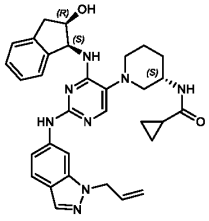
Example 25



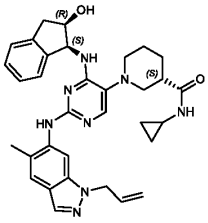
Example 26



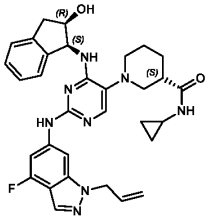
Example 27



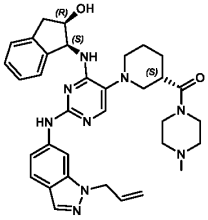
Example 28



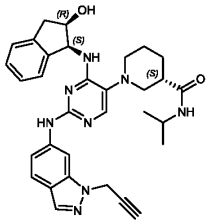
Example 29



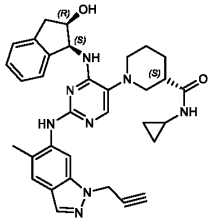
Example 30



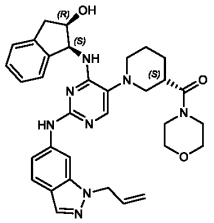
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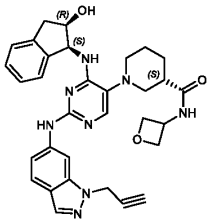
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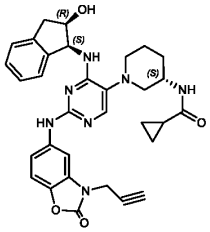
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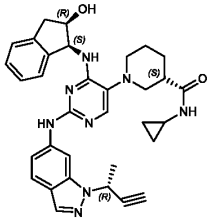
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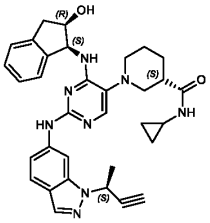
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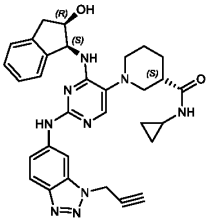
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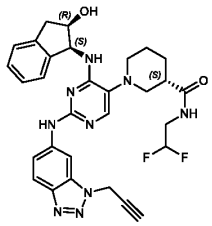
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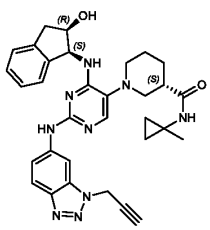
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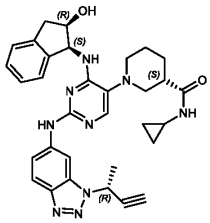
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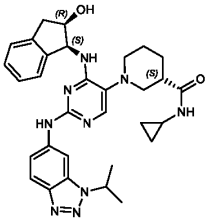
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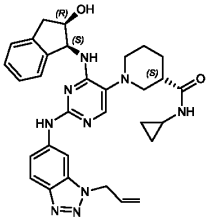
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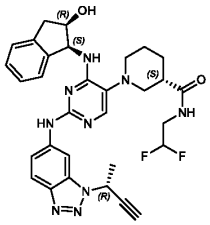
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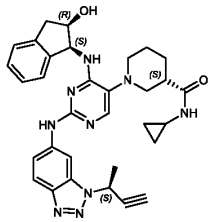
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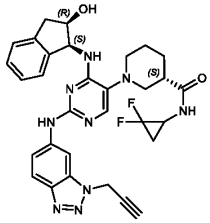
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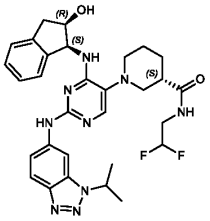
Example 45



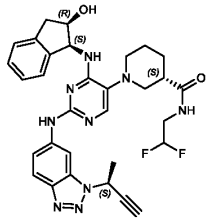
Example 46



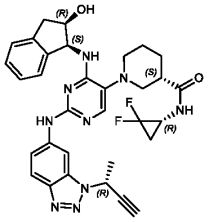
Example 47



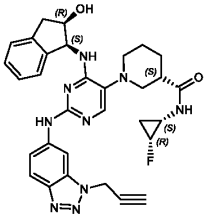
Example 48



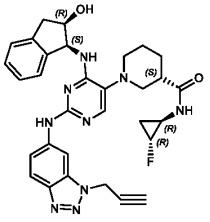
Example 49



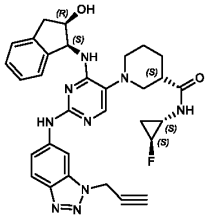
Example 50



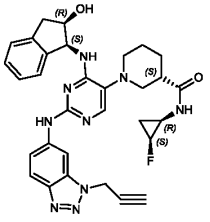
Example 51



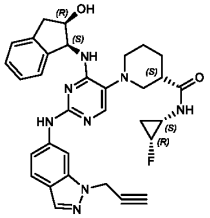
Example 52



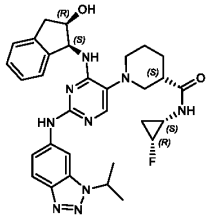
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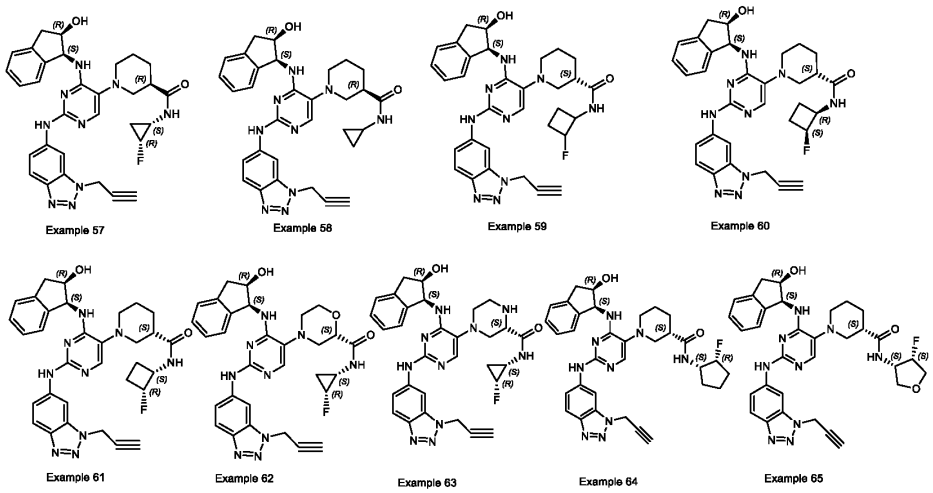
Example 54



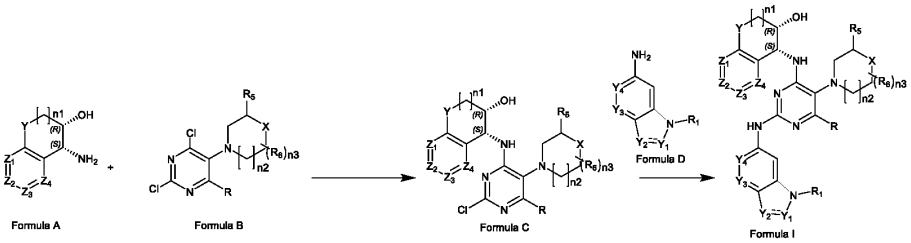
Example 55



Example 56



6. A process of preparation of compounds of Formula I as claimed in any one of the claims 1 to 5, the process comprising: reacting Formula (A) and Formula (B) followed by reacting with Formula (D) in the presence of a base to obtain the compound of Formula I,



wherein R_1 is selected from 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} alkoxy, C_{1-6} haloalkoxy, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl;

Y_1 is N or C(=O);

Y_2 is selected from N, O, CR_2 or NR_3, wherein R_2 and R_3 are independently selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

--- refers to single bond or double bond between Y_1 and Y_2;

Y_3 and Y_4 are independently N or CR_4, wherein R_4 is selected from hydrogen, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl; wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

R is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy;

R_5 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl, wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy or hydroxy;

n1 is 0, 1 or 2;

X is selected from CR_7, O, S, S=O, SO_2, or NR_7; R_7 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $NH(CO)_pR_8$, or $C(=O)R_8$; R_8 is selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, or C_{3-8} heterocyclyl, wherein C_{1-6} alkyl or C_{3-8} heterocyclyl is optionally substituted with hydroxy, amino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{3-8} heteroaryl; wherein C_{3-8} heterocyclyl is optionally substituted with one or more groups selected from oxo or C_{1-6} alkyl; p is 0 or 1;

R_6 is selected from hydrogen, amino, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} aminoalkyl, $C(=O)NR_{9a}R_{9b}$, -NH-C(=O) R_9 or $-NHCH_2R_9$; wherein C_{1-6} alkyl is optionally substituted with hydroxy, C_{1-6} alkoxy, or cyano;

R_9, R_{9a} and R_{9b} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, C_{3-12} heteroaryl, wherein C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{3-6} cycloalkyl, C_{3-8} heterocyclyl, or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from cyano, oxo, hydroxy, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, -S-C_{1-6} alkyl, -S(O)-C_{1-6} alkyl, -$S(O)_2$-C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{3-12} heteroaryl or C_{3-8} heterocyclyl, wherein C_{3-8} heterocyclyl or C_{3-12} heteroaryl is optionally substituted with one or more substituents selected from C_{1-6} alkyl; or R_{9a} and R_{9b} are combined together to form a C_{3-8} heterocyclyl optionally substituted with one or more substituents selected from oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} aminoalkyl;

Z_1, Z_2, Z_3, and Z_4 are independently selected from N or CR_{10};

R_{10} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;

Y is selected from O, S, S=O, SO_2, N-CH_3, N-C(=O)CH_3, or CR_{11};

R_{11} is hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy;
n2 is 0, 1 or 2; and
n3 is selected from 0 to 3.

7. The process as claimed in claim 6, wherein the base is selected from the group consisting of triethylamine, diisopropylethylamine, pyridine, sodium hydride, potassium tertiary butoxide, sodium carbonate, potassium carbonate, and combinations thereof.

8. The compound as claimed in any one of the claims 1 to 5, for use in the manufacture of a medicament.

9. The compound as claimed in any one of the claims 1 to 5, wherein the compound is an inhibitor of cyclin dependent kinase 7 or cyclin dependent kinase 7 with cyclin H and MAT1 or CDK-activating kinase (CAK) or combinations thereof.

10. The compound as claimed in any one of the claims 1 to 5, for use in treating cancer mediated at least in part by cyclin dependent kinase 7 or cyclin dependent kinase 7 with cyclin H and MAT1 or CDK-activating kinase (CAK) or combinations thereof.

11. The compound as claimed in claim 10, wherein said cancer is selected from cancer of adrenal gland, brain, bladder, breast, bone, colon, oesophagus, head, gastric, kidney, liver, lung, muscle, neck, pancreas, prostate, skin, thyroid or white blood cells.

12. A combination comprising of compounds of Formula I as claimed in any one of the claims 1 to 5, with at least one additional therapeutic agent.

13. A combination comprising of compounds of Formula Ia and Ib as claimed in claims 2 to 5, with at least one additional therapeutic agent.

14. The combination as claimed in any one of the claims 12 or 13, wherein the additional therapeutic agent is selected from chemotherapeutic agent or immune checkpoint inhibitors.

15. The combination as claimed in claim 14, wherein chemotherapeutic agent is selected from CDK4/6 inhibitor, BCl2 (B-cell lymphoma-2) inhibitor, Bcl-XL

(B-cell lymphoma-extra-large) inhibitor, anti-estrogen, anti-progesterone, KRas inhibitor, Braf inhibitor, EGFR inhibitor, angiogenesis inhibitor, 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 (PARP) inhibitor, cisplatin, oxaplatin or combinations thereof.

16. The combination as claimed in claim 14, wherein the immune checkpoint inhibitors 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 (CTL4), inhibitor, anti-CTL4 antibody, T cell immunoglobulin and ITIM domain (TIGIT) inhibitor, ecto-nucleoside triphosphate diphosphohydrolase 1(E-NTPDase, CD39) inhibitor, ecto-5'-nucleotidase(Ecto5'NTase, CD79) inhibitor, protein tyrosine phosphatases non-receptor type 1/2 (PTPN1/2) inhibitors, or combinations thereof.

17. A pharmaceutical composition comprising the compound as claimed in claim 1 to 5, with at least one pharmaceutically acceptable excipient.

18. The composition as claimed in claim 17, wherein the composition is in the form of powder, tablet, liquid, or emulsion.

19. A method of treating cancer to a subject in need thereof, the method comprising administering the compound as claimed in claim 1 to 5 or the combination as claimed in claim 12 to 16 or the pharmaceutical composition as claimed in claim 18 to 19 to the subject.

20. The method as claimed in claim 19, wherein the cancer is selected from cancer of adrenal gland, brain, bladder, breast, bone, colon, oesophagus, head, gastric, kidney, liver, lung, muscle, neck, pancreas, prostate, skin, thyroid or white blood cells.

21. A method of treating a disease or condition mediated by cyclin dependent kinase 7 or cyclin dependent kinase 7 with cyclin H and MAT1 or CDK-activating kinase (CAK) or combinations thereof to a subject in need thereof, the method

comprising administering the compound as claimed in claim 1 to 5 or the combination as claimed in claim 12 to 16 or the pharmaceutical composition as claimed in claim 17 to 18 to the subject.

22. The method as claimed in claim 21, wherein the disease or condition is selected from cancer of adrenal gland, brain, bladder, breast, bone, colon, oesophagus, head, gastric, kidney, liver, lung, muscle, neck, pancreas, prostate, skin, thyroid or white blood cells.