BICYCLIC HETEROCYCLYL DERIVATIVES AS IRAK4 INHIBITORS

This application claims the benefit of Indian provisional applications 158/CHE/2014 filed on January 13, 2014 and 3000/CHE/2014 filed on June 20, 2014 which hereby incorporated by reference.

FIELD OF THE INVENTION

This invention relates to compounds useful for treatment of cancer and inflammatory diseases associated with interleukin-1 receptor associated kinase (IRAK) and more particularly compounds that modulate the function of IRAK-4. The invention also provides pharmaceutically acceptable compositions comprising compounds of the present invention and methods of using said compositions in the treatment of diseases associated with IRAK-4.

BACKGROUND OF THE INVENTION

Interleukin-1 (IL-1) Receptor-Associated Kinase-4 (IRAK-4) is a serine/threonine kinase enzyme that plays an essential role in signal transduction by Toll/IL-1 receptors (TIRs). Diverse IRAK enzymes are key components in the signal transduction pathways mediated by interleukin-1 receptor (IL-1R) and Toll-like receptors (TLRs) (Janssens, S, et al. Mol. Cell. 11, 2003, 293–302). There are four members in the mammalian IRAK family: IRAK-1, IRAK-2, IRAK-M and IRAK-4. These proteins are characterized by a typical N-terminal death domain that mediates interaction with MyD88-family adaptor proteins and a centrally located kinase domain. The IRAK proteins, as well as MyD88, have been shown to play a role in transducing signals other than those originating from IL-1R receptors, including signals triggered by activation of IL-18 receptors (Kanakaraj, et al. J. Exp. Med. 189(7):1999, 1129-38) and LPS receptors (Yang, et al., J. Immunol. 163, 1999, 639-643). Out of four members in the mammalian IRAK family, IRAK-4 is considered to be the "master IRAK". Under overexpression conditions, all IRAKs can mediate the activation of nuclear factor-kB (NF-kB) and stress-induced mitogen activated protein kinase (MAPK)-signaling cascades. However, only IRAK-1 and IRAK-4 have been shown to have active kinase activity. While IRAK-1 kinase activity could be dispensable for its function in IL-1-induced NF-kB activation (Kanakaraj et al, J. Exp. Med. 187(12), 1998, 2073–2079) and (Xiaoxia Li, et al. Mol. Cell. Biol. 19(7), 1999, 4643–4652), IRAK-4 requires its kinase activity for signal transduction (Li S, et al. Proc. Natl. Acad. Sci. USA 99(8), 2002, 5567–5572) and (Lye, E et al, J. Biol. Chem. 279(39); 2004, 40653-8). Given the central role of IRAK4 in Toll-like/IL-1R signalling and immunological protection, IRAK4 inhibitors have been implicated as

valuable therapeutics in inflammatory diseases, sepsis and autoimmune disorders (Wietek C, et al, Mol. Interv. 2: 2002, 212–215).

Mice lacking IRAK-4 are viable and show complete abrogation of inflammatory cytokine production in response to IL-1, IL-18 or LPS (Suzuki et al. Nature, 416(6882), 2002, 750-756). Similarly, human patients lacking IRAK-4 are severely immunecompromised and are not responsive to these cytokines (Medvedev et al. J. Exp. Med., 198(4), 2003, 521-531 and Picard et al. Science 299(5615), 2003, 2076-2079). Knock-in mice containing inactive IRAK4 were completely resistant to lipopolysaccharide- and CpG-induced shock (Kim TW, et al. J Exp Med 204: 2007, 1025 -36) and (Kawagoe T, et al. J Exp Med 204(5): 2007, 1013-1024) and illustrated that IRAK4 kinase activity is essential for cytokine production, activation of MAPKs and induction of NF- κ B regulated genes in response to TLR ligands (Koziczak-Holbro M, et al. J Biol Chem; 282(18): 2007;13552-13560). Inactivation of IRAK4 kinase (IRAK4 KI) in mice leads to resistance to EAE due to reduction in infiltrating inflammatory cells into CNS and reduced antigen specific CD4+ T-cell mediated IL-17 production (Kirk A et al. The Journal of Immunology, 183(1), 2009, 568-577).

The crystal structures revealed that IRAK-4 contains characteristic structural features of both serine/threonine and tyrosine kinases, as well as additional novel attributes, including the unique tyrosine gatekeeper residue. Structural analysis of IRAK-4 revealed the underlying similarity with kinase family; ATP-binding cleft sandwiched between a bilobal arrangement. The N-terminal lobe consists of mainly of a twisted five-stranded antiparallel beta-sheet and one alpha-helix and the larger C-terminal lobe are predominantly alpha-helical. Yet, the structure reveals a few unique features for IRAK-4 kinase, including an additional alpha-helix from the N-terminal extension in the N-terminal lobe, a longer loop between helices alpha-D and alpha-E and a significantly moved helix alpha G as well as its adjoining loops. The ATP-binding site in IRAK-4 has no deep pocket in the back but has a featured front pocket. This uniquely shaped binding pocket provides an excellent opportunity for designing IRAK-4 inhibitors.

The development of IRAK-4 kinase inhibitors has generated several novel classes of protein binders which includes thiazole and pyridine amides (George M Buckley, et al. Bioorg. Med. Chem. Lett., 18(11), 2008, 3211-3214), aminobenzimidazoles (Powers JP, et al. Bioorg. Med. Chem. Lett., 16(11), 2006, 2842-2845), Imidazo[1,2-a] pyridines (Buckley G M, et al. Bioorg. Med. Chem. Lett. 18(11), 2008, 3656-3660) and (Buckley G, et al. Bioorg. Med. Chem.

Lett. 18(11), 2008, 3291-3295), imidazo[1,2-b]pyridazines and benzimidazole-indazoles (WO2008030579; WO2008030584). Apparently, all of them are still in the early preclinical stage.

Despite various disclosures on different kinase inhibitors, however, with the rise in number of patients affected by kinase enzyme mediated diseases, there appears to be unmet need for newer drugs that can treat such diseases more effectively. There is still need for newer kinase inhibitors including multikinase inhibitors, which may be further useful in treatment of disorders owing to variations in various kinases activity and possessing broader role. They may also be useful as part of other therapeutic regimens for the treatment of disorders, alone or in combination with protein kinase compounds well known by the one skilled in the art.

OBJECTIVES OF THE INVENTION

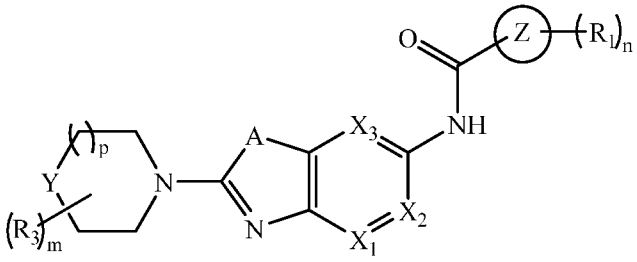
One objective herein is to provide bicyclic heterocyclyl compounds of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, as kinase inhibitors, particularly IRAK4 inhibitors.

Another objective is to provide a pharmaceutical composition comprising the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof and atleast one pharmaceutically acceptable excipient such as a pharmaceutically acceptable carrier or diluent.

Yet another objective is to provide a use of bicyclic heterocyclyl derivativesof formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, for the treatment and prevention of diseases or disorders, in particular their use in diseases or disorder where there is an advantage in inhibiting kinase enzyme, more particularly IRAK4 enzyme.

SUMMARY OF THE INVENTION

In one aspect according to the present invention, it comprises bicyclic heterocyclyl derivatives of formula (I)



(I)

or a pharmaceutically acceptable salt or a stereoisomer thereof;

wherein,

X_1 and X_3 independently are CH or N; X_2 is CR_2 or N; provided one and not more than one of X_1, X_2 or X_3 is N;

A is O or S;

Y is $-CH_2-$ or O;

Ring Z is aryl or heterocyclyl;

R_1, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or $-NR_aR_b$;

R_2 is hydrogen, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or $-NR_aR_b$; wherein the substituent is alkyl, amino, halo or hydroxyl;

R_3, at each occurrence, is alkyl or hydroxyl;

R_a and R_b are independently hydrogen, alkyl, acyl or heterocyclyl;

'm' and 'n' are independently 0, 1 or 2;

'p' is 0 or 1.

In yet another aspect, the present invention provides a pharmaceutical composition comprising the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof and atleast one pharmaceutically acceptable excipient such as a pharmaceutically acceptable carrier or diluent.

In yet another aspect, the present invention relates to the preparation of the compounds of formula (I).

In yet further aspect of the present application, it provides use of bicyclic heterocyclyl derivativesof formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, for the treatment and prevention of diseases or disorder mediated by IRAK4 enzyme.

More particularly, the invention relates to the use of bicyclic heterocyclyl derivatives of formula (I) pharmaceutically acceptable salts and stereoisomers thereof, including mixtures thereof in all ratios, as a medicament, by inhibiting IRAK or IRAK4 or other related kinases.

Bicyclic heterocyclyl derivatives of formula (I) of the present invention possess therapeutic role of inhibiting IRAK or IRAK4 or other related kinases useful in the area ofdiseases and/or disorders include, but are not limited to cancers, allergic diseases and/or disorders, autoimmune diseases and/or disorders, inflammatory diseases and/or disorder and/or conditions associated with inflammation and pain, proliferative diseases, hematopoietic disorders, haematological malignancies, bone disorders, fibrosis diseases and/or disorders, metabolic disorders, muscle diseases and/or disorders, respiratory diseases and/or disorders, pulmonary diseases and/or disorders, genetic developmental diseases and/or, neurological and neurodegenerative diseases and/or disorders, chronic inflammatory demyelinating neuropathies, cardiovascular, vascular or heart diseases and/or disorders, ophthalmic/ocular diseases and/or disorders, wound repair, infection and viral diseases. Therefore, inhibition of one or more kinases would have multiple therapeutic indications.

DETAILED DESCRIPTION OF THE INVENTION

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in art to which the subject matter herein belongs. As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated in order to facilitate the understanding of the present invention.

The singular forms “a”, “an” and “the” encompass plural references unless the context clearly indicates otherwise.

As used herein, the terms “optional” or “optionally” mean that the subsequently described event or circumstance may occur or may not occur and that the description includes instances where the event or circumstance occurs as well as instances in which it does not. For

example, "optionally substituted alkyl" refers to that 'alkyl' may be substituted as well as where the alkyl is not substituted.

It is understood that substituents and substitution patterns on the compounds of the present invention can be selected by one of ordinary skilled person in the art to result chemically stable compounds which can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results.

As used herein, the term "optionally substituted" refers to the replacement of one to six hydrogen radicals in a given structure with the radical of a specified substituent including, but not limited to: halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, aryl, heterocyclyl, amino, cyano, nitro, alkylamino, arylamino, alkylaminoalkyl, arylaminoalkyl, hydroxyl, hydroxyalkyl, cycloalkyl, aryl, heterocyclic and aliphatic. It is understood that the substituent may be further substituted.

As used herein, the term "alkyl" refers to saturated aliphatic groups, including but not limited C_1-C_{10} straight-chain alkyl groups or C_1-C_{10} branched-chain alkyl groups. Preferably, the "alkyl" group refers to C_1-C_6 straight-chain alkyl groups or C_1-C_6 branched-chain alkyl groups. Most preferably, the "alkyl" group refers to C_1-C_4 straight-chain alkyl groups or C_1-C_4 branched-chain alkyl groups. Examples of "alkyl" include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, n-butyl, sec-butyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl or 4-octyl and the like. The "alkyl" group may be optionally substituted.

The term "acyl" refers to a group R-CO- wherein R is an alkyl group defined above. Examples of 'acyl' groups are, but not limited to, CH_3CO-, CH_3CH_2CO-, $CH_3CH_2CH_2CO$- or $(CH_3)_2CHCO$-.

As used herein, the term "alkoxy" refers to a straight or branched, saturated aliphatic C_1-C_{10} hydrocarbon radical bonded to an oxygen atom that is attached to a core structure. Preferably, alkoxy groups have one to six carbon atoms. Examples of alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, 3-methyl butoxy and the like.

As used herein, the term "haloalkyl" refers to alkyl group (as defined above) is substituted with one or more halogens. A monohaloalkyl radical, for example, may have a chlorine, bromine, iodine or fluorine atom. Dihalo and polyhaloalkyl radicals may have two or more of the same or different halogen atoms. Examples of haloalkyl include, but are not limited to, chloromethyl, dichloromethyl, trichloromethyl, dichloroethyl, dichloropropyl, fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl and the like.

As used herein, the term "haloalkoxy" refers to radicals wherein one or more of the hydrogen atoms of the alkoxy groups are substituted with one or more halogens. Representative examples of "haloalkoxy" groups include, but not limited to, difluoromethoxy (-$OCHF_2$), trifluoromethoxy (-OCF_3) or trifluoroethoxy (-OCH_2CF_3).

As used herein, the term "aryl" alone or in combination with other term(s) means a carbocyclic aromatic system containing one or two rings wherein such rings may be fused. The term "fused" means that the second ring is attached or formed by having two adjacent atoms in common with the first ring. The term "fused" is equivalent to the term "condensed". Examples of aryl groups include but are not limited to phenyl, naphthyl, indanyl and the like. Unless otherwise specified, all aryl groups described herein may be substituted or unsubstituted.

As used herein, "Amino" refers to an $-NH_2$ group.

As used herein, "alkylamino" refers to amino group wherein one of the hydrogen atom of amino group is replaced with alkyl group.

As used herein, "arylamino" refers to amino group wherein one of hydrogen atoms is substituted with aryl group.

As used herein, "alkylaminoalkyl" refers to alkyl group substituted with "alkylamino" group defined above.

As used herein, "arylaminoalkyl" refers to arylamino group, as defined above, substituted with alkyl group.

As used herein, "nitro" refers to an $-NO_2$ group.

As used herein, "alkylamino" or "cycloalkylamino", refer to an –N-group, wherein nitrogen atom of said group being attached to alkyl or cycloalkyl respectively. Representative

examples of an "Alkylamino" and "Cycloalkylamino" groups include, but are not limited to -$NHCH_3$ and -NH-cyclopropyl. An amino group can be optionally substituted with one or more of the suitable groups.

"Aminoalkyl" refers to an alkyl group, as defined above, wherein one or more of the alkyl group's hydrogen atom has been replaced with an amino group as defined above. Representative examples of an aminoalkyl group include, but are not limited to $–CH_2NH_2$, -$CH_2CH_2NH_2$, -$CH(CH_3)NH_2$, -$CH_2CH(CH_3)NH_2$. An aminoalkyl group can be unsubstituted or substituted with one or more suitable groups.

As used herein the term "cycloalkyl" alone or in combination with other term(s) means C_3-C_{10} saturated cyclic hydrocarbon ring. A cycloalkyl may be a single ring, which typically contains from 3 to 7 carbon ring atoms. Examples of single-ring cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. A cycloalkyl may alternatively be polycyclic or contain more than one ring. Examples of polycyclic cycloalkyls include bridged, fused and spirocyclic carbocyclyls.

As used herein, the term "cyano" refers to -CN group.

As used herein, the term "hydroxy" or "Hydroxyl" refers to -OH group.

As used herein the term "hydroxyalkyl" or "hydroxylalkyl" means alkyl substituted with one or more hydroxyl groups, wherein the alkyl groups are as defined above. Examples of "hydroxyalkyl" include but are not limited to hydroxymethyl, hydroxyethyl, hydroxypropyl, propan-2-ol and the like.

As used herein, the term "halo" or "halogen" alone or in combination with other term(s) means fluorine, chlorine, bromine or iodine.

As used herein, the term "heterocyclyl" includes definitions of "heterocycloalkyl" and "heteroaryl".

The term "heterocycloalkyl" refers to a non-aromatic, saturated or partially saturated, monocyclic or polycyclic ring system of 3 to 15 members having at least one heteroatom or heterogroup selected from O, N, S, S(O), $S(O)_2$, NH or C(O) with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen and sulfur. Examples of "Heterocycloalkyl" include, but are not limited to azetidinyl, oxetanyl,

imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl,1,4-dioxanyl, dioxidothiomorpholinyl, oxapiperazinyl, oxapiperidinyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl, indolinyl, indolinylmethyl, azepanyl, 2-aza-bicyclo[2.2.2]octanyl, azocinyl, chromanyl, xanthenyl and N-oxides thereof. Attachment of a heterocycloalkyl substituent can occur via either a carbon atom or a heteroatom. A heterocycloalkyl group can be optionally substituted with one or more suitable groups by one or more aforesaid groups. Preferably "heterocycloalkyl" refers to 4- to 7-membered ring selected from the group consisting of azetidinyl, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, 1,4-dioxanyl, azepanyl and N-oxides thereof. More preferably, "heterocycloalkyl" includes azetidinyl, pyrrolidinyl, morpholinyl, piperidinyl or azepanyl. All heterocycloalkyl are optionally substituted by one or more aforesaid groups.

The term "heteroaryl" refers to an aromatic heterocyclic ring system containing 5 to 20 ring atoms, suitably 5 to 10 ring atoms, which may be a single ring (monocyclic) or multiple rings (bicyclic, tricyclic or polycyclic) fused together or linked covalently. Preferably, "heteroaryl" is a 5- to 6-membered ring. The rings may contain from 1 to 4 heteroatoms selected from N, O and S, wherein the N or S atom is optionally oxidized, or the N atom is optionally quarternized. Any suitable ring position of the heteroaryl moiety may be covalently linked to the defined chemical structure.

Examples of heteroaryl include, but are not limited to: furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, cinnolinyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzoxazolyl, benzisoxazolyl; benzothiazolyl, benzofuranyl, benzothienyl, benzotriazinyl, phthalazinyl, thianthrene, dibenzofuranyl, dibenzothienyl, benzimidazolyl, indolyl, isoindolyl, indazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, purinyl, pteridinyl, 9H-carbazolyl, α-carboline, indolizinyl, benzoisothiazolyl, benzoxazolyl, pyrrolopyridyl, furopyridinyl, purinyl, benzothiadiazolyl, benzooxadiazolyl, benzotriazolyl, benzotriadiazolyl, carbazolyl, dibenzothienyl, acridinyl and the like. Preferably "heteroaryl" refers to 5- to 6-membered ring selected from the group consisting of furanyl, thiophene, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, cinnolinyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl,

pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl. More preferably, pyrazolyl, pyridyl, oxazolyl and furanyl. All heteroaryls are optionally substituted by one or more aforesaid groups.

As used herein, the term "including" as well as other forms, such as "include", "includes" and "included" is not limiting.

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

The term "pharmaceutically acceptable salt" refers to a product obtained by reaction of the compound of the present invention with a suitable acid or a base. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic bases such as Li, Na, K, Ca, Mg, Fe, Cu, Al, Zn and Mn salts; Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, 4-methylbenzenesulfonate or p-toluenesulfonate salts and the like. Certain compounds of the invention (compounds of formula (I)) can form pharmaceutically acceptable salts with various organic bases such as lysine, arginine, guanidine, diethanolamine or metformin. Suitable base salts include, but are not limited to, aluminum, calcium, lithium, magnesium, potassium, sodium, or zinc, salts.

As used herein, the term "stereoisomer" is a term used for all isomers of individual compounds of formula (I) that differ only in the orientation of their atoms in space. The term stereoisomer includes mirror image isomers (enantiomers) of compound of formula (I), mixtures of mirror image isomers (racemates, racemic mixtures) compound of formula (I), geometric (cis/trans or E/Z, R/S) isomers compound of formula (I) and isomers of compound of formula (I) with more than one chiral center that are not mirror images of one another (diastereoisomers).

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

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

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

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

As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions {e.g., such as an oil/water or water/oil emulsions) and various types of wetting agents. The compositions also can include stabilizers and preservatives. The examples of carriers, stabilizers and adjuvant are mentioned in literature like, Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975].

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

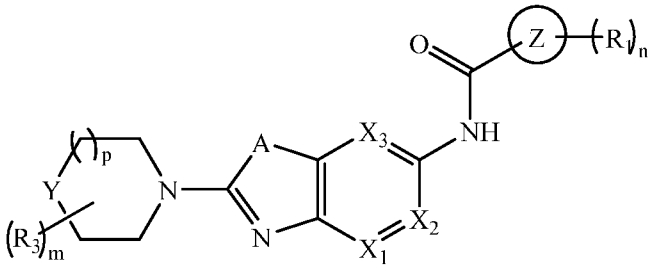
As used herein, the term "prevent", "preventing" and "prevention" refer to a method of preventing the onset of a disease and/or its attendant symptoms or barring a subject from acquiring a disease. As used herein, "prevent", "preventing" and "prevention" also include

delaying the onset of a disease and/or its attendant symptoms and reducing a subject's risk of acquiring a disease.

As used herein, the term "subject" refers to an animal, preferably a mammal and most preferably a human.

As used herein, the term, "therapeutically effective amount" refers to an amount of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof; or a composition comprising the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, effective in producing the desired therapeutic response in a particular patient suffering from a disease or disorder mediated by kinase enzymes, particularly IRAK or IRAK4 enzyme. Particularly, the term "therapeutically effective amount" includes the amount of the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, when administered, that induces a positive modification in the disease or disorder to be treated or is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disease or disorder being treated in a subject. In respect of the therapeutic amount of the compound, the amount of the compound used for the treatment of a subject is low enough to avoid undue or severe side effects, within the scope of sound medical judgment can also be considered. The therapeutically effective amount of the compound or composition will be varied with the particular condition being treated, the severity of the condition being treated or prevented, the duration of the treatment, the nature of concurrent therapy, the age and physical condition of the end user, the specific compound or composition employed and the particular pharmaceutically acceptable carrier utilized.

In one embodiment, the present invention provides the compound of formula (I);



(I)

or a pharmaceutically acceptable salt or a stereoisomer thereof;

wherein,

X_1 and X_3 independently are CH or N; X_2 is CR_2 or N; provided one and not more than one of X_1, X_2 or X_3 is N;

A is O or S;

Y is $-CH_2-$ or O;

Ring Z is aryl or heterocyclyl;

R_1, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or $-NR_aR_b$;

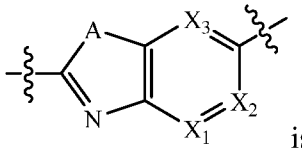
R_2 is hydrogen, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or $-NR_aR_b$; wherein the substituent is alkyl, amino, halo or hydroxyl;

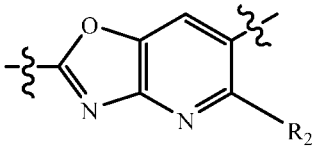
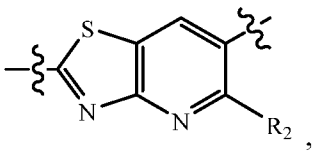
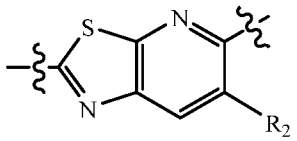
R_3, at each occurrence, is alkyl or hydroxyl;

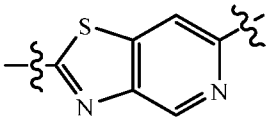
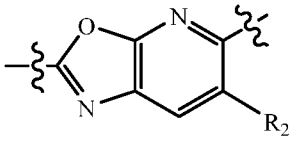
R_a and R_b are independently hydrogen, alkyl, acyl or heterocyclyl;

'm' and 'n' are independently 0, 1 or 2;

'p' is 0 or 1.

In one embodiment, the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the group  is

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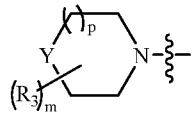
 or  ;

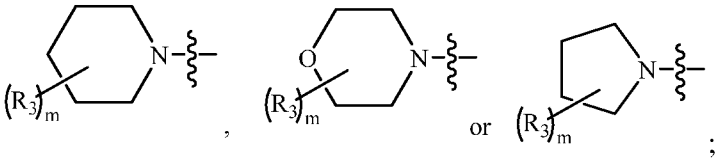
wherein R_2 are as defined in compound of formula (I).

In another embodiment, the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the Ring Z is aryl or 5- or 6-membered heterocyclyl.

In another embodiment, the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the Ring Z is phenyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl,1,4-dioxanyl, dioxidothiomorpholinyl, oxapiperazinyl, oxapiperidinyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl or dihydropyranyl; each of which is optionally substituted with alkyl, alkoxy, halo, hydroxyl, hydroxyalkyl or $-NR_aR_b$; R_a and R_b are independently are hydrogen, alkyl or acyl.

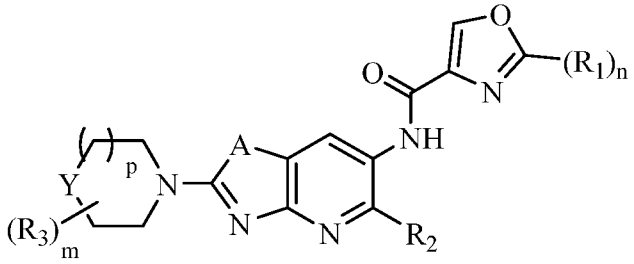
In another embodiment, the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the Ring Z is phenyl, oxazolyl, furanyl, thienyl or pyridyl; each of which is optionally substituted with one or more R_1.

In another embodiment, the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein  is

 ;

wherein R_3 and 'm' are defined in compound of formula (I).

In another embodiment, the compound of formula (I) is a compound of formula (IA):

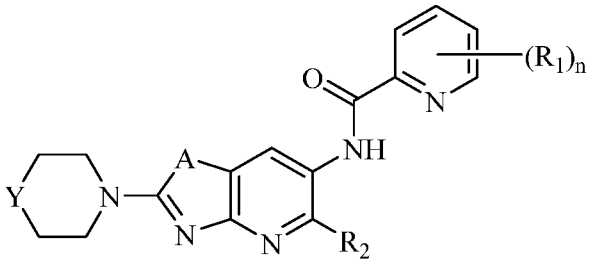


(IA)

or a pharmaceutically acceptable salt or a stereoisomer thereof;

wherein, A, Y, R_1, R_2, R_3, 'm', 'p' and 'n' are same as defined in compound of formula (I).

In another embodiment, the compound of formula (I) is a compound of formula (IB):

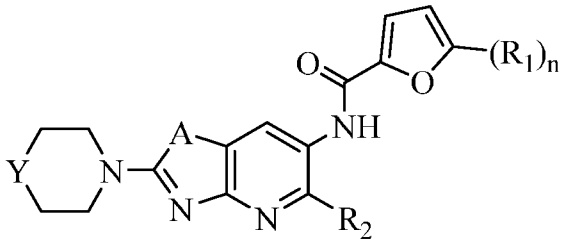


(IB)

or a pharmaceutically acceptable salt or a stereoisomer thereof;

wherein, A, Y, R_1, R_2 and 'n' are same as defined in compound of formula (I).

In yet another embodiment, the compound of formula (I) is a compound of formula (IC):



(IC)

or a pharmaceutically acceptable salt or a stereoisomer thereof;

wherein, A, Y, R_1, R_2, R_3 and 'n' are same as defined compounds of formula (I).

The embodiments below are illustrative of the present invention and are not intended to limit the claims to the specific embodiments exemplified.

According to one embodiment, specifically provided are compounds of formula (I) or (IA) or (IB) or (IC), wherein Y is O or CH_2.

According to one embodiment, specifically provided are compounds of formula (I) wherein R_1 is optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or $-NR_aR_b$; R_a and R_b are independently hydrogen, alkyl or acyl.

According to one embodiment, specifically provided are compounds of formula (I) wherein R_1 is pyridyl, pyrazolyl, pyrrolidinyl or piperidinyl; each of which is optionally

substituted with alkyl, alkoxy, halo, hydroxyl, hydroxyalkyl or -NR_aR_b; R_a and R_b are independently hydrogen or acyl.

According to one embodiment, specifically provided are compounds of formula (I) wherein R_2 is hydrogen.

According to one embodiment, specifically provided are compounds of formula (I) wherein R_2 is optionally substituted cycloalkyl.

According to one embodiment, specifically provided are compounds of formula (I) wherein R_2 is cyclopropyl.

According to one embodiment, specifically provided are compounds of formula (I) wherein R_2 is optionally substituted heterocyclyl; wherein the substituent is alkyl, amino, halo or hydroxyl.

According to one embodiment, specifically provided are compounds of formula (I) wherein R_2 is piperidinyl, pyrrolidinyl, morpholinyl, piperazinyl, azetidinyl, pyrazolyl, furanyl, pyridyl, azepanyl or azabicyclo[3.2.1]octanyl; wherein the substituent is alkyl, amino, halo or hydroxyl.

According to one embodiment, specifically provided are compounds of formula (I) wherein R_2 is optionally substituted aryl; wherein the substituent is halo.

According to one embodiment, specifically provided are compounds of formula (I) wherein R_2 is optionally substituted phenyl; wherein the substituent is fluoro.

According to one embodiment, specifically provided are compounds of formula (I) wherein R_2 is -NR_aR_b; wherein R_a and R_b are independently hydrogen or heterocyclyl.

According to one embodiment, specifically provided are compounds of formula (I) wherein R_2 is -NR_aR_b; wherein R_a and R_b are independently hydrogen or pyrrolidinyl.

According to one embodiment, specifically provided are compounds of formula (IA) wherein A is O or S; Y is -CH_2- or O; R_1 is halo, pyridyl, pyrazolyl, pyrrolidinyl each of which is optionally substituted with alkyl, alkoxy, halo, hydroxyl, hydroxyalkyl or -NR_aR_b; R_2 is hydrogen, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or -NR_aR_b; wherein the substituent is alkyl, amino, halo or hydroxyl; R_a and R_b are independently hydrogen or alkyl.

According to one embodiment, specifically provided are compounds of formula (IB) wherein A is O or S; Y is $-CH_2-$ or O; R_1 is pyridyl, pyrazolyl, pyrrolidinyl; each of which is optionally substituted with alkyl, hydroxyl, hydroxyalkyl or $-NR_aR_b$; R_a and R_b are independently hydrogen; R_2 is hydrogen, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or $-NR_aR_b$; wherein the substituent is alkyl, amino, halo or hydroxyl; R_a and R_b are independently hydrogen, alkyl, acyl or heterocyclyl.

According to one embodiment, specifically provided are compounds of formula (IA), (IB) and (IC), wherein 'n' is 0, 1 or 2.

According to one embodiment, specifically provided are compounds of formula (IA) and (IB), wherein 'p' is 0 or 1.

According to one embodiment, specifically provided are compounds of formula (IA) and (IB), wherein 'm' is 0 or 2.

In yet further embodiment, the present invention relates to a process for preparing bicyclic heterocyclyl derivatives of formula (I).

In yet further embodiment, the present invention relates to a pharmaceutical composition, comprising at least one compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof and a pharmaceutically acceptable carrier or excipient.

In further embodiment, the present invention provides a method of treating IRAK4 mediated disorders or diseases or condition in a subject comprising administering a therapeutically effective amount of a compound of formula (I).

In further embodiment, the IRAK4-mediated disorder or disease or condition is selected from the group consisting of cancer, an inflammatory disorder, an autoimmune disease, metabolic disorder, a hereditary disorder, a hormone-related disease, immunodeficiency disorders, a condition associated with cell death, a destructive bone disorder, thrombin-induced platelet aggregation, liver disease and a cardiovascular disorder.

In further embodiment, the cancer is selected the group consisting of a solid tumor, benign or malignant tumor, carcinoma of the brain, kidney, liver, stomach, vagina, ovaries, gastric tumors, breast, bladder colon, prostate, pancreas, lung, cervix, testis, skin, bone or thyroid; sarcoma, glioblastomas, neuroblastomas, multiple myeloma, gastrointestinal cancer, a

tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphomas, Hodgkins and Non-Hodgkins, a mammary carcinoma, follicular carcinoma, papillary carcinoma, seminoma, melanoma; hematological malignancies selected from leukemia, diffuse large B-cell lymphoma (DLBCL), activated B-cell-like DLBCL, chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, acute lymphocytic leukemia, B-cell pro lymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenstrom's macroglobulnemia (WM), splenic marginal zone lymphoma, intravascular large B-cell lymphoma, plasmacytoma and multiple myeloma.

In further embodiment, the inflammatory disorder is selected from the group consisting of ocular allergy, conjunctivitis, keratoconjunctivitis sicca, vernal conjunctivitis, allergic rhinitis, autoimmune hematological disorders (e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven- Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, multiple sclerosis, endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren's syndrome, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, nephritis, vasculitis, diverticulitis, interstitial cystitis, glomerulonephritis (e.g. including idiopathic nephrotic syndrome or minimal change nephropathy), chronic granulomatous disease, endometriosis, leptospirosis renal disease, glaucoma, retinal disease, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle wasting, catabolic disorders, obesity, fetal growth retardation, hypercholesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ecodermal dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma, acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, fibrositis, gastritis, gastroenteritis, nasal sinusitis, ocular allergy, silica induced diseases, chronic obstructive pulmonary disease (COPD), cystic fibrosis, acid-induced lung injury, pulmonary hypertension,

polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, juvenile rheumatoid arthritis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, vasculitis, vulvitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Cryopyrin Associated Periodic Syndrome (CAPS) and osteoarthritis.

In further embodiment, the present invention provides a compound or a pharmaceutically acceptable salt or a stereoisomer thereof, for use for the treatment of a cancer, an inflammatory disorder, a an autoimmune disease, metabolic disorder, a hereditary disorder, a hormone-related disease, immunodeficiency disorders, a condition associated with cell death, a destructive bone disorder, thrombin-induced platelet aggregation, liver disease and a cardiovascular disorder.

In further embodiment, the present invention relates to a use of the compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof, in the manufacture of a medicament for the treatment of a cancer, an inflammatory disorder, a an autoimmune disease, metabolic disorder, a hereditary disorder, a hormone-related disease, immunodeficiency disorders, a condition associated with cell death, a destructive bone disorder, thrombin-induced platelet aggregation, liver disease and a cardiovascular disorder.

In further embodiment, the neurodegenerative disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia and neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity, hypoxia, epilepsy and graft versus host disease.

An embodiment of the present invention provides the IRAK4 inhibitor compounds according to formula (I) may be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred experimental conditions (i.e. reaction temperatures, time, moles of reagents, solvents etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by the person skilled in the art, using routine optimisation procedures. Moreover, by utilizing the procedures described in detail, one of ordinary skill in the art can prepare additional compounds of the present invention claimed herein. All temperatures are in degrees Celsius (^{o}C) unless otherwise noted.

In a further embodiment, the compounds of the present invention can also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the present invention also embraces isotopically-labeled variants of the present invention which are identical to those recited herein, but for the fact that one or more atoms of the compounds are replaced by an atom having the atomic mass or mass number different from the predominant atomic mass or mass number usually found in nature for the atom. All isotopes of any particular atom or element as specified are contemplated within the scope of the compounds of the invention and their uses. Exemplary isotopes that can be incorporated in to compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine and iodine, such as ^{2}H ("D"), ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I and ^{125}I. Isotopically labeled compounds of the present inventions can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

The **MS** (Mass Spectral) data provided in the examples were obtained using the equipments-

API 2000 LC/MS/MS/Triplequad,

Agilent (1100) Technologies/LC/MS/DVL/Singlequad and

Shimadzu LCMS-2020/Singlequad.

The **NMR** data provided in the examples were obtained using the equipment -` ^{1}H-NMR: Varian -300,400 and 600 MHz.

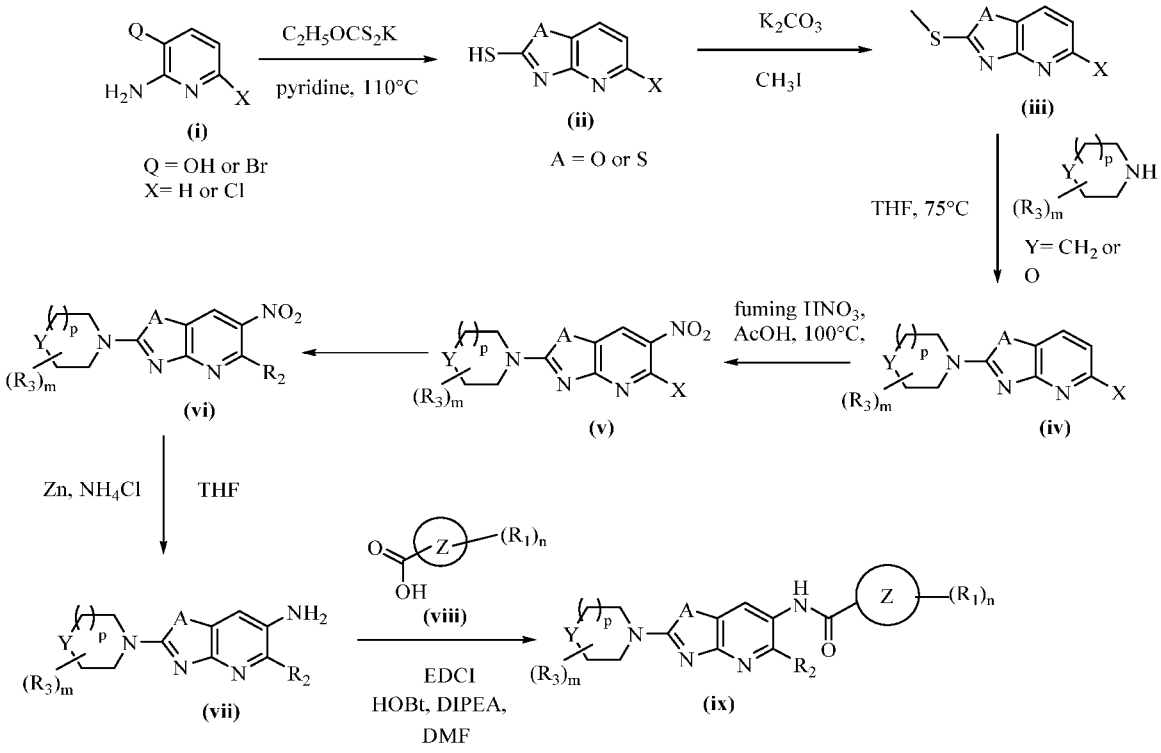
The **abbreviations** used in the entire specification may be summarized herein below with their particular meaning.

°C (degree Celsius); δ (delta); % (percentage); Ac_2O (Acetic anhydride); $(Boc)_2O$ (boc anhydride); bs (Broad singlet); $CDCl_3$ (Deuteriated chloroform); CH_2Cl_2/DCM (Dichloromethane); DMF (Dimethyl formamide); DMSO (Dimethyl sulphoxide) ; DIPEA/DIEA (N, N- Diisopropyl ethylamine); DAST (Diethylaminosulfur trifluoride); DMAP (Dimethyl amino pyridine); DMSO-d_6 (Deuteriated DMSO); d (Doublet); dd (Doublet of doublet); EDCI. HCl (1-(3-Dimethyl aminopropyl)-3-carbodiimide hydrochloride); EtOAc (Ethyl acetate); EtOH (Ethanol); Fe (Iron powder); g (gram); H or H_2 (Hydrogen); H_2O (Water); HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate); HOBt (1-Hydroxy benzotriazole); H_2SO_4 (Sulphuric acid); HCl (Hydrochloric acid or Hydrochloride salt); h or hr (Hours); Hz (Hertz); HPLC (High-performance liquid chromatography); J (Coupling constant); K_2CO_3 (Potassium carbonate); KOAc (Potassium Acetate); KNO_3 (Potassium nitrate); LiOH (Lithium hydroxide); NaHMDS (Sodiumbis(trimethylsilyl)amide); MeOH/CH_3OH (Methanol); mmol (Millimol); M (Molar); ml (Millilitre); mg (Milli gram); m (Multiplet); mm (Millimeter); MHz (Megahertz); MS (ES) (Mass spectroscopy-electro spray); min (Minutes); NaH (Sodium hydride); $NaHCO_3$ (Sodium bicarbonate); Na_2SO_4 (Sodium sulphate); NH_4Cl (Ammonium Chloride); N_2 (Nitrogen); NMR (Nuclear magnetic resonance spectroscopy); $Pd(PPh_3)_2Cl_2$ (Bis(triphenylphosphine)palladium(II) dichloride); $Pd(OAc)_2$ (Palladium diacetate); $Pd(dppf)Cl_2$ (1,1'-Bis(diphenylphosphino)ferrocene) palladium(II) dichloride; RT (Room Temperature); s (Singlet); TBAF (Tetra-n-butylammonium fluoride); TEA (Triethylamine); TFA (Trifluoroaceticacid); TLC (Thin Layer Chromatography); THF (Tetrahydrofuran); TFA (Trifluoro acetic acid); t (Triplet); and $Zn(CN)_2$ (Zinc Cyanide).

Compounds of this invention may be made by synthetic chemical processes, examples of which are shown herein. It is meant to be understood that the order of the steps in the processes may be varied, that reagents, solvents and reaction conditions may be substituted for those specifically mentioned and that vulnerable moieties may be protected and deprotected, as necessary.

A general approach for the synthesis of some of the compounds of general formula (ix) is depicted in below schemes. As used herein the below schemes the terms Z, Y, R_1, R_2, R_3, m, n and p represents all the possible substitutions as disclosed in formula (I).

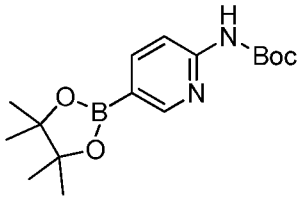
SCHEME 1:



The first general approach for the synthesis of compounds of general formula (ix) is depicted in scheme-1. Compound of formula (ii) can be obtained from compound of formula (i) by reacting with potassium ethyl xanthate in appropriate solvent like pyridine at a higher temperature. Compound of formula (ii) on alkylation with methyl iodide using base like potassium carbonate can give compound of formula (iii) can be subjected to nucleophilic displacement with suitable nucleophile to give compound of formula (iv). Compound of formula (iv) on nitration can give compound of formula (v). Compound of formula (v) can be subjected to Suzuki reaction to give compound of formula (vi) which on reduction with suitable reducing reagents like Zn and ammonium chloride can give compound of formula (vii). Compound of formula vii can be subjected to Amide coupling with a suitable acid of compound of formula (viii) by using a standard amide coupling reagent known in the literature to give compound of formula (ix).

INTERMEDIATES

Intermediate 1: Synthesis of tert-butyl (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate



Step 1: Preparation of tert-butyl (5-bromopyridin-2-yl)carbamate

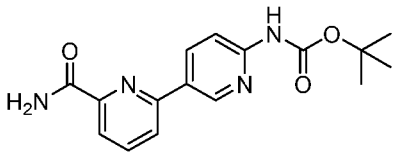
To a solution of 5-bromopyridin-2-amine (5.0g, 28.901 mmol) in DCM (50mL) was added DMAP (5.28g, 43.351 mmol) and Boc anhydride (7.56g, 34.682 mmol) and stirred at RT for overnight. The solvent was distilled out and purified by 60-120 silica gel column chromatography using 30% ethyl acetate in hexane as eluent to obtain the title compound (5.5g, 69.62%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 8.327-8.320 (d, 1H), 8.10 (bs, 1H), 7.92-7.89 (d, 1H), 7.76-7.73 (dd, 1H), 1.55 (s, 9H). **LCMS:** m/z: 217.0 $(M\text{-}Boc)^+$.

Step 2: Preparation of tert-butyl (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate

In a sealed tube, tert-butyl (5-bromopyridin-2-yl)carbamate (5.0g, 0.18315 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (6.02g, 23.8 mmol) and potassium acetate (5.38mg, 54.945 mmol) were taken in 1,4-dioxane (50mL) and purged argon for 10 min. Added $Pd(dppf)Cl_2$ (669mg, 0.915 mmol) and heated at 100°C for 2 h. The solvent was distilled out and purified by 60-120 silica gel column chromatography using 40% ethyl acetate in hexane as eluent to obtain the title compound (5.0g, 85.32%).

Intermediate 2: Synthesis of tert-butyl (6-carbamoyl-[2,3'-bipyridin]-6'-yl)carbamate



Step 1: Preparation of 6-bromopicolinamide

Using the same reaction conditions as described in step 6 of example 1, 6-bromopicolinic acid (2g, 9.9 mmol) was coupled with ammonium chloride (787mg, 14.851 mmol) using EDCI.HCl (2.8g, 14.851 mmol), HOBt (2.0g, 14.851 mmol) and DIPEA (3.8g, 29.750 mmol) in

DMF (10mL) to get the crude product. The resultant crude was purified using 60-120 silica-gel column chromatography and compound was eluted using 50% ethyl acetate in hexane as eluent to afford the title compound (2.0g, 100%).

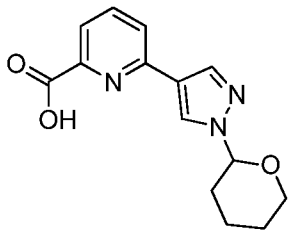
^{1}HNMR ($CDCl_3$, 300MHz): δ 8.18-8.16 (d, 1H), 7.7.63-7.5656-7.63 (m, 2H), 5.80-5.60 (bs, 2H).

Step 2: Preparation of tert-butyl (6-carbamoyl-[2,3'-bipyridin]-6'-yl)carbamate

Using the same reaction conditions as described in step 7 of example 1, 6-bromopicolinamide (2.0g, 9.95 mmol) was coupled with tert-butyl (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (intermediate 1) (3.8g, 11.94 mmol) using sodium carbonate (3.2g, 29.85 mmol) and $Pd(PPh_3)_2Cl_2$ (363mg, 0.5 mmol) in 1,2-dimethoxyethane (10mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent to obtain the title compound (2.8g, 90.3%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 8.908-8.901 (d, 1H), 8.30-8.26 (dd, 1H), 8.18-8.16 (d, 1H), 8.09-8.06 (d, 1H), 7.97-7.68 (m, 3H), 7.26 (s, 1H), 5.70-5.60 (s, 1H), 1.55 (s, 9H). **LCMS:** m/z: 259.1 (de-t-butyl).

Intermediate 3: Synthesis of 6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinic acid



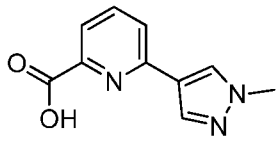
Step 1:Preparation of methyl 6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinate

Using the same reaction conditions as described in step 7 of example 1, methyl 6-bromopicolinate (900mg, 4.166 mmol) was coupled with 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.39g, 5 mmol) using sodium carbonate (1.324g, 12.49 mmol) and $Pd(PPh_3)_2Cl_2$ (339mg, 0.416 mmol) in 1,2-dimethoxyethane (10mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 30% ethyl acetate in hexane as eluent to obtain the title compound (450mg, 38%). **LCMS:** m/z: 288.1 $(M+1)^+$.

Step 2:Preparation of 6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinic acid

A solution of methyl 6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinate (450mg, 1.567 mmol) and lithium hydroxide (500mg, 7.839 mmol) in THF methanol/H_2O (10mL/4ml/1ml) was stirred at RT for 2 hrs. The reaction mixture was acidified with citric acid and extracted with DCM (2 X 100mL) dried over sodium sulphate and distilled out the solvent to get the title compound (300mg, 70%). **LCMS:** m/z: 274.3 $(M+1)^+$.

Intermediate 4: Synthesis of 6-(1-methyl-1H-pyrazol-4-yl)picolinic acid



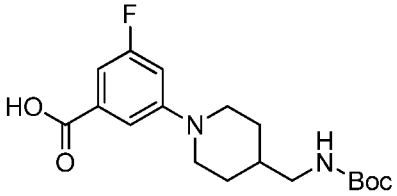
Step 1:Preparation of methyl 6-(1-methyl-1H-pyrazol-4-yl)picolinate

Using the same reaction conditions as described in step 7 of example 1, methyl 6-bromopicolinate (3.5g, 16.28 mmol) was coupled with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (4.06g, 19.53 mmol) using sodium carbonate (5.177g, 48.846 mmol) and Pd(dppf)Cl_2 (1.328g, 1.628 mmol) in 1,2-dimethoxyethane (20mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 30% ethyl acetate in hexane as eluent to obtain the title compound (1.2g, 33.9%). **LCMS:** m/z: 218.2 $(M+1)^+$.

Step 2:Preparation of 6-(1-methyl-1H-pyrazol-4-yl)picolinic acid

Using the same reaction conditions as described in step 2 of intermediate 5, 6-(1-methyl-1H-pyrazol-4-yl)picolinic acid (1.2g, 5.529 mmol) was hydrolysed using lithium hydroxide (696mg, 16.58 mmol) in THF/methanol (8/2 mL) at RT for 2h to obtain the title compound (900mg, 80.3%). **LCMS:** m/z: 204.0 $(M+1)^+$.

Intermediate 5: Synthesis of 3-(4-(((tert-butoxycarbonyl)amino)methyl)piperidin-1-yl)-5-fluorobenzoic acid



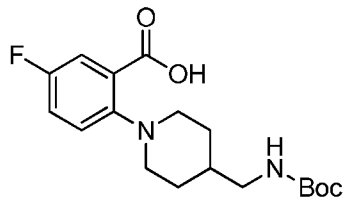
Step 1: Preparation of methyl 3-(4-(((tert-butoxycarbonyl)amino)methyl)piperidin-1-yl)-5-fluorobenzoate

Using the same reaction conditions as described in step 4 of example 12, methyl 3-bromo-5-fluorobenzoate (100mg, 0.429 mmol) was coupled with tert-butyl (piperidin-4-ylmethyl)carbamate (110mg, 0.515 mmol) using cesium carbonate (209mg, 0.643 mmol), xantphos (14mg, 0.025 mmol) and $Pd_2(dba)_3$ (8mg, 0.0085 mmol) in toluene (5mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent to obtain the title compound (110mg, 70.06%). **LCMS:** 94.13%, m/z = 367.5 $(M+1)^+$.

Step 2: Preparation of 3-(4-(((tert-butoxycarbonyl)amino)methyl)piperidin-1-yl)-5-fluorobenzoic acid

A solution of methyl 3-(4-(((tert-butoxycarbonyl)amino)methyl)piperidin-1-yl)-5-fluorobenzoate (110mg, 0.02 mmol), lithium hydroxide (5mg, 0.104 mmol), methanol (3mL), THF (2mL) and water (1mL) was stirred at RT for 1h., acidified with 2N HCl, distilled the solvent and filtered the solid to get the crude product. This was then purified by prep HPLC to obtain the title compound (105mg, 100%). **LCMS:** m/z: 353.4 $(M+1)^+$.

Intermediate 6: Synthesis of 2-(4-(((tert-butoxycarbonyl)amino)methyl)piperidin-1-yl)-5-fluorobenzoic acid



Step 1: Preparation of methyl 2-(4-(((tert-butoxycarbonyl)amino)methyl)piperidin-1-yl)-5-fluorobenzoate

Using the same reaction conditions as described in step 1 of example 11, methyl 2,5-difluorobenzoate (1g, 4.6 mmol), was coupled with tert-butyl (piperidin-4-ylmethyl)carbamate (803mg, 4.6 mmol) using potassium carbonate (1.289mg, 9.3 mmol), in DMF (10mL) at 90°C overnight to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using ethyl acetate in hexane as eluent to obtain the title compound (300mg, 20%).

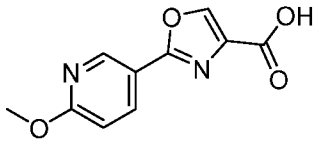
^{1}HNMR (DMSO-d_6, 400MHz): δ 7.38-7.28 (m, 2H), 7.16-7.12 (m, 1H), 6.90-6.85 (t, 1H), 3.80 (s, 3H), 3.13-3.10 (d, 2H), 2.87-2.84 (m, 2H), 2.64-2.58 (t, 2H), 1.67-1.64 (d, 2H), 1.40 (s, 9H), 1.26-1.09 (m, 2H). **LCMS:** m/z: 367.3 $(M+1)^+$.

Step 2: Preparation of 2-(4-(((tert-butoxycarbonyl)amino)methyl)piperidin-1-yl)-5-fluorobenzoic acid

Using the same reaction conditions as described in step 2 of intermediate 5, methyl 2-(4-(((tert-butoxycarbonyl)amino)methyl)piperidin-1-yl)-5-fluorobenzoate (300mg, 0.819 mmol), was hydrolysed using lithium hydroxide (172mg, 4.098 mmol) in THF/methanol/H_2O (5mL/1ml/0.5ml) at RT for 2h to obtain the title compound (220mg, 77%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 7.86-7.83 (m, 1H), 7.74-7.70 (m, 1H), 7.55-7.54 (m, 1H), 7.01 (bs, 1H), 3.11-3.08 (m, 4H), 2.93-2.89 (t, 2H), 1.87-1.83 (d, 2H), 1.70-1.60 (bs, 1H), 1.40 (s, 9H), 1.35-1.30 (m, 2H). **LCMS:** m/z: 353.4 $(M+1)^+$.

Intermediate 7: Synthesis of 2-(6-methoxypyridin-3-yl)oxazole-4-carboxylic acid



Step 1:Preparation of ethyl 2-(6-fluoropyridin-3-yl)oxazole-4-carboxylate

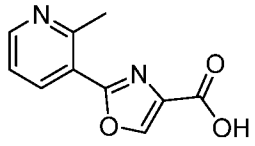
Using the same reaction conditions as described in step 7 of example 1, 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (200mg, 1.41 mmol) was coupled with ethyl 2-chlorooxazole-4-carboxylate (298mg, 1.70 mmol) using sodium carbonate (451 mg, 4.25 mmol) and $Pd(PPh_3)_4$ (289mg, 0.332 mmol) in 1,2-dimethoxyethane/water (15/3mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 20% ethyl acetate in hexane as eluent to obtain the title compound (200mg, 59.8%).

Step 2:Preparation of 2-(6-methoxypyridin-3-yl)oxazole-4-carboxylic acid

Using the same reaction conditions as described in step 2 of intermediate 5, ethyl 2-(6-fluoropyridin-3-yl)oxazole-4-carboxylate (300mg, 0.127 mmol) was hydrolysed using lithium hydroxide (160mg, 3.91 mmol) in THF/methanol/water (5/1/2mL) at RT for 2h to obtain the title compound (160mg, 57.3%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 13.5-12.5 (bs, 1H), 8.85 (s, 1H), 8.80-8.79 (d, 1H), 8.26-8.23 (dd, 1H), 7.02-6.99 (dd, 1H), 3.95 (s, 3H). **LCMS:** m/z = 221.1 $(M+1)^+$.

Intermediate 8: Synthesis of 2-(2-methylpyridin-3-yl)oxazole-4-carboxylic acid



Step 1:Preparation of ethyl 2-(2-methylpyridin-3-yl)oxazole-4-carboxylate

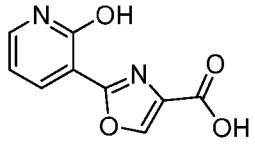
Using the same reaction conditions as described in step 7 of example 1, 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1g, 7.09 mmol) was coupled with ethyl 2-chlorooxazole-4-carboxylate (1.86g, 0.851 mmol) using sodium carbonate (2.25g, 21.2 mmol) and $Pd(dppf)Cl_2$ (289mg, 0.332 mmol) in 1,2-dimethoxyethane/water (30/6mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 20% ethyl acetate in hexane as eluent to obtain the title compound (1g, 59.8%).

Step 2:Preparation of 2-(2-methylpyridin-3-yl)oxazole-4-carboxylic acid

Using the same reaction conditions as described in step 2 of intermediate 5, ethyl 2-(2-methylpyridin-3-yl)oxazole-4-carboxylate (1g, 4.3 mmol) was hydrolysed using lithium hydroxide (542mg, 12.9 mmol) in THF/water (25/4mL) at RT for 2h to obtain the title compound (550mg, 62.5%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 13.3 (s, 1H), 8.96 (s, 1H), 8.64-8.62 (dd, 1H), 8.32-8.03 (dd, 1H), 7.47-7.44 (q, 1H), 2.86 (s, 3H). **LCMS:** m/z = 205.0 $(M+1)^+$.

Intermediate 9: Synthesis of 2-(2-hydroxypyridin-3-yl)oxazole-4-carboxylic acid



Step 1:Preparation of ethyl 2-(2-fluoropyridin-3-yl)oxazole-4-carboxylate

Using the same reaction conditions as described in step 7 of example 1, (2-fluoropyridin-3-yl)boronic acid (400mg, 2.83 mmol) was coupled with ethyl 2-chlorooxazole-4-carboxylate (596mg, 3.40 mmol) using sodium carbonate (902mg, 8.51 mmol) and $Pd(dppf)Cl_2$ (115mg, 0.141 mmol) in 1,2-dimethoxyethane/water (25/4mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 30% ethyl acetate in hexane as eluent to obtain the title compound (400mg, 60.6%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.11 (s, 1H), 8.64-8.59 (m, 1H), 8.48-8.47 (d, 1H), 7.62-7.59 (m, 1H), 4.38-4.33 (q, 2H), 1.35-1.32 (t, 3H).

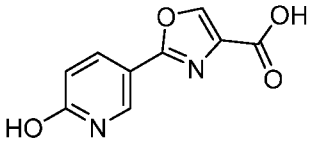
Step 2:Preparation of 2-(2-hydroxypyridin-3-yl)oxazole-4-carboxylic acid

Using the same reaction conditions as described in step 2 of intermediate 5, ethyl 2-(2-fluoropyridin-3-yl)oxazole-4-carboxylate (400mg, 1.69 mmol) was hydrolysed using lithium

hydroxide (213mg, 5.07 mmol) in THF/water (10/2mL) at RT for 2h to obtain the title compound (250mg, 71.6%).

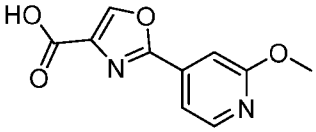
^{1}HNMR (DMSO-d_6, 400MHz): δ 13.3-12.9 (bs, 1H), 12.4-12.2 (s, 1H), 8.81 (s, 1H), 8.20-8.17 (dd, 1H), 7.68-7.66 (dd, 1H), 6.41-6.37 (t, 1H). **LCMS:** m/z = 207.1 $(M+1)^+$.

Intermediate 10: Synthesis of 2-(2-hydroxypyridin-5-yl)oxazole-4-carboxylic acid



Using the same reaction conditions as described in step 2 of intermediate 5, ethyl 2-(6-fluoropyridin-3-yl)oxazole-4-carboxylate (product of step 1 of intermediate 7) (400mg, 1.69 mmol) was hydrolysed using lithium hydroxide (400mg, 10.3 mmol) in THF/water (2/2mL) at RT for 2h to obtain the crude title compound (300mg). **LCMS:** m/z = 207.1 $(M+1)^+$.

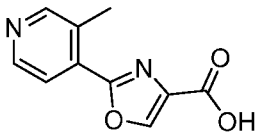
Intermediate 11: Synthesis of 2-(2-methoxypyridin-4-yl)oxazole-4-carboxylic acid

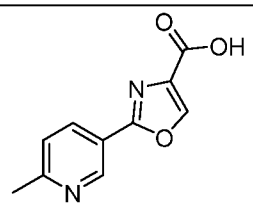


The title compound was prepared by using the similar conditions and reagents according to the procedure described in the synthesis of Intermediate-7.

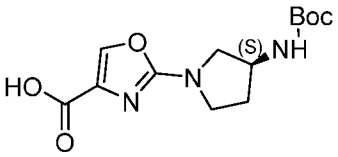
^{1}HNMR (DMSO-d_6, 300MHz): δ 8.38 (s, 1H) 8.34-8.32 (d, 1H) 7.53-7.52 (d, 1H) 7.33 (s, 1H) 3.91 (s, 3H)**. LCMS:** m/z = 221.1 $(M+1)^+$.

The below intermediates were prepared by using appropriate reagents according to the above protocol depicted in Intermediate 8.

Intermediate No.	Structure	Characterization Data
12		**^{1}HNMR** (DMSO-d_6, 300MHz): δ13.3 (bs, 1H) 8.97 (s,1H) 8.64 (s,1H) 8.58-8.57 (d,1H) 7.86-7.84 (d,1H) 2.62 (s,3H). **LCMS:** m/z = 205.0 $(M+1)^+$, **HPLC:** 98.44%.

13		**^{1}HNMR** (DMSO-d_6, 300MHz): δ13.3 (bs,1H) 9.03 (s,1H) 8.88 (s,1H) 8.24-8.20 (d,1H) 7.46-7.43 (d,1H) 2.54 (s,3H). **LCMS:** m/z = 205.1 $(M+1)^+$, **HPLC:** 97.33%.

Intermediate 14: Synthesis of (S)-2-(3-((tert-butoxycarbonyl)amino)pyrrolidin-1-yl)oxazole-4-carboxylic acid



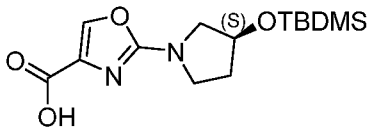
Step 1: Preparation of ethyl (S)-2-(3-((tert-butoxycarbonyl)amino)pyrrolidin-1-yl)oxazole-4-carboxylate

The mixture of ethyl 2-chlorooxazole-4-carboxylate (100mg, 0.5698 mmol), tert-butyl (S)-pyrrolidin-3-ylcarbamate (127mg, 0.6837 mmol), DIPEA (0.284mL, 1.4245 mmol) and DMF (5mL) were heated at 120°C for 2h. The reaction mass was quenched with ice water and extracted with DCM. The solvent was distilled out to get the title compound (170mg, 91.89%). **LCMS:** m/z = 270.1 (M - t-butyl +1)$^+$.

Step 2: Preparation of (S)-2-(3-((tert-butoxycarbonyl)amino)pyrrolidin-1-yl)oxazole-4-carboxylic acid

Using the same reaction conditions as described in step 2 of intermediate 5, ethyl (S)-2-(3-((tert-butoxycarbonyl)amino)pyrrolidin-1-yl)oxazole-4-carboxylate (170mg, 0.5224 mmol) was hydrolysed using lithium hydroxide (33mg, 0.7837 mmol) in THF/methanol/water (10/1/2mL) at RT for 12h to obtain the title compound (150mg, 96.77%). **LCMS:** m/z = 242.0(M- t-butyl+1)$^+$.

Intermediate 15: Synthesis of (S)-2-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)oxazole-4-carboxylic acid



Step 1:Preparation of ethyl (S)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxylate

Using the same reaction conditions as described in step 1 of intermediate 14, ethyl 2-chlorooxazole-4-carboxylate (500mg, 2.8490 mmol) was reacted with (S)-pyrrolidin-3-ol

(298mg, 3.4188 mmol) using, sodium carbonate (453mg, 4.2735 mmol) in DMF (10mL) to get the title compound (535mg, 83.07%).

LCMS: m/z = 227.1 $(M+1)^+$.

Step 2:Preparation of ethyl (S)-2-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)oxazole-4-carboxylate

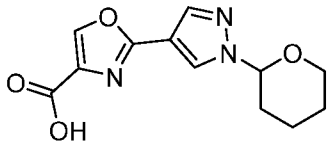
Using the same reaction conditions as described in step 2 of example 41, ethyl(S)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxylate (535mg, 2.3672 mmol) was protected using TBDMS chloride (429mg, 2.8407 mmol), imidazole (396mg, 5.8072 mmol) and DMAP (29mg, 0.2367 mmol) in DMF (5mL) at RT for 2h to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 20% ethyl acetate in hexane as eluent to obtain the title compound (520mg, 64.5%). **LCMS:** m/z = 341.2 $(M+1)^+$.

Step 3: Preparation of (S)-2-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)oxazole-4-carboxylic acid

Using the same reaction conditions as described in step 2 of intermediate 5, ethyl (S)-2-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)oxazole-4-carboxylate (520mg, 1.5294 mmol) was hydrolysed using lithium hydroxide (97mg, 2.2941 mmol) in THF/methanol/water (10/5/5mL) at RT for 2h to obtain the title compound (350mg, 73.37%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 7.88 (s, 1H), 4.55-4.50(s, 1H), 3.75-3.60 (m, 3H), 3.5-3.4 (d, 1H), 2.05-1.90 (m, 2H), 0.9 (s, 9H). **LCMS:** m/z = 313.1 $(M+1)^+$.

Intermediate 16: Synthesis of 2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)oxazole-4-carboxylic acid



Step 1: Preparation of ethyl 2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)oxazole-4-carboxylate

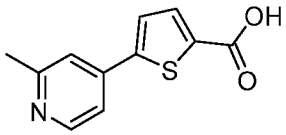
Using the same reaction conditions as described in step 7 of example 1, 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (273mg, 0.982 mmol) was coupled with ethyl 2-chlorooxazole-4-carboxylate (125mg, 0.892 mmol) using sodium carbonate (283mg, 2.676 mmol) and $Pd(dppf)Cl_2$ (65mg, 0.089 mmol) in 1,2-dimethoxyethane/water (5/1mL) to get the crude product. The resultant crude was purified by 60-

120 silica gel column chromatography using 20% ethyl acetate in hexane as eluent to obtain the title compound (200mg, 43.9%). **LCMS:** m/z = 292.3 $(M+1)^+$.

Step 2: Preparation of 2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)oxazole-4-carboxylic acid

Using the same reaction conditions as described in step 2 of intermediate 5, ethyl 2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)oxazole-4-carboxylate (200mg, 0.784 mmol) was hydrolysed using lithium hydroxide (50mg, 1.176 mmol) in THF/methanol/water (5/2/1mL) at RT for 1h to obtain the title compound (206mg, 100%). **LCMS:** m/z = 263.9 $(M+1)^+$.

Intermediate 17: Synthesis of 5-(2-methylpyridin-4-yl)thiophene-2-carboxylic acid



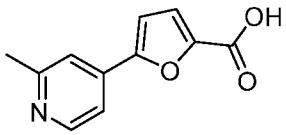
Step 1: Preparation of methyl 5-(2-methylpyridin-4-yl)thiophene-2-carboxylate

Using the similar reaction conditions as described in step 7 of example 1, methyl 5-bromothiophene-2-carboxylate (460mg, 2.08 mmol) was coupled with 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (680mg, 3.10 mmol) using potassium carbonate (576mg, 4.17 mmol) TBAB (100mg, 0.310 mmol) and $Pd(dppf)Cl_2$ (108mg, 0.1538 mmol) in dioxane/water (10/3mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 50%ethyl acetate in hexane as eluent to obtain the title compound (552mg, 91%). **LCMS:** m/z = 234.0 $(M+1)^+$.

Step 2: Preparation of 5-(2-methylpyridin-4-yl)thiophene-2-carboxylic acid

Using the same reaction conditions as described in step 2 of intermediate 5, 5-(2-methylpyridin-4-yl)thiophene-2-carboxylate (550mg, 2.36 mmol) was hydrolysed using lithium hydroxide (200mg, 4.72 mmol) in THF/methanol/water (10/5/5 mL) at 50°C for 15 min to obtain the title compound (501mg, 97%). **LCMS:** m/z = 220.0 $(M+1)^+$.

Intermediate 18: Synthesis of 5-(2-methylpyridin-4-yl)furan-2-carboxylic acid



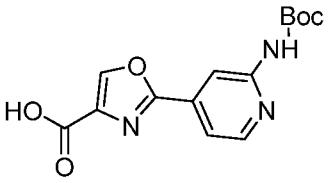
Step 1: Preparation of methyl 5-(2-methylpyridin-4-yl)furan-2-carboxylate

Using the similar reaction conditions as described in step 7 of example 1, methyl 5-bromofuran-2-carboxylate (214mg, 1.0406 mmol) was coupled with 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (340mg, 1.561 mmol) using potassium carbonate (288mg, 2.08 mmol) TBAB (50mg, 0.156 mmol) and $Pd(dppf)Cl_2$ (54mg, 0.078 mmol) in dioxane/water (10/3mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 50% ethyl acetate in hexane as eluent to obtain the title compound (301mg, 89%). **LCMS:** 100%, m/z = 217.8 $(M+1)^+$.

Step 2: Preparation of 5-(2-methylpyridin-4-yl)furan-2-carboxylic acid

Using the same reaction conditions as described in step 2 of intermediate 5, methyl 5-(2-methylpyridin-4-yl)furan-2-carboxylate (300mg, 1.38 mmol) was hydrolysed using lithium hydroxide (116mg, 2.76 mmol) in THF/methanol/water (10/5/5 mL) at 50°C for 0.25h to obtain the title compound (260mg, 92.8%). **LCMS:** 100%, m/z = 204.1 $(M+1)^+$.

Intermediate 19: Synthesis of 2-(2-((tert-butoxycarbonyl)amino)pyridin-4-yl)oxazole-4-carboxylic acid



Step 1: Preparation of ethyl 2-(2-((tert-butoxycarbonyl)amino)pyridin-4-yl)oxazole-4-carboxylate

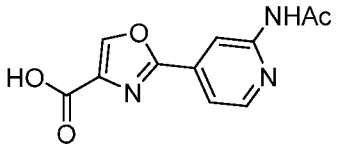
Using the same reaction conditions as described in step 7 of example 1, tert-butyl (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (487mg, 1.5223 mmol) was coupled with ethyl 2-chlorooxazole-4-carboxylate (165mg, 1.1710 mmol) using sodium carbonate (373mg, 3.5131 mmol) and $Pd(dppf)Cl_2$ (43mg, 0.0585 mmol) in 1,2-dimethoxyethane/water (10/5mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 30% ethyl acetate in hexane as eluent to obtain the title compound (200mg, 43.9%). **LCMS:** m/z = 278.0 $(M+1\text{-t-butyl})^+$.

Step 2: Preparation of 2-(2-((tert-butoxycarbonyl)amino)pyridin-4-yl)oxazole-4-carboxylic acid

Using the same reaction conditions as described in step 2 of intermediate 5, ethyl 2-(2-((tert-butoxycarbonyl)amino)pyridin-4-yl)oxazole-4-carboxylate (145mg, 0.4349 mmol) was

hydrolysed using 10% sodium hydroxide solution (1mL) in THF/methanol/water (10/5/2mL) at RT for 10min to obtain the title compound (75mg, 56.81%). **LCMS**: m/z: 250.0 $(M+1\text{-de-t-butyl})^+$.

Intermediate 20: Synthesis of 2-(2-acetamidopyridin-4-yl)oxazole-4-carboxylic acid



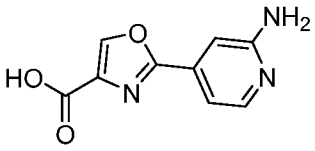
Step 1: Preparation of ethyl 2-(2-acetamidopyridin-4-yl)oxazole-4-carboxylate

Using the same reaction conditions as described in step 7 of example 1, N-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)acetamide (2.78g, 10.04 mmol) was coupled with ethyl 2-chlorooxazole-4-carboxylate (1g, 7.09 mmol) using sodium carbonate (106mg, 21.2 mmol) and $Pd(dppf)Cl_2$ (259mg, 0.354 mmol) in 1,2-dimethoxyethane/water (30/5mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 50% ethyl acetate in hexane as eluent to obtain the title compound (680mg, 36%). **LCMS**: m/z: 276.3 $(M+1)^+$.

Step 2: Preparation of 2-(2-acetamidopyridin-4-yl)oxazole-4-carboxylic acid

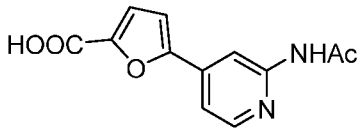
Using the same reaction conditions as described in step 2 of intermediate 5, ethyl 2-(2-acetamidopyridin-4-yl)oxazole-4-carboxylate (500mg, 1.81 mmol) was hydrolysed using lithium hydroxide (84mg, 2 mmol) in THF/methanol/water (10/1/5mL) at RT for 4h to obtain the title compound (360mg, 81.08%). **LCMS**: m/z: 248.1 $(M+1)^+$.

Intermediate 21: Synthesis of 2-(2-aminopyridin-4-yl)oxazole-4-carboxylic acid



Using the same reaction conditions as described in step 2 of intermediate 5, ethyl 2-(2-acetamidopyridin-4-yl)oxazole-4-carboxylate (product of step 1 of intermediate 20) (900mg, 3.27 mmol) was hydrolysed using lithium hydroxide (329mg, 7.85 mmol) in THF/methanol/water (30/1/5mL) at RT for 4h to obtain the title compound (750mg, 96%). **LCMS**: m/z: 206.2 $(M+1)^+$.

Intermediate 22: Synthesis of 5-(2-acetamidopyridin-4-yl)furan-2-carboxylic acid



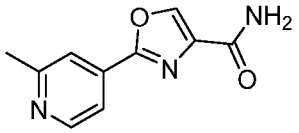
Step 1: Preparation of methyl 5-(2-acetamidopyridin-4-yl)furan-2-carboxylate

Using the same reaction conditions as described in step 7 of example 1, N-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)acetamide (1.91g, 7.317 mmol) was coupled with methyl 5-bromofuran-2-carboxylate (1g, 4.87 mmol) using sodium carbonate (1.54g, 14.61 mmol) and Pd(dppf)Cl_2 (178mg, 0.243 mmol) in 1,2-dimethoxyethane/water (20/4mL) at 80°C for 3h to get the crude product. The resultant crude was purified by flash chromatography using 35% ethyl acetate in hexane as eluent to obtain the title compound (451mg, 35.6%). **LCMS**: m/z: 261.1 $(M+1)^+$.

Step 2: Preparation of 5-(2-acetamidopyridin-4-yl)furan-2-carboxylic acid

Using the same reaction conditions as described in step 2 of intermediate 5, ethyl 2-(2-acetamidopyridin-4-yl)oxazole-4-carboxylate (450mg, 1.73 mmol) was hydrolysed using lithium hydroxide (73mg, 1.73 mmol) in THF/methanol/water (10/5/5mL) at RT for 2h to obtain the title compound (396mg, 93.17%). **LCMS**: m/z: 247.2 $(M+1)^+$.

Intermediate 23: Synthesis of 2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



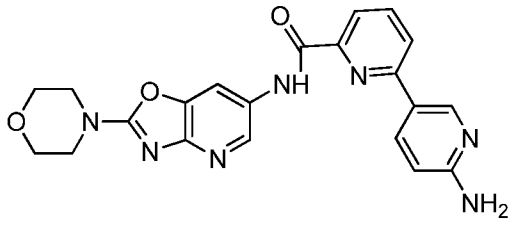
To a solution of 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (WO2011/043371) (0.25 g, 1.22 mmol) in DMF were added ammonium chloride (0.131 g, 2.45 mmol), EDCI.HCl (0.351 g, 1.83 mmol), HOBT (0.248 g, 1.83 mmol) and DIPEA (0.790 g, 6.12 mmol). The reaction mixture was stirred for 12 h at room temperature and was diluted with EtOAc, washed with brine and dried over Na_2SO_4 and concentrated to afford the title compound (0.180 g, 75 %) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (d, 1H), 7.81-7.79 (m, 2H), 7.72 (d, 1H), 7.65 (s, 1H), 2.55 (s, 3H); **MS (ES):** m/z: 204 $(M+1)^+$; HPLC: 93.5%

EXAMPLES

Example 1

6'-amino-N-(2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide



Step 1: Preparation of oxazolo[4,5-b]pyridine-2-thiol

A solution of 2-aminopyridin-3-ol (5.0g, 45.45 mmol) and potassium ethyl xanthate (8.0g, 49.99 mmol) in pyridine (50mL) was heated at 110°C overnight. The reaction mixture was cooled to 0°C, added ice water and acidified with Conc. HCl. The solid was filtered and dried under vacuum to afford the title compound (6.0g, 86.95%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 8.24-8.22 (d, 1H), 7.90-7.87 (d, 1H), 7.30-7.26 (m, 1H). **LCMS:** m/z: 153.0 $(M+1)^+$.

Step 2: Preparation of 2-(methylthio)oxazolo[4,5-b]pyridine

To a stirred solution of oxazolo[4,5-b]pyridine-2-thiol (3.0g, 19.73 mmol) in ethyl acetate (30mL) was added potassium carbonate (3.81g, 27.62 mmol) and methyl iodide (3.08g, 21.71 mmol) and stirred at RT overnight. The reaction mixture was diluted with water (100ml), extracted with ethyl acetate (2x50mL), dried over sodium sulphate and concentrated to afford the title compound (3.0g, 93.75%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 8.46-8.44 (d, 1H), 7.71-7.68 (d, 1H), 7.20-7.15 (m, 1H), 2.81 (s, 3H). **LCMS:** m/z: 167.0$(M+1)^+$.

Step 3: Preparation of 2-morpholinooxazolo[4,5-b]pyridine

To a solution of 2-(methylthio)oxazolo[4,5-b]pyridine (2.0g, 12.12 mmol) in THF (5mL) was added morpholine (5mL) and heated at 75°C overnight. The solvent was distilled off to afford the title compound (2.0g, 83.3%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 8.20-8.10 (d, 1H), 7.80-7.70 (d, 1H), 7.15-7.00 (m, 1H), 3.75-3.72 (m, 4H), 3.63-3.52 (m, 4H). **LCMS:** m/z: 206.5 $(M+1)^+$.

Step 4: Preparation of 2-morpholino-6-nitrooxazolo[4,5-b]pyridine

To a solution of 2-morpholinooxazolo[4,5-b]pyridine (1.0g, 4.854 mmol) in acetic acid (10mL), was added fuming nitric acid (6mL) and heated at 100°C for 4 hrs. The reaction mixture was cooled to 0°C, added ice and filtered the solid to afford the title compound (800mg, 66.6%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 9.11-9.10 (d, 1H), 8.567-8.560 (d, 1H), 3.75 (s, 8H). **LCMS:** m/z: 250.9$(M+1)^+$.

Step 5: Preparation of 2-morpholinooxazolo[4,5-b]pyridin-6-amine

To a solution of 2-morpholino-6-nitrooxazolo[4,5-b]pyridine (700mg, 2.8 mmol) in THF was added ammonium chloride (2.37g, 44.80 mmol) in water (5mL) and zinc dust (1.82g, 28.0 mmol) and stirred at 50°C for 1 hr. The catalyst was filtered through Celite®, extracted with DCM (2 X 100mL) and distilled out the solvent to get the title compound (600mg, 97.4%). **LCMS:** m/z: 221.1 $(M+1)^+$.

Step 6: Preparation of 6-bromo-N-(2-morpholinooxazolo[4,5-b]pyridin-6-yl)picolinamide

The solution of 2-morpholinooxazolo[4,5-b]pyridin-6-amine (600mg, 2.727 mmol), 6-bromopicolinic acid (661mg, 3.27 mmol), EDCI.HCl (797mg, 4.09 mmol), HOBt (552mg, 4.09 mmol), DIPEA (1.05g, 8.181 mmol) in DMF (5mL) was stirred at RT overnight. Thr reaction mixture was quenched with ice water and extracted the compound in ethyl acetate (2x25 mL), dried over sodium sulphate and concentrated. The resultant crude was filtered by using 60-120 silica-gel column chromatography and compound was eluted using 5% methanol in DCM as eluent to afford the title compound (350mg, 31.8%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 9.79 (s, 1H), 8.46-8.45 (d, 1H), 8.32-8.31 (d, 1H), 8.26-8.23 (d, 1H), 7.82-7.68 (m, 2H), 3.85-3.67 (m, 8H). **LCMS:** m/z: 405.6 $(M+1)^+$.

Step 7: Preparation of tert-butyl (6-((2-morpholinooxazolo[4,5-b]pyridin-6-yl)carbamoyl)-[2,3'-bipyridin]-6'-yl)carbamate

To a sealed tube 6-bromo-N-(2-morpholinooxazolo[4,5-b]pyridin-6-yl)picolinamide (350mg, 0.866 mmol), tert-butyl (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (360mg, 1.126 mmol) (intermediate 1), sodium carbonate (275mg, 2.598 mmol) in 1,2-dimethoxyethane (10mL) and water (2mL) were added. The reaction mixture was purged with argon for 10 min, added $Pd(PPh_3)_2Cl_2$ (31mg, 0.043 mmol) and heated at 95°C overnight. The solvent was distilled out. The resultant crude was purified by 60-120 silica gel column chromatography using 5% methanol in DCM as eluent to obtain the title compound (300mg, 67.11%). **LCMS:** m/z: 517.7$(M+1)^+$.

Step 8: 6'-amino-N-(2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide

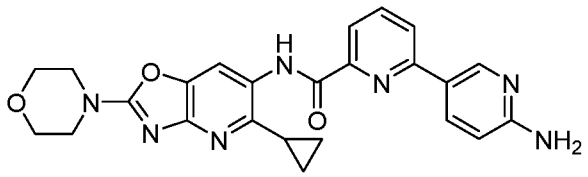
TFA (5mL) was added to the solution of tert-butyl (6-((2-morpholinooxazolo[4,5-b]pyridin-6-yl)carbamoyl)-[2,3'-bipyridin]-6'-yl)carbamate (300mg, 0.580 mmol) in DCM (1mL)

and stirred at RT for 1 hr. After completion of the reaction, this was then purified by prep. HPLC to obtain the title compound (34mg, 14.05%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 10.06 (s, 1H), 8.96-8.95 (d, 1H), 8.58-8.44 (d, 1H), 8.44-8.40 (dd, 1H), 8.31-8.30 (d, 1H), 8.11-7.95 (m, 3H), 6.59-6.56 (d, 1H), 6.38 (s, 2H), 3.75-3.66 (m, 8H). **LCMS:** 98.20%, m/z = 418.1 $(M+1)^+$. **HPLC:** 98.32%.

Example 2

6'-amino-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide hydrochloride



.HCl

Step 1:Preparation of 2-amino-6-chloropyridin-3-ol

Using the same reaction conditions as described in step 5 of example 1, 6-chloro-2-nitropyridin-3-ol (35mg, 0.201 mmol) was reduced with zinc dust (65mg, 1.005 mmol) and ammonium chloride (54mg, 1.005 mmol) in THF (2mL) to get the title compound (25mg, 89%). **LCMS:** m/z: 145.2 $(M+1)^+$.

Step 2:Preparation of 5-chlorooxazolo[4,5-b]pyridine-2-thiol

Using the same reaction conditions as described in step 1 of example 1 2-amino-6-chloropyridin-3-ol (25mg, 0.173 mmol) was cyclised using potassium ethyl xanthate (33mg, 0.208 mmol) in pyridine (1mL) to afford the title compound (25mg, 78%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 7.94-7.90 (d, 1H), 7.38-7.35 (d, 1H). **LCMS:** m/z: 187.1$(M+1)^+$.

Step 3:Preparation of 5-chloro-2-(methylthio)oxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 2 of example 1, 5-chlorooxazolo[4,5-b]pyridine-2-thiol (620mg, 3.33 mmol) was methylated using potassium carbonate (689mg, 4.99 mmol) and methyl iodide (567mg, 3.99 mmol) in ethyl acetate (10mL) to afford the title compound (720mg, 90%). **LCMS:** m/z: 201.1 $(M+1)^+$.

Step 4:Preparation of 5-chloro-2-morpholinooxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 3 of example 1, 5-chloro-2-(methylthio)oxazolo[4,5-b]pyridine was substituted using morpholine (2mL) and THF (10mL) to afford the title compound (750mg, 88%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 7.82-7.80 (d, 1H), 7.08-7.06 (d, 1H), 3.74-3.64 (m, 8H). **LCMS:** m/z: 240.2(M+1)$^+$.

Step 5:Preparation of 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 4 of example 1 5-chloro-2-morpholinooxazolo[4,5-b]pyridine (50mg) was nitrated using acetic acid (0.2mL) and fuming nitric acid (0.1mL) at 100°C for 2h to afford the title compound (25mg, 43%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 8.60 (s, 1H), 3.72 (s, 8H)$^+$.

Step 6:Preparation of 5-cyclopropyl-2-morpholino-6-nitrooxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 7 of example 1 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (25mg, 0.088 mmol) was coupled with cyclopropyl boronic acid (9mg, 0.105 mmol) using potassium carbonate (24mg, 0.176 mmol) and $Pd(PPh_3)_4$ (5mg, 0.004 mmol) in xylene (2mL) to get the crude product (50mg). **LCMS:** m/z: 291.1 (M+1)$^+$.

Step 7:Preparation of 5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 5-cyclopropyl-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (220mg, 0.758 mmol) was reduced with zinc dust (394mg , 6.068 mmol) and ammonium chloride (327mg, 6.068 mmol) in THF/methanol/H_2O (5mL/1ml/0.5mL)to get the title compound (160mg, 84%). **LCMS:** m/z: 261.0 (M+1)$^+$.

Step 8: Preparation of 6-bromo-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)picolinamide

Using the same reaction conditions as described in step 6 of example 1, 5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-amine (100mg, 0.384 mmol), was coupled with 6-bromopicolinic acid (85mg, 0.423 mmol) using EDCI.HCl (110mg, 0.576 mmol), HOBt (77mg, 0.576 mmol), TEA (0.22mL, 1.538 mmol) in DMF (2mL) to afford the title compound (75mg, 44%). **LCMS:** m/z: 444.2(M+1)$^+$.

Step 9: Preparation of tert-butyl (6-((5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)carbamoyl)-[2,3'-bipyridin]-6'-yl)carbamate

Using the same reaction conditions as described in step 7 of example 1, 6-bromo-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)picolinamide (75mg, 0.169 mmol) was coupled with tert-butyl (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (65mg, 0.203 mmol) (intermediate 1) using sodium carbonate (53mg, 0.507 mmol) and $Pd(PPh_3)_2Cl_2$ (7mg, 0.0084 mmol) in 1,2-dimethoxyethane (5mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 50% ethyl acetate in hexane as eluent to obtain the title compound (50mg, 54%). **LCMS:** m/z: 558.2 $(M+1)^+$.

Step 10: Preparation of 6'-amino-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide

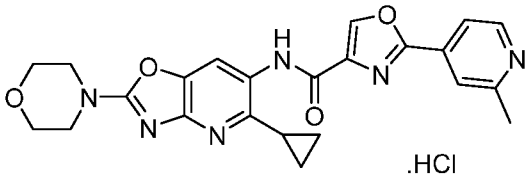
Using the same reaction conditions as described in step 8 of example 1 tert-butyl (6-((5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)carbamoyl)-[2,3'-bipyridin]-6'-yl)carbamate (50mg, 0.089 mmol) was deprotected using methanolic HCl (5mL) to get the crude product. This was then purified by prep HPLC to get the title compound (40mg, 90%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 10.78 (s, 1H), 9.059-9.055 (d, 1H), 8.93-8.90 (dd, 1H), 8.40-8.25 (bs, 2H), 8.21-8.20 (d, 1H), 8.15-8.11 (t, 1H), 8.07-8.05 (d, 1H), 7.83 (s, 1H), 7.12-7.09 (d, 1H), 3.71-3.60 (m, 8H), 2.20-2.16 (m, 1H), 0.91-0.87 (m, 4H).

LCMS: 96.48%, m/z = 458.2 $(M+1)^+$. **HPLC:** 98.7%.

Example 3

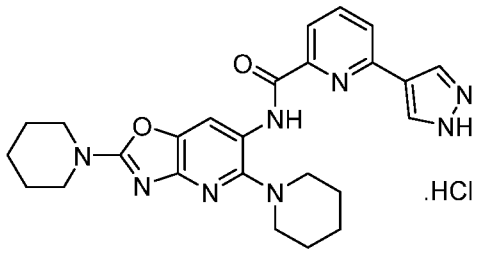
N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride



Using the same reaction conditions as described in step 6 of example 1, 5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-amine (product of step 7 of example 2) (60mg, 0.23 mmol), was coupled with 2-(2-methyl-pyridin-4-yl)oxazole-4-carboxylic acid (71mg, 0.396 mmol) using EDCI.HCl (66mg, 0.396 mmol), HOBt (46mg, 0.396 mmol), TEA (0.13mL, 0.923 mmol) in DMF (2mL) to afford the crude product. This was then purified by prep HPLC and treated with methanolic HCl to get the title compound (20mg, 20%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 10.22 (s, 1H), 9.27 (s, 1H), 8.85-8.83 (d, 1H), 8.25 (s, 1H), 8.14-8.13 (d, 1H), 7.72 (s, 1H), 3.71-3.59 (m, 8H), 2.63 (s, 3H), 2.17-2.14 (m, 1H), 0.89-0.86 (m, 4H). **LCMS:** 93.91%, m/z = 447.1 $(M+1)^+$. **HPLC:** 99.0%.

Example 4: N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide hydrochloride



Step 1:Preparation of 5-chloro-2-(piperidin-1-yl)oxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 3 of example 1, 5-chloro-2-(methylthio)oxazolo[4,5-b]pyridine (product of step 3 of example 2) (3g, 14.95 mmol) was substituted using piperidine (8mL) and THF (30mL) to afford the title compound (3g, 90%). **LCMS:** m/z = 238.1 $(M+1)^+$.

Step 2: Preparation of 5-chloro-6-nitro-2-(piperidin-1-yl)oxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 4 of example 20, 5-chloro-2-(piperidin-1-yl)oxazolo[4,5-b]pyridine (4g, 168 mmol) was nitrated using potassium nitrate (3.4g, 337 mmol) and conc. sulphuric acid (20mL) at RT for 3h to afford the crude title compound (4g). **LCMS:** m/z = 283.0 $(M+1)^+$.

Step 3:Preparation of 6-nitro-2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridine

A mixture of 5-chloro-6-nitro-2-(piperidin-1-yl)oxazolo[4,5-b]pyridine (product of step 5 of example 2) (300mg, 1.056 mmol) was heated with piperidine (3mL) at 100°C for 2h. Reaction was quenched with ice water and filtered the solid to get the title compound (300mg, 86%). **LCMS:** m/z: 332.1$(M+1)^+$.

Step 4:Preparation of 2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 6-nitro-2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridine (300mg, 0.90 mmol) was reduced with zinc dust (468mg, 7.207 mmol) and ammonium chloride (389mg, 7.207 mmol) in THF/methanol/H_2O (5mL/1mL/0.5mL) to get the title compound (250mg, 92%). **LCMS:** m/z: 302.4 $(M+1)^+$.

Step 5:Preparation of N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinamide

Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (100mg, 0.33 mmol), was coupled with 6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinic acid (intermediate 3) (108mg, 0.396 mmol) using EDCI.HCl (94mg, 0.495 mmol), HOBt (66mg, 0.495 mmol), TEA (0.2mL, 1.324 mmol) in DMF (2mL) to afford the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 1% methanol in DCM as eluent to obtain the title compound (100mg, 55%). **LCMS:** m/z: 557.4 $(M+1)^+$.

Step 6: Preparation of N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide hydrochloride

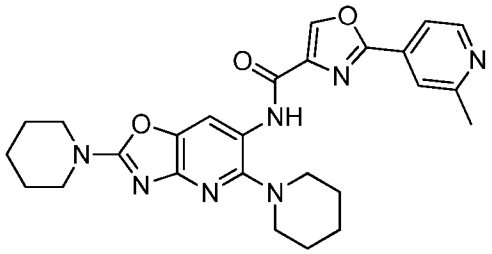
Using the same reaction conditions as described in step 8 of example 1, N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinamide (100mg, 0.179 mmol) was deprotected using methanolic HCl to get the crude product. This was then purified by prep HPLC to get the title compound (40mg, 50%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 10.8 (s, 1H), 8.66 (s, 1H), 8.39 (s, 1H), 8.04-7.94 (m, 3H), 3.62 (s, 4H), 2.94 (s, 4H), 1.75 (s, 4H), 1.62-1.55 (m, 8H).

LCMS: 97.91%, m/z = 473.5 $(M+1)^+$.**HPLC:** 96.5%.

Example 5

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



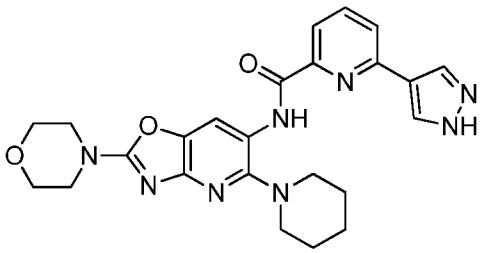
Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 4 of example 4) (100mg, 0.33 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (74mg, 0.363 mmol) using EDCI.HCl (94mg, 0.495 mmol), HOBt (66mg, 0.495 mmol), TEA (0.2mL, 1.324 mmol) in DMF

(2mL) to afford the crude product. This was then purified by prep HPLC to get the title compound (30mg, 20%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 9.98 (s, 1H), 9.21 (s, 1H), 8.91-8.89 (d, 1H), 8.51 (s, 1H), 8.21 (s, 1H), 8.09-8.08 (d, 1H), 3.61 (m, 7H), 2.98 (s, 3H), 2.71 (s, 3H), 1.81 (s, 3H), 1.61 (s, 7H).**LCMS:** 100%, m/z = 488.2 $(M+1)^+$. **HPLC:** 92.1%.

Example 6

N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide



Step 1: Preparation of 2-morpholino-6-nitro-5-(piperidin-1-yl)oxazolo[4,5-b]pyridine

To a solution of 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (product of step-5 of example 2) (30mg, 0.1056 mmol) in THF (2mL) was added piperidine (11mg, 0.126 mmol) and stirred at RT overnight. The reaction mixture was quenched with ice water and extracted with ethyl acetate (2X10mL), dried over sodium sulphate and distilled out the solvent to obtain the title compound (30mg, 89%). **LCMS:** m/z: 334.5 $(M+1)^+$.

Step 2: Preparation of 2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 2-morpholino-6-nitro-5-(piperidin-1-yl)oxazolo[4,5-b]pyridine (300mg, 0.900 mmol) was reduced with zinc dust (468mg, 7.207 mmol) and ammonium chloride (389mg, 7.207 mmol) in THF/methanol/H_2O (5mL/1mL/0.5mL) to get the title compound (260mg, 96%). **LCMS:** m/z: 304.1 $(M+1)^+$.

Step 3: Preparation of N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinamide

Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (90mg, 0.297 mmol), was coupled with 6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinic acid (intermediate 3) (97mg, 0.356 mmol) using EDCI.HCl (85mg, 0.445 mmol), HOBt (60mg, 0.445 mmol), TEA (0.2mL, 1.188 mmol) in DMF (4mL) to afford the crude product. The resultant crude was purified by 60-120 silica gel

column chromatography using 1% methanol in DCM as eluent to obtain the title compound (60mg, 38%). **LCMS:** m/z: 559.6 $(M+1)^+$.

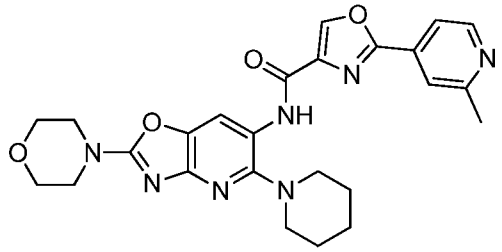
Step 4: Preparation of N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide

Using the same reaction conditions as described in step 8 of example 1, N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinamide (60mg, 0.107 mmol) was deprotected using methanolic HCl (2mL) to get the title compound (50mg, 90%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 10.80 (s, 1H), 8.65 (s, 1H), 8.43 (s, 2H), 8.05-7.93 (m, 3H), 3.76-3.62 (m, 8H), 2.98 (s, 4H), 1.76 (s, 4H), 1.54 (s, 2H). **LCMS:** 92.69%, m/z = 475.5 $(M+1)^+$. **HPLC:** 90.31%.

Example 7

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

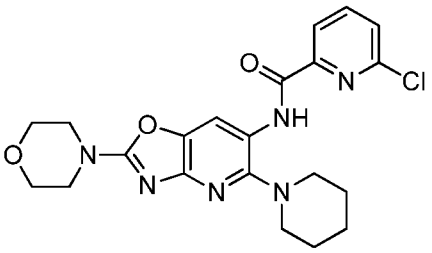


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 6) (100mg, 0.331 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (81mg, 0.397 mmol) using EDCI.HCl (94mg, 0.496 mmol), HOBt (66mg, 0.496 mmol), TEA (0.2mL, 1.302 mmol) in DMF (2mL) to afford the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 1% methanol in DCM as eluent to obtain the title compound (35mg, 22%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 9.80 (s, 1H), 9.20 (s, 1H), 8.90-8.88 (d, 1H), 8.57 (s, 1H), 8.18 (s, 1H), 8.06-8.04 (d, 1H), 3.72-3.61 (m, 8H), 2.96 (s, 4H), 2.73 (s, 3H), 1.81 (s, 4H), 1.63 (s, 2H). **LCMS:** 81.6%, m/z = 490.2 $(M+1)^+$. **HPLC:** 94.3%.

Example 8

6-chloro-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide

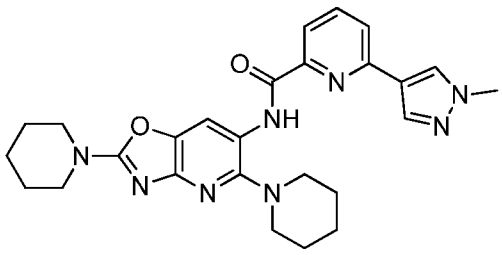


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 6) (70mg, 0.2317 mmol), was coupled with 6-chloropicolinic acid (44mg, 0.278 mmol) using EDCI.HCl (66mg, 0.347 mmol), HOBt (46mg, 0.347 mmol), TEA (0.2mL, 0.926 mmol) in DMF (4mL) to afford the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 1% methanol in DCM as eluent to obtain the title compound (35mg, 35%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 10.60 (s, 1H), 8.70 (s, 1H), 8.15-8.14 (t, 2H), 7.84-7.81 (m, 1H), 3.77-3.60 (m, 8H), 2.93-2.10 (t, 4H), 1.81 (s, 4H), 1.58 (s, 2H). **LCMS:** 99.3%, m/z = 443.2 $(M+1)^+$. **HPLC:** 93.0%.

Example 9

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)picolinamide

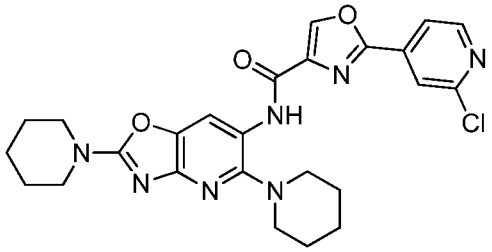


Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 4) (75mg, 0.2483 mmol), was coupled with 6-(1-methyl-1H-pyrazol-4-yl)picolinic acid (intermediate 4)(61mg, 0.298 mmol) using EDCI.HCl (72mg, 0.372 mmol), HOBt (51mg, 0.372 mmol), DIPEA (0.17mL, 0.9933 mmol) in DMF (2mL) to afford the crude product. This was then purified by prep HPLC to get the title compound (41mg, 33.0%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 10.80 (s, 1H), 8.67 (s, 1H), 8.44 (s, 1H), 8.21 (s, 1H), 8.06-8.02 (t, 1H), 7.98-7.96 (d, 1H), 7.92-7.91 (d, 1H), 3.92 (s, 3H), 3.63 (s, 4H), 2.94 (s, 4H), 1.76 (s, 4H), 1.63 (s, 6H), 1.55 (s, 2H). **LCMS:** 98.9%, m/z = 487.2 $(M+1)^+$. **HPLC:** 94.0%.

Example 10

2-(2-chloropyridin-4-yl)-N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

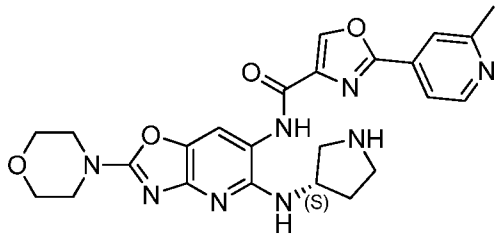


Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 4) (75mg, 0.2483 mmol), was coupled with 2-(2-chloropyridin-4-yl)oxazole-4-carboxylic acid (71mg, 0.298 mmol) using EDCI.HCl (72mg, 0.372 mmol), HOBt (51mg, 0.372 mmol), DIPEA (0.17mL, 0.9933 mmol) in DMF (2mL) to afford the crude product. This was then purified by prep HPLC to get the title compound (62mg, 45.9%).

^{1}HNMR (CD_3OD, 400MHz): δ 8.82 (s, 1H), 8.64-8.62 (d, 1H), 8.14 (s, 1H), 8.04-8.03 (d, 1H), 3.81 (s, 8H), 2.06-1.96 (m, 4H), 1.79 (s, 8H). **LCMS:** 84.1%, m/z = 508.2 $(M+1)^+$. **HPLC:** 97.6%.

Example 11

(S)-2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-3-ylamino)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide



Step 1:Preparation of (S)-tert-butyl 3-((2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)amino)pyrrolidine-1-carboxylate

A solution of 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (300mg, 1.0563 mmol) (S)-tert-butyl 3-aminopyrrolidine-1-carboxylate (237mg, 1.267 mmol) and potassium carbonate (292mg, 2.112 mmol) in DMF (2mL) was heated at 100°C for 2h. Reaction was quenched with ice water and filtered the solid. The resultant crude was purified by 60-120 silica

gel column chromatography using 1% methanol in DCM as eluent to obtain the title compound (350mg, 76.25%). **LCMS:** m/z: 435.4 $(M+1)^+$.

Step 2:Preparation of (S)-tert-butyl 3-((6-amino-2-morpholinooxazolo[4,5-b]pyridin-5-yl)amino)pyrrolidine-1-carboxylate

Using the same reaction conditions as described in step 5 of example 1, (S)-tert-butyl 3-((2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)amino)pyrrolidine-1-carboxylate (350mg, 0.806 mmol) was reduced with zinc dust (422mg, 6.451 mmol) and ammonium chloride (691mg, 12.903 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the title compound (240mg, 71.8%). **LCMS:** m/z: 405.2 $(M+1)^+$.

Step 3:Preparation of (S)-tert-butyl 3-((6-(2-(2-methylpyridin-4-yl)oxazole-4-carboxamido)-2-morpholinooxazolo[4,5-b]pyridin-5-yl)amino)pyrrolidine-1-carboxylate

Using the same reaction conditions as described in step 6 of example 1, (S)-tert-butyl 3-((6-amino-2-morpholinooxazolo[4,5-b]pyridin-5-yl)amino)pyrrolidine-1-carboxylate (115mg, 0.284 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (70mg, 0.341 mmol) using EDCI.HCl (82mg, 0.426 mmol), HOBt (58mg, 0.426 mmol), DIPEA (0.199mL, 1.138 mmol) in DMF (2mL) to afford the title compound (100mg, 59.52%). **LCMS:** m/z: 591.4 $(M+1)^+$.

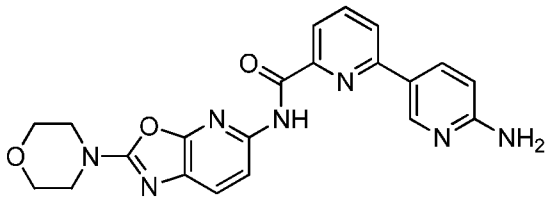
Step 4: Preparation of (S)-2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-3-ylamino)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 8 of example 1, (S)-tert-butyl 3-((6-(2-(2-methylpyridin-4-yl)oxazole-4-carboxamido)-2-morpholinooxazolo[4,5-b]pyridin-5-yl)amino)pyrrolidine-1-carboxylate (100mg, 0.169 mmol) was deprotected using methanolic HCl (5mL) to get the crude product. This was then purified by prep HPLC to get the title compound (9mg, 10.84%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.91 (s, 1H), 8.78 (s, 1H), 8.74-8.73 (d, 1H), 8.45 (s, 1H), 7.82 (s, 1H), 7.76-7.74 (d, 1H), 4.50 (s, 1H), 4.04-4.03 (d, 4H), 3.30-3.00 (m, 7H), 2.70 (s, 3H), 2.40-1.80 (m, 4H), 1.00-0.08 (m, 1H). **LCMS:** 100%, m/z = 491.3 $(M+1)^+$.

Example 12

6'-amino-N-(2-morpholinooxazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide



Step 1:Preparation of 3-amino-6-chloropyridin-2-ol

Using the same reaction conditions as described in step 5 of example 1 6-chloro-3-nitropyridin-2-ol (1.0g, 5.747 mmol was reduced with zinc dust (3.0g ,45.977 mmol) and ammonium chloride (4.92g, 91.952 mmol) in THF/methanol/H_2O (20m/4mL/2mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 10% methanol in DCM as eluent to obtain the title compound (500mg, 60.97%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 6.84-6.81 (d, 1H), 6.55-6.52 (d, 1H). **LCMS:** m/z: 145.0$(M+1)^+$.

Step 2:Preparation of 5-chlorooxazolo[5,4-b]pyridine-2-thiol

Using the same reaction conditions as described in step 1 of example 1, 3-amino-6-chloropyridin-2-ol (900mg, 6.25 mmol) was cyclised using potassium ethyl xanthate (1.1g, 6.875 mmol) in pyridine (8mL) to afford the title compound (1.0g, 86.2%). **LCMS:** m/z: 185.0 $(M-1)^+$.

Step 3:Preparation of 5-chloro-2-morpholinooxazolo[5,4-b]pyridine

The mixture of 5-chlorooxazolo[5,4-b]pyridine-2-thiol (550mg, 2.956 mmol), morpholine (5mL) and heated at 110°C overnight. Solvent was distilled off. The resultant crude was purified by 60-120 silica gel column chromatography using 40% ethyl acetate in hexane as eluent to obtain the title compound (200mg, 28.5%). **LCMS:** m/z: 240.0 $(M+1)^+$.

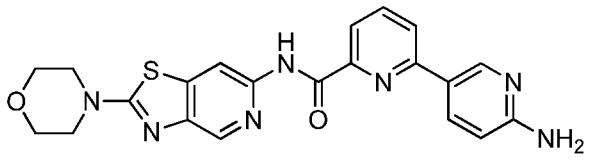
Step 4:Preparation of 6'-amino-N-(2-morpholinooxazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide

In a sealed tube, taken 5-chloro-2-morpholinooxazolo[5,4-b]pyridine (76mg, 0.316 mmol), tert-butyl (6-carbamoyl-[2,3'-bipyridin]-6'-yl)carbamate (100mg, 0.316 mmol) (intermediate 2) and caesium carbonate (257mg, 0.79 mmol) in toluene (5mL) and purged argon for 10 min. Added X-Phos (15 mg, 0.32 mmol) and heated at 110°C overnight. The solvent was distilled out. The resultant crude was purified by 60-120 silica gel column chromatography using 5% methanol in DCM as eluent. Further The resultant crude was purified by prep HPLC to obtain the title compound (11mg, 10.0%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 8.81 (s, 1H), 8.25-8.24 (d, 1H), 8.10 (s, 1H), 7.80-7.75 (m, 3H), 7.50-7.44 (m, 1H), 7.25 (s, 1H), 3.77-3.62 (m, 8H). **LCMS:** 72.3%, m/z = 418.2 $(M+1)^+$.**HPLC:** 96.1%.

Example 13

6'-amino-N-(2-morpholinothiazolo[4,5-c]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide



Step-1: Synthesis of 6-chloro thiazolo[4,5-c]pyridine-2(3*H*)-thione

Using the same reaction conditions as described in step 1 of example 1, 4,6-dichloropyridin-3-amine (1.3 g, 7 mmol) was cyclised using potassium ethyl xanthate (2.55 g, 15 mmol) in DMF (25mL) at 150°C for 8h to afford the title compound (1.3 g, 86.6 %) as a light brown solid.

^{1}HNMR (400 MHz, DMSO-d_6): δ 14.2-14.0 (b, 1H), 8.274 (s, 1H), 7.931 (s, 1H); **LCMS:** 100%, m/z = 201.3 $(M+1)^+$.

Step-2: Synthesis of 4-(6-chloro thiazolo[4,5-c]pyridin-2-yl) morpholine

To a suspension of 6-chlorothiazolo[4,5-c]pyridine-2(3H)-thione (0.3 g, 1.16 mmol) in DCM (4 mL), oxalyl chloride (0.2 mL, 2.38 mmol) and DMF (1.5 mL) were added at 0°C. The resulting mixture was slowly allowed to warm to room temperature and stirred there for 1 h. The reaction mixture was again cooled to 0°C and triethyl amine (0.66 mL, 4.76 mmol) and morpholine (0.13 mL, 1.75 mmol) were added. The reaction mixture was stirred at RT for 1 h and quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography (EtOAc/*n*-hexanes 3:7) to afford the title compound (0.14 g, 39.6 %) as a light brown solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.04 (s, 1H), 3.74-3.72 (m, 4H), 3.61-3.59 (m, 4H); **LCMS:** m/z = 256.1 $(M+1)^+$.

Step-3: Synthesis of 6'-amino-*N*-(2-morpholino thiazolo [4,5-c]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide

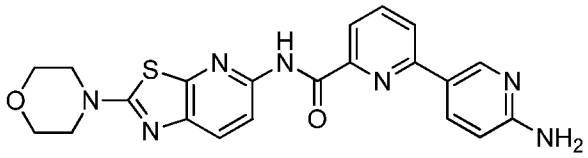
Using the same reaction conditions as described in step 4 of example 12, 4-(6-chlorothiazolo[4,5-c] pyridin-2-yl) morpholine (0.081 g, 0.32 mmol), was coupled with tert-butyl

(6-carbamoyl-[2,3'-bipyridin]-6'-yl)carbamate (intermediate 2) (0.1 g, 0.32 mmol) using cesium carbonate (0.21 g, 0.64 mmol), XantPhos (0.028g, 0.047mmol) and $Pd_2(dba)_3$ (0.015 mg, 0.015 mmol) in toluene : dioxane (2:2mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent. Further the resultant crude was purified by prep HPLC to afford title compound (0.01 g, 6 %) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.88 (d, 1H), 8.85 (dd, 1H), 8.71 (s, 1H), 8.55 (s, 1H), 8.22-8.13 (m, 4 H), 7.09 (d, 1H), 3.73 (t, 4H), 3.58 (t, 4H). **LCMS:** 100%, m/z = 434.2 $(M+1)^+$.

Example 14

6'-amino-N-(2-morpholinothiazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide



Step 1:Preparation of 5-chlorothiazolo[5,4-b]pyridine-2-thiol

Using the same reaction conditions as described in step 1 of example 1, 2,6-dichloropyridin-3-amine (5g, 30 mmol) was cyclised using potassium ethyl xanthate (9.81g, 61 mmol) in NMP (40mL) at 150°C for overnight to afford the title compound (5.5gr, 92%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 14.10 (bs, 1H), 7.66-7.62 (d, 1H), 7.53-7.48 (d, 1H). **LCMS:** m/z: 202.9 $(M+1)^+$.

Step 2:Preparation of 4-(5-chlorothiazolo[5,4-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 1 of example 4, 5-chlorothiazolo[5,4-b]pyridine-2-thiol (5.5g, 27.22 mmol) was substituted using morpholine (40mL) to afford the title compound (4gr, 58%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 7.83-7.80 (d, 1H), 7.42-7.39 (d, 1H), 3.75-3.71 (m, 4H), 3.61-3.58 (m, 4H). **LCMS:** m/z: 256.0$(M+1)^+$.

Step 3: Preparation of 6'-amino-N-(2-morpholinothiazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide

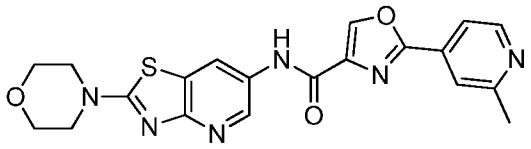
Using the same reaction conditions as described in step 4 of example 12, 6'-amino-N-(2-morpholinothiazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide (200mg, 0.632 mmol), was coupled with tert-butyl (6-carbamoyl-[2,3'-bipyridin]-6'-yl)carbamate (intermediate 2)

(177mg, 0.692 mmol) using cesium carbonate (514mg, 1.582 mmol), X-Phos (30mg, 0.063 mmol) and $Pd_2(dba)_3$ (28mg, 0.031 mmol) in toluene (5mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent. Further The resultant crude was purified by prep HPLC to obtain the title compound (13mg, 5%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 10.06 (s, 1H), 9.17-9.16 (d, 1H), 8.64-8.60 (m, 1H), 8.39 (s, 1H), 8.15-8.13 (d, 1H), 8.04-7.99 (t, 1H), 7.93-7.91 (d, 1H), 7.80-7.69 (m, 4H), 3.75-3.72 (t, 4H), 3.55-3.52 (t, 4H). **LCMS:** 96.5%, m/z = 434.4 $(M+1)^+$. **HPLC:** 95.1%.

Example 15

2-(2-methylpyridin-4-yl)-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide



Step 1:Preparation of thiazolo[4,5-b]pyridine-2-thiol

Using the same reaction conditions as described in step 1 of example 1, 3-bromopyridin-2-amine (5gr, 28 mmol) was cyclised using potassium ethyl xanthate (9.24gr, 57 mmol) in NMP (40mL) at 150°C for overnight to afford the title compound (4.2gr, 88%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 8.37-8.35 (m, 1H), 8.15-8.12 (m, 1H), 7.32-7.28 (q, 1H) **LCMS:** m/z: 169.1$(M+1)^+$.

Step 2:Preparation of 4-(thiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 1 of example 4, thiazolo[4,5-b]pyridine-2-thiol (4.2gr, 25 mmol) was substituted using morpholine (20mL) at 110°C to afford the title compound (3g, 55%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 8.32-8.30 (dd, 1H), 8.22-8.18 (dd, 1H), 7.07-7.03 (q, 1H), 3.76-3.72 (m, 4H), 3.62-3.59 (m, 4H). **LCMS:** m/z: 222.3 $(M+1)^+$.

Step 3: Preparation of 4-(6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 4 of example 1 4-(thiazolo[4,5-b]pyridin-2-yl)morpholine (2.5g, 11.3 mmol) was nitrated using acetic acid (5mL) and fuming nitric acid (10mL) at 100°C for overnight to afford the title compound (1.5g, 50%). **^{1}HNMR** (DMSO-d_6, 300MHz): δ 9.15-9.09 (m, 2H), 3.70-3.60 (bs, 8H).

Step 4: Preparation of 2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1 4-(6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (500mg, 1.879 mmol) was reduced with zinc dust (977mg, 15.03 mmol) and ammonium chloride (812mg, 15.03 mmol) in THF/methanol/H_2O(10mL/2mL/1mL) to get the title compound (430mg, 97%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 7.75-7.74 (d, 1H), 7.36-7.35 (d, 1H), 5.10-5.05 (bs, 2H), 3.73-3.70 (m, 4H), 3.48-3.34 (m, 4H). **LCMS:** m/z: 237.4 $(M+1)^+$.

Step 5: Preparation of 2-(2-methylpyridin-4-yl)-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

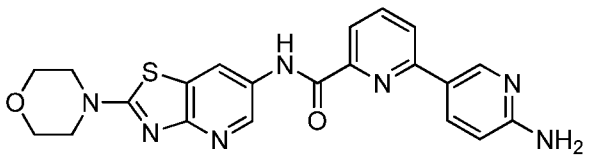
Using the same reaction conditions as described in step 6 of example 1, 2-morpholinothiazolo[4,5-b]pyridin-6-amine (110mg, 0.466 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (95mg, 0.466 mmol) using EDCI.HCl (133mg, 0.699 mmol), HOBt (94mg, 0.69 mmol), DIPEA (0.2mL, 1.165 mmol) in DMF (2mL) to afford the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent. The crude was further purified by prep HPLC to obtain the title compound (28mg, 15%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 10.45 (s, 1H), 9.01 (s, 1H), 8.70-8.63 (d, 1H), 8.65-8.62 (dd, 2H), 7.89 (s, 1H), 7.80-7.75 (d, 1H), 3.77-3.72 (t, 4H), 3.62-3.60 (t, 4H), 2.60 (s, 3H).

LCMS: 100%, m/z = 423.2 $(M+1)^+$. **HPLC:** 96.9%.

Example 16

6'-amino-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide



Step 1: Preparation of 6-bromo-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)picolinamide

Using the same reaction conditions as described in step 6 of example 1, 2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 4 of example 15) (320mg, 1.35 mmol), was coupled with 6-bromopicolinic acid (356mg, 1.76 mmol) using EDCI.HCl (698mg, 5.4 mmol), HOBt (239mg, 1.76 mmol), DIPEA (338mL, 1.76 mmol) in DMF (5mL) to afford the title compound (250mg, 43.9%). **LCMS:** m/z: 421.6 $(M+1)^+$.

Step 2:Preparation of tert-butyl (6-((2-morpholinothiazolo[4,5-b]pyridin-6-yl)carbamoyl)-[2,3'-bipyridin]-6'-yl)carbamate

Using the same reaction conditions as described in step 7 of example 1 6-bromo-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)picolinamide (250mg, 0.59 mmol) was coupled with tert-butyl (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (151mg, 0.71 mmol) (intermediate 1) using sodium carbonate (188mg, 1.77 mmol) and $Pd(PPh_3)_2Cl_2$ (22mg, 0.029 mmol) in 1,2-dimethoxyethane (8mL) to get the crude product. The resultant crude was purified by Combiflash using 0.2-2.0% methanol in chloroform as eluent to obtain the title compound (120mg, 37.8%). **LCMS:** m/z: 534.2$(M+1)^+$.

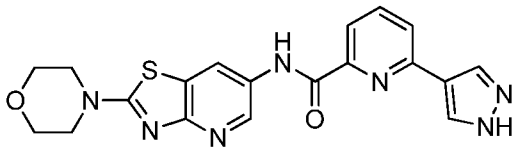
Step 3: Preparation of 6'-amino-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide

Using the same reaction conditions as described in step 8 of example 1, tert-butyl (6-((2-morpholinothiazolo[4,5-b]pyridin-6-yl)carbamoyl)-[2,3'-bipyridin]-6'-yl)carbamate (120mg, 0.22 mmol) was deprotected using TFA (12mL) to get the title compound (80mg, 82%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 10.65 (s, 1H), 8.96 (s, 1H), 8.71 (s, 1H), 8.45-8.42 (d, 1H), 8.08-7.95 (m, 3H), 6.59-6.56 (d, 1H), 6.38 (s, 2H), 3.76-3.74 (t, 4H), 3.63-3.62 (t, 4H). **LCMS:** 98.9%, m/z = 434.1 $(M+1)^+$. **HPLC:** 95.9%.

Example 17

N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide

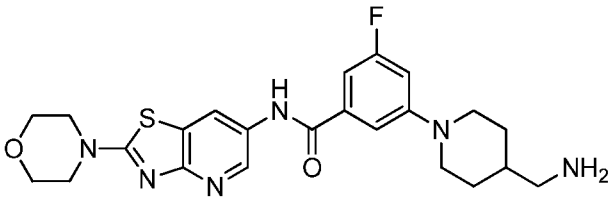


Using the same reaction conditions as described in step 7 of example 1, 6-bromo-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)picolinamide (product of step 1 of example 16) (200mg, 0.477 mmol) was coupled with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (111mg, 0.572 mmol) using sodium carbonate (151mg, 1.431 mmol) and $Pd(PPh_3)_2Cl_2$ (35mg, 0.0477 mmol) in 1,2-dimethoxyethane (5mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent. Further it was purified by prep HPLC to obtain the title compound (14mg, 8%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 13.2 (s, 1H), 10.60 (s, 1H), 8.70-8.60 (m, 3H), 8.40 (s, 1H), 8.02-7.91 (m, 3H), 3.76-3.74 (t, 4H), 3.62-3.60 (t, 4H). **LCMS:** 100%, m/z = 408.1 $(M+1)^+$. **HPLC:** 97.9%.

Example 18

3-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide



Step 1: tert-butyl ((1-(3-fluoro-5-((2-morpholinothiazolo[4,5-b]pyridin-6-yl)carbamoyl)phenyl)piperidin-4-yl)methyl)carbamate

Using the same reaction conditions as described in step 6 of example 1, 2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 4 of example 15) (60mg, 0.254 mmol), was coupled with 3-(4-(((tert-butoxycarbonyl)amino)methyl)piperidin-1-yl)-5-fluorobenzoic acid (intermediate 5) (98mg, 0.279 mmol) using EDCI.HCl (72mg, 0.381 mmol), HOBt (52mg, 0.381 mmol), DIPEA (98mg, 0.762 mmol) in DMF (5mL) to afford the title compound (130mg, 90.2%). **LCMS:** m/z: 571.2$(M+1)^+$.

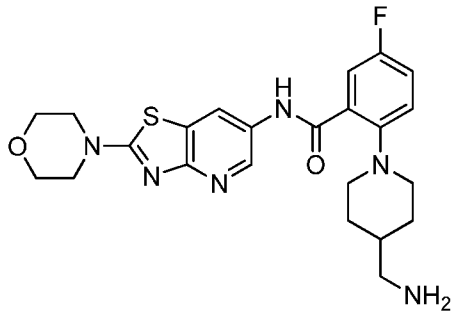
Step 2:3-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide

Using the same reaction conditions as described in step 8 of example 1, tert-butyl ((1-(3-fluoro-5-((2-morpholinothiazolo[4,5-b]pyridin-6-yl)carbamoyl)phenyl)piperidin-4-yl)methyl)carbamate (130mg, 0.228 mmol) was deprotected using methanolic HCl (4.7mL) to get the crude compound. The resultant crude was purified by prep HPLC to obtain the title compound (55mg, 47.8%).

^{1}HNMR (DMSO-d_6, $3^0$0MHz): δ 10.74 (s, 1H), 8.87 (s, 1H), 8.69 (s, 1H), 7.96 (s, 3H), 7.41 (s, 1H), 7.14-7.01 (m, 2H), 3.69-3.68 (m, 6H), 2.83-2.73 (m, 5H), 2.27 (s, 1H), 1.85-1.81 (m, 4H), 1.30-1.23 (m, 3H). **LCMS:** 100%, m/z = 471.5$(M+1)^+$. **HPLC:** 97.9%.

Example 19

2-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide



Step 1: Preparation of tert-butyl ((1-(4-fluoro-2-((2-morpholinothiazolo[4,5-b]pyridin-6-yl)carbamoyl)phenyl)piperidin-4-yl)methyl)carbamate

Using the same reaction conditions as described in step 6 of example 1, 2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 4 of example 15) (100mg, 0.423 mmol), was coupled with 2-(4-(((tert-butoxycarbonyl)amino)methyl)piperidin-1-yl)-5-fluorobenzoic acid (intermediate 6) (164mg, 0.466 mmol) using EDCI.HCl (121mg, 0.65 mmol), HOBt (85mg, 0.635 mmol), TEA (0.3mL, 1.694 mmol) in DMF (4mL) to afford the title compound (50mg, 21%). **LCMS:** m/z: 571.3 $(M+1)^+$.

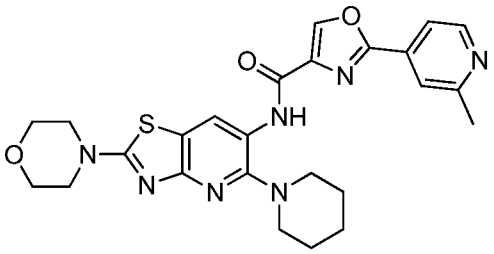
Step 2: Preparation of 2-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide hydrochloride

Using the same reaction conditions as described in step 8 of example 1, tert-butyl ((1-(4-fluoro-2-((2-morpholinothiazolo[4,5-b]pyridin-6-yl)carbamoyl)phenyl)piperidin-4-yl)methyl)carbamate (50mg, 0.087 mmol) was deprotected using methanolic HCl (4.7mL) to get the title compound (40mg, 90%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 11.93 (s, 1H), 8.87-8.86 (d, 1H), 8.70-8.69 (d, 1H), 8.20-7.98 (m, 3H), 7.65-7.61 (m, 1H), 7.49-7.43 (m, 2H), 3.77-3.75 (t, 4H), 3.75-3.67 (t, 4H), 3.22-3.19 (m, 2H), 2.82-2.72 (m, 4H), 1.89-1.85 (m, 3H), 1.40-1.36 (m, 2H). **LCMS:** 100%, m/z = 471.3 $(M+1)^+$. **HPLC:** 96.8%.

Example 20

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide



Step 1:Preparation of 5-chlorothiazolo[4,5-b]pyridine-2-thiol

Using the same reaction conditions as described in step 1 of example 1, 3-bromo-6-chloropyridin-2-amine (1.8g, 8.653 mmol) was cyclised using potassium ethyl xanthate (2.35g, 14.71 mmol) in in NMP (5mL) at 165°C for overnight to afford the crude product (2.0g).

LCMS: m/z: 202.9 $(M+1)^+$.

Step 2:Preparation of 5-chloro-2-(methylthio)thiazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 2 of example 1, 5-chlorothiazolo[4,5-b]pyridine-2-thiol (2g, 9.850 mmol) was methylated using potassium carbonate (2.71g, 19.7 mmol) and methyl iodide (2.1g, 14.775 mmol) in ethyl acetate (10mL) to afford the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 20% ethyl acetate in hexane as eluent to obtain the title compound (500mg, 23.8%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 8.02-8.00 (d, 1H), 7.37-7.24 (m, 2H), 2.85 (s, 3H).

Step 3:Preparation of 4-(5-chlorothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 3 of example 1 5-chloro-2-(methylthio)thiazolo[4,5-b]pyridine(500mg, 2.314 mmol) was substituted using morpholine (1mL) and THF (1mL) to afford the title compound (450mg, 76.2%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 7.82-7.80 (d, 1H), 7.04-7.01 (d, 1H), 3.84-3.83 (m, 4H), 3.75-3.71 (m, 4H). **LCMS:** m/z: 256.0 $(M+1)^+$.

Step 4: Preparation of 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Potassium nitrate (266mg, 2.64 mmol) was added to a solution of 4-(5-chlorothiazolo[4,5-b]pyridin-2-yl)morpholine (450mg, 1.764 mmol) in conc. sulphuric acid (5mL) and stirred at RT overnight. Ice water was added to the RM and filtered the solid to afford the title compound (450mg, 86.0%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.06 (s, 1H), 3.75 (s, 8H). **LCMS:** m/z: 301.0 $(M+1)^+$.

Step 5:Preparation of 4-(6-nitro-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 1 of example 6 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (450mg, 1.50 mmol) was substituted using piperidine (0.5mL) in THF (5mL) 75°C for 2h to obtain the title compound (450mg, 85.7%). **LCMS:** m/z: 350.1 $(M+1)^+$.

Step 6:Preparation of 2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 4-(6-nitro-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-2-yl)morpholine (400mg, 1.142 mmol) was reduced with zinc dust (600mg, 9.136 mmol) and ammonium chloride (1.0g, 18.272 mmol) in THF/methanol/H_2O (10/2mL/1mL) to get the crude product (400mg). **LCMS:** m/z: 320.25 $(M+1)^+$.

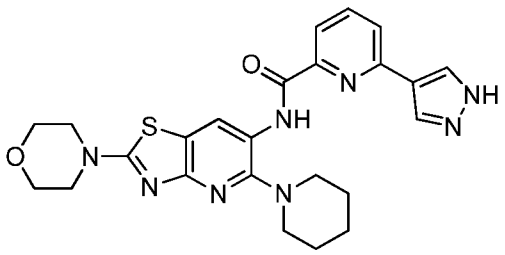
Step 7: Preparation of 2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (100mg, 0.313 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (64mg, 0.313 mmol) using EDCI.HCl (90mg, 0.47 mmol), HOBt (64mg, 0.47 mmol), DIPEA (101mg, 0.782 mmol) in DMF (5mL) to afford the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (40mg, 47.5%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.80 (s, 1H), 9.21 (s, 1H), 8.90-8.88 (m, 2H), 8.19 (s, 1H), 8.07-8.06 (m, 1H), 3.73-3.72 (t, 4H), 3.60-3.58 (t, 4H), 3.03-2.90 (t, 4H), 2.66 (s, 3H), 1.88-1.79 (t, 4H), 1.65-1.58 (m, 2H). **LCMS:** 90.4%, m/z = 506.3 $(M+1)^+$. **HPLC:** 92.6%.

Example 21

N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide



Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 6 of example 20) (100mg, 0.313

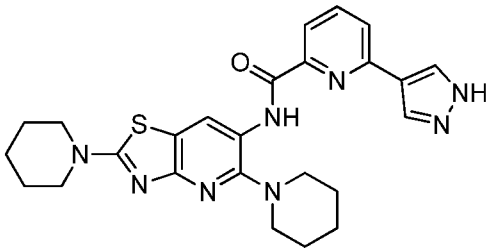
mmol) was coupled with 6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinic acid (intermediate 3) (90mg, 0.313 mmol) using EDCI.HCl (90mg, 0.47 mmol), HOBt (64mg, 0.47 mmol), DIPEA (101mg, 0.782 mmol) in DMF (5mL) to afford the crude coupled product. Using the same reaction conditions as described in step 8 of example 1, the above crude product was deprotected using methanolic HCl (5mL) to get the crude compound. The resultant crude was purified by prep HPLC to obtain the title compound (30mg, 43.5%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 10.80 (s, 1H), 9.05 (s, 1H), 8.39 (s, 2H), 8.05-7.98 (m, 3H), 3.73-3.58 (m, 8H), 2.99-2.90 (m, 4H), 1.75-1.68 (m, 4H), 1.54-1.48 (m, 2H).

LCMS: 85.0%, m/z = 491.3 $(M+1)^+$. **HPLC:** 95.7%.

Example 22

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide



Step 1:Preparation of 5-chloro-2-(piperidin-1-yl)thiazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 3 of example 1 5-chloro-2-(methylthio)thiazolo[4,5-b]pyridine(450mg, 2.314 mmol) was substituted using piperidine (1mL) and THF (mL) at 75°C for 2h to afford the crude product (500mg). **LCMS:** m/z: 254.0 $(M+1)^+$.

Step 2:Preparation of 5-chloro-6-nitro-2-(piperidin-1-yl)thiazolo[4,5-b]pyridine

Potassium nitrate (71mg, 2.657 mmol) was added to the solution of 5-chloro-2-(piperidin-1-yl)thiazolo[4,5-b]pyridine (450mg, 1.771 mmol) in conc. sulphuric acid (5mL) and stirred at RT overnight. The ice water was added to the RM and filtered the solid to afford the title compound (400mg, 75.5%). **LCMS:** m/z: 299.0 $(M+1)^+$.

Step 3:Preparation of 6-nitro-2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 1 of example 6, 5-chloro-6-nitro-2-(piperidin-1-yl)thiazolo[4,5-b]pyridine (400mg, 1.337 mmol) was substituted using piperidine (2.0mL) in THF (5mL) 75°C for 30min to obtain the crude product (400mg). **LCMS:** m/z: 348.1 $(M+1)^+$.

Step 4:Preparation of 2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 6-nitro-2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridine (400mg, 1.149 mmol) was reduced with zinc dust (597mg, 9.192 mmol) and ammonium chloride (974mg, 18.384 mmol) in THF (10mL) to get the crude product (320mg). **LCMS:** m/z: 318.1$(M+1)^+$.

Step 5: Preparation of N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinamide

Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (100mg, 0.315 mmol) was coupled with 6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinic acid (intermediate 3) (77mg, 0.378 mmol) using EDCI.HCl (90mg, 0.472 mmol), HOBt (63mg, 0.472 mmol), DIPEA (101mg, 0.787 mmol) in DMF (5mL) to afford the crude product (140mg).**LCMS:** m/z: 573.3 $(M+1)^+$.

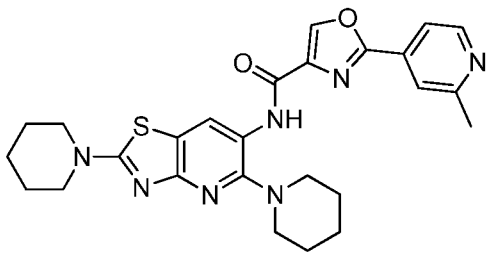
Step 6: Preparation of N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide

Using the same reaction conditions as described in step 8 of example 1, N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinamide (140mg, 0.244) was deprotected using methanolic HCl (5mL) to get the crude compound. The resultant crude was purified by prep HPLC to obtain the title compound (40mg, 32.3%).

^{1}HNMR (CD_3OD, 400MHz): δ 8.94 (s, 1H), 8.74 (s, 2H), 8.17-8.03 (m, 3H), 3.90-3.82 (m, 4H), 3.33-3.32 (m, 4H), 1.90-1.83 (m, 10H), 1.69-1.68 (m, 2H). **LCMS:** 99.0%, m/z = 489.5 $(M+1)^+$. **HPLC:** 96.2%.

Example 23

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 4 of example 22) (100mg, 0.315 mmol) was

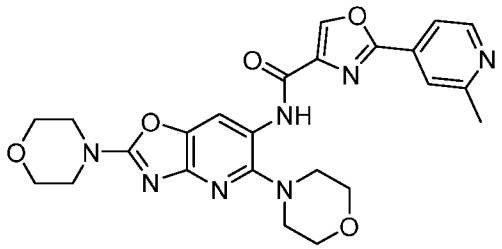
coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (77mg, 0.378 mmol) using EDCI.HCl (90mg, 0.472 mmol), HOBt (63mg, 0.472 mmol), DIPEA (101mg, 0.787 mmol) in DMF (5mL) to afford the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (45mg, 26.5%).

^{1}HNMR (CD_3OD, 400MHz): δ 9.00 (s, 1H), 8.96-8.94 (d, 1H), 8.77 (s, 1H), 8.59 (s, 1H), 8.52-8.50 (d, 1H), 3.90-3.81 (m, 4H), 3.50-3.41 (m, 4H), 2.94 (s, 3H), 1.89-1.75 (m, 12H).

LCMS: 80.0%, m/z = 504.2 $(M+1)^+$. **HPLC:** 98.4%.

Example 24

N-(2,5-dimorpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1:Preparation of 2,5-dimorpholino-6-nitrooxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 1 of example 4, 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (product of step 5 of example 2) (175mg, 0.6147 mmol) was heated with morpholine (2mL) at 110°C for 3h. The solvent was distilled to afford the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 1% methanol in DCM as eluent to obtain the title compound (190mg, 92.23%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 8.14 (s, 1H), 3.84-3.81 (m, 12H), 3.49-3.45 (m, 4H). **LCMS:** m/z = 336.0 $(M+1)^+$.

Step 2:Preparation of 2,5-dimorpholinooxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 2,5-dimorpholino-6-nitrooxazolo[4,5-b]pyridine (190mg, 0.5666 mmol) was reduced with zinc dust (297mg, 4.5329 mmol) and ammonium chloride (485mg, 9.0659 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the title compound (150mg, 86.70%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 6.97 (s, 1H), 3.87-3.66 (m, 14H), 3.12-3.10 (t, 4H). **LCMS:** m/z = 306.1 $(M+1)^+$.

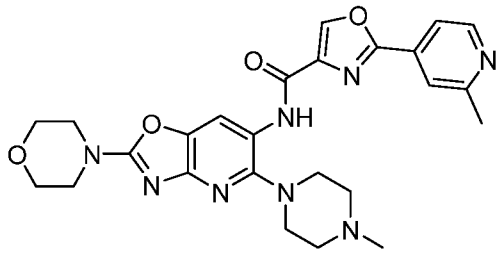
Step 3:Preparation of N-(2,5-dimorpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride

Using the same reaction conditions as described in step 6 of example 1, 2,5-dimorpholinooxazolo[4,5-b]pyridin-6-amine (70mg, 0.229 mmol), was coupled with 2-(pyridin-4-yl)oxazole-4-carboxylic acid (56mg, 0.275 mmol) using EDCI.HCl (66mg, 0.343 mmol), HOBt (47mg, 0.343 mmol), DIPEA (0.16mL, 0.917 mmol) in DMF (2mL) to get the crude product. This was then treated with methanolic HCl to afford the title compound (61mg, 50.41%).

^{1}HNMR (CD_3OD, 400MHz): δ 8.90-8.88 (m, 2H), 8.7 (s, 1H), 8.6 (s, 1H), 8.5 (d, 1H), 3.99-3.95 (t, 4H), 3.84-3.83 (t, 4H), 3.78-3.76 (t, 4H), 3.20-3.18 (t, 4H), 2.92 (s, 3H). **LCMS:** m/z = 492.0 $(M+1)^+$. **HPLC:** 95.10%.

Example 25

N-(5-(4-methylpiperazin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of 5-(4-methylpiperazin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 1 of example 4, 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (product of step 5 of example 2) (175mg, 0.6147 mmol) was heated with N-methylpiperazine (185mg, 1.844 mmol) at 75°C for 3h. The solvent was distilled to afford the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 5% methanol in DCM as eluent to obtain the title compound (200mg, 93.45%). m/z = 349.3 $(M+1)^+$.

Step 2:Preparation of 5-(4-methylpiperazin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 5-(4-methylpiperazin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (200mg, 0.5747 mmol) was

reduced with zinc dust (301mg, 4.5977 mmol) and ammonium chloride (492mg, 9.1954 mmol) in THF/methanol/H_2O (10mL/2mL/1mL)to get the title compound (150mg, 81.96%). **LCMS:** m/z = 319.4 $(M+1)^+$.

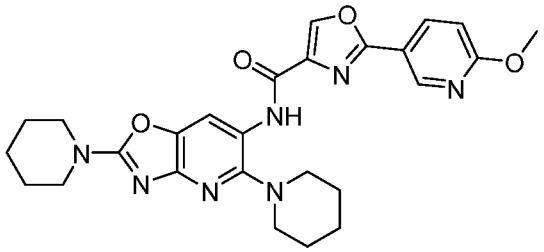
Step 3:Preparation of N-(5-(4-methylpiperazin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride

Using the same reaction conditions as described in step 6 of example 1, 5-(4-methylpiperazin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine (70mg, 0.2198 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (54mg, 0.2638 mmol) using EDCI.HCl (64mg, 0.3298 mmol), HOBt (45mg, 0.3298 mmol), DIPEA (0.145mL, 0.8794 mmol) in DMF (2mL) to get the crude product. This was then purified by prep HPLC and treated with methanolic HCl to afford the title compound (50mg, 42.01%).

^{1}HNMR (CD_3OD, 400MHz): δ 8.91 (m, 2H), 8.70 (s, 1H), 8.60-8.55 (m, 2H), 3.85-3.82 (t, 4H), 3.76-3.74 (t, 4H), 3.67-3.30 (m, 8H), 3.04 (s, 3H), 2.93 (s, 3H). m/z = 505.3 $(M+1)^+$. **HPLC:** 97.92%.

Example 26

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide

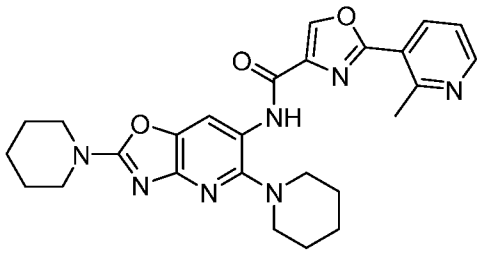


Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 4 of example 4) (70mg, 0.2317 mmol), was coupled with 2-(6-methoxypyridin-3-yl)oxazole-4-carboxylic acid (intermediate 7) (62mg, 0.2781 mmol) using EDCI.HCl (67mg, 0.3476 mmol), HOBt (47mg, 0.3476 mmol), DIPEA (0.162mL, 0.9271 mmol) in DMF (2mL) to afford the crude product. This was then purified by prep HPLC to get the title compound (10mg, 8.54%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.77 (s, 1H), 8.84 (s, 1H), 8.85-8.84 (d, 1H), 8.60 (s, 1H), 8.27-8.24 (dd, 1H), 7.10-7.07 (d, 1H), 3.95 (s, 3H), 3.62-3.60 (t, 4H), 2.94-2.91 (t, 4H), 1.90 (s, 4H), 1.77-1.50 (s, 8H). **LCMS:** m/z = 504.2 $(M+1)^+$. **HPLC:** 97.23%.

Example 27

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-3-yl)oxazole-4-carboxamide

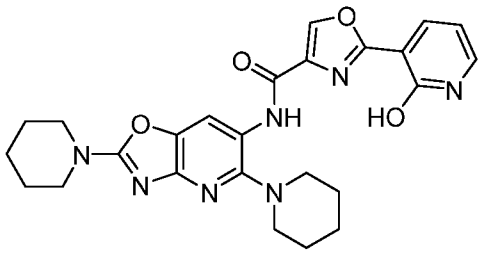


Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 4 of example 4) (70mg, 0.2317 mmol), was coupled with 2-(2-methylpyridin-3-yl)oxazole-4-carboxylic acid (intermediate 8) (57mg, 0.2781 mmol) using EDCI.HCl (67mg, 0.3476 mmol), HOBt (47mg, 0.3476 mmol), DIPEA (0.162mL, 0.9271 mmol) in DMF (2mL) to afford the crude product. This was then purified by prep HPLC to get the title compound (50mg, 44.24%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.79 (s, 1H), 9.02 (s, 1H), 8.639-8.631 (d, 2H), 8.33-8.30 (d, 1H), 7.50-7.45 (m, 1H), 3.61-3.60 (m, 4H), 2.97 (s, 3H), 2.90-2.88 (t, 4H), 1.80-1.70 (m, 4H), 1.61-1.50 (m, 8H). **LCMS:** m/z = 488.2 $(M+1)^+$. **HPLC:** 97.55%.

Example 28

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-hydroxypyridin-3-yl)oxazole-4-carboxamide

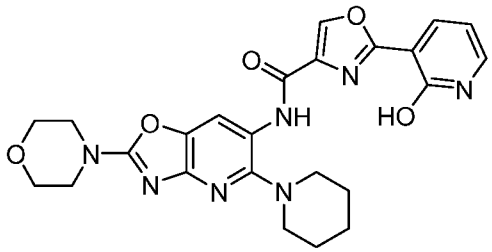


Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 4 of example 4) (70mg, 0.232 mmol), was coupled with 2-(2-hydroxypyridin-3-yl)oxazole-4-carboxylic acid (intermediate 9) (48mg, 0.232 mmol) using EDCI.HCl (67mg, 0.348 mmol), HOBt (47mg, 0.348 mmol), DIPEA (75mg, 0.581 mmol) in DMF (2mL) to afford the title compound (75mg, 66.3%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 12.4 (s, 1H), 9.80 (s, 1H), 8.87 (s, 1H), 8.61 (s, 1H), 8.22-8.20 (d, 1H), 7.70-7.69 (d, 1H), 6.45-6.42 (t, 1H), 3.62 (s, 4H), 2.90-2.89 (m, 4H), 1.90-1.77 (m, 4H), 1.69-1.55 (m, 8H). **LCMS:** m/z = 490.1 $(M+1)^+$. **HPLC:** 90.22%.

Example 29

2-(2-hydroxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

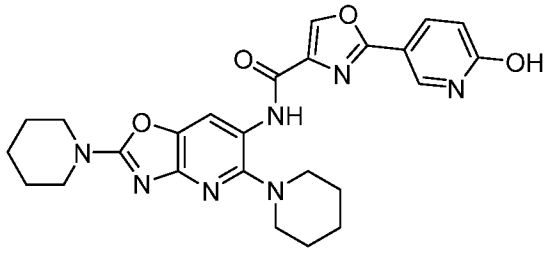


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 6) (70mg, 0.232 mmol), was coupled with 2-(2-hydroxypyridin-3-yl)oxazole-4-carboxylic acid (intermediate 9) (48mg, 0.232 mmol) using EDCI.HCl (67mg, 0.348 mmol), HOBt (47mg, 0.348 mmol), DIPEA (75mg, 0.581 mmol) in DMF (2mL) to afford the title compound (65mg, 57.5%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 12.30 (s, 1H), 9.80 (s, 1H), 8.88 (s, 1H), 8.65 (s, 1H), 8.24-8.13 (d, 1H), 7.70-7.64 (d, 1H), 6.50-6.30 (t, 1H), 3.73-3.72 (m, 4H), 3.63-3.62 (m, 4H), 2.90-2.89 (m, 4H), 1.90-1.76 (m, 4H), 1.64-1.54 (m, 2H). **LCMS:** m/z = 492.0 $(M+1)^+$. **HPLC:** 90.53%.

Example 30

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-hydroxypyridin-3-yl)oxazole-4-carboxamide



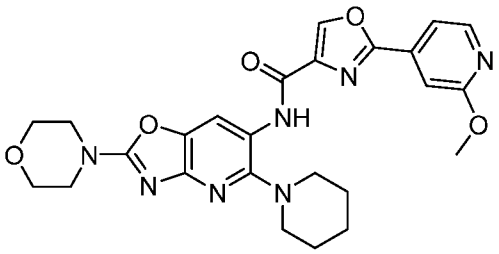
Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 4 of example 4) (75mg, 0.247 mmol), was coupled with 2-(2-hydroxypyridin-5-yl)oxazole-4-carboxylic acid (intermediate 10) (61mg,

0.297 mmol) using EDCI.HCl (70mg, 0.371 mmol), HOBt (50mg, 0.371 mmol), DIPEA (0.2mL, 0.99 mmol) in DMF (4mL) to afford the crude product. This was then purified by prep HPLC to get the title compound (25mg, 21%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 12.30 (s, 1H), 9.90 (s, 1H), 8.84 (s, 1H), 8.59 (s, 1H), 8.14-8.02 (d, 1H), 7.98-7.88 (d, 1H), 6.68-6.53 (d, 1H), 3.64-3.52 (m, 4H), 2.94-2.92 (t, 4H), 1.84-1.73 (m, 4H), 1.70-1.54 (m, 8H). **LCMS:** m/z = 490.2 $(M+1)^+$. **HPLC:** 93.74%.

Example 31

2-(2-methoxypyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

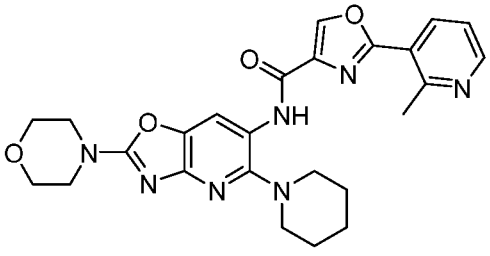


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 6) (70mg, 0.230 mmol), was coupled with 2-(2-methoxypyridin-4-yl)oxazole-4-carboxylic acid (intermediate 11) (57mg, 0.276 mmol) using EDCI.HCl (67mg, 0.346 mmol), HOBt (47mg, 0.346 mmol), DIPEA (0.161mL, 0.929 mmol) in DMF (2mL) to afford the crude product. This was then purified by prep HPLC to get the title compound (7mg, 6.03%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 10.0 (s, 1H), 8.76 (s, 1H), 8.38-8.33 (d, 2H), 7.51 (s, 1H), 7.38 (s, 1H), 5.34 (s, 1H), 4.10 (s, 3H), 3.80-3.70 (d, 8H), 3.05 (s, 4H), 1.89-1.82 (m, 4H), 1.65-1.63 (bs, 2H). **LCMS:** m/z = 506.2 $(M+1)^+$. **HPLC:** 95.81%.

Example 32

2-(2-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

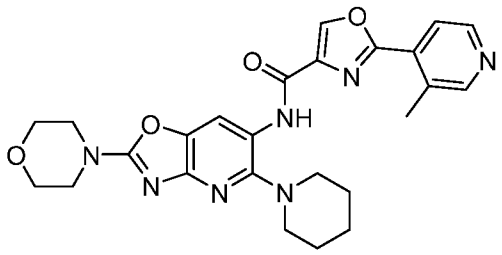


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 6) (70mg, 0.230 mmol), was coupled with 2-(2-methoxypyridin-3-yl)oxazole-4-carboxylic acid (intermediate 8) (57mg, 0.276 mmol) using EDCI.HCl (67mg, 0.346 mmol), HOBt (47mg, 0.346 mmol), DIPEA (0.161mL, 0.929 mmol) in DMF (2mL) to afford the crude product. This was then purified by prep HPLC to get the title compound (7mg, 6.03%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.91 (s, 1H), 9.11 (s, 1H), 8.78-8.77 (d, 1H), 8.65-8.62 (m, 2H), 7.76-7.75 (t, 1H), 3.73-3.61 (m, 8H), 3.08 (s, 3H), 2.94-2.75 (m, 4H), 1.76-1.65 (m, 4H), 1.60-1.55 (m, 2H). **LCMS:** m/z = 490.2 $(M+1)^+$. **HPLC:** 96.28%.

Example 33

2-(3-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

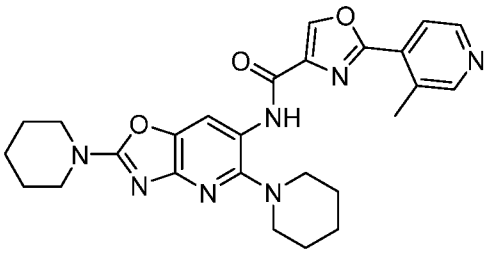


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 6) (54mg, 0.265 mmol), was coupled with 2-(3-methylpyridin-4-yl)oxazole-4-carboxylic acid (intermediate 12) (80mg, 0.265 mmol) using EDCI.HCl (77mg, 0.397 mmol), HOBt (38mg, 0.278 mmol), DIPEA (0.12mL, 0.927 mmol) in DMF (5mL) to afford the title compound (121mg, 93%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 9.90 (s, 1H), 9.10 (s, 1H), 8.75-8.60 (m, 3H), 7.95-7.86 (d, 1H), 3.80-3.52 (m, 8H), 2.95-2.85 (m, 4H), 2.80 (s, 3H), 1.80-1.68 (m, 4H), 1.66-1.50 (m, 2H). **LCMS:** m/z = 490.4 $(M+1)^+$. **HPLC:** 95.93%.

Example 34

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(3-methylpyridin-4-yl)oxazole-4-carboxamide

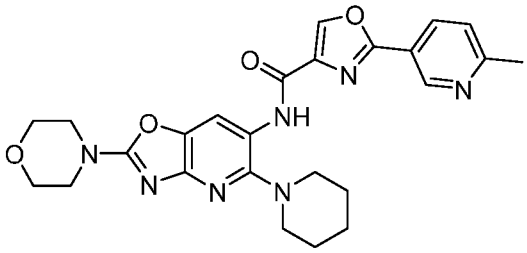


Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 4 of example 4) (54mg, 0.265 mmol), was coupled with 2-(3-methylpyridin-4-yl)oxazole-4-carboxylic acid (intermediate 12) (80mg, 0.265 mmol) using EDCI.HCl (77mg, 0.397 mmol), HOBt (38mg, 0.278 mmol), DIPEA (0.12mL, 0.927 mmol) in DMF (5mL) to afford the title compound (117mg, 91%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 9.90 (s, 1H), 9.05 (s, 1H), 8.77 (s, 1H), 8.68-8.60 (m, 2H), 7.90-7.85 (d, 1H),3.70-3.60 (m, 4H), 2.95-2.85 (m, 4H), 2.80 (s, 3H), 1.80-1.70 (m, 4H), 1.68-1.50 (m, 8H). **LCMS:** 98.99%, m/z = 488.4 $(M+1)^+$. **HPLC:** 97.00%.

Example 35

2-(6-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

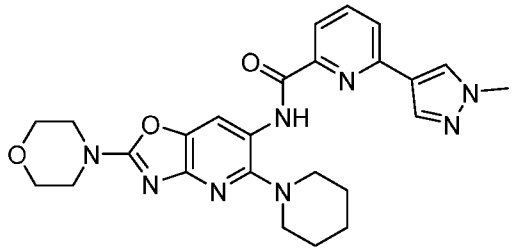


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 6) (70mg, 0.230 mmol), was coupled with 2-(6-methylpyridin-3-yl)oxazole-4-carboxylic acid (intermediate 13) (57mg, 0.276 mmol) using EDCI.HCl (67mg, 0.346 mmol), HOBt (47mg, 0.346 mmol), DIPEA (0.201mL, 1.153 mmol) in DMF (2mL) to afford crude product. This was then purified by prep HPLC to get the title compound (30mg, 24.79%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.85 (s, 1H), 9.147-9.142 (d, 1H), 9.04 (s, 1H), 8.64 (s, 1H), 8.37-8.35 (dd, 1H), 7.64-7.62 (d, 1H), 3.74-3.72 (m, 4H), 3.64-3.62 (m, 4H), 3.15-2.90 (m, 4H), 2.62 (s, 3H), 1.90-1.75 (m, 4H), 1.70-1.55 (m, 2H). **LCMS:** 98.39%, m/z = 490.0 $(M+1)^+$. **HPLC:** 95.97%.

Example 36

6-(1-methyl-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide

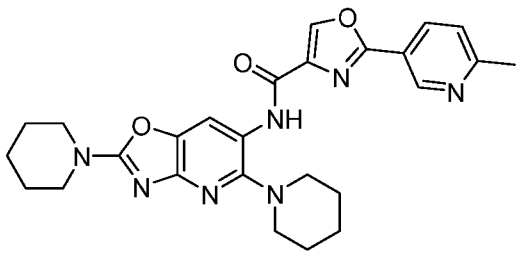


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 6) (80mg, 0.2640 mmol), was coupled with 6-(1-methyl-1H-pyrazol-4-yl)picolinic acid (intermediate 4) (65mg, 0.3168 mmol) using EDCI.HCl (76mg, 0.3960 mmol), HOBt (38mg, 0.2772 mmol), DIPEA (0.103mg, 0.7920 mmol) in DMF (4mL) to afford title compound (75mg, 58.59%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 10.9 (s, 1H), 8.70 (s, 1H), 8.43 (s, 1H), 8.22 (s, 1H), 8.10-7.90 (m, 3H), 4.00 (s, 3H), 3.80-3.70 (m, 4H), 3.69-3.60 (m, 4H), 3.0 (s, 4H), 1.80 (s, 4H), 1.55 (s, 2H). **LCMS:** 100%, m/z = 489.3 $(M+1)^+$. **HPLC:** 96.26%.

Example 37

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-methylpyridin-3-yl)oxazole-4-carboxamide

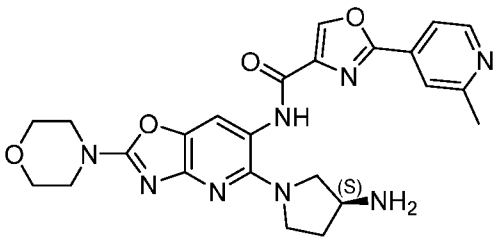


Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 4 of example 4) (80mg, 0.265 mmol), was coupled with 2-(2-methylpyridin-5-yl)oxazole-5-carboxylic acid (intermediate 13) (60mg, 0.292 mmol) using EDCI.HCl (77mg, 0.398 mmol), HOBt (38mg, 0.279 mmol), DIPEA (0.102mg, 0.797 mmol) in DMF (4mL) to afford the title compound (90mg, 69.7%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.83 (s, 1H), 9.11 (s, 1H), 9.00 (s, 1H), 8.61 (s, 1H), 8.27-8.25 (dd, 1H), 7.54-7.52 (d, 1H), 3.63 (s, 4H), 2.94-2.93 (t, 4H), 2.58 (s, 3H), 1.82 (s, 4H), 1.63 (s, 8H). **LCMS:** 98.89%, m/z = 488.2 $(M+1)^+$. **HPLC:** 98.54%.

Example 38

(S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of tert-butyl (S)-(1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate

In a round bottom flask, taken 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (product of step 5 of example 2) (157mg, 0.555 mmol), tert-butyl (S)-pyrrolidin-3-ylcarbamate (125mg, 0.555 mmol) potassium carbonate (238mg, 1.722 mmol) and DMF (5mL) and stirred at RT overnight. The ice water was added and filtered the solid and dried under vacuum to afford the crude product which was used as such for next step.

LCMS: m/z = 435.2 $(M+1)^+$. **HPLC:** 80.36%.

Step 2:Preparation of tert-butyl (S)-(1-(6-amino-2-morpholinooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate

The crude tert-butyl (S)-(1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate obtained above was dissolved in methanol (30mL) and added 10% Pd/C (25mg) and stirred under hydrogen balloon for two hours. The reaction mass was filtered through Celite® and concentrated to get the title compound (71mg, 32%).

LCMS: m/z = 405.2 $(M+1)^+$.**HPLC:**79.86%.

Step 3: Preparation of tert-butyl (S)-(1-(6-(2-(2-methylpyridin-4-yl)oxazole-4-carboxamido)-2-morpholinooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate

Using the same reaction conditions as described in step 6 of example 1, tert-butyl (S)-(1-(6-amino-2-morpholinooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate (70mg, 0.341 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (115mg, 0.284

mmol) using EDCI.HCl (98mg, 0.512 mmol), HOBt (46mg, 0.341 mmol), DIPEA (0.148mg, 1.1384 mmol) in DMF (4mL) to get the title compound (152mg, 91%).

LCMS: m/z = 591.6 $(M+1)^+$. **HPLC:** 86.43%.

Step 4: Preparation of (S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride

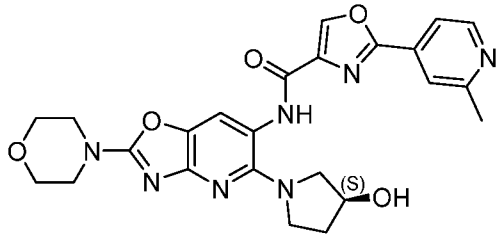
Using the same reaction conditions as described in step 8 of example 1, tert-butyl (S)-(1-(6-(2-(2-methylpyridin-4-yl)oxazole-4-carboxamido)-2-morpholinooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate (150mg, 0.2542 mmol) was deprotected using methanolic HCl (5mL) to get the crude product. This was then purified by prep HPLC to get the title compound (58mg, 97%).

^{1}HNMR (CD_3OD, 400MHz): δ 8.97 (s, 1H), 8.93-8.91 (d, 1H), 8.64 (s, 1H), 8.56-8.55 (d, 1H), 8.02 (s, 1H), 4.02-3.67 (m, 13H), 2.90 (s, 3H), 2.50-2.40 (m, 1H), 2.25-2.05 (m, 1H).

LCMS: 96.74%, m/z = 491.4 $(M+1)^+$. **HPLC:** 95.27%.

Example 39

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of (S)-1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol

Using the same reaction conditions as described in step 1 of example 38, 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (product of step 5 of example 2) (200mg, 0.704 mmol) was substituted with(S)-pyrrolidin-3-ol (61mg, 0.704 mmol) using potassium carbonate (291mg, 2.112 mmol) and DMF (5mL) to afford the title product (195mg, 82%) **LCMS:** m/z = 335.9 $(M+1)^+$.

Step 2: Preparation of (S)-1-(6-amino-2-morpholinooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol

Using the same reaction conditions as described in step 2 of example 38, (S)-1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol (194mg, 0.579 mmol) was reduced using 10% Pd/C (50mg) in methanol (40mL) to get the title compound (162mg, 92%). **LCMS:** m/z = 306.1 $(M+1)^+$.

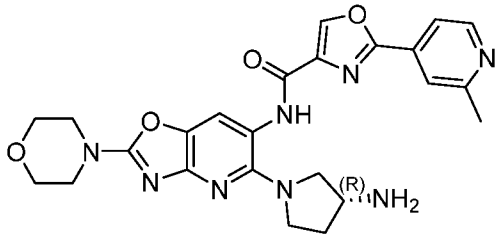
Step 3: Preparation of (S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, (S)-1-(6-amino-2-morpholinooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol (160mg, 0.526 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (108mg, 0.526 mmol) using EDCI.HCl (151mg, 0.789 mmol), HOBt (75mg, 0.5523 mmol), DIPEA (0.272mg, 2.104 mmol) in DMF (5mL) to get the title compound (45mg, 17%).

^{1}HNMR (CD_3OD, 400MHz): δ 8.70 (s, 1H), 8.64-8.63 (d, 1H), 8.02 (s, 1H), 7.94-7.93 (d, 1H), 7.87 (s, 1H), 4.49-4.45 (m, 1H), 3.84-3.71 (m, 10H), 3.70-3.47 (m, 2H), 2.67 (s, 3H), 2.13-2.10 (m, 1H), 2.00-1.80 (m, 1H). **LCMS:** 100%, m/z = 492.2 $(M+1)^+$. **HPLC:** 97.90%.

Example 40

(R)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of tert-butyl (R)-(1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate

Using the same reaction conditions as described in step 1 of example 38, 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (product of step 5 of example 2) (126mg, 0.444 mmol) was substituted with tert-butyl (R)-pyrrolidin-3-ylcarbamate (100mg, 0.444 mmol) using potassium carbonate (183mg, 1.33 mmol) and DMF (5mL) to afford the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 1% methanol in DCM as eluent to obtain the title compound (127mg, 66%). **LCMS:** m/z = 435.2 $(M+1)^+$.

Step 2: Preparation of tert-butyl (R)-(1-(6-amino-2-morpholinooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate

Using the same reaction conditions as described in step 2 of example 38, (R)-(1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate (126mg, 0.290 mmol) was reduced using 10% Pd/C (25mg) in methanol (20mL) to get the title compound (102mg, 87%). **LCMS:** m/z = 405.3 $(M+1)^+$.

Step 3: Preparation of tert-butyl (R)-(1-(6-(2-(2-methylpyridin-4-yl)oxazole-4-carboxamido)-2-morpholinooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate

Using the same reaction conditions as described in step 6 of example 1, tert-butyl (R)-(1-(6-amino-2-morpholinooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate (100mg, 0.2475 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (51mg, 0.2475 mmol) using EDCI.HCl (72mg, 0.3712 mmol), HOBt (35mg, 0.2599 mmol), DIPEA (0.128mg, 0.990 mmol) in DMF (5mL) to get the title compound (73mg, 51%). **LCMS:** m/z = 591.1 $(M+1)^+$.

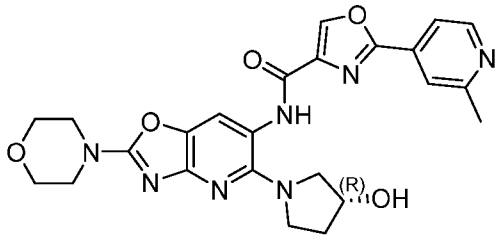
Step 4: Preparation of (R)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride

Using the same reaction conditions as described in step 8 of example 1, tert-butyl (R)-(1-(6-(2-(2-methylpyridin-4-yl)oxazole-4-carboxamido)-2-morpholinooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate (73mg, 0.123 mmol) was deprotected using methanolic HCl (5mL) to get the title compound (32mg, 53%).

^{1}HNMR (CD_3OD, 400MHz): δ 9.72 (s, 1H), 8.65-8.63 (d, 1H), 8.01 (s, 1H), 7.93-7.90 (t, 2H), 3.84-3.81 (t, 4H), 3.70-3.64 (m, 7H), 3.60-3.50 (m, 2H), 2.67 (s, 3H), 2.30-2.20 (m, 1H), 1.90-1.80 (m, 1H). **LCMS:** 96.75%, m/z = 491.2 $(M+1)^+$. **HPLC:** 95.80%.

Example 41

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of (R)-1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol

Using the same reaction conditions as described in step 1 of example 38, 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (product of step 5 of example 2) (200mg, 0.704 mmol) was substituted with (R)-pyrrolidin-3-ol (61mg, 0.704 mmol) using potassium carbonate (291mg, 2.112 mmol) and DMF (5mL) to afford the title product (231mg, 98.7%). **LCMS:** m/z = 336.1 $(M+1)^+$.

Step 2: Preparation of (R)-5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine

To the solution of (R)-1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol (230mg, 0.698 mmol) in DMF (5mL) was added TBDMS chloride (124mg, 0.822 mmol) and imidazole (116mg, 1.70 mmol) and stirred at RT overnight. Reaction mass was quenched with water and extracted with ethyl acetate to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 1% methanol in DCM as eluent to obtain the title compound (310mg, 99%). **LCMS:** m/z = 450.3 $(M+1)^+$.

Step 3: Preparation of (R)-5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 2 of example 38, (R)-5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (308mg, 0.685 mmol) was reduced using 10% Pd/C (30mg) in methanol (20mL) to get the title compound (235mg, 81%). **LCMS:** m/z = 420.2 $(M+1)^+$.

Step 4: Preparation of (R)-N-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, (R)-5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine (234mg, 0.5587 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (114mg, 0.5584 mmol) using EDCI.HCl (180mg, 0.840 mmol), HOBt (81mg, 0.5863 mmol), DIPEA (0.290mg, 2.237 mmol) in DMF (5mL) to get the title compound (167mg, 50%). **LCMS:** m/z = 606.2 $(M+1)^+$.

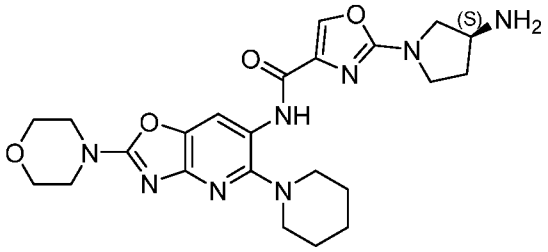
Step 5: Preparation of (R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 8 of example 1, (R)-N-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide (167mg, 0.276 mmol) was deprotected using methanolic HCl (5mL) to get the title compound (106mg, 78%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 9.82 (s, 1H), 8.96 (s, 1H), 8.68-8.67 (d, 1H), 7.86 (s, 1H), 7.80-7.77 (d, 1H), 7.66 (s, 1H), 4.86 (s, 1H), 4.27 (s, 1H), 3.72-3.6.0 (m, 11H), 3.25-3.21 (m, 1H), 2.58 (s, 3H), 1.89-1.78 (m, 2H). **LCMS:** 98.95%, m/z = 492.2 $(M+1)^+$. **HPLC:** 95.08%.

Example 42

(S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide



Step 1: Preparation of tert-butyl (S)-(1-(4-((2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)carbamoyl)oxazol-2-yl)pyrrolidin-3-yl)carbamate

Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 6) (100mg, 0.3296 mmol), was coupled with (S)-2-(3-((tert-butoxycarbonyl)amino)pyrrolidin-1-yl)oxazole-4-carboxylic acid (intermediate 14) (147mg, 0.4944 mmol) using EDCI.HCl (95mg, 0.4944 mmol), HOBt (67mg, 0.4944 mmol), DIPEA (0.23mL, 1.3185 mmol) in DMF (2mL) to afford crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 1% methanol in DCM as eluent to obtain the title compound (130mg, 67.7%). **LCMS:** m/z = 583.5 $(M+1)^+$.

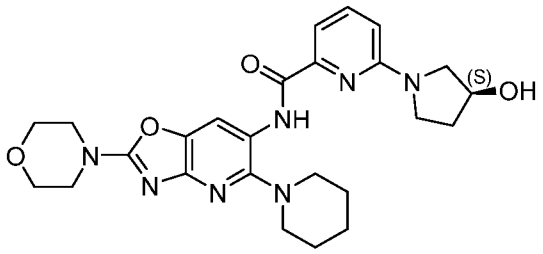
Step 2: Preparation of (S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 8 of example 1, tert-butyl (S)-(1-(4-((2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)carbamoyl)oxazol-2-yl)pyrrolidin-3-yl)carbamate (130mg, 4.482 mmol) was deprotected using TFA (5mL) and DCM (5mL) to get the title compound (73mg, 68.22%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.90 (s, 1H), 8.77 (s, 1H), 7.82 (s, 1H), 3.81-3.73 (m, 10H), 3.69-3.59 (m, 1H), 3.38-3.28 (m, 1H), 3.02 (s, 4H), 2.30-2.15 (m, 1H), 1.82 (m, 5H), 1.70-1.60 (m, 3H). **LCMS:** 99.52%, m/z = 483.2 $(M+1)^+$. **HPLC:** 98.70%.

Example 43

(S)-6-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide



Step 1: Preparation of 6-bromo-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide

Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 6) (400mg, 1.3245 mmol), was coupled with 6-bromopicolinic acid (321mg, 1.5894 mmol) using EDCI.HCl (321mg, 1.9867 mmol), HOBt (268mg, 1.9867 mmol), DIPEA (683mg, 5.2980 mmol) in DMF (20mL) to afford the title compound (487mg, 75%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 10.86 (s, 1H), 8.82 (s, 1H), 8.24-8.22 (d, 1H), 7.80-7.86 (t, 1H), 7.67-7.65 (d, 1H), 3.83-3.73 (m, 8H), 3.06-3.03 (t, 4H), 1.90-1.88 (m, 4H), 1.70-1.60 (m, 2H). **LCMS:** m/z = 489.1 $(M+2)^+$. **HPLC:** 97.69%.

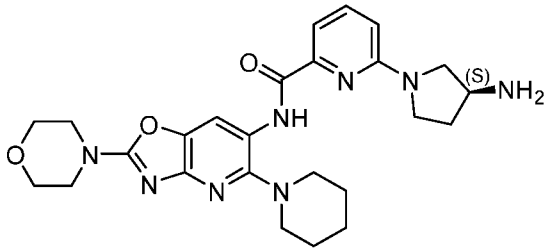
Step 2: Preparation of (S)-6-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide

The mixture of 6-bromo-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide (130mg, 0.2269 mmol), (S)-pyrrolidin-3-ol (35mg, 0.4 mmol) and sodium carbonate (85mg, 0.8 mmol) in DMF (2mL) was heated at 140°C for 12h. The reaction was quenched with ice water, filtered and purified by 60-120 silica gel column chromatography using 1% methanol in DCM as eluent to obtain the title compound (80mg, 60.79%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 10.66 (s, 1H), 8.83 (s, 1H), 7.64-7.62 (t, 1H), 7.58-7.56 (d, 1H), 6.58-6.56 (d, 1H), 3.83-3.79 (m, 4H), 3.76-3.72 (m, 7H), 3.04-3.03 (m, 4H), 2.30-2.10 (m, 2H), 1.77-1.72 (m, 4H), 1.61-1.57 (m, 3H). **LCMS:** 96.72%, m/z = 494.2 $(M+1)^+$. **HPLC:** 98.60%.

Example 44

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide



Step 1: Preparation of tert-butyl (S)-(1-(6-((2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)carbamoyl)pyridin-2-yl)pyrrolidin-3-yl)carbamate

Using the same reaction conditions as described in step 2 of example 43, 6-bromo-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide (product of step 2 of example 6) (100mg, 0.2053 mmol) was substituted with tert-butyl (S)-pyrrolidin-3-ylcarbamate (57mg, 0.3080 mmol) using sodium carbonate (65mg, 0.6160 mmol) in DMF (2mL) at 140°C for 12h to obtain the title compound (60mg, 49.34%).

Step 2: Preparation of (S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide

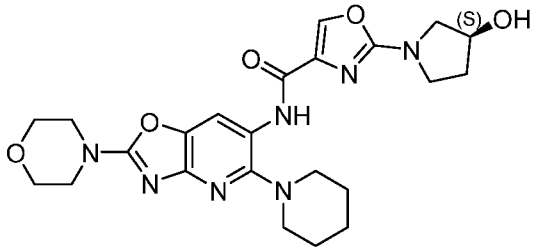
Using the same reaction conditions as described in step 8 of example 1, tert-butyl (S)-(1-(6-((2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)carbamoyl)pyridin-2-yl)pyrrolidin-3-yl)carbamate (60mg, 0.1013 mmol) was deprotected using TFA (2mL) and DCM (2mL) to get the title compound (30mg, 60.16%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 10.70 (s, 1H), 8.84 (s, 1H), 7.65-7.61 (t, 1H), 7.57-7.55 (d, 1H), 6.56-6.54 (d, 1H), 3.87-3.63 (m, 9H), 3.39-3.37 (m, 1H), 3.04-3.01 (t, 4H), 2.28-2.25 (m, 2H), 1.90-1.87 (m, 1H), 1.771-1.76 (m, 5H), 1.60-1.56 (m, 3H).

LCMS: 98.72%, m/z = 493.3 $(M+1)^+$. **HPLC:** 97.84%.

Example 45

(S)-2-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

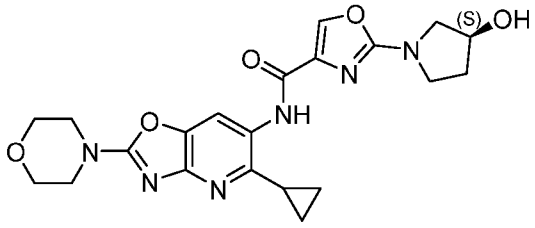


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 6) (100mg, 0.3296 mmol), was coupled with (S)-2-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)oxazole-4-carboxylic acid (intermediate 15) (124mg, 0.3955 mmol) using EDCI.HCl (95mg, 0.4944 mmol), HOBt (67mg, 0.4944 mmol), DIPEA (0.23mL, 1.3185 mmol) in DMF (2mL) to afford crude product. Using the same reaction conditions as described in step 8 of example 1, this crude product was deprotected using methanolic HCl (5mL) to get the title compound (128mg, 80.5%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 9.78 (s, 1H), 8.76 (s, 1H), 7.82 (s, 1H), 4.70-4.60 (m, 1H), 3.82-3.56 (m, 12H), 3.03-3.00 (t, 4H), 2.19-2.11 (m, 2H), 1.81-1.78 (m, 6H). **LCMS:** 95.04%, m/z = 484.2 $(M+1)^+$. **HPLC:** 95.55%.

Example 46

(S)-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxamide



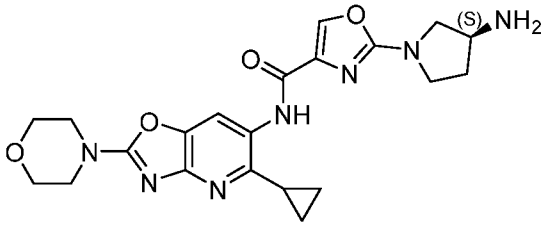
Using the same reaction conditions as described in example 45, 5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-amine (product of step 7 of example 2) (100mg, 0.384 mmol), was coupled with (S)-2-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)oxazole-4-carboxylic acid (intermediate 15) (145mg, 0.4615 mmol) using EDCI.HCl (110mg, 0.5769 mmol), HOBt (78mg, 0.5769 mmol), DIPEA (0.268mL, 1.5384 mmol) in DMF (2mL) followed by deprotection using methanolic HCl (5mL) to get the title compound (56mg, 50.4%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 9.17 (s, 1H), 8.33 (s, 1H), 7.84 (s, 1H), 4.70-4.60 (m, 1H), 3.82-3.56 (m, 12H), 2.13-2.03 (m, 3H), 1.86-1.84 (d, 1H), 1.16-1.13 (m, 2H), 1.04-1.00 (m, 2H).

LCMS: 93.32%, m/z = 440.8 $(M+1)^+$. **HPLC:** 95.51%.

Example 47

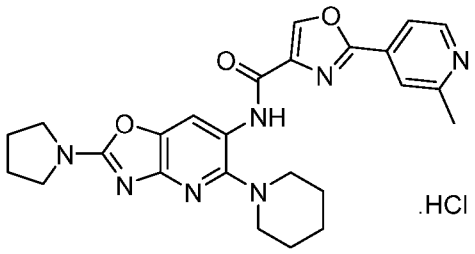
(S)-2-(3-aminopyrrolidin-1-yl)-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide



Using the same reaction conditions as described in example 45, 5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-amine (product of step 7 of example 2) (100mg, 0.384 mmol), was coupled with (S)-2-(3-((tert-butoxycarbonyl)amino)pyrrolidin-1-yl)oxazole-4-carboxylic acid (intermediate 14) (137mg, 0.4615 mmol) using EDCI.HCl (110mg, 0.5769 mmol), HOBt (78mg, 0.5769 mmol), DIPEA (0.268mL, 1.5384 mmol) in DMF (2mL) followed by deprotection using TFA (5mL) and DCM (5mL) to get the title compound (27mg, 18.49%). **^{1}HNMR** ($CDCl_3$, 400MHz): δ 9.17 (s, 1H), 8.34 (s, 1H), 7.83 (s, 1H), 3.82-3.72 (m, 10H), 3.61-3.59 (m, 1H), 3.29-3.26 (m, 1H), 2.30-2.18 (m, 2H), 2.10-2.00 (m, 1H), 1.90-1.78 (m, 1H), 1.16-1.15 (m, 2H), 1.04-1.00 (m, 2H). **LCMS:** 100%, m/z = 440.2 $(M+1)^+$. **HPLC:** 98.06%.

Example 48

2-(2-methylpyridin-4-yl)-N-(5-(piperidin-1-yl)-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride



Step 1:Preparation of 5-chloro-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 3 of example 1, 5-chloro-2-(methylthio)oxazolo[4,5-b]pyridine (250mg) was substituted using pyrrolidine (2mL) and THF (5mL) at 75°C for 2h to afford the title compound (250mg).

^{1}HNMR ($CDCl_3$, 400MHz): δ 7.35-7.33 (d, 1H), 6.89-6.87 (d, 1H), 3.70-3.60 (m, 4H), 2.10-2.00 (m, 4H). **LCMS:** m/z = 224.1 $(M+1)^+$.

Step 2:Preparation of 5-chloro-6-nitro-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 4 of example 20, 5-chloro-6-nitro-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridine (250mg, 1.121 mmol) was nitrated using potassium nitrate (226mg, 2.242 mmol) and conc. sulphuric acid (3mL) at RT for 24h to afford the crude title compound (180mg, 60%).

Step 3:Preparation of 6-nitro-5-(piperidin-1-yl)-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 1 of example 6, 5-chloro-6-nitro-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridine (180mg, 0.6716 mmol) was substituted using piperidine (57mg) in THF (3mL) at RT for 12h to obtain the title compound (150mg, 70.7%). **LCMS:** m/z = 318.45 $(M+1)^+$.

Step 4:Preparation of 5-(piperidin-1-yl)-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 6-nitro-5-(piperidin-1-yl)-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridine (150mg, 0.4731 mmol) was reduced with zinc dust (247mg, 3.7854 mmol) and ammonium chloride (404mg, 7.5696 mmol) in THF/methanol/H_2O (5m/1mL/0.5mL) to get the crude title product (152mg). **LCMS:** m/z = 288.2 $(M+1)^+$.

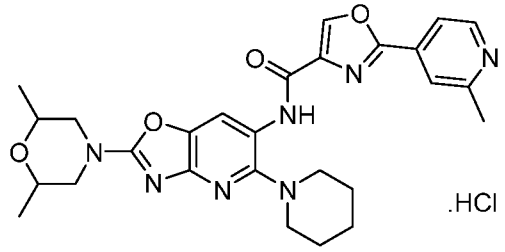
Step 5: Preparation of 2-(2-methylpyridin-4-yl)-N-(5-(piperidin-1-yl)-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride

Using the same reaction conditions as described in step 6 of example 1, 5-(piperidin-1-yl)-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (150mg, 0.5226 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (127mg, 0.6271 mmol) using EDCI.HCl (149mg, 0.7839 mmol), HOBt (108mg, 0.7839 mmol), DIPEA (0.18mL, 1.0452 mmol) in DMF (2mL) to afford the crude product. The resultant crude was purified by prep HPLC and treated with methanolic HCl to obtain the title compound (38mg, 14.28%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 13.4-12.8 (bs, 1H), 11.80 (s, 1H), 9.19 (s, 1H), 8.74 (s, 1H), 8.47-8.42 (m, 2H), 7.93 (s, 1H), 3.74 (s, 4H), 3.65 (s, 4H), 3.08 (s, 3H), 2.48 (s, 2H), 2.12 (s, 4H), 1.99 (s, 2H), 1.90-1.70 (m, 2H). **LCMS:** 100%, m/z = 474.2 $(M+1)^+$. **HPLC:** 97.93%.

Example 49

N-(2-(2,6-dimethylmorpholino)-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride



Step 1:Preparation of 5-chloro-2-(2,6-dimethylmorpholino)oxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 3 of example 1, 5-chloro-2-(methylthio)oxazolo[4,5-b]pyridine (product of step 3 example 2) (250mg, 1.25 mmol) was substituted using 2,6-dimethylmorpholine (2mL) and THF (5mL) at 75°C for 2h to afford the title compound (251mg).

^{1}HNMR ($CDCl_3$, 400MHz): δ 7.38-7.36 (d, 1H), 6.94-6.92 (d, 1H), 4.17-4.14 (d, 2H), 3.75-3.68 (m, 2H), 2.90-2.84 (t, 2H), 1.27-1.26 (d, 6H). **LCMS:** m/z = 268.0 $(M+1)^+$.

Step 2:Preparation of 5-chloro-2-(2,6-dimethylmorpholino)-6-nitrooxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 4 of example 20, 5-chloro-2-(2,6-dimethylmorpholino)oxazolo[4,5-b]pyridine (250mg, 0.9363 mmol) was nitrated using potassium nitrate (189mg, 1.8726 mmol) and conc. sulphuric acid (3mL) at RT for 24h to afford the title compound (150mg, 51.3%). **LCMS:** m/z = 313.0 $(M+1)^+$.

Step 3:Preparation of 2-(2,6-dimethylmorpholino)-6-nitro-5-(piperidin-1-yl)oxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 1 of example 6, 5-chloro-2-(2,6-dimethylmorpholino)-6-nitrooxazolo[4,5-b]pyridine (150mg, 0.1602 mmol) was substituted using piperidine (45mg) in THF (3mL) at RT for 12h to obtain the title compound (152mg, 86.2%).

LCMS: m/z = 362.4 $(M+1)^+$.

Step 4:Preparation of 2-(2,6-dimethylmorpholino)-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 2-(2,6-dimethylmorpholino)-6-nitro-5-(piperidin-1-yl)oxazolo[4,5-b]pyridine (152mg, 0.4143 mmol)

was reduced with zinc dust (216mg, 3.3147 mmol) and ammonium chloride (353mg, 6.6288 mmol) in THF/methanol/H_2O (5mL/1mL/0.5mL) to get the crude title compound (160mg).

^{1}HNMR ($CDCl_3$, 400MHz): δ 6.96 (s, 1H), 4.11-4.07 (dd, 2H), 3.74-3.70 (m, 2H), 3.02-3.01 (m, 4H), 2.83-2.77 (t, 2H), 1.76-1.68 (m, 4H), 1.64-1.56 (m, 2H), 1.26-1.24 (d, 6H). **LCMS:** m/z = 332.2 $(M+1)^+$.

Step 5: Preparation of N-(2-(2,6-dimethylmorpholino)-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride

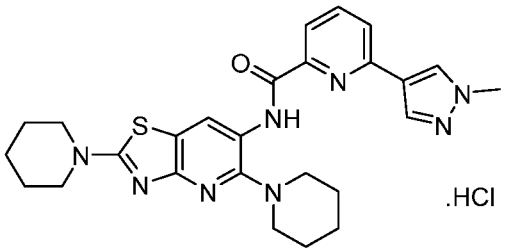
Using the same reaction conditions as described in step 6 of example 1, 2-(2,6-dimethylmorpholino)-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine(152mg, 0.6024 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (147mg, 0.7228 mmol) using EDCI.HCl (172mg, 0.9036 mmol), HOBt (125mg, 0.9036 mmol), DIPEA (0.2mL, 1.2048 mmol) in DMF (2mL) to afford the crude product. The resultant crude was purified by prep HPLC and treated with methanolic HCl to obtain the title compound (80mg).

^{1}HNMR ($CDCl_3$, 400MHz): δ 13.15-12.90 (bs, 1H), 11.90 (s, 1H), 9.18 (s, 1H), 8.74 (s, 1H), 8.46-8.42 (d, 1H), 7.96 (s, 1H), 4.21-4.18 (m, 2H), 3.76-3.60 (m, 6H), 3.08 (s, 3H), 2.99-2.92 (t, 2H), 2.60-2.41 (m, 2H), 2.08-1.90 (m, 2H), 1.60-1.80 (m, 2H), 1.29-1.27 (d, 6H).

LCMS: 100%, m/z = 518.5 $(M+1)^+$. **HPLC:** 98.81%.

Example 50

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)picolinamide hydrochloride

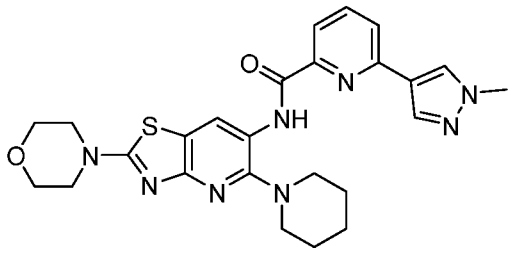


Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 4 of example 22) (70mg, 0.220 mmol) was coupled 6-(1-methyl-1H-pyrazol-4-yl)picolinic acid (intermediate 4) (53mg, 0.264 mmol) using EDCI.HCl (63mg, 0.33 mmol), HOBt (45mg, 0.33 mmol), DIPEA (78mg, 0.66 mmol) in DMF (5mL) to afford the crude product. The resultant crude was purified by prep HPLC and treated with methanolic HCl to obtain the title compound (25mg, 21.2%).

^{1}HNMR (CD_3OD, 300MHz): δ 9.01 (s, 1H), 8.42 (s, 1H), 8.30 (s, 1H), 8.10-8.01 (m, 2H), 7.92-7.89 (dd, 1H), 4.01 (s, 3H), 3.80 (s, 4H), 3.39-3.30 (m, 4H), 1.82 (s, 10H), 1.69-1.67 (d, 2H). **LCMS:** 98.92%, m/z = 503.3 $(M+1)^+$. **HPLC:** 98.03%.

Example 51

6-(1-methyl-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide

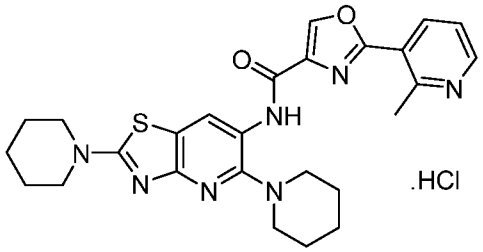


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 6 of example 20) (70mg, 0.313 mmol) was coupled with 6-(1-methyl-1H-pyrazol-4-yl)picolinic acid (intermediate 4) (53mg, 0.262 mmol) using EDCI.HCl (62mg, 0.327 mmol), HOBt (45mg, 0.327 mmol), DIPEA (85mg, 0.654 mmol) in DMF (5mL) to afford the crude coupled product. The resultant crude was purified by prep HPLC to obtain the title compound (35mg, 30%).

^{1}HNMR (CD_3OD, 300MHz): δ 8.96 (bs, 1H), 8.46 (s, 1H), 8.34 (s, 1H), 8.11-8.01 (m, 2H), 7.94-7.91 (d, 1H), 4.02 (s, 3H), 3.88-3.82 (m, 8H), 3.55-3.21 (m, 4H), 1.87 (s, 4H), 1.80-1.60 (m, 2H). **LCMS:** 82.87%, m/z = 505.2 $(M+1)^+$. **HPLC:** 97.63%.

Example 52

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-3-yl)oxazole-4-carboxamide hydrochloride



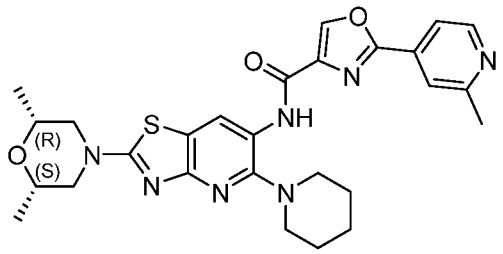
Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 4 of example 22) (70mg, 0.220 mmol) was coupled with 2-(2-methylpyridin-3-yl)oxazole-4-carboxylic acid (intermediate 8) (50mg, 0.242

mmol) using EDCI.HCl (63mg, 0.33 mmol), HOBt (45mg, 0.33 mmol), DIPEA (85mg, 0.66 mmol) in DMF (5mL) to afford the crude product. The resultant crude was purified by prep HPLC and treated with methanolic HCl to obtain the title compound (30mg, 27.2%).

^{1}HNMR (CD_3OD, 400MHz): δ 9.21-9.19 (d, 2H), 8.91-8.88 (m, 3H), 8.80 (bs, 1H), 8.15-8.11 (t, 2H), 3.78 (s, 8H), 3.18 (s, 3H), 1.80 (s, 8H), 1.71-1.70 (m, 4H). **LCMS:** 85.44%, m/z = 504.2 $(M+1)^+$. **HPLC:** 98.54%.

Example 53

N-(2-((2S,6R)-2,6-dimethylmorpholino)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of (2R, 6S)-4-(5-chlorothiazolo[4,5-b]pyridin-2-yl)-2,6-dimethylmorpholine

Using the same reaction conditions as described in step 3 of example 1, 5-chloro-2-(methylthio)thiazolo[4,5-b]pyridine (product of step 2 of example 20) (170mg, 0.784 mmol) was substituted using (2R,6S)-2,6-dimethylmorpholine (1mL) and THF (2mL) at 75°C for 16h to afford the crude title compound (260mg). **LCMS:** m/z = 284.1 $(M+1)^+$.

Step 2:Preparation of (2R,6S)-4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)-2,6-dimethylmorpholine

Using the same reaction conditions as described in step 4 of example 20, (2R,6S)-4-(5-chlorothiazolo[4,5-b]pyridin-2-yl)-2,6-dimethylmorpholine (260mg, 0.916 mmol) was nitrated using potassium nitrate (277mg, 2.74 mmol) and conc. sulphuric acid (5mL) at RT for 2 days to afford the crude title compound (120mg). **LCMS:** m/z = 328.9 $(M+1)^+$.

Step 3:Preparation of (2R,6S)-2,6-dimethyl-4-(6-nitro-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 1 of example 6, (2R,6S)-4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)-2,6-dimethylmorpholine (120mg, 0.365 mmol) was

substituted using piperidine (0.5mL) in THF (2mL) at RT for 30min to obtain the title compound (190mg). m/z = 378.0 $(M+1)^+$.

Step 4:Preparation of 2-((2R,6S)-2,6-dimethylmorpholino)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, (2R,6S)-2,6-dimethyl-4-(6-nitro-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-2-yl)morpholine (190mg, 0.503 mmol) was reduced with zinc dust (260mg, 4.026 mmol) and ammonium chloride (430mg, 8.04 mmol) in THF/methanol/H_2O (3mL/0.8mL/0.3mL) to get the crude product (170mg). **LCMS:** m/z = 348.2 $(M+1)^+$.

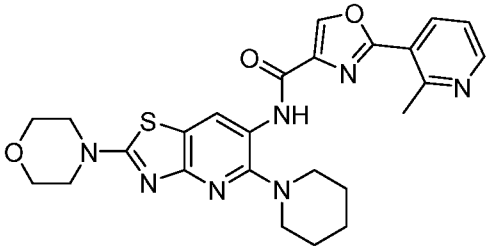
Step 5: Preparation of N-(2-((2S,6R)-2,6-dimethylmorpholino)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride

Using the same reaction conditions as described in step 6 of example 1, 2-((2R,6S)-2,6-dimethylmorpholino)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (85mg, 0.244 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (60mg, 0.293 mmol) using EDCI.HCl (70mg, 0.366 mmol), HOBt (50mg, 0.366 mmol), DIPEA (0.94mg, 0.732 mmol) in DMF (2mL) to afford the crude product. The resultant crude was purified by prep HPLC and treated with methanolic HCl to obtain the title compound (25mg, 19.20%).

^{1}HNMR (CD_3OD, 300MHz): δ 9.05 (s, 1H), 8.90-8.85 (d, 1H), 8.70 (s, 1H), 8.60 (s, 1H), 8.58-8.45 (d, 1H), 4.06-3.97 (m, 2H), 3.85-3.79 (m, 2H), 3.49 (s, 4H), 3.21-3.05 (t, 2H), 2.93 (s, 3H), 1.89 (s, 4H), 1.76 (s, 2H), 1.29-1.21 (d, 6H). **LCMS:** 98.99%, m/z = 534.3 $(M+1)^+$. **HPLC:** 96.10%.

Example 54

2-(2-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

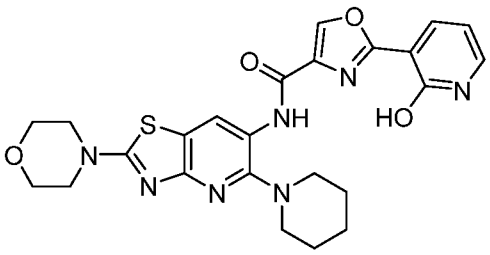


Using the same reaction conditions as described in step 6 of example 1,2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 6 of example 20) (70mg, 0.219 mmol) was coupled with 2-(2-methylpyridin-3-yl)oxazole-4-carboxylic acid (intermediate 8) (45mg, 0.219 mmol) using EDCI.HCl (63mg, 0.329 mmol), HOBt (45mg, 0.329 mmol), DIPEA (71mg, 0.548 mmol) in DMF (5mL) to afford the crude title compound. The resultant crude was purified by prep HPLC to obtain the title compound (35mg, 30%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.70 (s, 1H), 9.12 (s, 1H), 8.95 (s, 1H), 8.82-8.74 (d, 1H), 8.68-8.62 (d, 1H), 7.83-7.72 (t, 1H), 3.74-3.72 (m, 4H), 3.59-3.57 (m, 4H), 3.08 (s, 3H), 2.99 (s, 4H), 1.74 (s, 4H), 1.65-1.52 (m, 2H). **LCMS:** 88.8%, m/z = 506.2 $(M+1)^+$. **HPLC:** 97.66%.

Example 55

2-(2-hydroxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

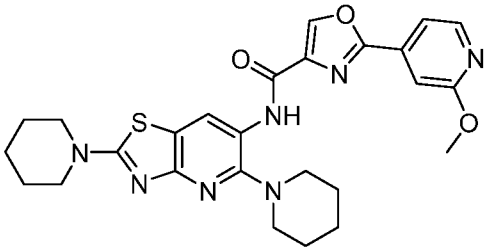


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 6 of example 20) (70mg, 0.219 mmol) was coupled with 2-(2-hydroxypyridin-3-yl)oxazole-4-carboxylic acid (intermediate 9) (45mg, 0.219 mmol) using EDCI.HCl (63mg, 0.329 mmol), HOBt (45mg, 0.329 mmol), DIPEA (71mg, 0.548 mmol) in DMF (5mL) to afford the crude title compound. The resultant crude was purified by prep HPLC to obtain the title compound (35mg, 31.5%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 12.40 (s, 1H), 9.62 (s, 1H), 8.97 (s, 1H), 8.89 (s, 1H), 8.23-8.21 (dd, 1H), 7.73-7.62 (m, 1H), 3.75-3.73 (m, 4H), 3.58-3.56 (m, 4H), 2.99-2.96 (, 4H), 1.80 (s, 4H), 1.68-1.53 (m, 2H). **LCMS:** 100%, m/z = 508.0 $(M+1)^+$. **HPLC:** 96.21%.

Example 56

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methoxypyridin-4-yl)oxazole-4-carboxamide

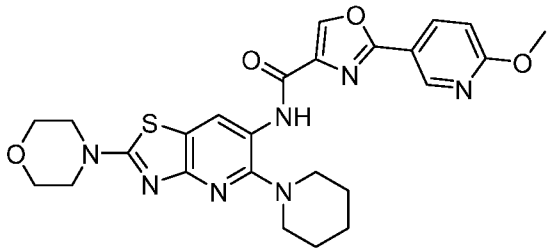


Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 4 of example 22) (70mg, 0.220 mmol) was coupled with 2-(2-methoxypyridin-4-yl)oxazole-4-carboxylic acid (intermediate 11) (53mg, 0.242 mmol) using EDCI.HCl (57mg, 0.30 mmol), HOBt (41mg, 0.30 mmol), DIPEA (85mg, 0.66 mmol) in DMF (5mL) to afford the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (13mg, 11%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 9.84 (s, 1H), 9.00 (s, 1H), 8.37 (s, 1H), 8.34-8.33 (d, 1H), 7.52-7.50 (dd, 1H), 7.38 (s, 1H), 4.01 (s, 3H), 3.66 (s, 4H), 3.12-3.09 (t, 4H), 1.88 (s, 4H), 1.69 (s, 8H). **LCMS:** 100%, m/z = 520.0 $(M+1)^+$. **HPLC:** 94.16%.

Example 57

2-(6-methoxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

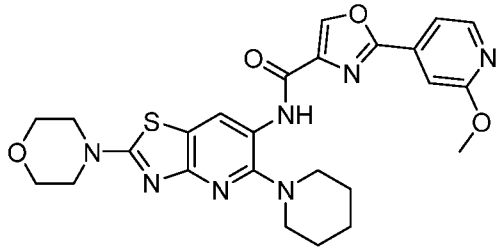


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 6 of example 20) (540mg, 1.692 mmol) was coupled with 2-(2-methoxypyridin-5-yl)oxazole-4-carboxylic acid (intermediate 7) (442mg, 2.031 mmol) using EDCI.HCl (484mg, 25.39 mmol), HOBt (228mg, 1.692 mmol), DIPEA (1.3g, 6.771 mmol) in DMF (5mL) to afford the title compound (400mg, 45%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.65 (s, 1H), 8.98-8.97 (d, 2H), 8.87 (s, 1H), 8.35-8.30 (dd, 1H), 7.117.09 (d, 1H), 3.96 (s, 3H), 3.75-3.73 (m, 4H), 3.59-3.58 (m, 4H), 3.10-3.00 (t, 4H), 1.82 (s, 4H), 1.20-1.10 (m, 2H). **LCMS:** 95.26%, m/z = 522.2 $(M+1)^+$. **HPLC:** 95.37%.

Example 58

2-(2-methoxypyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

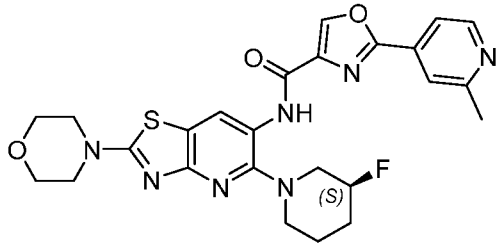


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 6 of example 20) (70mg, 0.22 mmol) was coupled with 2-(2-methoxypyridin-4-yl)oxazole-4-carboxylic acid (intermediate 11) (53mg, 0.242 mmol) using EDCI.HCl (63mg, 0.33 mmol), HOBt (45mg, 0.33 mmol), DIPEA (85mg, 0.66 mmol) in DMF (5mL) to afford the title compound (25mg, 21%).

^{1}HNMR (CD_3OD, 300MHz): δ 8.99 (s, 1H), 8.59 (s, 1H), 8.35-8.30 (d, 1H), 7.60-7.52 (d, 1H), 7.42 (s, 1H), 3.99 (s, 3H), 3.84-3.81 (t, 4H), 3.67-3.64 (t, 4H), 3.11-3.08 (t, 4H), 1.90-1.85 (m, 4H), 1.80-1.70 (m, 2H). **LCMS:** 88.28%, m/z = 522.2 $(M+1)^+$. **HPLC:** 91.56%.

Example 59

(S)-N-(5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1:Preparation of (S)-1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)piperidin-3-ol

Using the same reaction conditions as described in step 2 of example 43, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (250mg, 1.50 mmol) was substituted using (S)-piperidin-3-ol hydrochloride (137mg, 0.9976 mmol) using sodium carbonate (265mg, 2.4940 mmol) in DMF (2mL) at 140°C for 4h to obtain the title compound (190mg, 62.70%). **LCMS:** m/z = 366.1 $(M+1)^+$.

Step 2:Preparation of (S)-4-(5-(3-fluoropiperidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

DAST (0.17mL, 1.3013 mmol) was added to the cooled (-78°C) solution of (S)-1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)piperidin-3-ol (190mg, 0.5205 mmol) in DCM (5mL). The reaction was quenched with ice water after stirring at -78°C for 30min. The compound was extracted with DCM and purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent to obtain the title compound (100mg, 52.35%). **LCMS:** m/z = 368.1 $(M+1)^+$.

Step 3:Preparation of (S)-5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, (S)-4-(5-(3-fluoropiperidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (100mg, 0.2724 mmol) was reduced with zinc dust (143mg, 2.1798 mmol) and ammonium chloride (233mg, 4.3596 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the crude product (100mg). **LCMS:** m/z = 338.1 $(M+1)^+$.

Step 4: Preparation of (S)-N-(5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

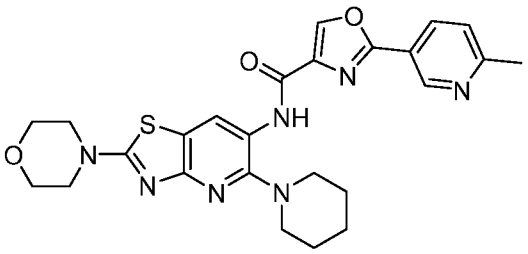
Using the same reaction conditions as described in step 6 of example 1, (S)-5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (100mg, 0.2724 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (84mg, 0.4087 mmol) using EDCI.HCl (79mg, 0.4087 mmol), HOBt (56mg, 0.4087 mmol), DIPEA (0.19mL, 1.0899 mmol) in DMF (2mL) to afford the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (26mg, 18.30%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.94 (s, 1H), 9.09 (s, 1H), 8.69-8.68 (d, 1H), 8.39 (s, 1H), 7.87 (s, 1H), 7.76-7.75 (d, 1H), 5.04-4.92 (m, 1H), 3.84-3.82 (t, 4H), 3.71-3.68 (t, 4H), 3.45-3.36 (m, 2H), 3.15-3.02 (m, 2H), 2.67 (s, 3H), 2.26-1.83 (m, 4H). **LCMS:** 97.00%, m/z = 524.1 $(M+1)^+$.

HPLC: 95.24%.

Example 60

2-(6-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

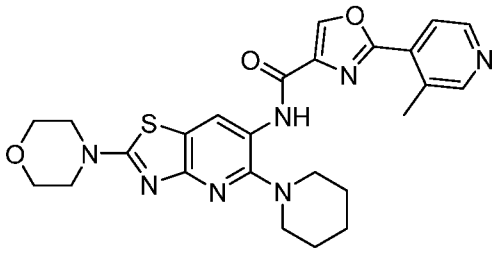


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 6 of example 20) (70mg, 0.22 mmol) was coupled with 2-(2-methylpyridin-5-yl)oxazole-4-carboxylic acid (intermediate 13) (54mg, 0.264 mmol) using EDCI.HCl (63mg, 0.33 mmol), HOBt (40mg, 0.33 mmol), DIPEA (85mg, 0.66 mmol) in DMF (5mL) to afford the title compound (30mg, 26%).

^{1}HNMR (CD_3OD, 400MHz): δ 9.36 (s, 1H), 9.08-9.05 (dd, 1H), 8.85 (s, 1H), 8.70 (s, 1H), 8.15-8.13 (d, 1H), 3.85-3.83 (t, 8H), 3.50-3.48 (m, 4H), 2.88 (s, 3H), 1.85 (s, 4H), 1.80-1.70 (m, 2H). **LCMS:** 98.51%, m/z = 506.2 $(M+1)^+$. **HPLC:** 94.43%.

Example 61

2-(3-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

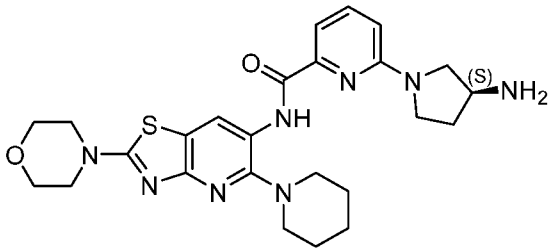


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 6 of example 20) (80mg, 0.25 mmol) was coupled with 2-(3-methylpyridin-4-yl)oxazole-4-carboxylic acid (intermediate 12) (61mg, 0.3 mmol) using EDCI.HCl (72mg, 0.376 mmol), HOBt (36mg, 0.263 mmol), DIPEA (97mg, 0.75 mmol) in DMF (3.4mL) to afford the title compound (29mg, 23%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.70 (s, 1H), 9.09 (s, 1H), 8.99 (s, 1H), 8.71 (s, 1H), 8.65-8.64 (d, 1H), 7.92-7.91 (d, 1H), 3.73-3.72 (m, 4H), 3.65-3.55 (m, 4H), 2.96-2.95 (m, 4H), 2.78 (s, 3H), 1.76 (s, 4H), 1.59 (s, 2H). **LCMS:** 99.47%, m/z = 506.2 $(M+1)^+$. **HPLC:** 98.79%.

Example 62

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide



Step 1:Preparation of 6-bromo-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide

Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 6 of example 20) (35mg, 0.994 mmol) was coupled with 6-bromopicolinic acid (301mg, 1.49 mmol) using EDCI.HCl (285mg, 1.49 mmol), HOBt (141mg, 1.04 mmol), DIPEA (384mg, 2.98 mmol) in DMF (10mL) to afford the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 1% methanol in DCM as eluent to obtain the title compound (220mg, 40%). **LCMS:** m/z = 503.0 $(M)^+$.

Step 2: Preparation of tert-butyl (S)-(1-(6-((2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)carbamoyl)pyridin-2-yl)pyrrolidin-3-yl)carbamate

Using the same reaction conditions as described in step 2 of example 43, 6-bromo-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide (70mg, 0.139 mmol) was substituted with tert-butyl (S)-pyrrolidin-3-ylcarbamate (39mg, 0.209 mmol) using sodium carbonate (59mg, 0.556 mmol) in DMF (3mL) at 140°C for 4h to obtain the title compound (40mg, 46.5%).

Step 3: Preparation of (S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide

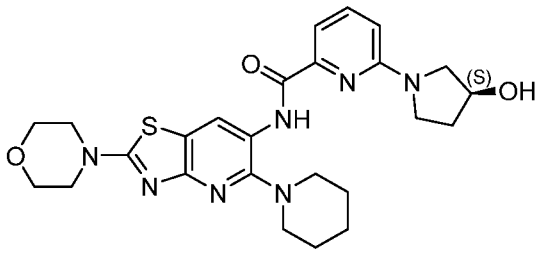
Using the same reaction conditions as described in step 8 of example 1, tert-butyl (S)-(1-(6-((2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)carbamoyl)pyridin-2-yl)pyrrolidin-3-yl)carbamate (65mg, 9.3655) was deprotected using TFA (2mL) and DCM (8mL) to get the title compound (45mg, 83.3%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 10.58 (s, 1H), 9.11 (s, 1H), 7.65-7.55 (m, 2H), 6.57-6.55 (d, 1H), 3.87-3.77 (m, 6H), 3.68-3.3.63 (m, 5H), 3.38-3.37 (m, 1H), 3.10-3.07 (t, 4H), 2.28-2.25 (m, 1H),

1.90-1.87 (m, 1H), 1.77 (s, 4H), 1.57-1.55 (m, 3H). **LCMS:** 100%, m/z = 509.1 $(M+1)^+$. **HPLC:** 95.95%.

Example 63

(S)-6-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide



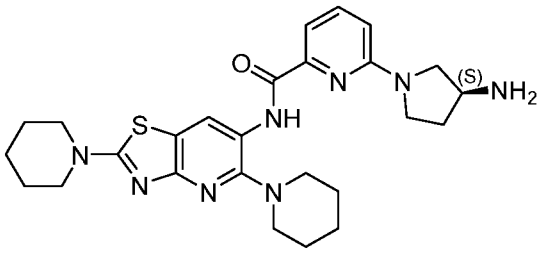
Using the same reaction conditions as described in step 2 of example 43, 6-bromo-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide (product of step 1 of example 63) (70mg, 0.139 mmol) was substituted with (S)-pyrrolidin-3-ol (19mg, 0.208 mmol) using sodium carbonate (59mg, 0.556 mmol) in DMF (3mL) at 140°C for 12h to obtain the title compound (50mg, 71.4%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 10.45 (s, 1H), 9.05 (s, 1H), 7.74-7.70 (t, 1H), 7.38-7.37 (d, 1H), 6.75-6.74 (d, 1H), 5.06-5.05 (d, 1H), 4.44 (s, 1H), 3.75-3.72 (m, 4H), 3.64-3.56 (m, 7H), 2.94-2.93 (d, 4H), 2.09-2.07 (m, 1H), 1.98-1.95 (m, 1H), 1.72 (s, 4H), 1.57 (s, 2H).

LCMS: 94.83%, m/z = 510.2 $(M+1)^+$. **HPLC:** 95.34%.

Example 64

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide



Step 1: Preparation of 6-bromo-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide

Using the same reaction conditions as described in step 6 of example 1, 2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 4 of example 22) (300mg, 0.946 mmol) was

coupled with 6-bromopicolinic acid (286mg, 1.419 mmol) using EDCI.HCl (270mg, 1.419 mmol), HOBt (191mg, 1.419 mmol), DIPEA (370mg, 2.838 mmol) in DMF (5mL) to afford the title compound (350mg, 73.83%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 10.7 (s, 1H), 9.06 (s, 1H), 8.24-8.21 (d, 1H), 7.80-7.75 (t, 1H), 7.67-7.64 (d, 1H), 3.65 (s, 4H), 3.12-3.08 (t, 4H), 1.95-1.85 (m, 4H), 1.69 (s, 8H). **LCMS:** m/z = 503.1 $(M+2)^+$.

Step 2: Preparation of tert-butyl (S)-(1-(6-((2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)carbamoyl)pyridin-2-yl)pyrrolidin-3-yl)carbamate

Using the same reaction conditions as described in step 2 of example 43, 6-bromo-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide (100mg, 0.2 mmol) was substituted with tert-butyl (S)-pyrrolidin-3-ylcarbamate (56mg, 0.3 mmol) using sodium carbonate (64mg, 0.6 mmol) in DMF (2mL) at 100°C for 4h to obtain the title compound (120mg, 100%). **LCMS:** m/z = 607.3 $(M+1)^+$.

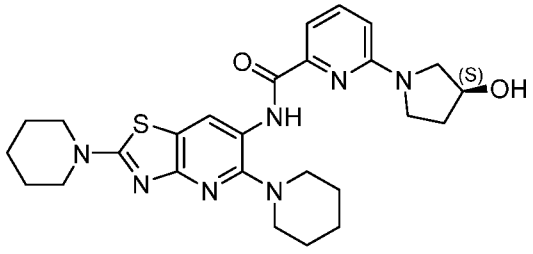
Step 3: Preparation of (S)-6-(3-aminopyrrolidin-1-yl)-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide

Using the same reaction conditions as described in step 8 of example 1, tert-butyl (S)-(1-(6-((2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)carbamoyl)pyridin-2-yl)pyrrolidin-3-yl)carbamate (120mg, 0.197 mmol) was deprotected using TFA (1mL) and DCM (1mL) to afford the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (65mg, 65%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 10.53 (s, 1H), 9.05 (s, 1H), 7.65-7.54 (m, 2H), 6.55-6.53 (d, 1H), 3.84-3.73 (m, 3H), 3.64 (s, 6H), 3.50-3.35 (m, 1H), 3.08-3.04 (t, 4H), 2.31-2.25 (m, 1H), 2.10-1.85 (m, 1H), 1.80-1.60 (m, 11H). **LCMS:** 92.92%, m/z = 507.2 $(M+1)^+$. **HPLC:** 96.92%.

Example 65

(S)-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide

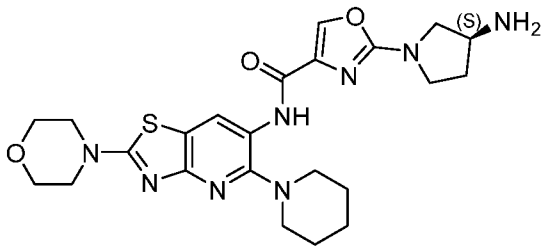


Using the same reaction conditions as described in step 2 of example 43, 6-bromo-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide (product of step 1 of example 65) (70mg, 0.14 mmol) was substituted with (S)-pyrrolidin-3-ol (20mg, 0.209 mmol) using sodium carbonate (45mg, 0.42 mmol) in DMF (2mL) at 100°C for 4h to obtain the title compound (60mg, 84.5%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 10.57 (s, 1H), 9.06 (s, 1H), 7.66-7.62 (t, 1H), 7.59-7.57 (d, 1H), 6.58-6.56 (d, 1H), 4.68 (s, 1H), 3.79-3.74 (m, 4H), 3.65 (s, 4H), 3.09-3.07 (m, 4H), 2.24-2.12 (m, 2H), 1.77-1.76 (m, 4H), 1.69 (s, 6H), 1.61-1.56 (m, 3H). **LCMS:** 99.49%, m/z = 508.2 $(M+1)^+$. **HPLC:** 99.62%.

Example 66

(S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide



Step 1: Preparation of tert-butyl (S)-(1-(4-((2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)carbamoyl)oxazol-2-yl)pyrrolidin-3-yl)carbamate

Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 6 of example 20) (100mg, 0.3134 mmol), was coupled with (S)-2-(3-((tert-butoxycarbonyl)amino)pyrrolidin-1-yl)oxazole-4-carboxylic acid (intermediate 14) (140mg, 0.4702 mmol) using EDCI.HCl (91mg, 0.4702 mmol), HOBt (64mg, 0.4702 mmol), DIPEA (0.218mL, 1.2539 mmol) in DMF (2mL) to afford crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 1% methanol in DCM as eluent to obtain the title compound (170mg, 90.9%). **LCMS:** m/z = 599.3 $(M+1)^+$. **HPLC:** 88.43%.

Step 2: Preparation of (S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 8 of example 1,tert-butyl (S)-(1-(4-((2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)carbamoyl)oxazol-2-

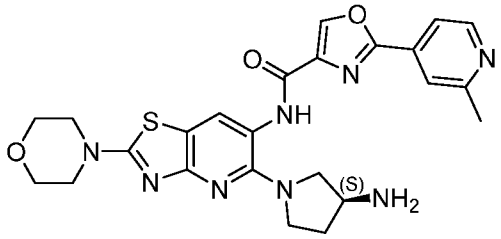
yl)pyrrolidin-3-yl)carbamate (170mg, 0.2839 mmol) was deprotected using TFA (5mL) and DCM (5mL) to get the title compound (69mg, 48.93%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.07 (s, 1H), 9.06 (s, 1H), 7.82 (s, 1H), 3.82-3.68 (m, 11H), 3.30-3.28 (m, 1H), 3.15-3.03 (m, 4H), 2.30-2.20 (m, 1H), 1.90-1.80 (m, 5H), 1.62-1.55 (m, 3H).

LCMS: 98.35%, m/z = 499.2 $(M+1)^+$. **HPLC:** 97.34%.

Example 67

(S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of tert-butyl (S)-(1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate

Using the same reaction conditions as described in step 1 of example 38, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (150mg, 0.5 mmol) was substituted with tert-butyl (S)-pyrrolidin-3-ylcarbamate (93mg, 0.5 mmol) using potassium carbonate (207mg, 1.5 mmol) and DMF (5mL) to afford the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 1% methanol in DCM as eluent to obtain the title compound (195mg, 87%). **LCMS:** m/z = 451.3 $(M+1)^+$.

Step 2: Preparation of tert-butyl tert-butyl (S)-(1-(6-amino-2-morpholinothiazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate

Using the same reaction conditions as described in step 2 of example 38, tert-butyl (S)-(1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate (194mg, 0.431 mmol) was reduced with zinc dust (224mg , 3.448 mmol) and ammonium chloride (366mg, 6.8977 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the title compound (171mg, 94%). **LCMS:** m/z = 421.2 $(M+1)^+$.

Step 3: Preparation of tert-butyl (S)-(1-(6-(2-(2-methylpyridin-4-yl)oxazole-4-carboxamido)-2-morpholinothiazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate

Using the same reaction conditions as described in step 6 of example 1, tert-butyl (S)-(1-(6-amino-2-morpholinothiazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate (83mg, 0.4047 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (170mg, 0.4047 mmol) using EDCI.HCl (117mg, 0.6155 mmol), HOBt (58mg, 0.4293 mmol), DIPEA (209mg, 1.624 mmol) in DMF (5mL) to get the title compound (162mg, 66%). **LCMS:** m/z = 607.2 $(M+1)^+$. **HPLC:** 95.47%.

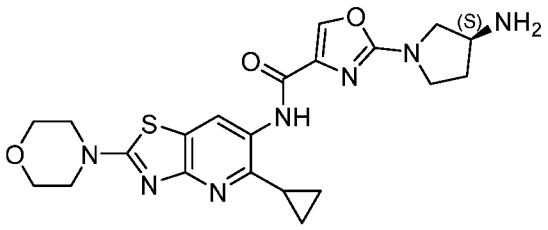
Step 4: Preparation of (S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 8 of example 1, tert-butyl (S)-(1-(6-(2-(2-methylpyridin-4-yl)oxazole-4-carboxamido)-2-morpholinothiazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-yl)carbamate (161mg, 0.2656 mmol) was deprotected using methanolic HCl (5mL) to get the title compound (83mg, 62%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 8.97 (s, 1H), 8.69-8.68 (d, 1H), 8.53 (s, 1H), 8.40 (s, 1H), 7.79 (s, 1H), 7.73-7.71 (d, 1H), 3.84-3.80 (t, 4H), 3.72-3.68 (m, 8H), 3.63-3.54 (m, 2H), 3.33-3.26 (m, 1H), 2.67 (s, 3H), 2.28-2.24 (m, 1H), 1.82-1.78 (m, 1H). **LCMS:** 100%, m/z = 507.1 $(M+1)^+$. **HPLC:** 97.85%.

Example 68

(S)-2-(3-aminopyrrolidin-1-yl)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide



Step 1:Preparation of 4-(5-cyclopropyl-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 7 of example 1,4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (500mg, 1.666 mmol) was coupled with cyclopropyl boronic acid (286mg, 3.333 mmol) using potassium phosphate (882mg, 4.165 mmol) and $Pd(OAc)_2$ (57mg, 0.254 mmol) and tricyclohexyl phosphine (70mg, 0.254 mmol) in toluene : water (10/1mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 30% ethyl

acetate in hexane as eluent to obtain the title compound (400mg, 80%). **LCMS:** m/z = 306.9 $(M+1)^+$.

Step 2:Preparation of 5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1,4-(5-cyclopropyl-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (400mg, 1.307 mmol) was reduced with zinc dust (680mg , 10.457 mmol) and ammonium chloride (1.13g, 20.916 mmol) in THF (10mL) to get the title compound (350mg, 100%). **LCMS:** m/z = 277.1 $(M+1)^+$.

Step 3: Preparation of tert-butyl (S)-(1-(4-((5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)carbamoyl)oxazol-2-yl)pyrrolidin-3-yl)carbamate

Using the same reaction conditions as described in step 6 of example 1, 5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-amine (100mg, 0.362 mmol), was coupled with (S)-2-(3-((tert-butoxycarbonyl)amino)pyrrolidin-1-yl)oxazole-4-carboxylic acid (intermediate 14) (129mg, 0.434 mmol) using EDCI.HCl (102mg, 0.54 mmol), HOBt (73mg, 0.54 mmol), DIPEA (0.280mL, 2.16 mmol) in DMF (5mL) to afford the title compound (180mg, 85.1%). **LCMS:** m/z = 556.2 $(M+1)^+$.

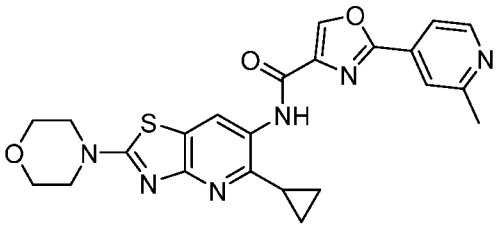
Step 4: Preparation of (S)-2-(3-aminopyrrolidin-1-yl)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 8 of example 1, tert-butyl (S)-(1-(4-((5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)carbamoyl)oxazol-2-yl)pyrrolidin-3-yl)carbamate (180mg, 0.324 mmol) was deprotected using TFA (1mL) and DCM (0.5mL) to get the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (60mg, 40.8%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 9.20 (s, 1H), 8.72 (s, 1H), 7.83 (s, 1H), 3.83-3.56 (m, 12H), 3.28-3.25 (m, 1H), 2.22-2.18 (m, 1H), 2.10-2.03 (m, 1H), 1.88-1.77 (m, 1H), 1.33-1.21 (m, 2H), 1.07-1.00 (m, 2H). **LCMS:** 98.66%, m/z = 456.2 $(M+1)^+$. **HPLC:** 95.53%.

Example 69

N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

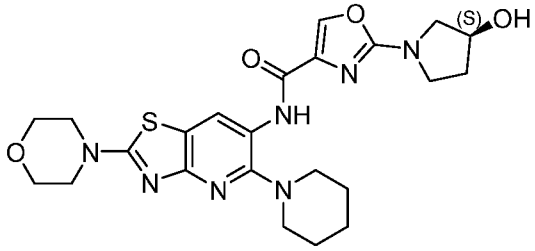


Using the same reaction conditions as described in step 6 of example 1, 5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 2 of example 69) (100mg, 0.362 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (110mg, 0.54 mmol) using EDCI.HCl (102mg, 0.54 mmol), HOBt (73mg, 0.54 mmol), DIPEA (280mg, 2.16 mmol) in DMF (5mL) to afford the title compound (45mg, 26.94%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.30 (s, 1H), 8.75-8.57 (m, 2H), 8.48 (s, 1H), 7.85 (s, 1H), 7.75-7.72 (d, 1H), 3.90-3.80 (t, 4H), 3.78-3.70 (t, 4H), 2.75 (s, 3H), 2.25-2.15 (m, 1H), 1.35-1.25 (m, 2H), 1.15-1.05 (m, 2H). **LCMS:** 98.37%, m/z = 463.1 $(M+1)^+$. **HPLC:** 97.74%.

Example 70

(S)-2-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide



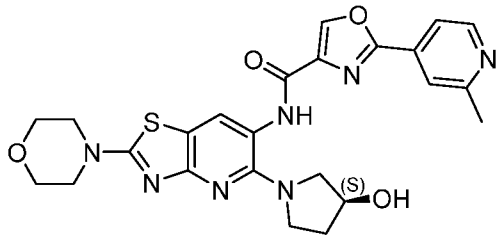
Using the same reaction conditions as described in example 45, 2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 6 of example 20) (90mg, 0.281 mmol), was coupled with (S)-2-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)oxazole-4-carboxylic acid (intermediate 15) (105mg, 0.3375 mmol) using EDCI.HCl (81mg, 0.4218 mmol), HOBt (57mg, 0.4218 mmol), DIPEA (145mg, 1.125 mmol) in DMF (2mL) followed by deprotection using methanolic HCl (2mL) to get the title compound (63mg, 84%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.75 (s, 1H), 9.07 (s, 1H), 7.85 (s, 1H), 4.67 (bs, 1H), 3.843.59 (m, 12H), 3.12-3.09 (t, 4H), 2.30-2.10 (m, 2H), 1.85 (s, 4H), 1.63-1.59 (m, 3H).

LCMS: 100%, m/z = 500.3 $(M+1)^+$. **HPLC:** 97.36%.

Example 71

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of (S)-1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol

Using the same reaction conditions as described in step 1 of example 38, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (150mg, 0.5 mmol) was substituted with (S)-pyrrolidin-3-ol (43mg, 0.5 mmol) using potassium carbonate (207mg, 1.5 mmol) and DMF (2mL) to afford the title product (171mg, 97%). **LCMS:** m/z = 352.1 $(M+1)^+$.

Step 2: Preparation of (S)-1-(6-amino-2-morpholinothiazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol

Using the same reaction conditions as described in step 2 of example 38, (S)-1-(6-amino-2-morpholinothiazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol (167mg, 0.475 mmol) was reduced with zinc dust (247mg , 3.806 mmol) and ammonium chloride (403mg, 7.6 mmol) in THF (10mL) to get the title compound (147mg, 96.7%). **LCMS:** m/z = 322.1 $(M+1)^+$.

Step 3: Preparation of (S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

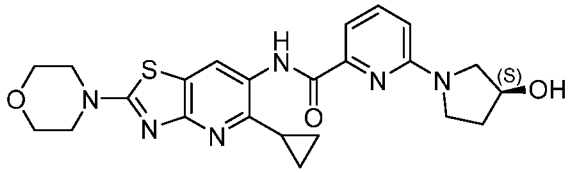
Using the same reaction conditions as described in step 6 of example 1, (S)-1-(6-amino-2-morpholinothiazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol (146mg, 0.6074 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (124mg, 0.6074 mmol) using EDCI.HCl (175mg, 0.911 mmol), HOBt (82mg, 0.6074 mmol), DIPEA (354mg, 2.429 mmol) in DMF (5mL) to get the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (30mg, 10%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.17 (s, 1H), 8.71-8.70 (d, 1H), 8.67 (s, 1H), 8.43 (s, 1H), 7.83 (s, 1H), 7.76-7.75 (d, 1H), 4.60 (bs, 1H), 3.86-3.83 (t, 4H), 3.76-3.68 (m, 6H), 3.60-3.54 (m, 3H), 2.69 (s, 3H), 2.26-2.24 (m, 1H), 2.10-2.01 (m, 1H). **LCMS:** 100%, m/z = 508.4 $(M+1)^+$.

HPLC: 98.23%.

Example 72

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide



Step 1: Preparation of 6-bromo-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)picolinamide

Using the same reaction conditions as described in example 45, 5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 2 of example 69) (220mg, 0.797 mmol), was coupled with 6-bromopicolinic acid (193mg, 0.956 mmol) using EDCI.HCl (228mg, 1.19 mmol), HOBt (112mg, 0.836 mmol), DIPEA (308mg, 2.39 mmol) in DMF (10mL) to get the title compound (200mg, 54.64%).

LCMS: m/z = 460.0 $(M+1)^+$.

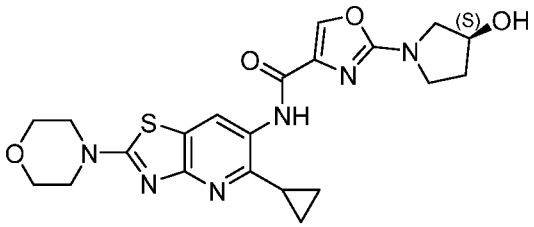
Step 2: Preparation of (S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide

Using the same reaction conditions as described in step 2 of example 43, 6-bromo-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)picolinamide (100mg, 0.217 mmol) was substituted with (S)-pyrrolidin-3-ol (40mg, 0.325 mmol) using sodium carbonate (92mg, 0.868 mmol) in DMF (2mL) at 100°C for 4h to obtain the title compound (55mg, 54.45%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 10.41 (s, 1H), 8.60 (s, 1H), 7.71-7.67 (t, 1H), 7.32-7.30 (d, 1H), 6.72-6.70 (d, 1H), 5.00-4.99 (d, 1H), 4.40 (s, 1H), 3.73-3.70 (t, 4H), 3.58-3.51 (m, 7H), 2.19-2.16 (m, 1H), 2.18-2.00 (m, 2H), 0.98-0.96 (m, 4H). **LCMS:** 100%, m/z = 467.2 $(M+1)^+$. **HPLC:** 95.50%.

Example 73

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxamide

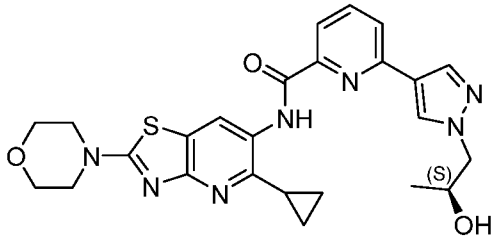


Using the same reaction conditions as described in example 45, 5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 2 of example 69) (80mg, 0.289 mmol), was coupled with (S)-2-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)oxazole-4-carboxylic acid (intermediate 15) (90mg, 0.289 mmol) using EDCI.HCl (83mg, 0.433 mmol), HOBt (59mg, 0.433 mmol), DIPEA (149mg, 1.156 mmol) in DMF (5mL) followed by deprotection using methanolic HCl (5mL) to get the title compound (40mg, 44.4%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 9.19 (s, 1H), 8.71 (s, 1H), 7.84 (s, 1H), 4.65 (s, 1H), 3.83-3.74 (t, 4H), 3.71-3.60 (m, 9H), 2.10-2.08 (m, 3H), 1.21-1.19 (m, 2H), 1.06-1.02 (m, 2H). **LCMS:** 97.34%, m/z = 457.4 (M+1). **HPLC:** 95.05%.

Example 74

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)picolinamide



Step 1: Preparation of N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinamide

Using the same reaction conditions as described in step 7 of example 1, 6-bromo-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)picolinamide (product of step 1 of example 73) (100mg, 0.217 mmol) was coupled with 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (79mg, 0.282 mmol) using sodium carbonate (69mg, 0.651 mmol) and $Pd(PPh_3)_2Cl_2$ (8mg, 0.108 mmol) in 1,2-dimethoxyethane/water (5/1mL) to get the crude product. The resultant crude was purified by 60-120 silica gel column

chromatography using 30% ethyl acetate in hexane as eluent to obtain the title compound (100mg, 86.9%). **LCMS:** m/z = 531.7 $(M+1)^+$.

Step 2: Preparation of N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide hydrochloride

Using the same reaction conditions as described in step 8 of example 1, N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)picolinamide (100mg, 0.188 mmol) was deprotected using methanolic HCl (8mL) to get the title compound (90mg, 94.7%). **LCMS:** m/z = 447.7 $(M+1)^+$.

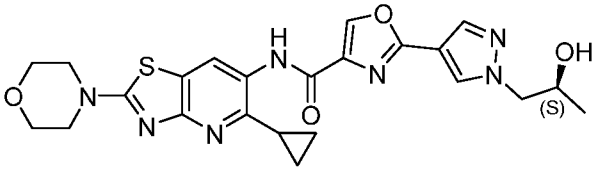
Step 3: Preparation of(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)picolinamide

Using the same reaction conditions as described in step 2 of example 43, N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide hydrochloride (90mg, 0.201 mmol) was substituted with (S)-2-methyloxirane (24mg, 0.402 mmol) using sodium carbonate (107mg, 1.00 mmol) in DMF (2mL) at 140°C for 4h to obtain the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (35mg, 34.6%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 10.8 (s, 1H), 8.61 (s, 1H), 8.31-8.30 (d, 2H), 8.00-7.98 (m, 1H), 7.93-7.89 (m, 2H), 5.02-5.01 (d, 1H), 4.05-4.02 (m, 3H), 3.75 (s, 4H), 3.61 (s, 4H) 2.33-2.23(m, 1H), 1.08-1.07 (d, 3H), 0.99-0.95 (m, 4H). **LCMS:** m/z = 505.7 $(M+1)^+$. **HPLC:** 98.67%.

Example 75

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)oxazole-4-carboxamide



Step 1: Preparation ofN-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(1H-pyrazol-4-yl)oxazole-4-carboxamide hydrochloride

Using the same reaction conditions as described in example 45, 6-bromo-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)picolinamide (product of step 1 of example 73) (100mg, 0.362 mmol) was coupled with 2-(1-(tetrahydro-2H-pyran-2-yl)-1H-

pyrazol-4-yl)oxazole-4-carboxylic acid (intermediate 16) (95mg, 0.362 mmol) using EDCI.HCl (103mg, 0.543 mmol), HOBt (73mg, 0.543 mmol), DIPEA (187mg, 1.448 mmol) in DMF (5mL) followed by deprotection using methanol/methanolic HCl (1/5mL) to get the title compound (145mg, 85.1%). **LCMS:** m/z = 437.7 $(M+1)^+$.

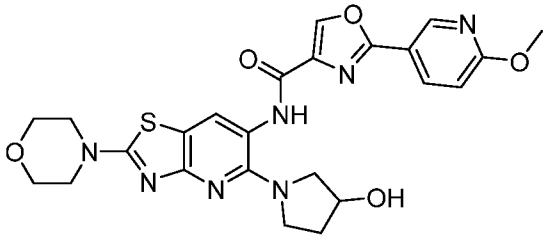
Step 2: Preparation of(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 2 of example 43, N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(1H-pyrazol-4-yl)oxazole-4-carboxamide hydrochloride (145mg, 0.306 mmol) was substituted with (S)-2-methyloxirane (35mg, 0.613 mmol) using sodium carbonate (162mg, 1.53 mmol) in DMF (2mL) at 100°C for 14h to obtain the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (50mg, 21.2%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.18 (s, 1H), 8.70 (s, 1H), 8.25 (s, 1H), 8.05-8.03 (d, 2H), 4.28-4.25 (d, 3H), 3.83-3.81 (m, 4H), 3.70-3.69 (m, 4H), 2.22-2.15 (m, 2H), 1.28-1.27 (m, 4H) 1.11-1.09 (d, 2H). **LCMS:** 98.69%, m/z = 496.2 $(M+1)^+$. **HPLC:** 97.79%.

Example 76

N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide



Step 1: Preparation of 1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol

Using the same reaction conditions as described in step 1 of example 38, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (125mg, 0.4166 mmol) was substituted with pyrrolidin-3-ol hydrochloride (54mg, 0.437 mmol) using potassium carbonate (230mg, 1.666 mmol) and DMF (5mL) to afford the title product (102mg, 70%). **LCMS:** m/z = 351.8 $(M+1)^+$.

Step 2: Preparation of 4-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 2 of example 41, 1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol (100mg, 0.2857 mmol) was protected using TBDMS chloride (52mg, 0.3428 mmol) and imidazole (43mg, 0.712 mmol) in DMF (5mL) at RT for 14h to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 40% ethyl acetate in hexane as eluent to obtain the title compound (111mg, 84%). **LCMS:** m/z = 465.7 $(M+1)^+$.

Step 3: Preparation of 5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 2 of example 38, 4-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (110mg, 0.2365 mmol) was reduced with zinc dust (123mg, 1.8923 mmol) and ammonium chloride (200mg, 3.7816 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the title compound (101mg, 99%). **LCMS:** m/z = 436.2 $(M+1)^+$.

Step 4: Preparation of N-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (60mg, 0.2727 mmol), was coupled with 2-(6-methoxypyridin-3-yl)oxazole-4-carboxylic acid (intermediate 7) (100mg, 0.2298 mmol) using EDCI.HCl (80mg, 0.4108 mmol), HOBt (39mg, 0.2865 mmol), DIPEA (142mg, 1.095 mmol) in DMF (5mL) to get the title compound (103mg, 70%). **LCMS:** m/z = 637.6 $(M+1)^+$.

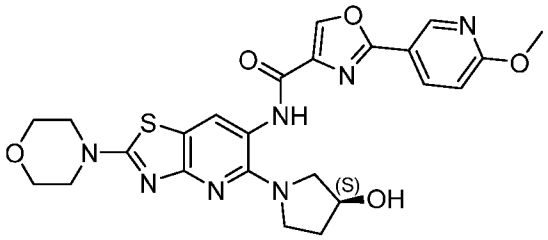
Step 5: Preparation of N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide

TBAF (0.3mL) was added to the stirred solution of N-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide (100mg, 0.1569 mmol) in THF (5mL) and stirred at RT for 1 hr. The reaction mass was diluted with saturated ammonium chloride solution and the solid was filtered and suck dried to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent to obtain the title compound (35mg, 43%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.17 (s, 1H), 8.88 (s, 1H), 8.69 (s, 1H), 8.33 (s, 1H), 8.22-8.20 (d, 1H), 6.88-6.86 (d, 1H), 4.57 (s, 1H), 4.02 (s, 3H), 3.84-3.53 (m, 9H) 2.50-2.49 (d, 1H), 2.31-2.21 (m, 2H), 2.09-2.01 (m, 2H). **LCMS**: 100%, m/z = 524.3 $(M+1)^+$. **HPLC**: 97.99%.

Example 77

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide



Step 1: Preparation of (S)-4-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 2 of example 41, (S)-1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol (product of step 1 of example 72) (100mg, 0.2857 mmol) was protected using TBDMS chloride (52mg, 0.3428 mmol) and imidazole (43mg, 0.712 mmol) in DMF (5mL) at RT for 14h to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 40% ethyl acetate in hexane as eluent to obtain the title compound (113mg, 85%). **LCMS:** m/z = 465.7 $(M+1)^+$.

Step 2: Preparation of (S)-5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 2 of example 38, (S)-4-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (110mg, 0.2365 mmol) was reduced with zinc dust (123mg, 1.8923 mmol) and ammonium chloride (200mg, 3.7816 mmol) in THF/methanol/H_2O (20mL/2mL/1mL) to get the title compound (100mg, 98%). **LCMS:** m/z = 436.3 $(M+1)^+$.

Step 3: Preparation of (S)-N-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, (S)-5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (60mg,

0.2727 mmol), was coupled with 2-(6-methoxypyridin-3-yl)oxazole-4-carboxylic acid (intermediate 7) (100mg, 0.2298 mmol) using EDCI.HCl (80mg, 0.4108 mmol), HOBt (39mg, 0.2865 mmol), DIPEA (142mg, 1.095 mmol) in DMF (5mL) to get the title compound (102mg, 70%). **LCMS:** m/z = 637.6 $(M+1)^+$.

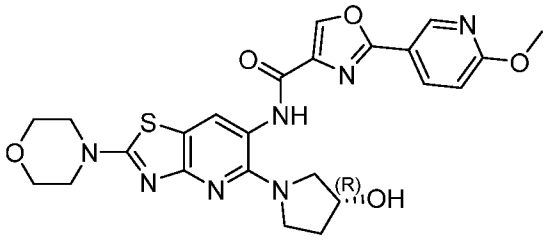
Step 4: Preparation of (S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide

TBAF (0.3mL) was added to the stirred solution of (S)-N-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide (100mg, 0.1569 mmol) in THF (5mL) and stirred at RT for 1 hr. The reaction mass was diluted with saturated ammonium chloride solution and the solid was filtered and suck dried to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent to obtain the title compound (15mg, 18%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.17 (s, 1H), 8.88 (s, 1H), 8.69 (s, 1H), 8.33 (s, 1H), 8.22-8.20 (d, 1H), 6.88-6.86 (d, 1H), 4.57 (s, 1H), 4.02 (s, 3H), 3.83-3.81 (m, 4H),3.76-3.69 (m, 4H), 3.68-3.51 (m, 4H), 2.47-2.46 (d, 1H), 2.27-2.21 (m, 1H), 2.04-2.02 (m, 1H). **LCMS:** 100%, m/z = 524.1 $(M+1)^+$. **HPLC:** 99.55%.

Example 78

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide



Step 1: Preparation of (R)-1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol

Using the same reaction conditions as described in step 1 of example 38, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (125mg, 0.4166 mmol) was substituted with (R)-pyrrolidin-3-ol (38mg, 0.437 mmol) using potassium carbonate

(230mg, 1.666 mmol) and DMF (5mL) to afford the title product (101mg, 70%). **LCMS:** m/z = 351.8 $(M+1)^+$.

Step 2: Preparation of (R)-4-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 2 of example 41, (R)-1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol(100mg, 0.2857 mmol) was protected using TBDMS chloride (52mg, 0.3428 mmol) and imidazole (43mg, 0.712 mmol) in DMF (5mL) at RT for 14h to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 40% ethyl acetate in hexane as eluent to obtain the title compound (115mg, 85.5%). **LCMS:** m/z = 465.7 $(M+1)^+$.

Step 3: Preparation of (R)-5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 2 of example 38, (R)-4-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (110mg, 0.2365 mmol) was reduced with zinc dust (123mg, 1.8923 mmol) and ammonium chloride (200mg, 3.7816 mmol) in THF/methanol/H_2O (20mL/2mL/1mL) to get the title compound (100mg, 98%). **LCMS:** m/z = 436.5 $(M+1)^+$.

Step 4: Preparation of (R)-N-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, (R)-5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (60mg, 0.2727 mmol), was coupled with 2-(6-methoxypyridin-3-yl)oxazole-4-carboxylic acid (intermediate 7) (100mg, 0.2298 mmol) using EDCI.HCl (79mg, 0.4108 mmol), HOBt (39mg, 0.2865 mmol), DIPEA (141mg, 1.095 mmol) in DMF (5mL) to get the title compound (110mg, 75%). **LCMS:** m/z = 637.6 $(M+1)^+$.

Step 5: Preparation of (R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide

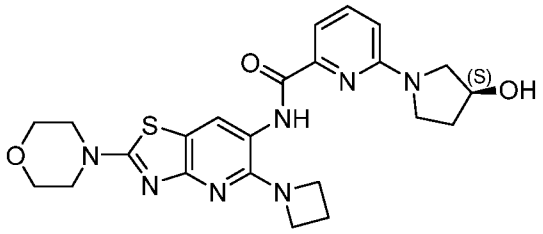
TBAF (0.3mL) was added to the stirred solution of (R)-N-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide (100mg, 0.1569 mmol) in THF (5mL) and stirred at RT for 1 hr. The reaction mass was diluted with saturated ammonium chloride solution and the

solid was filtered and suck dried to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent to obtain the title compound (45mg, 55%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.17 (s, 1H), 8.88 (s, 1H), 8.69 (s, 1H), 8.33 (s, 1H), 8.22-8.20 (dd, 1H), 6.88-6.86 (d, 1H), 4.57 (s, 1H), 4.02 (s, 3H), 3.84-3.81 (m, 4H),3.76-3.63 (m, 4H), 3.61-3.48 (m, 4H), 2.50-2.49 (d, 1H), 2.44-2.22 (m, 1H), 2.04-2.03 (m, 1H). **LCMS: 100%**, m/z = 524.1 $(M+1)^+$. **HPLC:**98.62%.

Example 79

(S)-N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide



Step 1: Preparation of 4-(5-(azetidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 1 of example 38, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (200mg, 0.666 mmol) was substituted with azetidine (76mg, 1.333 mmol) using sodium carbonate (283mg, 2.664 mmol) and DMF (5mL) to afford the title product (150mg, 71.4%). **LCMS:** m/z = 322.1 $(M+1)^+$.

Step 2: Preparation of 5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 2 of example 38, 4-(5-(azetidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (150mg, 0.465 mmol) was reduced with zinc dust (243mg, 3.726 mmol) and ammonium chloride (402mg, 7.440 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the title compound (150mg, crude). **LCMS:** m/z = 292.1 $(M+1)^+$.

Step 3: Preparation of N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-bromopicolinamide

Using the same reaction conditions as described in example 45, 5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (80mg, 0.2373 mmol), was coupled with 6-bromopicolinic acid (83mg, 0.410 mmol) using EDCI.HCl (80mg, 0.41 mmol), HOBt (55mg,

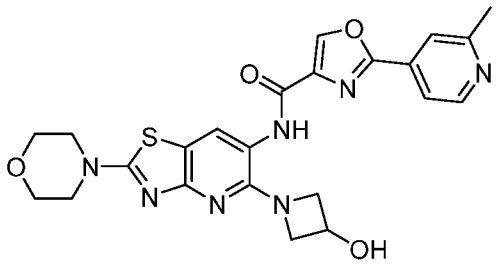
0.410 mmol), DIPEA (141mg, 1.092 mmol) in DMF (5mL) to get the title compound (130mg, 100%). **LCMS:** m/z = 477.1 $(M+2)^+$.

Step 4: Preparation of (S)-N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide

Using the same reaction conditions as described in step 2 of example 43, N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-bromopicolinamide (100mg, 0.210 mmol) was substituted with (S)-pyrrolidin-3-ol hydrochloride (40mg, 0.315 mmol) using sodium carbonate (90mg, 0.840 mmol) in DMF (2mL) at 100°C for 14h to obtain the title compound (35mg, 35%). **^{1}HNMR** ($CDCl_3$, 300MHz): δ 9.79 (s, 1H), 8.59 (s, 1H), 7.66-7.60 (m, 1H), 7.55-7.53 (d, 1H), 6.59-6.56 (d, 1H), 4.71 (s, 1H), 4.26-4.12 (m, 4H), 3.83-3.76 (m, 4H), 3.74-3.65 (m, 8H),2.32-2.19 (m, 4H). **LCMS:** 97.98%, m/z = 482.2 $(M+1)^+$. **HPLC:** 97.38%.

Example 80

N-(5-(3-hydroxyazetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of 1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)azetidin-3-ol

Using the same reaction conditions as described in step 1 of example 38, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (200mg, 0.6666 mmol) was substituted with azetidin-3-ol hydrochloride (109mg, 1.0 mmol) using sodium carbonate (212mg, 3.0 mmol) and DMF (2mL) at 80°C for 1h to afford the title product (160mg, 71.11%). **LCMS:** m/z = 338.1 $(M+1)^+$.

Step 2: Preparation of 4-(5-(3-((tert-butyldimethylsilyl)oxy)azetidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 2 of example 41, 1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)azetidin-3-ol(160mg, 0.4742 mmol) was protected using TBDMS chloride (86mg, 0.5691 mmol) and imidazole (113mg, 1.658 mmol) and

DAMP (64mg, 0.5217 mmol) in DMF (5mL) at RT for 1h to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 1% methanol in DCM as eluent to obtain the title compound (210mg, 98.59%). **LCMS:** m/z = 452.2 $(M+1)^+$.

Step 3: Preparation of 5-(3-((tert-butyldimethylsilyl)oxy)azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 2 of example 38, 4-(5-(3-((tert-butyldimethylsilyl)oxy)azetidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (210mg, 0.4656 mmol) was reduced with zinc dust (244mg, 3.725 mmol) and ammonium chloride (399mg, 7.4501 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the title compound (180mg, 91.83%). **LCMS:** m/z = 422.2 $(M+1)^+$.

Step 4: Preparation of N-(5-(3-((tert-butyldimethylsilyl)oxy)azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 5-(3-((tert-butyldimethylsilyl)oxy)azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (180mg, 0.4275 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (131mg, 0.6413 mmol) using EDCI.HCl (123mg, 0.6413 mmol), HOBt (87mg, 0.6413 mmol), DIPEA (0.297mL, 1.7102 mmol) in DMF (2mL) to get the title compound (150mg, 57.91%).

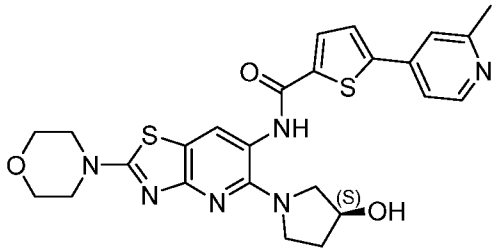
Step 5: Preparation of N-(5-(3-hydroxyazetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

TBAF (1M in THF) (0.5mL) was added to the stirred solution of N-(5-(3-((tert-butyldimethylsilyl)oxy)azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide (150mg, 0.2467 mmol) in THF (20mL) and stirred at RT for 1 hr. The reaction mass was diluted with saturated ammonium chloride solution and the solid was filtered and dried to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent to obtain the title compound (35mg, 28.92%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 9.71 (s, 1H), 8.96 (s,1H), 8.68-8.66 (d, 1H), 7.90 (s, 1H), 7.85 (s, 1H), 7.77-7.75 (d, 1H), 5.51-5.49 (d, 1H), 4.48-4.42 (m, 1H), 4.19-4.14 (t, 2H),3.76-3.70(m, 6H), 3.56-3.54 (m, 4H), 2.57 (s, 3H). **LCMS:** 100%, m/z = 494.1 $(M+1)^+$. **HPLC:** 98.83%.

Example 81

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide



Step 1: Preparation of (S)-N-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide

Using the same reaction conditions as described in step 6 of example 1, (S)-5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 2 of compound 78) (90mg, 0.206 mmol), was coupled with 5-(2-methylpyridin-4-yl)thiophene-2-carboxylic acid (intermediate 17) (54mg, 0.248 mmol) using EDCI.HCl (59mg, 0.309 mmol), HOBt (42mg, 0.309 mmol), DIPEA (106mg, 0.824 mmol) in DMF (5mL) to get the title compound (120mg, crude). **LCMS:** m/z = 637.2 $(M+1)^+$.

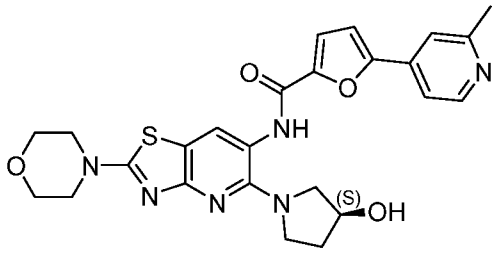
Step 2: Preparation of (S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide

Using the same reaction conditions as described in step 8 of example 1 (S)-N-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide (120mg, 0.188 mmol) was deprotected using methanolic HCl/methanol (5/1mL) to get the crude product. This was then purified by prep HPLC to get the title compound (45mg, 45.4%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 8.66 (s, 1H), 8.54-8.53 (d, 1H), 8.38 (s, 1H), 7.70-7.69 (d, 1H), 7.489-7.480 (d, 1H), 7.38 (s, 1H), 7.34-7.32 (s, 1H), 4.59 (s, 1H), 3.83-3.81 (m, 4H),3.69-3.67(m, 4H), 3.64-3.61 (m, 1H), 3.53-3.50 (m, 3H), 2.62 (s, 3H), 229-2.19 (m, 1H), 2.18-1.90 (m, 1H). **LCMS**: 99.27%, m/z = 523.1 $(M+1)^+$. **HPLC:** 96.58%.

Example 82

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide



Step 1: Preparation of (S)-N-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide

Using the same reaction conditions as described in step 6 of example 1, (S)-5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 2 of compound 78) (90mg, 0.206 mmol), was coupled with 5-(2-methylpyridin-4-yl)furan-2-carboxylic acid (intermediate 18) (50mg, 0.248 mmol) using EDCI.HCl (59mg, 0.309 mmol), HOBt (42mg, 0.309 mmol), DIPEA (106mg, 0.824 mmol) in DMF (5mL) to get the title compound (130mg, crude).

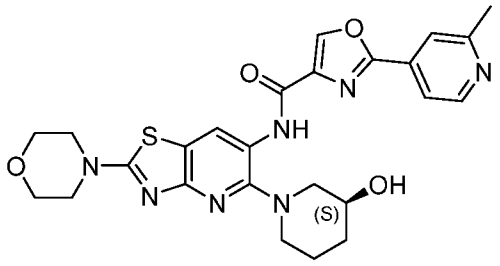
Step 2: Preparation of (S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide

Using the same reaction conditions as described in step 8 of example 1 (S)-N-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide (130mg, 0.209 mmol) was deprotected using methanolic HCl/methanol (5/1mL) to get the crude product. This was then purified by prep HPLC to get the title compound (50mg, 47.16%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 8.72 (s, 2H), 8.57-8.55 (d, 1H), 7.51 (s, 1H), 7.44-7.42 (d, 1H), 7.36-7.34 (d, 1H), 7.00-6.99 (d, 1H), 4.62 (s, 1H), 3.84-3.75 (m, 4H), 3.75-3.65 (m, 6H),3.55-3.43(m, 2H), 2.63 (s, 3H), 2.42-2.39 (m, 1H), 2.26-2.21 (m, 1H), 2.06-1.99 (m, 1H). **LCMS:** 97.85%, m/z = 507.2 $(M+1)^+$. **HPLC:** 99.02%.

Example 83

(S)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of (S)-4-(5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 2 of example 41, (S)-1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)piperidin-3-ol (product of step 1 of example 59) (210mg, 0.575 mmol) was protected using TBDMS chloride (108mg, 0.719 mmol) and imidazole (98mg, 1.438 mmol) and DMAP (88mg, 0.719 mmol) in DMF (5mL) at RT for 14h to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 1% methanol in DCM as eluent to obtain the title compound (177mg, 64%). **LCMS:** m/z = 480.3 $(M+1)^+$.

Step 2: Preparation of (S)-5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 2 of example 38, (S)-4-(5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (175mg, 0.3645 mmol) was reduced with zinc dust (190mg, 2.916 mmol) and ammonium chloride (312mg, 5.833 mmol) in THF / methanol / water (20/10/5mL) to get the title compound (162mg, 98.7%). **LCMS:** m/z = 450.2 $(M+1)^+$.

Step 3: Preparation of (S)-N-(5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, (S)-5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (160mg, 0.355 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (91mg, 0.444 mmol) using HATU (202mg, 0.532 mmol) and DIPEA (183mg, 1.42 mmol) in DMF (5mL) to get the title compound (198mg, 88%). **LCMS:** m/z = 634.3 $(M-1)^+$.

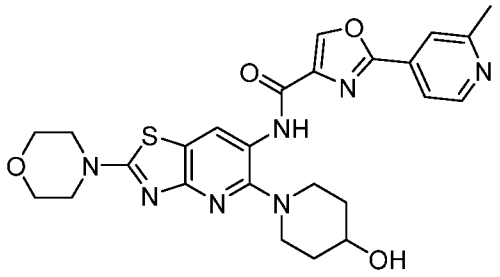
Step 4: Preparation of (S)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 8 of example 1 (S)-N-(5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide (197mg, 0.3102 mmol) was deprotected using methanolic HCl/methanol (5/5mL) to get the title compound (138mg, 85.7%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 9.78 (s, 1H), 9.05 (s, 1H), 8.71-8.69 (d, 1H), 8.41 (s, 1H), 7.86 (s, 1H), 7.77-7.75 (d, 1H), 4.19-4.12 (m, 1H), 3.84-3.81 (m, 4H), 3.71-3.67 (m, 4H),3.33-3.32 (m, 1H), 3.24-3.13 (m, 4H), 2.68 (s, 3H), 2.21-2.00 (m, 1H), 1.86-1.83 (m, 3H). **LCMS:** 98.40%, m/z = 522.2 $(M+1)^+$. **HPLC:** 98.37%.

Example 84

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of 1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)piperidin-4-ol

Using the same reaction conditions as described in step 1 of example 38, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (200mg, 0.6666 mmol) was substituted with piperidine-4-ol(68mg, 0.666 mmol) using potassium carbonate (311mg, 2.66 mmol) and DMF (5mL) at RT for 14h to afford the title product (211mg, 87%). **LCMS:** m/z = 366.1 $(M+1)^+$.

Step 2: Preparation of 4-(5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 2 of example 41, 1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)piperidin-4-ol(210mg, 0.575 mmol) was protected using TBDMS chloride (108mg, 0.7191 mmol) and imidazole (98mg, 1.438 mmol) and DMAP (88mg, 0.719 mmol) in DMF (5mL) at RT for 1h to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 1% methanol in DCM as eluent to obtain the title compound (216mg, 78.2%). **LCMS:** m/z = 480.2 $(M+1)^+$.

Step 3: Preparation of 5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 2 of example 38, 4-(5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (215mg, 0.448 mmol) was reduced with zinc dust (233mg, 3.583 mmol) and ammonium chloride (387mg, 7.16 mmol) in THF/methanol/H_2O (20mL/5mL/2mL) to get the title compound (161mg, 80%). **LCMS:** m/z = 450.2 $(M+1)^+$.

Step 4: Preparation of N-(5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (160mg, 0.355 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (91mg, 0.444 mmol) using HATU (202mg, 0.532 mmol) and DIPEA (0.183mg, 1.42 mmol) in DMF (5mL) to get the title compound (192mg, 68%). **LCMS:** m/z = 634.3 $(M-1)^+$.

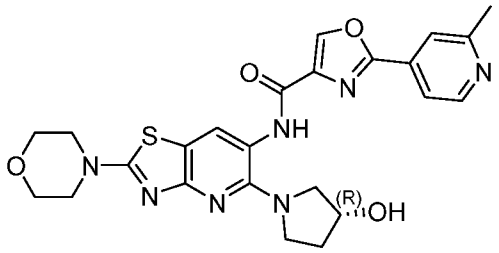
Step 5: Preparation of N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 8 of example 1 N-(5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide (191mg, 0.3 mmol) was deprotected using methanolic HCl/methanol (5/5mL) to get the title compound (130mg, 83.3%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 9.87 (s, 1H), 9.05 (s, 1H), 8.70-8.68 (d, 1H), 8.40 (s, 1H), 7.85 (s, 1H), 7.75-7.73 (d, 1H), 3.99-3.93 (m, 1H), 3.84-3.81 (m, 4H), 3.70-3.67 (m, 4H),3.35-3.30 (m, 2H), 3.11-3.08 (m, 2H), 2.68 (s, 3H), 2.22-2.15 (m, 2H), 2.13-1.97 (m, 2H), 1.69-1.68 (m, 1H). **LCMS:** 94.22%, m/z = 522.2 $(M+1)^+$. **HPLC:** 97.51%.

Example 85

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of (R)-N-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, (R)-5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 3 of example 79) (150mg, 0.34 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (85mg, 0.413 mmol) using HATU (196mg, 0.517 mmol) and DIPEA (177mg, 1.37 mmol) in DMF (8mL) to get the title compound (120mg, 52.1%). **LCMS:** m/z = 622.3 $(M+1)^+$.

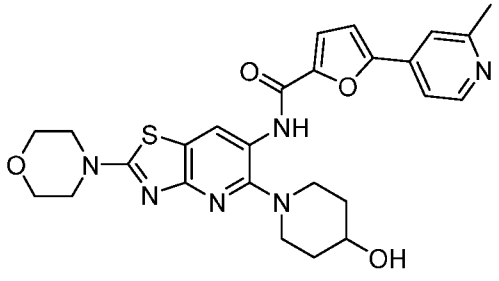
Step 2: Preparation of (R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 8 of example 1,(R)-N-(5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide (120mg, 0.1759 mmol) was deprotected using methanolic HCl/methanol (5/5mL) to get the title compound (77mg, 65%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.99 (s, 1H), 8.96 (s, 1H), 8.69-8.68 (d, 1H), 7.86 (s, 2H), 7.78-7.76 (d, 1H), 4.48 (s, 1H), 4.27 (s, 1H), 3.74-3.72 (m, 4H), 3.64-3.52 (m, 6H),2.59 (s, 3H), 2.09 (s, 1H), 1.89-1.87 (m, 1H), 1.84-1.77 (m, 1H). **LCMS:** 97.25%, m/z = 508.2 $(M+1)^+$. **HPLC:** 95.18%.

Example 86

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide



Step 1: Preparation of N-(5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 3 of example 85) (150mg, 0.334 mmol), was coupled with 5-(2-methylpyridin-4-yl)furan-2-carboxylic acid (intermediate 18) (68mg, 0.334 mmol) using HATU (190mg, 0.501 mmol) and DIPEA (172mg, 1.336 mmol) in DMF (5mL) to get the title compound (165mg, 77.8%). **LCMS:** m/z = 633.3 $(M-1)^+$.

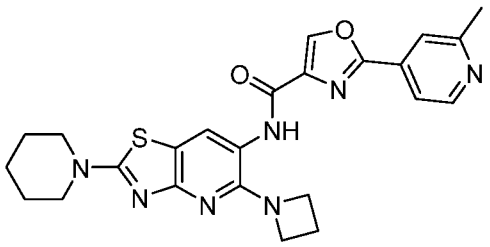
Step 2: Preparation of N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide

Using the same reaction conditions as described in step 8 of example 1 N-(5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide (160mg, 0.252 mmol) was deprotected using methanolic HCl/metahnol (5/5mL) to get the title compound (107mg, 81.6%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 9.61 (s, 1H), 8.58 (s, 1H), 8.55-8.53 (d, 1H), 7.74 (s, 1H), 7.68-7.67 (d, 1H), 7.45-7.44 (d, 2H), 4.74 (s, 1H), 3.74-3.73 (m, 4H), 3.66-3.58 (m, 5H),2.90-2.83 (m, 2H), 2.56 (s, 3H), 2.71-1.88 (m, 2H), 1.64-1.61 (m, 2H). **LCMS:** 99.09%, m/z = 521.2 $(M+1)^+$. **HPLC:** 95.12%.

Example 87

N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of 5-(azetidin-1-yl)-6-nitro-2-(piperidin-1-yl)thiazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 1 of example 38, 5-chloro-6-nitro-2-(piperidin-1-yl)thiazolo[4,5-b]pyridine (product of step 2 of example 22) (250mg, 0.8389 mmol) was substituted with azetidine hydrochloride (117mg, 1.2583 mmol) using sodium

carbonate (267mg, 2.5167 mmol) and DMF (5mL) at RT overnight to afford the title product (170mg, 63.43%). **LCMS:** m/z = 320.1 $(M+1)^+$.

Step 2: Preparation of 5-(azetidin-1-yl)-2-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 2 of example 38, 5-(azetidin-1-yl)-6-nitro-2-(piperidin-1-yl)thiazolo[4,5-b]pyridine (170mg, 0.5329 mmol) was reduced with zinc dust (228mg, 4.2633 mmol) and ammonium chloride (558mg, 8.5266 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the title compound (140mg, 90.9%). **LCMS:** m/z = 290.1 $(M+1)^+$.

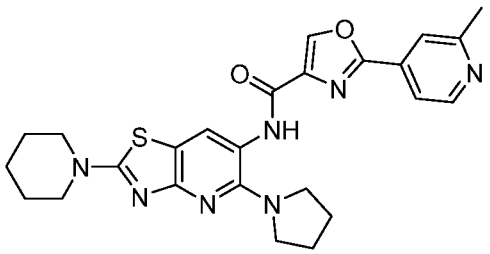
Step 3: Preparation of N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 5-(azetidin-1-yl)-2-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (140mg, 0.4844 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (119mg, 0.5813 mmol) using HATU (294mg, 0.6297 mmol) and DIPEA (0.338mL, 1.9377 mmol) in DMF (3mL) to get the title compound (96mg, 41.73%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 8.70-8.69 (d, 1H), 8.55 (s, 1H), 8.38-8.36 (d, 2H), 7.81 (s, 1H), 7.78-7.76 (d, 1H), 4.24-4.20 (t, 4H), 3.65 (s, 4H), 2.69 (s, 3H), 2.40-2.33 (m, 2H),1.69(s, 6H). **LCMS:** 100%, m/z = 476.1 $(M+1)^+$. **HPLC:** 97.70%.

Example 88

2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide



Step 1: Preparation of6-nitro-2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 1 of example 38, 5-chloro-6-nitro-2-(piperidin-1-yl)thiazolo[4,5-b]pyridine (product of step 2 of example 22) (250mg, 0.8389 mmol) was substituted with pyrrolidine (90mg, 1.2583 mmol) using sodium carbonate (178mg,

1.6778 mmol) and DMF (5mL) at RT overnight to afford the title product (200mg, 71.42%). **LCMS:** m/z = 334.1 $(M+1)^+$.

Step 2: Preparation of 2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 2 of example 38, 6-nitro-2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridine (200mg, 0.5998 mmol) was reduced with zinc dust (257mg, 4.7988 mmol) and ammonium chloride (628mg, 9.5977 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the title compound (140mg, 76.92%). **LCMS:** m/z = 304.1 $(M+1)^+$.

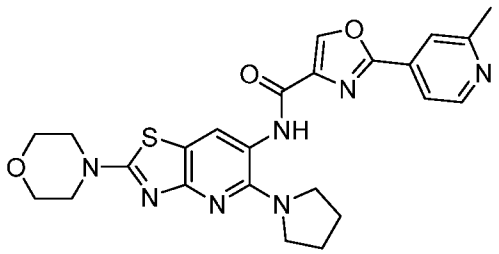
Step 3: Preparation of2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (100mg, 0.3300 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (81mg, 0.3960 mmol) using HATU (163mg, 0.4290 mmol) and DIPEA (0.23mL, 1.3201 mmol) in DMF (3mL) to get the title compound (59mg, 36.64%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 8.95 (s, 1H), 8.69-8.68 (d, 1H), 8.48 (s, 1H), 8.39 (s, 1H), 7.79 (s, 1H), 7.73-7.71 (d, 1H), 3.75-3.65 (m, 4H), 3.55-3.49 (m, 4H), 2.67 (s, 3H), 1.99-1.94(m, 4H), 1.69 (s, 6H). **LCMS:** 98.26%, m/z = 490.1 $(M+1)^+$. **HPLC:** 97.87%.

Example 89

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide



Step 1: Preparation of4-(6-nitro-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 1 of example 38, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (200mg, 0.666 mmol) was substituted with pyrrolidine (71mg, 0.999 mmol) using potassium carbonate (275mg,

1.998 mmol) and DMF (5mL) at RT overnight to afford the title product (200mg, 89.68%). **LCMS:** m/z = 336.0 $(M+1)^+$.

Step 2: Preparation of 2-morpholino-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 2 of example 38, 4-(6-nitro-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-2-yl)morpholine (200mg, 0.597 mmol) was reduced with zinc dust (310mg, 4.776 mmol) and ammonium chloride (515mg, 9.552 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the title compound (200mg, crude). **LCMS:** m/z = 306.1 $(M+1)^+$.

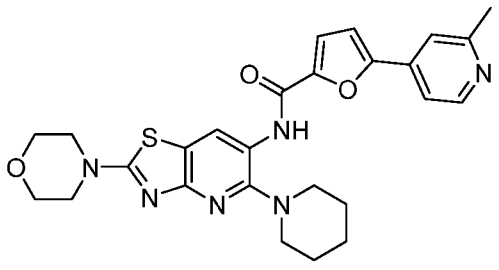
Step 3: 2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (100mg, 0.327 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (80mg, 0.393 mmol) using HATU (186mg, 0.490 mmol) and DIPEA (169mg, 1.3081 mmol) in DMF (5mL) to get the title compound (90mg, 56.2%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 8.94 (s, 1H), 8.70-8.68 (d, 1H), 8.52 (s, 1H), 8.40 (s, 1H), 7.79 (s, 1H), 7.73-7.71 (d, 1H), 3.83-3.80 (m, 4H), 3.70-3.65 (m, 4H), 3.56-3.52 (m, 4H),2.68(s, 3H), 2.00-1.95 (m, 4H). **LCMS:** 100%, m/z = 492.1 $(M+1)^+$. **HPLC:** 97.29%.

Example 90

5-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)furan-2-carboxamide

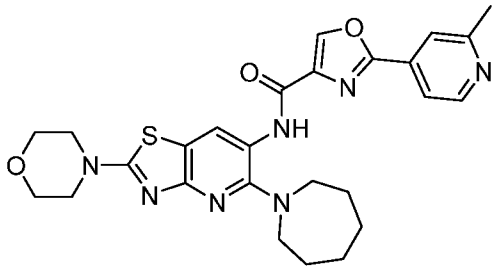


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 6 of example 20) (150mg, 0.468 mmol) was coupled with 5-(2-methylpyridin-4-yl)furan-2-carboxylic acid (intermediate 18) (114mg, 0.562 mmol) using HATU (267mg, 0.702 mmol) and DIPEA (241mg, 1.872 mmol) in DMF (5mL) to afford the title compound (60mg, 25.4%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.08 (s, 1H), 8.58-8.57 (d, 1H), 7.58 (s, 1H), 7.44-7.42 (d, 1H), 7.35-7.34 (d, 1H), 7.02-7.01 (d, 1H), 3.84-3.82 (m, 4H), 3.71-3.68 (m, 4H), 3.13-3.10 (m, 4H),2.64(s, 3H), 1.99-1.86 (m, 4H), 1.69 (s, 2H). **LCMS:** 100%, m/z = 505.3 $(M+1)^+$. **HPLC:** 95.52%.

Example 91

N-(5-(azepan-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of4-(5-(azepan-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 1 of example 38, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (250mg, 0.8333 mmol) was substituted with azepane (165mg, 1.6666 mmol) using sodium carbonate (221mg, 2.0833 mmol) and DMF (4mL) at 80°C for 2h to afford the title product (200mg, 66.22%). **LCMS:** m/z = 364.0 $(M+1)^+$.

Step 2: Preparation of 5-(azepan-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 2 of example 38, 4-(5-(azepan-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (200mg, 0.550 mmol) was reduced with zinc dust (236mg, 4.407 mmol) and ammonium chloride (577mg, 8.8154 mmol) in THF/methanol/H_2O(10mL/2mL/2mL) to get the title compound (100mg, 52.93). **LCMS:** m/z = 334.3 $(M+1)^+$.

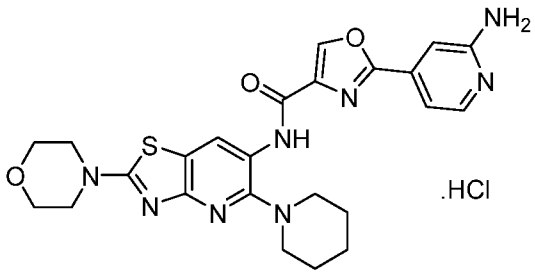
Step 3: Preparation ofN-(5-(azepan-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 5-(azepan-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (100mg, 0.300 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (74mg, 0.360 mmol) using HATU (149mg, 0.390 mmol) and DIPEA (0.21mL, 1.2012 mmol) in DMF (5mL) to get the title compound (84mg, 53.84%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 9.85 (s, 1H), 9.07 (s, 1H), 8.69-8.67 (d, 1H), 8.40 (s, 1H), 7.83 (s, 1H), 7.72-7.71 (d, 1H), 3.84-3.81 (m, 4H), 3.70-3.67 (m, 4H), 3.39-3.32 (m, 4H),2.67(s, 3H), 1.93 (s, 8H). **LCMS:** 89.19%, m/z = 520.2 $(M+1)^+$. **HPLC:** 95.29%.

Example 92

2-(2-aminopyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride

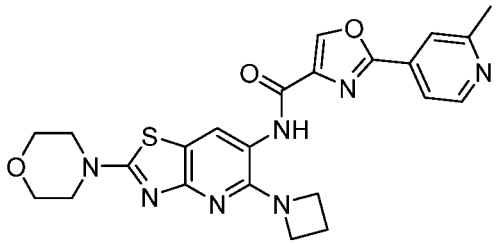


Using the same reaction conditions as described in example 45, 2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-amine (product of step 6 of example 20) (70mg, 0.2191 mmol), was coupled with 2-(2-((tert-butoxycarbonyl)amino)pyridin-4-yl)oxazole-4-carboxylic acid (intermediate 19) (74mg, 0.2410 mmol) using HATU (108mg, 0.2848 mmol) and DIPEA (0.153mL, 0.8765 mmol) in DMF (2mL) followed by deprotection using methanolic HCl/DCM (2/5mL) to get the crude product. This was then purified by prep HPLC and treated with methanolic HCl to get the title compound (47mg, 52.80%).

^{1}HNMR ($DMSO-d_6$, 400MHz): δ 9.61 (s, 1H), 9.19 (s, 1H), 8.91 (s, 1H), 8.49-8.41 (m, 2H), 8.21-8.19 (d, 1H), 7.53 (s, 1H), 7.30-7.28 (d, 1H), 3.74-3.73 (m, 4H), (3.52-3.60 (m, 4H), 3.06-3.01 (m, 4H), 1.82-1.78 (m, 4H), 1.64-1.61 (m, 2H). **LCMS:** 93.04%, m/z = 507.2 $(M+1)^+$. **HPLC:** 98.15%.

Example 93

N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

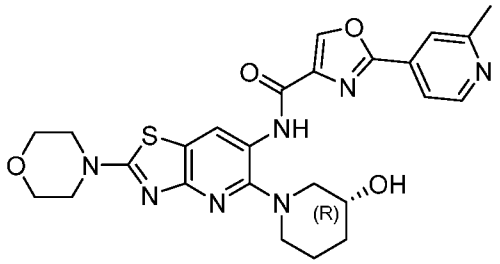


Using the same reaction conditions as described in step 6 of example 1, 5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 2 of example 80) (100mg, 0.344 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (105mg, 0.517 mmol) using HATU (196mg, 0.517 mmol) and DIPEA (177mg, 1.376 mmol) in DMF (5mL) to afford title compound (40mg, 25.0%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 8.71-8.69 (d, 1H), 8.57 (s, 1H), 8.42-8.39 (d, 2H), 7.81 (s, 1H), 7.75-7.73 (d, 1H), 4.26-4.21 (t, 4H), 3.84-3.80 (m, 4H), 3.69-3.66 (m, 4H), 2.69 (s, 3H),2.39-2.34(m, 2H). **LCMS:** 94.95%, m/z = 478.1 $(M+1)^+$. **HPLC:** 98.37%.

Example 94

(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1:Preparation of (R)-1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)piperidin-3-ol

Using the same reaction conditions as described in step 2 of example 43, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (400mg, 1.333 mmol) was substituted using (R)-piperidin-3-ol hydrochloride (218mg, 1.6 mmol) using potassium carbonate (552mg, 4 mmol) in DMF (5mL) at RT for 14h to obtain the title compound (420mg, 86.4%). **LCMS:** m/z = 365.3 $(M+1)^+$.

Step 2: Preparation of (R)-4-(5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 2 of example 41, (R)-1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)piperidin-3-ol(420mg, 0.903 mmol) was protected using TBDMS chloride (110mg, 0.903 mmol) and imidazole (92mg, 1.354 mmol) and DMAP (204mg, 1.354 mmol) in DMF/DCM (10/2mL) at RT for 0.5h to get the crude product. The

resultant crude was purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent to obtain the title compound (520mg, 94.5%). **LCMS:** m/z = 480.2 $(M+1)^+$.

Step 3: Preparation of (R)-5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 2 of example 38, (R)-4-(5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (520mg, 0.898 mmol) was reduced with zinc dust (467mg, 7.184 mmol) and ammonium chloride (776mg, 14.368 mmol) in THF / water (20/5mL) to get the title compound (500mg crude). **LCMS:** m/z = 450.0 $(M+1)^+$.

Step 4: Preparation of (R)-N-(5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, (R)-5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (120mg, 0.266 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (81mg, 0.399 mmol) using HATU (152mg, 0.399 mmol) and DIPEA (137mg, 1.064 mmol) in DMF (3mL) to get the crude title compound (200mg). **LCMS:** m/z = 636.2 $(M+1)^+$.

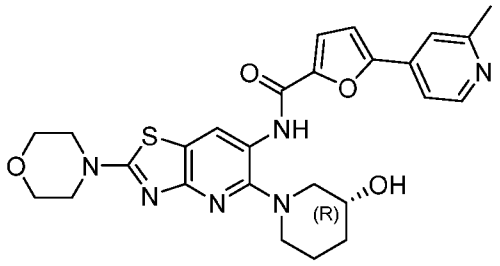
Step 5: Preparation of (R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 5 of example 77,(R)-N-(5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide (200mg, 0.314 mmol) was deprotected using TBAF / THF (2/5mL) to get the crude product. The resultant crude was purified by prep plate using 5% methanol in DCM as eluent to obtain the title compound (50mg, 30.4%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.92 (s, 1H), 9.05 (s, 1H), 8.75 (s, 1H), 8.40 (s, 1H), 7.87 (s, 1H), 7.69-7.67 (d, 1H), 4.15 (s, 1H), 3.84-3.82 (m, 4H), 3.71-3.69 (m, 4H),3.39-3.36(m, 1H), 3.34-3.31 (m, 3H), 3.12-3.05 (m, 1H), 2.68 (s, 3H), 2.20-2.10 (m, 1H), 1.90-1.60 (m, 3H). **LCMS:** 97.74%, m/z = 522.2 $(M+1)^+$. **HPLC:** 98.12%.

Example 95

(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide

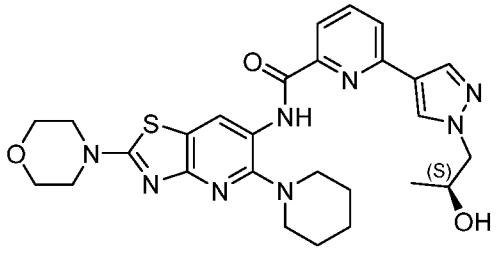


Using the same reaction conditions as described in example 45, (R)-5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 3 of example 95) (100mg, 0.209 mmol), was coupled with 5-(2-methylpyridin-4-yl)furan-2-carboxylic acid (intermediate 18) (51mg, 0.250 mmol) using HATU (120mg, 0.315 mmol) and DIPEA (108mg, 0.840 mmol) in DMF (5mL) followed by deprotection using TBAF / THF (1/2mL) to get the crude product. This was then purified by prep plate using 5% methanol in DCM as eluent to obtain the title compound (50mg, 59.5%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 9.33 (s, 1H), 9.09 (s, 1H), 8.57-8.56 (d, 1H), 7.59 (s, 1H), 7.45-7.44 (d, 1H), 7.37-7.35 (d, 1H), 7.00-6.99 (d, 1H), 4.13 (s, 1H), 3.84-3.81 (m, 4H),3.71-3.69(m, 4H), 3.36-3.11 (m, 1H), 3.19-3.10 (m, 3H), 2.64 (s, 3H), 2.39 (s, 1H) 2.17-2.11 (m, 1H), 1.99-1.90 (m, 1H), 1.80-1.77 (m, 2H). **LCMS:** 93.43%, m/z = 521.4 $(M+1)^+$. **HPLC:** 95.34%.

Example 96

(S)-6-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide

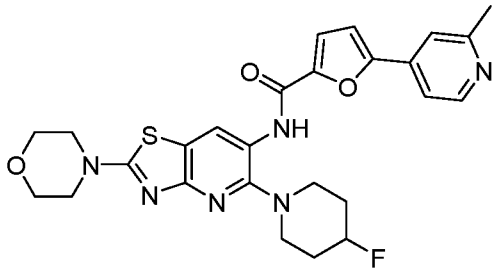


Using the same reaction conditions as described in step 2 of example 43, N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide (example 21) (200mg, 0.380 mmol) was substituted with (S)-2-methyloxirane (34mg, 0.570 mmol) using sodium carbonate (201mg, 1.900 mmol) in DMF (5mL) at 100°C for 14h to obtain the crude product. The resultant crude was purified by prep plate using 5% methanol in DCM as eluent to obtain the title compound (50mg, 24.5%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 10.59 (s, 1H), 9.03 (s, 1H), 8.42 (s, 1H), 8.22 (s, 1H), 8.04-8.01 (m, 1H), 7.97-7.96 (m, 2H), 5.02 (s, 1H), 4.06-4.04 (m, 3H), 3.72-3.70 (m, 4H),3.58-3.55 (m, 4H), 3.02-2.89 (m, 4H), 1.78-1.73 (m, 4H), 1.61-1.55 (m, 2H), 1.11-1.04 (m, 3H). **LCMS:** 92.56%, m/z = 549.3 $(M+1)^+$. **HPLC:** 96.98%.

Example 97

N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide



Step 1: Preparation of 4-(5-(4-fluoropiperidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 2 of example 59,1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)piperidin-4-ol (product of step 1 of example 85) (450mg, 1.3846 mmol) was fluorinated using DAST (0.3mL, 2.353 mmol) in DCM (10mL) at -78°C for 30min. The resultant crude was purified by 60-120 silica gel column chromatography using 50% ethyl acetate in hexane as eluent to obtain the crude title compound (360mg). **LCMS:** m/z = 368.0 $(M+1)^+$.

Step 2: Preparation of 5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 4-(5-(4-fluoropiperidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (360mg, 0.9809 mmol) was reduced with zinc dust (510mg, 0.7847 mmol) and ammonium chloride (423mg, 0.7847 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the crude product (240mg). **LCMS:** m/z = 338.3 $(M+1)^+$.

Step 3: Preparation of N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide

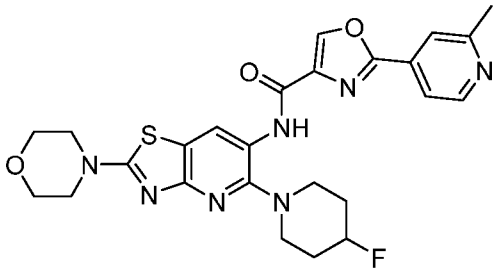
Using the same reaction conditions as described in step 6 of example 1, 5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (120mg, 0.3560 mmol) was

coupled with 5-(2-methylpyridin-4-yl)furan-2-carboxylic acid (intermediate 18) (86mg, 0.4272 mmol) using HATU (202mg, 0.5341 mmol) and DIPEA (0.3mL, 1.424 mmol) in DMF (5mL) to afford the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (75mg, 40%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.85 (s, 1H), 8.55-8.53 (d, 2H), 7.77 (s, 1H), 7.69-7.68 (d, 1H), 7.46 (s, 2H), 4.95-4.79 (m, 1H), 3.75-3.73 (m, 4H), 3.60-3.58 (m, 4H), 3.28-3.27 (m, 2H),3.06-3.02(m, 2H), 2.53 (s, 3H), 2.06-2.02 (m, 2H), 1.92-1.90 (m, 2H). **LCMS:** 100%, m/z = 523.2 $(M+1)^+$. **HPLC:** 97.39%.

Example 98

N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

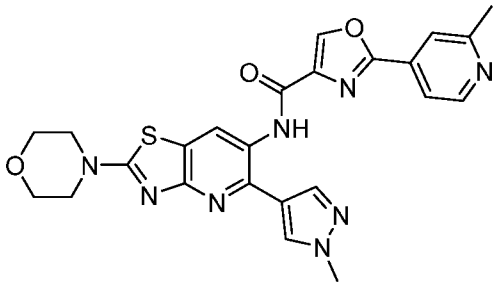


Using the same reaction conditions as described in step 6 of example 1, 5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 2 of 98) (120mg, 0.3560 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (87mg, 0.4272 mmol) using HATU (202mg, 0.5341 mmol) and DIPEA (183mg, 1.024 mmol) in DMF (5mL) to afford the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (30mg, 20%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.72 (s, 1H), 9.25 (s, 1H), 8.91-8.89(m, 2H), 8.24 (s, 1H), 8.14-8.12 (d, 1H), 5.08-4.91 (m, 1H), 3.7-3.73 (m, 4H), 3.60-3.58 (m, 4H),3.27-3.23 (m, 2H), 3.16 (s, 1H), 3.06-3.03 (m, 2H), 2.76 (s, 2H), 2.25-2.15 (m, 2H), 2.10-2.02 (m, 2H). **LCMS:** 99.32%, m/z = 524.0 $(M+1)^+$. **HPLC:** 98.71%.

Example 99

N-(5-(1-methyl-1H-pyrazol-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of 4-(5-(1-methyl-1H-pyrazol-4-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 7 of example 1, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (200mg, 0.66 mmol) was coupled with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (200mg, 0.99 mmol) using sodium iodide (200mg, 1.33 mmol), potassium carbonate (220mg, 1.99 mmol) and Pd(dppf)Cl_2 (48mg, 0.066 mmol) in 1,2-dimethoxyethane/water (0.5/0.2mL) to get the title compound (150mg, %). **LCMS:** m/z = 346.9 $(M+1)^+$.

Step 2:Preparation of5-(1-methyl-1H-pyrazol-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 4-(5-(1-methyl-1H-pyrazol-4-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (150mg, 0.43 mmol) was reduced with zinc dust (220mg, 3.4 mmol) and ammonium chloride (360mg, 6.9 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) (2mL) to get the crude product (100mg). **LCMS:** m/z = 317.3 $(M+1)^+$.

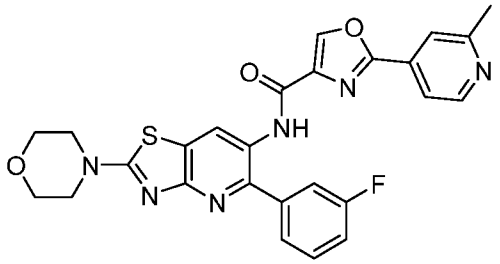
Step 3: Preparation of N-(5-(1-methyl-1H-pyrazol-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 5-(1-methyl-1H-pyrazol-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (100mg, 0.316 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (77mg, 0.38 mmol) using HATU (156mg, 0.41 mmol) and DIPEA (122mg, 0.94 mmol) in DMF (5mL) to afford the title compound (40mg, %).

^{1}HNMR (DMSO-d_6, 400MHz): δ 10.1 (s, 1H), 9.05 (s, 1H), 8.71-8.70 (d, 1H), 8.30 (s, 1H), 8.21 (s, 1H), 7.94 (s, 1H), 7.88 (s, 1H), 7.80-7.79 (d, 1H), 3.87 (s, 3H),3.82-3.76(m, 4H), 3.69-3.64 (m, 4H), 2.60 (s, 3H). **LCMS:** 97.70%, m/z = 503.2 $(M+1)^+$. **HPLC:** 96.20%.

Example 100

N-(5-(3-fluorophenyl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of 4-(5-(3-fluorophenyl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 7 of example 1, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (250mg, 0.83 mmol) was coupled with 3-fluoro phenyl boronic acid (173mg, 1.25 mmol) using sodium iodide (375mg, 2.5 mmol), potassium carbonate (517mg, 3.7 mmol) and $Pd(dppf)Cl_2$ (61mg, 0.1056 mmol) in 1,2-dimethoxyethane/water (0.5/0.2mL) to get the title compound (200mg, %). **LCMS:** m/z = 361.2 $(M+1)^+$.

Step 2: Preparation of5-(3-fluorophenyl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 4-(5-(3-fluorophenyl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (360mg, 0.9809 mmol) was reduced with zinc dust (510mg, 0.7847 mmol) and ammonium chloride (423mg, 0.7847 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the crude product (240mg). **LCMS:** m/z = 330.9 $(M+1)^+$.

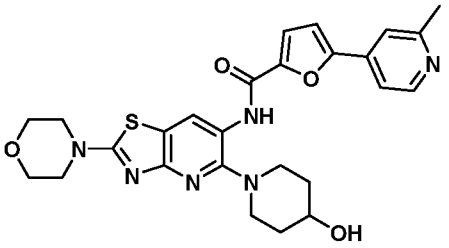
Step 3:Preparation of N-(5-(3-fluorophenyl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 5-(3-fluorophenyl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (120mg, 0.36 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (89mg, 0.43 mmol) using HATU (180mg, 0.47 mmol) and DIPEA (190mg, 1.45 mmol) in DMF (5mL) to afford the title compound (50mg).

^{1}HNMR (DMSO-d_6, 400MHz): δ 10.10 (s, 1H), 8.94 (s, 1H), 8.68-8.67 (d, 1H), 8.51 (s, 1H), 7.79 (s, 1H), 7.71-7.70 (d, 1H), 7.53-7.48 (m, 2H), 7.27-7.24 (t, 1H), 3.77-3.75 (m, 4H),3.70-3.66(m, 4H), 2.54 (s, 3H). **LCMS:** 97.4%, m/z = 517.0 $(M+1)^+$. **HPLC:** 98.80%.

Example 101

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide

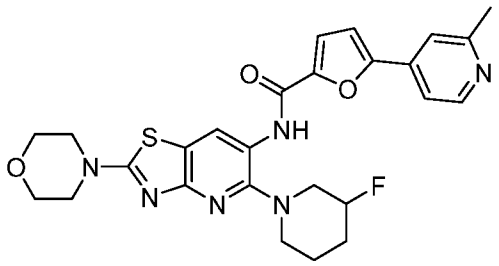


Using the same reaction conditions as described in example 45, 5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 3 of example 85) (200mg, 0.445 mmol), was coupled with 5-(2-methylpyridin-4-yl)furan-2-carboxylic acid (intermediate 18) (135mg, 0.668 mmol) using HATU (253mg, 0.668 mmol) and DIPEA (230mg, 1.780 mmol) in DMF (5mL) followed by deprotection using methanol / methanolic HCl (1/5mL) to get the crude product. This was then purified by prep HPLC to obtain the title compound (50mg, 30.4%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.33 (s, 1H), 9.10 (s, 1H), 8.58-8.57 (d, 1H), 7.60 (s, 1H), 7.46-7.45 (d, 1H), 7.37-7.36 (d, 1H), 7.01-7.00 (d, 1H), 4.13 (s, 1H), 3.85-3.82 (m, 4H),3.71-3.69(m, 4H), 3.35-3.33 (m, 1H), 3.20-3.10 (m, 3H), 2.65 (s, 3H), 2.35 (s, 1H), 2.14-2.12 (m, 1H), 1.97-1.91 m, 1H), 1.79-1.77 (m, 2H). **LCMS:** 99.89%, m/z = 521.20 $(M+1)^+$. **HPLC:** 97.27%.

Example 102

N-(5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide



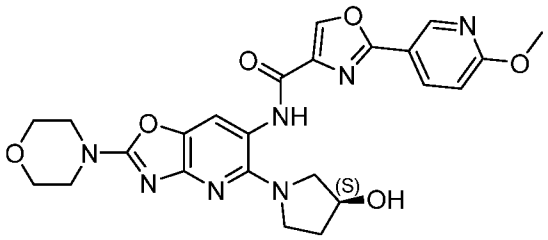
Using the same reaction conditions as described in step 6 of example 1, (S)-5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 4 of example 59) (200mg, 0.593 mmol) was coupled with 5-(2-methylpyridin-4-yl)furan-2-carboxylic acid (intermediate 18) (180mg, 0.890 mmol) using HATU (338mg, 0.890 mmol) and DIPEA (305mg,

2.372 mmol) in DMF (5mL) to afford the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (40mg, 12.9%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 9.51 (s, 1H), 9.14 (s, 1H), 8.56-8.54 (d, 1H), 7.65 (s, 1H), 7.48-7.46 (d, 1H), 7.35-7.34 (d, 1H), 7.00-6.99 (d, 1H), 5.05-4.90 (m, 1H), 3.85-3.81 (m, 4H), 3.71-3.68 (m, 4H), 3.49-3.44 (m, 2H), 3.23-3.08 (m, 2H), 2.63 (s, 3H), 2.20-2.17 (m, 2H), 1.79-1.75 (m, 2H). **LCMS:** 98.09%, m/z = 523.0 $(M+1)^+$. **HPLC:** 99.18%.

Example 103

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide

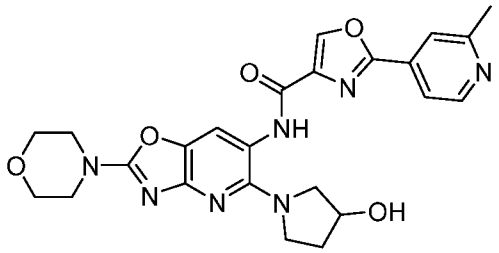


Using the same reaction conditions as described in example 45, (S)-5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 39) (130mg, 0.3090 mmol), was coupled with 2-(2-methoxypyridin-5-yl)oxazole-4-carboxylic acid (intermediate 7) (80mg, 0.3636 mmol) using EDCI.HCl (105mg, 0.5454 mmol), HOBt (52mg, 0.3817 mmol), DIPEA (188mg, 1.454 mmol) in DMF (5mL) to get the coupled product followed by deprotection using 1M TBAF in THF / THF (0.3/5mL) to get the title compound (59mg, 33%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 9.46 (s, 1H), 8.89-8.88 (d, 1H), 8.55 (s, 1H), 8.32 (s, 1H), 8.23-8.19 (dd, 1H), 6.88-6.85 (dd, 1H), 4.55 (m, 1H), 4.02 (s, 1H), 3.83-3.80 (m, 4H),3.75-3.72(m, 4H), 3.50-3.48 (m, 4H), 2.85 (s, 1H), 2.26-2.22 (m, 1H), 2.05-2.01 (m, 1H). **LCMS:** 100%, m/z = 508.1 $(M+1)^+$. **HPLC:** 98.32%.

Example 104

N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of 1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol

Using the same reaction conditions as described in step 1 of example 38, 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (product of step 5 of example 2) (250mg, 0.880 mmol) was substituted with pyrrolidin-3-ol (108mg, 0.880 mmol) using potassium carbonate (183mg, 1.320 mmol) and DMF (5mL) to afford the title product (210mg, 72.41%). **LCMS:** m/z = 335.8 $(M+1)^+$.

Step 2: Preparation 5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 2 of example 41, 1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)pyrrolidin-3-ol (150mg, 0.447 mmol) was protected using TBDMS chloride (102mg, 0.6716 mmol), imidazole (60mg, 0.8955 mmol) and DMAP (10mg, 0.089 mmol) in DMF (5mL) at RT for 2h to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using ethyl acetate in hexane as eluent to obtain the title compound (160mg, 80%). **LCMS:** m/z = 449.8 $(M+1)^+$.

Step 3: Preparation of 5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (160mg, 0.3555 mmol) was reduced with zinc dust (0.1859mg, 2.8444 mmol) and ammonium chloride (304mg, 5.688 mmol) in THF/methanol/H_2O (5mL/2mL/1mL) to get the title product (90mg, 60.44%). **LCMS:** m/z = 420.5 $(M+1)^+$.

Step 4:Preparation of N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

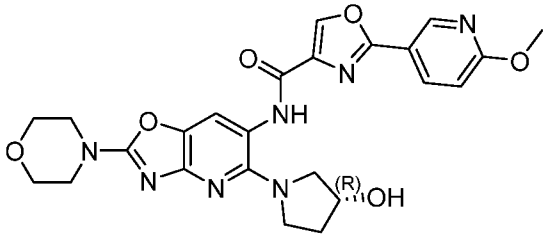
Using the same reaction conditions as described in example 45, 5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine (80mg, 0.190 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (42mg, 0.229

mmol) using EDCI.HCl (54mg, 0.286 mmol), HOBt (38mg, 0.2863 mmol), DIPEA (99mg, 0.7637 mmol) in DMF (3mL) to get the coupled product followed by deprotection using TBAF / THF (0.173/5mL) to get the title compound (30mg, 53.57%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.46 (s, 1H), 8.69-8.68 (d, 1H), 8.52 (s, 1H), 8.40 (s, 1H), 7.81 (s, 1H), 7.74-7.70 (d, 1H), 4.57 (s, 1H), 3.82-3.81 (m, 4H), 3.75-3.74 (m, 4H),3.61-3.59(m, 1H), 3.57-3.46 (m, 1H), 3.42-3.33 (m, 1H), 2.80-2.78 (d, 1H), 2.68 (s, 1H), 2.27-2.24 (m, 2H), 2.05-2.02 (m, 2H), 1.03-0.99 (m, 1H). **LCMS:** 100%, m/z = 492.1 $(M+1)^+$. **HPLC:** 98.80%.

Example 105

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide

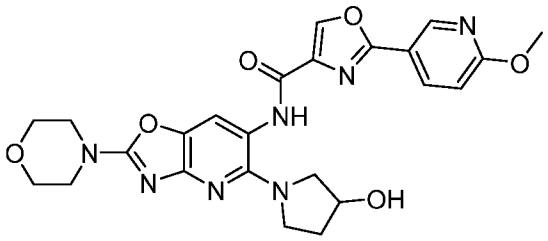


Using the same reaction conditions as described in step example 45, (R)-5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine(product of step 3 of example 41) (57mg, 0.1357 mmol), was coupled with 2-(2-methoxypyridin-5-yl)oxazole-4-carboxylic acid (intermediate 7) (35mg, 0.1628 mmol) using EDCI.HCl (38mg, 0.2035 mmol), HOBt (27mg, 0.2035 mmol), DIPEA (70mg, 0.542 mmol) in DMF (5mL) to get the coupled product followed by deprotection using TBAF / THF (0.144/5mL) to get the title compound (10mg, 20.44%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.47 (s, 1H), 8.89 (s, 1H), 8.55 (s, 1H), 8.33 (s, 1H), 8.22-8.20 (d, 1H), 6.88-6.86 (d, 1H), 4.56-4.45 (m, 1H), 4.02 (s, 3H), 3.82-3.81 (m, 4H),3.75-3.74(m, 4H), 3.65-3.47 (m, 3H), 2.35-2.26 (m, 2H), 2.20-2.01 (m, 2H). **LCMS:** 94.67%, m/z = 507.7 $(M+1)^+$. **HPLC:** 97.15%.

Example 106

N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide

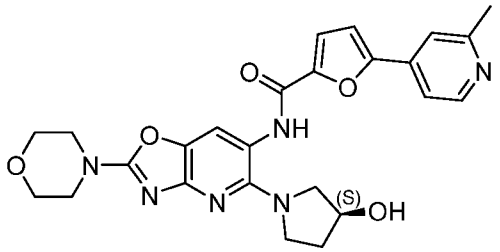


Using the same reaction conditions as described in step 6 of example 1, 5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine (product of step 3 of example 105) (90mg, 0.2142 mmol), was coupled with 2-(2-methoxypyridin-5-yl)oxazole-4-carboxylic acid (intermediate 7) (56mg, 0.2571 mmol) using EDCI.HCl (62mg, 0.3214 mmol), HOBt (43mg, 0.3214 mmol), DIPEA (110mg, 0.8571 mmol) in DMF (3mL) to get the coupled product followed by deprotection using TBAF / THF (0.144/5mL) to get the title compound (15mg, 31.25%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.47 (s, 1H), 8.89 (s, 1H), 8.55 (s, 1H), 8.33 (s, 1H), 8.22-8.20 (d, 1H), 6.88-6.86 (d, 1H), 4.56 (s, 1H), 4.02 (s, 3H), 3.83-3.81 (m, 4H),3.75-3.73(m, 4H), 3.55-3.45 (m, 4H), 2.94-2.93 (d, 1H), 2.30-2.25 (m, 1H), 2.09-2.01 (m, 1H). **LCMS:** 98.15%, m/z = 507.7 $(M+1)^+$. **HPLC:** 98.95%.

Example 107

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide

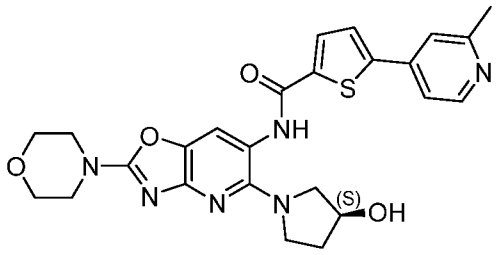


Using the same reaction conditions as described in example 45, (S)-5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 39) (109mg, 0.261 mmol), was coupled with 5-(2-methylpyridin-4-yl)furan-2-carboxylic acid (intermediate 18) (53mg, 0.261 mmol) using EDCI.HCl (75mg, 0.3916 mmol), HOBt (37mg, 0.2741 mmol), DIPEA (135mg, 1.046 mmol) in DMF (5mL) to get the coupled product followed by deprotection using TBAF / THF (1/5mL) to get the title compound (26mg, 41.2%).

^{1}HNMR (CD_3OD, 400MHz): δ 8.49-8.47 (d, 1H), 7.85 (s, 1H), 7.74-7.72 (d, 1H), 7.70 (s, 1H), 7.40-7.39 (d, 1H), 7.33-7.32 (d, 1H), 4.45 (s, 1H), 3.83-3.77 (m, 4H), 3.74-3.69 (m, 4H),3.49-3.47(m, 1H), 3.42-3.40 (m, 1H), 3.21-3.16 (m, 1H), 2.61 (s, 3H), 2.09-2.07 (m, 1H), 1.89-1.86 (m, 1H), 1.88-1.72 (m, 1H), 1.43-1.37 (m, 1H). **LCMS:** 100%, m/z = 491.2 $(M+1)^+$. **HPLC:** 97.91%.

Example 108

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide

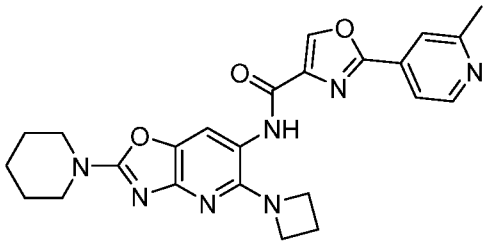


Using the same reaction conditions as described in example 45, (S)-5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 39) (109mg, 0.261 mmol), was coupled with 5-(2-methylpyridin-4-yl)thiophene-2-carboxylic acid (intermediate 17) (57mg, 0.261 mmol) using EDCI.HCl (75mg, 0.3916 mmol), HOBt (37mg, 0.2741 mmol), DIPEA (135mg, 1.046 mmol) in DMF (5mL) to get the coupled product followed by deprotection using TBAF / THF (1/5mL) to get the title compound (55mg, 66%).

^{1}HNMR (CD_3OD, 400MHz): δ 8.46-8.45 (d, 1H), 7.93-7.92 (d, 1H), 7.76-7.75 (d, 1H), 7.65 (s, 1H), 7.61 (s, 1H), 7.57-7.56 (d, 1H), 4.43 (s, 1H), 3.83-3.75 (m, 4H), 3.72-3.68 (m, 6H),3.51-3.50 (m, 1H), 3.42-3.36 (m, 1H), 2.60 (s, 3H), 2.07-2.05 (m, 1H), 1.93-1.92 (m, 1H). **LCMS:** 92.94%, m/z = 507.2 $(M+1)^+$. **HPLC:**96.09%.

Example 109

N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1:Preparation of 5-chloro-2-(piperidin-1-yl)oxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 3 of example 1, 5-chloro-2-(methylthio)oxazolo[4,5-b]pyridine (product of step 3 of example 2) (3g) was substituted using piperidine (8mL) and THF (30mL) to afford the title compound (3g, 90%).

LCMS: m/z = 238.1 $(M+1)^+$.

Step 2: Preparation of 5-chloro-6-nitro-2-(piperidin-1-yl)oxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 4 of example 20, 5-chloro-2-(piperidin-1-yl)oxazolo[4,5-b]pyridine (4g, 168 mmol) was nitrated using potassium nitrate (3.4g, 337 mmol) and conc. sulphuric acid (20mL) at RT for 3h to afford the crude title compound (4g). **LCMS:** m/z = 283.0 $(M+1)^+$.

Step 3: Preparation of 5-(azetidin-1-yl)-6-nitro-2-(piperidin-1-yl)oxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 1 of example 38, 5-chloro-6-nitro-2-(piperidin-1-yl)oxazolo[4,5-b]pyridine (400mg, 1.418 mmol) was substituted with azetidine hydrochloride (161mg, 1.7021 mmol) using potassium carbonate (391mg, 2.836 mmol) and THF (5mL) to afford the crude product (300mg). **LCMS:** m/z = 304.3 $(M+1)^+$.

Step 4: Preparation of 5-(azetidin-1-yl)-2-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 5-(azetidin-1-yl)-6-nitro-2-(piperidin-1-yl)oxazolo[4,5-b]pyridine (300mg, 0.990 mmol) was reduced with zinc dust (514mg, 7.92 mmol) and ammonium chloride (427mg, 7.92 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the crude product (200mg). **LCMS:** m/z = 274.1 $(M+1)^+$.

Step 5:Preparation of N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

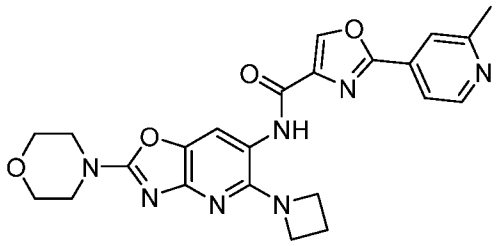
Using the same reaction conditions as described in step 6 of example 1, 5-(azetidin-1-yl)-2-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (100mg, 0.366 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (90mg, 0.439 mmol) using HATU (208mg, 0.549

mmol) and DIPEA (0.3mL, 1.465 mmol) in DMF (5mL) to afford the title compound (60mg, 36%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.81 (s, 1H), 8.97 (s, 1H), 8.69-8.68 (d, 1H), 7.86 (s, 1H), 7.78-7.77 (d, 1H), 7.60 (s, 1H), 3.97-3.93 (t, 4H), 3.65-3.60 (m, 4H), 2.59 (s, 3H),2.20-2.17(t, 2H), 1.62 (s, 6H). **LCMS:** 97.60%, m/z = 460.1 $(M+1)^+$. **HPLC:** 96.38%.

Example 110

N-(5-(azetidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of 5-(azetidin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 3 of example 1, 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (product of step 5 of example 2) (200mg, 0.701 mmol) was substituted with azetidine (81mg, 0.140 mmoland THF (5mL) at RT for 2h to afford the title compound (160mg, 73.39%). **LCMS:** m/z = 306.1 $(M+1)^+$.

Step 2: Preparation of 5-(azetidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 5-(azetidin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (160mg, 0.5245 mmol) was reduced with zinc dust (274mg, 4.196 mmol) and ammonium chloride (448mg, 8.393 mmol) in THF/methanol/H_2O (8mL/2mL/1mL)to get the title product (138mg, 95.83%). **LCMS:** m/z = 274.1 $(M-1)^+$.

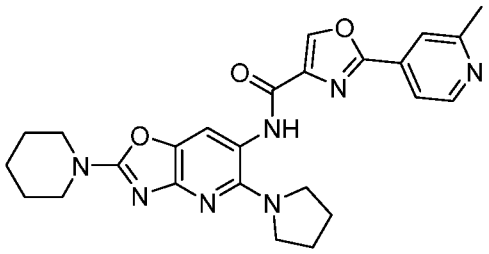
Step 3:Preparation of N-(5-(azetidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 5-(azetidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine (150mg, 0.5454 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (166mg, 0.818 mmol) using EDCI.HCl (156mg, 0.818 mmol), HOBt (110mg, 0.818 mmol) and DIPEA (282mg, 2.1818 mmol) in DMF (5mL) to afford the title compound (20mg, 8.0%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 8.70-8.69 (d, 1H), 8.62 (s, 1H), 8.39 (s, 1H), 8.17 (s, 1H), 7.81 (s, 1H), 7.75-7.74 (d, 1H), 4.19-4.15 (t, 4H), 3.82-3.81 (m, 4H), 3.74-3.73 (m, 4H),2.69(s, 3H), 2.37-2.33 (t, 2H). **LCMS:** 83.88%, m/z = 462.1 $(M+1)^+$. **HPLC:** 95.19%.

Example 111

2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide



Step 1: Preparation of 6-nitro-2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 1 of example 38, 5-chloro-6-nitro-2-(piperidin-1-yl)oxazolo[4,5-b]pyridine (product of step 2 of example 110) (400mg, 1.418 mmol) was substituted with pyrrolidine (120mg, 1.7021 mmol) in THF (10mL) to afford the crude product (300mg). **LCMS:** m/z = 318.2 $(M+1)^+$.

Step 2: Preparation of 2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 6-nitro-2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridine (300mg, 0.946 mmol) was reduced with zinc dust (492mg, 7.57 mmol) and ammonium chloride (409mg, 7.57 mmol) in THF/methanol/H_2O (5mL/2mL/1mL) to get the crude product (200mg). **LCMS:** m/z = 288.1 $(M+1)^+$.

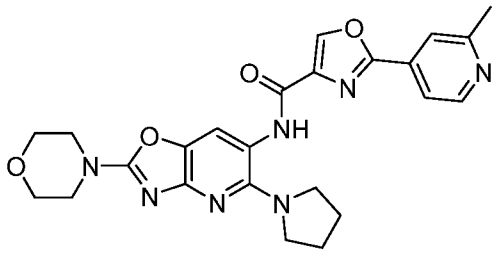
Step 3:Preparation of 2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (100mg, 0.348 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (80mg, 0.418 mmol) using HATU (198mg, 0.522 mmol) and DIPEA (0.3mL, 1.393 mmol) in DMF (5mL) to afford the title compound (140mg, 86%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.80 (s, 1H), 8.97 (s, 1H), 8.69-8.68 (d, 1H), 7.85 (s, 1H), 7.77-7.76 (d, 1H), 7.66 (s, 1H), 3.61-3.60 (m, 4H), 3.39-3.34 (m, 4H), 2.59 (s, 3H), 1.83(s, 4H), 1.62 (s, 6H). **LCMS:** 97.7%, m/z = 474.2 $(M+1)^+$. **HPLC:** 95.05%.

Example 112

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide



Step 1: Preparation of 2-morpholino-6-nitro-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 3 of example 1, 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (product of step 5 of example 2) (200mg, 0.701 mmol) was substituted with pyrrolidine (100mg, 0.7403 mmoland THF (5mL) at RT for 2h to afford the title compound (160mg, 71.11%). **LCMS:** m/z = 320.1 $(M+1)^+$.

Step 2: Preparation of 2-morpholino-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 2-morpholino-6-nitro-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridine (160mg, 0.5015 mmol) was reduced with zinc dust (262mg, 0.4012 mmol) and ammonium chloride (430mg, 8.0250 mmol) in THF/methanol/H_2O (5mL/2mL/1mL) to get the title product (130mg, 92.85%).

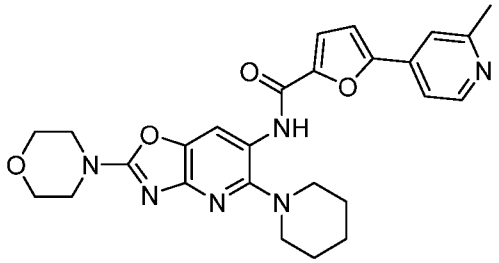
Step 3: Preparation of 2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (148mg, 0.5172 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (158mg, 0.7758 mmol) using EDCI.HCl (148mg, 0.7758 mmol), HOBt (104mg, 0.7758 mmol) and DIPEA (267mg, 2.0689 mmol) in DMF (5mL) to afford the title compound (80mg, 33.05%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.82 (s, 1H), 8.96 (s, 1H), 8.69-8.68 (s, 1H), 7.85 (s, 1H), 7.77-7.76 (d, 1H), 7.69 (s, 1H), 3.73-3.72 (m, 4H), 3.69-3.68 (m ,4H), 3.62-3.59 (m, 4H), 2.59 (s, 3H),1.84-1.81 (m, 4H). **LCMS**: 98.97%, m/z = 476.2 $(M+1)^+$. **HPLC:** 99.34%.

Example 113

5-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)furan-2-carboxamide

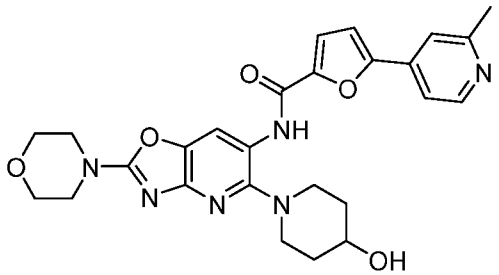


Using the same reaction conditions as described in step 6 of example 1, 2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-amine (product of step 2 of example 6) (70mg, 0.3448 mmol), was coupled with 5-(2-methylpyridin-4-yl)furan-2-carboxylic acid (intermediate 18) using HATU (196mg, 0.5172 mmol), DIPEA (134mg, 1.034 mmol) in DMF (5mL) to afford the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent to obtain the title compound (46mg, 29.8%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.85 (s, 1H), 8.79 (s, 1H), 8.58-8.56 (d, 1H), 7.59 (s, 1H), 7.44-7.43 (d, 1H), 7.34-7.33 (d, 1H), 7.02-7.01 (d, 1H), 3.84-3.81 (m, 4H), 3.76-3.74 (m, 4H),3.07-3.04(t, 4H), 2.64 (s, 3H), 1.88-1.85 (m, 4H), 1.69 (s, 2H). **LCMS:** 100%, m/z = 489.2 $(M+1)^+$. **HPLC:** 98.98%.

Example 114

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide



Step 1: Preparation of 1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)piperidin-4-ol

Using the same reaction conditions as described in step 3 of example 1, 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (product of step 5 of example 2) (250mg, 0.8802 mmol) was substituted with piperidin-4-ol (178mg, 1.760 mmol) and THF (10mL) at RT for 2h to afford the title compound (300mg, 97.71%). **LCMS:** m/z = 350.1 $(M+1)^+$.

Step 2: Preparation of 5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 2 of example 41, 1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)piperidin-4-ol(300mg, 0.859 mmol) was protected using TBDMS chloride (194mg, 1.289 mmol) and imidazole (117mg, 1.7191 mmol) and DMAP (21mg, 1.719 mmol) in DMF (5mL) at RT for 2h to get the title compound (300mg, 76%). **LCMS:** m/z = 464.2 $(M+1)^+$.

Step 3: Preparation of 5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 5-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (300mg, 0.6479 mmol) was reduced with zinc dust (330mg, 5.183 mmol) and ammonium chloride (554mg, 10.367 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the title product (150mg, 53.57%). **LCMS:** m/z = 434.2 $(M+1)^+$.

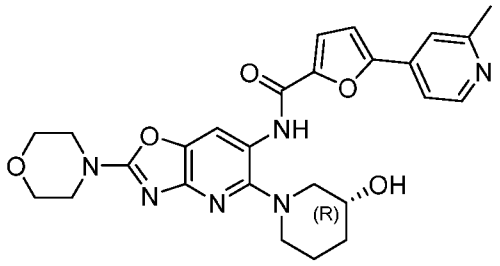
Step 4:Preparation of N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide

Using the same reaction conditions as described in example 45, 5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine (150mg, 0.346 mmol), was coupled with 5-(2-methylpyridin-4-yl)furan-2-carboxylic acid (intermediate 18) (84mg, 0.415 mmol) using HATU (171mg, 0.4503 mmol) and DIPEA (178mg, 1.385 mmol) in DMF (3mL) to get the coupled product followed by deprotection using TBAF / THF (63mg/5mL) to get the title compound (40mg, 50%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.62 (s, 1H), 8.55-8.54 (d, 1H), 8.37 (s, 1H), 7.74 (s, 1H), 7.68-7.67 (d, 1H), 7.48-7.45 (d, 2H), 4.80-4.79 (d, 1H), 3.73-3.63 (m, 8H), 3.20-3.17 (m, 3H),2.86-2.81(t, 2H), 2.56 (s, 3H), 1.91 (s, 2H), 1.67-1.65 (m, 2H). **LCMS:** 100%, m/z = 505.2 $(M+1)^+$. **HPLC:**96.82%.

Example 115

(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide



Step 1: Preparation of (R)-1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)piperidin-3-ol

Using the same reaction conditions as described in step 3 of example 1, 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (product of step 5 of example 2) (250mg, 0.8802 mmol) was substituted with (R)-piperidin-3-ol (121mg, 1.88 mmol) and THF (10mL) at RT for 2h to afford the title compound (230mg, 74.91%). **LCMS:** m/z = 350.1 $(M+1)^+$.

Step 2: Preparation of (R)-5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 2 of example 41, (R)-1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)piperidin-3-ol (230mg, 0.659 mmol) was protected using TBDMS chloride (149mg, 0.9885 mmol) and imidazole (89mg, 1.318 mmol) and DMAP (16mg, 0.1318 mmol) in DMF (5mL) at RT for 2h to get the title compound (300mg, 99.5%). **LCMS:** m/z = 464.2 $(M+1)^+$.

Step 3: Preparation of (R)-5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, (R)-5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (300mg, 0.6479 mmol) was reduced with zinc dust (330mg, 5.183 mmol) and ammonium chloride (554mg, 10.367 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the title product (150mg, 53.57%). **LCMS:** m/z = 434.2 $(M+1)^+$.

Step 4:Preparation of (R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide

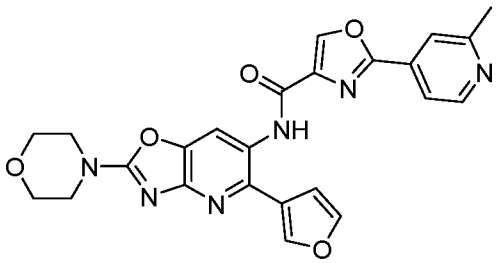
Using the same reaction conditions as described in example 45, (R)-5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine (150mg, 0.346 mmol), was coupled with 5-(2-methylpyridin-4-yl)furan-2-carboxylic acid (intermediate

18) (84mg, 0.415 mmol) using HATU (171mg, 0.4503 mmol) and DIPEA (178mg, 1.385 mmol) in DMF (3mL) to get the coupled product followed by deprotection using TBAF / THF (63mg/5mL) to get the title compound (32mg, 30.18%).

^{1}HNMR (DMSO-d_6, 400MHz): δ +.85 (s, 1H), 8.55-8.54 (d, 1H), 8.42 (s, 1H), 7.81 (s, 1H), 7.70-7.68 (d, 1H), 7.48-7.46 (m, 2H), 4.92-4.91 (d, 1H), 3.83 (s, 1H), 3.74-3.64 (m, 4H),3.64-3.62(m, 4H), 3.17-3.15 (m, 1H), 3.02-2.99(m, 1H), 2.83-2.79 (m, 1H), 2.73-2.70 (m, 1H), 2.55 (s,3H), 1.90-1.84 (m, 2H), 1.66-1.64 (m, 1H), 1.45-1.43 (m, 1H). **LCMS:** 98.47%, m/z = 505.2 $(M+1)^+$. **HPLC:** 98.78%.

Example 116

N-(5-(furan-3-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of 5-(furan-3-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 7 of example 1, 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (product of step 5 of example 2) (300mg, 1.0563 mmol) was coupled with furan-3-boronic acid (177mg, 1.5845 mmol) using sodium iodide (237mg, 1.5843 mmol) and Pd(dppf)Cl_2 (86mg, 0.1056 mmol) in 1,2-dimethoxyethane/water (5/1mL) to get the crude title compound (170mg). **LCMS:** m/z = 317.1 $(M+1)^+$.

Step 2:Preparation of 5-(furan-3-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (170mg, 0.5379 mmol) was reduced with zinc dust (281mg, 4.303 mmol) and ammonium chloride (460mg, 8.607 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the title product (130mg, 43.33%).

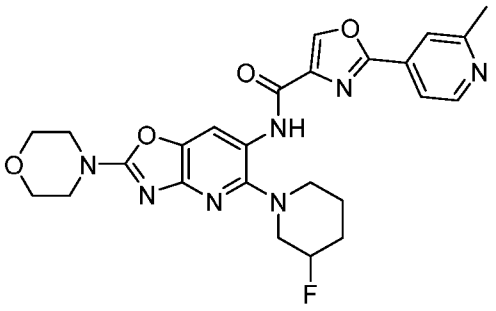
Step 3:Preparation of N-(5-(furan-3-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 5-(furan-3-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine (100mg, 0.3496 mmol) was coupled with 2-(2-

methylpyridin-4-yl)oxazole-4-carboxylic acid (106mg, 0.5244 mmol) using HATU (172mg, 0.4545 mmol) and DIPEA (180mg) in DMF (5mL) to afford the title compound (70mg, 42.42%). **^{1}HNMR** (DMSO-d_6, 400MHz): δ 10.19 (s, 1H), 9.02 (s, 1H), 8.71-8.69 (d, 1H), 8.14 (s, 1H), 7.94-7.87 (d, 2H), 7.79-7.75 (m, 2H), 7.01 (s, 1H), 3.76-3.65 (m, 8H), 2.60 (s, 3H). **LCMS:** 100%, m/z = 473.1 $(M+1)^+$. **HPLC:** 95.76%.

Example 117

N-(5-(3-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of 1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)piperidin-3-ol

Using the same reaction conditions as described in step 3 of example 1, 5-chloro-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (product of step 5 of example 2) (300mg, 1.056 mmol) was substituted with piperidin-3-ol (211mg, 2.110 mmol) and THF (5mL) at RT for 14h to afford the title compound (298mg, 81%). **LCMS:** m/z = 350.3 $(M+1)^+$.

Step 2: Preparation of 5-(3-fluoropiperidin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 2 of example 59,1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)piperidin-3-ol (270mg, 0.7736 mmol) was fluorinated using DAST (218mg, 1.353 mmol) in DCM (20mL) at -78°C for 1h to obtain the title compound (240mg, 88.4%).

Step 3: Preparation of 5-(3-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 5-(3-fluoropiperidin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (230mg, 0.6552 mmol) was reduced with zinc dust (340mg, 5.24 mmol) and ammonium chloride (555mg, 10.48 mmol) in THF/water (20/5mL) to get the title compound (145mg, 69%).

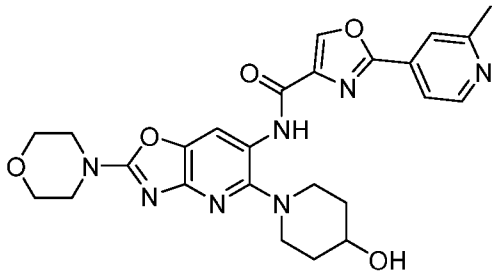
Step 4:Preparation of N-(5-(3-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 5-(3-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine (120mg, 0.3738 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (95mg, 0.4672 mmol) using HATU (213mg, 0.5605 mmol) and DIPEA (193mg) in DMF (5mL) to afford the crude compound. This was then purified by prep TLC using 3.5% methanol in chloroform to obtain the title compound (81mg, 34%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 9.86 (s, 1H), 9.05 (s, 1H), 8.70-8.68 (d, 1H), 8.62 (s, 1H), 7.85 (s, 1H), 7.75-7.74 (d, 1H), 5.10-4.90 (d, 1H), 3.73-3.70 (t, 4H), 3.62-3.61 (t, 4H), 3.26-3.10 (m, 2H), 2.80-2.90 (m, 2H), 2.57 (s, 3H), 2.20-1.70 (m, 4H). **LCMS:** 100%, m/z = 508.0 $(M+1)^+$. **HPLC:** 99.27%.

Example 118

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

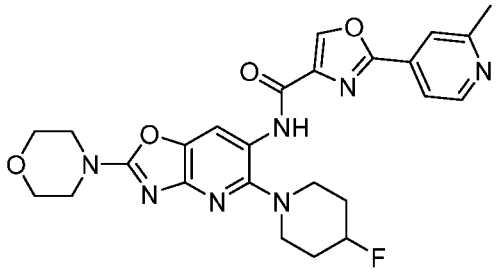


Using the same reaction conditions as described in example 45, 5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine (product of step 3 of example 115) (140mg, 0.3233 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (66mg, 0.3233 mmol) using HATU (185mg, 0.4868 mmol) and DIPEA (167mg, 1.295 mmol) in DMF (5mL) to get the coupled product followed by deprotection using methanol/MeOH. HCl (5/5mL) to get the title compound (127mg, 88%).

^{1}HNMR (DMSO-d_6, 300MHz): δ 9.90 (s, 1H), 9.00 (s, 1H), 8.66-8.64 (d, 1H), 8.58 (s, 1H), 7.83 (s, 1H), 7.74-7.72 (d, 1H), 4.90 (s, 1H), 3.71-3.70 (m, 5H), 3.61-3.59 (d, 4H), 3.12-3.08 (m, 2H), 2.85-2.78 (t, 2H), 2.57 (s, 3H), 1.99-1.96 (m, 2H),1.79-1.76 (m, 2H). **LCMS:** 100%, m/z = 506.1 $(M+1)^+$. **HPLC:** 98.00%.

Example 119

N-(5-(4-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of 5-(4-fluoropiperidin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 2 of example 59,1-(2-morpholino-6-nitrooxazolo[4,5-b]pyridin-5-yl)piperidin-4-ol (product of step 1 of example 115) (200mg, 0.5730 mmol) was fluorinated using DAST (161mg, 1.002 mmol) in DCM (20mL) at -78°C for 1h to obtain the title compound (191mg, 95%). **LCMS:** m/z = 352.1 $(M+1)^+$.

Step 2: Preparation of 5-(4-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 5-(4-fluoropiperidin-1-yl)-2-morpholino-6-nitrooxazolo[4,5-b]pyridine (190mg, 0.5413 mmol) was reduced with zinc dust (281mg, 4.33 mmol) and ammonium chloride (460mg, 8.66 mmol) in THF/water (20/5mL) to get the title product (90mg, 52%).

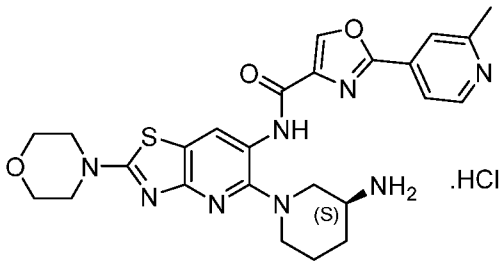
Step 3:Preparation of N-(5-(4-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 5-(4-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-amine (85mg, 0.2647 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (67mg, 0.328 mmol) using HATU (149mg, 0.394 mmol) and DIPEA (135mg, 1.050 mmol) in DMF (5mL) to afford the crude compound. This was then purified by prep TLC using 3.5% methanol in chloroform to obtain the title compound (81mg, 34%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 10.00 (s, 1H), 8.76 (s, 1H), 8.70-8.69 (d, 1H), 8.39 (s, 1H), 7.82 (s, 1H), 7.71-7.69 (dd, 1H), 5.00-4.70 (m, 1H), 3.84-3.81 (t, 4H), 3.76-3.73 (t, 4H), 3.29-3.21 (m, 2H), 3.10-3.05 (m, 2H), 2.67 (s, 3H), 2.27-2.18 (m, 4H). **LCMS:** 100%, m/z = 508.3 $(M+1)^+$. **HPLC:** 90.17%.

Example 120

(S)-N-(5-(3-aminopiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride



Step 1: Preparation of tert-butyl (S)-(1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)piperidin-3-yl)carbamate

Using the same reaction conditions as described in step 1 of example 38, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (200mg, 0.66mol) was substituted with tert-butyl (S)-piperidin-3-ylcarbamate (199mg, 0.99 mmol) using potassium carbonate (276mg, 1.99 mmol) and THF (10mL) to afford the crude product which was taken as such for next step.

Step 2: Preparation of tert-butyl (S)-(1-(6-amino-2-morpholinothiazolo[4,5-b]pyridin-5-yl)piperidin-3-yl)carbamate

Using the same reaction conditions as described in step 5 of example 1, crude tert-butyl (S)-(1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)piperidin-3-yl)carbamate was reduced with zinc dust (338mg , 5.1724 mmol) and ammonium chloride (553mg, 10.344 mmol) in THF/methanol/H_2O (10mL/2mL/1mL) to get the title compound (180mg, 64.48%). **LCMS:** m/z = 435.4 $(M+1)^+$.

Step 3: Preparation of tert-butyl (S)-(1-(6-(2-(2-methylpyridin-4-yl)oxazole-4-carboxamido)-2-morpholinothiazolo[4,5-b]pyridin-5-yl)piperidin-3-yl)carbamate

Using the similar reaction conditions as described in step 6 of example 1, tert-butyl (S)-(1-(6-amino-2-morpholinothiazolo[4,5-b]pyridin-5-yl)piperidin-3-yl)carbamate (450mg, 0.464 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (296mg, 1.4547 mmol) using HATU (479mg, 1.2607 mmol) and DIPEA (501mg, 3.8793 mmol) in DMF (5mL) to get the title compound (400mg, 66.66%). **LCMS:** m/z = 621.4 $(M+1)^+$.

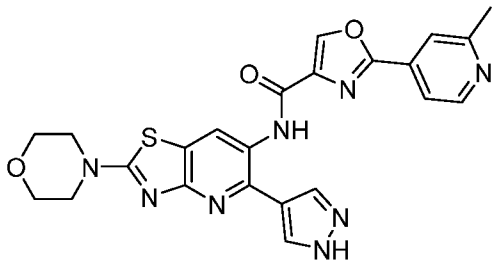
Step 4: Preparation of (S)-N-(5-(3-aminopiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride

Using the same reaction conditions as described in step 8 of example 1, tert-butyl (S)-(1-(6-(2-(2-methylpyridin-4-yl)oxazole-4-carboxamido)-2-morpholinothiazolo[4,5-b]pyridin-5-yl)piperidin-3-yl)carbamate (400mg, 0.6451 mmol) was deprotected using methanolic HCl/methanol (5/5mL) to get the title compound (100mg, 94.33%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.71 (s, 1H), 9.24 (s, 1H), 8.85-8.83 (d, 1H), 8.75 (s, 1H), 8.26 (s, 2H), 8.13 (s, 1H), 8.05-8.03 (d, 1H), 3.75-3.73 (m, 5H), 3.42-3.39 (m, 4H), 3.16-3.04 (m, 3H), 2.90-2.80 (m, 2H), 2.72 (s, 3H), 2.04-1.90 (m, 3H), 1.79-1.69 (m, 2H). **LCMS:** 86.06%, m/z = 521.4 $(M+1)^+$. **HPLC:** 98.61%.

Example 121

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(1H-pyrazol-4-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide



Step 1: Preparation of 4-(6-nitro-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)thiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 7 of example 1, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (250mg, 0.833 mmol) was coupled with 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (579mg, 2.083 mmol) using sodium iodide (375mg, 2.5 mmol), potassium carbonate (345mg, 2.5 mmol) and Pd(dppf)Cl_2 (304mg, 0.4166 mmol) in 1,2-dimethoxyethane/water (5/1mL) to get the title compound (150mg, 43.35%). **LCMS:** m/z = 417.15 $(M+1)^+$.

Step 2: Preparation of2-morpholino-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)thiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 4-(6-nitro-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)thiazolo[4,5-b]pyridin-2-yl)morpholine (150mg, 0.360 mmol) was reduced with zinc dust (188mg, 2.8846 mmol) and ammonium chloride

(308mg, 5.769 mmol) in THF/water (5/1mL) to get the crude product (110mg, 79.23%). **LCMS:** m/z = 387.2 $(M+1)^+$.

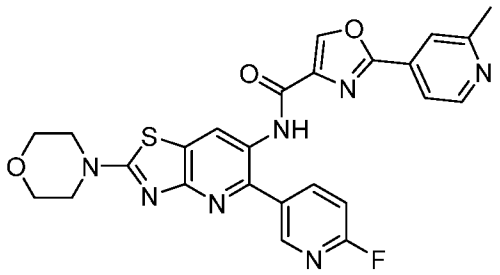
Step 3: Preparation of 2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(1H-pyrazol-4-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in example 45, 2-morpholino-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)thiazolo[4,5-b]pyridin-6-amine(130mg, 0.336 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (103mg, 0.505 mmol) using HATU (166mg, 0.4378 mmol) and DIPEA (174mg, 1.347 mmol) in DMF (5mL) to get the coupled product followed by deprotection using methanol/MeOH HCl (2/5mL) to get the title compound (75mg, 67.56%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 13.0 (s, 1H), 10.18 (s, 1H), 9.02 (s, 1H), 8.69-8.68 (d, 1H), 8.31 (s, 1H), 8.20-8.00 (bs, 2H), 7.87 (s, 1H), 7.79-7.78 (d, 1H), 3.76-3.64 (m, 8H), 2.60 (s, 3H). **LCMS:** 100%, m/z = 489.3 $(M+1)^+$. **HPLC:** 95.64%.

Example 122

N-(5-(6-fluoropyridin-3-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of 4-(5-(6-fluoropyridin-3-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 7 of example 1, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (200mg, 0.666 mmol) was coupled with (6-fluoropyridin-3-yl)boronic acid (234mg, 1.66 mmol) using sodium iodide (299mg, 1.99 mmol), potassium carbonate (276mg, 1.99 mmol) and Pd(dppf)Cl_2 (243mg, 0.333 mmol) in 1,2-dimethoxyethane/water (5/1mL) to get the title compound (152mg, 63.33%).

Step 2:Preparation of5-(6-fluoropyridin-3-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 4-(5-(6-fluoropyridin-3-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (152mg, 0.4210 mmol) was

reduced with zinc dust (220mg, 3.368 mmol) and ammonium chloride (360mg, 6.736 mmol) in THF/water (5/1mL) to get the crude product (150mg). **LCMS:** m/z = 331.9 $(M+1)^+$.

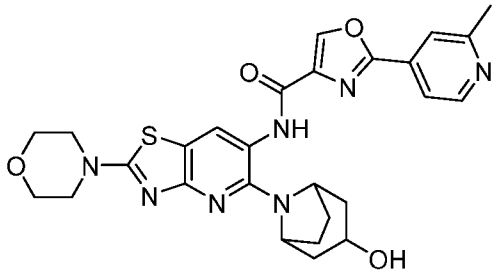
Step 3:Preparation of N-(5-(6-fluoropyridin-3-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the similar reaction conditions as described in step 6 of example 1, crude 5-(6-fluoropyridin-3-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (150mg, 0.4531 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (138mg, 6.797 mmol) using HATU (223mg, 0.589 mmol) and DIPEA (234mg, 1.812 mmol) in DMF (5mL) to get the title compound (110mg, 47%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 10.4 (s, 1H), 8.91 (s, 1H), 8.74 (s, 1H), 8.68-8.66 (d, 1H), 8.589-8.582 (d, 1H), 8.427 (s, 1H), 8.00-7.98 (d, 1H), 7.82 (s, 1H), 7.74-7.73 (d, 1H),3.76-3.75 (t, 4H), 3.67-3.66 (t, 4H), 2.58 (s, 3H). **LCMS:** 79.07%, m/z = 518.3 $(M+1)^+$. **HPLC:** 95.64%.

Example 123

N-(5-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of 8-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)-8-azabicyclo[3.2.1]octan-3-ol

Using the same reaction conditions as described in step 1 of example 38, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (300mg, 1 mmol) was substituted with 8-azabicyclo[3.2.1]octan-3-ol hydrochloride (195mg, 1.2 mmol) using potassium carbonate (552mg, 4 mmol) and DMF (5mL) to afford the title product (360mg, 92.3%). **LCMS:** m/z = 392.1 $(M+1)^+$.

Step 2: Preparation of 8-(6-amino-2-morpholinothiazolo[4,5-b]pyridin-5-yl)-8-azabicyclo[3.2.1]octan-3-ol

Using the same reaction conditions as described in step 2 of example 38, 8-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)-8-azabicyclo[3.2.1]octan-3-ol (350mg, 0.8951 mmol) was reduced with zinc dust (468mg, 7.161 mmol) and ammonium chloride (766mg, 14.321 mmol) in THF/water (10/2mL) to get the title compound (280mg, 86.68%). **LCMS:** m/z = 362.1 $(M+1)^+$.

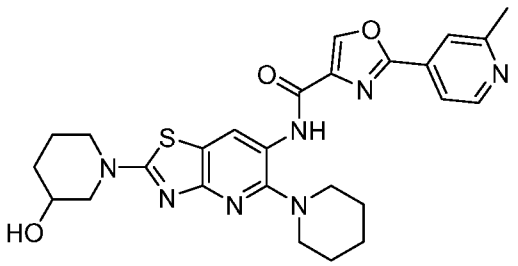
Step 3: Preparation of N-(5-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 8-(6-amino-2-morpholinothiazolo[4,5-b]pyridin-5-yl)-8-azabicyclo[3.2.1]octan-3-ol (100mg, 0.2770 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (85mg, 0.4155 mmol) using HATU (136mg, 0.3601 mmol) and DIPEA (143mg, 1.108 mmol) in DMF (5mL) to get the title compound (120mg, 79.47%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.52 (s, 1H), 9.08 (s, 1H), 8.78 (s, 1H), 8.71-8.70 (d, 1H), 7.81 (s, 1H), 7.73-7.72 (s, 1H), 4.568-4.563 (d, 1H), 4.10 (s, 1H), 4.03 (s, 2H), 3.74-3.72 (t, 4H), 3.58-3.55 (m, 4H), 2.59 (s, 3H), 2.42-2.39 (m, 2H), 2.20-2.18 (m, 2H), 1.94-1.93 (m, 2H), 1.83-1.80 (m, 2H). **LCMS:** 100%, m/z = 548.5 $(M+1)^+$. **HPLC:** 95.67%.

Example 124

N-(2-(3-hydroxypiperidin-1-yl)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1:Preparation of 6-bromo-5-chlorothiazolo[4,5-b]pyridine-2-thiol

Using the same reaction conditions as described in step 1 of example 1, 3,5-dibromo-6-chloropyridin-2-amine (3g, 10.489 mmol) was cyclised using potassium ethyl xanthate (3g, 18.881 mmol) in DMF (50mL) at 155°C for 3h to afford the title product (2.95g, 100%). **LCMS:** m/z = 280.8 $(M-1)^+$.

Step 2: Preparation of 6-bromo-5-chloro-2-(methylthio)thiazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 2 of example 1, 6-bromo-5-chlorothiazolo[4,5-b]pyridine-2-thiol (3g, 10.676 mmol) was methylated using potassium carbonate (2.94g, 21.352 mmol) and methyl iodide (2.29g, 16.014 mmol) in ethyl acetate (100mL) to afford the title compound (3.16g, 100%). **LCMS:** m/z = 296.7 $(M+1)^+$.

Step 3: Preparation of 2-(3-(benzyloxy)piperidin-1-yl)-6-bromo-5-chlorothiazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 1 of example 38, 6-bromo-5-chloro-2-(methylthio)thiazolo[4,5-b]pyridine (500mg, 1.689 mmol) was substituted with 3-(benzyloxy)piperidine hydrochloride (322mg, 1.689 mmol) using potassium carbonate (932mg, 6.756 mmol) and THF (5mL) at 85°C for 14h to afford the crude product. The crude product was purified by using 60-120 silica-gel column chromatography and compound was eluted using 30% ethyl acetate in hexane as eluent to afford the title compound (280mg, 37.8%). **LCMS:** m/z = 438.2 $(M)^+$.

Step 4: Preparation of 2-(3-(benzyloxy)piperidin-1-yl)-6-bromo-5-(piperidin-1-yl)thiazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 1 of example 6,2-(3-(benzyloxy)piperidin-1-yl)-6-bromo-5-chlorothiazolo[4,5-b]pyridine (280mg, 0.639 mmol) was substituted using piperidine (1mL) in THF (1mL) 125°C for 14h to obtain the crude product (280mg). **LCMS:** m/z = 489.1 $(M+2)^+$.

Step 5: Preparation of N-(2-(3-(benzyloxy)piperidin-1-yl)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

To the solution of 2-(3-(benzyloxy)piperidin-1-yl)-6-bromo-5-(piperidin-1-yl)thiazolo[4,5-b]pyridine (50mg, 0.102 mmol), 2-(2-methylpyridin-4-yl)oxazole-4-carboxamide (31mg, 0.154 mmol) (intermediate 23) and potassium phosphate (65mg, 0.306 mmol) in 1,4-dioxane (4mL) was added copper iodide (2mg, 0.01 mmol) and trans-N1,N2-dimethylcyclohexane-1,2-diamine (5mg, 0.030 mmol) and heated at 110°C for 14h. The solvent was distilled out and purified by 60-120 silica gel column chromatography using 5% methanol in DCM as eluent to obtain the title compound (40mg, 64.5%). **LCMS:** m/z = 610.3 $(M+1)^+$.

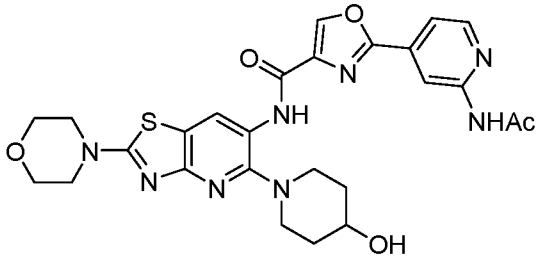
Step 6: Preparation of N-(2-(3-hydroxypiperidin-1-yl)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the similar reaction conditions as described in step 8 of example 1, N-(2-(3-(benzyloxy)piperidin-1-yl)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide (200mg, 0.328 mmol) was deprotected using TFA (5mL) and toluene (1mL) at 110°C for 14h to afford the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (50mg, 29.4%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 9.90 (s, 1H), 9.00 (s, 1H), 8.70-8.69 (d, 1H), 8.39 (s, 1H), 7.83 (s, 1H), 7.74-7.25 (s, 1H), 4.05-3.94 (m, 2H), 3.85-3.70 (m, 1H), 3.53-3.51 (m, 2H), 3.14-3.10 (t, 4H), 2.67 (s, 3H), 1.92-1.58 (m, 11H). **LCMS:** 96.10%, m/z = 520.4 $(M+1)^+$. **HPLC:** 97.47%.

Example 125

2-(2-acetamidopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

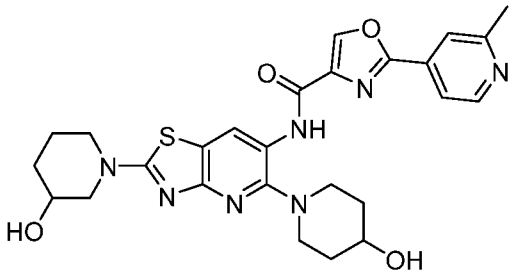


Using the same reaction conditions as described in example 45, 5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 3 of example 85) (155mg, 0.3452 mmol), was coupled with 2-(2-acetamidopyridin-4-yl)oxazole-4-carboxylic acid (intermediate 20) (106mg, 0.4315 mmol) using HATU (197mg, 0.5188 mmol) and DIPEA (179mg, 1.3835 mmol) in DMF (5mL) to get the crude compound followed by deprotection using TBAF / THF (1/10mL) to get the title compound (42mg, 46%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 9.10 (s, 1H), 8.60 (s, 1H), 8.32-8.31 (d, 1H), 7.42-7.41 (d, 1H), 7.33-7.32 (d, 1H), 7.07-7.06 (d, 1H), 3.18 (s, 4H), 3.69-3.67 (m, 4H), 3.30-3.26 (m, 2H), 3.09-3.01 (t, 2H), 2.26 (s, 3H), 2.19-2.16 (m, 2H), 2.00-1.87 (m, 4H). **LCMS:** 96.40%, m/z = 564.4 $(M+1)^+$. **HPLC:** 96.95%.

Example 126

N-(2-(3-hydroxypiperidin-1-yl)-5-(4-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1:Preparation of 1-(2-(3-(benzyloxy)piperidin-1-yl)-6-bromothiazolo[4,5-b]pyridin-5-yl)piperidin-4-ol

Using the same reaction conditions as described in step 1 of example 38, 2-(3-(benzyloxy)piperidin-1-yl)-6-bromo-5-(piperidin-1-yl)thiazolo[4,5-b]pyridine (product of step 3 of example 125) (200mg, 0.456 mmol) was substituted with 4-hydroxypiperidine (56mg, 0.547 mmol) using potassium carbonate (126mg, 0.912 mmol) and DMF (5mL) at 150°C for 5h to afford the crude product (250mg). **LCMS:** m/z = 505.3 $(M+2)^+$.

Step 2: Preparation of2-(3-(benzyloxy)piperidin-1-yl)-6-bromo-5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)thiazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 2 of example 41, 1-(2-(3-(benzyloxy)piperidin-1-yl)-6-bromothiazolo[4,5-b]pyridin-5-yl)piperidin-4-ol (250mg, 0.496 mmol) was protected using TBDMS chloride (149mg, 0.992 mmol), imidazole (50mg, 0.744 mmol) and DMAP (60mg, 0.496 mmol) in DMF (5mL) at RT for 2h to get the crude product (306mg).

Step 3: Preparation of N-(2-(3-(benzyloxy)piperidin-1-yl)-5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 5 of example 125, 2-(3-(benzyloxy)piperidin-1-yl)-6-bromo-5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)thiazolo[4,5-b]pyridine (306mg, 0.495 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxamide (120mg, 0.595 mmol) (intermediate 23) using potassium phosphate (314mg, 1.485 mmol), copper iodide (10mg, 0.049 mmol) and trans-N1,N2-dimethylcyclohexane-1,2-diamine (21mg, 0.148 mmol) in 1,4-dioxane (5mL) at 110°C for 14hand purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent to obtain the title compound (300mg, 84.2%).

Step 4: Preparation of N-(2-(3-(benzyloxy)piperidin-1-yl)-5-(4-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 8 of example 1,N-(2-(3-(benzyloxy)piperidin-1-yl)-5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide (150mg, 0.202 mmol) was deprotected using methanolic.HCl/methanol (1/1mL) to get the crude compound (120mg). **LCMS:** m/z = 626.4 $(M+1)^+$.

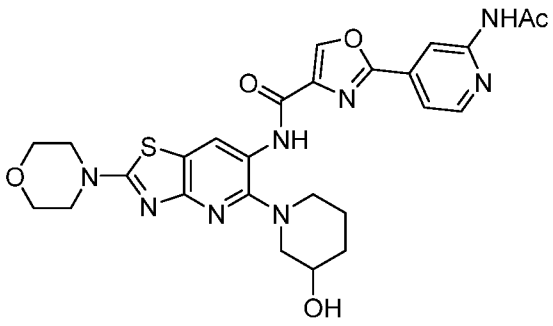
Step 5: Preparation of N-(2-(3-hydroxypiperidin-1-yl)-5-(4-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the similar reaction conditions as described in step 8 of example 1, N-(2-(3-(benzyloxy)piperidin-1-yl)-5-(4-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide (120mg, 0.191 mmol) was deprotected using TFA (5mL) and toluene (1mL) at 110°C for 1h to afford the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (40mg, 39.2%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.76(s, 1H), 9.08 (s, 1H), 8.91 (s, 1H), 8.70-8.69 (d, 1H), 7.89 (s, 1H), 7.79-7.77 (d, 1H), 5.09-5.08 (d, 1H), 4.90-4.89 (d, 1H), 3.88-3.86 (m, 1H), 3.73-3.62 (m, 3H), 3.21-3.11 (m, 4H), 2.89-2.86 (t, 2H), 2.67 (s, 3H), 2.02-1.99 (m, 2H), 1.90-1.77 (m, 4H), 1.53-1.23 (m, 2H). **LCMS:** 81.88%, m/z = 536.3 $(M+1)^+$. **HPLC:** 98.31%.

Example 127

2-(2-acetamidopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide



Step 1:Preparation of 1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)piperidin-3-ol

Using the same reaction conditions as described in step 2 of example 43, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (500mg, 1.66mol) was substituted using piperidin-3-ol (202mg, 1.99 mmol) using potassium carbonate (691mg,

4.99 mmol) in DMF (5mL) at RT for 2h to obtain the title compound (500mg, 83.33%). **LCMS:** m/z = 366.2 $(M+1)^+$.

Step 2: Preparation of 4-(5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 2 of example 41, 1-(2-morpholino-6-nitrothiazolo[4,5-b]pyridin-5-yl)piperidin-3-ol(300mg, 0.8219 mmol) was protected using TBDMS chloride (185mg, 1.232 mmol) and imidazole (111mg, 1.643 mmol) and DMAP (20mg, 0.1643 mmol) in DMF (5mL) at RT for 0.5h to get the crude product. The resultant crude was purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent to obtain the title compound (350mg, 89.74%). **LCMS:** m/z = 480.2 $(M+1)^+$.

Step 3: Preparation of 5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 2 of example 38, 4-(5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (400mg, 0.8333 mmol) was reduced with zinc dust (435mg, 6.66 mmol) and ammonium chloride (713mg, 13.3 mmol) in THF / water (10/2mL) to get the title compound (290mg, 77.33%). **LCMS:** m/z = 451.0 $(M+1)^+$.

Step 4: Preparation of 2-(2-acetamidopyridin-4-yl)-N-(5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (100mg, 0.222 mmol), was coupled with 2-(2-acetamidopyridin-4-yl)oxazole-4-carboxylic acid (intermediate 20) (82mg, 0.332 mmol) using HATU (108mg, 0.288 mmol) and DIPEA (115mg, 0.888 mmol) in DMF (5mL) to get the crude title compound (132mg, 88%). **LCMS:** m/z = 679.5 $(M+1)^+$.

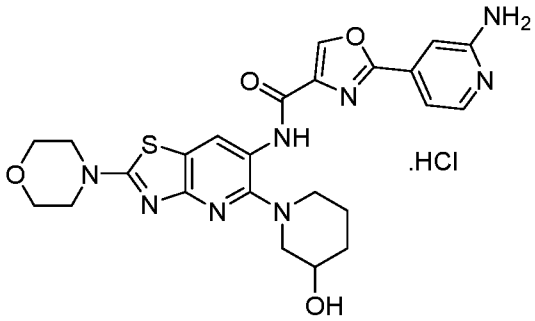
Step 5: Preparation of 2-(2-acetamidopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 8 of example 12-(2-acetamidopyridin-4-yl)-N-(5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-

morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide (132mg, 0.1946 mmol) was deprotected using methanolic HCl/methanol (3mL) to get the title compound (20mg, 18.34%). **^{1}HNMR** (DMSO-d_6, 400MHz): δ 10.81 (s, 1H), 9.61 (s, 1H), 9.07 (s, 1H), 8.93 (s, 1H), 8.79 (s, 1H), 8.56-8.55 (d, 1H), 7.66-7.65 (d, 1H), 4.81 (s, 1H), 3.88 (s, 1H), 3.74 (s, 4H), 3.58 (s, 4H), 3.30-3.20 (m, 1H), 3.14-3.11 (d, 1H), 2.72-2.60 (m, 3H), 2.15 (s, 3H), 2.05 (s, 1H), 1.86 (s, 1H), 1.40-1.20 (m, 1H). **LCMS:** 49.65%, m/z = 565.4 $(M+1)^+$. **HPLC:** 95.43%.

Example 128

2-(2-aminopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride



Step 1: Preparation of 2-(2-aminopyridin-4-yl)-N-(5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 6 of example 1, 5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 3 of example 128) (100mg, 0.222 mmol), was coupled with 2-(2-aminopyridin-4-yl)oxazole-4-carboxylic acid (intermediate 21) (68mg, 0.333 mmol) using HATU (109mg, 0.288 mmol) and DIPEA (114mg, 0.888 mmol) in DMF (5mL) to get the title compound (120mg, 85.71%). **LCMS:** m/z = 637.4$(M+1)^+$.

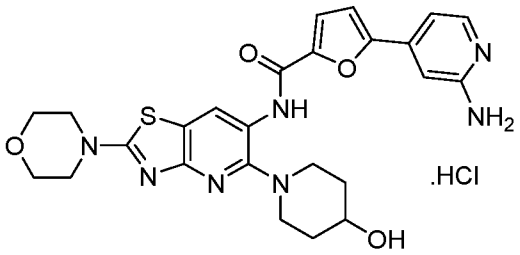
Step 2: Preparation of 2-(2-aminopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride

Using the same reaction conditions as described in step 8 of example 1, 2-(2-aminopyridin-4-yl)-N-(5-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide (120mg, 0.188 mmol) was deprotected using methanolic HCl/methanol (5/2mL) to get the title compound (20mg, 37.73%).

^{1}HNMR (DMSO-d_6, 400MHz): δ 9.58 (s, 1H), 9.16 (s, 1H), 8.87 (s, 1H), 8.20-8.19 (d, 1H), 7.53 (s, 1H), 7.28-7.27 (d, 1H), 3.90-3.80 (m, 1H), 3.74 (s, 2H), 3.58 (s, 2H), 3.27-3.25 (m, 2H), 3.14-3.09 (m, 1H), 2.90-2.70 (m, 2H), 2.76-2.73 (m, 2H), 2.10-1.70 (m, 6H). **LCMS:** 93.20%, m/z = 523.4 $(M+1)^+$. **HPLC:** 97.01%.

Example 129

5-(2-aminopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)furan-2-carboxamide hydrochloride

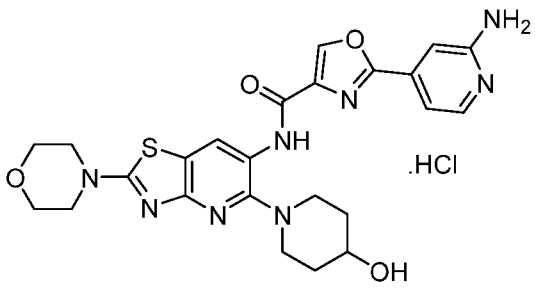


Using the same reaction conditions as described in example 45, 5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 3 of example 85) (155mg, 0.3452 mmol), was coupled with 5-(2-acetamidopyridin-4-yl)furan-2-carboxylic acid (intermediate 22) (106mg, 0.4315 mmol) using HATU (197mg, 0.5188 mmol) and DIPEA (179mg, 1.3835 mmol) in DMF (5mL) to get the crude compound followed by deprotection using HCl / MeOH (5/5mL) to get the title compound (50mg, 55%).

^{1}HNMR (CD_3OD, 300MHz): δ 8.58 (s, 1H), 7.93-7.91 (d, 1H), 7.55-7.52 (m, 2H), 7.48 (s, 1H), 7.41-7.38 (dd, 1H), 3.88-3.78 (m, 12H), 2.04-1.81 (m, 5H). **LCMS:** 99.14%, m/z = 522.3 $(M+1)^+$. **HPLC:** 97.06%.

Example 130

2-(2-aminopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride

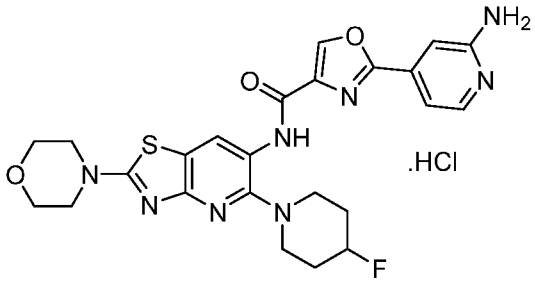


Using the same reaction conditions as described in example 45, 5-(4-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 3 of example 85) (100mg, 0.222 mmol), was coupled with 2-(2-aminopyridin-4-yl)oxazole-4-carboxylic acid (intermediate 21) (50mg, 0.244 mmol) using HATU (126mg, 0.333 mmol) and DIPEA (114mg, 0.888 mmol) in DMF (3mL) to get the crude compound followed by deprotection using methanolic HCl / MeOH (2/1mL) to get the crude compound. This was then purified by prep HPLC and treated with methanolic HCl to get the title compound (27mg, 31%).

^{1}HNMR (CD_3OD, 300MHz): δ 8.95 (s, 1H), 8.868-8.864 (d, 1H), 8.05-8.03 (d, 1H), 7.687-7.684(d, 1H), 7.53-7.50 (dd, 1H), 3.87-3.84 (t, 4H), 3.73 (s, 4H), 3.54-3.33 (m, 2H), 3.12-3.07 (m, 3H), 2.12-2.09 (m, 2H),1.90-1.87 (m, 2H). **LCMS:** 99.56%, m/z = 523.2 $(M+1)^+$. **HPLC:** 97.24%.

Example 131

2-(2-aminopyridin-4-yl)-N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride

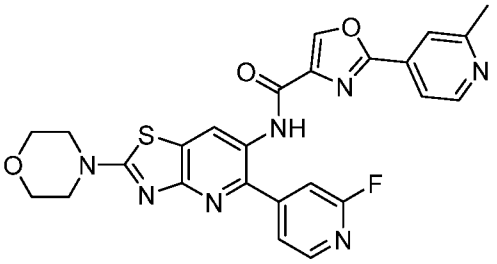


Using the same reaction conditions as described in example 45, 5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (product of step 2 of example 98) (70mg, 0.2 mmol) was coupled with 2-(2-acetamidopyridin-4-yl)oxazole-4-carboxylic acid (intermediate 20) (62mg, 0.24 mmol) using HATU (100mg, 0.27 mmol) and DIPEA (110mg, 0.83 mmol) in DMF (0.3mL) to afford the crude product followed by deprotection using HCl / MeOH (0.5/2mL) to get the crude compound. This was then purified by prep HPLC and treated with methanol/ether HCl (0.5/0.5mL) to get the title compound (30mg).

^{1}HNMR (CD_3OD, 300MHz): δ 8.90 (s, 1H), 8.86 (s, 1H), 8.03-8.02 (d, 1H), 7.64-7.63 (d, 1H), 7.50-7.06 (dd, 1H), 3.86-3.83 (m, 4H), 3.73-3.70 (t, 4H), 3.37-3.31 (m, 2H), 3.24-3.23 (m, 5H), 2.30-2.20 (m, 4H). **LCMS:** 58.28%, m/z = 525.2 $(M+1)^+$. **HPLC:** 98.31%.

Example 132

N-(5-(2-fluoropyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of 4-(5-(2-fluoropyridin-4-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine

Using the same reaction conditions as described in step 7 of example 1, 4-(5-chloro-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (product of step 4 of example 20) (200mg, 0.666 mmol) was coupled with (2-fluoropyridin-4-yl)boronic acid (223mg, 1 mmol) using sodium iodide (200mg, 1.3 mmol), potassium carbonate (276mg, 2 mmol) and $Pd(dppf)Cl_2$ (48mg, 0.067 mmol) in 1,2-dimethoxyethane/water (1/0.2mL) to get the title compound (100mg).

Step 2:Preparation of5-(2-fluoropyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine

Using the same reaction conditions as described in step 5 of example 1, 4-(5-(2-fluoropyridin-4-yl)-6-nitrothiazolo[4,5-b]pyridin-2-yl)morpholine (90mg, 0.25 mmol) was reduced with zinc dust (130mg, 1.99 mmol) and ammonium chloride (212mg, 3.98 mmol) in THF/water (2/1mL) to get the title product (70mg). **LCMS:** m/z = 332.3 $(M+1)^+$.

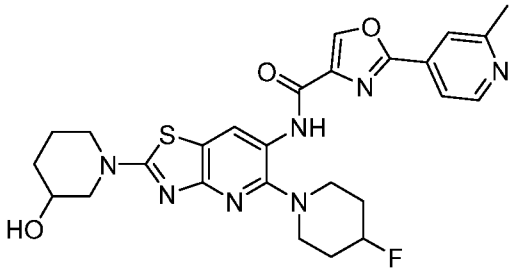
Step 3:Preparation of N-(5-(2-fluoropyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the similar reaction conditions as described in step 6 of example 1, crude 5-(2-fluoropyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-amine (70mg, 0.21 mmol), was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxylic acid (52mg, 0.25 mmol) using HATU (104mg, 0.27 mmol) and DIPEA (110mg, 0.84 mmol) in DMF (0.3mL) to get the title compound (100mg).

^{1}HNMR (DMSO-d_6, 300MHz): δ 10.40 (s, 1H), 8.92 (s, 1H), 8.67-8.65 (d, 1H), 8.44 (s, 1H), 8.28-8.26 (d, 1H), 7.81 (s, 1H), 7.73-7.71 (d, 1H), 7.63-7.61 (d, 1H), 7.44 (s, 1H), 3.75 (s, 4H), 3.65 (s, 4H), 2.56 (s, 3H). **LCMS:** 100%, m/z = 518.4 $(M+1)^+$. **HPLC:** 96.41%.

Example 133

N-(5-(4-fluoropiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide



Step 1: Preparation of 1-(6-bromo-5-chlorothiazolo[4,5-b]pyridin-2-yl)piperidin-3-ol

Using the same reaction conditions as described in step 1 of example 6,6-bromo-5-chloro-2-(methylthio)thiazolo[4,5-b]pyridine (product of step 2 of example 125) (1g, 3.370 mmol) was substituted using 3-hydroxypiperidine (510mg, 5.06 mmol) in THF (10mL) at 100°C for 5h to obtain the crude product (280mg). The crude product was purified by using 60-120 silica-gel column chromatography and compound was eluted using 5% methanol in DCM as eluent to afford the title compound (1.1g, 94%).

Step 2: Preparation of6-bromo-2-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-5-chlorothiazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 2 of example 41, 1-(6-bromo-5-chlorothiazolo[4,5-b]pyridin-2-yl)piperidin-3-ol (1g, 2.865 mmol) was protected using TBDMS chloride (863mg, 5.73 mmol), imidazole (292mg, 4.297 mmol) and DMAP (350mg, 2.865 mmol) in DMF (5mL) at RT for 1h to get the title compound (1.3g, 100%). **LCMS:** m/z = 464.2 $(M+2)^+$.

Step 3: Preparation of 1-(6-bromo-2-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)thiazolo[4,5-b]pyridin-5-yl)piperidin-4-ol

Using the same reaction conditions as described in step 1 of example 38, 6-bromo-2-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-5-chlorothiazolo[4,5-b]pyridine(500mg, 1.082 mmol) was substituted with 4-hydroxypiperidine (162mg, 1.623 mmol) using potassium carbonate (298mg, 2.164 mmol) and DMF (1mL) at 160°C for 14h to afford the crude product. The crude product was purified by using 60-120 silica-gel column chromatography and compound was eluted using 2% methanol in DCM as eluent to afford the title compound (200mg, 35%). **LCMS:** m/z = 527.2 $(M+2)^+$.

Step 4:Preparation of 6-bromo-2-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-5-(4-fluoropiperidin-1-yl)thiazolo[4,5-b]pyridine

Using the same reaction conditions as described in step 2 of example 59,1-(6-bromo-2-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)thiazolo[4,5-b]pyridin-5-yl)piperidin-4-ol (200mg, 0.378 mmol) was fluorinated using DAST (0.2mL) in DCM (5mL) at -20°C for 1h. The resultant crude was purified by 60-120 silica gel column chromatography using 50% ethyl acetate in hexane as eluent to obtain the title compound (120mg). **LCMS:** m/z = 529.3 $(M)^+$.

Step 5: Preparation of N-(2-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-5-(4-fluoropiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the same reaction conditions as described in step 5 of example 125, 6-bromo-2-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-5-(4-fluoropiperidin-1-yl)thiazolo[4,5-b]pyridine (120mg, 0.226 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxamide (60mg, 0.294 mmol) (Intermediate 23) using potassium phosphate (143mg, 0.678 mmol), copper iodide (4mg, 0.022 mmol) and trans-N1,N2-dimethylcyclohexane-1,2-diamine (10mg, 0.067 mmol) in 1,4-dioxane (5mL) at 110°C for 14h and purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent to obtain the crude compound (100mg). **LCMS:** m/z = 652.4 $(M+1)^+$.

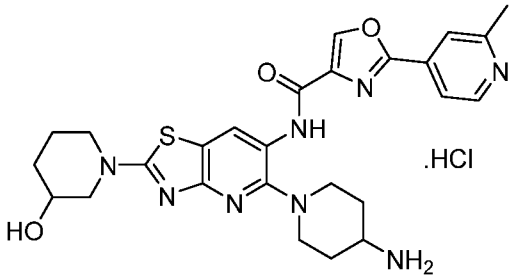
Step 6: Preparation of N-(5-(4-fluoropiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide

Using the similar reaction conditions as described in step 8 of example 1, N-(2-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-5-(4-fluoropiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide (100mg, 0.153 mmol) was deprotected using methanolic HCl (5mL) and methanol (1mL) at RT for 0.5h to afford the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (24mg, 29.2%).

^{1}HNMR ($CDCl_3$, 400MHz): δ 9.83 (s, 1H), 9.02 (s, 1H), 8.71-8.69 (d, 1H), 8.41 (s, 1H), 7.83 (s, 1H), 7.72-7.70 (d, 1H), 5.00-4.75 (m, 1H), 3.97-3.94 (m, 2H), 3.85-3.75 (m, 1H), 3.54-3.50 (m, 2H), 3.40-3.30 (m, 2H), 3.13-3.11 (m, 2H), 2.68 (s, 3H), 2.24-2.20 (m, 4H), 2.00-1.99 (m, 3H), 1.69-1.64 (m, 2H). **LCMS:** 93.92%, m/z = 538.4 $(M+1)^+$. **HPLC:** 95.18%.

Example 134

N-(5-(4-aminopiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride



Step 1: Preparation of tert-butyl (1-(6-bromo-2-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)thiazolo[4,5-b]pyridin-5-yl)piperidin-4-yl)carbamate

Using the same reaction conditions as described in step 1 of example 38, 6-bromo-2-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)-5-chlorothiazolo[4,5-b]pyridine (product of step 2 of example 134) (500mg, 1.082 mmol) was substituted with tert-butyl piperidin-4-ylcarbamate (324mg, 1.623 mmol) using potassium carbonate (298mg, 2.164 mmol) and DMF (1mL) at 150°C for 14h to afford the crude product. The crude product was purified by using 60-120 silica-gel column chromatography and compound was eluted using 50% ethyl acetate in hexane as eluent to afford the title compound (100mg, 14.7%). **LCMS:** m/z = 628.4 $(M+2)^+$.

Step 2: Preparation of tert-butyl (1-(2-(3-hydroxypiperidin-1-yl)-6-(2-(2-methylpyridin-4-yl)oxazole-4-carboxamido)thiazolo[4,5-b]pyridin-5-yl)piperidin-4-yl)carbamate

Using the same reaction conditions as described in step 5 of example 125, tert-butyl (1-(6-bromo-2-(3-((tert-butyldimethylsilyl)oxy)piperidin-1-yl)thiazolo[4,5-b]pyridin-5-yl)piperidin-4-yl)carbamate (100mg, 0.159 mmol) was coupled with 2-(2-methylpyridin-4-yl)oxazole-4-carboxamide (42mg, 0.207 mmol) (Intermediate 23) using potassium phosphate (101mg, 0.477 mmol), copper iodide (3mg, 0.015 mmol) and trans-N1,N2-dimethylcyclohexane-1,2-diamine (7mg, 0.047 mmol) in 1,4-dioxane (5mL) at 110°C for 14h and purified by 60-120 silica gel column chromatography using 2% methanol in DCM as eluent to obtain the crude compound (100mg).

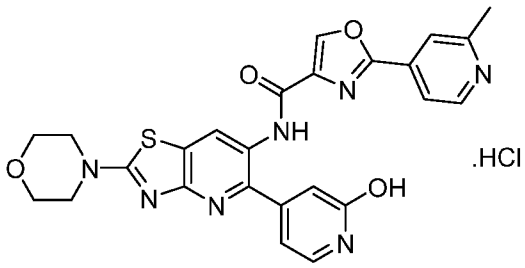
Step 3: Preparation of N-(5-(4-aminopiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride

Using the similar reaction conditions as described in step 8 of example 1, tert-butyl (1-(2-(3-hydroxypiperidin-1-yl)-6-(2-(2-methylpyridin-4-yl)oxazole-4-carboxamido)thiazolo[4,5-b]pyridin-5-yl)piperidin-4-yl)carbamate (100mg, 0.153 mmol) was deprotected using methanolic HCl (5mL) and methanol (1mL) at RT for 0.5h to afford the crude product. The resultant crude was purified by prep HPLC to obtain the title compound (20mg, 28.1%).

^{1}HNMR (CD_3OD, 300MHz): δ 8.96-8.92 (m, 2H), 8.76 (s, 1H), 8.60-8.58 (m, 2H), 3.98-3.88 (m, 2H), 3.76-3.66 (m, 5H), 3.50-3.40 (m, 1H), 3.17-3.09 (t, 2H), 2.94 (s, 3H), 2.13-1.96 (m, 7H), 2.35-2.20 (m, 2H). **LCMS:** 98.18%, m/z = 535.4 $(M+1)^+$. **HPLC:** 96.08%.

Example 135

N-(5-(2-hydroxypyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride



The solution of N-(5-(2-fluoropyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide (example 133) (100mg, 0.19 mmol) in methanolic HCl (10mL) was stirred at RT for 1h and distilled out the solvent. The resultant crude was purified by prep HPLC and treated with methanolic HCl to obtain the title compound (50mg).

^{1}HNMR (CD_3OD, 300MHz): δ 8.91-8.88 (m, 2H), 8.78 (s, 1H), 8.56 (s, 1H), 8.48-8.46 (d, 1H), 7.83-7.80 (d, 1H), 7.12 (s, 1H), 7.97-7.95 (d, 1H), 3.88 (s, 8H), 2.91 (s, 3H). **LCMS:** 100%, m/z = 516.2 $(M+1)^+$. **HPLC:** 98.02%.

IRAK-4 Biochemical assay

Compounds were tested for their potential to inhibit IRAK-4 enzyme in a TR-FRET assay using recombinant IRAK-4 kinase from Millipore, USA. The assay buffer was 50mM Tris-HCl pH 7.5, 20mM $MgCl_2$, 1mM EGTA, 2mM DTT, 3mM $MnCl_2$ and 0.01% Tween20. 5ng of IRAK-4 kinase was used for the assay. After pre-incubation of enzyme with test compound for 30 minutes at room temperature, a substrate mix containing 100nM Biotin Histone H3 (Millipore, USA) and 20μM ATP (Sigma, USA) was added and the reaction was incubated for 30 minutes. Post incubation, the reaction was stopped by the addition of stop mix containing

40mM EDTA, 1nM of Europium-Anti-Phospho-Histone H3 (Ser10) antibody (Perkin Elmer, USA) and 20 nM Sure Light Allophycocyanin-Streptavidin (Perkin Elmer, USA). The fluorescence emission at 615 nm and 665 nm were measured at an excitation of 340nm and the percent inhibition was estimated from the ratio of the fluorescence intensities [(F665/F615)*10000]. The compounds were initially screened at 1µM and 10µM concentrations and potent compounds (>50% inhibition at 1µM) were taken for dose response studies. The IC_{50} values were estimated by fitting the dose-response data to sigmoidal dose response (variable slope), curve fitting program using Graphpad Prism software Version 6.01.

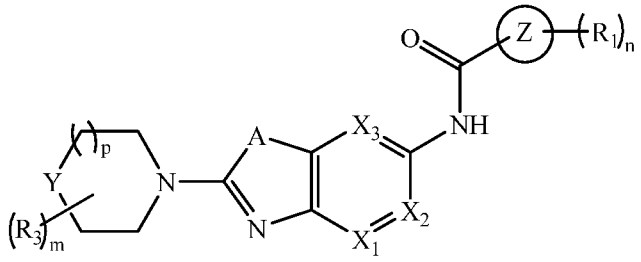
The compounds of the present invention were screened in the above mentioned assay and the results (IC_{50}) are summarized in the table 1. The IC_{50} values of the compounds of examples are set forth below wherein "A" refers to an IC_{50} value of less than or equal to 50nM, "B" refers to IC_{50} value ranges from 50.01 nM to 100nM and "C" refers to an IC50 value of greater than 100 nM.

Table 1: IC_{50} values for IRAK4 activity of the selected compounds.

Group	Example No
A	3, 5, 7-8, 10-14, 16, 20-27, 29, 32-41, 43-45, 47, 50-67, 69-78, 80, 82-102, 104, 110-111, 113-131 and 133-134.
B	4, 6, 9, 42, 68 and 79
C	17, 28, 30-31, 46, 48, 81, 103, 105-109 and 112

WE CLAIM:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt or a stereoisomer thereof;

wherein,

X_1 and X_3 independently are CH or N; X_2 is CR_2 or N; provided one and not more than one of X_1, X_2 or X_3 is N;

A is O or S;

Y is $-CH_2-$ or O;

Ring Z is aryl or heterocyclyl;

R_1, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or $-NR_aR_b$;

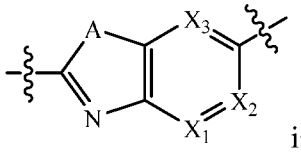
R_2 is hydrogen, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or $-NR_aR_b$; wherein the substituent is alkyl, amino, halo or hydroxyl;

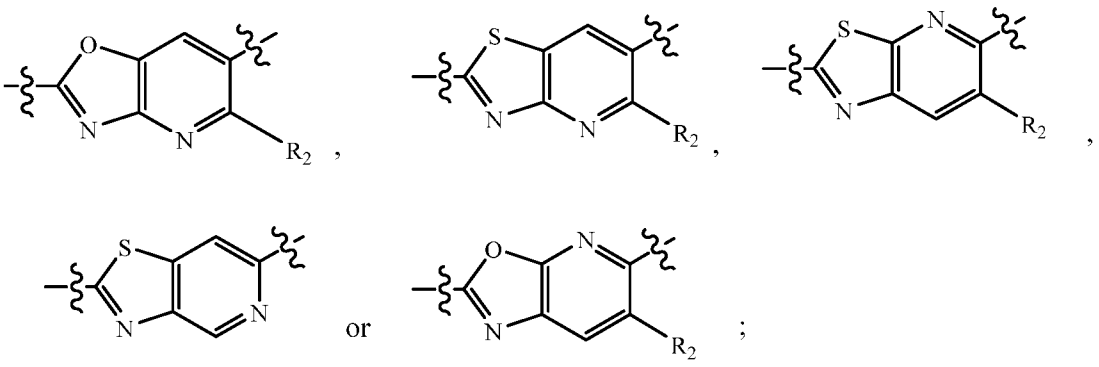
R_3, at each occurrence, is alkyl or hydroxyl;

R_a and R_b are independently hydrogen, alkyl, acyl or heterocyclyl;

'm' and 'n' are independently 0, 1 or 2;

'p' is 0 or 1.

2. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the group  is

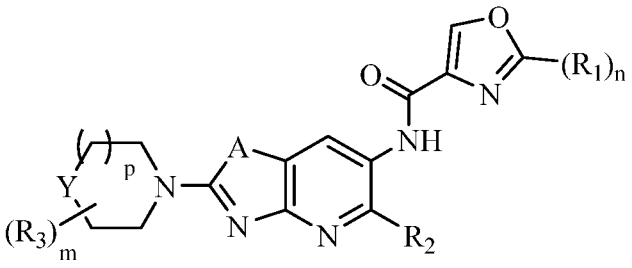


wherein R_2 is as defined in claim 1.

3. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1, wherein the Ring Z is aryl or 5- or 6-membered heterocyclyl.

4. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 or 3, wherein Ring Z is optionally substituted groups selected from phenyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, azetidinyl, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl,1,4-dioxanyl, dioxidothiomorpholinyl, oxapiperazinyl, oxapiperidinyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl or azabicyclo[3.2.1]octanyl; each of which is optionally substituted with alkyl, alkoxy, halo, hydroxyl, hydroxyalkyl or $-NR_aR_b$; R_a and R_b are independently hydrogen, alkyl or acyl.

5. The compound of formula (I) according to claim 1, is a compound of formula (IA):

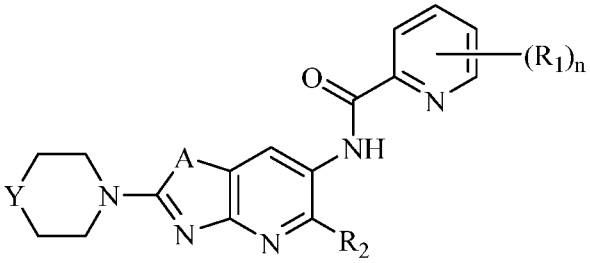


(IA)

or a pharmaceutically acceptable salt or a stereoisomer thereof;

wherein, A, Y, R_1, R_2, R_3, 'm', 'p' and 'n' are same as defined in claim 1.

6. The compound of formula (I) according to claim 1 is a compound of formula (IB):

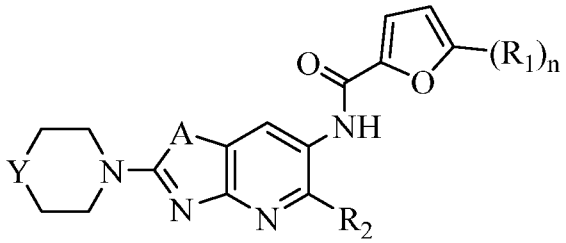


(IB)

or a pharmaceutically acceptable salt or a stereoisomer thereof;

wherein, A, Y, R_1, R_2 and 'n' are same as defined in claim 1.

7. The compound of formula (I) according to claim 1, is a compound of formula (IC)



(IC)

or a pharmaceutically acceptable salt or a stereoisomer thereof;

wherein, A, Y, R_1, R_2 and 'n' are same as defined in claim1.

8. The compounds of formula (I) or a pharmaceutically acceptable salt thereof, according to any one of claims 1, 5, 6 or 7 wherein Y is O or CH_2.

9. The compounds of formula (I) or a pharmaceutically acceptable salt thereof, according to any one of claims 1, 5 or 6 wherein R_2 is hydrogen.

10. The compounds of formula (I) or a pharmaceutically acceptable salt thereof, according to any one of claims 1, 5, 6 or 7 wherein R_2 is optionally substituted heterocyclyl selected from piperidinyl, pyrrolidinyl, morpholinyl, piperazinyl, azetidinyl, pyrazolyl, furanyl or azabicyclo[3.2.1]octanyl; wherein the substituent is hydroxyl, halo, alkyl or amino.

11. The compounds of formula (I) or a pharmaceutically acceptable salt thereof, according to any one of claims 1, 5, 6 or 7 wherein R_2 is cycloalkyl.

12. The compounds of formula (I) or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 11, wherein R_1 is optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or $-NR_aR_b$; R_a and R_b are independently hydrogen or acyl.

13. The compounds of formula (I) or a pharmaceutically acceptable salt thereof, according to claim 12, wherein R_1 is pyridyl, pyrazolyl, pyrrolidinyl or piperidinyl.

14. The compounds of formula (I) or a pharmaceutically acceptable salt thereof, according to any one of claims 1, 3, 4 or 6 wherein R_1 is halo.

15. A compound is selected from the group consisting of:

Example No	IUPAC name
1.	6'-amino-N-(2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;
2.	6'-amino-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide hydrochloride;
3.	N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;
4.	N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide hydrochloride;
5.	N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
6.	N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;
7.	2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
8.	6-chloro-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;
9.	N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1-methyl-1H-pyrazol-4-

	yl)picolinamide;
10.	2-(2-chloropyridin-4-yl)-N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
11.	(S)-2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-3-ylamino)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
12.	6'-amino-N-(2-morpholinooxazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide;
13.	6'-amino-N-(2-morpholinothiazolo[4,5-c]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;
14.	6'-amino-N-(2-morpholinothiazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide;
15.	2-(2-methylpyridin-4-yl)-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
16.	6'-amino-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;
17.	N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;
18.	3-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide;
19.	2-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide;
20.	2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
21.	N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;
22.	N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;
23.	N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

24.	N-(2,5-dimorpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
25.	N-(5-(4-methylpiperazin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
26.	N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;
27.	N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-3-yl)oxazole-4-carboxamide;
28.	N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-hydroxypyridin-3-yl)oxazole-4-carboxamide;
29.	2-(2-hydroxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
30.	N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-hydroxypyridin-3-yl)oxazole-4-carboxamide;
31.	2-(2-methoxypyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
32.	2-(2-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
33.	2-(3-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
34.	N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(3-methylpyridin-4-yl)oxazole-4-carboxamide;
35.	2-(6-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
36.	6-(1-methyl-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;
37.	N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-methylpyridin-3-yl)oxazole-4-carboxamide;
38.	(S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

39.	(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
40.	(R)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
41.	(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
42.	(S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
43.	(S)-6-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;
44.	(S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;
45.	(S)-2-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
46.	(S)-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxamide;
47.	(S)-2-(3-aminopyrrolidin-1-yl)-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
48.	2-(2-methylpyridin-4-yl)-N-(5-(piperidin-1-yl)-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;
49.	N-(2-(2,6-dimethylmorpholino)-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;
50.	N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)picolinamide hydrochloride;
51.	6-(1-methyl-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;
52.	N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-3-yl)oxazole-4-carboxamide hydrochloride;

53.	N-(2-((2S,6R)-2,6-dimethylmorpholino)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
54.	2-(2-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
55.	2-(2-hydroxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
56.	N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methoxypyridin-4-yl)oxazole-4-carboxamide;
57.	2-(6-methoxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
58.	2-(2-methoxypyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
59.	(S)-N-(5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
60.	2-(6-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
61.	2-(3-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
62.	(S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;
63.	(S)-6-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;
64.	(S)-6-(3-aminopyrrolidin-1-yl)-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;
65.	(S)-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;

66.	(S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
67.	(S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
68.	(S)-2-(3-aminopyrrolidin-1-yl)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
69.	N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
70.	(S)-2-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
71.	(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
72.	(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;
73.	(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxamide;
74.	(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)picolinamide;
75.	(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)oxazole-4-carboxamide;
76.	N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;
77.	(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;
78.	(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;
79.	(S)-N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;

80.	N-(5-(3-hydroxyazetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
81.	(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide;
82.	(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
83.	(S)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
84.	N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide
85.	(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
86.	N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
87.	N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
88.	2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
89.	2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
90.	5-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)furan-2-carboxamide;
91.	N-(5-(azepan-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
92.	2-(2-aminopyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;
93.	N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
94.	(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

95.	(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
96.	(S)-6-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide
97.	N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide
98.	N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride
99.	N-(5-(1-methyl-1H-pyrazol-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
100.	N-(5-(3-fluorophenyl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
101.	N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
102.	N-(5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
103.	(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;
104.	N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
105.	(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;
106.	N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;
107.	(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
108.	(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide;
109.	N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

110.	2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
111.	5-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)furan-2-carboxamide;
112.	N-(5-(azetidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
113.	2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
114.	N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
115.	(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
116.	N-(5-(furan-3-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
117.	N-(5-(3-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
118.	N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
119.	N-(5-(4-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
120.	(S)-N-(5-(3-aminopiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
121.	2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(1H-pyrazol-4-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
122.	N-(5-(6-fluoropyridin-3-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
123.	N-(5-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
124.	N-(2-(3-hydroxypiperidin-1-yl)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

125.	2-(2-acetamidopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
126.	N-(2-(3-hydroxypiperidin-1-yl)-5-(4-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
127.	2-(2-acetamidopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
128.	2-(2-aminopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;
129.	5-(2-aminopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)furan-3-carboxamide hydrochloride;
130.	2-(2-aminopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;
131.	2-(2-aminopyridin-4-yl)-N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;
132.	N-(5-(2-fluoropyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
133.	N-(5-(4-fluoropiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
134.	N-(5-(4-aminopiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride; and
135.	N-(5-(2-hydroxypyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

16. A pharmaceutical composition, comprising at least one compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt or a stereoisomer thereof and a pharmaceutically acceptable carrier or excipient.

17. The compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt or a stereoisomer thereof, for use as a medicament.

18. A method of treating IRAK4 mediated disorders or diseases or condition in a subject comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 15.

19. The method of claim 18, wherein the IRAK4-mediated disorder or disease or condition is selected from the group consisting of cancer, an inflammatory disorder, an autoimmune disease, metabolic disorder, a hereditary disorder, a hormone-related disease, immunodeficiency disorders, a condition associated with cell death, a destructive bone disorder, thrombin-induced platelet aggregation, liver disease and a cardiovascular disorder.

20. The method of claim 19, wherein the cancer is selected from the group consisting of a solid tumor, benign or malignant tumor, carcinoma of the brain, kidney, liver, stomach, vagina, ovaries, gastric tumors, breast, bladder colon, prostate, pancreas, lung, cervix, testis, skin, bone or thyroid; sarcoma, glioblastomas, neuroblastomas, multiple myeloma, gastrointestinal cancer, a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphomas, Hodgkins and Non-Hodgkins, a mammary carcinoma, follicular carcinoma, papillary carcinoma, seminoma, melanoma; haematological malignancies selected from leukemia, diffuse large B-cell lymphoma (DLBCL), activated B-cell-like DLBCL, chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, acute lymphocytic leukemia, B-cell pro lymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenstrom's macroglobulinemia (WM), splenic marginal zone lymphoma, intravascular large B-cell lymphoma, plasmacytoma and multiple myeloma.

21. The method of claim 19, wherein the inflammatory disorder is selected from the group consisting of ocular allergy, conjunctivitis, keratoconjunctivitis sicca, vernal conjunctivitis, allergic rhinitis, autoimmune hematological disorders (e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven- Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease,

glomerular disease, alcoholic liver disease, multiple sclerosis, endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren's syndrome, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, nephritis, vasculitis, diverticulitis, interstitial cystitis, glomerulonephritis (e.g. including idiopathic nephrotic syndrome or minimal change nephropathy), chronic granulomatous disease, endometriosis, leptospirosis renal disease, glaucoma, retinal disease, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle wasting, catabolic disorders, obesity, fetal growth retardation, hypercholesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ecodermal dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma, acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, fibrositis, gastritis, gastroenteritis, nasal sinusitis, ocular allergy, silica induced diseases, chronic obstructive pulmonary disease (COPD), cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, juvenile rheumatoid arthritis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, vasculitis, vulvitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Cryopyrin Associated Periodic Syndrome (CAPS) and osteoarthritis.

22. The compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt or a stereoisomer thereof, for use in the treatment of a cancer, an inflammatory disorder, an

autoimmune disease, metabolic disorder, a hereditary disorder, a hormone-related disease, immunodeficiency disorders, a condition associated with cell death, a destructive bone disorder, thrombin-induced platelet aggregation, liver disease and a cardiovascular disorder.

23. Use of the compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt or a stereoisomer thereof, in the manufacture of a medicament for the treatment of a cancer, an inflammatory disorder, a an autoimmune disease, metabolic disorder, a hereditary disorder, a hormone-related disease, immunodeficiency disorders, a condition associated with cell death, a destructive bone disorder, thrombin-induced platelet aggregation, liver disease and a cardiovascular disorder.