CHEMICAL COMPOUNDS AND USES THEREOF

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/611,649 filed December 18, 2023, which is incorporated herein in its entirety and for all purposes.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] NOT APPLICABLE

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

[0003] NOT APPLICABLE

BACKGROUND

[0004] Mutational or non-mutational alterations in epigenetic genes encoding for key histone modifications such as acetylation and methylation have the ability to disrupt normal gene expression and cellular processes (Yoo *et al. Nat Rev Drug Discov. 2006 Feb;5(2):121).* The most recent iteration of the cancer hallmarks further highlighted a growing body of literature supporting the role for epigenetic regulation in promoting inter and intratumor heterogeneity (Hanahan D. *Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022;12(1):31-46*). With already several approved drugs for chromatin modifying proteins (e.g.: HMTs, HDACs), targeting histone modifying proteins is an exciting and attainable approach for several cancer types with unmet clinical need.

[0005] KAT6A (also referred to as MOZ/MYST3 in the literature) and KAT7 (also referred to as HBO1/MYST2 in the literature) are lysine (K) acetyltransferase (AT) enzymes that via a tetrameric complex formation with BRPF1/2/3, ING5, and EAF6, acetylate key lysine residues on histones H3 and H4. *See*, Yerra and Advani *et al. Cell Mol Life Sci.* 2018; 75(17): 3193–3213. KAT6 and/or KAT7-mediated acetylation creates an open chromatin conformation, typically promoting gene transcription, with specific roles for KAT6 and KAT7 identified in the regulation of genes associated with cell cycle, stem cell maintenance, and cellular differentiation (Sheikh et al. *Oncogene.* 2015;34(47):5807-5820, and

MacPherson et al. *Nature*. 2020;577(7789):266-270) Dysregulation of these proteins has in addition been associated with rare developmental disorders and cancer (Avakuumov *et al. Oncogene. 2007; **26**, 5395–5407)*.

[0006] KAT6A is located on the chromosome arm 8p11, and its primary oncogenic potential was discovered in acute myeloid leukemia (AML), where KAT6A is predisposed to creating fusion proteins with other histone modifying enzymes such as CBP, MLL, and p300. (Borrow *et al. Nat Genet. 1996;14(1):33-41. doi:10.1038/ng0996-33)*. Several studies have since further demonstrated that arm-level chromosomal amplification of the 8p11 loci (Garcia *et al. Oncogene. 2005;24(33):5235-5245,* and Gelsi-Boyer *et al. Mol Cancer Res. 2005;3(12):655-667)* is oncogenic and predicts worse tumor survival among patients. Upregulation of KAT6A or KAT7 gene overexpression has been noted in a number of cancers including lung, bladder, testicular, breast, ovarian, and gastric cancer. *See*, for example, Gao *et al. Biochem Biophys Res Commun.* 2017; 489(2):235-241, and Huang *et al. Mol Cell Biol.* 2016;36(14):1900-7.

[0007] Despite earlier reports linking the activity of KAT6A or KAT7 to cancer and other diseases, there are no approved inhibitors of KAT6A or KAT7. As such, there is a need in the art to identify and develop compounds that can act as inhibitors of KAT6A and/or KAT7. The present disclosure addresses these needs and provides related advantages as well.

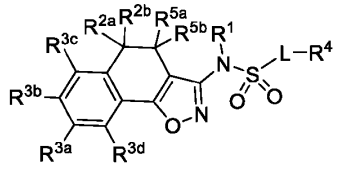
BRIEF SUMMARY

[0008] The present disclosure provides, in part, compounds of Formula (Y) or (I) and pharmaceutically acceptable salts thereof. Such compounds can inhibit the activity of KAT6A and/or KAT7, thereby affecting biological functions. Also provided are pharmaceutical compositions and medicaments comprising the compounds or pharmaceutically acceptable salts of the present disclosure, alone or in combination with additional therapeutic agents.

[0009] The present disclosure also provides, in part, methods for preparing the compounds, pharmaceutically acceptable salts thereof, and compositions comprising the compounds, and methods of using the foregoing.

[0010] The present disclosure also provides therapeutic methods and uses comprising administering a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[0011] In one aspect, the present disclosure provides a compound, represented by Formula (Y):



(Y),

or a pharmaceutically acceptable salt thereof, wherein:

L is a bond, C_{1-3} alkylene, or $-N(R^6)-$;

R^1 is selected from the group consisting of H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{2a} and R^{2b} together with the carbon atom to which they are attached form cyclopropyl or cyclobutyl, wherein each of said cyclopropyl and cyclobutyl is independently unsubstituted or substituted with from 1 to 3 R^g; or

R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-6} alkyl, hydroxyC_{1-6}alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, hydroxyC_{1-6}alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-5} cycloalkyl, $-O-C_{3-5}$ cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, 5- to 6-membered heteroaryl–C_{1-3} alkylene–, $-C(O)NHR^a$, $-NR^{a1}R^{a2}$, and cyano, wherein each of said C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl, by itself or as part of another group, is independently unsubstituted or substituted with from 1 to 4 R^b;

R^{3d} is selected from the group consisting of H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^4 is selected from the group consisting of C_{1-6} alkyl, C_{4-7} cycloalkyl, bridged C_{5-10} cycloalkyl, phenyl, 5- to 6-membered heteroaryl, 3- to 7-membered heterocyclyl, and fused heterocyclyl, wherein each of said cycloalkyl, bridged cycloalkyl, phenyl, heteroaryl, heterocyclyl, and fused heterocyclyl is independently unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently selected from the

group consisting of C_{1-6} alkyl, C_{2-6} alkynyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, 3- to 7-membered heterocyclyl, 3- to 7-membered heterocyclyl–O–, –C(O)R^c, –C(O)OR^d, –C(O)N$R^e$$R^f$, –$C_{1-3}$ alkylene–C(O)N$R^e$$R^f$, C_{3-6} cycloalkyl–C(O)NH–, and C_{1-6} alkyl–S(O)$_2$–C_{0-3} alkylene–; or two R^{4a} groups on adjacent carbon atoms are optionally combined to form 5- to 6-membered cycloalkyl or 3- to 7-membered heterocyclyl, each of which is independently unsubstituted or substituted with from 1 to 3 R^{4a1}, wherein each R^{4a1} is independently selected from halo, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{5a} and R^{5b} are each independently selected from the group consisting of H, C_{1-6} alkyl, hydroxyC_{1-6}alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^6 is selected from the group consisting of H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^a is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

R^{a1} and R^{a2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^b is independently selected from the group consisting of oxo, halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and C_{1-6} alkyl–S(O)$_2$–C_{0-3} alkylene–;

each R^c is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^d is independently selected from the group consisting of H and C_{1-6} alkyl;

R^e and R^f are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3- to 7-membered heterocyclyl, wherein each of said cycloalkyl and heterocyclyl is independently unsubstituted or substituted with 1 or 2 R^h; or R^e and R^f together with the nitrogen atom to which they are attached form 3- to 10-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^i;

each R^g is independently selected from the group consisting of C_{1-6} alkyl, halo, hydroxy, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and cyano;

each R^h is independently selected from the group consisting of halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkoxy, and cyano;

each R^i is independently selected from the group consisting of halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkoxy, and cyano;

each heteroaryl has 1 to 4 heteroatoms each independently selected from N, O, and S;

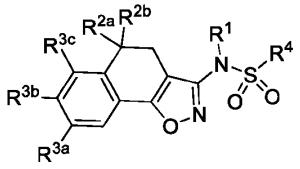
each heterocyclyl has 1 to 4 heteroatoms or groups each independently selected from N, O, S, S(O), and $S(O)_2$;

each bridged heterocyclyl has 1 to 3 heteroatoms each independently selected from N, O, and S;

the fused heterocyclyl is a 4- to 7-membered heterocyclyl having 1 to 3 heteroatoms each independently selected from N, O, and S, and the 4- to 7-membered heterocyclyl is fused to two adjacent ring members of C_{3-6} cycloalkyl, phenyl, or 5- to 6-membered heteroaryl; and

each spiroheterocyclyl has 1 to 3 heteroatoms each independently selected from N, O, and S.

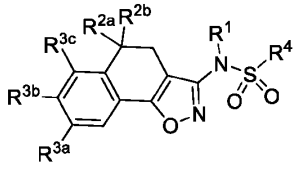
[0012] In some embodiments, the compound is represented by Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{3c}, and R^4 are each defined and described herein.

[0013] In one aspect, provided herein are compounds of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of H, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{2a} and R^{2b} together with the carbon atom to which they are attached form cyclopropyl or cyclobutyl, wherein each of said cyclopropyl and cyclobutyl, is independently unsubstituted or substituted with from 1 to 3 R^g; or

R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, and C_{1-4} haloalkyl;

R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, –C(O)NHR[a], and cyano; and wherein each of said 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl have from 1 to 4 ring members independently selected from N, O, and S, and wherein each of said C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl, is independently unsubstituted or substituted with from 1 to 4 R^b;

R^4 is selected from the group consisting of C_{4-7} cycloalkyl, phenyl, heteroaryl, heterocyclyl, and fused heterocyclyl, wherein each of phenyl, heteroaryl, heterocyclyl, and fused heterocyclyl, is independently unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently selected from the group consisting of C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, –C(O)R^c, –C(O)OR^d, and –C(O)N$R^e$$R^f$; or two R^{4a} groups on adjacent carbon atoms are optionally combined to form a 5- to 6-membered cycloalkyl or heterocyclyl, each of which is independently unsubstituted or substituted with 1-3 groups independently selected from halo, C_{1-4} alkyl, and C_{1-4} haloalkyl;

each R^a is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^b is independently selected from the group consisting of oxo, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^c is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^d is independently selected from the group consisting of H and C_{1-6} alkyl;

each R^e and R^f is independently selected from the group consisting of H, C_{1-6} alkyl and C_{3-6} cycloalkyl; or R^e and R^f together with the nitrogen atom to which they are attached form 4- to 6-membered ring; and

each R^g is independently selected from the group consisting of C_{1-6} alkyl, halo, hydroxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and cyano.

[0014] In another aspect, provided herein is a pharmaceutical composition comprising a compound of Formula (Y) or (I) (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0015] In another aspect, provided herein is a compound of Formula (Y) or (I) (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in therapy.

[0016] In another aspect, provided herein is a compound of Formula (Y) or (I) (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of cancer. In one embodiment, the cancer is a human cancer.

[0017] In another aspect, provided herein is a compound of Formula (Y) or (I) (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the production of a KAT6A and/or KAT7 inhibitory effect.

[0018] In another aspect, provided herein is the use of a compound of Formula (Y) or (I) (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of cancer. Suitably, the medicament is for use in the treatment of human cancers.

[0019] In another aspect, provided herein is the use of a compound of Formula (Y) or (I) (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein in the manufacture of a medicament for the production of a KAT6A and/or KAT7 inhibitory effect.

[0020] In another aspect, provided herein is a method of inhibiting KAT6A and/or KAT7 *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound of Formula (Y) or (I) (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[0021] In another aspect, provided herein is a method of inhibiting cell proliferation *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound of

Formula (Y) or (I) (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[0022] In another aspect, provided herein is a method of treating abnormal cell growth in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of the present disclosure, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[0023] In another aspect, provided herein is a method of treating a disorder mediated by KAT6A and/or KAT7 in a patient, comprising administering to said patient a therapeutically effective amount of a compound of Formula (Y) or (I) (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein. In one embodiment, the disorder is cancer.

[0024] In another aspect, provided herein is a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound of Formula (Y) or (I) (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[0025] In another aspect, provided herein is a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound of Formula (Y) or (I) (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, wherein the cancer is characterized by an overexpression of KAT6A and/or KAT7, an amplification of KAT6A gene and/or KAT7 gene, an increased activity of KAT6A and/or KAT7, or a combination thereof.

[0026] In another aspect, provided herein is a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound of Formula (Y) or (I) (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, wherein the cancer is characterized by an overexpression of KAT6A, an amplification of KAT6A gene, an increased activity of KAT6A, or a combination thereof.

[0027] In another aspect, provided are methods of synthesizing a compound of Formula (Y) or (I) (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, as defined herein.

[0028] In another aspect, provided herein is a compound as defined herein, or a pharmaceutically acceptable salt, obtainable by, or obtained by, or directly obtained by a method of synthesis as defined herein.

[0029] In another aspect, provided herein are novel intermediates as defined herein which are suitable for use in any one of the synthetic methods as set out herein.

[0030] Preferred, suitable, and optional features of any one particular aspect of the present disclosure are also preferred, suitable, and optional features of any other aspect.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] **FIG. 1** shows a general method for preparing a compound of Formula (Y) by Method 1.

[0032] **FIG. 2** shows a general method for preparing a compound of Formula (Y) by Method 2.

[0033] **FIG. 3** shows a general method for preparing a compound of Formula (Y) by Method 3.

DETAILED DESCRIPTION

[0034] Before the present disclosure is further described, it is to be understood that the disclosure is not limited to the particular embodiments set forth herein, and it is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0035] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0036] As used herein, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology such as "solely," "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation.

[0037] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Further, the dates of publication provided may be different from the actual publication dates, which may need to be independently confirmed.

General

[0038] Provided herein, for example, are compounds and compositions for inhibition of KAT6A and/or KAT7, and pharmaceutical compositions comprising the same. Also provided herein are, for example, methods of treating or preventing a disease, disorder or condition, or a symptom thereof, mediated by inhibition of KAT6A and/or KAT7.

Definitions

[0039] Unless otherwise indicated, the following terms are intended to have the meaning set forth below. Other terms are defined elsewhere throughout the specification.

[0040] Unless specifically indicated otherwise, the group "  " as used in any one of the structures in Table 1, the Examples, or moieties disclosed herein, refers to methyl ($-CH_3$) where the wavy line is the point of attachment to the remainder of the molecule.

[0041] The term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a saturated straight or branched chain hydrocarbon radical, having the number of carbon atoms designated (*i.e.* C_{1-8} means one to eight carbons). Alkyl can include any number of carbons, such as C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{1-6}, C_{1-7}, C_{1-8}, C_{1-9}, C_{1-10}, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{3-4}, C_{3-5}, C_{3-6}, C_{4-5}, C_{4-6} and C_{5-6}. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

[0042] The term "alkylene" refers to a straight or branched, saturated hydrocarbon radical having the number of carbon atoms indicated, and linking at least two other groups, *i.e.*, a divalent hydrocarbon radical. The two moieties linked to the alkylene can be linked to the

same atom or different atoms of the alkylene group. Representative alkylene groups include, but are not limited to, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, sec-butylene, pentylene and hexylene.

[0043] "Bridged heterocyclyl" means a saturated 5 to 7 membered monocyclic heterocycle having two non-adjacent ring atoms linked by a $(X)_n$ group where n is 1, 2, or 3, each X is CRR', NR, $S(O)_{n1}$, or O wherein no more than one X is NR, $S(O)_{n1}$ or O, and R and R' are independently H or methyl (also may be referred to herein as "bridging" group). In some embodiments, a 6- to 9-membered bridged heterocycle has 6 to 9 ring atoms including the bridging carbon atom(s) of (CRR')n where n is 1 to 3, and the indicated number of ring atoms does not include the carbon atom of each R (i.e., methyl). The 5 to 7 membered heterocycle or the 6- to 9-membered bridged heterocycle has from one to three heteroatoms independently selected from N, O, and $S(O)_{n1}$, the remaining ring atoms being carbon, where n1 is 0, 1, or 2. Examples include, but are not limited to, 2-azabicyclo[2.2.2]octane, quinuclidine, 7-oxabicyclo[2.2.1]heptane, and the like. Additional examples include 3,8-diazabicyclo[3.2.1]octane, and the like.

[0044] The term "cycloalkyl" refers to a saturated or partially unsaturated hydrocarbon ring having the indicated number of ring atoms (*e.g.*, C_{3-6} cycloalkyl). Cycloalkyl is optionally substituted with one, two, or three substituents independently selected from C_{1-6} alkyl, halo, hydroxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or cyano, unless stated otherwise. Representative examples include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, and the like.

[0045] The term "bridged cycloalkyl" means a saturated monocyclic 4- to 7-membered hydrocarbon radical in which two non-adjacent ring atoms are linked by a (CRR')n group where n is 1 to 3 and each R is independently H or methyl (also referred to herein as the bridging group). "Bridged C_{5-10} cycloalkyl" has 5 to 10 carbon ring atoms including the bridging carbon atom(s) of (CRR')n where n is 1 to 3. The indicated number of ring atoms (e.g., C_{5-10}) does not include the carbon atom of each R (i.e., methyl). Examples of bridged cycloalkyl include but are not limited to bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc.

[0046] As used herein, the term "cyano" refers to the group -CN.

[0047] The term "fused heterocyclyl" as used herein, means a saturated monocyclic ring of 4 to 7 ring atoms having from one to three heteroatoms independently selected from N, O, and S, and the remaining ring atoms being carbon, and further wherein the heterocyclyl ring

is fused to two adjacent ring members of a phenyl, a five or six membered heteroaryl, or C_{3-6} cycloalkyl, each as defined herein, unless stated otherwise. The fused heterocyclyl can be attached to the remainder of the molecule through any ring atom. For sake of clarity, the number of ring atoms in the saturated monocyclic ring includes the two common ring vertices shared with the fused group (e.g., the phenyl, five or six membered heteroaryl, or C_{3-6} cycloalkyl). Additionally, a cycloalkyl moiety in a fused heterocyclyl group is substituted as defined in the claims. Non limiting examples of the fused heterocyclyl include 2,3-dihydrobenzo[b][1,4]-dioxinyl, 2-oxabicyclo[3.1.0]hexanyl, and the like.

[0048] The term "halo" or "halogen," by itself or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

[0049] The term "haloalkyl," means alkyl, as defined above, that is substituted with one to five halo atoms and includes monohaloalkyl and polyhaloalkyl. For example, the term "C_{1-4} haloalkyl" includes trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0050] The terms "alkoxy," and "haloalkoxy" refer to alkyl and haloalkyl groups respectively, each as defined herein, that is attached to the remainder of the molecule via an oxygen atom.

[0051] The term "aryl" means, unless otherwise stated, an aromatic, hydrocarbon group which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. Non-limiting examples of aryl groups include phenyl, naphthyl and biphenyl.

[0052] The term "heteroaryl" refers to a 5- to 10-membered aromatic ring that contains from one to five heteroatoms selected from N, O, and S. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of heteroaryl groups include pyridyl, pyridazinyl, pyrazinyl, pyrimindinyl, triazinyl, quinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, benzotriazinyl, purinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiaxolyl, benzofuranyl, benzothienyl, indolyl, quinolyl, isoquinolyl, isothiazolyl, pyrazolyl, indazolyl, pteridinyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, thiazolyl, furyl, thienyl and the like.

[0053] The term "heterocycloalkyl" or "heterocyclyl" refers to a saturated or partially unsaturated 3 to 10 membered monocyclic or bicyclic ring having from one to four heteroatoms independently selected from N, O, and $S(O)_{n1}$, and the remaining ring atom being carbon, where n1 is 0, 1, or 2. In some embodiments, the term "heterocycloalkyl" or "heterocyclyl" refers to a saturated or partially unsaturated 4 to 10 membered monocyclic or bicyclic ring having from one to four heteroatoms independently selected from N, O, and S and the remaining ring atoms being carbon. The one or two ring carbon atoms of the heterocyclic ring may be replaced by -C=(O) group. Non limiting examples of heterocycloalkyl groups include pyrrolidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, piperidine, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S,S-oxide, piperazine, pyran, pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, tetrahydrothiophene, , and the like. A heterocycloalkyl group can be attached to the remainder of the molecule through a ring carbon or a heteroatom. Non limiting examples of heterocycloalkyl groups include pyridine-2(H)-one.

[0054] The term "spiro heterocyclyl" as used herein, means a saturated or partially unsaturated bicyclic ring of 5 to 12 ring atoms wherein one to three ring atoms are heteroatoms independently selected from N, O, and S, and the remaining ring atoms being carbon and further wherein the 2 rings are linked together by one common atom. Non limiting examples of the spiro heterocyclyl include 6-azaspiro[3.4]octane, 2-oxa-6-azaspiro[3.4]octan-6-yl, 4-oxaspiro[2.4]heptanyl, spiro[3.5]non-6-ene, and 2,7-diazaspiro[4.4]nonanyl.

[0055] The term "hydroxyalkyl," means alkyl, as defined above, that is substituted with one or two hydroxy. For example, the term " hydroxyC_{1-4} alkyl" is mean to include hydroxymethyl, 1-, or 2-hydroxyethyl, 1,2-dihydroxyethyl, hydroxypropyl, and the like.

[0056] As used herein, a wavy line, "$\sim\!\!\sim$", that intersects a single, double or triple bond in any chemical structure depicted herein, represent the point attachment of the single, double, or triple bond to the remainder of the molecule. Additionally, a bond extending to the center of a ring (e.g., a phenyl ring) is meant to indicate attachment at any of the available ring vertices. One of skill in the art will understand that multiple substituents shown as being attached to a ring will occupy ring vertices that provide stable compounds and are otherwise sterically compatible.

[0057] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0058] As used herein, the phrase "substituted with 1-3 R groups" (e.g., substituted with 1-3 R^{4a}) has the same meaning as the phrase "substituted with from 1 to 3 R" (e.g., substituted with from 1 to 3 R^{4a}).

[0059] The term "pharmaceutically acceptable salts" is meant to include salts of the compounds of Formula (Y) or (I) which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of Formula (Y) or (I) contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of Formula (Y) or (I) contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al,

"Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0060] The neutral forms of the compounds of Formula (Y) or (I) may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present disclosure.

[0061] In addition to salt forms, provided herein are compounds of Formula (Y) or (I) which are in a prodrug form. Prodrugs of the compounds of Formula (Y) or (I) are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of Formula (Y) or (I). Additionally, prodrugs can be converted to the compounds of Formula (Y) or (I) by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of Formula (Y) or (I) when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are described in more detail elsewhere herein.

[0062] Certain compounds of Formula (Y) or (I) can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present disclosure. Certain compounds of Formula (Y) or (I) may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

[0063] Certain compounds of Formula (Y) or (I) possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers, regioisomers and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present disclosure. When a stereochemical depiction is shown, it is meant to refer the compound in which one of the isomers is present and substantially free of the other isomer. 'Substantially free of' another isomer indicates at least an 80/20 ratio of the two isomers, more preferably 90/10, or 95/5 or more. In some embodiments, one of the isomers will be present in an amount of at least 99%.

[0064] The compounds of Formula (Y) or (I) may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. Unnatural proportions of an isotope may be defined as ranging from the amount found in nature to an amount consisting of 100% of the atom in question. For example, the compounds may incorporate radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C), or non-radioactive isotopes, such as deuterium (^{2}H) or carbon-13 (^{13}C). Such isotopic variations can provide additional utilities to those described elsewhere within this application. For instance, isotopic variants of the compounds of the disclosure may find additional utility, including but not limited to, as diagnostic and/or imaging reagents, or as cytotoxic/radiotoxic therapeutic agents. Additionally, isotopic variants of the compounds of Formula (Y) or (I) can have altered pharmacokinetic and pharmacodynamic characteristics which can contribute to enhanced safety, tolerability or efficacy during treatment. All isotopic variations of the compounds of Formula (Y) or (I), whether radioactive or not, are intended to be encompassed within the scope of the present disclosure.

[0065] The terms "patient" or "subject" are used interchangeably to refer to a human or a non-human animal (e.g., a mammal). In one embodiment, the patient or subject is a human.

[0066] The terms "administration", "administer" and the like, as they apply to, for example, a subject, cell, tissue, organ, or biological fluid, refer to contact of, for example, an inhibitor of KAT6A and/or KAT7, a pharmaceutical composition comprising same, or a diagnostic agent to the subject, cell, tissue, organ, or biological fluid. In the context of a cell, administration includes contact (e.g., in vitro or ex vivo) of a reagent to the cell, as well as contact of a reagent to a fluid, where the fluid is in contact with the cell.

[0067] The terms "treat", "treating", treatment" and the like refer to a course of action (such as administering an inhibitor of KAT6A and/or KAT7 or a pharmaceutical composition comprising same) initiated after a disease, disorder or condition, or a symptom thereof, has been diagnosed, observed, and the like so as to eliminate, reduce, suppress, mitigate, or ameliorate, either temporarily or permanently, at least one of the underlying causes of a disease, disorder, or condition afflicting a subject, or at least one of the symptoms associated with a disease, disorder, condition afflicting a subject. Thus, treatment includes inhibiting (e.g., arresting the development or further development of the disease, disorder or condition or clinical symptoms association therewith) an active disease.

[0068] The term "in need of treatment" as used herein refers to a judgment made by a physician or other caregiver that a subject requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of the physician's or caregiver's expertise.

[0069] The terms "prevent", "preventing", "prevention" and the like refer to a course of action (such as administering a KAT6A and/or KAT7 inhibitor or a pharmaceutical composition comprising same) initiated in a manner (e.g., prior to the onset of a disease, disorder, condition or symptom thereof) so as to prevent, suppress, inhibit or reduce, either temporarily or permanently, a subject's risk of developing a disease, disorder, condition or the like (as determined by, for example, the absence of clinical symptoms) or delaying the onset thereof, generally in the context of a subject predisposed to having a particular disease, disorder or condition. In certain instances, the terms also refer to slowing the progression of the disease, disorder or condition or inhibiting progression thereof to a harmful or otherwise undesired state.

[0070] The term "in need of prevention" as used herein refers to a judgment made by a physician or other caregiver that a subject requires or will benefit from preventative care. This judgment is made based on a variety of factors that are in the realm of a physician's or caregiver's expertise.

[0071] The terms "inhibiting" and "reducing," or any variation of these terms in relation of KAT6A and/or KAT7, includes any measurable decrease or complete inhibition to achieve a desired result. For example, there may be a decrease of about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more, reduction of KAT6A and/or KAT7 activity compared to normal. About as used herein means within ± 10%, preferably ± 5% of a given value.

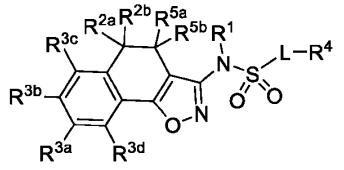
[0072] The phrase "therapeutically effective amount" refers to the administration of an agent to a subject, either alone or as part of a pharmaceutical composition and either in a single dose or as part of a series of doses, in an amount capable of having any detectable, positive effect on any symptom, aspect, or characteristic of a disease, disorder or condition when administered to the subject. The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and diagnostic analysis of the subject's condition, and the like. By way of example,

measurement of the serum level of a KAT6A and/or KAT7 inhibitor (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been used.

[0073] The term "substantially pure" indicates that a component makes up greater than about 50% of the total content of the composition, and typically greater than about 60% of the total content. More typically, "substantially pure" refers to compositions in which at least 75%, at least 85%, at least 90% or more of the total composition is the component of interest.

COMPOUNDS

[0074] In one aspect, the present disclosure provides a compound, represented by Formula (Y):



(Y),

or a pharmaceutically acceptable salt thereof, wherein:

L is a bond, C_{1-3} alkylene, or $-N(R^6)-$;

R^1 is selected from the group consisting of H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{2a} and R^{2b} together with the carbon atom to which they are attached form cyclopropyl or cyclobutyl, wherein each of said cyclopropyl and cyclobutyl is independently unsubstituted or substituted with from 1 to 3 R^g; or

R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-6} alkyl, hydroxyC_{1-6}alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^{3a}, R^{3b}, R^{3c}, and R^{3d} are each independently selected from the group consisting of H, halo, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, hydroxyC_{1-6}alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-5} cycloalkyl, $-O-C_{3-5}$ cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, 5- to 6-membered heteroaryl–C_{1-3} alkylene–, $-C(O)NHR^a$, $-NR^{a1}R^{a2}$, and cyano, wherein each of said C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl, by itself or as part of another group, is independently unsubstituted or substituted with from 1 to 4 R^b;

R^4 is selected from the group consisting of C_{1-6} alkyl, C_{4-7} cycloalkyl, bridged C_{5-10} cycloalkyl, phenyl, 5- to 6-membered heteroaryl, 3- to 7-membered heterocyclyl, and fused heterocyclyl, wherein each of said cycloalkyl, bridged cycloalkyl, phenyl, heteroaryl, heterocyclyl, and fused heterocyclyl is independently unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkynyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, 3- to 7-membered heterocyclyl, 3- to 7-membered heterocyclyl–O–, $–C(O)R^c$, $–C(O)OR^d$, $–C(O)NR^eR^f$, $–C_{1-3}$ alkylene–$C(O)NR^eR^f$, C_{3-6} cycloalkyl–C(O)NH–, and C_{1-6} alkyl–$S(O)_2$–C_{0-3} alkylene–; or two R^{4a} groups on adjacent carbon atoms are optionally combined to form 5- to 6-membered cycloalkyl or 3- to 7-membered heterocyclyl, each of which is independently unsubstituted or substituted with from 1 to 3 R^{4a1}, wherein each R^{4a1} is independently selected from halo, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{5a} and R^{5b} together with the carbon atom to which they are attached form cyclopropyl or cyclobutyl, wherein each of said cyclopropyl and cyclobutyl is independently unsubstituted or substituted with from 1 to 3 R^{g1}; or

R^{5a} and R^{5b} are each independently selected from the group consisting of H, C_{1-6} alkyl, hydroxyC_{1-6}alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^6 is selected from the group consisting of H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^a is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

R^{a1} and R^{a2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^b is independently selected from the group consisting of oxo, halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and C_{1-6} alkyl–$S(O)_2$–C_{0-3} alkylene–;

each R^c is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^d is independently selected from the group consisting of H and C_{1-6} alkyl;

R^e and R^f are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3- to 7-membered heterocyclyl, wherein each of said cycloalkyl and heterocyclyl is independently unsubstituted or substituted with 1 or 2 R^h; or R^e and R^f together with the nitrogen atom to which they are attached form 3- to 10-

membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^i;

each R^g is independently selected from the group consisting of C_{1-6} alkyl, halo, hydroxy, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and cyano;

each R^{g1} is independently selected from the group consisting of C_{1-6} alkyl, halo, hydroxy, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and cyano;

each R^h is independently selected from the group consisting of halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkoxy, and cyano;

each R^i is independently selected from the group consisting of halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkoxy, and cyano;

each heteroaryl has 1 to 4 heteroatoms each independently selected from N, O, and S;

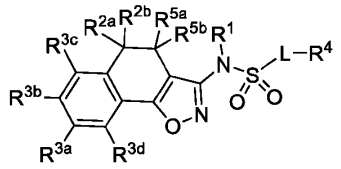
each heterocyclyl has 1 to 4 heteroatoms or groups each independently selected from N, O, S, S(O), and $S(O)_2$;

each bridged heterocyclyl has 1 to 3 heteroatoms each independently selected from N, O, and S;

the fused heterocyclyl is a 4- to 7-membered heterocyclyl having 1 to 3 heteroatoms each independently selected from N, O, and S, and the 4- to 7-membered heterocyclyl is fused to two adjacent ring members of C_{3-6} cycloalkyl, phenyl, or 5- to 6-membered heteroaryl; and

each spiroheterocyclyl has 1 to 3 heteroatoms each independently selected from N, O, and S.

[0075] In another aspect, the present disclosure provides a compound, represented by Formula (Y):



(Y),

or a pharmaceutically acceptable salt thereof, wherein:

L is a bond, C_{1-3} alkylene, or $–N(R^6)–$;

R^1 is selected from the group consisting of H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{2a} and R^{2b} together with the carbon atom to which they are attached form cyclopropyl or cyclobutyl, wherein each of said cyclopropyl and cyclobutyl is independently unsubstituted or substituted with from 1 to 3 R^g; or

R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-6} alkyl, hydroxyC_{1-6}alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, hydroxyC_{1-6}alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, 5- to 6-membered heteroaryl–C_{1-3} alkylene–, –C(O)NHR^a, –NR^{a1}R^{a2}, and cyano, wherein each of said C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl, by itself or as part of another group, is independently unsubstituted or substituted with from 1 to 4 R^b;

R^{3d} is selected from the group consisting of H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^4 is selected from the group consisting of C_{1-6} alkyl, C_{4-7} cycloalkyl, bridged C_{5-10} cycloalkyl, phenyl, 5- to 6-membered heteroaryl, 3- to 7-membered heterocyclyl, and fused heterocyclyl, wherein each of said cycloalkyl, bridged cycloalkyl, phenyl, heteroaryl, heterocyclyl, and fused heterocyclyl is independently unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkynyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, 3- to 7-membered heterocyclyl, 3- to 7-membered heterocyclyl–O–, –C(O)R^c, –C(O)OR^d, –C(O)NR^{e}R^f, –C_{1-3} alkylene–C(O)NR^{e}R^f, C_{3-6} cycloalkyl–C(O)NH–, and C_{1-6} alkyl–$S(O)_2$–C_{0-3} alkylene–; or two R^{4a} groups on adjacent carbon atoms are optionally combined to form 5- to 6-membered cycloalkyl or 3- to 7-membered heterocyclyl, each of which is independently unsubstituted or substituted with from 1 to 3 R^{4a1}, wherein each R^{4a1} is independently selected from halo, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{5a} and R^{5b} are each independently selected from the group consisting of H, C_{1-6} alkyl, hydroxyC_{1-6}alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^6 is selected from the group consisting of H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^a is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

R^{a1} and R^{a2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^b is independently selected from the group consisting of oxo, halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and C_{1-6} alkyl–$S(O)_2$–C_{0-3} alkylene–;

each R^c is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^d is independently selected from the group consisting of H and C_{1-6} alkyl;

R^e and R^f are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3- to 7-membered heterocyclyl, wherein each of said cycloalkyl and heterocyclyl is independently unsubstituted or substituted with 1 or 2 R^h; or R^e and R^f together with the nitrogen atom to which they are attached form 3- to 10-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^i;

each R^g is independently selected from the group consisting of C_{1-6} alkyl, halo, hydroxy, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and cyano;

each R^h is independently selected from the group consisting of halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkoxy, and cyano;

each R^i is independently selected from the group consisting of halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkoxy, and cyano;

each heteroaryl has 1 to 4 heteroatoms each independently selected from N, O, and S;

each heterocyclyl has 1 to 4 heteroatoms or groups each independently selected from N, O, S, S(O), and $S(O)_2$;

each bridged heterocyclyl has 1 to 3 heteroatoms each independently selected from N, O, and S;

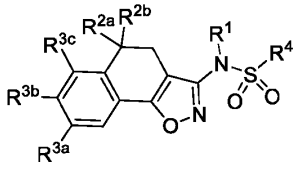
the fused heterocyclyl is a 4- to 7-membered heterocyclyl having 1 to 3 heteroatoms each independently selected from N, O, and S, and the 4- to 7-membered heterocyclyl is fused to two adjacent ring members of C_{3-6} cycloalkyl, phenyl, or 5- to 6-membered heteroaryl; and

each spiroheterocyclyl has 1 to 3 heteroatoms each independently selected from N, O, and S.

[0076] In some embodiments, R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-6} alkyl, hydroxyC_{1-6}alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy; and R^{5a} and R^{5b} are each H. In some embodiments, R^{2a} and R^{2b} together with the carbon atom to which they are attached form cyclopropyl or cyclobutyl, wherein each of said cyclopropyl and cyclobutyl is independently unsubstituted or substituted with from 1 to 3 R^g; and R^{5a} and R^{5b} are each H.

[0077] In some embodiments, R^{5a} and R^{5b} are each independently selected from the group consisting of H, C_{1-6} alkyl, hydroxyC_{1-6}alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy; and R^{2a} and R^{2b} are each H. In some embodiments, R^{5a} and R^{5b} together with the carbon atom to which they are attached form cyclopropyl or cyclobutyl, wherein each of said cyclopropyl and cyclobutyl is independently unsubstituted or substituted with from 1 to 3 R^{g1}; and R^{2a} and R^{2b} are each H.

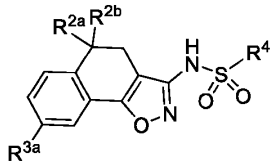
[0078] In some embodiments of Formula (Y), L is a bond; and each of R^{3d}, R^{5a}, and R^{5b} is H. In some embodiments, the compound is represented by Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{3c}, and R^4 are each defined in Formula (Y) and described in any one of embodiments herein. In some embodiments of Formula (I), R^1 is H.

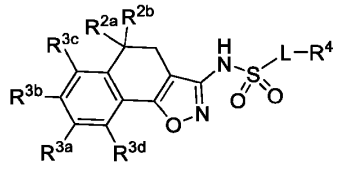
[0079] In some embodiments of Formula (Y), L is a bond; R^1 is H; R^{3b}, R^{3c}, and R^{3d} are each H; and R^{5a} and R^{5b} are each H. In some embodiments of Formula (I), R^1 is H; and R^{3b} and R^{3c} are each H. In some embodiments, the compound is represented by Formula (I-1):



(I-1),

or a pharmaceutically acceptable salt thereof, wherein each of R^{2a}, R^{2b}, R^{3a}, and R^4 are each defined in Formula (Y) and described in any one of embodiments herein.

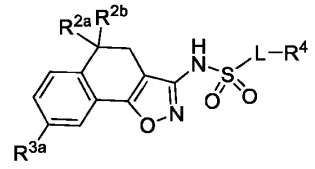
[0080] In some embodiments of Formula (Y), R^1 is H; and R^{5a} and R^{5b} are each H. In some embodiments, the compound is represented by Formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein each of L, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{3c}, R^{3d}, and R^4 are each defined in Formula (Y) and described in any one of embodiments herein.

[0081] In some embodiments of Formula (Y), R^1 is H; R^{3b}, R^{3c}, and R^{3d} are each H; and R^{5a} and R^{5b} are each H. In some embodiments of Formula (II), R^{3b}, R^{3c}, and R^{3d} are each H. In some embodiments, the compound is represented by Formula (II-1):

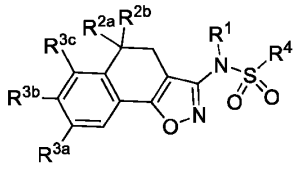


(II-1),

or a pharmaceutically acceptable salt thereof, wherein each of L, R^{2a}, R^{2b}, R^{3a}, and R^4 are each defined in Formula (Y) and described in any one of embodiments herein.

[0082] In some embodiments of any one of Formulae (Y), (I), (I-1), (II), and (II-1), each heteroaryl has 1 to 3 heteroatoms each independently selected from N, O, and S; and each heterocyclyl has 1 to 3 heteroatoms or groups each independently selected from N, O, S, S(O), and $S(O)_2$.

[0083] In one aspect, provided herein are compounds of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of H, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{2a} and R^{2b} together with the carbon atom to which they are attached form cyclopropyl or cyclobutyl, wherein each of said cyclopropyl and cyclobutyl is independently unsubstituted or substituted with from 1 to 3 R^g; or

R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, and C_{1-4} haloalkyl;

R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, –C(O)NHR[a], and cyano; and wherein each of said 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl has from 1 to 4 ring members independently selected from N, O and S, and wherein each of said C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl is independently unsubstituted or substituted with from 1 to 4 R^b;

R^4 is selected from the group consisting of C_{4-7} cycloalkyl, phenyl, heteroaryl, heterocyclyl, and fused heterocyclyl, wherein each of said phenyl, heteroaryl, heterocyclyl, and fused heterocyclyl is independently unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, –C(O)R^c, –C(O)OR^d, or –C(O)N$R^e$$R^f$; or two R^{4a} groups on adjacent carbon atoms are optionally combined to form a 5- to 6-membered cycloalkyl or heterocycloalkyl, each of which is independently unsubstituted or substituted with from 1 to 3 R^{4a1}, wherein each R^{4a1} is independently selected from halo, C_{1-4} alkyl, and C_{1-4} haloalkyl;

each R^a is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^b is independently selected from the group consisting of oxo, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

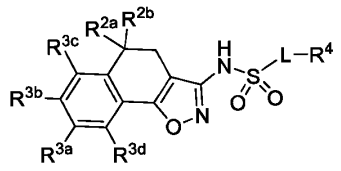
each R^c is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^d is independently selected from the group consisting of H and C_{1-6} alkyl;

each R^e and R^f is independently selected from the group consisting of H, C_{1-6} alkyl and C_{3-6} cycloalkyl; or R^e and R^f together with the nitrogen atom to which they are attached form 4- to 6-membered ring; and

each R^g is independently selected from the group consisting of C_{1-6} alkyl, halo, hydroxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and cyano.

[0084] In another aspect, the preset disclosure provides a compound represented by Formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

L is a bond or C_{1-3} alkylene;

R^{2a} and R^{2b} together with the carbon atom to which they are attached form unsubstituted cyclopropyl; or

R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{3a} is selected from the group consisting of H, halo, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, 5- to 6-membered heteroaryl–C_{1-3} alkylene–, and –C(O)NHR[a], wherein each of said C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl is independently unsubstituted or substituted with 1 or 2 R^b;

R^{3b} is selected from the group consisting of H, halo, and C_{1-4} alkyl;

R^{3c} is selected from the group consisting of H, halo, C_{1-4} alkyl, and C_{1-4} hydroxyalkyl;

R^{3d} is selected from the group consisting of H and halo;

R^4 is selected from the group consisting of C_{1-6} alkyl, C_{4-7} cycloalkyl, bridged C_{5-10} cycloalkyl, phenyl, 5- to 6-membered heteroaryl, and 3- to 7-membered heterocyclyl, wherein each of said cycloalkyl, phenyl, heteroaryl, and heterocyclyl is independently unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halo, CN, C_{1-4} haloalkoxy, 3- to 7-membered heterocyclyl, 3- to 7-membered heterocyclyl–O–, –C(O)NR^eR^f, –C_{1-3} alkylene–C(O)NR^eR^f, C_{3-6} cycloalkyl–C(O)NH–, and C_{1-4} alkyl–$S(O)_2$–C_{0-3} alkylene–; or two R^{4a} groups on adjacent carbon atoms are optionally combined to form 5- to 6-membered cycloalkyl or 3- to 7-membered heterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 halo;

R^a is C_{1-4} alkyl;

each R^b is independently selected from the group consisting of oxo, halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} alkyl–$S(O)_2$–C_{0-3} alkylene–;

each R^e and R^f is independently selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, and 3- to 7-membered heterocyclyl, wherein each of said C_{3-6} cycloalkyl and heterocyclyl is independently unsubstituted or substituted with 1 or 2 R^h; or R^e and R^f together with the nitrogen atom to which they are attached form 3- to 10-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^i;

each R^h is independently selected from the group consisting of hydroxy and C_{1-4} alkoxy;

each R^i is independently selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, and C_{1-4} alkoxy;

each heteroaryl has 1 or 2 heteroatoms each independently selected from N and O;

each heterocyclyl has 1 or 2 heteroatoms or groups each independently selected from N, O, and $S(O)_2$;

each bridged heterocyclyl has 1 or 2 heteroatoms each independently selected from N and O;

the fused heterocyclyl is a 4- to 7-membered heterocyclyl having 1 or 2 heteroatoms each independently selected from N and O, and the 4- to 7-membered heterocyclyl is fused to two adjacent ring members of C_{3-6} cycloalkyl, phenyl, or 5- to 6-membered heteroaryl; and

each spiroheterocyclyl has 1 or 2 heteroatoms each independently selected from N and O.

[0085] In some embodiments of any one of Formulae (Y), (II), and (II-1), L is a bond.

[0086] In some embodiments of any one of Formulae (Y), (II), and (II-1), L is C_{1-3} alkylene. In some embodiments, L is CH_2. In some embodiments, L is $CH(CH_3)$.

[0087] In some embodiments of Formula (Y), or any one of the embodiments thereof, R^{2a} and R^{2b} are each independently H, C_{1-4} alkyl, or C_{1-4} haloalkyl; and R^{5a} and R^{5b} are each H. In some embodiments, R^{2a} and R^{2b} are each independently H or C_{1-4} alkyl; and R^{5a} and R^{5b} are each H. In some embodiments, R^{2a} and R^{2b} are each independently H or methyl; and R^{5a} and R^{5b} are each H. In some embodiments, R^{2a} R^{2b}, R^{5a}, and R^{5b} are each H. In some

embodiments, R^{2a} is H and R^{2b} is methyl; and R^{5a} and R^{5b} are each H. In some embodiments, R^{2a} and R^{2b} are each methyl; and R^{5a} and R^{5b} are each H.

[0088] With reference to any one of Formulae (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^{2a} and R^{2b} are each independently H, C_{1-4} alkyl, or C_{1-4} haloalkyl. In some embodiments, R^{2a} and R^{2b} are each independently H or C_{1-4} alkyl. In some embodiments, R^{2a} and R^{2b} are each independently H or methyl. In some embodiments, R^{2a} and R^{2b} are each H. In some embodiments, R^{2a} is H and R^{2b} is methyl. In some embodiments, R^{2a} and R^{2b} are each methyl.

[0089] In some embodiments of Formula (Y), or any one of the embodiments thereof, R^{5a} and R^{5b} are each H; R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl, which is unsubstituted or substituted with 1 or 2 R^g; and each R^g is independently selected from the group consisting of C_{1-4} alkyl, halo, hydroxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, and cyano. In some embodiments, R^{5a} and R^{5b} are each H; R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl, which is unsubstituted or substituted with 1 or 2 R^g; and each R^g is independently C_{1-4} alkyl or halo. In some embodiments, R^{5a} and R^{5b} are each H; R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl, which is substituted with 1 or 2 R^g; and each R^g is independently C_{1-4} alkyl or halo. In some embodiments, R^{5a} and R^{5b} are each H; R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl, which is substituted with 1 or 2 R^g; and each R^g is independently methyl or F. In some embodiments, R^{5a} and R^{5b} are each H; and R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl, which is unsubstituted.

[0090] With reference to any one of Formulae (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl, which is unsubstituted or substituted with 1 or 2 R^g; and each R^g is independently selected from the group consisting of C_{1-4} alkyl, halo, hydroxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, and cyano. In some embodiments, R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl, which is unsubstituted or substituted with 1 or 2 R^g; and each R^g is independently C_{1-4} alkyl or halo. In some embodiments, R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl, which is substituted with 1 or 2 R^g; and each R^g is independently C_{1-4} alkyl or halo. In some embodiments, R^{2a} and R^{2b} are combined with the

carbon atom to which they are attached to form cyclopropyl, which is substituted with 1 or 2 R^g; and each R^g is independently methyl or F. In some embodiments, R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl, which is unsubstituted.

[0091] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-4} alkyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, hydroxyC_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, 5- to 6-membered heteroaryl–C_{1-3} alkylene–, –C(O)NHR^a, –NR^{a1}R^{a2}, and cyano, wherein each of said C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl, by itself or as part of another group, is independently unsubstituted or substituted with from 1 to 3 R^b; and R^{3d} (when present) is selected from the group consisting of H, halo, C_{1-4} alkyl, and C_{1-4} alkoxy. In some embodiments, R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-4} alkyl, C_{2-4} alkynyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, 5- to 6-membered heteroaryl–C_{1-3} alkylene–, –C(O)NHR^a, and –NR^{a1}R^{a2}, wherein each of said C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl, by itself or as part of another group, is independently unsubstituted or substituted with 1 or 2 R^b; and R^{3d} (when present) is selected from the group consisting of H, halo, and C_{1-4} alkyl. In some embodiments, R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-4} alkyl, C_{2-4} alkynyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, 5- to 6-membered heteroaryl–C_{1-3} alkylene–, –C(O)NHR^a, and –NR^{a1}R^{a2}, wherein each of said C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl, by itself or as part of another group, is independently unsubstituted or substituted with 1 or 2 R^b; R^{3d} (when present) is selected from the group

consisting of H, halo, and C_{1-4} alkyl; each R^a is independently C_{1-4} alkyl; and R^{a1} and R^{a2} are each independently selected from the group consisting of H and C_{1-4} alkyl.

[0092] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^{3a} is selected from the group consisting of H, halo, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, 5- to 6-membered heteroaryl–C_{1-3} alkylene–, –C(O)NHR^a, and , –$NR^{a1}R^{a2}$, wherein each of said C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl, by itself or as part of another group, is independently unsubstituted or substituted with 1 or 2 R^b; R^a is C_{1-4} alkyl; R^{a1} and R^{a2} are each independently selected from the group consisting of H and C_{1-4} alkyl; each R^b is independently selected from the group consisting of oxo, halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} alkyl–$S(O)_2$–C_{0-3} alkylene–; R^{3b} is selected from the group consisting of H, halo, and C_{1-4} alkyl; R^{3c} is selected from the group consisting of H, halo, C_{1-4} alkyl, and C_{1-4} hydroxyalkyl; and R^{3d} (when present) is selected from the group consisting of H and halo.

[0093] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^{3a} is selected from the group consisting of 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, and 5- to 6-membered heteroaryl–C_{1-3} alkylene–, wherein each of the 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl, by itself or as part of another group, is independently unsubstituted or substituted with 1 or 2 R^b.

[0094] In some embodiments of Formula (Y), (I), or (II), or any one of the embodiments thereof, R^{3a} is selected from the group consisting of 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, and 5- to 6-membered heteroaryl–C_{1-3} alkylene–, wherein each of the 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl, by itself or as part of another group, is independently unsubstituted or substituted with 1 or 2 R^b; and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

[0095] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, R^{3a} is 3- to 7-membered heterocyclyl, which is unsubstituted or substituted with 1 or 2 R^b.

[0096] In some embodiments of Formula (Y), (I), or (II), or any one of the embodiments thereof, R^{3a} is 3- to 7-membered heterocyclyl, which is unsubstituted or substituted with 1 or 2 R^b; and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

[0097] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, wherein R^{3a} is 6- to 9-membered bridged heterocyclyl or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^b.

[0098] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, wherein R^{3a} is 6- to 9-membered bridged heterocyclyl or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^b; and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

[0099] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, R^{3a} is 6- to 9-membered bridged heterocyclyl, which is unsubstituted or substituted with 1 or 2 R^b.

[0100] In some embodiments of Formula (Y), (I), or (II), or any one of the embodiments thereof, R^{3a} is 6- to 9-membered bridged heterocyclyl, which is unsubstituted or substituted with 1 or 2 R^b; and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

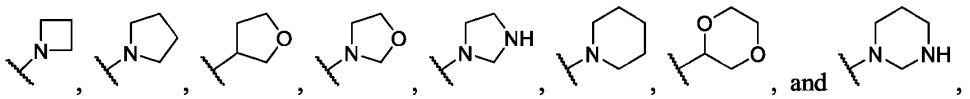
[0101] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, R^{3a} is 6- to 10-membered spiroheterocyclyl, which is unsubstituted or substituted with 1 or 2 R^b.

[0102] In some embodiments of Formula (Y), (I), or (II), or any one of the embodiments thereof, R^{3a} is 6- to 10-membered spiroheterocyclyl, which is unsubstituted or substituted with 1 or 2 R^b; and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

[0103] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, R^{3a} is 5- to 6-membered heteroaryl or 5- to 6-membered heteroaryl–$C_{1\text{-}3}$ alkylene–, each of heteroaryl is unsubstituted or substituted with 1 or 2 R^b.

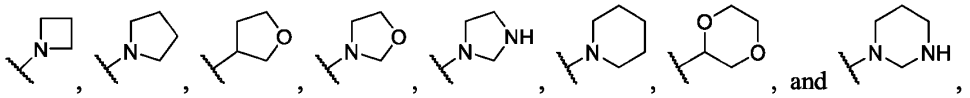
[0104] In some embodiments of Formula (Y), (I), or (II), or any one of the embodiments thereof, R^{3a} is 5- to 6-membered heteroaryl or 5- to 6-membered heteroaryl–C_{1-3} alkylene–, each of heteroaryl is unsubstituted or substituted with 1 or 2 R^b; and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

[0105] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of embodiments thereof, in some embodiments, R^{3a} is selected from the group consisting of:



each of which is independently unsubstituted or substituted with 1 or 2 R^b.

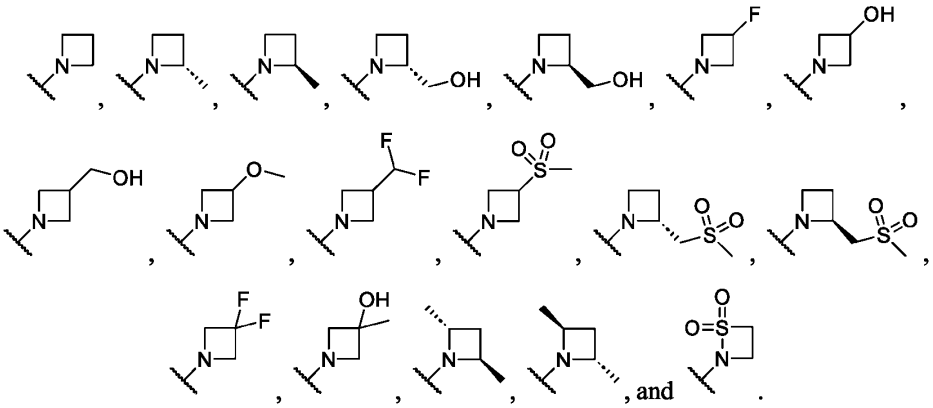
[0106] In some embodiments of Formula (Y), (I), or (II), or any one of the embodiments thereof, R^{3a} is selected from the group consisting of:



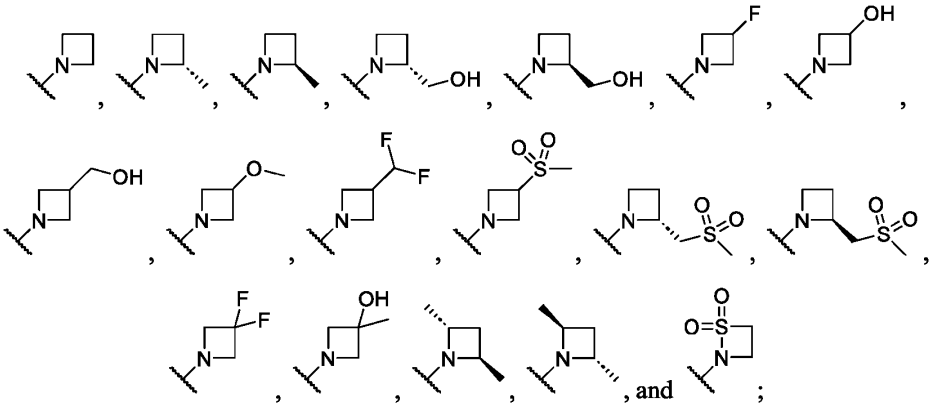
each of which is independently unsubstituted or substituted with 1 or 2 R^b; and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

[0107] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1) and any one of the embodiments thereof, in some embodiments, each R^b is independently selected from the group consisting of oxo, halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} alkyl–$S(O)_2$–C_{0-3} alkylene–. In some embodiments, each R^b is independently selected from the group consisting of oxo, halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4} alkyl, and C_{1-4} alkoxy. In some embodiments, each R^b is independently oxo or halo. In some embodiments, each R^b is independently selected from the group consisting of oxo, fluoro, hydroxy, methyl, ethyl, $–CHF_2$, $–CH_2F$, $–CF_3$, $–CH_2OH$, $–OCH_3$, $–S(O)_2CH_3$, and $–CH_2S(O)_2CH_3$. In some embodiments, each R^b is independently selected from the group consisting of oxo, fluoro, hydroxy, methyl, $–CHF_2$, $–CH_2OH$, and $–OCH_3$. In some embodiments, at least one R^b is oxo. In some embodiments, each R^b is independently oxo or fluoro. In some embodiments, each R^b is independently oxo or methyl. In some embodiments, each R^b is independently oxo or hydroxy.

[0108] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^{3a} is selected from the group consisting of:



[0109] In some embodiments of Formula (Y), (I), or (II), or any one of the embodiments thereof, R^{3a} is selected from the group consisting of:

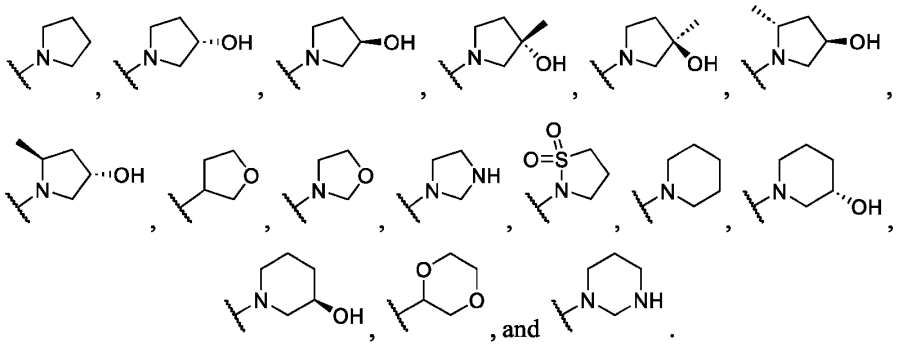


and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

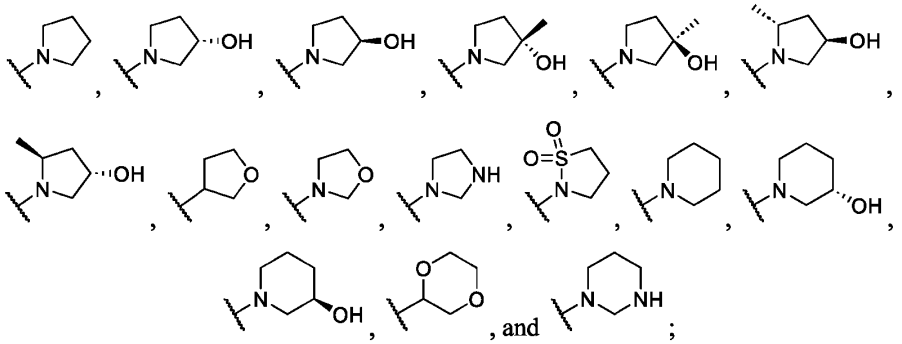
[0110] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^{3a} is  .

[0111] In some embodiments of Formula (Y), (I), or (II), or any one of the embodiments thereof, R^{3a} is  ; and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

[0112] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^{3a} is selected from the group consisting of:

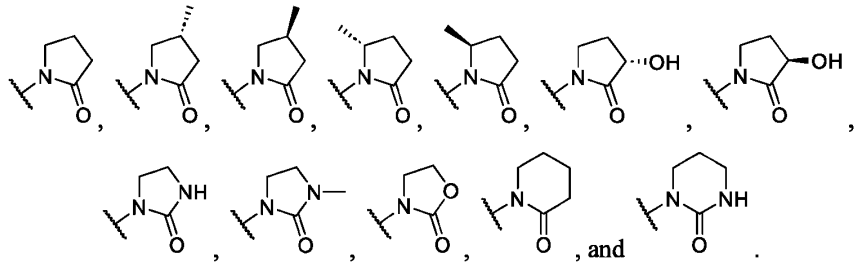


[0113] In some embodiments of Formula (Y), (I), or (II), or any one of the embodiments thereof, R^{3a} is selected from the group consisting of:

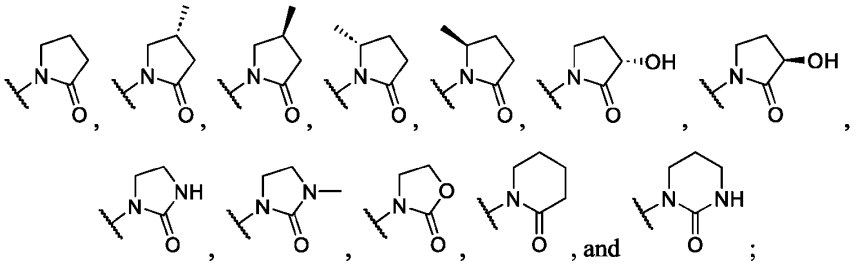


and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

[0114] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^{3a} is selected from the group consisting of:

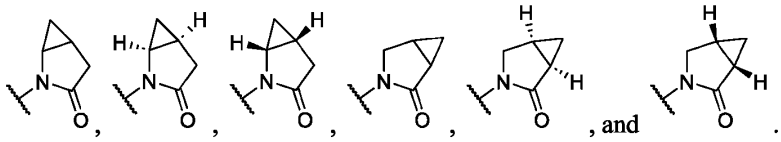


[0115] In some embodiments of Formula (Y), (I), or (II), or any one of the embodiments thereof, R^{3a} is selected from the group consisting of:

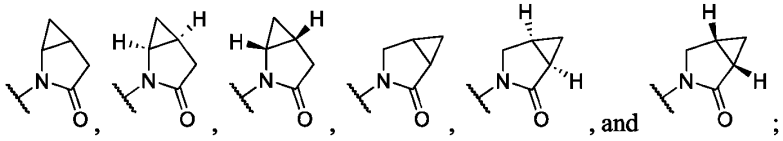


and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

[0116] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^{3a} is selected from the group consisting of:

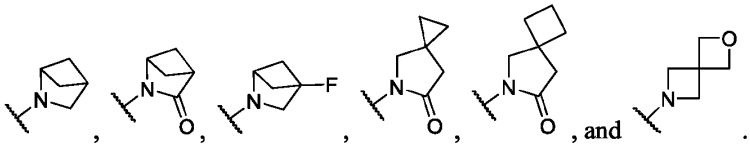


[0117] In some embodiments of Formula (Y), (I), or (II), or any one of embodiments thereof, R^{3a} is selected from the group consisting of:

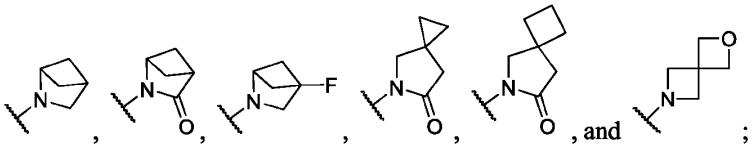


and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

[0118] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^{3a} is selected from the group consisting of:



[0119] In some embodiments of Formula (Y), (I), or (II), or any one of the embodiments thereof, R^{3a} is selected from the group consisting of:

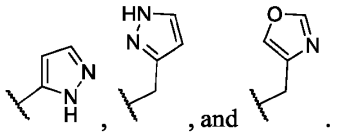


and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

[0120] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^{3a} is 5- to 6-membered heteroaryl or 5- to 6-membered heteroaryl–C_{1-3} alkylene–, each of which is unsubstituted.

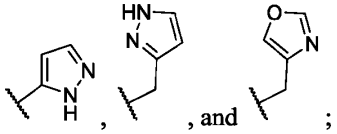
[0121] In some embodiments of Formula (Y), (I), or (II), or any one of the embodiments thereof, R^{3a} is 5- to 6-membered heteroaryl or 5- to 6-membered heteroaryl–C_{1-3} alkylene–, each of which is unsubstituted; and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

[0122] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^{3a} is selected from the group consisting of:



, , and .

[0123] In some embodiments of Formula (Y), (I), or (II), or any one of the embodiments thereof, R^{3a} is selected from the group consisting of:



, , and ;

and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

[0124] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^{3a} is selected from the group consisting of H, halo, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, –C(O)NHR^a, and –NR^{a1}R^{a2}; R^a is C_{1-4} alkyl; and R^{a1} and R^{a2} are each independently H or C_{1-4} alkyl.

[0125] In some embodiments of Formula (Y), (I), or (II), or any one of the embodiments thereof, R^{3a} is selected from the group consisting of H, halo, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, –C(O)NHR^a, and –NR^{a1}R^{a2}; R^a is C_{1-4} alkyl; R^{a1} and R^{a2} are each independently H or C_{1-4} alkyl; and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

[0126] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^{3a} is selected from the group consisting of

H, Cl, Br, $-CH_3$, $-CH_2OH$, $-CH(CH_3)OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCHF_2$, $-OCF_3$, cyclopropyl, –O–cyclopropyl, $-C(O)NHCH_3$, $-NH_2$, $-NHCH_3$, and $-N(CH_3)_2$.

[0127] In some embodiments of Formula (Y), (I), or (II), or any one of embodiments thereof, R^{3a} is selected from the group consisting of H, Cl, Br, $-CH_3$, $-CH_2OH$, $-CH(CH_3)OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCHF_2$, $-OCF_3$, cyclopropyl, –O–cyclopropyl, $-C(O)NHCH_3$, $-NH_2$, $-NHCH_3$, and $-N(CH_3)_2$; and R^{3b}, R^{3c}, and R^{3d} (when present) are each H.

[0128] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl, which is unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halo, CN, C_{1-4} haloalkoxy, 3- to 7-membered heterocyclyl, 3- to 7-membered heterocyclyl–O–, $-C(O)NR^eR^f$, $-C_{1-3}$ alkylene–$C(O)NR^eR^f$, C_{3-6} cycloalkyl–C(O)NH–, and C_{1-4} alkyl–$S(O)_2$–C_{0-3} alkylene–; each R^e and R^f is independently selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, and 3- to 7-membered heterocyclyl, wherein each of cycloalkyl and heterocyclyl is independently unsubstituted or substituted with 1 or 2 R^h; or R^e and R^f together with the nitrogen atom to which they are attached form 3- to 10-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^i; each R^h is independently selected from the group consisting of hydroxy and C_{1-4} alkoxy; and each R^i is independently selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy.

[0129] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with 1 or 2 R^{4a}; and each R^{4a} is independently C_{1-4} alkoxy. In some embodiments, each R^{4a} is methoxy. In some embodiments, R^4 is phenyl substituted with 1 or 2 methoxy. In some embodiments, R^4 is phenyl substituted with two (2) methoxy.

[0130] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy; and the remaining R^{4a} is $-C(O)NR^eR^f$. In some embodiments, the remaining R^{4a} is $-C(O)NR^eR^f$; R^e is H; and R^f is C_{1-4} alkyl. In some embodiments, two R^{4a} are each methoxy; and the remaining R^{4a} is $-C(O)NHCH_3$.

[0131] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each methoxy; and the remaining R^{4a} is $-C(O)NHCH_3$.

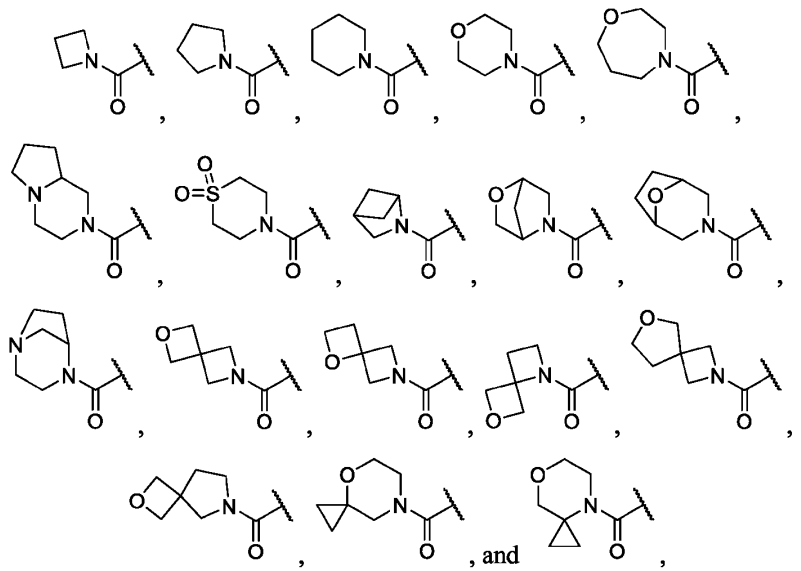
[0132] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is $-C(O)NR^eR^f$; and R^e and R^f together with the nitrogen atom to which they are attached form 5- to 10-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^i.

[0133] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is $-C(O)NR^eR^f$; R^e and R^f together with the nitrogen atom to which they are attached form 5- to 6-membered heterocyclyl, which is unsubstituted or substituted with 1 or 2 R^i; and each R^i is independently halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy.

[0134] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is $-C(O)NR^eR^f$; R^e and R^f together with the nitrogen atom to which they are attached form 6- to 9-membered bridged heterocyclyl, which is unsubstituted or substituted with 1 or 2 R^i; and each R^i is independently halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy.

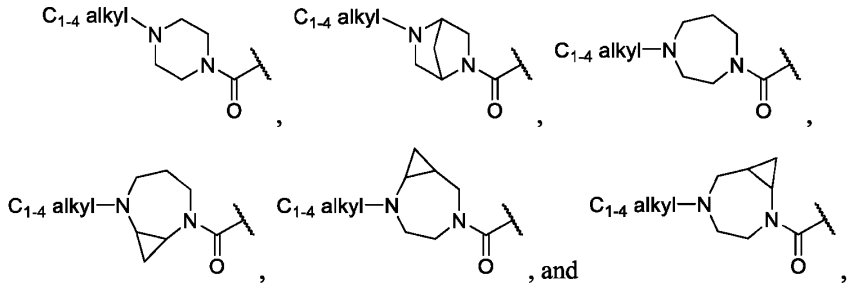
[0135] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is $-C(O)NR^eR^f$; R^e and R^f together with the nitrogen atom to which they are attached form 6- to 10-membered spiroheterocyclyl, which is unsubstituted or substituted with 1 or 2 R^i; and each R^i is independently halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy.

[0136] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is selected from the group consisting of:



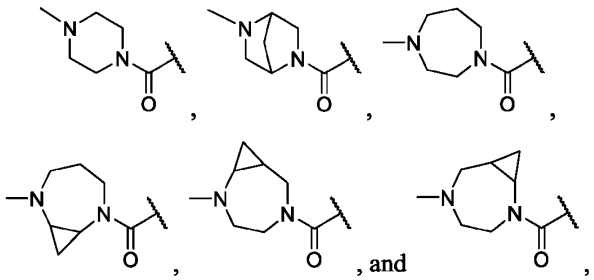
each of which is independently unsubstituted or substituted with 1 or 2 R^i; and each R^i is independently halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy.

[0137] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is selected from the group consisting of:



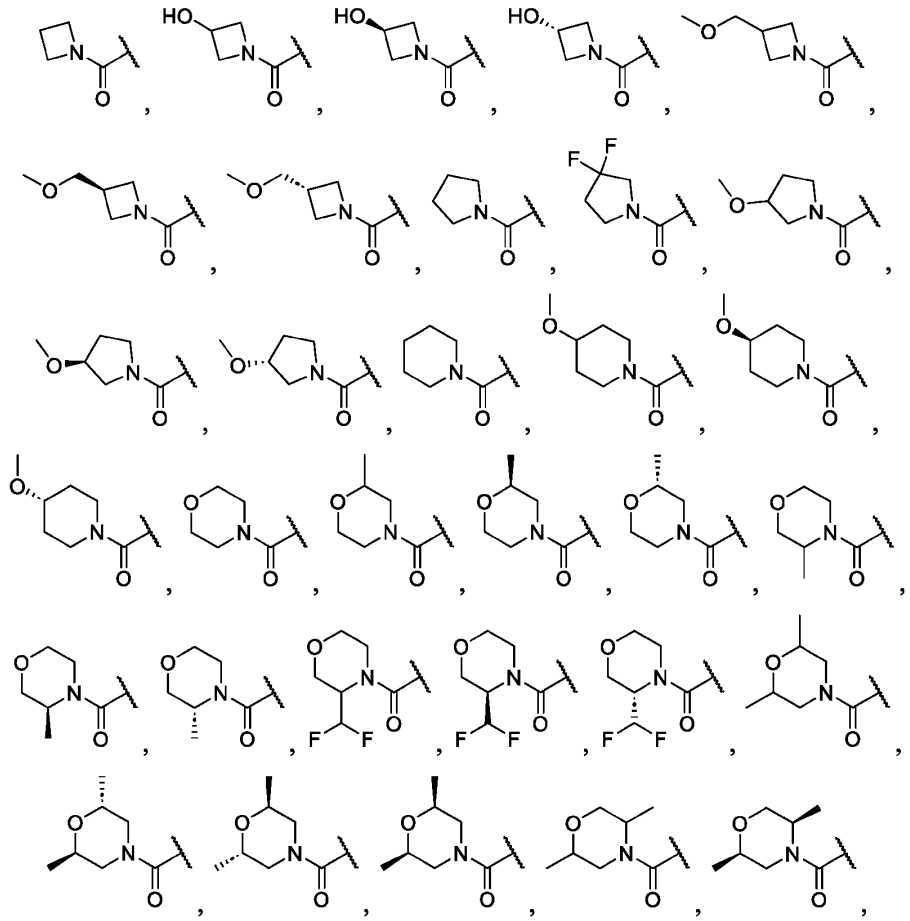
each of which is optionally substituted with one additional R^i; and R^i is halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy. In some embodiments, the one additional R^i is halo, C_{1-4} alkyl, or C_{1-4} alkoxy. In some embodiments, the one additional R^i is C_{1-4} alkyl.

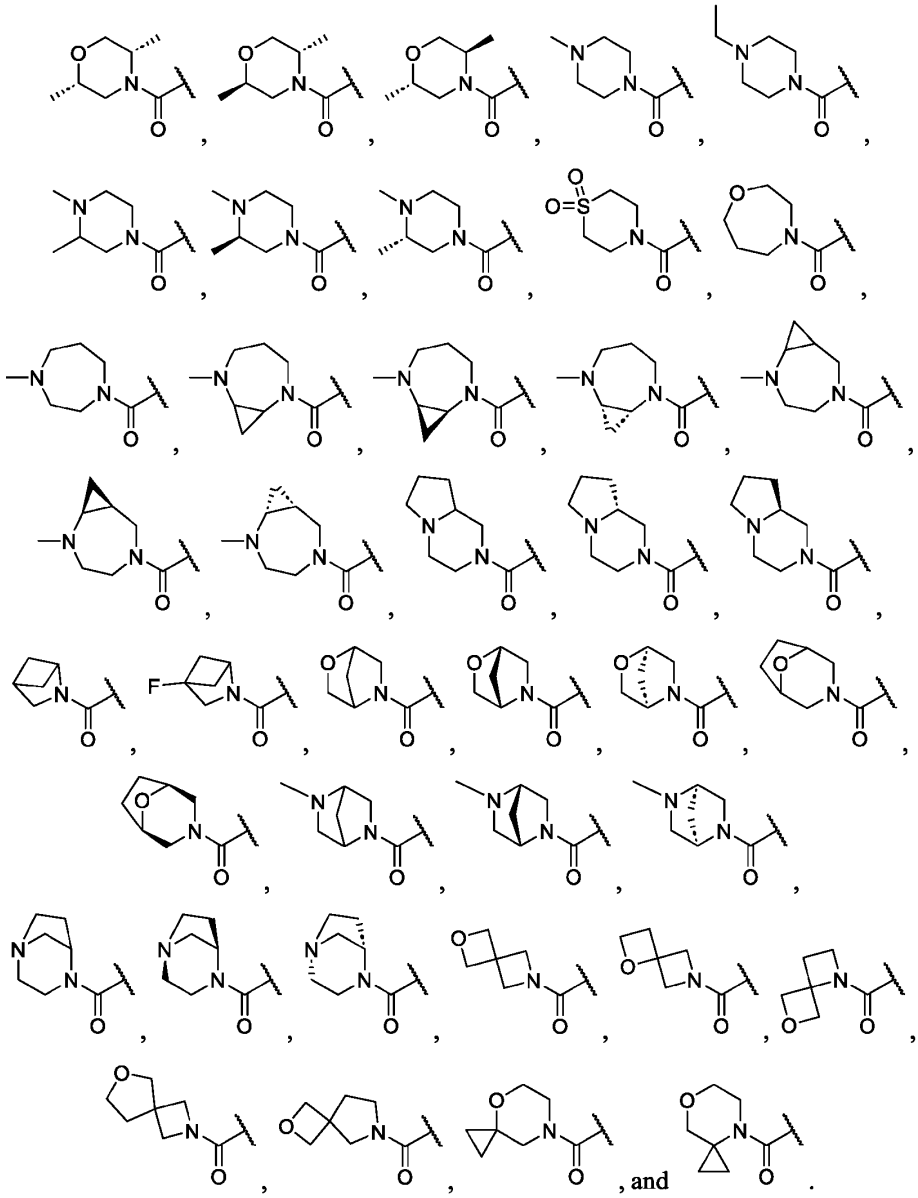
[0138] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is selected from the group consisting of:



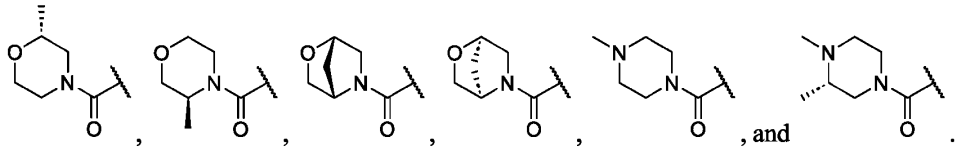
each of which is optionally substituted with one additional methyl.

[0139] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; and two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is selected from the group consisting of:

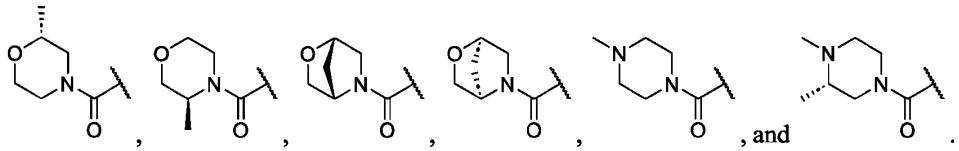




[0140] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; and two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is selected from the group consisting of:



[0141] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; and two R^{4a} are each methoxy and the remaining R^{4a} is selected from the group consisting of:

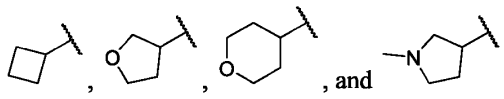


[0142] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is $-C(O)NR^eR^f$; R^e is H or C_{1-4} alkyl; and R^f is C_{3-6} cycloalkyl or 3- to 7-membered heterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^h.

[0143] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is $-C(O)NR^eR^f$; R^e is H or C_{1-4} alkyl; R^f is C_{3-6} cycloalkyl unsubstituted or substituted with 1 or 2 R^h; and each R^h is independently hydroxy or C_{1-4} alkoxy.

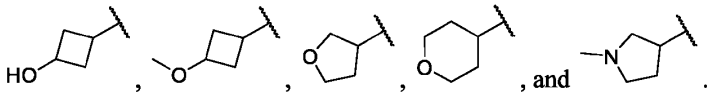
[0144] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is $-C(O)NR^eR^f$; R^e is H or C_{1-4} alkyl; R^f is 3- to 7-membered heterocyclyl unsubstituted or substituted with 1 or 2 R^h; and each R^h is independently hydroxy or C_{1-4} alkoxy.

[0145] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is $-C(O)NR^eR^f$; R^e is H or C_{1-4} alkyl; R^f is selected from the group consisting of:

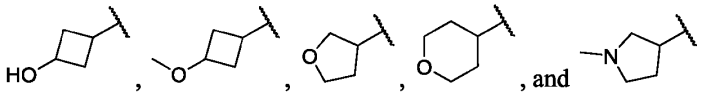


each of which is unsubstituted or substituted with 1 or 2 R^h; and each R^h is independently hydroxy or C_{1-4} alkoxy.

[0146] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is $-C(O)NR^eR^f$; R^e is H or methyl; R^f is selected from the group consisting of:



[0147] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each methoxy and the remaining R^{4a} is $-C(O)NR^eR^f$; R^e is H or methyl; R^f is selected from the group consisting of:



[0148] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each methoxy; and the remaining R^{4a} is $-C(O)NR^eR^f$, wherein each R^e and R^f are described in any one of embodiments.

[0149] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is 5- to 6-membered heteroaryl, which is unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halo, CN, C_{1-4} haloalkoxy, 3- to 7-membered heterocyclyl, 3- to 7-membered heterocyclyl–O–, $-C(O)NR^eR^f$, $-C_{1-3}$ alkylene–$C(O)NR^eR^f$, C_{3-6} cycloalkyl–C(O)NH–, and C_{1-4} alkyl–$S(O)_2$–C_{0-3} alkylene–; each R^e and R^f is independently selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, and 3- to 7-membered heterocyclyl, wherein each of cycloalkyl and heterocyclyl is independently unsubstituted or substituted with 1 or 2 R^h; or R^e and R^f together with the nitrogen atom to which they are attached form 3- to 10-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, or 6- to 10-membered spiroheterocyclyl, each of which is independently

unsubstituted or substituted with 1 or 2 R^i; each R^h is independently selected from the group consisting of hydroxy and C_{1-4} alkoxy; and each R^i is independently selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy.

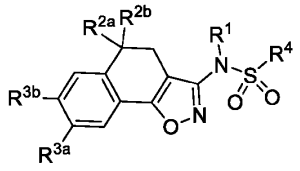
[0150] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is 6-membered heteroaryl, which is unsubstituted or substituted with 1 or 2 R^{4a}; and each R^{4a} is independently C_{1-4} alkoxy. In some embodiments, R^4 is 6-membered heteroaryl substituted with 1 or 2 R^{4a}; and each R^{4a} is independently C_{1-4} alkoxy. In some embodiments, each R^{4a} is methoxy. In some embodiments, R^4 is 6-membered heteroaryl substituted with 1 or 2 methoxy. In some embodiments, R^4 is 6-membered heteroaryl substituted with one (1) methoxy. In some embodiments, R^4 is 6-membered heteroaryl substituted with two (2) methoxy.

[0151] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is pyridyl substituted with 1 or 2 R^{4a}; and each R^{4a} is independently C_{1-4} alkoxy. In some embodiments, each R^{4a} is methoxy. In some embodiments, R^4 is pyridyl substituted with 1 or 2 methoxy. In some embodiments, R^4 is pyridyl substituted with one (1) methoxy. In some embodiments, R^4 is pyridyl substituted with two (2) methoxy.

[0152] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is pyrazinyl substituted with 1 or 2 R^{4a}; and each R^{4a} is independently C_{1-4} alkoxy. In some embodiments, each R^{4a} is methoxy. In some embodiments, R^4 is pyrazinyl substituted with 1 or 2 methoxy. In some embodiments, R^4 is pyrazinyl substituted with one (1) methoxy. In some embodiments, R^4 is pyrazinyl substituted with two (2) methoxy.

[0153] With reference to any one of Formulae (Y), (I), (I-1), (II), and (II-1), and any one of the embodiments thereof, in some embodiments, R^4 is 5-membered heteroaryl, which is unsubstituted or substituted with 1 or 2 R^{4a}; and each R^{4a} is independently C_{1-4} alkoxy. In some embodiments, each R^{4a} is methoxy. In some embodiments, R^4 is 5-membered heteroaryl, which is unsubstituted.

[0154] In one group of embodiments, provided herein are compounds represented by Formula (Ia),



(Ia)

or a pharmaceutically acceptable salt thereof, wherein the groups R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b} and R^4, have the meanings provided with reference to Formula (I).

[0155] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl or cyclobutyl, wherein each of said cyclopropyl and cyclobutyl is independently unsubstituted or substituted with from 1 to 3 R^g.

[0156] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl, wherein cyclopropyl is unsubstituted or substituted with from 1 to 3 R^g.

[0157] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl, wherein cyclopropyl is unsubstituted.

[0158] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclobutyl, wherein cyclobutyl is unsubstituted or substituted with from 1 to 3 R^g.

[0159] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclobutyl, wherein cyclobutyl is unsubstituted.

[0160] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{2a} and R^{2b} are

each independently selected from the group consisting of H, C_{1-4} alkyl, hydroxyC_{1-4} alkyl, and C_{1-4} haloalkyl.

[0161] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0162] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{2a} and R^{2b} are each independently selected from the group consisting of H and C_{1-4} alkyl.

[0163] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{2a} and R^{2b} are each H.

[0164] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{2a} and R^{2b} are each independently C_{1-4} alkyl.

[0165] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{2a} and R^{2b} are each independently methyl or ethyl.

[0166] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^1 is H.

[0167] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, and -O-C_{3-5} cycloalkyl.

[0168] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, and –C(O)NHR[a].

[0169] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, and –C(O)NHR^a.

[0170] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{3a} is selected from the group consisting of H, halo, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, and –C(O)NHR^a, and R^{3b} and R^{3c} are each independently H.

[0171] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^{3a} is selected from the group consisting of H, halo, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, and –C(O)NHR^a, and R^{3b} and R^{3c} are each independently selected from the group consisting of H and halo.

[0172] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein one of R^{3a} and R^{3b} is selected from the group consisting of 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl; and wherein each of said 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl has from 1 to 4 ring members independently selected from N, O and S, and are unsubstituted or substituted with from 1 to 4 R^b.

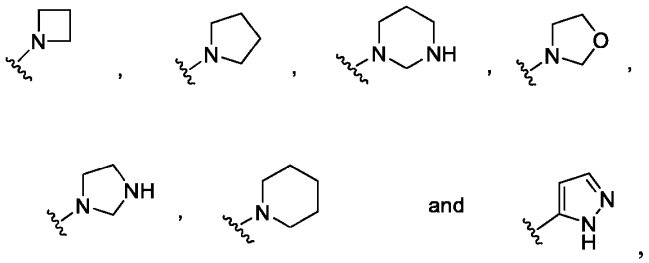
[0173] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein one of R^{3a} and R^{3b} is selected from the group consisting of 3- to 7-membered heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl; and wherein each of said 3- to 7-membered heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl has from 1 to 4 ring members independently selected from N, O and S, and is independently unsubstituted or substituted with from 1 to 4 R^b.

[0174] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein one of R^{3a} and

R^{3b} is selected from the group consisting of 3- to 7-membered heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl; and wherein each of said 3- to 7-membered heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl has from 1 to 4 ring members independently selected from N, O and S, and is unsubstituted.

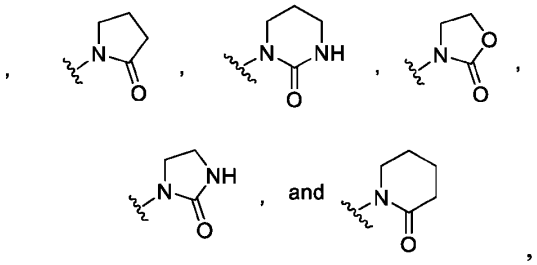
[0175] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein one of R^{3a} and R^{3b} is selected from the group consisting of 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl; and wherein each of said 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl has from 1 to 4 ring members independently selected from N, O and S, and is independently unsubstituted or substituted with from 1 to 4 R^b. In a further group of embodiments, one of R^{3a} and R^{3b} is selected from the group consisting of 3- to 7-membered heterocyclyl, having from 1 to 4 ring members independently selected from N, O and S, and which is unsubstituted or substituted with from 1 to 4 R^b. In another group of embodiments, one of R^{3a} and R^{3b} is selected from the group consisting of 6- to 9-membered bridged heterocyclyl, having from 1 to 4 ring members independently selected from N, O and S, and which is unsubstituted or substituted with from 1 to 4 R^b. In another group of embodiments, one of R^{3a} and R^{3b} is selected from the group consisting of 6- to 10-membered spiroheterocyclyl, having from 1 to 4 ring members independently selected from N, O and S, and which is unsubstituted or substituted with from 1 to 4 R^b. In another group of embodiments, one of R^{3a} and R^{3b} is selected from the group consisting of 5- to 6-membered heteroaryl having from 1 to 4 ring members independently selected from N, O and S, and which is unsubstituted or substituted with from 1 to 4 R^b.

[0176] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein one of R^{3a} and R^{3b} is selected from the group consisting of



wherein each cyclic moiety is independently unsubstituted or substituted with from 1 to 4 R^b.

[0177] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein one of R^{3a} and R^{3b} is selected from the group consisting of



wherein each cyclic moiety is independently unsubstituted or substituted with from 1 to 3 R^b.

[0178] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein each R^b is independently selected from the group consisting of oxo, hydroxyl, C_{1-6} alkyl, and C_{3-6} cycloalkyl.

[0179] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein each R^b is independently selected from the group consisting of oxo and C_{1-6} alkyl.

[0180] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^4 is phenyl, which is unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, $-C(O)R^c$, $-C(O)OR^d$, or $-C(O)NR^eR^f$.

[0181] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^4 is phenyl, which is unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or hydroxyC_{1-6} alkyl.

[0182] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^4 is phenyl, which is unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, C_{1-6} alkoxy, halo, CN, or C_{1-6} haloalkoxy.

[0183] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^4 is phenyl substituted with two R^{4a} groups on adjacent carbon atoms that combine to form a 5- to 6-membered cycloalkyl or heterocycloalkyl which is unsubstituted or substituted with 1-3 groups independently selected from halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0184] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^4 is a 5- or 6-membered heteroaryl, which is unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, $-C(O)R^c$, $-C(O)OR^d$, or $-C(O)NR^eR^f$.

[0185] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^4 is a 5- or 6-membered heteroaryl, which is unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, C_{1-6} alkoxy, halo, CN, or C_{1-6} haloalkoxy.

[0186] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^4 is pyridyl, which is unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, $-C(O)R^c$, $-C(O)OR^d$, or $-C(O)NR^eR^f$.

[0187] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^4 is pyridyl,

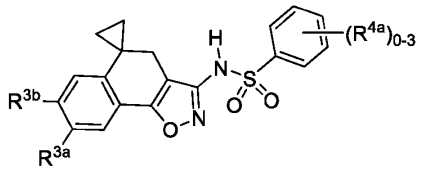
which is unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, C_{1-6} alkoxy, halo, CN, or C_{1-6} haloalkoxy.

[0188] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^4 is a 5- or 6-membered heterocyclyl, which is unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, $-C(O)R^c$, $-C(O)OR^d$, or $-C(O)NR^eR^f$.

[0189] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^4 is 5- or 6-membered heterocyclyl, which is unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, C_{1-6} alkoxy, halo, CN, or C_{1-6} haloalkoxy.

[0190] In another group of embodiments, provided herein are compounds or pharmaceutically acceptable salts of any of the embodiments above, wherein R^4 is C_{3-7} cycloalkyl.

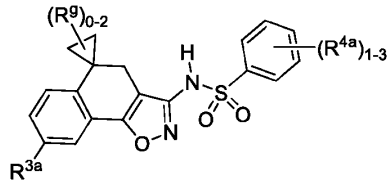
[0191] In another group of embodiments, provided herein are compounds represented by Formula (Ib), or a pharmaceutically acceptable salt thereof



(Ib)

wherein R^{3a}, R^{3b} and R^{4a} have the meaning provided for Formula (I) and the above paragraphs. In one group of embodiments, each R^{4a} is independently selected from the group consisting of C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and hydroxyC_{1-6} alkyl.

[0192] In some embodiments, the compound is represented by Formula (I-1a):



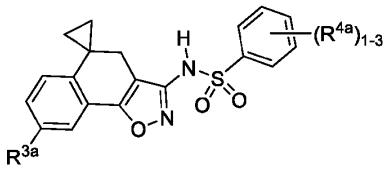
(I-1a),

or a pharmaceutically acceptable salt thereof, wherein R^{3a}, R^{4a}, and R^g are each defined in Formula (Y) and described in any one of the embodiments thereof.

[0193] In some embodiments of Formula (I-1a), R^{3a}, R^{4a}, and R^g are each described in any one of the embodiments related to Formula (I) or (I-1).

[0194] In some embodiments of Formula (I-1a), or any one of the embodiments thereof, the subscript of R^g is 1 or 2; and each R^g is independently C_{1-4} alkyl or halo. In some embodiments, the subscript of R^g is 1 or 2; and each R^g is independently methyl or F. In some embodiments, the subscript of R^g is 1; and R^g is C_{1-4} alkyl. In some embodiments, the subscript of R^g is 1; and R^g is methyl. In some embodiments, the subscript of R^g is 2; one R^g is C_{1-4} alkyl; and the other R^g is halo. In some embodiments, the subscript of R^g is 2; one R^g is methyl; and the other R^g is F.

[0195] In some embodiments, the subscript of R^g is 0. In some embodiments, the compound is represented by Formula (I-1b):



(I-1b),

or a pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{4a} are each defined in Formula (Y) and described in any one of embodiments thereof.

[0196] In some embodiments of Formula (I-1b), R^{3a} and R^{4a} are each described in any one of the embodiments related to Formula (I) or (I-1).

[0197] In some embodiments of Formula (I-Ia) or (I-1b), or any one of the embodiments thereof,

R^{3a} is selected from the group consisting of H, halo, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, 5- to 6-membered heteroaryl–C_{1-3} alkylene–, –C(O)NHR^a, and –N$R^{a1}R^{a2}$, wherein each of said C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl, by itself or as part of another group, is independently unsubstituted or substituted with 1 or 2 R^b;

each R^{4a} is independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halo, CN, C_{1-4} haloalkoxy, 3- to 7-membered heterocyclyl, 3- to 7-membered heterocyclyl–O–, -C(O)NR^eR^f, –C_{1-3} alkylene–C(O)NR^eR^f, C_{3-6} cycloalkyl–C(O)NH–, and C_{1-4} alkyl–$S(O)_2$–C_{0-3} alkylene–;

R^a is C_{1-4} alkyl;

each of R^{a1} and R^{a2} is independently selected from the group consisting of H and C_{1-4} alkyl,

each R^b is independently selected from the group consisting of oxo, halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} alkyl–$S(O)_2$–C_{0-3} alkylene–;

each R^e and R^f is independently selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, and 3- to 7-membered heterocyclyl, wherein each of C_{3-6} cycloalkyl and heterocyclyl is independently unsubstituted or substituted with 1 or 2 R^h; or R^e and R^f together with the nitrogen atom to which they are attached form 3- to 10-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^i;

each R^h is independently selected from the group consisting of hydroxy and C_{1-4} alkoxy; and

each R^i is independently selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy.

[0198] In some embodiments of Formula (I-1a) or (I-1b), R^{3a}, R^{4a}, R^a, R^{a1}, R^{a2}, R^b, R^e, R^f, R^h, and R^i are each described in any one of embodiments of Formula (I-1).

[0199] In some embodiments of Formula (I-1b), R^{3a} is  .

[0200] In some embodiments of Formula (I-1b), or any one of the embodiments thereof, two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is –C(O)NR^eR^f; R^e and R^f together with the nitrogen atom to which they are attached form 5- to 10-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^i; and each R^i is independently halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy. In some embodiments, two R^{4a} are each

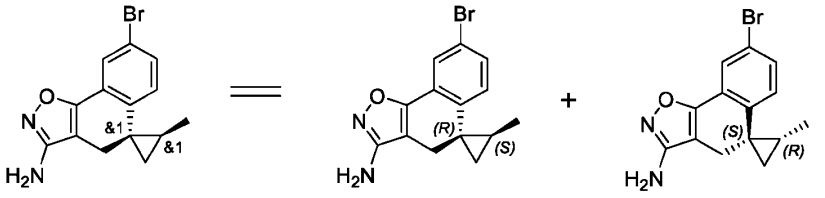
methoxy; and the remaining R^{4a} is $-C(O)NR^eR^f$, wherein each R^e and R^f are described in any one of embodiments of Formula (I-1).

[0201] In some embodiments, the compound of Formula (Y) or (I) or a pharmaceutically acceptable salt thereof is selected from the compounds in **Table 1** (Examples 1-311) or a pharmaceutically acceptable salt thereof. In some embodiments, compounds of Formula (Y) or (I) are selected from a compound of Examples 1 to 311.

[0202] A number of compounds in Table 1 include one or more stereocenters. When the absolute stereochemistry of a stereocenter is known, the stereocenter in the displayed chemical structure is represented by a wedged solid ( ) and/or dashed ( ) chemical bond(s) at the stereocenter without any markings or with the label of "(R)" or "(S)". When the absolute stereochemistry of one or more stereocenters in a compound is not known, the following labels are indicated at the stereocenter of the displayed structure: "&1," "or1," or "or2." Each of these labels is further described below.

[0203] When the same label "&1" is indicated in the displayed chemical structure (e.g., Intermediate L) having two stereocenters, the compound is a racemic mixture of two stereoisomers, where the relative stereochemistry between the two stereocenters is known.

[0204] For example, Intermediate L is a racemic mixture of (1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine and (1S,2R)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine, as shown below:



Intermediate L

[0205] When the label(s) "or1" or a combination of "or1" and "or2" are indicated in the displayed chemical structure having one or more stereocenters, the compound is a single stereoisomer but the absolute stereochemistry is not yet known. When one "or1" is indicated in the displayed chemical structure having one stereocenter, the compound is a single stereoisomer with unknown absolute stereochemistry. When the same label "or1" is indicated in the displayed chemical structure having two or three stereocenters, the relative

stereochemistry between the "or1" labeled stereocenters is known but not the absolute stereochemistry. When both "or1" and "or2" are indicated in the displayed chemical structure having three stereocenters, the relative stereochemistry between the stereocenters having "or1" and "or2" is not yet known.

[0206] For Example, Intermediate R is a single stereoisomer but the absolute stereochemistry is not yet known, wherein the relative stereochemistry at the two stereocenters with same label "or1" is known and –F is either cis- or trans- to the methyl group at the cyclopropyl. Intermediate R is one of four (4) possible stereoisomers, as shown below:

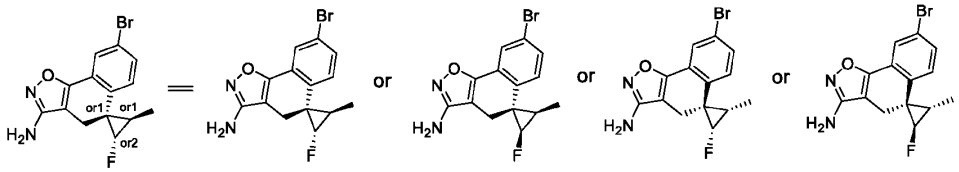
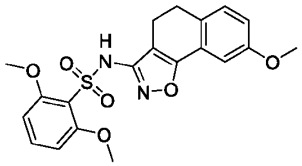
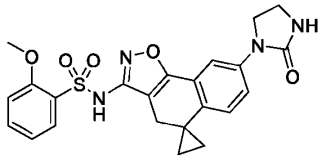
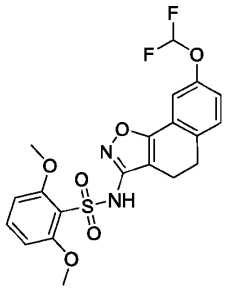
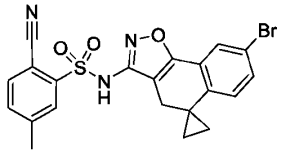
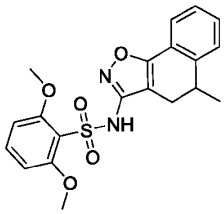
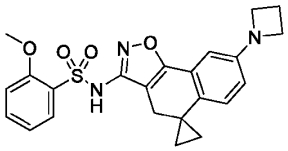
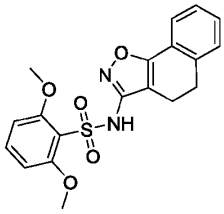
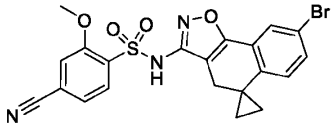
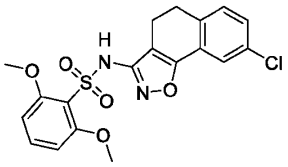
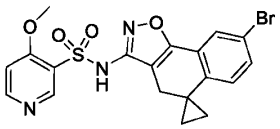
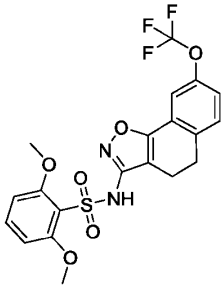
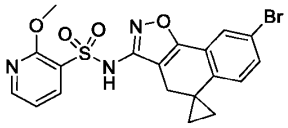
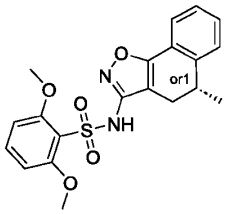
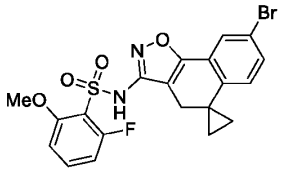
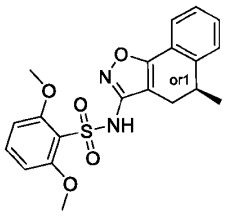
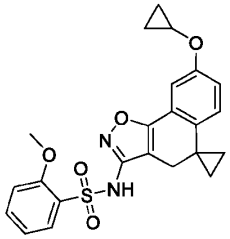
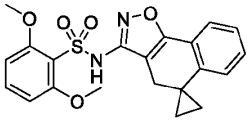
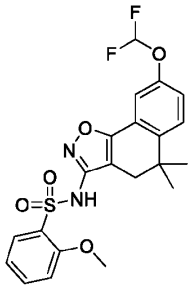
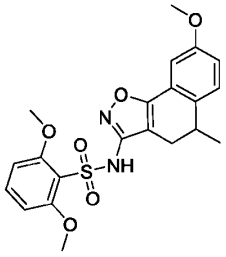
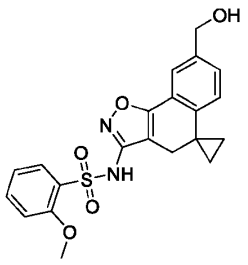
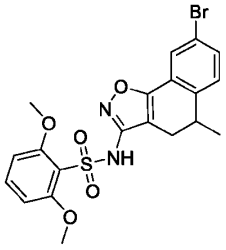
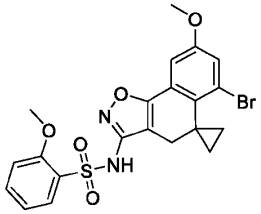
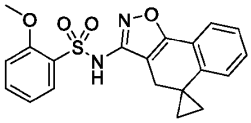
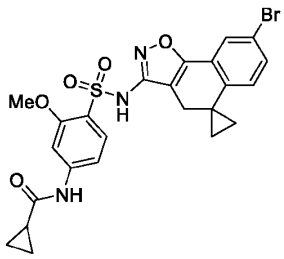
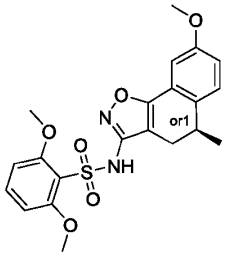
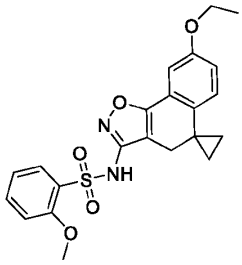
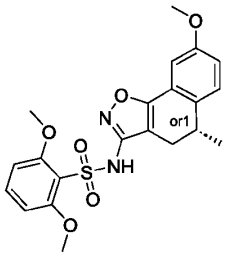
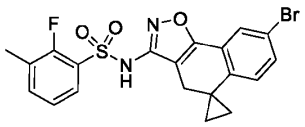
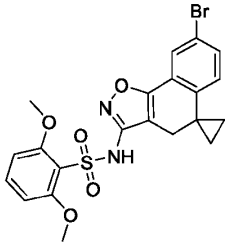
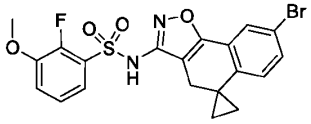
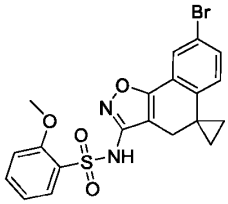
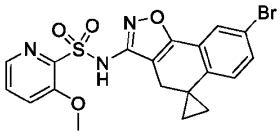
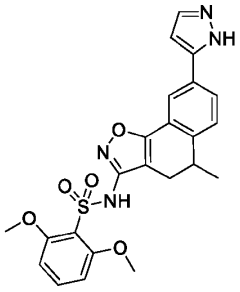
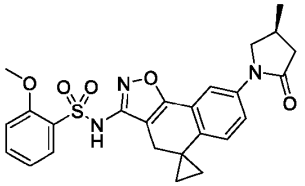


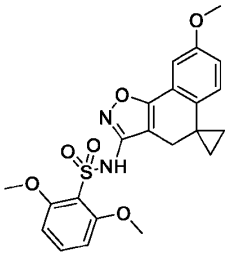
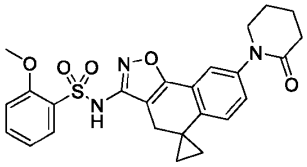
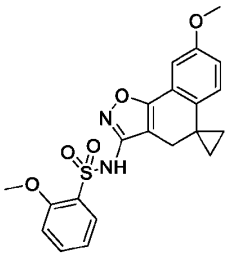
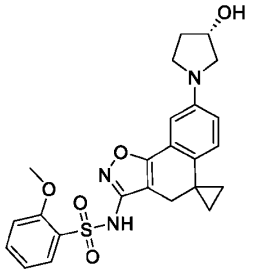
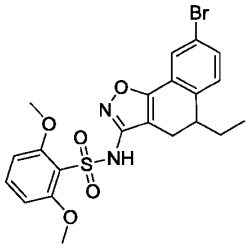
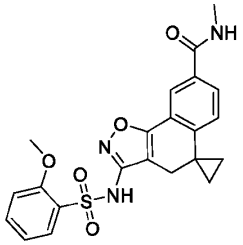
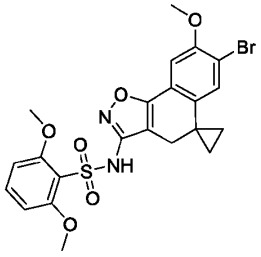
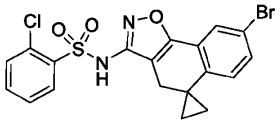
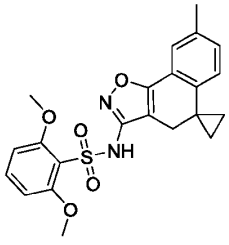
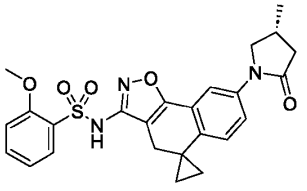
Table 1

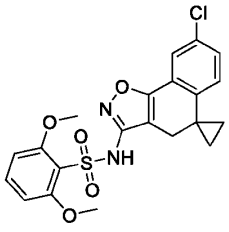
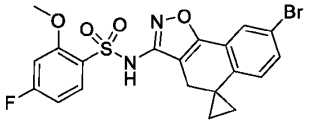
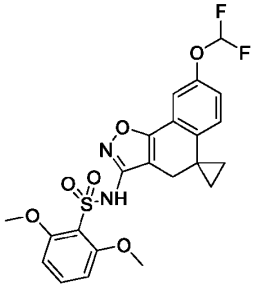
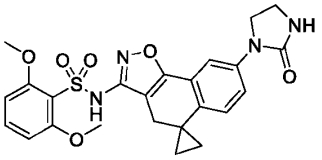
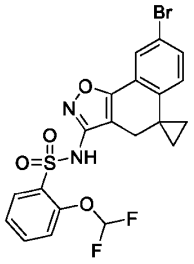
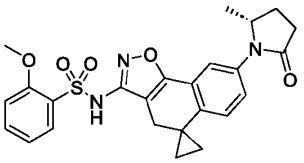
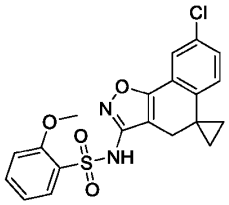
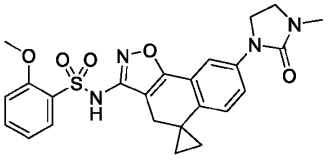
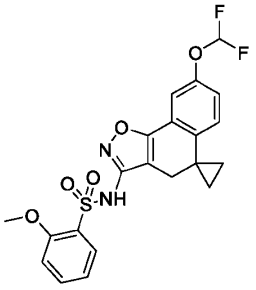
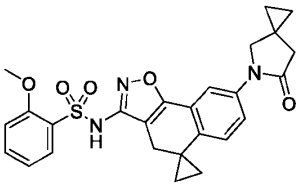
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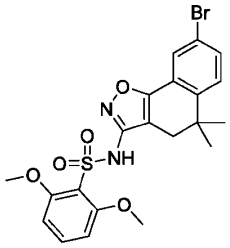
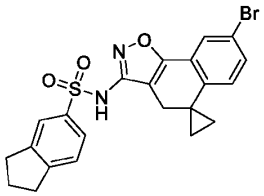
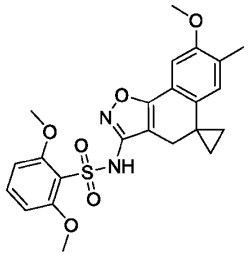
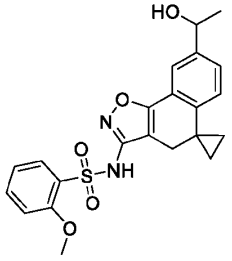
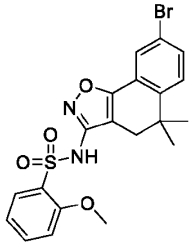
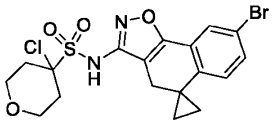
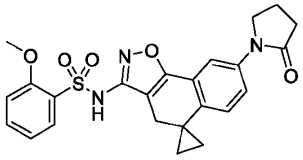
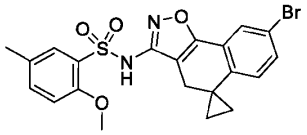
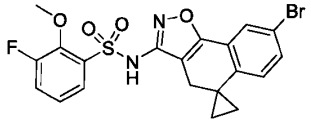
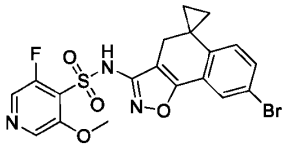
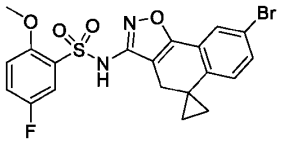
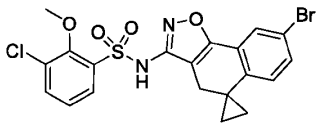
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7		45	

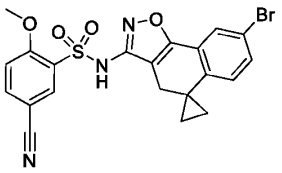
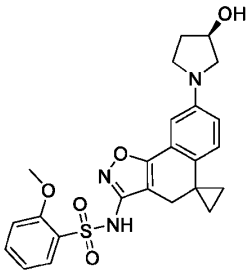
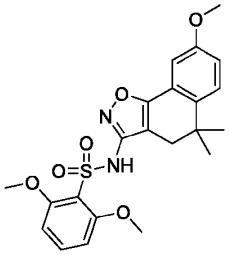
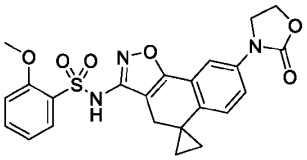
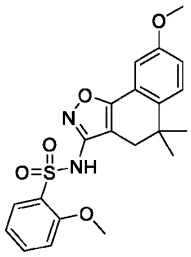
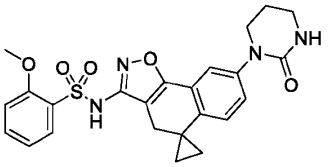
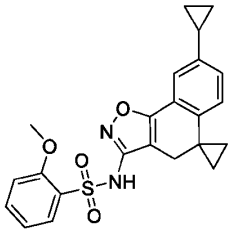
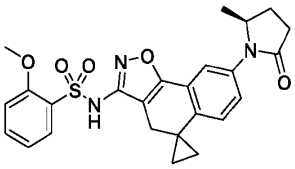
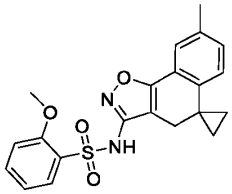
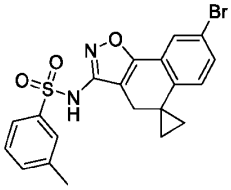
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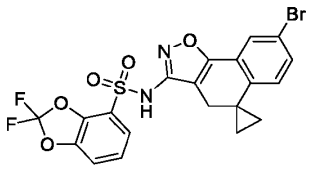
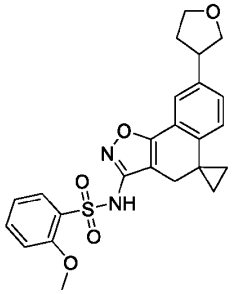
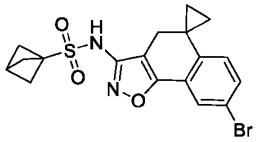
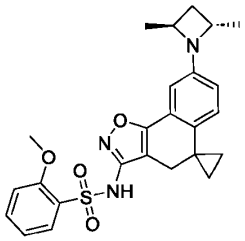
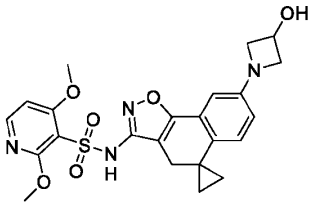
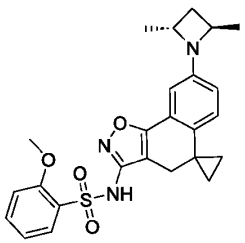
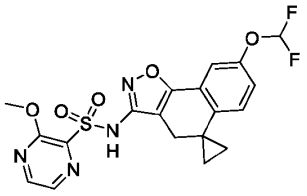
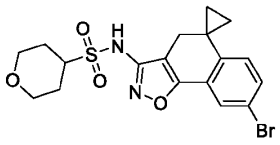
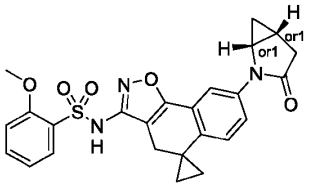
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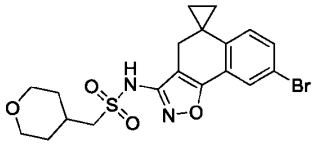
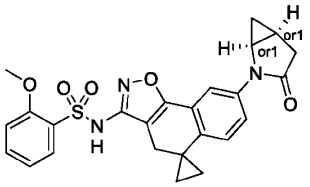
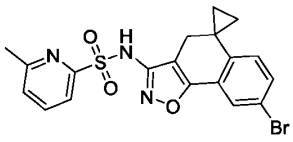
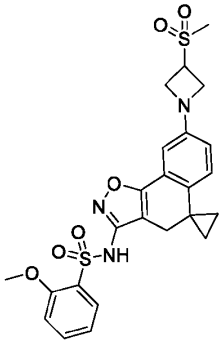
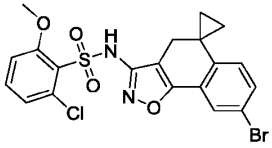
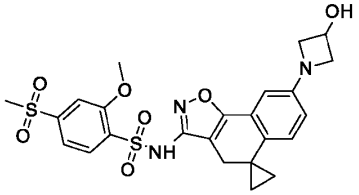
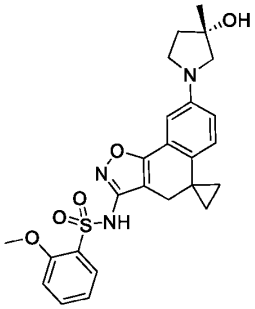
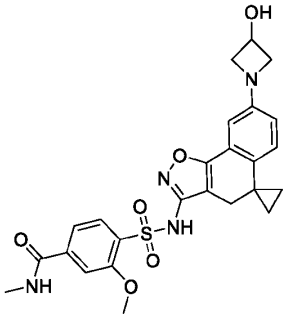
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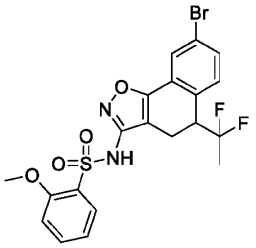
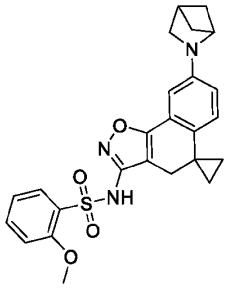
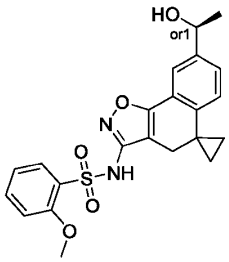
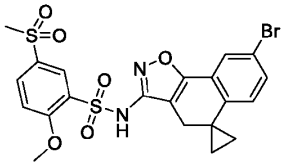
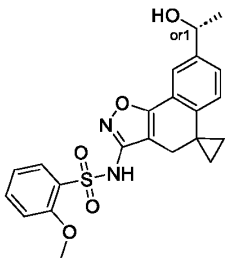
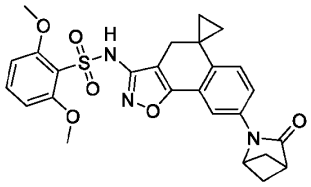
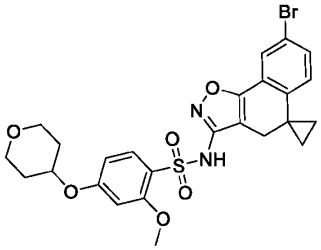
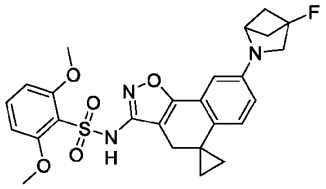
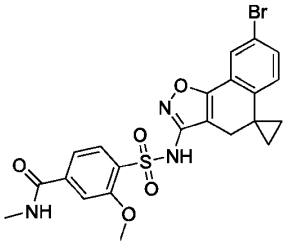
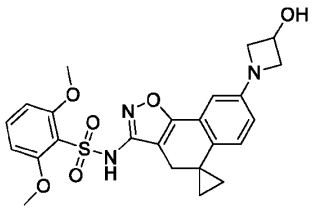
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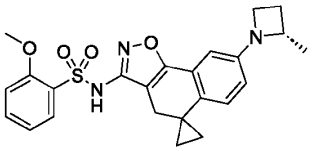
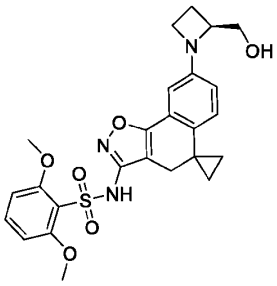
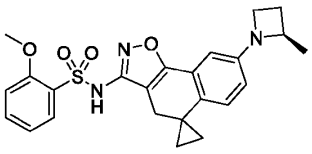
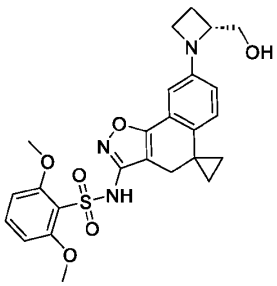
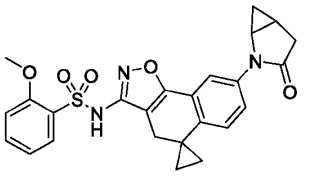
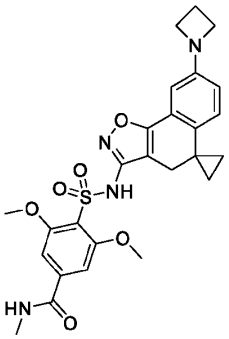
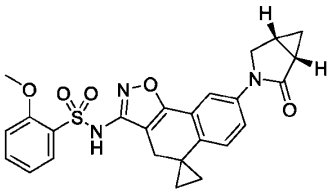
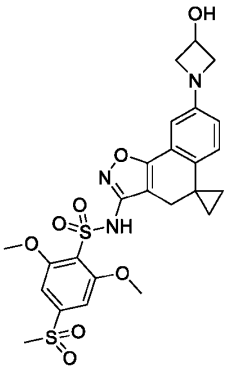
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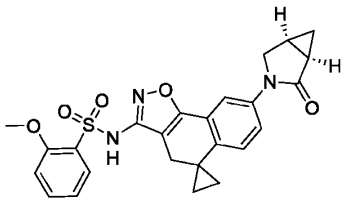
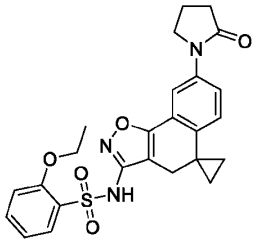
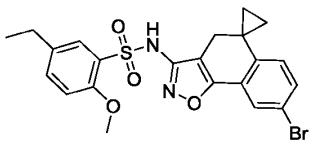
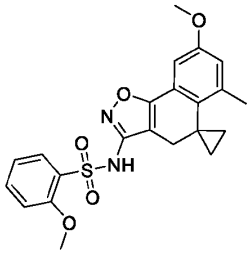
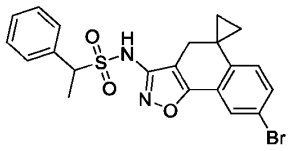
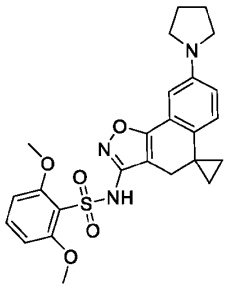
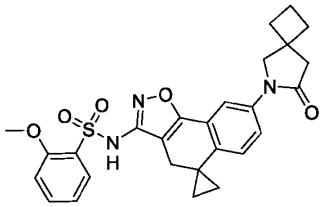
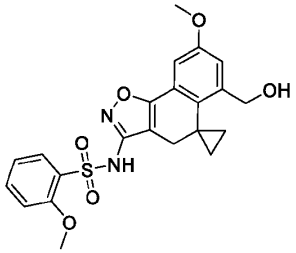
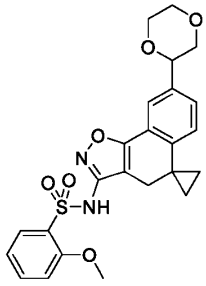
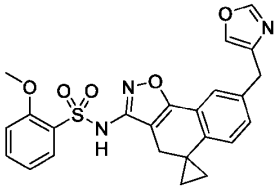
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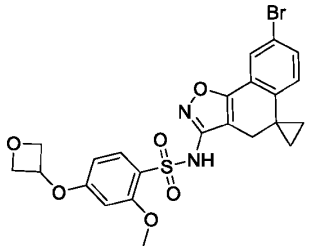
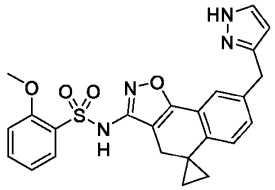
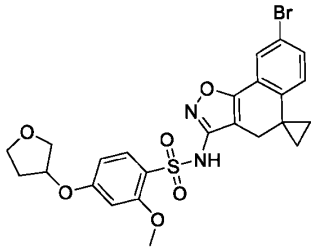
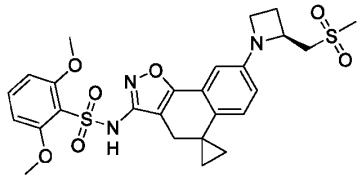
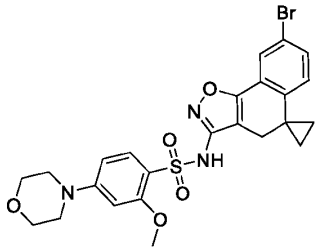
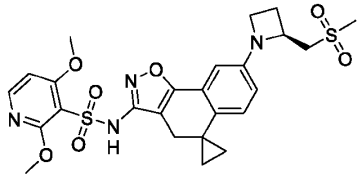
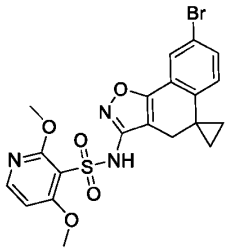
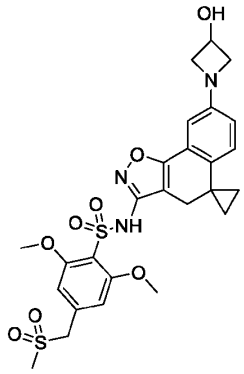
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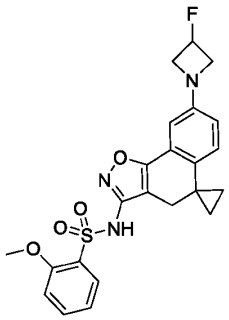
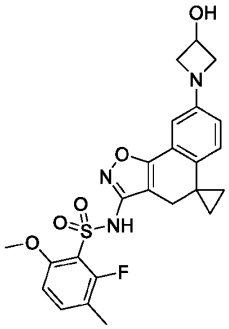
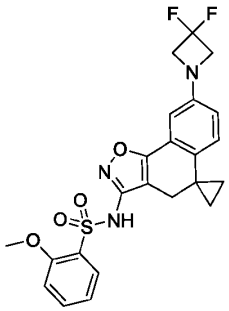
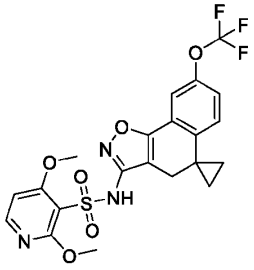
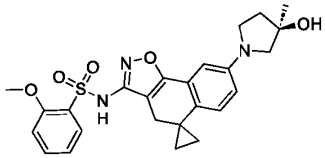
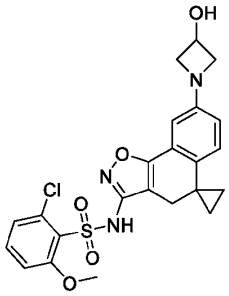
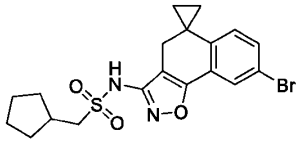
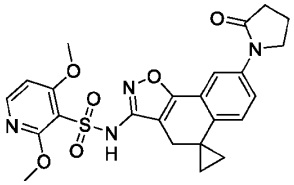
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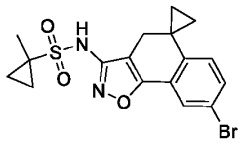
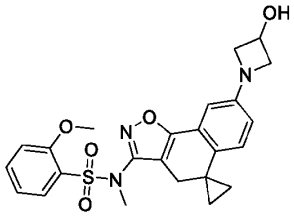
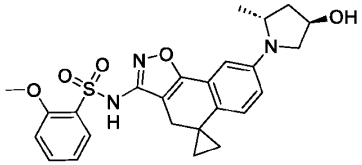
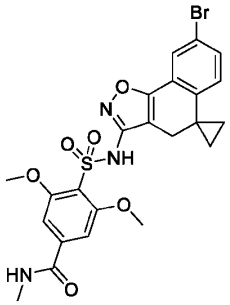
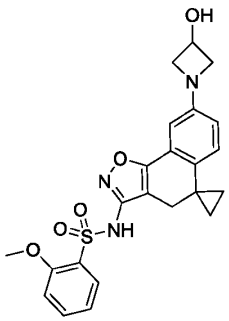
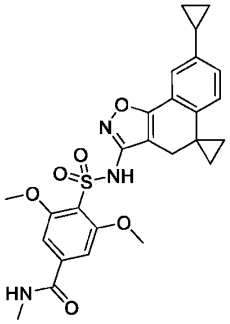
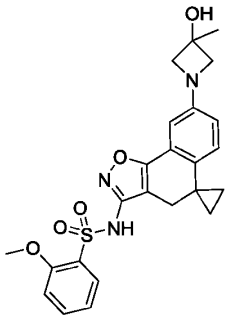
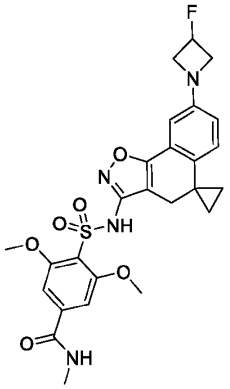
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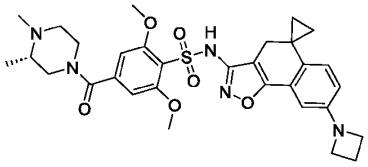
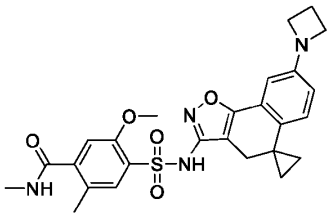
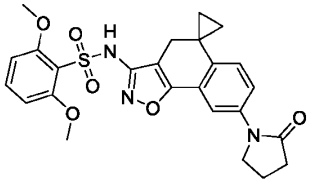
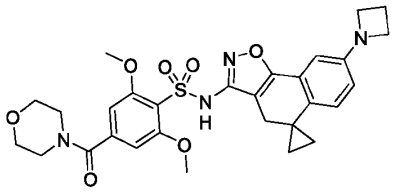
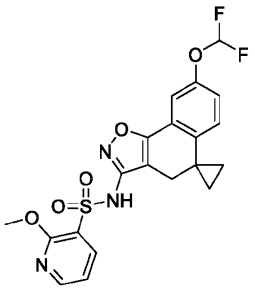
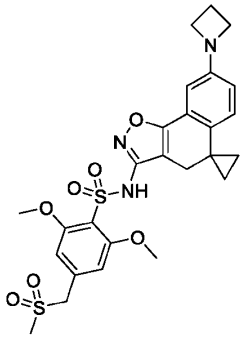
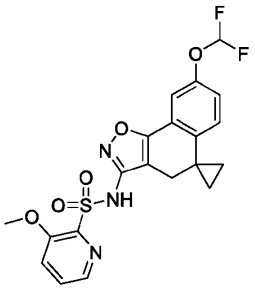
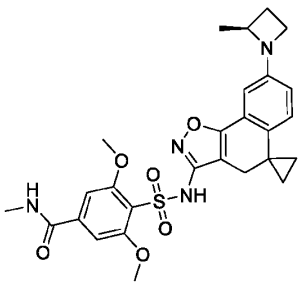
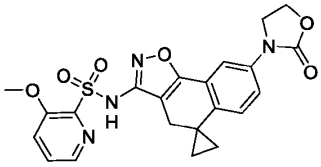
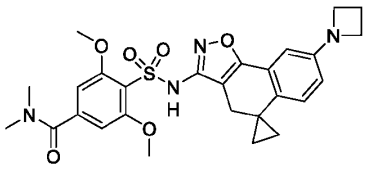
Ex No	Structure	Ex No	Structure
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94		178	

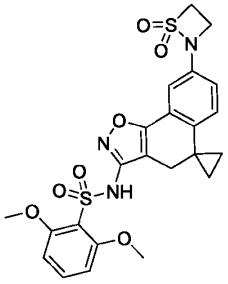
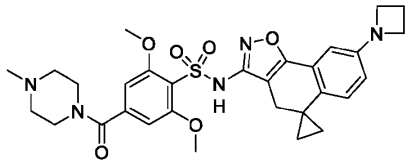
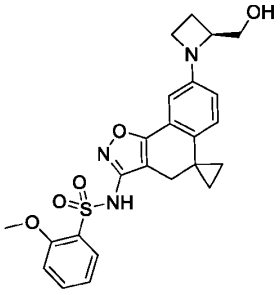
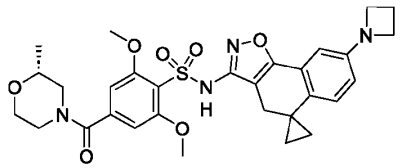
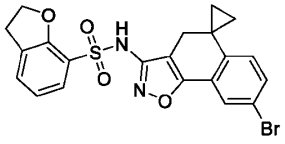
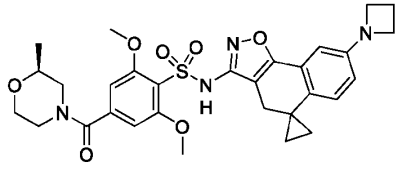
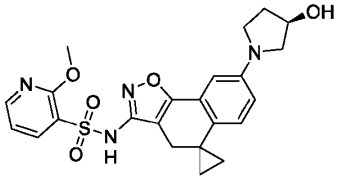
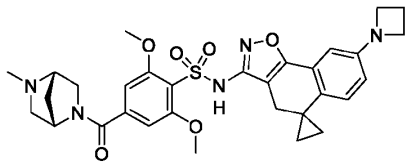
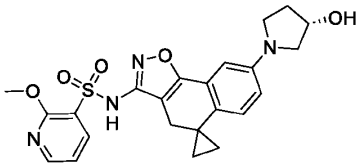
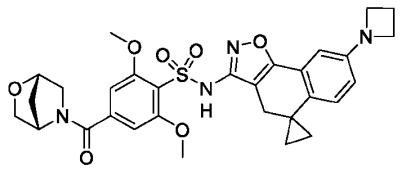
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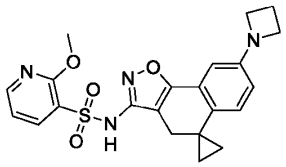
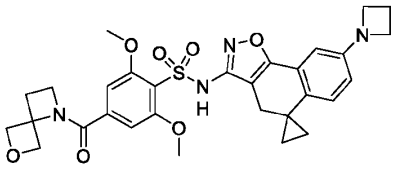
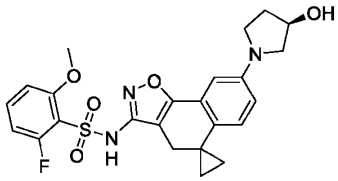
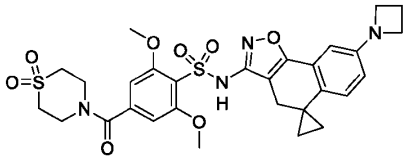
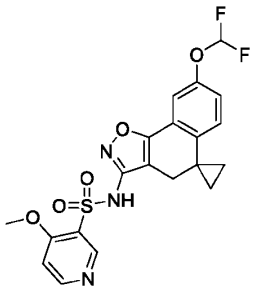
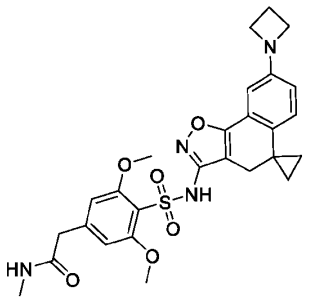
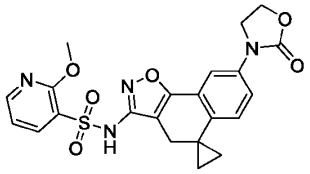
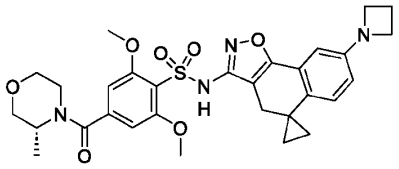
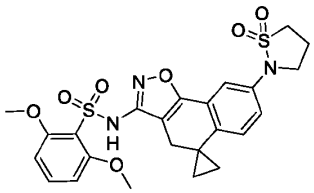
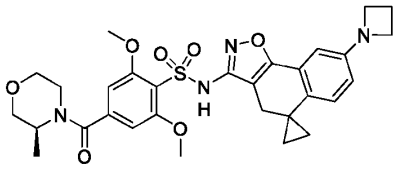
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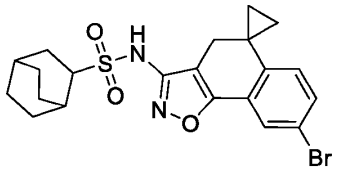
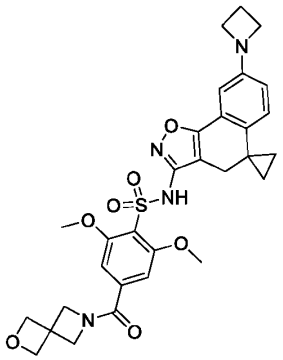
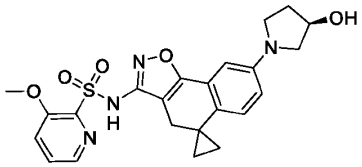
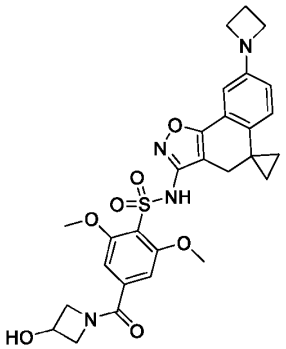
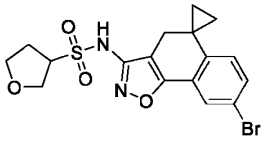
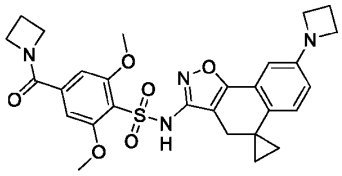
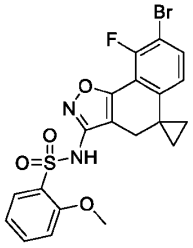
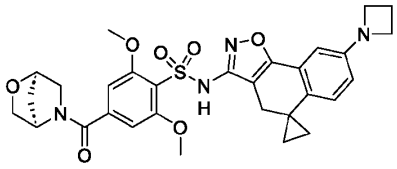
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107		191	

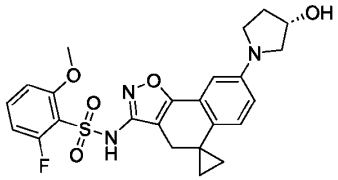
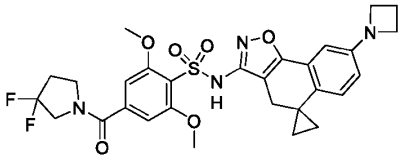
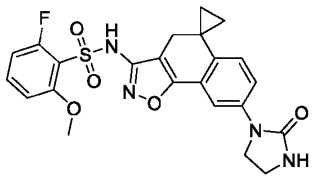
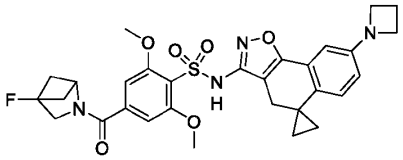
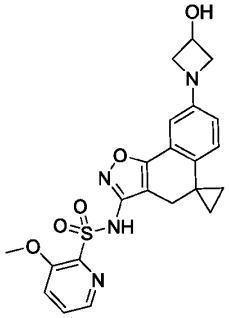
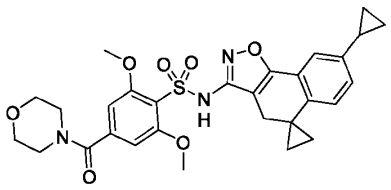
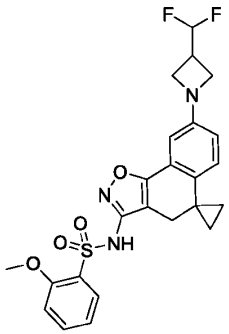
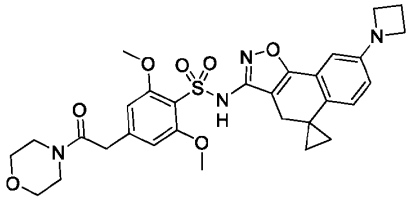
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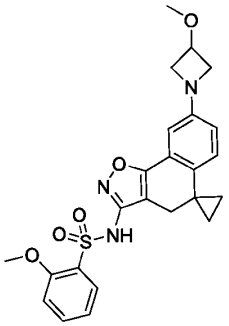
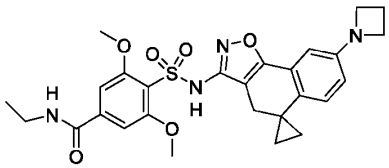
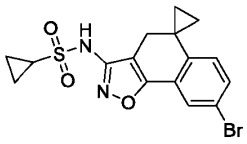
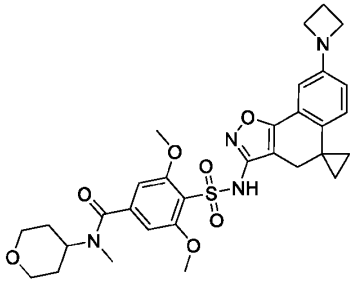
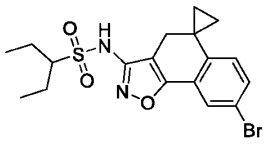
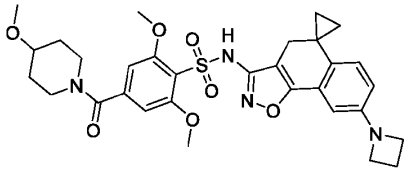
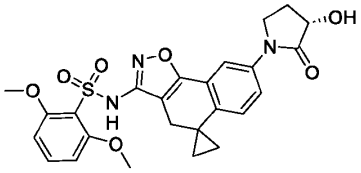
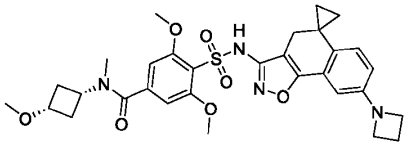
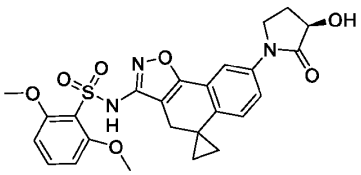
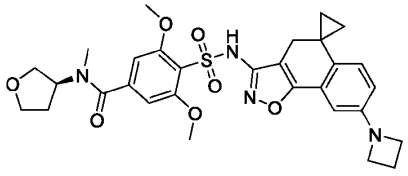
Ex No	Structure	Ex No	Structure
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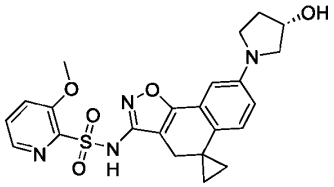
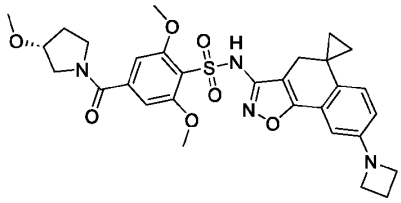
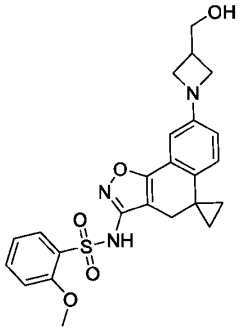
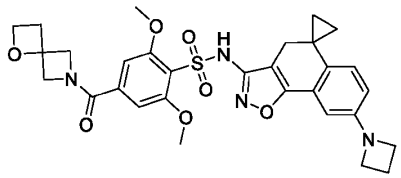
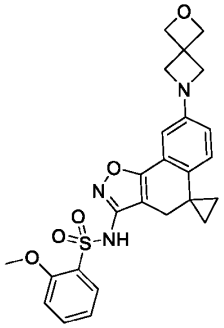
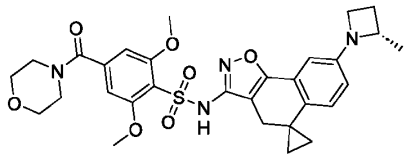
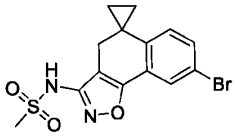
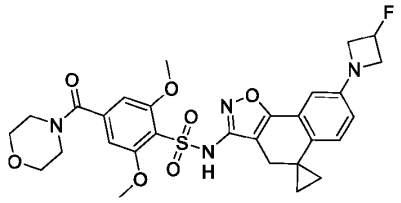
Ex No	Structure	Ex No	Structure
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121		205	

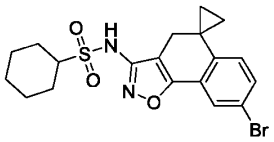
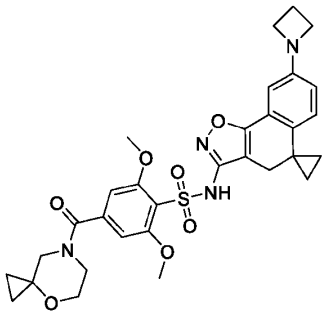
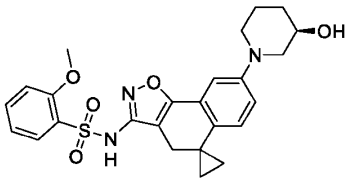
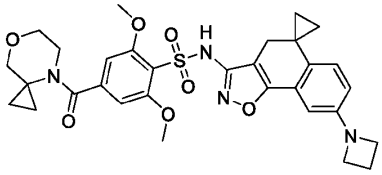
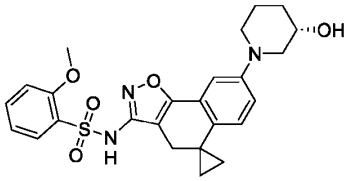
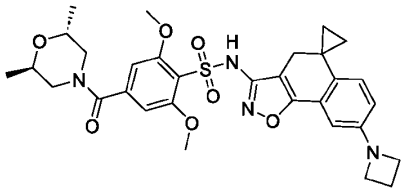
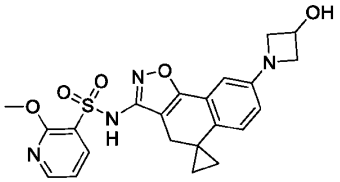
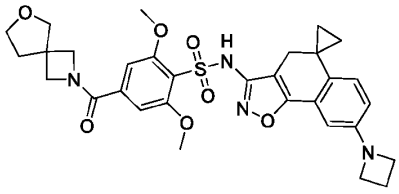
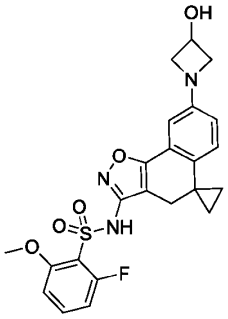
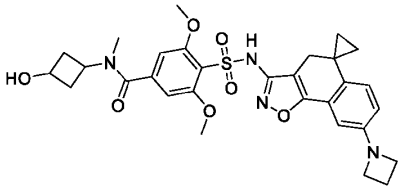
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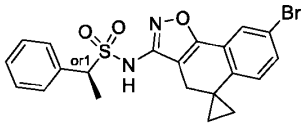
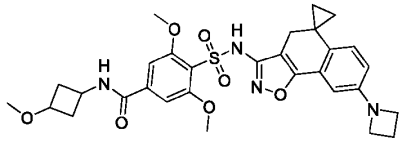
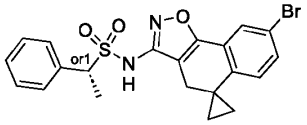
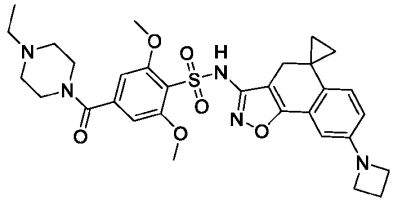
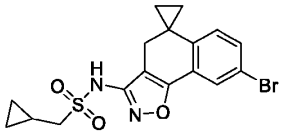
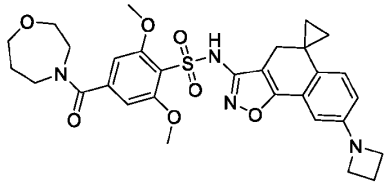
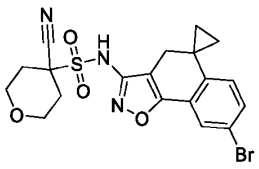
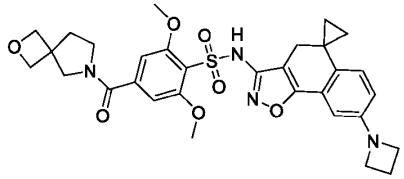
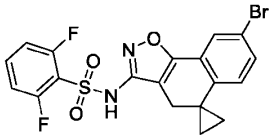
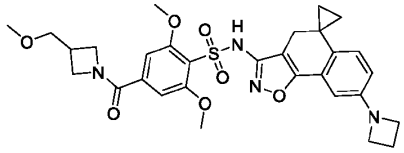
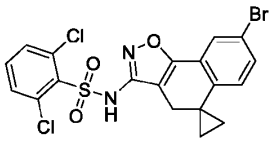
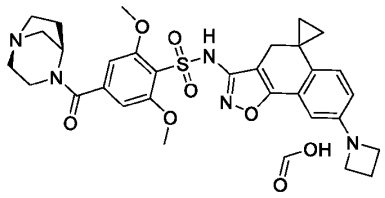
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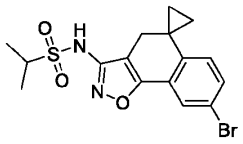
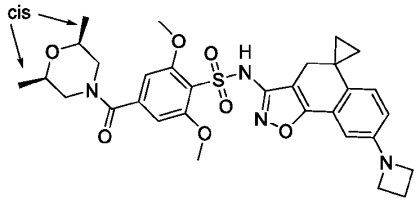
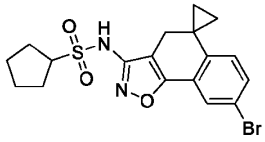
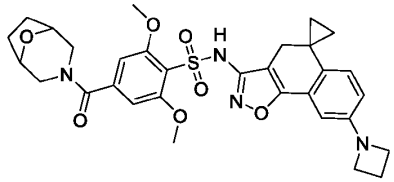
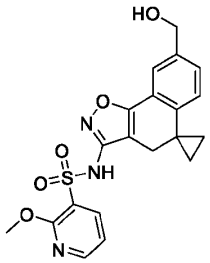
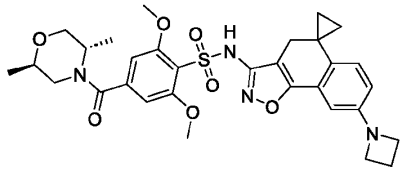
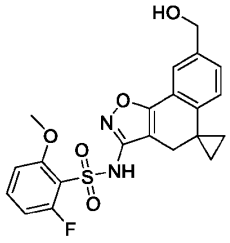
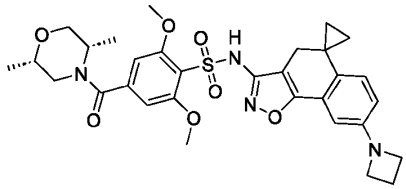
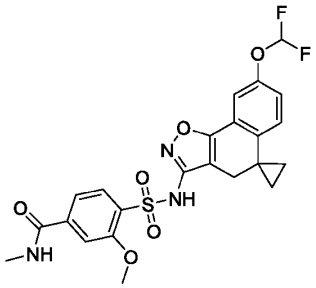
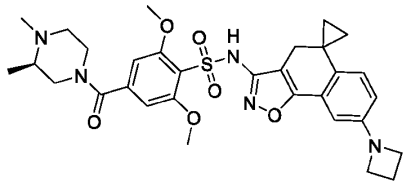
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132		216	
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134		218	

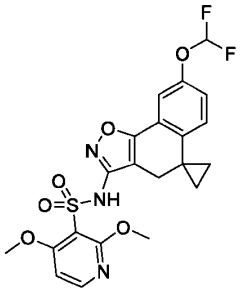
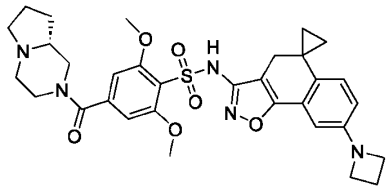
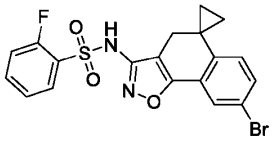
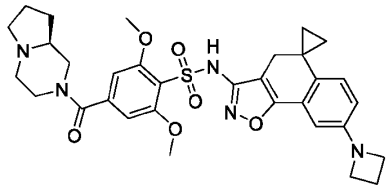
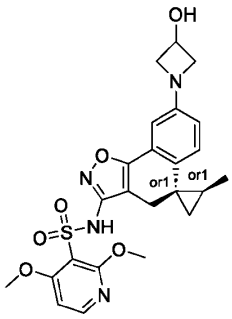
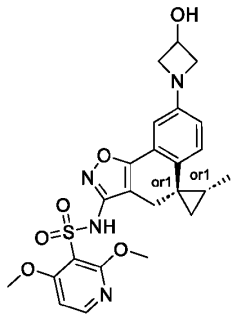
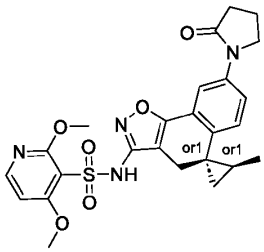
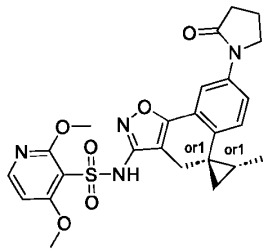
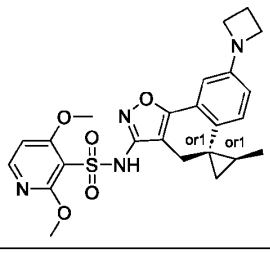
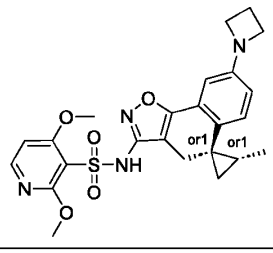
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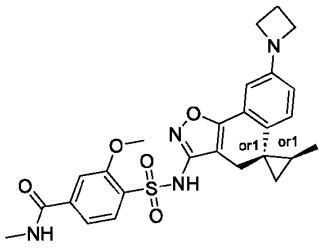
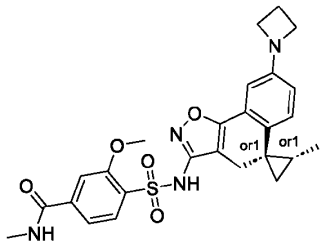
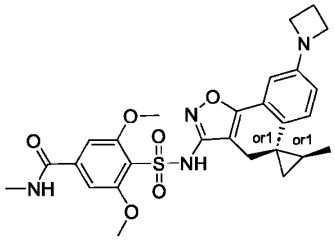
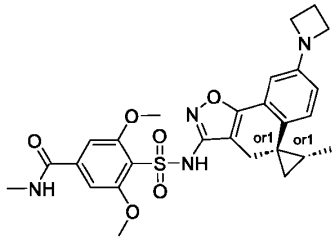
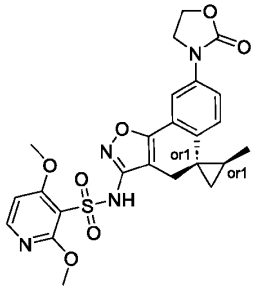
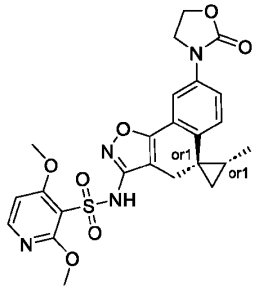
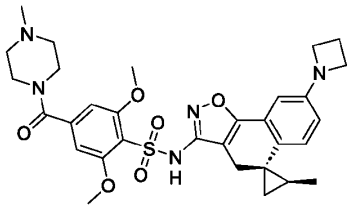
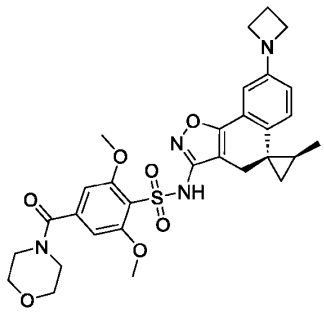
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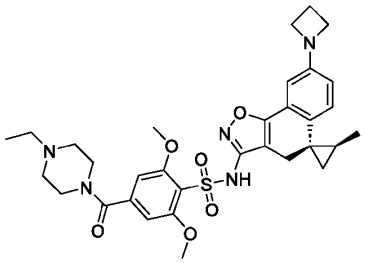
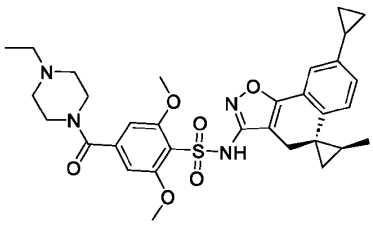
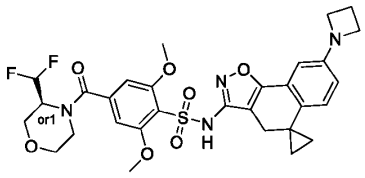
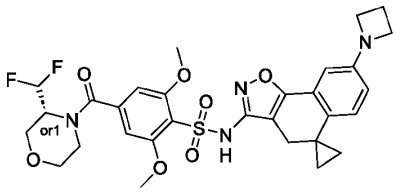
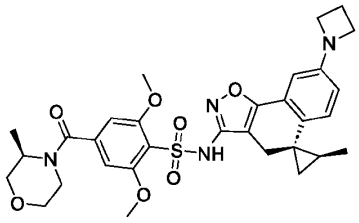
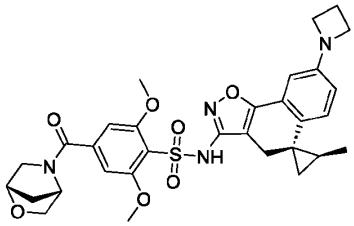
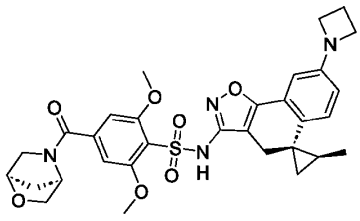
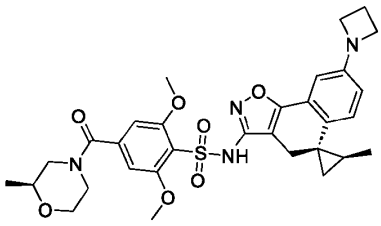
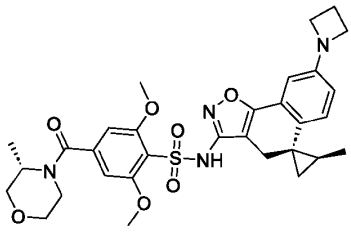
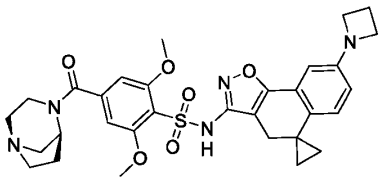
Ex No	Structure	Ex No	Structure
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145		229	
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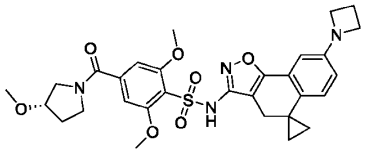
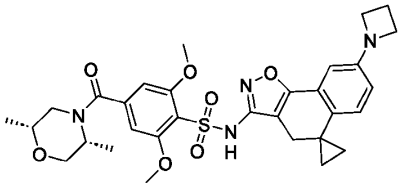
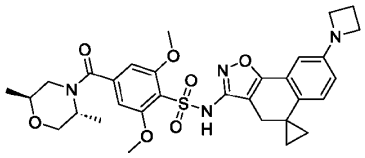
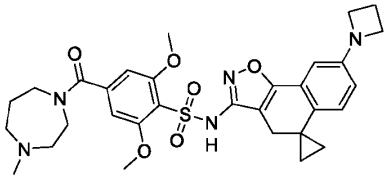
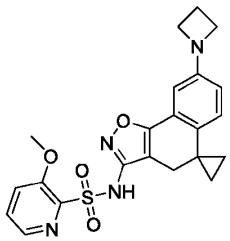
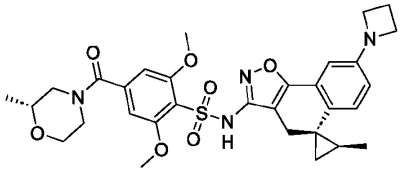
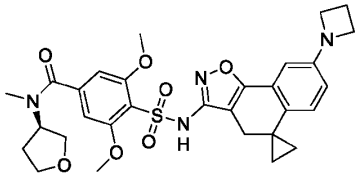
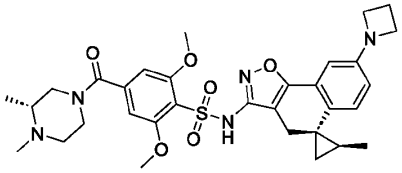
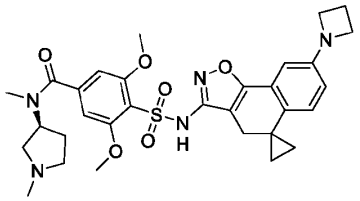
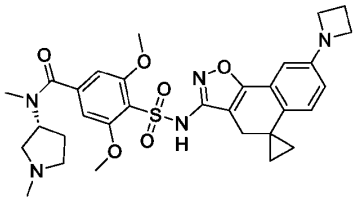
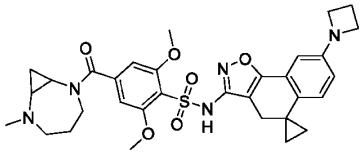
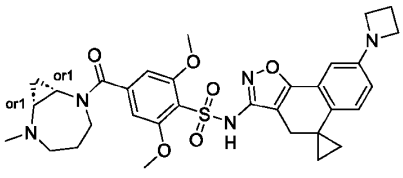
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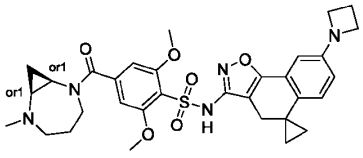
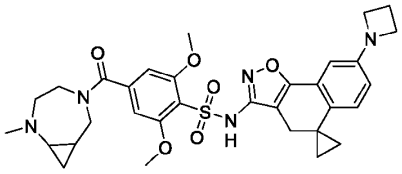
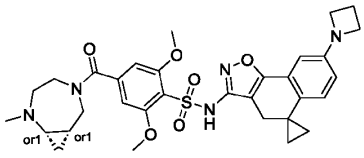
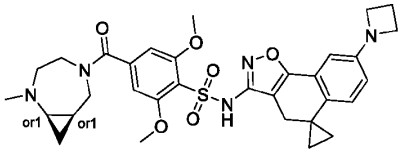
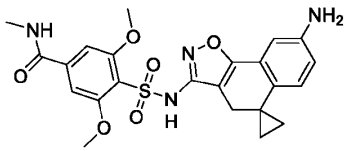
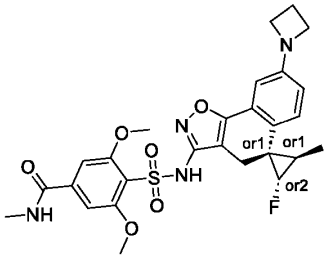
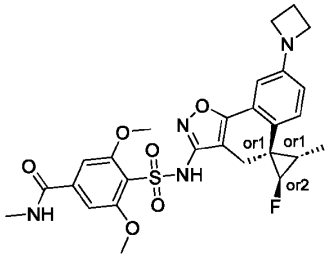
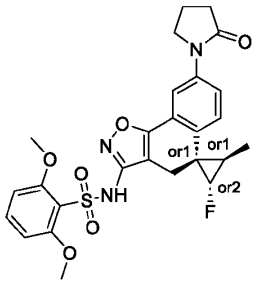
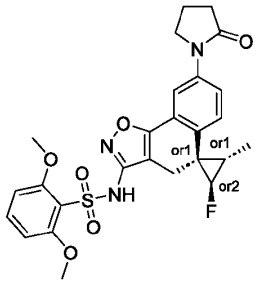
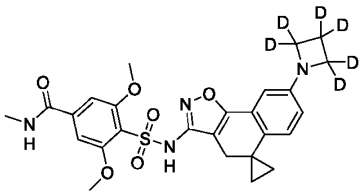
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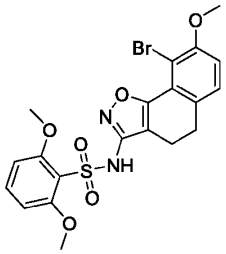
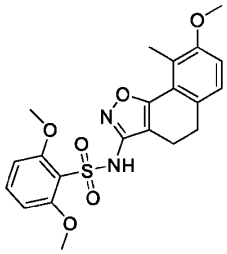
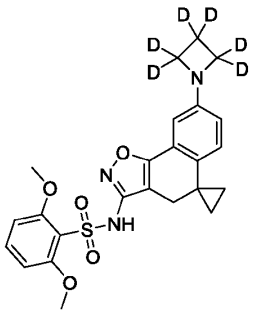
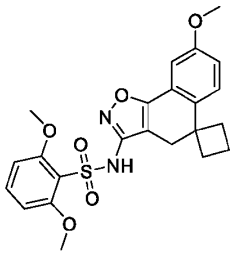
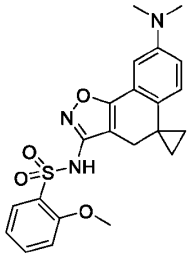
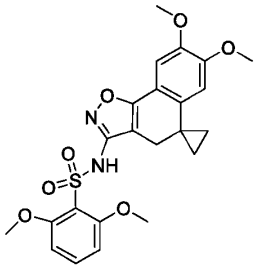
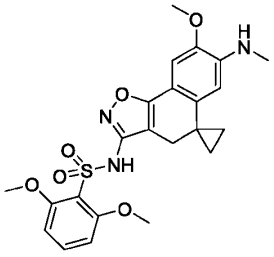
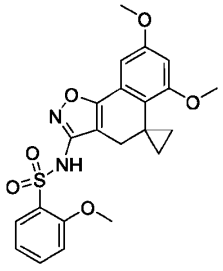
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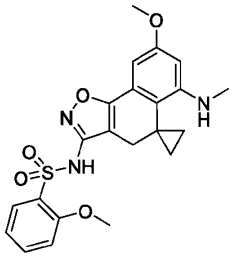
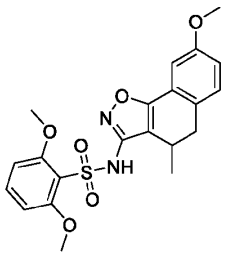
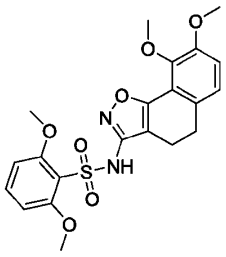
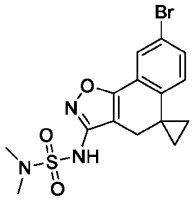
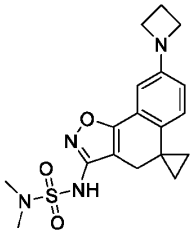
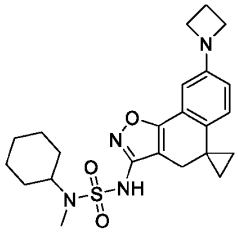
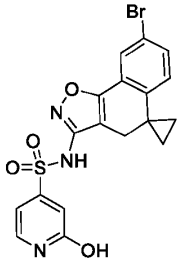
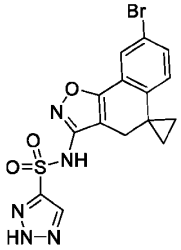
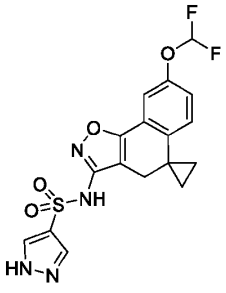
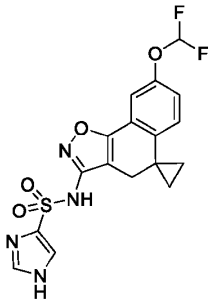
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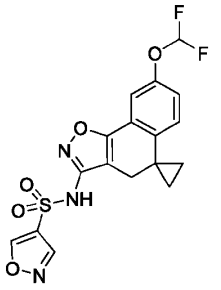
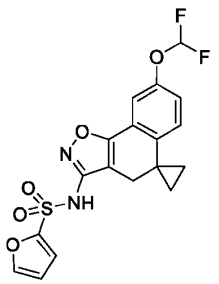
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Ex No	Structure	Ex No	Structure
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290		291	

Ex No	Structure	Ex No	Structure
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296		297	
298		299	

Ex No	Structure	Ex No	Structure
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302		303	
304		305	
306		307	
308		309	

Ex No	Structure	Ex No	Structure
310		311	

General Synthesis of Compounds

[0207] The compounds of Formula (Y) can prepared by methods known in the art. In some embodiments, the compound of Formula (Y) can be prepared according to at least one of general methods as disclosed herein.

[0208] **FIG. 1** shows a general method for preparing a compound of Formula (Y) by Method 1. Alkylation of tetralone 1 to afford Intermediate 2 is followed by condensation with hydroxylamine and cyclization to form isoxazole 3. Reaction with ammonium hydroxide gave carbamate 4, which undergoes Hoffman rearrangement to give primary amine 5. The compound of Formula (Y) is then formed after reacting amine 5 with the relevant sulfonyl chloride.

[0209] For example, in some embodiments, a compound of Formula (Y) can be prepared by Method 1, wherein R^1 is H; L is a bond; R^1 is H; R^{2a} and R^{2b} are independently H or C_{1-6} alkyl (e.g., methyl), or R^{2a} and R^{2b} together with the carbon atom to which they are attached form cyclopropyl unsubstituted or substituted with from 1 to 2 R^g; each R^g is independently C_{1-6} alkyl (e.g., methyl) or halo (e.g., F); R^{3a} is H, halo (e.g., Br), or C_{1-6} alkoxy (e.g., OMe); R^{3b}, R^{3c}, and R^{3d} are each H; R^{5a} and R^{5b} are each H; R^4 is phenyl or pyridyl unsubstituted or substituted with from 1 to 2 R^{4a}; and each R^{4a} is C_{1-6} alkoxy (e.g., OMe).

[0210] **FIG. 2** shows a general method for preparing a compound of Formula (Y) by Method 2. Alkylation of bromide 1a to afford Intermediate 2a is followed by condensation with hydroxylamine and cyclization to form isoxazole 3a. Reaction with ammonium hydroxide gave carbamate 4a, which undergoes Hoffman rearrangement to give primary

amine 5a. Sulfonamide 6a is formed after reacting amine 5a with the relevant sulfonyl chloride. Coupling of amines under Buchwald conditions leads to the final compound of Formula (Y).

[0211] For example, in some embodiments, a compound of Formula (Y) can be prepared by Method 2, wherein R^1 is H; L is a bond or C_{1-3} alkylene; R^1 is H; R^{2a} and R^{2b} together with the carbon atom to which they are attached form cyclopropyl unsubstituted or substituted with from 1 to 2 R^g; each R^g is independently C_{1-6} alkyl (e.g., methyl) or halo (e.g., F); R^{3a} is C_{1-6} alkyl, C_{3-5} cycloalkyl (e.g., cyclopropyl), 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, or –C(O)NHR^a; R^a is C_{1-6} alkyl; R^{3b}, R^{3c}, and R^{3d} are each H; R^{5a} and R^{5b} are each H; and R^4 is as defined and described in any one of embodiments related to Formula (Y).

[0212] **FIG. 3** shows a general method for preparing a compound of Formula (Y) by Method 3. Alkylation of bromide 1a to afford Intermediate 2a is followed by condensation with hydroxylamine and cyclization to form isoxazole 3a. Reaction with ammonium hydroxide gave carbamate 4a, which undergoes Hoffman rearrangement to give primary amine 5a. Sulfonamide 7a is formed after reacting amine 5a with the relevant sulfonyl chloride, which is followed by coupling with azetidine under Buchwald conditions. Saponification of ester 8 affords carboxylate 9, which is subjected to amide coupling with various amines to afford a compound of Formula (Y).

[0213] For example, in some embodiments, a compound of Formula (Y) can be prepared by Method 3, wherein R^1 is H; L is a bond; R^1 is H; R^{3a} is 1-azetyl; R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is –C(O)NR^{e}R^f; and R^{2a}, R^{2b}, R^{5a}, R^{5b}, R^{3b}, R^{3c}, R^{3d}, R^e, and R^f are each as defined and described in any one of embodiments related to Formula (Y).

[0214] Compounds of Formula (Y) wherein R^1 is other than H can be prepare in a similar manner to Example 192.

[0215] The preparation of specific compounds of Formula (Y) is further described in Examples 1 to 311.

Biological Activity

[0216] The KAT6A and/or KAT7 enzyme and cell assays described in accompanying Example section may be used to measure the pharmacological effects of the compounds of the present disclosure.

[0217] Although the pharmacological properties of the compounds of Formula (Y) or (I) vary with structural change, as expected, the compounds of the disclosure were found to be active in these KAT6A and/or KAT7 assays.

[0218] In general, the compounds of the disclosure demonstrate an IC_{50} of 10 μM or less in the KAT6A and/or KAT7 enzyme assay described herein, with preferred compounds of the disclosure demonstrating an IC_{50} of 1000nM or less, or 500 nM or less, and the most preferred compounds of the disclosure demonstrating an IC_{50} of 200 nM or less.

[0219] In general, the compounds of the disclosure demonstrate an IC_{50} of 1 μM or less in the KAT6A and/or KAT7 cell assay described herein, with preferred compounds of the disclosure demonstrating an IC_{50} of 500 nM or less and the most preferred compounds of the disclosure demonstrating an IC_{50} of 200 nM or less.

PHARMACEUTICAL COMPOSITIONS

[0220] The compounds of Formula (Y) or (I), or a pharmaceutically acceptable salt thereof, provided herein may be in the form of compositions suitable for administration to a subject. In general, such compositions are pharmaceutical compositions comprising a compound of Formula (Y) or (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients. The pharmaceutical compositions may be used in the methods disclosed herein; thus, for example, the pharmaceutical compositions can be administered *ex vivo* or *in vivo* to a subject in order to practice the therapeutic methods and uses described herein.

[0221] The pharmaceutical compositions can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein. Furthermore, the pharmaceutical compositions may be used in combination with other therapeutically active agents or compounds as described herein in order to treat the diseases, disorders and conditions contemplated by the present disclosure.

[0222] The pharmaceutical compositions containing the active ingredient (e.g., a compound of Formula (Y) or (I), a pharmaceutically acceptable salt thereof) may be in a form suitable

for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs. Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets and/or capsules contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets and/or capsules. These excipients may be, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

[0223] The pharmaceutical compositions typically comprise a therapeutically effective amount of a compound of Formula (Y) or (I), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipient. Suitable pharmaceutically acceptable excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that can be used in the pharmaceutical compositions and dosage forms contemplated herein. Typical buffers include, but are not limited to, pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. As an example, the buffer components can be water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof. Acceptable buffering agents include, for example, a Tris buffer, N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES), 2-(N-Morpholino)ethanesulfonic acid (MES), 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES), 3-(N-Morpholino)propanesulfonic acid (MOPS), and N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS).

[0224] All the compounds and pharmaceutical compositions provided herein can be used in all the methods provided herein. For example, the compounds and pharmaceutical compositions provided herein can be used in all the methods for treatment and/or prevention of all diseases or disorders provided herein. Thus, the compounds and pharmaceutical compositions provided herein are for use as a medicament.

THERAPEUTIC USES AND APPLICATIONS

[0225] Provided herein are compounds that function as inhibitors of KAT6A and/or KAT7.

[0226] The present disclosure therefore provides a method of inhibiting KAT6A and/or KAT7 enzyme activity *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein.

[0227] The present disclosure also provides a method of treating a disease or disorder in which KAT6A and/or KAT7 activity is implicated in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein.

[0228] The present disclosure also provides a method of treating a disorder mediated by KAT6A and/or KAT7 in a subject in need thereof, said method comprising administering to said subject a therapeutically effective amount of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein. In some embodiments the disorder is cancer.

[0229] Provided herein is a method of inhibiting cell proliferation, *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein.

[0230] Provided herein is a method of treating a proliferative disorder in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein.

[0231] Provided herein is a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a

compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein.

[0232] Provided herein is a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound of Formula (Y) or (I) (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, wherein the cancer is characterized by an overexpression of KAT6A and/or KAT7, an amplification of KAT6A gene and/or KAT7 gene, an increased activity of KAT6A and/or KAT7, or a combination thereof.

[0233] Provided herein is a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound of Formula (Y) or (I) (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, wherein the cancer is characterized by an overexpression of KAT6A, an amplification of KAT6A gene, an increased activity of KAT6A, or a combination thereof.

[0234] In some embodiments, the cancer is treatable by inhibition of KAT6 and/or KAT7. In some embodiments, KAT6 is KAT6A.

[0235] In some embodiments, the cancer is treatable by inhibition of KAT6A and/or KAT7. In some embodiments, the cancer is treatable by inhibition of KAT6A and KAT7.

[0236] Provided herein is a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein for use in therapy.

[0237] Provided herein is a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of a proliferative condition.

[0238] Provided herein is a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of cancer. In a particular embodiment, the cancer is human cancer.

[0239] Provided herein is a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein for use in the inhibition of KAT6 and/or KAT7 enzyme activity. In some embodiments, KAT6 is KAT6A.

[0240] Provided herein is a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein for use in the inhibition of KAT6A and/or KAT7 enzyme activity. Provided herein is a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein for use in the inhibition of KAT6A and KAT7 enzyme activity.

[0241] Provided herein is a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, as defined herein, or a pharmaceutical composition as defined herein for use in the treatment of a disease or disorder in which KAT6A and/or KAT7 activity is implicated.

[0242] Provided herein is a use of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of a proliferative condition.

[0243] Provided herein is a use of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein, as defined herein in the manufacture of a medicament for the treatment of cancer. Suitably, the medicament is for use in the treatment of human cancers.

[0244] Provided herein is a use of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein in the manufacture of a medicament for the inhibition of KAT6 and/or KAT7 enzyme activity. In some embodiments, KAT6 is KAT6A.

[0245] Provided herein is a use of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein in the manufacture of a medicament for the inhibition of KAT6A and/or KAT7 enzyme activity. Provided herein is a use of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein in the manufacture of a medicament for the inhibition of KAT6A and KAT7 enzyme activity.

[0246] Provided herein is a use of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein in the manufacture of a medicament for the selective inhibition of KAT6A and/or KAT7 enzyme activity over PARP1 or ARH3 enzyme activity.

[0247] Provided herein is a use of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of a disease or disorder in which KAT6A and/or KAT7 activity is implicated.

[0248] The terms "proliferative disorder" and "proliferative condition" are used interchangeably herein and pertain to an unwanted or uncontrolled cellular proliferation of excessive or abnormal cells which is undesired, such as, neoplastic or hyperplastic growth, whether in vitro or in vivo. Examples of proliferative conditions include, but are not limited to, pre-malignant and malignant cellular proliferation, including but not limited to, malignant neoplasms and tumors, cancers, leukemias, psoriasis, bone diseases, fibroproliferative disorders (e.g., of connective tissues), and atherosclerosis. Any type of cell may be treated, including but not limited to, lung, colon, breast, ovarian, prostate, liver, pancreas, brain, skin, head and neck, thyroid, bladder, esophagus, uterine, gastric, rhabdoid, bone, and cancers associated with the central nervous system.

[0249] In some embodiments, the cancer is selected from the group consisting of lung cancer (for example non-small cell lung cancer (NSCLC), mesothelioma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, hepatic carcinoma, colon cancer, breast cancer, cervical cancer, brain cancer, gastric cancer, rhabdoid cancer, sarcoma, blood cancer, eye cancer, testis cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, hematology malignancy, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, glioblastoma, brain stem glioma, pituitary adenoma, or a combination of two or more of the foregoing cancers. In some embodiments, the cancer is non-small cell lung cancer (NSCLC). In some embodiments, the cancer is squamous NSCLC.

[0250] Additional embodiments relate to a method of treating cancer in a patient, and in particular a human, comprising administering to the patient an amount of a compound described herein, or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof, that is effective in treating cancer. In one embodiment of this method, the cancer, includes, but is not limited to, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. In one embodiment the method comprises comprising administering to a patient an amount of a compound described herein that is effective in treating said cancer solid tumor. In one preferred embodiment the solid tumor is breast, lung, colon, brain, prostate, stomach, pancreatic, ovarian, skin (melanoma), endocrine, uterine, testicular, and bladder cancer.

[0251] Additional embodiments relate to methods of treating hematologic tumors in a patient. Some embodiments relate to the treatment of hematologic tumors in a patient comprising administering to the patient an amount of a compound described herein that is effective in treating the hematologic tumor.

[0252] In one embodiment, the hematologic tumor is leukemia, lymphoma or multiple myeloma.

[0253] In one embodiment, the hematologic tumor is leukemia or lymphoma.

[0254] Additional embodiments relate to methods of treating solid tumors in a patient. Some embodiments relate to the treatment of solid tumors in a patient comprising administering to the patient an amount of a compound described herein that is effective in treating the solid tumor. In one embodiment, the solid tumor is breast, lung, colon, brain,

prostate, stomach, pancreatic, ovarian, melanoma, endocrine, uterine, testicular, or bladder. In an embodiment, the solid tumor is breast, lung, prostate, pancreatic, or ovarian. In an embodiment, the solid tumor is breast cancer. In an embodiment, the breast cancer is ER positive breast cancer.

[0255] The anti-proliferative effects of the compounds of Formula (Y) or (I) or a pharmaceutically salt thereof have particular application in the treatment of human cancers (by virtue of their inhibition of KAT6A and/or KAT7 enzyme activity).

[0256] The anti-cancer effect may arise through one or more mechanisms, including but not limited to, the regulation of cell proliferation, the inhibition of angiogenesis (the formation of new blood vessels), the inhibition of metastasis (the spread of a tumor from its origin), the inhibition of invasion (the spread of tumor cells into neighboring normal structures), or the promotion of apoptosis (programmed cell death).

[0257] In a particular embodiment of the disclosure, the proliferative condition to be treated is cancer. In an embodiment, the proliferative condition to be treated is cancer, wherein the cancer is selected from lung cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, liver cancer, pancreatic cancer, brain cancer, skin cancer, head and neck cancer, thyroid cancer, bladder cancer, esophageal cancer, stomach cancer, uterine cancer, melanoma, gastric cancer, rhabdoid cancer, bone cancer, and cancers associated with the central nervous system.

ROUTES OF ADMINISTRATION

[0258] The compounds of Formula (Y) or (I) or a pharmaceutically salt thereof or pharmaceutical compositions comprising these compounds may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or topically (i.e., at the site of desired action).

[0259] Routes of administration include, but are not limited to, oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eye drops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intra-arterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal,

intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

COMBINATION THERAPIES

[0260] The antiproliferative treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to a therapeutically effective amount of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumor agents: other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumor antibiotics (for example anthracyclines like bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine as well as taxol and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin); cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride; anti-invasion agents [for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), *N*-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide and bosutinib (SKI-606), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase]; inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti-erbB1

antibody cetuximab [Erbitux, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern *et al.* (Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006), tipifarnib (R115777) and lonafarnib (SCH66336)), inhibitors of MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors; antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW 786034) and 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin)]; vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213; an endothelin receptor antagonist, for example zibotentan (ZD4054) or atrasentan; antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense; gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using

cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and immunotherapy approaches, including for example *ex-vivo* and *in-vivo* approaches to increase the immunogenicity of patient tumor cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumor cell lines and approaches using anti-idiotypic antibodies.

[0261] In some embodiments, the disclosure relates to a method of treating cancer comprising administering to a patient in need thereof an amount of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, and an amount of CDK4 inhibitor, wherein the amounts together are therapeutically effective in treating cancer.

[0262] In some embodiments, the disclosure relates to a method of treating cancer comprising administering to a patient in need thereof an amount of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, and an amount of antiestrogen, wherein the amounts together are therapeutically effective in treating cancer.

[0263] In some embodiments, the disclosure relates to a method of treating cancer comprising administering to a patient in need thereof an amount of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, and an amount of CDK4 inhibitor and an amount of antiestrogen, wherein the amounts together are therapeutically effective in treating cancer.

[0264] In an embodiment, the CDK4 inhibitor is a CDK4 selective inhibitor. In an embodiment, the CDK4 selective inhibitor is 1,5-anhydro-3-({5-chloro-4-[4-fluoro-2-(2-hydroxypropan-2-yl)-1-(propan-2-yl)-1*H*-benzimidazol-6-yl]pyrimidin-2-yl}amino)-2,3-dideoxy-D-THEO-pentitol, or a pharmaceutically acceptable salt thereof.

[0265] In an embodiment, the CDK4 inhibitor is a CDK4/6 inhibitor. In an embodiment, the CDK4/6 inhibitor is abemaciclib, ribociclib and palbociclib, or a pharmaceutically acceptable salt thereof.

[0266] In an embodiment, the antiestrogen is an aromatase inhibitor, a selective estrogen receptor degrader (SERD) or a selective estrogen receptor modulator (SERM). In an embodiment, the antiestrogen is fulvestrant or letrozole.

[0267] Some embodiments relate to a method of (and to a pharmaceutical composition for) treating cancer in a patient which comprise an amount of a compound of Formula (Y) or (I) or a pharmaceutically salt thereof compound described herein, or a pharmaceutically acceptable salt, in combination with an amount of one or more substances selected from antiangiogenesis agents, signal transduction inhibitors (e.g., inhibiting the means by which regulatory molecules that govern the fundamental processes of cell growth, differentiation, and survival communicated within the cell), and antiproliferative agents, which amounts are together effective in treating said abnormal cell growth.

[0268] Anti-angiogenesis agents, such as MMP-2 (matrix-metalloprotienase 2) inhibitors, MMP-9 (matrix-metalloprotienase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors, can be used in combination with a compound of Formula (Y) or (I) or a pharmaceutically salt thereof described herein in the methods and pharmaceutical compositions described herein.

[0269] Tyrosine kinase inhibitors can also be combined with a compound of Formula (Y) or (I) or a pharmaceutically salt thereof described herein.

[0270] VEGF inhibitors, for example, sutent and axitinib, can also be combined with a compound of Formula (Y) or (I) or a pharmaceutically salt thereof described herein.

[0271] ErbB2 receptor inhibitors may be administered in combination with a compound of Formula (Y) or (I) or a pharmaceutically salt thereof described herein. Various other compounds, such as styrene derivatives, have also been shown to possess tyrosine kinase inhibitory properties, and some of tyrosine kinase inhibitors have been identified as erbB2 receptor inhibitors.

[0272] Epidermal growth factor receptor (EGFR) inhibitors may be administered in combination with a compound of Formula (Y) or (I) or a pharmaceutically salt thereof.

[0273] PI3K inhibitors, such as PI3K alpha or PI3K beta inhibitors, may be administered in combination with a compound of Formula (Y) or (I) or a pharmaceutically salt thereof.

[0274] Mammalian target of rapamycin (mTOR) inhibitors may be administered in combination with a compound of Formula (Y) or (I) or a pharmaceutically salt thereof.

[0275] c-Met inhibitors may be administered in combination with a compound of Formula (Y) or (I) or a pharmaceutically salt thereof.

[0276] MEK inhibitors may be administered in combination with a compound of Formula (Y) or (I) or a pharmaceutically salt thereof.

[0277] PARP inhibitors may be administered in combination with a compound of Formula (Y) or (I) or a pharmaceutically salt thereof.

[0278] JAK inhibitors may be administered in combination with a compound of Formula (Y) or (I) or a pharmaceutically salt thereof.

[0279] An antagonist of a Programmed Death 1 protein (PD-1) may be administered in combination with a compound of Formula (Y) or (I) or a pharmaceutically salt thereof.

[0280] An antagonist of Programmed Death-Ligand 1 (PD-L1) may be administered in combination with a compound of Formula (Y) or (I) or a pharmaceutically salt thereof.

[0281] Other antiproliferative agents that may be used with the compounds described herein include inhibitors of the enzyme farnesyl protein transferase and inhibitors of the receptor tyrosine kinase PDGFr.

[0282] A compound of Formula (Y) or (I) or a pharmaceutically salt thereof may also be used with other agents useful in treating abnormal cell growth or cancer, including, but not limited to, agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocyte antigen 4) antibodies, and other agents capable of blocking CTLA4; and anti-proliferative agents such as other farnesyl protein transferase inhibitors, for example the farnesyl protein transferase.

[0283] A compound of Formula (Y) or (I) or a pharmaceutically salt thereof may be applied as a sole therapy or may involve one or more other anti-tumor substances, for example those selected from, for example, mitotic inhibitors, alkylating agents, anti-metabolites, growth factor inhibitors, cell cycle inhibitors, intercalating antibiotics, enzymes, and anti-hormones.

[0284] A compound of Formula (Y) or (I) or a pharmaceutically salt thereof may be used alone or in combination with one or more of a variety of anti-cancer agents or supportive care agents. For example, the compounds described herein may be used with cytotoxic agents. Some embodiments also contemplate the use of the compounds described herein together with hormonal therapy.

[0285] In a particular embodiment, the antiproliferative treatment defined hereinbefore may involve, in addition to the compound of Formula (Y) or (I) or a pharmaceutically salt thereof, conventional surgery or radiotherapy or chemotherapy.

[0286] Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this disclosure within the dosage range described hereinbefore and the other pharmaceutically active agent within its approved dosage range.

[0287] According to this aspect of the disclosure there is provided a combination for use in the treatment of a cancer (for example a cancer involving a solid tumor) comprising a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, and another anti-tumor agent.

[0288] According to this aspect of the disclosure there is provided a combination for use in the treatment of a proliferative condition, such as cancer (for example a cancer involving a solid tumor), comprising a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, and any one of the anti-tumor agents listed herein above.

[0289] In a further aspect of the disclosure there is provided a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, for use in the treatment of cancer in combination with another anti-tumor agent, optionally selected from one listed herein above.

[0290] Additional embodiments relate to methods of treating cancer in a patient which comprises administering to the patient an amount of a compound described herein that is effective in treating cancer in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, antihormones, and anti-androgens.

[0291] Herein, where the term "combination" is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the disclosure "combination" refers to simultaneous administration. In another aspect of the disclosure "combination" refers to separate administration. In a further aspect of the disclosure "combination" refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination.

[0292] According to a further aspect of the disclosure there is provided a pharmaceutical composition which comprises a compound of Formula (Y) or (I) or a pharmaceutically salt thereof, in combination with an anti-tumor agent (optionally selected from one listed herein above), in association with a pharmaceutically acceptable diluent or carrier.

DOSING

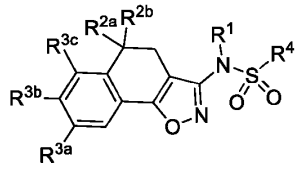
[0293] The compounds of Formula (Y) or (I), or a pharmaceutically acceptable salt thereof provided herein may be administered to a subject in an amount that is dependent upon, for example, the goal of administration (e.g., the degree of resolution desired); the age, weight, sex, and health and physical condition of the subject to which the formulation is being administered; the route of administration; and the nature of the disease, disorder, condition or symptom thereof. The dosing regimen may also take into consideration the existence, nature, and extent of any adverse effects associated with the agent(s) being administered.

[0294] An effective dose (ED) is the dose or amount of an agent that produces a therapeutic response or desired effect in some fraction of the subjects taking it. The "median effective dose" or ED_{50} of an agent is the dose or amount of an agent that produces a therapeutic response or desired effect in 50% of the population to which it is administered. Although the ED_{50} is commonly used as a measure of reasonable expectance of an agent's effect, it is not necessarily the dose that a clinician might deem appropriate taking into consideration all relevant factors. Thus, in some situations the effective amount is more than the calculated ED_{50}, in other situations the effective amount is less than the calculated ED_{50}, and in still other situations the effective amount is the same as the calculated ED_{50}.

[0295] In using a compound described herein, or a pharmaceutically acceptable salt thereof, for therapeutic or prophylactic purposes, it will generally be administered so that a total daily dose in the range, for example, 0.01 mg/kg to 100 mg/kg body weight is received. Contemplated routes of administration are discussed in a preceding section.

NON-LIMITING EXEMPLARY EMBODIMENTS

[0296] **Embodiment 1**: A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of H, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{2a} and R^{2b} together with the carbon atom to which they are attached form cyclopropyl or cyclobutyl, wherein each of said cyclopropyl and cyclobutyl, is independently unsubstituted or substituted with from 1 to 3 R^g; or

R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, and C_{1-4} haloalkyl;

R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, –C(O)NHR[a], and cyano; and wherein each of said 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroarylhas from 1 to 4 ring members independently selected from N, O and S, and wherein each of said C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl, is independently unsubstituted or substituted with from 1 to 4 R^b;

R^4 is selected from the group consisting of C_{4-7} cycloalkyl, phenyl, heteroaryl, heterocyclyl, and fused heterocyclyl, wherein each of phenyl, heteroaryl, heterocyclyl, and fused heterocyclyl, is independently unsubstituted or substituted with 1-3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, –C(O)R^c, –C(O)OR^d, or –C(O)N$R^e$$R^f$; or two R^{4a} groups on adjacent carbon atoms are optionally combined to form a 5- to 6-membered cycloalkyl or heterocycloalkyl which is unsubstituted or substituted with 1-3 groups independently selected from halo, C_{1-4} alkyl, and C_{1-4} haloalkyl;

each R^a is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^b is independently selected from the group consisting of oxo, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

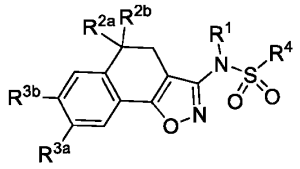
each R^c is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^d is independently selected from the group consisting of H and C_{1-6} alkyl;

each R^e and R^f is independently selected from the group consisting of H, C_{1-6} alkyl and C_{3-6} cycloalkyl; or R^e and R^f together with the nitrogen atom to which they are attached form 4- to 6-membered ring; and

each R^g is independently selected from the group consisting of C_{1-6} alkyl, halo, hydroxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and cyano.

[0297] **Embodiment 2**: The compound of embodiment **1**, wherein the compound is represented by Formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof.

[0298] **Embodiment 3**: The compound of embodiment **1** or embodiment **2** or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl or cyclobutyl, wherein each of said cyclopropyl and cyclobutyl is unsubstituted or substituted with from 1 to 3 R^g.

[0299] **Embodiment 4**: The compound of embodiment **1** or embodiment **2** or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl, wherein cyclopropyl is unsubstituted or substituted with from 1 to 3 R^g.

[0300] **Embodiment 5**: The compound of embodiment **1** or embodiment **2** or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl, wherein cyclopropyl is unsubstituted.

[0301] **Embodiment 6**: The compound of embodiment **1** or embodiment **2** or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are combined with the carbon

atom to which they are attached to form cyclobutyl, wherein cyclobutyl is unsubstituted or substituted with from 1 to 3 R^g.

[0302] **Embodiment 7**: The compound of embodiment **1** or embodiment **2** or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclobutyl, wherein cyclobutyl is unsubstituted.

[0303] **Embodiment 8**: The compound of embodiment **1** or embodiment **2** or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, and C_{1-4} haloalkyl.

[0304] **Embodiment 9**: The compound of embodiment **1** or embodiment **2** or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0305] **Embodiment 10**: The compound of embodiment **1** or embodiment **2** or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are each independently selected from the group consisting of H and C_{1-4} alkyl.

[0306] **Embodiment 11**: The compound of embodiment **1** or embodiment **2** or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are each H.

[0307] **Embodiment 12**: The compound of embodiment **1** or embodiment **2** or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are each independently C_{1-4} alkyl.

[0308] **Embodiment 13**: The compound of embodiment **1** or embodiment **2** or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are each independently methyl or ethyl.

[0309] **Embodiment 14**: The compound of any one of embodiments **1** to **13** or a pharmaceutically acceptable salt thereof, wherein R^1 is H.

[0310] **Embodiment 15**: The compound of any one of embodiments **1** to **14** or a pharmaceutically acceptable salt thereof, wherein R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, and -O-C_{3-5} cycloalkyl.

[0311] **Embodiment 16**: The compound of any one of embodiments **1** to **14** or a pharmaceutically acceptable salt thereof, wherein R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, and -C(O)NHR^a.

[0312] **Embodiment 17**: The compound of any one of embodiments **1** to **14** or a pharmaceutically acceptable salt thereof, wherein R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, and –C(O)NHR^a.

[0313] **Embodiment 18**: The compound of any one of embodiments **15** to **17** or a pharmaceutically acceptable salt thereof, wherein R^{3a} is selected from the group consisting of H, halo, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, and –C(O)NHR^a, and R^{3b} and R^{3c} are each independently H.

[0314] **Embodiment 19**: The compound of any one of embodiments **15** to **17** or a pharmaceutically acceptable salt thereof, wherein R^{3a} is selected from the group consisting of H, halo, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, and –C(O)NHR^a, and R^{3b} and R^{3c} are each independently selected from the group consisting of H and halo.

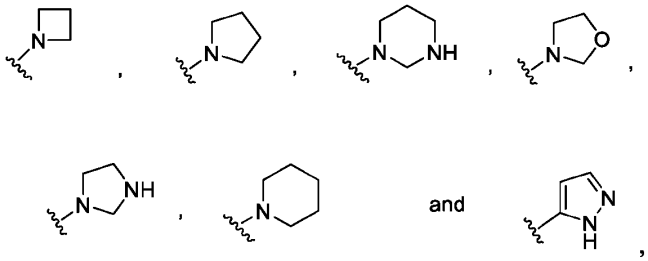
[0315] **Embodiment 20**: The compound of any one of embodiments **1** to **14** or a pharmaceutically acceptable salt thereof, wherein one of R^{3a} and R^{3b} is selected from the group consisting of 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl; and wherein each of said 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl has from 1 to 4 ring members independently selected from N, O and S, and is independently unsubstituted or substituted with from 1 to 4 R^b.

[0316] **Embodiment 21**: The compound of any one of embodiments **1** to **14** or a pharmaceutically acceptable salt thereof, wherein one of R^{3a} and R^{3b} is selected from the group consisting of 3- to 7-membered heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl; and wherein each of said 3- to 7-membered heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl has from 1 to 4 ring

members independently selected from N, O and S, and is independently unsubstituted or substituted with from 1 to 4 R^b.

[0317] **Embodiment 22**: The compound of any one of embodiments **1** to **14** or a pharmaceutically acceptable salt thereof, wherein one of R^{3a} and R^{3b} is selected from the group consisting of 3- to 7-membered heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl; and wherein each of said 3- to 7-membered heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl has from 1 to 4 ring members independently selected from N, O and S, and is unsubstituted.

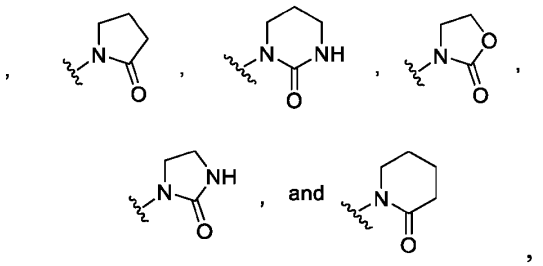
[0318] **Embodiment 23**: The compound of any one of embodiments **1** to **14** or a pharmaceutically acceptable salt thereof, wherein one of R^{3a} and R^{3b} is selected from the group consisting of



wherein each cyclic moiety is independently unsubstituted or substituted with from 1 to 4 R^b.

[0319] **Embodiment 24**: The compound of embodiment **23** or a pharmaceutically acceptable salt thereof, wherein each R^b is independently selected from the group consisting of oxo, hydroxyl, C_{1-6} alkyl, and C_{3-6} cycloalkyl.

[0320] **Embodiment 25**: The compound of any one of embodiments **1** to **14** or a pharmaceutically acceptable salt thereof, wherein one of R^{3a} and R^{3b} is selected from the group consisting of



wherein each cyclic moiety is unsubstituted or substituted with from 1 to 3 R^b.

[0321] Embodiment 26: The compound of embodiment **23** or **25** or a pharmaceutically acceptable salt thereof, wherein each R^b is independently selected from the group consisting of oxo and C_{1-6} alkyl.

[0322] Embodiment 27: The compound any one of embodiments **1** to **26** or a pharmaceutically acceptable salt thereof, wherein R^4 is phenyl, which is unsubstituted or substituted with 1-3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, –C(O)R^c, –C(O)OR^d, or –C(O)N$R^e R^f$.

[0323] Embodiment 28: The compound of any one of embodiments **1** to **26** or a pharmaceutically acceptable salt thereof, wherein R^4 is phenyl, which is unsubstituted or substituted with 1-3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or hydroxyC_{1-6} alkyl.

[0324] Embodiment 29: The compound of any one of embodiments **1** to **26** or a pharmaceutically acceptable salt thereof, wherein R^4 is phenyl, which is unsubstituted or substituted with 1-3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, C_{1-6} alkoxy, halo, CN, or C_{1-6} haloalkoxy.

[0325] Embodiment 30: The compound of any one of embodiments **1** to **26** or a pharmaceutically acceptable salt thereof, wherein R^4 is phenyl substituted with two R^{4a} groups on adjacent carbon atoms that combine to form a 5- to 6-membered cycloalkyl or heterocycloalkyl which is unsubstituted or substituted with 1-3 groups independently selected from halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

[0326] Embodiment 31: The compound of any one of embodiments **1** to **26** or a pharmaceutically acceptable salt thereof, wherein R^4 is a 5- or 6-membered heteroaryl, which is unsubstituted or substituted with 1-3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, –C(O)R^c, –C(O)OR^d, or –C(O)N$R^e R^f$.

[0327] Embodiment 32: The compound of any one of embodiments **1** to **26** or a pharmaceutically acceptable salt thereof, wherein R^4 is a 5- or 6-membered heteroaryl, which

is unsubstituted or substituted with 1-3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, C_{1-6} alkoxy, halo, CN, or C_{1-6} haloalkoxy.

[0328] **Embodiment 33**: The compound of any one of embodiments **1** to **26** or a pharmaceutically acceptable salt thereof, wherein R^4 is pyridyl, which is unsubstituted or substituted with 1-3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, –C(O)R^c, –C(O)OR^d, or –C(O)NR^eR^f.

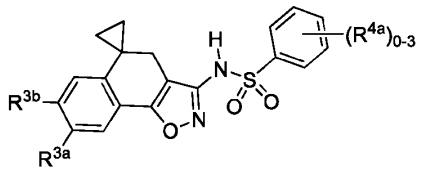
[0329] **Embodiment 34**: The compound of any one of embodiments **1** to **26** or a pharmaceutically acceptable salt thereof, wherein R^4 is pyridyl, which is unsubstituted or substituted with 1-3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, C_{1-6} alkoxy, halo, CN, or C_{1-6} haloalkoxy.

[0330] **Embodiment 35**: The compound of any one of embodiments **1** to **26** or a pharmaceutically acceptable salt thereof, wherein R^4 is a 5- or 6-membered heterocyclyl, which is unsubstituted or substituted with 1-3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, –C(O)R^c, –C(O)OR^d, or –C(O)NR^eR^f.

[0331] **Embodiment 36**: The compound of any one of embodiments **1** to **26** or a pharmaceutically acceptable salt thereof, wherein R^4 is 5- or 6-membered heterocyclyl, which is unsubstituted or substituted with 1-3 R^{4a}, wherein each R^{4a} is independently C_{1-6} alkyl, C_{1-6} alkoxy, halo, CN, or C_{1-6} haloalkoxy.

[0332] **Embodiment 37**: The compound of any one of embodiments **1** to **26** or a pharmaceutically acceptable salt thereof, wherein R^4 is C_{3-7} cycloalkyl.

[0333] **Embodiment 38**: The compound of any one of embodiments **1** and **14** to **29**, represented by Formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof, wherein each R^{4a} is independently selected from the group consisting of C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and hydroxyC_{1-6} alkyl.

[0334] Embodiment 39: A compound of embodiment **1** or a pharmaceutically acceptable salt thereof, wherein said compound is selected from compounds in Table 1 or from Examples 1 to 77.

[0335] Embodiment 40: A compound or a pharmaceutically acceptable salt thereof selected from the compounds of Table 1.

[0336] Embodiment 41: A pharmaceutical composition comprising a compound of any one of embodiments **1** to **40** or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[0337] Embodiment 42: A compound or pharmaceutically acceptable salt thereof of any one of embodiments **1** to **40** or a pharmaceutical composition of embodiment **41**, for use in therapy.

[0338] Embodiment 43: A method of treating cancer in a subject in need thereof, said method comprising administering to said subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt thereof of any one of embodiments **1** to **40,** or a pharmaceutical composition of embodiment **41**.

[0339] Embodiment 44: The method of embodiment **43**, wherein the cancer is characterized by an overexpression of KAT6A and/or KAT7, an amplification of KAT6A gene and/or KAT7 gene, an increased activity of KAT6A and/or KAT7, or a combination thereof.

[0340] Embodiment 45: The method of embodiment **43**, wherein the cancer is characterized by an overexpression of KAT6A, an amplification of KAT6A gene, an increased activity of KAT6A or a combination thereof.

[0341] Embodiment 46: The method of treating cancer of any one of embodiments **43** to **45**, wherein the cancer is treatable by inhibition of KAT6A and/or KAT7.

[0342] Embodiment 47: A method of treating a disorder mediated by KAT6A and/or KAT7 in a subject in need thereof, comprising administering to said subject a therapeutically

effective amount of a compound of any one of embodiments **1** to **40** or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment **41**.

[0343] **Embodiment 48**: The method of embodiment **47**, wherein the disorder is cancer.

[0344] **Embodiment 49**: The method of any one embodiments **43** to **48**, wherein the cancer is lung cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, liver cancer, pancreatic cancer, brain cancer, skin cancer, head and neck cancer, thyroid cancer, bladder cancer, esophageal cancer, stomach cancer, uterine cancer, melanoma, gastric cancer, rhabdoid cancer, bone cancer, or cancers associated with the central nervous system.

[0345] **Embodiment 50**: Use of a compound of any one of embodiments **1** to **40** or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of embodiment **41**, for use in the treatment of cancer.

[0346] **Embodiment 51**: Use of a compound of any one of embodiments **1** to **40** or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of embodiment **41**, in the manufacture of a medicament for the treatment of cancer.

[0347] **Embodiment 52**: The use of embodiment **50** or **51**, wherein the cancer is lung cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, liver cancer, pancreatic cancer, brain cancer, skin cancer, head and neck cancer, thyroid cancer, bladder cancer, esophageal cancer, stomach cancer, uterine cancer, melanoma, gastric cancer, rhabdoid cancer, bone cancer, or cancers associated with the central nervous system.

EXAMPLES

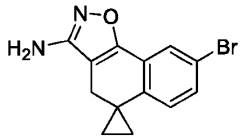
[0348] The following references (intermediates) and examples (final compounds) are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present disclosure, and are not intended to limit the scope of what the inventors regard as their disclosure, nor are they intended to represent that the experiments below were performed or that they are all of the experiments that may be performed. It is to be understood that exemplary descriptions written in the present tense were not necessarily performed, but rather that the descriptions can be performed to generate data and the like of a nature described therein. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.), but some experimental errors and deviations should be accounted for.

[0349] Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius (°C), and pressure is at or near atmospheric. Standard abbreviations are used, including the following: THF= tetrahydrofuran; DIEA = diisopropylethylamine; EtOAc = ethyl acetate; NMP = N-methylpyridine, TFA = trifluoroacetic acid; DCM = dichloromethane; Cs_2CO_3= cesium carbonate; Xphos Pd G3 = 2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)(2-(2′-amino-1,1′-biphenyl))palladium-(II) methanesulfonate; LiCl = lithium chloride; $POCl_3$ = phosphoryl chloride; PE = petroleum ether; DMSO = dimethylsulfoxide; HCl = hydrochloric acid; Na_2SO_4 = sodium sulfate; DMF = dimethylformamide; NaOH = sodium hydroxide; K_2CO_3 = potassium carbonate; MeCN= acetonitrile; BOC= tert-butoxycarbonyl; MTBE = methyl tert-butyl ether; MeOH = methanol; $NaHCO_3$ = sodium bicarbonate; $NaBH_3CN$ = sodium cyanoborohydride; EtOH = ethanol; PCl_5= phosphorus pentachloride; NH_4Oac = ammonium acetate; Et_2O = ether; HOAc = acetic acid; Ac_2O = acetic anhydride; *i*-PrOH = isopropanol; NCS = N-chlorosuccinimide; K_3PO_4 = potassium phosphate; Pd(dtbpf)Cl_2 =1,1′-Bis(di-tert-butylphosphino)ferrocene)dichloro-palladium(II); $Zn(CN)_2$ = Zinc cyanide; $Pd(PPh_3)_4$ =tetrakis(triphenylphosphine)palladium(0); Et_3N = triethylamine; CuCN = copper cyanide; *t*-BuONO = tert-butyl nitrite; HATU = 1-(bis(dimethylamino)methylene)-1H-1,2,3-triazolo(4,5-b)pyridinium 3-oxid hexafluorophosphate; DBU= 1,8-diazabicyclo(5.4.0)undec-7-ene; $LiAlH_4$ = lithium aluminium hydride; NH_3 = ammonia; H_2SO_4 = sulfuric acid; H_2O_2 = hydrogen peroxide; EDCI = N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride; HOBT = 1-hydroxybenzotriazole hydrate; DHP = dihydropyran; TsOH = p-Toluenesulfonic acid; FA = formic acid; TCFH = N,N,N,N'-tetramethylchloroformamidinium hexafluorophosphate ; NMI = N-methylimidazole; Pd(dppf)Cl_2 = (1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II); Pd(dppf)Cl_2-DCM = (1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II), complex with dichloromethane; DCE = dichloroethane; TEA = trimethylamine; MsCl = methanesulfonyl chloride; TFAA = trifluoroacetic anhydride; DIBAL-H = diisobutylaluminum hydride; NBS = N-Bromosuccinimide; THP = tetrahydropyran; TLC = thin layer chromatography; TMSCl = trimethylsilylchloride; TsOH = p-toluenesulfonic acid; U = unit; wt = wildtype.

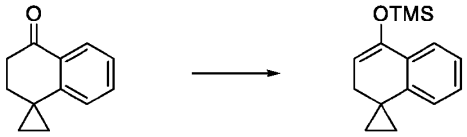
[0350] The chemical names in the present application are generated from the corresponding structures using software, for example, CHEMDRAW (e.g., version 22.2.0 or 23.1.1).

Intermediate A

4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine

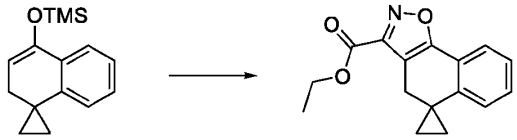


[0351] Step 1: Synthesis of ((2'H-spiro[cyclopropane-1,1'-naphthalen]-4'-yl)oxy)trimethylsilane



[0352] To a solution of 2'H,3'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (0.6 g, 3.48 mmol) in tetrahydrofuran (34.8 mL, 428 mmol) at -78 °C was added lithium bis(isopropyl)azanide (485 mg, 1.3 eq., 4.53 mmol), followed by chlorotris(methyl)silane (575 µL, 1.3 eq., 4.53 mmol). The reaction was allowed to warm to RT over 2 h. the reaction was quenched by addition of triethylamine (35.3 g, 100 eq., 348 mmol). The mixture was concentrated under reduced pressure, slurried with pentanes, filtered and concentrated to afford ((2'H-spiro[cyclopropane-1,1'-naphthalen]-4'-yl)oxy)trimethylsilane (910 mg, 107 % yield) as an orange oil. ^{1}H NMR (400 MHz, DMSO) δ 7.40 (s, 1H), 6.98 (dd, J = 8.6, 3.3 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 5.26 (q, J = 4.1 Hz, 1H), 2.27 – 2.06 (m, 2H), 0.91 – 0.70 (m, 4H), 0.24 (d, J = 5.2 Hz, 8H).

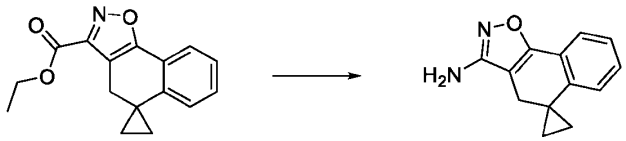
[0353] Step 2: Synthesis of ethyl 4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate



[0354] To a solution of trimethyl(2'H-spiro[cyclopropane-1,1'-naphthalen]-4'-yloxy)silane (910 mg, 3.72 mmol) and ethyl chloro(hydroxyimino)acetate (176 mg, 1.16 mmol) in n-hexanes (11.6 mL, 88.2 mmol) was added triethylamine (243 µL, 1.5 eq., 1.74 mmol) (1 M solution in hexanes) over 10 h via syringe pump. The reaction was stirred for 6 h. To the reaction was added p-toluenesulfonic acid monohydrate (1.32 g, 6 eq., 6.96 mmol) and the mixture heated at reflux for 6 h. The reaction was diluted with water (100 mL) and extracted

with EtOAc (200 mL X 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated. The mixture was subjected to normal phase purification (40-100% DCM in petroleum ether) to afford ethyl 4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (471 mg, 40 % yield) as a brown oil. MS (ESI, *m/z*): 348/350 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ ^1H NMR (400 MHz, MeOD) δ 7.83 (d, J = 2.2 Hz, 1H), 7.53 (dd, J = 8.4, 2.2 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 4.43 (td, J = 7.1, 4.7 Hz, 2H), 2.93 (s, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.07 – 1.02 (m, 2H), 1.01 – 0.95 (m, 2H).

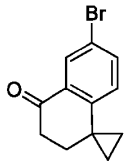
[0355] Step 3: Synthesis of 4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine



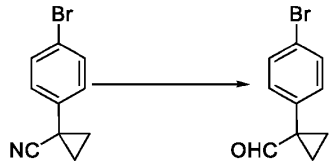
[0356] To a stirred solution of ethyl 4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (113 mg, 0.42 mmol, 1 equiv) in MeOH (1 mL) at 0 °C was added $NH_3 \cdot H_2O$ (1 mL). The reaction was allowed to warm to ambient temperature and stirred for 2 h. The resulting mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated under vacuum. The residue was dissolved in a combined solvent system of EtOAc (1.4 mL), acetonitrile (1.4 mL) and H_2O (0.7 mL) at ambient temperature and $PhI(Oac)_2$ (135 mg, 0.42 mmol, 1 equiv) was added. The resulting mixture was stirred at 70 °C for 16 h and then quenched with $Na_2S_2O_3$ solution. The mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated to afford 4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (21 mg, 24 % over two steps) as a yellow brown solid. MS (ESI, *m/z*): 213.2 $[M+H]^+$.

Intermediate B

6'-bromo-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one

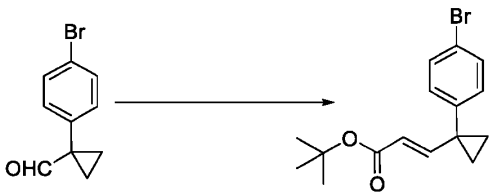


[0357] Step 1. Synthesis of 1-(4-bromophenyl)cyclopropane-1-carbaldehyde



[0358] To a stirred solution of 1-(4-bromophenyl)cyclopropane-1-carbonitrile (25 g, 112.57 mmol, 1 equiv) in THF (250 mL) at -78 °C was added dropwise DIBAL-H (146 mL, 1.0 mol/L in hexane, 146 mmol, 1.3 equiv) over 20 min under N_2 atmosphere. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 2 h. The mixture was quenched with aqueous HCl (1M) and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford 1-(4-bromophenyl)cyclopropane-1-carbaldehyde (25 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 225, 227 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d6) δ 8.88 (d, J = 0.5 Hz, 1H), 7.56-7.50 (m, 2H), 7.28-7.22 (m, 2H), 1.61-1.52 (m, 2H), 1.48-1.39 (m, 2H).

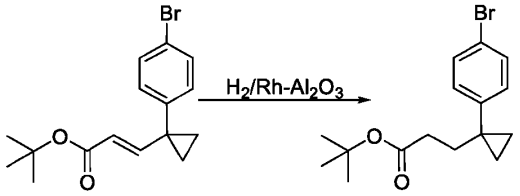
[0359] Step 2. Synthesis of tert-butyl (E)-3-(1-(4-bromophenyl)cyclopropyl)acrylate



[0360] To a stirred solution of tert-butyl 2-(diethoxyphosphoryl)acetate (44.83 g, 177.71 mmol, 2.0 equiv) in THF (220 mL) at 0 °C was added NaH (60% in mineral oil, 7.14 g, 178.6 mmol, 2.0 equiv) in portions over 30 min. The resulting mixture was stirred at this temperature for another 0.5 h and then to this was added dropwise a solution of 1-(4-bromophenyl)cyclopropane-1-carbaldehyde (20 g, 88.85 mmol, 1 equiv) in THF (20 mL) over 10 min. The resulting mixture was stirred at ambient temperature for 1 h and then quenched with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by trituration with petroleum ether to afford tert-butyl (E)-3-(1-(4-bromophenyl)cyclopropyl)acrylate (38 g, 65% yield over two steps) as a white solid. MS (ESI, *m/z*): 323, 325 $[M+H]^+$.^1H NMR (300 MHz, Chloroform-d) δ 7.56-7.42 (m, 2H), 7.24-

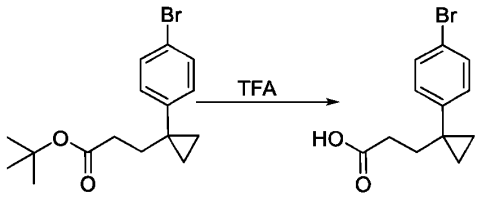
7.14 (m, 2H), 6.57 (d, J = 15.3 Hz, 1H), 5.21 (d, J = 15.3 Hz, 1H), 1.45 (s, 9H), 1.32-1.15 (m, 4H).

[0361] Step 3. Synthesis of tert-butyl 3-(1-(4-bromophenyl)cyclopropyl)propanoate



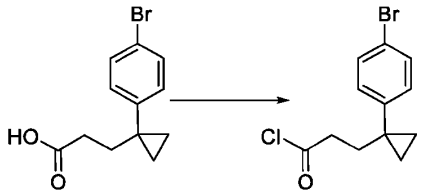
[0362] A mixture of tert-butyl (E)-3-(1-(4-bromophenyl)cyclopropyl)acrylate (20 g, 61.87 mmol, 1 equiv) and $Rh.Al_2O_3$ (2.0 g, 5% Rh on alumina, 10% w/w) in EtOH (100 mL) was stirred at ambient temperature for 24 h under H_2 (~3 atm) atmosphere and then filtered. The filtrate was concentrated under vacuum to afford tert-butyl 3-(1-(4-bromophenyl)cyclopropyl)propanoate (21 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 325, 327 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 7.43-7.36 (m, 2H), 7.20-7.14 (m, 2H), 2.21-2.12 (m, 2H), 1.86-1.78 (m, 2H), 1.40 (s, 9H), 0.83-0.68 (m, 4H).

[0363] Step 4. Synthesis of 3-(1-(4-bromophenyl)cyclopropyl)propanoic acid



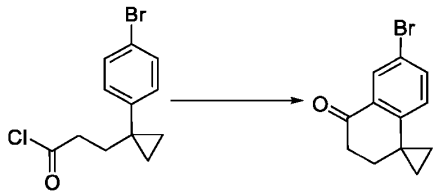
[0364] To a stirred solution of tert-butyl 3-(1-(4-bromophenyl)cyclopropyl)propanoate (20 g, 61.49 mmol, 1 equiv) in DCM (200 mL) at 0 °C was added trifluoroacetic acid (70 mL). The resulting mixture was stirred at ambient temperature for 2 h and then concentrated under vacuum. The residue was purified by trituration with petroleum ether to afford 3-(1-(4-bromophenyl)cyclopropyl)propanoic acid (15 g, 95% over two steps) as yellow solid. MS (ESI, *m/z*): 269, 271 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 7.43-7.36 (m, 2H), 7.19-7.13 (m, 2H), 7.08-6.50 (m, 1H), 2.33-2.26 (m, 2H), 1.91-1.84 (m, 2H), 0.83-0.76 (m, 2H), 0.76-0.70 (m, 2H).

[0365] Step 5. Synthesis of 3-(1-(4-bromophenyl)cyclopropyl)propanoyl chloride



[0366] To a stirred solution of 3-(1-(4-bromophenyl)cyclopropyl)propanoic acid (10 g, 37.16 mmol, 1 equiv) and DMF (0.14 g, 1.86 mmol, 0.05 equiv) in DCM (90 mL) at 0 °C was added dropwise oxalyl chloride (9.43 g, 74.31 mmol, 2 equiv) in DCM (10.0 mL) over 5 min. The resulting mixture was stirred at ambient temperature for another 2 h and then concentrated under vacuum to afford 3-(1-(4-bromophenyl)cyclopropyl)propanoyl chloride (12 g, crude) as brown oil, which was used for the next step without further purification. MS (ESI, *m/z*): 287, 289 $[M+H]^+$.

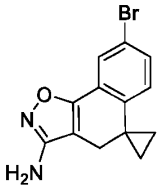
[0367] Step 6. Synthesis of 6'-bromo-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one



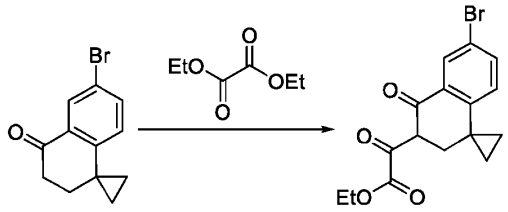
[0368] To a stirred mixture of 3-(1-(4-bromophenyl)cyclopropyl)propanoyl chloride (12 g, crude) in DCM (100.0 mL) at 0 °C was added $AlCl_3$ (3.97 g, 29.85 mmol, 0.8 equiv calculated from the purified carboxylic acid precursor) under N_2 atmosphere. The resulting mixture was stirred at this temperature for and then poured slowly into ice/water. The mixture was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-10% EtOAc in petroleum ether) to afford 6'-bromo-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (5.5 g, 59% yield overtwo steps) as an off-white solid. MS (ESI, *m/z*): 401 $[M+H]^+$. ^1H NMR (300 MHz, Chloroform-d) δ 8.15 (d, J = 2.1 Hz, 1H), 7.60-7.50 (m, 1H), 6.72 (d, J = 8.4 Hz, 1H), 2.83-2.73 (m, 2H), 2.04-1.94 (m, 2H), 1.14-1.06 (m, 2H), 1.06-0.97 (m, 2H).

Intermediate C

8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine

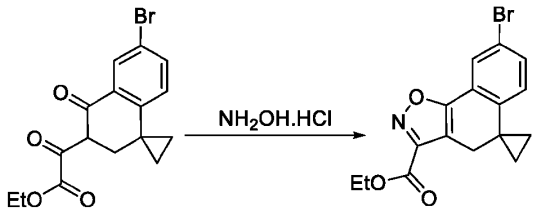


[0369] Step 1. Synthesis of ethyl 2-(6'-bromo-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate



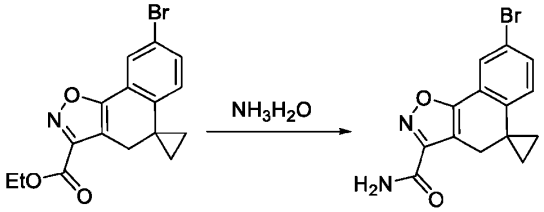
[0370] To a stirred solution of 6'-bromo-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (15 g, 59.73 mmol, 1 equiv, Intermediate B) in THF (150 mL) at 0 °C was added tBuOLi (6.22 g, 77.65 mmol, 1.30 equiv) under N_2 atmosphere. The resulting mixture was stirred at this temperature for 10 min and to this added dropwise a solution of diethyl oxalate (10.48 g, 71.68 mmol, 1.20 equiv) in THF (30 mL) over 5 min. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 2 h. The reaction mixture was then quenched with water and extracted with EtOAc three times. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum to afford ethyl 2-(6'-bromo-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (crude, 24 g) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 351, 353 $[M+H]^+$.

[0371] Step 2. Synthesis of ethyl 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate



[0372] A mixture of ethyl 2-(6'-bromo-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (24 g, 68.34 mmol, 1 equiv) and $NH_2OH{\cdot}HCl$ (5.70 g, 82.01 mmol, 1.20 equiv) in EtOH (300 mL) stirred at 80 °C for 2 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford ethyl 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (15.2 g, 73% yield over two steps) as a yellow solid. MS (ESI, *m/z*): 348, 350 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d6) δ 7.82 (d, J = 2.1 Hz, 1H), 7.60-7.50 (m, 1H), 7.06 (d, J = 8.4 Hz, 1H), 4.42-4.29 (m, 2H), 2.86 (s, 2H), 1.36-1.27 (m, 3H), 1.11-0.99 (m, 2H), 0.99-0.91 (m, 2H).

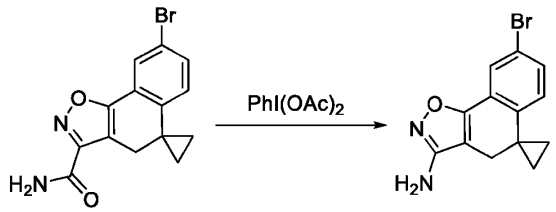
[0373] Step 3. Synthesis of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide



[0374] To a stirred solution of ethyl 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (15.20 g, 43.65 mmol, 1 equiv) in MeOH (200 mL) at 0 °C was added $NH_3{\cdot}H_2O$ (150 mL). The resulting mixture was allowed to warm up to ambient temperature and stirred for 2 h. The resulting mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0- 60% EtOAc:THF) (1:1) in petroleum ether) to afford 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (11.5 g, 83 %) as a yellow solid. MS (ESI, *m/z*): 319, 321 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d6) δ 8.15

(s, 1H), 7.88 (s, 1H), 7.81 (d, J = 2.1 Hz, 1H), 7.60-7.50 (m, 1H), 7.07 (d, J = 8.4 Hz, 1H), 2.87 (s, 2H), 1.08-0.99 (m, 2H), 0.99-0.91 (m, 2H).

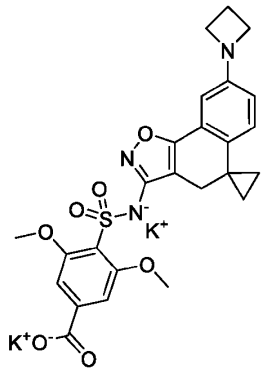
[0375] Step 4. Synthesis of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine



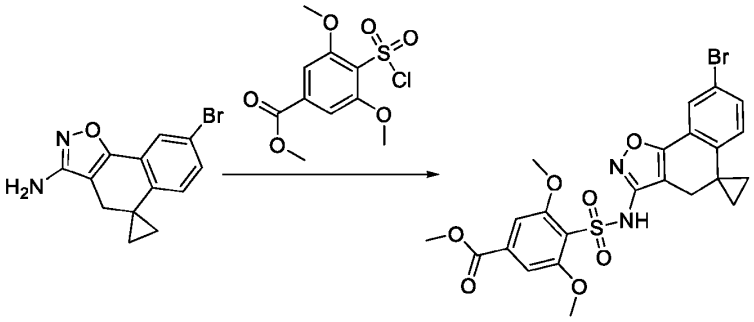
[0376] To a stirred mixture of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (3 g, 9.40 mmol, 1 equiv) and TEA (2.85 g, 28.30 mmol, 3 equiv) in combined solvent system of EtOAc (30 mL), acetonitrile (30 mL) and H_2O (10 mL) at ambient temperature was added $PhI(OAc)_2$ (4.54 g, 14.10 mmol, 1.50 equiv). The resulting mixture was stirred for 1 h and then quenched with $Na_2S_2O_3$ solution. The resulting mixture was extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) and further purified by reverse phase flash chromatography (0-100% CH3CN (0.1% HCOOH) in H2O (0.1% HCOOH)) to afford 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (0.76 g, 26% yield) as an off-white solid. 1.3 g of starting material was also recovered. MS (ESI, *m/z*): 291, 293 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d6) δ 7.63 (d, J = 2.1 Hz, 1H), 7.54-7.44 (m, 1H), 7.03 (d, J = 8.4 Hz, 1H), 5.75 (s, 2H), 2.57 (s, 2H), 1.10-0.94 (m, 2H), 0.94-0.85 (m, 2H).

Intermediate D

Potassium (8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)((4-carboxylato-2,6-dimethoxyphenyl)sulfonyl)amide

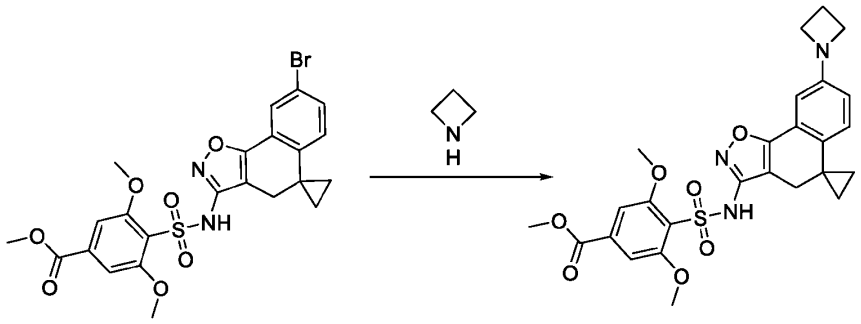


[0377] Step 1. Synthesis of methyl 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoate



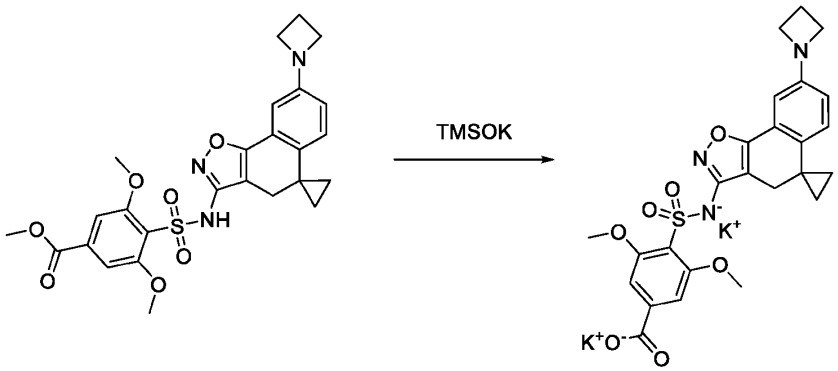
[0378] To a stirred mixture of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (3.5 g, 12.02 mmol, 1.00 equiv) and pyridine (9.51 g, 120.22 mmol, 10.00 equiv) in acetonitrile (50.0 mL) at 0 °C was added methyl 4-(chlorosulfonyl)-3,5-dimethoxybenzoate (4.25 g, 14.42 mmol, 1.20 equiv) in portions. The resulting mixture was stirred at this temperature for another 3 h and then combined with another batch (same scale) and concentrated under vacuum. The residue was resolved in acetonitrile and the solution was slowly added dropwise into saturated NH4Cl solution. The resulting mixture was stirred at ambient temperature for 0.5 h. The precipitate was collected by filtration and washed with water and dried under vacuum to afford methyl 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoate (13 g, 88% yield) as a white solid. MS (ESI, *m/z*): 549.0 $[M+H]^+$.

[0379] Step 2. Synthesis of methyl 4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoate



[0380] A mixture of methyl 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoate (1.0 g, 1.82 mmol, 1.00 equiv), azetidine (0.52 g, 9.10 mmol, 5.00 equiv), Pd-PEPPSI-IHeptCl (0.18 g, 0.18 mmol, 0.10 equiv) and Cs_2CO_3 (1.78 g, 5.46 mmol, 3.00 equiv) in DMF (20.0 mL) was stirred at 80 °C for 1 h under N_2 atmosphere. The resulting mixture was combined with another 12 batches (1.0 g scale) and diluted with ice water. The mixture was acidified with acetic acid to pH ~ 7. The precipitate was collected by filtration and washed with water and dried under vacuum. The crude material was purified by flash chromatography on silica gel (0-10% EtOAc in DCM) to afford methyl 4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoate (9 g, 70% yield) as a yellow solid. MS (ESI, *m/z*): 526.1 $[M+H]^+$.

[0381] Step 3. Synthesis of potassium (8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)((4-carboxylato-2,6-dimethoxyphenyl)sulfonyl)amide

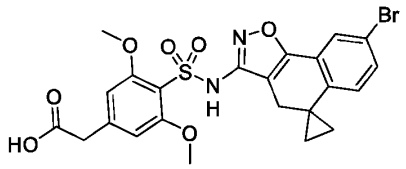


[0382] To a stirred solution of methyl 4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoate (9.0 g, 17.11 mmol, 1.00

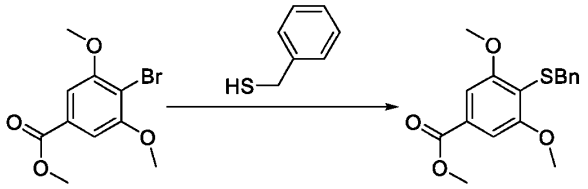
equiv) in THF (500.0 mL) at 0 °C were added dropwise a solution of potassium trimethylsilanolate (10.9 g, 85.55 mmol, 5.00 equiv) in THF (20.0 mL) over 5 min. The resulting mixture was allowed to warm up to ambient temperature and stirred at this temperature for another 3 h. The precipitate was collected by filtration and washed with hexane and dried under vacuum to afford potassium (8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)((4-carboxylato-2,6-dimethoxyphenyl)sulfonyl)amide (10.0 g, crude, Intermediate D) as a white solid, which was used for the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.04 (s, 2H), 6.76 (d, J = 8.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 6.28-6.25 (m, 1H), 3.78 (t, J = 7.1 Hz, 4H), 3.61 (s, 6H), 2.37 (s, 2H), 2.29-2.25 (m, 2H), 0.85-0.75 (m, 2H), 0.63-0.60 (m, 2H). MS (ESI, *m/z*): 512.1 [M+H]+.

Intermediate E

2-(4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxyphenyl)acetic acid



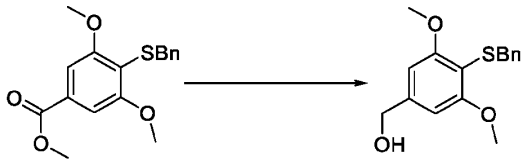
[0383] Step 1. Synthesis of methyl 4-(benzylthio)-3,5-dimethoxybenzoate



[0384] A mixture of methyl 4-bromo-3,5-dimethoxybenzoate (20.00 g, 72.70 mmol, 1.00 equiv), phenylmethanethiol (9.00 g, 72.70 mmol, 1.00 equiv), Pd2(dba)3 (3.33 g, 3.63 mmol, 0.05 equiv), DPPF (4 g, 7.27 mmol, 0.10 equiv) and DIEA (18.79 g, 145.40 mmol, 2.00 equiv) in toluene (200 mL) was stirred at 100 °C for 16 h under N2 atmosphere. The resulting mixture was allowed to cool down to ambient temperature and then to this was added saturated NaHCO3 aqueous solution. The mixture was stirred for another 1 h and then extracted with EtOAc three times. The combined organic layers were washed with brine three

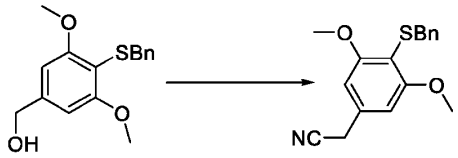
times, dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford methyl 4-(benzylthio)-3,5-dimethoxybenzoate (20 g, 86% yield) as a yellow solid. MS (ESI, *m/z*): 319 $[M+H]^+$+.

[0385] Step 2. Synthesis of (4-(benzylthio)-3,5-dimethoxyphenyl)methanol



[0386] To a stirred mixture of methyl 4-(benzylthio)-3,5-dimethoxybenzoate (15.00 g, 47.11 mmol, 1.00 equiv) in DCM (150 mL) at 0 °C was added dropwise DIBALH (1.0 M in hexane, 94 mL, 94 mmol, 2.00 equiv) over 20 min. The resulting mixture was stirred at this temperature for another 1 h and then quenched slowly at 0 °C with HCl (1.0 M aq) and extracted with EtOAc three times. The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-70% EtOAc in petroleum ether) to afford (4-(benzylthio)-3,5-dimethoxyphenyl)methanol (13 g, 95% yield) as yellow oil. MS (ESI, *m/z*): 291 $[M+H]^+$.

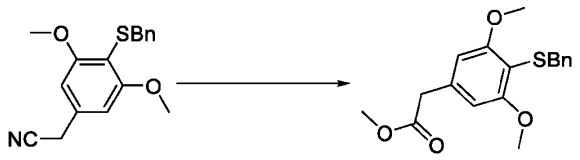
[0387] Step 3. Synthesis of 2-(4-(benzylthio)-3,5-dimethoxyphenyl)acetonitrile



[0388] To a stirred mixture of (4-(benzylthio)-3,5-dimethoxyphenyl)methanol (7.00 g, 24.10 mmol, 1.00 equiv), PPh3 (7.60 g, 28.92 mmol, 1.20 equiv), K2CO3 (10.00 g, 72.31 mmol, 3.00 equiv) and 1,2-diiodoethane (8.15 g, 28.92 mmol, 1.20 equiv) in DMF (70 mL) at ambient temperature was added dropwise TMSCN (9.57 g, 96.42 mmol, 4.00 equiv) over 10 min. The resulting mixture was stirred at this temperature for another 1 h and then diluted with EtOAc. The resulting mixture was washed with brine three times, dried over Na2SO4 and concentrated under vacuum. The residue was combined with another two batches (4.00 g and 0.5 g) and purified by flash chromatography on silica gel (0-50% EtOAc in petroleum

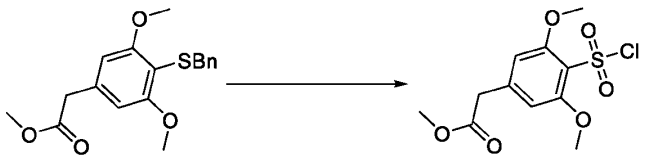
ether) to afford 2-(4-(benzylthio)-3,5-dimethoxyphenyl)acetonitrile (6.2 g, 54% yield) as a yellow solid. MS (ESI, *m/z*): 300 $[M+H]^{+\cdot}$

[0389] Step 4. Synthesis of methyl 2-(4-(benzylthio)-3,5-dimethoxyphenyl)acetate



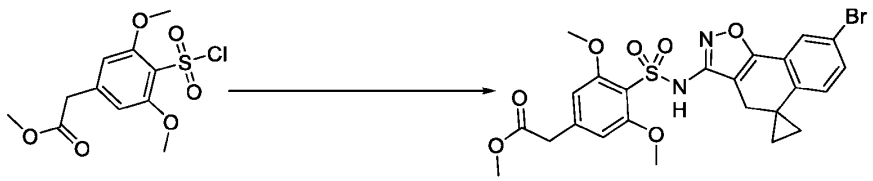
[0390] To a stirred methanol (60 mL) at 0 °C was added dropwise SOCl2 (9 mL) over 5 min and then to this was added 2-(4-(benzylthio)-3,5-dimethoxyphenyl)acetonitrile (6.20 g, 20.71 mmol, 1.00 equiv). The resulting mixture was stirred at 70 °C for another 2 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) and further purified by reverse phase flash chromatography on C18 gel (0-80% acetonitrile in water (contained 0.1% formic acid)) to afford methyl 2-(4-(benzylthio)-3,5-dimethoxyphenyl)acetate (5.0 g, 73% yield) as colorless oil. MS (ESI, *m/z*): 333 $[M+H]^{+}$.

[0391] Step 5. Synthesis of methyl 2-(4-(chlorosulfonyl)-3,5-dimethoxyphenyl)acetate



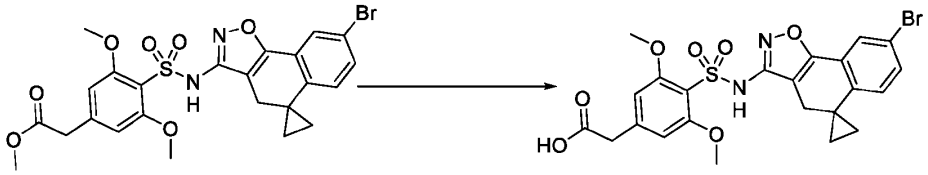
[0392] To a stirred solution of methyl 2-(4-(benzylthio)-3,5-dimethoxyphenyl)acetate (2.50 g, 7.52 mmol, 1.00 equiv) in AcOH (27 mL) and H2O (9 mL) at 0 °C was added NCS (3.00 g, 22.56 mmol, 3.00 equiv) in portions. The resulting mixture was stirred at this temperature for another 1 h and then diluted with EtOAc. The resulting mixture was washed with brine three times, dried over Na2SO4 and concentrated under vacuum. The residue was combined with another batch (2.50 g) and purified by flash chromatography on silica gel (0-80% DCM in petroleum ether) to afford methyl 2-(4-(chlorosulfonyl)-3,5-dimethoxyphenyl)acetate (2.8 g, 60% yield) as a white solid. MS (ESI, *m/z*): 309, 311 $[M+H]^{+}$.

[0393] Step 6. Synthesis of methyl 2-(4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxyphenyl)acetate



[0394] A mixture of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (300.0 mg, 1.030 mmol, 1.00 equiv, Intermediate C) and methyl 2-(4-(chlorosulfonyl)-3,5-dimethoxyphenyl)acetate (445.0 mg, 1.442 mmol, 1.40 equiv) in pyridine (8 mL) was stirred at 80 oC for 2 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-10% MeOH in DCM) to afford methyl 2-(4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxyphenyl)acetate (520.0 mg, 89 % yield) as a white solid. MS (ESI, *m/z*): 563, 565 $[M+H]^+$.

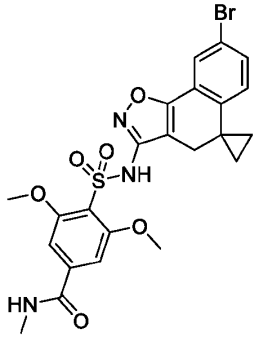
[0395] Step 7. Synthesis of 2-(4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxyphenyl)acetic acid



[0396] A mixture of methyl 2-(4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxyphenyl)acetate (520.0 mg, 0.923 mmol, 1.00 equiv) and LiOH (44.0 mg, 1.846 mmol, 2.00 equiv) in methanol (6 mL) and H2O (2 mL) was stirred at ambient temperature for 1 h and then diluted with water. The resulting mixture was acidified with HCl (1.0 M aq) to pH ~5 and then filtered. The filter cake was washed with water and dried under vacuum to afford 2-(4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxyphenyl)acetic acid (470.0 mg) as a white solid, which was used for the next step without further purification. MS (ESI, *m/z*): 549, 551 $[M+H]^+$.

Intermediate G (Example 193)

4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide

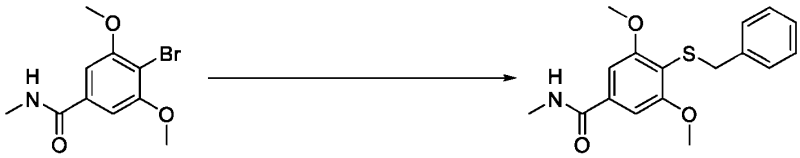


[0397] Step 1. Synthesis of 4-bromo-3,5-dimethoxy-N-methylbenzamide



[0398] To a stirred solution of 4-bromo-3,5-dimethoxybenzoic acid (4 g, 15.322 mmol, 1.00 equiv), methylamine (0.52 g, 16.854 mmol, 1.10 equiv) and DIEA (7.92 g, 61.288 mmol, 4.0 equiv) in DMF (30 mL) at 0 °C was added HATU (8.74 g, 22.983 mmol, 1.50 equiv) in portions. The resulting mixture was stirred at ambient temperature for 2 h and then diluted with EtOAc. The organic solution was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-70% EtOAc in petroleum ether) to afford 4-bromo-3,5-dimethoxy-N-methylbenzamide (3.8 g, 82% yield) as an off-white solid. MS (ESI, *m/z*): 274, 276 [M+H]+.

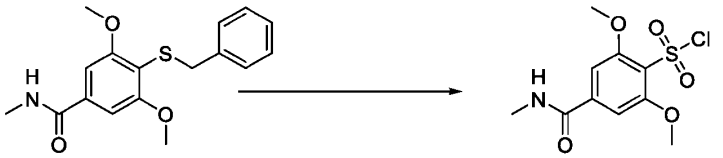
[0399] Step 2. Synthesis of 4-(benzylthio)-3,5-dimethoxy-N-methylbenzamide



[0400] A mixture of 4-bromo-3,5-dimethoxy-N-methylbenzamide (3.8 g, 13.863 mmol, 1.00 equiv), benzyl mercaptan (1.89 g, 15.249 mmol, 1.10 equiv), XantPhos (0.80 g, 1.386 mmol, 0.10 equiv), $Pd_2(dba)_3$ (1.27 g, 1.386 mmol, 0.10 equiv) and DIEA (5.38 g, 41.589 mmol, 3.00 equiv) in dioxane (30 mL) was stirred at 100 °C for 16 h under N_2 atmosphere. The resulting mixture was diluted with EtOAc, washed with saturated NaHCO3 solution three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by

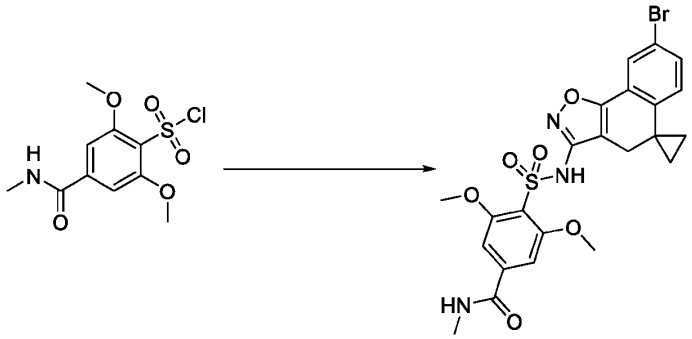
flash chromatography on silica gel (0-50% EtOAc in petroleum ether) and further purified by reverse phase flash chromatography on C18 gel (0-50% acetonitrile in water (contained 0.1% formic acid)) to afford 4-(benzylthio)-3,5-dimethoxy.

[0401] Step 3. Synthesis of 2,6-dimethoxy-4-(methylcarbamoyl)benzenesulfonyl chloride



[0402] To a stirred solution of 4-(benzylthio)-3,5-dimethoxy-N-methylbenzamide (2 g, 6.301 mmol, 1.00 equiv) in acetonitile (10 mL) and H_2O (2 mL) at 0 °C was added concentrated HCl (0.69 g, 18.903 mmol, 3.00 equiv). The reaction mixture was stirred for 10 mins and to this was added NCS (2.52 g, 18.903 mmol, 3.00 equiv) in portions. The resulting mixture was stirred at this temperature for another 1 hand then diluted with EtOAc. The organic solution was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford 2,6-dimethoxy-4-(methylcarbamoyl)benzenesulfonyl chloride (1.5 g, 61% yield) as an off-white solid. MS (ESI, *m/z*): 294, 296 [M+H]+.

[0403] Step 4. Synthesis of 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide

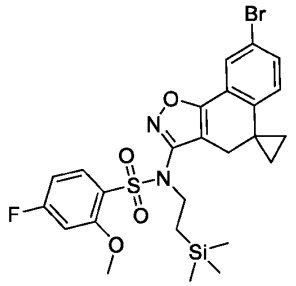


[0404] A mixture of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (400 mg, 1.375 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(methylcarbamoyl)benzenesulfonyl chloride (485 mg,1.649 mmol, 1.2 equiv) in pyridine (10 mL) was stirred at 80 oC for 2 h and then concentrated under vacuum. The residue was

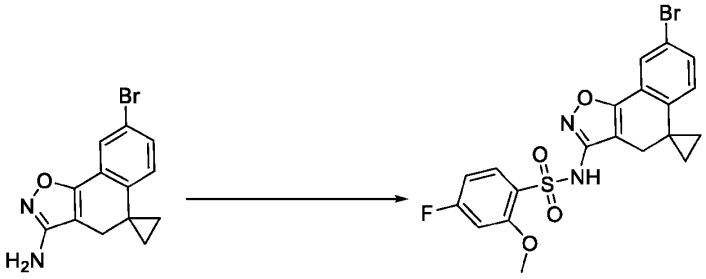
combined with another batch (100 mg) and purified by reverse phase flash chromatography on C18 gel (0-70% acetonitrile in water (contained 0.1% formic acid)) to afford 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (700 mg, 74.3% yield) as a yellow solid. MS (ESI, *m/z*): 548, 550 [M+H]+.1H NMR (300 MHz, DMSO-d6) δ 10.86 (s, 1H), 8.68-8.58 (m, 1H), 7.66 (d, J = 2.1 Hz, 1H), 7.51 (dd, J = 8.4, 2.1 Hz, 1H), 7.14 (s, 2H), 7.03 (d, J = 8.4 Hz, 1H), 3.85 (s, 6H), 3.17 (d, J = 5.1 Hz, 1H), 2.79 (d, J = 4.5 Hz, 3H), 2.62 (s, 2H), 1.05-0.95 (m, 2H), 0.86-0.76 (m, 2H).

Intermediate H

N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-fluoro-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide



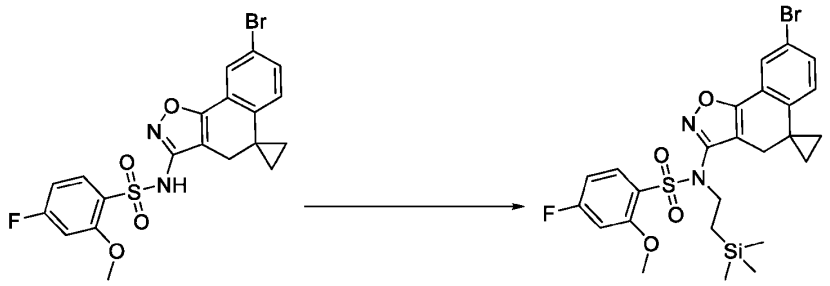
[0405] Step 1. Synthesis of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-fluoro-2-methoxybenzenesulfonamide



[0406] A mixture of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (500.0 mg, 1.72 mmol, 1.00 equiv, Intermediate C) and 4-fluoro-2-methoxybenzenesulfonyl chloride (1.2 g, 5.16 mmol, 3.00 equiv) in pyridine (10.0 mL) was stirred at 80 °C for 2 h. The resulting mixture was concentrated under vacuum. The residue

was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-fluoro-2-methoxybenzenesulfonamide (450.0 mg, 55% yield) as a green solid. MS (ESI, *m/z*): 479, 481 [M+H]+.

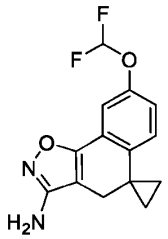
[0407] Step 2. Synthesis of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-fluoro-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide



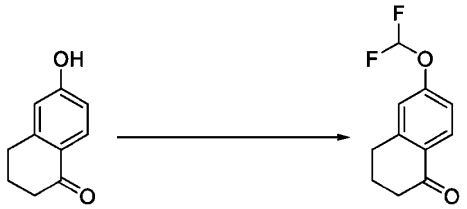
[0408] To a stirred mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-fluoro-2-methoxybenzenesulfonamide (460.0 mg, 0.96 mmol, 1.00 equiv), 2-(trimethylsilyl)ethan-1-ol (453.0 mg, 3.84 mmol, 4.00 equiv) and PPh3 (1.0 g, 3.84 mmol, 4.00 equiv) in THF (10.0 mL) at 0 °C was added DIAD (776.0 mg, 3.84 mmol, 4.00 equiv). The resulting mixture was stirred at ambient temperature for 1 h and then diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-fluoro-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (460.0 mg, 83% yield) as blue oil. MS (ESI, *m/z*): 579, 581 [M+H]+.

Intermediate I

8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine

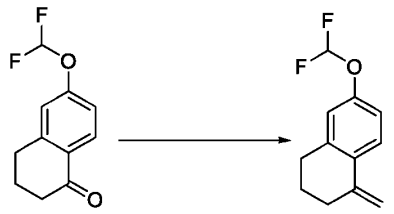


[0409] Step 1. Synthesis of 6-(difluoromethoxy)-3,4-dihydronaphthalen-1(2H)-one



[0410] A mixture of 6-hydroxy-3,4-dihydronaphthalen-1(2H)-one (25.0 g, 154.32 mol, 1.00 equiv), sodium 2-chloro-2,2-difluoroacetate (25.8 g, 169.75 mmol, 1.10 equiv), Bu_4NI (56.9 g, 154.32 mmol, 1.00 equiv), KI (25.6 g, 154.32 mmol, 1.00 equiv) and Cs_2CO_3 (100.6 g, 308.64 mmol, 2.00 equiv) in DMF (250.0 mL) was stirred at 100 °C for 2 h and then filtered through a pad of celite. The filtrate was diluted with brine and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford 6-(difluoromethoxy)-3,4-dihydronaphthalen-1(2H)-one (12.7 g, 38% yield) as yellow oil. MS (ESI, *m/z*): 213 [M+H]+.

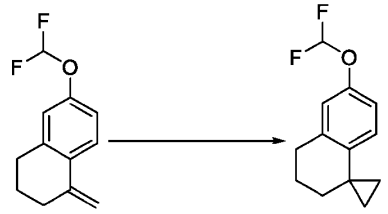
[0411] Step 2. Synthesis of 6-(difluoromethoxy)-1-methylene-1,2,3,4-tetrahydronaphthalene



[0412] To a stirred solution of bromo(methyl)triphenyl-lambda5-phosphane (200.2 g, 560.37 mmol, 1.20 equiv) in THF (2.0 L) at 0 °C were added t-BuOK (78.45 g, 700.47 mmol, 1.50 equiv) in portions under N_2 atmosphere. The resulting mixture was stirred at this

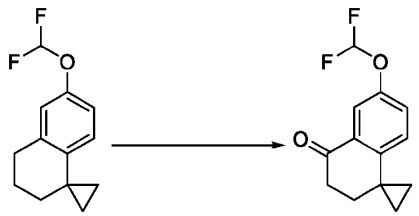
temperature for another 2 h and to this was added 6-(difluoromethoxy)-3,4-dihydronaphthalen-1(2H)-one (99.0 g, 466.98 mmol, 1.00 equiv). The resulting mixture was stirred at ambient temperature for 16 h and then quenched at 0 °C with saturated NH4Cl solution and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% DCM in petroleum ether) to afford 6-(difluoromethoxy)-1-methylene-1,2,3,4-tetrahydronaphthalene (66.0 g, 67% yield) as colorless oil. MS (ESI, *m/z*): 211 [M+H]+.

[0413] Step 3. Synthesis of 6'-(difluoromethoxy)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]



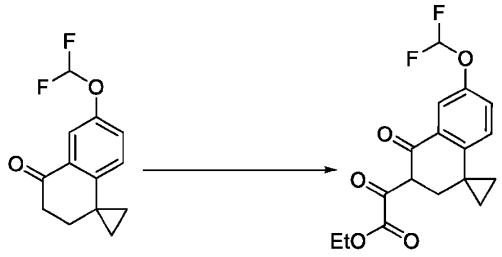
[0414] To a stirred solution of $ZnEt_2$ (142.8 mL, 142.85 mmol, 1.50 equiv, 1.0 M in hexane) in DCM (250.0 mL) at 0 °C was added dropwise TFA (16.3 g, 142.85 mmol, 1.50 equiv) over 0.5 h under N_2 atmosphere. The resulting mixture was stirred at this temperature for another 0.5 h and then to this was added dropwise CH_2I_2 (38.3 g, 142.85 mmol, 1.50 equiv) over 0.5 h. The resulting mixture was stirred for another 1 h and to this at 0 °C was added 6-(difluoromethoxy)-1-methylene-1,2,3,4-tetrahydronaphthalene (20.0 g, 95.23 mmol, 1.00 equiv) in portions. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 1 h. The reaction mixture was quenched at 0 °C with saturated NH4Cl solution and then extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford 6'-(difluoromethoxy)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene] (20.2 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 225 [M+H]+.

[0415] Step 4. Synthesis of 6'-(difluoromethoxy)-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one



[0416] To a stirred mixture of 6'-(difluoromethoxy)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene] (24.0 g, 107.14 mmol, 1.00 equiv) and $MgSO_4$ (15.4 g, 128.57 mmol, 1.20 equiv) in acetone (360.0 mL) and H_2O (240.0 mL) at 0 °C was added $KMnO_4$ (33.8 g, 214.28 mmol, 2.00 equiv) in portions. The resulting mixture was allowed to warm up to ambient temperature and for another 16 h. The resulting mixture was filtered through a pad of celite. The filtrate was diluted with EtOAc. The organic solution was washed with $Na_2S_2O_3$ solution three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford 6'-(difluoromethoxy)-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (13.9 g, 54% yield) as a yellow solid. MS (ESI, *m/z*): 239 [M+H]+.

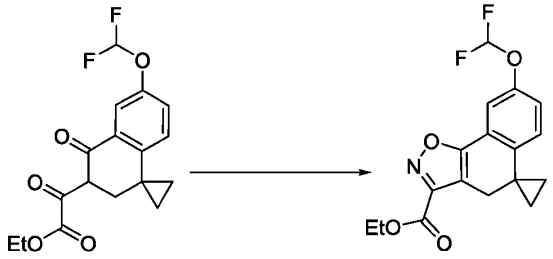
[0417] Step 5. Synthesis of ethyl 2-(6'-(difluoromethoxy)-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate



[0418] To a stirred solution of 6'-(difluoromethoxy)-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (25.0 g, 105.04 mmol, 1.00 equiv) and ethyl oxalate (23.0 g, 157.56 mmol, 1.50 equiv) in THF (500.0 mL) at 0 °C was added t-BuOLi (12.6 g, 157.56 mmol, 1.50 equiv) in portions under N_2 atmosphere. The resulting mixture was stirred at this temperature for another 1 h and then quenched with aqueous HCl (1.0 M aq) solution and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford ethyl 2-(6'-(difluoromethoxy)-4'-oxo-3',4'-dihydro-2'H-

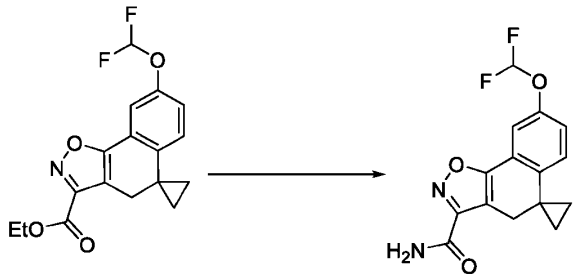
spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (40.7 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 339 [M+H]+.

[0419] Step 6. Synthesis of ethyl 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate



[0420] A mixture of ethyl 2-(6'-(difluoromethoxy)-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (28.0 g, 82.84 mmol, 1.00 equiv) and $NH_2OH.HCl$ (6.3 g, 91.12 mmol, 1.10 equiv) in EtOH (280.0 mL) was stirred at 80 °C for 2 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford ethyl 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (25.1 g, 90% yield) as yellow oil. MS (ESI, *m/z*): 336 [M+H]+.

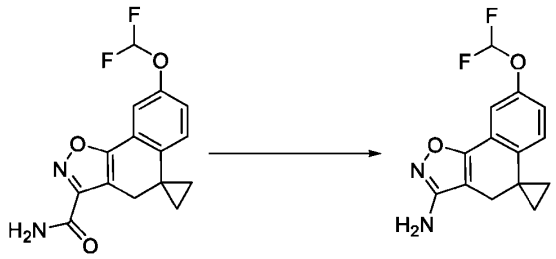
[0421] Step 7. Synthesis of 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide



[0422] A solution of ethyl 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (25.0 g, 246.27 mmol, 1.00 equiv) and $NH_3.H_2O$ (250.0 mL) in THF (250.0 mL) and MeOH (250.0 mL) was stirred at ambient temperature for 1 h. The resulting mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford 8'-

(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (22.1 g, crude) as a yellow solid, which was used for the next step without further purification. MS (ESI, *m/z*): 307 [M+H]+.

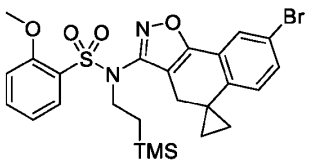
[0423] Step 8. Synthesis of 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (Intermediate I)



[0424] To a stirred solution of 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (5.0 g, 16.33 mmol, 1.00 equiv) and TEA (4.9 g, 49.01 mmol, 3.00 equiv) in EtOAc (50.0 mL), acetonitrile (50.0 mL) and H_2O (25.0 mL) at 0 °C was added $PhI(OAc)_2$ (7.8 g, 24.49 mmol, 1.50 equiv) under N_2 atmosphere. The resulting mixture was stirred at ambient temperature for 1 h and then filtered through a pad of celite. The filtrate was diluted with EtOAc. The organic layer was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (604.1 mg, 13% yield) as a brown solid. ^1H NMR (300 MHz, DMSO-d_6) δ 7.34-7.24 (m, 1H), 7.13-7.01 (m, 3H), 5.72 (s, 2H), 2.55 (s, 2H), 1.08-0.98 (m, 2H), 0.98-0.81 (m, 2H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -82.18. MS (ESI, *m/z*): 279 [M+H]+.

Intermediate J

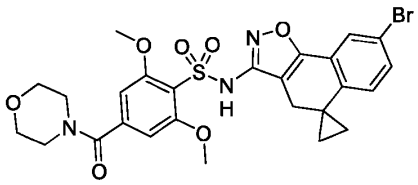
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide



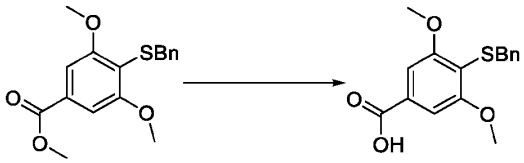
[0425] To a stirred solution of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (2.4 g, 5.20 mmol, 1.00 equiv), 2-(trimethylsilyl)ethan-1-ol (1.2 g, 10.40 mmol, 2.00 equiv) and PPh_3 (5.5 g, 20.81 mmol, 4.00 equiv) in THF (24.0 mL) at 0 °C was added dropwise a solution of DIAD (4.2 g, 20.81 mmol, 4.00 equiv) in THF (4.0 mL) over 10 min. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 2 h and then diluted with EtOAc. The resulting mixture was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~50% EtOAc in petroleum ether) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (2.7 g, 93% yield) as orange oil. MS (ESI, *m/z*): 561, 563 [M+H]+.

Intermediate K

N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonamide

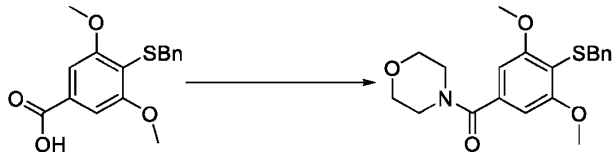


[0426] Step 1. Synthesis of 4-(benzylthio)-3,5-dimethoxybenzoic acid



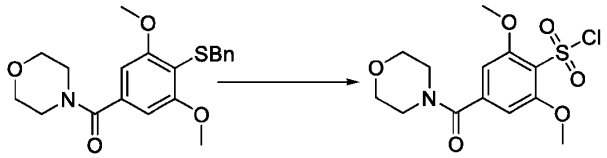
[0427] To a stirred solution of methyl 4-(benzylthio)-3,5-dimethoxybenzoate (5.00 g, 15.70 mmol, 1.00 equiv, Intermediate E Step 1) in MeOH (40 mL) and THF (40 mL) at ambient temperature was added a solution of LiOH (1.13 g, 47.2 mmol, 3.00 equiv) in H_2O (10 mL). The resulting mixture was stirred at this temperature for another 16 h and then acidified with HCl (1.0 M aq) to pH ~6 and extracted with DCM three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford 4-(benzylthio)-3,5-dimethoxybenzoic acid (5.10 g, 90% yield) as a yellow solid, which was used for the next step without further purification. MS (ESI, *m/z*): 305 [M+H]+.

[0428] Step 2. Synthesis of (4-(benzylthio)-3,5-dimethoxyphenyl)(morpholino)methanone



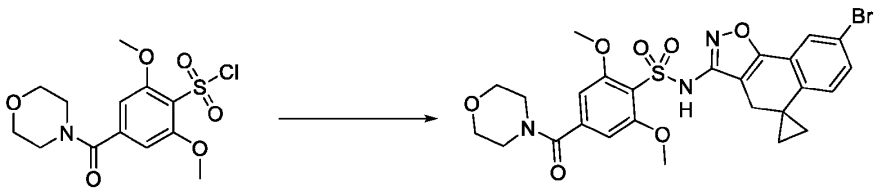
[0429] To a stirred mixture of 4-(benzylthio)-3,5-dimethoxybenzoic acid (5.10 g, 18.72 mmol, 1.00 equiv), morpholine (1.79 g, 20.60 mmol, 1.10 equiv) and DIEA (9.68 g, 74.89 mmol, 4.00 equiv) in DMF (60 mL) at 0 °C was added HATU (8.55 g, 22.48 mmol, 1.20 equiv) in portions. The resulting mixture was allowed to warm up to ambient temperature and stirred at this temperature for another 1 h. The resulting mixture was diluted with EtOAc and then washed with brine three times. The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-30% EtOAc in DCM) to afford (4-(benzylthio)-3,5-dimethoxyphenyl)(morpholino)methanone (5.10 g, 86% yield) as a white solid. MS (ESI, *m/z*): 374 [M+H]+.

[0430] Step 3. Synthesis of 2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonyl chloride



[0431] To a stirred solution of 4-[4-(benzylsulfanyl)-3,5-dimethoxybenzoyl]morpholine (5.10 g, 13.65 mmol, 1.00 equiv) in acetonitrile (50 mL), AcOH (2 mL) and H_2O (1 mL) at 0 °C was added DCDMH (3.77 g, 19.11 mmol, 1.40 equiv) in portions. The resulting mixture was stirred at this temperature for another 1 h and then diluted with EtOAc. The resulting mixture was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-30% EtOAc in DCM) to afford 2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonyl chloride (3.30 g, 69% yield) as a white solid. MS (ESI, *m/z*): 350 [M+H]+.

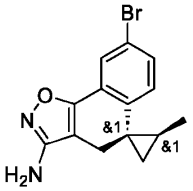
[0432] Step 4. Synthesis of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonamide



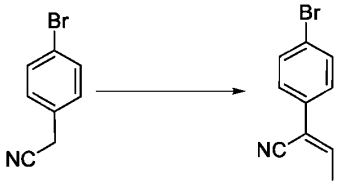
[0433] A mixture of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (1 g, 3.435 mmol, 1.00 equiv, Intermediate C) and 2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonyl chloride (1.68 g, 4.809 mmol, 1.40 equiv) in pyridine (15 mL) was stirred at 80 °C for 2 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-10% methanol in DCM) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonamide (2 g, 96% yield) as a white solid. MS (ESI, *m/z*): 604, 606 [M+H]+.

Intermediate L

Rac-(*cis*)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine



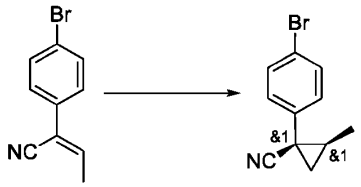
[0434] Step 1. (Z)-2-(4-bromophenyl)but-2-enenitrile



[0435] To a stirred solution of 2-(4-bromophenyl)acetonitrile (100.0 g, 512.82 mmol, 1.00 equiv) and K_2CO_3 (142.0 g, 1025.64 mmol, 2.00 equiv) in MeOH (1000.0 mL) at 0 °C was added acetaldehyde (68.0 g, 1538.46 mmol, 3.00 equiv). The resulting mixture was stirred at this temperature for 2 h. Color change was observed from colorless to light yellow. The resulting mixture was quenched with NH_4Cl solution and then extracted with EtOAc 3 times.

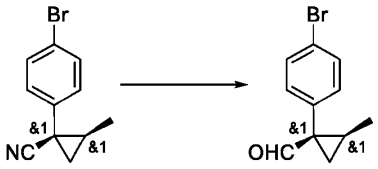
The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with other 3 batches (same scale) and then purified by re-crystallization from acetonitrile in H_2O (~1 : 10) at 0 °C and dried under vacuum at 30 - 40 °C for 0.5 h to afford (Z)-2-(4-bromophenyl)but-2-enenitrile (310 g, 68%) as a yellow solid. MS (ESI, *m/z*): 222, 224 $(M + H)^+$.

[0436] Step 2. (*cis*)-1-(4-bromophenyl)-2-methylcyclopropane-1-carbonitrile



[0437] To a stirred solution of trimethylsulfoxonium iodide (100.0 g, 452.48 mmol, 2.00 equiv) in DMSO (500.0 mL) at 0 °C was added tBuOK (1M in THF, 452.0 mL, 452.48 mmol, 2.00 equiv). The resulting mixture was stirred at 0 °C for 0.5 h and to this was added (Z)-2-(4-bromophenyl)but-2-enenitrile (50.0 g, 226.24 mmol, 1.00 equiv). The resulting mixture was stirred at ambient temperature for 16 h. Color change was observed from yellow to brown. The resulting mixture was quenched with NH_4Cl solution and combined with other 6 batches (same scale) and extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0 ~ 60% EtOAc in petroleum ether) to afford (cis)-1-(4-bromophenyl)-2-methylcyclopropane-1-carbonitrile (210 g, 65%) as yellow oil. MS (ESI, *m/z*): 236, 238 $(M + H)^+$.

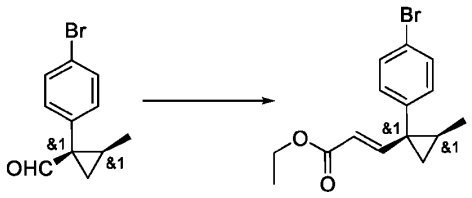
[0438] Step 3. (*cis*)-1-(4-bromophenyl)-2-methylcyclopropane-1-carbaldehyde



[0439] To a stirred solution of 1-(4-bromophenyl)-2-methylcyclopropane-1-carbonitrile (40.0 g, 170.21 mmol, 1.00 equiv) in THF (400.0 mL) at 0 °C was added dropwise DIBAL-H (1.0 M in hexanes, 221.0 mL, 221.27 mmol, 1.30 equiv) over 30 min under N_2 atmosphere. The resulting mixture was allowed to warm up to ambient temperature and stirred for another

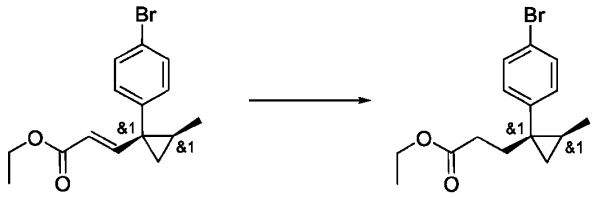
2 h. Color change was observed from yellow to colorless. The mixture was quenched slowly with HCl (1M, 340.0 mL, 2 eq.) for 0.5 h with vigorous gas releasing and then diluted with EtOAc. The mixture was filtered and the filter cake was rinsed with EtOAc. The combined filtrate was extracted with EtOAc 3 times and then combined with another 5 batches (same scale). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford (*cis*)-1-(4-bromophenyl)-2-methylcyclopropane-1-carbaldehyde (170 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 239, 241 $(M + H)^+$.

[0440] Step 4. ethyl (E)-3-((*cis*)-1-(4-bromophenyl)-2-methylcyclopropyl)acrylate



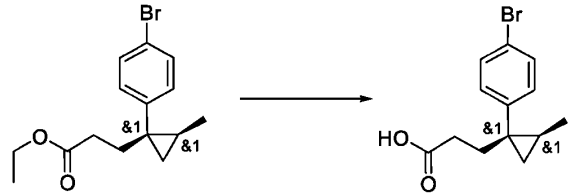
[0441] A mixture of (cis)-1-(4-bromophenyl)-2-methylcyclopropane-1-carbaldehyde (57.0 g, 239.0 mmol, 1 equiv) and ethyl (triphenylphosphoranylidene)acetate (87.0 g, 251.0 mmol, 1.05 equiv) in DCE (570.0 mL) was stirred at 50 °C for 2 h. Color change was observed from light yellow to yellow. The resulting mixture was concentrated under vacuum. The residue was slowly added to heptane (500 mL) at 0 °C. The mixture was stirred at this temperature for 30 mins and filtered. The filtrate was combined with another 2 batches (same scale) and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0 ~ 30% DCM in petroleum ether) to afford ethyl (E)-3-((*cis*)-1-(4-bromophenyl)-2-methylcyclopropyl)-acrylate (153.0 g, 69%, purity 70%) as colorless oil. MS (ESI, m/z): 309, 310 $(M + H)^+$.

[0442] Step 5. ethyl 3-((*cis*)-1-(4-bromophenyl)-2-methylcyclopropyl)propanoate



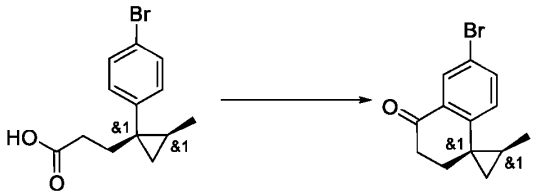
[0443] A mixture of ethyl (E)-3-((*cis*)-1-(4-bromophenyl)-2-methylcyclopropyl)acrylate (50 g, 170.06 mmol, 1 equiv) and Rh-C (10.0 g, 5% Rh/C, 20% w/w) in THF (250 mL) and 2-methylpropan-2-ol (250 mL) was stirred at ambient temperature for 24 h under H_2 (~15 atm) atmosphere and filtered. The filtrate was combined with other 2 batches (same scale) and then concentrated under vacuum to afford ethyl 3-((*cis*)-1-(4-bromophenyl)-2-methylcyclopropyl)propanoate (145.0 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, m/z): 297, 299 (M + H)+ .

[0444] Step 6. 3-((*cis*)-1-(4-bromophenyl)-2-methylcyclopropyl)propanoic acid



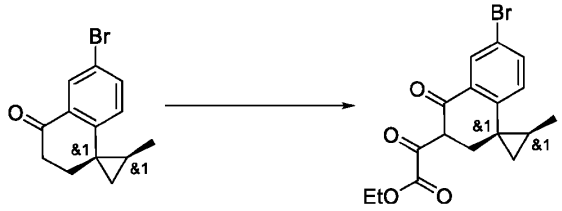
[0445] To a stirred solution of ethyl 3-((*cis*)-1-(4-bromophenyl)-2-methylcyclopropyl)propanoate (49.0 g, 158.06 mmol, 1.00 equiv) in methanol (250.0 mL) at 0 °C was added a solution of NaOH (13.0 g, 316.12 mmol, 2.00 equiv) in H_2O (42.0 mL). The resulting mixture was stirred at ambient temperature for 2 h. Color change was observed from light yellow to colorless. The mixture was diluted with H_2O (500.0 mL) and washed with petroleum ether 3 times. The aqueous layer was acidified with AcOH (2.5 eq.) and then extracted with EtOAc 3 times. The organic layers were combined with 3 batches (same scale), washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford 3-((*cis*)-1-(4-bromophenyl)-2-methylcyclopropyl)propanoic acid (96.0 g, crude) as a white solid, which was used for the next step without further purification. MS (ESI, *m/z*): 283, 285 $(M + H)^+$

[0446] Step 7. (*cis*)-6'-bromo-2-methyl-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one



[0447] To a stirred solution of 3-((*cis*)-1-(4-bromophenyl)-2-methylcyclopropyl)propanoic acid (15.0 g, 53.19 mmol, 1.00 equiv) and DMF (194.0 mg, 2.66 mmol, 0.05 equiv) in DCM (150.0 mL) at 0 °C was added dropwise oxalyl chloride (13.0 g, 106.38 mmol, 2.00 equiv) over 2 min. The resulting mixture was stirred at ambient temperature for another 2 h. Color change was observed from yellow to dark brown. The mixture was concentrated under vacuum and the residue was re-dissolved in DCM (150.0 mL). To this at 0 °C was added $AlCl_3$ (3.77 g, 28.37 mmol, 0.8 equiv (calculated from carboxylic acid precursor)) under N_2 atmosphere. The resulting dark brown mixture was stirred at this temperature for 2 h and then combined with another 5 batches (same scale). The mixture was slowly poured into ice/water. The resulting mixture was extracted with DCM 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford (*cis*)-6'-bromo-2-methyl-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (54 g, 64%) as an off-white solid. MS (ESI, *m/z*): 265, 267 $(M + H)^+$.

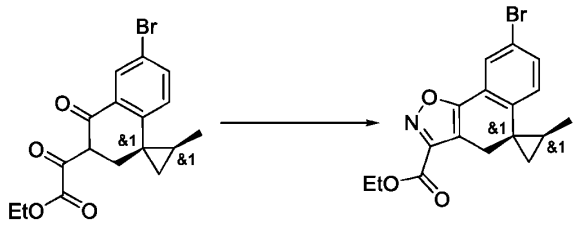
[0448] Step 8. ethyl 2-((*cis*)-6'-bromo-2-methyl-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate



[0449] To a stirred solution of (*cis*)-6'-bromo-2-methyl-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (27.0 g, 74.17 mmol, 1.00 equiv) in THF (270.0 mL) at 0 °C was added t-BuOLi (10.0 g, 126.10 mmol, 1.70 equiv). The resulting mixture was stirred at this temperature for 10 min and to this was added dropwise a solution of diethyl oxalate (16.0 g, 111.26 mmol, 1.50 equiv) over 2 min. The resulting yellow solution was allowed to warm up to ambient temperature and stirred for another 2 h. The reaction mixture was then quenched with water and combined with another batch (same scale) and extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford ethyl 2-((*cis*)-6'-bromo-2-methyl-4'-oxo-3',4'-dihydro-2'H-

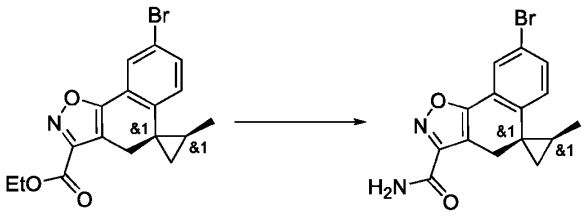
spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (76 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 365, 367 $(M + H)^+$.

[0450] Step 9. ethyl (*cis*)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate



[0451] A mixture of ethyl 2-((*cis*)-6'-bromo-2-methyl-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (38.0 g, 104.40 mmol, 1.00 equiv) and hydroxylamine hydrochloride (9.0 g, 125.27 mmol, 1.20 equiv) in EtOH (380.0 mL) was stirred at 80 °C for 2 h and allowed to cool down to ambient temperature. To the resulting yellow solution was added water (10 V). The mixture was stirred for further 0.5 h and allowed to stand for 0.5 h with yellow oil formed. Solvent was spilled out. The crude material was collected and combined with another batch (same scale) and co-evaporated with acetonitrile to afford ethyl (*cis*)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (83.0 g, crude) as a yellow solid, which was used for the next step without further purification. MS (ESI, *m/z*): 362, 364 $(M + H)^+$.

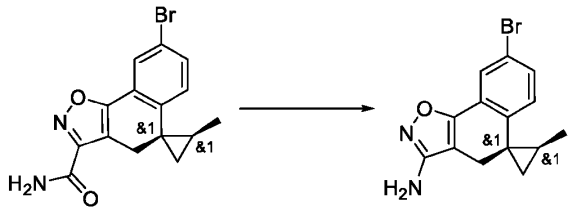
[0452] Step 10. (*cis*)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide



[0453] To a stirred solution of ethyl (*cis*)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (42.0 g, 116.34 mmol, 1.00 equiv) in methanol (210.0 mL) at 0 °C was added ammonia (7.0 M in methanol, 210.0 mL). The resulting brown

mixture was allowed to warm up to ambient temperature and stirred for 16 h. The resulting mixture was combined with another batch (same scale) and concentrated under vacuum to half volume with massive solid precipitated. The solid was collected by filtration and rinsed with methanol to afford (*cis*)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (58 g, crude) as a white solid, which was used for the next step without further purification. MS (ESI, *m/z*): 333, 335 $(M + H)^+$.

[0454] Step 11. Rac-(*cis*)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine

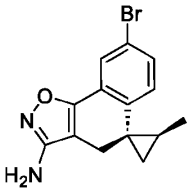


[0455] (*cis*)-8'-Bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (14.0 g, 42.17 mmol, 1.00 equiv), and 1-methyl-1H-imidazole (14.0 g, 168.68 mmol, 4.00 equiv) at ambient temperature was dissolved in NMP (150.0 mL), ethyl acetate (75.0 mL) and H_2O (75.0 mL) to prepare solution A. $PdI(OAc)_2$ (27.0 g, 84.34 mmol, 2.00 equiv) at ambient temperature was dissolved in NMP (200.0 mL) and EtOAc (100.0 mL) to prepare solution B. The solution A and B was pumped individually to a plastic tubing (~ 30 meters) for 10 h with peristaltic pumps. The resulting mixture was collected and then quenched with $Na_2S_2O_3$ solution. The resulting mixture was combined with other 3 batches (same scale) and extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0 ~ 30% EtOAc in petroleum ether) to afford (*cis*)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (34.0 g, 65%) as a white solid. ^1H NMR (300 MHz, DMSO-*d6*) δ 7.56 (d, $J = 2.1$ Hz, 1H), 7.49-7.41 (m, 1H), 6.97 (d, $J = 8.4$ Hz, 1H), 5.77 (s, 2H), 2.73-2.55 (m, 2H), 1.27-1.12 (m, 5H), 0.58-0.49 (m, 1H). MS (ESI, *m/z*): 305, 307 $(M + H)^+$.

Intermediate M

(1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-

amine



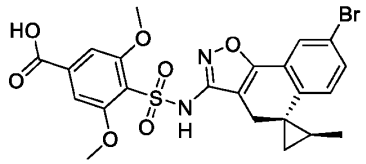
[0456] Rac-(*cis*)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (1.0 g, 3.29 mmol, 1.00 equiv, Intermediate L) was resolved with Prep-SFC.

[0457] (1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (0.50 g, 50%) as a yellow solid, the first elution peak from Prep-SFC. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.55 (d, *J* = 2.2 Hz, 1H), 7.45-7.43 (m, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 5.77 (s, 2H), 2.71-2.55 (m, 2H), 1.25-1.09 (m, 5H), 0.59-0.49 (m, 1H). MS (ESI, *m/z*): 305, 307 $(M + H)^+$.

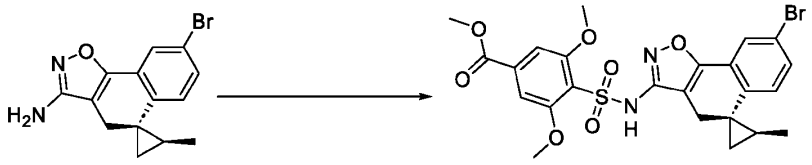
[0458] The absolute stereochemistry of Intermediate M was determined by crystallography based on the co-crystal structure of selected compounds disclosed herein with KAT7 enzyme, where the compounds were prepared using Intermediate M.

Intermediate N

4-(N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoic acid



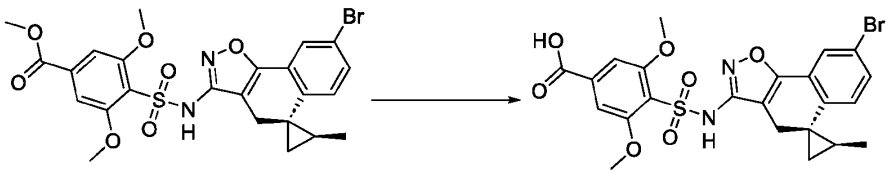
[0459] Step 1. methyl 4-(N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoate



[0460] A solution of (1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (1.0 g, 3.28 mmol, 1.00 equiv, Intermediate M) and methyl 4-

(chlorosulfonyl)-3,5-dimethoxybenzoate (1.3 g, 4.26 mmol, 1.30 equiv) in pyridine (10.0 mL) was stirred at 80 °C for 2 h. The resulting mixture was combined with another 4 batches (1 g x 3 + 0.2 g) and then concentrated under vacuum. The residue was re-disolved in acetonitrile. The organic solution was added dropwise into a stirred NH4Cl solution and the resulting mixture was stirred for another 30 mins. The precipitated solid was collected by filtration and purified by trituration with water and dried under vacuum to afford methyl 4-(N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoate (9.2 g, crude) as a yellow solid, which was used for the next step without further purification. MS (ESI, m/z): 563.1 (M + H)+.

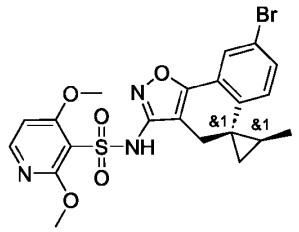
[0461] Step 2. 4-(N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoic acid



[0462] To a stirred solution of methyl 4-(N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoate (8.7 g, 15.44 mmol, 1.00 equiv) in methanol (72.0 mL) and THF (72.0 mL) at 0 °C was added a solution of LiOH (1.1 g, 46.32 mmol, 3.00 equiv) in H2O (18.0 mL). The resulting mixture was allowed to warm up to ambient temperature and stirred at this temperature for another 2 h and combined with another batch (0.5 g). The organic volatile was removed by vacuum. The aqueous residue was diluted with water and then acidified with AcOH to pH ~ 5. The precipitated solid was collected by filtration and washed with water 3 times and then dried under vacuum to afford 4-(N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoic acid (8.6 g, crude, Intermediate N) as a yellow solid, which was used for the next step without further purification. MS (ESI, m/z): 549.1 (M + H)+.

Intermediate O

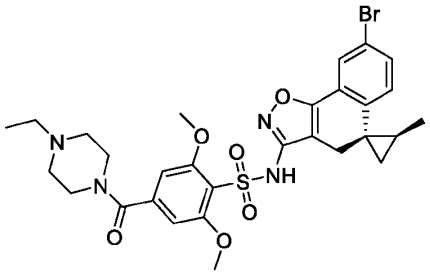
Rac- N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide



[0463] To a stirred solution of rec-*cis*-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (100.0 mg, 0.33 mmol, 1.00 equiv, Intermediate L) in THF (4.0 mL) at -78 °C was added t-BuOK (1.0 M in THF, 1.3 mL, 1.30 mmol, 4.00 equiv). The resulting mixture was stirred at this temperature for 0.5 h and then to this was added dropwise a solution of 2,4-dimethoxypyridine-3-sulfonyl chloride (155.8 mg, 0.66 mmol, 2.00 equiv) in THF (2.0 mL) over 1 min. The resulting mixture was stirred at this temperature for another 1 h and then quenched with NH_4Cl (aq.). The resulting mixture was combined with another 7 batches (same scale) and extracted with EtOAc 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford *cis*-N-(8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (820.0 mg, 61%, Intermediate O) as a yellow solid. MS (ESI, *m/z*): 506, 508 $(M + H)^+$.

Intermediate P

N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(4-ethylpiperazine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide

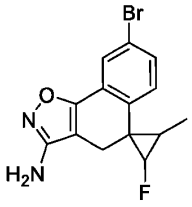


[0464] A mixture of 4-(N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoic acid (1.40 g, 2.55 mmol, 1.00 equiv, Intermediate N), 1-ethylpiperazine (436 mg, 3.82 mmol, 1.50 equiv), HATU

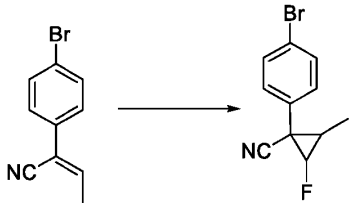
(1.45 g, 3.82 mmol, 1.50 equiv) and DIEA (988 mg, 7.64 mmol, 3.00 equiv) in DMF (10 mL) was stirred at ambient temperature for 2 h and then diluted with EtOAc. The resulting mixture was washed with brine 3 times, dried over Na2SO4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-70% acetonitrile in water) and further purified by flash chromatography on silica gel (0-10% MeOH in DCM) to afford N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(4-ethylpiperazine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide (1.20 g, 72.94%) as a white solid. MS (ESI, m/z): 645.6 (M + H)+.

Intermediate Q

8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine



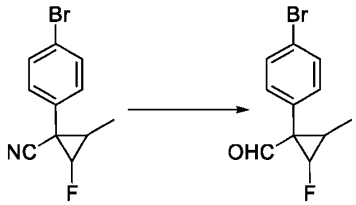
[0465] Step 1. 1-(4-bromophenyl)-2-fluoro-3-methylcyclopropane-1-carbonitrile



[0466] To a stirred solution of 2-(4-bromophenyl)but-2-enenitrile (15.0 g, 67.87 mmol, 1.00 equiv, Intermediate L, Step 1) and (fluoromethyl)(phenyl)(2,3,4,5-tetramethylphenyl)sulfonium tetrafluoroborate (24.2 g, 88.23 mmol, 1.30 equiv) in THF (150.0 mL) at 0 °C was added NaH (60% in mineral oil, 13.5 g, 339.3 mmol, 5.00 equiv) in portions. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 2 h. The reaction mixture was quenched with NH4Cl solution and extracted with EtOAc 3 times. The combined organic layers were washed with brine 3 times, dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography

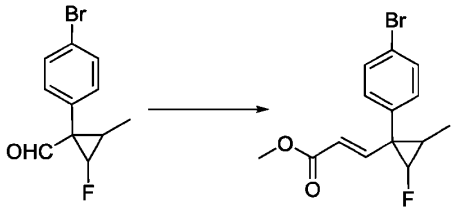
on silica gel (0-50% DCM in petroleum ether) to afford 1-(4-bromophenyl)-2-fluoro-3-methylcyclopropane-1-carbonitrile (4.8 g, 28%) as yellow oil. 1H NMR (300 MHz, DMSO-d6) δ 7.68 – 7.54 (m, 2H), 7.47 – 7.39 (m, 1H), 7.32 – 7.21 (m, 1H), 5.61 – 3.96 (m, 1H), 2.21 – 2.08 (m, 1H), 1.45 – 1.14 (m, 3H). 19F NMR (282 MHz, DMSO-d6) δ -205.49, -214.73.

[0467] Step 2. 1-(4-bromophenyl)-2-fluoro-3-methylcyclopropane-1-carbaldehyde



[0468] To a stirred solution of 1-(4-bromophenyl)-2-fluoro-3-methylcyclopropane-1-carbonitrile (10.0 g, 39.35 mmol, 1.00 equiv) in THF (100.0 mL) at -50 °C was added dropwise DIBAL-H (1.0 M in hexane, 118.1 mL, 118.05 mmol, 3.00 equiv). The resulting mixture was allowed to warm up to ambient temperature and stirred at this temperature for another 1 h. The resulting mixture was quenched with HCl (1.0 M) and filtered through a pad of celite. The filtrate was extracted with EtOAc 3 times. The combined organic layers were washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-28% DCM in petroleum ether) to afford 1-(4-bromophenyl)-2-fluoro-3-methylcyclopropane-1-carbaldehyde (6.3 g, 62%) as yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 – 9.34 (m, 1H), 7.63 – 7.50 (m, 2H), 7.39 – 7.32 (m, 1H), 7.29 – 7.20 (m, 1H), 5.66 – 4.99 (m, 1H), 2.21 – 1.64 (m, 1H), 1.63 – 1.26 (m, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -163.80, -167.00, -204.42.

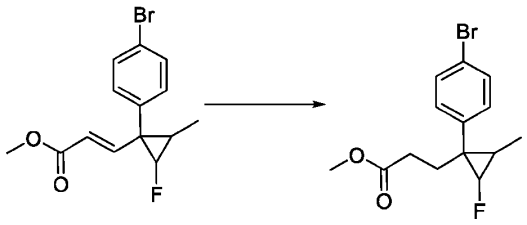
[0469] Step 3. methyl-3-(1-(4-bromophenyl)-2-fluoro-3-methylcyclopropyl)acrylate



[0470] A mixture of methyl 2-(diethoxyphosphoryl)acetate (14.6 g, 80.12 mmol, 2.50 equiv), LiCl (32.0 g, 64.10 mmol, 2.00 equiv) and DBU (9.7 g, 64.10 mmol, 2.00 equiv) in

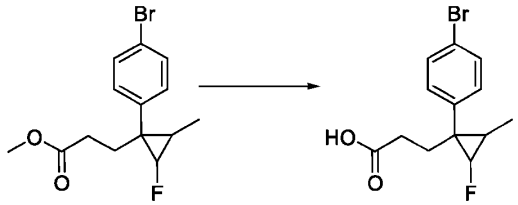
acetonitrile (40.0 mL) was stirred at ambient temperature for 0.5 h under N2 atmosphere and to this was added 1-(4-bromophenyl)-2-fluoro-3-methylcyclopropane-1-carbaldehyde (10.0 g, 32.05 mmol, 1.00 equiv). The resulting mixture was stirred at this temperature for another 2 h and then diluted with EtOAc. The resulting mixture was washed with brine 3 times, dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-28% DCM in petroleum ether) to afford methyl-3-(1-(4-bromophenyl)-2-fluoro-3-methylcyclopropyl)acrylate (6.2 g, 50%) as a yellow solid. MS (ESI, m/z): 313.0 (M + H)+.

[0471] Step 4. methyl 3-(1-(4-bromophenyl)-2-fluoro-3-methylcyclopropyl)propanoate



[0472] To a stirred solution of methyl-3-(1-(4-bromophenyl)-2-fluoro-3-methylcyclopropyl)acrylate (5.0 g, 16.02 mmol, 1.00 equiv) and $TsNHNH_2$ (28.2 g, 160.20 mmol, 10.00 equiv) in DME (25.0 mL) at ambient temperature was added a solution of NaOAc (12.4 g, 160.20 mmol, 10.00 equiv) in H_2O (25.0 mL). The resulting mixture was stirred at 90 °C for 2 h and then extracted with DCM 3 times. The combined organic layers were washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-40% DCM in petroleum ether) to afford methyl 3-(1-(4-bromophenyl)-2-fluoro-3-methylcyclopropyl)propanoate (3.8 g, 75%) as yellow oil. MS (ESI, *m/z*): 315.1 $(M + H)^+$.

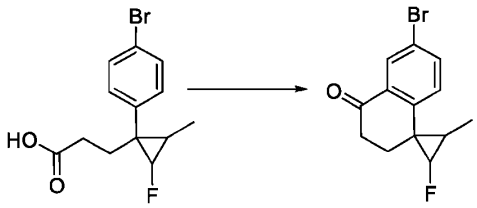
[0473] Step 5. 3-(1-(4-bromophenyl)-2-fluoro-3-methylcyclopropyl)propanoic acid



[0474] To a stirred solution of methyl 3-(1-(4-bromophenyl)-2-fluoro-3-methylcyclopropyl)propanoate (6.0 g, 19.10 mmol, 1.00 equiv) in methanol (36.0 mL) at 0 °C

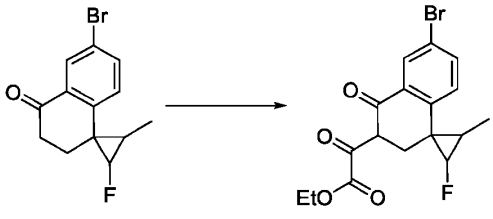
was added a solution of NaOH (1.6 g, 42.03 mmol, 2.20 equiv) in H_2O (6.0 mL). The resulting mixture was stirred at ambient temperature for 2 h and then acidified at 0 °C with AcOH to pH ~ 5 and extracted with EtOAc 3 times. The combined organic layers were washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum The residue was purified by flash chromatography on silica gel (0-50% DCM in petroleum ether) to afford 3-(1-(4-bromophenyl)-2-fluoro-3-methylcyclopropyl)propanoic acid (4.7 g, 82%) as light yellow oil. MS (ESI, *m/z*): 298.9 $(M - H)^-$.

[0475] Step 6. 6'-bromo-2-fluoro-3-methyl-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one



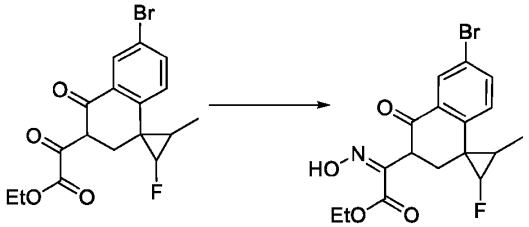
[0476] To a stirred solution of 3-(1-(4-bromophenyl)-2-fluoro-3-methylcyclopropyl)propanoic acid (5.0 g, 16.66 mmol, 1.00 equiv) in DCM (33.0 mL) at 0 °C was added dropwise $ClSO_3H$ (5.8 g, 50.00mmol, 3.00 equiv). The resulting mixture was stirred at ambient temperature for another 2 h. The reaction mixture was quenched at 0 °C with $NaHCO_3$ solution and extracted with DCM 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-45% DCM in petroleum ether) to afford 6'-bromo-2-fluoro-3-methyl-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (2.7 g, 58%) as a white solid. MS (ESI, *m/z*): 282.9 $(M + H)^+$.

[0477] Step 7. ethyl 2-(6'-bromo-2-fluoro-3-methyl-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate



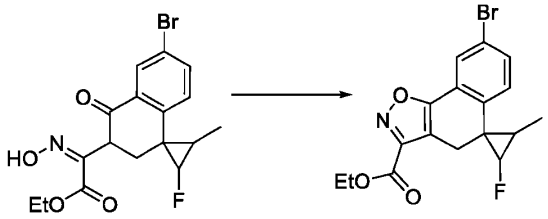
[0478] To a stirred solution of 6'-bromo-2-fluoro-3-methyl-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (3.0 g, 10.63 mmol, 1.00 equiv) and diethyl oxalate (2.3 g, 15.95 mmol, 1.50 equiv) in THF (30.0 mL) at 0 °C was added t-BuOLi (1.2 g, 15.95 mmol, 1.50 equiv). The resulting mixture was stirred at ambient temperature for 2 h and then quenched with a saturated aqueous solution of NH_4Cl. The resulting mixture was extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford ethyl 2-(6'-bromo-2-fluoro-3-methyl-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (4.5 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 383.0 $(M + H)^+$.

[0479] Step 8. ethyl-2-(6'-bromo-2-fluoro-3-methyl-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-(hydroxyimino)acetate



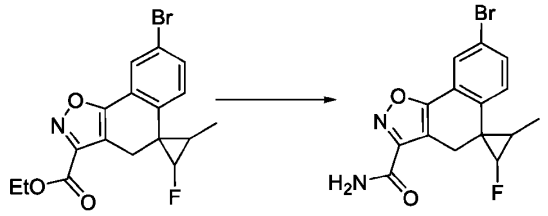
[0480] A mixture of ethyl 2-(6'-bromo-2-fluoro-3-methyl-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (7.0 g, 18.32 mmol, 1.00 equiv) and NH2OH.HCl (1.3 g, 20.15 mmol, 1.10 equiv) in EtOH (70.0 mL) was stirred at 80 oC for 2 h. The resulting mixture was diluted with water and then extracted with EtOAc 3 times. The combined organic layers were dried over Na2SO4 and concentrated under vacuum to afford ethyl-2-(6'-bromo-2-fluoro-3-methyl-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-(hydroxyimino)acetate (7.7 g, crude) as a yellow solid, which was used for the next step without further purification. MS (ESI, m/z): 398.2 (M + H)+.

[0481] Step 9. ethyl 8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate



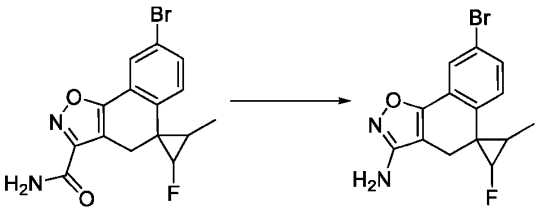
[0482] To a stirred solution of ethyl-2-(6'-bromo-2-fluoro-3-methyl-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-(hydroxyimino)acetate (5.0 g, 12.59 mmol, 1.00 equiv) and TEA (2.5 g, 25.18 mmol, 2.00 equiv) in DCM (40.0 mL) at 0 °C was added dropwise a solution of Ms_2O (3.2 g, 18.89 mmol, 1.50 equiv) in DCM (10.0 mL). The resulting mixture was stirred at ambient temperature for 2 h and then diluted DCM. The resulting mixture was washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-40% DCM in petroleum ether) to afford ethyl 8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (2.7 g, 56%) as yellow oil. MS (ESI, *m/z*): 380.1 $(M + H)^+$.

[0483] Step 10. 8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide



[0484] To a stirred solution of ethyl 8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (4.0 g, 10.55 mmol, 1.00 equiv) in methanol (40.0 mL) at 0 °C was added ammonia (40.0 mL, 7.0 M in methanol). The resulting brown mixture was stirred at ambient temperature for 2 h and then concentrated under vacuum to afford 8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (3.2 g, crude) as a white solid, which was used for the next step without further purification. MS (ESI, *m/z*): 351.0 $(M + H)^+$.

[0485] Step 11. 8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine



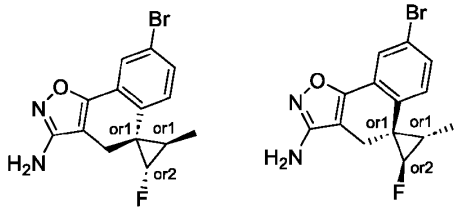
[0486] A mixture of 8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (1.0 g, 2.85 mmol, 1.00 equiv), $PhI(OAc)_2$ (2.7 g, 8.57 mmol, 3.00 equiv) and K_2CO_3 (1.5 g, 11.42 mmol, 4.00 equiv) in NMP (10.0 mL), EtOAc (2.0 mL) and H_2O (2.0 mL) was stirred at ambienttemperature for 2 h. The resulting mixture was quenched with $Na_2S_2O_3$ solution and extracted with EtOAc 3 times. The combined organic layers were washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) and further purified by reverse phase flash chromatography on C18 gel (5-90% acetonitrile in water) to afford 8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (0.3 g, 33.6%) as a white solid. MS (ESI, *m/z*): 323.1 $(M + H)^+$.

Intermediate R

Rel-(1S,2S,3R)-8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine

Intermediate S

Rel-(1R,2R,3S)-8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine



[0487] 8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (2.0 g, 6.21 mmol, 1.00 equiv, Intermediate Q) was resolved with Prep-SFC. The absolute stereochemistry was not determined. (Column: CHIRALPAK-IK, 3*25mm, 5μm; Mobile Phase A: CO_2, Mobile Phase B: IPA; Flow rate: 90 mL/min; Gradient (B%): isocratic

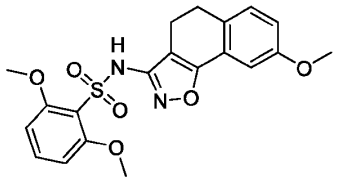
50% B; Wave Length: 220 nm; RT1(min): 3.5; RT2(min): 5.4; Sample Solvent: MEOH; Injection Volume: 4 mL)

[0488] rel-(1S,2S,3R)-8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (0.6 g, 30%) as a white solid (1st peak). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65 (d, J = 2.1 Hz, 1H), 7.56 – 7.47 (m, 1H), 7.28 (d, J = 8.4 Hz, 1H), 5.78 (s, 2H), 4.55 – 4.27 (m, 1H), 2.71 – 2.57 (m, 1H), 2.41 – 2.24 (m, 2H), 1.26 – 1.17 (m, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -208.12. MS (ESI, *m/z*): 323.1 $(M + H)^+$.

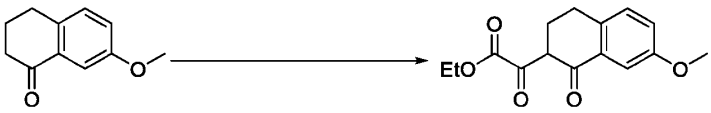
[0489] rel-(1R,2R,3S)-8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (0.6 g, 30%) as a white solid (2nd peak). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65 (d, J = 2.1 Hz, 1H), 7.56 – 7.47 (m, 1H), 7.28 (d, J = 8.4 Hz, 1H), 5.78 (s, 2H), 4.55 – 4.27 (m, 1H), 2.71 – 2.57 (m, 1H), 2.41 – 2.23 (m, 2H), 1.26 – 1.17 (m, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -208.12. MS (ESI, *m/z*): 323.1 $(M + H)^+$.

Example 1

2,6-dimethoxy-N-(8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide



[0490] Step 1. Synthesis of Ethyl 2-(7-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate



[0491] To a stirred mixture of t-BuOLi (2.9 g, 36.89 mmol, 1.30 equiv) in THF (30.0 mL) at 0 °C was added a solution of diethyl oxalate dropwise (5.0 g, 34.05 mmol, 1.20 equiv) in THF (10.0 mL). The resulting mixture was stirred at this temperature for 10 minutes and to this was added a solution of 7-methoxy-3,4-dihydro-2H-naphthalen-1-one dropwise (5.0 g, 28.37 mmol, 1.00 equiv) in THF (10.0 mL). The mixture was stirred at ambient temperature for another 2 h and then quenched with water and extracted with EtOAc three

times. The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford ethyl 2-(7-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate (7.4 g, 83% yield) as brown oil. MS (ESI, *m/z*): 277 $[M+H]^+$.

[0492] Step 2. Synthesis of Ethyl 8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate



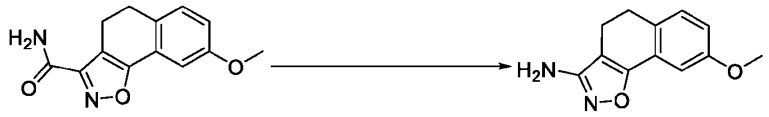
[0493] A mixture of ethyl 2-(7-methoxy-1-oxo-3,4-dihydro-2H-naphthalen-2-yl)-2-oxoacetate (5.7 g, 20.63 mmol, 1.00 equiv) and hydroxylamine hydrochloride (1.4 g, 20.63 mmol, 1.00 equiv) in EtOH (60.0 mL) was stirred at 80 °C for 1 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5--70% acetonitrile in water (contained 0.05% formic acid)) to afford ethyl 8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (6.2 g, 75% yield) as a yellow solid. MS (ESI, *m/z*): 274 $[M+H]^+$.

[0494] Step 3. Synthesis of 8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide



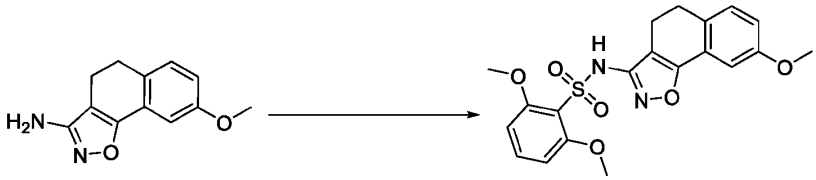
[0495] To a stirred solution of ethyl 8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (4.4 g, 16.10 mmol, 1.00 equiv) in MeOH (40.0 mL) at ambient temperature was added ammonia (28% in water, 40.0 mL). The resulting mixture was stirred at this temperature for 30 minutes and then concentrated under vacuum to afford 8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (4.1 g, crude) as yellow solid, which was used for the next step without further purification. MS (ESI, *m/z*): 245 $[M+H]^+$.

[0496] Step 4. Synthesis of 8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine



[0497] To a stirred solution of 8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (2.0 g, 8.18 mmol, 1.00 equiv) in EtOAc/acetonitrile/H_2O (20.0 mL/20.0 mL/20.0 mL) at ambient temperature was added $PhI(OAc)_2$ (4.7 g, 14.72 mmol, 1.80 equiv). The mixture was stirred at 50 °C for 2 h and then diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford 8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (710.0 mg, 40% yield) as brown solid. MS (ESI, *m/z*): 217 $[M+H]^+$.

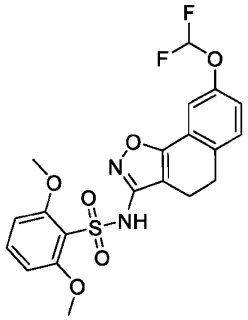
[0498] Step 5. Synthesis of 2,6-dimethoxy-N-(8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide



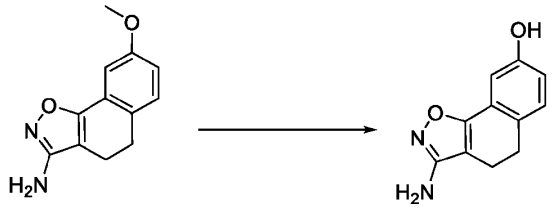
[0499] A mixture of 8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (700.0 mg, 3.24 mmol, 1.00 equiv) and 2,6-dimethoxybenzenesulfonyl chloride (917.8 mg, 3.89 mmol, 1.20 equiv) in pyridine (7.0 mL) was stirred at 80 °C for 2 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5--80% acetonitrile in water (contained 0.05% formic acid)) and further purified by Prep-HPLC (5-70% acetonitrile in water (contained 0.1% formic acid)) to afford 2,6-dimethoxy-N-(8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide (63.9 mg, 5% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (brs, 1H), 7.48 (t, J = 8.4 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 2.8 Hz, 1H), 6.92 (dd, J = 8.4, 2.8 Hz, 1H), 6.76 (d, J = 8.4 Hz, 2H), 3.79 (s, 6H), 3.77 (s, 3H), 2.86 (t, J = 8.0 Hz, 2H), 2.64 (t, J = 8.0 Hz, 2H). MS (ESI, *m/z*): 417 $[M+H]^+$.

Example 2

N-(8-(difluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide

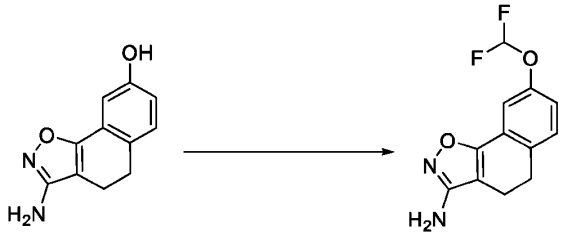


[0500] Step 1. Synthesis of 3-amino-4,5-dihydronaphtho[2,1-d]isoxazol-8-ol



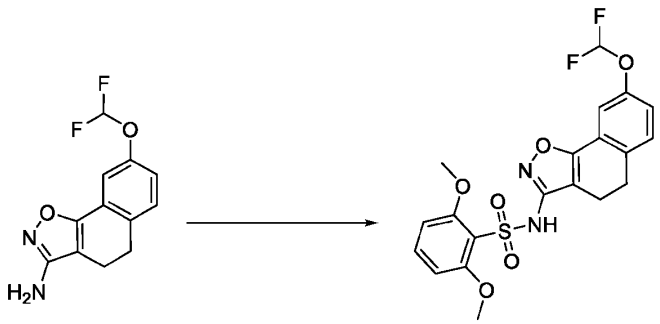
[0501] A solution of 8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (500.0 mg, 2.31 mmol, 1.00 equiv, Example 1, Step 4) and BBr_3 (1 M in DCM, 6.7 mL, 6.7 mmol, 3.0 equiv) in DCM (10.0 mL) was stirred at ambient temperature for 3 h under N_2 atmosphere and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-70%, acetonitrile in water (contained 0.05 % formic acid) to afford 3-amino-4,5-dihydronaphtho[2,1-d]isoxazol-8-ol (300.0 mg, 64% yield) as a white solid. MS (ESI, *m/z*): 203 $[M+H]^+$.

[0502] Step 2. Synthesis of 8-(difluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine



[0503] To a stirred mixture of 3-amino-4,5-dihydronaphtho[2,1-d]isoxazol-8-ol (260.0 mg, 1.29 mmol, 1.00 equiv) and NaOH (149.6 mg, 3.74 mmol, 2.90 equiv) in DMF (5.0 mL) at 0 °C was added dropwise a solution of sodium 2-chloro-2,2-difluoroacetate (294.1 mg, 1.94 mmol, 1.50 equiv) in DMF (2.0 mL) under N_2 atmosphere. The resulting mixture was stirred at 80 °C for 2 h and then diluted with brine and extracted with EtOAc three times. The organic layers were combined and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-85% acetonitrile in water (contained 0.1 % NH_4HCO_3) to afford 8-(difluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (40.0 mg, 12% yield) as a yellow solid. MS (ESI, *m/z*): 253 $[M+H]^+$.

[0504] Step 3. Synthesis of N-(8-(difluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide



[0505] A mixture of 8-(difluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (40.0 mg, 0.16 mmol, 1.00 equiv) and 2,6-dimethoxybenzenesulfonyl chloride (37.5 mg, 0.16 mmol, 1.00 equiv) in pyridine (1.0 mL) was stirred at 80 °C for 2 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5--80% acetonitrile in water (contained 0.05% formic acid)) and Prep-HPLC (5-72% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8-(difluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide (5.0 mg, 7% yield) as a white solid. MS (ESI, *m/z*): 453 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.47 (t, J = 8.4 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 2.8 Hz, 1H), 7.26 (t, J = 74.0 1H), 7.15 (dd, J = 8.4, 2.8 Hz, 1H), 6.75 (d, J = 8.4 Hz, 2H), 3.79 (s, 6H), 2.93 (t, J = 8.0 Hz, 2H), 2.68 (t, J = 8.0 Hz, 2H).

Example 3

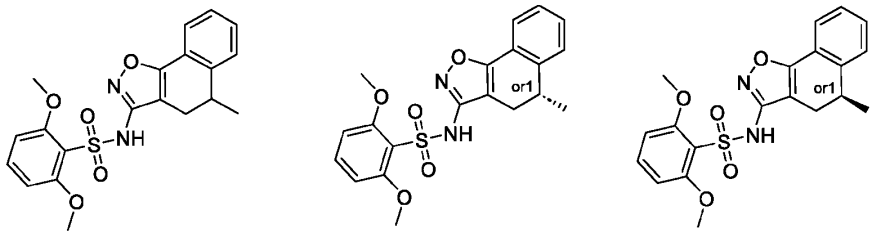
Rac-2,6-dimethoxy-N-(5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide,

Example 7

Rel-(R)-2,6-dimethoxy-N-(5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide and

Example 8

Rel-(S)-2,6-dimethoxy-N-(5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide

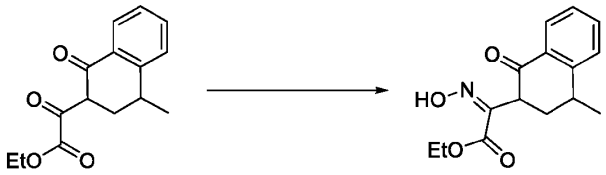


[0506] Step 1. Synthesis of rac-Ethyl 2-(4-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate



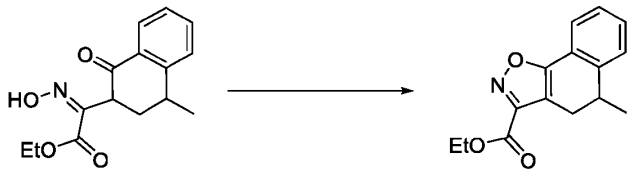
[0507] To a stirred mixture of t-BuOLi (3.25 g, 40.57 mmol, 1.30 equiv) in THF (30 mL) at 0 °C was added dropwise a solution of diethyl oxalate (5.47 g, 37.45 mmol, 1.20 equiv) in THF (10 mL). The resulting mixture was stirred at 0 °C for 10 minutes. To this was added dropwise a solution of 4-methyl-3,4-dihydro-2H-naphthalen-1-one (5 g, 31.20 mmol, 1 equiv) in THF (10 mL). The mixture was stirred at ambient temperature for 2 h and then quenched with water. The resulting mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford rac-ethyl 2-(4-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate (9.8 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 261 $[M+H]^+$.

[0508] Step 2. Synthesis of rac-Ethyl (2Z)-2-(N-hydroxyimino)-2-(4-methyl-1-oxo-3,4-dihydro-2H-naphthalen-2-yl) acetate



[0509] A mixture of ethyl 2-(4-methyl-1-oxo-3,4-dihydro-2H-naphthalen-2-yl)-2-oxoacetate (9.8 g, 37.65 mmol, 1 equiv) and hydroxylamine hydrochloride (2.60 g, 37.65 mmol, 1 equiv) in EtOH (100 mL) was stirred at 80 °C for 1 h and then concentrated under vacuum. The residue was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford rac-ethyl (2Z)-2-(N-hydroxyimino)-2-(4-methyl-1-oxo-3,4-dihydro-2H-naphthalen-2-yl) acetate (7.7 g, crude) as brown oil, which was used for the next step without further purification. MS (ESI, *m/z*): 276 $[M+H]^+$.

[0510] Step 3. Synthesis of rac-ethyl 5-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate



[0511] To a stirred solution of ethyl (2Z)-2-(N-hydroxyimino)-2-(4-methyl-1-oxo-3,4-dihydro-2H-naphthalen-2-yl) acetate (6.7 g, 24.34 mmol, 1.0 equiv) in DCM (40 mL) at ambient temperature was added TEA (9.85 g, 97.35 mmol, 4.0 equiv). The resulting mixture was stirred for 10 mins and to this at 0 °C was added dropwise a solution of MsCl (13.73 g, 48.67 mmol, 2.0 equiv) in DCM (10 mL) over 20 minutes. The mixture was stirred at ambient temperature for 1 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-30% EtOAc in petroleum ether) to afford rac-ethyl 5-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (4.1 g, 65% yield) as yellow oil. MS (ESI, *m/z*): 258 $[M+H]^+$.

[0512] Step 4. Synthesis of rac-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide



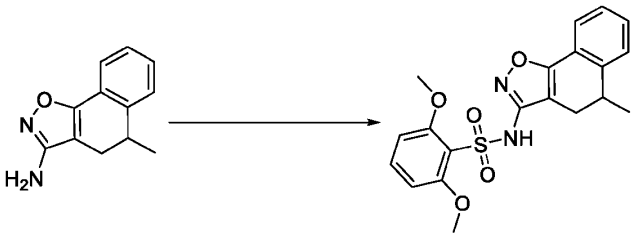
[0513] To a stirred solution of rac-ethyl 5-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (2 g, 7.77 mmol, 1 equiv) in MeOH (10 mL) at ambient temperature was added ammonia (28% in water, 10 mL). The resulting mixture was stirred at this temperature for 30 minutes and then concentrated under vacuum to afford rac-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (1.7 g, crude) as a white solid, which was used for the next step without further purification. MS (ESI, *m/z*): 229 $[M+H]^+$.

[0514] Step 5. Synthesis of rac-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine



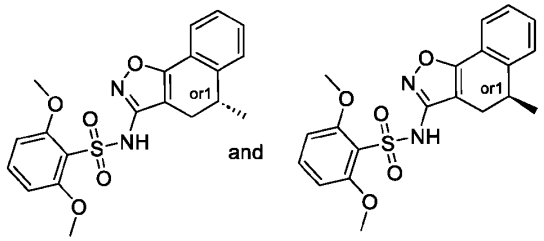
[0515] To a stirred solution of rac-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (1.7 g, 7.45 mmol, 1 equiv) in EtOAc/ACN/H_2O (10 mL/10 mL/5 mL) at ambient temperature, was added $PhI(OAc)_2$ (2.40 g, 7.45 mmol, 1 equiv). The mixture was stirred at 45 °C for 2 h and then diluted with water. The resulting mixture was extracted with EtOAc for three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography (5-70% acetonitrile in water (contained 0.05% formic acid)) to afford rac-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (110 mg, 7% yield) as yellow oil. MS (ESI, *m/z*): 201 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d6) δ 7.53-7.45 (m, 1H), 7.42-7.26 (m, 3H), 5.70 (s, 2H), 3.24-3.10 (m, 1H), 2.81-2.67 (m, 1H), 2.47-2.34 (m, 1H), 1.21 (d, $J = 7.2$ Hz, 3H).

[0516] Step 6. Synthesis of rac-2,6-dimethoxy-N-(5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide



[0517] To a stirred solution of rac-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (37 mg, 0.185 mmol, 1 equiv) in pyridine/DCM (0.5 mL/0.5 mL) at ambient temperature was added dropwise a solution of 2,6-dimethoxybenzenesulfonyl chloride (43.73 mg, 0.185 mmol, 1 equiv) in DCM (0.2 mL). The resulting mixture was stirred at this temperature for 16 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography (5-50% acetonitrile in water (contained 0.05% NH_4HCO_3)) and further purified by Prep-HPLC (formic acid system) to afford rac-2,6-dimethoxy-N-(5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide (8.2 mg, 11% yield) as a white solid. MS (ESI, *m/z*): 401 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.48-7.39 (m, 1H), 7.39-7.24 (m, 3H), 6.63 (d, J = 8.4 Hz, 2H), 3.93 (s, 6H), 3.24-3.11 (m, 1H), 3.11-2.98 (m, 1H), 2.82-2.77 (m, 1H), 1.25 (d, J = 7.2 Hz, 3H).

[0518] Step 7. Synthesis of rel-(R)-2,6-dimethoxy-N-(5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide and rel-(S)-2,6-dimethoxy-N-(5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide



[0519] The crude product of rac-2,6-dimethoxy-N-(5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide (100 mg, 0.25 mmol, 1 equiv) was resolved with Chiral-Prep-HPLC. The absolute stereochemistry was not determined.

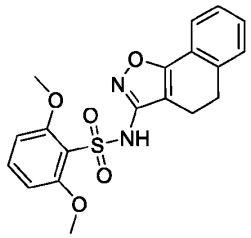
[0520] Rel-(R)-2,6-dimethoxy-N-(5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide (22.1 mg, 44% yield) as a white solid, 1st elution peak from Chiral-Prep-HPLC. MS (ESI, *m/z*): 401 $[M+H]^+$ ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.62-

7.53 (m, 1H), 7.47-7.39 (m, 1H), 7.39-7.24 (m, 3H), 6.64 (d, J = 8.4 Hz, 2H), 3.96 (s, 6H), 3.27-3.15 (m, 1H), 3.09-2.97 (m, 1H), 2.85-2.76 (m, 1H), 1.26 (d, J = 7.2 Hz, 3H).

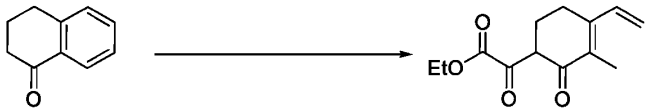
[0521] Rel-(S)-2,6-dimethoxy-N-(5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide (18.4 mg, 37% yield) as a white solid, 2nd elution peak from Chiral-Prep-HPLC. MS (ESI, *m/z*): 401 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.62-7.56 (m, 1H), 7.48-7.39 (m, 1H), 7.39-7.24 (m, 3H), 6.63 (d, J = 8.4 Hz, 2H), 3.96 (s, 6H), 3.25-3.11 (m, 1H), 3.11-2.99 (m, 1H), 2.82-2.73 (m, 1H), 1.26 (d, J = 7.2 Hz, 3H).

Example 4

N-(4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide



[0522] Step-1: Synthesis of ethyl 2-oxo-2-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate:



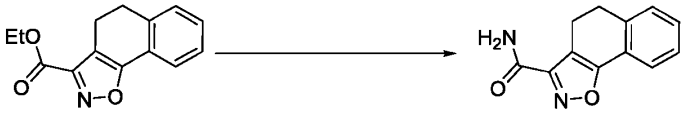
[0523] To a stirred solution of diethyl oxalate (24.0 g, 164.22 mmol, 1.2 equiv) in THF (600 mL) at 0 °C was added t-BuOLi (14.4 g, 179.86 mmol, 1.3 equiv) under N_2 atmosphere. The resulting mixture was stirred for 10 min and to this was added dropwise a solution of 1-tetralone (20.0 g, 136.80 mmol, 1.0 equiv) in THF (60 mL) over 10 min. The resulting mixture was stirred at ambient temperature for 16 h and then acidified with aqueous HCl (1M) to pH 1 and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford ethyl 2-oxo-2-(1-oxo-3,4-dihydro-2H-naphthalen-2-yl)acetate (25.0 g, crude) as a yellow solid, which was used for the next step without further purification. MS (ESI, *m/z*): 247 $[M+H]^+$.

[0524] Step-2: Synthesis of ethyl 4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate:



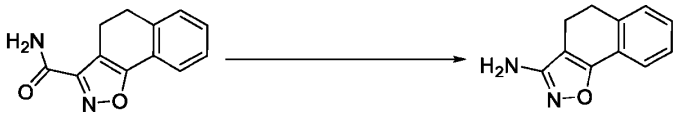
[0525] To a stirred solution of ethyl 2-oxo-2-(1-oxo-3,4-dihydro-2H-naphthalen-2-yl)acetate (25 g, 102.88 mmol, 1.0 equiv) in acetonitrile (300 mL) at ambient temperature was added hydroxylamine hydrochloride (7.7 g, 110.80 mmol, 1.1 equiv). The resulting mixture was stirred at 60 °C for 2 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-30% EtOAc in petroleum ether) to afford ethyl 4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxyl (20.0 g, 81% yield) as a light pink solid. MS (ESI, *m/z*): 244 $[M+H]^+$.

[0526] Step-3: Synthesis of 4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide:



[0527] To a stirred solution of ethyl 4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (4.0 g, 16.44 mmol, 1.0 equiv) in MeOH (20 mL) at ambient temperature was added $NH_3 \cdot H_2O$ (20.0 mL, 28% in H_2O). The resulting mixture was stirred for 2 and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-30% EtOAc in petroleum ether) to afford 4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (3.3 g, 93.6% yield) as a yellow solid. MS (ESI, *m/z*): 215 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d6) δ 8.09 (s, 1H), 7.84 (s, 1H), 7.64 (d, J = 6.8 Hz, 1H), 7.41-7.33 (m, 3H), 3.03-2.95 (m, 2H), 2.93-2.88 (m, 2H).

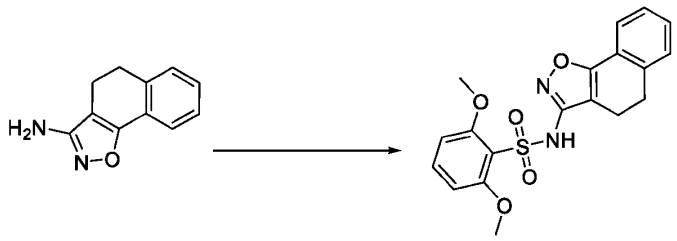
[0528] Step-4: Synthesis of 4,5-dihydronaphtho[2,1-d]isoxazol-3-amine:



[0529] To a stirred solution of 4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (3.2 g, 14.93 mmol, 1.0 equiv) in a combined solvent of EtOAc (10 ml), acetonitrile (10 mL) and water (10 mL) at ambient temperature was added $PhI(OAc)_2$ (7.2 g, 22.35 mmol, 1.5 equiv) under N_2 atmosphere. The resulting mixture was stirred for 2 h and then concentrated under

vacuum to afford 4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (4.0 g, crude) as a yellow solid, which was used for the next step without further purification. MS (ESI, *m/z*): 187 $[M+H]^+$.

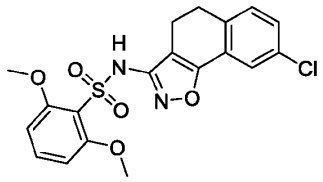
[0530] Step-5: Synthesis of N-(4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide:



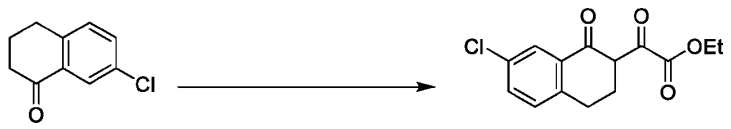
[0531] To a stirred solution of 4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (500.0 mg, 2.69 mmol, 1.0 equiv) in DCM (10 mL) at ambient temperature was added 2,6-dimethoxybenzenesulfonyl chloride (693.0 mg, 2.92 mmol 1.1 equiv) and pyridine (429.0 mg, 5.42 mmol, 2.0 equiv). The resulting mixture was stirred at 60 °C for 16 h and then diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by Prep-HPLC (5-50% acetonitrile in water (contained 0.1% formic acid)) to afford N-(4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide (30.9 mg, 2.9 % yield) MS (ESI, *m/z*): 387 $[M+H]^+$.as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (s, 1H), 7.51-7.46 (m, 2H), 7.35-7.32 (m, 3H), 6.76 (d, J = 8.8 Hz, 2H), 3.79 (s, 6H), 2.94 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 8.0 Hz, 2H).

Example 5

N-(8-chloro-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide

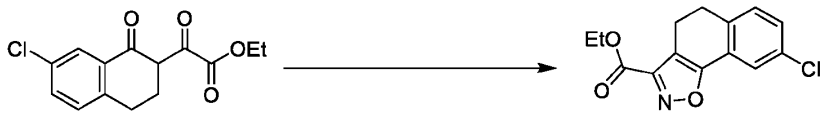


[0532] Step 1. Synthesis of ethyl 2-(7-chloro-1-oxo-3,4-dihydro-2H-naphthalen-2-yl)-2-oxoacetate



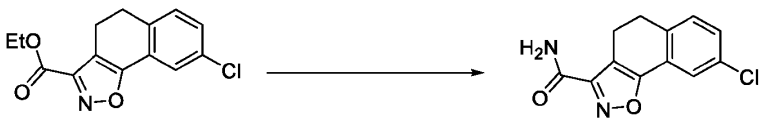
[0533] To a stirred solution of diethyl oxalate (9.8 g, 66.99 mmol, 1.2 equiv) in THF (200 mL) at 0 °C was added t-BuOLi (8.4 g, 105.19 mmol, 1.9 equiv) under N_2 atmosphere. The resulting mixture was stirred for 10 min and to this was added dropwise a solution of 7-chloro-3,4-dihydro-2H-naphthalen-1-one (10.0 g, 55.36 mmol, 1.0 equiv) in THF (200 mL) over 10 min. The resulting mixture was stirred at 50 °C for 3 h and then acidified with aqueous HCl (1 M) to pH 4 and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford ethyl 2-(7-chloro-1-oxo-3,4-dihydro-2H-naphthalen-2-yl)-2-oxoacetate (15.0 g, crude) as brown oil, which was used for the next step without further purification. MS (ESI, *m/z*): 281, 283 $[M+H]^+$.

[0534] Step 2. Synthesis of 8-chloro-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide



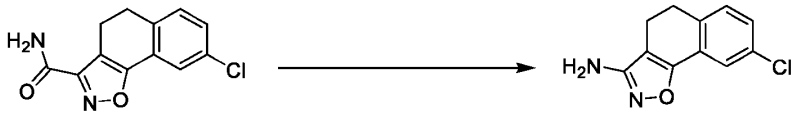
[0535] To a stirred solution of ethyl 2-(7-chloro-1-oxo-3,4-dihydro-2H-naphthalen-2-yl)-2-oxoacetate (6.0 g, 21.34 mmol, 1.0 equiv) in EtOH (100.0 mL) at ambient temperature was added NH_4OH (0.9 g, 25.65 mmol, 1.2 equiv). The resulting mixture was stirred at 80 °C for 16 h and then allowed to cool down to ambient temperature. The precipitated solid was collected by filtration and purified by trituration with EtOH to afford 8-chloro-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (4.6 g, crude) as an off-white solid, which was used for the next step without further purification. MS (ESI, *m/z*): 279, 281 $[M+H]^+$.

[0536] Step 3. Synthesis of 8-chloro-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide



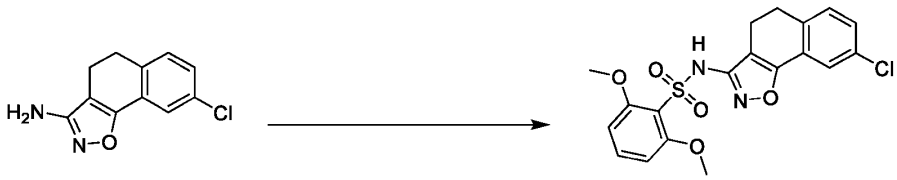
[0537] A mixture of ethyl 8-chloro-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (8.0 g, 28.81 mmol, 1.0 equiv) and NH_3 (7M in MeOH, 100.0 mL) was stirred at ambient temperature for 2 h. The resulting mixture was concentrated under vacuum to afford 8-chloro-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (4.6 g, crude) as an off-white solid, which was used for the next step without further purification. MS (ESI, *m/z*): 249, 251 $[M+H]^+$.

[0538] Step 4. Synthesis of 8-chloro-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine



[0539] To a stirred solution of 8-chloro-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (300.0 mg, 1.21 mmol, 1.0 equiv) in a combined solvent of acetonitrile (4.0 mL), EtOAc (4.0 mL) and H_2O (2.0 mL) at ambient temperature was added $PhI(OAc)_2$ (390.0 mg, 1.15 mmol, 0.95 equiv). The resulting solution was stirred for 2 h and then diluted with water. The mixture was basified with saturated NaHCO3 solution to pH 8 and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford 8-chloro-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (100.0 mg, crude) as a yellow solid, which was used for the next step without further purification. MS (ESI, *m/z*): 221, 223 $[M+H]^+$.

[0540] Step 5. Synthesis of N-(8-chloro-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide

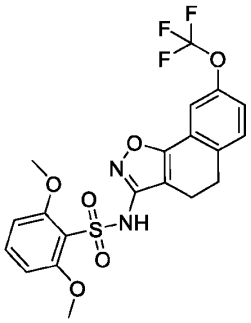


[0541] To a stirred solution of 8-chloro-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (100.0 mg, 0.45 mmol, 1.0 equiv) in pyridine (10.0 mL) at ambient temperature was added 2,6-dimethoxybenzenesulfonyl chloride (300.0 mg, 1.27 mmol, 2.8 equiv). The resulting mixture was stirred for 16 h and then concentrated under vacuum. The residue was purified flash chromatography on silica gel (0-50% EtOAc in petroleum ether) and further purified by Prep-

HPLC (5-50% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8-chloro-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide (22.4 mg, 12% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 7.53-7.37 (m, 4H), 6.77 (d, J = 8.4 Hz, 2H), 3.80 (s, 6H), 2.96-2.92 (m, 2H), 2.71-2.67 (m, 2H). MS (ESI, *m/z*): 421, 423 $[M+H]^+$.

Example 6

2,6-dimethoxy-N-(8-(trifluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide



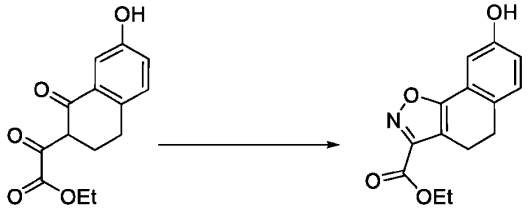
[0542] Step 1. Synthesis of Ethyl 2-(7-hydroxy-1-oxo-3,4-dihydro-2H-naphthalen-2-yl)-2-oxoacetate



[0543] To a stirred solution of t-BuOLi (11.9 g, 147.98 mmol, 2.40 equiv) in THF (100.0 mL) at 0 °C was added dropwise a solution of ethyl oxalate (10.8 g, 73.98 mmol, 1.20 equiv) in THF (100.0 mL). The resulting mixture was stirred at 0 °C for 10 minutes and to this was added dropwise a solution of 7-hydroxy-3,4-dihydro-2H-naphthalen-1-one (10.0 g, 61.66 mmol, 1.00 equiv) in THF (10.0 mL). The mixture was stirred at ambient temperature for 2 h and then quenched with water. The resulting mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford ethyl 2-(7-hydroxy-1-oxo-3,4-dihydro-2H-naphthalen-2-yl)-2-

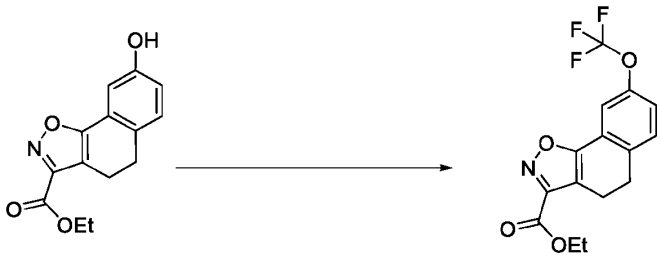
oxoacetate (21.5 g, crude) as a yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 263 $[M+H]^+$.

[0544] Step 2. Synthesis of ethyl 8-hydroxy-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate



[0545] A mixture of ethyl 2-(7-hydroxy-1-oxo-3,4-dihydro-2H-naphthalen-2-yl)-2-oxoacetate (20.0 g, 76.26 mmol, 1.00 equiv) and hydroxylamine hydrochloride (5.8 g, 83.89 mmol, 1.10 equiv) in EtOH (100.0 mL) was stirred at 80 °C for 16 h and then concentrated under vacuum. The residue was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-30% EtOAc in petroleum ether) to afford ethyl 8-hydroxy-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (13.5 g, 58% yield) as a brown solid. MS (ESI, *m/z*): 260 $[M+H]^+$.

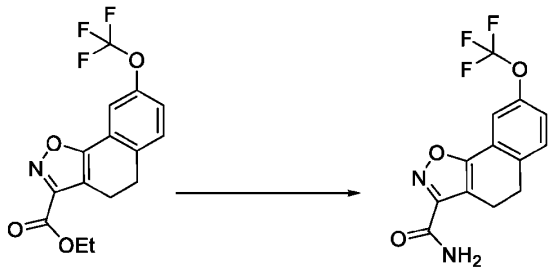
[0546] Step 3. Synthesis of ethyl 8-(trifluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate



[0547] To a stirred mixture of ethyl 8-hydroxy-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (2.0 g, 7.71 mmol, 1.00 equiv), silver trifluoromethanesulfonate (9.9 g, 38.57 mmol, 5.00 equiv), 4-(chloromethyl)-1-fluoro-1,4-diazabicyclo[2.2.2]octane-1,4-diium (5.8 g, 15.43 mmol, 2.00 equiv), N-(benzenesulfonyl)-S-phenylfluoranesulfonamido (4.9 g, 15.43 mmol, 2.00 equiv) and CsF (7.0 g, 46.28 mmol, 6.00 equiv) in toluene (20.0 mL) at ambient

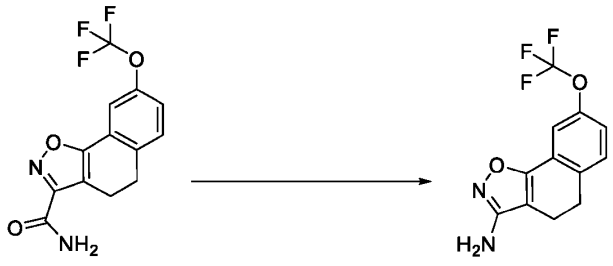
temperature was added trifluoromethyltrimethylsilane (5.5 g, 38.57 mmol, 5.00 equiv) and 2-fluoropyridine (3.7 g, 38.57 mmol, 5.00 equiv) under N_2 atmosphere. The resulting mixture was stirred at ambient temperature for 16 h and then filtered through a pad of celite. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5--70% acetonitrile in water (contain 0.1% formic acid)) to afford ethyl 8-(trifluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (1.1 g, 34% yield) as yellow oil. MS (ESI, *m/z*): 328 $[M+H]^+$.

[0548] Step 4. Synthesis of 8-(trifluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide



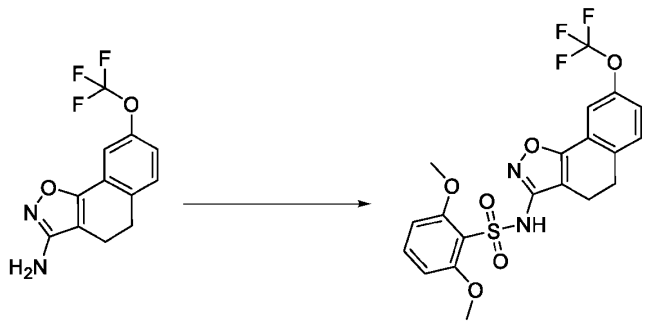
[0549] To a stirred solution of ethyl 8-(trifluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (1.0 g, 3.06 mmol, 1.00 equiv) in MeOH (5.0 mL) at ambient temperature was added $NH_4.H_2O$ (28%, 5.0 mL). The resulting mixture was stirred at this temperature for 1 h and then concentrated under vacuum to afford 8-(trifluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (1.8 g, crude) as a white solid, which was used for the next step without further purification. MS (ESI, *m/z*): 299 $[M+H]^+$.

[0550] Step 5. Synthesis of 8-(trifluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine



[0551] To a stirred solution of 8-(trifluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (810.0 mg, 2.72 mmol, 1.00 equiv) in EtOAc (5.0 mL), acetonitrile (5.0 mL) and H_2O (5.0 mL) at ambient temperature was added $PhI(OAc)_2$ (1.3 g, 4.07 mmol, 1.50 equiv). The mixture was stirred at this temperature for 2 h and then diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5--70% acetonitrile in water (contained 0.1% formic acid)) to afford 8-(trifluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (100.0 mg, 10% yield) as yellow oil. MS (ESI, *m/z*): 271 $[M+H]^+$.

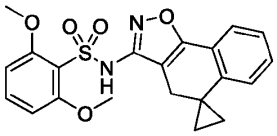
[0552] Step 6. Synthesis of 2,6-dimethoxy-N-(8-(trifluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide



[0553] To a stirred mixture of 8-(trifluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (100.0 mg, 0.37 mmol, 1.00 equiv) in pyridine (5.00 mL) was added 2,6-dimethoxybenzenesulfonyl chloride (87.6 mg, 0.37 mmol, 1.00 equiv). The resulting mixture was stirred at 80 °C for 1 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5--70% acetonitrile in water (contained 0.1% formic acid)) and Prep-HPLC (5--70% acetonitrile in water (contained 0.1% formic acid)) to afford 2,6-dimethoxy-N-(8-(trifluoromethoxy)-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide (14.5 mg, 8% yield) as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 10.76 (s, 1H), 7.51-7.47 (m, 3H), 7.40-7.31 (m, 1H), 6.78 (d, J = 8.4 Hz, 2H), 3.80 (s, 6H), 3.00-2.96 (m, 2H), 2.72-2.68 (m, 2H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -56.96. MS (ESI, *m/z*): 471 $[M+H]^+$.

Example 9

2,6-dimethoxy-N-(4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0554] Example 9 was prepared according to the procedure as described in Example 76, using 2,6-dimethoxybenzenesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, MeOD) δ 7.57 (dd, J = 7.6, 1.5 Hz, 1H), 7.50 (t, J = 8.5 Hz, 1H), 7.33 (td, J = 7.6, 1.5 Hz, 1H), 7.25 (td, J = 7.5, 1.2 Hz, 1H), 7.02 (dd, J = 7.7, 1.2 Hz, 1H), 6.77 (d, J = 8.5 Hz, 2H), 3.90 (s, 6H), 2.66 (s, 2H), 1.07 – 0.95 (m, 2H), 0.86 – 0.74 (m, 2H). MS (ESI, *m/z*): 413.2 $[M+H]^+$.

Example 10

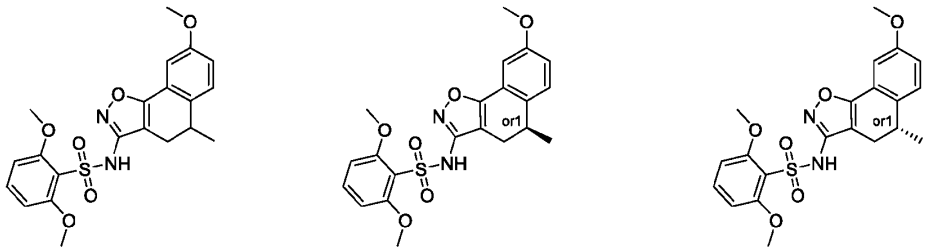
Rac-2,6-dimethoxy-N-(8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazol-3-yl) benzenesulfonamide,

Example 13

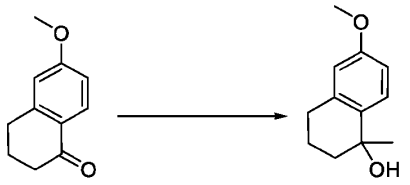
Rel-(S)-2,6-dimethoxy-N-(8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazol-3-yl) benzenesulfonamide,

Example 14

Rel-(R)-2,6-dimethoxy-N-(8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazol-3-yl) benzenesulfonamide

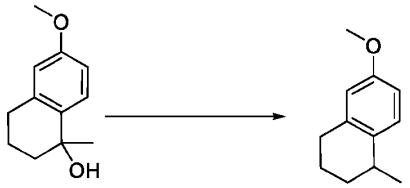


[0555] Step 1. Synthesis of rac-6-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol



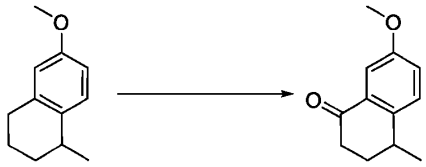
[0556] To a stirred solution of 6-methoxy-3,4-dihydronaphthalen-1(2H)-one (40.0 g, 226.99 mmol, 1.00 equiv) in THF (400.0 mL) at -78°C was added dropwise CH_3MgBr (3 M in THF, 302.9 mL, 907.98 mmol, 4.00 equiv) under N_2 atmosphere. The resulting mixture was stirred at this temperature for 1 h and then quenched with saturated NH_4Cl solution and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford rac-6-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (59.5 g, crude) as brown oil, which was used for the next step without further purification. MS (ESI, *m/z*): 175 $[M+H-H_2O]^+$.

[0557] Step 2. Synthesis of rac-6-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene



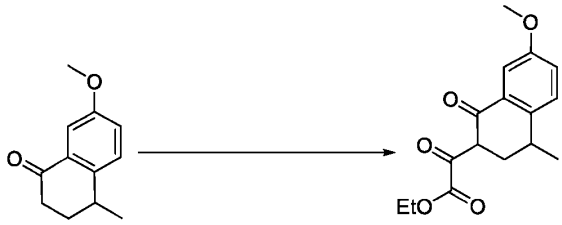
[0558] To a stirred solution of rac-6-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (49.0 g, 254.87 mmol, 1.00 equiv) and triethylsilane (118.5 g, 1.02 mol, 4.00 equiv) in DCM (500.0 mL) at 0 °C added TFA (58.1 g, 509.72 mmol, 2.00 equiv). The resulting mixture was stirred at ambient temperature for 2 h and then neutralized with $NaHCO_3$ solution to pH 7 and extracted with EtOAc three times. The combined organic layers were washed with brine dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% DCM in petroleum ether) to afford rac-6-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene (35.2 g, 72% yield) as colorless oil. MS (ESI, *m/z*): 177 $[M+H]^+$.

[0559] Step 3. Synthesis of rac-7-methoxy-4-methyl-3,4-dihydronaphthalen-1(2H)-one



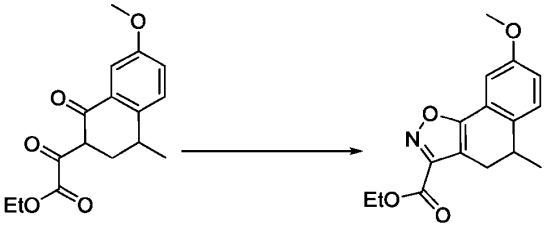
[0560] To a stirred solution of rac-6-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene (10.0 g, 56.73 mmol, 1.00 equiv) and $MgSO_4$ (13.6 g, 113.47 mmol, 2.00 equiv) in acetone (150.0 mL) and H_2O (100.0 mL) at 0 °C was added $KMnO_4$ (26.9 g, 170.20 mmol, 3.00 equiv) in portions. The resulting mixture was stirred at ambient temperature for 16 h and then filtered through a pad of celite. The filtrate was quenched with $Na_2S_2O_3$ solution and extracted with EtOac three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford rac-7-methoxy-4-methyl-3,4-dihydronaphthalen-1(2H)-one (1.1 g, 9% yield) as brown oil. MS (ESI, *m/z*): 191 $[M+H]^+$.

[0561] Step 4. Synthesis of rac-ethyl 2-(7-methoxy-4-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate



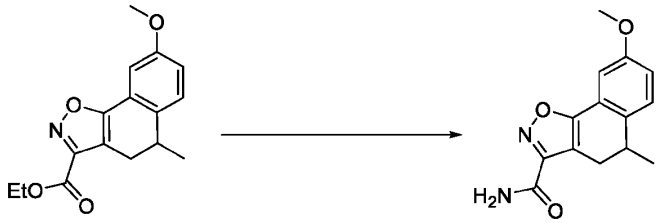
[0562] To a stirred solution of rac-7-methoxy-4-methyl-3,4-dihydronaphthalen-1(2H)-one (1.8 g, 9.46 mmol, 1.00 equiv) and ethyl oxalate (2.7 g, 18.92 mmol, 2.00 equiv) in THF (18.0 mL) at 0 °C was added t-BuOLi (1.5 g, 18.92 mmol, 2.00 equiv) in portions. The resulting reaction mixture was stirred at ambient temperature for 1 h and then acidified with aqueous HCl (1M) to pH 4 and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford rac-ethyl 2-(7-methoxy-4-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate (2.1 g, crude) as brown oil, which was used for the next step without further purification. MS (ESI, *m/z*): 291 $[M+H]^+$.

[0563] Step 5. Synthesis of rac-ethyl 8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazole-3-carboxylate



[0564] A mixture of rac-ethyl 2-(7-methoxy-4-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate (1.8 g, 6.20 mmol, 1.00 equiv) and $NH_2OH{\cdot}HCl$ (0.5 g, 6.82 mmol, 1.10 equiv) in EtOH (18.0 mL) was stirred at 80 °C for 2 h and then diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford rac-ethyl 8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazole-3-carboxylate (1.4 g, 71 % yield) as brown oil. MS (ESI, *m/z*): 288 $[M+H]^+$.

[0565] Step 6. Synthesis of rac-8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazole-3-carboxamide



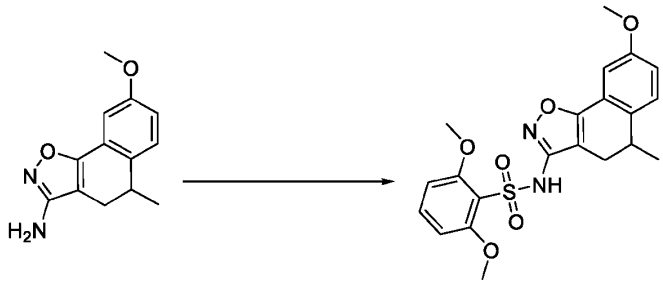
[0566] A mixture of rac-ethyl 8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazole-3-carboxylate (1.2 g, 4.17 mmol, 1.00 equiv) in $NH_3{\cdot}H_2O$ (12.0 mL) and MeOH (12.0 mL) was stirred at ambient temperature for 2 h. The resulting mixture was concentrated under vacuum to afford rac-8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazole-3-carboxamide (1.1 g, crude) as a yellow solid, which was used for the next step without further purification. MS (ESI, *m/z*): 259 $[M+H]^+$.

[0567] Step 7. Synthesis of rac-8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazol-3-amine



[0568] A mixture of rac-8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazole-3-carboxamide (1.1 g, 4.25 mmol, 1.00 equiv) and $PhI(OAc)_2$ (2.0 g, 6.38 mmol, 1.50 equiv) in EtOAc (3.6 mL), acetonitrile (3.6 mL) and H_2O (3.6 mL) was stirred at ambient temperature for 2 h. The resulting mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-70% acetonitrile in water (contained 0.1% formic acid)) to afford rac-8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazol-3-amine (410.0 mg, 28% yield over two steps) as a brown oil. MS (ESI, *m/z*): 231 $[M+H]^+$.

[0569] Step 8. Synthesis of rac-2,6-dimethoxy-N-(8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazol-3-yl) benzenesulfonamide

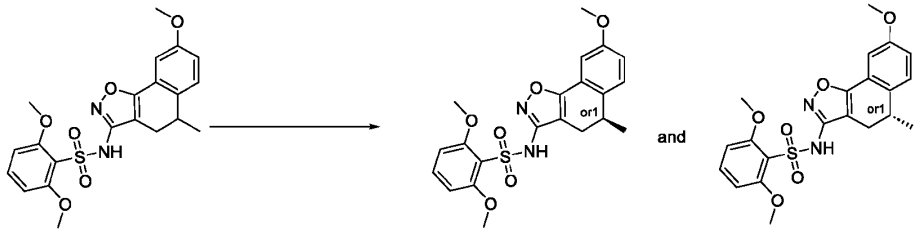


[0570] A mixture of rac-8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazol-3-amine (200.0 mg, 0.87 mmol, 1.00 equiv) and 2,6-dimethoxybenzenesulfonyl chloride (205.5 mg, 0.87 mmol, 1.00 equiv) in pyridine (2.0 mL) was stirred at 80 °C for 2 h. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-70%, acetonitrile in water (contained 0.1% formic acid)) to afford rac-2,6-dimethoxy-N-(8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazol-3-yl) benzenesulfonamide (97.0 mg, 25% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.66 (brs, 1H), 7.49 (t, J = 8.4 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 2.7 Hz, 1H),

6.96 (dd, J = 8.4, 2.7 Hz, 1H), 6.76 (d, J = 8.4 Hz, 2H), 3.82-3.75 (m, 9H), 3.04-3.00 (m, 1H), 2.82-2.68 (m, 1H), 2.49-2.45 (m, 1H), 1.10 (d, J = 7.2 Hz, 3H). MS (ESI, *m/z*): 431 $[M+H]^+$.

[0571] Step 9. Synthesis of (R)-2,6-dimethoxy-N-(8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazol-3-yl) benzenesulfonamide and (S)-2,6-dimethoxy-N-(8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazol-3-yl) benzenesulfonamide

[0572] The crude product of rac-2,6-dimethoxy-N-(8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazol-3-yl) benzenesulfonamide (97.0 mg) was resolved with Chiral-Prep-HPLC. The absolute stereochemistry was not determined.

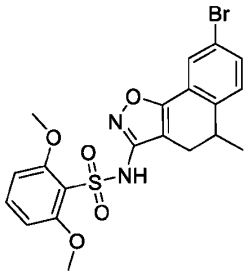


[0573] rel-(S)-2,6-dimethoxy-N-(8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazol-3-yl) benzenesulfonamide (16.2 mg, 18% yield) as a white solid, 1st elution peak from Chiral-Prep-HPLC MS (ESI, *m/z*): 431 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (brs, 1H), 7.49 (t, J = 8.4, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 2.8 Hz, 1H), 6.96 (dd, J = 8.4, 2.8 Hz, 1H), 6.76 (d, J = 8.4, 2H), 3.82-3.75 (m, 9H), 3.04-3.00 (m, 1H), 2.82-2.68 (m, 1H), 2.49-2.45 (m, 1H), 1.10 (d, J = 7.2 Hz, 3H).

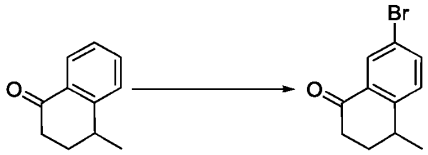
[0574] rel-(R)-2,6-dimethoxy-N-(8-methoxy-5-methyl-4,5-dihydronaphtho[2,1-d] isoxazol-3-yl) benzenesulfonamide (17.7 mg, 20% yield) as a white solid, 2nd elution peak from Chiral-Prep-HPLC. MS (ESI, *m/z*): 431 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (brs, 1H), 7.49 (t, J = 8.4 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 2.8 Hz, 1H), 6.96 (dd, J = 8.4, 2.8 Hz, 1H), 6.76 (d, J = 8.4 Hz, 2H), 3.82-3.75 (m, 9H), 3.04-3.00 (m, 1H), 2.82-2.68 (m, 1H), 2.49-2.45 (m, 1H), 1.10 (d, J = 6.8 Hz, 3H).

Example 11

Rac-N-(8-bromo-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide

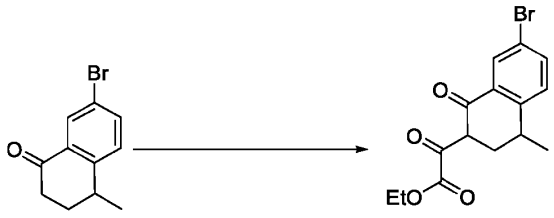


[0575] Step 1. Synthesis of rac-7-bromo-4-methyl-3,4-dihydronaphthalen-1(2H)-one



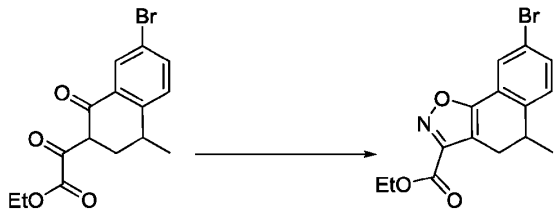
[0576] To a stirred mixture of 4-methyl-3,4-dihydronaphthalen-1(2H)-one (40.0 g, 250.00 mmol, 1.00 equiv) in DCM (400.0 mL) at ambient temperature was added $FeCl_3$ (81.0 g, 500.00 mmol, 2.00 equiv). The resulting mixture was stirred at ambient temperature for 10 minutes and to this was added a solution of bromine (100.0 g, 625.00 mmol, 2.50 equiv) in DCM (20.0 mL). The mixture was stirred at ambient temperature for 16 h and then diluted with aqueous HCl (2M) and extracted with EtOAc three times. The combined organic layers were washed with $Na_2S_2O_3$ solution, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-30% EtOAc in petroleum ether) to afford rac-7-bromo-4-methyl-3,4-dihydronaphthalen-1(2H)-one (38.0 g, 63% yield) as brown oil. MS (ESI, *m/z*): 239, 241 $[M+H]^+$.

[0577] Step 2. Synthesis of rac-Ethyl 2-(7-bromo-4-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate



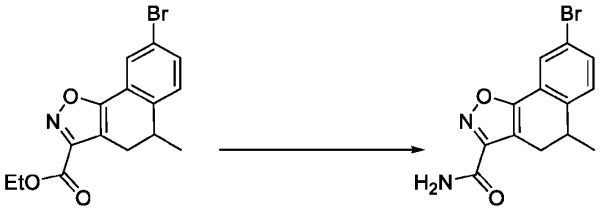
[0578] To a stirred mixture of t-BuOLi (15.6 g, 195.00 mmol, 1.30 equiv) in THF (150.0 mL) at 0 °C was added dropwise a solution of diethyl oxalate (25.8 g, 180.00 mmol, 1.20 equiv) in THF (20.0 mL). The resulting mixture was stirred at this temperature for 10 minutes and to this was added dropwise a solution of rac-7-bromo-4-methyl-3,4-dihydronaphthalen-1(2H)-one (35.0 g, 150.00 mmol, 1.00 equiv) in THF (20.0 mL). The mixture was stirred at ambient temperature for 2 h and then quenched with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford rac-ethyl 2-(7-bromo-4-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate (42.0 g, crude) as brown oil, which was used for the next step without further purification. MS (ESI, *m/z*): 339, 341 $[M+H]^+$.

[0579] Step 3. Synthesis of rac-Ethyl 8-bromo-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate



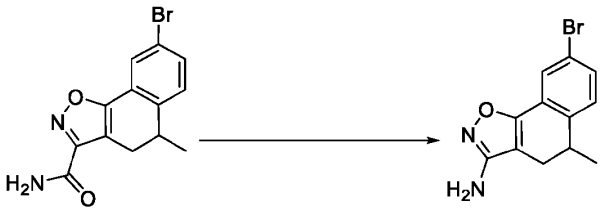
[0580] A mixture of ethyl 8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (42.0 g, 124.00 mmol, 1.00 equiv) and hydroxylamine hydrochloride (8.6 g, 124.00 mmol, 1.00 equiv) in EtOH (400.0 mL) was stirred at 80 °C for 1 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford rac-ethyl 8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (23.3 g, 56% yield) as a yellow solid. MS (ESI, *m/z*): 336, 338 $[M+H]^+$.

[0581] Step 4. Synthesis of rac-8-bromo-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide



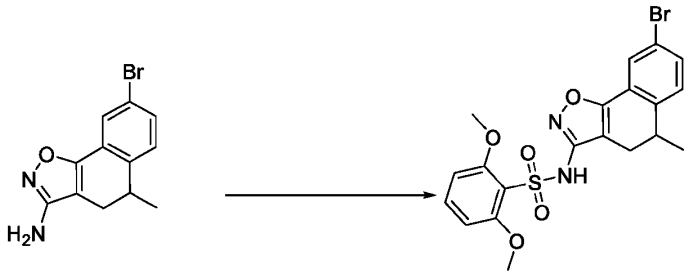
[0582] To a stirred solution of ethyl 8-bromo-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (20.0 g, 59.70 mmol, 1.00 equiv) in MeOH (200.0 mL) at ambient temperature was added ammonia (28%,200.0 mL). The resulting mixture was stirred at this temperature for 30 minutes and then concentrated under vacuum to afford rac-8-bromo-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (22.0 g, crude) as a yellow solid, which was used for the next step without further purification. MS (ESI, *m/z*): 307, 309 $[M+H]^+$.

[0583] Step 5. Synthesis of rac-8-bromo-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine



[0584] To a stirred solution of rac-8-bromo-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (10.0 g, 32.68 mmol, 1.00 equiv) in EtOAc/acetonitrile/H_2O (100.0 mL/100.0 mL/100.0 mL) at ambient temperature was added $PhI(OAc)_2$ (12.6 g, 39.22 mmol, 1.20 equiv). The mixture was stirred at 50 °C for 2 h and then diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford rac-8-bromo-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (2.1 g, 22% yield over two steps) as yellow solid. MS (ESI, *m/z*): 279, 281 $[M+H]^+$.

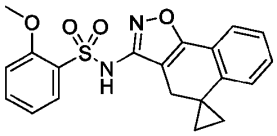
[0585] Step 6. Synthesis of rac-N-(8-bromo-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide



[0586] A mixture of rac-8-bromo-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (650.0 mg, 2.34 mmol, 1.00 equiv) and 2,6-dimethoxybenzenesulfonyl chloride (660.8 mg, 2.80 mmol, 1.20 equiv) in pyridine (4.0 mL) was stirred at 80 °C for 2 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5--80% acetonitrile in water (contained 0.05% formic acid)) and further purified by Prep-HPLC (5--66% acetonitrile in water (contained 0.1% formic acid)) to afford rac-2,6-dimethoxy-N-(8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide (108.0 mg, 9% yield) as a white solid. MS (ESI, *m/z*): 479, 481 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.74 (s, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.58 (dd, J = 8.4, 2.0 Hz, 1H), 7.50 (t, J = 8.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.4 Hz, 2H), 3.80 (s, 6H), 3.19-3.08 (m, 1H), 2.83-2.75 (m, 1H), 2.63-2.52 (m, 1H), 1.11 (d, J = 7.2 Hz, 3H).

Example 12

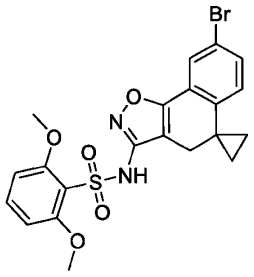
2-Methoxy-N-(4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0587] Example12 was prepared according to the procedure as described in Example 76, using 2-methoxybenzenesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 7.78 (dd, J = 7.8, 1.7 Hz, 1H), 7.57 (ddd, J = 8.9, 7.4, 1.8 Hz, 1H), 7.51 (dd, J = 7.4, 1.5 Hz, 1H), 7.29 (dtd, J = 25.5, 7.5, 1.4 Hz, 2H), 7.17 (d, J = 8.3 Hz, 1H), 7.09 – 7.00 (m, 2H), 3.81 (s, 3H), 2.58 (s, 2H), 1.01 – 0.94 (m, 2H), 0.85 – 0.77 (m, 2H). MS (ESI, *m/z*): 383.2 $[M+H]^+$.

Example 15

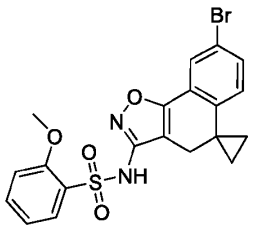
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide



[0588] A solution of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (400 mg, 1.37 mmol, 1 equiv, Intermediate C) and 2,6-dimethoxybenzenesulfonyl chloride (487.73 mg, 2.06 mmol, 1.50 equiv) in pyridine (10 mL) was stirred at 80 °C for 2 h under N_2 atmosphere and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography (5-95% acetonitrile in water (contained 0.5% formic acid)) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide (103.4 mg, 15% yield) as a white solid. MS (ESI, *m/z*): 491, 493 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d6) δ 10.73 (s, 1H), 7.65 (d, J = 2.1 Hz, 1H), 7.54-7.42 (m, 2H), 7.02 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 8.4 Hz, 2H), 3.77 (s, 6H), 2.59 (s, 2H), 1.03-0.88 (m, 2H), 0.82-0.72 (m, 2H).

Example 16

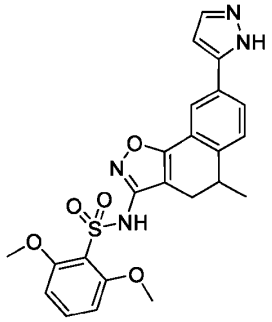
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



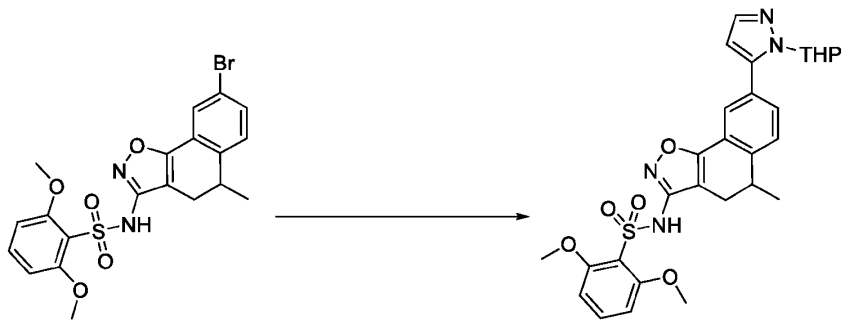
[0589] A solution of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (0.5 g, 1.72 mmol, 1 equiv, Intermediate C) and 2-methoxybenzenesulfonyl chloride (0.53 g, 2.58 mmol, 1.50 equiv) in pyridine (10 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. The resulting mixture was combined with another 6 batches (same scale) and acidified with aqueous HCl (1 M) to pH 4-5 and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-40% EtOAc (contained 50% tetrahydrofuran) in petroleum ether) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (3.7 g, 67% yield) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.93 (s, 1H), 7.82-7.72 (m, 1H), 7.68-7.56 (m, 2H), 7.55-7.45 (m, 1H), 7.25-7.15 (m, 1H), 7.13-6.98 (m, 2H), 3.81 (s, 3H), 2.62 (s, 2H), 1.04-0.91 (m, 2H), 0.91-0.79 (m, 2H). MS (ESI, *m/z*): 461, 463 $[M+H]^+$.

Example 17

Rac-2,6-dimethoxy-N-(5-methyl-8-(1H-pyrazol-5-yl)-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide

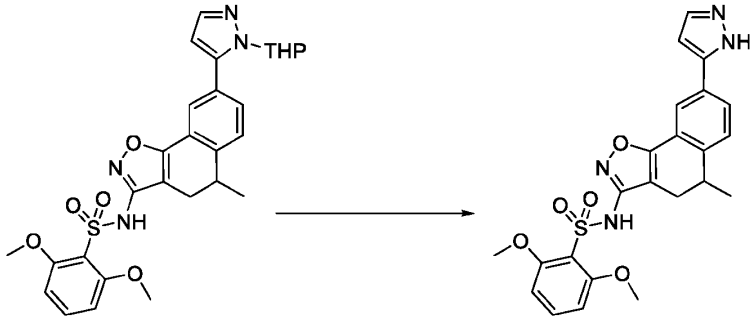


[0590] Step 1. Synthesis of rac-2,6-dimethoxy-N-(5-methyl-8-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide



[0591] A solution of rac-N-(8-bromo-5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamidee (150 mg, 0.31 mmol, 1 equiv, Example 11), 1-(oxan-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (104 mg, 0.37 mmol, 1.19 equiv), $Pd(PPh_3)_2Cl_2$ (22 mg, 0.03 mmol, 0.1 equiv) and Na_2CO_3 (66 mg, 0.62 mmol, 2 equiv) in DMF (11 mL) and H_2O (1 mL) was stirred at 80 °C for 4 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-70% EtOAc in petroleum ether) to afford rac-2,6-dimethoxy-N-(5-methyl-8-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide (70 mg, 41% yield) as a white solid. MS (ESI, *m/z*): 551 $[M+H]^+$.

[0592] Step 2. Synthesis of rac-2,6-dimethoxy-N-(5-methyl-8-(1H-pyrazol-5-yl)-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide

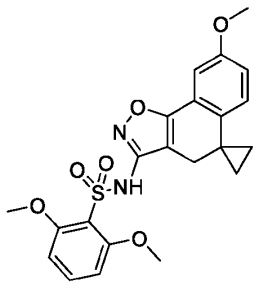


[0593] To a stirred solution of rac-2,6-dimethoxy-N-(5-methyl-8-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide (120 mg, 0.22 mmol, 1 equiv) in DCM (4 mL) at 0 °C was added aqueous HCl (4 M in 1,4-dioxane, 4 mL). The resulting mixture was stirred at 0 °C for 2 h and then concentrated under

vacuum. The residue was purified by reverse phase flash (5-70% acetonitrile in water (contained 0.05% formic acid)) to afford rac-2,6-dimethoxy-N-(5-methyl-8-(1H-pyrazol-5-yl)-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide (38.2 mg, 37% yield) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 12.93 (brs, 1H), 10.66 (brs, 1H), 7.94 (d, J = 1.8 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.74 (s, 1H), 7.49 (t, J = 8.4 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 6.83-6.70 (m, 3H), 3.81 (s, 6H), 3.22-3.08 (m, 1H), 2.91-2.76 (m, 1H), 2.63-2.53 (m, 1H), 1.16 (d, J = 6.9 Hz, 3H). MS (ESI, *m/z*): 467 $[M+H]^+$.

Example 18

2,6-Dimethoxy-N-(8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



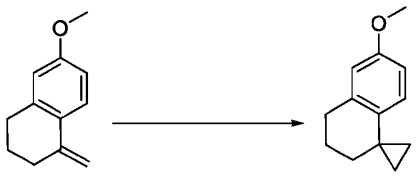
[0594] Step 1. Synthesis of 6-methoxy-1-methylene-1,2,3,4-tetrahydronaphthalene



[0595] To a stirred mixture of bromo(methyl)triphenyl-lambda5-phosphane (182.5 g, 510.74 mmol, 3.00 equiv) in THF (700 mL) at 0 °C was added t-BuOK (66.9 g, 595.86 mmol, 3.50 equiv) under N_2 atmosphere. The reaction mixture was stirred at this temperature for 1 h and to this was added 6-methoxy-3,4-dihydro-2H-naphthalen-1-one (30.0 g, 170.25 mmol, 1.00 equiv). The resulting mixture was stirred at ambient temperature for another 16 h and acidified with aqueous HCl (1 M) to pH 3 and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in

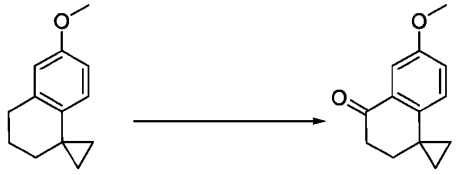
petroleum ether) to afford 6-methoxy-1-methylene-1,2,3,4-tetrahydronaphthalene (29.0 g, 95% yield) as light yellow oil. MS (ESI, *m/z*): 175 $[M+H]^+$.

[0596] Step 2. Synthesis of 6'-methoxy-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]



[0597] To a stirred solution of $ZnEt_2$ (86.0 mL, 1 M in hexane, 86 mmol, 1.50 equiv) in DCM (300 mL) at 0 °C was added dropwise TFA (9.8 g, 86.09 mmol, 1.50 equiv) over 20 mins. The resulting mixture was stirred at this temperature for 0.5 h and to this was added dropwise a solution of CH_2I_2 (23.1 g, 86.09 mmol, 1.50 equiv) in DCM (25.0 mL) over 5 mins. The resulting mixture was stirred for 1 h and to this was added dropwise a solution of 6-methoxy-1-methylene-1,2,3,4-tetrahydronaphthalene (10.0 g, 57.39 mmol, 1.00 equiv) in DCM (25.0 mL) over 5 mins. The resulting mixture was stirred for another 2 h and then diluted with water and filtered through a pad of celite. The filtrate was concentrated under vacuum to afford 6'-methoxy-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene] (15.5 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 189 $[M+H]^+$.

[0598] Step 3. Synthesis of 6'-methoxy-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one



[0599] To a stirred mixture of 6'-methoxy-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene] (10.0 g, 53.19 mmol, 1.00 equiv) in acetone (100.0 mL) at 0 °C was added a solution of $MgSO_4$ (6.4 g, 53.19 mmol, 1.00 equiv) in H_2O (50.0 mL). The resulting mixture was stirred at this temperature for 30 mins and to this was added $KMnO_4$ (15.1 g, 95.74 mmol, 1.80 equiv). The resulting mixture was stirred at ambient temperature for 16 h and

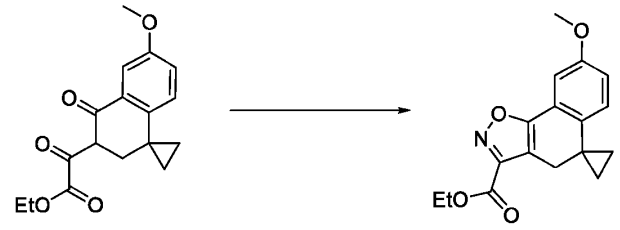
then filtered. The filtrate was quenched with $Na_2S_2O_3$ solution and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford 6'-methoxy-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (1.9 g, 82% yield) as yellow oil. ^{1}H NMR (300 MHz, DMSO-d6) δ 7.34 (d, J = 3.0 Hz, 1H), 7.10 (dd, J = 8.7, 3.0 Hz, 1H), 6.89 (d, J = 8.7 Hz, 1H), 3.76 (s, 3H), 2.72-2.61 (m, 2H), 1.93-1.82 (m, 2H), 1.04-0.97 (m, 2H), 0.96-0.88 (m, 2H). MS (ESI, *m/z*): 203 $[M+H]^+$.

[0600] Step 4. Synthesis of Ethyl 2-(6'-methoxy-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate



[0601] To a stirred mixture of t-BuOLi (5.9 g, 74.01 mmol, 1.30 equiv) in THF (80.0 mL) at 0 °C was added dropwise a solution of diethyl oxalate (10.0 g, 68.32 mmol, 1.20 equiv) in THF (10.0 mL). The resulting mixture was stirred at this temperature for 10 minutes and to this was added dropwise a solution of 4-methyl-3,4-dihydro-2H-naphthalen-1-one (11.5 g, 56.93 mmol, 1.00 equiv) in THF (10.0 mL). The mixture was stirred at ambient temperature for 2 h and then quenched with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford ethyl 2-(6'-methoxy-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (18.7 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 303 $[M+H]^+$.

[0602] Step 5. Synthesis of Ethyl 8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate



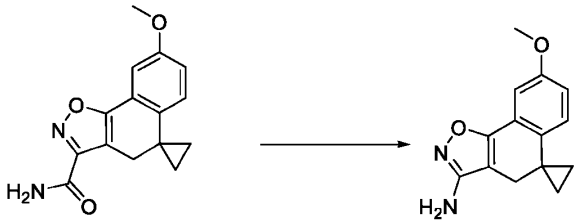
[0603] A mixture of ethyl 8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (20.0 g, 66.22 mmol, 1.00 equiv) and hydroxylamine hydrochloride (4.6 g, 66.22 mmol, 1.00 equiv) in EtOH (200.0 mL) was stirred at 80 °C for 1 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford ethyl 8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (15.0 g, 76% yield) as a yellow solid. MS (ESI, *m/z*): 300 $[M+H]^+$.

[0604] Step 6. Synthesis of 8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide



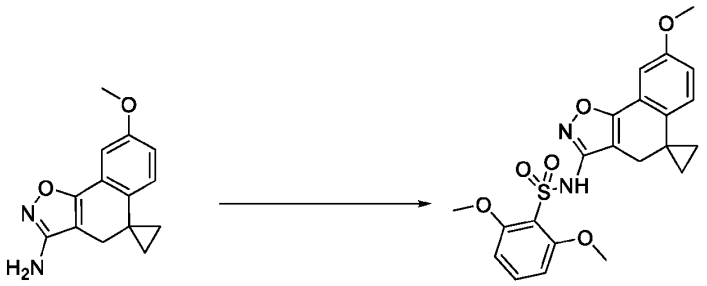
[0605] To a stirred solution of ethyl 8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (9.0 g, 30.10 mmol, 1.00 equiv) in MeOH (90.0 mL) at ambient temperature was added ammonia (28%, 90.0 mL). The resulting mixture was stirred at this temperature for 30 minutes and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford 8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (7.9 g, 97% yield) as a white solid. MS (ESI, *m/z*): 271 $[M+H]^+$.

[0606] Step 7. Synthesis of 8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine



[0607] To a stirred solution of 8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (5.0 g, 18.52 mmol, 1.00 equiv) in EtOAc/acetonitrile/H_2O (50.0 mL/50.0 mL/25.0 mL) at ambient temperature was added $PhI(OAc)_2$ (7.2 g, 22.22 mmol, 1.20 equiv). The mixture was stirred at 50 °C for 2 h and then diluted with water. The resulting mixture was extracted with EtOAc for three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography (5-70% acetonitrile in water (contained 0.05% formic acid)) to afford 8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (333.3 mg, 7% yield) as yellow oil. MS (ESI, *m/z*): 243 $[M+H]^+$.

[0608] Step 8. Synthesis of 2,6-dimethoxy-N-(8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl) benzenesulfonamide

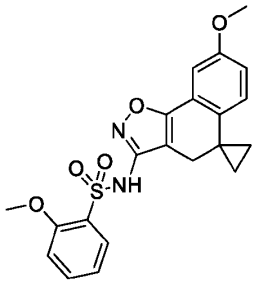


[0609] A mixture of 8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d] [1,2] oxazol]-3'-amine (150.0 mg, 0.62 mmol, 1.00 equiv) and 2,6-dimethoxybenzenesulfonyl chloride (175.3 mg, 0.74 mmol, 1.20 equiv) in pyridine (4.0 mL) was stirred at 80 °C for 2 h. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5--80% acetonitrile in water (contained 0.1 % formic acid)) and further purified by Prep-HPLC (5--60% acetonitrile in water (contained 0.1% formic acid)) to afford 2,6-dimethoxy-N-(8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide (80.4 mg, 29% yield) as a white solid. ^1H

NMR (300 MHz, DMSO-d_6) δ 10.68 (s, 1H), 7.50 (t, J = 8.4 Hz, 1H), 7.08 (d, J = 2.7 Hz, 1H), 6.99 (d, J = 8.7 Hz, 1H), 6.93-6.84 (m, 1H), 6.78 (d, J = 8.4 Hz, 2H), 3.87-3.72 (m, 9H), 2.55 (s, 2H), 0.93-0.83 (m, 2H), 0.75-0.63 (m, 2H). MS (ESI, *m/z*): 443 $[M+H]^+$.

Example 19

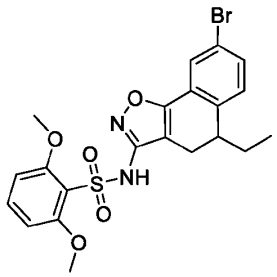
2-Methoxy-N-(8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



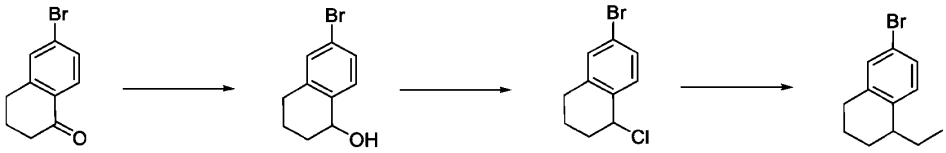
[0610] To a stirred mixture of 8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (150.0 mg, 0.62 mmol, 1.00 equiv, Example 18) in pyridine (2.0 mL) at ambient temperature was added 2-methoxybenzenesulfonyl chloride (153.5 mg, 0.74 mmol, 1.20 equiv). The resulting mixture was stirred at 80 °C for 1 h and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-45% acetonitrile in water (contained 0.1% formic acid)) and further purified by Prep-HPLC (5-60% acetonitrile in water (contain 0.1% formic acid)) to afford 2-methoxy-N-(8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide (54.5 mg, 21% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.86 (s, 1H), 7.79 (dd, J = 7.8, 1.8 Hz, 1H), 7.69-7.55 (m, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.12-7.04 (m, 2H), 7.00 (d, J = 8.7 Hz, 1H), 6.91 (dd, J = 8.7, 2.7 Hz, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 2.58 (s, 2H), 0.96-0.88 (m, 2H), 0.81-0.72 (m, 2H). MS (ESI, *m/z*): 413 $[M+H]^+$.

Example 20

Rac-N-(8-bromo-5-ethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide

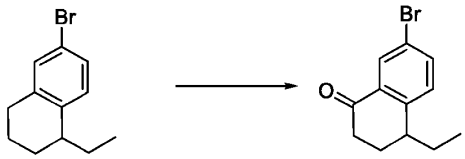


[0611] Steps 1-3: Synthesis of rac-6-bromo-1-ethyl-1,2,3,4-tetrahydronaphthalene



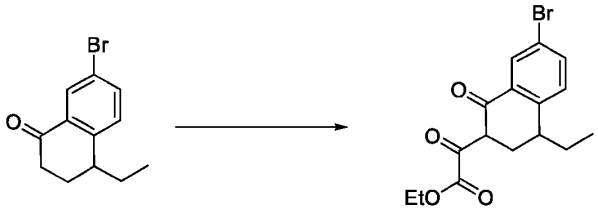
[0612] To a stirred solution of 6-bromo-3,4-dihydronaphthalen-1(2H)-one (6.3 g, 28 mmol) in ethanol (93.3 mL, 1.6 mol) was added sodium borohydride (4.24 g, 4 eq., 112 mmol) in small portions at 0 °C under inert atmosphere. The mixture was stirred for 2 hours at room temperature. The reaction was quenched with brine and extracted with EtOAc. The organic phase was dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The crude rac-6-bromo-1,2,3,4-tetrahydronaphthalen-1-ol (6.36 g, 28 mmol) was used in the next step without further purification. The flask containing crude rac-6-bromo-1,2,3,4-tetrahydronaphthalen-1-ol (6.36 g, 28 mmol) was back-filled with argon and cooled to 0 °C, and then thionyl chloride (5.08 mL, 2.5 eq., 70 mmol) was added slowly. The reaction mixture was stirred at 0 °C for 1 hour. The reaction progress was monitored by TLC, and thionyl chloride was removed by a rotavap upon completion. Then the crude rac-6-bromo-1-chloro-1,2,3,4-tetrahydronaphthalene was dissolved in CH_2Cl_2 (0.3 M) and the reaction mixture was cooled to –78 °C. Diethylzinc (1.0 M in hexanes, 56 mL, 56 mmol) was added dropwise. The reaction mixture was slowly warmed to 23 °C and stirred for 2 hours and then quenched with aqueous HCl solution (1.0 M) at 0 °C. The aqueous layer was extracted with CH_2Cl_2, dried over anhydrous MgSO4, filtered concentrated under reduced pressure, and purified by column chromatography (SiO2, 100% hexanes) to give rac-6-bromo-1-ethyl-1,2,3,4-tetrahydronaphthalene (6 g, 90% yield). ^{1}H NMR (400 MHz, CDCl3) δ 7.24 (dd, J = 10.3, 2.1 Hz, 2H), 7.06 (d, J = 8.1 Hz, 1H), 2.82 – 2.60 (m, 3H), 1.88 – 1.76 (m, 2H), 1.76 – 1.65 (m, 3H), 1.58 (ddq, J = 14.4, 9.2, 7.3 Hz, 1H), 0.98 (t, J = 7.4 Hz, 3H).

[0613] Step 4: Synthesis of rac-7-bromo-4-ethyl-3,4-dihydronaphthalen-1(2H)-one



[0614] The rac-6-bromo-1-ethyl-1,2,3,4-tetrahydronaphthalene (3.35 g, 14 mmol), MnO_2 (4.87 g, 4 eq., 56 mmol, loaded on 4.87 g silica gel) and DCM (140 mL, 0.1 M) were loaded in a 250 mL flask equipped with a magnetic stirring bar. The mixture was cooled to 0 °C and TBHP (11.6 mL, 84 mmol, 70 wt% in water) was added dropwise over 5 min. The reaction was stirred at 0 °C for 10 min, then it was allowed to warm to ambient temperature and stirred until gas formation ceased. The vial was sealed and the resulting black suspension was maintained at 23 °C for 2 h. Inorganic solids were removed by filtration. The filtrate was concentrated to dryness and purified by column chromatography (SiO2, 0-30% EtOAc in hexanes gradient) to afford rac-7-bromo-4-ethyl-3,4-dihydronaphthalen-1(2H)-one (634 mg, 18% yield) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 8.15 (d, J = 2.2 Hz, 1H), 7.60 (dd, J = 8.3, 2.3 Hz, 1H), 7.19 (dd, J = 8.2, 0.7 Hz, 1H), 2.86 – 2.80 (m, 1H), 2.79 – 2.71 (m, 1H), 2.59 (ddd, J = 17.8, 5.8, 4.8 Hz, 1H), 2.23 (ddt, J = 13.6, 11.4, 4.6 Hz, 1H), 2.08 (dq, J = 13.7, 5.2 Hz, 1H), 1.81 – 1.67 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H). MS (ESI, *m/z*): 253.0 $[M+H]^+$.

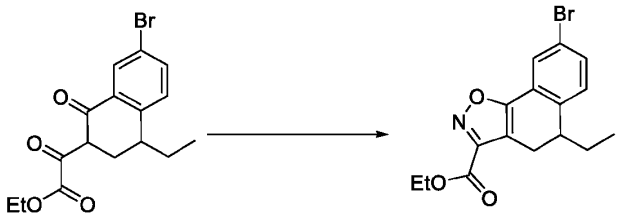
[0615] Step 5: Synthesis of rac-ethyl 2-(7-bromo-4-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate



[0616] To a stirred mixture of lithium tert-butoxide (38.5 mg, 1.3 eq., 481 μmol) in THF (1 mL) at 0 °C was added dropwise a solution of diethyl oxalate (64.9 mg, 1.2 eq., 444 μmol) in THF (1 mL). The resulting mixture was stirred at 0 °C for 30 minutes. To the reaction mixture was added dropwise a solution of rac-7-bromo-4-ethyl-1,2,3,4-tetrahydro-1-naphthalenone (93.7 mg, 370 μmol) in THF (1 mL). The mixture was stirred at ambient

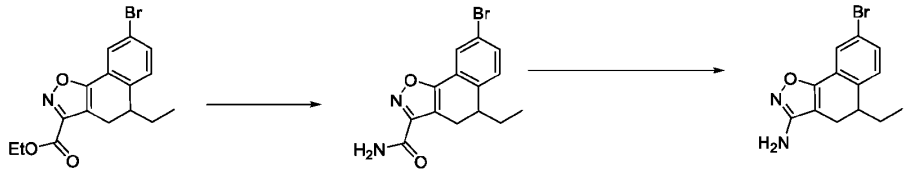
temperature for 2 h and then quenched with water. The resulting mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na2SO4 and concentrated under vacuum to afford rac-ethyl 2-(7-bromo-4-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate (131 mg, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 353.0 $[M+H]^+$.

[0617] Step 6: Synthesis of rac-ethyl 8-bromo-5-ethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate



[0618] A mixture of rac-ethyl 2-(7-bromo-4-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate (131 mg, 370 μmol) and hydroxylamine hydrochloride (25.7 mg, 370 μmol) in EtOH (4 mL) was stirred at 80 °C for 16 h and then concentrated under vacuum. The residue was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na2SO4 and concentrated under vacuum. The crude material was purified by silica gel chromatography (0-50% EtOAc in Hexanes) to afford rac-ethyl 8-bromo-5-ethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (41 mg, 32% yield) as a yellow solid, MS (ESI, *m/z*): 350.0 $[M+H]^+$.

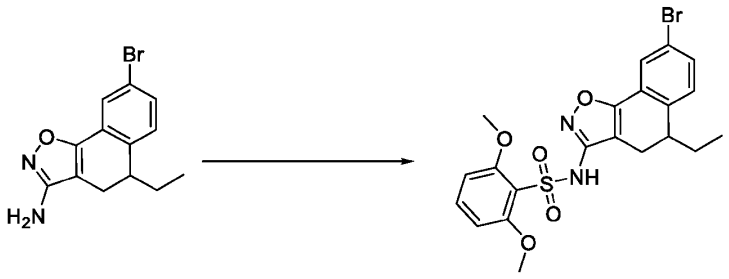
[0619] Step 7-8: Synthesis of rac-8-bromo-5-ethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine



[0620] To a stirred mixture of rac-ethyl 8-bromo-5-ethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (70 mg, 0.2 mmol) in MeOH (2 mL) at ambient temperature was added ammonium hydroxide (2 mL). The resulting mixture was stirred at 23 °C for 2 h and then concentrated under vacuum to afford crude rac-8-bromo-5-ethyl-4,5-

dihydronaphtho[2,1-d]isoxazole-3-carboxamide (64.2 mg, 0.2 mmol) as a white solid, which was used directly to next step. To a stirred mixture of rac-8-bromo-5-ethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (64.2 mg, 0.2 mmol) in combined solvent system of EtOAc (2 mL), acetonitrile (2 mL) and H2O (1 mL) was added (diacetoxyiodo)benzene (96.6 mg, 1.5 eq., 0.3 mmol). The resulting mixture was stirred at 23 °C for 16 h and then quenched with saturated sodium thiosulfate solution. The resulting mixture was extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash CHchCchromatography on silica gel (0 to 60% EtOAc in hexanes) to afford rac-8-bromo-5-ethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (10 mg, 17% yield) as a light yellow solid. 1H NMR (400 MHz, CDCl3) δ 7.75 (d, J = 2.1 Hz, 1H), 7.48 (dd, J = 8.2, 2.1 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 3.89 (s, 2H), 2.94 (tt, J = 6.8, 3.5 Hz, 1H), 2.85 (dd, J = 15.8, 6.9 Hz, 1H), 2.61 (dd, J = 15.9, 3.3 Hz, 1H), 1.65 – 1.54 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H). MS (ESI, *m/z*): 293.0 $[M+H]^+$.

[0621] Step 9: Synthesis of rac-N-(8-bromo-5-ethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide

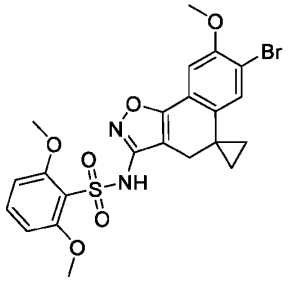


[0622] To a solution of rac-8-bromo-5-ethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (11.7 mg, 40 µmol) in dry THF (1 mL) at -78 °C under N_2 was added LiHMDS (1.0 M solution in THF, 0.12 mL, 0.12 mmol) dropwise and the mixture was stirred at -78 °C for 1 h. 2,6-dimethoxybenzenesulfonyl chloride (14.2 mg, 1.5 eq., 60 µmol) was then added dropwise and the mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was acidified to pH 4-5 with 1 M aqueous HCI and extracted with EtOAc. The organic layer was dried with Na2SO4, filtered, and concentrated in vacuo. The crude product was subsequently purified by prep-HPLC (0-60% CH3CN (0.1% FA) in H2O (0.1% FA)), and dried via lyophilization giving rac-N-(8-bromo-5-ethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-

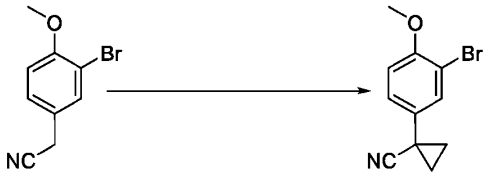
yl)-2,6-dimethoxybenzenesulfonamide as a white solid (5 mg, 24% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.64 (d, J = 2.1 Hz, 1H), 7.56 (dd, J = 8.2, 2.2 Hz, 1H), 7.47 (t, J = 8.4 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 6.75 (d, J = 8.5 Hz, 2H), 3.78 (s, 6H), 2.94 – 2.85 (m, 1H), 2.84 – 2.73 (m, 1H), 2.68 (dd, J = 16.6, 6.9 Hz, 1H), 1.38 (p, J = 7.4 Hz, 2H), 0.78 (t, J = 7.3 Hz, 3H). MS (ESI, *m/z*): 493.2 $[M+H]^+$.

Example 21

N-(7'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide



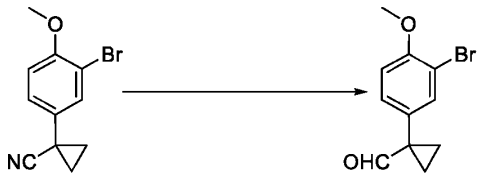
[0623] Step 1. Synthesis of 1-(3-bromo-4-methoxyphenyl)cyclopropane-1-carbonitrile



[0624] To a stirred solution of NaH (60% in mineral oil, 22.0 g, 917.8 mmol, 2.5 equiv) in DMF (900.0 mL) at 0 °C was added dropwise a solution of 2-(3-bromo-4-methoxyphenyl)acetonitrile (83.0 g, 367.1 mmol, 1.0 equiv) and 1,2-dibromoethane (103.4 g, 550.7 mmol, 1.5 equiv) in DMF (100.0 mL) over 10 mins under N_2 atmosphere. The resulting mixture was stirred at ambient temperature for another 2 h and then quenched with NH_4Cl solution and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-30% EtOAc in petroleum ether) to afford 1-(3-bromo-4-methoxyphenyl)cyclopropane-1-carbonitrile (47.5 g, 46% yield) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 (d, *J* = 2.4 Hz, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 6.89 (d, *J* =

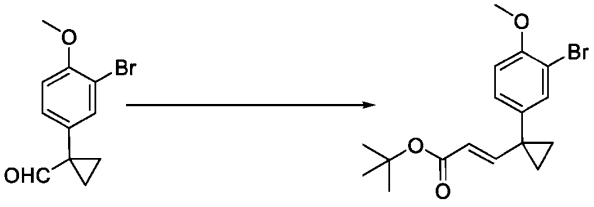
8.8 Hz, 1H), 3.92 (s, 3H), 1.75-1.63 (m, 2H), 1.44-1.32 (m, 2H).MS (ESI, *m/z*): 252, 254 $[M+H]^+$.

[0625] Step 2. Synthesis of 1-(3-bromo-4-methoxyphenyl)cyclopropane-1-carbaldehyde



[0626] To a stirred solution of 1-(3-bromo-4-methoxyphenyl)cyclopropane-1-carbonitrile (47.5 g, 188.4 mmol, 1.0 equiv) in DCM (1000.0 mL) at -78 °C was added dropwise DIBAL-H (237.5 mL, 1M in THF, 237.5 mmol, 1.3 eq) under N_2 atmosphere. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 2 h. The mixture was quenched with NH_4Cl solution and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford 1-(3-bromo-4-methoxyphenyl)cyclopropane-1-carbaldehyde (43.0 g, crude) as a yellow solid, which was used for the next step without further purification. ^1H NMR (300 MHz, Chloroform-*d*) δ 9.14 (s, 1H), 7.51-7.40 (m, 1H), 7.23-7.12 (m, 1H), 6.93-6.78 (m, 1H), 3.89 (s, 3H), 1.60-1.50 (m, 2H), 1.43-1.32 (m, 2H). MS (ESI, *m/z*): 255, 257 $[M+H]^+$.

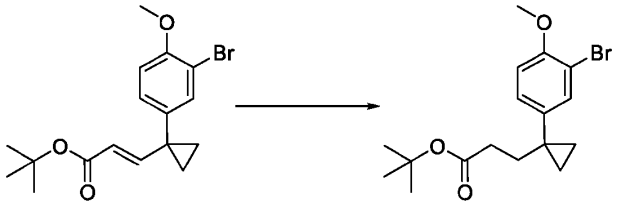
[0627] Step 3. Synthesis of tert-butyl (E)-3-(1-(3-bromo-4-methoxyphenyl)cyclopropyl)acrylate



[0628] To a stirred solution of tert-butyl 2-(diethoxyphosphoryl)acetate (85.0 g, 337.1 mmol, 2.0 equiv) in THF (500.0 mL) at 0 °C was added NaH (60% in mineral oil, 8.0 g, 337.1 mmol, 2.0 equiv) in portions The resulting reaction mixture was stirred at this temperature for 0.5 h and to this was added a solution of 1-(3-bromo-4-methoxyphenyl)cyclopropane-1-carbaldehyde (43.0 g, 168.5 mmol, 1.0 equiv) in THF (200.0

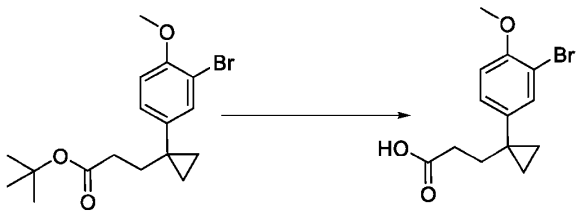
mL). The resulting mixture was stirred at ambient temperature for 1 h and then quenched with NH_4Cl solution and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-30% EtOAc in petroleum ether) to afford tert-butyl (E)-3-(1-(3-bromo-4-methoxyphenyl)cyclopropyl)acrylate (42.4 g, 64% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 2.1 Hz, 1H), 7.26-7.16 (m, 1H), 6.92-6.85 (m, 1H), 6.55 (d, *J* = 15.3 Hz, 1H), 5.23 (d, *J* = 15.3 Hz, 1H), 3.91 (d, *J* = 1.2 Hz, 3H), 1.48-1.42 (s, 9 H), 1.29-1.21 (m, 2H), 1.21-1.12 (m, 2H). MS (ESI, *m/z*): 353, 355 $[M+H]^+$.

[0629] Step 4. Synthesis of tert-butyl 3-(1-(3-bromo-4-methoxyphenyl)cyclopropyl)propanoate



[0630] A mixture of tert-butyl (E)-3-(1-(3-bromo-4-methoxyphenyl)cyclopropyl)acrylate (42.4 g, 120.0 mmol, 1 equiv) and $Rh.Al_2O_3$ (4.2 g, 5% Rh on alumina, 10% w/w) in EtOH (1000.0 mL) was stirred at ambient temperature for 1 h under H_2 (~3 atm) atmosphere and then filtered. The filtrate was concentrated under vacuum to afford tert-butyl 3-(1-(3-bromo-4-methoxyphenyl)cyclopropyl)propanoate (40.0 g, crude) as brown oil, which was used for the next step without further purification. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47 (d, *J* = 2.1 Hz, 1H), 7.24-7.16 (m, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 3.86 (s, 3H), 2.22-2.11 (m, 2H), 1.85-1.73 (m, 2H), 1.41 (s, 9H), 0.81-0.72 (m, 2H), 0.71-0.61 (m, 2H).MS (ESI, *m/z*): 355, 357 $[M+H]^+$.

[0631] Step 5. Synthesis of 3-(1-(3-bromo-4-methoxyphenyl)cyclopropyl)propanoic acid



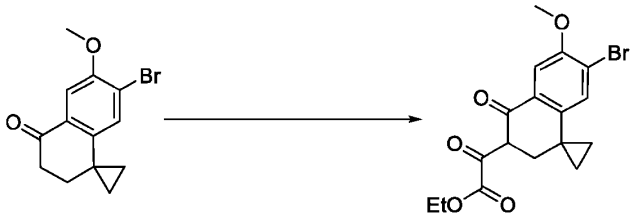
[0632] A mixture of tert-butyl 3-(1-(3-bromo-4-methoxyphenyl)cyclopropyl)propanoate (40.0 g, 112.5 mmol, 1.0 equiv) and TFA (200.0 mL) in DCM (500.0 mL) was stirred at ambient temperature for 2 h. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (0-70% acetonitrile in water (contained 0.1% formic acid)) to afford 3-(1-(3-bromo-4-methoxyphenyl)cyclopropyl)propanoic acid (31.0 g, 73% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 2.1 Hz, 1H), 7.25-7.15 (m, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 3.87 (s, 3H), 2.41-2.30 (m, 2H), 1.92-1.81 (m, 2H), 0.86-0.76 (m, 2H), 0.75-0.63 (m, 2H).MS (ESI, *m/z*): 299, 301 $[M+H]^+$.

[0633] Step 6. Synthesis of 7'-bromo-6'-methoxy-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one



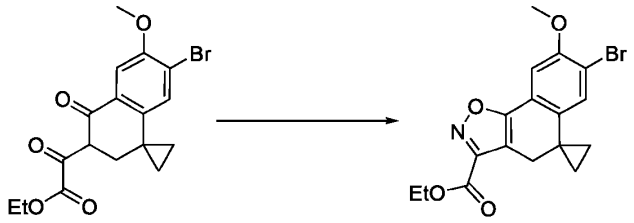
[0634] To a stirred mixture of 3-(1-(3-bromo-4-methoxyphenyl)cyclopropyl)propanoic acid (31.0 g, 103.6 mmol, 1.0 equiv) in DCM (250.0 mL) at 0 °C was added oxalic dichloride (26.3 g, 207.2 mmol, 2.0 equiv) and DMF (0.38 g, 5.1 mmol, 0.05 equiv) under N_2 atmosphere. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 2 h and then concentrated under vacuum. The residue was re-dissolved in DCM (250.0 mL) and to this at 0 °C was added $AlCl_3$ (11.0 g, 82.8 mmol, 0.8 equiv). The resulting mixture was allowed to warm up to ambient temperature and stirred for another 1 h. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-30% EtOAc in petroleum ether) to afford 7'-bromo-6'-methoxy-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (18.5 g, 60% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.52 (s, 1H), 7.03 (s, 1H), 3.93 (s, 3H), 2.81-2.71 (m, 2H), 2.01-1.91 (m, 2H), 1.09-0.99 (m, 2H), 0.99-0.91 (m, 2H). MS (ESI, *m/z*): 281, 283 $[M+H]^+$.

[0635] Step 7. Synthesis of ethyl 2-(7'-bromo-6'-methoxy-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate



[0636] To a stirred solution of 7'-bromo-6'-methoxy-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (18.5 g, 65.8 mmol, 1.0 equiv) in THF (1800.0 mL) at -78 °C was added LiHMDS (78.9 mL, 1M in THF, 78.9 mmol, 1.2 eq) under N_2 atmosphere. The resulting reaction mixture was stirred at this temperature for 0.5 h and to this was added dropwise a solution of ethyl oxalate (11.5 g, 78.9 mmol, 1.2 equiv). The resulting mixture was stirred at the temperature for another 2 h and then quenched with NH_4Cl solution and extracted with EtOAc for three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford ethyl 2-(7'-bromo-6'-methoxy-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (16.8 g, 60% yield) as a yellow solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.53 (s, 1H), 7.12 (s, 1H), 4.40-4.33 (m, 3H), 3.96 (s, 3H), 2.83 (s, 2H), 1.43-1.37 (m, 3H), 1.01-0.85 (m, 4H).MS (ESI, *m/z*): 381, 383 $[M+H]^+$.

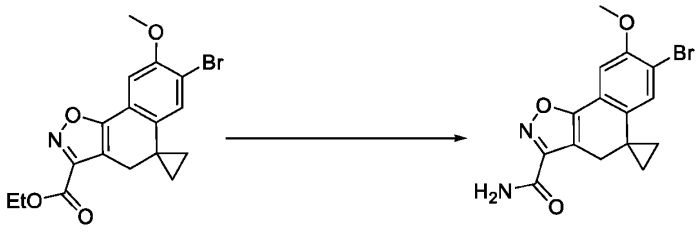
[0637] Step 8. Synthesis of ethyl 7'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate



[0638] A mixture of ethyl 2-(7'-bromo-6'-methoxy-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (16.8 g, 44.0 mmol, 1.0 equiv) and $NH_2OH{\cdot}HCl$ (3.3 g, 48.4 mmol, 1.1 equiv) in acetonitrile (1700.0 mL) was stirred at 70 °C for 2 h. The resulting mixture was concentrated under vacuum to afford ethyl 7'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (17.0 g, crude)

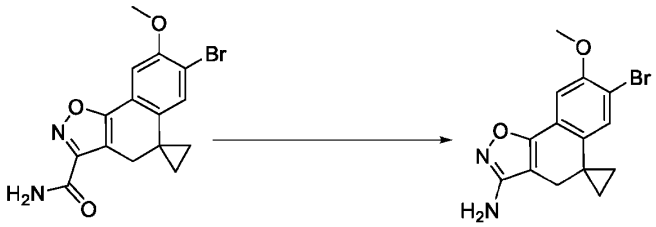
as brown oil, which was used for the next step without further purification. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.27 (s, 1H), 7.11 (s, 1H), 4.50-4.33 (m, 2H), 3.98 (s, 3H), 2.89 (s, 2H), 1.47-1.36 (m, 3H), 1.01-0.95 (m, 2H), 0.94-0.88 (m, 2H).MS (ESI, *m/z*): 378, 380 $[M+H]^+$.

[0639] Step 9. Synthesis of 7'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide



[0640] A mixture of (17.0 g, 44.947 mmol, 1 equiv) in $NH_3{\cdot}H_2O$ (1000.0 mL) and MeOH (2000.0 mL) was stirred at ambient temperature for 2 h. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (0-70% acetonitrile in water (contained 0.05% NH_4HCO_3)) to afford 7'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (5.5 g, 31.5% yield) as a brown solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.24 (s, 1H), 7.11 (s, 1H), 6.78 (s, 1H), 5.83 (s, 1H), 3.97 (s, 3H), 2.95 (s, 2H), 1.00-0.91 (m, 4H).MS (ESI, *m/z*): 349, 351 $[M+H]^+$.

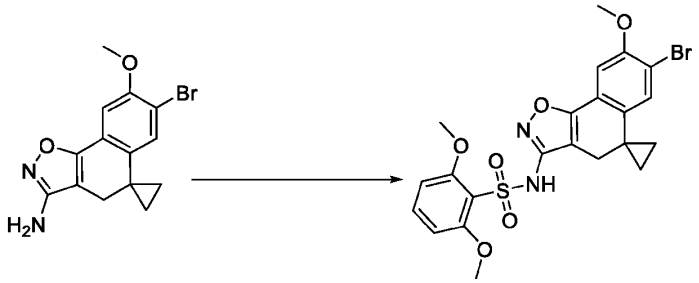
[0641] Step 10. Synthesis of 7'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine



[0642] A mixture of 7'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (5.5 g, 15.7 mmol, 1..0 equiv) and $PhI(OAc)_2$ (10.1 g, 31.5 mmol, 2 equiv) in EtOAc (100.0 mL)/acetonitrile (100.0 mL)/H_2O (30.0 mL) at ambient

temperature was stirred for 2 h and then diluted with water. The resulting mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford 7'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (3.0 g, 47% yield) as a brown solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.17 (s, 1H), 7.06 (s, 1H), 3.94 (s, 3H), 3.82 (d, *J* = 25.2 Hz, 2H), 2.51 (s, 2H), 1.02-0.94 (m, 2H), 0.90-0.83 (m, 2H).MS (ESI, *m/z*): 321, 323 $[M+H]^+$.

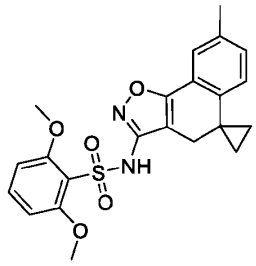
[0643] Step 11. Synthesis of N-(7'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide



[0644] A mixture of 7'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-Amine (150.0 mg, 0.4 mmol, 1. equiv) and 2,6-dimethoxybenzenesulfonyl chloride (132.6 mg, 0.5 mmol, 1.2 equiv) in pyridine (15.0 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (0-70% acetonitrile in water (contained 0.05% NH_4HCO_3)) to afford N-(7'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide (114.7 mg, 46% yield) as a brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.69 (s, 1H), 7.50 (t, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 9.9 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H), 3.89 (s, 3H), 3.80 (s, 6H), 2.57 (s, 2H), 1.03-0.93 (m, 2H), 0.77-0.67 (m, 2H). MS (ESI, *m/z*): 521, 523 $[M+H]^+$.

Example 22

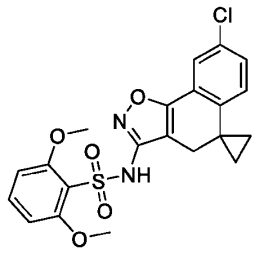
2,6-Dimethoxy-N-(8'-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



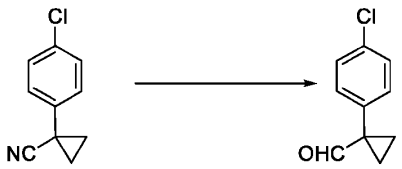
[0645] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide (50.0 mg, 0.1 mmol, 1.0 equiv, Example 15), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (19.1 mg, 0.1 mmol, 1.5 equiv), $Pd(dppf)Cl_2CH_2Cl_2$ (8.2 mg, 0.01 mmol, 0.1 equiv) and Cs_2CO_3 (66.3 mg, 0.2 mmol, 2.0 equiv) in dioxane (5.0 mL) and H_2O (1.0 mL) was stirred at 80 °C for 1 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (0-80% acetonitrile in water (contained 0.1% formic acid)) to afford 2,6-dimethoxy-N-(8'-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide(13.9 mg, 31% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.64 (s, 1H), 7.48 (t, J = 8.4 Hz, 1H), 7.35 (d, J = 1.8 Hz, 1H), 7.16-7.12 (m, 1H), 6.93 (d, J = 8.1 Hz, 1H), 6.75 (d, J = 8.4 Hz, 2H), 3.77 (s, 6H), 2.55 (s, 2H), 2.28 (s, 3H), 0.96-0.85 (m, 2H), 0.78-0.64 (m, 2H). MS (ESI, *m/z*): 427 $[M+H]^+$.

Example 23

N-(8'-chloro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6 dimethoxybenzenesulfonamide

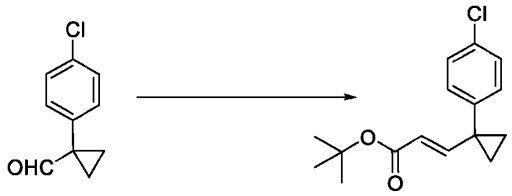


[0646] Step 1. Synthesis of ethyl 1-(4-chlorophenyl)cyclopropane-1-carbaldehyde



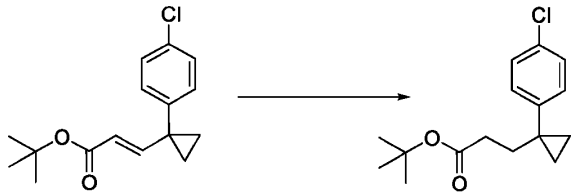
[0647] To a stirred solution of 1-(4-chlorophenyl)cyclopropane-1-carbonitrile (20.0 g, 112.59 mmol, 1 equiv) in DCM (300.0 mL) at -78 °C were added DIBAL-H (150.0 mL, 1.0 mol/L in hexane, 150 mmol, 1.3 equiv). The resulting solution was stirred at -78 °C for 1 h and then quenched with water. The residue was acidified with aqueous HCl (1 M) to pH 7 and extracted with DCM three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford ethyl 1-(4-chlorophenyl)cyclopropane-1-carbaldehyde (17.0 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 181, 183 $[M+H]^+$.

[0648] Step 2. Synthesis of tert-butyl (E)-3-(1-(4-chlorophenyl)cyclopropyl)acrylate



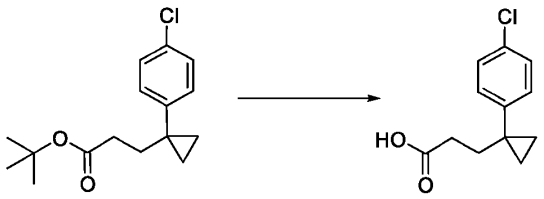
[0649] To a stirred solution of tert-butyl 2-(diethoxyphosphoryl)acetate (47.6 g, 188.71 mmol, 2.0 equiv) in THF (220 mL) at 0 °C was added NaH (60% in mineral oil, 7.5 g, 187.5 mmol, 2.0 equiv) in portions. The resulting mixture was stirred at 0 °C for 0.5 h and to this at ambient temperature was added chlorophenyl)cyclopropane-1-carbaldehyde (17.0 g, 94.12 mmol, 1.0 equiv). The resulting mixture was stirred for another 2 h and then quenched with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-20% DCM in petroleum ether) to afford tert-butyl (E)-3-(1-(4-chlorophenyl)cyclopropyl)acrylate (22.4 g, 85% yield) as a white solid. MS (ESI, *m/z*): 279, 281 $[M+H]^+$.

[0650] Step 3. Synthesis of tert-butyl 3-(1-(4-chlorophenyl)cyclopropyl)propanoate



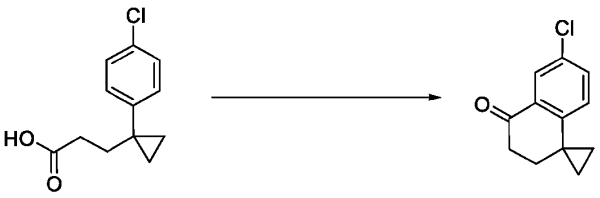
[0651] A stirred mixture of tert-butyl (E)-3-(1-(4-chlorophenyl)cyclopropyl)acrylate (22.4 g, 80.35 mmol, 1.0 equiv) and Rh.Al_2O_3 (wet, 10%, 3.0 g, 5% Rh on alumina) in a combined solvent of ethanol (50.0 mL), EtOAc (30.0 mL) and DCM (60.0 mL) were stirred at ambient temperature for 2 days under H_2 (~3 atm) atmosphere and then filtered. The filtrate was concentrated under vacuum to afford tert-butyl 3-(1-(4-chlorophenyl)cyclopropyl)propanoate (22.9 g, crude) as colorless oil, which was used for the next step without further purification. MS (ESI, *m/z*): 281, 283 $[M+H]^+$.

[0652] Step 4. Synthesis of 3-(1-(4-chlorophenyl)cyclopropyl)propanoic acid



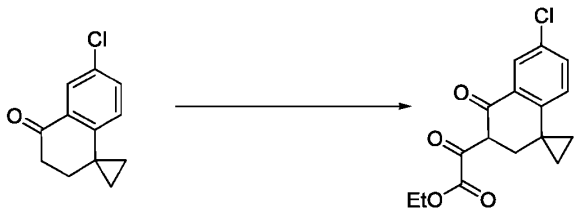
[0653] To a stirred solution of tert-butyl 3-(1-(4-chlorophenyl)cyclopropyl)propanoate (22.9 g, 81.56 mmol, 1.0 equiv) in DCM (200.0 mL) at 0 °C was added TFA (50.0 mL). The resulting mixture was stirred at ambient temperature for 2 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-20% EtOAc in petroleum ether) to afford 3-(1-(4-chlorophenyl)cyclopropyl)propanoic acid (15.6 g, 85% yield) as a white solid. MS (ESI, *m/z*): 225, 227 $[M+H]^+$.

[0654] Step 5. Synthesis of 6'-chloro-2',3'-dihydro-4'H-s'iro[cyclopropane-1,1'-naphthalen]-4'-one



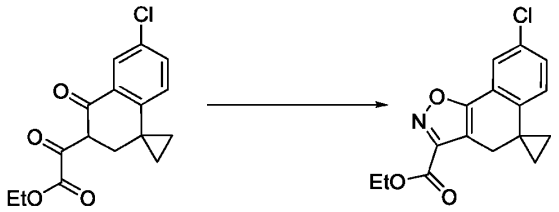
[0655] To a stirred solution of 3-(1-(4-chlorophenyl)cyclopropyl)propanoic acid (13.6 g, 60.53 mmol, 1.0 equiv) in TFA (100.0 mL) at ambient temperature was added TFAA (25.5 g, 121.06 mmol, 2.0 equiv). The resulting mixture was stirred at 80 °C for 4 h and then allowed to cool down to ambient temperature. The mixture was diluted with water and then neutralized with saturated NaHCO3 solution to pH 7.0 and extracted with DCM three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-20% EtOAc in petroleum ether) to afford 6'-chloro-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (3.68 g, 32% yield) as a light yellow solid. MS (ESI, *m/z*): 207, 209 $[M+H]^+$.

[0656] Step 6. Synthesis of ethyl 2-(6'-chloro-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate



[0657] To a stirred solution of 6'-chloro-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (3.1 g, 14.76 mmol, 1.0 equiv) in tetrahydrofuran (50.0 mL) at 0 °C was added t-BuOLi (3.0 g, 36.81 mmol, 2.5 equiv). The resulting mixture was stirred for 0.5 h and to this was added diethyl oxalate (4.3 g, 29.52 mmol, 2.0 equiv). The resulting mixture was stirred for another 2 h and then quenched with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-20% EtOAc in petroleum ether) to afford ethyl 2-(6'-chloro-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (3.5 g, 75% yield) as a yellow oil. MS (ESI, *m/z*): 307, 309 $[M+H]^+$.

[0658] Step 7. Synthesis of ethyl 8'-chloro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate



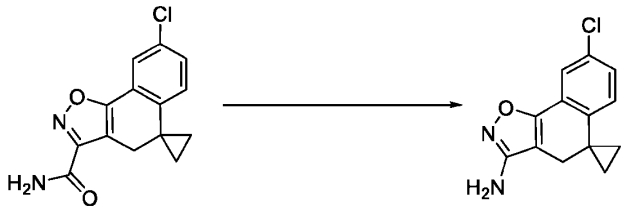
[0659] To a stirred solution of ethyl 2-(6'-chloro-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (3.5 g, 11.41 mmol, 1.0 equiv) in ethanol (40.0 mL) at ambient temperature was added hydroxylamine hydrochloride (1.4 g, 20.20 mmol, 1.8 equiv). The resulting mixture was stirred at 80 °C for 16 h and then allowed to cool down to ambient temperature and concentrated under vacuum. The residue was purified by lash chromatography on silica gel (0-15% EtOAc in petroleum ether) to afford ethyl 8'-chloro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (2.5 g, 72% yield) as yellow oil. MS (ESI, *m/z*): 304, 306 $[M+H]^+$.

[0660] Step 8. Synthesis of 8'-chloro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide



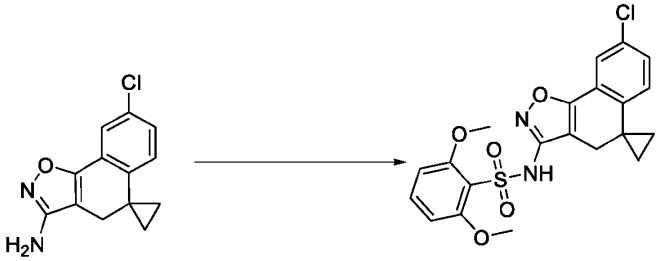
[0661] A mixture of ethyl 8'-chloro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (3.4 g, 11.19 mmol, 1.0 equiv) in NH_3 (7.0 M in MeOH, 80.0 mL) was stirred at ambient temperature for 16 h. The precipitated solids were collected by filtration and purified by trituration with methanol to afford 8'-chloro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (2.1 g, 68% yield) as a white solid. MS (ESI, *m/z*): 275, 277 $[M+H]^+$.

[0662] Step 9. Synthesis of 8'-chloro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine



[0663] To a stirred solution of 8'-chloro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (500.0 mg, 1.82 mmol, 1.0 equiv) and TEA (550.0 mg, 5.44 mmol, 3.0 equiv) in combined solvent system of EtOAc (10 mL), acetonitrile (10 mL) and H_2O (5 mL) at ambient temperature was added $PhI(OAc)_2$ (600.0 mg, 1.86 mmol, 1.0 equiv). The resulting solution was stirred for 1 h and quenched with NaS_2O_3 solution at 0 °C and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford 8'-chloro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (150.0 mg, crude) as a yellow solid. MS (ESI, *m/z*):247, 249 $[M+H]^+$.

[0664] Step 10. Synthesis of N-(8'-chloro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide

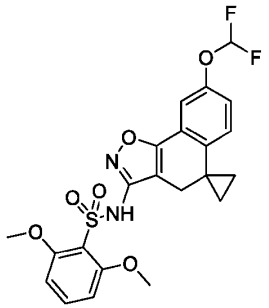


[0665] To a stirred solution of 8'-chloro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (200.0 mg, 0.81 mmol, 1.0 equiv) in pyridine (5.0 mL) at ambient temperature was added 2,6-dimethoxybenzenesulfonyl chloride (535.0 mg, 2.26 mmol, 2.8 equiv). The resulting mixture was stirred at 80 °C for 2 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) and further purified by Prep-HPLC (5-70% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-chloro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide (130.8 mg, 36% yield over two steps)

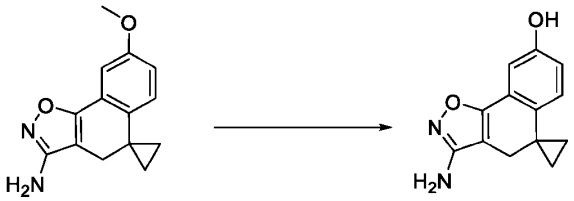
as a white solid. MS (ESI, *m/z*): 447, 449 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.53-7.48 (m, 1H), 7.40-7.37 (m, 1H), 7.40-7.37 (m, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 3.80 (s, 6H), 2.62 (s, 2H), 1.02-0.99 (m, 2H), 0.81-0.78 (m, 2H).

Example 24

N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide

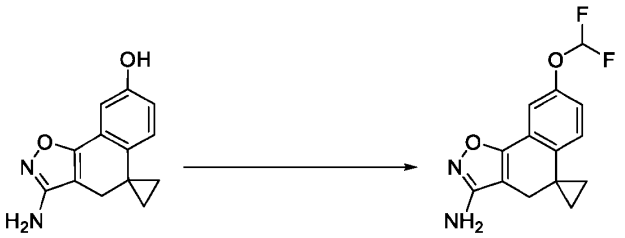


[0666] Step 1. Synthesis of 3'-amino-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-8'-ol



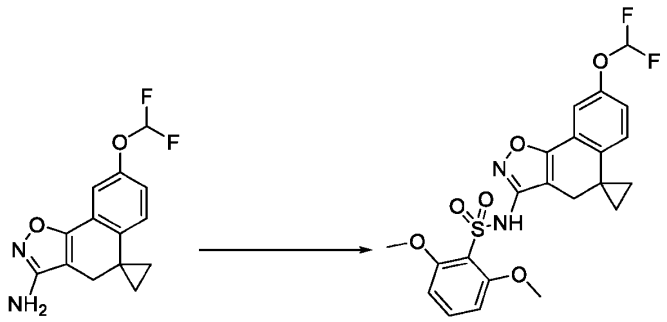
[0667] To a stirred solution of 8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (1.4 g, 5.78 mmol, 1.00 equiv, Example 18, Step 7) in DCM (20.0 mL) at -5 °C was added dropwise BBr_3 (1 M in DCM, 11.6 mL, 11.6 mmol, 2.00 equiv) under N_2 atmosphere. The resulting mixture was stirred at this temperature for 1 h and then quenched with saturated $NaHCO_3$ solution and extracted with EtOAc three times. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-50% acetonitrile in water (contained 0.1% formic acid)) to afford 3'-amino-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-8'-ol (740.5 mg, 56% yield) as a yellow solid. MS (ESI, *m/z*): 229 $[M+H]^+$.

[0668] Step 2. Synthesis of 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine



[0669] A mixture of 3'-amino-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-8'-ol (50.0 mg, 0.22 mmol, 1.00 equiv), NaOH (26.3 mg, 0.66 mmol, 3.00 equiv) and sodium 2-chloro-2,2-difluoroacetate (49.9 mg, 0.33 mmol, 1.50 equiv) in DMF (2.5 mL) was stirred at 60 °C for 3 h under N_2 atmosphere. The resulting mixture was diluted with water and extracted with EtOAc three times. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another 19 batch (same scale) and purified by reverse phase flash chromatography on C18 gel (5-60% acetonitrile in water (contained 0.1% formic acid)) to afford 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (210.1 mg, 17% yield) as a yellow solid. MS (ESI, *m/z*): 279 $[M+H]^+$.

[0670] Step 3. Synthesis of N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide

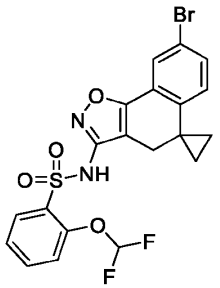


[0671] A mixture of 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (60.0 mg, 0.22 mmol, 1.00 equiv) and 2,6-dimethoxybenzenesulfonyl chloride (102.1 mg, 0.43 mmol, 2.00 equiv) in pyridine (1.0 mL) was stirred at 80 °C for 1 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The residue

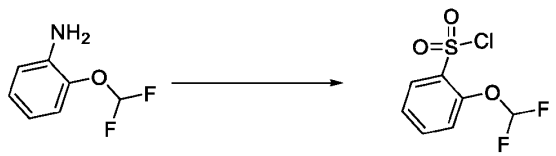
was diluted with water and acidified with aqueous HCl (1 M) to pH 3 and then extracted with EtOAc three times. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-55%, acetonitrile in water (contained 0.1% formic acid)) and further purified by Prep-HPLC (5-45% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide (35.6 mg, 34% yield) as a white solid. MS (ESI, *m/z*): 479 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-*d6*) δ 10.73 (s, 1H), 7.55–7.50 (m, 1H), 7.33 (d, J = 1.8 Hz, 1H), 7.28 (t, J = 60.0 Hz, 1H) 7.18-7.09 (m, 2H), 6.78 (d, J = 8.4 Hz, 2H), 3.80 (s, 6H), 2.61 (s, 2H), 1.04-0.94 (m, 2H), 0.82-0.73 (m, 2H). ^{19}F NMR (282 MHz, DMSO-*d6*) δ -82.34.

Example 25

N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-(difluoromethoxy)benzenesulfonamide



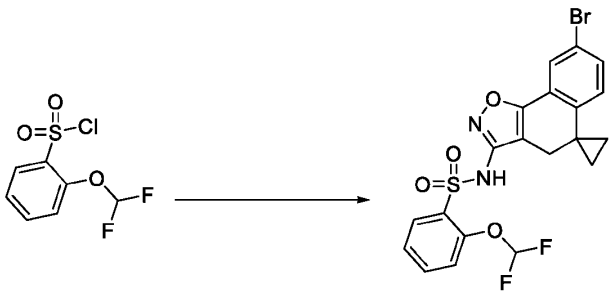
[0672] Step 1. Synthesis of 2-(difluoromethoxy)benzenesulfonyl chloride



[0673] To a stirred solution of CuCl (5 g, 50.3 mmol, 4.00 equiv) in water (20 mL) at 0 °C was bubbled through SO_2 for 30 min to prepare the SO_2 aqueous solution. To a stirred solution of 2-(difluoromethoxy)aniline (2 g, 12.6 mmol, 1.00 equiv) in AcOH (15 mL) and aqueous HCl (3 mL) at 0 °C was added $NaNO_2$ (1.7 g, 25.13 mmol, 2.00 equiv) in portions.

The resulting mixture was stirred at this temperature for 30 mins and to this was added dropwise half of the above SO_2 aqueous solution. The reaction mixture was stirred for further 30 min and then to this was added another half of the SO_2 aqueous solution. The resulting mixtures were stirred at ambient temperature for another 1 h and then diluted with water at 0 °C and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-30% EtOAc in petroleum ether) to afford 2-(difluoromethoxy)benzenesulfonyl chloride (1.4 g, 44% yield) as yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.78 (dd, J = 7.7, 1.8 Hz, 1H), 7.42-7.34 (m, 1H), 7.30-6.75 (m, 3H).

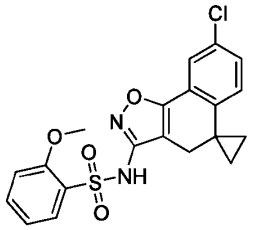
[0674] Step 2. Synthesis of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-(difluoromethoxy)benzenesulfonamide



[0675] A solution of 2-(difluoromethoxy)benzenesulfonyl chloride (125.0 mg, 0.52 mmol, 1.50 equiv) and 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (100.0 mg, 0.34 mmol, 1.000 equiv, Intermediate C) in pyridine (1.5 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-60% acetonitrile in water (contained 0.05% formic acid)) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-(difluoromethoxy)benzenesulfonamide (14.0 mg, 8% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 11.41 (s, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.74 (t, J = 7.8 Hz, 1H), 7.68-7.60 (m, 1H), 7.56-7.34 (m, 3H), 7.28 (s, 1H), 7.07-6.98 (m, 1H), 2.62 (s, 2H), 0.99 (d, J = 5.1 Hz, 2H), 0.86 (d, J = 5.1 Hz, 2H). MS (ESI, *m/z*): 497, 499 $[M+H]^+$.

Example 26

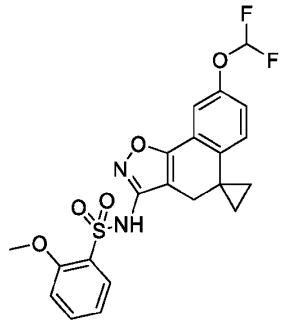
N-(8'-chloro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0676] To a stirred solution of 8'-chloro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (240.0 mg, 0.97 mmol, 1.0 equiv, Example 23, Step 9) in pyridine (5.0 mL) at ambient temperature was added 2-methoxybenzenesulfonyl chloride (600.0 mg, 2.90 mmol, 3.0 equiv). The resulting mixture was stirred at 80 °C for 2 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0- 50% EtOAc in petroleum ether) and further purified by Prep-HPLC (5-70% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-chloro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (67.1 mg, 16% yield) as a white solid. MS (ESI, *m/z*): 417, 419 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 7.80-7.78 (m, 1H), 7.64-7.59 (m, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.40-7.37 (m, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.11-7.06 (m, 1H), 3.82 (s, 3H), 2.62 (s, 2H), 1.02-0.99 (m, 2H), 0.86-0.84 (m, 2H).

Example 27

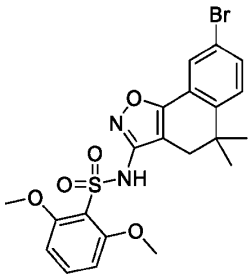
N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



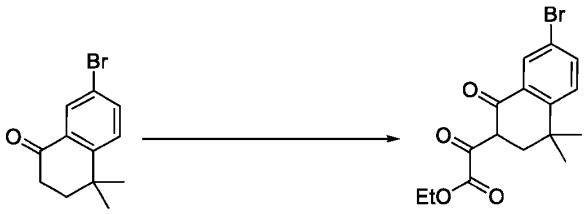
[0677] A mixture of 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (150.0 mg, 0.54 mmol, 1.00 equiv, Example 24, Step 2) and 2-methoxybenzenesulfonyl chloride (222.8 mg, 1.08 mmol, 2.00 equiv) in pyridine (2.0 mL) was stirred at 80 °C for 1 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The residue was diluted with water and acidified with aqueous HCl (1 M) to pH 3 and extracted with EtOAc three times. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-45% acetonitrile in water (contained 0.1% formic acid)) and further purified by Prep-HPLC (5-45% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (46.5 mg, 19% yield) as a white solid. MS (ESI, *m/z*): 449 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.94 (brs, 1H), 7.80 (dd, J = 7.8, 1.8 Hz, 1H), 7.68-7.59 (m, 1H), 7.32 (d, J = 2.1 Hz, 1H), 7.27 (t, J = 73.8, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.18-7.05 (m, 3H), 3.84 (s, 3H), 2.63 (s, 2H), 1.02-0.95 (m, 2H), 0.87-0.81 (m, 2H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -82.32.

Example 28

N-(8-bromo-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide

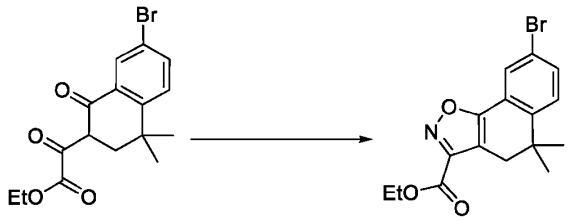


[0678] Step 1. Synthesis of ethyl 2-(7-bromo-4,4-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate



[0679] To a stirred mixture of 7-bromo-4,4-dimethyl-2,3-dihydronaphthalen-1-one (670 mg, 2.64 mmol, 1 equiv) and ethyl oxalate (773 mg, 5.29 mmol, 2 equiv) in THF (15 mL) at ambient temperature were added LiHMDS (1M in THF, 7.94 mL, 7.94 mmol, 3 equiv) under N_2 atmosphere. The resulting mixture was stirred at this temperature for 1 h and then quenched with saturated NH_4Cl solution and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford ethyl 2-(7-bromo-4,4-dimethyl-1-oxo-2,3-dihydronaphthalen-2-yl)-2-oxoacetate (1.5 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 353, 355 $[M+H]^+$.

[0680] Step 2. Synthesis of ethyl 8-bromo-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate



[0681] A mixture of ethyl 2-(7-bromo-4,4-dimethyl-1-oxo-2,3-dihydronaphthalen-2-yl)-2-oxoacetate (1.3 g, 3.681 mmol, 1 equiv) and $NH_2OH{\cdot}HCl$ (255.7 mg, 3.68 mmol, 1.0 equiv) in ethanol (15.0 mL) was stirred at 80 °C for 3 h. The resulting mixture was concentrated under vacuum to afford ethyl 8-bromo-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (1.3 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 350, 351 $[M+H]^+$.

[0682] Step 3. Synthesis of 8-bromo-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide



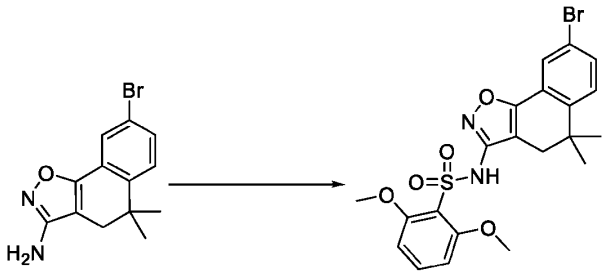
[0683] A mixture of ethyl 8-bromo-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (1.5 g, 4.28 mmol, 1 equiv) and $NH_3 \cdot H_2O$ (15.00 mL) in MeOH (30 mL) was stirred at ambient temperature for 5 h. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford 8-bromo-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (950 mg, 61% yield) as a yellow solid. MS (ESI, *m/z*):321, 323 $[M+H]^+$.

[0684] Step 4. Synthesis of 8-bromo-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine



[0685] To a stirred mixture of 8-bromo-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (400 mg, 1.24 mmol, 1 equiv) and TEA (378.0 mg, 3.73 mmol, 3 equiv) in EtOAc (6 mL)/acetonitrile(6 mL)/ H_2O (3 mL) at ambient temperature was added $PhI(OAc)_2$ (802.3 mg, 2.49 mmol, 2 equiv) in portions. The resulting solution was stirred for 1 h and quenched at 0 °C with NaS_2O_3 solution and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0%- 60% EtOAc in petroleum ether) to afford 8-bromo-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (230 mg, 61% yield) as a yellow solid. MS (ESI, *m/z*): 293, 295 $[M+H]^+$.

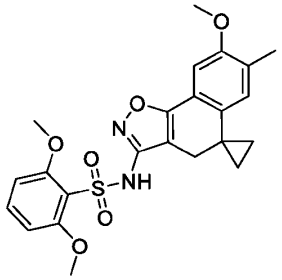
[0686] Step 5. Synthesis of N-(8-bromo-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide



[0687] A mixture of 8-bromo-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (100 mg, 0.34 mmol, 1 equiv) and 2,6-dimethoxybenzenesulfonyl chloride (161.4 mg, 0.68 mmol, 2 equiv) in pyridine (2 mL) was stirred at 80 °C for 1 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) and further purified by reverse phase flash chromatography (5-70% acetonitrile in water (contained 0.05% formic acid)) to afford N-(8-bromo-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide (58.7 mg, 34% yield) as a white solid. MS (ESI, *m/z*): 493, 495 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-*d6*) δ 10.72 (s, 1H), 7.65 (d, J = 2.1 Hz, 1H), 7.59 (dd, J = 8.4, 2.2 Hz, 1H), 7.48 (t, J = 8.4 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 8.5 Hz, 2H), 3.78 (s, 6H) 2.60 (s, 2H), 1.17 (s, 6H).

Example 29

2,6-Dimethoxy-N-(8'-methoxy-7'-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide

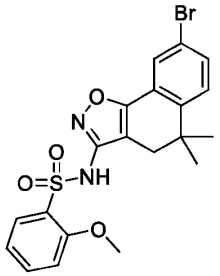


[0688] A mixture of N-(7'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide (110 mg, 0.2 mmol, 1.0 equiv, Example 22), trimethyl-1,3,5,2,4,6-trioxatriborinane (39.7 mg, 0.3 mmol, 1.5 equiv),

$Pd(dppf)Cl_2.CH_2Cl_2$ (17.1 mg, 0.02 mmol, 0.1 equiv) and Cs_2CO_3 (137.4 mg, 0.4 mmol, 2.0 equiv) in dioxane (5.0 mL) and H_2O (1.0 mL) was stirred at 80 °C for 1 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-70% acetonitrile in water (contained 0.1% formic acid)) to afford 2,6-dimethoxy-N-(8'-methoxy-7'-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide (35.9 mg, 37% yield) as a white solid. MS (ESI, *m/z*): 457 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.60 (s, 1H), 7.48 (t, J = 8.4 Hz, 1H), 7.05 (s, 1H), 6.87-6.81 (m, 1H), 6.75 (d, J = 8.4 Hz, 2H), 3.80 (s, 6H), 3.78 (s, 3H), 2.52 (s, 2H), 2.12 (s, 3H), 0.94-0.85 (m, 2H), 0.71-0.62 (m, 2H).

Example 30

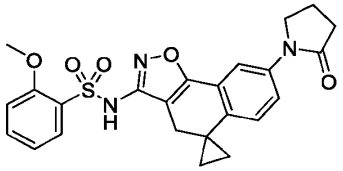
N-(8-bromo-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2-methoxybenzenesulfonamide



[0689] A mixture of 8-bromo-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (150 mg, 0.51 mmol, 1 equiv, Example 28, Step 4) and 2-methoxybenzenesulfonyl chloride (211.4 mg, 1.02 mmol, 2 equiv) in pyridine (3.0 mL) was stirred at 80 °C for 1 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-70% EtOAc in petroleum ether) and further purified by Prep-HPLC (5-60% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8-bromo-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2-methoxybenzenesulfonamide (96.5 mg, 40% yield) as a purple solid. MS (ESI, *m/z*): 463, 465 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.79-7.75 (m, 1H), 7.68-7.55 (m, 3H), 7.41 (d, J = 8.4 Hz, 1H), 7.22-1.18 (m, 1H), 7.08-7.04 (m, 1H), 3.83 (s, 3H), 2.61 (s, 2H), 1.19 (s, 6H).

Example 31

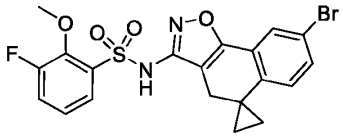
2-Methoxy-N-(8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0690] A solution of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (0.1 g, 217 μmol, Example 16), 2-pyrrolidinone (16.5 μL, 217 μmol) and Cs_2CO_3 (98.9 mg, 1.4 eq., 303 μmol) in 1,4-dioxane (2.17 mL, 25.4 mmol) was sparged with N_2 gas for 15 minutes. 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (25.1 mg, 0.2 eq., 43.4 μmol), tris(dibenzylideneacetone)dipalladium(0) (19.8 mg, 0.1 eq., 21.7 μmol) was added and the mixture heated at 100 °C for 16h. The residue was purified by reverse phase flash chromatography (30-70% acetonitrile in water (contained 0.05% formic acid)) to afford 2-methoxy-N-(8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide as a pale yellow solid (27 mg, 27 % yield). MS (ESI, *m/z*): 466.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 8.13 (s, 1H), 7.75 – 7.67 (m, 2H), 7.40 (dd, J = 8.7, 2.4 Hz, 1H), 7.32 (s, 1H), 6.94 (dd, J = 13.9, 8.5 Hz, 1H), 6.86 (t, J = 7.6 Hz, 1H), 6.51 (s, 1H), 3.76 (t, J = 7.0 Hz, 2H), 3.67 (s, 3H), 2.42 – 2.32 (m, 2H), 1.98 (p, J = 7.6 Hz, 2H), 1.17 (s, 2H), 0.86 (q, J = 4.3 Hz, 2H), 0.70 (q, J = 4.8, 4.4 Hz, 2H).

Example 32

N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-fluoro-2-methoxybenzenesulfonamide

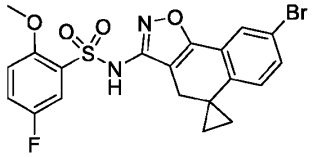


[0691] Example 32 was prepared according to the procedure as described in Example 76, using 3-fluoro-2-methoxybenzenesulfonyl chloride from a commercial source. Example 32 was purified using reverse phase chromatography (MeCN/H_2O, acidic modifiers). ^{1}H NMR (400 MHz, DMSO) δ 11.33 (s, 1H), 7.71 – 7.48 (m, 4H), 7.28 (td, J = 8.2, 4.7 Hz, 1H), 7.05

(d, J = 8.4 Hz, 1H), 3.93 (d, J = 2.2 Hz, 3H), 2.66 (s, 2H), 1.08 – 0.96 (m, 2H), 0.93 – 0.83 (m, 2H). MS (ESI, *m/z*): 479 $[M+H]^+$.

Example 33

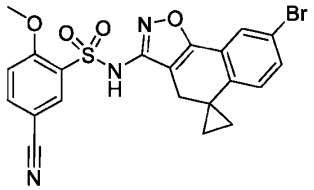
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-5-fluoro-2-methoxybenzenesulfonamide



[0692] Example 33 was prepared according to the procedure as described in Example 76, using 5-fluoro-2-methoxybenzenesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.33 (s, 1H), 7.71 – 7.48 (m, 4H), 7.28 (td, J = 8.2, 4.7 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 3.93 (d, J = 2.2 Hz, 3H), 2.66 (s, 2H), 1.08 – 0.96 (m, 2H), 0.93 – 0.83 (m, 2H). MS (ESI, *m/z*): 479 $[M+H]^+$.

Example 34

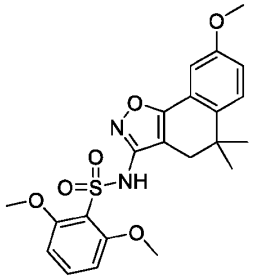
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-5-cyano-2-methoxybenzenesulfonamide



[0693] Example 34 was prepared according to the procedure as described in Example 76, using 5-cyano-2-methoxybenzenesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.26 (s, 1H), 8.14 – 8.02 (m, 2H), 7.60 (d, J = 2.2 Hz, 1H), 7.46 (dd, J = 8.4, 2.2 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 3.86 (s, 3H), 2.57 (s, 2H), 1.01 – 0.89 (m, 2H), 0.85 – 0.74 (m, 2H). MS (ESI, *m/z*): 486 $[M+H]^+$.

Example 35

2,6-Dimethoxy-N-(8-methoxy-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide

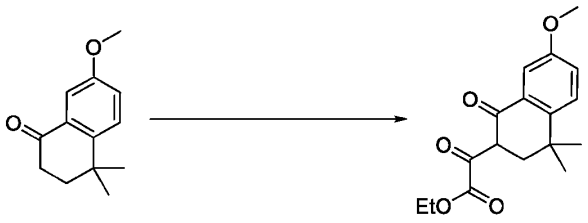


[0694] Step 1. Synthesis of 7-methoxy-4,4-dimethyl-2,3-dihydronaphthalen-1-one



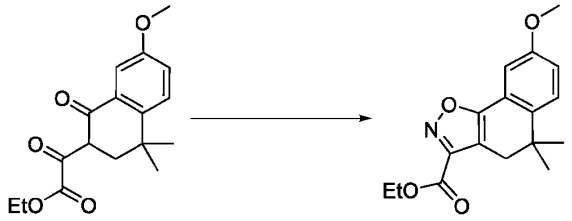
[0695] A mixture of 7-bromo-4,4-dimethyl-2,3-dihydronaphthalen-1-one (1.7 g, 6.71 mmol, 1 equiv), methanol (1.1 g, 33.58 mmol, 5 equiv), tBuONa (1 g, 10.07 mmol, 1.5 equiv), $Pd_2(dba)_3$ (0.6 g, 0.67 mmol, 0.1 equiv) and $Me_4tBuXPhos$ (0.6 g, 1.34 mmol, 0.2 equiv) in dioxane (20 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. The resulting mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-10% EtOAc in petroleum ether) to afford 7-methoxy-4,4-dimethyl-2,3-dihydronaphthalen-1-one (1.05 g, 55% yield) as yellow oil. MS (ESI, *m/z*): 205 $[M+H]^+$.

[0696] Step 2. Synthesis of ethyl 2-(7-methoxy-4,4-dimethyl-1-oxo-2,3-dihydronaphthalen-2-yl)-2-oxoacetate



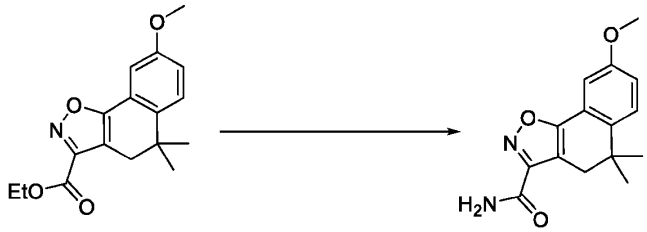
[0697] To a stirred solution of 7-methoxy-4,4-dimethyl-2,3-dihydronaphthalen-1-one (900.0 mg, 4.41 mmol, 1.0 equiv) and ethyl oxalate (1.28 g, 8.81 mmol, 2.0 equiv) in THF (10 mL) at ambient temperature was added dropwise LiHMDS (1 M in THF, 13.2 mL, 13.2 mmol, 3.0 equiv) under N_2 atmosphere. The resulting mixture was stirred at this temperature for 0.5 h and then quenched with saturated NH4Cl solution at 0 °C. The resulting mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford ethyl 2-(7-methoxy-4,4-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate (1.3 g, crude) as yellow oil, which was used for the next step directly without further purification. MS (ESI, *m/z*): 305 $[M+H]^+$.

[0698] Step 3. Synthesis of ethyl 8-methoxy-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate



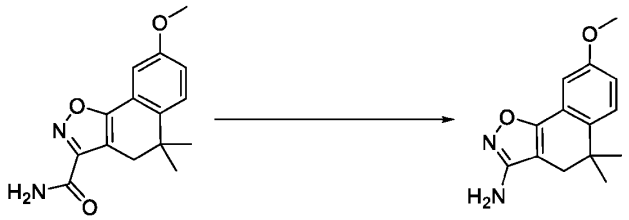
[0699] A solution of ethyl 2-(7-methoxy-4,4-dimethyl-1-oxo-2,3-dihydronaphthalen-2-yl)-2-oxoacetate (1.3 g, 4.27 mmol, 1.0 equiv) and hydroxylamine hydrochloride (0.3 g, 4.70 mmol, 1.1 equiv) in EtOH (13 mL) was stirred at 80 °C for 4 h and then concentrated under vacuum to afford ethyl 8-methoxy-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (1.4 g, crude) as yellow oil, which was used for the next step directly without further purification. MS (ESI, *m/z*): 302 $[M+H]^+$.

[0700] Step 4. Synthesis of 8-methoxy-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide



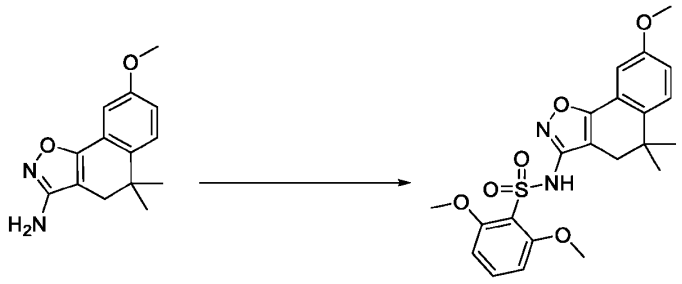
[0701] A solution of ethyl 8-methoxy-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (1.4 g, 4.58 mmol, 1.0 equiv) and $NH_3 \cdot H_2O$ (13 mL, 30%) in MeOH (13 mL) was stirred at ambient temperature for 2 h. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford 8-methoxy-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (500 mg, 30% yield) as a white solid. MS (ESI, *m/z*): 273 $[M+H]^+$.

[0702] Step 5. Synthesis of 8-methoxy-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine



[0703] To a stirred solution of 8-methoxy-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (450.0 mg, 1.65 mmol, 1.0 equiv) and TEA (501 mg, 4,96 mmol, 3 equiv) in combined solvent system of EtOAc (3 mL), acetonitrile (3 mL) and h_2O (1.5 mL) at 0 °C was added $PhI(OAc)_2$ (1.06 g, 3.31 mmol, 2.0 equiv). The resulting solution was stirred at ambient temperature for 2 h and then quenched with NaS_2O_3 solution at 0 °C and extracted with DCM three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-55% EtOAc in petroleum ether) to afford 8-methoxy-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (214 mg, 50.4% yield) as yellow oil. MS (ESI, *m/z*): 245 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d6) δ 7.36 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 2.7 Hz, 1H), 6.96-6.92 (m, 1H), 5.69 (s, 2H), 3.79 (s, 3H), 2.49 (s, 2H), 1.25 (s, 6H).

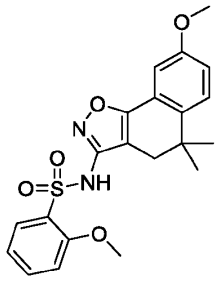
[0704] Step 6. Synthesis of 2,6-dimethoxy-N-(8-methoxy-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide



[0705] A solution of 8-methoxy-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (70.0 mg, 0.29 mmol, 1.000 equiv) and 2,6-dimethoxybenzenesulfonyl chloride (135.6 mg, 0.57 mmol, 2.000 equiv) in pyridine (2 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. The resulting was diluted with water and acidified with aqueous HCl (1 M) to pH 4-5 and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) and further purified by Prep-HPLC (5-55% acetonitrile in water (contained 0.1% formic acid)) to afford 2,6-dimethoxy-N-(8-methoxy-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide (46.2 mg, 36% yield) as a white solid. MS (ESI, *m/z*): 445 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d6) δ 10.66 (s, 1H), 7.47 (t, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.04 (d, *J* = 2.7 Hz, 1H), 6.98-6.93 (m, 1H), 6.75 (d, *J* = 8.4 Hz, 2H), 3.79 (s, 6H), 3.77 (s, 3H), 2.54 (s, 2H), 1.15 (s, 6H).

Example 36

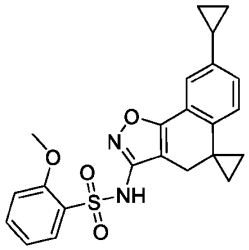
2-Methoxy-N-(8-methoxy-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide



[0706] A solution of 8-methoxy-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (100 mg, 0.41 mmol, 1 equiv) and 2-methoxybenzenesulfonyl chloride (169.2 mg, 0.82 mmol, 2 equiv) in pyridine (2 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. The resulting mixture was diluted with water and acidified with aqueous HCl (1 M) to pH 4-5 and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) and further purified by Prep-HPLC (5%- 50% acetonitrile in water (contained 0.1% formic acid)) to afford 2-methoxy-N-(8-methoxy-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide (31.2 mg, 18% yield) as a white solid. MS (ESI, *m/z*): 415 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.85 (s, 1H), 7.81-7.71 (m, 1H), 7.66-7.54 (m, 1H), 7.36 (d, J = 8.7 Hz, 1H), 7.24-7.15 (m, 1H), 7.11-7.01 (m, 2H), 7.01-6.91 (m, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 2.55 (s, 2H), 1.17 (s, 6H).

Example 37

N-(8'-cyclopropyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

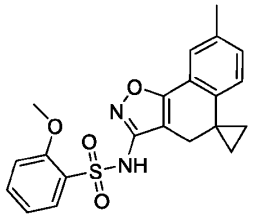


[0707] A solution of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (200 mg, 0.43 mmol, 1 equiv, Example 16), cyclopropylboronic acid (186.20 mg, 2.17 mmol, 5 equiv), $Pd(dppf)Cl_2$ (63.44 mg, 0.09 mmol, 0.20 equiv) and Cs_2CO_3 (282.50 mg, 0.87 mmol, 2 equiv) in dioxane (4 mL) and H_2O (1 mL) was stirred at 100 °C for 2 h under N_2 atmosphere and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography (5-70% acetonitrile in water (contained 0.05% formic acid)) and further purified by Prep-HPLC (5-70% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-cyclopropyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (40.1 mg, 21% yield) as an off-white solid. MS (ESI, *m/z*): 423 $[M+H]^+$. ^{1}H NMR (300 MHz,

DMSO-d6) δ 10.83 (s, 1H), 7.80-7.71 (m, 1H), 7.63-7.51 (m, 1H), 7.22-7.13 (m, 2H), 7.09-6.98 (m, 2H), 6.91 (d, J = 8.1 Hz, 1H), 3.80 (s, 3H), 2.54 (s, 2H), 1.98-1.83 (m, 1H), 0.98-0.81 (m, 4H), 0.80-0.70 (m, 2H), 0.70-0.59 (m, 2H).

Example 38

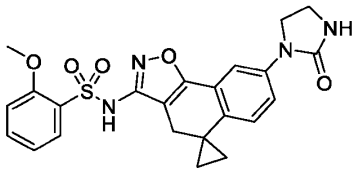
2-Methoxy-N-(8'-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0708] A solution of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (100 mg, 0.22 mmol, 1.00 equiv, Example 16), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (54.42 mg, 0.43 mmol, 2.00 equiv), $Pd(dppf)Cl_2$ (31.72 mg, 0.04 mmol, 0.20 equiv) and Cs_2CO_3 (141.25 mg, 0.43 mmol, 2.00 equiv) in dioxane (4 mL) and H_2O (1 mL) was stirred at 100 °C for 2 h under N_2 atmosphere and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography (5-80% acetonitrile in water (contained 0.05% formic acid)) and further purified by Prep-HPLC (5-70% acetonitrile in water (contained 0.1% formic acid)) to afford 2-methoxy-N-(8'-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide (52.2 mg, 60% yield) as an off-white solid. MS (ESI, *m/z*): 397 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d6) δ 10.82 (s, 1H), 7.80-7.73 (m, 1H), 7.65-7.57 (m, 1H), 7.34 (d, J = 1.8 Hz, 1H), 7.24-7.10 (m, 2H), 7.10-7.00 (m, 1H), 6.94 (d, J = 8.1 Hz, 1H), 3.81 (s, 3H), 2.56 (s, 2H), 2.28 (s, 3H), 0.97-0.86 (m, 2H), 0.86-0.72 (m, 2H).

Example 39

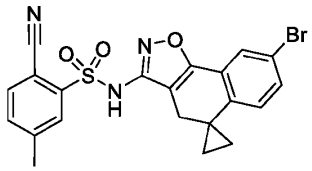
2-Methoxy-N-(8'-(2-oxoimidazolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0709] Example 39 was prepared according to the procedure as described in Example 31, starting from Example 16 and using imidazolidin-2-one from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 7.83 (d, J = 2.4 Hz, 1H), 7.79 (dd, J = 7.8, 1.7 Hz, 1H), 7.66 – 7.57 (m, 1H), 7.48 – 7.43 (m, 1H), 7.35 (d, J = 6.6 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 1.7 Hz, 1H), 3.84 (d, J = 9.9 Hz, 5H), 2.63 – 2.52 (m, 4H), 0.97 – 0.90 (m, 2H), 0.82 – 0.74 (m, 2H). MS (ESI, *m/z*): 467.2 $[M+H]^+$.

Example 40

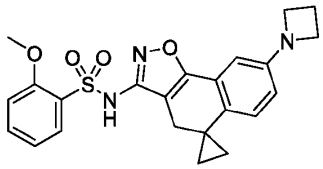
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-cyano-5-methylbenzenesulfonamide



[0710] Example 40 was prepared according to the procedure as described in Example 76, using 2-cyano-5-methylbenzenesulfonyl chloride from a commercial source (Combi-Blocks SS-6998). ^{1}H NMR (400 MHz, DMSO) δ 11.55 (br s, 1H), 7.86 (d, J = 11.8 Hz, 2H), 7.57 (dd, J = 11.2, 5.0 Hz, 2H), 7.44 (dd, J = 8.4, 2.2 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 2.56 (s, 2H), 2.42 (d, J = 8.9 Hz, 3H), 1.03 – 0.88 (m, 2H), 0.86 – 0.66 (m, 2H). MS (ESI, *m/z*): 470 $[M+H]^+$.

Example 41

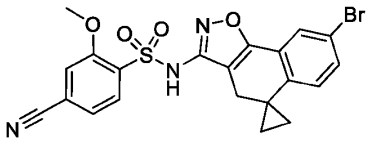
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0711] Example 41 was prepared according to the procedure as described in Example 31, starting from Example 16 and azetidine. ^{1}H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 7.81 – 7.73 (m, 1H), 7.59 (t, J = 8.2 Hz, 1H), 7.44 – 7.31 (m, 1H), 7.18 (d, J = 8.3 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.53 (d, J = 2.5 Hz, 1H), 6.37 (dd, J = 8.5, 2.5 Hz, 1H), 3.84 - 3.73 (m, 8H), 2.35 – 2.19 (m, 2H), 0.88 – 0.79 (m, 2H), 0.77 – 0.66 (m, 2H). MS (ESI, *m/z*): 438.2 $[M+H]^+$.

Example 42

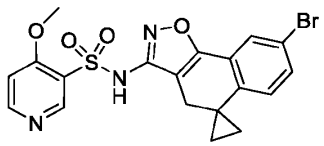
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-cyano-2-methoxybenzenesulfonamide



[0712] Example 42 was prepared according to the procedure as described in Example 76, using 4-cyano-2-methoxybenzenesulfonyl chloride from a commercial source (Enamine, EN300-139160). ^{1}H NMR (400 MHz, DMSO) δ 11.24 (br s, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.68 (s, 1H), 7.58 (d, J = 2.2 Hz, 1H), 7.47 (ddd, J = 17.4, 8.2, 1.8 Hz, 2H), 6.97 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 2.55 (s, 2H), 0.98 – 0.91 (m, 2H), 0.88 – 0.77 (m, 2H). MS (ESI, *m/z*): 486 $[M+H]^+$.

Example 43

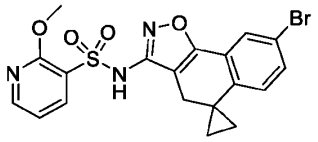
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-methoxypyridine-3-sulfonamide



[0713] Example 43 was prepared according to the procedure as described in Example 76, using 4-methoxypyridine-3-sulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.25 (s, 1H), 8.69 (s, 1H), 8.59 (d, J = 5.9 Hz, 1H), 7.59 (d, J = 2.2 Hz, 1H), 7.45 (dd, J = 8.4, 2.2 Hz, 1H), 7.21 (d, J = 5.9 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 3.84 (s, 3H), 2.57 (s, 2H), 0.98 – 0.91 (m, 2H), 0.88 – 0.77 (m, 2H). MS (ESI, *m/z*): 462 $[M+H]^+$.

Example 44

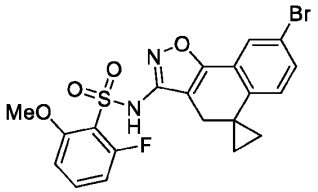
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxypyridine-3-sulfonamide



[0714] Example 44 was prepared according to the procedure as described in Example 76, using 2-methoxypyridine-3-sulfonyl chloride from a commercial source (Enamine, EN300-78550). ^{1}H NMR (400 MHz, DMSO) δ 11.23 (s, 1H), 8.37 (dd, J = 4.9, 1.9 Hz, 1H), 8.14 (dd, J = 7.6, 1.9 Hz, 1H), 7.60 (d, J = 2.2 Hz, 1H), 7.46 (dd, J = 8.4, 2.2 Hz, 1H), 7.13 (dd, J = 7.6, 5.0 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 3.86 (s, 3H), 2.57 (s, 2H), 0.98 – 0.91 (m, 2H), 0.88 – 0.77 (m, 2H). MS (ESI, *m/z*): 462 $[M+H]^+$.

Example 45

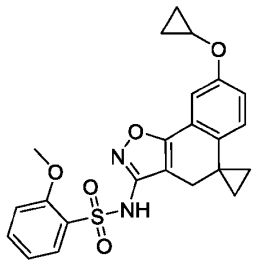
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-fluoro-6-methoxybenzenesulfonamide



[0715] Example 45 was prepared according to the procedure as described in Example 76, using 2-fluoro-6-methoxybenzenesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.21 (s, 1H), 7.68 (d, J = 2.1 Hz, 1H), 7.62 (q, J = 7.4 Hz, 1H), 7.53 (dd, J = 8.4, 2.2 Hz, 1H), 7.05 (d, J = 8.5 Hz, 2H), 6.99 – 6.90 (m, 1H), 3.85 (s, 3H), 2.64 (s, 2H), 1.06 – 0.98 (m, 2H), 0.89 – 0.82 (m, 2H). MS (ESI, *m/z*): 481 $[M+H]^+$.

Example 46

N-(8'-cyclopropoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0716] Step 1. Synthesis of 6'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-naphthalen]-4'-one



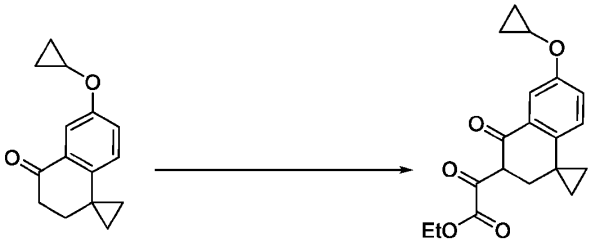
[0717] A mixture of 6'-bromo-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (1 g, 3.98 mmol, 1 equiv, Intermediate B), $Pd(dppf)Cl_2$ (0.22 g, 0.39 mmol, 0.1 equiv) and KOAc (0.78 g, 7.96 mmol, 2 equiv) in dioxane (10 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The residue was re-dissolved in MeOH (10 mL) and to this at ambient temperature was added H_2O_2 solution (30%, 10 mL). The resulting mixture was stirred for 16 h and then quenched with $Na_2S_2O_3$ solution at 0 °C and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0%- 60% EtOAc in petroleum ether) to afford 6'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-naphthalen]-4'-one (600 mg, 76% yield) as yellow oil. MS (ESI, *m/z*): 189 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.60 (d, $J = 3.0$ Hz, 1H), 7.06-7.02 (m, 1H), 6.77 (d, $J = 8.5$ Hz, 1H), 5.80 (s, 1H), 2.86-2.71 (m, 2H), 2.03-1.93 (m, 2H), 1.11-0.92 (m, 4H).

[0718] Step 2. Synthesis of 6'-cyclopropoxy-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one



[0719] A mixture of 6'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-naphthalen]-4'-one (1.5 g, 7.96 mmol, 1 equiv), bromocyclopropane (1.93 g, 15.95 mmol, 2.0 equiv) and Cs_2CO_3 (7.79 g, 23.91 mmol, 3.00 equiv) in DMF (20 mL) was stirred at 140 °C for 24 h under N_2 atmosphere. The resulting mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0--30% EtOAc in petroleum ether) to afford 6'-cyclopropoxy-2',3'-dihydrospiro[cyclopropane-1,1'-naphthalen]-4'-one (1.28 g, 68% yield) as yellow oil. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 2.8 Hz, 1H), 7.10 (dd, *J* = 8.5, 3.0 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 3.82-3.78 (m, 1H), 2.84-2.74 (m, 2H), 2.03-1.93 (m, 2H), 1.09-1.03 (m, 2H), 0.99-0.93 (m, 2H), 0.88-0.72 (m, 4H). MS (ESI, *m/z*): 229 $[M+H]^+$.

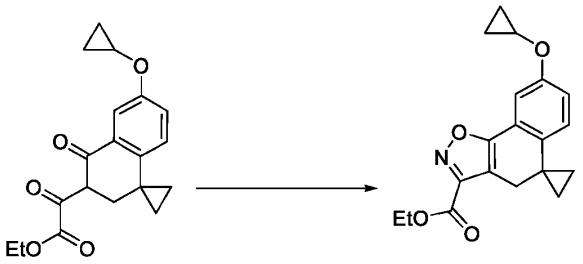
[0720] Step 3. Synthesis of ethyl 2-(6'-cyclopropoxy-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate



[0721] To a stirred mixture of 6'-cyclopropoxy-2',3'-dihydrospiro[cyclopropane-1,1'-naphthalen]-4'-one (1.28 g, 5.60 mmol, 1 equiv) and ethyl oxalate (1.64 g, 11.21 mmol, 2 equiv) in THF (20 mL) at ambient temperature was added dropwise LiHMDS (1M in THF, 16.8 mL, 16.8 mmol, 3 equiv) under N_2 atmosphere. The resulting mixture was stirred at this temperature for 1 h and then quenched with saturated NH4Cl solution and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford ethyl 2-(6'-cyclopropoxy-4'-oxo-3',4'-dihydro-2'H-

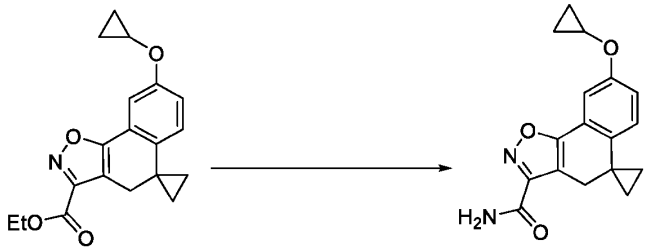
spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (2 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 329 $[M+H]^+$.

[0722] Step 4. Synthesis of ethyl 8'-cyclopropoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate



[0723] A mixture of ethyl 2-(6'-cyclopropoxy-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (2 g, 6.09 mmol, 1 equiv) and hydroxylamine hydrochloride (0.42 g, 6.09 mmol, 1 equiv) in EtOH (30 mL) was stirred at 80 °C for 3 h. The resulting mixture was concentrated under vacuum to afford ethyl 8'-cyclopropoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (2.1 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 326 $[M+H]^+$.

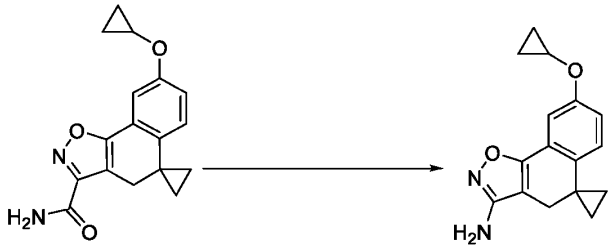
[0724] Step 5. Synthesis of 8'-cyclopropoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide



[0725] To a stirred mixture of ethyl 8'-cyclopropoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (2.1 g, 6.45 mmol, 1 equiv) in MeOH (40 mL) at ambient temperature was added ammonia (28% in water, 21 mL). The resulting mixture was stirred at this temperature for 5 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0%- 60% EtOAc in petroleum ether) to afford 8'-cyclopropoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (800

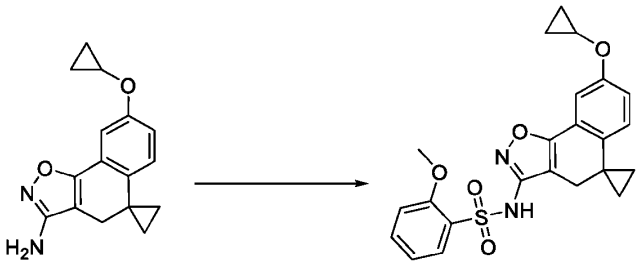
mg, 40% yield) as a yellow solid. MS (ESI, *m/z*): 297 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.86 (s, 1H), 7.35 (t, J = 1.5 Hz, 1H), 7.04 (d, J = 1.5 Hz, 2H), 3.96-3.92 (m, 1H), 2.83 (s, 2H), 1.01-0.77 (m, 6H), 0.77-0.63 (m, 2H).

[0726] Step 6. Synthesis of 8'-cyclopropoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine



[0727] To a stirred mixture of 8'-cyclopropoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (800 mg, 2.70 mmol, 1 equiv) and TEA (819.5 mg, 8.10 mmol, 3 equiv) in EtOAc (10 mL)/acetonitrile (10 mL)/H_2O (5 mL) at ambient temperature was added $(PhI(OAc)_2$ (1739.1 mg, 5.40 mmol, 2 equiv). The resulting solution was stirred for 1 h and then quenched with NaS_2O_3 solution at 0 °C and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford 8'-cyclopropoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (310 mg, 29% yield) as a yellow solid. MS (ESI, *m/z*): 269 $[M+H]^+$.

[0728] Step 7. Synthesis of N-(8'-cyclopropoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

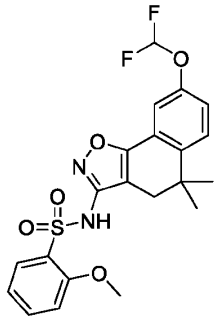


[0729] A mixture of 8'-cyclopropoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (200 mg, 0.74 mmol, 1 equiv) and 2-methoxybenzenesulfonyl chloride (308.0 mg,

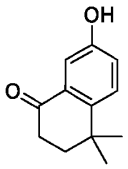
1.49 mmol, 2 equiv) in pyridine (5 mL) was stirred at 80 °C for 1 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) and further purified by (5-70% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-cyclopropoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (134.5 mg, 41% yield) as a white solid. MS (ESI, *m/z*): 439 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.86 (s, 1H), 7.77 (dd, J = 7.8, 1.8 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.22-7.16 (m, 2H), 7.06 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 1.8 Hz, 2H), 3.88-3.83 (m, 1H), 3.82 (s, 3H), 2.55 (s, 2H), 0.94-0.87 (m, 2H), 0.80-0.68 (m, 4H), 0.67-0.59 (m, 2H).

Example 47

N-(8-(difluoromethoxy)-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2-methoxybenzenesulfonamide



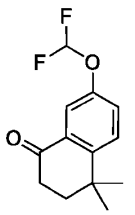
[0730] Step 1. Synthesis of 7-hydroxy-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one



[0731] A mixture of 7-bromo-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (1.6 g, 6.32 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.77 g, 6.95 mmol, 1.10 equiv), Pd(dppf)Cl_2 (0.92 mL, 1.26 mmol, 0.20 equiv) and KOAc (1.24 g, 12.64 mmol, 2 equiv) in dioxane (16 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum and then to

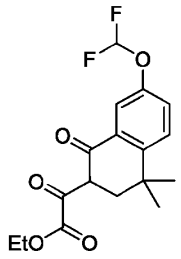
this was added dropwise H_2O_2 (1 mL) in MeOH (16 mL) at 0 °C over 3 min. The resulting solution was stirred at ambient temperature for 16 h and then quenched with $Na_2S_2O_3$ solution at 0 °C and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford 7-hydroxy-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (1.9 g, >100% yield) as a yellow solid. MS (ESI, *m/z*): 191 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d6) δ 9.56 (s, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.03-6.93 (m, 1H), 2.65-2.54 (m, 2H), 1.93-1.82 (m, 2H), 1.28 (s, 6H).

[0732] Step 2. Synthesis of 7-(difluoromethoxy)-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one



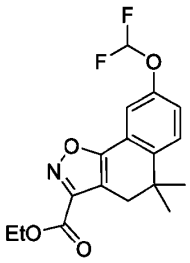
[0733] A mixture of 7-hydroxy-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (600 mg, 3.15 mmol, 1 equiv) and NaOH (378.44 mg, 9.46 mmol, 3 equiv) in DMF (6 mL) was stirred at ambient temperature for 15 min and to this was added dropwise a solution of sodium 2-chloro-2,2-difluoroacetate (721.26 mg, 4.73 mmol, 1.50 equiv) in DMF (4 mL). The resulting mixture was stirred at 80 °C for 2 h and then diluted with water and combined with another 2 batch (same scale). The resulting mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford 7-(difluoromethoxy)-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (547 mg, 35% yield overtwo steps) as yellow oil. MS (ESI, *m/z*): 241 [M+H]+. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.78-7.71 (m, 1H), 7.46 (d, J = 8.7 Hz, 1H), 7.35-7.28 (m, 1H), 2.82-2.71 (m, 2H), 2.09-1.99 (m, 2H), 1.41 (s, 6H).

[0734] Step 3. Synthesis of ethyl 2-(7-(difluoromethoxy)-4,4-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate



[0735] To a stirred solution of 7-(difluoromethoxy)-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (540 mg, 2.25 mmol, 1 equiv) and diethyl oxalate (656.95 mg, 4.49 mmol, 2 equiv) in THF (10 mL) at ambient temperature was added LiHMDS (1 M in THF, 6.75 ml, 6.75 mmol, 3 equiv) under N_2 atmosphere. The resulting mixture was stirred at ambient temperature for 1 h and then quenched with saturated NH4Cl solution and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-40% EtOAc in petroleum ether) to afford ethyl 2-(7-(difluoromethoxy)-4,4-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate (454 mg, 53% yield) as yellow oil. MS (ESI, *m/z*): 341 [M+H]+.

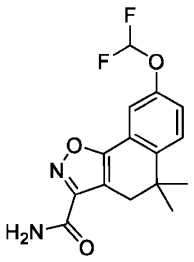
[0736] Step 4. Synthesis of ethyl 8-(difluoromethoxy)-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate



[0737] A mixture of ethyl 2-(7-(difluoromethoxy)-4,4-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate (454 mg, 1.33 mmol, 1 equiv) and $NH_2OH{\cdot}HCl$ (92.70 mg, 1.34 mmol, 1 equiv) in EtOH (10 mL) was stirred at 80 °C for 2 h. The resulting mixture was quenched with water and extracted with EtOAc three times. The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum to afford ethyl 8-(difluoromethoxy)-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (600 mg,

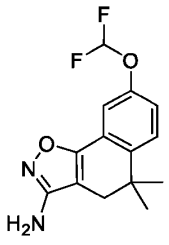
crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 338 [M+H]+.

[0738] Step 5. Synthesis of 8-(difluoromethoxy)-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide



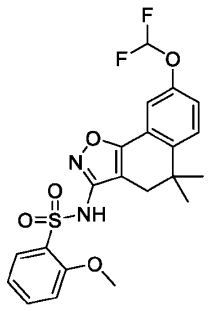
[0739] To a stirred solution of ethyl 8-(difluoromethoxy)-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (600 mg, 1.78 mmol, 1 equiv) in MeOH (15 mL) at 0 °C was added $NH_3 \cdot H_2O$ (6 mL). The resulting mixture was allowed to warm up to ambient temperature and stirred for 2 h. The mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0--60% EtOAc in petroleum ether) to afford 8-(difluoromethoxy)-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (300 mg, 72% yield over two steps) as a white solid. MS (ESI, *m/z*): 338 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.15 (s, 1H), 7.89 (s, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.46 (d, J = 2.4 Hz, 1H), 7.38-7.23 (m, 2H), 2.87 (s, 2H), 1.29 (s, 6H).

[0740] Step 6. Synthesis of 8-(difluoromethoxy)-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine



[0741] To a stirred mixture of 8-(difluoromethoxy)-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (300 mg, 0.97 mmol, 1 equiv) and TEA (393.89 mg, 3.89 mmol, 4 equiv) in combined solvent system of EtOAc (2 mL), acetonitrile (2 mL) and H_2O (1 mL) at ambient temperature was added $PhI(OAc)_2$ (626.88 mg, 1.95 mmol, 2 equiv). The resulting mixture was stirred for 1 h and then quenched with $Na_2S_2O_3$ solution and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford 8-(difluoromethoxy)-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (170 mg, 59% yield) as yellow oil. MS (ESI, *m/z*): 281 [M+H]+.

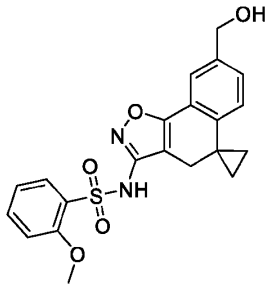
[0742] Step 7. Synthesis of N-(8-(difluoromethoxy)-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2-methoxybenzenesulfonamide



[0743] A solution of 8-(difluoromethoxy)-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (120 mg, 0.43 mmol, 1 equiv) and 2-methoxybenzenesulfonyl chloride (132.7 mg, 0.64 mmol, 1.5 equiv) in pyridine (2 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. The resulting mixture was diluted with water and acidified with aqueous HCl (1 M) to pH 4-5 and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) and further purified by Prep-HPLC (5-65% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8-(difluoromethoxy)-5,5-dimethyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2-methoxybenzenesulfonamide (89.4 g, 46% yield) as an off-white solid. MS (ESI, *m/z*): 451 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d6) δ 10.94 (s, 1H), 7.81-7.76 (m, 1H), 7.66-7.59 (m, 1H), 7.53-7.05 (m, 6H), 3.85 (s, 3H), 2.62 (s, 2H), 1.22 (s, 6H).

Example 48

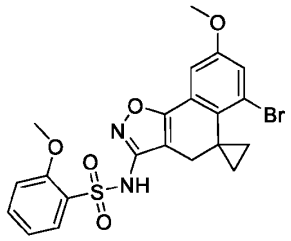
N-(8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



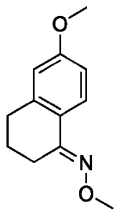
[0744] A solution of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (130 mg, 0.28 mmol, 1 equiv, Example 16), (tributylstannyl)methanol (180.96 mg, 0.56 mmol, 2 equiv) and $Pd(PPh_3)_4$ (65.13 mg, 0.06 mmol, 0.20 equiv) in dioxane (5 mL) was stirred at 100 °C for 2 h under N_2 atmosphere and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography (5-70% acetonitrile in water (contained 0.05% formic acid)) and further purified by Prep-HPLC (5-50% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (25.3 mg, 21% yield) as a white solid. MS (ESI, *m/z*): 413 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d6) δ 10.84 (s, 1H), 7.80-7.73 (m, 1H), 7.63-7.54 (m, 1H), 7.47 (d, J = 1.8 Hz, 1H), 7.30-7.15 (m, 2H), 7.10-6.98 (m, 2H), 5.26-5.17 (m, 1H), 4.47 (d, J = 5.7 Hz, 2H), 3.81 (s, 3H), 2.57 (s, 2H), 1.00-0.86 (m, 2H), 0.86-0.74 (m, 2H).

Example 49

N-(6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

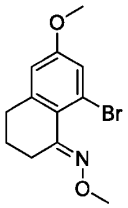


[0745] Step 1. Synthesis of (E)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime



[0746] A solution of 6-methoxy-3,4-dihydronaphthalen-1(2H)-one (50.0 g, 284.09 mmol, 1.00 equiv), pyridine (24.7 g, 312.50 mmol, 1.10 equiv) and O-methylhydroxylamine hydrochloride (28.5 g, 340.91 mmol, 1.20 equiv) in EtOH (0.8 L) was stirred at ambient temperature for 16 h. The resulting mixture was concentrated under vacuum. The residue was combined with another three batches (50.0 g scale) and purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford (E)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (180.0 g, 86% yield) as yellow oil. MS (ESI, *m/z*): 206 $[M+H]^+$.

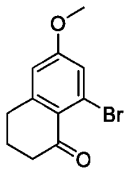
[0747] Step 2. Synthesis of (E)-8-bromo-6-methoxy-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime



[0748] A solution of (E)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (180.0 g, 878.05 mmol, 1.00 equiv), NBs (156.3 g, 878.05 mmol, 1.00 equiv) and $Pd(OAc)_2$ (9.9 g, 43.90 mmol, 0.05 equiv) in AcOH (4.5 L) was stirred at 80 °C for 3 h under N_2

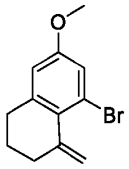
atmosphere. The resulting mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford (E)-8-bromo-6-methoxy-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (140.0 g, 87% yield) as a white solid. MS (ESI, *m/z*): 284, 286 $[M+H]^+$.

[0749] Step 3. Synthesis of 8-bromo-6-methoxy-3,4-dihydronaphthalen-1(2H)-one



[0750] A mixture of (E)-8-bromo-6-methoxy-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (30.0 g, 106.01 mmol, 1.00 equiv) and HCl (concentrated, 150.0 mL) in dioxane (150.0 mL) was stirred at 100 °C for 1 h under N_2 atmosphere. The organic volatile was removed under vacuum. The aqueous residue was neutralized with saturated NaHCO3 solution to pH 7 and extracted with DCM three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another three batches (30.3 g scale) and purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford 8-bromo-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (105.0 g, 83% yield) as a yellow solid. MS (ESI, *m/z*): 255, 257 $[M+H]^+$.

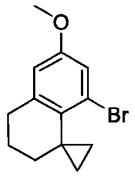
[0751] Step 4. Synthesis of 8-bromo-6-methoxy-1-methylene-1,2,3,4-tetrahydronaphthalene



[0752] To a stirred mixture of methyltriphenylphosphanium bromide (84.4 g, 236.22 mmol, 3.00 equiv) in THF (0.4 L) at 0 °C was added t-BuOK (30.9 g, 275.59 mmol, 3.50 equiv) under N_2 atmosphere. The resulting reaction mixture was stirred at this temperature for 1 h

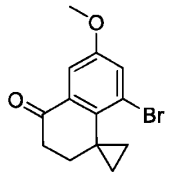
and to this was added 8-bromo-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (20.0 g, 78.74 mmol, 1.00 equiv). The resulting mixture was stirred at ambient temperature for another 16 h and then acidified with aqueous HCl (1 M) to pH 3 and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another two batches (20.0 g scale) and purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford 8-bromo-6-methoxy-1-methylene-1,2,3,4-tetrahydronaphthalene (59.0 g, 85% yield) as colorless oil. MS (ESI, *m/z*): 253, 255 $[M+H]^+$.

[0753] Step 5. Synthesis of 8'-bromo-6'-methoxy-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]



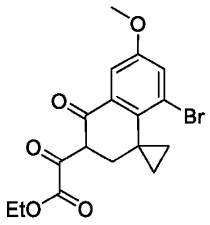
[0754] To a stirred mixture of 8-bromo-6-methoxy-1-methylene-1,2,3,4-tetrahydronaphthalene (10.0 g, 39.68 mmol, 1.00 equiv) in DCE (0.4 L) at 0 °C was added chloroiodomethane (31.5 g, 178.56 mmol, 4.50 equiv) under N_2 atmosphere. The reaction mixture was stirred at this temperature for 30 mins and to this was added $ZnEt_2$ (159 mL, 1 M in hexane, 159 mmol, 4.0 equiv). The resulting mixture was stirred for another 1.5 h and then quenched with saturated NH4Cl solution. The mixture was combined with another 6 batches (same scale) and extracted with DCM three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford 8'-bromo-6'-methoxy-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene] (72.3 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 267, 269 $[M+H]^+$.

[0755] Step 6. Synthesis of 8'-bromo-6'-methoxy-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one



[0756] To a stirred mixture of 8'-bromo-6'-methoxy-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene] (10.0 g, 37.59 mmol, 1.00 equiv) in acetone (100.0 mL) at ambient temperature was added a solution of $MgSO_4$ (5.4 g, 45.11 mmol, 1.20 equiv) in water (50.0 mL). The resulting mixture was stirred for 10 mins and to this was added $KMnO_4$ (10.7 g, 67.66 mmol, 1.80 equiv). The resulting mixture was stirred for further 16 h and then filtered. The filtrate was quenched with $Na_2S_2O_3$ solution and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another three batches (16.0 g scale) and purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford 8'-bromo-6'-methoxy-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (27.9 g, 87% yield) as yellow oil. MS (ESI, *m/z*): 281, 283 $[M+H]^+$.

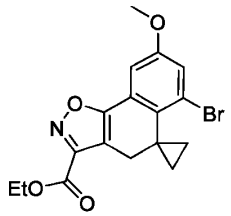
[0757] Step 7. Synthesis of ethyl 2-(8'-bromo-6'-methoxy-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate



[0758] To a stirred mixture of ethyl oxalate (3.1 g, 21.43 mmol, 1.20 equiv) in THF (300.0 mL) at 0 °C was added tBuOLi (2.1 g, 26.79 mmol, 1.50 equiv) under N_2 atmosphere. The reaction mixture was stirred at this temperature for 10 mins and to this was added 8'-bromo-6'-methoxy-2',3'-dihydro-4'H-spiro[cyclopropane-1,1'-naphthalen]-4'-one (5.0 g, 17.86 mmol, 1.00 equiv). The resulting mixture was stirred at ambient temperature for another 1 h and then quenched with water. The mixture was combined with another two batches (12.5 g scale) and acidified with aqueous HCl (1 M) to pH 3 and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated

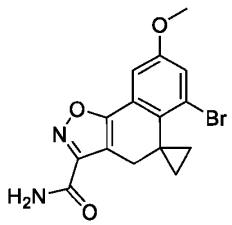
under vacuum to afford ethyl 2-(8'-bromo-6'-methoxy-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (45.2 g, crude) as a yellow solid, which was used for the next step without further purification. MS (ESI, *m/z*): 381, 383 $[M+H]^+$.

[0759] Step 8. Synthesis of ethyl 6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate



[0760] A solution of ethyl 2-(8'-bromo-6'-methoxy-4'-oxo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxoacetate (5.0 g, 13.16 mmol, 1.00 equiv) and hydroxylamine hydrochloride (1.3 g, 15.79 mmol, 1.20 equiv) in EtOH (50.0 mL) was stirred at 80 °C for 2 h under N_2 atmosphere and then concentrated under vacuum. The residue was combined with another two batches (20.0 g scale) and purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford ethyl 6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (36.5 g, 84% yield) as a white solid. MS (ESI, *m/z*): 378, 380 $[M+H]^+$.

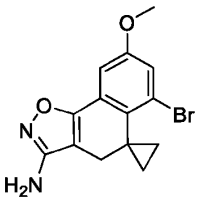
[0761] Step 9. Synthesis of 6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide



[0762] A solution of ethyl 6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate (14.0 g, 37.14 mmol, 1.00 equiv) and NH_4OH (140.0 mL) in MeOH (140.0 mL) and THF (140.0 mL) was stirred at ambient temperature for 1 h. The resulting mixture was combined with another three batches (500 mg scale) and concentrated

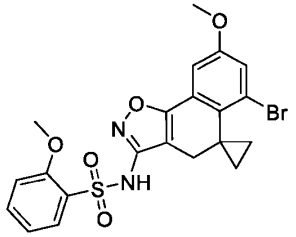
under vacuum to afford 6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (32.0 g, crude) as a white solid, which was used for the next step without further purification. MS (ESI, *m/z*): 349, 351 $[M+H]^+$.

[0763] Step 10. Synthesis of 6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine



[0764] To a stirred mixture of 6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (1.0 g, 2.87 mmol, 1.00 equiv) in EtOAc (10.0 mL), acetonitrile (10.0 mL) and water (10.0 mL) at 0 °C was added TEA (870.7 mg, 8.62 mmol, 3.00 equiv). The resulting mixture was stirred at this temperature for 30 mins and to this was added $PhI(OAc)_2$ (1.4 g, 4.31 mmol, 1.50 equiv). The resulting mixture was stirred at ambient temperature for another 1 h and then quenched with $Na_2S_2O_3$ solution and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another 6 batches (1.0 g scale) and purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford 6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (2.0 g, 86% yield) as yellow oil. MS (ESI, *m/z*): 321/323 $[M+H]^+$.

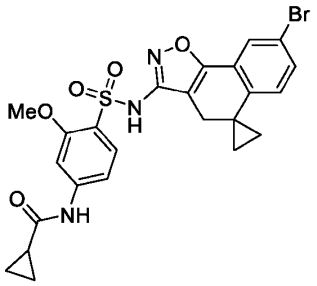
[0765] Step 11. Synthesis of N-(6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0766] A mixture of 6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (300.0 mg, 0.94 mmol, 1.00 equiv) and 2-methoxybenzenesulfonyl chloride (366.9 mg, 1.78 mmol, 1.90 equiv) in pyridine (3.0 mL) was stirred at ambient temperature for 1 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The residue was diluted with water and then acidified to pH 4 with aqueous HCl (1 M) and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another three batches (500 mg scale) and purified by reverse phase flash chromatography on C18 gel (5-40% acetonitrile in water (contained 0.05% formic acid)) to afford N-(6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (1.2421 g, 99.4% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.77 (dd, J = 7.8, 1.8 Hz, 1H), 7.66-7.53 (m, 1H), 7.23-7.03 (m, 4H), 3.81 (s, 3H), 3.77 (s, 3H), 2.43 (s, 2H), 1.44-1.32 (m, 2H), 0.84-0.75 (m, 2H).

Example 50

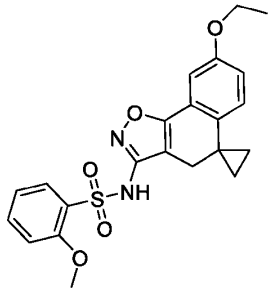
4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-N-cyclopropyl-3-methoxybenzamide



[0767] Example 50 was prepared according to the procedure as described in Example 76, using 4-cyclopropaneamido-2-methoxybenzene-1-sulfonyl chloride from a commercial source (Enamine, EN300-120766). ^{1}H NMR (400 MHz, DMSO) δ 10.81 (s, 1H), 10.59 (s, 1H), 7.73 – 7.63 (m, 2H), 7.59 (s, 1H), 7.52 (dd, J = 8.4, 2.2 Hz, 1H), 7.18 (dd, J = 8.7, 1.8 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 3.77 (s, 3H), 2.63 (s, 2H), 1.80 (p, J = 6.2 Hz, 1H), 1.00 (t, J = 3.1 Hz, 2H), 0.89 – 0.80 (m, 6H). MS (ESI, *m/z*): 543 $[M-H]^-$.

Example 51

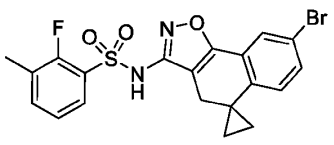
N-(8'-ethoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0768] To a mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (90.4 mg, 196 µmol), tBuXPhos, (4.16 mg, 0.05 eq., 9.79 µmol), tris(dibenzylideneacetonyl)bis-palladium (4.38 mg, 0.05 eq., 9.79 µmol), sodium tert-Butoxide (28.2 mg, 1.5 eq., 294 µmol) and ethanol (45.1 mg, 5 eq., 979 µmol) was added 1,4-dioxane (2.5 mL, 29.3 mmol). The reaction mixture was sparged with nitrogen for 5 minutes and heated at 80 °C for 1h and then concentrated under vacuum. The residue was purified by chromatography on silica gel (0 to 50% EtOAc in hexanes) to obtain N-(8'-ethoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (8.2 mg, 10% yield) as a white solid. MS (ESI, *m/z*): 427.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 7.79 (dd, J = 7.8, 1.7 Hz, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 7.14 – 7.02 (m, 2H), 6.98 (d, J = 8.6 Hz, 1H), 6.89 (dd, J = 8.6, 2.7 Hz, 1H), 4.04 (q, J = 6.9 Hz, 2H), 3.84 (s, 3H), 2.57 (s, 2H), 1.31 (t, J = 7.0 Hz, 3H), 0.99 – 0.84 (m, 2H), 0.84 – 0.67 (m, 2H).

Example 52

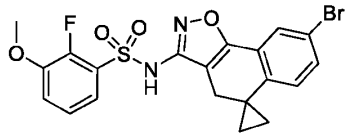
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-fluoro-3-methylbenzenesulfonamide



[0769] Example 52 was prepared according to the procedure as described in Example 76, using 2-fluoro-3-methylbenzenesulfonyl chloride from a commercial source (Enamine, EN300-1227745). ^{1}H NMR (400 MHz, DMSO) δ 11.51 (s, 1H), 7.67 – 7.53 (m, 3H), 7.45 (dd, J = 8.4, 2.2 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 2.56 (s, 2H), 2.21 (d, J = 2.1 Hz, 3H), 0.98 – 0.91 (m, 2H), 0.88 – 0.77 (m, 2H). MS (ESI, *m/z*): 463 $[M+H]^+$.

Example 53

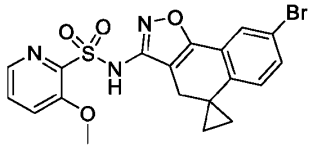
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-fluoro-3-methoxybenzenesulfonamide



[0770] Example 53 was prepared according to the procedure as described in Example 76, using 2-fluoro-3-methoxybenzenesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.55 (s, 1H), 7.59 (s, 1H), 7.45 (m, 2H), 7.32 (t, J = 6.7 Hz, 1H), 7.25 (m, 1H), 6.97 (d, J = 8.5 Hz, 1H), 3.81 (s, 3H), 2.55 (s, 2H), 0.97 – 0.90 (m, 2H), 0.84 – 0.76 (m, 2H). MS (ESI, *m/z*): 479 $[M+H]^+$.

Example 54

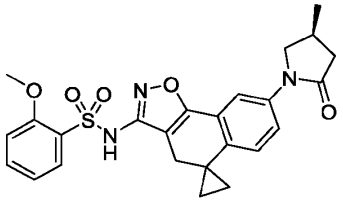
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-methoxypyridine-2-sulfonamide



[0771] Example 54 was prepared according to the procedure as described in Example 76, using 3-methoxypyridine-2-sulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.26 (s, 1H), 8.21 – 8.16 (m, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.69 (t, J = 3.5 Hz, 2H), 7.53 (dd, J = 8.4, 2.2 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 3.91 (s, 3H), 2.61 (s, 2H), 1.05 – 0.97 (m, 2H), 0.85 – 0.78 (m, 2H). MS (ESI, *m/z*): 462 $[M+H]^+$.

Example 55

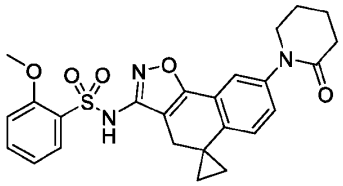
(S)-2-methoxy-N-(8'-(4-methyl-2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0772] Example 55 was prepared according to the procedure as described in Example 31, starting from Example 16 and (S)-4-methylpyrrolidin-2-one from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.87 (s, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.78 (dd, J = 7.9, 1.7 Hz, 1H), 7.62 (ddd, J = 8.8, 7.4, 1.7 Hz, 1H), 7.52 (dd, J = 8.6, 2.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.07 (td, J = 8.7, 8.3, 2.6 Hz, 2H), 3.93 (dd, J = 9.5, 7.6 Hz, 1H), 3.82 (s, 3H), 3.43 (dd, J = 9.5, 6.5 Hz, 1H), 2.71 – 2.57 (m, 3H), 2.46 (d, J = 7.2 Hz, 1H), 2.17 (dd, J = 16.5, 7.5 Hz, 1H), 1.10 (d, J = 6.7 Hz, 3H), 1.01 – 0.92 (m, 2H), 0.80 (q, J = 4.3 Hz, 2H). MS (ESI, *m/z*): 480.2 $[M+H]^+$.

Example 56

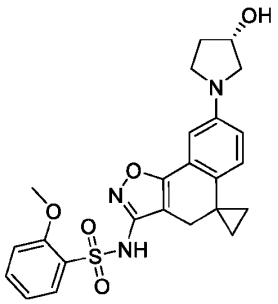
2-Methoxy-N-(8'-(2-oxopiperidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0773] Example 56 was prepared according to the procedure as described in Example 31, starting from Example 16 and piperidin-2-one from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.87 (s, 1H), 7.77 (dd, J = 7.8, 1.7 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 2.2 Hz, 1H), 7.26 – 7.16 (m, 2H), 7.06 (dt, J = 7.6, 3.5 Hz, 2H), 3.82 (s, 3H) 3.58 (t, J = 5.6 Hz, 2H), 2.59 (s, 2H), 2.37 (t, J = 6.2 Hz, 2H), 1.82 (dd, J = 8.3, 5.0 Hz, 4H), 0.99 (q, J = 4.4, 4.0 Hz, 2H), 0.86 – 0.78 (m, 2H). MS (ESI, *m/z*): 480.2 $[M+H]^+$.

Example 57

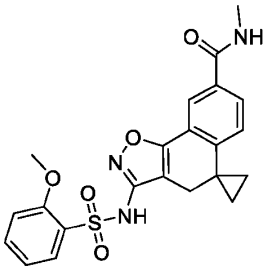
(S)-N-(8'-(3-hydroxypyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0774] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (50 mg, 108 µmol, Example 16), sodium 2-methyl-2-propanolate (31.2 mg, 3 eq., 325 µmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (3.14 mg, 0.05 eq., 5.42 µmol), (1E,4E)-1,5-diphenyl-1,4-pentadien-3-one-1,5-diphenyl-1,4-pentadien-3-one-palladium (1/2/2) (3.97 mg, 0.04 eq., 4.34 µmol), (S)-3-pyrrolidinol hydrochloride (1/1) (16.1 mg, 1.2 eq., 130 µmol) in 1,4-dioxane (1.08 mL, 12.7 mmol) was purged with N2 and stirred at 100°C for 16 h. The crude product was filtered, purified by prep-HPLC (0-100% CH3CN (0.1% HCOOH) in H2O (0.1% HCOOH)), and dried via lyophilization giving (S)-N-(8'-(3-hydroxypyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (3.4 mg, 6.3% yield) as a white solid. MS (ESI, *m/z*): 468.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 10.72 (s, 1H), 7.70 (dd, J = 7.9, 1.8 Hz, 1H), 7.51 (s, 1H), 7.11 (s, 1H), 6.98 (s, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.55 (s, 1H), 6.47 – 6.37 (m, 1H), 4.86 (d, J = 3.8 Hz, 1H), 4.31 (s, 1H), 3.74 (s, 3H), 3.34 (d, J = 4.9 Hz, 4H), 2.98 (d, J = 10.0 Hz, 1H), 2.00 – 1.91 (m, 1H), 1.81 (s, 1H), 0.76 (s, 2H), 0.62 (s, 2H).

Example 58

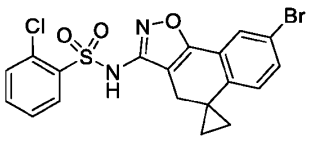
3'-((2-Methoxyphenyl)sulfonamido)-N-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-8'-carboxamide



[0775] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (50 mg, 108 µmol, Example 16), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (5.64 mg, 0.09 eq., 9.75 µmol), palladium bis(acetate) (1.46 mg, 0.06 eq., 6.5 µmol), potassium fluoride (15.7 mg, 2.5 eq., 271 µmol), 1,1-dioxo-3-oxo-1,2-dihydro-3H,1H,1H-1λ⁶,2-benzisothiazole-2-carbaldehyde (27.5 mg, 1.2 eq., 130 µmol) in dimethylformamide (542 µL, 7 mmol) was purged with N2 and stirred at 80°C in a capped vial for 16 h. The mixture was cooled to rt and treated with triethylamine (37.8 µL, 2.5 eq., 271 µmol) and methylamine (6.73 mg, 2 eq., 217 µmol) 2M in THF. The mixture was stirred for 2h at rt. The crude mixture was filtered and purified on C18 (water in ACN 0% to 100% with 0.1% HCOOH) to afford 3'-((2-methoxyphenyl)sulfonamido)-N-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-8'-carboxamide (14.0 mg, 29% yield) as a white solid. MS (ESI, *m/z*): 440.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.45 (d, J = 4.7 Hz, 1H), 7.93 (d, J = 1.9 Hz, 1H), 7.73 (dt, J = 7.9, 2.1 Hz, 2H), 7.55 (s, 1H), 7.14 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 3.75 (s, 3H), 2.70 (d, J = 4.5 Hz, 3H), 2.57 (s, 2H), 1.02 – 0.95 (m, 2H), 0.84 – 0.77 (m, 2H).

Example 59

N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-chlorobenzenesulfonamide

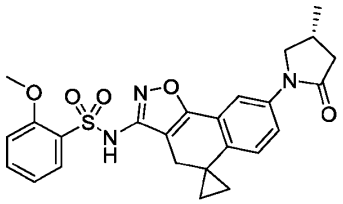


[0776] Example 59 was prepared according to the procedure as described in Example 76, using 2-chlorobenzenesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.57 (s, 1H), 8.06 – 7.99 (m, 1H), 7.67 – 7.57 (m, 3H), 7.55 – 7.39 (m, 2H), 6.97

(d, J = 8.4 Hz, 1H), 2.57 (s, 2H), 1.02 – 0.87 (m, 2H), 0.83 – 0.76 (m, 2H). MS (ESI, *m/z*): 465 $[M+H]^+$.

Example 60

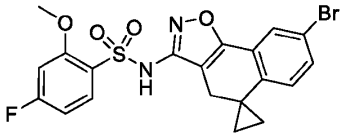
(R)-2-methoxy-N-(8'-(4-methyl-2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0777] Example 60 was prepared according to the procedure as described in Example 31, starting from Example 16 and (R)-4-methylpyrrolidin-2-one from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 7.89 (d, J = 2.4 Hz, 1H), 7.78 (dd, J = 7.8, 1.7 Hz, 1H), 7.61 (td, J = 7.9, 7.4, 1.8 Hz, 1H), 7.53 (dd, J = 8.6, 2.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.07 (t, J = 8.6 Hz, 2H), 3.93 (dd, J = 9.5, 7.6 Hz, 1H), 3.82 (s, 3H), 3.43 (dd, J = 9.5, 6.5 Hz, 1H), 2.69 – 2.58 (m, 3H), 2.49 – 2.35 (m, 1H), 2.17 (dd, J = 16.5, 7.5 Hz, 1H), 1.11 (d, J = 6.7 Hz, 3H), 0.96 (t, J = 3.0 Hz, 2H), 0.80 (q, J = 4.3 Hz, 2H). MS (ESI, *m/z*): 480.2 $[M+H]^+$.

Example 61

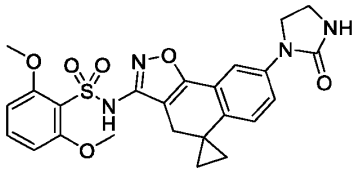
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-fluoro-2-methoxybenzenesulfonamide



[0778] Example 61 was prepared according to the procedure as described in Example 76, using 4-fluoro-2-methoxybenzenesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 7.78 (dd, J = 8.8, 6.5 Hz, 1H), 7.59 (d, J = 2.2 Hz, 1H), 7.45 (dd, J = 8.4, 2.2 Hz, 1H), 7.10 (dd, J = 11.2, 2.4 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.86 (td, J = 8.5, 2.4 Hz, 1H), 3.78 (s, 3H), 2.56 (s, 2H), 1.02 – 0.91 (m, 2H), 0.83 – 0.76 (m, 2H). MS (ESI, *m/z*): 479 $[M+H]^+$.

Example 62

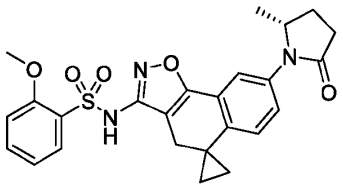
2,6-Dimethoxy-N-(8'-(2-oxoimidazolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0779] Example 62 was prepared according to the procedure as described in Example 31, starting from Example 16 and imidazolidin-2-one from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 8.39 (s, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.40 – 7.28 (m, 2H), 6.99 – 6.90 (m, 2H), 6.66 (d, J = 8.4 Hz, 2H), 3.84 (dd, J = 9.3, 6.7 Hz, 2H), 3.69 (s, 6H), 3.6 - 3.2 (m, 4 H) 0.89 (q, J = 4.3 Hz, 2H), 0.70 (q, J = 4.3 Hz, 2H). MS (ESI, *m/z*): 497.2 $[M+H]^+$.

Example 63

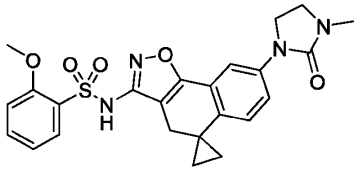
(R)-2-methoxy-N-(8'-(2-methyl-5-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0780] Example 63 was prepared according to the procedure as described in Example 31, starting from Example 16 and (R)-5-methylpyrrolidin-2-one from a commercial source (Pharmablock 21395-93-7). ^{1}H NMR (400 MHz, DMSO) δ 10.87 (s, 1H), 7.78 (dd, J = 7.8, 1.7 Hz, 1H), 7.70 – 7.57 (m, 2H), 7.38 (dd, J = 8.5, 2.3 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.14 – 7.03 (m, 2H), 4.46 – 4.34 (m, 1H), 3.83 (s, 3H), 2.61 (s, 2H), 2.59 – 2.52 (m, 1H), 2.45 – 2.21 (m, 2H), 1.66 (ddt, J = 12.0, 9.5, 6.0 Hz, 1H), 1.11 (d, J = 6.1 Hz, 3H), 0.98 (t, J = 3.1 Hz, 2H), 0.82 (q, J = 4.0 Hz, 2H). MS (ESI, *m/z*): 480.2 $[M+H]^+$.

Example 64

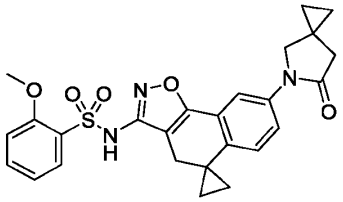
2-Methoxy-N-(8'-(3-methyl-2-oxoimidazolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0781] Example 64 was prepared according to the procedure as described in Example 31, starting from Example 16 and 1-methylimidazolidin-2-one from a commercial source (Combi-Blocks 694-32-6). ^{1}H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 7.84 – 7.74 (m, 2H), 7.61 (t, J = 7.9 Hz, 1H), 7.45 (dd, J = 8.7, 2.5 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.11 – 6.97 (m, 2H), 3.85 – 3.74 (m, 5H), 3.43 (dd, J = 9.2, 6.7 Hz, 2H), 2.76 (s, 3H), 2.57 (s, 2H), 0.97 – 0.86 (m, 2H), 0.81 – 0.74 (m, 2H). MS (ESI, *m/z*): 481.2 $[M+H]^+$.

Example 65

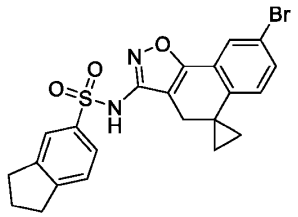
2-Methoxy-N-(8'-(6-oxo-5-azaspiro[2.4]heptan-5-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0782] Example 65 was prepared according to the procedure as described in Example 31, starting from Example 16 and 5-azaspiro[2.4]heptan-6-one from a commercial source (Enamine 1783637-53-5). ^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.78 (dd, J = 7.8, 1.7 Hz, 1H), 7.62 (ddd, J = 8.7, 7.4, 1.8 Hz, 1H), 7.55 (dd, J = 8.7, 2.4 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.08 (dd, J = 8.4, 6.8 Hz, 2H), 3.82 (s, 3H), 3.75 (s, 2H), 2.58 (d, J = 16.3 Hz, 4H), 1.00 – 0.93 (m, 2H), 0.84 – 0.77 (m, 2H), 0.68 (q, J = 2.0 Hz, 4H). MS (ESI, *m/z*): 492.2 $[M+H]^+$.

Example 66

N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,3-dihydro-1H-indene-5-sulfonamide



[0783] Example 66 was prepared according to the procedure as described in Example 76, using 2,3-dihydro-1H-indene-5-sulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 8.13 (s, 1H), 7.69 (s, 1H), 7.61 (dd, J = 8.0, 1.9 Hz, 2H), 7.48 (dd, J = 8.4, 2.2 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 2.90 (td, J = 7.5, 2.8 Hz, 4H), 2.56 (s, 2H), 2.07 – 2.00 (m, 2H), 1.02 – 0.94 (m, 2H), 0.84 (p, J = 4.1 Hz, 2H). MS (ESI, *m/z*): 470 [M-H]$^-$.

Example 67

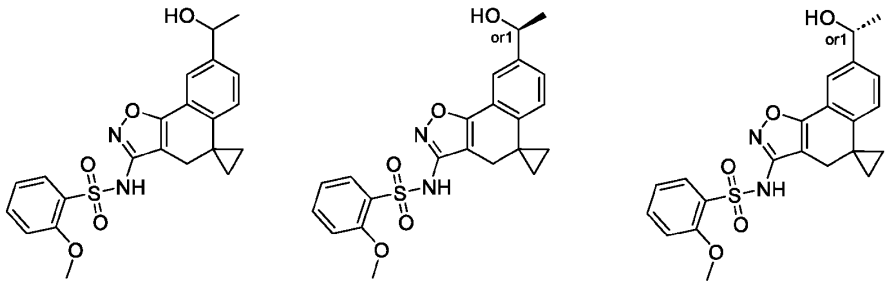
N-(8'-(1-hydroxyethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

Example 87

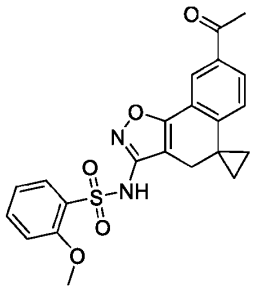
Rel-(S)-N-(8'-(1-hydroxyethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

Example 88

Rel-(R)-N-(8'-(1-hydroxyethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

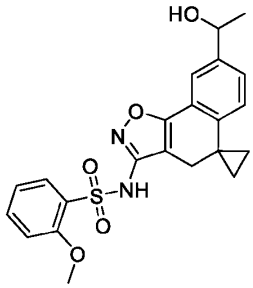


[0784] Step 1. Synthesis of N-(8'-acetyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0785] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (280 mg, 0.607 mmol, 1.00 equiv, Example 16), tributyl(1-ethoxyethenyl)stannane (439.0 mg, 1.215 mmol, 2.00 equiv) and $Pd(PPh_3)_4$ (70.0 mg, 0.061 mmol, 0.10 equiv) in dioxane (5.0 mL) was stirred at 90 °C for 16 h under N_2 atmosphere. The resulting mixture was cooled to ambient temperature and to this was added concentrated aqueous HCl (1 mL). The resulting mixture was stirred at this temperature for 1 h and then diluted with EtOAc. The resulting mixture was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford N-(8'-acetyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (120 mg, 46% yield) as yellow oil. MS (ESI, *m/z*): 425 [M+H]+.

[0786] Step 2. Synthesis of N-(8'-(1-hydroxyethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

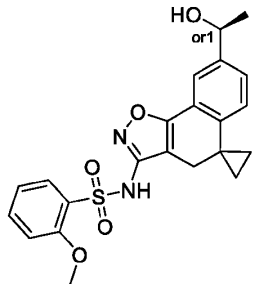


[0787] To a stirred mixture of N-(8'-acetyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (120.0 mg, 0.283 mmol, 1.0 equiv) in EtOH (6.0 mL) at 0 °C was added $NaBH_4$ (32.0 mg, 0.849 mmol, 3.0 equiv) in portions. The resulting mixture was stirred at ambient temperature for 2 h and then quenched with saturated NH4Cl solution and extracted with EtOAc three times. The combined organic layers were

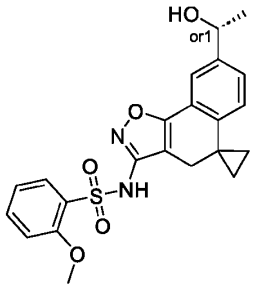
washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-80% acetonitrile in water (contained 0.05% formic acid)) to afford N-(8'-(1-hydroxyethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (80.0 mg, 66% yield) as a white solid. MS (ESI, *m/z*): 427 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.85 (s, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.63 (t, J = 8.1 Hz, 1H), 7.51 (s, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 8.7 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 5.21 (d, J = 4.5 Hz, 1H), 4.73-4.69 (m, 1H), 3.84 (s, 3H), 2.59 (s, 2H), 1.30 (d, J = 6.3 Hz, 3H), 0.96 (s, 2H), 0.80 (s, 2H).

[0788] Step 3. Synthesis of rel-(S)-N-(8'-(1-hydroxyethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide and rel-(R)-N-(8'-(1-hydroxyethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

[0789] The crude product of rac-N-(8'-(1-hydroxyethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (80.0 mg) was resolved with Chiral-Prep-HPLC. The absolute stereochemistry was not determined.



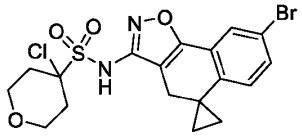
[0790] rel-(S)-N-(8'-(1-hydroxyethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (25.6 mg, 30% yield) as a white solid (1st peak). MS (ESI, *m/z*): 427.2 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.84 (s, 1H), 7.80-7.77 (m, 1H), 7.66-7.60 (m, 1H), 7.52 (d, J = 1.8 Hz, 1H), 7.32-7.29 (m, 1H), 7.23-7.20 (m, 1H), 7.11-7.05 (m, 1H), 7.02 (d, J = 8.1 Hz, 1H), 5.20 (d, J = 4.2 Hz, 1H), 4.77-4.65 (m, 1H), 3.84 (s, 3H), 2.59 (s, 2H), 1.30 (d, J = 6.3 Hz, 3H), 1.03-0.92 (m, 2H), 0.86-0.74 (m, 2H).



[0791] rel-(R)-N-(8'-(1-hydroxyethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (17.8 mg, 25% yield) as a white solid (2nd peak). MS (ESI, *m/z*): 427.2 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.84 (s, 1H), 7.80-7.77 (m, 1H), 7.66-7.60 (m, 1H), 7.52 (d, J = 1.8 Hz, 1H), 7.32-7.29 (m, 1H), 7.23-7.20 (m, 1H), 7.11-7.05 (m, 1H), 7.02 (d, J = 8.1 Hz, 1H), 5.20 (d, J = 4.2 Hz, 1H), 4.77-4.65 (m, 1H), 3.84 (s, 3H), 2.59 (s, 2H), 1.30 (d, J = 6.3 Hz, 3H), 1.02-0.89 (m, 2H), 0.89-0.76 (m, 2H).

Example 68

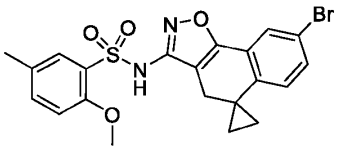
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-chlorotetrahydro-2H-pyran-4-sulfonamide



[0792] To 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (40 mg, 137 μmol, Intermediate C) dissolved in THF was added 1.0 M LiHMDS in THF (0.4 mL, 412 μmol) at -78 °C and stirred for 10 min. 4-(chlorosulfonyl)tetrahydro-2H-pyran (50.7 mg, 275 μmol) solution in THF (1 mL) was then added to the light yellow solution at -78 °C and the reaction was stirred at rt overnight. The resulting mixture was concentrated under reduced pressure to afford residue. The residue was purified by prep-HPLC (0-90% MeCN in water with 0.1% formic acid) to give N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-chlorotetrahydro-2H-pyran-4-sulfonamide (12.6 mg, 19% yield) as a white solid. MS (ESI, *m/z*): 473 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 11.34 (s, 1H), 7.77 (d, J = 2.1 Hz, 1H), 7.56 (dd, J = 8.4, 2.2 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 3.97 (dd, J = 11.9, 4.9 Hz, 2H), 3.57 (dd, J = 12.6, 10.7 Hz, 2H), 2.73 (s, 2H), 2.42 – 2.29 (m, 2H), 1.98 (m, 2H), 1.07 – 0.88 (m, 4H).

Example 69

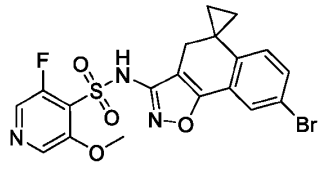
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-5-methylbenzenesulfonamide



[0793] Example 69 was prepared according to the procedure as described in Example 76, using 2-methoxy-5-methylbenzenesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 7.67 (d, J = 2.1 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 7.52 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 3.78 (s, 3H), 2.62 (s, 2H), 2.29 (s, 3H), 1.05 – 0.97 (m, 2H), 0.88 – 0.81 (m, 2H). MS(ESI, *m/z*): 475 $[M+H]^+$.

Example 70

N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-fluoro-5-methoxypyridine-4-sulfonamide

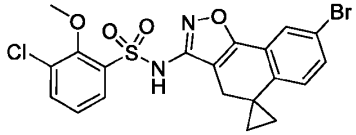


[0794] To 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (40 mg, 137 μmol, Intermediate C) dissolved in 1.0 mL THF was added 1.0 M LiHMDS in THF (0.4 mL, 412 μmol) at -78 °C and stirred for 10 min. Later, 3-fluoro-4-(fluorosulfonyl)-5-methoxypyridine (28.7 mg, 137 μmol) solution in 2 mL of THF was added to the light yellow solution at -78 °C and the reaction was stirred at rt overnight. The resulting mixture was concentrated under reduced pressure to afford a residue. The residue was purified by prep-HPLC (0-90% MeCN in water with 0.1% formic acid) to give N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-fluoro-5-methoxypyridine-4-sulfonamide (27 mg, 41% yield) as a white solid. MS (ESI, *m/z*): 480 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 11.73 (s, 1H), 8.55 (s, 1H), 8.45 (d, J = 1.3 Hz, 1H), 7.69 (d, J = 2.2 Hz,

1H), 7.54 (dd, J = 8.4, 2.2 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 3.99 (s, 3H), 2.66 (s, 2H), 1.07 – 1.00 (m, 2H), 0.96 – 0.85 (m, 2H).

Example 71

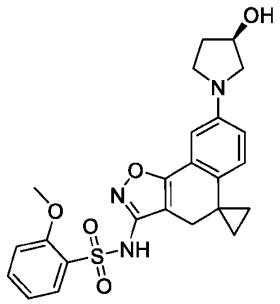
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-chloro-2-methoxybenzenesulfonamide



[0795] Example 71 was prepared according to the procedure as described in Example 76, using 2,2-difluorobenzo[d][1,3]dioxole-4-sulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.46 (s, 1H), 7.91 (ddd, J = 7.9, 6.2, 1.7 Hz, 2H), 7.75 (d, J = 2.1 Hz, 1H), 7.61 (dd, J = 8.4, 2.2 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 4.01 (s, 3H), 2.72 (s, 2H), 1.14 – 1.06 (m, 2H), 0.99 – 0.92 (m, 2H). MS (ESI, *m/z*): 495 $[M+H]^+$.

Example 72

(R)-N-(8'-(3-hydroxypyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

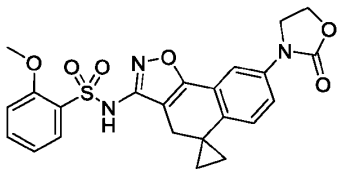


[0796] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (50 mg, 108 µmol, Example 16), sodium 2-methyl-2-propanolate (31.2 mg, 3 eq., 325 µmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (3.14 mg, 0.05 eq., 5.42 µmol), (1E,4E)-1,5-diphenyl-1,4-pentadien-3-one-1,5-diphenyl-1,4-pentadien-3-one-palladium (1/2/2) (3.97 mg, 0.04 eq., 4.34 µmol), (R)-3-

pyrrolidinol (16.1 mg, 1.2 eq., 130 µmol) in 1,4-dioxane (1.08 mL, 12.7 mmol) was purged with N2 and stirred at 100°C for 16 h. The crude product was diluted with DMSO, filtered, purified by prep-HPLC (0-100% CH3CN (0.1% HCOOH) in H2O (0.1% HCOOH)), and dried via lyophilization giving (R)-N-(8'-(3-hydroxypyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (7.9 mg, 16% yield) as a white solid. MS (ESI, *m/z*): 468.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 10.71 (s, 1H), 7.71 (dd, J = 7.9, 1.8 Hz, 1H), 7.55 (s, 1H), 7.14 (s, 1H), 7.00 (s, 1H), 6.78 (d, J = 8.6 Hz, 1H), 6.56 (d, J = 2.5 Hz, 1H), 6.47 – 6.38 (m, 1H), 4.86 (d, J = 3.8 Hz, 1H), 4.31 (s, 1H), 3.75 (s, 3H), 3.33 (dd, J = 10.0, 5.0 Hz, 1H), 3.25 – 3.20 (m, 3H), 2.98 (d, J = 9.8 Hz, 1H), 2.00 – 1.91 (m, 1H), 1.81 (s, 1H), 0.76 (s, 2H), 0.64 (d, J = 5.3 Hz, 2H).

Example 73

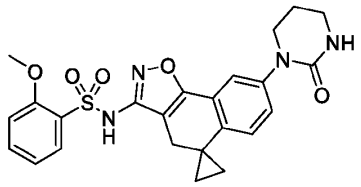
2-Methoxy-N-(8'-(2-oxooxazolidin-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0797] Example 73 was prepared according to the procedure as described in Example 31, starting from Example 16 and oxazolidin-2-one from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 7.81 – 7.72 (m, 2H), 7.56 (s, 1H), 7.45 (dd, J = 8.6, 2.5 Hz, 1H), 7.17 (t, J = 8.7 Hz, 1H), 7.05 (dd, J = 12.0, 7.9 Hz, 2H), 4.43 (dd, J = 9.0, 6.9 Hz, 2H), 4.07 (dd, J = 9.0, 6.9 Hz, 2H), 3.80 (d, J = 6.0 Hz, 3H), 2.55 (d, J = 10.6 Hz, 2H), 0.95 (q, J = 4.4 Hz, 2H), 0.81 (p, J = 5.0 Hz, 2H). MS (ESI, *m/z*): 468.2 $[M+H]^+$.

Example 74

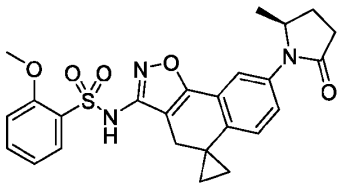
2-Methoxy-N-(8'-(2-oxotetrahydropyrimidin-1(2H)-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0798] Example 74 was prepared according to the procedure as described in Example 31, starting from Example 16 and tetrahydropyrimidin-2(1H)-one from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 7.77 (dd, J = 7.8, 1.8 Hz, 1H), 7.67 – 7.53 (m, 1H), 7.43 (d, J = 2.3 Hz, 1H), 7.25 – 7.12 (m, 2H), 7.07 – 6.94 (m, 2H), 6.62 (d, J = 2.9 Hz, 1H), 3.80 (s, 3H), 3.61 (t, J = 5.7 Hz, 2H), 3.21 (td, J = 5.9, 2.4 Hz, 2H), 2.54 (d, J = 2.7 Hz, 3H), 1.93 (p, J = 5.7 Hz, 2H), 0.95 (q, J = 4.4 Hz, 2H), 0.79 (q, J = 4.4 Hz, 2H). MS (ESI, *m/z*): 481.6 $[M+H]^+$.

Example 75

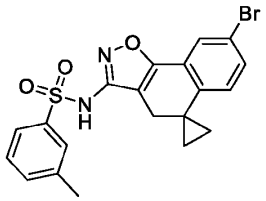
(S)-2-methoxy-N-(8'-(2-methyl-5-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0799] Example 75 was prepared according to the procedure as described in Example 31, starting from Example 16 and (S)-5-methylpyrrolidin-2-one from a commercial source (Pharmablock 1558-60-7). ^{1}H NMR (400 MHz, DMSO) δ 10.87 (s, 1H), 7.78 (dd, J = 7.9, 1.7 Hz, 1H), 7.69 – 7.57 (m, 2H), 7.37 (dd, J = 8.6, 2.3 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.07 (dd, J = 8.1, 5.9 Hz, 2H), 4.46 – 4.34 (m, 1H), 3.83 (s, 3H), 2.60 (s, 2H), 2.58 – 2.52 (m, 1H), 2.45 – 2.21 (m, 2H), 1.75 – 1.59 (m, 1H), 1.10 (d, J = 6.1 Hz, 3H), 0.98 (t, J = 3.1 Hz, 2H), 0.91 – 0.78 (m, 2H). MS (ESI, *m/z*): 480.2 $[M+H]^+$.

Example 76

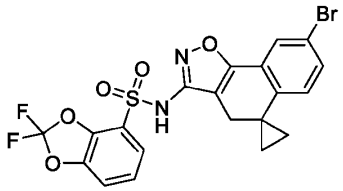
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-methylbenzenesulfonamide



[0800] To a solution of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (40mg, 0.14 mmol, Intermediate C) in pyridine (0.5 mL) was added m-(chlorosulfonyl)toluene (105 mg, 0.55 mmol) and DMAP (1 mg). The mixture was stirred at 30°C for 16 hours. The mixture was concentrated under reduced pressure to afford a residue. The residue was purified by reverse phase HPLC (0-90% MeCN in water with 0.1% formic acid) to give N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-methylbenzenesulfonamide (3.7 mg, 6% yield) as a white solid. MS (ESI, *m/z*): 444 $[M-H]^-$. ^{1}H NMR (400 MHz, DMSO) δ 11.21 (s, 1H), 7.72 – 7.63 (m, 3H), 7.56 – 7.45 (m, 3H), 7.04 (d, J = 8.4 Hz, 1H), 2.62 (s, 2H), 2.39 (s, 3H), 1.04 – 0.97 (m, 2H), 0.86 (dt, J = 6.9, 4.9 Hz, 2H).

Example 77

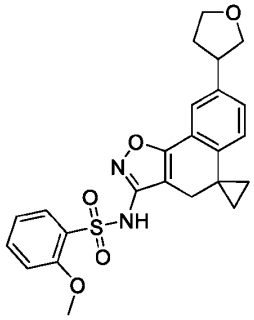
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,2-difluorobenzo[d][1,3]dioxole-4-sulfonamide



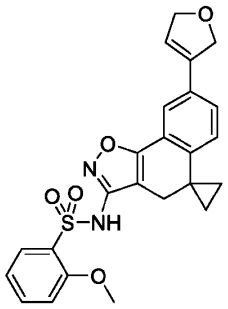
[0801] Example 77 was prepared according to the procedure as described in Example 76, using 2,2-difluorobenzo[d][1,3]dioxole-4-sulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.82 (s, 1H), 7.76 (dd, J = 8.1, 1.1 Hz, 1H), 7.70 (d, J = 2.2 Hz, 1H), 7.61 (dd, J = 8.3, 1.1 Hz, 1H), 7.54 (dd, J = 8.4, 2.2 Hz, 1H), 7.44 (t, J = 8.2 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 2.66 (s, 2H), 1.06 – 0.98 (m, 2H), 0.93 – 0.85 (m, 2H). MS (ESI, *m/z*): 511 $[M+H]^+$

Example 78

2-Methoxy-N-(8'-(tetrahydrofuran-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide

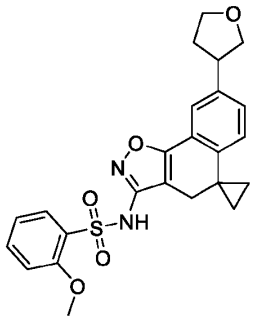


[0802] Step 1. Synthesis of N-(8'-(2,5-dihydrofuran-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0803] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (100.0 mg, 0.22 mmol, 1.00 equiv), 2-(2,5-dihydrofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (85.0 mg, 0.43 mmol, 2.00 equiv), $Pd(dppf)Cl_2$ (31.7 mg, 0.04 mmol, 0.20 equiv) and K_3PO_4 (92.0 mg, 0.43 mmol, 2.00 equiv) in dioxane (4.0 mL) and H_2O (1.0 mL) was stirred at 100 °C for 2 h under N_2 atmosphere and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-95% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-(2,5-dihydrofuran-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (75 mg, 71% yield) as a yellow solid. MS (ESI, *m/z*): 451 [M+H]+

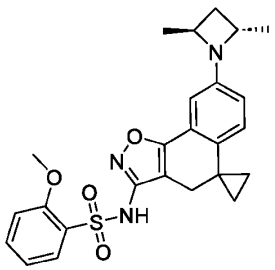
[0804] Step 2. Synthesis of 2-methoxy-N-(8'-(tetrahydrofuran-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0805] A mixture of N-(8'-(2,5-dihydrofuran-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (65.0 mg, 0.14 mmol, 1.00 equiv) and Pd/C (wet, 10%, 6 mg, 10% w/w) in EtOH (15.0 mL) was stirred at ambient temperature for 24 h under H2 (~3 atm) atmosphere and then filtered. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-70% acetonitrile in water (contained 0.05% formic acid)) and further purified by Prep-HPLC (5-70% acetonitrile in water (contained 0.1% formic acid)) to afford 2-methoxy-N-(8'-(tetrahydrofuran-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide (10 mg, 15% yield) as a white solid. MS (ESI, *m/z*): 453.2 [M+H]+. 1H NMR (300 MHz, DMSO-d6) δ 10.87 (br s, 1H), 7.82-7.73 (m, 1H), 7.68-7.56 (m, 1H), 7.42 (d, J = 1.8 Hz, 1H), 7.30-7.17 (m, 2H), 7.12-7.02 (m, 1H), 7.00 (d, J = 8.1 Hz, 1H), 4.05-3.95 (m, 1H), 3.95-3.87 (m, 1H), 3.83 (s, 3H), 3.80-3.71 (m, 1H), 3.55-3.48 (m, 1H), 3.46-3.41 (m, 1H), 2.58 (s, 2H), 2.35-2.21 (m, 1H), 1.95-1.80 (m, 1H), 1.01-0.84 (m, 2H), 0.84-0.74 (m, 2H).

Example 79

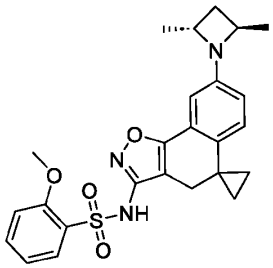
N-(8'-((2S,4S)-2,4-dimethylazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0806] Example 79 was prepared according to the procedure as described in Example 31, starting from Example 16 and (2S,4S)-2,4-dimethylazetidine from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.75 (s, 1H), 7.70 (dd, J = 7.9, 1.8 Hz, 1H), 7.59 – 7.47 (m, 1H), 7.13 (d, J = 8.3 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 6.76 (d, J = 8.5 Hz, 1H), 6.47 (d, J = 2.5 Hz, 1H), 6.33 (dd, J = 8.5, 2.5 Hz, 1H), 4.18 (h, J = 6.2 Hz, 2H), 3.76 (s, 3H), 2.49 (s, 2H), 1.95 (t, J = 6.4 Hz, 2H), 1.16 (d, J = 6.1 Hz, 6H), 0.78 (p, J = 3.4 Hz, 2H), 0.64 (t, J = 3.4 Hz, 2H). MS (ESI, *m/z*): 466.2 $[M+H]^+$.

Example 80

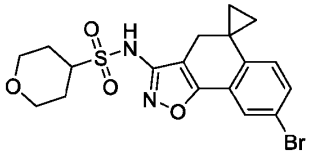
N-(8'-((2R,4R)-2,4-dimethylazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0807] Example 80 was prepared according to the procedure as described in Example 31, starting from Example 16 and (2R,4R)-2,4-dimethylazetidine from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.81 (s, 1H), 7.77 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.65 – 7.53 (m, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.53 (d, *J* = 2.5 Hz, 1H), 6.40 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.24 (h, *J* = 6.2 Hz, 2H), 3.82 (s, 3H), 2.51 (s, 2H), 2.02 (t, *J* = 6.4 Hz, 2H), 1.23 (d, *J* = 6.1 Hz, 6H), 0.84 (p, *J* = 3.4 Hz, 2H), 0.70 (t, *J* = 3.4 Hz, 2H). MS (ESI, *m/z*): 466.2 $[M+H]^+$.

Example 81

N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)tetrahydro-2H-pyran-4-sulfonamide

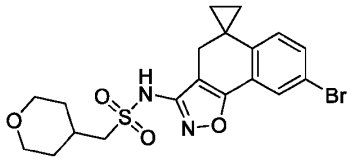


[0808] Example 81 was prepared according to the procedure as described in Example 76, using tetrahydro-2H-pyran-4-sulfonyl chloride from a commercial source. ^{1}H NMR (400

MHz, DMSO) δ 7.60 (d, J = 2.2 Hz, 1H), 7.44 (dd, J = 8.4, 2.2 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.09 – 3.70 (m, 2H), 3.48 (d, J = 12.1 Hz, 1H), 2.54 (s, 2H), 1.81 (d, J = 12.9 Hz, 2H), 1.60 (qd, J = 12.2, 4.6 Hz, 2H), 1.01 – 0.90 (m, 2H), 0.86 – 0.73 (m, 2H). MS (ESI, *m/z*): 439 [M+H]+.

Example 82

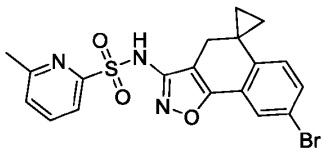
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-1-(tetrahydro-2H-pyran-4-yl)methanesulfonamide



[0809] Example 82 was prepared according to the procedure as described in Example 76, using (tetrahydro-2H-pyran-4-yl)methanesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 7.62 (d, J = 2.2 Hz, 1H), 7.45 (dd, J = 8.4, 2.2 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 3.74 (ddd, J = 11.6, 4.3, 2.1 Hz, 2H), 3.19 (d, J = 6.7 Hz, 5H), 2.54 (s, 2H), 2.05 (dt, J = 11.2, 6.4 Hz, 1H), 1.83 – 1.43 (m, 2H), 1.44 – 1.10 (m, 3H), 1.15 – 0.64 (m, 4H). MS (ESI, *m/z*): 453 [M+H]+.

Example 83

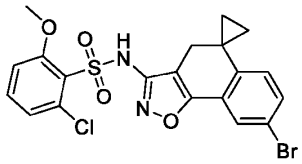
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-6-methylpyridine-2-sulfonamide



[0810] Example 83 was prepared according to the procedure as described in Example 70, using 6-methylpyridine-2-sulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.42 (s, 1H), 7.88 (t, J = 7.8 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.56 (s, 1H), 7.43 (dd, J = 8.6, 2.3 Hz, 2H), 6.96 (d, J = 8.5 Hz, 1H), 2.54 (s, 2H), 2.52 (s, 3H), 0.93 (q, J = 4.5 Hz, 2H), 0.85 – 0.59 (m, 2H). MS (ESI, *m/z*): 446 [M+H]+.

Example 84

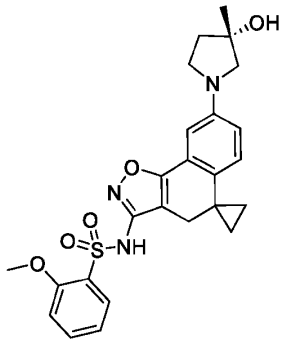
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-chloro-6-methoxybenzenesulfonamide



[0811] Example 84 was prepared according to the procedure as described in Example 76, using 2-chloro-6-methoxybenzenesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.04 (s, 1H), 7.59 (d, J = 2.2 Hz, 1H), 7.44 (dd, J = 8.4, 2.1 Hz, 2H), 7.10 (dd, J = 15.2, 8.3 Hz, 2H), 6.96 (d, J = 8.4 Hz, 1H), 3.77 (s, 3H), 2.55 (s, 2H), 0.97 – 0.90 (m, 2H), 0.84 – 0.73 (m, 2H). MS (ESI, *m/z*): 495 [M+H]+.

Example 85

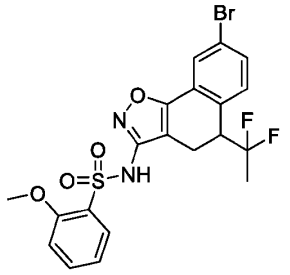
(S)-N-(8'-(3-hydroxy-3-methylpyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



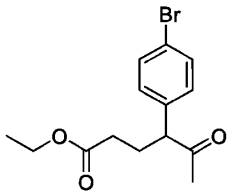
[0812] Example 85 was prepared according to the procedure as described in Example 31, starting from Example 16 and (S)-3-methylpyrrolidin-3-ol from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.78 (s, 1H), 7.78 (dd, J = 7.8, 1.8 Hz, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.08 (t, J = 7.7 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 6.60 (d, J = 2.6 Hz, 1H), 6.46 (dd, J = 8.6, 2.6 Hz, 1H), 4.77 (s, 1H), 3.83 (s, 3H), 3.39 – 3.33 (m, 2H), 3.32 – 3.26 (m, 2H), 3.16 (q, J = 9.7 Hz, 2H), 1.95 – 1.83 (m, 2H), 1.34 (s, 3H), 0.83 (t, J = 3.0 Hz, 2H), 0.74 – 0.67 (m, 2H). MS (ESI, *m/z*): 482.2 [M+H]+.

Example 86

N-(8-bromo-5-(1,1-difluoroethyl)-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2-methoxybenzenesulfonamide

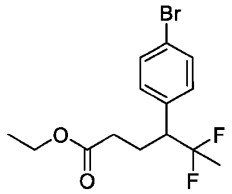


[0813] Step 1. Synthesis of ethyl 4-(4-bromophenyl)-5-oxohexanoate



[0814] A mixture of 1-(4-bromophenyl)propan-2-one (10.0 g, 46.93 mmol, 1.00 equiv), ethyl 3-iodopropanoate (13.9 g, 61.01 mmol, 1.30 equiv) and Cs_2CO_3 (45.9 g, 140.80 mmol, 3.00 equiv) in DMF (100.0 mL) was stirred at ambient temperature for 3 h. The resulting mixture was filtered. The filtrate was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-25% EtOAc in petroleum ether) to afford ethyl 4-(4-bromophenyl)-5-oxohexanoate (12.0 g, 81% yield) as yellow oil. MS (ESI, *m/z*): 313, 315 [M+H]+.

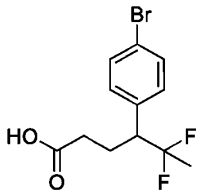
[0815] Step 2. Synthesis of ethyl 4-(4-bromophenyl)-5,5-difluorohexanoate



[0816] A mixture of ethyl 4-(4-bromophenyl)-5-oxohexanoate (12.0 g, 38.32 mmol, 1.00 equiv) and BAST (93.3 g, 421.47 mmol, 11.00 equiv) in DCM (180.0 mL) was stirred at

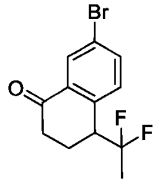
ambient temperature for 18 h. T resulting reaction mixture was quenched at 0 °C with water and then extracted with DCM three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-15% EtOAc in petroleum ether) to afford ethyl 4-(4-bromophenyl)-5,5-difluorohexanoate (6.0 g, 46% yield) as yellow oil. MS (ESI, *m/z*): 335, 337 [M+H]+.

[0817] Step 3. Synthesis of 4-(4-bromophenyl)-5,5-difluorohexanoic acid



[0818] A mixture of ethyl 4-(4-bromophenyl)-5,5-difluorohexanoate (6.0 g, 17.90 mmol, 1.00 equiv) and LiOH (1.3 g, 53.70 mmol, 3.00 equiv) in THF (30.0 mL), water (30.0 mL) and MeOH (30.0 mL) was stirred at ambient temperature for 2 h. The resulting mixture was diluted with water and then cooled to 0 °C, acidified with aqueous HCl (1 M) to pH ~ 2 and extracted with DCM three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-15% MeOH in DCM) to afford 4-(4-bromophenyl)-5,5-difluorohexanoic acid (4.5 g, 82% yield) as yellow oil. MS (ESI, *m/z*): 307, 309 [M+H]+.

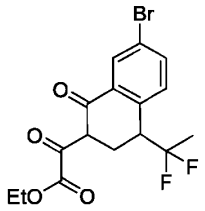
[0819] Step 4. Synthesis of 7-bromo-4-(1,1-difluoroethyl)-3,4-dihydronaphthalen-1(2H)-one



[0820] A solution of 4-(4-bromophenyl)-5,5-difluorohexanoic acid (4.5 g, 14.65 mmol, 1.00 equiv) in Eaton's reagent (30.0 mL) was stirred at 60 °C for 8 h. The resulting mixture was slowly poured into ice water and the mixture was extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-15% EtOAc in petroleum

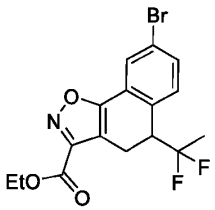
ether) to afford 7-bromo-4-(1,1-difluoroethyl)-3,4-dihydronaphthalen-1(2H)-one (1.3 g, 31% yield) as yellow oil. MS (ESI, *m/z*): 289, 291 [M+H]+.

[0821] Step 5. Synthesis of ethyl 2-(7-bromo-4-(1,1-difluoroethyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate



[0822] To a stirred solution of 7-bromo-4-(1,1-difluoroethyl)-3,4-dihydronaphthalen-1(2H)-one (1.3 g, 4.50 mmol, 1.00 equiv) and ethyl oxalate (1.0 g, 6.74 mmol, 1.50 equiv) in THF (20.0 mL) at 0 °C was added *t*-BuOLi (1.1 g, 13.49 mmol, 3.00 equiv) in portions. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 4 h. The resulting mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford ethyl 2-(7-bromo-4-(1,1-difluoroethyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate (900.0 mg, 51% yield) as yellow oil. MS (ESI, *m/z*):389, 391 [M+H]+.

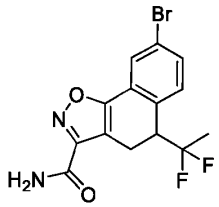
[0823] Step 6. Synthesis of ethyl 8-bromo-5-(1,1-difluoroethyl)-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate



[0824] A mixture of ethyl 2-(7-bromo-4-(1,1-difluoroethyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate (900.0 mg, 1.29 mmol, 1.00 equiv) and hydroxylamine (84.0 mg, 1.29 mmol, 1.00 equiv) in EtOH (15.0 mL) was stirred at 80 °C for 6 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-30% EtOAc in petroleum ether) to afford ethyl 8-bromo-5-(1,1-

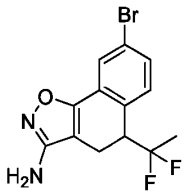
difluoroethyl)-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (500.0 mg, 61% yield) as yellow oil. MS (ESI, *m/z*): 386, 388 [M+H]+.

[0825] Step 7. Synthesis of 8-bromo-5-(1,1-difluoroethyl)-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide



[0826] A mixture of ethyl 8-bromo-5-(1,1-difluoroethyl)-4H,5H-naphtho[2,1-d][1,2]oxazole-3-carboxylate (500.0 mg, 1.29 mmol, 1.00 equiv) and ammonia (0.7 mL, 4.55 mmol, 3.53 equiv, 25% aq) in MeOH (5.0 mL) was stirred at ambient temperature for 5 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-10% MeOH in DCM) to afford 8-bromo-5-(1,1-difluoroethyl)-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (400.0 mg, 50% yield) as a white solid. MS (ESI, *m/z*): 357, 359 [M+H]+.

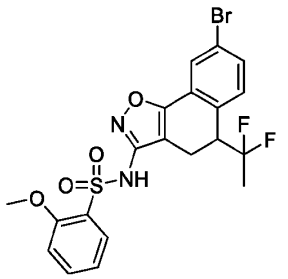
[0827] Step 8. Synthesis of 8-bromo-5-(1,1-difluoroethyl)-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine



[0828] To a stirred solution of 8-bromo-5-(1,1-difluoroethyl)-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (400.0 mg, 1.08 mmol, 1.00 equiv) in EtOAc (6.0 mL), acetonitrile (6.0 mL) and water (3.0 mL) at 0 °C was added $PhI(OAc)_2$ (385.0 mg, 1.08 mmol, 1.00 equiv) and K_2CO_3 (440.0 mg, 3.21 mmol, 3.00 equiv). The resulting mixture was allowed to warm up to ambient emperature and stirred for another 3 h. The mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-10% MeOH in DCM) to afford 8-bromo-5-(1,1-

difluoroethyl)-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (120.0 mg, 44% yield) as a white solid. MS (ESI, *m/z*): 329, 331 [M+H]+.

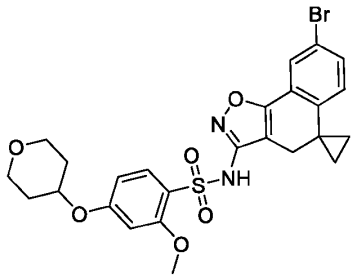
[0829] Step 9. Synthesis of N-(8-bromo-5-(1,1-difluoroethyl)-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2-methoxybenzenesulfonamide



[0830] To a stirred solution of 8-bromo-5-(1,1-difluoroethyl)-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (60.0 mg, 0.18 mmol, 1.00 equiv) in THF (1.50 mL) at 0 °C was added LiHMDS (1M in THF, 0.22 mL, 0.22 mmol, 1.2 equiv). The resulting mixture was stirred at this temperature for 30 min and then quenched with AcOH and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (10-60% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8-bromo-5-(1,1-difluoroethyl)-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2-methoxybenzenesulfonamide (6.4 mg, 7% yield) as a white solid. MS (ESI, *m/z*): 499, 501 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.03 (s, 1H), 7.79 (dd, J = 7.8, 1.6 Hz, 1H), 7.71 (d, 1.6 Hz, 1H), 7.65-7.62 (m, 2H), 7.41 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 3.83 (s, 3H), 3.73-3.55 (m, 1H), 3.20 (d, J = 18.4 Hz, 1H), 2.89-2.80 (m, 1H), 1.35 (t, J = 19.2 Hz, 3H). 19F NMR (376 MHz, DMSO-d6) δ -92.21, -92.32.

Example 89

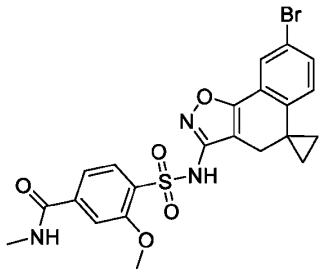
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-4-((tetrahydro-2H-pyran-4-yl)oxy)benzenesulfonamide



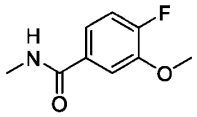
[0831] To a stirred mixture of tetrahydro-2H-pyran-4-ol (86 mg, 0.84 mmol, 3.00 equiv) in DMSO (2.0 mL) at 0 °C was added NaH (60% in mineral oil, 34 mg, 0.84 mmol, 3.00 equiv). The resulting mixture was stirred at this temperature for 1 h and then to this was added N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-fluoro-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (160.0 mg, 0.28 mmol, 1.00 equiv, Intermediate H). The resulting mixture was allowed to warm up to ambient temperature and stirred for another 16 h. The mixture was quenched with saturated NH4Cl solution and extracted with EtOAc three times. The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5--75% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-4-((tetrahydro-2H-pyran-4-yl)oxy)benzenesulfonamide (13.6 mg, 9% yield) as a white solid. MS (ESI, *m/z*): 561, 563 [M+H]+. 1H NMR (300 MHz, DMSO-d6) δ 7.73-7.65 (m, 1H), 7.63 (d, J = 2.1 Hz, 1H), 7.50 (dd, J = 8.4, 2.1 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.72-6.61 (m, 2H), 4.78-4.62 (m, 1H), 3.90-3.79 (m, 2H), 3.78 (s, 3H), 3.55-3.41 (m, 2H), 2.59 (s, 2H), 2.04-1.90 (m, 2H), 1.67-1.48 (m, 2H), 1.06-0.93 (m, 2H), 0.91-0.75 (m, 2H).

Example 90

4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide

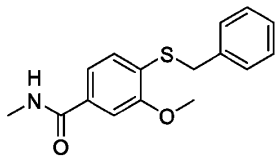


[0832] Step 1. Synthesis of -fluoro-3-methoxy-N-methylbenzamide



[0833] To a stirred solution of 4-fluoro-3-methoxybenzoic acid (10.0 g, 58.775 mmol, 1.00 equiv), $CH_3NH_2.HCl$ (4.66 g, 69.02 mmol, 1.17 equiv) and DIEA (22.7 g, 175.63 mmol, 2.99 equiv) in DMF (100 mL) at 0 °C was added HATU (24.6 g, 64.70 mmol, 1.10 equiv) in portions. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 1 h and then diluted with EtOAc. The resulting mixture was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum to afford 4-fluoro-3-methoxy-N-methylbenzamide (11 g, crude) as a white solid, which was used for the next step without further purification. MS (ESI, *m/z*): 184 [M+H]+.

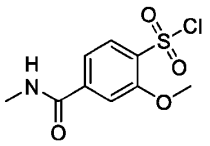
[0834] Step 2. Synthesis of 4-(benzylthio)-3-methoxy-N-methylbenzamide



[0835] A mixture of 4-fluoro-3-methoxy-N-methylbenzamide (11.0 g, 60.050 mmol, 1.00 equiv), phenylmethanethiol (8.2 g, 66.05 mmol, 1.10 equiv) and K_2CO_3 (9.96 g, 72.06 mmol, 1.20 equiv) in DMF (100 mL) was stirred at 120 °C for 3 h under N_2 atmosphere. The resulting mixture was cooled to ambient temperature and then to this was added $NaHCO_3$ aqueous solution. The resulting mixture was stirred at ambient temperature for another 1 h and extracted with EtOAc three times. The combined organic layers were washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-70% EtOAc in petroleum ether) to afford 4-

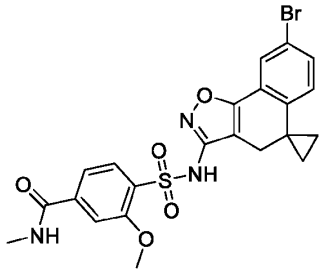
(benzylsulfanyl)-3-methoxy-N-methylbenzamide (11 g, 61% yield) as a white solid. MS (ESI, *m/z*): 288 [M+H]+.

[0836] Step 3. Synthesis of 2-methoxy-4-(methylcarbamoyl)benzenesulfonyl chloride



[0837] To a stirred solution of 4-(benzylsulfanyl)-3-methoxy-N-methylbenzamide (5.0 g, 17.40 mmol, 1.00 equiv) in AcOH (37.5 mL) and H_2O (12.5 mL) at 0 °C was added NCS (8.31 g, 52.20 mmol, 3.00 equiv) in portions. The resulting mixture was stirred at ambient temperature for anther1 h and then diluted with EtOAc. The mixture was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another batch (same scale) and purified by flash chromatography on silica gel (0-100% EtOAc in petroleum ether) to afford 2-methoxy-4-(methylcarbamoyl)benzenesulfonyl chloride (10 g, 91% yield) as a white solid. MS (ESI, *m/z*): 264. 266 [M+H]+ .

[0838] Step 4. Synthesis of 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide

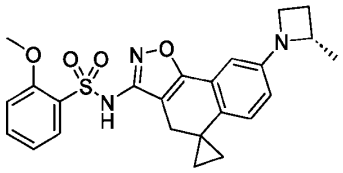


[0839] A mixture of 2-methoxy-4-(methylcarbamoyl)benzenesulfonyl chloride (100.0 mg, 0.38 mmol, 1.80 equiv) and 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (61.3 mg, 0.21 mmol, 1.00 equiv, Intermediate C) in pyridine (1 mL) was stirred at 80 °C for 1 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) and further purified by Prep-HPLC (formic acid system) to afford 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide (14.0 mg, 5% yield) as a white solid. MS (ESI, *m/z*): 518, 520 [M+H]+.1H NMR (300 MHz, DMSO-d6) δ

8.61 (d, J = 4.8 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 2.1 Hz, 1H), 7.50 (d, J = 16.2, 8.1, 1.5 Hz, 3H), 7.02 (d, J = 8.4 Hz, 1H), 3.87 (s, 3H), 2.79 (d, J = 4.5 Hz, 3H), 2.61 (s, 2H), 2.07 (s, 1H), 0.99 (q, J = 4.5, 4.2 Hz, 2H), 0.84 (d, J = 4.8, 4.5 Hz, 2H).

Example 91

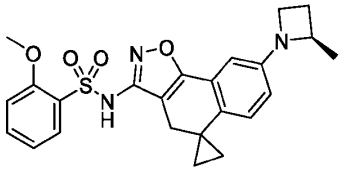
(S)-2-methoxy-N-(8'-(2-methylazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0840] Example 91 was prepared according to the procedure as described in Example 31, starting from Example 16 and (S)-2-methylazetidine from a commercial source (Pharmablock PBZ4357-1). ^{1}H NMR (400 MHz, DMSO) δ 10.81 (s, 1H), 7.78 (dd, J = 7.9, 1.7 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 6.57 (d, J = 2.5 Hz, 1H), 6.44 (dd, J = 8.5, 2.5 Hz, 1H), 4.05 (p, J = 6.7 Hz, 1H), 3.83 (s, 4H), 3.49 (q, J = 7.9 Hz, 1H), 2.35 (d, J = 8.9 Hz, 2H), 2.08 (s, 1H), 1.98 (p, J = 8.2 Hz, 1H), 1.39 (d, J = 6.1 Hz, 3H), 0.86 (d, J = 5.2 Hz, 2H), 0.72 (d, J = 2.2 Hz, 2H). MS (ESI, *m/z*): 452.2 [M+H]+.

Example 92

(R)-2-methoxy-N-(8'-(2-methylazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide

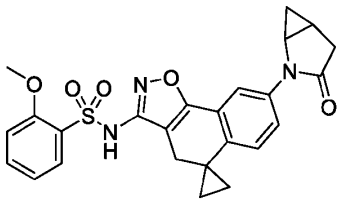


[0841] Example 92 was prepared according to the procedure as described in Example 31, starting from Example 16 and (R)-2-methylazetidine from a commercial source (Pharmablock PBZ4358-1). ^{1}H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 7.79 (td, J = 7.8, 7.4, 1.8 Hz, 1H), 7.70 – 7.57 (m, 1H), 7.21 (dd, J = 8.4, 3.4 Hz, 1H), 7.11 – 7.04 (m, 1H), 6.86 (d, J = 8.5 Hz, 1H), 6.57 (d, J = 2.4 Hz, 1H), 6.44 (dd, J = 8.4, 2.5 Hz, 1H), 4.05 (h, J =

6.0 Hz, 1H), 3.83 (d, J = 4.8 Hz, 4H), 3.48 (q, J = 7.9 Hz, 1H), 2.53 (s, 2H), 2.35 (dtd, J = 11.1, 8.3, 3.6 Hz, 1H), 1.98 (dq, J = 10.7, 8.1 Hz, 1H), 1.38 (d, J = 6.1 Hz, 3H), 0.91 – 0.79 (m, 2H), 0.72 (t, J = 3.0 Hz, 2H). MS (ESI, *m/z*): 452.2 $[M+H]^+$.

Example 93

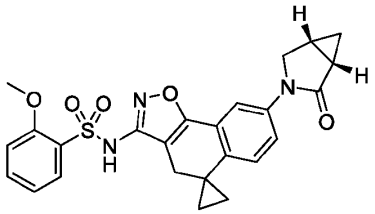
2-methoxy-N-(8'-(3-oxo-2-azabicyclo[3.1.0]hexan-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0842] Example 93 was prepared according to the procedure as described in Example 31, starting from Example 16 and 2-azabicyclo[3.1.0]hexan-3-one from a commercial source (Pharmablock 1558-60-7). ^{1}H NMR (400 MHz, DMSO) δ 7.81 (s, 1H), 7.77 (dd, J = 7.8, 1.8 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.51 (s, 1H), 7.12 (s, 1H), 7.06 (d, J = 8.7 Hz, 1H), 7.00 (s, 1H), 3.78 (s, 3H), 3.57 (s, 1H), 2.97 (dd, J = 18.2, 7.3 Hz, 1H), 2.54 (s, 2H), 1.62 – 1.52 (m, 1H), 1.08 (dt, J = 8.4, 5.4 Hz, 1H), 0.95 (s, 2H), 0.80 (m, 3H), 0.48 (dd, J = 7.0, 3.5 Hz, 1H). MS (ESI, *m/z*): 478.2 $[M+H]^+$.

Example 94

2-Methoxy-N-(8'-((1S,5R)-2-oxo-3-azabicyclo[3.1.0]hexan-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide

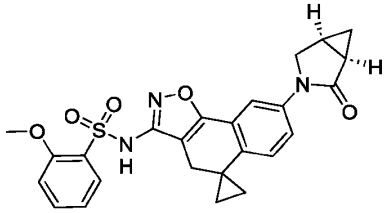


[0843] Example 94 was prepared according to the procedure as described in Example 31, starting from Example 16 and (1S,5R)-3-azabicyclo[3.1.0]hexan-2-one from a commercial source (AA Blocks 154001-70-4). ^{1}H NMR (400 MHz, DMSO) δ 10.87 (s, 1H), 7.82 – 7.74 (m, 2H), 7.58 (t, J = 7.9 Hz, 1H), 7.45 (dd, J = 8.7, 2.4 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 7.09

– 6.98 (m, 2H), 4.02 (dd, J = 10.2, 5.8 Hz, 1H), 3.80 (s, 3H), 3.77 – 3.70 (m, 1H), 2.56 (s, 2H), 2.03 (ddt, J = 13.3, 9.5, 4.7 Hz, 2H), 1.15 (td, J = 8.0, 4.3 Hz, 1H), 0.93 (t, J = 3.0 Hz, 2H), 0.79 (t, J = 3.0 Hz, 2H), 0.72 (q, J = 3.9 Hz, 1H). MS (ESI, *m/z*): 478.2 $[M+H]^+$.

Example 95

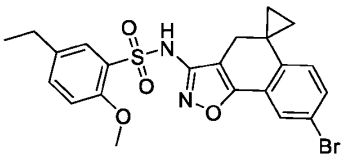
2-Methoxy-N-(8'-((1R,5S)-2-oxo-3-azabicyclo[3.1.0]hexan-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0844] Example 95 was prepared according to the procedure as described in Example 31, starting from Example 16 and (1R,5S)-3-azabicyclo[3.1.0]hexan-2-one from a commercial source (AA Blocks 169532-12-1). ^{1}H NMR (400 MHz, DMSO) δ 7.87 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.47 (d, J = 7.0 Hz, 1H), 7.17 (s, 1H), 7.07 - 6.96 (d, J = 8.9 Hz, 2H), 4.02 (dd, J = 10.2, 5.8 Hz, 1H), 3.77 - 3.68 (m, 4H), 2.54 (s, 2H), 2.01 (s, 2H), 1.14 (s, 1H), 0.90 (s, 2H), 0.78 – 0.69 (m, 3H). MS (ESI, *m/z*): 478.2 [M+H]+.

Example 96

N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-5-ethyl-2-methoxybenzenesulfonamide

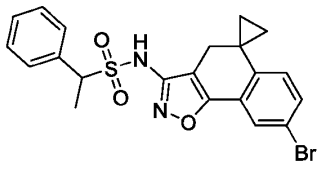


[0845] Example 96 was synthesized in an analogous manner to the preparation described in Example 76, using 5-ethyl-2-methoxybenzenesulfonyl chloride from a commercial source. Example 96 was purified using reverse phase chromatography (MeCN/H_2O, acidic modifiers). ^{1}H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 7.57 (dd, J = 17.4, 2.2 Hz, 2H), 7.41 (ddd, J = 25.4, 8.5, 2.2 Hz, 2H), 7.00 (dd, J = 33.7, 8.5 Hz, 2H), 3.70 (s, 3H), 2.57 – 2.47

(m, 4H), 1.07 (t, J = 7.6 Hz, 3H), 0.97 – 0.89 (m, 2H), 0.80 – 0.73 (m, 2H). MS (ESI, *m/z*): 489.2 [M+H]+.

Example 97

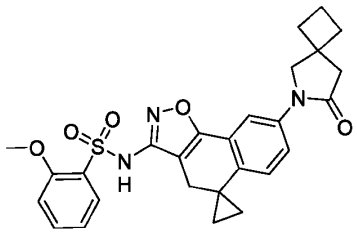
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-1-phenylethane-1-sulfonamide



[0846] Example 97 was prepared according to the procedure as described in Example 70, using 1-phenylethane-1-sulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.66 (s, 1H), 7.67 (d, J = 2.2 Hz, 1H), 7.47 (dd, J = 8.4, 2.2 Hz, 1H), 7.38 – 7.23 (m, 5H), 6.98 (d, J = 8.5 Hz, 1H), 4.74 (q, J = 7.1 Hz, 1H), 2.46 (s, 2H), 1.64 (d, J = 7.1 Hz, 3H), 0.94 (dd, J = 5.5, 2.9 Hz, 2H), 0.78 (t, J = 3.8 Hz, 2H). MS (ESI, *m/z*): 459 $[M+H]^+$.

Example 98

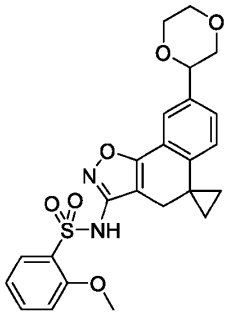
2-Methoxy-N-(8'-(7-oxo-6-azaspiro[3.4]octan-6-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



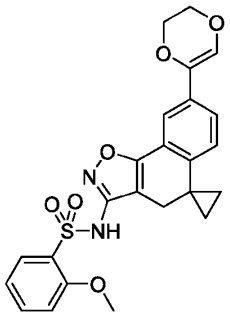
[0847] Example 98 was synthesized in an analogous manner to the preparation described in Example 31, starting from Example 16 and 6-azaspiro[3.4]octan-7-one from a commercial source (Enamine 1465480-75-4). Example 98 was purified using reverse phase chromatography (MeCN/H_2O, acidic modifiers). ^{1}H NMR (400 MHz, DMSO) δ 7.84 (s, 1H), 7.78 (dd, J = 7.8, 1.8 Hz, 1H), 7.58 – 7.49 (m, 2H), 7.16 (d, J = 8.3 Hz, 1H), 7.04 (d, J = 8.5 Hz, 2H), 3.85 (s, 2H), 3.80 (s, 3H), 2.62 (s, 2H), 2.55 (s, 2H), 2.12 – 1.96 (m, 4H), 1.93 – 1.82 (m, 2H), 0.97 – 0.92 (m, 2H), 0.81 – 0.77 (m, 2H). MS (ESI, *m/z*): 506.2 $[M+H]^+$.

Example 99

N-(8'-(1,4-dioxan-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

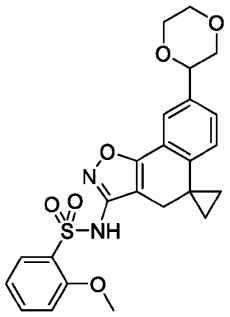


[0848] Step 1. Synthesis of N-(8'-(5,6-dihydro-1,4-dioxin-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0849] A mixture of 2-(5,6-dihydro-1,4-dioxin-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (140.0 mg, 0.66 mmol, 1.00 equiv), N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (304.6 mg, 0.66 mmol, 1.00 equiv, Example 16), $Pd(dppf)Cl_2$ (96.7 mg, 0.13 mmol, 0.20 equiv) and K_3PO_4 (280.3 mg, 1.32 mmol, 2.00 equiv) in dioxane (4.0 mL) and H_2O (1.0 mL) was stirred at 100 °C for 2 h under N_2 atmosphere and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-70% acetonitrile in water (contained 0.05% formic acid)) to afford N-(8'-(5,6-dihydro-1,4-dioxin-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (145 mg, 41% yield) as a brown solid. MS (ESI, *m/z*): 467 [M+H]+.

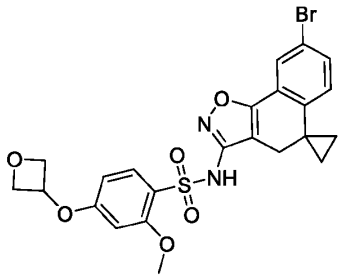
[0850] Step 2. Synthesis of N-(8'-(1,4-dioxan-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0851] A mixture of N-(8'-(5,6-dihydro-1,4-dioxin-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (145.0 mg, 0.31 mmol, 1.00 equiv) and Pd/C (wet, 10%, 14.5 mg, 10% w/w) in EtOAc (10.0 mL) was stirred at ambient temperature for 24 h under H_2 (~3 atm) atmosphere and then filtered. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-70% acetonitrile in water (contained 0.05% formic acid)) and further purified by Prep-HPLC (5-60% acetonitrile in water (contained 0.05% formic acid)) to afford N-(8'-(1,4-dioxan-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (1.6 mg, 1% yield) as a white solid. MS (ESI, *m/z*): 469 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d6) δ 7.80-7.71 (m, 1H), 7.64-7.52 (m, 1H), 7.50 (d, J = 1.8 Hz, 1H), 7.34-7.25 (m, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.10-6.98 (m, 2H), 4.62-4.51 (m, 1H), 3.92-3.65 (m, 7H), 3.61-3.52 (m, 1H), 3.25-3.21 (m, 1H), 2.57 (s, 2H), 1.01-0.84 (m, 2H), 0.83-0.74 (m, 2H).

Example 100

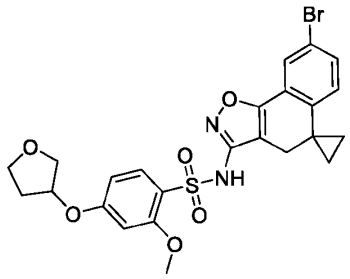
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-4-(oxetan-3-yloxy)benzenesulfonamide



[0852] To a stirred mixture of oxetan-3-ol (38.0 mg, 0.51 mmol, 3.00 equiv) in DMSO (2.0 mL) at 0 °C was added NaH (60% in mineral oil, 20.8 mg, 0.51 mmol, 3.00 equiv,). The resulting mixture was stirred at this temperature for 1 h and then to this was added dropwise a solution of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-fluoro-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (100.0 mg, 0.17 mmol, 1.00 equiv, Intermediate H) in DMSO (1.0 mL) over 1 min. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 1 h. The resulting mixture was quenched with NH_4Cl solution and extracted with EtOAc three times. The combined organic layers were washed with brine and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5---75% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-4-(oxetan-3-yloxy)benzenesulfonamide (9.9 mg, 11% yield) as a white solid. MS (ESI, *m/z*): 533, 534 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 7.49 (dd, J = 8.4, 2.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.40 (dd, J = 8.8, 2.4 Hz, 1H), 5.45-5.31 (m, 1H), 5.01-4.86 (m, 2H), 4.61-4.47 (m, 2H), 3.78 (s, 3H), 2.58 (s, 2H), 1.04-0.95 (m, 2H), 0.88-0.79 (m, 2H).

Example 101

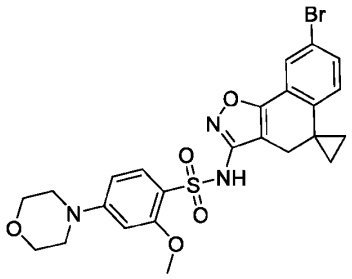
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-4-((tetrahydrofuran-3-yl)oxy)benzenesulfonamide



[0853] To a stirred mixture of tetrahydrofuran-3-ol (68.6 mg, 0.78 mmol, 3.00 equiv) in DMSO (2.0 mL) at 0 °C was added NaH (60% in mineral oil, 31.0 mg, 0.78 mmol, 3.00 equiv). The resulting mixture was stirred at this temperature for 1 h and then to this was added a solution of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-fluoro-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (150.0 mg, 0.26 mmol, 1.00 equiv) in DMSO (1.0 mL). The resulting mixture was allowed to warm up to ambient temperature and stirred for another 16 h. The mixture was quenched with saturated NH4Cl solution and extracted with EtOAc three times. The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was combined with another batch (same scale) and purified by reverse phase flash chromatography on C18 gel (0-64% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-4-((tetrahydrofuran-3-yl)oxy)benzenesulfonamide (80.7 mg, 28% yield) as a white solid. MS (ESI, *m/z*): 547, 549 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 10.81 (s, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 2.4Hz, 1H), 7.52 (dd, J = 8.4, 2.4Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 2.4Hz, 1H), 6.63 (dd, J = 8.8, 2.4Hz, 1H), 5.18-5.11 (m, 1H), 3.96-3.66 (m, 7H), 2.63 (s, 2H), 2.32-2.18 (m, 1H), 2.03-1.89 (m, 1H), 1.07-0.96 (m, 2H), 0.89-0.79 (m, 2H).

Example 102

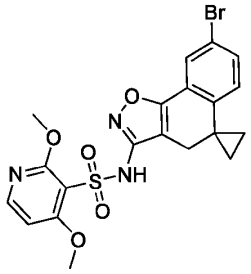
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-4-morpholinobenzenesulfonamide



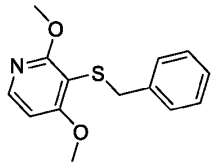
[0854] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-fluoro-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (100.0 mg, 0.17 mmol, 1.00 equiv, Intermediate H) and K2CO3 (71.0 mg, 0.51 mmol, 3.00 equiv) in DMSO (2.0 mL) was stirred at 80 °C for 16 h and then to this was add Cs2CO3 (166.0 mg, 0.51 mmol, 3.00 equiv). The resulting mixture was stirred at 100 °C for 16 h and then purified directly by reverse phase flash chromatography on C18 gel (10-80% acetonitrile in water (contained 0.05% formic acid)) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-4-morpholinobenzenesulfonamide (22.7 mg, 24% yield) as a white solid. MS (ESI, *m/z*): 546, 548 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 10.65 (s, 1H), 7.65 (d, J = 2.4 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.51 (dd, J = 8.4, 2.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 8.4 Hz, 2H), 3.80 (s, 3H), 3.76-3.65 (m, 4H), 3.28 (d, J = 9.6 Hz, 5H), 2.63 (s, 2H), 1.04-0.97 (m, 2H), 0.88-0.81 (m, 2H).

Example 103

N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide

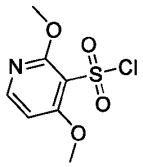


[0855] Step 1. Synthesis of 3-(benzylthio)-2,4-dimethoxypyridine



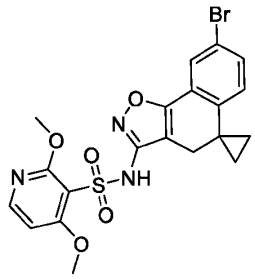
[0856] A mixture of 3-bromo-2,4-dimethoxypyridine (2.0 g, 9.17 mmol, 1.00 equiv), phenylmethanethiol (1.4 g, 11.01 mmol, 1.20 equiv), BrettPhos (0.5 g, 0.92 mmol, 0.10 equiv), BrettPhos Pd G_3 (0.8 g, 0.92 mmol, 0.10 equiv) and Cs_2CO_3 (8.9 g, 27.52 mmol, 3.00 equiv) in dioxane (20.0 mL) was stirred at 100 °C for 6 h under N_2 atmosphere and then filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-20% EtOAc in petroleum ether) to afford 3-(benzylthio)-2,4-dimethoxypyridine (1.8 g, 75% yield) as brown oil. MS (ESI, *m/z*): 262 [M+H]+.

[0857] Step 2. Synthesis of 2,4-dimethoxypyridine-3-sulfonyl chloride



[0858] To a stirred solution of 3-(benzylsulfanyl)-2,4-dimethoxypyridine (1.0 g, 3.83 mmol, 1.00 equiv) in AcOH (10.0 mL) at 5 °C was added NCS (2.0 g, 15.30 mmol, 4.00 equiv) in portions. The resulting mixture was stirred at ambient temperature for another 1 h and then diluted with water and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-25% EtOAc in petroleum ether) to afford 2,4-dimethoxypyridine-3-sulfonyl chloride (390.2 mg, 42% yield) as a yellow solid. MS (ESI, *m/z*): 238, 240 [M+H]+.

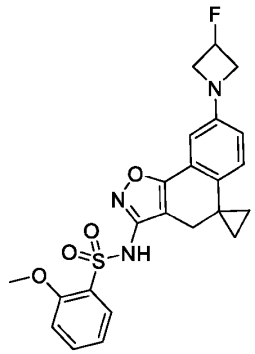
[0859] Step 3. Synthesis of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide



[0860] A mixture of 2,4-dimethoxypyridine-3-sulfonyl chloride (183.7 mg, 0.77 mmol, 1.50 equiv) and 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-amine (150.0 mg, 0.52 mmol, 1.00 equiv) in pyridine (3.0 mL) was stirred at 80 °C for 1 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum and the residue was re-dissolved in DCM. The organic solution mixture was washed with aqueous HCl (1 M) three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-85% EtOAc in petroleum ether) and further purified by Prep-HPLC (formic acid system) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (63.7 mg, 25% yield) as a white solid. MS (ESI, *m/z*): 492, 494 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.23 (d, J = 6.0 Hz, 1H), 7.68 (d, J = 2.1 Hz, 1H), 7.52 (dd, J = 8.4, 2.1 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 6.0 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.64 (s, 2H), 1.07–0.92 (m, 2H), 0.88 – 0.79 (m, 2H).

Example 104

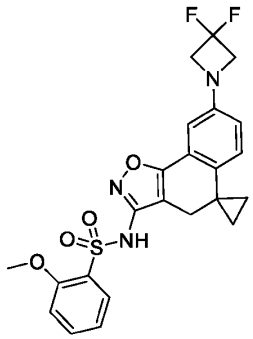
N-(8'-(3-fluoroazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0861] Example 104 was prepared according to the procedure as described in Example 31, starting from Example 16 and 3-fluoroazetidine from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 7.78 (dd, J = 7.8, 1.7 Hz, 1H), 7.61 (ddd, J = 8.8, 7.4, 1.8 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.13 – 7.00 (m, 1H), 6.90 (d, J = 8.5 Hz, 1H), 6.63 (d, J = 2.5 Hz, 1H), 6.46 (dd, J = 8.4, 2.5 Hz, 1H), 5.54 (tt, J = 5.9, 3.1 Hz, 1H), 5.40 (tt, J = 6.0, 3.2 Hz, 1H), 4.15 (dddd, J = 20.5, 9.3, 5.8, 1.3 Hz, 2H), 3.91 (ddd, J = 9.4, 3.3, 1.3 Hz, 1H), 3.88 – 3.78 (m, 4H), 2.53 (s, 2H), 0.92 – 0.83 (m, 2H), 0.77 – 0.67 (m, 2H). MS (ESI, *m/z*): 456.2 $[M+H]^+$.

Example 105

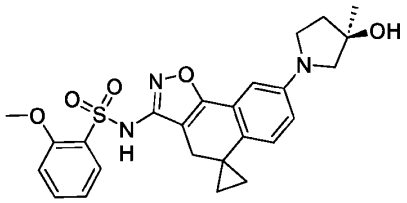
N-(8'-(3,3-difluoroazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0862] Example 105 was prepared according to the procedure as described in Example 31, starting from Example 16 and 3,3-difluoroazetidine from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 7.78 (dd, J = 7.9, 1.7 Hz, 1H), 7.62 (ddd, J = 8.8, 7.4, 1.8 Hz, 1H), 7.42 – 7.29 (m, 1H), 7.21 (dd, J = 8.5, 1.0 Hz, 1H), 7.07 (td, J = 7.7, 1.0 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 2.5 Hz, 1H), 6.55 (dd, J = 8.5, 2.6 Hz, 1H), 4.27 (t, J = 12.3 Hz, 4H), 3.83 (s, 3H), 2.55 (s, 2H), 2.08 (s, 1H), 0.93 – 0.83 (m, 2H), 0.79 – 0.69 (m, 2H). MS (ESI, *m/z*): 474.2 $[M+H]^+$.

Example 106

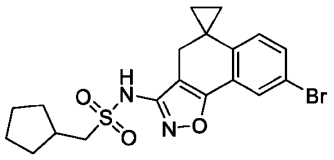
(R)-N-(8'-(3-hydroxy-3-methylpyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0863] Example 106 was prepared according to the procedure as described in Example 31, starting from Example 16 and (R)-3-methylpyrrolidin-3-ol from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.71 (s, 1H), 7.71 (dd, J = 7.9, 1.8 Hz, 1H), 7.55 (td, J = 7.9, 7.3, 1.8 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.05 – 6.96 (m, 1H), 6.78 (d, J = 8.6 Hz, 1H), 6.52 (d, J = 2.6 Hz, 1H), 6.38 (dd, J = 8.6, 2.6 Hz, 1H), 4.70 (s, 1H), 3.76 (s, 3H), 3.34 – 3.25 (m, 2H), 3.25 – 3.16 (m, 2H), 3.08 (q, J = 9.7 Hz, 2H), 1.90 – 1.74 (m, 2H), 1.26 (s, 3H), 0.80 – 0.73 (m, 2H), 0.73 – 0.59 (m, 2H). MS (ESI, *m/z*): 482.2 $[M + H]^+$.

Example 107

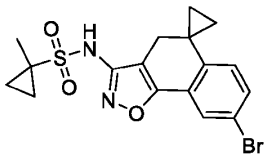
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-1-cyclopentylmethanesulfonamide



[0864] Example 107 was prepared according to the procedure as described in Example 76, using cyclopentylmethanesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, CDCl3) δ 7.73 (d, J = 2.1 Hz, 1H), 7.36 (dd, J = 8.4, 2.1 Hz, 1H), 6.90 (s, 1H), 6.73 (d, J = 8.4 Hz, 1H), 3.28 (d, J = 7.0 Hz, 2H), 2.66 (s, 2H), 2.35 (ddq, J = 16.1, 8.9, 7.2 Hz, 1H), 1.98 – 1.87 (m, 3H), 1.66 – 1.45 (m, 4H), 1.33 – 1.16 (m, 2H), 0.93 (td, J = 6.0, 1.6 Hz, 2H), 0.89 (m, 2H). MS (ESI, *m/z*): 437 $[M+H]^+$.

Example 108

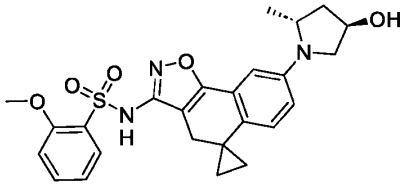
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-1-methylcyclopropane-1-sulfonamide



[0865] Example 108 was prepared according to the procedure as described in Example 76, using 1-methylcyclopropane-1-sulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 7.74 (d, J = 2.2 Hz, 1H), 7.54 (dd, J = 8.4, 2.2 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 2.67 (s, 2H), 1.47 (s, 3H), 1.23 (q, J = 4.8 Hz, 2H), 1.06 – 0.99 (m, 2H), 0.98 – 0.82 (m, 4H). MS (ESI, *m/z*): 409 $[M+H]^+$.

Example 109

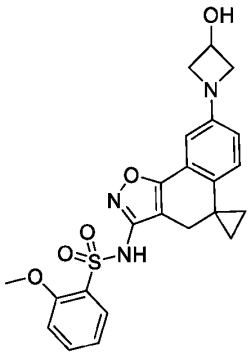
N-(8'-((2R,4R)-4-hydroxy-2-methylpyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0866] Example 109 was prepared according to the procedure as described in Example 31, starting from Example 16 and (3R,5R)-5-methylpyrrolidin-3-ol from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.79 (s, 1H), 7.78 (dd, J = 7.8, 1.8 Hz, 1H), 7.62 (s, 1H), 7.43 – 7.35 (m, 0H), 7.07 (s, 1H), 6.85 (d, J = 8.6 Hz, 1H), 6.65 (s, 1H), 6.52 (d, J = 9.0 Hz, 1H), 4.95 (d, J = 4.3 Hz, 1H), 4.45 – 4.38 (m, 1H), 3.91 (d, J = 5.8 Hz, 1H), 3.83 (s, 3H), 3.57 (dd, J = 9.8, 5.7 Hz, 1H), 3.50-3.20 (m, 2H), 2.97 (dd, J = 9.8, 4.4 Hz, 1H), 2.04 – 1.97 (m, 1H), 1.82 (dd, J = 11.4, 5.9 Hz, 1H), 1.11 (d, J = 6.1 Hz, 3H), 0.84 (s, 2H), 0.70 (s, 2H). MS (ESI, *m/z*): 482.2 $[M+H]^+$.

Example 110

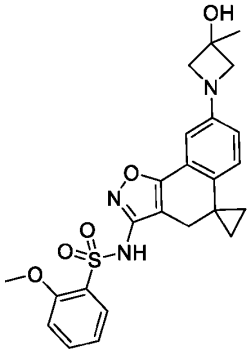
N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0867] Example 110 was prepared according to the procedure as described in Example 31, starting from Example 16 and azetidin-3-ol from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 7.78 (dd, J = 7.8, 1.8 Hz, 1H), 7.69 – 7.52 (m, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.56 (d, J = 2.5 Hz, 1H), 6.40 (dd, J = 8.4, 2.6 Hz, 1H), 5.59 (d, J = 6.6 Hz, 1H), 4.54 (h, J = 5.7 Hz, 1H), 4.07 (dd, J = 7.7, 6.3 Hz, 2H), 3.82 (s, 3H), 3.48 (dd, J = 7.7, 5.0 Hz, 2H), 0.85 (q, J = 4.3 Hz, 2H), 0.71 (q, J = 4.3 Hz, 2H). MS (ESI, *m/z*): 454.2 $[M+H]^+$.

Example 111

N-(8'-(3-hydroxy-3-methylazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

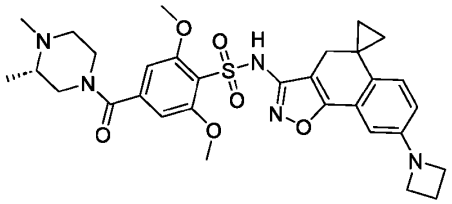


[0868] Example 111 was prepared according to the procedure as described in Example 31, starting from Example 16 and 3-methylazetidin-3-ol from a commercial source. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.77 (br s, 1H), 7.76 (dd, J = 7.8, 1.8 Hz, 1H), 7.65-7.53 (m, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.59-6.53 (m, 1H),

6.39 (dd, J = 8.4, 2.4 Hz, 1H), 5.48 (s, 1H), 3.80 (s, 3H), 3.73 (d, J = 7.2 Hz, 2H), 3.56 (d, J = 7.2 Hz, 2H), 2.50 (s, 2H), 1.42 (s, 3H), 0.86-0.64 (m, 4H). MS (ESI, *m/z*): 468.2 $[M+H]^+$.

Example 112

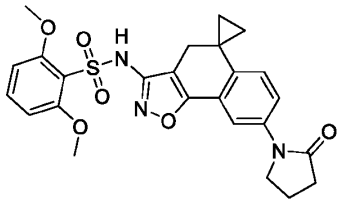
(S)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(3, 4-dimethylpiperazine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide



[0869] Example 112 was prepared according to General Procedure 1 of Example 220, using (S)-1,2-dimethylpiperazine from a commercial source (Firster Biopharm, CF-30178). ^{1}H NMR (300 MHz, DMSO) δ 10.72 (br s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.72 (s, 2H), 5.58 – 5.53 (m, 1H), 6.39 (dd, J = 8.4, 2.4 Hz, 1H), 4.31 – 4.10 (m, 1H), 3.94 – 3.63 (m, 10H), 3.27 – 2.71 (m, 4H), 2.67 – 2.58 (m, 1H), 2.47 – 2.23 (m, 3H), 2.19 (s, 3H), 2.11 – 1.98 (m, 2H), 1.13 – 0.97 (m, 2H), 0.88 – 0.81 (m, 3H), 0.71 – 0.62 (m, 2H). MS (ESI, *m/z*): 608.0 [M+H]+.

Example 113

2,6-Dimethoxy-N-(8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide

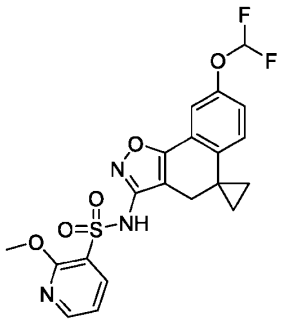


[0870] Example 113 was prepared according to the procedure as described in Example 31, starting from Example 15 and pyrrolidin-2-one from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.69 (br s, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.59 – 7.43 (m, 2H), 7.06 (d, J = 8.7 Hz, 1H), 6.77 (d, J = 8.4 Hz, 2H), 3.83 (t, J = 6.9 Hz, 2H), 3.79 (s, 6H), 2.59 (s, 2H),

2.47 (s, 2H), 2.13 – 1.97(m, 2H), 1.0 – 0.91 (m, 2H), 0.80 – 0.70 (m, 2H). MS (ESI, *m/z*): 496.3 $[M+H]^+$.

Example 114

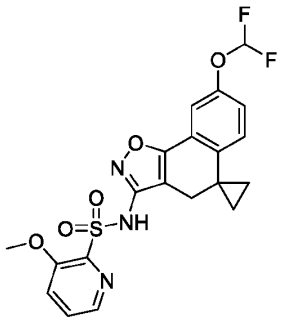
N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxypyridine-3-sulfonamide



[0871] A mixture of 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (100.0 mg, 0.36 mmol, 1.00 equiv, Intermediate I) and 2-methoxypyridine-3-sulfonyl chloride (111.9 mg, 0.54 mmol, 1.50 equiv) in pyridine (1.5 mL) was stirred at 80 oC for 1 h under N2 atmosphere and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-25% acetonitrile in water (contained 0.1% formic acid)) and further purified by Prep-HPLC (5-20% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxypyridine-3-sulfonamide (50.0 mg, 31% yield) as a white solid. MS (ESI, *m/z*): 450 [M+H]+. 1H NMR (300 MHz, DMSO-d6) δ 11.30 (br s, 1H), 8.43 (dd, J = 4.8, 1.8 Hz, 1H), 8.20 (dd, J = 7.5, 1.8 Hz, 1H), 7.54-7.00 (m, 6H), 3.93 (s, 3H), 2.63 (s, 2H), 1.05-0.80 (m, 4H). 19F NMR (282 MHz, DMSO-d6) δ -82.36.

Example 115

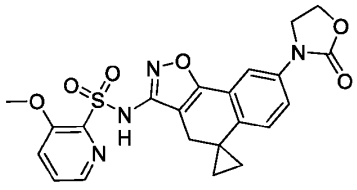
N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-methoxypyridine-2-sulfonamide



[0872] To a stirred solution of 3-methoxypyridine-2-sulfonyl chloride (560.8 mg, 2.71 mmol, 1.50 equiv) in DCM (5 mL) was added 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-amine (501 mg, 1.80 mmol, 1 equiv, Intermediate I) and pyridine (5 mL) under N2 atmosphere. The reaction mixture was stirred at 20 °C for 1 h and then concentrated under vacuum. The mixture was diluted with water. The aqueous mixture was acidified with aqueous HCl (1 M) to pH 5 and then extracted with EtOAc three times. The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-85% acetonitrile in water (contained 0.05% formic acid)) and then further purified by Prep-HPLC (5%~64% acetonitrile in water (contained 0.1% formic acid)) to afford N-[8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]-3-methoxypyridine-2-sulfonamide (352.2 mg, 43% yield) as a white solid. MS (ESI, *m/z*): 450 [M+H]+. 1H NMR (300 MHz, DMSO-d6) δ 11.26 (br s, 1H), 8.19 (dd, J = 4.5, 1.2 Hz, 1H), 7.84-7.74 (m, 1H), 7.73-7.63 (m, 1H), 7.55-7.01 (m, 4H), 7.14 (d, J = 1.8 Hz, 2H), 3.91 (s, 3H), 2.60 (s, 2H), 1.04-0.75 (m, 4H). 19F NMR (282 MHz, DMSO-d6) δ -82.35.

Example 116

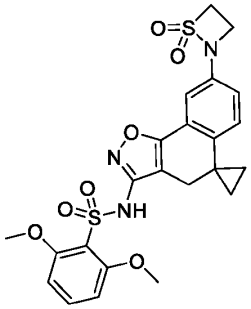
3-Methoxy-N-(8'-(2-oxooxazolidin-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-2-sulfonamide



[0873] Example 116 was prepared according to the procedure as described in Example 31, starting from Example 54 and oxazolidin-2-one from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 8.21 – 8.11 (m, 1H), 7.83 – 7.74 (m, 2H), 7.67 (dd, J = 8.5, 4.5 Hz, 1H), 7.47 (dd, J = 8.6, 2.5 Hz, 1H), 7.09 (d, J = 8.7 Hz, 1H), 4.43 (dd, J = 9.1, 6.9 Hz, 2H), 4.08 (dd, J = 9.0, 6.9 Hz, 2H), 3.91 (s, 3H), 2.58 (s, 2H), 1.01 – 0.89 (m, 2H), 0.81 – 0.74 (m, 2H). MS (ESI, *m/z*): 469.5 $[M-H]^+$.

Example 117

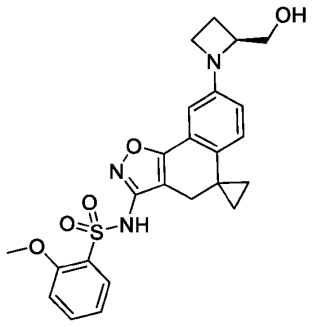
N-(8'-(1,1-dioxido-1,2-thiazetidin-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide



[0874] Example 117 was prepared according to the procedure as described in Example 31, starting from Example 15 and 1,2-thiazetidine 1,1-dioxide from a commercial source (Enamine, EN300-41338). ^{1}H NMR (400 MHz, DMSO) δ 7.43 (t, J = 8.4 Hz, 1H), 6.98 (d, J = 9.0 Hz, 1H), 6.75 (d, J = 8.5 Hz, 2H), 6.70 – 6.64 (m, 2H), 4.46 (t, J = 6.6 Hz, 2H), 3.72 (d, J = 7.6 Hz, 8H), 2.73 (s, 2H), 0.98 (s, 2H), 0.90 (s, 2H). MS (ESI, *m/z*): 518.2 $[M-H]^+$.

Example 118

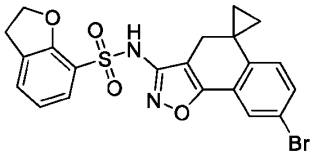
(S)-N-(8'-(2-(hydroxymethyl)azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0875] Example 118 was prepared according to the procedure as described in Example 31, starting from Example 16 and (S)-azetidin-2-ylmethanol from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.72 (s, 1H), 7.70 (dd, J = 7.8, 1.7 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.20 – 7.05 (m, 1H), 6.99 (t, J = 7.5 Hz, 1H), 6.81 – 6.66 (m, 2H), 6.55 – 6.35 (m, 1H), 4.87 (t, J = 5.4 Hz, 1H), 3.91 (p, J = 6.2 Hz, 1H), 3.75 (s, 3H), 3.54 (td, J = 5.4, 2.6 Hz, 2H), 3.43 (q, J = 7.9 Hz, 1H), 2.23 – 2.09 (m, 1H), 2.09 – 1.95 (m, 1H), 0.76 (t, J = 9.5 Hz, 2H), 0.63 (s, 2H). MS (ESI, *m/z*): 466.2 $[M-H]^+$.

Example 119

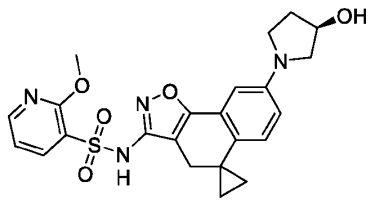
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,3-dihydrobenzofuran-7-sulfonamide



[0876] Example 119 was prepared according to the procedure as described in Example 76, using 2,3-dihydrobenzofuran-7-sulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.16 (s, 1H), 7.66 (d, J = 2.1 Hz, 1H), 7.55 – 7.47 (m, 3H), 7.03 (d, J = 8.4 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 4.63 (t, J = 8.8 Hz, 2H), 3.22 (t, J = 8.8 Hz, 2H), 2.61 (s, 2H), 1.04 – 0.96 (m, 2H), 0.88 – 0.81 (m, 2H). MS (ESI, *m/z*): 471 $(M-H)^+$.

Example 120

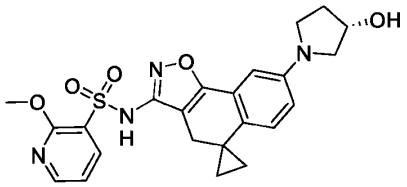
(R)-N-(8'-(3-hydroxypyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxypyridine-3-sulfonamide



[0877] Example 120 was prepared according to the procedure as described in Example 31, starting from Example 44 and using the relevant amine from a commercial source. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.17 (br s, 1H), 8.45 – 8.39 (m, 1H), 8.24 – 8.15 (m, 1H), 7.22 – 7.14 (m, 1H), 6.86 (d, J = 8.8 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 6.53 – 6.45 (m, 1H), 4.95 (d, J = 3.6 Hz, 1H), 4.41 – 4.34 (m, 1H), 3.93 (s, 3H), 3.44 – 3.35 (m, 1H), 3.32 – 3.21 (m, 2H), 3.08 – 3.01 (m, 1H), 2.54 (s, 2H), 2.10 – 1.96 (m, 1H), 1.93 – 1.82 (m, 1H), 0.89 – 0.82 (m, 2H), 0.82 – 0.69 (m, 2H). MS (ESI, *m/z*): 469.2 $[M+H]^+$.

Example 121

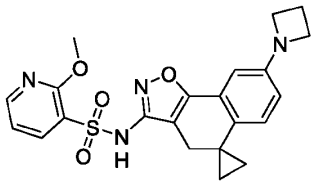
(S)-N-(8'-(3-hydroxypyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxypyridine-3-sulfonamide



[0878] Example 121 was prepared according to the procedure as described in Example 31, starting from Example 44 and (R)-pyrrolidin-3-ol from a commercial source. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.35 (dd, *J* = 5.1, 1.8 Hz, 1H), 8.05 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.50 (s, 1H), 6.98 (dd, *J* = 7.5, 5.1 Hz, 1H), 6.88 (br s, 1H), 6.84-6.77 (m, 1H), 6.68-6.58 (m, 1H), 4.65-4.58 (m, 1H), 4.17 (s, 3H), 3.59-3.46 (m, 2H), 3.44-3.25 (m, 2H), 2.73 (s, 2H), 2.30-2.09 (m, 1H), 2.14-2.02 (m, 1H), 0.95-0.79 (m, 4H). MS (ESI, *m/z*): 469.2 $[M + H]^+$.

Example 122

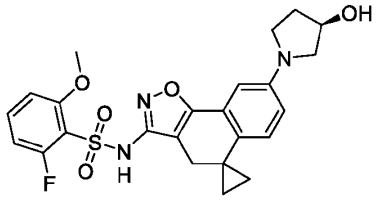
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxypyridine-3-sulfonamide



[0879] Example 122 was prepared according to the procedure as described in Example 31, starting from Example 44 and azetidine. Example 122 was purified using reverse phase chromatography (MeCN/H_2O, acidic modifiers). ^{1}H NMR (300 MHz, Chloroform-d) δ 8.39 – 8.33 (m, 1H), 8.08 – 7.99 (m, 1H), 7.48 (s, 1H), 7.01 – 6.94 (m, 1H), 6.83 – 6.73 (m, 2H), 6.49 (s, 1H), 4.18 (s, 3H), 3.92 (t, J = 7.2 Hz, 4H), 2.74 (s, 2H), 2.47 – 2.34 (m, 2H), 0.98 – 0.80 (m, 4H). MS (ESI, *m/z*): 469.2 [M+H]+.

Example 123

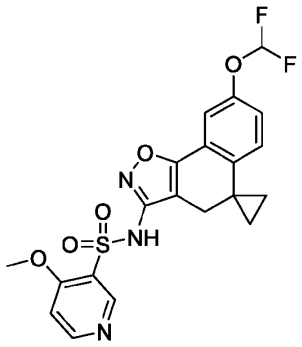
(R)-2-fluoro-N-(8'-(3-hydroxypyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-6-methoxybenzenesulfonamide



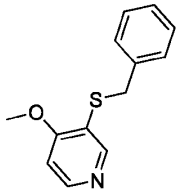
[0880] Example 123 was prepared according to the procedure as described in Example 31, starting from Example 45 and (R)-pyrrolidin-3-ol from a commercial source. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.96 (br s, 1H), 7.67 – 7.54 (m, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.92 (dd, J = 10.8, 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 6.49 (dd, J = 8.4, 2.4 Hz, 1H), 4.94 (d, J = 3.6 Hz, 1H), 4.44 – 4.33 (m, 1H), 3.85 (s, 3H), 3.40 (dd, J = 10.0, 4.8 Hz, 1H), 3.33 – 3.20 (m, 1H), 3.09 – 3.01 (m, 1H), 2.53 (s, 2H), 2.09-1.96 (m, 1H), 1.93-1.82 (m, 1H), 0.91 – 0.64 (m, 4H). ^{19}F NMR (377 MHz, DMSO-d6) δ -108.98. MS (ESI, *m/z*): 486.3 $[M+H]^+$.

Example 124

N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-methoxypyridine-3-sulfonamide

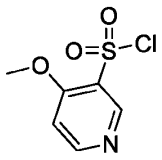


[0881] Step 1. Synthesis of 3-(benzylthio)-4-methoxypyridine



[0882] A mixture of 3-bromo-4-methoxypyridine (1.0 g, 5.3 mmol, 1.0 equiv), phenylmethanethiol (1.65 g, 13.3 mmol, 2.50 equiv), BrettPhos Pd G_3 (0.48 g, 0.53 mmol, 0.10 equiv), BrettPhos (0.29 g, 0.53 mmol, 0.10 equiv) and Cs_2CO_3 (5.2 g, 15.9 mmol, 3.00 equiv) in 1,4-dioxane (15.0 mL) was stirred at 100 °C for 16 h. The resulting mixture was diluted with EtOAc. The organic solution was washed with saturated NaHCO3 solution three times, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-25% acetonitrile in water (contained 0.1% formic acid)) to afford 3-(benzylthio)-4-methoxypyridine (0.3 g, 24% yield) as yellow oil. MS (ESI, *m/z*): 232 [M+H]+.

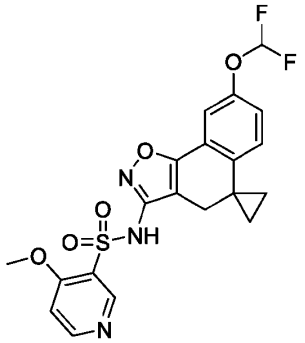
[0883] Step 2. Synthesis of -methoxypyridine-3-sulfonyl chloride



To a stirred solution of 3-(benzylthio)-4-methoxypyridine (1.0 g, 4.3 mmol, 1.00 equiv) in AcOH (8.0 mL) at 0 °C was added NCS (2.31 g, 17.3 mmol, 4.00 equiv) in portions. The resulting mixture was stirred at this temperature for another 2 h and then poured into ice water.

The mixture was extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-80% EtOAc in petroleum ether) to afford 4-methoxypyridine-3-sulfonyl chloride (403 mg, 45% yield) as a white solid. MS (ESI, *m/z*): 208, 210 [M+H]+.

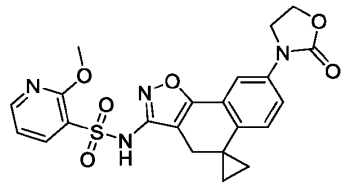
[0884] Step 3. Synthesis of N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-methoxypyridine-3-sulfonamide



[0885] A mixture of 4-methoxypyridine-3-sulfonyl chloride (191.0 mg, 0.92 mmol, 2.00 equiv) in DCM (1.0 mL) and 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (128.0 mg, 0.46 mmol, 1.00 equiv, Intermediate I) in pyridine (1.0 mL) was stirred at ambient temperature for 16 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-50% acetonitrile in water (contained 0.05% NH4HCO3)) and further purified by Prep-HPLC (30-40% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-methoxypyridine-3-sulfonamide (65.5 mg, 31% yield) as a white solid. MS (ESI, *m/z*): 450 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d6) δ 8.76 (s, 1H), 8.65 (d, J = 6.0 Hz, 1H), 7.34– 7.27 (m, 2H), 7.26 (t, J = 74.1 Hz, 1H), 7.18 – 7.09 (m, 2H),3.91 (s, 3H), 2.63 (s, 2H), 1.04 – 0.80 (m, 4H). ^{19}F NMR (282 MHz, DMSO-d6) δ -82.32.

Example 125

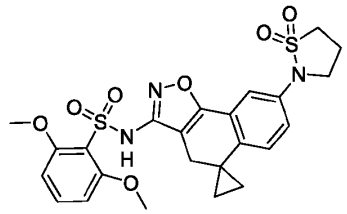
2-Methoxy-N-(8'-(2-oxooxazolidin-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide



[0886] Example 125 was prepared according to the procedure as described in Example 31, starting from Example 44 and oxazolidin-2-one from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.42 (d, J = 5.1 Hz, 1H), 8.24 – 8.17 (m, 1H), 7.79 (d, J = 2.4 Hz, 1H), 7.53 – 7.44 (m, 1H), 7.19 (dd, J = 7.5, 5.1 Hz, 1H), 7.11 (d, J = 8.7 Hz, 1H), 4.44 (t, J = 8.1 Hz, 2H), 4.08 (t, J = 8.1 Hz, 2H), 3.93 (s, 3H), 2.62 (s, 2H), 1.00 – 0.95 (m, 2H), 0.89 – 0.84 (m, 2H). MS (ESI, *m/z*): 469.2 $[M+H]^+$.

Example 126

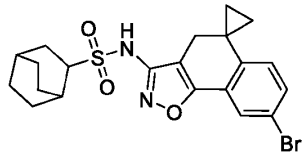
N-(8'-(1,1-dioxidoisothiazolidin-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide



[0887] Example 126 was prepared according to the procedure as described in Example 31, starting from Example 15 and isothiazolidine 1,1-dioxide from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 7.40 (q, J = 10.9, 9.7 Hz, 2H), 7.08 – 6.85 (m, 2H), 6.83 – 6.67 (m, 2H), 3.72 (s, 6H), 3.50 (t, J = 7.4 Hz, 3H), 2.70 (s, 2H), 2.39 (p, J = 6.9 Hz, 3H), 0.98 (d, J = 4.6 Hz, 2H), 0.90 (d, J = 4.6 Hz, 2H). MS (ESI, *m/z*): 532.2 $[M + H]^+$.

Example 127

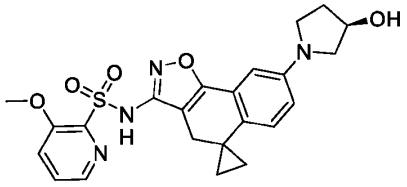
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)bicyclo[2.2.2]octane-2-sulfonamide



[0888] Example 127 was prepared according to the procedure as described in Example 70, using bicyclo[2.2.2]octane-2-sulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.65 (s, 1H), 7.74 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 8.4, 2.2 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 3.64 (t, J = 9.0 Hz, 1H), 2.67 (s, 2H), 2.05 (s, 1H), 1.86 (d, J = 9.5 Hz, 2H), 1.73 (s, 1H), 1.51 (dt, J = 34.2, 16.9 Hz, 8H), 1.04 (q, J = 4.2 Hz, 2H), 0.97 – 0.71 (m, 2H). MS (ESI, *m/z*): 463.2 $[M + H]^+$.

Example 128

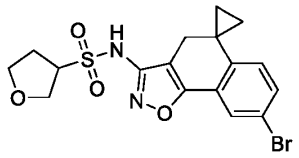
(R)-N-(8'-(3-hydroxypyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-methoxypyridine-2-sulfonamide



[0889] Example 128 was prepared according to the procedure as described in Example 31, starting from Example 54 and (R)-pyrrolidin-3-ol from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 8.08 (dd, J = 4.5, 1.2 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.52 (dd, J = 8.4, 4.5 Hz, 1H), 6.68 (d, J = 8.3 Hz, 1H), 6.20 (d, J = 8.5 Hz, 2H), 4.87 (d, J = 3.7 Hz, 1H), 4.32 (s, 1H), 3.76 (s, 3H), 3.31 (dd, J = 10.3, 5.1 Hz, 2H), 3.26 – 3.12 (m, 1H), 3.00 – 2.93 (m, 1H), 2.55 (s, 2H), 2.03 – 1.89 (m, 1H), 1.82 (dd, J = 11.6, 7.8 Hz, 1H), 1.07 – 0.52 (m, 4H). MS (ESI, *m/z*): 469.2 $[M + H]^+$.

Example 129

N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)tetrahydrofuran-3-sulfonamide

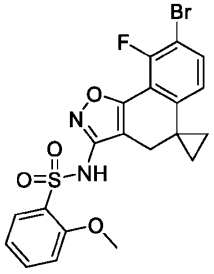


[0890] Example 129 was prepared according to the procedure as described in Example 76, using tetrahydrofuran-3-sulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 7.60 (s, 1H), 7.43 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.45 (s, 1H), 4.12

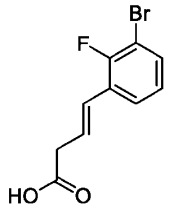
(dt, J = 14.0, 7.6 Hz, 1H), 3.91 (dd, J = 9.8, 4.9 Hz, 1H), 3.87 – 3.80 (m, 1H), 3.73 (q, J = 7.1 Hz, 1H), 3.59 (q, J = 7.2 Hz, 1H), 2.53 (s, 2H), 2.11 (q, J = 7.0 Hz, 2H), 0.92 (d, J = 4.8 Hz, 2H), 0.85 – 0.74 (m, 2H). MS (ESI, *m/z*): 426 $[M+H]^+$.

Example 130

N-(8'-bromo-9'-fluoro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



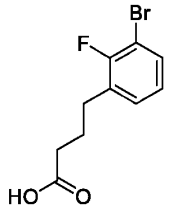
[0891] Step 1. Synthesis of (E)-4-(3-bromo-2-fluorophenyl)but-3-enoic acid



[0892] To a stirred solution of 3-bromo-2-fluorobenzaldehyde (20.0 g, 98.52 mmol, 1.00 equiv) and 3-(bromotriphenyl-l5-phosphaneyl)propanoic acid (40.9 g, 98.52 mmol, 1.00 equiv) in THF (100.0 mL) at 0 °C was added NaH (60% in mineral oil, 7.6 g, 190.01 mmol, 1.90 equiv) in portions under N_2 atmosphere. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 4 h. The resulting mixture was quenched with saturated NH4Cl solution and then basified with $NaHCO_3$ solution (1 M) to pH ~10 and washed with petroleum ether/DCM (3/1) three times. The aqueous layer was acidified with HCl (concentrated) to pH ~ 3 and then extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another three batches (20.0 g x 3) and purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford (E)-4-(3-bromo-2-fluorophenyl)but-3-enoic acid (50.0 g, 49% yield) as a yellow solid. MS (ESI, *m/z*): 257, 259

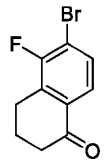
$[M - H]^-$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.41 (q, *J* = 8.0 Hz, 2H), 6.98 (t, *J* = 8.0 Hz, 1H), 6.66 (d, *J* = 16.0 Hz, 1H), 6.44-6.34 (m, 1H), 3.35 (d, *J* = 7.2 Hz, 2H).

[0893] Step 2. Synthesis of 4-(3-bromo-2-fluorophenyl)butanoic acid



[0894] A mixture of (E)-4-(3-bromo-2-fluorophenyl)but-3-enoic acid (37.0 g, 142.30 mmol, 1.00 equiv) and Rh/Al_2O_3 (3.7 g, 5% Rh on alumina, 10% w/w) in MeOH (370.0 mL) was stirred at ambient temperature for 6 h under H_2 atmosphere and then filtered. The filtrate was concentrated under vacuum to afford 4-(3-bromo-2-fluorophenyl)butanoic acid (37.0 g, crude) as a yellow solid, which was used for the next step without further purification. MS (ESI, *m/z*): 259, 261 $[M - H]^-$.

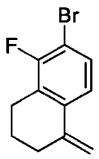
[0895] Step 3. Synthesis of 6-bromo-5-fluoro-3,4-dihydronaphthalen-1(2*H*)-one



[0896] To a stirred solution of 4-(3-bromo-2-fluorophenyl)butanoic acid (37.0 g, 141.71 mmol, 1.00 equiv) and DMF (catalytic amount, 0.5 mL, 6.46 mmol, 0.05 equiv) in DCM (370.0 mL) at 0 °C was added dropwise oxalyl chloride (94.5 mL, 283.50 mmol, 2.00 equiv). The resulting mixture was allowed to warm up to ambient temperature and stirred for another 1 h and then concentrated under vacuum. The residue was dissolved in DCM (370.0 mL). The solution was cooled to 0 °C and to this was added $AlCl_3$ (18.9 g, 141.75 mmol, 1.00 equiv) in portions. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 1 h and then quenched with NaOH solution (1M). The resulting mixture was extracted with DCM three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-25% EtOAc in petroleum ether) to afford 6-bromo-5-fluoro-

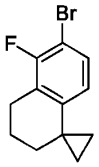
3,4-dihydronaphthalen-1(2*H*)-one (20.0 g, 58% over two steps) as a yellow solid. MS (ESI, *m/z*): 243, 245 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73-7.67 (m, 1H), 7.67-7.61 (m, 1H), 2.95 (t, J = 6.0 Hz, 2H), 2.66-2.58 (m, 2H), 2.11-2.03 (m, 2H).

[0897] Step 4. Synthesis of 6-bromo-5-fluoro-1-methylene-1,2,3,4-tetrahydronaphthalene



[0898] To a stirred solution of *t*-BuOK (20.0 g, 90.90 mmol, 1.10 equiv) in THF (200.0 mL) at 0 °C was added $MePPh_3I$ (36.6 g, 90.54 mmol, 1.10 equiv) in portions under N_2 atmosphere. The resulting mixture was stirred at this temperature for another 30 min and then to this was added 6-bromo-5-fluoro-3,4-dihydronaphthalen-1(2*H*)-one (20.0 g, 82.28 mmol, 1.00 equiv). The resulting mixture was allowed to warm up to ambient temperature and stirred for another 30 min and then filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-10% EtOAc in petroleum ether) to afford 6-bromo-5-fluoro-1-methylene-1,2,3,4-tetrahydronaphthalene (15.8 g, 80% yield) as yellow oil. MS (ESI, *m/z*): 241, 243 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52-7.42 (m, 2H), 5.62 (s, 1H), 5.09 (s, 1H), 2.81-2.74 (m, 2H), 2.49-2.43 (m, 2H), 1.84-1.75 (m, 2H).

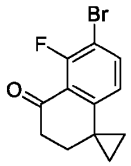
[0899] Step 5. Synthesis of 6'-bromo-5'-fluoro-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-naphthalene]



[0900] To a stirred solution of $ZnEt_2$ (1.0 M in hexane, 207.4 mL, 207.38 mmol, 5.00 equiv) in DCM (100.0 mL) at 0 °C was added dropwise TFA (69.1 mL, 207.38 mmol, 5.00 equiv) over 1 h. The resulting mixture was stirred at this temperature for another 30 min and then to this was added CH_2I_2 (16.7 mL, 207.38 mmol, 5.00 equiv). The resulting mixture was stirred at this temperature for another 1 h and to this was added 6-bromo-5-fluoro-1-methylene-1,2,3,4-tetrahydro-naphthalene (10.0 g, 41.48 mmol, 1.00 equiv). The reaction

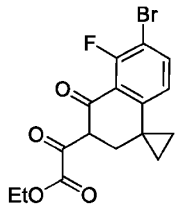
mixture was stirred for another 16 h and then quenched with water and extracted with DCM three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-20% EtOAc in petroleum ether) to afford 6'-bromo-5'-fluoro-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-naphthalene] (10.5 g, 100% yield) as yellow oil. MS (ESI, *m/z*): 255, 257 [M+H]+.^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (t, J = 8.0 Hz, 1H), 6.52 (d, J = 8.4 Hz, 1H), 2.78 (t, J = 6.4 Hz, 2H), 1.88-1.75 (m, 2H), 1.63-1.55 (m, 2H), 0.98-0.93 (m, 2H), 0.87-0.81 (m, 2H).

[0901] Step 6. Synthesis of 6'-bromo-5'-fluoro-2',3'-dihydro-4'*H*-spiro[cyclopropane-1,1'-naphthalen]-4'-one



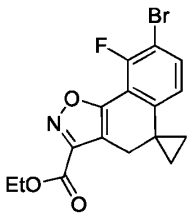
[0902] To a stirred solution of 6'-bromo-5'-fluoro-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-naphthalene] (10.5 g, 41.16 mmol, 1.00 equiv) in acetone (50.0 mL) and water (50.0 mL) at 0 °C was added $MgSO_4$ (12.4 g, 103.02 mmol, 2.50 equiv). The resulting mixture was stirred at this temperature for 10 min and then to this was added $KMnO_4$ (32.5 g, 205.66 mmol, 5.00 equiv) in portions. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 24 h. The resulting mixture was quenched with saturated Na_2SO_3 solution and diluted with DCM and filtered. The filtrate was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-30% EtOAc in petroleum ether) to afford 6'-bromo-5'-fluoro-2',3'-dihydro-4'*H*-spiro[cyclo-propane-1,1'-naphthalen]-4'-one (6.0 g, 54% yield) as a white solid. MS (ESI, *m/z*): 269, 271 [M+H]+.

[0903] Step 7. Synthesis of 2-(6'-bromo-5'-fluoro-4'-oxo-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxo-acetate



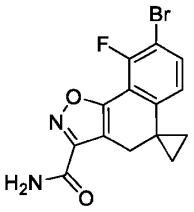
[0904] To a stirred solution of 6'-bromo-5'-fluoro-2',3'-dihydro-4'*H*-spiro[cyclopropane-1,1'-naphthalen]-4'-one (6.0 g, 22.30 mmol, 1.00 equiv) and ethyl oxalate (4.6 mL, 33.87 mmol, 1.50 equiv) in THF (60.0 mL) at 0 °C was added dropwise LiHMDS solution (1.0 M in THF, 33.4 mL, 33.40 mmol, 1.50 equiv) over 20 min. The resulting mixture was stirred at this temperature for another 0.5 h and then quenched with HCl solution (1 M) and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford ethyl 2-(6'-bromo-5'-fluoro-4'-oxo-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxo-acetate (3.0 g, 36% yield) as yellow oil. MS (ESI, *m/z*): 369, 371 [M+H]+.

[0905] Step 8. Synthesis of ethyl 8'-bromo-9'-fluoro-4'*H*-spiro[cyclopropane-1,5'-naphtho[2,1-*d*]isoxazole]-3'-carboxylate



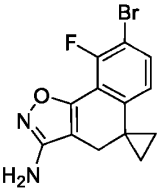
[0906] A mixture of 2-(6'-bromo-5'-fluoro-4'-oxo-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-naphthalen]-3'-yl)-2-oxo-acetate (3.0 g, 8.13 mmol, 1.00 equiv) and $NH_2OH.HCl$ (847.0 mg, 12.19 mmol, 1.50 equiv) in EtOH (30.0 mL) was stirred at 80 °C for 16 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford ethyl 8'-bromo-9'-fluoro-4'*H*-spiro[cyclopropane-1,5'-naphtho[2,1-*d*]isoxazole]-3'-carboxylate (2.0 g, 67% yield) as a yellow solid. MS (ESI, *m/z*): 366, 368 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 4.38 (q, J = 7.2 Hz, 2H), 2.89 (s, 2H), 1.34 (t, J = 7.2 Hz, 3H), 1.11-1.05 (m, 2H), 1.04-0.97 (m, 2H).

[0907] Step 9. Synthesis of 8'-bromo-9'-fluoro-4'*H*-spiro[cyclopropane-1,5'-naphtho[2,1-*d*]isoxazole]-3'-carboxamide



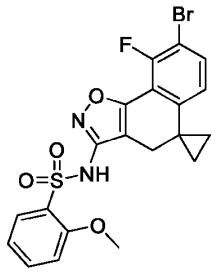
[0908] A mixture of ethyl 8'-bromo-9'-fluoro-4'*H*-spiro[cyclopropane-1,5'-naphtho[2,1-*d*]isoxazole]-3'-carboxylate (2.0 g, 5.50 mmol, 1.00 equiv) and a solution of NH_3 in MeOH (7.0 M in MeOH, 20.0 mL) was stirred at ambient temperature for 2 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-15% MeOH in DCM) to afford 8'-bromo-9'-fluoro-4'*H*-spiro[cyclopropane-1,5'-naphtho[2,1-*d*][1,2]-oxazole]-3'-carboxamide (1.0 g, 54% yield) as a white solid. MS (ESI, *m/z*): 337, 339 [M+H]+.

[0909] Step 10. Synthesis of 8'-bromo-9'-fluoro-4'*H*-spiro[cyclopropane-1,5'-naphtho[2,1-*d*][1,2]oxazol]-3'-amine



[0910] To a stirred solution of 8'-bromo-9'-fluoro-4'*H*-spiro[cyclopropane-1,5'-naphtho[2,1-*d*][1,2]oxazole] -3'-carboxamide (1.0 g, 2.97 mmol, 1.00 equiv) and K_2CO_3 (1.2 g, 8.68 mmol, 3.00 equiv) in EtOAc (4.0 mL), acetonitrile (4.0 mL) and water (2.0 mL) at ambient temperature was added $PhI(OAc)_2$ (1.9 g, 5.90 mmol, 2.00 equiv). The resulting mixture was stirred at 50 °C for 2 h and then diluted with EtOAc. The resulting mixture was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (0-50% acetonitrile in water (contained 0.1% formic acid)) to afford 8'-bromo-9'-fluoro-4'*H*-spiro[cyclopropane-1,5'-naphtho[2,1-*d*][1,2]oxazol]-3'-amine (400.0 mg, 44% yield). MS (ESI, *m/z*): 309, 311 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 5.75 (s, 2H), 2.55 (s, 2H), 1.08-1.03 (m, 2H), 0.92-0.87 (m, 2H).

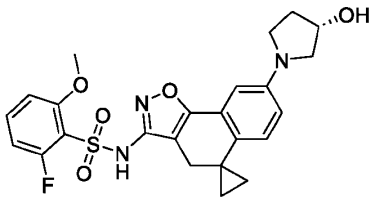
[0911] Step 11. Synthesis of N-(8'-bromo-9'-fluoro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0912] To a stirred solution of 8'-bromo-9'-fluoro-4'*H*-spiro[cyclopropane-1,5'-naphtho[2,1-*d*][1,2]oxazol]-3'-amine (360.0 mg, 1.17 mmol, 1.00 equiv) and 2-methoxybenzene-sulfonyl chloride (481.0 mg, 2.33 mmol, 2.00 equiv) in THF (10.0 mL) at 0 °C was added dropwise LiHMDS solution (1.0 M in THF, 3.5 mL, 3.50 mmol, 3.01 equiv) under N_2 atmosphere. The resulting mixture was stirred at this temperature for another 0.5 h and then quenched with saturated NH_4Cl solution and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-10% MeOH in DCM) and further purified by Prep-HPLC (NH_4HCO_3 system) to afford N-(8'-bromo-9'-fluoro-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (45.4 mg, 8% yield) as a white solid. MS (ESI, *m/z*): 479, 481 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 7.79 (dd, J = 8.0, 1.6 Hz, 1H), 7.69 -7.59 (m, 2H), 7.22 (d, J = 8.4 Hz, 1H), 7.13-7.05 (m, 1H), 6.91 (d, J = 8.4 Hz, 1H), 3.83 (s, 3H), 2.64 (s, 2H), 1.07-0.96 (m, 2H), 0.95-0.84 (m, 2H).

Example 131

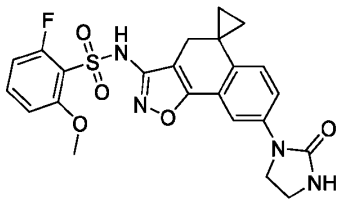
(S)-2-fluoro-N-(8'-(3-hydroxypyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-6-methoxybenzenesulfonamide



[0913] Example 131 was prepared according to the procedure as described in Example 31, starting from Example 45 and (S)-pyrrolidin-3-ol from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 11.03 (br s, 1H), 7.68 – 7.54 (m, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.93 (dd, J = 10.8, 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 6.50 (dd, J = 8.4, 2.4 Hz, 1H), 4.94 (d, J = 3.6 Hz, 1H), 4.38 (br s, 1H), 3.85 (s, 3H), 3.46 – 3.35 (m, 1H), 3.31 – 3.19 (m, 2H), 3.10 – 3.01 (m, 1H), 2.54 (s, 2H), 2.06 – 1.95 (m, 1H), 1.94 – 1.81 (m, 1H), 0.89 – 0.80 (m, 2H), 0.80 – 0.65 (m, 2H). ^{19}F NMR (282 MHz, DMSO-d6) δ -109.01. MS (ESI, *m/z*): 486.3 [M+H]+.

Example 132

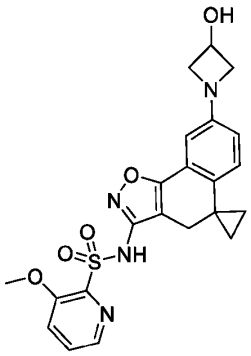
2-Fluoro-6-methoxy-N-(8'-(2-oxoimidazolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0914] Example 132 was prepared according to the procedure as described in Example 31, starting from Example 45 and imidazolidin-2-one from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 11.12 (br s, 1H), 7.85 (d, J = 2.4 Hz, 1H), 7.68 – 7.58 (m, 1H), 7.44 (dd, J = 8.7, 2.4 Hz, 1H), 7.09 – 6.99 (m, 3H), 6.98 – 6.89 (m, 1H), 3.91 – 3.77 (m, 5H), 3.46 – 3.38 (m, 2H), 2.60 (s, 2H), 0.99 – 0.89 (m, 2H), 0.85 – 0.74 (m, 2H). ^{19}F NMR (282 MHz, DMSO-d6) δ -109.01. MS (ESI, *m/z*): 485.1 [M+H]+.

Example 133

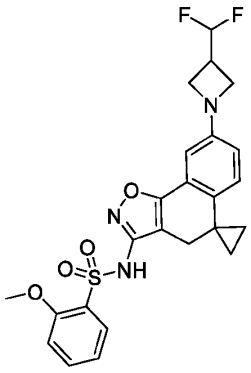
N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-methoxypyridine-2-sulfonamide



[0915] Example 133 was prepared according to the procedure as described in Example 31, starting from Example 54 and azetidin-3-ol from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.82 (br s, 1H), 8.17 (dd, J = 4.5, 1.2 Hz, 1H), 7.81 – 7.72 (m, 1H), 7.71 – 7.60 (m, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 2.4 Hz, 1H), 6.40 (dd, J = 8.4, 2.4 Hz, 1H), 5.60 (d, J = 6.6 Hz, 1H), 4.61 – 4.47 (m, 1H), 4.11 – 4.02 (m, 2H), 3.90 (s, 3H), 3.48 (dd, J = 7.8, 5.1 Hz, 2H), 0.90 – 0.62 (m, 4H). MS (ESI, *m/z*): 455.1 $[M + H]^+$.

Example 134

N-(8'-(3-(difluoromethyl)azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

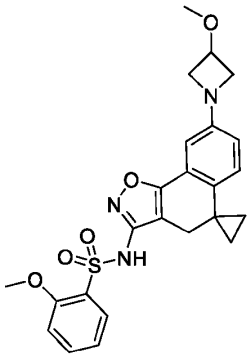


[0916] Example 134 was prepared according to the procedure as described in Example 31, starting from Example 16 and 3-(difluoromethyl)azetidine from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.74 (s, 1H), 7.70 (dd, J = 7.8, 1.7 Hz, 1H), 7.54 (ddd, J = 8.9, 7.5, 1.8 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 7.00 (td, J = 7.6, 1.0 Hz, 1H), 6.82 (d, J = 8.5 Hz, 1H), 6.53 (d, J = 2.5 Hz, 1H), 6.37 (dd, J = 8.5, 2.5 Hz, 1H), 3.86 (t, J = 8.1 Hz, 2H), 3.75 (s, 3H), 3.68 (dd, J = 7.8, 5.5

Hz, 2H), 3.18 – 3.01 (m, 1H), 2.46 (d, J = 6.2 Hz, 2H), 0.86 – 0.70 (m, 2H), 0.70 – 0.55 (m, 2H). MS (ESI, *m/z*): 488.2 $[M+H]^+$.

Example 135

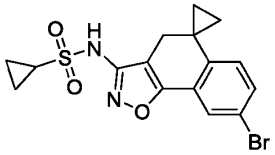
2-Methoxy-N-(8'-(3-methoxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0917] Example 135 was prepared according to the procedure as described in Example 31, starting from Example 16 and 3-methoxyazetidine from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.79 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 8.1 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.60 – 6.41 (m, 1H), 6.35 (dd, J = 8.5, 2.6 Hz, 1H), 4.25 (p, J = 5.4 Hz, 1H), 3.99 (t, J = 7.2 Hz, 2H), 3.77 (s, 3H), 3.54 (dd, J = 8.2, 4.3 Hz, 2H), 3.18 (s, 3H), 2.49 (s, 2H), 0.80 (d, J = 5.1 Hz, 2H), 0.67 (d, J = 4.8 Hz, 2H). MS (ESI, *m/z*): 468.2 $[M+H]^+$.

Example 136

N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)cyclopropanesulfonamide

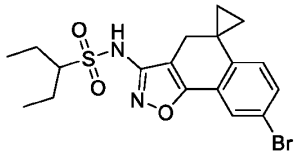


[0918] Example 136 was prepared according to the procedure as described in Example 70, using cyclopropanesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.62 (s, 1H), 7.66 (s, 1H), 7.46 (d, J = 8.5 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 2.81

(q, J = 6.2 Hz, 1H), 2.59 (s, 2H), 0.96 (t, J = 6.4 Hz, 6H), 0.83 (d, J = 5.4 Hz, 2H). MS (ESI, *m/z*): 395 $[M + H]^+$.

Example 137

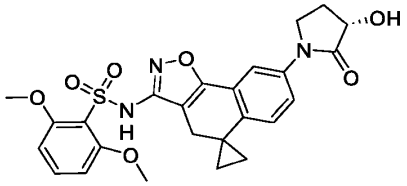
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pentane-3-sulfonamide



[0919] Example 137 was prepared according to the procedure as described in Example 70, using pentane-3-sulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, CDCl3) δ 7.82 (s, 1H), 7.49 – 7.42 (m, 1H), 6.82 (d, J = 7.7 Hz, 2H), 3.23 – 3.15 (m, 1H), 2.77 (d, J = 1.4 Hz, 2H), 1.96 (ddq, J = 47.5, 14.5, 7.1 Hz, 4H), 1.10 (ddd, J = 9.0, 7.0, 1.4 Hz, 6H), 1.05 – 0.92 (m, 4H). MS (ESI, *m/z*): 425.2 $[M + H]^+$.

Example 138

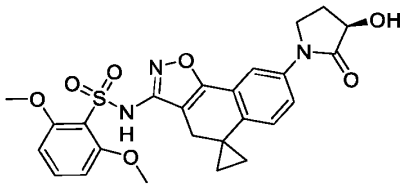
(S)-N-(8'-(3-hydroxy-2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide



[0920] Example 138 was prepared according to the procedure as described in Example 31, starting from Example 15 and (S)-3-hydroxypyrrolidin-2-one from a commercial source (Combi-blocks 77510-50-0). ^{1}H NMR (400 MHz, DMSO) δ 7.89 (s, 1H), 7.57 – 7.50 (m, 1H), 7.38 (t, J = 8.2 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.70 (d, J = 8.4 Hz, 2H), 5.76 (s, 1H), 4.30 (d, J = 10.7 Hz, 1H), 3.72 (s, 6H), 2.47 (s, 2H), 2.37 (m, 2H), 2.06 – 1.73 (m, 2H), 0.94 (s, 2H), 0.74 (s, 2H). MS (ESI, *m/z*): 512.2 $[M+H]^+$.

Example 139

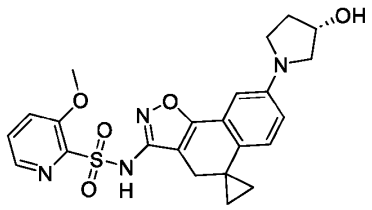
(R)-N-(8'-(3-hydroxy-2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide



[0921] Example 139 was prepared according to the procedure as described in Example 31, starting from Example 15 and (R)-3-hydroxypyrrolidin-2-one from a commercial source (Combi-Blocks 34368-52-0). ^{1}H NMR (400 MHz, DMSO) δ 7.87 (s, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.34 (t, J = 8.3 Hz, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.67 (d, J = 8.4 Hz, 2H), 5.76 (s, 1H), 4.29 (t, J = 8.7 Hz, 1H), 3.70 (s, 6H), 2.47 (s, 2H), 2.40 (m, 2H), 1.91 – 1.78 (m, 2H), 0.93 (s, 2H), 0.74 (s, 2H). MS (ESI, *m/z*): 512.2 [M+H]+.

Example 140

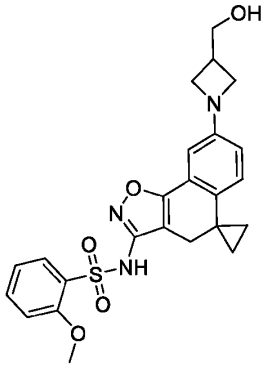
(S)-N-(8'-(3-hydroxypyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-methoxypyridine-2-sulfonamide



[0922] Example 140 was prepared according to the procedure as described in Example 31, starting from Example 54 and (S)-pyrrolidin-3-ol from a commercial source. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (dd, J = 4.5, 1.0 Hz, 1H), 7.62 (br s, 1H), 7.56 – 7.50 (m, 1H), 7.50 – 7.45 (m, 1H), 6.81 – 6.77 (m, 2H), 6.52 (dd, J = 8.5, 2.5 Hz, 1H), 4.65 (s, 1H), 4.10 (s, 3H), 3.57 – 3.48 (m, 2H), 3.39 – 3.34 (m, 1H), 3.25 (d, J = 10.5 Hz, 1H), 2.80 (s, 2H), 2.26 – 2.17 (m, 1H), 2.12 – 2.03 (m, 1H), 1.27 (s, 1H), 0.96 – 0.78 (m, 4H). MS (ESI, *m/z*): 469.2 $[M+H]^+$.

Example 141

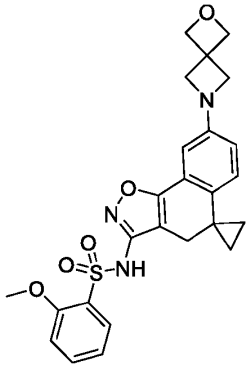
N-(8'-(3-(hydroxymethyl)azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0923] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (50 mg, 108 µmol, Example 16), (azetidin-3-yl)methanol hydrochloride (14.7 mg, 1.1 eq., 119 µmol), Sodium tert-Butoxide (31.2 mg, 3 eq., 325 µmol) and DavePhos Pd G3, CAS 1445085-87-9,Methanesulfonato[2-(dicyclohexylphosphino)-2'-(N,N-dimethylamino)-1,1'-biphenyl](2'-amino-1,1'-biphenyl-2-yl)palladium(II) (4.14 mg, 0.05 eq., 5.42 µmol) in 1,4-dioxane (1.5 mL, 17.6 mmol) was purged with N2 for 5 minutes, then heated at 80 °C for 2 hrs. Concentrated in vacuo, the residue purified by prep-HPLC (0-80% CH3CN (0.1% TFA) in H2O (0.1% TFA)), and dried via lyophilization to afford N-(8'-(3-(hydroxymethyl)azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (4.1 mg, 8% yield) as an off white solid. MS (ESI, *m/z*): 468.2 [M+H]+ 1H NMR (400 MHz, DMSO) δ 10.71 (s, 1H), 7.70 (dd, J = 7.8, 1.7 Hz, 1H), 7.50 (s, 1H), 7.10 (d, J = 8.6 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.55 – 6.37 (m, 1H), 6.37 – 6.20 (m, 1H), 4.66 (t, J = 5.3 Hz, 1H), 3.74 (d, J = 3.5 Hz, 4H), 3.54 – 3.40 (m, 4H), 2.69 (p, J = 7.3 Hz, 1H), 2.49 (s, 2H), 0.86 – 0.68 (m, 2H), 0.68 – 0.47 (m, 2H).

Example 142

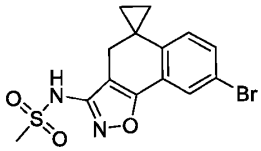
N-(8'-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0924] Example 142 was prepared according to the procedure as described in Example 31, starting from Example 16 and 2-oxa-6-azaspiro[3.3]heptane from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.73 (s, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.54 (t, J = 7.9 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.54 – 6.40 (m, 1H), 6.40 – 6.24 (m, 1H), 4.62 (s, 4H), 3.89 (s, 4H), 3.75 (d, J = 1.5 Hz, 3H), 2.51 (s, 2H),0.77 (d, J = 4.9 Hz, 2H), 0.65 (d, J = 5.2 Hz, 2H). NMRMS (ESI, *m/z*): 480.2 [M+H]+.

Example 143

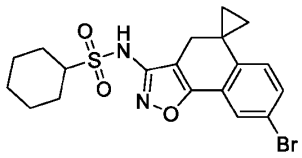
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)methanesulfonamide



[0925] Example 143 was prepared according to the procedure as described in Example 70, using methanesulfonyl chloride. ^{1}H NMR (400 MHz, DMSO) δ 10.78 (s, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.55 (dt, J = 8.3, 2.0 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 3.25 (d, J = 1.5 Hz, 3H), 2.66 (s, 2H), 1.02 (d, J = 5.1 Hz, 2H), 0.91 (d, J = 5.4 Hz, 2H). MS (ESI, *m/z*): 370 [M + H]$^+$.

Example 144

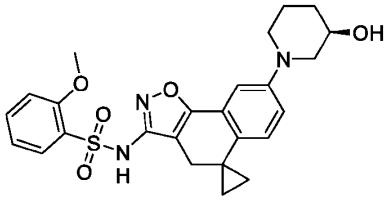
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)cyclohexanesulfonamide



[0926] Example 144 was synthesized in an analogous manner to the preparation described in Example 70, using cyclohexanesulfonyl chloride from a commercial source. Example 144 was purified using reverse phase chromatography (MeCN/H_2O, acidic modifiers). ^{1}H NMR (400 MHz, DMSO) δ 10.65 (s, 1H), 7.74 (d, J = 2.1 Hz, 1H), 7.55 (dd, J = 8.6, 2.1 Hz, 1H), 7.07 (d, J = 8.5 Hz, 1H), 2.67 (s, 2H), 2.08 (d, J = 12.4 Hz, 2H), 1.81 (d, J = 12.7 Hz, 2H), 1.63 (d, J = 12.8 Hz, 1H), 1.45 (q, J = 12.4 Hz, 2H), 1.37 – 1.25 (m, 2H), 1.03 (d, J = 5.4 Hz, 2H), 0.98 – 0.80 (m, 4H). MS (ESI, *m/z*): 435 $[M-H]^+$.

Example 145

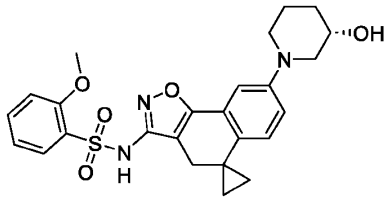
(R)-N-(8'-(3-hydroxypiperidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0927] Example 145 was prepared according to the procedure as described in Example 31, starting from Example 16 and (R)-piperidin-3-ol from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.59 (s, 1H), 7.78 (dd, J = 7.8, 1.8 Hz, 1H), 7.69 – 7.53 (m, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.04 – 6.98 (m, 1H), 6.93 – 6.84 (m, 2H), 4.81 (d, J = 4.2 Hz, 1H), 3.84 (s, 3H), 3.64 – 3.40 (m, 3H), 2.74 – 2.59 (m, 1H), 2.58 – 2.51 (m, 3H), 1.93 – 1.80 (m, 1H), 1.79 – 1.67 (m, 1H), 1.58 – 1.41 (m, 1H), 1.34 – 1.16 (m, 1H), 0.93 – 0.83 (m, 2H), 0.83 – 0.68 (m, 2H). MS (ESI, *m/z*): 482.2 [M+H]+.

Example 146

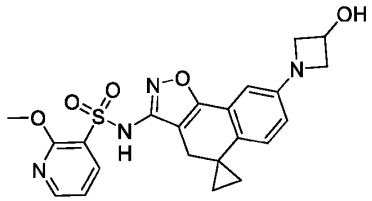
(S)-N-(8'-(3-hydroxypiperidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0928] Example 146 was prepared according to the procedure as described in Example 31, starting from Example 16 and (S)-piperidin-3-ol from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.66 (s, 1H), 7.78 (dd, J = 7.8, 1.8 Hz, 1H), 7.68 – 7.57 (m, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.04 – 6.97 (m, 1H), 6.92 – 6.85 (m, 2H), 4.82 (d, J = 4.2 Hz, 1H), 3.84 (s, 3H), 3.64 – 3.40 (m, 3H), 2.73 – 2.56 (m, 1H), 2.57 – 2.52 (m, 3H), 1.93 – 1.81 (m, 1H), 1.78 – 1.66 (m, 1H), 1.58 – 1.41 (m, 1H), 1.36 – 1.17 (m, 1H), 0.92 – 0.86 (m, 2H), 0.78 – 0.67 (m, 2H). MS (ESI, *m/z*): 482.2 [M+H]+.

Example 147

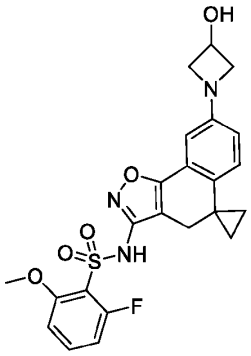
N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxypyridine-3-sulfonamide



[0929] Example 147 was prepared according to the procedure as described in Example 31, starting from Example 44 and azetidin-3-ol from a commercial source. ^{1}H NMR (400 MHz, CDCl3) δ 8.39-8.35 (m, 1H), 8.08-8.04 (m, 1H), 7.02-6.97 (m, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.45-6.40 (m, 1H), 4.80-4.73 (m, 1H), 4.18 (d, J = 3.0 Hz, 5H), 3.71-3.64 (m, 2H), 2.75 (s, 2H), 0.93-0.83 (m, 4H). MS (ESI, *m/z*): 455 $[M+H]^+$.

Example 148

2-Fluoro-N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-6-methoxybenzenesulfonamide



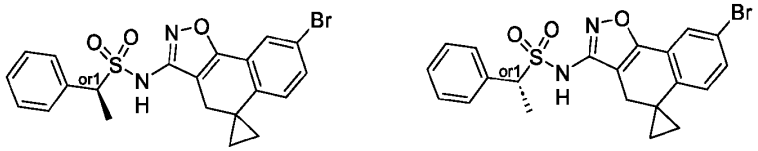
[0930] Example 148 was prepared according to the procedure as described in Example 31, starting from Example 45 and azetidin-3-ol from a commercial source. ^{1}H NMR (500 MHz, DMSO-d6) δ 11.09 (br s, 1H), 7.61-7.57 (m, 1H), 7.05 (d, J = 8.5 Hz, 1H), 6.94 (dd, J = 11.0, 8.5 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.58 (d, J = 2.5 Hz, 1H), 6.42 (dd, J = 8.5, 2.5 Hz, 1H), 5.62 (d, J = 6.5 Hz, 1H), 4.60-4.50 (m, 1H), 4.07 (dd, J = 7.5, 6.5 Hz, 2H), 3.86 (s, 3H), 3.51-3.46 (m, 2H), 2.55 (s, 2H), 0.89-0.84 (m, 2H), 0.76-0.67 (m, 2H). MS (ESI, *m/z*): 472 $[M+H]^+$.

Example 149

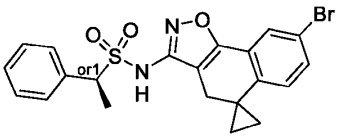
Rel-(1S)-N-{8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}-1-phenylethanesulfonamide

Example 150

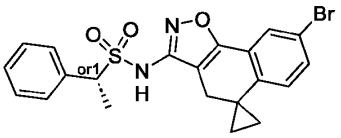
Rel-(1R)-N-{8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}-1-phenylethanesulfonamide



[0931] The product N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-1-phenylethane-1-sulfonamide (20.0 mg, 0.04 mmol, 1.00 equiv, **Example 97**) was resolved with Chiral-Prep-HPLC. The absolute stereochemistry was not determined. (Column: CHIRALPAK IH-3; Mobile Phase A: Hex(0.1%FA): IPA=70: 30; Flow rate: 1.0mL/min mL/min; Gradient: isocratic ; Injection Volume: 3μL mL)



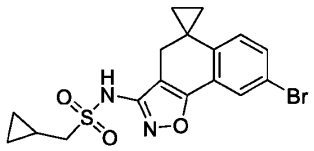
[0932] Rel-(1S)-N-{8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}-1-phenylethanesulfonamide (7.1 mg, 35% yield) as a white solid (1st peak). MS (ESI, *m/z*): 459, 461 [M+H]+. 1H NMR (300 MHz, DMSO-d6) δ 7.74 (d, J = 2.1 Hz, 1H), 7.54 (dd, J = 8.4, 2.1 Hz, 1H), 7.44-7.31 (m, 5H), 7.05 (d, J = 8.4 Hz, 1H), 4.88-4.74 (m, 1H), 2.50-2.43 (m, 2H), 1.71 (d, J = 7.2 Hz, 3H), 1.04-0.96 (m, 2H), 0.88-0.83 (m, 2H).



[0933] Rel-(1R)-N-{8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}-1-phenylethanesulfonamide (6.4 mg, 32% yield) as a white solid (2nd peak). MS (ESI, *m/z*): 459, 461 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.74 (d, J = 2.1 Hz, 1H), 7.54 (dd, J = 8.4, 2.1 Hz, 1H), 7.44-7.31 (m, 5H), 7.05 (d, J = 8.4 Hz, 1H), 4.88-4.74 (m, 1H), 1.71 (d, J = 7.2 Hz, 3H), 1.04-0.96 (m, 2H), 0.88-0.83 (m, 2H).

Example 151

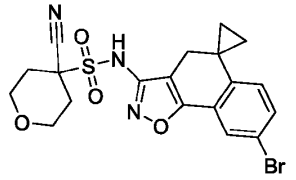
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-1-cyclopropylmethanesulfonamide



[0934] Example 151 was prepared according to the procedure as described in Example 70, using cyclopropylmethanesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.72 (s, 1H), 7.66 (d, J = 2.1 Hz, 1H), 7.48 (dd, J = 8.4, 2.2 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 3.26 (s, 2H), 2.60 (s, 2H), 1.04 – 0.93 (m, 3H), 0.87 – 0.73 (m, 2H), 0.56 – 0.47 (m, 2H), 0.27 (dt, J = 6.4, 4.5 Hz, 2H). MS (ESI, *m/z*): 409 $[M+H]^+$.

Example 152

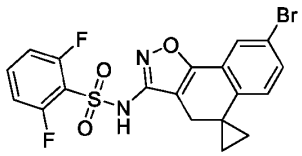
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-cyanotetrahydro-2H-pyran-4-sulfonamide



[0935] Example 152 was prepared according to the procedure as described in Example 70, using 4-cyanotetrahydro-2H-pyran-4-sulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.78 (s, 1H), 7.74 (d, J = 2.1 Hz, 1H), 7.51 (dd, J = 8.4, 2.1 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 3.97 (dd, J = 11.6, 4.5 Hz, 2H), 3.37 – 3.26 (m, 2H), 2.68 (s, 2H), 2.31 – 2.10 (m, 4H), 0.97 (d, J = 5.1 Hz, 2H), 0.90 – 0.83 (m, 2H). MS (ESI, *m/z*): 464.0 [M +H]+.

Example 153

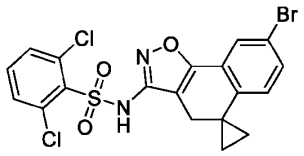
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-difluorobenzenesulfonamide



[0936] Example 153 was prepared according to the procedure as described in Example 76, using 2,6-difluorobenzenesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.88 (s, 1H), 7.76 – 7.65 (m, 1H), 7.62 (d, J = 2.2 Hz, 1H), 7.47 (dd, J = 8.4, 2.2 Hz, 1H), 7.34 – 7.17 (m, 2H), 6.98 (d, J = 8.5 Hz, 1H), 2.58 (s, 2H), 1.00 – 0.89 (m, 2H), 0.89 – 0.78 (m, 2H). MS (ESI, *m/z*): 468.0 $[M+H]^+$.

Example 154

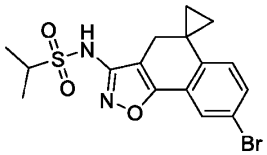
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dichlorobenzenesulfonamide



[0937] Example 154 was prepared according to the procedure as described in Example 76, using 2,6-dichlorobenzenesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.98 (s, 1H), 7.81 – 7.73 (m, 3H), 7.69 (dd, J = 9.1, 6.8 Hz, 1H), 7.62 (dd, J = 8.4, 2.2 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 2.73 (s, 2H), 1.23 – 1.04 (m, 2H), 1.04 – 0.81 (m, 2H). MS (ESI, *m/z*): 501.0 $[M+H]^+$.

Example 155

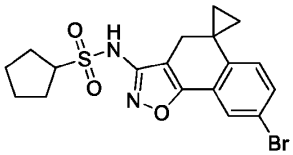
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)propane-2-sulfonamide



[0938] Example 155 was synthesized in an analogous manner to the preparation described in Example 70, using propane-2-sulfonyl chloride from a commercial source. Example 155 was purified using reverse phase chromatography (MeCN/H_2O, acidic modifiers). ^{1}H NMR (400 MHz, DMSO) δ 10.66 (s, 1H), 7.73 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 8.4, 2.2 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 3.61 (hept, J = 6.8 Hz, 1H), 2.67 (s, 2H), 1.31 (d, J = 6.8 Hz, 6H), 1.12 – 0.96 (m, 2H), 0.96 – 0.82 (m, 2H). MS (ESI, *m/z*): 397.0 $[M+H]^+$.

Example 156

N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)cyclopentanesulfonamide

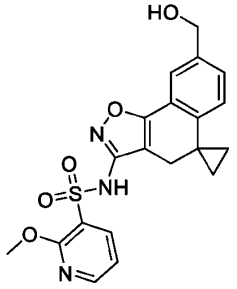


[0939] Example 156 was prepared according to the procedure as described in Example 70, using cyclopentanesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz,

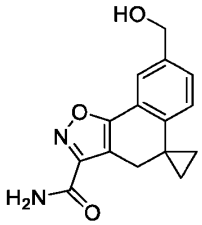
DMSO) δ 10.60 (s, 1H), 7.67 (d, J = 2.1 Hz, 1H), 7.48 (dd, J = 8.4, 2.2 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 3.95 – 3.70 (m, 1H), 2.60 (s, 2H), 2.01 (s, 1H), 1.87 (q, J = 6.2 Hz, 3H), 1.70 – 1.39 (m, 4H), 1.08 – 0.91 (m, 2H), 0.91 – 0.74 (m, 2H). MS (ESI, *m/z*): 423.0 $[M+H]^+$.

Example 157

N-(8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxypyridine-3-sulfonamide

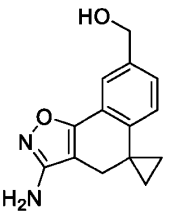


[0940] Step 1. Synthesis of 8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide



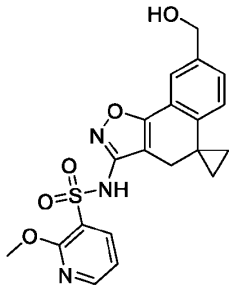
[0941] A solution of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (1.00 g, 3.13 mmol, 1.00 equiv, Intermediate C Step 3), (tributylstannyl)methanol (1.11 g, 3.45 mmol, 1.10 equiv) and XPhos Pd G2 (246.0 mg, 0.31 mmol, 0.10 equiv) in dioxane (10 mL) was stirred at 80 °C for 2 h under N_2 atmosphere and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-70% EtOAc in petroleum ether) to afford 8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (450 mg, 50% yield) as a yellow solid. MS (ESI, *m/z*): 271 [M+H]+.

[0942] Step 2. Synthesis of (3'-amino-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-8'-yl)methanol



[0943] To a stirred mixture of 8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide (400.0 mg, 1.48 mmol, 1.00 equiv) and TEA (449.0 mg, 4.44 mmol, 3.00 equiv) in combined solvent system of EtOAc (4 mL), acetonitrile (4 mL) and H_2O (2 mL) at 0 °C was added $PhI(OAc)_2$ (953.0 mg, 2.96 mmol, 2.00 equiv) in portions. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 2 h and then quenched with $Na_2S_2O_3$ solution. The resulting mixture was extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~70% EtOAc in petroleum ether) to afford (3'-amino-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-8'-yl)methanol (170 mg, 35% yield) as a yellow solid. MS (ESI, *m/z*): 243 [M+H]+.

[0944] Step 3. Synthesis of N-(8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxypyridine-3-sulfonamide

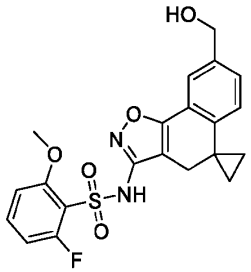


[0945] A mixture of 3'-amino-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-8'-ylmethanol (300.0 mg, 1.24 mmol, 1.00 equiv) and 2-methoxypyridine-3-sulfonyl chloride (309.0 mg, 1.49 mmol, 1.20 equiv) in pyridine (6.0 mL) was stirred at ambient temperature for 1 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5~50% acetonitrile in water (contained 0.05% formic acid)) and further purified by Prep-HPLC (25~40% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-

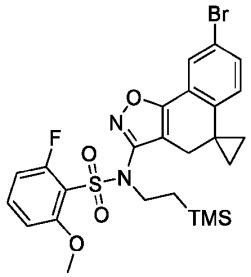
2-methoxypyridine-3-sulfonamide (58.6 mg, 34% yield) as a white solid. MS (ESI, *m/z*): 414 [M+H]+. 1H NMR (300 MHz, DMSO-d6) δ 11.05 (br s, 1H), 8.42 (dd, J = 4.8, 1.8 Hz, 1H), 8.21-8.18 (m, 1H), 7.48 (d, J = 1.8 Hz, 1H), 7.27-7.17 (m, 2H), 7.02 (d, J = 8.1 Hz, 1H), 5.24 (t, J = 6.0 Hz, 1H), 4.47 (d, J = 4.2 Hz, 2H), 3.92 (s, 3H), 2.60 (s, 2H), 0.96-0.81 (m, 4H).

Example 158

2-Fluoro-N-(8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-6-methoxybenzenesulfonamide



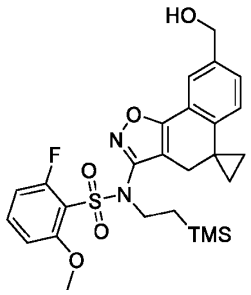
[0946] Step 1. Synthesis of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-fluoro-6-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide



[0947] To a stirred mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-fluoro-6-methoxybenzenesulfonamide (200.0 mg, 0.42 mmol, 1.00 equiv, Example 45), 2-(trimethylsilyl)ethan-1-ol (198.0 mg, 1.68 mmol, 4.00 equiv) and PPh_3 (441.8 mg, 1.68 mmol, 4.00 equiv) in THF (3.0 mL) at 0 °C was added dropwise a solution of DIAD (339.4 mg, 1.68 mmol, 4.00 equiv) in THF (1.0 mL). The resulting mixture was allowed to warm up to ambient temperature and stirred for another1 h and then diluted EtOAc. The resulting mixture was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-

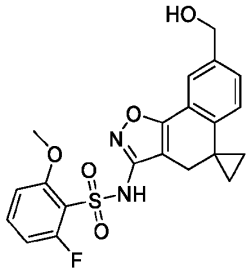
d]isoxazol]-3'-yl)-2-fluoro-6-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (192.0 mg, 79% yield) as colorless oil. MS (ESI, *m/z*): 579 [M+H]+.

[0948] Step 2. Synthesis of 2-fluoro-N-(8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-6-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide



[0949] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-fluoro-6-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (130.0 mg, 0.22 mmol, 1.00 equiv), (tributylstannyl)methanol (141.7 mg, 0.44 mmol, 2.00 equiv) and $Pd(AMPhos)_2Cl_2$ (28.3 mg, 0.04 mmol, 0.2 equiv) in dioxane (2.0 mL) was stirred at 100 °C for 16 h under N_2 atmosphere and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (10-60% acetonitrile in water (contained 0.05% formic acid)) to afford 2-fluoro-N-(8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-6-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (74.0 mg, 62% yield) as yellow oil. MS (ESI, *m/z*): 531 [M+H]+.

[0950] Step 3. Synthesis of 2-fluoro-N-(8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-6-methoxybenzenesulfonamide

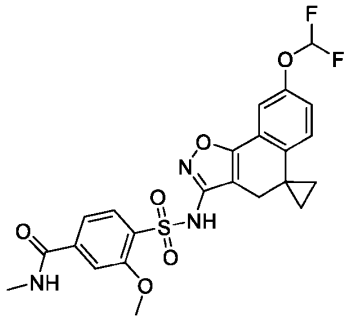


[0951] A mixture of 2-fluoro-N-(8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-6-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide

(80.0 mg, 0.15 mmol, 1.00 equiv) and Cs2CO3 (147.0 mg, 0.45 mmol, 3.00 equiv) in DMSO (1.0 mL) was stirred at 100 °C for 2 h. The resulting mixture was directly purified by reverse phase flash chromatography on C18 gel (10-60% acetonitrile in water (contained 0.05% formic acid)) to afford 2-fluoro-N-(8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-6-methoxybenzenesulfonamide (23.1 mg, 36% yield) as a white solid. MS (ESI, *m/z*): 431 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d6) δ 11.10 (br s, 1H), 7.68-7.55 (m, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.29 (dd, J = 8.1, 1.8 Hz, 1H), 7.04 (dd, J = 8.4, 3.6 Hz, 2H), 6.99-6.89 (m, 1H), 5.30-5.20 (m, 1H), 4.49 (d, J = 5.4 Hz, 2H), 3.85 (s, 3H), 2.61 (s, 2H), 1.03-0.93 (m, 2H), 0.86-0.75 (m, 2H). 19F NMR (377 MHz, DMSO-d6) δ -108.97.

Example 159

4-(N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide

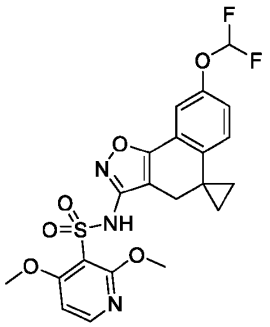


[0952] A mixture of 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-amine (150.0 mg, 0.54 mmol, 1.00 equiv, Intermediate I) and 2-methoxy-4-(methylcarbamoyl)benzenesulfonyl chloride (256.0 mg, 0.97 mmol, 1.80 equiv) in pyridine (2.0 mL) was stirred at 80 °C for 2 h under N2 atmosphere. The resulting mixture was concentrated under vacuum. The residue was re-dissolved in a small amount of DCM. The organic solution and acidified with aqueous HCl (1 M) to pH ~3. The mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na2SO4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5~55% acetonitrile in water (contained 0.1% formic acid) and further purified by Prep-HPLC (35~50% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-

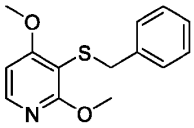
yl)sulfamoyl)-3-methoxy-N-methylbenzamide (45.7 mg, 16% yield) as a white solid. MS (ESI, *m/z*): 506 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.70 – 8.59 (m, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.57 – 7.44 (m, 2H), 7.32 – 7.25 (m, 1H), 7.23 (t, J = 74.1 Hz, 1H), 7.18 – 7.07 (m, 2H), 3.87 (s, 3H), 2.78 (d, J = 4.5 Hz, 3H), 2.61 (s, 2H), 1.08 – 0.93 (m, 2H), 0.93 – 0.79 (m, 2H). ^{19}F NMR (282 MHz, DMSO-d6) δ -82.26.

Example 160

N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide

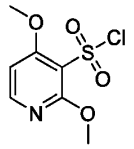


[0953] Step 1. Synthesis of 3-(benzylthio)-2,4-dimethoxypyridine



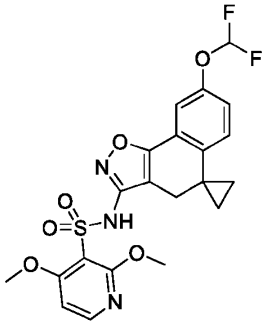
[0954] A mixture of 3-bromo-2,4-dimethoxypyridine (2.0 g, 9.17 mmol, 1.00 equiv), phenylmethanethiol (1.4 g, 11.00 mmol, 1.20 equiv), Cs_2CO_3 (8.9 g, 27.51 mmol, 3.00 equiv), BrettPhos (0.5 g, 0.91 mmol, 0.10 equiv) and BrettPhos Pd G3 (0.8 g, 0.91 mmol, 0.10 equiv) in dioxane (30.0 mL) was stirred at 100 °C for 3 h under N_2 atmosphere and then filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford 3-(benzylthio)-2,4-dimethoxypyridine (1.8 g, 75% yield) as brown oil. MS (ESI, *m/z*): 262 [M+H]+.

[0955] Step 2. Synthesis of 2,4-dimethoxypyridine-3-sulfonyl chloride



[0956] To a stirred mixture of 3-(benzylthio)-2,4-dimethoxypyridine (390.0 mg, 1.49 mmol, 1.00 equiv) in AcOH (4.8 mL) and water (1.6 mL) at 0 °C was added NCS (797.1 mg, 5.97 mmol, 4.00 equiv). The resulting mixture was allowed to warm up to ambient temperature and stirred for another 2 h. The resulting solution was basified with saturated NaHCO3 solution to pH ~8 and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another batch (same scale) and purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford 2,4-dimethoxypyridine-3-sulfonyl chloride (504.0 mg, 71% yield) as a white solid. MS (ESI, *m/z*): 238 [M+H]+.

[0957] Step 3. Synthesis of N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide

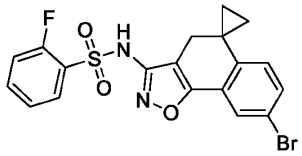


[0958] A mixture of 2,4-dimethoxypyridine-3-sulfonyl chloride (180.0 mg, 0.76 mmol, 2.10 equiv) and 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (100.0 mg, 0.36 mmol, 1.00 equiv) in pyridine (2.0 mL) was stirred at 80 °C for 2 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5~40% acetonitrile in water (contained 0.05% formic acid) and further purified by Prep-HPLC (38-58% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (52.5 mg, 22% yield) as a white solid. MS (ESI, *m/z*): 480 [M+H]+.1H NMR (300 MHz, DMSO-d6) δ 10.98 (br s, 1H), 8.22 (d, J = 6.0, 1H),

7.54-6.99 (m, 4H), 6.90 (d, J = 6.0 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.61 (s, 2H), 1.05-0.93 (m, 2H), 0.93-0.75 (m, 2H). 19F NMR (282 MHz, DMSO-d6) δ -82.35.

Example 161

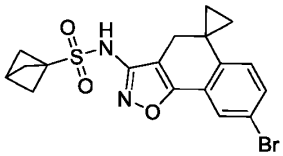
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-fluorobenzenesulfonamide



[0959] Example 161 was prepared according to the procedure as described in Example 70, using 2-fluorobenzenesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.55 (s, 1H), 7.83 (td, J = 7.7, 1.8 Hz, 1H), 7.69 (tdd, J = 7.4, 5.0, 1.8 Hz, 1H), 7.61 (d, J = 2.1 Hz, 1H), 7.46 (dd, J = 8.4, 2.2 Hz, 1H), 7.44 – 7.30 (m, 2H), 6.98 (d, J = 8.5 Hz, 1H), 2.57 (s, 2H), 1.05 – 0.88 (m, 2H), 0.88 – 0.69 (m, 2H). MS (ESI, *m/z*): 449.0 [M +H]$^+$.

Example 162

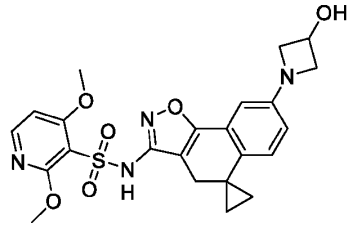
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)bicyclo[1.1.1]pentane-1-sulfonamide



[0960] Example 162 was synthesized in an analogous manner to the preparation described in Example 70, using bicyclo[1.1.1]pentane-1-sulfonyl chloride from a commercial source. Example 162 was purified using reverse phase chromatography (MeCN/H_2O, acidic modifiers). ^{1}H NMR (400 MHz, DMSO) δ 10.74 (s, 1H), 7.74 (d, J = 2.2 Hz, 1H), 7.54 (dd, J = 8.4, 2.2 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 2.69 (s, 1H), 2.66 (s, 2H), 2.15 (s, 6H), 1.02 (d, J = 4.5 Hz, 2H), 0.94 – 0.87 (m, 2H). MS (ESI, *m/z*): 421.0 [M +H]$^+$.

Example 163

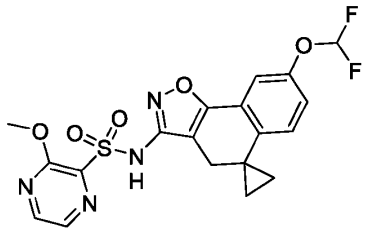
N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide



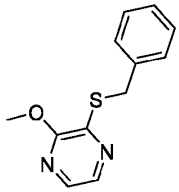
[0961] Example 163 was prepared according to the procedure as described in Example 31, starting from Example 103 and azetidin-3-ol from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.89 (s, 1H), 8.22 (d, J = 6.0 Hz, 1H), 6.96 – 6.83 (m, 2H), 6.58 (d, J = 2.4 Hz, 1H), 6.45 – 6.36 (m, 1H), 5.60 (d, J = 6.6 Hz, 1H), 4.60 – 4.48 (m, 1H), 4.12 – 4.01 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.53 – 3.43 (m, 2H), 2.54 (s, 2H), 0.91 – 0.77 (m, 2H), 0.75 – 0.65 (m, 2H). MS (ESI, *m/z*): 485.2 [M+H]+.

Example 164

N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-methoxypyrazine-2-sulfonamide



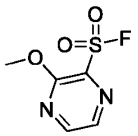
[0962] Step 1. Synthesis of 2-(benzylthio)-3-methoxypyrazine



[0963] To a stirred solution of NaOEt (4.5 g, 66.13 mmol, 1.99 equiv) in EtOH (40 mL) at 40 °C was added 2-chloro-3-methoxypyrazine (4.8 g, 33.20 mmol, 1.00 equiv) and phenylmethanethiol (4.9 g, 39.45 mmol, 1.19 equiv). The resulting mixture was stirred at this

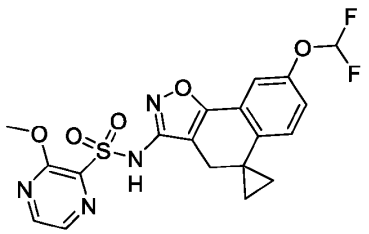
temperature for 2 h and then diluted with water and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-80% EtOAc in petroleum ether) to afford 2-(benzylthio)-3-methoxypyrazine (6.0 g, 78% yield) as a white solid. MS (ESI, *m/z*): 233 [M+H]+.

[0964] Step 2. Synthesis of 3-methoxypyrazine-2-sulfonyl fluoride



[0965] To a stirred mixture of 2-(benzylthio)-3-methoxypyrazine (100.0 mg, 0.43 mmol, 1.00 equiv) in AcOH (0.1 mL) and H_2O (0.2 mL) at 0 °C was added 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (254.0 mg, 1.29 mmol, 3.00 equiv) in portions. The resulting mixture was stirred at this temperature for another 3 h and to this was added KF (50.0 mg, 0.86 mmol, 2.00 equiv). The resulting mixture was allowed to warm up to ambient temperature and stirred for another 8 h. The mixture was diluted with EtOAc. The organic mixture was washed with brine three times, dried over Na_2SO_4, and concentrated under vacuum. The residue was combined with another 9 batches (same scale) and purified by flash chromatography on silica gel (0-35% EtOAc in petroleum ether) to afford 3-methoxypyrazine-2-sulfonyl fluoride (450.0 mg, 54% yield) as a white solid. MS (ESI, *m/z*): 193 [M+H]+.

[0966] Step 3. Synthesis of N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-methoxypyrazine-2-sulfonamide



[0967] To a stirred solution of 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (193.0 mg, 0.69 mmol, 1.00 equiv) in THF (2.0 mL) at 0 oC was added dropwise LiHMDS (1 M in THF, 4.2 mL, 4.2 mmol, 6.09 equiv). The resulting

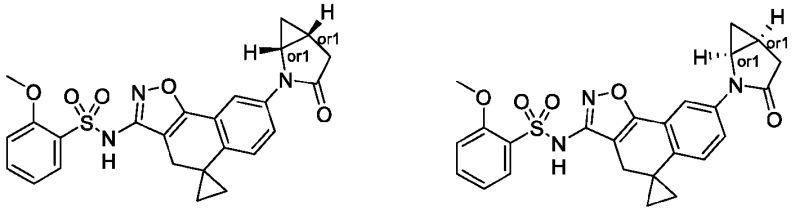
mixture was stirred at this temperature for another 15 min and to this was added dropwise a solution of 3-methoxypyrazine-2-sulfonyl fluoride (200.0 mg, 1.04 mmol, 1.51 equiv) in THF (1.0 mL). The resulting mixture was stirred for another 2 h and then concentrated under vacuum. The residue was purified by Prep-TLC (5% MeOH in DCM) and further purified by Achiral-SFC to afford N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-methoxypyrazine-2-sulfonamide (8.7 mg, 2% yield) as a white solid. MS (ESI, *m/z*): 451 [M+H]+.1H NMR (300 MHz, DMSO-d6) δ 8.43 (s, 1H), 8.25 (br s, 1H), 7.30 (br s, 0H), 7.53-6.99 (m, 3H), 3.97 (s, 3H), 3.09 (q, J = 7.2 Hz, 1H), 2.56 (s, 2H), 1.26-1.12 (m, 2H), 1.03-0.77 (m, 4H). 19F NMR (282 MHz, DMSO-d6) δ -82.21.

Example 165

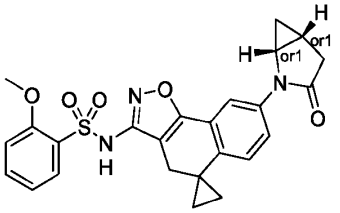
Rel-2-methoxy-N-(8'-((1R,5R)-3-oxo-2-azabicyclo[3.1.0]hexan-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide

Example 166

Rel-2-methoxy-N-(8'-((1S,5S)-3-oxo-2-azabicyclo[3.1.0]hexan-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide

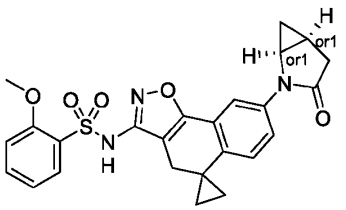


[0968] The product 2,6-dimethoxy-N-(5-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide (42.0 mg, 0.087 mmol, 1.00 equiv, **Example 93**) was resolved with Chiral-Prep-HPLC. The absolute stereochemistry was not determined.



[0969] rel-2-methoxy-N-(8'-((1R,5R)-3-oxo-2-azabicyclo[3.1.0]hexan-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide (12.3 mg, 29%

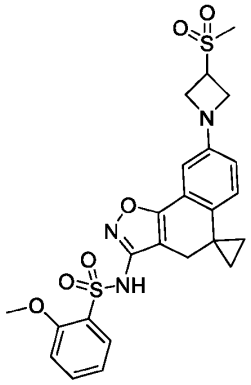
yield) as a white solid (1st peak). MS (ESI, *m/z*): 478 [M+H]+ . ^{1}H NMR (300 MHz, DMSO-d6) δ 10.83 (br s, 3H), 7.86 (d, J = 2.4 Hz, 1H), 7.78 (dd, J = 7.8, 1.8 Hz, 1H), 7.68 – 7.56 (m, 2H), 7.25 – 7.16 (m, 1H), 7.13 – 7.02 (m, 2H), 3.83 (s, 3H), 3.57 (t, J = 6.0 Hz, 1H), 2.97 (dd, J = 18.3, 7.2 Hz, 1H), 2.60 (s, 2H), 2.48 – 2.39 (m, 1H), 1.13 – 1.01 (m, 1H), 1.01 – 0.91 (m, 2H), 0.86 – 0.73 (m, 2H), 0.52 – 0.42 (m, 1H).



[0970] rel-2-methoxy-N-(8'-((1S,5S)-3-oxo-2-azabicyclo[3.1.0]hexan-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide (13.6 mg, 32% yield) as a white solid (2nd peak). MS (ESI, *m/z*): 478 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.82 (br s, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.78 (dd, J = 7.8, 1.8 Hz, 1H), 7.68 – 7.56 (m, 2H), 7.25 – 7.16 (m, 1H), 7.14 – 7.01 (m, 2H), 3.82 (s, 3H), 3.62 – 3.50 (m, 1H), 2.97 (dd, J = 18.3, 7.2 Hz, 1H), 2.60 (s, 2H), 2.49 – 2.40 (m, 1H), 1.66 – 1.51 (m, 1H), 1.14 – 1.01 (m, 1H), 1.01 – 0.91 (m, 2H), 0.87 – 0.75 (m, 2H), 0.51 – 0.42 (m, 1H).

Example 167

2-Methoxy-N-(8'-(3-(methylsulfonyl)azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide

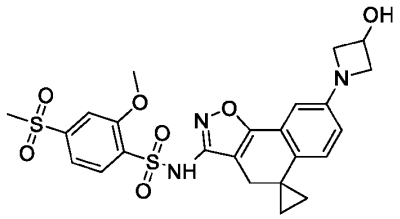


[0971] Example 167 was synthesized in an analogous manner to the preparation described in Example 31, starting from Example 16 and 3-(methylsulfonyl)azetidine from a commercial

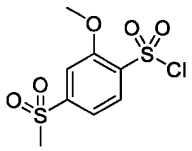
source. Example 167 was purified using reverse phase chromatography (MeCN/H_2O, acidic modifiers). ^{1}H NMR (400 MHz, DMSO) δ 10.81 (s, 1H), 7.78 (dd, J = 7.9, 1.7 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 8.5 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.48 (dd, J = 8.4, 2.6 Hz, 1H), 4.41 (ddd, J = 13.7, 8.2, 5.3 Hz, 1H), 4.13 (t, J = 8.4 Hz, 2H), 4.04 (dd, J = 8.6, 5.3 Hz, 2H), 3.83 (s, 3H), 3.04 (s, 3H), 2.54 (s, 2H), 0.92 – 0.85 (m, 2H), 0.77 – 0.69 (m, 2H). MS (ESI, *m/z*): 516.2 $[M+H]^+$.

Example 168

N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-4-(methylsulfonyl)benzenesulfonamide



[0972] Step 1. 2-methoxy-4-(methylsulfonyl)benzenesulfonyl chloride

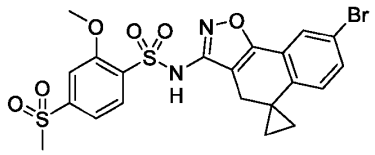


[0973] To a stirred mixture of 2-methoxy-4-(methylsulfonyl)aniline (1.5 g, 7.46 mmol, 1.00 equiv) in HCl (conc., 9.0 mL) and AcOH (7.5 mL) at -15 °C was added dropwise a solution of $NaNO_2$ (566.2 mg, 8.21 mmol, 1.10 equiv) in water (5.0 mL). The reaction mixture was stirred at this temperature for 30 mins to afford solution A.

[0974] To water (5.0 mL) under string at 0 °C was added dropwise $SOCl_2$ (8.9 g, 75.00 mmol, 10.00 equiv) over 10 min. The resulting mixture was stirred at ambient temperature for another 1 h and then to this was added CuCl (369.3 mg, 3.73 mmol, 0.50 equiv). To this at 0 °C was slowly added dropwise solution A. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 1 h. The mixture was then diluted with water and extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford 2-methoxy-4-

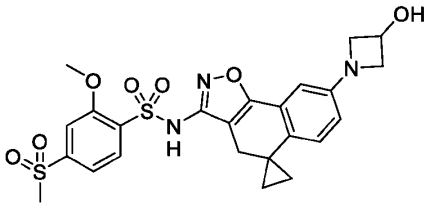
(methylsulfonyl)benzenesulfonyl chloride (1.8 g, 42%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (d, J = 8.4 Hz, 1H), 7.46-7.40 (m, 2H), 3.87 (s, 3H), 3.22 (s, 3H).

[0975] Step 2. N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-4-(methylsulfonyl)benzenesulfonamide



[0976] A mixture of 4-methanesulfonyl-2-methoxybenzenesulfonyl chloride (443.0 mg, 1.56 mmol, 3.00 equiv) and 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-amine (150.0 mg, 0.52 mmol, 1.00 equiv, Intermediate C) in pyridine (2.5 mL) was stirred at 80 °C for 2 h. The resulting mixture was concentrated under vacuum. The residue was re-dissolved in DCM. The organic solution was acidified with HCl (3 M) to pH ~3 and extracted with EtOAc 3 times. The combined organic layers were concentrated under vacuum. The residue was combined with another batch (160.0 mg scale) and purified by reverse phase flash chromatography on C18 gel (0-70% acetonitrile in water (contained 0.05% formic acid)) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-4-(methylsulfonyl)benzenesulfonamide (290.0 mg, 50%) as a yellow solid. MS (ESI, *m/z*):539, 541 $(M + H)^+$.

[0977] Step 3. N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-4-(methylsulfonyl)benzenesulfonamide

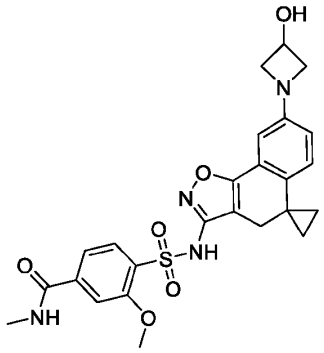


[0978] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-4-(methylsulfonyl)benzenesulfonamide (150.0 mg, 0.28 mmol, 1.00 equiv), azetidin-3-ol (61.0 mg, 0.84 mmol, 3.00 equiv), Pd-PEPPSI-IHeptCl (27.0 mg, 0.028 mmol, 0.10 equiv) and Cs_2CO_3 (183.0 mg, 0.56 mmol, 2.00 equiv) in NMP (5 mL) was stirred at 100 °C for 2 h under N_2 atmosphere. The resulting mixture was combined with

another batch (30.0 mg scale) and purified by reverse phase flash chromatography on C18 gel (5%-65% acetonitrile in water (contained 0.05% formic acid)) to afford N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-4-(methylsulfonyl)benzenesulfonamide (69.1 mg, 39%) as a light yellow solid. ^{1}HNMR (300 MHz, DMSO-d_6) δ 11.16 (br s, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.71-7.56 (m, 2H), 6.88 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 2.4 Hz, 1H), 6.47-6.35 (m, 1H), 5.60 (d, J = 6.3 Hz, 1H), 4.63-4.46 (m, 1H), 4.15-4.01 (m, 2H), 3.96 (s, 3H), 3.53-3.41 (m, 2H), 3.36-3.28 (s, 3H), 2.55 (s, 2H), 0.92-0.83 (m, 2H), 0.79-0.70 (m, 2H). MS (ESI, *m/z*):532 $(M + H)^+$.

Example 169

4-(N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide

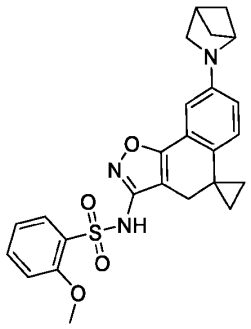


[0979] A mixture of 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide (100.0 mg, 0.19 mmol, 1.00 equiv, **Example 90**), azetidin-3-ol (71.0 mg, 0.95 mmol, 5.00 equiv), Cs2CO3 (189.0 mg, 0.58 mmol, 3.00 equiv), and Pd-PEPPSI-IHeptCl 3-chloropyridine (19.0 mg, 0.02 mmol, 0.10 equiv) in NMP (4.0 mL) was stirred at 100 oC for 2 h under N2 atmosphere. The resulting mixture was combined with another two batches (same scale) and purified directly by reverse phase flash chromatography (5-80% acetonitrile in water (contained 0.05% formic acid)) to afford 4-(N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide (68.6 mg, 21% yield) as a yellow solid. MS (ESI, *m/z*): 511 [M+H]+. 1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.64 (d, J = 4.8 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 1.5 Hz, 1H), 7.53-7.43 (m, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 2.4 Hz, 1H), 6.46-6.35 (m, 1H), 5.60 (d, J = 6.6 Hz, 1H),

4.60-4.48 (m, 1H), 4.11-4.01 (m, 2H), 3.52-3.42 (m, 2H), 2.80 (d, J = 4.5 Hz, 3H), 2.54 (s, 2H), 0.86 (d, J = 4.5 Hz, 2H), 0.74 (d, J = 4.8 Hz, 2H).

Example 170

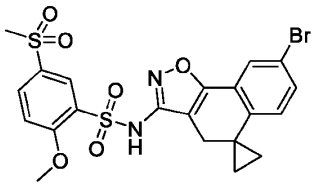
N-(8'-(2-azabicyclo[2.1.1]hexan-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[0980] Example 170 was prepared according to the procedure as described in Example 31, starting from Example 16 and 2-azabicyclo[2.1.1]hexane from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.79 (s, 1H), 7.77 (dd, J = 7.8, 1.7 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.88 – 6.81 (m, 2H), 6.70 (dd, J = 8.6, 2.6 Hz, 1H), 4.40 (d, J = 6.7 Hz, 1H), 3.83 (s, 3H), 3.22 (s, 2H), 2.52 (s, 3H), 1.89 (s, 2H), 1.27 (dd, J = 4.4, 1.9 Hz, 2H), 0.90 – 0.83 (m, 2H), 0.74 – 0.67 (m, 2H). MS (ESI, *m/z*): 464.3 [M+H]+

Example 171

N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-5-(methylsulfonyl)benzenesulfonamide

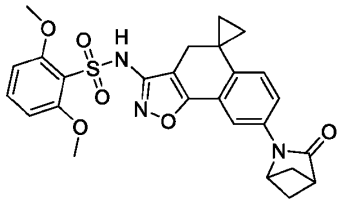


[0981] Example 171 was prepared according to the procedure as described in Example 76, using 2-methoxy-5-(methylsulfonyl)benzenesulfonyl chloride from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 11.32 (s, 1H), 8.27 (d, J = 2.4 Hz, 1H), 8.20 (dd, J = 8.8, 2.4 Hz,

1H), 7.69 (d, J = 2.2 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.05 (d, J = 8.4 Hz, 1H), 3.94 (s, 3H), 3.26 (s, 3H), 2.65 (s, 2H), 1.07 – 0.95 (m, 2H), 0.95 – 0.76 (m, 2H). MS (ESI, *m/z*): 541.0 $[M+H]^+$.

Example 172

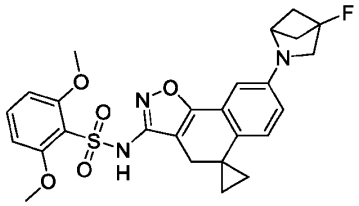
2,6-Dimethoxy-N-(8'-(3-oxo-2-azabicyclo[2.1.1]hexan-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[0982] Example 172 was prepared according to the procedure as described in Example 31, starting from Example 15 and 2-azabicyclo[2.1.1]hexan-3-one from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.67 (s, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.49 (t, J = 8.4 Hz, 1H), 7.39 (dd, J = 8.4, 2.4 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 6.76 (d, J = 8.5 Hz, 2H), 4.73 – 4.67 (m, 1H), 3.79 (s, 6H), 2.84 – 2.76 (m, 1H), 2.69 – 2.60 (m, 2H), 2.56 (s, 2H), 2.36 – 2.30 (m, 2H), 0.98 – 0.83 (m, 2H), 0.77 – 0.67 (m, 2H). MS (ESI, *m/z*): 508.2 $[M+H]^+$.

Example 173

N-(8'-(4-fluoro-2-azabicyclo[2.1.1]hexan-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide

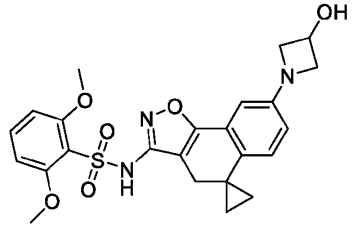


[0983] Example 173 was prepared according to the procedure as described in Example 31, starting from Example 15 and 4-fluoro-2-azabicyclo[2.1.1]hexane from a commercial source. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.65 (br s, 1H), 7.48 (t, J = 8.4 Hz, 1H), 6.91 – 6.84 (m, 2H), 6.76 (d, J = 8.4 Hz, 2H), 6.71 (dd, J = 8.4, 2.4 Hz, 1H), 4.44 – 4.34 (m, 1H), 3.78 (s, 6H), 3.30 (s, 2H), 2.52 (s, 2H), 2.15 – 2.07 (m, 2H), 1.94 – 1.87 (m, 2H), 0.90 – 0.83 (m, 2H),

0.70 – 0.62 (m, 2H). ^{19}F NMR (377 MHz, DMSO-d6) δ -161.71. MS (ESI, *m/z*): 512.2 $[M+H]^+$.

Example 174

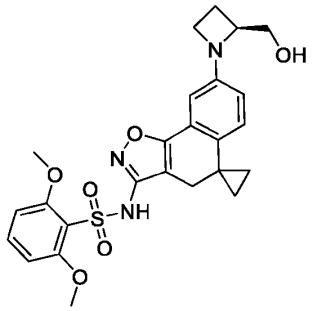
N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide



[0984] Example 174 was prepared according to the procedure as described in Example 31, starting from Example 15 and azetidin-3-ol from a commercial source. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.88 (s, 1H), 7.41 (t, J = 8.4 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 6.62 (d, J = 8.4 Hz, 2H), 6.40 (dd, J = 8.4, 2.4 Hz, 1H), 4.81 – 4.68 (m, 1H), 4.21 – 4.10 (m, 2H), 3.94 (s, 6H), 3.70 – 3.60 (m, 2H), 2.78 (s, 2H), 0.90 – 0.76 (m, 4H). MS (ESI, *m/z*): 482.2 $(M - H)^-$.

Example 175

(S)-N-(8'-(2-(hydroxymethyl)azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide

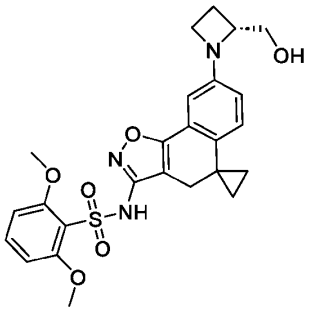


[0985] Example 175 was prepared according to the procedure as described in Example 31, starting from Example 15 and (S)-azetidin-2-ylmethanol from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 7.46 (s, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.79 (s, 1H), 6.75 (d, J =

8.5 Hz, 2H), 6.56 (d, J = 7.3 Hz, 1H), 4.95 (t, J = 5.3 Hz, 1H), 3.99 (s, 1H), 3.85 (s, 1H), 3.77 (s, 6H), 3.66 – 3.58 (m, 3H), 3.50 (d, J = 8.2 Hz, 1H), 2.23 (s, 1H), 2.11 (s, 1H), 0.84 (d, J = 7.6 Hz, 2H), 0.65 (s, 2H). MS (ESI, *m/z*): 498.2 $[M+H]^+$.

Example 176

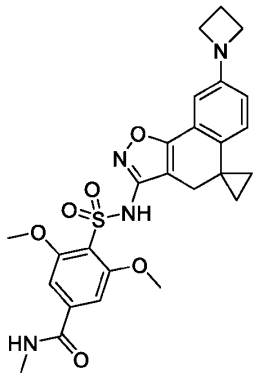
(R)-N-(8'-(2-(hydroxymethyl)azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide



[0986] Example 176 was prepared according to the procedure as described in Example 31, starting from Example 15 and (R)-azetidin-2-ylmethanol from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.6 (s, 1H), 7.46 (s, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.79 (s, 1H), 6.75 (d, J = 8.5 Hz, 2H), 6.56 (d, J = 7.3 Hz, 1H), 4.95 (t, J = 5.3 Hz, 1H), 3.99 (s, 1H), 3.85 (s, 1H), 3.77 (s, 6H), 3.66 – 3.58 (m, 3H), 3.50 (d, J = 8.2 Hz, 1H), 2.23 (s, 1H), 2.11 (s, 1H), 0.84 (d, J = 7.6 Hz, 2H), 0.65 (s, 2H). MS (ESI, *m/z*): 498.2 $[M+H]^+$.

Example 177

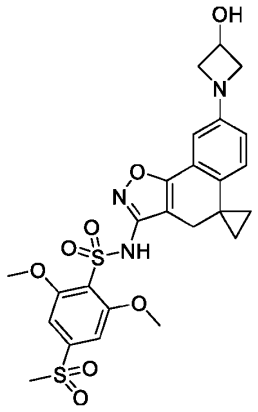
4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



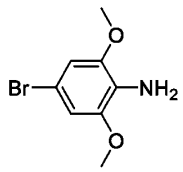
[0987] A mixture of 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (700 mg, 1.277 mmol, 1.00 equiv, Intermediate G), azetidine (728 mg, 12.77 mmol, 10.0 equiv), Pd-PEPPSI-IHept (249 mg, 0.255 mmol, 0.20 equiv) and Cs_2CO_3 (833 mg, 2.555 mmol, 2.00 equiv) in NMP (12 mL) was stirred at 100 °C for 4 h under N_2 atmosphere. The resulting mixture was diluted with EtOAc. The organic solution was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (0-70% acetonitrile in water (contained 0.1% formic acid)) and further purified by Prep-HPLC (10-35% acetonitrile in water (contained 0.1% formic acid)) to afford 4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (132.2 mg, 19.7% yield) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.74 (br s, 1H), 8.67 – 8.57 (m, 1H), 7.14 (s, 2H), 6.86 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 6.38 (dd, J = 8.4, 2.4 Hz, 1H), 3.84 (s, 6H), 3.78 (t, J = 7.2 Hz, 4H), 3.76 (s, 1H), 2.79 (d, J = 4.5 Hz, 3H), 2.35-2.20 (m, 2H), 2.07 (s, 2H), 0.89 – 0.62 (m, 4H). MS (ESI, m/z): 523.3 $(M-H)^-$.

Example 178

N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(methylsulfonyl)benzenesulfonamide

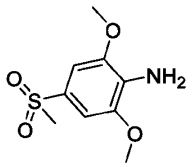


[0988] Step 1. Synthesis of 4-bromo-2,6-dimethoxyaniline



[0989] To a stirred mixture of 2,6-dimethoxyaniline (5.0 g, 32.64 mmol, 1.00 equiv) in chloroform (150.0 mL) at 0 °C was added dropwise a solution of Br_2 (5.2 g, 32.64 mmol, 1.00 equiv) in chloroform (10.0 mL) over 10 min. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 16 h. The reaction mixture was basified with NaOH (1.0 M) to pH ~11 and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another batch (10.0 g scale) and purified by flash chromatography on silica gel (0~50% EtOAc in petroleum ether) to afford 4-bromo-2,6-dimethoxyaniline (17.2 g, 76% yield) as a brown solid. MS (ESI, *m/z*): 232, 234 [M+H]+.

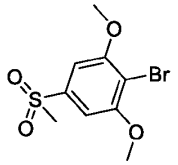
[0990] Step 2. Synthesis of 2,6-dimethoxy-4-(methylsulfonyl)aniline



[0991] A mixture of 4-bromo-2,6-dimethoxyaniline (1.0 g, 4.30 mmol, 1.00 equiv), sodium methanesulfinate (0.7 g, 6.46 mmol, 1.5 equiv), CuI (0.3 g, 1.29 mmol, 0.30 equiv) and NaOH (0.2 g, 4.30 mmol, 1.00 equiv) in DMSO (10.0 mL) was stirred at 95 °C for 16

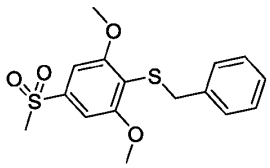
h under N_2 atmosphere. The resulting mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another batch (17.2 g scale) and purified by flash chromatography on silica gel (0~100% EtOAc in petroleum ether) to afford 4-methanesulfonyl-2,6-dimethoxyaniline (8.6 g, 47% yield) as a yellow solid. MS (ESI, *m/z*): 232 [M+H]+.

[0992] Step 3. Synthesis of 2-bromo-1,3-dimethoxy-5-(methylsulfonyl)benzene



[0993] A mixture of 4-methanesulfonyl-2,6-dimethoxyaniline (4.0 g, 17.29 mmol, 1.00 equiv), *t*-BuONO (2.7 g, 25.94 mmol, 1.50 equiv) and $CuBr_2$ (5.8 g, 25.94 mmol, 1.50 equiv) in acetonitrile (40.0 mL) was stirred at 60 °C for 2 h under N_2 atmosphere. The resulting mixture was filtered through a pad celite. The filtrate was concentrated under vacuum. The residue was combined with another batch (same scale) and purified by flash chromatography on silica gel (0~50% EtOAc in petroleum ether) to afford 2-bromo-5-methanesulfonyl-1,3-dimethoxybenzene (7.1 g, 70% yield) as a light yellow solid. MS (ESI, *m/z*): 295, 297 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.21 (s, 2H), 3.96 (s, 6H), 3.29 (s, 3H).

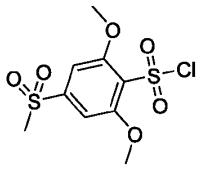
[0994] Step 4. Synthesis of benzyl(2,6-dimethoxy-4-(methylsulfonyl)phenyl)sulfane



[0995] A mixture of 2-bromo-5-methanesulfonyl-1,3-dimethoxybenzene (6.0 g, 20.32 mmol, 1.00 equiv), phenylmethanethiol (3.8 g, 30.49 mmol, 1.50 equiv), $Pd_2(dba)_3$ (2.3 g, 4.06 mmol, 0.20 equiv), XantPhos (2.4 g, 4.06 mmol, 0.20 equiv) and DIEA (5.2 g, 40.65 mmol, 2.00 equiv) in dioxane (60.0 mL) was stirred at 100 °C for 16 h under N_2 atmosphere. The resulting mixture was cooled to room temperature and then added saturated NaHCO3 aqueous solution and stirred at ambient temperature for another 1 h under air condition. The resulting mixture was extracted with EtOAc three times, and the combined organic layers

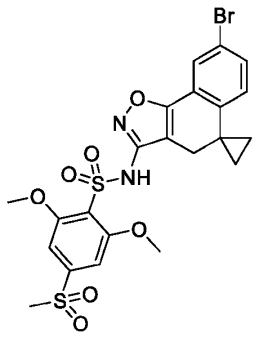
were dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another batch (1.0 g sacle) and was purified by flash chromatography on silica gel (0~100% EtOAc in petroleum ether) to afford 2-(benzylsulfanyl)-5-methanesulfonyl-1,3-dimethoxybenzene (6.9 g, 85% yield) as a yellow solid. MS (ESI, *m/z*): 339 [M+H]+.

[0996] Step 5. Synthesis of 2,6-dimethoxy-4-(methylsulfonyl)benzenesulfonyl chloride



[0997] To a stirred mixture of 2-(benzylsulfanyl)-5-methanesulfonyl-1,3-dimethoxybenzene (1.0 g, 2.95 mmol, 1.00 equiv) in AcOH (9.0 mL) and H_2O (3.0 mL) at 0 °C was added NCS (1.2 g, 8.86 mmol, 3.00 equiv) in portions. The resulting mixture was stirred at this temperature for another 2 h and then diluted with EtOAc. The organic solution was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another batch (2.0 g scale) and purified by trituration with petroleum ether to afford 4-methanesulfonyl-2,6-dimethoxybenzenesulfonyl chloride (2.2 g, 79% yield) as a yellow solid. MS (ESI, *m/z*): 315 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d6) δ 7.10 (s, 2H), 3.81 (s, 6H), 3.24 (s, 3H).

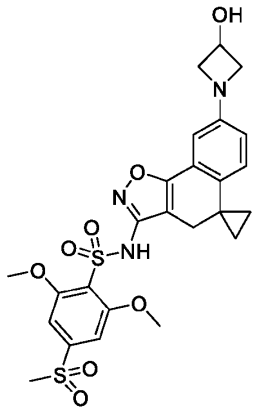
[0998] Step 6. Synthesis of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(methylsulfonyl)benzenesulfonamide



[0999] A mixture of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-amine (100.0 mg, 0.34 mmol, 1.00 equiv, Intermediate C) and 4-methanesulfonyl-2,6-dimethoxybenzenesulfonyl chloride (216.0 mg, 0.68 mmol, 2.00 equiv) in pyridine (1.0

mL) was stirred at 80 °C for 2 h and then concentrated under vacuum. The residue was re-dissolved in DCM. The organic solution was washed with aqueous HCl (1 M) three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another batch (same scale) and purified by flash chromatography on silica gel (0~60% EtOAc in DCM) to afford N-{8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}-4-methanesulfonyl-2,6-dimethoxybenzenesulfonamide (256.0 mg, 65% yield) as a yellow solid. MS (ESI, *m/z*): 569, 571 [M+H]+.

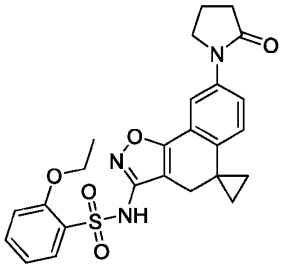
[1000] Step 7. Synthesis of N-[8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]-4-methanesulfonyl-2,6-dimethoxybenzenesulfonamide



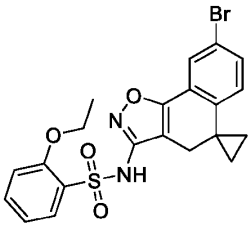
[1001] A mixture of N-{8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}-4-methanesulfonyl-2,6-dimethoxybenzenesulfonamide (100.0 mg, 0.18 mmol, 1.00 equiv), azetidin-3-ol (51.3 mg, 0.71 mmol, 4.00 equiv), Pd-PEPPSI-IHeptCl (18.2 mg, 0.02 mmol, 0.10 equiv) and Cs_2CO_3 (114.0 mg, 0.35 mmol, 2.00 equiv) in NMP (1.0 mL) was stirred at 100 °C for 2 h under N_2 atmosphere. The resulting mixture was combined with another batch (same scale) and purified directly by reverse phase flash chromatography on C18 gel (5~50% acetonitrile in water (10 mmol/L NH_4HCO_3) to afford N-[8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]-4-methanesulfonyl-2,6-dimethoxybenzenesulfonamide (31.0 mg, 15% yield) as a light yellow solid. MS (ESI, *m/z*): 562 [M+H]+.^{1}H NMR (300 MHz, DMSO-d_6) δ 10.92 (br s, 1H), 7.23 (s, 2H), 6.87 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 2.4 Hz, 1H), 6.45-6.36 (m, 1H), 5.61 (d, J = 6.6 Hz, 1H), 4.56-4.47 (m, 1H), 4.08 (t, J = 7.2 Hz, 2H), 3.90 (s, 6H), 3.54-3.45 (m, 2H), 3.33 (s, 3H), 2.54 (s, 2H), 0.93-0.81 (m, 2H), 0.72-0.66 (m, 2H).

Example 179

2-Ethoxy-N-(8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide

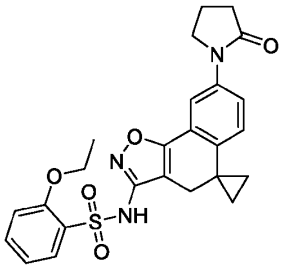


[1002] Step 1. Synthesis of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-ethoxybenzenesulfonamide



[1003] A solution of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (150 mg, 515 µmol, Intermediate C) and o-(chlorosulfonyl)ethoxybenzene (114 mg, 515 µmol) in pyridine (5.15 mL) was stirred at rt for 16 hours. Reaction mixture concentrated and purified via reverse phase flash column chromatography (MeCN (0.1 % FA) in H2O (0.1 % FA), 10-100 %)) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-ethoxybenzenesulfonamide as a white solid (91 mg, 37% yield). ESI, *m/z*): 474.1, 476.1 [M+H]+

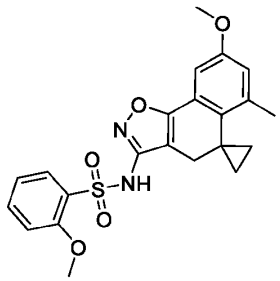
[1004] Step 2. Synthesis of 2-ethoxy-N-(8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[1005] A solution of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-ethoxybenzenesulfonamide (91 mg, 191 μmol), 2-pyrrolidinone (16.3 mg, 191 μmol), 2-pyrrolidinone (16.3 mg, 191 μmol) and dicaesium carbonate (187 mg, 3 eq., 574 μmol) in 1,4-dioxane (1.91 mL, 22.4 mmol) was sparged with N2 gas for 10 minutes before adding 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (22.2 mg, 0.2 eq., 38.3 μmol) tris(dibenzylideneacetone)dipalladium(0) (17.5 mg, 0.1 eq., 19.1 μmol). The mixture was heated at 100 °Cfor 16 h and concentrated. The mixture was purified via reverse phase flash column chromatography (MeCN (0.1 % FA) in water (0.1 % FA), 10-100 %)) to afford 2-ethoxy-N-(8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide (35.8 mg, 39 % yield) as an orange solid MS (ESI, *m/z*): 480.0 [M+H]+. 1H NMR (400 MHz, DMSO) δ 10.78 (s, 1H), 7.92 (s, 1H), 7.84 – 7.77 (m, 1H), 7.62 – 7.50 (m, 2H), 7.21 (s, 1H), 7.07 (d, J = 8.5 Hz, 2H), 4.11 (dd, J = 17.1, 6.2 Hz, 2H), 3.84 (t, J = 7.0 Hz, 2H), 2.61 (s, 2H), 2.05 (p, J = 7.6 Hz, 2H), 1.23 (t, J = 6.9 Hz, 3H), 0.96 (s, 2H), 0.80 (s, 2H).

Example 180

2-Methoxy-N-(8'-methoxy-6'-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide

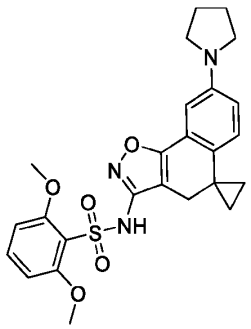


[1006] A solution of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide, methylboranediol (12.9 mg, 216 μmol, 1.00 eq, Example

49) and dicaesium carbonate (211 mg, 3 eq., 649 µmol) in 1,4-dioxane (2.16 mL, 25.4 mmol) was sparged with N2 gas for 15 minutes. Pd(dppf)Cl2 (31.7 mg, 0.2 eq., 43.3 µmol) was added and the mixture heated at 100 degrees for 2 h. The resulting mixture was concentrated under reduced pressure and purified on reverse phase column chromatography (10 -90 % MeCN (0.1 % FA) in water (0.1 % FA)) to afford 2-methoxy-N-(8'-methoxy-6'-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide (10.8 mg, 12 % yield) as a pale yellow solid. MS (ESI, *m/z*): 427.0 [M+H]+. 1H NMR (400 MHz, CD3CN) δ 7.76 (dd, J = 7.9, 1.8 Hz, 1H), 7.66 – 7.55 (m, 1H), 7.17 (d, J = 8.3 Hz, 1H), 7.08 – 6.98 (m, 2H), 6.70 (d, J = 2.8 Hz, 1H), 3.97 (s, 3H), 3.76 (s, 4H), 2.36 (s, 3H), 1.00 (q, J = 4.6 Hz, 2H), 0.84 – 0.75 (m, 2H).

Example 181

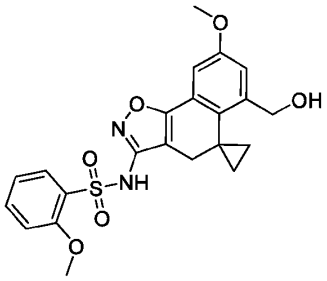
2,6-Dimethoxy-N-(8'-(pyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



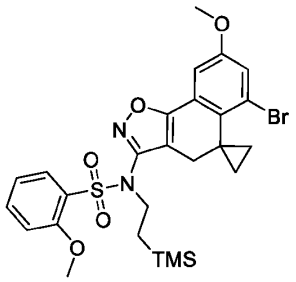
[1007] Example 181 was prepared according to the procedure as described in Example 31, starting from Example 15 and pyrrolidine. ^{1}H NMR (400 MHz, CD3CN) δ 7.49 (t, J = 8.5 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 6.78 – 6.65 (m, 3H), 6.53 (dd, J = 8.7, 2.6 Hz, 1H), 3.88 (s, 6H), 3.28 – 3.20 (m, 4H), 2.57 (s, 2H), 1.97 (q, J = 3.4 Hz, 4H), 0.95 – 0.75 (m, 2H), 0.75 – 0.65 (m, 2H). MS (ESI, *m/z*): 482.0 $[M+H]^+$.

Example 182

N-(6'-(hydroxymethyl)-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

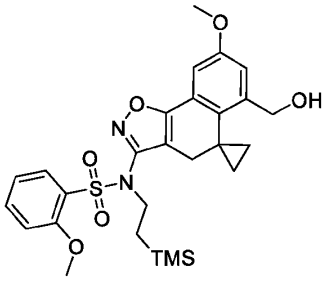


[1008] Step 1. Synthesis of N-(6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide



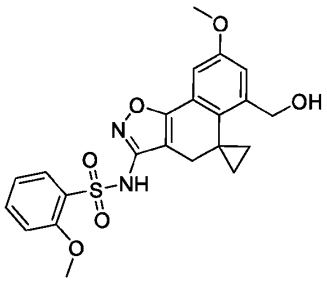
[1009] To a solution of N-(6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (0.2 g, 407 µmol, Example 49), 2-(trimethylsilyl)ethanol (117 µL, 2 eq., 814 µmol) and triphenylphosphine (214 mg, 2 eq., 814 µmol) in tetrahydrofuran (2.71 mL, 33.3 mmol) at 0 degrees was added (isopropyl)(oxycarbonylamino) 2-propanecarbamate (0.4 mL, 5 eq., 2.04 mmol) portionwise. The reaction was allowed to warm to ambient temperature and stirred for 4. Reaction mixture was concentrated under reduced pressure and purified using normal phase column chromatography (0-100 % EtOAc in hexanes) to afford N-(6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (150 mg, 63 % yield) as a pale yellow gum. MS (ESI, *m/z*): 591/593 [M+H]+.

[1010] Step 2. Synthesis of N-(6'-(hydroxymethyl)-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide



[1011] A solution of N-(6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide, and (tributylstannyl)methanol (163 mg, 2 eq., 507 μmol) in 1,4-dioxane (2.54 mL, 29.7 mmol) was sparged with N2 gas for 15 minutes. $Pd(PPh_3)_4$ (58.6 mg, 0.2 eq., 50.7 μmol) was added and the mixture heated at 100 degrees for 16 h. The resulting mixture was concentrated under reduced pressure and purified using normal phase column chromatography (0-100 % EtOAc in hexanes) to afford N-(6'-(hydroxymethyl)-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (23 mg, 17 % yield) as a pale yellow solid. MS (ESI, *m/z*): 543.2 [M+H]+.

[1012] Step 3. Synthesis of N-(6'-(hydroxymethyl)-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

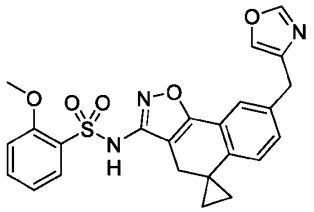


[1013] A solution of (N-(6'-(hydroxymethyl)-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (23 mg, 42.4 μmol) and tetrabutylammonium fluoride (111 mg, 10 eq., 424 μmol) in tetrahydrofuran (1 mL, 12.3 mmol) was heated at 60 degrees for 16h. Reaction concentrated and purified using reverse phase flash column chromatography (10-70 % MeCN (0.1 % FA) in water (0.1 % FA) to afford N-(6'-(hydroxymethyl)-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (11.3 mg, 60 % yield) as a pale yellow solid. MS (ESI, *m/z*): 443.0 [M+H]+. 1H NMR (400 MHz, CD3CN) δ 7.76 (dd, J = 7.8, 1.7

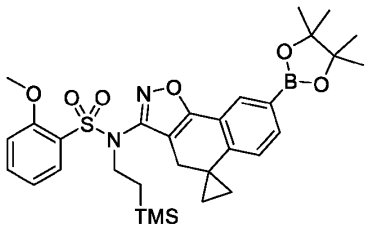
Hz, 1H), 7.61 (td, J = 8.0, 1.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.10 – 6.99 (m, 2H), 6.98 (d, J = 2.9 Hz, 1H), 4.62 (s, 2H), 3.97 (s, 3H), 3.78 (s, 3H), 2.42 (s, 2H), 1.08 – 1.00 (m, 2H), 0.80 – 0.72 (m, 2H).

Example 183

2-Methoxy-N-(8'-(oxazol-4-ylmethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide

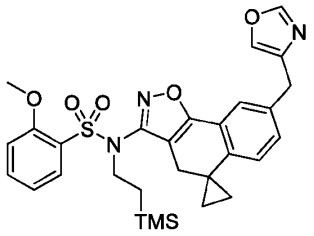


[1014] Step 1. Synthesis of 2-methoxy-N-(8'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide



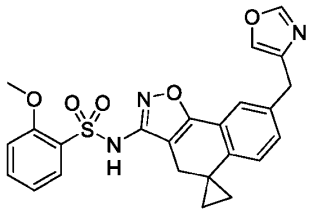
[1015] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (500.0 mg, 0.89 mmol, 1.00 equiv, Intermediate J), 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (271.0 mg, 1.07 mmol, 1.20 equiv), $Pd(dppf)Cl_2.CH_2Cl_2$ (73.0 mg, 0.09 mmol, 0.10 equiv) and AcOK (262.0 mg, 2.67 mmol, 3.00 equiv) in 1,4-dioxane (5.0 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~50% EtOAc in petroleum ether) to afford 2-methoxy-N-(8'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (360.0 mg, 87% yield) as yellow oil. MS (ESI, *m/z*): 609 [M+H]+.

[1016] Step 2. Synthesis of 2-methoxy-N-(8'-(oxazol-4-ylmethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide



[1017] A mixture of 2-methoxy-N-(8'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (340.0 mg, 0.56 mmol, 1.00 equiv), 4-(chloromethyl)oxazole hydrochloride (258.0 mg, 1.68 mmol, 3.00 equiv), $Pd(PPh_3)_2Cl_2$ (78.0 mg, 0.11 mmol, 0.20 equiv) and K_2CO_3 (232.0 mg, 1.67 mmol, 3.00 equiv) in THF (8.0 mL) and H_2O (1.0 mL) was stirred at 65 °C for 3 h under N_2 atmosphere. The resulting mixture was allowed to cool down to ambient temperature and then diluted with EtOAc. The mixture was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5~40% acetonitrile in water (contained 0.05% formic acid)) to afford 2-methoxy-N-(8'-(oxazol-4-ylmethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (100.0 mg, 32% yield) as brown oil. MS (ESI, *m/z*): 564 [M+H]+.

[1018] Step 3. Synthesis of 2-methoxy-N-(8'-(oxazol-4-ylmethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide

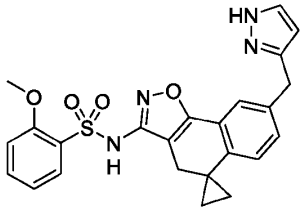


[1019] A solution of 2-methoxy-N-[8'-(1,3-oxazol-4-ylmethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]-N-[2-(trimethylsilyl)ethyl]benzenesulfonamide (90.0 mg, 0.16 mmol, 1.00 equiv) and TBAF (83.4 mg, 0.32 mmol, 2.00 equiv) in THF (5 mL) was stirred at 60 °C for 1 h. The mixture was concentrated under vacuum. The residue was

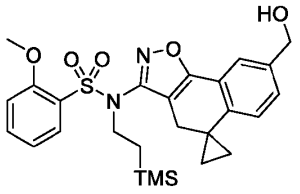
purified by reverse phase flash chromatography on C18 gel (5~40% acetonitrile in water (contained 0.05% formic acid)) to afford 2-methoxy-N-[8'-(1,3-oxazol-4-ylmethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]benzenesulfonamide (20.3 mg, 28% yield) as a white solid. MS (ESI, *m/z*): 464 [M+H]+.^{1}H NMR (300 MHz, DMSO-d6) δ 10.84 (s, 1H), 8.27 (s, 1H), 7.88 (d, *J* = 1.2 Hz, 1H), 7.77 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.64-7.57 (m, 1H), 7.41 (d, *J* = 1.8 Hz, 1H), 7.24-7.18 (m, 2H), 7.10-7.03 (m, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 3.83 (s, 5H), 2.58 (s, 2H), 0.98-0.92 (m, 2H), 0.82-0.77 (m, 2H).

Example 184

N-(8'-((1H-pyrazol-3-yl)methyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

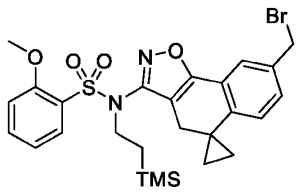


[1020] Step 1. Synthesis of N-(8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide



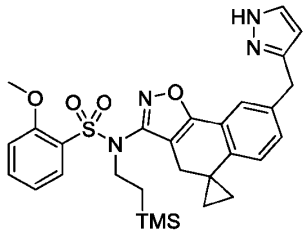
[1021] A solution of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (900.0 mg, 1.60 mmol, 1.00 equiv, Intermediate J), (tributylstannyl)methanol (566.0 mg, 1.76 mmol, 1.10 equiv) and XPhos Pd G_2 (126.0 mg, 0.16 mmol, 0.10 equiv) in dioxane (5.0 mL) was stirred at 100 °C for 2 h under N_2 atmosphere and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~50% EtOAc in petroleum ether) to afford N-(8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (473.7 mg, 57% yield) as yellow oil. MS (ESI, *m/z*): 513 [M+H]+.

[1022] Step 2. Synthesis of N-(8'-(bromomethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide



[1023] To a stirred solution of N-(8'-(hydroxymethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (600.0 mg, 1.17 mmol, 1.00 equiv) in DCM (6.0 mL) at 0 °C was added PBr_3 (158.0 mg, 0.58 mmol, 0.50 equiv). The resulting mixture was stirred at this temperature for 1 h and then quenched with water and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~50% EtOAc in petroleum ether) to afford N-(8'-(bromomethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (275.8 mg, 41% yield) as yellow oil. MS (ESI, *m/z*): 575, 577 [M+H]+.

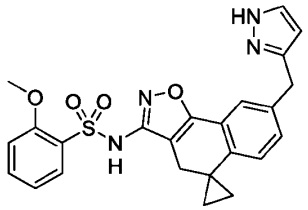
[1024] Step 3. Synthesis of N-(8'-((1H-pyrazol-3-yl)methyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide



[1025] A mixture of N-(8'-(bromomethyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (150.0 mg, 0.20 mmol, 1.00 equiv), tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (153.0 mg, 0.50 mmol, 2.00 equiv), $Pd(PPh_3)_4$ (30.0 mg, 0.02 mmol, 0.10 equiv) and Na_2CO_3 (55.0 mg, 0.50 mmol, 2.00 equiv) in DME (6.0 mL) and H_2O (2.0 mL) was stirred at 110 °C for 2 h under N_2 atmosphere. The resulting mixture was diluted with EtOAc. The mixture was washed with brine three times, dried over Na_2SO_4 and concentrated under

vacuum. The residue was purified by flash chromatography on silica gel (0-90% EtOAc in petroleum ether) to afford N-(8'-((1H-pyrazol-3-yl)methyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (120.0 mg, 82% yield) as colorless oil. MS (ESI, *m/z*): 563 [M+H]+.

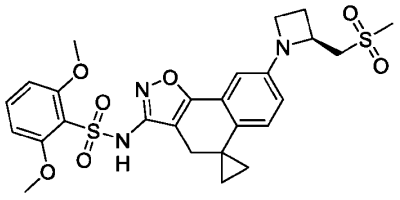
[1026] Step 4. Synthesis of N-(8'-((1H-pyrazol-3-yl)methyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide



[1027] A mixture of N-(8'-((1H-pyrazol-3-yl)methyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-(2-(trimethylsilyl)ethyl)benzenesulfonamide (110.0 mg, 0.10 mmol, 1.00 equiv) and TBAF (256.0 mg, 0.90 mmol, 5.00 equiv) in THF (3.0 mL) was stirred at ambient temperature for 1 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-100% acetonitrile in water (contained 0.5% NH_4HCO_3)) to afford N-(8'-((1H-pyrazol-3-yl)methyl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (12.4 mg, 13% yield) as a white solid. MS (ESI, *m/z*): 463 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d6) δ 12.56 (br s, 1H), 10.83 (br s, 1H), 7.76 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.65-7.55 (m, 1H), 7.47 (br s, 1H), 7.37 (d, *J* = 1.8 Hz, 1H), 7.19 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.09-7.00 (m, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.00 (d, *J* = 2.1 Hz, 1H), 3.90 (s, 2H), 3.81 (s, 3H), 2.55 (s, 2H), 0.98-0.88 (m, 2H), 0.81-0.71 (m, 2H).

Example 185

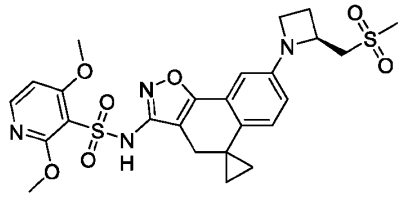
(S)-2,6-dimethoxy-N-(8'-(2-((methylsulfonyl)methyl)azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[1028] Example 185 was prepared according to the procedure as described in Example 31, starting from Example 15 and (S)-2-((methylsulfonyl)methyl)azetidine from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.37 (s, 1H), 7.39 (t, J = 8.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 2.4 Hz, 1H), 6.49 (dd, J = 8.4, 2.4 Hz, 1H), 4.45 – 4.32 (m, 1H), 4.00 – 3.90 (m, 1H), 3.85 – 3.69 (m, 7H), 3.68 – 3.53 (m, 2H), 3.03 (s, 3H), 2.47 – 2.37 (m, 4H), 0.90 – 0.77 (m, 2H), 0.72 – 0.61 (m, 2H). MS (ESI, *m/z*): 560.2 [M+H]+.

Example 186

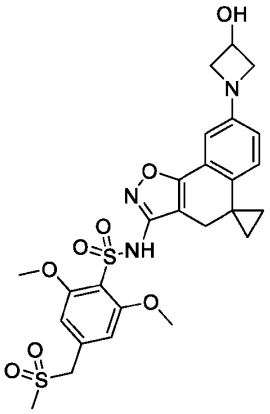
(S)-2,4-dimethoxy-N-(8'-(2-((methylsulfonyl)methyl)azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide



[1029] Example 186 was prepared according to the procedure as described in Example 31, starting from Example 103 and (S)-2-((methylsulfonyl)methyl)azetidine from a commercial source. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.91 (br s, 1H), 8.21 (d, J = 6.0 Hz, 1H), 6.94-6.86 (m, 2H), 6.68 (d, J = 2.4 Hz, 1H), 6.53 (dd, J = 8.4, 2.4 Hz, 1H), 4.46 – 4.34 (m, 1H), 4.01 – 3.92 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.82 – 3.74 (m, 1H), 3.66 – 3.53 (m, 2H), 3.04 (s, 3H), 2.58 – 2.37 (m, 4H), 0.94 – 0.79 (m, 2H), 0.76 – 0.66 (m, 2H). MS (ESI, *m/z*): 561.2 [M+H]+.

Example 187

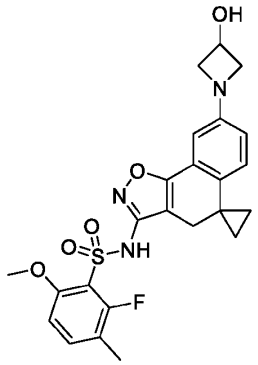
N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((methylsulfonyl)methyl)benzenesulfonamide



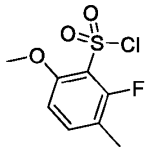
[1030] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((methylsulfonyl)methyl)benzenesulfonamide (150.0 mg, 0.25 mmol, 1.00 equiv, Intermediate F), azetidin-3-ol (56.0 mg, 0.77 mmol, 3.00 equiv), Pd-PEPPSI-IHeptCl (25.0 mg, 0.03 mmol, 0.10 equiv) and Cs_2CO_3 (168.0 mg, 0.52 mmol, 2.00 equiv) in NMP (5.0 mL) was stirred at 80 °C for 4 h under N_2 atmosphere. The resulting mixture was directly purified by reverse phase flash chromatography on C18 gel (0-80% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((methylsulfonyl)methyl)benzenesulfonamide (59.6 mg, 40% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.70 (br s, 1H), 6.90-6.80 (m, 3H), 6.58 (d, J = 2.4 Hz, 1H), 6.40 (dd, J = 8.4, 2.4 Hz, 1H), 5.60 (d, J = 6.6 Hz, 1H), 4.6-4.46 (m, 3H), 4.12-4.01 (m, 2H), 3.78 (s, 6H), 3.48 (dd, J = 7.8, 5.1 Hz, 2H), 3.33 (s, 3H), 2.95 (s, 2H), 0.89-0.80 (m, 2H), 0.72-0.62 (m, 2H). MS (ESI, *m/z*): 576 [M+H]+.

Example 188

2-fluoro-N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-6-methoxy-3-methylbenzenesulfonamide

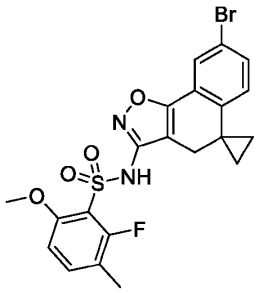


[1031] Step 1. Synthesis of 2-fluoro-6-methoxy-3-methylbenzenesulfonyl chloride



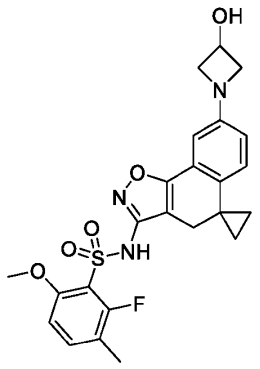
[1032] To a stirred solution of DIPA (2.2 g, 21.41 mmol, 1.50 equiv) in THF (10.0 mL) at -78 °C was added dropwise n-BuLi (2.5 M in n-hexane, 8.6 mL, 2.5 mmol, 1.50 equiv) over 10 min under N_2 atmosphere. The resulting mixture was stirred at this temperature for another 10 min and to this was added dropwise a solution of 2-fluoro-4-methoxy-1-methylbenzene (2.00 g, 14.27 mmol, 1.00 equiv) in THF (10 mL) over 10 min. The resulting mixture was stirred for another 30 min and to this was added sulfur (0.50 g, 15.70 mmol, 1.10 equiv). The resulting mixture was allowed to warm up to ambient temperature and the stirred for 2 h. To this at 0 °C was added acetonitrile (20.0 mL), H_2O (4.0 mL), 1M HCl (aq) (4.0 mL) and NCS (5.6 g, 34.84 mmol, 3.0 equiv) sequentially. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 1 h and then diluted with EtOAc. The organic solution was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford 2-fluoro-6-methoxy-3-methylbenzenesulfonyl chloride (1.3 g, 47% yield) as a yellow solid. MS (ESI, *m/z*): 239 [M+H]+.

[1033] Step 2. Synthesis of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-fluoro-6-methoxy-3-methylbenzenesulfonamide



[1034] To a stirred solution of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (240.0 mg, 0.82 mmol, 1.00 equiv) in THF (2.0 mL) at -78 °C was added dropwise a solution of t-BuOK (1.0 M in THF, 3.3 mL, 3.30 mmol, 4.00 equiv) over 2 min under N_2 atmosphere. The resulting mixture was stirred at this temperature for 10 min and then to this was added 2-fluoro-6-methoxy-3-methylbenzenesulfonyl chloride (787.0 mg, 3.30 mmol, 4.00 equiv). The resulting mixture was stirred for another 1 h and then quenched with Saturated NH4Cl solution and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-fluoro-6-methoxy-3-methylbenzenesulfonamide (190.0 mg, 47% yield) as yellow oil. MS (ESI, *m/z*): 493, 495 [M+H]+.

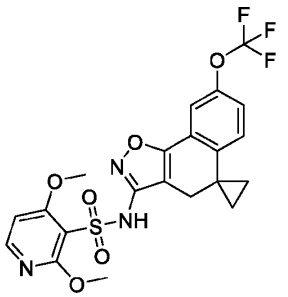
[1035] Step 3. Synthesis of 2-fluoro-N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-6-methoxy-3-methylbenzenesulfonamide



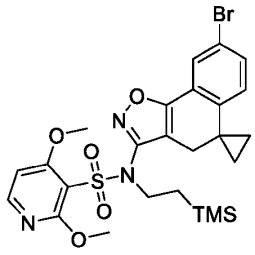
[1036] A mixture of N-{8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}-2-fluoro-6-methoxy-3-methylbenzenesulfonamide (170.0 mg, 0.35 mmol, 1.00 equiv), azetidin-3-ol (126.0 mg, 1.73 mmol, 5.0 equiv), EPhos Pd G4 (58.0 mg, 0.07 mmol, 0.20 equiv), EPhos (37.0 mg, 0.07 mmol, 0.2 equiv) and K2CO3 (225.0 mg, 0.69 mmol, 2.00 equiv) in dioxane (5.0 mL) was stirred at 100 °C for 1 h under N2 atmosphere and then diluted with EtOAc. The resulting mixture was extracted with water three times. The combined aqueous layers were concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (10-60% acetonitrile in water (contained 0.05% formic acid)) to afford 2-fluoro-N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-6-methoxy-3-methylbenzenesulfonamide (48.8 mg, 29% yield) as an off-white solid. MS (ESI, *m/z*): 486 [M+H]+. 1H NMR (300 MHz, DMSO-d6) δ 11.04 (br s, 1H), 7.49 (t, J = 8.4 Hz, 1H), 6.94 (dd, J = 8.7, 1.2 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 2.4 Hz, 1H), 6.40 (dd, J = 8.4, 2.4 Hz, 1H), 5.61 (d, J = 6.6 Hz, 1H), 4.60-4.48 (m, 1H), 4.12-4.01 (m, 2H), 3.48 (dd, J = 7.8, 5.1 Hz, 2H), 2.53 (s, 2H), 2.16 (d, J = 2.4 Hz, 3H), 0.91-0.74 (m, 2H), 0.74-0.65 (m, 2H). 19F NMR (282 MHz, DMSO-d6) δ -111.92.

Example 189

2,4-Dimethoxy-N-(8'-(trifluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide

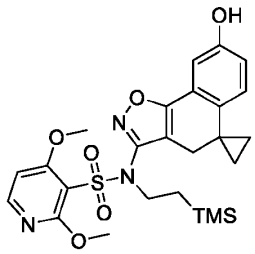


[1037] Step 1. Synthesis of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxy-N-(2-(trimethylsilyl)ethyl)pyridine-3-sulfonamide



[1038] To a stirred mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (1.4 g, 2.84 mmol, 1.00 equiv, **Example 103**), 2-(trimethylsilyl) ethanol (0.67 g, 5.68 mmol, 2.00 equiv), and PPh_3 (1.5 g, 5.69 mmol, 2.00 equiv) in THF (14.0 mL) at 0 °C was added DIAD (1.2 g, 5.68 mmol, 2.00 equiv) under N_2 atmosphere. The resulting mixture was stirred at ambient temperature for 2 h and then diluted with water and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxy-N-(2-(trimethylsilyl)ethyl)pyridine-3-sulfonamide (1.3 g, 77% yield) as brown oil. MS (ESI, *m/z*): 592, 594 [M+H]+.

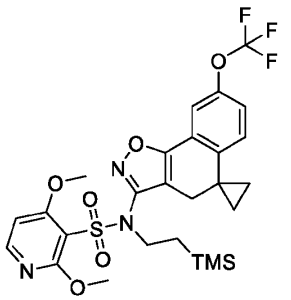
[1039] Step 2. Synthesis of N-(8'-hydroxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxy-N-(2-(trimethylsilyl)ethyl)pyridine-3-sulfonamide



[1040] A mixture of N-{8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}-2,4-dimethoxy-N-[2-(trimethylsilyl)ethyl]pyridine-3-sulfonamide (1.2 g, 2.02 mmol, 1.00 equiv), KOH (0.34 g, 6.07 mmol, 3.00 equiv), $Pd_2(dba)_3$ (0.2 g, 0.21 mmol, 0.10 equiv) and t-BuXPhos (0.1 g, 0.20 mmol, 0.10 equiv) in dioxane (10.0 mL) and H_2O (2.0 mL) was stirred at 100 °C for 2 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-80% acetonitrile in water (contained 0.05% formic acid)) to afford N-(8'-hydroxy-4'H-spiro[cyclopropane-1,5'-

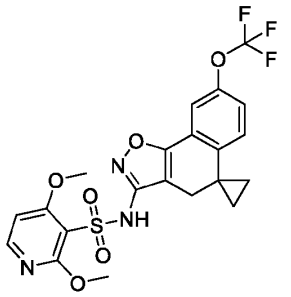
naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxy-N-(2-(trimethylsilyl)ethyl)pyridine-3-sulfonamide (540.0 mg, 50% yield) as yellow oil. MS (ESI, *m/z*): 530 [M+H]+.

[1041] Step 3. Synthesis of N-(9'-(difluoromethoxy)-5'H-spiro[cyclopropane-1,6'-[1,2,4]triazolo[3,4-a]isoquinolin]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide



[1042] A mixture of N-{8'-hydroxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}-2,4-dimethoxy-N-[2-(trimethylsilyl)ethyl]pyridine-3-sulfonamide (50.0 mg, 0.09 mmol, 1.00 equiv), $TMSCF_3$ (40.2 mg, 0.28 mmol, 3.00 equiv), 2-fluoropyridine (45.83 mg, 0.47 mmol, 5.00 equiv), $Ag(OTf)_2$ (121.0 mg, 0.47 mmol, 5.00 equiv), N-Fluorobenzenesulfonimide (60.0 mg, 0.18 mmol, 2.00 equiv), CsF (86.0 mg, 0.56 mmol, 6.00 equiv) and Selectfluor (66.9 mg, 0.19 mmol, 2.00 equiv) in toluene (1.6 mL) was stirred at ambient temperature for 16 h under N_2 atmosphere and then filtered. The filtrate was concentrated under vacuum. The residue was combined with another 5 batch (400.0 mg scale in total) and purified by reverse phase flash chromatography on C18 gel (5-40% acetonitrile in water (contained 0.1% formic acid)) to afford 2,4-dimethoxy-N-[8'-(trifluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]-N-[2-(trimethylsilyl)ethyl]pyridine-3-sulfonamide (260.0 mg, 51% yield) as a yellow solid. MS (ESI, *m/z*): 598 [M+H]+.

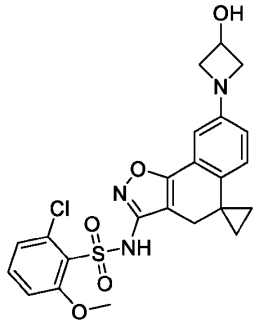
[1043] Step 4. Synthesis of 2,4-dimethoxy-N-(8'-(trifluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide



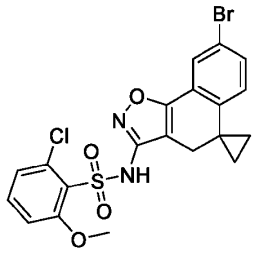
[1044] A mixture of 2,4-dimethoxy-N-[8'-(trifluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]-N-[2-(trimethylsilyl)ethyl]pyridine-3-sulfonamide (260.0 mg, 0.43 mmol, 1.00 equiv) and Cs_2CO_3 (425.0 mg, 1.30 mmol, 3.00 equiv) in DMSO (3.0 mL) was stirred at 100 °C for 1 h and then filtered. The filtrate was purified directly by reverse phase flash chromatography on C18 gel (5-70% acetonitrile in water (contained 0.1% formic acid)) and further purified by Prep-HPLC (44~61% acetonitrile in water (contained 0.1% formic acid)) to afford 2,4-dimethoxy-N-[8'-(trifluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]pyridine-3-sulfonamide (38.4 mg, 17% yield) as a white solid. MS (ESI, *m/z*): 480 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.01 (br s, 1H), 8.22 (d, J = 6.0 Hz, 1H), 7.53-7.44 (m, 1H), 7.35 (d, J = 8.7 Hz, 1H), 7.20 (d, J = 8.7 Hz, 1H), 6.93 (d, J = 6.0 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 2.67 (s, 2H), 1.14-0.99 (m, 2H), 0.93-0.78 (m, 2H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -56.95.

Example 190

2-Chloro-N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-6-methoxybenzenesulfonamide

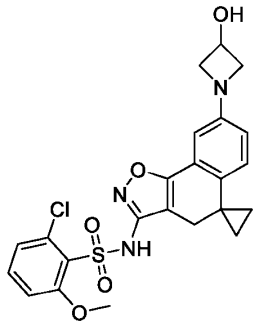


[1045] Step 1. Synthesis of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-chloro-6-methoxybenzenesulfonamide



[1046] A mixture of 2-chloro-6-methoxybenzenesulfonyl chloride (81.0 mg, 0.34 mmol, 1.50 equiv) and 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (65.0 mg, 0.22 mmol, 1.00 equiv) in pyridine (4.0 mL) was stirred at 80 °C for 2 h. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-80% acetonitrile in water) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-chloro-6-methoxybenzenesulfonamide (80.0 mg, 72% yield) as an off-white solid. MS (ESI, *m/z*): 495, 497 [M+H]+.

[1047] Step 2. Synthesis of 2-chloro-N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-6-methoxybenzenesulfonamide

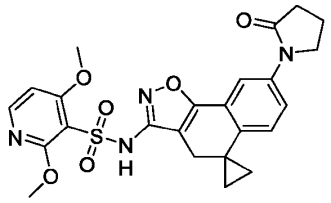


[1048] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-chloro-6-methoxybenzenesulfonamide (70.0 mg, 0.14 mmol, 1.00 equiv), azetidin-3-ol (31.0 mg, 0.42 mmol, 3.00 equiv), Pd-PEPPSI-IHeptCl (14.0 mg, 0.01 mmol, 0.10 equiv) and Cs_2CO_3 (138.0 mg, 0.42 mmol, 3.00 equiv) in NMP (5.0 mL) was stirred at 100 °C for 16 h under N_2 atmosphere. The resulting mixture was directly purified by reverse phase flash chromatography on C18 gel (5-70% acetonitrile in water (contain 0.1% formic acid) and further purified by flash chromatography on silica gel (0-80% EtOAc in petroleum ether) to afford 2-chloro-N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-

d]isoxazol]-3'-yl)-6-methoxybenzenesulfonamide (11.8 mg, 17% yield) as a white solid. MS (ESI, *m/z*): 488, 490 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.99 (br s, 1H), 7.54 (t, J = 8.4 Hz, 1H), 7.25-7.12 (m, 2H), 6.86 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 2.4 Hz, 1H), 6.41 (dd, J = 8.4, 2.4 Hz, 1H), 5.60 (d, J = 6.6 Hz, 1H), 4.61-4.46 (m, 1H), 4.11-4.01 (m, 2H), 3.86 (s, 3H), 3.48 (dd, J = 7.8, 5.1 Hz, 2H), 2.53 (s, 2H), 0.91-0.65 (m, 4H).

Example 191

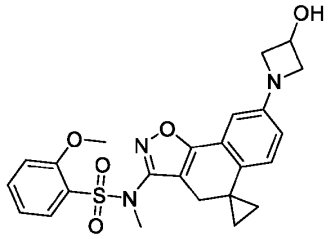
2,4-Dimethoxy-N-(8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide



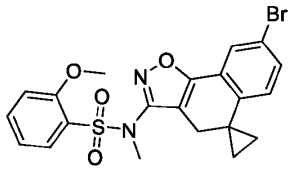
[1049] Example 191 was prepared according to the procedure as described in Example 31, starting from Example 103 and pyrrolidin-2-one from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.19 (d, J = 6.0 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.54 (dd, J = 8.7, 2.4 Hz, 1H), 7.06 (d, J = 8.7 Hz, 1H), 6.90 (d, J = 6.0 Hz, 1H), 3.93 – 3.75 (m, 8H), 3.78 (s, 1H), 2.59 (s, 2H), 2.49 – 2.43 (m, 1H), 2.13 – 1.97 (m, 2H), 1.01 – 0.92 (m, 2H), 0.83 – 0.74 (m, 2H). MS (ESI, *m/z*): 497.2 $[M+H]^+$.

Example 192

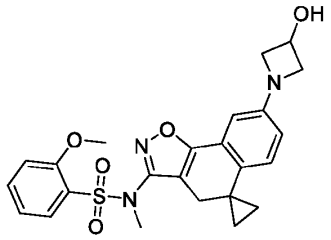
N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-methylbenzenesulfonamide



[1050] Step 1. Synthesis of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-methylbenzenesulfonamide



[1051] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (100.0 mg, 0.21 mmol, 1.00 equiv, Example 16), CH_3I (62.0 mg, 0.43 mmol, 2.00 equiv) and K_2CO_3 (90.0 mg, 0.65 mmol, 3.00 equiv) in acetonitrile (4.00 mL) was stirred at 80 °C for 2 h and then diluted with EtOAc. The resulting mixture was washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-methylbenzenesulfonamide (50.0 mg, 49% yield) as a yellow solid. MS (ESI, *m/z*): 475, 477 [M+H]+.**[1052]** Step 2. Synthesis of N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-methylbenzenesulfonamide

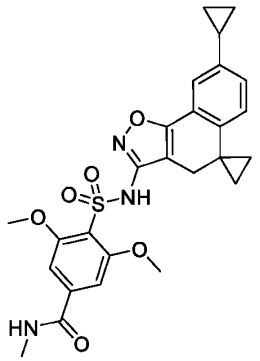


[1053] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-methylbenzenesulfonamide (50.0 mg, 0.105 mmol, 1.00 equiv), azetidin-3-ol (38.0 mg, 0.525 mmol, 5.00 equiv), Cs_2CO_3 (103.0 mg, 0.315 mmol, 3.00 equiv) and Pd-PEPPSI-IHept (9.0 mg, 0.011 mmol, 0.10 equiv) in NMP (2.00 mL) was stirred at 100 °C for 1 h under N_2 atmosphere. The resulting mixture was purified directly by reverse phase flash chromatography on C18 gel (0-70% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-(3-hydroxyazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxy-N-methylbenzenesulfonamide (22.9 mg, 46% yield) as an off-white solid. MS (ESI, *m/z*): 468 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.77 (dd, J = 7.8, 1.7 Hz, 1H), 7.72-7.63 (m, 1H), 7.25 (dd, J = 8.7, 1.2 Hz, 1H), 7.16-7.07 (m, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 6.44 (dd, J = 8.4, 2.4 Hz, 1H), 5.61 (d, J = 6.3 Hz, 1H),

4.64-4.47 (m, 1H), 4.14-4.04 (m, 2H), 3.68 (s, 3H), 3.51 (dd, *J* = 7.8, 5.1 Hz, 2H), 3.21 (s, 3H), 2.62 (s, 2H), 0.91-0.72 (m, 4H).

Example 194

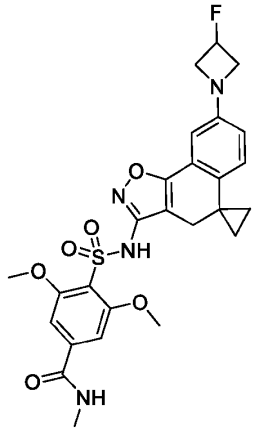
4-(N-(8'-cyclopropyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



[1054] A mixture of 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (150.0 mg, 0.27 mmol, 1.00 equiv, Intermediate G), cyclopropylboronic acid (94.0 mg, 1.09 mmol, 4.00 equiv), Pd(dppf)Cl2 (44.0 mg, 0.05 mmol, 0.20 equiv) and K_2CO_3 (75.0 mg, 0.54 mmol, 2.00 equiv) in dioxane (5.0 mL) and H_2O (1.0 mL) was stirred at 100 °C for 2 h under N2 atmosphere. The resulting mixture was directly purified by reverse phase flash chromatography (5-70% acetonitrile in water (contained 0.05% formic acid)) and further purified by Prep-HPLC (28-43% acetonitrile in water (contained 0.08% NH_4HCO_3)) to afford 4-(N-(8'-cyclopropyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (7.9 mg, 5% yield) as an off-white solid. MS (ESI, *m/z*): 510 [M+H]+. 1H NMR (300 MHz, DMSO-d6) δ 10.73 (br s, 1H), 8.61 (d, J = 4.8 Hz, 1H), 7.20 (d, J = 1.8 Hz, 1H), 7.13 (s, 2H), 7.07-6.97 (m, 1H), 6.91 (d, J = 8.1 Hz, 1H), 3.82 (s, 6H), 2.78 (d, J = 4.5 Hz, 3H), 2.55 (s, 2H), 1.98-1.84 (m, 1H), 0.97-0.77 (m, 4H), 0.77-0.59 (m, 4H).

Example 195

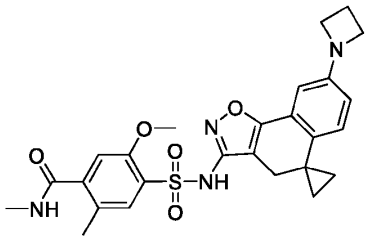
4-(N-(8'-(3-fluoroazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



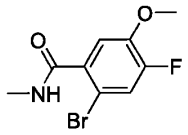
[1055] A mixture of 4-({8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (350.00 mg, 0.638 mmol, 1.00 equiv, Intermediate G), 3-fluoroazetidine hydrochloride (427.00 mg, 3.828 mmol, 6.00 equiv), EPhos Pd G4 (117.00 mg, 0.128 mmol, 0.20 equiv), EPhos (68.00 mg, 0.128 mmol, 0.20 equiv) and sodium benzenolate (593.0 mg, 5.104 mmol, 8.00 equiv) in NMP (20.00 mL) was stirred at 100 oC for 1 h under N2 atmosphere. The resulting mixture was directly purified by reverse phase flash chromatography on C18 gel (5---40% acetonitrile in water (contained 0.1% formic acid)) and further purified by reverse phase flash chromatography on C18 gel (5---40% acetonitrile in water (contained 0.05% NH_4HCO_3)) to afford 4-{[8'-(3-fluoroazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]sulfamoyl}-3,5-dimethoxy-N-methylbenzamide (148.8 mg, 43% yield) as a white solid. MS (ESI, *m/z*): 543 [M+H]+ . 1H NMR (300 MHz, DMSO-d6) δ 10.76 (s, 1H), 8.63 (d, J = 4.8 Hz, 1H), 7.14 (s, 2H), 6.89 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 6.45 (dd, J = 8.4, 2.4 Hz, 1H), 5.64-5.29 (m, 1H), 4.26-4.02 (m, 2H), 3.96-3.87 (m, 1H), 3.87-3.71 (m, 7H), 2.79 (d, J = 4.5 Hz, 3H), 2.53 (s, 2H), 0.91-0.81 (m, 2H), 0.75-0.63 (m, 2H). 19F NMR (282 MHz, DMSO-d6) δ -179.22.

Example 196

4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-5-methoxy-N,2-dimethylbenzamide

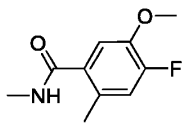


[1056] Step 1. Synthesis of 2-bromo-4-fluoro-5-methoxy-N-methylbenzamide



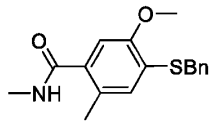
[1057] To a stirred mixture of 2-bromo-4-fluoro-5-methoxybenzoic acid (10.0 g, 40.15 mmol, 1.00 equiv), hydroxylamine hydrochloride (5.6 g, 80.31 mmol, 2.00 equiv) and HATU (30.4 g, 80.31 mmol, 2.00 equiv) in DMF (100.0 mL) at 0 °C was added DIEA (10.5 g, 80.31 mmol, 2.00 equiv). The resulting mixture was stirred at ambient temperature for 2 h and diluted with water and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~50% EtOAc in petroleum ether) to afford 2-bromo-4-fluoro-5-methoxy-N-methylbenzamide (10.0 g, 95% yield) as a white solid. MS (ESI, *m/z*): 262, 264 [M+H]+.

[1058] Step 2. Synthesis of 4-fluoro-5-methoxy-N,2-dimethylbenzamide



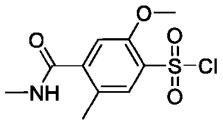
[1059] A mixture of 2-bromo-4-fluoro-5-methoxy-N-methylbenzamide (9.0 g, 34.34 mmol, 1.00 equiv), $Pd(dppf)Cl_2CH_2Cl_2$ (5.6 g, 6.86 mmol, 0.20 equiv) and Cs_2CO_3 (22.3 g, 68.68 mmol, 2.00 equiv), trimethyl-1,3,5,2,4,6-trioxatriborinane (8.6 g, 68.68 mmol, 2.00 equiv) in dioxane (90.0 mL) and H_2O (10.0 mL) was stirred at 100 °C for 2 h under N_2 atmosphere and then filtered. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5~70% acetonitrile in water (contained 0.1% formic acid)) to afford 4-fluoro-5-methoxy-N,2-dimethylbenzamide (3.5 g, 51% yield) as a yellow solid. MS (ESI, *m/z*): 198 [M+H]+.

[1060] Step 3. Synthesis of 4-(benzylthio)-5-methoxy-N,2-dimethylbenzamide



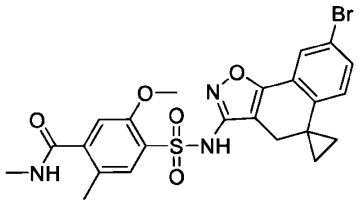
[1061] A mixture of 4-fluoro-5-methoxy-N,2-dimethylbenzamide (3.5 g, 17.74 mmol, 1.00 equiv), K_2CO_3 (4.9 g, 35.49 mmol, 2.00 equiv) and benzyl mercaptan (2.6 g, 21.29 mmol, 1.20 equiv) in DMF (35.0 mL) was stirred at 100 °C for 16 h under nitrogen and then filtered. The filtrate was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~40% EtOAc in petroleum ether) to afford 4-(benzylsulfanyl)-5-methoxy-N,2-dimethylbenzamide (3.3 g, 30% yield) as a yellow semi-solid. MS (ESI, *m/z*): 302 [M+H]+.

[1062] Step 4. Synthesis of 2-methoxy-5-methyl-4-(methylcarbamoyl)benzenesulfonyl chloride



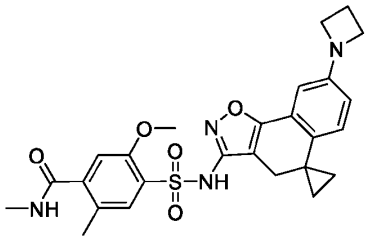
[1063] To a stirred mixture of 4-(benzylsulfanyl)-5-methoxy-N,2-dimethylbenzamide (4.0 g, 13.27 mmol, 1.00 equiv) in AcOH (30.0 mL) and H_2O (10.0 mL) at 0 °C was added NCS (3.6 g, 26.54 mmol, 2.00 equiv). The resulting mixture was stirred at ambient temperature for 2 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~80% EtOAc in petroleum ether) to afford 2-methoxy-5-methyl-4-(methylcarbamoyl)benzenesulfonyl chloride (1.7 g, 47% yield) as a yellow semi-solid. MS (ESI, *m/z*): 278, 280 [M+H]+.

[1064] Step 5. Synthesis of 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-5-methoxy-N,2-dimethylbenzamide



[1065] A mixture of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-amine (150.0 mg, 0.51 mmol, 1.00 equiv) and 2-methoxy-5-methyl-4-(methylcarbamoyl)benzenesulfonyl chloride (572.3 mg, 2.06 mmol, 4.00 equiv) in pyridine (2.0 mL) was stirred at 80 °C for 2 h and then concentrated under vacuum. The resulting solution was acidified with AcOH to pH 4 and extracted with DCM three times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~70% EtOAc in petroleum ether) to afford 4-({8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}sulfamoyl)-5-methoxy-N,2-dimethylbenzamide (60.0 mg, 21% yield) as an off-white solid. MS (ESI, *m/z*): 532, 534 [M+H]+.

[1066] Step 6. Synthesis of 4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-5-methoxy-N,2-dimethylbenzamide

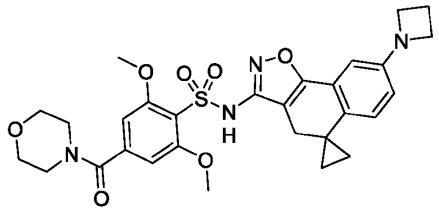


[1067] A mixture of 4-({8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}sulfamoyl)-5-methoxy-N,2-dimethylbenzamide (160.0 mg, 0.30 mmol, 1.00 equiv), azetidine (171.6 mg, 3.01 mmol, 10.00 equiv), Pd-PEPPSI-IHeptCl (58.5 mg, 0.06 mmol, 0.20 equiv) and Cs_2CO_3 (195.8 mg, 0.60 mmol, 2.00 equiv) in NMP (2.0 mL) was stirred at 100 °C for 1 h under N_2 atmosphere. The resulting mixture was purified by reverse phase flash chromatography on C18 gel (5~40% acetonitrile in water (contained 0.1% NH_4HCO_3)) and further purified by Prep-HPLC (36% ~51% acetonitrile in water (contained 0.1% formic acid)) to afford 4-{[8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]sulfamoyl}-5-methoxy-N,2-dimethylbenzamide (21.4 mg, 14% yield) as

a light yellow solid. MS (ESI, *m/z*): 509 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.92 (s, 1H), 8.28-8.37 (m, 1H), 7.62 (s, 1H), 7.08 (s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 6.39 (dd, J = 8.4, 2.4 Hz, 1H), 3.93-3.69 (m, 7H), 2.75 (d, J = 4.5 Hz, 3H), 2.55 (s, 2H), 2.34-2.22 (m, 5H), 0.90-0.81 (m, 2H), 0.78-0.66 (m, 2H).

Example 197

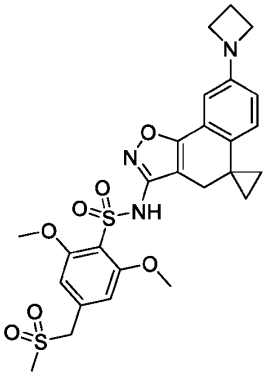
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonamide



[1068] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonamide (500 mg, 0.827 mmol, 1.00 equiv, Intermediate K), azetidine (141.68 mg, 2.481 mmol, 3.00 equiv), Pd-PEPPSI-IHeptCl (80.55 mg, 0.083 mmol, 0.10 equiv) and Cs_2CO_3 (539.02 mg, 1.654 mmol, 2.00 equiv) in NMP (10 mL) was stirred at 100 °C for 1 h under N_2 atmosphere. The resulting mixture was combined with another 7 batches (same scale) and then diluted with water, acidified with AcOH to pH ~ 4 and extracted with EtOAc three times. The combined organic layers were washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) and further purified by reverse phase chromatography on C18 gel (0-50% acetonitrile in water) to afford N-[8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]-2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonamide (1.1 g, 29.59% yield) as a light yellow solid. MS (ESI, *m/z*): 581 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.72 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.76 (s, 2H), 6.56 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 8.4, 2.4 Hz, 1H), 3.87-3.73 (m, 10H), 3.70-3.45 (m, 6H), 3.25 (br s, 2H), 2.52 (s, 2H), 2.35-2.20 (m, 2H), 2.07 (s, 3H), 0.90-0.80 (m, 2H), 0.71-0.62 (m, 2H).

Example 198

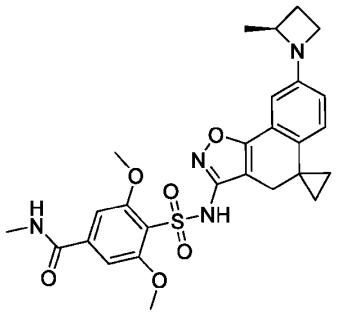
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((methylsulfonyl)methyl)benzenesulfonamide



[1069] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((methylsulfonyl)methyl)benzenesulfonamide (120 mg, 0.21 mmol, 1.00 equiv, Intermediate F), azetidine (59 mg, 1.03 mmol, 5.00 equiv), Pd-PEPPSI-IHeptCl (20 mg, 0.02 mmol, 0.10 equiv) and Cs_2CO_3 (201 mg, 0.62 mmol, 3.00 equiv) in NMP (5 mL) was stirred at 100 °C for 3 h under N_2 atmosphere. The resulting mixture was purified directly by reverse phase flash chromatography on C18 gel (5---60% acetonitrile in water (contained 0.1% formic acid)) and further purified by Prep-HPLC (5---60% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((methylsulfonyl)methyl)benzenesulfonamide (41.3 mg, 36% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.72 (br s, 1H), 6.93-6.79 (m, 3H), 6.55 (d, J = 2.4 Hz, 1H), 6.42-6.33 (m, 1H), 4.49 (s, 2H), 3.92-3.65 (m, 10H), 2.95 (s, 3H), 2.51 (s, 2H), 2.35-2.20 (m, 2H), 0.89-0.75 (m, 2H), 0.72-0.62 (m, 2H). MS (ESI, *m/z*): 560 [M+H]+.

Example 199

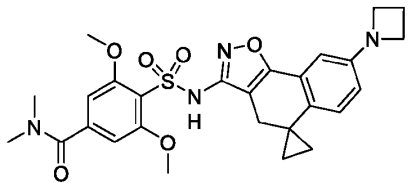
(S)-3,5-dimethoxy-N-methyl-4-(N-(8'-(2-methylazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)benzamide



[1070] A mixture of 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (140.0 mg, 0.255 mmol, 1.00 equiv, Intermediate F), (S)-2-methylazetidine hydrogen chloride (166.0 mg, 1.533 mmol, 6.00 equiv), $Pd_2(dba)_3$ (24.0 mg, 0.026 mmol, 0.10 equiv), t-BuXPhos (22.0 mg, 0.051 mmol, 0.20 equiv) and t-BuONa (123.0 mg, 1.275 mmol, 5.00 equiv) in NMP (10.0 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. The resulting mixture was directly purified by reverse phase chromatography on C18 gel (0-70% acetonitrile in water (contained 0.05% NH_4HCO_3)) to afford (S)-3,5-dimethoxy-N-methyl-4-(N-(8'-(2-methylazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)benzamide (7.7 mg, 5.6% yield) as an off-white solid. MS (ESI, *m/z*): 539 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.65-8.59 (m, 1H), 7.15 (s, 2H), 6.86 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 2.4 Hz, 1H), 6.46-6.40 (m, 1H), 4.12-4.00 (m, 1H), 3.84 (s, 7H), 3.54-3.42 (m, 1H), 2.80 (d, J = 4.5 Hz, 3H), 2.39-2.30 (m, 1H), 2.06-1.94 (m, 1H), 1.39 (d, J = 6.0 Hz, 3H), 0.90-0.81 (m, 2H), 0.73-0.64 (m, 2H).

Example 200

4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N,N-dimethylbenzamide

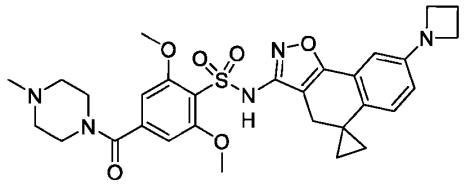


[1071] Example 200 was prepared according to General Procedure 1 of Example 220, using dimethylamine. ^{1}H NMR (400 MHz, DMSO) δ 10.70 (s, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.75 (s, 2H), 6.57 (s, 1H), 6.39 (d, J = 8.9 Hz, 1H), 3.81 (d, J = 5.9 Hz, 10H), 3.30 (s, 1H),

2.98 (s, 3H), 2.87 (s, 3H), 2.33 (br s, 1H), 2.29 (t, J = 7.2 Hz, 2H), 0.85 (s, 2H), 0.67 (s, 2H). MS (ESI, *m/z*): 539.2 $[M+H]^+$.

Example 201

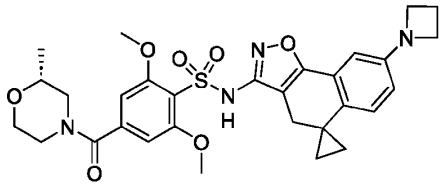
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(4-methylpiperazine-1-carbonyl)benzenesulfonamide – Prepared by General Procedure 2



[1072] To a stirred solution of 4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoic acid (103.0 mg, 0.201 mmol, 1.00 equiv, Intermediate D), 1-methylpiperazine (22.2 mg, 1.1 eq., 221 μmol) and DIEA (0.071 mL , 0.403 mmol, 2.00 equiv) in DMF (5.00 mL) at 0 °C was added HATU (115 mg, 0.30 mmol, 1.50 equiv). The resulting mixture was allowed to warm up to ambient temperature and stirred at this temperature for another 1 h. The resulting mixture was diluted with EtOAc and then washed with brine three times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(4-methylpiperazine-1-carbonyl)benzenesulfonamide (37.30 mg, 31.2% yield) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.66 (br s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.72 (s, 2H), 6.55 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 8.4, 2.4 Hz, 1H), 3.87 – 3.71 (m, 10H), 3.66 – 3.52 (m, 2H), 3.29 – 3.14 (m, 2H), 2.52 (s, 2H), 2.42 – 2.20 (m, 6H), 2.18 (s, 3H), 0.89 – 0.61 (m, 4H). MS (ESI, m/z): 594.5 $(M+H)^+$.

Example 202

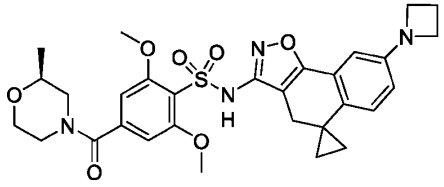
(R)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(2-methylmorpholine-4-carbonyl)benzenesulfonamide



[1073] Example 202 was prepared according to General Procedure 1 of Example 220, using (R)-2-methylmorpholine from a commercial source (Chongqing Firster Biopharm Co., Ltd., CF-130411). ^{1}H NMR (400 MHz, DMSO) δ 10.72 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.75 (s, 3H), 6.56 (s, 1H), 6.38 (d, J = 8.6 Hz, 1H), 4.31 (s, 1H), 3.80 (d, J = 6.1 Hz, 10H), 3.68 (s, 1H), 3.50 (br s, 3H), 3.30 (s, 1H), 2.94 – 2.82 (m, 1H), 2.33 (s, 1H), 2.29 (t, J = 7.2 Hz, 2H), 1.15 (s, 2H), 0.97 (s, 2H), 0.85 (s, 2H), 0.67 (d, J = 5.3 Hz, 2H). MS (ESI, *m/z*): 595.2 $[M+H]^+$.

Example 203

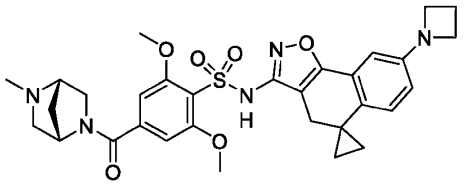
(S)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(2-methylmorpholine-4-carbonyl)benzenesulfonamide



[1074] Example 203 was prepared according to General Procedure 1 of Example 220, using (S)-2-methylmorpholine from a commercial source (Bide Pharmatech Co., Ltd, BD34808). ^{1}H NMR (400 MHz, DMSO) δ 6.86 (d, J = 8.4 Hz, 1H), 6.73 (s, 2H), 6.55 (s, 1H), 6.37 (d, J = 8.5 Hz, 1H), 4.30 (s, 1H), 3.79 (d, J = 14.2 Hz, 1H), 3.79 (s, 11H), 3.50 (s, 3H), 3.22 – 3.14 (m, 1H), 2.94 – 2.82 (m, 1H), 2.33 (br s, 1H), 2.29 (t, J = 7.2 Hz, 2H), 1.20 - 1.10 (m, 2H), 1.04 - 0.98 (m, 2H), 0.85 (br s, 2H), 0.66 (br s, 2H). MS (ESI, *m/z*): 595.2 $[M+H]^+$.

Example 204

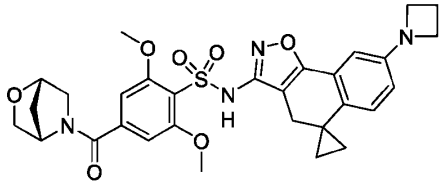
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-carbonyl)benzenesulfonamide



[1075] Example 204 was synthesized according to General Procedure 1 of Example 220, using (1S,4S)-2-methyl-2,5-diazabicyclo[2.2.1]heptane from a commercial source. Example 204 was purified using reverse phase chromatography (MeCN/H_2O, no modifiers). ^{1}H NMR (400 MHz, DMSO) δ 10.68 (s, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 16.7 Hz, 2H), 6.56 (d, J = 2.5 Hz, 1H), 6.39 (dd, J = 8.6, 2.5 Hz, 1H), 4.08 (s, 1H), 3.81 (d, J = 12.4 Hz, 11H), 3.65 – 3.41 (m, 3H), 2.86 (s, 2H), 2.41 (s, 4H), 2.29 (p, J = 7.8 Hz, 2H), 1.76 (d, J = 15.0 Hz, 2H), 0.85 (s, 2H), 0.67 (s, 2H). MS (ESI, *m/z*): 606.2 $[M+H]^+$.

Example 205

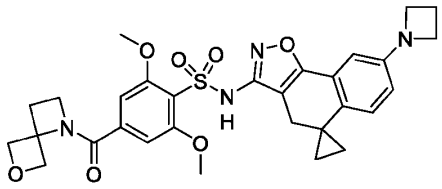
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1076] Example 205 was prepared according to General Procedure 1 of Example 220, using (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane from a commercial source (Accela ChemBio Co., Ltd., SY020085). ^{1}H NMR (400 MHz, DMSO) δ 10.73 (s, 1H), 6.85 (dd, J = 15.7, 8.0 Hz, 3H), 6.57 (d, J = 2.5 Hz, 1H), 6.39 (dd, J = 8.4, 2.5 Hz, 1H), 4.61 (d, J = 44.9 Hz, 1H), 4.28 (s, 1H), 3.94 (d, J = 7.5 Hz, 1H), 3.90 – 3.70 (m, 11H), 3.64 (d, J = 7.5 Hz, 1H), 3.47 (t, J = 10.1 Hz, 1H), 3.19 (d, J = 9.8 Hz, 1H), 2.29 (p, J = 7.1 Hz, 2H), 2.00 – 1.80 (m, 2H), 1.74 (d, J = 10.0 Hz, 1H), 0.85 (d, J = 4.9 Hz, 2H), 0.68 (d, J = 5.1 Hz, 2H). MS (ESI, *m/z*): 593.2 $[M+H]^+$.

Example 206

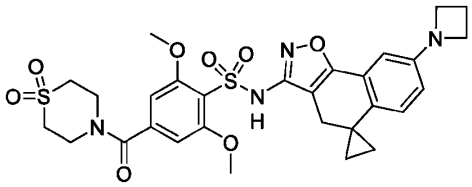
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(6-oxa-1-azaspiro[3.3]heptane-1-carbonyl)benzenesulfonamide



[1077] Example 206 was prepared according to General Procedure 1 of Example 220, using 6-oxa-1-azaspiro[3.3]heptane from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.66 (d, J = 12.4 Hz, 1H), 6.85 – 6.76 (m, 3H), 6.49 (d, J = 2.5 Hz, 1H), 6.31 (dd, J = 8.3, 2.5 Hz, 1H), 5.26 (d, J = 6.6 Hz, 2H), 4.50 (d, J = 6.6 Hz, 2H), 4.00 (t, J = 7.4 Hz, 2H), 3.74 (d, J = 15.9 Hz, 11H), 2.49 - 2.46 (m, 3H), 2.21 (p, J = 7.6 Hz, 2H), 0.78 (s, 2H), 0.59 (q, J = 4.3 Hz, 2H). MS (ESI, *m/z*): 593.2 $[M+H]^+$.

Example 207

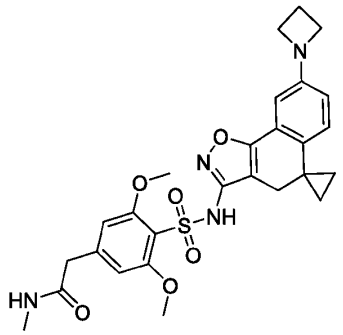
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(1,1-dioxidothiomorpholine-4-carbonyl)-2,6-dimethoxybenzenesulfonamide



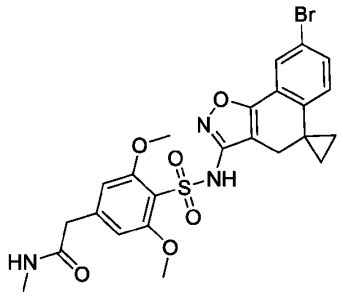
[1078] Example 207 was prepared according to General Procedure 1 of Example 220, using thiomorpholine 1,1-dioxide from a commercial source. ^{1}H NMR (400 MHz, CD_3CN) δ 8.47 (s, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.74 (d, *J* = 3.1 Hz, 2H), 6.65 (d, *J* = 2.5 Hz, 1H), 6.40 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.08 (s, 2H), 3.90 (s, 6H), 3.83 (t, *J* = 7.1 Hz, 2H), 3.68 (s, 2H), 3.06 (br m, 8H), 2.57 (s, 2H), 0.84 (d, *J* = 4.8 Hz, 2H), 0.80 – 0.68 (m, 2H). MS (ESI, *m/z*): 629.2 $[M+H]^+$.

Example 208

2-(4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxyphenyl)-N-methylacetamide

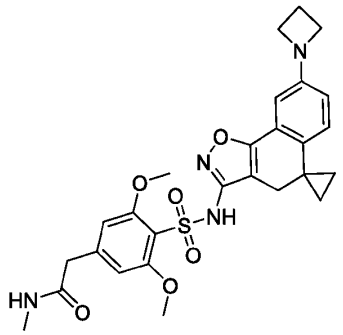


[1079] Step 1. Synthesis of 2-(4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxyphenyl)-N-methylacetamide



[1080] To a stirred solution of 2-(4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxyphenyl)acetic acid (224.0 mg, 0.41 mmol, 1.10 equiv, Intermediate E), methylamine hydrochloride (25.0 mg, 0.37 mmol, 1.00 equiv) and DIEA (191.0 mg, 1.48 mmol, 4.00 equiv) in DMF (2.0 mL) at 0 oC was added HATU (211.0 mg, 0.56 mmol, 1.50 equiv) in portions. The resulting mixture was allowed to warm up to ambient temperature and stirred for another 1 h. The resulting mixture was directly purified by reverse phase flash chromatography on C18 gel (0-60% acetonitrile in water (contained 0.1% FA)) to afford 2-(4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxyphenyl)-N-methylacetamide (166.0 mg, 79% yield)% yield) as a yellow solid. MS (ESI, *m/z*): 562, 563 $[M+H]^+$ [M+H]+.

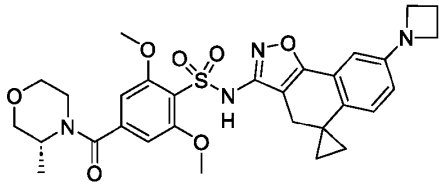
[1081] Step 2. Synthesis of 2-(4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxyphenyl)-N-methylacetamide



[1082] A mixture of 2-(4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxyphenyl)-N-methylacetamide (220.0 mg, 0.39 mmol, 1.00 equiv), azetidine (112.0 mg, 1.96 mmol, 5.00 equiv), Pd-PEPPSI-IHeptCl (76.0 mg, 0.08 mmol, 0.20 equiv) and Cs2CO3 (382.0 mg, 1.17 mmol, 3.00 equiv) in NMP (8.0 mL) was stirred at 100 °C for 1 h under N2 atmosphere. The resulting mixture was directly purified by reverse phase flash chromatography on C18 gel (0-60% acetonitrile in water (contained 0.05% NH_4HCO_3)) to afford 2-(4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxyphenyl)-N-methylacetamide (43.6 mg, 21% yield) as a yellow solid. MS (ESI, *m/z*): 539 $[M+H]^+$ [M+H]+. 1H NMR (300 MHz, DMSO-d6) δ 10.35 (br s, 1H), 7.96 (d, J = 4.8 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.64 (s, 2H), 6.54 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 8.4, 2.4 Hz, 1H), 3.77 (d, J = 9.2 Hz, 9H), 3.39 (s, 1H), 2.57 (d, J = 4.5 Hz, 3H), 2.28 (p, J = 7.2 Hz, 2H), 0.87-0.79 (m, 2H), 0.69-0.61 (m, 2H).

Example 209

(R)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(3-methylmorpholine-4-carbonyl)benzenesulfonamide

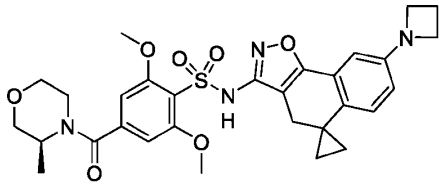


[1083] Example 209 was prepared according to General Procedure 1 of Example 220, using (R)-3-methylmorpholine from a commercial source (Balmxy Pharmaceutic Co. Ltd, BX12731). ^{1}H NMR (400 MHz, DMSO) δ 10.71 (s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.74 (s,

2H), 6.61 – 6.51 (m, 1H), 6.39 (dd, *J* = 8.6, 2.5 Hz, 1H), 4.48 (s, 1H), 4.13 (s, 1H), 3.81 (d, *J* = 10.8 Hz, 11H), 3.56 (d, *J* = 9.7 Hz, 2H), 3.40 (s, 3H), 3.15 (s, 1H), 2.29 (p, *J* = 7.3 Hz, 2H), 1.26 (d, *J* = 6.8 Hz, 4H), 0.85 (d, *J* = 5.0 Hz, 2H), 0.67 (d, *J* = 5.2 Hz, 2H). MS (ESI, *m/z*): 595.2 $[M+H]^+$.

Example 210

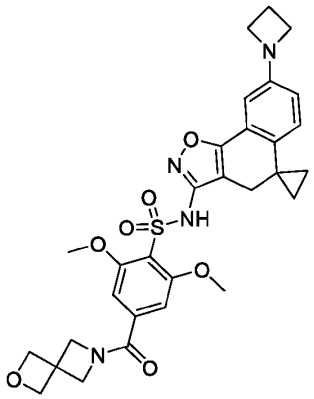
(S)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(3-methylmorpholine-4-carbonyl)benzenesulfonamide



[1084] Example 210 was prepared according to General Procedure 1 of Example 220, using (S)-3-methylmorpholine from a commercial source (Firster Biopharm, CF-130109). ^{1}H NMR (400 MHz, DMSO) δ 10.72 (s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.74 (s, 2H), 6.57 (d, J = 2.5 Hz, 1H), 6.39 (dd, J = 8.4, 2.5 Hz, 1H), 4.72 – 4.34 (br m, 1H), 4.27 – 4.03 (br m, 1H), 3.81 (d, J = 11.2 Hz, 11H), 3.56 (d, J = 9.9 Hz, 2H), 3.38 (d, J = 10.3 Hz, 2H), 3.2 – 2.98 (br s, 2H), 2.29 (p, J = 7.3 Hz, 2H), 1.25 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 5.1 Hz, 2H), 0.67 (s, 2H). MS (ESI, *m/z*): 595.2 $[M+H]^+$.

Example 211

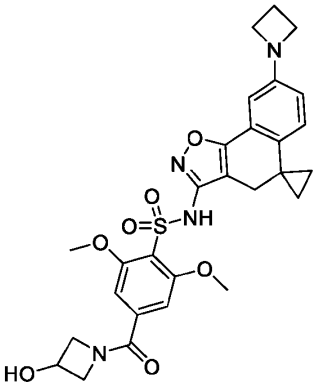
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(2-oxa-6-azaspiro[3.3]heptane-6-carbonyl)benzenesulfonamide



[1085] Example 211 was prepared according to General Procedure 1 of Example 220, using 2-oxa-6-azaspiro[3.3]heptane from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.75 (s, 1H), 6.90 – 6.83 (m, 3H), 6.56 (t, J = 1.8 Hz, 1H), 6.42 – 6.35 (m, 1H), 4.72 – 4.63 (m, 4H), 4.47 (s, 2H), 4.21 (s, 2H), 3.82 (d, J = 19.4 Hz, 10H), 2.53 (s, 2H), 2.28 (p, J = 7.2 Hz, 2H), 0.86 (s, 2H), 0.68 (s, 2H). MS (ESI, *m/z*): 593.2 $[M+H]^+$.

Example 212

N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(3-hydroxyazetidine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide

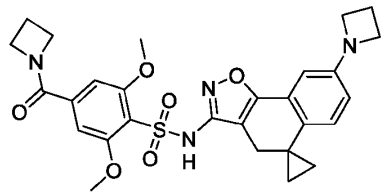


[1086] Example 212 was prepared according to General Procedure 1 of Example 220, using azetidin-3-ol from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.75 (s, 1H), 6.87 (d, *J* = 9.8 Hz, 3H), 6.56 (d, *J* = 2.4 Hz, 1H), 6.38 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.78 (d, *J* = 5.8 Hz, 1H), 4.47 (dt, *J* = 24.0, 6.6 Hz, 2H), 4.24 (dd, *J* = 10.6, 6.7 Hz, 1H), 4.05 (dt, *J* = 9.5,

4.7 Hz, 1H), 3.84 (s, 6H), 3.79 (t, J = 7.3 Hz, 5H), 2.52 (s, 2H), 2.28 (p, J = 7.2 Hz, 2H), 0.85 (d, J = 5.1 Hz, 2H), 0.68 (d, J = 5.1 Hz, 2H MS (ESI, *m/z*): 567.2 $[M+H]^+$.

Example 213

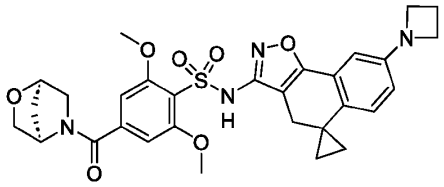
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(azetidine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1087] A mixture of methyl 4-({8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}sulfamoyl)-3,5-dimethoxybenzoate (3.5 g, 6.37 mmol, 1.00 equiv, Intermediate D, Step 1), azetidine (1.8 g, 31.86 mmol, 5.00 equiv), Cs2CO3 (6.2 g, 19.11 mmol, 3.00 equiv) and Pd-PEPPSI-IHeptCl (620.0 mg, 0.64 mmol, 0.10 equiv) in DMF (35.0 mL) was stirred at 100 °C for 1 h under nitrogen. The residue was purified by reverse phase flash chromatography on C18 gel (5-70% acetonitrile in water (contained 0.1% formic acid)) and further purified by Prep-HPLC (40-60% acetonitrile in water (contained 0.1% formic acid)) to afford N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(azetidine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide (109.6 mg, 3%) as a light yellow solid. 1H NMR (300 MHz, DMSO-d6) δ 10.76 (s, 1H), 6.91-6.84 (m, 3H), 6.56 (d, J = 2.4 Hz, 1H), 6.41-6.34 (m, 1H), 4.29 (t, J = 7.8 Hz, 2H), 4.04 (t, J = 7.8 Hz, 2H), 3.84 (s, 6H), 3.81 – 3.75 (m, 4H), 2.50 (s, 2H), 2.36-2.17 (m, 4H), 0.90-0.80 (m, 2H), 0.72-0.62 (m, 2H). MS (ESI, m/z): 551 (M + H)+.

Example 214

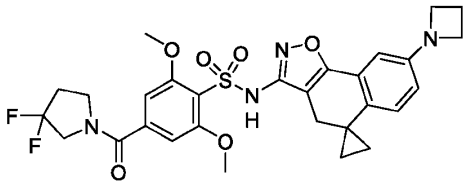
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1088] Example 214 was prepared according to General Procedure 1 of Example 220, using (1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptane from a commercial source (Shanghai Balmxy Pharmaceutic Co., Ltd, BX30831). ^{1}H NMR (400 MHz, DMSO) δ 10.75 (s, 1H), 6.85 (dd, J = 15.4, 8.1 Hz, 3H), 6.56 (d, J = 2.4 Hz, 1H), 6.39 (dd, J = 8.5, 2.5 Hz, 1H), 4.61 (d, J = 44.4 Hz, 1H), 4.28 (s, 1H), 3.94 (d, J = 7.5 Hz, 1H), 3.89 – 3.72 (m, 11H), 3.64 (d, J = 7.4 Hz, 1H), 3.47 (t, J = 10.0 Hz, 1H), 3.19 (d, J = 9.9 Hz, 1H), 2.29 (p, J = 7.2 Hz, 2H), 1.98 – 1.79 (m, 2H), 1.74 (d, J = 10.1 Hz, 1H), 0.85 (d, J = 5.0 Hz, 2H), 0.68 (d, J = 5.0 Hz, 2H). MS (ESI, *m/z*): 593.2 $[M+H]^+$.

Example 215

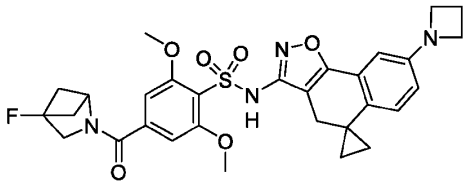
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(3,3-difluoropyrrolidine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1089] Example 215 was prepared according to General Procedure 1 of Example 220, using 3,3-difluoropyrrolidine from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 6.86 (dd, J = 8.5, 3.7 Hz, 3H), 6.56 (d, J = 2.5 Hz, 1H), 6.38 (dd, J = 8.5, 2.5 Hz, 1H), 3.95 – 3.75 (m, 12H), 3.71 (t, J = 7.6 Hz, 1H), 3.64 (t, J = 7.3 Hz, 1H), 2.43 (tt, J = 14.3, 7.2 Hz, 2H), 2.55 – 2.49 9m, 2H), 2.29 (p, J = 7.2 Hz, 2H), 0.85 (d, J = 5.1 Hz, 2H), 0.68 (d, J = 4.1 Hz, 2H). MS (ESI, *m/z*): 601.2 $[M+H]^+$.

Example 216

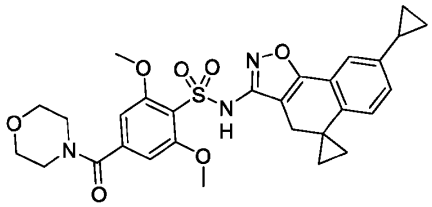
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(4-fluoro-2-azabicyclo[2.1.1]hexane-2-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1090] Example 216 was prepared according to General Procedure 1 of Example 220, using 4-fluoro-2-azabicyclo[2.1.1]hexane from a commercial source. ^{1}H NMR (400 MHz, DMSO) δ 10.74 (s, 1H), 6.98 – 6.83 (m, 2H), 6.78 (s, 1H), 6.56 (d, J = 2.4 Hz, 1H), 6.38 (dd, J = 8.5, 2.5 Hz, 1H), 4.66 (d, J = 23.8 Hz, 1H), 4.14 (d, J = 21.9 Hz, 1H), 3.94 – 3.69 (m, 10H), 3.54 (d, J = 16.5 Hz, 2H), 2.53 (s, 1H), 2.29 (p, J = 7.2 Hz, 2H), 2.19 (d, J = 15.0 Hz, 3H), 2.09 – 2.00 (m, 1H), 0.85 (d, J = 5.0 Hz, 2H), 0.68 (d, J = 5.0 Hz, 2H). MS (ESI, *m/z*): 595.2 $[M+H]^+$.

Example 217

N-(8'-cyclopropyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonamide

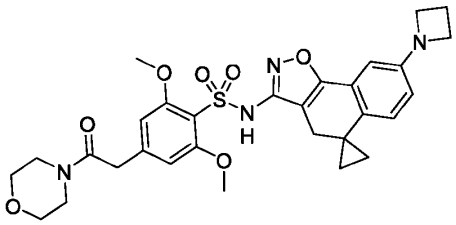


[1091] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonamide (260.00 mg, 0.43 mmol, 1.00 equiv, Intermediate K), cyclopropylboronic acid (110.80 mg, 1.29 mmol, 3.00 equiv), $Pd(dppf)Cl_2.CH_2Cl_2$ (35.10 mg, 0.04 mmol, 0.10 equiv) and Cs_2CO_3 (420.40 mg, 1.29 mmol, 3.00 equiv) in dioxane (5.00 mL) and H_2O (1.00 mL) was stirred at 100 °C for 2 h under N_2 atmosphere. The resulting mixture was diluted with water and extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (10-60% acetonitrile in water (contained 0.10% formic acid)) to afford N-(8'-cyclopropyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonamide (30.00 mg, 12%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.77 (br s, 1H), 7.22 (d, J = 1.9 Hz, 1H), 7.08-7.01 (m, 1H), 6.97-6.88 (m, 1H),

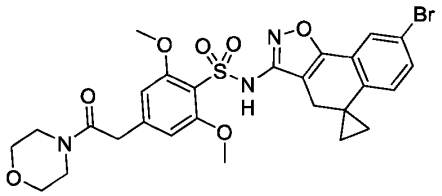
6.75 (s, 2H), 3.80 (s, 6H), 3.70-3.45 (m, 5H), 3.26 (br s, 2H), 2.55 (s, 2H), 2.00-1.86 (m, 1H), 0.98-0.87 (m, 4H), 0.83-0.61 (m, 4H). MS (ESI, *m/z*): 566 $(M + H)^+$.

Example 218

N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(2-morpholino-2-oxoethyl)benzenesulfonamide

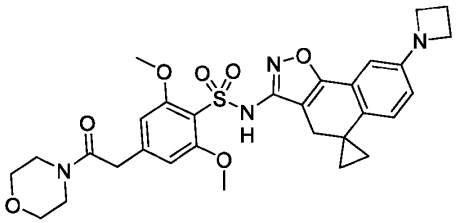


[1092] Step 1. Synthesis of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(2-morpholino-2-oxoethyl)benzenesulfonamide



[1093] To a stirred solution of 2-(4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxyphenyl)acetic acid (220.0 mg, 0.400 mmol, 1.00 equiv, Intermediate E), morpholine (41.0 mg, 0.480 mmol, 1.20 equiv) and DIEA (155.0 mg, 1.200 mmol, 3.00 equiv) in DMF (8 mL) at 0 °C was added HATU (228.0 mg, 0.600 mmol, 1.50 equiv). The resulting mixture was stirred at ambient temperature for 2 h and then diluted with EtOAc. The resulting solution was washed with brine three times, dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-10% MeOH in DCM) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(2-morpholino-2-oxoethyl)benzenesulfonamide (220.0 mg, 88 % yield) as a white solid. MS (ESI, *m/z*): 618, 620 $[M+H]^+$[M+H]+.

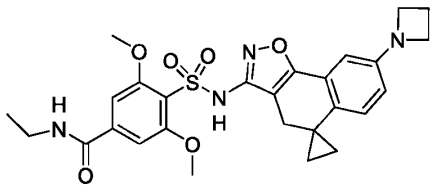
[1094] Step 2. Synthesis of N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(2-morpholino-2-oxoethyl)benzenesulfonamide



[1095] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(2-morpholino-2-oxoethyl)benzenesulfonamide (220.0 mg, 0.356 mmol, 1.00 equiv), azetidine (101.0 mg, 1.780 mmol, 5.00 equiv), Pd-PEPPSI-IHept (35.0 mg, 0.036 mmol, 0.10 equiv) and Cs2CO3 (231.0 mg, 0.712 mmol, 2.00 equiv) in NMP (6 mL) was stirred at 100 °C for 1 h under N2 atmosphere. The resulting mixture was diluted with water and then acidified with AcOH to pH ~6 and then extracted with EtOAc three times. The combined organic layers were washed with brine three times, dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-10% MeOH in DCM) and further purified by reverse phase flash chromatography on C18 gel (0-70% acetonitrile in water) to afford N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(2-morpholino-2-oxoethyl)benzenesulfonamide (79.6 mg, 37.6% yield) as a white solid. MS (ESI, *m/z*): 595 $[M+H]^+$[M+H]+.1H NMR (400 MHz, DMSO-d6) δ 10.58 (s, 1H), 6.86 (d, J = 8.5 Hz, 1H), 6.62 (s, 2H), 6.55 (d, J = 2.6 Hz, 1H), 6.37 (dd, J = 8.5, 2.5 Hz, 1H), 3.83-3.77 (m, 4H), 3.76 (s, 6H), 3.72 (s, 2H), 3.52 (d, J = 4.8 Hz, 2H), 3.44 (d, J = 4.8 Hz, 2H), 2.36-2.21 (m, 2H), 0.89-0.79 (m, 2H), 0.70-0.60 (m, 2H).

Example 219

4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-N-ethyl-3,5-dimethoxybenzamide

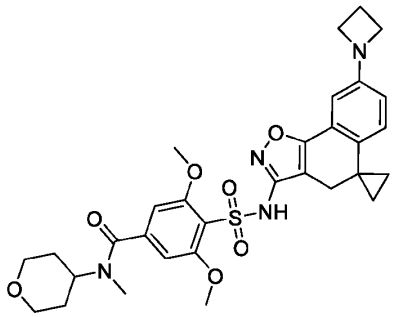


[1096] Example 219 was prepared according to General Procedure 1 of Example 220, using ethylamine. ^{1}H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.64 (t, J = 5.6 Hz, 1H), 7.14 (s, 2H), 6.86 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.38 (dd, J = 8.5, 2.5 Hz, 1H), 3.85

(s, 6H), 3.79 (t, J = 7.1 Hz, 4H), 3.29 (d, J = 6.7 Hz, 2H), 2.53 (s, 2H), 2.28 (p, J = 7.2 Hz, 2H), 1.13 (t, J = 7.2 Hz, 3H), 0.85 (s, 2H), 0.68 (s, 2H). MS (ESI, *m/z*): 539.2 $[M+H]^+$.

Example 220

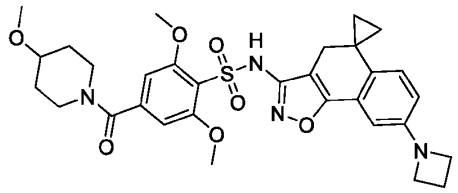
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonamide – Prepared by General Procedure 1



[1097] To a stirred mixture of potassium (8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)((4-carboxylato-2,6-dimethoxyphenyl)sulfonyl)amide (130.0 mg, 0.25 mmol, 1.00 equiv, Intermediate D), N-methyloxan-4-amine (35.1 mg, 0.30 mmol, 1.20 equiv) and 1-methyl-1H-imidazole (104.3 mg, 1.27 mmol, 5.00 equiv) in acetonitrile (13.0 mL) at 0 °C was added TCFH (107.0 mg, 0.38 mmol, 1.50 equiv). The resulting mixture was allowed to warm up to ambient temperature and then stirred at this temperature for another 1 h and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-55% acetonitrile in water) to afford 4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methyl-N-(tetrahydro-2H-pyran-4-yl)benzamide (39.1 mg, 25% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.69 (br s, 1H), 6.90 – 6.80 (m, 1H), 6.71 (s, 2H), 6.58 – 6.52 (m, 1H), 6.44 – 6.33 (m, 1H), 4.10 – 3.88 (m, 1H), 3.87 – 3.67 (m, 10H), 3.50 – 3.23 (m, 3H), 3.10 – 2.95 (m, 1H), 2.90 – 2.60 (m, 3H), 2.50 (s, 2H), 2.35 – 2.20 (m, 2H), 1.90 – 1.70 (m, 2H), 1.65 – 1.50 (m, 2H), 0.88 – 0.80 (m, 2H), 0.70 – 0.65 (m, 2H). MS (ESI, *m/z*): 609.3 [M+H]+.

Example 221

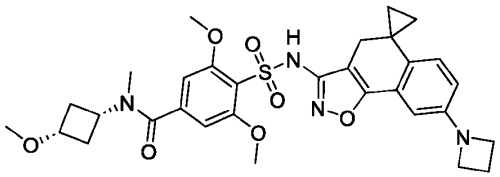
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(4-methoxypiperidine-1-carbonyl)benzenesulfonamide



[1098] Example 221 was prepared according to General Procedure 1 of Example 220, using 4-methoxypiperidine from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.69 (br s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.73 (s, 2H), 6.56 (d, J = 2.4 Hz, 1H), 6.38 (dd, J = 8.4, 2.4 Hz, 1H), 3.90 – 3.76 (m, 11H), 3.49 – 3.29 (m, 3H), 3.25 (s, 3H), 3.14 – 3.02 (m, 1H), 2.52 (s, 2H), 2.33 – 2.23 (m, 2H), 1.93 – 1.71 (m, 2H), 1.56 – 1.36 (m, 2H), 0.88 – 0.81 (m, 2H), 0.68 – 0.63 (m, 2H). MS (ESI, *m/z*): 609.2 [M+H]+.

Example 222

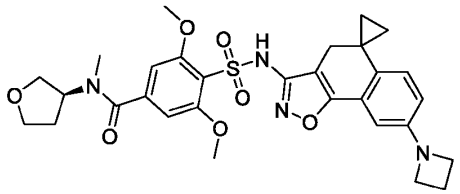
4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-((1s,3s)-3-methoxycyclobutyl)-N-methylbenzamide



[1099] Example 222 was prepared according to General Procedure 1 of Example 220, using the relevant amine from a commercial source (Chiral Reagent for Innovation Life Science Inc./CRI, C72673). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.70 (br s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.77 – 6.62 (m, 2H), 6.56 (d, J = 2.4 Hz, 1H), 6.38 (dd, J = 8.4, 2.4 Hz, 1H), 3.91 – 3.74 (m, 10H), 3.74 – 3.58 (m, 1H), 3.22 – 3.02 (m, 3H), 2.99 – 2.71 (m, 3H), 2.60 – 2.19 (m, 7H), 2.15 – 1.94 (m, 2H), 0.93 – 0.80 (m, 2H), 0.73 – 0.62 (m, 2H). MS (ESI, *m/z*): 609.4 $[M+H]^+$.

Example 223

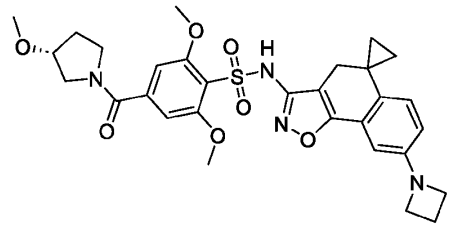
(S)-4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methyl-N-(tetrahydrofuran-3-yl)benzamide



[1100] Example 222 was prepared according to General Procedure 1 of Example 220, using the relevant amine from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.70 (s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.77 – 6.90 (m, 2H), 6.56 (d, J = 2.4 Hz, 1H), 6.41 – 6.36 (m, 1H), 5.23– 4.10 (m, 1H), 4.01 – 3.88 (m, 1H), 3.87 – 3.67 (m, 11H), 3.66 – 3.16 (m, 2H), 2.95 – 2.68 (m, 3H), 2.50 (s, 2H), 2.36 – 2.22 (m, 2H), 2.10 – 1.90 (m, 2H), 0.87 – 0.82 (m, 2H), 0.69 – 0.64 (m, 2H). MS (ESI, *m/z*): 595.2 [M+H]+.

Example 224

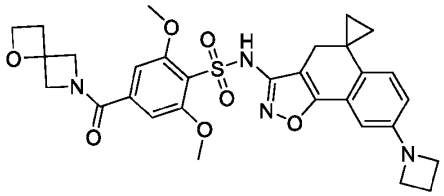
(R)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(3-methoxypyrrolidine-1-carbonyl)benzenesulfonamide



[1101] Example 224 was prepared according to General Procedure 1 of Example 220, using (R)-3-methoxypyrrolidine from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.73 (br s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 2.4 Hz, 2H), 6.55 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 8.4, 2.4 Hz, 1H), 4.03 – 3.90 (m, 1H), 3.84 – 3.75 (m, 10H), 3.60 – 3.40 (m, 4H), 3.29 – 3.13 (m, 3H), 2.60 – 2.43 (m, 2H), 2.52 (s, 2H), 2.01 – 1.88 (m, 2H), 0.87 – 0.81 (m, 2H), 0.70 – 0.62 (m, 2H). MS (ESI, *m/z*): 595.3 [M+H]+.

Example 225

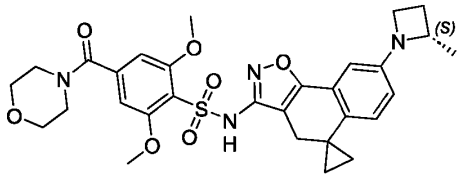
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(1-oxa-6-azaspiro[3.3]heptane-6-carbonyl)benzenesulfonamide



[1102] Example 225 was prepared according to General Procedure 1 of Example 220, using 1-oxa-6-azaspiro[3.3]heptane from a commercial source. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.76 (br s, 1H), 6.94 – 6.83 (m, 3H), 6.59 – 6.51 (m, 1H), 6.42 – 6.34 (m, 1H), 4.48 (d, J = 4.8 Hz, 2H), 4.45 – 4.36 (m, 2H), 4.32 – 4.26 (m, 1H), 4.14 – 4.07 (m, 1H), 3.90 – 3.75 (m, 10H), 2.86 – 2.77 (m, 2H), 2.51 (s, 2H), 2.34 – 2.22 (m, 2H), 0.89 – 0.80 (m, 2H), 0.71 – 0.63 (m, 2H). MS (ESI, *m/z*): 593.1 $[M+H]^+$.

Example 226

(S)-2,6-dimethoxy-N-(8'-(2-methylazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(morpholine-4-carbonyl)benzenesulfonamide

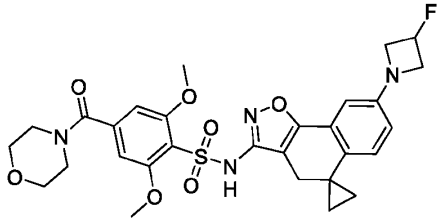


[1103] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonamide (100 mg, 0.165 mmol, 1.00 equiv, Intermediate K), (2S)-2-methylazetidine (58.83 mg, 0.825 mmol, 5.00 equiv), $Pd_2(dba)_3$ (15.15 mg, 0.017 mmol, 0.10 equiv), t-BuXPhos (14.05 mg, 0.033 mmol, 0.20 equiv) and t-BuONa (95.39 mg, 0.990 mmol, 6.00 equiv) in NMP (8 mL) was stirred at 100 °C for 2 h under N_2 atmosphere. The resulting mixture was purified directly by reverse phase flash chromatography on C18 gel (5-55% acetonitrile in water (contained 0.1% formic acid)) to afford (S)-2,6-dimethoxy-N-(8'-(2-methylazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(morpholine-4-carbonyl)benzenesulfonamide (15.3 mg, 15.55% yield) as an off-white solid. MS (ESI, *m/z*): 595.3 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.81 (br s, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.75 (s, 2H), 6.58 (d, J = 2.4 Hz, 1H), 6.43 (dd, J = 8.4, 2.4 Hz, 1H), 4.12-3.97 (m, 1H), 3.91 – 3.76 (m, 7H), 3.70 – 3.42 (m, 7H),

3.26 (br s, 2H), 2.41 – 2.24 (m, 1H), 2.06 – 1.89 (m, 1H), 1.38 (d, J = 6.0 Hz, 3H), 0.89 – 0.80 (m, 2H), 0.71 – 0.62 (m, 2H).

Example 227

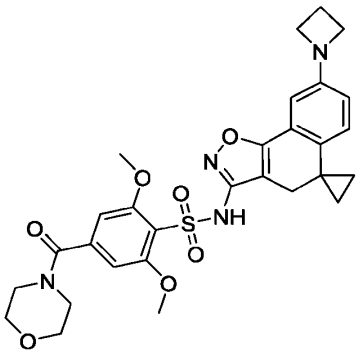
N-(8'-(3-fluoroazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonamide



[1104] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonamide (100.0 mg, 0.10 mmol, 1.00 equiv, Intermediate K), 3-fluoroazetidine hydrochloride (73.0 mg, 0.66 mmol, 4.00 equiv), EPhos (17.0 mg, 0.03 mmol, 0.20 equiv), EPhos Pd G_4 (30.0 mg, 0.03 mmol, 0.20 equiv) and sodium benzenolate (153.0 mg, 1.32 mmol, 8.00 equiv) in NMP (8.00 mL) was stirred at 100 °C for 1 h under N_2 atmosphere. The resulting mixture was purified directly by reverse phase chromatography on C18 gel (0-50% acetonitrile in water (no additive)) to afford N-(8'-(3-fluoroazetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonamide (12.7 mg, 12.8% yield) as a white solid. MS (ESI, *m/z*): 599.2 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.75 (br s, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.75 (s, 2H), 6.67 – 6.61 (m, 1H), 6.50 – 6.41 (m, 1H), 5.58 – 5.39 (m, 1H), 4.42 – 4.06 (m, 2H), 3.99 – 3.87 (m, 2H), 3.87 – 3.77 (m, 6H), 3.69 – 3.51 (m, 8H), 2.78 – 2.70 (m, 2H), 1.24 (s, 1H), 0.90 – 0.84 (m, 2H), 0.71 – 0.65 (m, 2H). ^{19}F NMR (282 MHz, DMSO-d6) δ -179.21.

Example 228

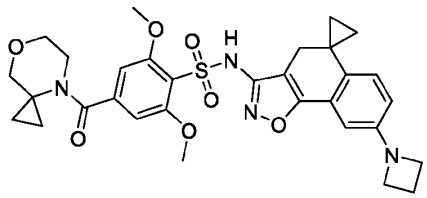
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(4-oxa-7-azaspiro[2.5]octane-7-carbonyl)benzenesulfonamide



[1105] Example 228 was prepared according to General Procedure 1 of Example 220, using 4-oxa-7-azaspiro[2.5]octane from a commercial source. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.72 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 10.2 Hz, 2H), 6.55 (d, J = 2.4 Hz, 1H), 6.38 (dd, J = 8.4, 2.4 Hz, 1H), 3.88 – 3.73 (m, 10H), 3.69 (br s, 2H), 3.64 – 3.52 (s, 2H), 3.42 – 3.34 (s, 3H), 3.26 (s, 1H), 2.36 – 2.20 (m, 2H), 0.89 – 0.80 (m, 2H), 0.78 – 0.58 (m, 5H), 0.43 (s, 1H). MS (ESI, *m/z*): 607.2 [M+H]+.

Example 229

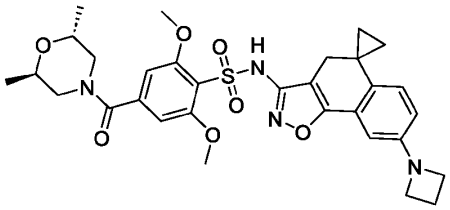
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(7-oxa-4-azaspiro[2.5]octane-4-carbonyl)benzenesulfonamide



[1106] Example 228 was prepared according to General Procedure 1 of Example 220, using 7-oxa-4-azaspiro[2.5]octane from a commercial source. Example 228 was purified using reverse phase chromatography (MeCN/H_2O, no modifiers). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.71 (br s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.75 (s, 2H), 6.55 (d, J = 2.4 Hz, 1H), 6.43 – 6.33 (m, 1H), 3.96 – 3.65 (m, 13H), 3.54 (s, 3H), 2.33 – 2.24 (m, 2H), 0.98 – 0.57 (m, 8H). MS (ESI, *m/z*): 607.2 [M+H]+.

Example 230

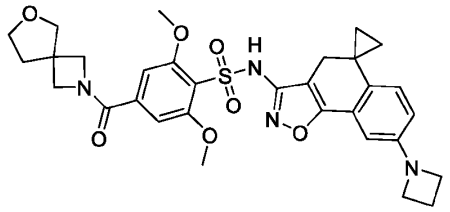
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-((2R,6R)-2,6-dimethylmorpholine-4-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1107] Example 230 was prepared according to General Procedure 2 of Example 201, using (2R,6R)-2,6-dimethylmorpholine from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.72 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.73 (s, 2H), 6.55 (d, J = 2.4 Hz, 1H), 6.38 (dd, J = 8.4, 2.4 Hz, 1H), 3.97 (s, 1H), 3.89 – 3.63 (m, 13H), 3.70 (s, 1H), 3.29 – 3.14 (m, 2H), 3.07 – 2.92 (m, 1H), 2.35 – 2.20 (m, 2H), 1.23 (s, 1H), 1.18 – 1.11 (m, 4H), 1.03 (d, J = 6.3 Hz, 3H), 0.89 – 0.80 (m, 2H), 0.71 – 0.61 (m, 2H). MS (ESI, *m/z*): 609.3 [M+H]+.

Example 231

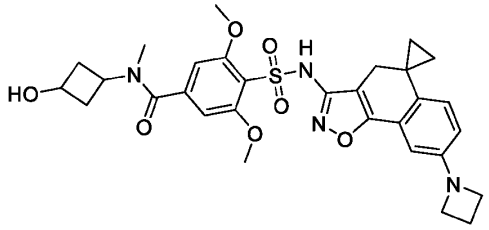
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(6-oxa-2-azaspiro[3.4]octane-2-carbonyl)benzenesulfonamide



[1108] Example 231 was prepared according to General Procedure 1 of Example 220, using the relevant amine from a commercial source. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.76 (br s, 1H), 6.89 (s, 2H), 6.85 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 6.40 – 6.32(m, 1H), 4.34 – 4.22 (m, 2H), 4.01 (s, 2H), 3.81 (s, 6H), 3.80 – 3.73 (m, 6H), 3.73 – 3.64 (m, 2H), 2.32 – 2.22 (m, 2H), 2.16 – 2.05 (m, 2H), 0.88 – 0.81 (m, 2H), 0.70 – 0.63 (m, 2H). MS (ESI, *m/z*): 607.3 $[M+H]^+$.

Example 232

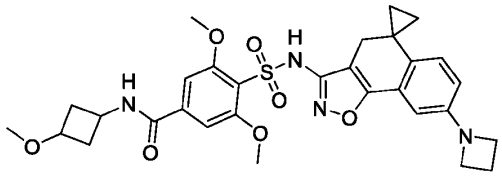
4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-N-(3-hydroxycyclobutyl)-3,5-dimethoxy-N-methylbenzamide



[1109] Example 232 was prepared according to General Procedure 2 of Example 201, using the relevant amine from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.73 (br s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.74 – 6.61 (m, 2H), 6.56 (d, J = 2.4 Hz, 1H), 6.38 (dd, J = 8.4, 2.5 Hz, 1H), 5.08 (s, 1H), 4.52 – 4.05 (s, 1H), 3.84 – 3.74 (s, 11H), 3.71 – 3.51 (m, 1H), 3.03 – 2.75 (m, 3H), 2.46 – 2.37 (m, 1H), 2.36 – 2.20 (m, 3H), 2.15 – 1.94 (m, 2H), 0.89 – 0.80 (m, 2H), 0.71 – 0.61 (m, 2H). MS (ESI, *m/z*): 595.2 [M+H]+.

Example 233

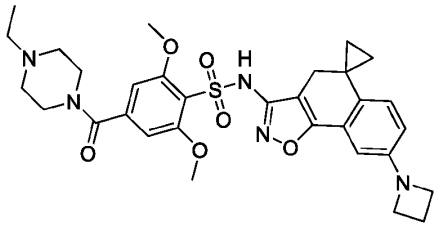
4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-(3-methoxycyclobutyl)benzamide



[1110] Example 233 was prepared according to General Procedure 2 of Example 201, using the relevant amine from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.73 (s, 1H), 8.82 – 8.68 (m, 1H), 7.16 – 7.09 (m, 2H), 6.86 (d, J = 8.5 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 6.38 (dd, J = 8.4, 2.5 Hz, 1H), 4.50 – 3.94 (m, 2H), 3.85 (s, 6H), 3.76 (t, J = 7.2 Hz, 3H), 3.69 – 3.57 (m, 1H), 3.15 (s, 1H), 3.14 (s, 2H), 2.67 – 2.54 (m, 2H), 2.52 (s, 2H), 2.35 – 2.19 (m, 3H), 2.00 – 1.86 (m, 1H), 0.89 – 0.62 (m, 4H). MS (ESI, *m/z*): 594.9 $[M+H]^+$.

Example 234

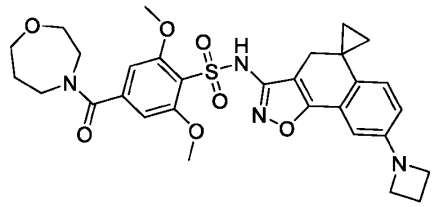
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(4-ethylpiperazine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1111] Example 234 was prepared according to General Procedure 2 of Example 201, using 1-ethylpiperazine from a commercial source. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.88 (br s, 1H), 6.86 (d, J = 8.5 Hz, 1H), 6.72 (s, 2H), 6.56 (d, J = 2.4 Hz, 1H), 6.32 (dd, J = 8.4, 2.4 Hz, 1H), 3.84 – 3.76 (m, 10H), 3.60 – 3.56 (m, 2H), 3.24 – 3.20 (m, 2H), 2.50 (s, 2H), 2.45 – 2.38 (m, 2H), 2.37 – 2.21 (m, 6H), 0.92 (t, J = 7.2 Hz, 3H), 0.88 – 0.80 (m, 2H), 0.68 – 0.64 (m, 2H). MS (ESI, *m/z*): 608.2 $[M+H]^+$.

Example 235

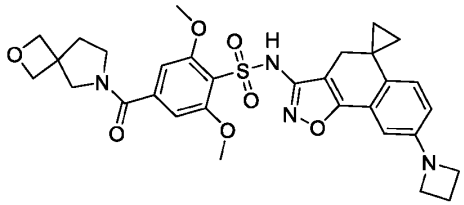
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(1,4-oxazepane-4-carbonyl)benzenesulfonamide



[1112] Example 235 was prepared according to General Procedure 1 of Example 220, using the relevant amine from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.73 (br s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 4.0 Hz, 2H), 6.56 (d, J = 2.5 Hz, 1H), 6.38 (dd, J = 8.5, 2.4 Hz, 1H), 3.82 – 3.67 (m, 3H), 3.73 (s, 2H), 3.67 (d, J = 5.5 Hz, 3H), 3.59 (t, J = 5.0 Hz, 1H), 3.36 (s, 3H), 3.34 (s, 16H), 2.32 – 2.22 (m, 2H), 1.93 – 1.82 (m, 1H), 1.76 – 1.66 (m, 1H), 0.90 – 0.81 (m, 2H), 0.70 – 0.61 (m, 2H). MS (ESI, *m/z*): 595.2 [M+H]+.

Example 236

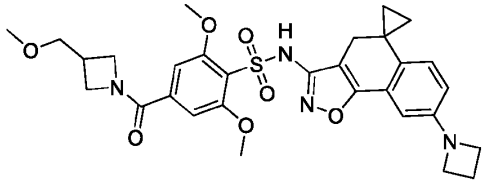
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(2-oxa-6-azaspiro[3.4]octane-6-carbonyl)benzenesulfonamide



[1113] Example 236 was prepared according to General Procedure 1 of Example 220, using the relevant amine from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 6.85 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 2.1 Hz, 2H), 6.55 (d, J = 3.0 Hz, 1H), 6.37 – 6.35 (m, 1H), 4.72 – 4.28 (m, 5H), 4.12-3.58 (m, 10H), 3.47 (d, J = 7.2 Hz, 2H), 3.44 (s, 4H), 2.34 – 2.23 (m, 2H), 2.21 – 2.06 (m, 2H), 0.84 (s, 2H), 0.66 (s, 2H). MS (ESI, *m/z*): 607.3 [M+H]+.

Example 237

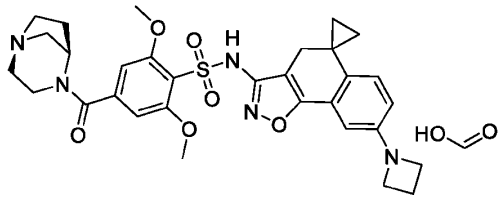
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(3-(methoxymethyl)azetidine-1-carbonyl)benzenesulfonamide



[1114] Example 237 was prepared according to General Procedure 1 of Example 220, using 3-(methoxymethyl)azetidine from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.8 (br s, 1H), 6.88 – 6.83 (m, 3H), 6.54 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 8.4, 2.4 Hz, 1H), 4.43 – 3.92 (m, 4H), 3.89 – 3.69 (m, 10H), 3.48 (d, J = 6.3 Hz, 2H), 3.27 (s, 3H), 2.51 (s, 2H), 2.35 – 2.23 (m, 3H), 0.93 – 0.77 (m, 2H), 0.69 – 0.64 (m, 2H). MS (ESI, *m/z*): 595.2 $[M+H]^+$.

Example 238

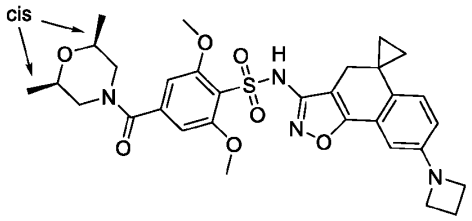
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-((1R,5R)-1,4-diazabicyclo[3.2.1]octane-4-carbonyl)-2,6-dimethoxybenzenesulfonamide formate



[1115] Example 238 was prepared according to General Procedure 1 of Example 220, using the relevant amine from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.18 (d, J = 3.3 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 4.5 Hz, 2H), 6.56 (d, J = 2.4 Hz, 1H), 6.39 – 6.35 (m, 1H), 3.80 (d, J = 3.6 Hz, 12H), 3.02 (d, J = 13.2 Hz, 3H), 2.92 (s, 3H), 2.34 – 2.23 (m, 4H), 2.00 (s, 1H), 0.85 (s, 2H), 0.71 – 0.63 (m, 2H). MS (ESI, *m/z*): 606.6 [M+H]+.

Example 239

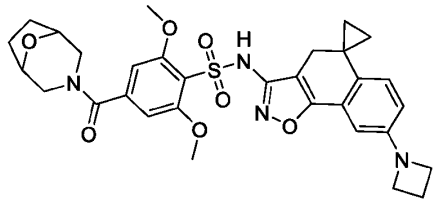
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(cis-2,6-dimethylmorpholine-4-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1116] Example 239 was prepared according to General Procedure 2 of Example 201, using cis-2,6-dimethylmorpholine from a commercial source. ^{1}H NMR (500 MHz, DMSO-d6) δ 10.75 (s, 1H), 6.86 (d, J = 8.5 Hz, 1H), 6.74 (s, 2H), 6.55 (d, J = 2.5 Hz, 1H), 6.38 – 6.36 (m, 1H), 4.34 (d, J = 13.0 Hz, 1H), 3.82 – 3.75 (m, 10H), 3.55 (s, 2H), 3.26 (d, J = 13.0 Hz, 1H), 2.84 – 2.75 (m, 1H), 2.44 (d, J = 11.5 Hz, 1H), 2.29 – 2.23 (m, 2H), 1.14 (d, J = 6.5 Hz, 3H), 0.96 (d, J = 6.5 Hz, 3H), 0.87 – 0.81 (m, 2H), 0.69 – 0.63 (m, 2H). MS (ESI, *m/z*): 609.3 $[M+H]^+$.

Example 240

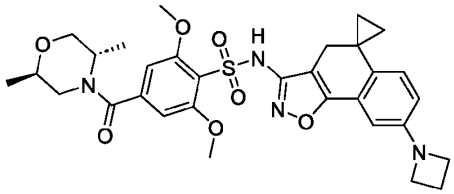
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1117] Example 240 was prepared according to General Procedure 1 of Example 220, using 8-oxa-3-azabicyclo[3.2.1]octane from a commercial source. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.85 (d, J = 8.4 Hz, 1H), 6.72 (s, 2H), 6.55 (d, J = 2.4 Hz, 1H), 6.38 – 6.35 (m, 1H), 4.38 (s, 1H), 4.12 (d, J = 16.4 Hz, 3H), 3.79 (d, J = 2.8 Hz, 10H), 3.05 – 2.84 (m, 3H), 2.86 (d, J = 12.0 Hz, 1H), 2.31 – 2.22 (m, 2H), 1.86 – 1.62 (m, 5H), 0.87 – 0.80 (m, 2H), 0.69 – 0.61 (m, 2H). MS (ESI, *m/z*): 607.2 [M+H]+.

Example 241

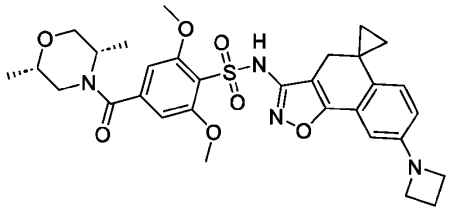
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-((2R,5S)-2,5-dimethylmorpholine-4-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1118] Example 241 was prepared according to General Procedure 1 of Example 220, using (2R,5S)-2,5-dimethylmorpholine from a commercial source. ^{1}H NMR (300 MHz, DMSO-d6) δ 6.85 (d, J = 8.4 Hz, 1H), 6.69 (s, 2H), 6.54 (d, J = 2.4 Hz, 1H), 6.44 – 6.34 (m, 1H), 3.95 (s, 2H), 3.89 – 3.84 (m, 1H), 3.84 – 3.71 (m, 10H), 3.47 – 3.33 (m, 2H), 3.28 (d, J = 11.7 Hz, 1H), 2.35 – 2.19 (m, 2H), 1.24 (d, J = 6.9 Hz, 3H), 1.16 (d, J = 6.6 Hz, 3H), 0.89 – 0.79 (m, 2H), 0.71 – 0.61 (m, 2H). MS (ESI, *m/z*): 609.0 [M+H]+.

Example 242

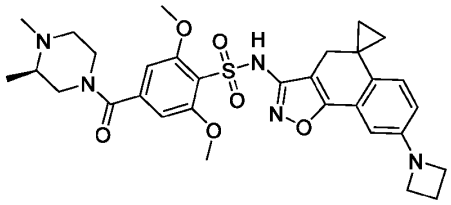
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-((2S,5S)-2,5-dimethylmorpholine-4-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1119] Example 242 was prepared according to General Procedure 1 of Example 220, using (2S,5S)-2,5-dimethylmorpholine from a commercial source. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.74 (br s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.75 (s, 1H), 6.68 (s, 1H), 6.55 (t, J = 2.4 Hz, 1H), 6.38 (dd, J = 8.4, 2.4 Hz, 1H), 4.54 – 4.12 (m, 1H), 3.85 – 3.75 (m, 10H), 3.72 – 3.55 (m, 2H), 3.54 – 3.40 (m, 2H), 3.18 – 2.92 (m, 1H), 2.77 – 2.63 (m, 1H), 2.54 (s, 1H), 2.36 – 2.20 (m, 2H), 1.28 – 1.13 (m, 5H), 0.98 (d, J = 6.0 Hz, 1H), 0.90 – 0.81 (m, 2H), 0.66 (d, J = 3.7 Hz, 2H). MS (ESI, *m/z*): 609.1 $[M+H]^+$.

Example 243

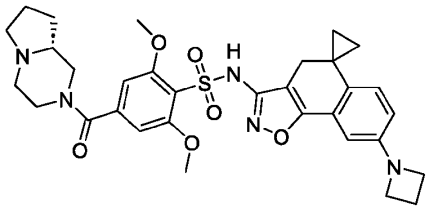
(R)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(3,4-dimethylpiperazine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1120] Example 243 was prepared according to General Procedure 1 of Example 220, using (R)-1,2-dimethylpiperazine from a commercial source (Firster Biopharm, CF-30177). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.71 (br s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.71 (s, 2H), 6.55 (d, J = 2.4 Hz, 1H), 6.38 (dd, J = 8.4, 2.4 Hz, 1H), 4.26 – 4.11 (s, 1H), 3.85 – 3.72 (s, 11H), 3.27 – 2.90 (m, 2H), 2.89 – 2.57 (m, 2H), 2.36 – 2.20 (m, 1H), 2.10 – 1.93 (m, 2H), 2.04 (s, 2H), 1.24 (d, J = 6.9 Hz, 1H), 1.04 (d, J = 6.1 Hz, 2H), 0.90 – 0.77 (m, 4H), 0.70 – 0.61 (s, 2H). MS (ESI, *m/z*): 608.1 [M+H]+.

Example 244

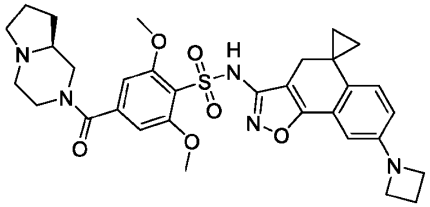
(R)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(octahydropyrrolo[1,2-a]pyrazine-2-carbonyl)benzenesulfonamide



[1121] Example 244 was prepared according to General Procedure 1 of Example 220, using (R)-octahydropyrrolo[1,2-a]pyrazine from a commercial source (Bide Pharmatech Co., Ltd, BD167044). ^{1}H NMR (500 MHz, DMSO-d6) δ 10.78 (s, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.72 (s, 2H), 6.56 (d, J = 2.5 Hz, 1H), 6.40 – 6.35 (m, 1H), 4.60 – 4.40 (m, 1H), 3.89 – 3.70 (m, 10H), 3.52 – 3.43 (m, 1H), 3.19 – 2.78 (m, 4H), 2.38 – 2.21 (m, 2H), 2.12 – 1.98 (m, 2H), 1.98 – 1.78 (m, 1H), 1.75 – 1.54 (m, 3H), 1.38 – 1.31 (m, 1H), 1.25 – 1.21 (m, 1H), 1.21 – 1.11 (m, 1H), 0.96 – 0.84 (m, 2H), 0.68 – 0.61 (m, 2H). MS (ESI, *m/z*): 620.0 $[M+H]^+$.

Example 245

(S)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(octahydropyrrolo[1,2-a]pyrazine-2-carbonyl)benzenesulfonamide



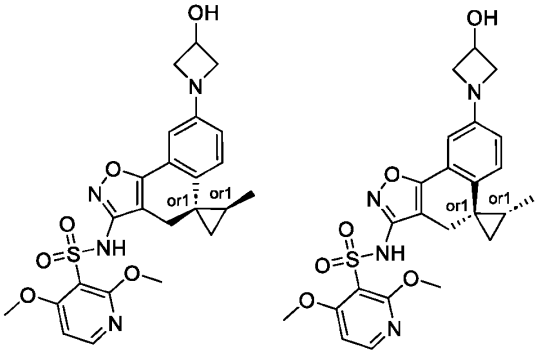
[1122] Example 245 was prepared according to General Procedure 1 of Example 220, using (S)-octahydropyrrolo[1,2-a]pyrazine from a commercial source (Accela ChemBio Co., Ltd, SY003947). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.74 (br s, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.67 – 6.46 (m, 3H), 6.37 – 6.27 (m, 1H), 4.62 – 4.31 (m, 2H), 3.91 – 3.68 (m, 9H), 3.63 – 3.43 (m, 1H), 3.19 – 2.94 (m, 2H), 2.91 – 2.69 (s, 1H), 2.43 (s, 2H), 2.34 – 2.19 (m, 2H), 2.13 – 1.97 (m, 2H), 1.97 – 1.73 (m, 2H), 1.73 – 1.50 (m, 3H), 1.44 – 1.07 (m, 2H), 0.94 – 0.77 (m, 2H), 0.69 – 0.58 (m, 2H). MS (ESI, *m/z*): 620.1 [M+H]+.

Example 246

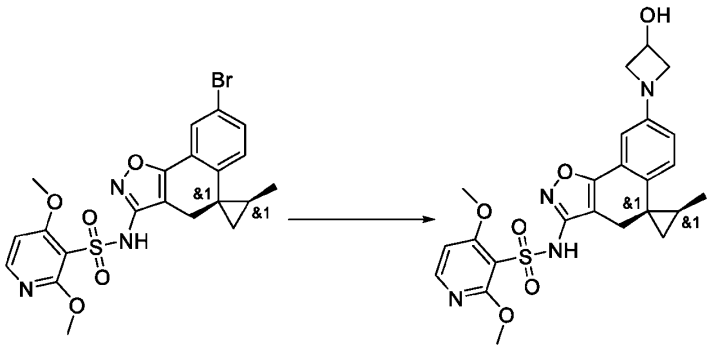
Rel-N-((1R,2S)-8'-(3-hydroxyazetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide

Example 247

Rel-N-((1S,2R)-8'-(3-hydroxyazetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide

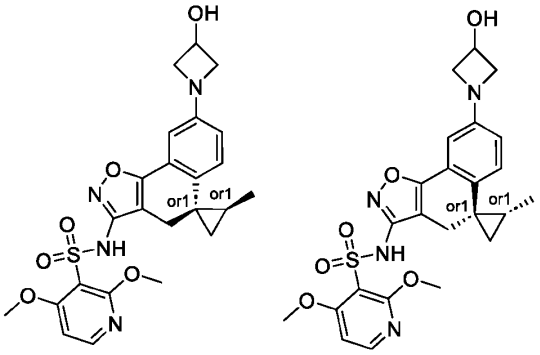


[1123] Step 1. Rac-*cis*-N-(8'-(3-hydroxyazetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide



[1124] A mixture of rac-*cis*-N-(8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (150.0 mg, 0.30 mmol, 1.00 equiv, Intermediate O), azetidin-3-ol (217.0 mg, 2.96 mmol, 10.00 equiv), Pd-PEPPSI-IHeptCl (58.0 mg, 0.06 mmol, 0.20 equiv) and Cs_2CO_3 (290.0 mg, 0.89 mmol, 3.00 equiv) in NMP (2.0 mL) was stirred at 100 °C for 2 h under N_2 atmosphere. The resulting mixture was combined with another 4 batches (670.0 mg in total) and directly purified by reverse phase flash chromatography on C18 gel (5-30% acetonitrile in water (contained 0.1 % NH_4HCO_3) to afford *cis*-N-(8'-(3-hydroxyazetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (400.0 mg, 29%) as a yellow solid. MS (ESI, *m/z*): 499 $(M + H)^+$.

[1125] Step 2. rel-N-((1R,2S)-8'-(3-hydroxyazetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide and rel-N-((1S,2R)-8'-(3-hydroxyazetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide



[1126] Rac-*cis*-N-(8'-(3-hydroxyazetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (400.0 mg, 0.80 mmol, 1.00 equiv) was resolved with Chiral-Prep-HPLC. The absolute stereochemistry was not determined. (Column: CHIRAL ART Amylose-SA, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MEOH(0.1% 2M NH_3-MEOH); Flow rate: 100 mL/min; Gradient: isocratic 50% B; RT1(min): 8; RT2(min): 12; Sample Solvent: MEOH; Injection Volume: 3 mL; Number Of Runs: 10)。

[1127] rel-N-((1R,2S)-8'-(3-hydroxyazetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (116.0 mg, 29%) as a yellow solid (1st peak). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.90 (br s, 1H), 8.22 (d, J = 6.0 Hz, 1H), 6.92 (d, J = 6.0 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.40 (dd, J = 8.4, 2.4 Hz, 1H), 5.59 (d, J = 6.6 Hz, 1H), 4.61-4.46 (m, 1H), 4.10-4.00 (m, 2H), 3.92-3.84 (m, 6H), 3.47 (dd, J = 7.8, 5.1 Hz, 2H), 2.74-2.52 (m, 2H), 1.15-1.00 (m, 5H), 0.38-0.32 (m, 1H). MS (ESI, *m/z*): 499 $(M + H)^+$.

[1128] rel-N-((1S,2R)-8'-(3-hydroxyazetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (84.5 mg, 21%) as a yellow solid (2nd peak). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.90 (br s, 1H), 8.22 (d, J = 6.0 Hz, 1H), 6.92 (d, J = 6.0 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.40 (dd, J = 8.4, 2.4 Hz, 1H), 5.59 (d, J = 6.6 Hz, 1H), 4.61-4.46 (m, 1H), 4.10-4.00 (m, 2H), 3.92-

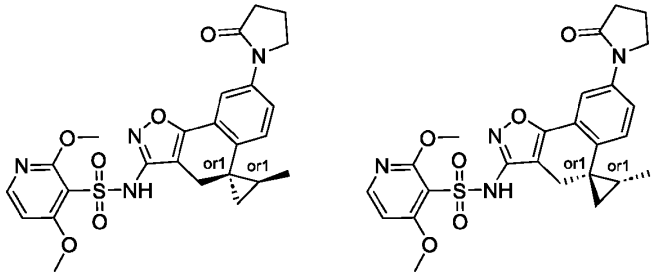
3.84 (m, 6H), 3.47 (dd, J = 7.8, 5.1 Hz, 2H), 2.74-2.52 (m, 2H), 1.15-1.00 (m, 5H), 0.38-0.32 (m, 1H). MS (ESI, m/z): 499 $(M + H)^+$.

Example 248

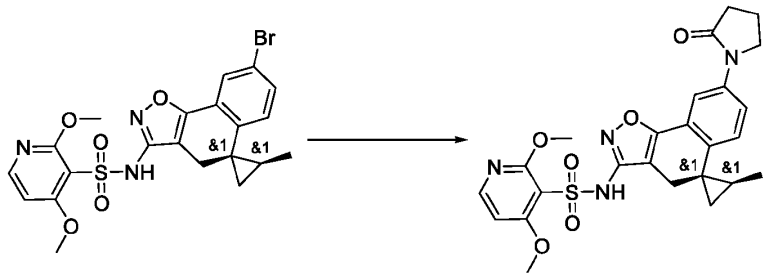
Rel-2,4-dimethoxy-N-((1R,2S)-2-methyl-8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide

Example 249

Rel-2,4-dimethoxy-N-((1S,2R)-2-methyl-8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide



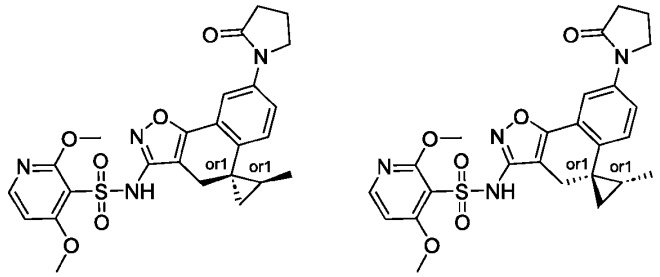
[1129] Step 1. Rac-*cis*-2,4-dimethoxy-N-2-methyl-8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide



[1130] A mixture of cis-N-(8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (100.0 mg, 0.20 mmol, 1.00 equiv, Intermediate O), BrettPhos Pd G3 (35.8 mg, 0.04mmol, 0.2 equiv), pyrrolidin-2-one (84.1 mg, 0.99 mmol, 5.00 equiv) and Cs2CO3 (195.6 mg, 0.60 mmol, 3.00 equiv) in 1,4-dioxane (2.5 mL) was stirred at 100 oC for 2 h under N2 atmosphere. The resulting mixture was combined with another 2 batches (same scale) and diluted with EtOAc. The organic solution was washed with brine 3 times, dried over Na2SO4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5-85% acetonitrile

in water (contained 0.05 % NH4HCO3) to afford cis-2,4-dimethoxy-N-(2-methyl-8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide (120.0 mg, 40%) as a yellow solid. MS (ESI, m/z): 511 (M + H)+.

[1131] Step 2. rel-2,4-dimethoxy-N-((1R,2S)-2-methyl-8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide and rel-2,4-dimethoxy-N-((1S,2R)-2-methyl-8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide.



[1132] Rac-cis-2,4-dimethoxy-N-(2-methyl-8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide (100.0 mg, 0.20 mmol, 1.00 equiv) was resolved with Chiral-Prep-HPLC. The absolute stereochemistry was not determined. (Column: CHIRAL ART Amylose-SA, 3*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: MEOH(0.1% 2M NH3-MEOH); Flow rate: 100 mL/min; Gradient: isocratic 60% B; RT1(min): 4.5; RT2(min): 6.5; Sample Solvent: MEOH; Injection Volume: 4.9 mL; Number Of Runs: 4).

[1133] rel-2,4-dimethoxy-N-((1R,2S)-2-methyl-8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide (isomer 1) (26.7 mg, 26%) as a yellow solid (1st peak). 1H NMR (300 MHz, DMSO-d6) δ 10.97 (br s, 1H), 8.22 (d, J = 6.0 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.54 (dd, J = 8.7, 2.4 Hz, 1H), 7.02 (d, J = 8.7 Hz, 1H), 6.92 (d, J = 6.0 Hz, 1H), 3.92-3.77 (m, 8H), 2.82-2.56 (m, 2H), 2.52-2.45 (m, 2H), 2.13-1.97 (m, 2H), 1.26-1.08 (m, 5H), 0.50-0.42 (m, 1H). MS (ESI, m/z): 511

[1134] rel-2,4-dimethoxy-N-((1S,2R)-2-methyl-8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide (isomer 2) (22.0 mg, 22%) as a yellow solid (2nd peak). 1H NMR (300 MHz, DMSO-d6) δ 10.97 (br s, 1H), 8.22 (d, J = 6.0 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.54 (dd, J = 8.7, 2.4 Hz, 1H), 7.02 (d, J = 8.7 Hz, 1H), 6.92 (d, J = 6.1 Hz, 1H), 3.92-3.77 (m, 8H), 2.82-2.56 (m, 2H), 2.52-2.45

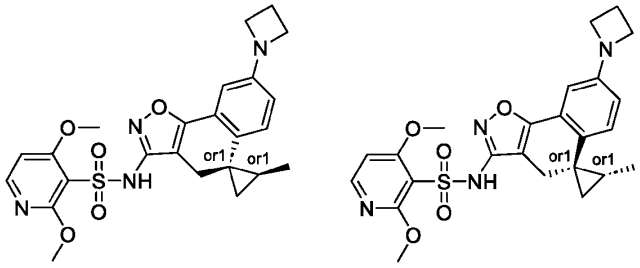
(m, 2H), 2.13-1.97 (m, 2H), 1.26-1.08 (m, 5H), 0.50-0.42 (m, 1H). MS (ESI, m/z): 511 (M + H)+.

Example 250

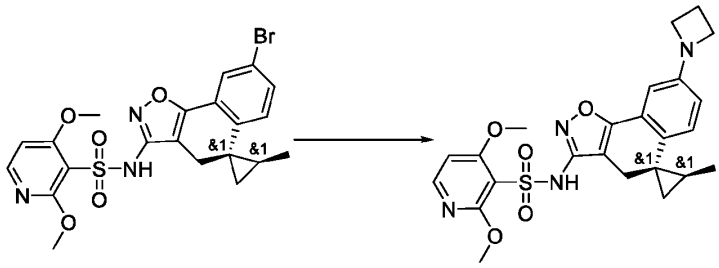
Rel-N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide

Example 251

Rel-N-((1S,2R)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide



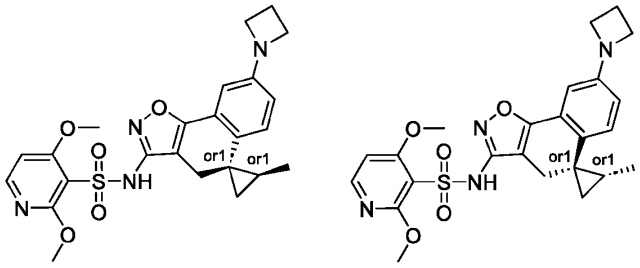
[1135] Step 1. Rac-*cis*-N-(8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide



[1136] A mixture of rac-cis-N-(8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (160.0 mg, 0.32 mmol, 1.00 equiv, Intermediate O), azetidine (91.2 mg, 1.60 mmol, 5.00 equiv), Pd-PEPPSI-IHeptCl (29.2 mg, 0.03 mmol, 0.10 equiv) and Cs2CO3 (313.0 mg, 0.96 mmol, 3.00 equiv) in NMP (5.0 mL) was stirred at 100 °C for 2 h under N2 atmosphere. The resulting mixture was purified directly by reverse phase flash chromatography on C18 gel (5% to 90% acetonitrile in water (contained 0.1% NH4HCO3)) to afford cis-N-(8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (88.8 mg, 58%) as an off-white solid. 1H NMR (300 MHz, DMSO-d6) δ 8.09 (d, J = 6.0 Hz,

1H), 7.68 (br s, 1H), 6.86 – 6.75 (m, 2H), 6.47 (d, J = 2.4 Hz, 1H), 6.32 (dd, J = 8.4, 2.4 Hz, 1H), 3.92 – 3.64 (m, 10H), 2.77 – 2.40 (m, 2H), 2.36 – 2.16 (m, 2H), 1.30 – 0.85 (m, 5H), 0.37 – 0.29 (m, 1H). MS (ESI, m/z): 483.1 (M + H)+.

[1137] Step 2. rel-N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide and rel-N-((1S,2R)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide



[1138] The rac-cis-N-(8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (100.0 mg) was resolved with SFC.

[1139] The absolute stereochemistry was not determined. Column: CHIRAL ART Amylose-SA, 3*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: IPA: DCM=1: 1(0.1% 2M NH3.MEOH); Flow rate: 100 mL/min; Gradient: isocratic 50% B; RT1(min): 3.4; RT2(min): 4.7; Sample Solvent: MEOH; Injection Volume: 3 mL; Number of Runs: 15

[1140] rel-N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (22.4 mg, 22%) as an off-white solid. (1st peak). 1H NMR (300 MHz, DMSO-d6) δ 10.92 (br s, 1H), 8.23 (d, J = 6.0 Hz, 1H), 6.92 (d, J = 6.0 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 6.38 (dd, J = 8.4, 2.4 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.83 – 3.73 (m, 4H), 2.78 – 2.53 (m, 2H), 2.32 – 2.21 (m, 2H), 1.19 – 0.96 (m, 5H), 0.41 – 0.27 (m, 1H). MS (ESI, m/z): 483.1 (M + H)+.

[1141] rel-N-((1S,2R)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (7.2 mg, 7%) as a white solid. (2nd peak). 1H NMR (400 MHz, DMSO-d6) δ 10.84 (br s, 1H), 8.21 (d, J = 6.0 Hz, 1H), 6.91 (d, J = 6.0 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 2.4 Hz, 1H), 6.37 (dd, J =

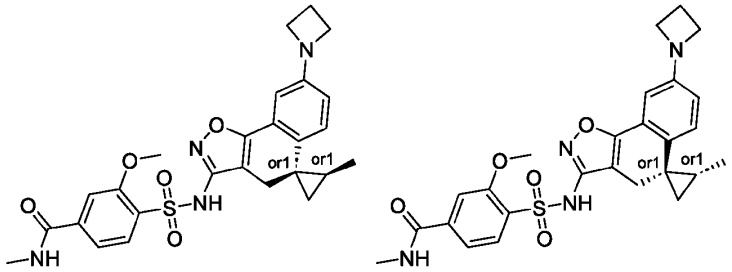
8.4, 2.4 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.83 – 3.73 (m, 4H), 2.75 – 2.52 (m, 2H), 2.32 – 2.21 (m, 2H), 1.18 – 0.98 (m, 5H), 0.41 – 0.27 (m, 1H). MS (ESI, m/z): 483.1 (M + H)+.

Example 252

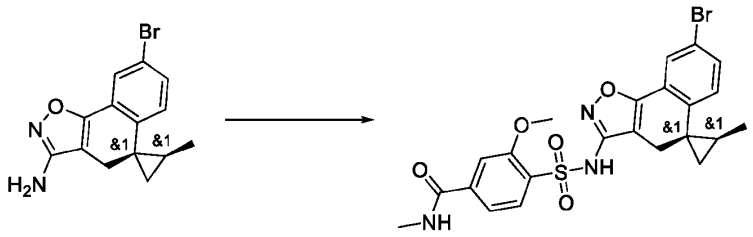
Rel-4-(N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide

Example 253

Rel-4-(N-((1S,2R)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide

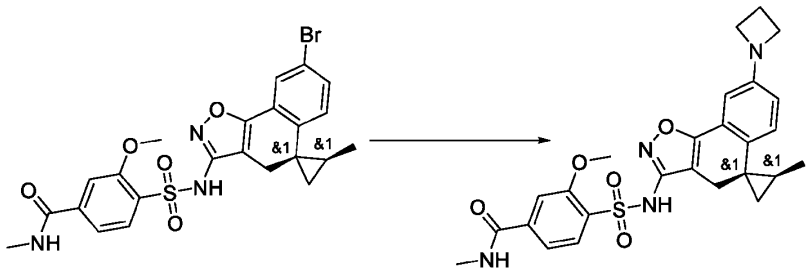


[1142] Step 1. Rac-*cis*-4-(N-(8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide



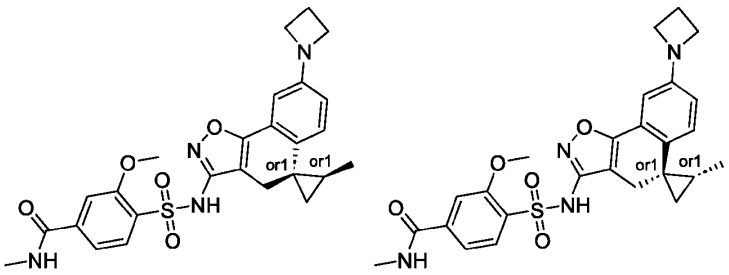
[1143] A mixture of rac-cis-8'-bromo-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-amine (250.0 mg, 0.819 mmol, 1.00 equiv, Intermediate L) and 2-methoxy-4-(methylcarbamoyl)benzenesulfonyl chloride (302.0 mg, 1.147 mmol, 1.40 equiv) in pyridine (5 mL) was stirred at 80 °C for 2 h. The resulting mixture was combined with another batch (10.0 mg) and purified directly by reverse phase flash chromatography on C18 gel (0-80% acetonitrile in water (contained 0.05% NH4HCO3)) to afford cis-4-(N-(8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide (210.0 mg, 48.1%) as a white solid. MS (ESI, m/z): 532.0 (M + H)+.

[1144] Step 2. Rac-*cis*-4-(N-(-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide



[1145] A mixture of rac-cis-4-(N-(8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide (200.0 mg, 0.376 mmol, 1.00 equiv), azetidine (107.0 mg, 1.880 mmol, 5.00 equiv), Pd-PEPPSI-IHeptCl (37.0 mg, 0.038 mmol, 0.1 equiv) and Cs2CO3 (490.0 mg, 1.504 mmol, 4.00 equiv) in NMP (10 mL) was stirred at 100 °C for 1 h under N2 atmosphere. The resulting mixture was combined with another batch (10.0 mg) and purified directly by reverse phase flash chromatography on C18 gel (0-60% acetonitrile in water (contained 0.05% NH4HCO3)) and further purified by Prep-HPLC (5-50% acetonitrile in water (contained 0.05% NH4HCO3)) to afford cis-4-(N-(-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide (90.0 mg, 47.1%) as a white solid. MS (ESI, m/z): 509.1 (M + H)+.

[1146] Step 3. rel-4-(N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide and rel-4-(N-((1S,2R)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide



[1147] Rac-*cis*-2,4-dimethoxy-N-(2-methyl-8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide (100.0 mg,

0.20 mmol, 1.0 equiv) was resolved with Chiral-Prep-HPLC. The absolute stereochemistry was not determined.

[1148] rel-4-(N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide (29.2 mg, 32.4%) as an off-white solid (1st peak). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.02 (br s, 1H), 8.63 (d, J = 5.1 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.55 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 6.42 – 6.31 (m, 1H), 3.89 (s, 3H), 3.77 (t, J = 7.2 Hz, 4H), 2.79 (d, J = 4.5 Hz, 3H), 2.74 – 2.56 (m, 2H), 2.35 – 2.17 (m, 2H), 1.34 – 0.97 (m, 6H), 0.42 – 0.35 (m, 1H). MS (ESI, m/z): 509.1 $(M + H)^+$.

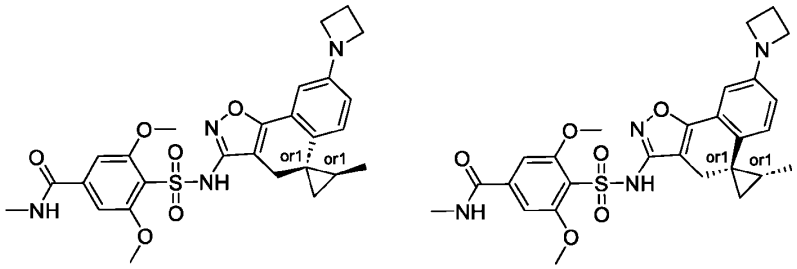
[1149] rel-4-(N-((1S,2R)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3-methoxy-N-methylbenzamide (27.3 mg, 30.33%) as a yellow solid (2nd peak). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.02 (br s, 1H), 8.64 (d, J = 4.8 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 1.5 Hz, 1H), 7.48 (dd, J = 8.1, 1.5 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 8.4, 2.4 Hz, 1H), 3.90 (s, 3H), 3.77 (t, J = 7.2 Hz, 4H), 2.79 (d, J = 4.5 Hz, 3H), 2.74 – 2.56 (m, 2H), 2.35 – 2.17 (m, 2H), 1.34 – 0.97 (m, 6H), 0.42 – 0.35 (m, 1H). MS (ESI, m/z): 509.1 $(M + H)^+$.

Example 254

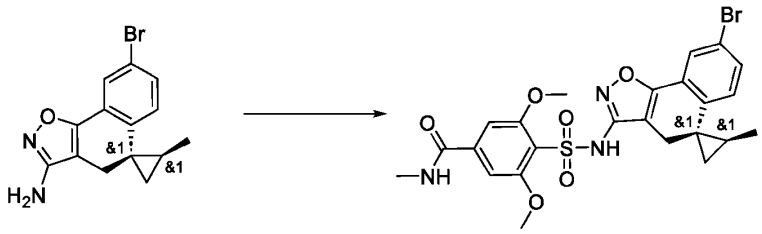
Rel-4-(N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide

Example 255

Rel-4-(N-((1S,2R)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide

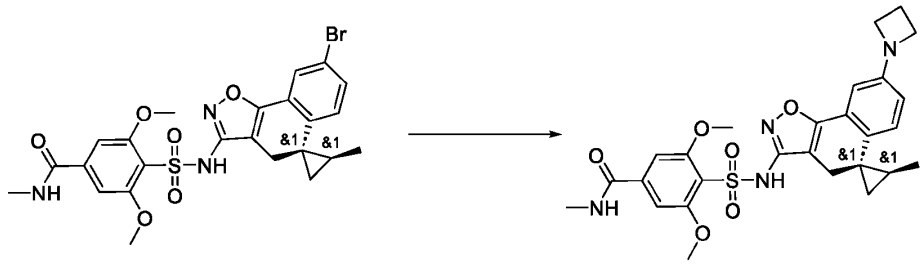


[1150] Step 1. Rac-cis-4-(N-(8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



[1151] To a mixture of rac-cis-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (100.0 mg, 0.32 mmol, 1.00 equiv, Intermediate L) in THF (4.0 mL) was added t-AmONa (144.0 mg, 1.31 mmol, 4.00 equiv) in THF (4.0 mL) at 0 oC over 10 min and to this solution was added dropwise a solution of 2,6-dimethoxy-4-(methylcarbamoyl)benzenesulfonyl chloride (192.0 mg, 0.65 mmol, 2.00 equiv) at 0 oC over 10 min in THF (2.0 mL). The resulting mixture was stirred at 0 oC for 1 h under N2 atmosphere and then combined with another 3 batch (same scale) and diluted with NH4Cl4 solution. The resulting mixture was filtered; the filter cake was washed with water. The residue was purified by flash chromatography on silica gel (0-20% DCM in MeOH) to afford cis-4-(N-(8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (380 mg, 51%) as a white solid. MS (ESI, m/z): 562.0 (M + H)+.

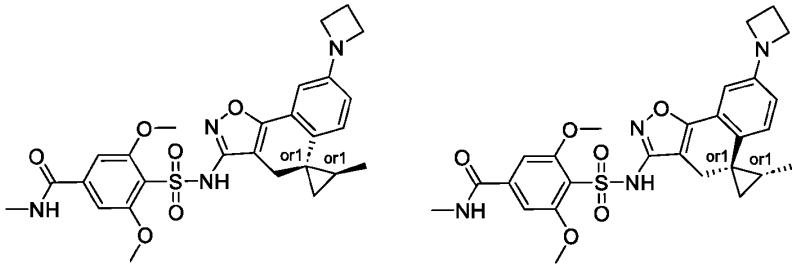
[1152] Step 2. Rac-cis-4-(N-(8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



[1153] A mixture of rac-cis- 4-(N-(8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (350.0 mg, 0.62 mmol, 1.00 equiv), azetidine (177.0 mg, 3.11 mmol, 5.00 equiv), Pd-PEPPSI-IHeptCl (60.0 mg, 0.06 mmol, 0.10 equiv) and Cs2CO3 (608.0 mg, 1.86 mmol, 3.00 equiv) in NMP (5.0 mL) was stirred at 100 °C for 2 h under N2 atmosphere and then allowed to rt and diluted with water. The resulting mixture was acidified to pH ~ 7 with acetic acid and then

extracted with EtOAc 3 times. The combined organic layers were washed with brine, dried over Na2SO4, concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-10% MeOH in DCM) to afford cis-4-(N-(8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (144 mg, 42%) as a yellow solid. MS (ESI, m/z): 539.1 (M + H)+.

[1154] Step 3. rel-4-(N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide; and rel-4-(N-((1S,2R)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



[1155] Rac-cis-4-(N-(8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (144 mg) was resolved with Chiral-Prep-HPLC. The absolute stereochemistry was not determined. Column: CHIRAL ART Cellulose-SC, 3*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: MeOH: ACN=1: 1(0.1% 2M NH3-MeOH); Flow rate: 100 mL/min; Gradient (B%): isocratic 50% B; RT1(min): 5.5; RT2(min): 7; Sample Solvent: MEOH; Injection Volume: 2 mL; Number Of Runs: 15

[1156] rel-4-(N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (60.7 mg, 42%) as a brown solid (1st peak). 1H NMR (400 MHz, DMSO-d6) δ 10.78 (br s, 1H), 8.62 (q, J = 4.4 Hz, 1H), 7.15 (s, 2H), 6.82 (d, J = 8.8 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 6.39 – 6.35 (m, 1H), 3.85 (s, 6H), 3.78 (t, J = 7.2 Hz, 4H), 2.79 (d, J = 4.4 Hz, 3H), 2.67 (d, J = 16.8 Hz, 1H), 2.56 (s, 1H), 2.28 – 2.26 (m, 2H), 1.23 (s, 1H), 1.10 (d, J = 5.2 Hz, 3H), 1.05 – 1.03 (m, 2H). MS (ESI, m/z): 539.1 (M + H)+.

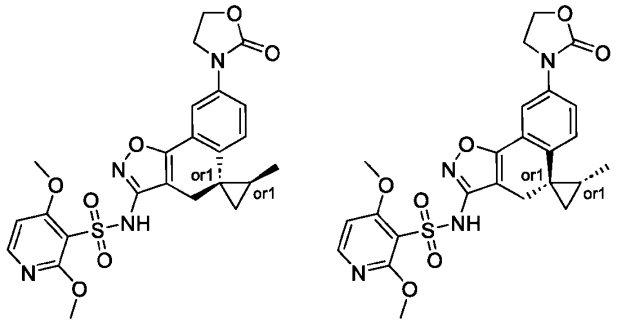
[1157] rel-4-(N-((1S,2R)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (63.1 mg, 43%) as a brown solid (2nd peak). 1H NMR (400 MHz, DMSO-d6) δ 10.78 (br s, 1H), 8.62 (d, J = 4.8 Hz, 1H), 7.15 (s, 2H), 6.82 (d, J = 8.4 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 6.37 – 6.35 (m, 1H), 3.85 (s, 6H), 3.78 (t, J = 7.2 Hz, 4H), 2.79 (d, J = 4.4 Hz, 3H), 2.72 – 2.54 (m, 2H), 2.28 – 2.26 (m, 2H), 1.24 (s, 1H), 1.10 (d, J = 5.2 Hz, 3H), 1.04 (d, J = 3.2 Hz, 2H). MS (ESI, m/z): 539.1 (M + H)+.

Example 256

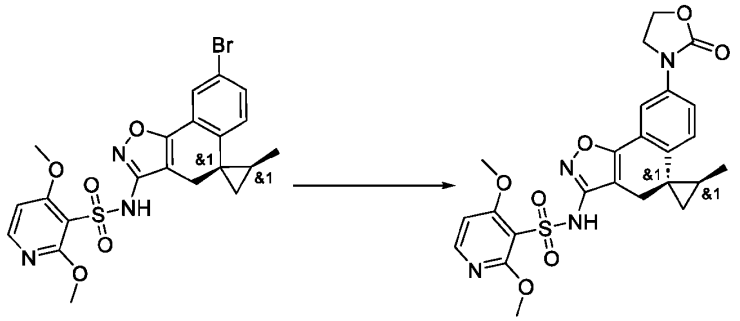
Rel-2,4-dimethoxy-N-((1R,2S)-2-methyl-8'-(2-oxooxazolidin-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide

Example 257

Rel-2,4-dimethoxy-N-((1S,2R)-2-methyl-8'-(2-oxooxazolidin-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide

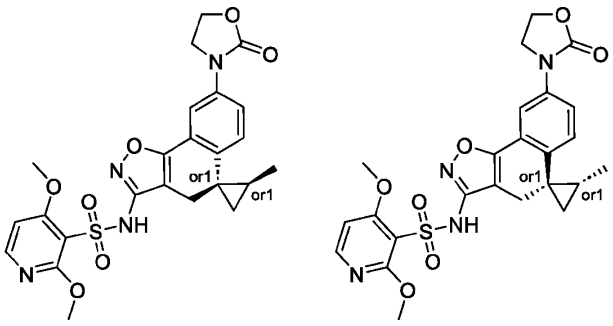


[1158] Step 1: Rac-cis-2,4-dimethoxy-N-(2-methyl-8'-(2-oxooxazolidin-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide



[1159] A mixture of rac-cis-N-(8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,4-dimethoxypyridine-3-sulfonamide (200.0 mg, 0.40 mmol, 1.00 equiv, **Example 247**, Step 1), oxazolidin-2-one (174.0 mg, 2.00 mmol, 5.00 equiv), Pd-PEPPSI-IHeptCl (38.9 mg, 00.04 mmol, 0.10 equiv) and Cs2CO3 (391.2 mg, 1.20 mmol, 3.00 equiv) in NMP (2.0 mL) was stirred at 100 °C for 2 h under N2 atmosphere. The resulting mixture was purified directly by reverse phase flash chromatography on C18 gel (0-40% acetonitrile in water (contained 0.05% NH4HCO3)) to afford to afford cis-2,4-dimethoxy-N-(2-methyl-8'-(2-oxooxazolidin-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide (70.8 mg, 35%) as a white solid. 1H NMR (400 MHz, DMSO-d6) δ 11.00 (br s, 1H), 8.20 (d, J = 6.0 Hz, 1H), 7.74 (d, J = 2.4 Hz, 1H), 7.45 (dd, J = 8.6, 2.4 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 6.90 (d, J = 6.0 Hz, 1H), 4.43 (dd, J = 9.2, 6.8 Hz, 2H), 4.06 (dd, J = 9.2, 6.8 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 2.81 – 2.54 (m, 2H), 1.26 – 1.02 (m, 5H), 0.53 – 0.39 (m, 1H). MS (ESI, m/z): 513.1 (M + H)+.

[1160] Step 2. rel-2,4-dimethoxy-N-((1R,2S)-2-methyl-8'-(2-oxooxazolidin-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide andrel-2,4-dimethoxy-N-((1S,2R)-2-methyl-8'-(2-oxooxazolidin-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide



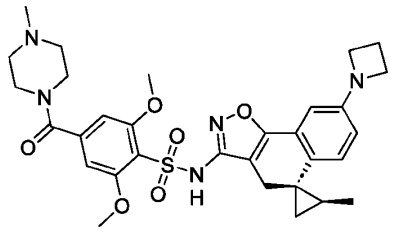
[1161] The product rac-cis-2,4-dimethoxy-N-(2-methyl-8'-(2-oxooxazolidin-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide (80.0 mg, 0.16 mmol, 1.00 equiv) was resolved with Chiral-Prep-HPLC. The absolute stereochemistry was not determined. (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: HEX(0.5% 2M NH3-MeOH), Mobile Phase B: ETOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient (B%): isocratic 50; Wave Length: 220/254 nm; RT1(min): 18.619; RT2(min): 25.438; Sample Solvent: EtOH; Injection Volume: 1.5 mL; Number Of Runs: 5)

[1162] rel-2,4-dimethoxy-N-((1R,2S)-2-methyl-8'-(2-oxooxazolidin-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide (17.4 mg, 22%) as a white solid (1st peak). 1H NMR (400 MHz, DMSO-d6) δ 11.00 (br s, 1H), 8.20 (d, J = 6.0 Hz, 1H), 7.74 (d, J = 2.4 Hz, 1H), 7.45 (dd, J = 8.6, 2.4 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 6.90 (d, J = 6.0 Hz, 1H), 4.43 (dd, J = 9.2, 6.8 Hz, 2H), 4.06 (dd, J = 9.2, 6.8 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 2.81 – 2.54 (m, 2H), 1.26 – 1.02 (m, 5H), 0.53 – 0.39 (m, 1H). MS (ESI, m/z): 513.1 (M + H)+.

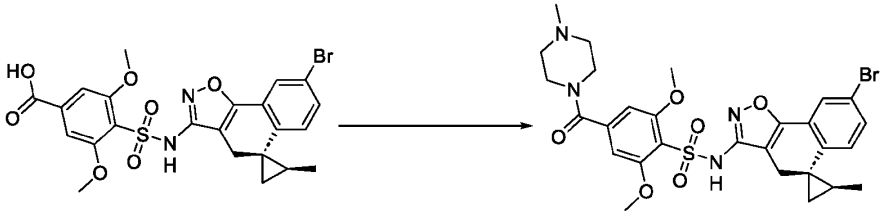
[1163] rel-2,4-dimethoxy-N-((1S,2R)-2-methyl-8'-(2-oxooxazolidin-3-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)pyridine-3-sulfonamide (19.8 mg, 25%) as a white solid (2nd peak). 1H NMR (400 MHz, DMSO-d6) δ 11.00 (br s, 1H), 8.21 (d, J = 6.0 Hz, 1H), 7.74 (d, J = 2.4 Hz, 1H), 7.45 (dd, J = 8.6, 2.4 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 6.90 (d, J = 6.0 Hz, 1H), 4.43 (dd, J = 9.2, 6.8 Hz, 2H), 4.06 (dd, J = 9.2, 6.8 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 2.81 – 2.54 (m, 2H), 1.26 – 1.02 (m, 5H), 0.53 – 0.39 (m, 1H). MS (ESI, m/z): 513.1 (M + H)+.

Example 258

N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(4-methylpiperazine-1-carbonyl)benzenesulfonamide – Prepared by General Procedure 3

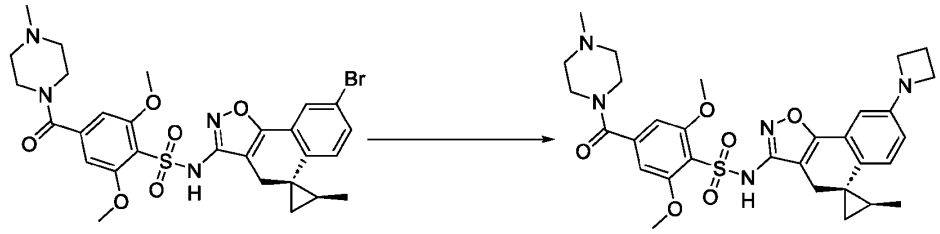


[1164] Step 1. N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(4-methylpiperazine-1-carbonyl)benzenesulfonamide



[1165] To a stirred solution of 4-(N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoic acid (5 g, 9.10 mmol, 1.00 equiv, Intermediate N), 1-methylpiperazine (1.8 g, 18.20 mmol, 2.00 equiv) and DIEA (3.5 g, 27.30 mmol, 3.00 equiv) in DMF (50.0 mL) at 0 °C was added HATU (6.9 g, 18.20 mmol, 2.00 equiv) in portions. The resulting mixture was allowed to warm up to ambient temperature and stirred at this temperature for another 2 h and then combined with another batch (0.5 g). The mixture was diluted with EtOAc. The organic solution was washed with brine 3 times, dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-10% methanol in DCM) to afford N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(4-methylpiperazine-1-carbonyl)benzenesulfonamide (7 g, >100%) as a yellow solid. MS (ESI, m/z): 631.2 (M + H)+.

[1166] Step 2. N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(4-methylpiperazine-1-carbonyl)benzenesulfonamide

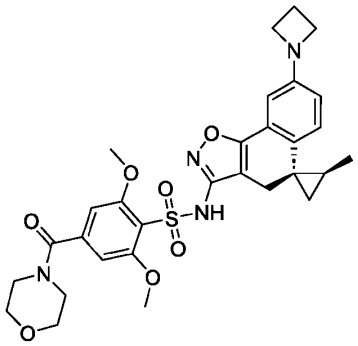


[1167] A mixture of N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(4-methylpiperazine-1-carbonyl)benzenesulfonamide (850.0 mg, 1.35 mmol, 1.00 equiv), azetidine (384.0 mg, 6.73 mmol, 5.00 equiv), Pd-PEPPSI-IHeptCl (131.0 mg, 0.14 mmol, 0.10 equiv) and Cs2CO3 (877.0 mg, 2.69 mmol, 2.0 equiv) in NMP (16.0 mL) was stirred at 100 °C for 1 h under N2 atmosphere. The resulting mixture was combined with another 7 batches (same scale) and then slowly poured into NH4Cl solution at 0 oC. The mixture was extracted with EtOAc 3 times. The combined organic layers were washed with brine 3 times, dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-10% methanol in DCM) to afford N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(4-methylpiperazine-1-carbonyl)benzenesulfonamide (1.56 g, 24%) as a yellow solid. 1H NMR

(300 MHz, DMSO-d6) δ 10.76 (br s, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.72 (s, 2H), 6.52 (d, J = 2.4 Hz, 1H), 6.40 – 6.33 (m, 1H), 3.86 – 3.70 (m, 10H), 3.58 (d, J = 8.4 Hz, 2H), 3.28 – 3.17 (m, 2H), 2.74 – 2.53 (m, 2H), 2.41 – 2.33 (m, 2H), 2.33 – 2.21 (m, 4H), 2.19 (s, 3H), 1.15 – 0.96 (m, 5H), 0.32 (s, 1H). MS (ESI, m/z): 608.1 (M + H)+.

Example 259

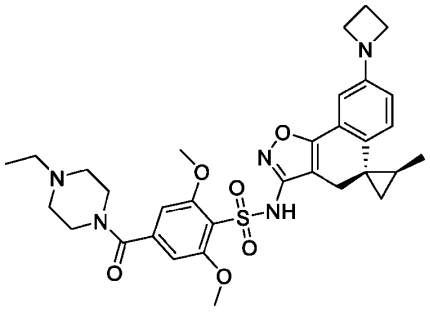
N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(morpholine-4-carbonyl)benzenesulfonamide



[1168] Example 259 was prepared according to General Procedure 3, using Intermediate N and morpholine (Step 1) and azetidine (step 2). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.79 (s, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.77 (s, 2H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.43-6.33 (m, 1H), 3.85-3.73 (m, 10H), 3.71-3.58 (m, 4H), 3.57-3.48 (m, 2H), 3.33-3.22 (m, 2H), 2.77-2.56 (m, 2H), 2.35-2.20 (m, 2H), 1.15-1.01 (m, 5H), 0.33 (s, 1H). MS (ESI, *m/z*): 595.2 $(M + H)^+$.

Example 260

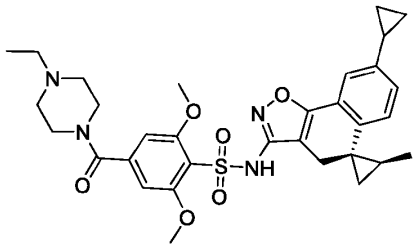
N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(4-ethylpiperazine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1169] A mixture of N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(4-ethylpiperazine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide (160.0 mg, 0.25 mmol, 1.00 equiv, Intermediate P), azetidine (142.0 mg, 2.48 mmol, 10.00 equiv), Pd-PEPPSI-IHeptCl (24.0 mg, 0.03 mmol, 0.10 equiv) and Cs_2CO_3 (404.0 mg, 1.24 mmol, 5.00 equiv) in NMP (10.0 mL) was stirred at 100 °C for 1 h under N_2 atmosphere. The resulting mixture was purified by reverse phase flash chromatography on C18 gel (0% to 60% acetonitrile in water) to afford N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(4-ethylpiperazine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide (20.5 mg, 13%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.75 (d, J = 8.5 Hz, 1H), 6.58 (s, 2H), 6.44 (d, J = 2.5 Hz, 1H), 6.28 (dd, J = 8.4, 2.5 Hz, 1H), 3.91 – 3.71 (m, 5H), 3.66 (s, 6H), 3.58 (br s, 2H), 2.57 (s, 1H), 2.61 – 2.51 (m, 2H), 2.45 – 2.19 (m, 9H), 1.15 – 0.89 (m, 7H), 0.31 (d, J = 5.4 Hz, 1H). MS (ESI, *m/z*): 622.1 $(M + H)^+$. MS (ESI, *m/z*): 622.1 $(M + H)^+$.

Example 261

N-((1R,2S)-8'-cyclopropyl-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(4-ethylpiperazine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1170] A mixture of N-((1R,2S)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(4-ethylpiperazine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide (130 mg, 0.20 mmol, 1.00 equiv, Intermediate P), cyclopropylboronic acid (52 mg, 0.60 mmol, 3.00 equiv), Pd(OAc)2 (0.90 mg, 0.004 mmol, 0.02 equiv), S-Phos (2 mg, 0.006 mmol, 0.03 equiv) and Cs2CO3 (197 mg, 0.60 mmol, 3.00 equiv) in toluene (5 mL) and H2O (0.5 mL) was stirred at 100 °C for 2 h under N2 atmosphere. The resulting mixture was diluted with water and neutralized with NH4Cl solution to pH ~ 7 and then extracted with EtOAc 3 times. The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-10% MeOH in DCM) and further purified by Prep-HPLC

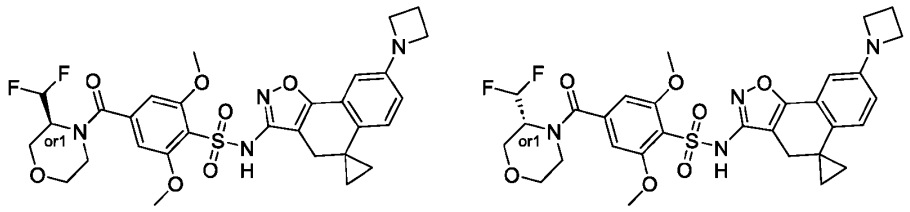
(10-70% acetonitrile in water (contained 0.05% NH4HCO3)) to afford N-((1R,2S)-8'-cyclopropyl-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(4-ethylpiperazine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide (16.1 mg, 13.18%) as a white solid. 1H NMR (300 MHz, DMSO-d6) δ 10.82 (br s, 1H), 7.18 (d, J = 2.1 Hz, 1H), 7.08 – 6.98 (m, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.71 (s, 2H), 3.79 (s, 6H), 3.60 (s, 2H), 2.75 – 2.62 (m, 1H), 2.60 (s, 1H), 2.46 – 2.37 (m, 2H), 2.36 – 2.26 (m, 3H), 2.00 – 1.85 (m, 1H), 1.12 (s, 5H), 1.05 – 0.87 (m, 5H), 0.72 – 0.60 (m, 2H), 0.43 – 0.37 (m, 1H). MS (ESI, m/z): 607.0 (M + H)+ .

Example 262

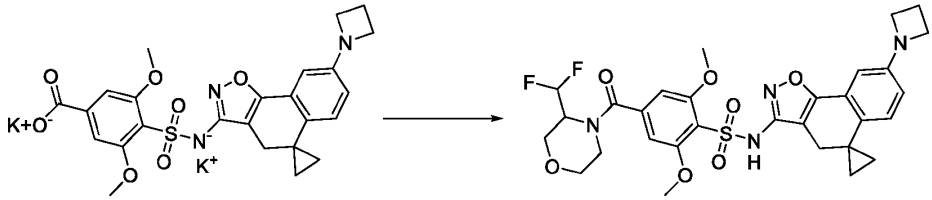
Rel-(*R*)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(3-(difluoromethyl)morpholine-4-carbonyl)-2,6-dimethoxybenzenesulfonamide

Example 263

Rel-(*S*)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(3-(difluoromethyl)morpholine-4-carbonyl)-2,6-dimethoxybenzenesulfonamide



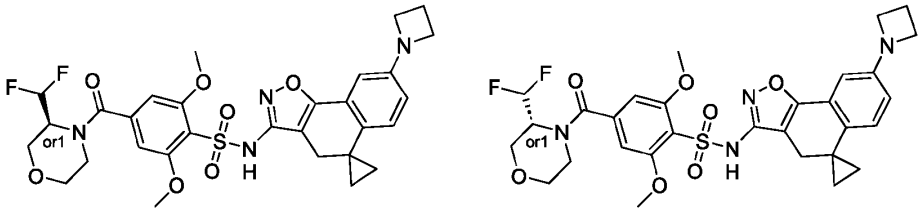
[1171] Step 1. N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(3-(difluoromethyl)morpholine-4-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1172] To a stirred mixture of potassium (8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)((4-carboxylato-2,6-dimethoxyphenyl)sulfonyl)amide (180.0 mg, 0.35 mmol, 1.00 equiv, Intermediate D), 3-(difluoromethyl)morpholine (72.3 mg, 0.53 mmol, 1.50 equiv) and 1-methyl-1H-imidazole (144.4 mg, 1.76 mmol, 5.00 equiv) in acetonitrile (15.0 mL) at ambient temperature was added TCFH (148.1 mg, 0.52

mmol, 1.50 equiv). The resulting mixture was stirred at 70 °C for 1 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5~70% acetonitrile in water) to afford N-[8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]-4-[3-(difluoromethyl)morpholine-4-carbonyl]-2,6-dimethoxybenzenesulfonamide (70.0 mg, 31%) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.74 (br s, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.72 (s, 2H), 6.66 – 6.24 (m, 3H), 4.78 – 3.10 (m, 17H), 2.51 (s, 2H), 2.33 – 2.21 (m, 2H), 0.87 – 0.82 (m, 2H), 0.69 – 0.63 (m, 2H). MS (ESI, *m/z*): 631.1 $(M + H)^+$.

[1173] Step 2. rel-(S)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(3-(difluoromethyl)morpholine-4-carbonyl)-2,6-dimethoxybenzenesulfonamide andrel-(R)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(3-(difluoromethyl)morpholine-4-carbonyl)-2,6-dimethoxybenzenesulfonamide



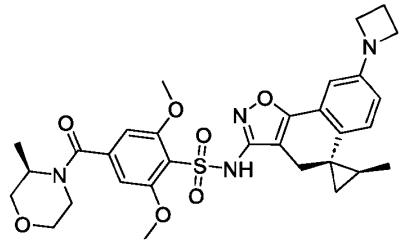
[1174] N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(3-(difluoromethyl)morpholine-4-carbonyl)-2,6-dimethoxybenzenesulfonamide (62.0 mg) was resolved with SFC. The absolute stereochemistry was not determined. Column: CHIRALPAK IH 3*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: IPA; Flow rate: 70 mL/min; Gradient (B%): isocratic 50% B; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 8.68; RT2(min): 13.15; Sample Solvent: MEOH; Injection Volume: 4..49 mL

[1175] rel-(S)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(3-(difluoromethyl)morpholine-4-carbonyl)-2,6-dimethoxybenzenesulfonamide (27.2 mg, 45%) as an off-white solid (1st peak). 1H NMR (300 MHz, DMSO-d6) δ 10.74 (br s, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.72 (s, 2H), 6.66 – 6.24 (m, 3H), 4.78 – 3.10 (m, 17H), 2.51 (s, 2H), 2.33 – 2.21 (m, 2H), 0.87 – 0.82 (m, 2H), 0.69 – 0.63 (m, 2H). 19F NMR (282 MHz, DMSO-d6) δ -124.98, -125.42. MS (ESI, m/z): 631.1 (M + H)+.

[1176] rel-(R)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(3-(difluoromethyl)morpholine-4-carbonyl)-2,6-dimethoxybenzenesulfonamide (23.7 mg, 38%) as an off-white solid (2nd peak). 1H NMR (400 MHz, DMSO-d6) δ 10.75 (br s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.73 (s, 2H), 6.60 – 6.28 (m, 3H), 4.75 – 3.13 (m, 17H), 2.50 (s, 2H), 2.36 – 2.21 (m, 2H), 0.89 – 0.80 (m, 2H), 0.70 – 0.62 (m, 2H). 19F NMR (282 MHz, DMSO-d6) δ -124.99, -125.43. MS (ESI, m/z): 631.1 (M + H)+.

Example 264

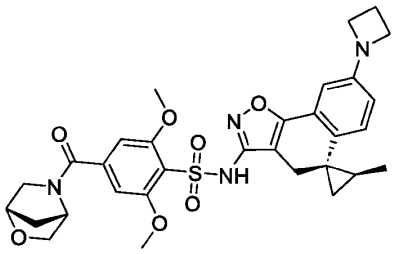
N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((R)-3-methylmorpholine-4-carbonyl)benzenesulfonamide



[1177] Example 264 was prepared according to General Procedure 3, using Intermediate N and (R)-3-methylmorpholine (Step 1) and azetidine (Step 2). ^{1}H NMR (300 MHz, DMSO) δ 10.78 (s, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.78 – 6.70 (m, 2H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.37 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.88 – 3.73 (m, 11H), 3.60 – 3.51 (m, 2H), 3.45 – 3.34 (m, 2H), 3.26 – 3.00 (m, 2H), 2.71 – 2.52 (m, 2H), 2.35 – 2.23 (m, 2H), 1.31 – 1.19 (m, 4H), 1.13 – 1.00 (m, 5H), 0.32 (s, 1H). MS (ESI, *m/z*): 609.0 $(M + H)^+$.

Example 265

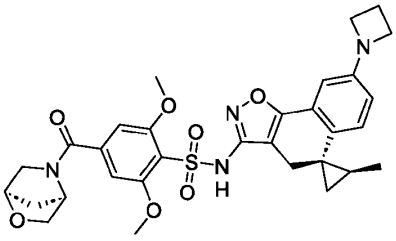
N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1178] Example 265 was prepared according to General Procedure 3, using Intermediate N and (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane (Step 1) and azetidine (Step 2). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.77 (br s, 1H), 6.88 – 6.74 (m, 3H), 6.51 (d, J = 2.4 Hz, 1H), 6.40 – 6.29 (m, 1H), 4.84 – 4.24 (m, 2H), 3.96 – 3.59 (m, 12H), 3.52 – 3.39 (m, 1H), 3.29 – 3.14 (m, 1H), 2.75 – 2.53 (m, 2H), 2.34 – 2.17 (m, 2H), 1.95 – 1.68 (m, 2H), 1.13 – 0.95 (m, 5H), 0.32 (s, 1H). MS (ESI, *m/z*): 607.2 $(M + H)^+$.

Example 266

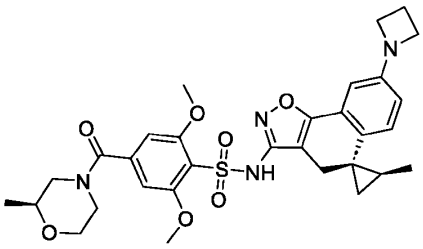
N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1179] Example 266 was prepared according to General Procedure 3, using Intermediate N and (1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptane (Step 1) and azetidine (Step 2). ^{1}H NMR (300 MHz, DMSO) δ 10.78 (s, 1H), 6.87 – 6.79 (m, 3H), 6.53 (d, J = 2.4 Hz, 1H), 6.42 – 6.33 (m, 1H), 4.88 – 4.64 (m, 1H), 4.56 – 4.22 (m, 1H), 4.05 – 3.61 (m, 12H), 3.59 – 3.44 (m, 1H), 3.30 – 3.01 (m, 1H), 2.78 – 2.55 (m, 2H), 2.37 – 2.19 (m, 2H), 1.98 – 1.66 (m, 2H), 1.13 – 0.98 (m, 5H), 0.34 (s, 1H). MS (ESI, *m/z*): 606.9 $(M + H)^+$.

Example 267

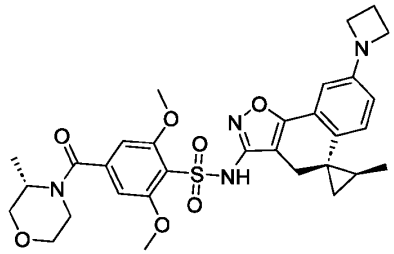
N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((S)-2-methylmorpholine-4-carbonyl)benzenesulfonamide



[1180] Example 267 was prepared according to General Procedure 3, using Intermediate N and (S)-2-methylmorpholine (Step 1) and azetidine (Step 2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.78 (s, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.76 (s, 2H), 6.52 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 8.4, 2.4 Hz, 1H), 4.29 (t, J = 15.6 Hz, 1H), 3.95 – 3.63 (m, 11H), 3.58 – 3.38 (m, 2H), 3.06 – 3.30 (m, 2H), 2.88 (t, J = 12.0 Hz, 1H), 2.75 – 2.51 (m, 2H), 2.35 – 2.19 (m, 2H), 1.20 – 0.91 (m, 8H), 0.38 – 0.27 (m, 1H). MS (ESI, *m/z*): 609.2 $(M + H)^+$.

Example 268

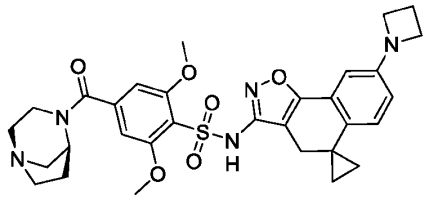
N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((S)-3-methylmorpholine-4-carbonyl)benzenesulfonamide



[1181] Example 268 was prepared according to General Procedure 3, using Intermediate N and (S)-3-methylmorpholine (Step 1) and azetidine (Step 2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (s, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.74 (s, 2H), 6.53 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 8.4, 2.4 Hz, 1H), 4.47, 4.13 (2 br s, 1H), 3.95 – 3.51 (m, 14H), 3.19 – 2.99 (m, 1H), 2.71 – 2.55 (m, 2H), 2.35 – 2.21 (m, 2H), 1.33 – 1.18 (m, 4H), 1.14 – 1.00 (m, 5H), 0.37 – 0.27 (m, 1H). MS (ESI, m/z): 609.2 $(M + H)^+$.

Example 269

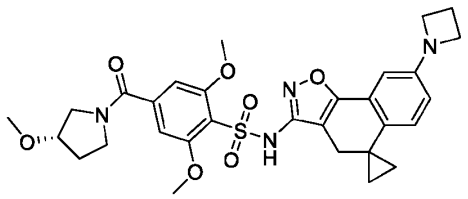
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-((1S,5S)-1,4-diazabicyclo[3.2.1]octane-4-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1182] Example 269 was prepared according to General Procedure 1, using Intermediate D and ((1S,5S)-1,4-diazabicyclo[3.2.1]octane. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 4.2 Hz, 2H), 6.57 (d, J = 2.4 Hz, 1H), 6.42 – 6.33 (m, 1H), 4.30 – 3.27 (m, 13H), 3.15 – 2.61 (m, 6H), 2.51 (s, 2H), 2.40 – 2.19 (m, 2H), 2.07 – 1.71 (m, 2H), 0.90 – 0.81 (m, 2H), 0.69 – 0.63 (m, 2H). MS (ESI, *m/z*): 606.2 $(M + H)^+$.

Example 270

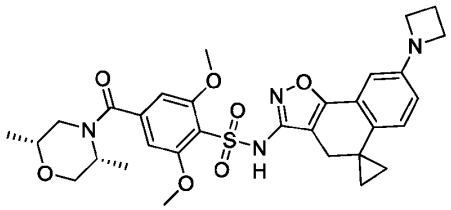
(S)-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(3-methoxypyrrolidine-1-carbonyl)benzenesulfonamide



[1183] Example 270 was prepared according to General Procedure 1, using Intermediate D and (S)-3-methoxypyrrolidine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.72 (br s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 2.4 Hz, 2H), 6.57 (d, J = 2.4 Hz, 1H), 6.45 – 6.35 (m, 1H), 4.05 – 3.90 (m, 1H), 3.85 – 3.75 (m, 10H), 3.63 – 3.13 (m, 7H), 2.50 (s, 2H), 2.35 – 2.20 (m, 2H), 2.05 – 1.90 (m, 2H), 0.90 – 0.76 (m, 2H), 0.70 – 0.65 (m, 2H). MS (ESI, m/z): 595.3 $(M + H)^+$.

Example 271

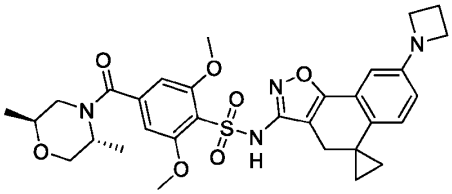
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-((2R,5R)-2,5-dimethylmorpholine-4-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1184] Example 271 was prepared according to General Procedure 1, using Intermediate D and (2R,5R)-2,5-dimethylmorpholine hydrochloride. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.72 (br s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.72 (s, 2H), 6.56 (d, J = 2.4 Hz, 1H), 6.39 (dd, J = 8.4, 2.4 Hz, 1H), 4.09 – 3.73 (m, 13H), 2.47 – 3.27 (m, 3H), 2.51 (s, 2H) 2.38 – 2.16 (m, 2H), 1.26 (d, J = 6.6Hz, 3H), 1.18 (d, J = 6.6 Hz, 3H), 0.92 – 0.79 (m, 2H), 0.72 – 0.59 (m, 2H). MS (ESI, *m/z*): 609.2 $(M + H)^+$.

Example 272

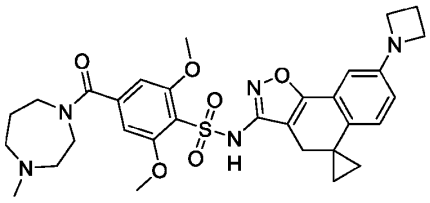
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-((2S,5R)-2,5-dimethylmorpholine-4-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1185] Example 272 was prepared according to General Procedure 1, using Intermediate D and (2S,5R)-2,5-dimethylmorpholine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.68 (br s, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.71 (s, 2H), 6.54 (d, J = 2.4 Hz, 1H), 6.36 (dd, J = 8.4, 2.4 Hz, 1H), 4.02 – 3.72 (m, 13H), 3.44 – 3.21 (m, 3H), 2.50 (s, 2H), 2.37 – 2.19 (m, 2H), 1.23 (d, J = 6.6 Hz, 3H), 1.17 (d, J = 6.6 Hz, 3H), 0.87 – 0.78 (m, 2H), 0.72 – 0.60 (m, 2H). MS (ESI, *m/z*): 609.2 $(M + H)^+$.

Example 273

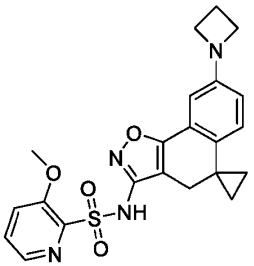
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(4-methyl-1,4-diazepane-1-carbonyl)benzenesulfonamide



[1186] Example 273 was prepared according to General Procedure 1, using Intermediate D and N-methylhomopiperazine. ^{1}H NMR (300 MHz, DMSO-*d*6) δ 6.86 (d, *J* = 8.4 Hz, 1H), 6.74 – 6.67 (m, 2H), 6.56 (d, *J* = 2.4 Hz, 1H), 6.42 – 6.32 (m, 1H), 3.91 – 3.70 (m, 10H), 3.60 (d, J = 7.8 Hz, 2H), 3.32 – 3.13 (m, 4H), 2.68 (s, 1H), 2.53 (d, J = 11.4 Hz, 3H), 2.35 – 2.21 (m, 5H), 1.92 – 1.63 (m, 2H), 1.23 (s, 1H), 0.89 – 0.79 (m, 2H), 0.70 – 0.59 (m, 2H). MS (ESI, m/z): 608.1 $(M + H)^+$.

Example 274

N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-methoxypyridine-2-sulfonamide

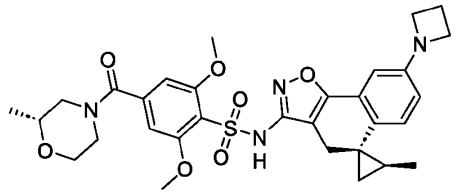


[1187] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-methoxypyridine-2-sulfonamide (180.0 mg, 0.39 mmol, 1.00 equiv, Intermediate C), azetidine (111.2 mg, 1.95 mmol, 5.00 equiv), Pd-PEPPSI-IHeptCl (37.9 mg, 0.04 mmol, 0.10 equiv) and Cs_2CO_3 (380.6 mg, 1.17 mmol, 3.00 equiv) in DMF (5.0 mL) was stirred at 80 °C for 1h under N_2 atmosphere. The resulting mixture was diluted with water and acidified with AcOH to pH ~ 6 and extracted with EtOAc 3 times. The combined organic layers were washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another 2 batches (20.0 mg x 2) and purified by reverse phase flash chromatography on C18 gel (5~40% acetonitrile in water (contained 0.05% formic acid)) to afford N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-3-methoxypyridine-2-sulfonamide (37.7 mg, 18%) as a yellow solid. ^{1}H NMR (300 MHz,

DMSO-d6) δ 8.19 (s, 1H), 8.22 – 8.16 (m, 1H), 7.83 – 7.74 (m, 1H), 7.71 – 7.65 (m, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.42 – 6.36 (m, 1H), 3.93 (s, 3H), 3.84 – 3.75 (m, 4H), 2.50 (s, 2H), 2.34 – 2.22 (m, 2H), 0.90 – 0.81 (m, 2H), 0.72 – 0.63 (m, 2H). MS (ESI, m/z): 439.0 $(M + H)^+$.

Example 275

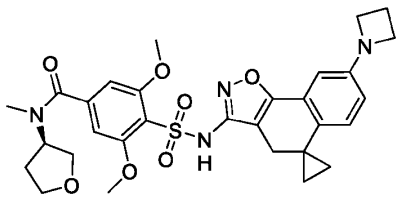
N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((R)-2-methylmorpholine-4-carbonyl)benzenesulfonamide



[1188] Example 275 was prepared according to General Procedure 3, using Intermediate N and (R)-2-methylmorpholine (Step 1) and azetidine (Step 2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.76 (s, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.76 (s, 2H), 6.52 (d, *J* = 2.4 Hz, 1H), 6.37 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.29 (t, *J* = 15.9 Hz, 1H), 3.94 – 3.61 (m, 11H), 3.59 – 3.40 (m, 3H), 3.05 – 3.29 (m, 1H), 2.96 – 2.77 (m, 1H), 2.72 – 2.51 (m, 2H), 2.35 – 2.17 (m, 2H), 1.27 – 0.89 (m, 9H), 0.37 – 0.26 (m, 1H). MS (ESI, *m/z*): 609.3 $(M + H)^+$.

Example 276

(R)-4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methyl-N-(tetrahydrofuran-3-yl)benzamide

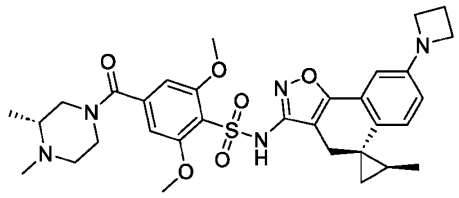


[1189] Example 276 was prepared according to General Procedure 1, using Intermediate D and (R)-N-methyltetrahydrofuran-3-amine. ^{1}H NMR (300 MHz, DMSO) δ 10.72 (s, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.81 – 6.65 (m, 2H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.43 – 6.33 (m, 1H), 5.15, 4.18 (2s, 1H), 3.99 – 3.88 (m, 1H), 3.87 – 3.71 (m, 11H), 3.71 – 3.38 (m, 3H), 3.31 (s,

1H), 2.93 – 2.70 (m, 3H), 2.37 – 2.21 (m, 2H), 2.14 – 1.79 (m, 2H), 0.90 – 0.81 (m, 2H), 0.71 – 0.62 (m, 2H). MS (ESI, *m/z*): 595.2 $(M + H)^+$.

Example 277

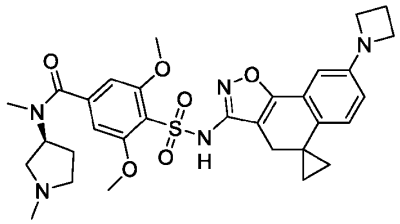
N-((1R,2S)-8'-(azetidin-1-yl)-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-((R)-3,4-dimethylpiperazine-1-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1190] Example 277 was prepared according to General Procedure 3, using Intermediate N and (R)-1,2-dimethylpiperazine (Step 1) and azetidine (Step 2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.77 (br s, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.72 (s, 2H), 6.52 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 8.4, 2.4 Hz, 1H), 4.27 – 4.10 (m, 1H), 3.88 – 3.69 (m, 10H), 3.28 – 3.11 (m, 1H), 3.07 – 2.92 (m, 2H), 2.90 – 2.72 (m, 1H), 2.71 – 2.53 (m, 2H), 2.34 – 2.21 (m, 2H), 2.18 (s, 3H), 2.05 (br s, 2H), 1.78 – 1.68 (m, 1H), 1.13 – 1.00 (m, 6H), 0.84 (d, J = 6.0 Hz, 1H), 0.32 (s, 1H). MS (ESI, *m/z*): 622.2 $(M + H)^+$.

Example 278

(S)-4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methyl-N-(1-methylpyrrolidin-3-yl)benzamide

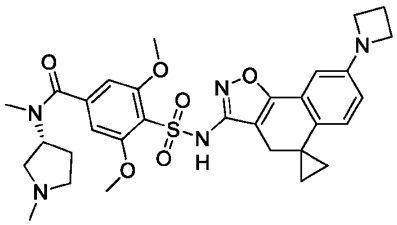


[1191] Example 278 was prepared according to General Procedure 1, using Intermediate D and (S)-N,1-dimethylpyrrolidin-3-amine. ^{1}H NMR (300 MHz, DMSO) δ 6.86 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 16.2 Hz, 2H), 6.56 (d, J = 2.4 Hz, 1H), 6.39 – 6.37 (m, 1H), 5.10 – 4.05 (m, 1H), 3.80 (d, J = 2.1 Hz, 10H), 2.93 – 2.80 (m, 4H), 2.72 (s, 2H), 2.35 – 2.22 (m, 4H), 2.17

(s, 2H), 2.07 – 1.85 (m, 4H), 0.89 – 0.79 (m, 2H), 0.70 – 0.60 (m, 2H). MS (ESI, *m/z*): 608.4 $(M + H)^+$.

Example 279

(R)-4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methyl-N-(1-methylpyrrolidin-3-yl)benzamide



[1192] Example 279 was prepared according to General Procedure 1, using Intermediate D and (R)-N,1-dimethylpyrrolidin-3-amine. ^{1}H NMR (300 MHz, DMSO) δ 10.37 (br s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 15.3 Hz, 2H), 6.57 (d, J = 2.4 Hz, 1H), 6.41 – 6.37 (m, 1H), 5.02 – 4.20 (m, 1H), 3.81 (d, J = 7.5 Hz, 10H), 3.08 – 3.04 (m, 2 H), 2.92 – 2.83 (m, 4H), 2.64 (s, 2H), 2.46 (s, 1H), 2.33 – 2.24 (m, 3H), 2.00 (s, 2H), 0.90 – 0.78 (m, 2H), 0.73 – 0.63 (m, 2H). MS (ESI, *m/z*): 608.4 $(M + H)^+$.

Example 280

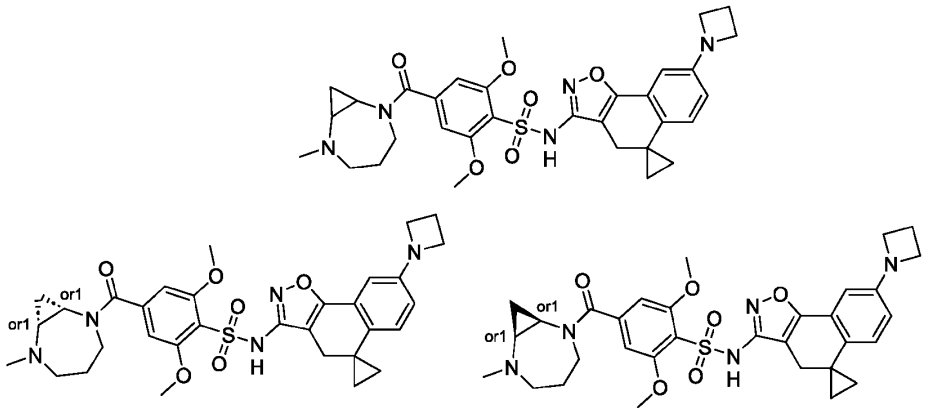
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(6-methyl-2,6-diazabicyclo[5.1.0]octane-2-carbonyl)benzenesulfonamide

Example 281

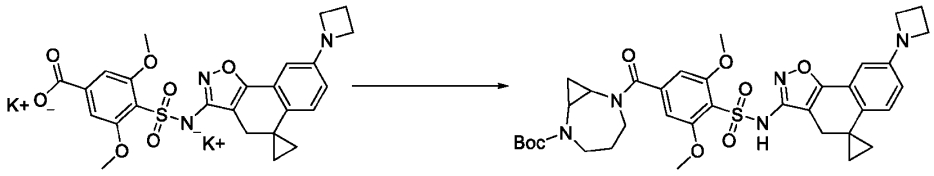
Rel-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((1S,7R)-6-methyl-2,6-diazabicyclo[5.1.0]octane-2-carbonyl)benzenesulfonamide

Example 282

Rel-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((1R,7S)-6-methyl-2,6-diazabicyclo[5.1.0]octane-2-carbonyl)benzenesulfonamide

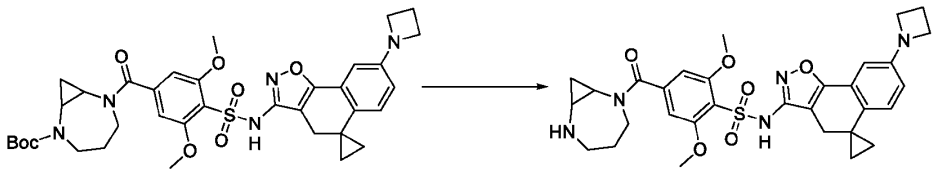


[1193] Step 1. tert-butyl 6-(4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoyl)-2,6-diazabicyclo[5.1.0]octane-2-carboxylate



[1194] tert-butyl 6-(4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoyl)-2,6-diazabicyclo[5.1.0]octane-2-carboxylate was prepared according to General Procedure 1, using Intermediate D and tert-butyl 2,6-diazabicyclo[5.1.0]octane-2-carboxylate. MS (ESI, *m/z*): 706.2 $(M + H)^+$.

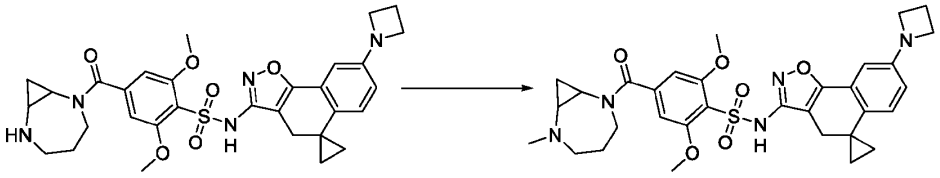
[1195] Step 2. N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazole]-3'-yl)-4-(2,6-diazabicyclo[5.1.0]octane-2-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1196] To a stirred solution of tert-butyl 6-(4-{[8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]sulfamoyl}-3,5-dimethoxybenzoyl)-2,6-diazabicyclo[5.1.0]octane-2-carboxylate (270.0 mg, 0.38 mmol, 1.00 equiv) in EtOAc (6.0 mL) at 0 oC was added HMDS (246.9 mg, 1.532 mmol, 4.00 equiv) and TMSOTf (340.0 mg,

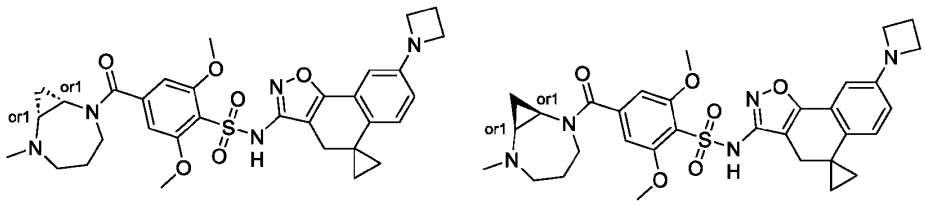
1.53 mmol, 4.00 equiv) sequentially. The resulting mixture was stirred at ambient temperature for 30 min and combined with another batch (20 mg scale) and then diluted with EtOAc. The resulting mixture was washed with brine 3 times, dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~30% MeOH in DCM) to afford N-[8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]-4-{2,6-diazabicyclo[5.1.0]octane-2-carbonyl}-2,6-dimethoxybenzenesulfonamide (170.0 mg, 73%) as a yellow solid. MS (ESI, m/z): 606.3 (M + H)+.

[1197] Step 3. N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(6-methyl-2,6-diazabicyclo[5.1.0]octane-2-carbonyl)benzenesulfonamide



[1198] To a stirred solution of N-[8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]-4-{2,6-diazabicyclo[5.1.0]octane-2-carbonyl}-2,6-dimethoxybenzenesulfonamide (160.0 mg, 0.26 mmol, 1.00 equiv) and formaldehyde solution (198.2 mg, 2.64 mmol, 10.00 equiv, 40%) in DCM (6.0 mL) and methanol (1.5 mL) at 0 oC was added NaBH3CN (66.4 mg, 1.05 mmol, 4.00 equiv) in portions. The resulting mixture was stirred at ambient temperature for another 0.5 h and then diluted with EtOAc. The resulting mixture was washed with brine 3 times, dried over Na2SO4 and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5~40% acetonitrile in water (contained 0.05% formic acid)) and flash chromatography on silica gel (0~50% EtOAc in petroleum ether) to afford rac-N-[8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]-2,6-dimethoxy-4-{6-methyl-2,6-diazabicyclo[5.1.0]octane-2-carbonyl}benzenesulfonamide (60.5 mg, 36%) as a white solid. 1H NMR (400 MHz, DMSO-d6) δ 10.68 (br s, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.82 (s, 2H), 6.54 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 8.4, 2.4 Hz, 1H), 3.92 – 2.52 (m, 16H), 2.50 (s, 2H), 2.32 – 2.25 (m, 2H), 2.20 (s, 3H), 1.95 – 1.66 (m, 3H), 0.88 – 0.81 (m, 2H), 0.70 – 0.65 (m, 2H), 0.45 – 0.38 (m, 1H). MS (ESI, m/z): 620.2 (M + H)+.

[1199] Step 4. rel-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((1S,7R)-6-methyl-2,6-diazabicyclo[5.1.0]octane-2-carbonyl)benzenesulfonamide and rel- N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((1R,7S)-6-methyl-2,6-diazabicyclo[5.1.0]octane-2-carbonyl)benzenesulfonamide



[1200] N-[8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]-2,6-dimethoxy-4-{6-methyl-2,6-diazabicyclo[5.1.0]octane-2-carbonyl}benzenesulfonamide (110.0 mg) was resolved with SFC. The absolute stereochemistry was not determined. Column: CHIRALPAK IK 2*25 cm, 5 μm; Mobile Phase A: MtBE (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: ETOH; Flow rate: 20 mL/min; Gradient (B%): isocratic 50; Wave Length: 220/254 nm; RT1(min): 6.677; RT2(min): 8.5; Sample Solvent: EtOH-HPLC; Injection Volume: 0.5 mL; Number Of Runs: 14

[1201] rel-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((1S,7R)-6-methyl-2,6-diazabicyclo[5.1.0]octane-2-carbonyl)benzenesulfonamide (43.3 mg, 39%) as a white solid (1st peak). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (brs, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.82 (s, 2H), 6.54 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 8.4, 2.4 Hz, 1H), 3.92 – 2.52 (m, 16H), 2.50 (s, 2H), 2.32 – 2.25 (m, 2H), 2.20 (s, 3H), 1.95 – 1.66 (m, 3H), 0.88 – 0.81 (m, 2H), 0.70 – 0.65 (m, 2H), 0.45 – 0.38 (m, 1H). MS (ESI, *m/z*): 620.3 $(M + H)^+$.

[1202] rel- N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((1R,7S)-6-methyl-2,6-diazabicyclo[5.1.0]octane-2-carbonyl)benzenesulfonamide (35.1 mg, 31%) as a white solid (2nd peak). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (brs, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.82 (s, 2H), 6.54 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 8.4, 2.4 Hz, 1H), 3.92 – 2.52 (m, 16H), 2.50 (s, 2H), 2.32 – 2.25 (m, 2H), 2.20 (s, 3H), 1.95 – 1.66 (m, 3H), 0.88 – 0.81 (m, 2H), 0.70 – 0.65 (m, 2H), 0.45 – 0.38 (m, 1H). MS (ESI, *m/z*): 620.1 $(M + H)^+$.

Example 283

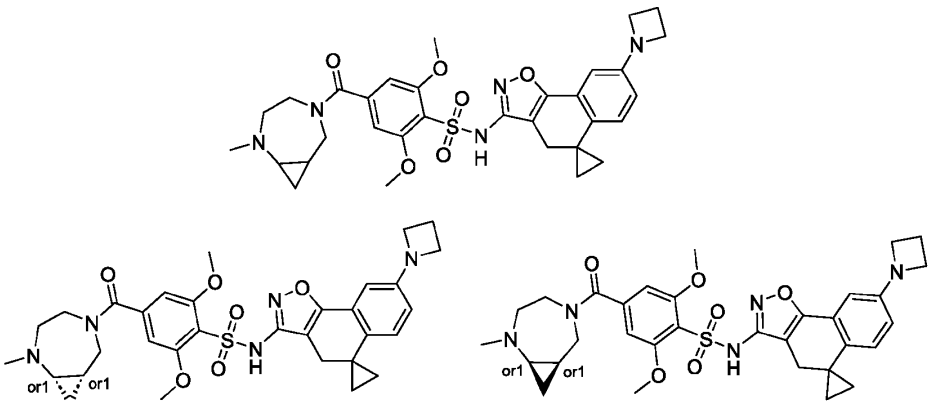
N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(2-methyl-2,5-diazabicyclo[5.1.0]octane-5-carbonyl)benzenesulfonamide

Example 284

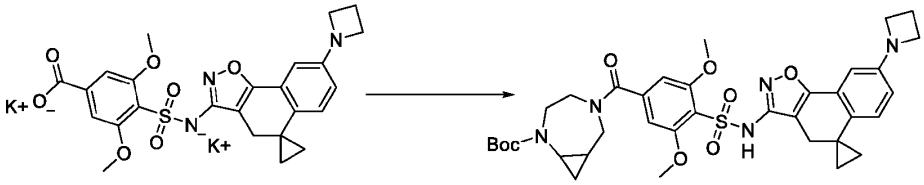
Rel-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((1S,7S)-2-methyl-2,5-diazabicyclo[5.1.0]octane-5-carbonyl)benzenesulfonamide

Example 285

Rel-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((1R,7R)-2-methyl-2,5-diazabicyclo[5.1.0]octane-5-carbonyl)benzenesulfonamide

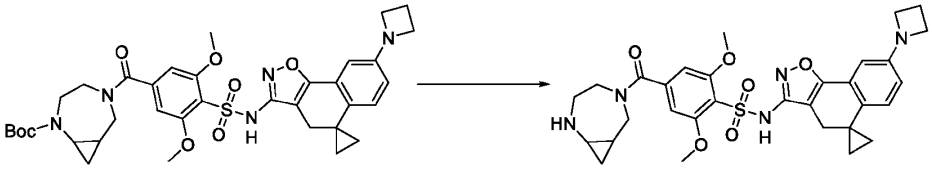


[1203] Step 1. tert-butyl 5-(4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoyl)-2,5-diazabicyclo[5.1.0]octane-2-carboxylate



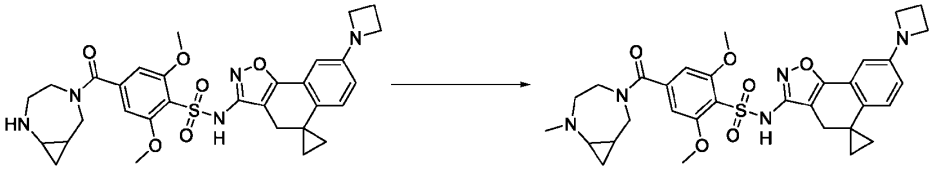
[1204] tert-butyl 5-(4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoyl)-2,5-diazabicyclo[5.1.0]octane-2-carboxylate was prepared according to General Procedure 1, using Intermediate D and tert-butyl 2,5-diazabicyclo[5.1.0]octane-2-carboxylate. MS (ESI, m/z): 706.1 (M + H)+.

[1205] Step 2. N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(2,5-diazabicyclo[5.1.0]octane-5-carbonyl)-2,6-dimethoxybenzenesulfonamide



[1206] To a stirred solution of tert-butyl 5-(4-(N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxybenzoyl)-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (700.0 mg, 0.99 mmol, 1.00 equiv) in DCM (10.0 mL) at 0 °C was added TMSOTf (440.0 mg, 1.98 mmol, 2.00 equiv) and HMDS (640.0 mg, 3.96 mmol, 4.00 equiv). The resulting mixture was stirred at ambient temperature for 1 h and then concentrated under vacuum. The residue was purified by reverse phase chromatography on C18 gel (0-50% acetonitrile in water (contained 0.05% NH4HCO3)) to afford N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(2,5-diazabicyclo[5.1.0]octane-5-carbonyl)-2,6-dimethoxybenzenesulfonamide (290.0 mg, 48%) as a white solid. MS (ESI, m/z): 606.2 (M + H)+.

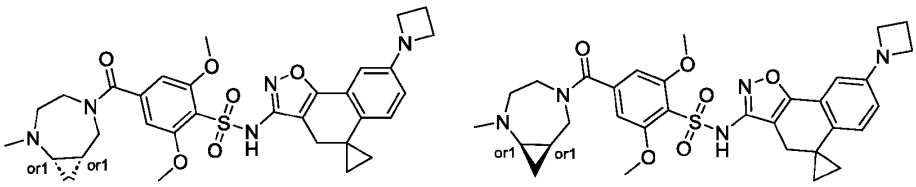
[1207] Step 3. N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(2-methyl-2,5-diazabicyclo[5.1.0]octane-5-carbonyl)benzenesulfonamide



[1208] To a stirred solution of N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-4-(2,5-diazabicyclo[5.1.0]octane-5-carbonyl)-2,6-dimethoxybenzenesulfonamide (280.0 mg, 0.46 mmol, 1.00 equiv) in DCM (10.0 mL) and MeOH (1.0 mL) at ambient temperature was added formaldehyde solution (10% in water, 0.3 mL, 0.92 mmol, 2.00 equiv). The resulting mixture was stirred at this temperature for 10 min and then to this was added $NaBH(OAc)_3$ (391.8 mg, 1.84 mmol, 4.00 equiv) in portions. The resulting mixture was stirred for another 1 h and then quenched with NH_4Cl solution and extracted with EtOAc 3 times. The combined organic layers were washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash

chromatography on silica gel (0-10% MeOH in DCM) to afford N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(2-methyl-2,5-diazabicyclo[5.1.0]octane-5-carbonyl)benzenesulfonamide (100.0 mg, 34%) as an off-white solid. MS ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.71 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 17.4 Hz, 2H), 6.56 (d, J = 2.4 Hz, 1H), 6.38 (dd, J = 8.4, 2.4 Hz, 1H), 4.58 – 4.30 (m, 1H), 3.87 – 3.73 (m, 10H), 3.46 – 3.34 (m, 1H), 3.17 – 3.02 (m, 1H), 2.96 – 2.79 (m, 1H), 2.77 – 2.64 (m, 1H), (s, 3H), 2.41 – 2.20 (m, 5H), 1.84 (s, 1H), 1.23 (s, 1H), 0.94 (s, 1H), 0.80 – 0.33 (m, 6H). MS (ESI, *m/z*): 620.3 $(M + H)^+$.

[1209] Step 4. rel-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((1S,7S)-2-methyl-2,5-diazabicyclo[5.1.0]octane-5-carbonyl)benzenesulfonamide and rel-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((1R,7R)-2-methyl-2,5-diazabicyclo[5.1.0]octane-5-carbonyl)benzenesulfonamide



[1210] N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-(2-methyl-2,5-diazabicyclo[5.1.0]octane-5-carbonyl)benzenesulfonamide (100.0 mg, 0.16 mmol, 1.00 equiv) was resolved with Chiral-Prep-HPLC. The absolute stereochemistry was not determined. Column: CHIRALPAK IA, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient (B%): isocratic 25; Wave Length: 220/254 nm; RT1(min): 24.202; RT2(min): 32.99; Sample Solvent: EtOH--HPLC; Injection Volume: 0.5 mL; Number Of Runs: 16

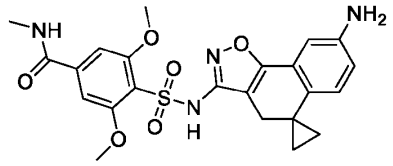
[1211] rel-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((1S,7S)-2-methyl-2,5-diazabicyclo[5.1.0]octane-5-carbonyl)benzenesulfonamide (22.5 mg, 22%) as an off-white solid (1st peak). 1H NMR (400 MHz, DMSO-d6) δ 10.72 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.73 (s, 1H), 6.67 (s, 1H), 6.59 – 6.53 (m, 1H), 6.38 (dd, J = 8.4, 2.4 Hz, 1H), 4.57 – 4.30 (m, 1H), 3.87 – 3.74 (m, 10H), 3.48 – 3.37 (m, 1H), 3.17 – 3.03 (m, 1H), 2.95 – 2.80 (m, 1H), 2.77 – 2.62 (m, 2H), 2.41 – 2.21

(m, 6H), 1.84 (br s, 1H), 1.43 (s, 1H), 1.24 (s, 1H), 0.98 – 0.32 (m, 6H). MS (ESI, m/z): 620.3 (M + H)+.

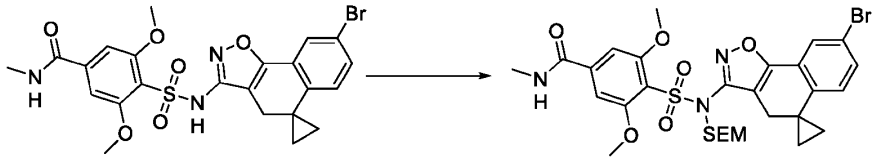
[1212] rel-N-(8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-4-((1R,7R)-2-methyl-2,5-diazabicyclo[5.1.0]octane-5-carbonyl)benzenesulfonamide (13.3 mg, 13%) as a white solid (2nd peak). 1H NMR (300 MHz, DMSO-d6) δ 10.71 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 17.4 Hz, 2H), 6.56 (d, J = 2.4 Hz, 1H), 6.38 (dd, J = 8.4, 2.4 Hz, 1H), 4.59 – 4.30 (m, 1H), 3.89 – 3.69 (m, 10H), 3.59 – 3.34 (m, 2H), 3.18 – 2.80 (m, 2H), 2.78 – 2.62 (m, 2H), 2.41 – 2.20 (m, 5H), 1.91 – 1.79 (s, 1H), 1.01 – 0.30 (m, 6H). MS (ESI, m/z): 620.3 (M + H)+.

Example 286

4-(N-(8'-amino-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



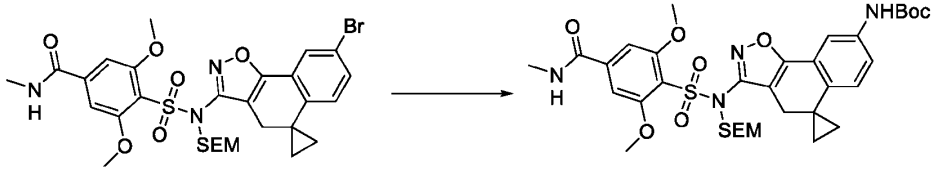
[1213] Step 1. 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



[1214] To a stirred mixture of 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (450.0 mg, 0.82 mmol, 1.00 equiv, Intermediate G) and Cs2CO3 (401.0 mg, 1.23 mmol, 1.50 equiv) in DMF (10.0 mL) at 0 °C was added dropwise a solution of SEMCl (164.0 mg, 0.98 mmol, 1.20 equiv) in DMF (1.0 mL). The resulting mixture was stirred at ambient temperature for 1 h and then diluted with EtOAc. The resulting mixture was washed with brine 3 times, dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-6% MeOH in DCM) to afford 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-

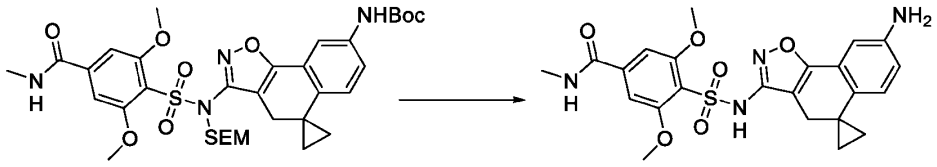
d]isoxazol]-3'-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (0.4 g, 72%) as colorless oil. MS (ESI, m/z): 678.0 (M + H)+.

[1215] Step 2. tert-butyl (3'-((2,6-dimethoxy-4-(methylcarbamoyl)-N-((2-(trimethylsilyl)ethoxy)methyl)phenyl)sulfonamido)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-8'-yl)carbamate



[1216] A mixture of 4-({8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}({[2-(trimethylsilyl)ethoxy]methyl})sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (300.0 mg, 0.44 mmol, 1.00 equiv), tert-butyl carbamate (78.0 mg, 0.66 mmol, 1.50 equiv), $Pd(OAc)_2$ (10.0 mg, 0.04 mmol, 0.10 equiv), XantPhos (26.0 mg, 0.04 mmol, 0.10 equiv) and Cs_2CO_3 (288.0 mg, 0.88 mmol, 2.00 equiv) in dioxane (10.0 mL) was stirred at 100 °C for 16 h under N_2 atmosphere. The resulting mixture was diluted with EtOAc. The mixture was washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford tert-butyl (3'-((2,6-dimethoxy-4-(methylcarbamoyl)-N-((2-(trimethylsilyl)ethoxy)methyl)phenyl)sulfonamido)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-8'-yl)carbamate (180.0 mg, 57%) as a white solid. MS (ESI, m/z): 715.0 $(M + H)^+$.

[1217] Step 3. 4-(N-(8'-amino-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide

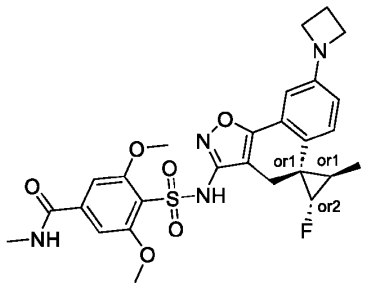


[1218] A mixture of tert-butyl N-[3'-(N-{[2-(trimethylsilyl)ethoxy]methyl}2,6-dimethoxy-4-(methylcarbamoyl)benzenesulfonamido)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-8'-yl]carbamate (160.0 mg, 0.22 mmol, 1.00 equiv) and TBAF (1.0 M in THF, 5.0 mL, 0.67 mmol, 20.0 equiv) in THF (5.0 mL) was stirred at 60 °C for 16 h and then

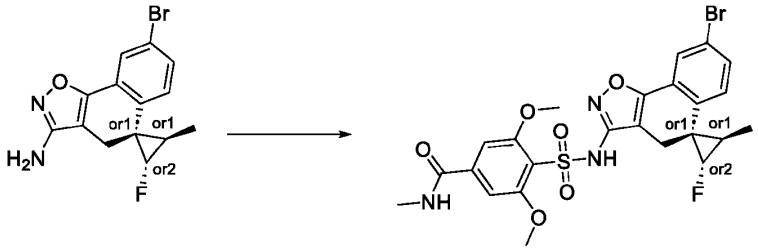
concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% MeOH in DCM) and further purified by reverse phase flash chromatography (5%-60% acetonitrile in water (contained 0.1% formic acid)) to afford 4-({8'-amino-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (21.9 mg, 20%) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d*6) δ 10.71 (br s, 1H), 8.64 –8.58 (m, 1H), 7.14 (s, 2H), 6.77 (d, *J* = 2.5 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.56 – 6.50 (m, 2.4 Hz, 1H), 5.19 (br s, 2H), 3.84 (s, 6H), 2.79 (d, *J* = 4.5 Hz, 3H), 2.49 (s, 2H), 0.84 – 0.78 (m, 2H), 0.66 – 0.61 (m, 2H). MS (ESI, m/z): 485.2 $(M + H)^+$.

Example 287

Rel-4-(N-((1S,2S,3R)-8'-(azetidin-1-yl)-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



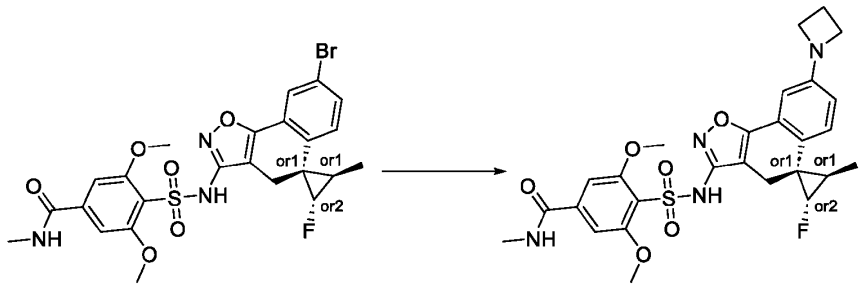
[1219] Step 1. rel-4-(N-((1S,2S,3R)-8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



[1220] A solution of rel-(1S,2S,3R)-8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (200.0 mg, 0.62 mmol, 1.00 equiv, Intermediate R) and 2,6-dimethoxy-4-(methylcarbamoyl)benzenesulfonyl chloride (308.8 mg, 1.05 mmol, 1.70 equiv) in pyridine (4.0 mL) was stirred at 80 °C for 2 h and then concentrated under vacuum. The residue was purified by trituration with acetonitrile to afford 4-(N-((1S,2S,3R)-8'-bromo-

2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (116.0 mg, 32%) as a white solid. MS (ESI, *m/z*): 580.0 $(M + H)^+$.

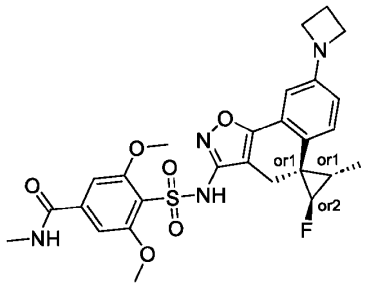
[1221] Step 2. rel-4-(N-((1S,2S,3R)-8'-(azetidin-1-yl)-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



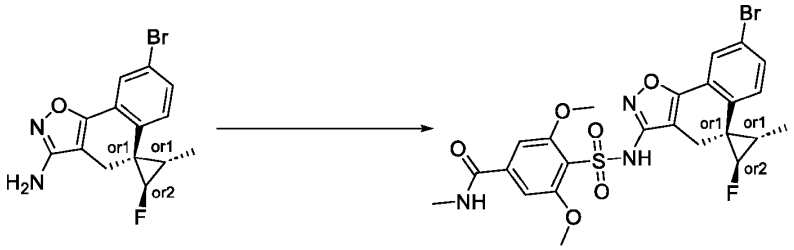
[1222] A mixture of N-(8'-bromo-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (80.0 mg, 0.13 mmol, 1.00 equiv), azetidine (39.3 mg, 0.69 mmol, 5.00 equiv), Pd-PEPPSI-IHeptCl (9.7 mg, 0.01 mmol, 0.10 equiv) and Cs_2CO_3 (84.5 mg, 0.26 mmol, 2.00 equiv) in NMP (2.0 mL) was stirred at 80 °C for 45 min under N_2 atmosphere. The resulting mixture was combined with another batch (80 mg) and purified directly by reverse phase flash chromatography on C18 gel (5-90% acetonitrile in water) and further purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford rel-4-(N-((1S,2S,3R)-8'-(azetidin-1-yl)-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (22.9 mg, 14%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.78 (br s, 1H), 8.68 – 8.58 (m, 1H), 7.16 (s, 2H), 7.11 (d, J = 8.7 Hz, 1H), 6.57 (d, J = 2.4 Hz, 1H), 6.44 – 6.35(m, 1H), 4.28 – 4.00 (m, 1H), 3.94 – 3.74 (m, 10H), 2.80 (d, J = 4.5 Hz, 3H), 2.61 – 2.02 (m, 5H), 1.25 – 1.11 (m, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -208.54. MS (ESI, *m/z*): 557.1 $(M + H)^+$.

Example 288

rel-4-(N-((1R,2R,3S)-8'-(azetidin-1-yl)-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide

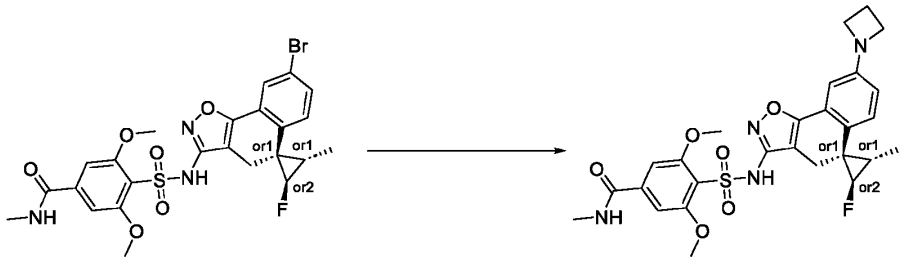


[1223] Step 1. rel-4-(N-((1R,2R,3S)-8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



[1224] A mixture of rel-(1R,2R,3S)-8'-bromo-3-fluoro-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-amine (250.0 mg, 0.77 mmol, 1.00 equiv, Intermediate S), 2,6-dimethoxy-4-(methylcarbamoyl)benzenesulfonyl chloride (340.8 mg, 1.16 mmol, 1.50 equiv, Intermediate G Step 3) and pyridine (305.9 mg, 3.87 mmol, 5.00 equiv) in acetonitrile (10.0 mL) was stirred at 80 °C for 1 h. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~100% EtOAc in petroleum ether) to afford rel-4-{[(1S,2S,3R)-8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]sulfamoyl}-3,5-dimethoxy-N-methylbenzamide (140.0 mg, 31%) as a white solid. MS (ESI, m/z): 581.4 (M + H)+.

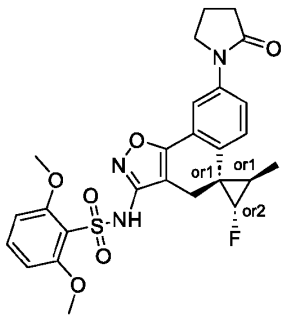
[1225] Step 2. rel-4-(N-((1R,2R,3S)-8'-(azetidin-1-yl)-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



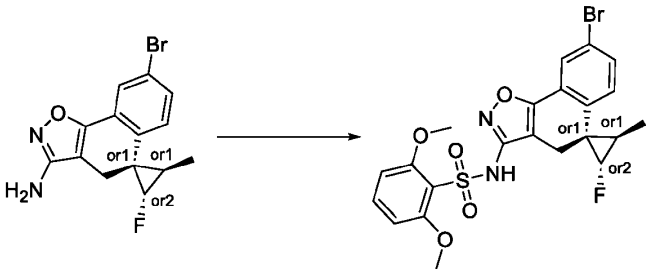
[1226] A mixture of rel-4-{[(1R,2R,3S)-8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]sulfamoyl}-3,5-dimethoxy-N-methylbenzamide (120.0 mg, 0.21 mmol, 1.00 equiv), azetidine (59.0 mg, 1.03 mmol, 5.00 equiv), Pd-PEPPSI-IHeptCl 3-chloropyridine (16.3 mg, 0.02 mmol, 0.10 equiv) and Cs2CO3 (134.7 mg, 0.41 mmol, 2.00 equiv) in NMP (3.0 mL) was stirred at 100 °C for 30 min under N2 atmosphere. The resulting mixture was purified directly by reverse phase flash chromatography on C18 gel (5~70% acetonitrile in water) to afford rel-4-{[(1R,2R,3S)-8'-(azetidin-1-yl)-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]sulfamoyl}-3,5-dimethoxy-N-methylbenzamide (15.7 mg, 13%) as an off-white solid. 1H NMR (300 MHz, DMSO-d6) δ 8.55 – 8.49 (m, 1H), 7.11 – 7.02 (m, 3H), 6.51 (d, J = 2.4 Hz, 1H), 6.33 (dd, J = 8.4, 2.4 Hz, 1H), 4.23 – 3.96 (m, 1H), 3.87 – 3.66 (m, 10H), 2.79 (d, J = 4.5 Hz, 3H), 2.50 – 1.99 (m, 4H), 1.27 – 1.19 (m, 1H), 1.17 – 1.08 (m, 3H). 19F NMR (282 MHz, DMSO-d6) δ -208.87. MS (ESI, m/z): 595.2 (M + H)+.

Example 289

Rel-N-((1S,2S,3R)-2-fluoro-3-methyl-8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide

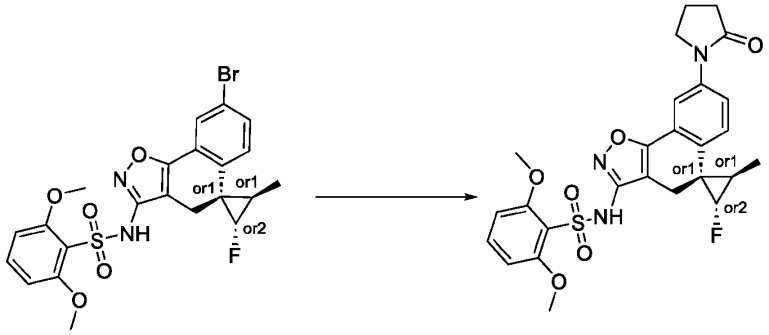


[1227] Step 1. rel-N-((1S,2S,3R)-8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide



[1228] A solution of (1S,2S,3R)-8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (150.0 mg, 0.46 mmol, 1.00 equiv, Intermediate R) and 2,6-dimethoxybenzenesulfonyl chloride (164.9 mg, 0.69 mmol, 1.50 equiv) in pyridine (2.0 mL) was stirred at 80 °C for 1 h under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5%-40% acetonitrile in water) to afford N-((1S,2S,3R)-8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide (210.0 mg, 86%) as a white solid. MS (ESI, *m/z*): 523.1 $(M + H)^+$.

[1229] Step 2. rel-N-((1S,2S,3R)-2-fluoro-3-methyl-8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide

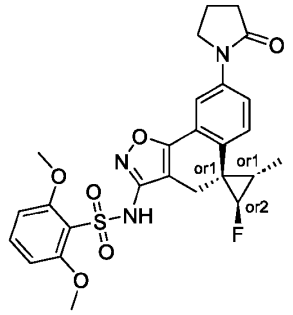


[1230] A mixture of N-((1S,2S,3R)-8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide (100.0 mg, 0.19 mmol, 1.00 equiv), pyrrolidin-2-one (81.4 mg, 0.95 mmol, 5.00 equiv), Pd-PEPPSI-IHeptCl (18.3 mg, 0.02 mmol, 0.10 equiv) and Cs_2CO_3 (122.3 mg, 0.38 mmol, 2.00 equiv) in DMF (3.0 mL) was stirred at 80 °C for 16 h under N_2 atmosphere. The resulting mixture was combined with another batch (100 mg) and purified directly by reverse phase flash chromatography on C18 gel (5%-50% acetonitrile in water) to afford (41.4 mg, 19%) as a

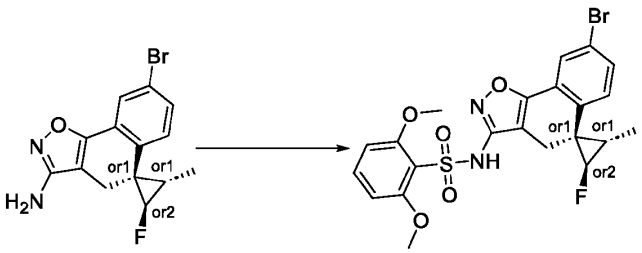
yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.84 (d, J = 2.4 Hz, 1H), 7.51 – 7.42 (m, 1H), 7.28 – 7.16 (m, 2H), 6.61 (d, J = 8.4 Hz, 2H), 4.28 – 3.99 (m, 1H), 3.90 – 3.80 (m, 2H), 3.63 (s, 6H), 2.50 – 2.42 (m, 2H), 2.23 – 2.01 (m, 5H), 1.17 – 1.08 (m, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -208.30. MS (ESI, *m/z*): 528.2 $(M + H)^+$.

Example 290

Rel-N-((1R,2R,3S)-2-fluoro-3-methyl-8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide

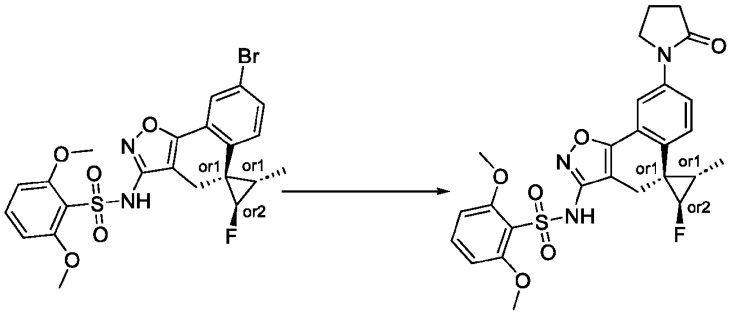


[1231] Step 1. rel-N-((1R,2R,3S)-8'-bromo-2-fluoro-3-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide



[1232] A mixture of (2S,3R)-8'-bromo-3-fluoro-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-amine (150.0 mg, 0.46 mmol, 1.00 equiv, Intermediate S) and 2,6-dimethoxybenzenesulfonyl chloride (164.7 mg, 0.69 mmol, 1.50 equiv) in pyridine (8.0 mL) was stirred at 80 °C for 1 h and then concentrated under vacuum. The residue was purified by reverse phase flash chromatography on C18 gel (5~100% acetonitrile in water) to afford N-[(2S,3R)-8'-bromo-3-fluoro-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]-2,6-dimethoxybenzenesulfonamide (220.0 mg, 90%) as a light yellow solid. MS (ESI, m/z): 525.0 $(M + H)^+$.

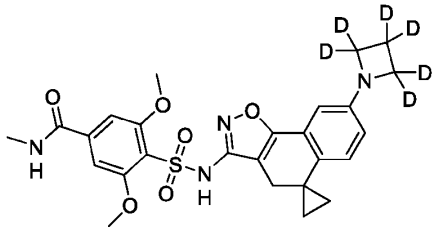
[1233] Step 2. rel-N-((1R,2R,3S)-2-fluoro-3-methyl-8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide



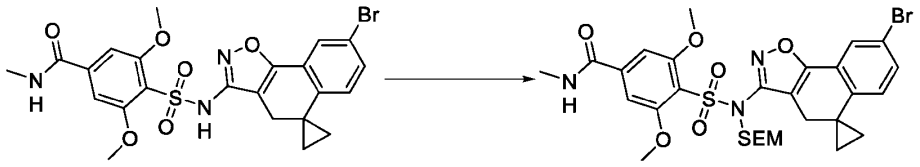
[1234] A mixture of N-[(2S,3R)-8'-bromo-3-fluoro-2-methyl-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]-2,6-dimethoxybenzenesulfonamide (150.0 mg, 0.29 mmol, 1.00 equiv), pyrrolidone (121.9 mg, 1.43 mmol, 5.00 equiv), Pd-PEPPSI-IHeptCl (27.9 mg, 0.03 mmol, 0.10 equiv) and Cs_2CO_3 (186.7 mg, 0.57 mmol, 2.00 equiv) in DMF (8.0 mL) was stirred at 100 °C for 16 h under N_2 atmosphere. The resulting mixture was purified directly by reverse phase flash chromatography on C18 gel (5~50% acetonitrile in water) to afford N-((1R,2R,3S)-2-fluoro-3-methyl-8'-(2-oxopyrrolidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide (37.9 mg, 25 %) as a brown solid. ^{1}H NMR (300 MHz, DMSO) δ 7.83 (d, J = 2.4 Hz, 1H), 7.47 (dd, J = 8.7, 2.4 Hz, 1H), 7.27 – 7.14 (m, 2H), 6.60 (d, J = 8.4 Hz, 2H), 4.29 – 3.99 (m, 1H), 3.93 – 3.81(m, 2H), 3.63 (s, 6H), 2.52– 2.40 (m, 2H), 2.22 – 2.01(m, 5H), 1.17 – 1.08 (m, 3H).^{19}F NMR (282 MHz, DMSO) δ -208.30. MS (ESI, *m/z*): 528.3 $(M + H)^+$.

Example 291

4-(N-(8'-(azetidin-1-yl-d6)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide

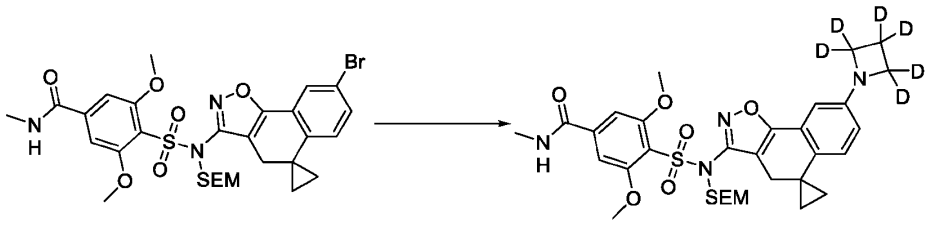


[1235] Step 1. 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



[1236] To a stirred mixture of 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (450.0 mg, 0.82 mmol, 1.00 equiv, Intermediate G) and Cs_2CO_3 (401.0 mg, 1.23 mmol, 1.50 equiv) in DMF (10.0 mL) at 0 °C was added dropwise a solution of SEMCl (164.0 mg, 0.98 mmol, 1.20 equiv) in DMF (1.0 mL). The resulting mixture was stirred at ambient temperature for 1 h and diluted with EtOAc. The resulting mixture was washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-6% MeOH in DCM) to afford 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (0.4 g, 72%) as colorless oil. MS (ESI, *m/z*): 678.0 $(M + H)^+$.

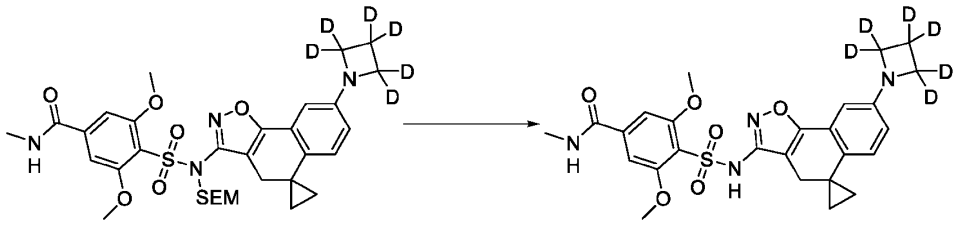
[1237] Step 2. 4-(N-(8'-(azetidin-1-yl-d6)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



[1238] A mixture of 4-(N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (100.0 mg, 0.14 mmol, 1.00 equiv), azetidine-2,2,3,3,4,4-d6 (29.65 mg, 0.294 mmol, 2 equiv), Pd-PEPPSI-IPentCl (11.0 mg, 0.01 mmol, 0.10 equiv) and Cs_2CO_3 (120.0 mg, 0.36 mmol, 2.50 equiv) in NMP (5.0 mL) was stirred at 80 °C for 16 h under N_2 atmosphere. The resulting mixture was diluted with EtOAc and washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica

gel (0-5% MeOH in DCM) to afford 4-(N-(8'-(azetidin-1-yl-d6)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (45 mg, 46 %) as yellow oil. MS (ESI, *m/z*): 661.3 $(M + H)^+$.

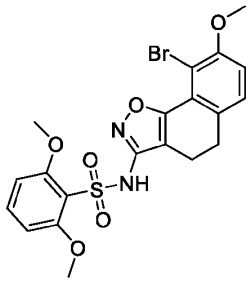
[1239] Step 3. 4-(N-(8'-(azetidin-1-yl-d6)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide



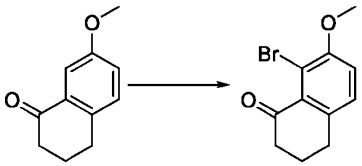
[1240] A mixture of 4-(N-(8'-(azetidin-1-yl-d6)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-N-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (40.0 mg, 0.06 mmol, 1.00 equiv) and TBAF (.0 M in THF, 1.8 mL, 30.00 equiv) in THF (3.0 mL) was stirred at 80 °C for 48 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-5% MeOH in DCM) to afford 4-(N-(8'-(azetidin-1-yl-d6)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)sulfamoyl)-3,5-dimethoxy-N-methylbenzamide (16.6 mg, 51%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO) δ 10.74 (s, 1H), 8.63 (d, J = 4.8 Hz, 1H), 7.15 (s, 2H), 6.86 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.39 – 6.36 (m, 1H), 3.85 (s, 6H), 2.80 (d, J = 4.5 Hz, 3H), 0.90 – 0.81 (m, 2H), 0.74 – 0.64 (m, 2H). MS (ESI, *m/z*): 531.4 $(M + H)^+$.

Example 292

N-(9-bromo-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide

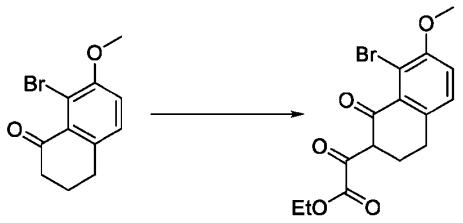


[1241] Step 1. 8-bromo-7-methoxy-3,4-dihydronaphthalen-1(2H)-one



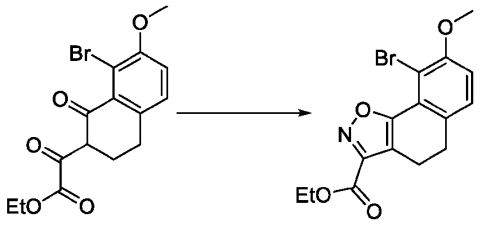
[1242] A mixture of 7-methoxy-3,4-dihydro-2H-naphthalen-1-one (25.0 g, 141.87 mmol, 1.00 equiv), $FeCl_3$ (920.4 mg, 5.67 mmol, 0.04 equiv) and NBS (25.2 g, 141.86 mmol, 1.00 equiv) in acetonitrile (125.0 mL) was stirred at ambient temperature for 4 h and then slowly poured into ice water. The precipitated solid was collected by filtration and dried under vacuum to afford 8-bromo-7-methoxy-3,4-dihydro-2H-naphthalen-1-one (crude, 30.0 g) as a brown solid, which was used for the next step without further purification. MS (ESI, *m/z*): 255.0 $(M + H)^+$.

[1243] Step 2. ethyl 2-(8-bromo-7-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate



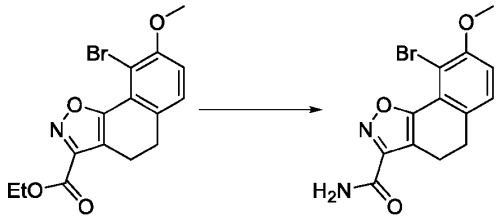
[1244] To a stirred mixture of 8-bromo-7-methoxy-3,4-dihydro-2H-naphthalen-1-one (20.0 g, 78.39 mmol, 1.00 equiv) and ethyl oxalate (22.9 g, 156.79 mmol, 2.00 equiv) in THF (200.0 mL) at 0 °C was added t-BuOLi (12.5 g, 156.79 mmol, 2.00 equiv). The resulting mixture was stirred at ambient temperature for 1 h. The resulting mixture was quenched at 0 °C with NH_4Cl solution and extracted with EtOAc 3 times. The combined organic layers were dried over with Na_2SO_4 and concentrated under vacuum to afford ethyl 2-(8-bromo-7-methoxy-1-oxo-3,4-dihydro-2H-naphthalen-2-yl)-2-oxoacetate (crude, 39.0 g) as a brown solid, which was used for the next step without further purification. MS (ESI, *m/z*): 355.0 $(M + H)^+$.

[1245] Step 3. ethyl 9-bromo-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate



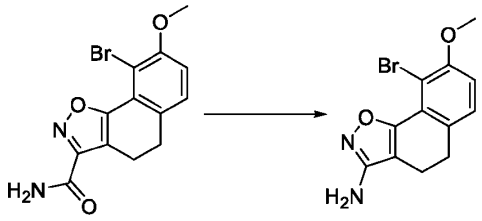
[1246] A mixture of ethyl 2-(8-bromo-7-methoxy-1-oxo-3,4-dihydro-2H-naphthalen-2-yl)-2-oxoacetate (39.0 g, 109.80 mmol, 1.00 equiv) and hydroxylamine hydrochloride (15.2 g, 219.60 mmol, 2.00 equiv) in EtOH (390.0 mL) was stirred at 80 °C for 16 h. The resulting mixture was concentrated under vacuum. The residue was redissolved in EtOAc. The organic solution was washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~50% EtOAc in petroleum ether) to afford ethyl 9-bromo-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (32.0 g, 82.7%) as a brown solid. MS (ESI, *m/z*): 352.0 $(M + H)^+$.

[1247] Step 4. 9-bromo-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide



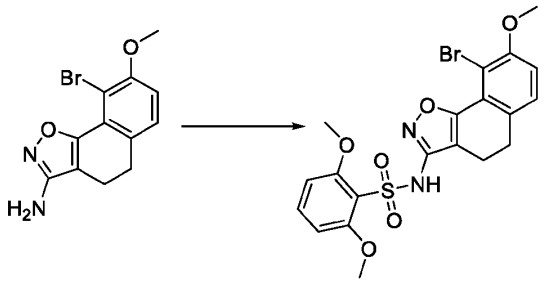
[1248] A mixture of ethyl 9-bromo-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (15.0 g, 42.59 mmol, 1.00 equiv) and ammonia (, 7.0 M in MeOH, 375.0 mL) in THF (275.0 mL) was stirred at ambient temperature for 30 min. The resulting mixture was concentrated under vacuum. The residue was purified by trituration with MeOH to afford 9-bromo-8-methoxy-4H,5H-naphtho[2,1-d][1,2]oxazole-3-carboxamide (11.8 g, 86%) as an off-white solid. MS (ESI, *m/z*): 323.0 $(M + H)^+$.

[1249] Step 5. 9-bromo-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine



[1250] To a stirred mixture of 9-bromo-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (500.0 mg, 1.54 mmol, 1.00 equiv) and K_2CO_3 (508.1 mg, 3.67 mmol, 2.38 equiv) in NMP (5.0 mL), EtOAc (1.0 mL) and H_2O (1.0 mL) at 0 °C was added $PhI(OAc)_2$ (1495.1 mg, 4.64 mmol, 3.00 equiv). The resulting mixture was stirred at ambient temperature for 1 h and then diluted with water. The resulting mixture was extracted with EtOAc 3 times. The combined organic layers were washed with brine 3 times, dried over with Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~50% EtOAc in petroleum ether) to afford 9-bromo-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (166.0 mg, 36%) as a yellow solid. MS (ESI, *m/z*): 295.0 $(M + H)^+$.

[1251] Step 6. N-(9-bromo-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide

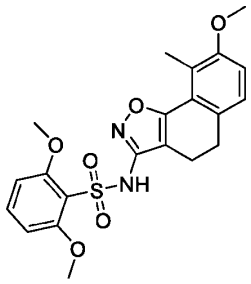


[1252] A mixture of 9-bromo-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (400.0 mg, 1.35 mmol, 1.00 equiv) and 2,6-dimethoxybenzenesulfonyl chloride (481.1 mg, 2.03 mmol, 1.50 equiv) in pyridine (4.0 mL) was stirred at 80 °C for 1 h. The resulting mixture was concentrated under vacuum. The residue was purified by trituration with acetonitrile to afford N-{9-bromo-8-methoxy-4H,5H-naphtho[2,1-d][1,2]oxazol-3-yl}-2,6-dimethoxybenzenesulfonamide (36.5 mg, 5.44%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 10.55 (br s, 1H), 7.48 (t, J = 8.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.08 (d, J =

8.4 Hz, 1H), 6.76 (d, J = 8.4 Hz, 2H), 3.85 (s, 3H), 3.79 (s, 6H), 2.92 – 2.84 (m, 2H), 2.65 – 2.57 (m, 2H). MS (ESI, *m/z*): 494.9 $(M + H)^+$.

Example 293

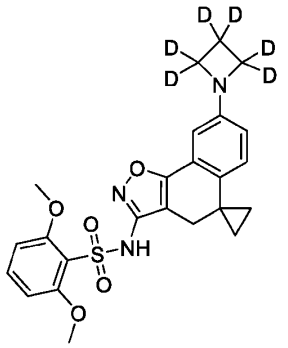
2,6-Dimethoxy-N-(8-methoxy-9-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide



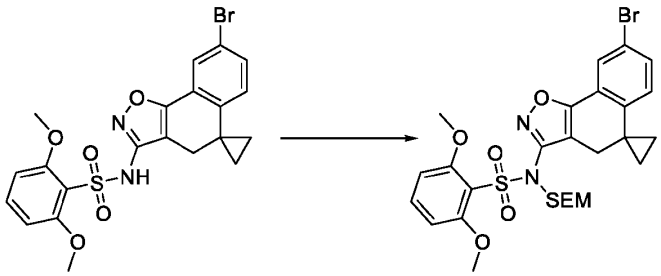
[1253] A mixture of N-{9-bromo-8-methoxy-4H,5H-naphtho[2,1-d][1,2]oxazol-3-yl}-2,6-dimethoxybenzenesulfonamide (150.0 mg, 0.30 mmol, 1.00 equiv, Example 292, trimethyl-1,3,5,2,4,6-trioxatriborinane (304.1 mg, 1.21 mmol, 4.00 equiv, 50% in THF), $Pd(dppf)Cl_2CH_2Cl_2$ (24.7 mg, 0.03 mmol, 0.10 equiv) and Cs_2CO_3 (296.0 mg, 0.91 mmol, 3.00 equiv) in dioxane (1.2 mL) and H_2O (0.3 mL) was stirred at 80 °C for 2 h under N_2 atmosphere and then diluted EtOAc. The resulting mixture was washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~50% EtOAc in petroleum ether) and further purified by Prep-HPLC (30% to 50% acetonitrile in water (contained 0.05% NH_4HCO_3)) to afford 2,6-dimethoxy-N-(8-methoxy-9-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide (33.6 mg, 25.77%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 8.71 (br s, 1 H), 7.43 (t, J = 8.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 2H), 3.77 (s, 3H), 3.76 (s, 6H), 2.80 (t, J = 7.6 Hz, 2H), 2.59 – 2.53 (m, 2H), 2.37 (s, 3H). MS (ESI, *m/z*): 431.1 $(M + H)^+$.

Example 294

N-(8'-(azetidin-1-yl-d6)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide

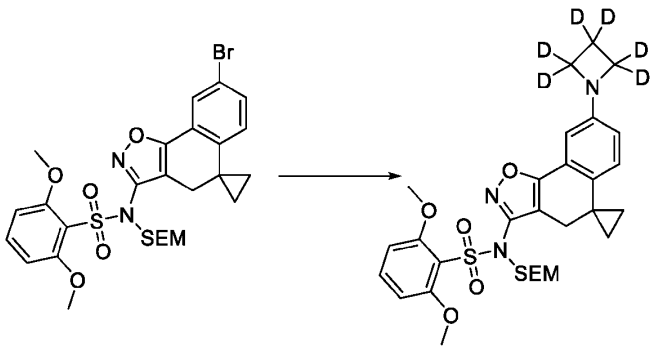


[1254] Step 1. N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzenesulfonamide



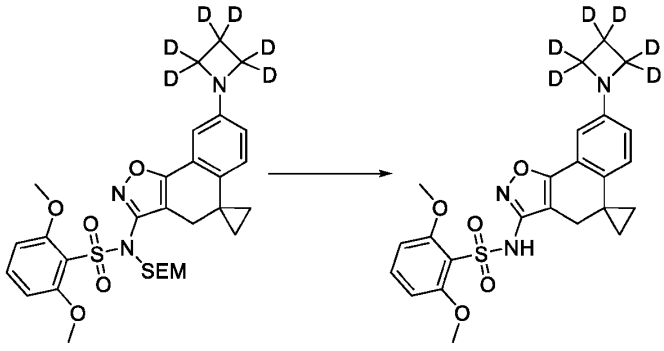
[1255] To a stirred mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide (280.0 mg, 0.57 mmol, 1.00 equiv, Example 15) and Cs_2CO_3 (371.0 mg, 1.14 mmol, 2.00 equiv) in DMF (6.0 mL) at 0 °C was added dropwise a solution of [2-(chloromethoxy)ethyl]trimethylsilane (142.0 mg, 0.85 mmol, 1.50 equiv) DMF (1.0 mL). The resulting mixture was stirred at ambient temperature for another 1 h and then diluted with EtOAc. The resulting mixture was washed with brine 3 times, dried over Na_2SO_4, concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-3% MeOH in DCM) to afford N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzenesulfonamide (320 mg, 90%) as an off-white solid. MS (ESI, *m/z*): 621.1 $(M + H)^+$.

[1256] Step 2. N-(8'-(azetidin-1-yl-d6)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzenesulfonamide



[1257] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzenesulfonamide (50.0 mg, 0.08 mmol, 1.00 equiv), (2,2,3,3,4,4-2H6)azetidine chloro(2H) (16.0 mg, 0.16 mmol, 2.00 equiv), Pd-PEPPSI-IPentCl (11.0 mg, 0.01 mmol, 0.10 equiv) and Cs_2CO_3 (65.0 mg, 0.20 mmol, 2.50 equiv) in NMP (5.0 mL) was stirred at 80 °C for 16 h under N_2 atmosphere and then diluted EtOAc. The resulting mixture was washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-40% EtOAc in petroleum ether) to afford N-(8'-(azetidin-1-yl-d6)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzenesulfonamide (15 mg, 30 %) as yellow oil. MS (ESI, *m/z*): 604.4 $(M + H)^+$.

[1258] Step 3. N-(8'-(azetidin-1-yl-d6)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide

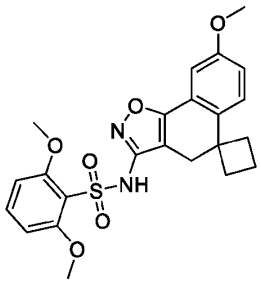


[1259] A mixture of N-(8'-(azetidin-1-yl-d6)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzenesulfonamide (15.0 mg, 0.03 mmol, 1.00 equiv) and TBAF (1.0 M in THF, 0.49 mL, 20 equiv) in THF (5.0

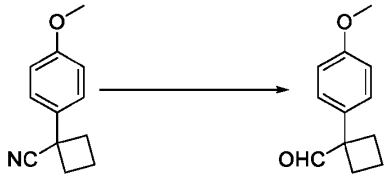
mL) was stirred at 80 °C for 48 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford N-(8'-(azetidin-1-yl-d6)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide (2.0 mg, 17%) as a white solid. ^{1}H NMR (300 MHz, DMSO) δ 10.62 (br s, 1 H), 7.49 (t, J = 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.4 Hz, 2H), 6.55 (d, J = 2.4 Hz, 1H), 6.40 – 6.36 (m, 1 H), 3.79 (s, 6H), 2.28 (s, 2H), 0.84 (s, 2H), 0.65 (s, 2H). MS (ESI, *m/z*): 474.2 $(M + H)^+$.

Example 295

2,6-dimethoxy-N-(8'-methoxy-4'H-spiro[cyclobutane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide

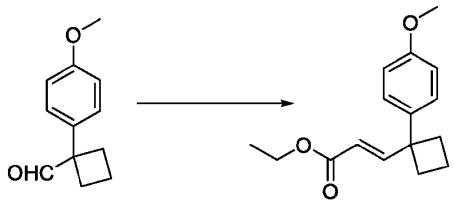


[1260] Step 1. 1-(4-methoxyphenyl)cyclobutane-1-carbaldehyde



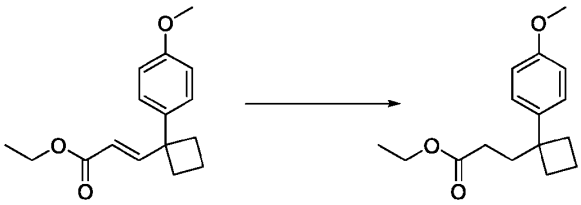
[1261] To a stirred solution of 1-(4-methoxyphenyl)cyclobutane-1-carbonitrile (1.0 g, 5.35 mmol, 1.00 equiv) in THF (10.0 mL) at -50 °C was added dropwise DIBAL-H solution (1.0 M in hexanes, 13.4 mL, 13.37 mmol, 2.50 equiv) over 5 min under N_2 atmosphere. The resulting mixture was stirred at this temperature for another 2 h and then quenched by dropwise addition of HCl (1.0 M, 13.4 mL, 2.5 eq) over 10 min and then filtered. The filtrate was extracted with EtOAc 3 times. The combined organic layers were washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum to afford 1-(4-methoxyphenyl)cyclobutane-1-carbaldehyde (1.0 g, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 191.2 $(M + H)^+$.

[1262] Step 2. ethyl (E)-3-(1-(4-methoxyphenyl)cyclobutyl)acrylate



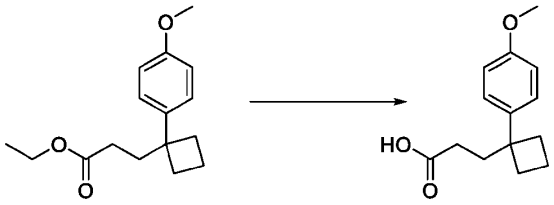
[1263] A mixture of 1-(4-methoxyphenyl)cyclobutane-1-carbaldehyde (1.0 g, 5.26 mmol, 1.00 equiv) and ethyl (triphenylphosphoranylidene)acetate (2.0 g, 5.53 mmol, 1.05 equiv) in DCE (20.0 mL) was stirred at 50 °C for 2 h. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0 ~ 30% EtOAc in petroleum ether) to afford ethyl (E)-3-(1-(4-methoxyphenyl)cyclobutyl)acrylate (0.9 g, 66%) as colorless oil. MS (ESI, i): 261.1 $(M + H)^+$.

[1264] Step 3. ethyl 3-(1-(4-methoxyphenyl)cyclobutyl)propanoate



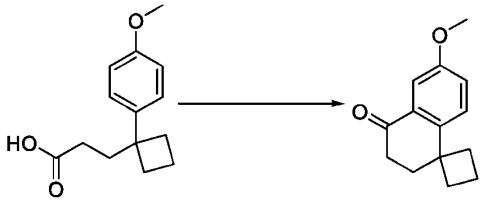
[1265] To a stirred mixture of ethyl (E)-3-(1-(4-methoxyphenyl)cyclobutyl)acrylate (0.9 g, 3.46 mmol, 1.00 equiv) and $TsNHNH_2$ (1.6 g, 8.65 mmol, 2.50 equiv) in THF (10.0 mL) and H_2O (10.0 mL) at ambient temperature was added NaOAc (2.4 g, 17.3 mmol, 5.00 equiv). The resulting mixture was stirred at 70 °C for 16 h and then diluted with water and extracted with EtOAc 3 times. The combined organic layers were washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0 ~ 30% EtOAc in petroleum ether) to afford ethyl 3-(1-(4-methoxyphenyl)cyclobutyl)propanoate (550.0 mg, 60%) as yellow oil. MS (ESI, *m/z*): 263.2 $(M + H)^+$.

[1266] Step 4. 3-(1-(4-methoxyphenyl)cyclobutyl)propanoic acid



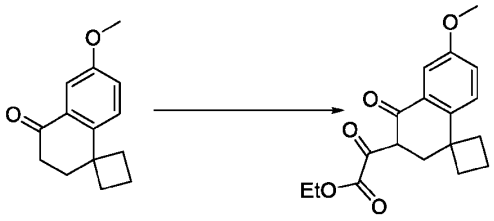
[1267] To a stirred solution of ethyl 3-(1-(4-methoxyphenyl)cyclobutyl)propanoate (550.0 mg, 2.10 mmol, 1.00 equiv) in methanol (2.50 mL) at 0 °C was added a solution of NaOH (168.0 mg, 4.20 mmol, 2.00 equiv) in H_2O (2.50 mL). The resulting mixture was stirred at ambient temperature for 2 h and then diluted with water. The resulting mixture was washed with EtOAc 3 times and the aqueous layer was acidified with AcOH to pH ~ 6 and then extracted with EtOAc 3 times. The organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford 3-(1-(4-methoxyphenyl)cyclobutyl)propanoic acid (390.0 mg, crude) as a white solid, which was used for the next step without further purification. MS (ESI, *m/z*): 234 $(M + H)^+$.

[1268] Step 5. 6'-methoxy-2',3'-dihydro-4'H-spiro[cyclobutane-1,1'-naphthalen]-4'-one



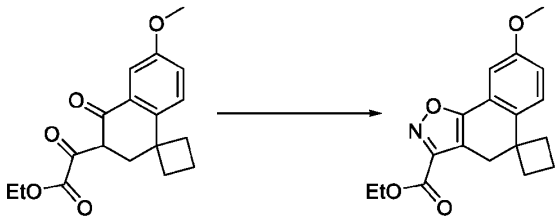
[1269] To a stirred solution of 3-(1-(4-methoxyphenyl)cyclobutyl)propanoic acid (390.0 mg, 1.67 mmol, 1.00 equiv) in TFA (10.0 mL) at 0 °C was added TFAA (526.0 mg, 2.51 mmol, 1.50 equiv). The resulting mixture was stirred at 40 °C for 2 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0 ~ 50% EtOAc in petroleum ether) to afford 6'-methoxy-2',3'-dihydro-4'H-spiro[cyclobutane-1,1'-naphthalen]-4'-one (260.0 mg, 72%) as yellow oil. MS (ESI, *m/z*): 217.3 $(M + H)^+$.

[1270] Step 6. ethyl 2-(6'-methoxy-4'-oxo-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalen]-3'-yl)-2-oxoacetate



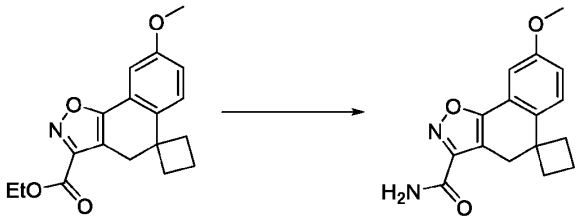
[1271] To a stirred mixture of 6'-methoxy-2',3'-dihydrospiro[cyclobutane-1,1'-naphthalen]-4'-one (240.0 mg, 1.11 mmol, 1.00 equiv) and t-BuOLi (151.3 mg, 1.89 mmol, 1.70 equiv) in THF (5.00 mL) at 0 °C was added dropwise a solution of ethyl oxalate (243.3 mg, 1.67 mmol, 1.50 equiv) in THF (5.00 mL). The resulting mixture was stirred at ambient temperature for another 1 h and then quenched with NH_4Cl solution and extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford ethyl 2-{6'-methoxy-4'-oxo-2',3'-dihydrospiro[cyclobutane-1,1'-naphthalen]-3'-yl}-2-oxoacetate (200.0 mg, 57%) as yellow oil. MS (ESI, *m/z*): 317.2 $(M + H)^+$.

[1272] Step 7. ethyl 8'-methoxy-4'H-spiro[cyclobutane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxylate



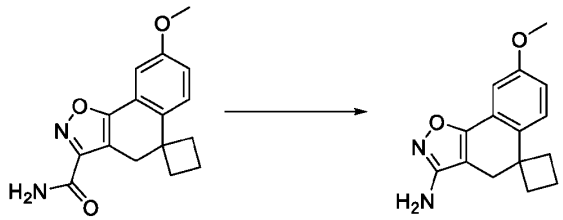
[1273] A solution of ethyl 2-{6'-methoxy-4'-oxo-2',3'-dihydrospiro[cyclobutane-1,1'-naphthalen]-3'-yl}-2-oxoacetate (190.0 mg, 0.60 mmol, 1.00 equiv) and hydroxylamine hydrochloride (50.1 mg, 0.72 mmol, 1.20 equiv) in EtOH (2.0 mL) was stirred at ambient temperature for 16 h and then stirred at 60 °C for another 3 h and then diluted with EtOAc. The resulting mixture was washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum to afford ethyl 8'-methoxy-4'H-spiro[cyclobutane-1,5'-naphtho[2,1-d][1,2]oxazole]-3'-carboxylate (200 mg, crude) as yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 314.5 $(M + H)^+$.

[1274] Step 8. 8'-methoxy-4'H-spiro[cyclobutane-1,5'-naphtho[2,1-d]isoxazole]-3'-carboxamide



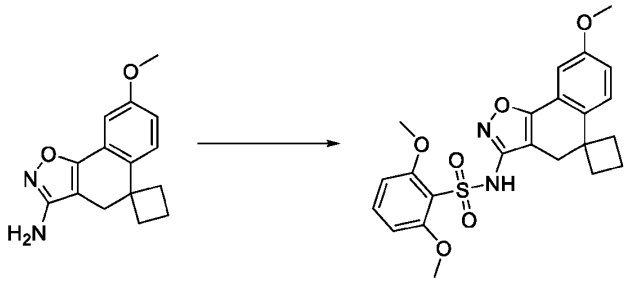
[1275] A solution of ethyl 8'-methoxy-4'H-spiro[cyclobutane-1,5'-naphtho[2,1-d][1,2]oxazole]-3'-carboxylate (200.0 mg, 0.64 mmol, 1.00 equiv) and ammonia (7.0 M in methanol, 2.0 mL) in methanol (2.0 mL) was stirred at ambient temperature for 1 h. The resulting mixture was concentrated under vacuum to afford 8'-methoxy-4'H-spiro[cyclobutane-1,5'-naphtho[2,1-d][1,2]oxazole]-3'-carboxamide (125 mg) as a brown solid, which was used for the next step without further purification. MS (ESI, *m/z*): 285.6 $(M + H)^+$.

[1276] Step 9. 8'-methoxy-4'H-spiro[cyclobutane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine



[1277] To a stirred mixture of 8'-methoxy-4'H-spiro[cyclobutane-1,5'-naphtho[2,1-d][1,2]oxazole]-3'-carboxamide (125.0 mg, 0.44 mmol, 1.00 equiv) and 1-methyl-1H-imidazole (144.4mg, 1.76 mmol, 4.00 equiv) in NMP (1.0 mL), EtOAc (1.0 mL) and H_2O (0.5 mL) at 0 °C was added $PhI(OAc)_2$ (424.8 mg, 1.32 mmol, 3.00 equiv). The resulting mixture was stirred at this temperature for 1 h and then diluted with EtOAc. The resulting mixture was washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-40% EtOAc in petroleum ether) to afford 8'-methoxy-4'H-spiro[cyclobutane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-amine (55.0 mg, 49%) as yellow oil. MS (ESI, *m/z*): 257.5 $(M + H)^+$.

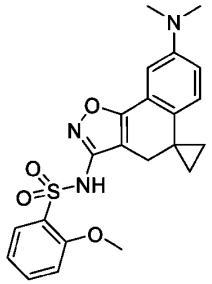
[1278] Step 10. 2,6-dimethoxy-N-(8'-methoxy-4'H-spiro[cyclobutane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[1279] A solution of 8'-methoxy-4'H-spiro[cyclobutane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-amine (50 mg, 0.195 mmol, 1.00 equiv) and 2,6-dimethoxybenzenesulfonyl chloride (129.3 mg, 0.55 mmol, 2.80 equiv) in pyridine (2.00 mL) was stirred at 80 °C for 3 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford 2,6-dimethoxy-N-{8'-methoxy-4'H-spiro[cyclobutane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}benzenesulfonamide (26.5 mg, 30%) as a white solid. ^{1}H NMR (300 MHz, DMSO) δ 10.75 (br s, 1H), 7.68 – 7.40 (m, 2H), 7.13 – 6.96 (m, 2H), 6.78 (d, J = 8.4 Hz, 2H), 3.80 (d, J = 7.5 Hz, 9H), 2.83 (s, 2H), 2.15 – 2.08 (m, 2H), 1.89 – 1.86 (m, 4H). MS (ESI, m/z): 457.1 $(M + H)^+$.

Example 296

N-(8'-(dimethylamino)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

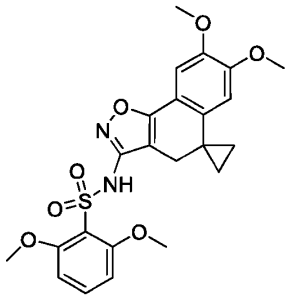


[1280] A mixture of N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (154 mg, 334 µmol, Example 16), dimethylamine solution, 2.0 M in THF (22.6 mg, 1.5 eq., 501 µmol), cesium carbonate (326 mg, 3 eq., 1 mmol) and Pd-PEPPSI-IHept-Cl, CAS 1814936-54-3 (61.9 mg, 0.2 eq., 66.8 µmol) in N-methyl-2-pyrrolidone (3 mL, 31.1 mmol) was sparged with N2(g) for 5 minutes and the mixture heated to 100°C for 18 hrs.

[1281] The resulting mixture was concentrated under reduced pressure and the residue was purified via reverse phase column chromatography (Waters XSelect CSH C18) using 0.1% FA in H2O and ACN (gradient 40 - 60) to obtain N-(8'-(dimethylamino)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (13.8 mg, 10%), as an off-white solid. MS(ESI, m/z) = 426.2 $[M+H]^+$ 1H NMR (400 MHz, DMSO) δ 10.81 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.58 (s, 1H), 7.18 (d, J = 8.5 Hz, 1H), 7.05 (t, J = 7.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.83 (s, 1H), 6.69 (d, J = 8.5 Hz, 1H), 3.82 (s, 3H), 2.89 (s, 6H), 2.55 (s, 2H), 0.85 (s, 2H), 0.72 (d, J = 4.9 Hz, 2H).

Example 297

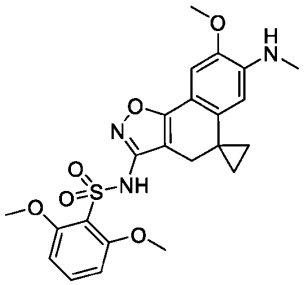
N-(7',8'-dimethoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide



[1282] A mixture of N-(7'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide (120 mg, 230 µmol, Example 21), methanol (36.9 mg, 5 eq., 1.15 mmol), tBuXPhos, (9.77 mg, 0.1 eq., 23 µmol), tris(dibenzylideneacetone)dipalladium(0), (21.1 mg, 0.1 eq., 23 µmol) and sodium tert-butoxide (33.2 mg, 1.5 eq., 345 µmol) in 1,4-dioxane (3 mL, 35.2 mmol) was sparged with N2(g) for 5 min. and was heated to 80°C for 1 hr. Reaction mixture was filtered, washed with EtOAc, concentrated and the residue was purified via reverse phase column chromatography (Waters XSelect CSH C18) using 0.1% formic Acid in water and pure ACN (gradient 50 - 70) to obtain N-(7',8'-dimethoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide (15.9 mg, 15) as a white solid. MS (ESI, m/z) = 473.2 $[M+H]^+$ 1H NMR (400 MHz, DMSO) δ 7.47 (t, J = 8.5 Hz, 1H), 7.08 (s, 1H), 6.75 (d, J = 8.5 Hz, 2H), 6.57 (s, 1H), 3.78 (s, 13H), 1.24 (s, 2H), 0.98 (s, 2H), 0.70 (s, 2H).

Example 298

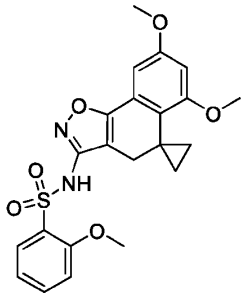
2,6-dimethoxy-N-(8'-methoxy-7'-(methylamino)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



[1283] A mixture of N-(7'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2,6-dimethoxybenzenesulfonamide (121 mg, 232 µmol, Example 21), methyl amine, 2M solution in THF (230 µL, 2 eq., 464 µmol), cesium carbonate (227 mg, 3 eq., 696 µmol) and Pd-PEPPSI-IHept-Cl (43.1 mg, 0.2 eq., 46.4 µmol) in N-methyl-2-pyrrolidone (1.67 mL, 17.3 mmol) was sparged with N2(g) and heated to 100oC for 18 hrs. The resulting mixture was concentrated under reduced pressure and the residue was purified via reverse phase column chromatography (Waters XSelect CSH C18) using 0.1% Formic Acid in Water and pure ACN (gradient 50 - 70) to obtain 2,6-dimethoxy-N-(8'-methoxy-7'-(methylamino)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide (10.7 mg, 10%) as a light yellow solid. MS(ESI, m/z) = 472.2 $[M+H]^+$ 1H NMR (400 MHz, DMSO) δ 7.50 - 7.43 (m, 1H), 6.91 (s, 1H), 6.75 (d, J = 8.5 Hz, 2H), 6.04 (s, 1H), 5.52 (br s, 1H), 3.79 (s, 9H), 2.72 (d, J = 5.0 Hz, 3H), 2.47 (s, 2H), 0.91 (s, 2H), 0.65 (s, 2H).

Example 299

N-(6',8'-dimethoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide

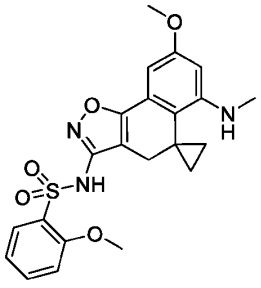


[1284] A mixture of N-(6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (121 mg, 246 µmol, Example 49) methanol (39.5 mg, 5 eq., 1.23 mmol), tBuXPhos, (5.23 mg, 0.05 eq., 12.3 µmol), tris(dibenzylideneacetone)dipalladium(0), (11.3 mg, 0.05 eq., 12.3 µmol) and sodium tert-butoxide (35.5 mg, 1.5 eq., 369 µmol) in 1,4-dioxane (1.92 mL, 22.5 mmol) was sparged with N2(g) for 5 min. and was heated to 80°C for 1 hr.

[1285] Reaction mixture was filtered, washed with EtOAc, concentrated and the residue was purified via reverse phase column chromatography (Waters XSelect CSH C18) using 0.1% Formic Acid in Water and pure ACN (gradient 50 - 70) to obtain N-(6',8'-dimethoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (7.4 mg, 7% yield) as an off-white solid. MS (ESI, m/z) = 443.1 $[M+H]^+$ 1H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.59 (s, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.05 (t, J = 7.9 Hz, 1H), 6.72 (s, 1H), 6.56 (s, 1H), 3.82 (s, 3H), 3.78 (d, J = 2.1 Hz, 3H), 3.72 (d, J = 2.1 Hz, 3H), 2.40 (s, 2H), 1.39 (s, 2H), 0.63 (s, 2H).

Example 300

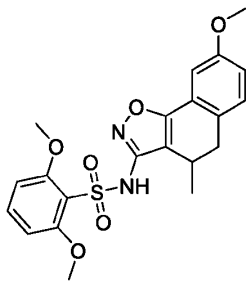
2-methoxy-N-(8'-methoxy-6'-(methylamino)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide



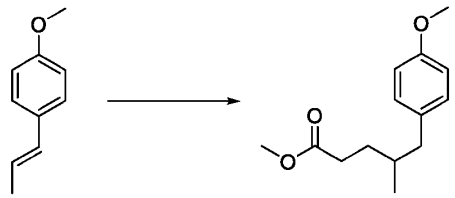
[1286] A mixture of N-(6'-bromo-8'-methoxy-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-methoxybenzenesulfonamide (120 mg, 245 µmol, Intermediate 49), methyl amine, 2M solution in THF (245 µL, 2 eq., 489 µmol), cesium carbonate (239 mg, 3 eq., 734 µmol) and Pd-PEPPSI-IHept-Cl, (45.4 mg, 0.2 eq., 48.9 µmol) in N-methyl-2-pyrrolidone (2 mL, 20.7 mmol) was sparged with N2(g) and heated to 100°C for 18 hrs. The resulting mixture was concentrated under reduced pressure and the residue was purified via reverse phase column chromatography (Waters XSelect CSH C18) using 0.1% formic acid in water and pure ACN (gradient 50 - 70) to obtain 2-methoxy-N-(8'-methoxy-6'-(methylamino)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)benzenesulfonamide (4.5 mg, 4%) as a light brown solid. MS(ESI, m/z) = 442.2 $[M+H]^+$ 1H NMR (400 MHz, DMSO) δ 7.75 (d, J = 8.0 Hz, 1H), 7.58 (br s, 1H), 7.19 (s, 1H), 7.06 (s, 1H), 6.46 (s, 1H), 6.12 (s, 1H), 5.16 (s, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 2.64 (s, 3H), 2.35 - 2.24 (m, 2H), 0.91 (s, 2H), 0.74 (s, 2H).

Example 301

2,6-dimethoxy-N-(8-methoxy-4-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide



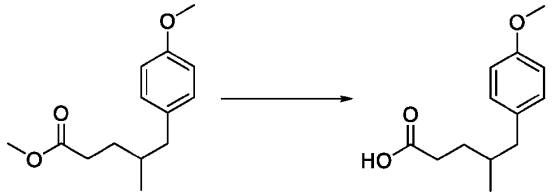
[1287] Step 1. methyl 5-(4-methoxyphenyl)-4-methylpentanoate



[1288] To a stirred solution of diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3.4 g, 13.50 mmol, 2.00 equiv), tris(2,2'-bipyridine) dichlororuthenium hexahydrate (0.25 g, 0.34 mmol, 0.050 equiv) and 4-methylbenzene-1-thiol (0.20 g, 1.35 mmol, 0.20 equiv) in

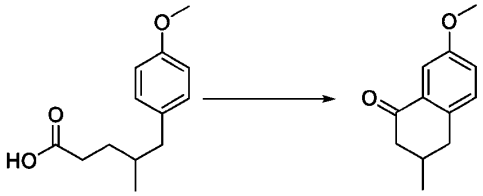
DCM (21.0 mL) was added anethole (1.0 g, 6.75 mmol, 1.00 equiv) and ethyl diazoacetate (1.5 g, 13.50 mmol, 2.00 equiv) under N_2 atmosphere. The resulting mixture was irradiated under 455 nm blue LED with stirring at 25 °C for 16 h. The resulting mixture was combined with another batch (1.0 g) and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~30% EtOAc in petroleum ether) to afford methyl 5-(4-methoxyphenyl)-4-methylpentanoate (1.23 g, 38%) as colorless oil. MS (ESI, *m/z*): 237.1 (M + H)$^+$.

[1289] Step 2. 5-(4-methoxyphenyl)-4-methylpentanoic acid



[1290] To a stirred solution of methyl 5-(4-methoxyphenyl)-4-methylpentanoate (1.23 g, 5.20 mmol, 1.00 equiv) in methanol (10.0 mL) at 0 °C was added a solution of NaOH (0.40 g, 10.41 mmol, 2.00 equiv) in H_2O (2.5 mL). The resulting mixture was stirred at ambient temperature for 2 h and then diluted with water. The resulting mixture was acidified at 0 °C with HCl (1.0 M) to pH 5-6 and then extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford 5-(4-methoxyphenyl)-4-methylpentanoic acid (970.0 mg, crude) as a yellow oil, which was used for the next step without further purification. MS (ESI, *m/z*): 223.1(M + H)$^+$.

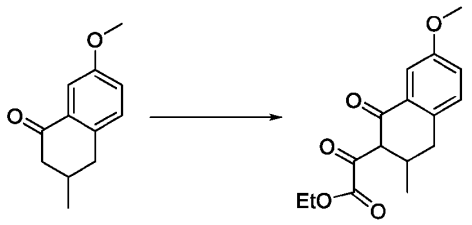
[1291] Step 3. 7-methoxy-3-methyl-3,4-dihydronaphthalen-1(2H)-one



[1292] A mixture of 5-(4-methoxyphenyl)-4-methylpentanoic acid (970.0 mg, 4.36 mmol, 1.00 equiv) and TFAA (3.70 g, 17.46 mmol, 4.00 equiv) in TFA (10.0 mL) was stirred at 40 °C for 6 h and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-30% EtOAc in petroleum ether) to afford 7-methoxy-3-

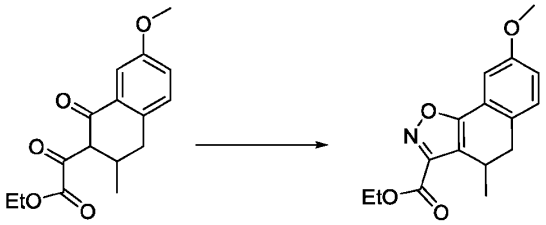
methyl-3,4-dihydronaphthalen-1(2H)-one (350.0 mg, 42%) as an off-white solid. MS (ESI, *m/z*): 191.1 $(M + H)^+$.

[1293] Step 4. ethyl 2-(7-methoxy-3-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate



[1294] To a stirred solution of 7-methoxy-3-methyl-3,4-dihydronaphthalen-1(2H)-one (350.0 mg, 1.84 mmol, 1.00 equiv) and EtONa (20% in EtOH, 5.0 mL) at 0 °C was added ethyl oxalate (431.0 mg, 2.95 mmol, 1.70 equiv). The resulting mixture was stirred at ambient temperature for 1 h and then quenched at 0 °C with NH_4Cl solution and extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-40% EtOAc in petroleum ether) to afford ethyl 2-(7-methoxy-3-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoacetate (124.0 mg, 24%) as a yellow solid. MS (ESI, *m/z*): 291.1$(M + H)^+$.

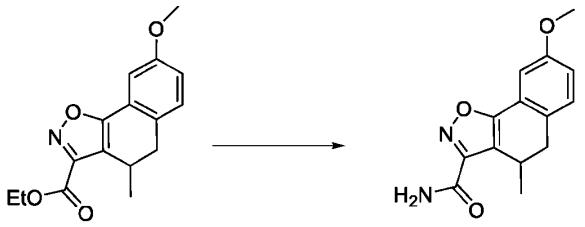
[1295] Step 5. ethyl 8-methoxy-4-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate



[1296] A mixture of ethyl 2-(7-methoxy-3-methyl-1-oxo-3,4-dihydro-2H-naphthalen-2-yl)-2-oxoacetate (124.0 mg, 0.43 mmol, 1.00 equiv) and hydroxylamine hydrochloride (36.0 mg, 0.51 mmol, 1.20 equiv) in EtOH (7.0 mL) was stirred at 80 °C for 2 h and then concentrated under vacuum. The residue was redissolved in DCM (5.0 mL) and then cooled down to 0 °C. To this was added Et_3N (173.0 mg, 1.71 mmol, 4.00 equiv) and Ms_2O (298.0 mg, 1.71 mmol, 4.00 equiv) sequentially. The resulting mixture was stirred at ambient temperature for another

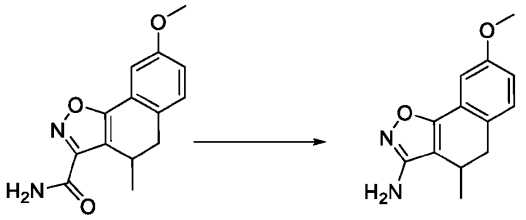
1 h and then quenched with NH_4HCO_3 solution and then extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford ethyl 8-methoxy-4-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (117.0 mg, 95%) as brown oil. MS (ESI, *m/z*): 288.0 $(M + H)^+$.

[1297] Step 6. 8-methoxy-4-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide



[1298] To a stirred solution of ethyl 8-methoxy-4-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (117.0 mg, 0.41 mmol, 1.00 equiv) in MeOH (2.5 mL) at 0 °C was added ammonia (7.0 M in MeOH, 2.5 mL). The resulting mixture was stirred at ambient temperature for 1 h and then concentrated under vacuum to afford 8-methoxy-4-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (95.0 mg, crude) as a white solid, which was used for the next step without further purification. MS (ESI, *m/z*): 259.1 $(M + H)^+$.

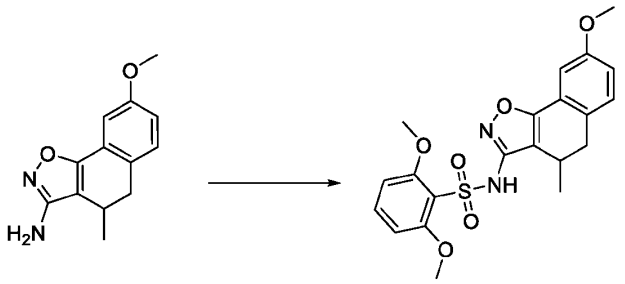
[1299] Step 7. 8-methoxy-4-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine



[1300] To a stirred mixture of 8-methoxy-4-methyl-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide (95.0 mg, 0.37 mmol, 1.00 equiv) and K_2CO_3 (204.0 mg, 1.47 mmol, 4.00 equiv) in combined solvent system of NMP (2.5 mL), EtOAc (0.5 mL) and H_2O (0.5 mL) at ambient temperature was added $PhI(OAc)_2$ (356.0 mg, 1.10 mmol, 3.00 equiv). The resulting mixture was stirred for 3 h and then diluted with EtOAc. The resulting mixture was washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-60% EtOAc in petroleum ether) to afford 8-

methoxy-4-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (31.0 mg, 36%) as a brown solid. MS (ESI, *m/z*): 231.1 $(M + H)^+$.

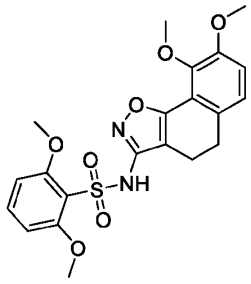
[1301] Step 8. 2,6-dimethoxy-N-(8-methoxy-4-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide



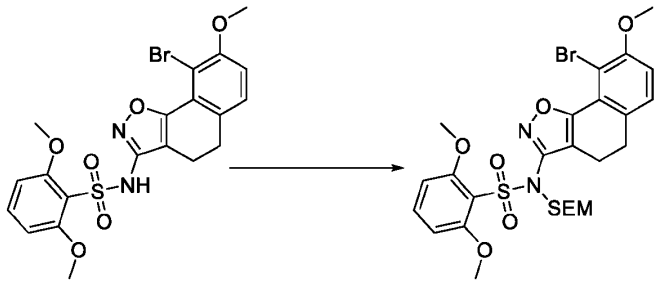
[1302] To a stirred solution of 8-methoxy-4-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-amine (30 mg, 0.13 mmol, 1.00 equiv) in THF (2.5 mL) at -78 °C was added dropwise t-BuOK solution (1.0 M in THF, 0.5 mL, 0.52 mmol, 4.00 equiv). The resulting mixture was stirred at this temperature for another 10 min and then to this was added dropwise a solution of 2,6-dimethoxybenzenesulfonyl chloride (124.0 mg, 0.52 mmol, 4.00 equiv) in THF (1.0 mL). The resulting mixture was stirred for another 1 h and then neutralized with NH_4Cl solution to pH 6~7 and then extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford 2,6-dimethoxy-N-(8-methoxy-4-methyl-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)benzenesulfonamide (11.6 mg, 20%) as an off-white solid. ^1H NMR (300 MHz, DMSO) δ 10.65 (s, 1H), 7.50 (t, J = 8.4 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 2.7 Hz, 1H), 6.97 – 6.91 (m, 1H), 6.77 (d, J = 8.4 Hz, 2H), 3.87 – 3.75 (m, 9H), 3.25 – 3.13 (m, 1H), 3.10 – 2.97 (m, 1H), 2.77 – 2.65 (m, 1H), 0.94 (d, J = 6.9 Hz, 3H). MS (ESI, *m/z*): 431.0 $(M + H)^+$.

Example 302

N-(8,9-dimethoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide

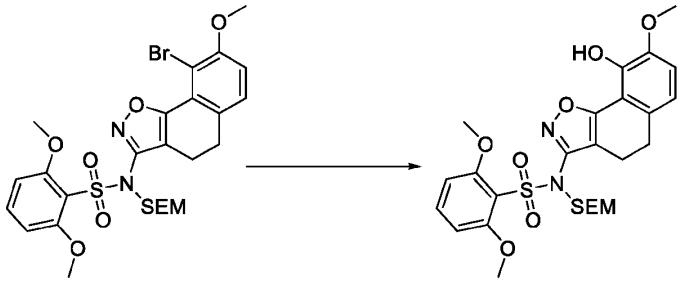


[1303] Step 1. N-(9-bromo-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzenesulfonamide



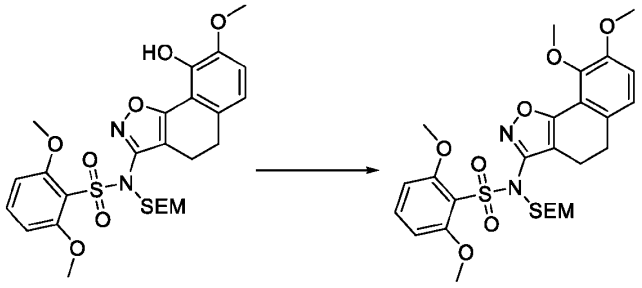
[1304] To a stirred mixture of N-(9-bromo-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide (700.0 mg, 1.42 mmol, 1.00 equiv, Example 292) and Cs_2CO_3 (921.1 mg, 2.84 mmol, 2.00 equiv) in DMF (7.0 mL) at 0 °C was added (2-(chloromethoxy)ethyl)trimethylsilane (352.83 mg, 2.13 mmol, 1.50 equiv). The resulting mixture was stirred at ambient temperature for 1 h and then diluted with water and extracted with EtOAc 3 times. The combined organic layers were washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-8% MeOH in DCM) to afford N-(9-bromo-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzenesulfonamide (680.0 mg, 76%) as a white solid. MS (ESI, *m/z*): 652.9 $(M + H)^+$.

[1305] Step 2. N-(9-hydroxy-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzenesulfonamide



[1306] A mixture of N-(9-bromo-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzenesulfonamide (450.0 mg, 0.72 mmol, 1.00 equiv), KOH (201.8 mg, 3.60 mmol, 5.00 equiv) and BrettPhos Pd G_3 (65.2 mg, 0.07 mmol, 0.10 equiv) in dioxane (3.7 mL) and water (0.8 mL) was stirred at 90 °C for 1 h under N_2 atmosphere. The resulting mixture was diluted with water and extracted with EtOAc 3 times. The combined organic layers were washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was combined with another 3 batches (totally 220.0 mg) and purified by flash chromatography on silica gel (0~80% EtOAc in petroleum ether) to afford N-(9-hydroxy-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzenesulfonamide (310.0 mg, 51%) as a brown solid. MS (ESI, *m/z*): 563.2 $(M + H)^+$.

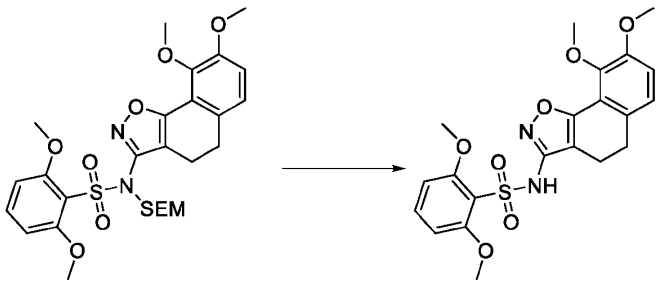
[1307] Step 3. N-(8,9-dimethoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzenesulfonamide



[1308] A mixture of N-(9-hydroxy-8-methoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzenesulfonamide (300.0 mg, 0.53 mmol, 1.00 equiv), CH_3I (113.5 mg, 0.80 mmol, 1.50 equiv) and K_2CO_3 (147.3 mg, 1.06 mmol, 2.00 equiv) in DMF (3.0 mL) was stirred at ambient temperature for 2 h and then diluted with EtOAc. The resulting mixture was combined with another batch (10.0 mg scale),

washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. to afford N-(8,9-dimethoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzenesulfonamide (310.0 mg, crude) as a brown solid, which was used for the next step without further purification. MS (ESI, *m/z*): 577.3 $(M + H)^+$.

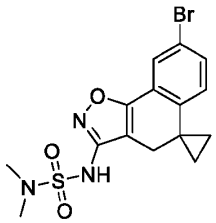
[1309] Step 4. N-(8,9-dimethoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide



[1310] A mixture of N-(8,9-dimethoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxy-N-((2-(trimethylsilyl)ethoxy)methyl)benzenesulfonamide (150.0 mg, 0.26 mmol, 1.00 equiv) and TBAF (1.0 M in THF, 10.4 mL, 10.4 mmol, 40.00 equiv) in THF (5.0 mL) was stirred at 80 °C for 4 h and then concentrated under vacuum. The residue was combined with another 2 batches (totally 160.0 mg scale) and purified by flash chromatography on silica gel (0~50% EtOAc in petroleum ether) to afford N-(8,9-dimethoxy-4,5-dihydronaphtho[2,1-d]isoxazol-3-yl)-2,6-dimethoxybenzenesulfonamide (87.4 mg, 36%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.56 (s, 1H), 7.53 – 7.44 (m, 1H), 7.11 – 6.96 (m, 2H), 6.78 (d, J = 8.4 Hz, 2H), 3.84 – 3.69 (m, 12H), 2.85 – 2.76 (m, 2H), 2.64 – 2.55 (m, 2H). MS (ESI, *m/z*): 447.0 $(M + H)^+$.

Example 303

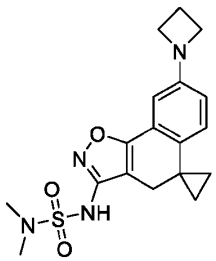
({8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}sulfamoyl)dimethylamine



[1311] To a stirred mixture of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-amine (100.0 mg, 0.34 mmol, 1.00 equiv) in THF (2.0 mL) at 0 °C was added dropwise t-BuOK solution (1.0 M in THF, 1.4 mL, 0.07 mmol, 2.00 equiv). The resulting mixture was stirred at this temperature for another 30 min and then to this was added dimethylsulphamoyl-chloride (147.9 mg, 1.03 mmol, 3.00 equiv). The resulting mixture was stirred for another 2 h and then quenched with NaH_2PO_4 solution and extracted with EtOAc 3 times. The combined organic layers were washed with brine 3 times, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~50% EtOA in petroleum ether) to afford ({8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d] [1,2]oxazol]-3'-yl}sulfamoyl)dimethylamine (32.1 mg, 22%) as an off-white solid. ^{1}H NMR (300 MHz, DMSO) δ 10.62 (s, 1H), 7.74 (d, J = 2.1 Hz, 1H), 7.56 (dd, J = 8.4, 2.1 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 2.82 (s, 6H), 2.67 (s, 2H), 1.05 – 0.87 (m, 4H). MS (ESI, *m/z*): 399.8 $(M + H)^+$.

Example 304

{[8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]sulfamoyl}dimethylamine

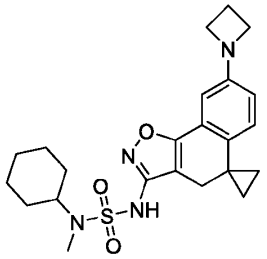


[1312] A mixture of ({8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl}sulfamoyl)dimethylamine (130.0 mg, 0.33 mmol, 1.00 equiv, Example 303), azetidine (186.3 mg, 3.26 mmol, 10.00 equiv), Pd-PEPPSI-IHeptCl 3-chloropyridine (31.7 mg, 0.03 mmol, 0.10 equiv) and Cs_2CO_3 (212.7 mg, 0.65 mmol, 2.00 equiv) in DMF (2.0 mL) was

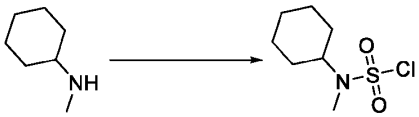
stirred at 80 °C for 2 h under N_2 atmosphere. The resulting mixture was purified directly by reverse phase flash chromatography on C18 gel (5~70% acetonitrile in water (contained 0.1% formic acid)) to afford {[8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-yl]sulfamoyl}dimethylamine (17.1 mg, 14%) as a brown solid. ^{1}H NMR (300 MHz, DMSO) δ 10.58 (br s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 6.42 (dd, J = 8.4, 2.4 Hz, 1H), 3.89 – 3.74 (m, 4H), 2.79 (s, 6H), 2.60 (s, 2H), 2.37 – 2.22 (m, 2H), 0.90 – 0.72 (m, 4H). (ESI, *m/z*): 375.0 $(M + H)^+$.

Example 305

N-cyclohexyl-N-methyl[8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-ylamino]sulfonamide

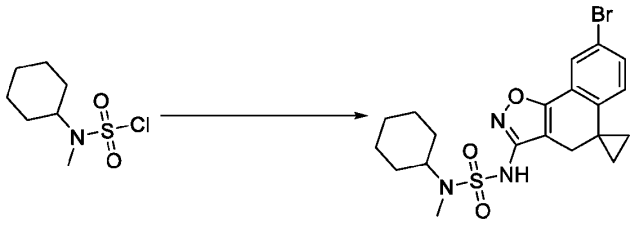


[1313] Step 1. cyclohexyl(methyl)sulfamoyl chloride



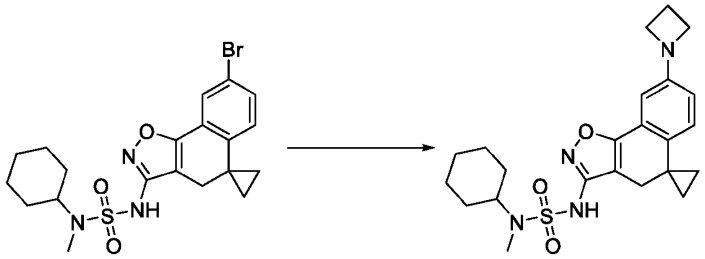
[1314] To a stirred solution of N-methylcyclohexanamine (1.0 g, 8.83 mmol, 1.00 equiv) and Et_3N (1.8 g, 17.66 mmol, 2.00 equiv) in DCM (20.0 mL) at 0 °C was added dropwise sulfonyl dichloride (1.2 g, 8.83 mmol, 1.00 equiv). The resulting mixture was stirred at this temperature for another 1 h and then quenched with NH_4Cl solution and extracted with EtOAc 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~30% EtOAc in petroleum ether) to afford N-cyclohexyl-N-methylsulfamoyl chloride (600.0 mg, 32%) as colorless oil.

[1315] Step 2. N-cyclohexyl-N-methyl{8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-ylamino}sulfonamide



[1316] A mixture of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-amine (200.0 mg, 0.68 mmol, 1.00 equiv, Intermediate C) and N-cyclohexyl-N-methylsulfamoyl chloride (363.0 mg, 1.72 mmol, 2.50 equiv) in pyridine (5.0 mL) was stirred at 80 °C for 16 h. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0~30% EtOAc in petroleum ether) to afford N-cyclohexyl-N-methyl{8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-ylamino}sulfonamide (175 mg, 54%) as a white solid. MS (ESI, *m/z*): 466.4 $(M + H)^+$.

[1317] Step 3. N-cyclohexyl-N-methyl[8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-ylamino]sulfonamide

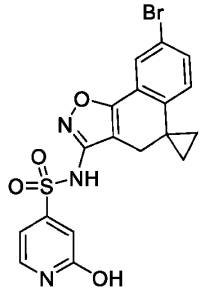


[1318] A mixturte of N-cyclohexyl-N-methyl{8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-ylamino}sulfonamide (145.0 mg, 0.31 mmol, 1.00 equiv), azetidine (177.5 mg, 3.11 mmol, 10.00 equiv), Pd-PEPPSI-IHeptCl (30.3 mg, 0.03 mmol, 0.10 equiv) and Cs_2CO_3 (303.9 mg, 0.93 mmol, 3.00 equiv) in dioxane (5.0 mL) was stirred at 100 °C for 2 h under N_2 atmosphere. The resulting mixture was diluted with EtOAc and washed with brine 3 times. The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to afford N-cyclohexyl-N-methyl[8'-(azetidin-1-yl)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d][1,2]oxazol]-3'-ylamino]sulfonamide (47.0 mg, 34%) as a yellow solid. ^1H NMR (300 MHz, DMSO-*d6*) δ 10.44 (s, 1H), 6.89 (d, $J = 8.4$ Hz, 1H), 6.62 (d, $J = 2.4$ Hz, 1H), 6.44 – 6.35 (m, 1H), 3.87 –3.76 (m, 4H), 3.64 – 3.51 (m, 1H), 2.75 (s, 3H), 2.59 (s, 2H),

2.35 – 2.24 (m, 2H), 1.72 (d, *J* = 12.3 Hz, 2H), 1.64 – 1.50 (m, 3H), 1.46 – 1.31 (m, 2H), 1.29 – 1.16 (m, 2H), 1.11 – 1.06 (m, 1H), 0.89 (d, J = 6.0 Hz, 2H), 0.79 – 0.71 (m, 2H). MS (ESI, *m/z*): 443.1 $(M + H)^+$.

Example 306

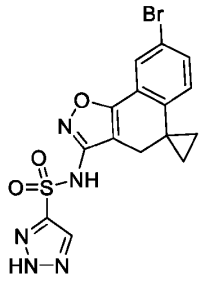
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-hydroxypyridine-4-sulfonamide



[1319] To a mixture of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (158 mg, 543 µmol, Intermediate C) and 4-Pyridinesulfonyl fluoride, 1,2-dihydro-2-oxo-, hydrochloride (1:1), (139 mg, 1.2 eq., 651 µmol) in tetrahydrofuran (4 mL, 49.1 mmol) at 0°C was added lithium bis(trimethylsilyl)amide solution, 1.0 M in THF (2.71 mL, 5 eq., 2.71 mmol) and stirred at rt for 18 hrs. Quenched with slow addition of water (2 ml) then citric acid (521 mg, 5 eq., 2.71 mmol) was added and stirred for 5 minutes, extracted with EtOAc, washed with brine, dried (MgSO4), concentrated and the residue was purified by revered phase HPLC (10 - 90% ACN-Water, w / 0.1% Formic Acid) to obtain N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2-hydroxypyridine-4-sulfonamide (31 mg, 13%) as a white solid. MS (ESI, m/z): 447.2 $[M-H]^+$ 1H NMR (400 MHz, DMSO) δ 12.22 (s, 1H), 11.59 (s, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 6.9 Hz, 1H), 7.55 (dd, J = 8.3, 2.1 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.73 (s, 1H), 6.47 (d, J = 6.9 Hz, 1H), 2.66 (s, 2H), 1.02 (d, J = 5.0 Hz, 2H), 0.91 (d, J = 5.2 Hz, 2H).

Example 307

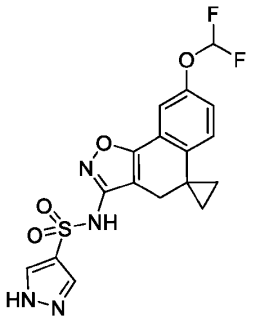
N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2H-1,2,3-triazole-4-sulfonamide



[1320] To a mixture of 8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (156 mg, 536 µmol, Intermediate C) in tetrahydrofuran (3 mL, 36.9 mmol) at 0°C was added Lithium bis(trimethylsilyl)amide solution, 1.0 M in THF (2.68 mL, 5 eq., 2.68 mmol) and stirred at rt for 18 hrs. The reaction was quenched by slow addition of water (2 ml) then citric acid (515 mg, 5 eq., 2.68 mmol) was added and stirred for 5 minutes, extracted with EtOAc, washed with brine, dried (MgSO4), concentrated and the residue was purified by revered phase HPLC (10 - 90% ACN-Water, w / 0.1% Formic Acid) to obtain N-(8'-bromo-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-2H-1,2,3-triazole-4-sulfonamide (23.5 mg, 10%) as a white solid. MS (ESI, m/z): 423.0 1H NMR (400 MHz, DMSO) δ 16.03 (s, 1H), 11.63 (s, 1H), 8.67 (s, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 2.63 (s, 2H), 1.01 (d, J = 5.2 Hz, 2H), 0.89 (d, J = 5.2 Hz, 2H).

Example 308

N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-1H-pyrazole-4-sulfonamide

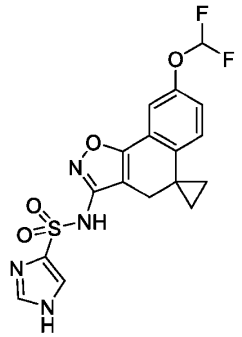


[1321] To a mixture of 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (113 mg, 406 µmol, Intermediate I) in dichloromethane (2 mL, 31.2 mmol) was added 1H-pyrazole-4-sulfonyl chloride (81.2 mg, 1.2 eq., 487 µmol) at 0°C , then

followed by slow addition of pyridine (328 µL, 10 eq., 4.06 mmol). Ice-bath removed and stirring continue at 80°C for another 18 hrs. Solvent removed under reduced pressure and the residue was purified by revered phase HPLC (10 - 90% ACN-Water, w / 0.1% Formic Acid) to obtain N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-1H-pyrazole-4-sulfonamide (39.5 mg, 24%) as a white solid. MS(ESI,m/z): 407.2 $[M-H]^-$ 1H NMR (400 MHz, DMSO) δ 7.28 (t, J = 73 Hz, 1H), 7.27 (s, 1H), 7.14 (s, 1H), 7.09 (d, J = 1.8 Hz, 2H), 5.71 (s, 1H), 2.55 (s, 2H), 1.05 – 0.95 (m, 2H), 0.86 (d, J = 4.9 Hz, 2H).

Example 309

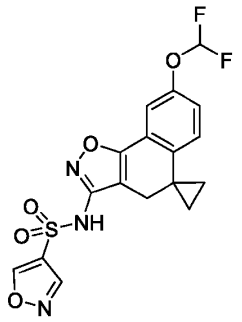
N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-1H-imidazole-4-sulfonamide



[1322] To a mixture of 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (110 mg, 395 µmol, Intermediate I) in dichloromethane (2 mL, 31.2 mmol) at 0°C , was added 1H-imidazole-4-sulfonyl chloride (79 mg, 1.2 eq., 474 µmol) then followed by slow addition of pyridine (320 µL, 10 eq., 3.95 mmol). Ice-bath removed and stirring continue at 80°C for another 18 hrs. Solvent removed under reduced pressure and the residue was purified by revered phase HPLC (10 - 90% ACN-Water, w / 0.1% Formic Acid) to obtain N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)-1H-imidazole-4-sulfonamide (5.5 mg, 3%), as a light brown solid. MS(ESI,m/z): 409.2 1H NMR (400 MHz, DMSO) δ 12.80 (s, 1H), 11.02 (s, 1H), 7.83 (s, 2H), 7.32 (s, 1H), 7.28 (s, J = 74 Hz, 1H), 7.14 (t, 2H), 2.62 (s, 2H), 0.98 (d, J = 5.0 Hz, 2H), 0.85 (d, J = 5.2 Hz, 2H).

Example 310

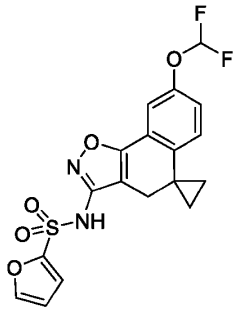
N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)isoxazole-4-sulfonamide



[1323] To a mixture of 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (111 mg, 399 µmol, Interemediate I) in dichloromethane (2 mL, 31.2 mmol) at 0°C , was added 1,2-oxazole-4-sulfonyl chloride (80.2 mg, 1.2 eq., 479 µmol then followed by slow addition of pyridine (323 µL, 10 eq., 3.99 mmol). Ice-bath removed and stirring continue at 80°C for another 18 hrs. Solvent removed under reduced pressure and the residue was purified by revered phase HPLC (10 - 90% ACN-Water, w / 0.1% Formic Acid) to obtain N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)isoxazole-4-sulfonamide (5.5 mg, 3%) as a light brown solid. MS (ESI,m/z): 408.0 $[M-H]^-$ 1H NMR (400 MHz, DMSO) δ 10.11 (s, 1H), 8.69 (s, 1H), 7.69 (d, J = 2.5 Hz, 1H), 7.44 – 7.36 (m, 1H), 7.30 (t, J = 74 Hz, 1H), 7.29 (s, 1H), 7.13 (d, J = 14.8 Hz, 1H), 2.97 (s, 2H), 1.14 (d, J = 3.8 Hz, 2H), 1.09 (d, J = 7.5 Hz, 2H).

Example 311

N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)furan-2-sulfonamide



[1324] To a mixture of 8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-amine (117 mg, 420 µmol, Intermediate I) in dichloromethane (2 mL, 31.2 mmol) at 0°C was added furan-2-sulfonyl chloride (70 mg, 420 µmol) followed by slow addition of pyridine (340 µL, 10 eq., 4.2 mmol). Ice-bath removed and stirring continue at 80°C for 18 hrs. Solvent removed under reduced pressure and the residue was purified by revered phase HPLC (10 - 90% ACN-Water, w / 0.1% Formic Acid) to obtain N-(8'-(difluoromethoxy)-4'H-spiro[cyclopropane-1,5'-naphtho[2,1-d]isoxazol]-3'-yl)furan-2-sulfonamide (12.5 mg, 7%) as a light brown solid. MS(ESI,m/z): 409.2 $[M+H]^+$ 1H NMR (400 MHz, DMSO) δ 11.60 (s, 1H), 8.03 (s, 1H), 7.37 (s, 1H), 7.29 (t, J = 74 Hz, 1H), 7.24 (d, J = 3.5 Hz, 1H), 7.16 (d, J = 3.0 Hz, 2H), 6.71 (dd, J = 3.7, 1.7 Hz, 1H), 2.62 (s, 2H), 1.00 (d, J = 5.0 Hz, 2H), 0.88 (d, J = 5.2 Hz, 2H).

Biological Example 1

KAT6A biochemical assay

[1325] KAT6A radiometric HotSpot assay was conducted at a starting concentration of 10µM in 10-points and 4-fold serial dilutions for test compounds, and a 10-point, 3-fold serial dilution starting at 100 µM for the control inhibitor. DMSO was used as the high signal control.

[1326] The enzymatic reaction was carried out at a final concentration of KAT6A (488-778) (Active Motif, Inc.) of 10nM, in a reaction mixture buffer and incubated for 30 minutes at 30°C; the mixture consisted on 5µM Histone H3 (Sigma, Inc.), and [Acetyl-3H]Acetyl-Coenzyme A in assay buffer; assay buffer consisted of 50mM Tris-HCl (pH 8), 50mM NaCl, 0.1mM EDTA, and 1mM DTT. After 30 minutes, the reaction was detected using the filter binding method.

[1327] Percent inhibition for each concentration of test compound was determined by calculating the ratio between the test compound and high control signal; the resulting data was fitted and the IC_{50} estimated. Results are shown in **Table 2**, wherein A <= 100 nM, 100 nM < B <= 200 nM, 200 nM < C <= 500 nM, 500 nM < D <= 1 µM, 1 µM < E <= 2 µM, 2 µM < F <= 5 µM.

Biological Example 2

KAT7 biochemical assay

[1328] KAT7 AlphaScreen biochemical assay was conducted in 384-well, assay-ready compound plates with a final enzymatic reaction volume of 10µL; plates were prepared a priori, starting at 10µM in 11-points and 3-fold serial dilutions for test compounds, and single concentrations for the controls. The controls were defined as Low Control and High Control; low control is a known inhibitor at 10µM, and the High control is vehicle or DMSO.

[1329] The enzymatic reaction was carried out at a final concentration of Full-length KAT7 (SignalChem, Inc.) of 20nM, in a reaction mixture buffer and incubated for 30 minutes at RT; the mixture consisted on 7µM of Acetyl-CoA (Sigma, Inc.), 10µg/mL anti-H4K8Ac and Histone H4 peptide (Anaspec, Inc.) at 150nM in assay buffer; assay buffer consisted of 100mM Tris-HCl (pH 8), 15mM NaCl, 1mM EDTA, 0.01% Tween-20, 0.01% w/v chicken egg white albumin (Sigma, Inc). After 30 minutes, the reaction was stopped using 50µM of Anacardic acid. Detection of the enzymatic reaction was done using and 20µg/mL AlphaScreen Streptavidin donor beads (Perkin-Elmer, Inc.) 20µg/mL of AlphaScreen anti-rabbit IgG Acceptor beads (Perkin-Elmer, Inc.), and 20µg/mL AlphaScreen Streptavidin donor beads (Perkin-Elmer, Inc.), added separately and incubated each for 60 minutes at RT. Following the donor beads incubation step, signal was measured in a plate reader with AlphaScreen capabilities.

[1330] Percent inhibition for each concentration of test compound was determined by calculating the ratio between the test compound, low control, and high control signals; the resulting data was fitted and the IC_{50} was estimated using Levenberg-Marquardt algorithm. Results are shown in **Table 2**, wherein A <= 100 nM, 100 nM < B <= 200 nM, 200 nM < C <= 500 nM, 500 < D <= 1 µM, 1 µM < E <= 2 µM, 2 µM < F <= 5 µM.

Table 2

Example Number	KAT6A IC_{50}	KAT7 IC_{50}
1	A	B
2	C	C
3	C	C
4	A	E
5	A	C
6	C	F
7	A	D
8	A	A
9	A	A

Example Number	KAT6A IC_{50}	KAT7 IC_{50}
10	A	A
11	A	A
12	A	
13	A	B
14	A	A
15	A	A
16	A	A
17	A	A
18	A	A
19	A	A
20	A	A
21	A	A
22	A	B
23	A	A
24	A	A
25	B	A
26	A	A
27	A	A
28	A	A
29	A	A
30	B	A
31	A	A
32	B	A
33	A	A
34	A	A
35	A	A
36	A	A
37	A	A
38	A	A
39	A	A
40	E	C
41	A	A
42	A	A
43	A	B
44	A	A
45	A	A
46	A	A
47	B	A
48	A	A
49	C	A
50	A	A
51	A	A
52	B	A
53	B	B
54	A	A
55	A	A

Example Number	KAT6A IC_{50}	KAT7 IC_{50}
56	A	A
57	A	A
58	B	A
59	B	A
60	A	A
61	A	A
62	A	A
63	C	A
64	A	A
65	A	A
66	D	B
67	A	A
68	C	B
69	A	A
70	A	A
71	C	A
72	A	A
73	A	A
74	B	A
75	A	A
76	D	B
77	E	C

Biological Example 3

KAT6A/7 Surface Plasmon Resonance (SPR) assay

[1331] The binding affinity (K_D) determination of Examples 1 to 311 was conducted by Surface Plasmon Resonance on a Biacore 8K+ instrument (Cytiva) at a temperature of 15 °C.

[1332] Recombinant human protein KAT6a (497-780) and protein complex KAT7 (336-611); BRPF2 (31-80; R38G) were in vitro biotinylated (EZ-Link™ Sulfo NHS-LC-LC-Biotin; Thermo Fisher Scientific) and immobilized onto a Series S Streptavidin sensor chip (Cytiva). The protein capture was performed in PBS-P+ buffer (Cytiva) at a flow rate of 15 µL/min and 100 s contact time, obtaining consistent capture levels of ca. 4,000 RU for both preparations across experimental days.

[1333] After the capture step, remaining unoccupied surface sites were blocked by a 100 µM Biotin-PEO3-amine (Biotium) injection to prevent non-specific interactions. Subsequently, the surface of the sensor chip was washed with PBS-P+ buffer, supplemented

with 1 mM TCEP and 1% DMSO, at a steady flow of 30 µL /min for approx. 4 hours to eliminate unbound species and reach a stable baseline (measured drift < 0.005 RU/s).

[1334] For K_D determination, compounds were assayed in single cycle kinetic mode with varying top concentrations (50, 100, 500 or 2000 nM) using PBS-P+ buffer supplemented with 1 mM TCEP and 1% DMSO as running buffer at a 50 µL/min flow rate. In addition, given the duration of these assay runs, a surface control sample was included and distributed throughout the experiment to monitor binding level over time.

[1335] The SPR absolute responses were subjected to blank/reference subtraction, solvent correction, and ultimately a 1:1 binding model was employed to fit the experimental data using Biacore™ Insight version 6.0 evaluation software (Cytiva). An unbiased post-analysis was also performed to normalize experimental R_{max} to account for surface activity decay, as well as to apply quality control criteria for fit acceptance. All K_D values reported herein originate from at least two independent replicates.

[1336] Results are shown in **Table 3**, wherein AAA <=1 nM, 1 nM <AA <= 10 nM, 10 nM < A <= 50 nM, 50 nM < B <= 100 nM, 100 nM < C <= 250 nM, 250 nM < D <= 500 nM, 500 nM < E <= 1 µM, 1 µM < F <= 2 µM, and G > 2 µM.

Biological Example 4

H3K14ac and H3K23ac Immunofluorescence Pharmacodynamics (IFPD) Assay

[1337] H3K14ac and H3K23ac IFPD assay was performed using CAMA-1 cells seeded in 384 well plates at a concentration of 3,000 cells per well (60,000 cells per ml). After overnight incubation at 37° Celsius, the cells were dosed with a starting concentration of 20 µM in a 10-point dose response with 2.7-fold serial dilutions in triplicate fashion, and a 10-point. DMSO was used as a negative control.

[1338] After 24 hours of incubation at 37° Celsius, dosed cells were fixed for 10 minutes at room temperature using a 1:2 dilution of 8% Paraformaldehyde (PFA) solution which was then washed out with PBS 5x. PBS was then removed from the plates by plate flicking followed by centrifugation for 15 seconds. Cells were then permeabilized for 10 minutes with 100% ice-cold methanol. After washing 5x with PBS, cells were blocked in Buffer A (10% Goat Serum, 1% Bovine Serum Albumin, 0.1% Triton X-100, and 0.01% NaN_3 in PBS).

Cells were washed with PBS, and primary antibody solutions prepared in Buffer A with final dilutions of 1:2,000 (H3k23ac – ab177275) and 1:4,000 (H3K14ac – CST-7627S). Plates were incubated at room temperature for 1 hour while being shaken on a plate shaker. After 1 hour, cells were again washed 5x with PBS. A solution consisting of a secondary antibody labelled with AlexaFluor488 (Invitrogen, A32731), and DAPI (Invitrogen, D21490) was prepared in Buffer A and added to the cell plates at 1:1,000 and 1:10,000 final dilutions respectively. Cell plates were sealed and incubated at room temperature for 1 hour while being shaken on a plate shaker. After 1 hour, plates were washed with PBS and resealed. Fluorescence was detected using a Molecular Devices IXMicro digital microscope.

[1339] Percent inhibition of acetylation for each concentration of test compound was calculated using InCarta Image analysis software. Nuclei were segmented using the DAPI signal. Acetylation was calculated using the cell average total integrated AlexaFluor488 intensity per nuclei. Percent response was calculated by dividing well average by the average negative control (DMSO). IC_{50} values were calculated using a 4-parameter logarithmic regression.

[1340] Results are shown in **Table 3**, wherein AAA <=1 nM, 1 nM <AA <= 10 nM, 10 nM < A <= 50 nM, 50 nM < B <= 100 nM, 100 nM < C <= 250 nM, 250 nM < D <= 500 nM, 500 nM < E <= 1 μM, 1 μM < F <= 2 μM, and G > 2 μM.

Biological Example 5

Cell viability assay (CyQuant Direct Cell Proliferation) in CAMA-1 cells

[1341] CyQuant Direct Cell Proliferation (Invitrogen) was conducted following the manufacturer's product protocol.

[1342] Cells were cultured in EMEM (Gibco) supplemented with 10% Fetal Bovine Serum (FBS). Cells were seeded in 96-well tissue culture plates, at a density of 400 cells/well. Cell plates were incubated overnight at 37°C with 5% CO_2.

[1343] Cells were treated starting at a 40μM in 9-points and 3-fold serial dilutions for test compounds and one control compound, and a single concentration for the negative and positive control; all compounds and controls had a final DMSO concentration of 0.25%. The

single concentration high control was defined as 0.25% DMSO. Cells were incubated for 10 days at 37°C with 5% CO_2.

[1344] As per product protocol, 2x detection reagent was mixed in OBS or cell culture media. Reagent was added as 1:1 to each well. Plates were incubated for 60 minutes at 37°C with 5% CO_2. After the incubation period, plates were read in a plate reader with fluorescence capabilities.

[1345] Percent inhibition for each concentration of test compound was determined by calculating the ratio between the test compound/high control; the resulting data was fitted and the IC50 was estimated using the xlfit.

[1346] Results are shown in **Table 3**, wherein A <= 100 nM, 100 nM < B <= 200 nM, 200 nM < C <= 500 nM, 500 < D <= 1 μM, 1 μM < E <= 2 μM, 2 μM < F <= 5 μM, and G > 5 μM.

Table 3

Example Number	KAT6A (SPR) IC_{50}	KAT7 (SPR) IC_{50}	K14 (IFPD) IC_{50}	K23 (IFPD) IC_{50}	Cell Viability IC_{50}
1	A	B	--	--	--
2	--	--	--	--	--
3	A	B	F	F	--
4	D	D	G	F	--
5	A	B	G	F	--
6	C	G	G	G	--
7	D	D	G	G	--
8	A	B	--	--	--
9	--	--	--	--	--
10	A	AA	--	--	--
11	AA	A	--	--	--
12	AA	AA	--	--	--
13	A	B	F	E	--
14	AA	AA	--	--	--
15	AA	AA	--	--	--
16	AA	AA	--	--	--

Example Number	KAT6A (SPR) IC_{50}	KAT7 (SPR) IC_{50}	K14 (IFPD) IC_{50}	K23 (IFPD) IC_{50}	Cell Viability IC_{50}
17	B	A	--	--	--
18	AAA	AAA	--	--	--
19	AAA	AAA	--	--	--
20	AA	A	--	--	--
21	AA	AA	--	--	--
22	AAA	AAA	B	A	C
23	AA	AA	--	--	--
24	AA	AAA	--	--	--
25	A	A	--	--	--
26	AA	AA	--	--	--
27	AA	AAA	--	--	--
28	AA	A	--	--	--
29	AAA	AAA	--	--	--
30	A	C	--	--	--
31	A	AAA	--	--	--
32	A	A	--	--	--
33	AA	A	--	--	--
34	A	B	--	--	--
35	AA	A	--	--	--
36	A	B	--	--	--
37	--	AAA	--	--	F
38	AA	AAA	--	--	--
39	AA	AAA	A	D	E
40	C	G	--	--	--
41	AAA	AAA	B	C	D
42	A	B	--	--	--
43	A	B	--	--	--
44	A	A	--	--	--
45	A	A	--	--	--
46	A	AA	--	--	--
47	A	A	--	--	--

Example Number	KAT6A (SPR) IC_{50}	KAT7 (SPR) IC_{50}	K14 (IFPD) IC_{50}	K23 (IFPD) IC_{50}	Cell Viability IC_{50}
48	AA	AAA	--	--	--
49	C	C	G	G	G
50	AA	B	--	--	--
51	AA	AAA	--	--	--
52	B	C	--	--	--
53	A	C	G	G	--
54	A	A	--	--	--
55	--	AAA	A	C	F
56	--	AAA	--	--	--
57	AA	AA	--	--	--
58	C	A	--	--	--
59	A	G	--	--	--
60	--	AA	--	--	--
61	A	A	--	--	--
62	--	AAA	AA	D	E
63	C	A	E	F	G
64	A	AA	--	--	--
65	--	AAA	--	--	--
66	C	F	--	--	--
67	--	AA	C	A	C
68	C	D	G	F	F
69	AAA	AA	D	B	D
70	B	C	--	--	--
71	C	C	G	G	G
72	AA	AAA	--	--	--
73	AA	AA	C	C	C
74	--	AA	A	E	--
75	B	A	--	--	--
76	C	E	--	--	--
77	F	G	--	--	--
78	A	AA	G	G	--

Example Number	KAT6A (SPR) IC_{50}	KAT7 (SPR) IC_{50}	K14 (IFPD) IC_{50}	K23 (IFPD) IC_{50}	Cell Viability IC_{50}
79	AA	A	--	--	--
80	G	A	E	G	--
81	--	--	--	--	--
82	D	F	--	--	--
83	C	D	--	--	--
84	--	--	--	--	--
85	--	AA	E	F	--
86	F	E	--	--	--
87	AAA	AAA	A	A	C
88	--	AA	C	B	D
89	AA	A	G	E	--
90	--	AA	F	D	--
91	--	AAA	E	C	F
92	AA	AAA	F	G	F
93	AA	AAA	D	G	--
94	--	AAA	C	AA	--
95	B	AA	E	F	--
96	AAA	AA	G	D	--
97	D	G	--	--	--
98	B	AA	D	G	--
99	AA	AA	E	G	--
100	AA	A	E	E	--
101	AA	A	E	D	--
102	AA	A	E	D	--
103	AA	AA	D	C	--
104	AAA	AAA	C	E	--
105	--	AAA	--	E	--
106	--	AA	--	E	--
107	D	F	--	--	--
108	D	E	--	--	--
109	A	AA	--	E	--

Example Number	KAT6A (SPR) IC_{50}	KAT7 (SPR) IC_{50}	K14 (IFPD) IC_{50}	K23 (IFPD) IC_{50}	Cell Viability IC_{50}
110	AAA	AAA	B	D	E
111	AAA	AAA	A	A	E
112	AAA	AAA	AA	A	A
113	AA	AAA	AA	F	F
114	B	A	--	G	--
115	B	A	--	G	--
116	A	A	--	--	--
117	--	--	--	--	--
118	AA	AAA	A	A	--
119	AA	A	--	G	--
120	--	AA	--	G	--
121	--	A	--	G	--
122	AAA	AAA	A	C	--
123	--	AAA	--	G	--
124	B	A	--	G	--
125	--	A	--	--	--
126	G	G	--	--	--
127	D	C	--	--	--
128	D	AA	--	--	--
129	E	F	--	--	--
130	AA	AA	E	F	--
131	AA	AA	E	G	--
132	--	AAA	A	E	--
133	AA	AAA	--	--	F
134	AA	AA	C	E	--
135	--	AA	C	D	--
136	D	D	--	--	--
137	D	E	--	--	--
138	--	AA	B	F	--
139	C	AA	B	G	--
140	--	A	--	--	--

Example Number	KAT6A (SPR) IC_{50}	KAT7 (SPR) IC_{50}	K14 (IFPD) IC_{50}	K23 (IFPD) IC_{50}	Cell Viability IC_{50}
141	A	AA	D	F	--
142	B	A	--	--	--
143	G	G	--	--	--
144	D	D	--	--	--
145	--	AA	C	F	--
146	B	AA	D	G	--
147	AA	AAA	A	D	F
148	AAA	AAA	B	E	--
149	B	G	--	--	--
150	C	G	--	--	--
151	D	G	--	--	--
152	F	G	--	--	--
153	C	C	--	--	--
154	B	B	--	--	--
155	D	G	--	--	--
156	D	D	--	--	--
157	A	A	--	--	--
158	AA	AA	D	D	--
159	--	AA	D	D	--
160	A	AA	D	E	--
161	B	C	--	--	--
162	E	F	--	--	--
163	AAA	AAA	A	A	C
164	--	A	--	--	--
165	--	AA	E	F	--
166	AA	AAA	A	F	F
167	A	AA	B	D	--
168	AAA	AAA	E	G	--
169	AAA	AAA	C	D	--
170	AA	AAA	D	F	G
171	A	C	--	--	--

Example Number	KAT6A (SPR) IC_{50}	KAT7 (SPR) IC_{50}	K14 (IFPD) IC_{50}	K23 (IFPD) IC_{50}	Cell Viability IC_{50}
172	AA	AAA	D	F	F
173	AA	AA	F	G	G
174	AAA	AAA	A	B	E
175	AAA	AAA	A	C	F
176	AAA	AA	E	F	F
177	AAA	AAA	AA	A	A
178	AAA	AAA	C	E	--
179	A	AAA	B	G	--
180	A	A	G	G	--
181	AA	AAA	C	E	--
182	--	AA	G	G	--
183	AA	AA	E	F	--
184	AA	AAA	D	E	--
185	AA	AA	B	E	--
186	A	AA	C	E	--
187	AAA	AAA	A	B	D
188	AAA	AAA	B	B	F
189	B	C	--	--	--
190	AAA	AAA	B	E	G
191	A	AAA	AA	E	F
192	G	G	--	--	--
193	AA	AA	C	B	--
194	AA	AAA	C	C	C
195	AAA	AAA	AA	A	C
196	AAA	AAA	AA	AA	A
197	AAA	AAA	AA	AA	B
198	--	AAA	AA	AA	B
199	AAA	AAA	B	A	--
200	AAA	AAA	AA	AA	A
201	AAA	AAA	AAA	A	A
202	AAA	AAA	AA	A	B

Example Number	KAT6A (SPR) IC_{50}	KAT7 (SPR) IC_{50}	K14 (IFPD) IC_{50}	K23 (IFPD) IC_{50}	Cell Viability IC_{50}
203	AAA	AAA	AA	A	C
204	AAA	AAA	AA	AA	B
205	AAA	AAA	AA	A	A
206	AAA	AAA	AA	A	B
207	AAA	AAA	AA	A	D
208	AAA	AAA	AA	AA	A
209	AAA	AAA	AA	A	A
210	--	AAA	AA	A	A
211	AAA	AAA	AA	AA	A
212	--	AAA	AA	AA	B
213	--	AAA	AA	A	C
214	AAA	AAA	AA	B	B
215	AAA	AAA	AA	A	A
216	AAA	AAA	AA	AA	C
217	AA	AAA	C	C	B
218	--	AAA	AA	A	B
219	--	AAA	AA	A	B
220	AAA	AAA	AAA	AA	A
221	AAA	AAA	AA	A	A
222	AAA	AAA	AA	A	A
223	AAA	AAA	AA	AA	A
224	AAA	AAA	AA	A	A
225	AAA	AAA	AA	A	A
226	AA	AA	C	B	B
227	AAA	AAA	AA	A	--
228	AAA	AAA	AA	A	A
229	AAA	AAA	AA	AA	A
230	AAA	AAA	AA	C	A
231	AAA	AAA	AA	A	A
232	AAA	AAA	AA	A	A
233	AAA	AAA	AA	A	A

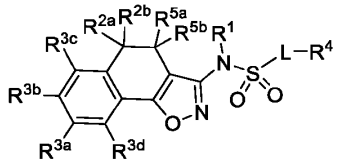
Example Number	KAT6A (SPR) IC_{50}	KAT7 (SPR) IC_{50}	K14 (IFPD) IC_{50}	K23 (IFPD) IC_{50}	Cell Viability IC_{50}
234	AAA	AAA	AA	A	A
235	AAA	AAA	AA	AA	A
236	AAA	AAA	AA	A	A
237	AAA	AAA	AA	A	C
238	AAA	AAA	AA	A	A
239	AAA	AAA	AA	A	--
240	AAA	AAA	AA	A	--
241	AAA	AAA	AA	B	A
242	AAA	AAA	AA	AA	A
243	AAA	AAA	AA	A	A
244	AAA	AAA	AA	A	A
245	AAA	AAA	AA	AA	A
246	AAA	AAA	AA	A	A
247	AAA	AAA	--	--	D
248	--	--	--	--	--
249	--	--	--	--	--
250	AAA	AAA	AA	AA	A
251	AAA	AAA	AA	A	B
252	AAA	AAA	AA	AA	B
253	AAA	AAA	AA	A	C
254	AAA	AAA	AA	AA	B
255	--	AAA	AAA	AAA	A
256	--	--	--	--	D
257	--	--	--	--	D
258	--	AAA	AAA	AA	A
259	--	--	AAA	AA	A
260	--	--	--	--	--
261	--	--	--	--	D
262	AAA	AAA	AA	AA	A
263	AAA	AAA	AA	A	B
264	AAA	AAA	AA	AA	A

Example Number	KAT6A (SPR) IC_{50}	KAT7 (SPR) IC_{50}	K14 (IFPD) IC_{50}	K23 (IFPD) IC_{50}	Cell Viability IC_{50}
265	AAA	AAA	AA	AA	A
266	AAA	AAA	AA	AA	A
267	AAA	AAA	AA	AA	A
268	AAA	AAA	AA	AA	A
269	AAA	AAA	AA	AA	A
270	AAA	AAA	AA	AA	A
271	AAA	AAA	AA	AA	C
272	AAA	AAA	AA	AA	B
273	AAA	AAA	AA	AA	A
274	AAA	AAA	C	D	E
275	AAA	AAA	AA	AA	A
276	AAA	AAA	AA	AA	A
277	AAA	AAA	AA	AA	A
278	AAA	AAA	AA	AA	A
279	AAA	AAA	AA	A	A
280	AAA	AAA	AA	AA	A
281	AAA	AAA	AA	A	A
282	AAA	AAA	AA	AA	A
283	AAA	AAA	AA	AA	A
284	AAA	AAA	AA	A	A
285	AAA	AAA	AA	A	B
286	AA	AA	C	E	G
287	--	AAA	AAA	AA	A
288					
289	A	AAA	AA	C	D
290	D	--	D	G	F
291	--	AAA	--	--	A
292	E	G	--	--	--
293	C	B	--	--	--
294	--	--	--	--	--
295	A	B	--	--	--

Example Number	KAT6A (SPR) IC_{50}	KAT7 (SPR) IC_{50}	K14 (IFPD) IC_{50}	K23 (IFPD) IC_{50}	Cell Viability IC_{50}
296	AAA	AAA	--	--	--
297	B	AA	--	--	--
298	AA	AA			
299	--	A	--	--	--
300	C	E	--	--	--
301	C	D	--	--	--
302	E	F	--	--	--
303	--	AA	--	--	--
304	E	--	--	--	--
305	AAA	AA	--	--	--
306	D	G	--	--	--
307	A	A	--	--	--
308	--	D	--	--	--
309	C	C	--	--	--
310	G	G	--	--	--
311	D	C	--	--	--

WHAT IS CLAIMED IS:

1. A compound, represented by Formula (Y):



(Y),

or a pharmaceutically acceptable salt thereof, wherein:

L is a bond, C_{1-3} alkylene, or $–N(R^6)–$;

R^1 is selected from the group consisting of H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{2a} and R^{2b} together with the carbon atom to which they are attached form cyclopropyl or cyclobutyl, wherein each of said cyclopropyl and cyclobutyl is independently unsubstituted or substituted with from 1 to 3 R^g; or

R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-6} alkyl, hydroxyC_{1-6}alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, hydroxyC_{1-6}alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-5} cycloalkyl, $–O–C_{3-5}$ cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, 5- to 6-membered heteroaryl–C_{1-3} alkylene–, $–C(O)NHR^a$, $–NR^{a1}R^{a2}$, and cyano, wherein each of said C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl, by itself or as part of another group, is independently unsubstituted or substituted with from 1 to 4 R^b;

R^{3d} is selected from the group consisting of H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^4 is selected from the group consisting of C_{1-6} alkyl, C_{4-7} cycloalkyl, bridged C_{5-10} cycloalkyl, phenyl, 5- to 6-membered heteroaryl, 3- to 7-membered heterocyclyl, and fused heterocyclyl, wherein each of said cycloalkyl, bridged cycloalkyl, phenyl, heteroaryl, heterocyclyl, and fused heterocyclyl is independently unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkynyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, 3- to 7-membered heterocyclyl, 3- to 7-membered heterocyclyl–O–, $–C(O)R^c$, $–C(O)OR^d$, $–C(O)NR^eR^f$,

–C_{1-3} alkylene–C(O)NR^eR^f, C_{3-6} cycloalkyl–C(O)NH–, and C_{1-6} alkyl–$S(O)_2$–C_{0-3} alkylene–; or two R^{4a} groups on adjacent carbon atoms are optionally combined to form 5- to 6-membered cycloalkyl or 3- to 7-membered heterocyclyl, each of which is independently unsubstituted or substituted with from 1 to 3 R^{4a1}, wherein each R^{4a1} is independently selected from halo, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{5a} and R^{5b} are each independently selected from the group consisting of H, C_{1-6} alkyl, hydroxyC_{1-6}alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

R^6 is selected from the group consisting of H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^a is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

R^{a1} and R^{a2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^b is independently selected from the group consisting of oxo, halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and C_{1-6} alkyl–$S(O)_2$–C_{0-3} alkylene–;

each R^c is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^d is independently selected from the group consisting of H and C_{1-6} alkyl;

R^e and R^f are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3- to 7-membered heterocyclyl, wherein each of said cycloalkyl and heterocyclyl is independently unsubstituted or substituted with 1 or 2 R^h; or R^e and R^f together with the nitrogen atom to which they are attached form 3- to 10-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^i;

each R^g is independently selected from the group consisting of C_{1-6} alkyl, halo, hydroxy, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and cyano;

each R^h is independently selected from the group consisting of halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkoxy, and cyano;

each R^i is independently selected from the group consisting of halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkoxy, and cyano;

each heteroaryl has 1 to 4 heteroatoms each independently selected from N, O, and S;

each heterocyclyl has 1 to 4 heteroatoms or groups each independently selected from N, O, S, S(O), and $S(O)_2$;

each bridged heterocyclyl has 1 to 3 heteroatoms each independently selected from N, O, and S;

the fused heterocyclyl is a 4- to 7-membered heterocyclyl having 1 to 3 heteroatoms each independently selected from N, O, and S, and the 4- to 7-membered heterocyclyl is fused to two adjacent ring members of C_{3-6} cycloalkyl, phenyl, or 5- to 6-membered heteroaryl; and

each spiroheterocyclyl has 1 to 3 heteroatoms each independently selected from N, O, and S.

2. The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein:

L is a bond, C_{1-3} alkylene, or $–N(R^6)–$;

R^{2a} and R^{2b} together with the carbon atom to which they are attached form cyclopropyl or cyclobutyl, wherein each of said cyclopropyl and cyclobutyl is independently unsubstituted or substituted with from 1 to 2 R^g; or

R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{3a} is selected from the group consisting of H, halo, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, $–O–C_{3-5}$ cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, 5- to 6-membered heteroaryl–C_{1-3} alkylene–, $–C(O)NHR^a$, and $–NR^{a1}R^{a2}$, wherein each of said C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl, by itself or as part of another group, is independently unsubstituted or substituted with 1 or 2 R^b;

R^{3b} is selected from the group consisting of H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, and $–NR^{a1}R^{a2}$;

R^{3c} is selected from the group consisting of H, halo, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, and $–NR^{a1}R^{a2}$;

R^{3d} is selected from the group consisting of H, halo, C_{1-4} alkyl, and C_{1-4} alkoxy;

R^4 is selected from the group consisting of C_{1-6} alkyl, C_{4-7} cycloalkyl, bridged C_{5-10} cycloalkyl, phenyl, 5- to 6-membered heteroaryl, and 3- to 7-membered heterocyclyl,

wherein each of said cycloalkyl, bridged cycloalkyl, phenyl, heteroaryl, and heterocyclyl is independently unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halo, CN, C_{1-4} haloalkoxy, 3- to 7-membered heterocyclyl, 3- to 7-membered heterocyclyl–O–, $–C(O)NR^eR^f$, $–C_{1-3}$ alkylene–$C(O)NR^eR^f$, C_{3-6} cycloalkyl–C(O)NH–, and C_{1-4} alkyl–$S(O)_2$–C_{0-3} alkylene–; or two R^{4a} groups on adjacent carbon atoms are optionally combined to form 5- to 6-membered cycloalkyl or 3- to 7-membered heterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 halo;

R^{5a} and R^{5b} are each independently selected from the group consisting of H and C_{1-4} alkyl;

R^6 is C_{1-4} alkyl;

R^a is C_{1-4} alkyl;

R^{a1} and R^{a2} are each independently selected from the group consisting of H and C_{1-6} alkyl;

each R^b is independently selected from the group consisting of oxo, halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} alkyl–$S(O)_2$–C_{0-3} alkylene–;

each R^e and R^f is independently selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, and 3- to 7-membered heterocyclyl, wherein each of said C_{3-6} cycloalkyl and heterocyclyl is independently unsubstituted or substituted with 1 or 2 R^h; or R^e and R^f together with the nitrogen atom to which they are attached form 3- to 10-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^i;

each R^g is independently selected from the group consisting of C_{1-4} alkyl and halo;

each R^h is independently selected from the group consisting of hydroxy and C_{1-4} alkoxy;

each R^i is independently selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy;

each heteroaryl has 1 or 2 heteroatoms each independently selected from N and O;

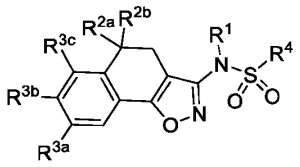
each heterocyclyl has 1 or 2 heteroatoms or groups each independently selected from N, O, and $S(O)_2$;

each bridged heterocyclyl has 1 or 2 heteroatoms each independently selected from N and O;

the fused heterocyclyl is a 4- to 7-membered heterocyclyl having 1 or 2 heteroatoms each independently selected from N and O, and the 4- to 7-membered heterocyclyl is fused to two adjacent ring members of C_{3-6} cycloalkyl, phenyl, or 5- to 6-membered heteroaryl; and

each spiroheterocyclyl has 1 or 2 heteroatoms each independently selected from N and O.

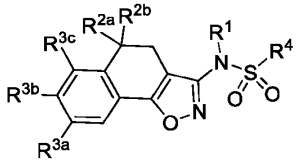
3. The compound of claim **1**, wherein R^{3d} is H and the compound is represented by Formula (I):



(I),

or a pharmaceutically acceptable salt thereof.

4. The compound of claim **1** or **3**, wherein the compound is represented by Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of H, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{2a} and R^{2b} together with the carbon atom to which they are attached form cyclopropyl or cyclobutyl, wherein each of said cyclopropyl and cyclobutyl is independently unsubstituted or substituted with from 1 to 3 R^g; or

R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, and C_{1-4} haloalkyl;

R^{3a}, R^{3b}, and R^{3c} are each independently selected from the group consisting of H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, –C(O)NHR^a, and cyano; and wherein each of said 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered

spiroheterocyclyl, and 5- to 6-membered heteroaryl has from 1 to 3 heteroatoms eachindependently selected from N, O and S, and wherein each of said C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl is independently unsubstituted or substituted with from 1 to 4 R^b;

R^4 is selected from the group consisting of C_{4-7} cycloalkyl, phenyl, heteroaryl, heterocyclyl, and fused heterocyclyl, wherein each of said phenyl, heteroaryl, heterocyclyl, and fused heterocyclyl is independently unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently selected from the group consisting of C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, CN, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxyC_{1-6} alkyl, –C(O)R^c, –C(O)OR^d, and –C(O)N$R^e$$R^f$; or two R^{4a} groups on adjacent carbon atoms are optionally combined to form a 5- to 6-membered cycloalkyl or heterocyclyl, each of which is independently unsubstituted or substituted with from 1 to 3 R^{4a1}, wherein each R^{4a1} is independently selected from halo, C_{1-4} alkyl, and C_{1-4} haloalkyl;

each R^a is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^b is independently selected from the group consisting of oxo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

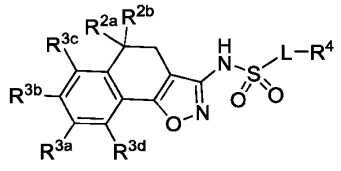
each R^c is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl;

each R^d is independently selected from the group consisting of H and C_{1-6} alkyl;

each R^e and R^f is independently selected from the group consisting of H, C_{1-6} alkyl and C_{3-6} cycloalkyl; or R^e and R^f together with the nitrogen atom to which they are attached form 4- to 6-membered ring; and

each R^g is independently selected from the group consisting of C_{1-6} alkyl, halo, hydroxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and cyano.

5. The compound of claim **1**, wherein R^1 is H and the compound is represented by formula (II):



(II),

or a pharmaceutically acceptable salt thereof.

6. The compound of any one of claims **1** to **5**, or a pharmaceutically acceptable salt thereof, wherein each heteroaryl has 1 to 3 heteroatoms each independently selected from N, O, and S; and each heterocyclyl has 1 to 3 heteroatoms or groups each independently selected from N, O, S, S(O), and $S(O)_2$.

7. The compound of claim **5** or **6**, or a pharmaceutically acceptable salt thereof, wherein:

L is a bond or C_{1-3} alkylene;

R^{2a} and R^{2b} together with the carbon atom to which they are attached form unsubstituted cyclopropyl; or

R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^{3a} is selected from the group consisting of H, halo, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, 5- to 6-membered heteroaryl–C_{1-3} alkylene–, and –C(O)NHR[a], wherein each of said C_{3-5} cycloalkyl, 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl, by itself or as part of another group, is independently unsubstituted or substituted with 1 or 2 R^b;

R^{3b} is selected from the group consisting of H, halo, and C_{1-4} alkyl;

R^{3c} is selected from the group consisting of H, halo, C_{1-4} alkyl, and C_{1-4} hydroxyalkyl;

R^{3d} is selected from the group consisting of H and halo;

R^4 is selected from the group consisting of C_{1-6} alkyl, C_{4-7} cycloalkyl, bridged C_{5-10} cycloalkyl, phenyl, 5- to 6-membered heteroaryl, and 3- to 7-membered heterocyclyl, wherein each of said cycloalkyl, phenyl, heteroaryl, and heterocyclyl is independently unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halo, CN, C_{1-4}

haloalkoxy, 3- to 7-membered heterocyclyl, 3- to 7-membered heterocyclyl–O–, –C(O)NR^{e}R^f, –C$_{1-3}$ alkylene–C(O)NR^{e}R^f, C$_{3-6}$ cycloalkyl–C(O)NH–, and C$_{1-4}$ alkyl–S(O)$_2$–C$_{0-3}$ alkylene–; or two R^{4a} groups on adjacent carbon atoms are optionally combined to form 5- to 6-membered cycloalkyl or 3- to 7-membered heterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 halo;

R^a is C$_{1-4}$ alkyl;

each R^b is independently selected from the group consisting of oxo, halo, hydroxy, C$_{1-4}$ alkyl, C$_{1-4}$ haloalkyl, hydroxyC$_{1-4}$ alkyl, C$_{1-4}$ alkoxy, and C$_{1-4}$ alkyl–S(O)$_2$–C$_{0-3}$ alkylene–;

each R^e and R^f is independently selected from the group consisting of H, C$_{1-4}$ alkyl, C$_{3-6}$ cycloalkyl, and 3- to 7-membered heterocyclyl, wherein each of said C$_{3-6}$ cycloalkyl and heterocyclyl is independently unsubstituted or substituted with 1 or 2 R^h; or R^e and R^f together with the nitrogen atom to which they are attached form 3- to 10-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^i;

each R^h is independently selected from the group consisting of hydroxy and C$_{1-4}$ alkoxy;

each R^i is independently selected from the group consisting of halo, hydroxy, C$_{1-4}$ alkyl, and C$_{1-4}$ alkoxy;

each heteroaryl has 1 or 2 heteroatoms each independently selected from N and O;

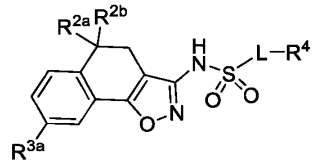
each heterocyclyl has 1 or 2 heteroatoms or groups each independently selected from N, O, and S(O)$_2$;

each bridged heterocyclyl has 1 or 2 heteroatoms each independently selected from N and O;

the fused heterocyclyl is a 4- to 7-membered heterocyclyl having 1 or 2 heteroatoms each independently selected from N and O, and the 4- to 7-membered heterocyclyl is fused to two adjacent ring members of C$_{3-6}$ cycloalkyl, phenyl, or 5- to 6-membered heteroaryl; and

each spiroheterocyclyl has 1 or 2 heteroatoms each independently selected from N and O.

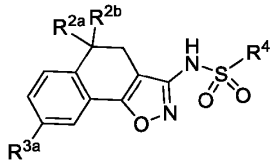
8. The compound of any one of claims **1** to **2** and **5** to **7**, represented by Formula (II-1):



(II-1),

or a pharmaceutically acceptable salt thereof.

9. The compound of any one of claims **1** to **7**, represented by Formula (I-1):



(I-1),

or a pharmaceutically acceptable salt thereof.

10. The compound of any one of claims **1** to **2** and **5** to **8**, or a pharmaceutically acceptable salt thereof, wherein L is a bond.

11. The compound of any one of claims **1** to **10**, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are each independently H or C_{1-4} alkyl.

12. The compound of any one of claims **1** to **11**, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are each H.

13. The compound of any one of claims **1** to **11**, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is H; and R^{2b} is methyl.

14. The compound of any one of claims **1** to **11**, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are each methyl.

15. The compound of any one of claims **1** to **10**, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form cyclopropyl substituted with 1 or 2 R^g; and each R^g is independently C_{1-4} alkyl or halo.

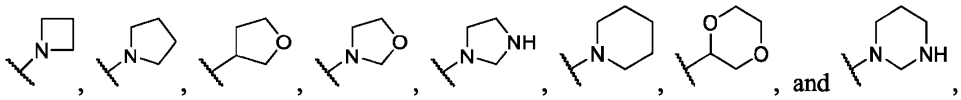
16. The compound claim **15**, or a pharmaceutically acceptable salt thereof, wherein each R^g is independently methyl or F.

17. The compound of any one of claims **1** to **10**, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are combined with the carbon atom to which they are attached to form unsubstituted cyclopropyl.

18. The compound of any one of claims **1** to **3** and **5** to **17**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is selected from the group consisting of 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, 5- to 6-membered heteroaryl, and 5- to 6-membered heteroaryl–C_{1-3} alkylene–, wherein each of the 3- to 7-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, 6- to 10-membered spiroheterocyclyl, and 5- to 6-membered heteroaryl is independently unsubstituted or substituted with 1 or 2 R^b.

19. The compound of claim **18**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is 3- to 7-membered heterocyclyl, which is unsubstituted or substituted with 1 or 2 R^b.

20. The compound of claim **18** or **19**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is selected from the group consisting of:

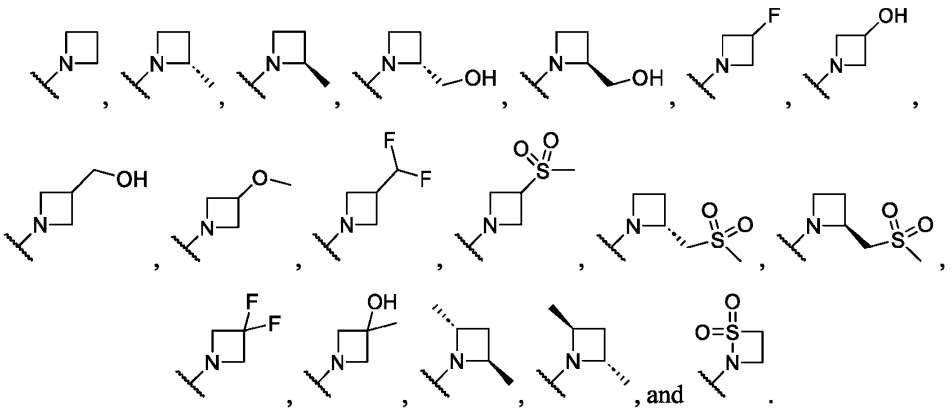


each of which is independently unsubstituted or substituted with 1 or 2 R^b.

21. The compound of any one of claims **18** to **20**, or a pharmaceutically acceptable salt thereof, wherein each R^b is independently selected from the group consisting of oxo, halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} alkyl–$S(O)_2$–C_{0-3} alkylene–.

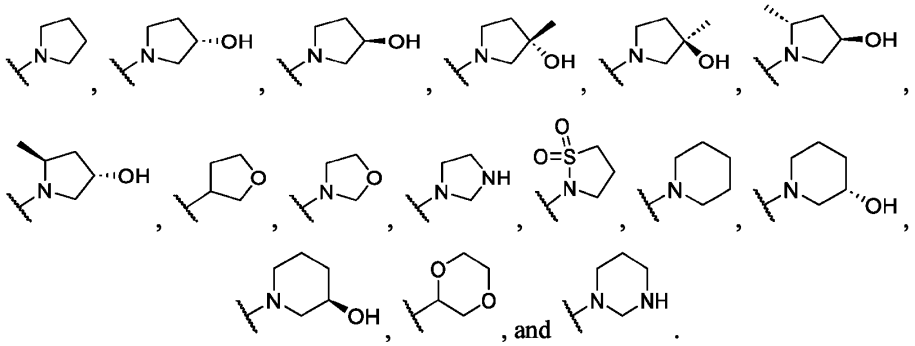
22. The compound of any one of claims **18** to **21**, or a pharmaceutically acceptable salt thereof, wherein each R^b is independently selected from the group consisting of oxo, halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyC_{1-4} alkyl, and C_{1-4} alkoxy.

23. The compound of claim **18** or **19**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is selected from the group consisting of:

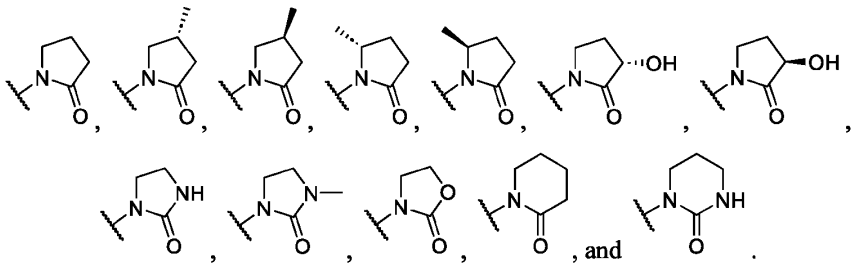


24. The compound of any one of claims **1** to **23**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is  .

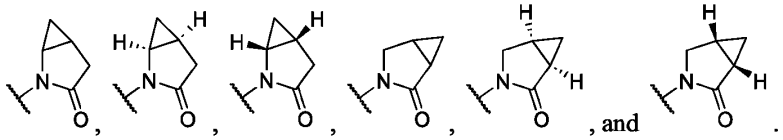
25. The compound of claim **18** or **19**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is selected from the group consisting of:



26. The compound of any one of claims **1** to **22**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is selected from the group consisting of:



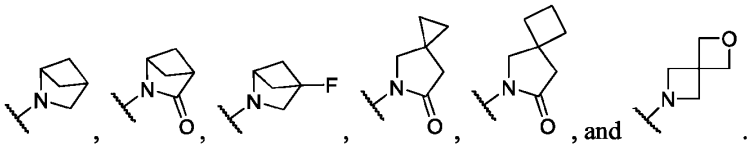
27. The compound of any one of claims **1** to **19**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is selected from the group consisting of:



28. The compound of claim **18**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is 6- to 9-membered bridged heterocyclyl or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^b.

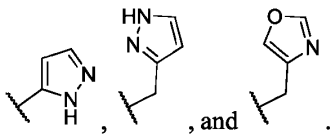
29. The compound of claim **28**, or a pharmaceutically acceptable salt thereof, wherein each R^b is independently oxo or halo.

30. The compound of claim **28** or **29**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is selected from the group consisting of:



31. The compound of claim **18**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is 5- to 6-membered heteroaryl or 5- to 6-membered heteroaryl–C_{1-3} alkylene–, each of which is unsubstituted.

32. The compound of claim **31**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is selected from the group consisting of:



33. The compound of any one of claims **1** to **17**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is selected from the group consisting of H, halo, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, and –C(O)NHR^a; and R^a is C_{1-4} alkyl.

34. The compound of claim **33**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is selected from the group consisting of H, Cl, Br, $–CH_3$, $–CH_2OH$, $–CH(CH_3)OH$, $–OCH_3$, $–OCH_2CH_3$, $–OCHF_2$, $–OCF_3$, cyclopropyl, –O–cyclopropyl, and $–C(O)NHCH_3$.

35. The compound of any one of claims **1** to **3** and **8** to **17**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is selected from the group consisting of H, halo, C_{1-4} alkyl, hydroxyC_{1-4}alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-5} cycloalkyl, –O–C_{3-5} cycloalkyl, $–C(O)NHR^a$, and $–NR^{a1}R^{a2}$; R^a is C_{1-4} alkyl; and R^{a1} and R^{a2} are each independently H or C_{1-4} alkyl.

36. The compound of claim **35**, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is selected from the group consisting of H, Cl, Br, $–CH_3$, $–CH_2OH$, $–CH(CH_3)OH$, $–OCH_3$, $–OCH_2CH_3$, $–OCHF_2$, $–OCF_3$, cyclopropyl, –O–cyclopropyl, $–C(O)NHCH_3$, $–NH_2$, $–NHCH_3$, and $–N(CH_3)_2$.

37. The compound of any one of claims **1** to **3** and **5** to **36**, or a pharmaceutically acceptable salt thereof, wherein:

R^4 is phenyl, which is unsubstituted or substituted with from 1 to 3 R^{4a}, wherein each R^{4a} is independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halo, CN, C_{1-4} haloalkoxy, 3- to 7-membered heterocyclyl, 3- to 7-membered heterocyclyl–O–, $–C(O)NR^eR^f$, $–C_{1-3}$ alkylene–$C(O)NR^eR^f$, C_{3-6} cycloalkyl–C(O)NH–, and C_{1-4} alkyl–$S(O)_2$–C_{0-3} alkylene–;

each R^e and R^f is independently selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, and 3- to 7-membered heterocyclyl, wherein each of cycloalkyl and heterocyclyl is independently unsubstituted or substituted with 1 or 2 R^h; or R^e and R^f together with the nitrogen atom to which they are attached form 3- to 10-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^i;

each R^h is independently selected from the group consisting of hydroxy and C_{1-4} alkoxy; and

each R^i is independently selected from the group consisting of halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy.

38. The compound of any one of claims **1** to **37**, or a pharmaceutically acceptable salt thereof, wherein R^4 is phenyl substituted with 1 or 2 R^{4a}; and each R^{4a} is independently C_{1-4} alkoxy.

39. The compound of claim **38**, or a pharmaceutically acceptable salt thereof, wherein each R^{4a} is methoxy.

40. The compound of any one of claims **1** to **37**, or a pharmaceutically acceptable salt thereof, wherein R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy; and the remaining R^{4a} is $-C(O)NR^eR^f$.

41. The compound of claim **40**, or a pharmaceutically acceptable salt thereof, wherein the remaining R^{4a} is $-C(O)NR^eR^f$; R^e is H; and R^f C_{1-4} alkyl.

42. The compound of claim **40** or **41**, or a pharmaceutically acceptable salt thereof, wherein two R^{4a} are each methoxy; and the remaining R^{4a} is $-C(O)NHCH_3$.

43. The compound of any one of claims **1** to **3** and **5** to **37**, or a pharmaceutically acceptable salt thereof, wherein R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is $-C(O)NR^eR^f$; and R^e and R^f together with the nitrogen atom to which they are attached form 5- to 10-membered heterocyclyl, 6- to 9-membered bridged heterocyclyl, or 6- to 10-membered spiroheterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^i.

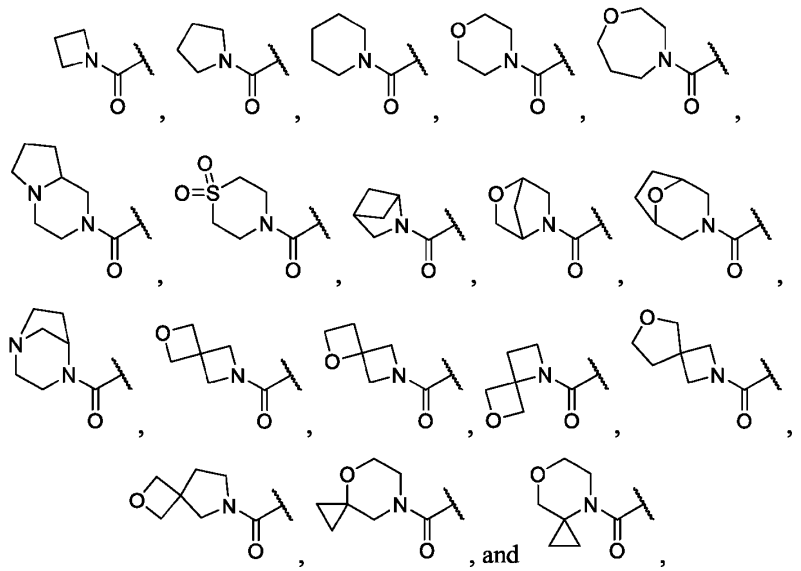
44. The compound of claim **43**, or a pharmaceutically acceptable salt thereof, wherein R^e and R^f together with the nitrogen atom to which they are attached form 5- to 6-membered heterocyclyl, which is unsubstituted or substituted with 1 or 2 R^i; and each R^i is independently halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy.

45. The compound of claim **43**, or a pharmaceutically acceptable salt thereof, wherein R^e and R^f together with the nitrogen atom to which they are attached form 6- to 9-membered bridged heterocyclyl, which is unsubstituted or substituted with 1 or 2 R^i; and each R^i is independently halo, hydroxy, C_{1-4} alkyl, , C_{1-4} haloalkyl, or C_{1-4} alkoxy.

46. The compound of claim **43**, or a pharmaceutically acceptable salt thereof, wherein R^e and R^f together with the nitrogen atom to which they are attached form 6-

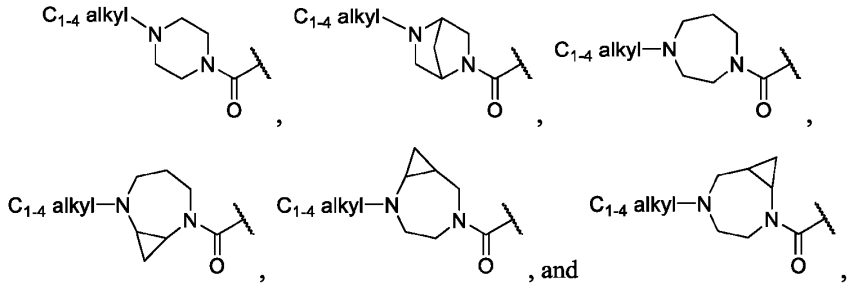
to 10-membered spiroheterocyclyl, which is unsubstituted or substituted with 1 or 2 R^i; and each R^i is independently halo, hydroxy, C_{1-4} alkyl, , C_{1-4} haloalkyl, or C_{1-4} alkoxy.

47. The compound of claim **43**, or a pharmaceutically acceptable salt thereof, wherein the remaining R^{4a} is selected from the group consisting of:



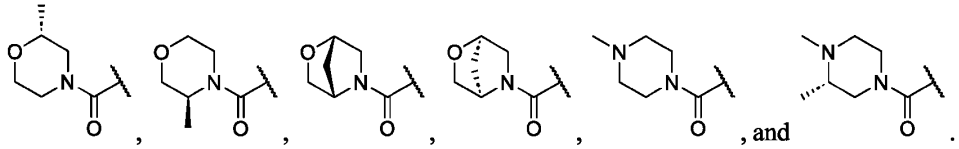
each of which is independently unsubstituted or substituted with 1 or 2 R^i; and each R^i is independently halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy.

48. The compound of claim **43**, or a pharmaceutically acceptable salt thereof, wherein the remaining R^{4a} is selected from the group consisting of:



each of which is optionally substituted with one additional R^i; and R^i is halo, C_{1-4} alkyl, or C_{1-4} alkoxy.

49. The compound of claim **47** or **48**, or a pharmaceutically acceptable salt thereof, wherein R^4 is phenyl substituted with three (3) R^{4a}; and two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is selected from the group consisting of:

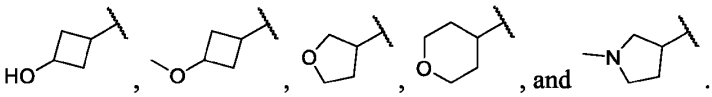


50. The compound of any one of claims **1** to **3** and **5** to **37**, or a pharmaceutically acceptable salt thereof, wherein R^4 is phenyl substituted with three (3) R^{4a}; two R^{4a} are each C_{1-4} alkoxy and the remaining R^{4a} is $-C(O)NR^eR^f$; R^e is H or C_{1-4} alkyl; and R^f is C_{3-6} cycloalkyl or 3- to 7-membered heterocyclyl, each of which is independently unsubstituted or substituted with 1 or 2 R^h.

51. The compound of claim **50**, or a pharmaceutically acceptable salt thereof, wherein R^f is C_{3-6} cycloalkyl unsubstituted or substituted with 1 or 2 R^h; and each R^h is independently hydroxy or C_{1-4} alkoxy.

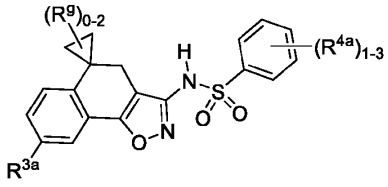
52. The compound of claim **50**, or a pharmaceutically acceptable salt thereof, wherein R^f is 3- to 7-membered heterocyclyl unsubstituted or substituted with 1 or 2 R^h; and each R^h is independently hydroxy or C_{1-4} alkoxy.

53. The compound of claim **50** or **52**, or a pharmaceutically acceptable salt thereof, wherein R^f is selected from the group consisting of:



54. The compound of any one of claims **43** to **53**, or a pharmaceutically acceptable salt thereof, wherein two R^{4a} are each methoxy.

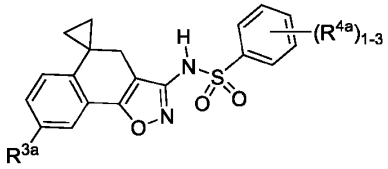
55. The compound of any one of claims **1** to **3**, **5** to **10**, and **15** to **54**, wherein the compound is represented by Formula (I-1a):



(I-1a),

or a pharmaceutically acceptable salt thereof.

56. The compound of any one of claims **1**, **3**, **5** to **10**, and **17** to **34**, wherein the compound is represented by Formula (I-1a):



(I-1b),

or a pharmaceutically acceptable salt thereof.

57. A compound of claim **1** or a pharmaceutically acceptable salt thereof, wherein said compound is a compound from **Table 1** or a compound of Examples 1 to 311.

58. A pharmaceutical composition comprising a compound of any one of claims **1** to **57**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

59. A compound or pharmaceutically acceptable salt thereof of any one of claims **1** to **57** or a pharmaceutical composition of claim **58**, for use in therapy.

60. A method of treating cancer in a subject in need thereof, said method comprising administering to said subject a therapeutically effective amount of a compound of any one of claims **1** to **57** or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim **58**.

61. The method of claim **60**, wherein the cancer is characterized by an overexpression of KAT6A and/or KAT7, an amplification of KAT6A gene and/or KAT7 gene, an increased activity of KAT6A and/or KAT7, or a combination thereof.

62. The method of claim **60**, wherein the cancer is characterized by an overexpression of KAT6A, an amplification of KAT6A gene, an increased activity of KAT6A, or a combination thereof.

63. The method of any one of claims **60** to **62**, wherein the cancer is treatable by inhibition of KAT6A and/or KAT7.

64. A method of treating a disorder mediated by KAT6A and/or KAT7 in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a compound of any one of claims **1** to **57**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim **58**.

65. The method of claim **64**, wherein the disorder is cancer.

66. The method of any one claims **60** to **65**, wherein the cancer is lung cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, liver cancer, pancreatic cancer, brain cancer, skin cancer, head and neck cancer, thyroid cancer, bladder cancer, esophageal cancer, stomach cancer, uterine cancer, melanoma, gastric cancer, rhabdoid cancer, or bone cancer; or the cancer is associated with the central nervous system.

67. A compound of any one of claims **1** to **57**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim **58**, for use in the treatment of cancer.

68. Use of a compound of any one of claims **1** to **57**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim **58**, in the manufacture of a medicament for the treatment of cancer.

69. The use of claim **67** or **68**, wherein the cancer is lung cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, liver cancer, pancreatic cancer, brain cancer, skin cancer, head and neck cancer, thyroid cancer, bladder cancer, esophageal cancer, stomach cancer, uterine cancer, melanoma, gastric cancer, rhabdoid cancer, or bone cancer; or the cancer is associated with the central nervous system.