

NICOTINAMIDE RIPK1 INHIBITORS

RELATED APPLICATION

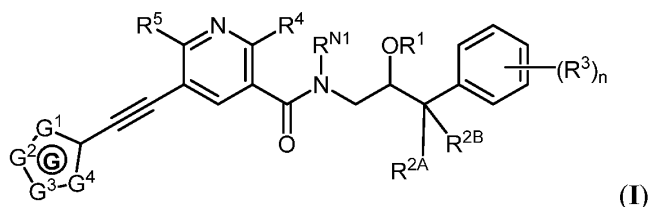
[0001] This application claims the benefit of priority to U.S. Provisional Patent Application No. 63/231,590, filed August 10, 2021, the contents of which are hereby incorporated by reference.

BACKGROUND

[0002] Receptor-interacting protein kinase (RIPK1) is a key regulator of inflammation involved in the induction of necroptosis, apoptosis, and pro-inflammatory cytokine production. Necroptosis is a pro-inflammatory form of regulated cell death characterized by breakdown of the cellular membrane and the release of intracellular contents into the local cellular environment. The intracellular contents, known as damage associated molecular patterns (DAMPs), activate various immune cells leading to the onset of an inflammatory response and the production of inflammatory cytokines that contribute to additional cell death, thus driving a cycle of inflammation. The most studied pathway for induction of necroptosis by RIPK1 is the tumor necrosis factor (TNF) pathway, but RIPK1 is also involved in necroptosis induction by other TNF superfamily members (FAS/TRAIL) and Toll-like receptors (TLRs; TLR3/TLR4). Phosphorylation of RIPK1 leads to subsequent phosphorylation of RIPK3 and formation of an amyloid structure that subsequently recruits and activates the pseudokinase MLKL (mixed lineage kinase domain-like), a critical component of necroptotic cell death. Inhibition of RIPK1 is associated with inhibition of this necroptotic induced cascade of events and the ensuing inflammatory response. See, *e.g.*, Li, *et al.*, Necroptosis in inflammatory bowel disease and other intestinal diseases. *World J. Clin. Cases* (2018) 6(14):745-752. Accordingly, there exists a need to develop further inhibitors of RIPK1 useful for treating Ulcerative Colitis.

SUMMARY

[0003] Described herein are compounds of Formula (I), and pharmaceutically acceptable salts thereof:



wherein:

R^1 is hydrogen, or
 R^1 is $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2OR^{P1}$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$, wherein each instance of R^{P1} is independently selected from the group consisting of hydrogen and substituted or unsubstituted C_{1-4} alkyl, and R^{P2} is substituted or unsubstituted C_{1-4} alkyl;
 R^{2A} and R^{2B} are each independently hydrogen or halo;
each R^3 is independently selected from the group consisting of halo and substituted or unsubstituted C_{1-4} alkyl, wherein n is 0, 1, or 2;
 R^{N1} is hydrogen or substituted or unsubstituted C_{1-4} alkyl;
 R^4 is independently selected from the group consisting of hydrogen, $-OR^{4A}$, and substituted or unsubstituted C_{1-4} alkyl, wherein R^{4A} is hydrogen or substituted or unsubstituted C_{1-4} alkyl;
 R^5 is independently selected from the group consisting of hydrogen, $-OR^{5A}$, and substituted or unsubstituted C_{1-4} alkyl, wherein R^{5A} is hydrogen or substituted or unsubstituted C_{1-4} alkyl;
Ring G is a 5-membered heteroaryl ring, wherein each G^1 , G^2 , G^3 , and G^4 is, independently, CH, CR^{G1} , N, NR^{N2} , O, or S, provided at least one of G^1 , G^2 , G^3 , and G^4 is N, NR^{N2} , O, or S, and wherein no more than two of G^1 , G^2 , G^3 , and G^4 is O or S;
each instance of R^{G1} is independently selected from the group consisting of halo, $-OR^{G2}$, $-NR^7$, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted 3-4-membered carbocyclyl, or substituted or unsubstituted 4-membered heterocyclyl, wherein R^{G2} is hydrogen or substituted or unsubstituted C_{1-4} alkyl;
or two vicinal R^{G1} groups, taken together with the atoms to which they are attached, form a fused substituted or unsubstituted 5-6 membered carbocyclyl or fused substituted or unsubstituted 5-6 membered heterocyclyl;
or a vicinal R^{G1} group and R^{N2} group, taken together with the atoms to which they are attached, form a fused substituted or unsubstituted 5-6 membered heterocyclyl;
each R^{N2} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted 3-4-membered carbocyclyl, and substituted or unsubstituted 4-membered heterocyclyl;
each R^7 is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted 3-4-membered carbocyclyl, and substituted or unsubstituted 4-membered heterocyclyl; and

each instance of substituted or unsubstituted is optionally and independently substituted by 0, 1, 2, or 3 substituents selected from the group consisting of halo, $-OH$, $-O(C_{1-4}alkyl)$, and $-O(C_{1-4}haloalkyl)$.

[0004] In certain embodiments, in Ring G, at least one of G^1 , G^2 , G^3 , and G^4 is N or NR^{N2} .

[0005] In certain embodiments, in Ring G, at least one of G^2 or G^3 is N or NR^{N2} .

[0006] In certain embodiments, in Ring G, at least two of G^1 , G^2 , G^3 , and G^4 are N or NR^{N2} .

[0007] In certain embodiments, Ring G is a diazole. In certain such embodiments, G^2 and G^3 are each independently N or NR^{N2} .

[0008] In further embodiments, Ring G is a triazole. In certain such embodiments, G^2 , G^3 , and G^4 are each independently N or NR^{N2} .

[0009] In certain embodiments, R^{N2} is alkyl or haloalkyl.

[0010] In certain embodiments, one of G^1 and G^2 is CR^{G1} . In certain such embodiments, R^{G1} is methyl or cyclopropyl.

[0011] In certain embodiments, R^4 is hydrogen.

[0012] In certain embodiments, R^5 is hydrogen, alkoxy, or haloalkyl.

[0013] In further embodiments, R^5 is hydrogen, methyl, methoxy, or difluoromethyl. In still further embodiments, R^5 is hydrogen.

[0014] In certain embodiments, R^{N1} is hydrogen or methyl. For example, in some embodiments, R^{N1} is hydrogen; alternatively, in some embodiments, R^{N1} is methyl.

[0015] In certain embodiments, R^{2A} and R^{2B} are each hydrogen.

[0016] In certain embodiments, one of R^{2A} and R^{2B} is hydrogen and the other is fluoro.

[0017] In certain embodiments, n is 0 or 1.

[0018] In certain embodiments, n is 1. In certain such embodiments, R^3 is halo.

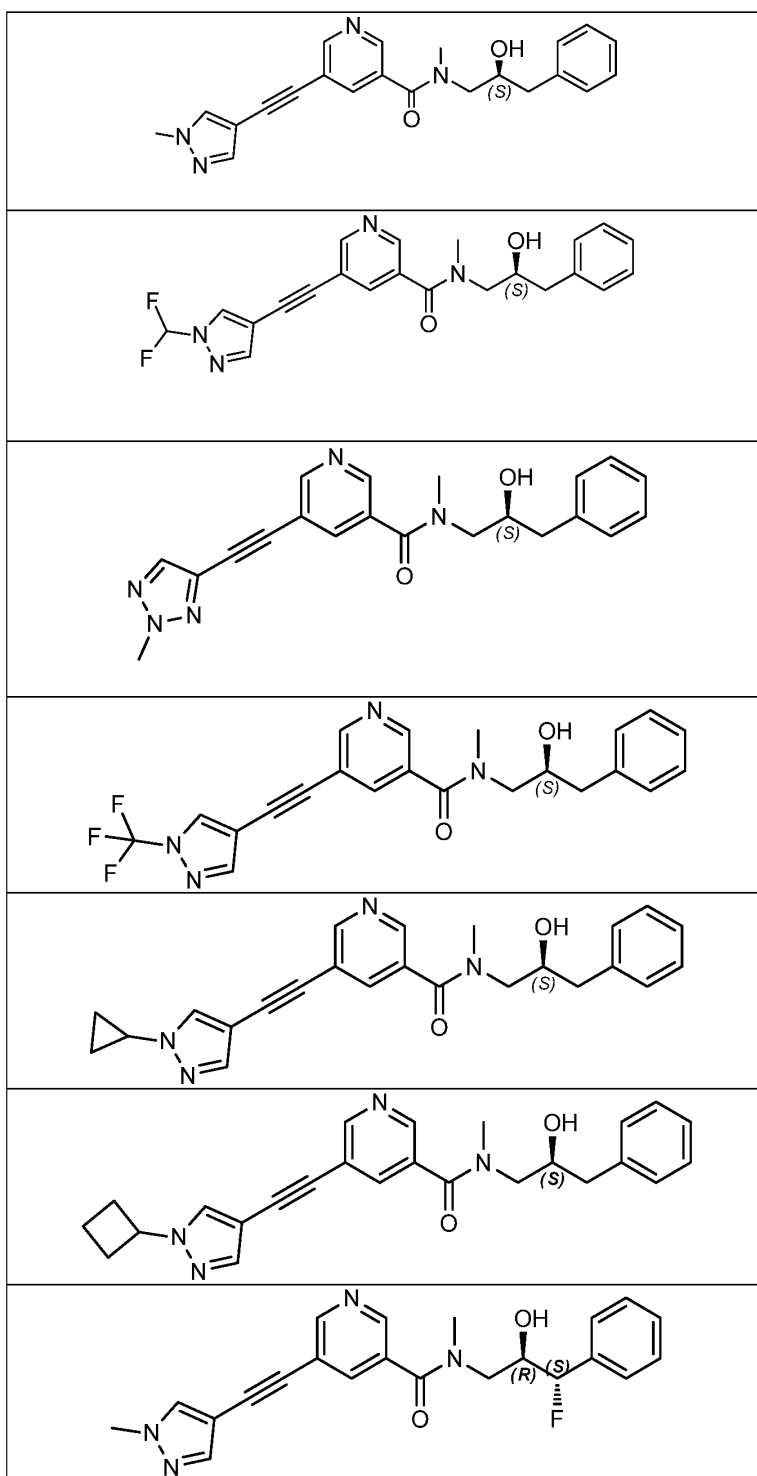
[0019] In alternative embodiments, n is 0.

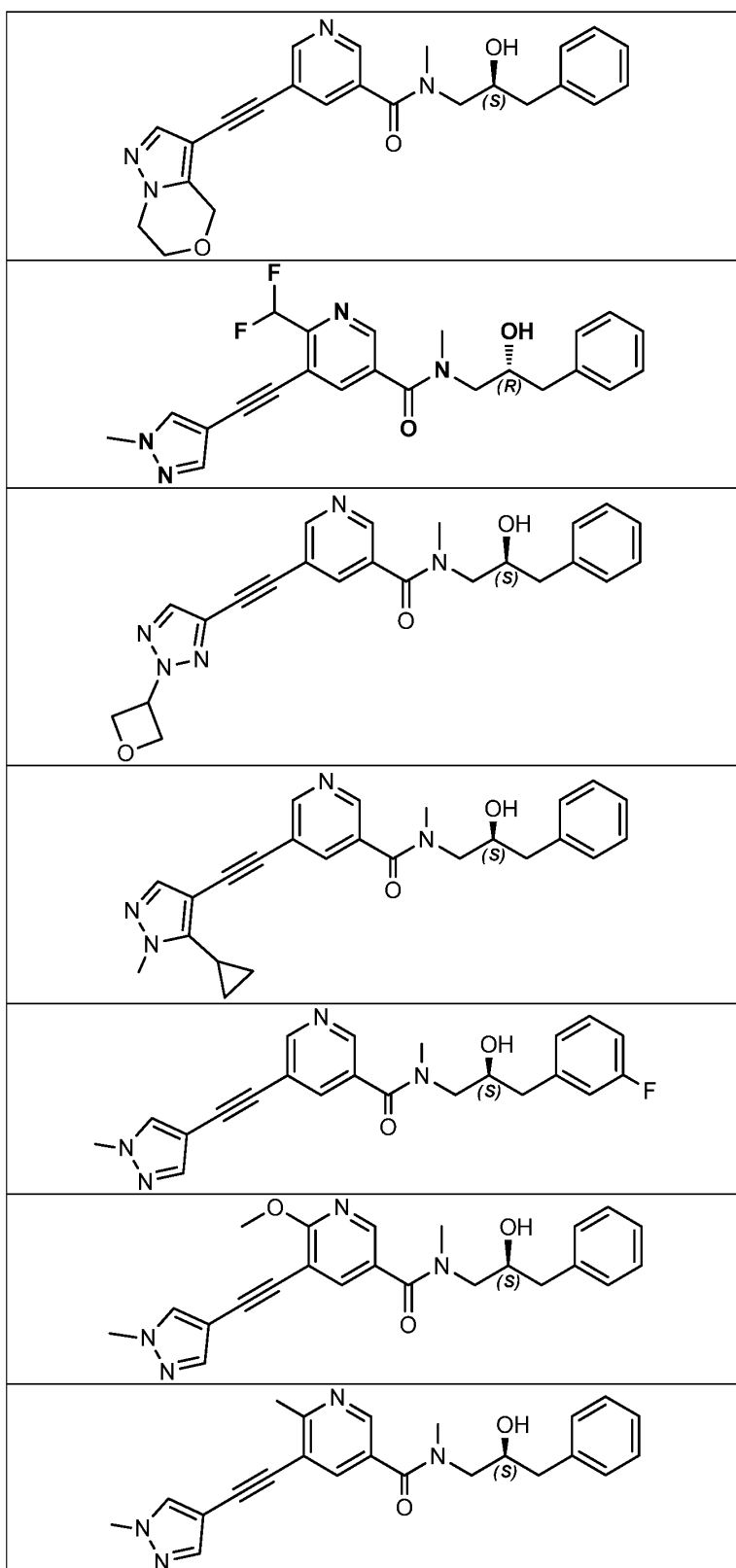
[0020] In certain embodiments, R^1 is hydrogen.

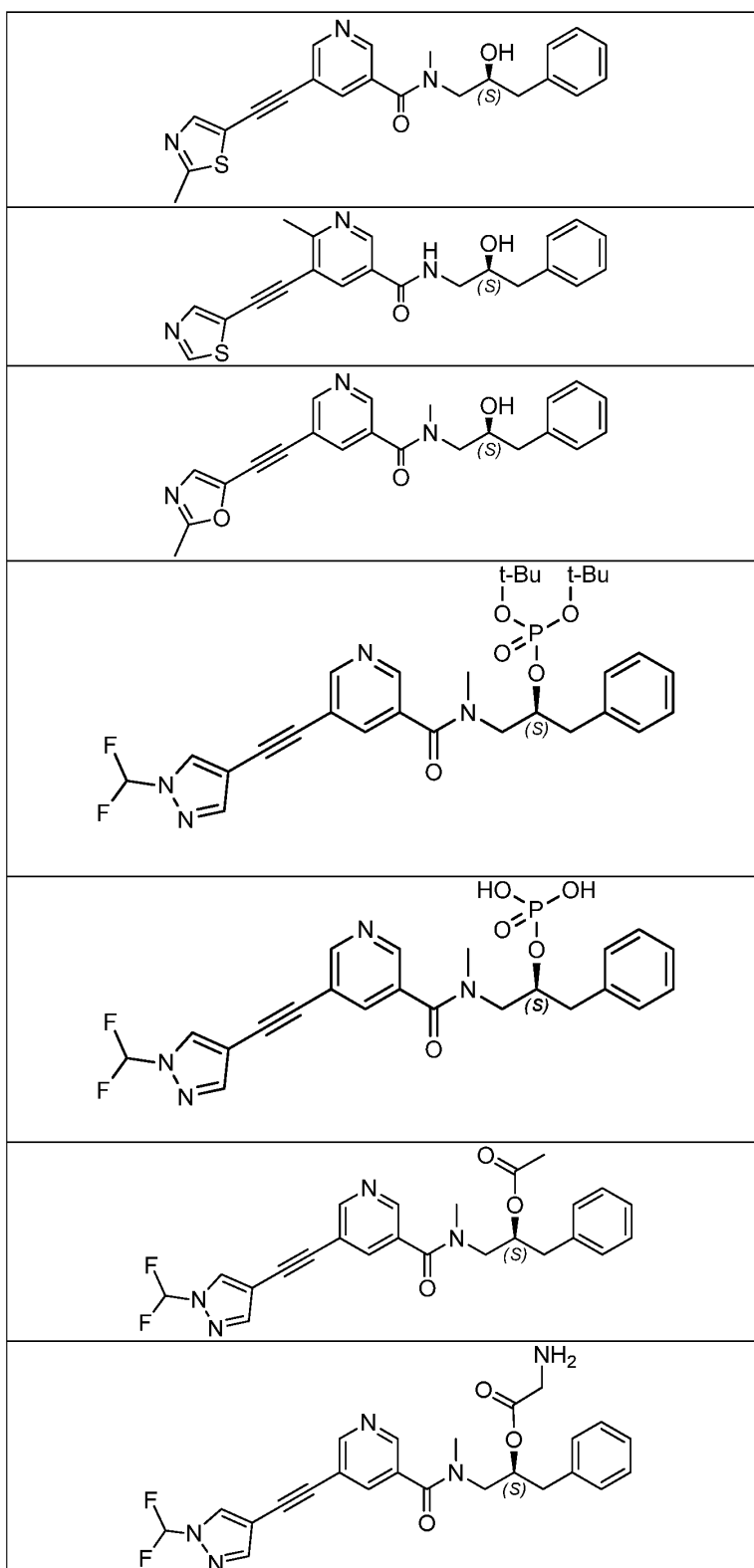
[0021] In alternative embodiments, R^1 is $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$.

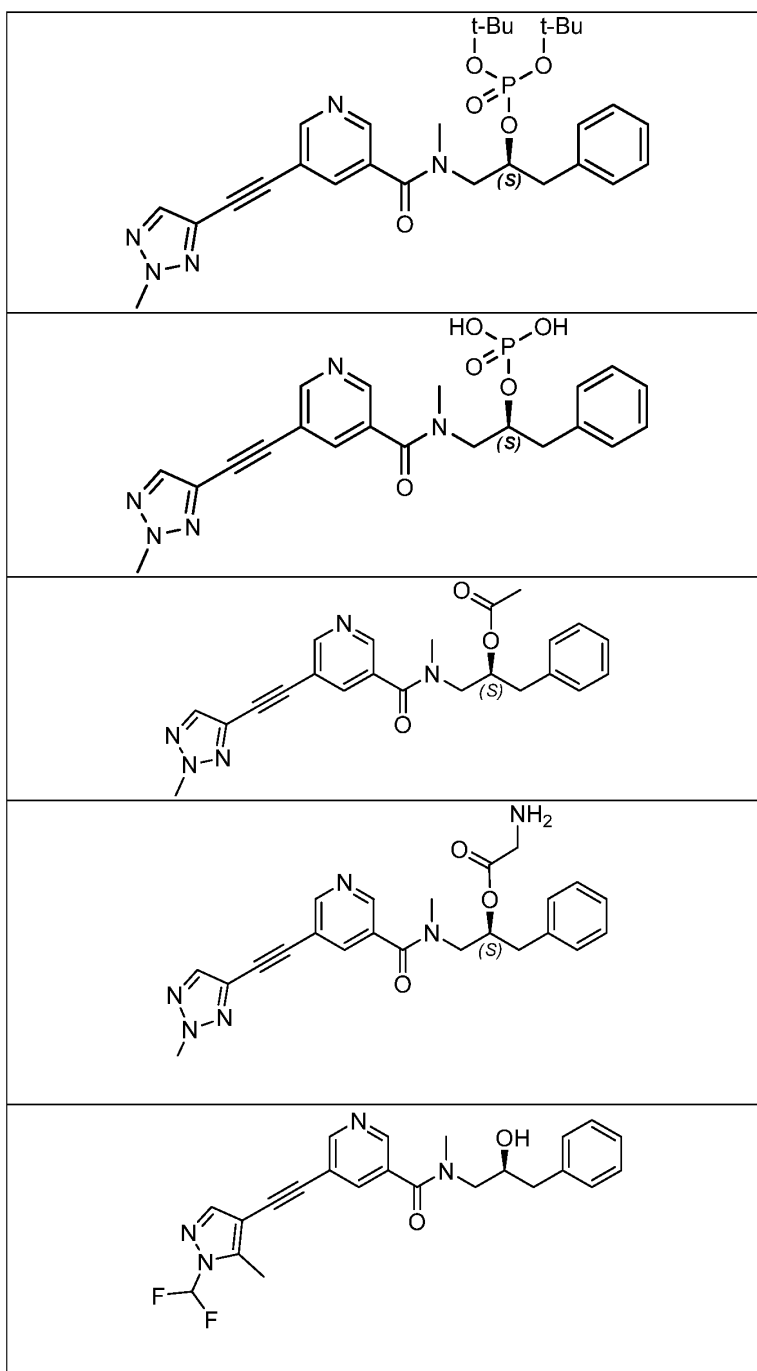
For example, R^1 is $-P(=O)(OR^{P1})_2$. In certain such embodiments, each R^{P1} is independently selected from the group consisting of hydrogen and unsubstituted $C_{1-4}alkyl$. In further such embodiments, each R^{P1} is hydrogen. Alternatively, each R^{P1} can be unsubstituted $C_{1-4}alkyl$.

[0022] In certain embodiments, the compound is selected from the following table:









or a pharmaceutically acceptable salt thereof.

[0023] Also provided herein are pharmaceutical compositions comprising a compound of Formula (I).

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] **Fig. 1** depicts a modeled binding mode of a compound of Formula (I), wherein R¹ is hydrogen, in the ATP (adenoside triphosphate) binding pocket of RIPK1, providing a working hypothesis for the observed RIPK1 binding activity and selectivity over other kinases. In particular, and without wishing to be bound by any particular theory, it is believed several interactions serve as anchor points for binding, from right to left: (1) the terminal phenyl ring fills the volume in a lipophilic back pocket in addition to making an edge-to-face aromatic interaction with the side chain ring of His136; (2) the hydroxyl group makes a hydrogen bond interaction with the backbone carbonyl of the Val76 residue; (3) the carbonyl group makes a hydrogen bond interaction with the backbone Asp156 residue of the DLG motif (Asp156–Leu157–Gly158); and (4) an electron donating group of the heteroaryl ring (designated as “Ring G”) makes an interaction with the backbone NH of the Met95 residue in the hinge region. While DLG motif is not unique to RIPK1, it is found in only a small subset of kinases; the majority of kinases instead comprise a DFG (Asp–Phe–Gly) motif. Without wishing to be bound by any particular theory, it further hypothesized that the shape of the lipophilic pocket and interaction with the His136 residue, in addition to the presence of the more accommodating DLG motif (which lacks the bulky phenylalanine ring), drive RIPK1 selectivity by contributing to and accommodating the overall curved binding conformation, thereby allowing for more specific RIPK1 contacts and binding.

[0025] **Fig. 2** contains a plot that shows prodrug loss, based on peak area ratios, for Example 19. The inhibition of phosphatase activity by 1 mM orthovanadate as demonstrated by effect on substrate depletion is also shown.

[0026] **Fig. 3** contains a plot that shows parent formation, based on peak area ratios, for Example 19. The inhibition of phosphatase activity by 1 mM orthovanadate as demonstrated by effect on parent formation is also shown.

DEFINITIONS

[0027] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March

March's Advanced Organic Chemistry, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0028] Compounds described herein may comprise one or more asymmetric centers, and thus may exist in various stereoisomeric forms, e.g., enantiomers and/or diastereomers and/or geometric (cis/trans or E/Z) isomers in a composition. For example, compositions may comprise a mixture of stereoisomers, including racemic (equal) mixtures, mixtures enriched in one or more stereoisomer, or may comprise an individual stereoisomer in substantially pure (>99%) form. As used herein, "enriched" refers to a composition which comprises greater than (>) 50% of one stereoisomer over the sum total of other stereoisomer(s) which may be present in the composition. In certain embodiments, a composition may comprise >60%, >65%, >70%, >75%, >80%, >85%, >90%, >91%, >92%, >93%, >94%, >95%, >96%, >97%, >98%, >99%, >99.5%, >99.9%, or even up to 100% of one stereoisomer over the sum total of other stereoisomer(s) which may be present in the composition; or may comprise 0% or less than (<) 0.1%, <0.5%, <1%, <2%, <3%, <4%, <5%, <6%, <7%, <8%, <9%, <10%, <15%, <20%, <25%, <30%, <35%, <40%, <45%, or <50% of one stereoisomer over the sum total of other stereoisomer(s) which may be present in the composition. For simplicity, calculating enriched amounts of any of the stereoisomer(s), if provided as pharmaceutically acceptable salt(s) in a composition, are based on the hypothetical amount of free base form. In certain embodiments, a composition is enriched in its (*S*)-enantiomer. In other embodiments, a composition is enriched in its (*R*)-enantiomer.

[0029] Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, replacement of ¹⁹F with ¹⁸F, replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon, and/or replacement of an oxygen atom with ¹⁸O, are within the scope of the disclosure.

[0030] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, "C₁₋₆ alkyl" is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl.

[0031] "Alkyl" refers to a monovalent radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 4 carbon atoms ("C₁₋₄ alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C₁₋₃ alkyl"). In some embodiments, an alkyl group has 1

to 2 carbon atoms (“C₁₋₂ alkyl”). In some embodiments, an alkyl group has 1 carbon atom (“C₁ alkyl”). Examples of C₁₋₄ alkyl groups include methyl (C₁), ethyl (C₂), n-propyl (C₃), isopropyl (C₃), n-butyl (C₄), *tert*-butyl (C₄), *sec*-butyl (C₄), and iso-butyl (C₄) groups.

[0032] “Haloalkyl” is an alkyl group wherein one or more of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. “Perhaloalkyl” is a subset of haloalkyl, and refers to an alkyl group wherein all of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, the haloalkyl moiety has 1 to 4 carbon atoms (“C₁₋₄ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 3 carbon atoms (“C₁₋₃ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms (“C₁₋₂ haloalkyl”). In some embodiments, all of the haloalkyl hydrogen atoms are replaced with fluoro to provide a perfluoroalkyl group. Examples of haloalkyl groups include –CF₃, –CHF₂, –CFH₂, –CF₂CF₃, –CH₂CF₃, –CF₂CF₂CF₃, –CCl₃, –CFCl₂, and –CF₂Cl.

[0033] “Carbocyclyl” or “carbocyclic” refers to a monovalent radical of a monocyclic, non-aromatic, 3- to 6- membered ring system having from 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”) and zero ring heteroatoms. In some embodiments, a carbocyclyl group has 3 to 4 ring carbon atoms (“C₃₋₄ carbocyclyl”). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms (“C₄₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms (“C₅₋₆ carbocyclyl”). Exemplary C₃₋₆ carbocyclyl groups include, without limitation, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), and cyclohexadienyl (C₆).

[0034] “Heterocyclyl” or “heterocyclic” refers to a monovalent radical of a monocyclic, non-aromatic, 4- to 6-membered ring system having ring carbon atoms and 1 to 3 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“4- to 6-membered heterocyclyl”). Exemplary 4-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azetidiny, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyl groups containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidiny, and dihydropyrrolyl. Exemplary 5-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5-membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazoliny, oxadiazoliny, and thiadiazoliny. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidiny, tetrahydropyranyl, dihydropyridiny, and

thianyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazinanyl.

[0035] A “5-membered heteroaryl” refers to a radical of a 5 membered monocyclic $4n+2$ aromatic ring system (*e.g.*, having 6 pi electrons shared in a cyclic array) having ring carbon atoms and 1–3 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur. In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. In some embodiments, the 5-membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-membered heteroaryl has 2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Exemplary 5-membered heteroaryl groups containing 1 heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5-membered heteroaryl groups containing 2 heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing 3 heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl.

[0036] “Halo” refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[0037] “Substituted” means that the specified group or moiety bears one or more substituents. Where any group may carry multiple substituents, and a variety of possible substituents is provided, the substituents are independently selected, and need not to be the same. Exemplary substituents include, but are not limited to, hydroxyl, halo, cyano, nitro, thiol, alkyl, alkenyl, carbocyclyl, heterocyclyl, heteroaryl, aryl, heteroarylalkyl, arylalkyl, alkoxy, phosphate, phosphonate, amino, amido, carboxylate, and ester.

[0038] “Unsubstituted” means that the specified group bears no substituents.

[0039] “Optionally and independently substituted” means that the specified group may or may not be further substituted by one or more substituents and that those substituents need not to be the same, if more than one substituent is present.

[0040] “Salt” refers to any and all salts, and is produced from the ionic complexation of a basic compound with an inorganic or organic acid, or an acidic compound with an inorganic or organic base, to provide a compound which is electronically neutral. “Pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment,

suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. See also Berge *et al.*, *J. Pharmaceutical Sciences* (1977) 66:1–19. A “free base” of a compound is the neutral and salt-free form of the compound. In certain embodiments, a compound of Formula (I) may be a salt (*e.g.*, a pharmaceutically acceptable salt). In certain embodiments, *e.g.*, in the absence of reference to a pharmaceutically acceptable salt, a compound of Formula (I) may be present as the free base form.

[0041] A “leaving group” refers to a molecular fragment that departs with a pair of electrons in heterolytic bond cleavage wherein the molecular fragment is an anion or neutral molecule. A “leaving group” also refers to a molecular fragment which departs via a cross-coupling reaction. Exemplary leaving groups which depart with a pair of electrons in heterolytic bond cleavage include, but are not limited to, halo (*e.g.*, chloro, bromo, iodo) and activated hydroxyl groups, such as a trifluoromethanesulfonyl activated hydroxyl group (–OTf) 4-toluenesulfonyl activated hydroxyl group (–OTs), methanesulfonyl activated hydroxyl group (–OMs), benzenesulfonyl activated hydroxyl group (–OBs), or –OS(O)₂OCH₃. Exemplary leaving groups which depart via a cross-coupling reaction, include, but are not limited to, boronic acids or boronic esters (*e.g.*, a dioxoborolane group, *e.g.*, tetramethyl dioxoborolane), trialkyl stannanes (*e.g.*, (R')₃Sn–, wherein R' is C_{1–3}alkyl), and halo (*e.g.*, chloro, bromo, iodo).

[0042] Hydroxyl protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999. Exemplary “hydroxyl protecting groups”, as used herein, include but are not limited to, methoxymethyl (MOM), methylthiomethyl (MTM), *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (*p*-AOM), guaiacolmethyl (GUM), *t*-butoxymethyl, 4-pentenylloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), allyl, benzyl (Bn), *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, diphenylmethyl, triphenylmethyl, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylhexylsilyl, *t*-

butyldimethylsilyl (TBDMS), *t*-butyldiphenylsilyl (TBDPS), tribenzylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*-butylmethoxyphenylsilyl (TBMPS), acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), ethyl carbonate, 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-(phenylsulfonyl) ethyl carbonate (Psec), 2-(triphenylphosphonio) ethyl carbonate (Peoc), isobutyl carbonate, vinyl carbonate, allyl carbonate, *t*-butyl carbonate (BOC), *p*-nitrophenyl carbonate, benzyl carbonate, *p*-methoxybenzyl carbonate, 3,4-dimethoxybenzyl carbonate, *o*-nitrobenzyl carbonate, and *p*-nitrobenzyl carbonate.

[0043] A “subject” refers to a mammal, and includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult or senior adult)) and/or other non-human mammals, for example, primates (*e.g.*, cynomolgus monkeys, rhesus monkeys), cats, and/or dogs.

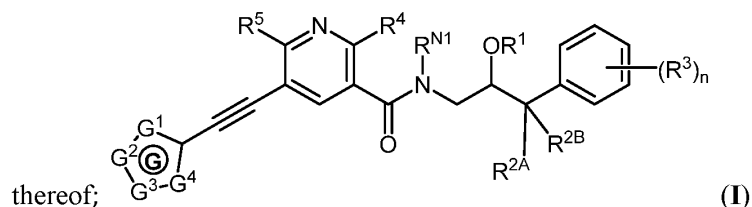
[0044] “Treat,” “treating” and “treatment” refers to an action that occurs while a subject is suffering from the disease, and which reduces the severity of the disease, or retards or slows the progression of the disease or associated symptoms.

[0045] An “effective amount” of a compound, or a pharmaceutically acceptable salt thereof, is an amount, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of a disease from which the subject suffers, or to delay or minimize one or more symptoms associated with the disease from which the subject suffers.

DETAILED DESCRIPTION OF THE INVENTION

(i) *Compounds*

Described herein are compounds of Formula (I) and pharmaceutically acceptable salts



or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is hydrogen, or

R^1 is $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2OR^{P1}$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$, wherein each instance of R^{P1} is independently selected from the group consisting of hydrogen and substituted or unsubstituted C_{1-4} alkyl, and R^{P2} is substituted or unsubstituted C_{1-4} alkyl;

R^{2A} and R^{2B} are each independently hydrogen or halo;

each R^3 is independently selected from the group consisting of halo and substituted or unsubstituted C_{1-4} alkyl, wherein n is 0, 1, or 2;

R^{N1} is hydrogen or substituted or unsubstituted C_{1-4} alkyl;

R^4 is independently selected from the group consisting of hydrogen, $-OR^{4A}$, and substituted or unsubstituted C_{1-4} alkyl, wherein R^{4A} is hydrogen or substituted or unsubstituted C_{1-4} alkyl;

R^5 is independently selected from the group consisting of hydrogen, $-OR^{5A}$, and substituted or unsubstituted C_{1-4} alkyl, wherein R^{5A} is hydrogen or substituted or unsubstituted C_{1-4} alkyl;

Ring G is a 5-membered heteroaryl ring, wherein each G^1 , G^2 , G^3 , and G^4 is, independently, CH, CR^{G1} , N, NR^{N2} , O, or S, provided at least one of G^1 , G^2 , G^3 , and G^4 is N, NR^{N2} , O, or S, and wherein no more than two of G^1 , G^2 , G^3 , and G^4 is O or S;

each instance of R^{G1} is independently selected from the group consisting of halo, $-OR^{G2}$, $-NR^7$, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted 3-4-membered carbocyclyl, or substituted or unsubstituted 4-membered heterocyclyl, wherein R^{G2} is hydrogen or substituted or unsubstituted C_{1-4} alkyl;

or two vicinal R^{G1} groups, taken together with the atoms to which they are attached, form a fused substituted or unsubstituted 5-6 membered carbocyclyl or fused substituted or unsubstituted 5-6 membered heterocyclyl;

or a vicinal R^{G1} group and R^{N2} group, taken together with the atoms to which they are attached, form a fused substituted or unsubstituted 5-6 membered heterocyclyl;

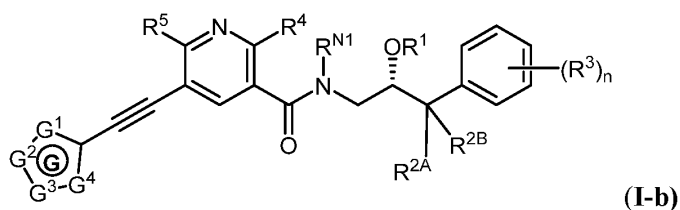
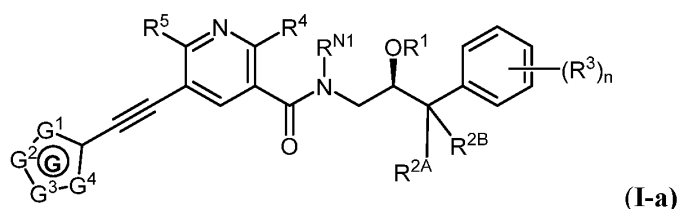
each R^{N2} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted 3-4-membered carbocyclyl, and substituted or unsubstituted 4-membered heterocyclyl;

each R^7 is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted 3-4-membered carbocyclyl, and substituted or unsubstituted 4-membered heterocyclyl; and

each instance of substituted or unsubstituted is optionally and independently substituted by 0, 1, 2, or 3 substituents selected from the group consisting of halo, $-OH$, $-O(C_{1-4}alkyl)$, and $-O(C_{1-4}haloalkyl)$.

[0046] Compounds of Formula (I) may selectively bind to and inhibit RIPK1 (*see* **FIG. 1**; RIPK1 Binding Assay in Assays and Activity Data). By inhibiting RIPK1, the compounds of the invention may prevent TNF-induced necroptosis (*see* U937 TNF/zVAD Cytotoxicity Cell Assay in Assays and Activity Data).

[0047] Compounds of Formula (I) may further comprise one or more stereocenters. In certain embodiments, the compound comprises a stereocenter on the carbon to which group OR^1 is attached. For example, in certain embodiments, the compound is a stereoisomer of Formula (I-a), or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a stereoisomer of Formula (I-b), or a pharmaceutically acceptable salt thereof.



Ring G

[0048] In certain embodiments, in Ring G, at least one of G^1 , G^2 , G^3 , and G^4 is N or NR^{N2} .

[0049] In certain embodiments, in Ring G, at least one of G^2 or G^3 is N or NR^{N2} .

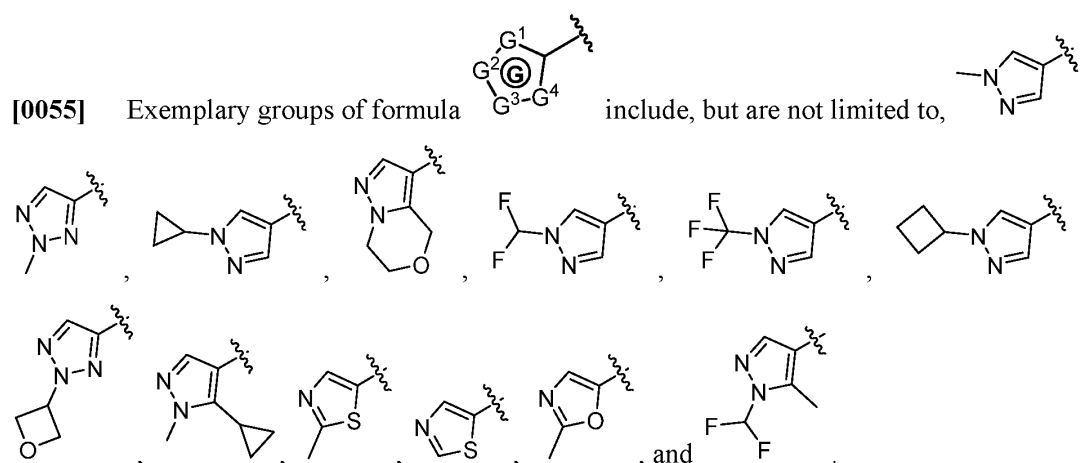
[0050] In certain embodiments, in Ring G, at least two of G^1 , G^2 , G^3 , and G^4 is N or NR^{N2} .

[0051] In certain such embodiments, Ring G is a diazole. In certain such embodiments, G^2 and G^3 are each independently N or NR^{N2} .

[0052] In further embodiments, Ring G is a triazole. In certain such embodiments, G^2 , G^3 , and G^4 are each independently N or NR^{N2} .

[0053] In certain embodiments, R^{N2} is alkyl or haloalkyl.

[0054] In certain embodiments, e.g., in which at least one of G^1 , G^2 , G^3 , and G^4 is N or NR^{N2} or in which Ring G is a diazole, one of G^1 and G^2 is CR^{G1} . In certain such embodiments, R^{G1} is methyl or cyclopropyl.

**R⁴ and R⁵**

[0056] In certain embodiments, R⁴ is hydrogen.

[0057] In certain embodiments, R⁵ is hydrogen, alkoxy, or haloalkyl.

[0058] In certain embodiments, R⁵ is hydrogen, methyl, methoxy, or difluoromethyl. For example, R⁵ may be hydrogen.

R^{N1}

[0059] In certain embodiments, R^{N1} is hydrogen or methyl. For example, R^{N1} may be hydrogen. Alternatively, R^{N1} is methyl.

R^{2A} and R^{2B}

[0060] In certain embodiments, R^{2A} and R^{2B} are each hydrogen. Alternatively, one of R^{2A} and R^{2B} is hydrogen and the other is fluoro.

R³ and n

[0061] In certain embodiments, n is 0 or 1.

[0062] In some embodiments, n is 1. In certain such embodiments, R³ is halo. Alternatively, n is 0.

R¹

[0063] In certain embodiments, R¹ is hydrogen.

[0064] Alternatively, R¹ may be $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$. For example, in some embodiments, R¹ is $-P(=O)(OR^{P1})_2$. In certain such embodiments, each R^{P1} is independently selected from the group consisting of hydrogen and unsubstituted C₁₋₄alkyl. For example, each R^{P1} may be hydrogen. Alternatively, each R^{P1} may be unsubstituted C₁₋₄alkyl.

[0065] In certain embodiments of Formula (I), at least one of G² or G³ is N or NR^{N2}; R⁴ is hydrogen; R⁵ is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R¹ is hydrogen.

[0066] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$.

[0067] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$. In certain such embodiments, each R^{P1} is independently selected from the group consisting of hydrogen and unsubstituted C_{1-4} alkyl. In certain preferred embodiments, each R^{P1} is H.

[0068] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 0; and R^1 is hydrogen.

[0069] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 0; and R^1 is $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$.

[0070] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 0; and R^1 is $-P(=O)(OR^{P1})_2$. In certain such embodiments, each R^{P1} is independently selected from the group consisting of hydrogen and unsubstituted C_{1-4} alkyl. In certain preferred embodiments, each R^{P1} is H.

[0071] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 1; R^3 is halo; and R^1 is hydrogen.

[0072] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 1; R^3 is halo; and R^1 is $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$.

[0073] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 1; R^3 is halo; and R^1 is $-P(=O)(OR^{P1})_2$. In certain such embodiments, each R^{P1} is independently selected from the group consisting of hydrogen and unsubstituted C_{1-4} alkyl. In certain preferred embodiments, each R^{P1} is H.

[0074] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; one of R^{2A} and R^{2B} is hydrogen and the other is fluoro; n is 0 or 1; and R^1 is hydrogen.

[0075] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; one of R^{2A} and R^{2B} is hydrogen and the other is fluoro; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$.

[0076] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; one of R^{2A} and R^{2B} is hydrogen and the other is fluoro; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$. In certain such embodiments, each R^{P1} is independently selected from the group consisting of hydrogen and unsubstituted C_{1-4} alkyl. In certain preferred embodiments, each R^{P1} is H.

[0077] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is hydrogen.

[0078] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$.

[0079] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$. In certain such embodiments, each R^{P1} is independently selected from the group consisting of hydrogen and unsubstituted C_{1-4} alkyl. In certain preferred embodiments, each R^{P1} is H.

[0080] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is hydrogen.

[0081] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$.

[0082] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$. In certain such embodiments, each R^{P1} is independently selected from the group consisting of hydrogen and unsubstituted C_{1-4} alkyl. In certain preferred embodiments, each R^{P1} is H.

[0083] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, methyl, methoxy, or difluoromethyl; R^{N1} is methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is hydrogen.

[0084] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, methyl, methoxy, or difluoromethyl; R^{N1} is methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$.

[0085] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, methyl, methoxy, or difluoromethyl; R^{N1} is methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$. In certain such embodiments, each R^{P1} is independently selected from the group consisting of hydrogen and unsubstituted C_{1-4} alkyl. In certain preferred embodiments, each R^{P1} is H.

[0086] In certain embodiments of Formula (I), G^2 and G^3 are each independently N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is hydrogen.

[0087] In certain embodiments of Formula (I), G^2 and G^3 are each independently N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$.

[0088] In certain embodiments of Formula (I), G^2 and G^3 are each independently N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$. In certain such embodiments, each R^{P1} is independently selected from the group consisting of hydrogen and unsubstituted C_{1-4} alkyl. In certain preferred embodiments, each R^{P1} is H.

[0089] In certain embodiments of Formula (I), G^2 and G^3 are each independently N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, methyl, methoxy; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is hydrogen.

[0090] In certain embodiments of Formula (I), G^2 and G^3 are each independently N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, methyl, methoxy; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$.

[0091] In certain embodiments of Formula (I), G^2 and G^3 are each independently N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, methyl, methoxy; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$. In certain such embodiments, each R^{P1} is independently selected from the group consisting of hydrogen and unsubstituted C_{1-4} alkyl. In certain preferred embodiments, each R^{P1} is H.

[0092] In certain embodiments of Formula (I), G^2 and G^3 are each independently N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is hydrogen.

[0093] In certain embodiments of Formula (I), G^2 and G^3 are each independently N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$.

[0094] In certain embodiments of Formula (I), G^2 and G^3 are each independently N or NR^{N2} ; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is $-P(=O)(OR^{P1})_2$. In certain such embodiments, each R^{P1} is independently selected from the group consisting of hydrogen and unsubstituted C_{1-4} alkyl. In certain preferred embodiments, each R^{P1} is H.

[0095] In certain embodiments of Formula (I), at least one of G^2 or G^3 is N or NR^{N2} ; G^1 is CR^{G1} ; R^{G1} is methyl or cyclopropyl; R^4 is hydrogen; R^5 is hydrogen, alkoxy, or haloalkyl; R^{N1} is hydrogen or methyl; R^{2A} and R^{2B} are each hydrogen; n is 0 or 1; and R^1 is hydrogen.

[0096] In certain embodiments, the compound is selected from the group consisting of:

(S)-N-(2-hydroxy-3-phenylpropyl)-N-methyl-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)nicotinamide;

(S)-5-((1-(difluoromethyl)-1H-pyrazol-4-yl)ethynyl)-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide;

(S)-N-(2-hydroxy-3-phenylpropyl)-N-methyl-5-((2-methyl-2H-1,2,3-triazol-4-yl)ethynyl)nicotinamide;

(S)-N-(2-hydroxy-3-phenylpropyl)-N-methyl-5-((1-(trifluoromethyl)-1H-pyrazol-4-yl)ethynyl)nicotinamide;

(S)-5-((1-cyclopropyl-1H-pyrazol-4-yl)ethynyl)-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide;

(S)-5-((1-cyclobutyl-1H-pyrazol-4-yl)ethynyl)-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide;

N-((2R,3S)-3-fluoro-2-hydroxy-3-phenylpropyl)-N-methyl-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)nicotinamide;

(S)-5-((6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-3-yl)ethynyl)-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide;

(R)-6-(difluoromethyl)-N-(2-hydroxy-3-phenylpropyl)-N-methyl-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)nicotinamide;

(*S*)-*N*-(2-hydroxy-3-phenylpropyl)-*N*-methyl-5-((2-(oxetan-3-yl)-2*H*-1,2,3-triazol-4-yl)ethynyl)nicotinamide;

(*S*)-5-((5-cyclopropyl-1-methyl-1*H*-pyrazol-4-yl)ethynyl)-*N*-(2-hydroxy-3-phenylpropyl)-*N*-methylnicotinamide;

(*S*)-*N*-(3-(3-fluorophenyl)-2-hydroxypropyl)-*N*-methyl-5-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)nicotinamide;

(*S*)-*N*-(2-hydroxy-3-phenylpropyl)-6-methoxy-*N*-methyl-5-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)nicotinamide;

(*S*)-*N*-(2-hydroxy-3-phenylpropyl)-*N*,6-dimethyl-5-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)nicotinamide;

(*S*)-*N*-(2-hydroxy-3-phenylpropyl)-*N*-methyl-5-((2-methylthiazol-5-yl)ethynyl)nicotinamide;

(*S*)-*N*-(2-hydroxy-3-phenylpropyl)-6-methyl-5-(thiazol-5-ylethynyl)nicotinamide;

(*S*)-*N*-(2-hydroxy-3-phenylpropyl)-*N*-methyl-5-((2-methyloxazol-5-yl)ethynyl)nicotinamide;

(*S*)-di-*tert*-butyl (1-(5-((1-(difluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)-*N*-methylnicotinamido)-3-phenylpropan-2-yl) phosphate;

(*S*)-1-(5-((1-(difluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)-*N*-methylnicotinamido)-3-phenylpropan-2-yl dihydrogen phosphate;

(*S*)-1-(5-((1-(difluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)-*N*-methylnicotinamido)-3-phenylpropan-2-yl acetate;

(*S*)-1-(5-((1-(difluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)-*N*-methylnicotinamido)-3-phenylpropan-2-yl glycinate;

(*S*)-di-*tert*-butyl (1-(*N*-methyl-5-((2-methyl-2*H*-1,2,3-triazol-4-yl)ethynyl)nicotinamido)-3-phenylpropan-2-yl) phosphate;

(*S*)-1-(*N*-methyl-5-((2-methyl-2*H*-1,2,3-triazol-4-yl)ethynyl)nicotinamido)-3-phenylpropan-2-yl dihydrogen phosphate;

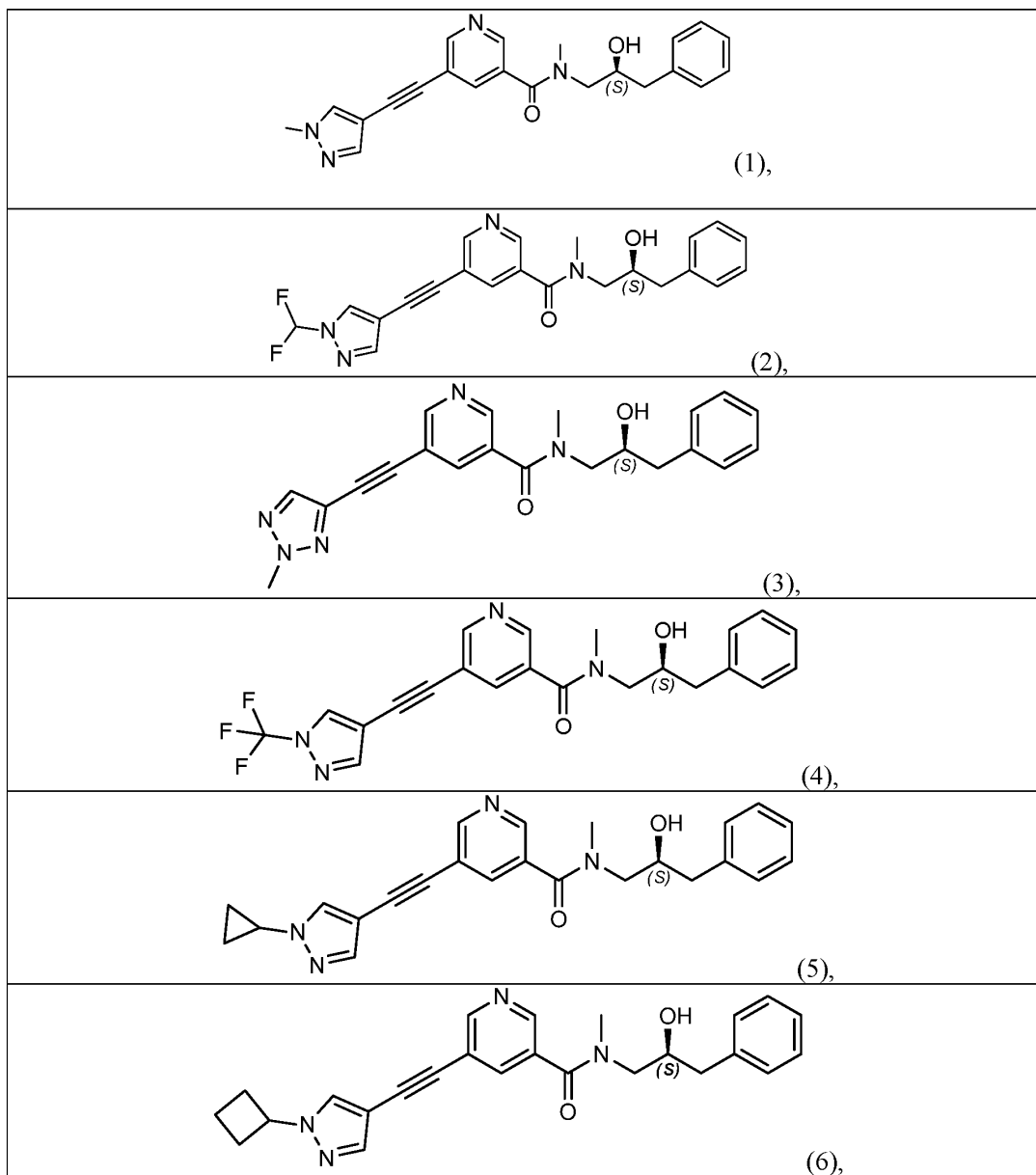
(*S*)-1-(*N*-methyl-5-((2-methyl-2*H*-1,2,3-triazol-4-yl)ethynyl)nicotinamido)-3-phenylpropan-2-yl acetate;

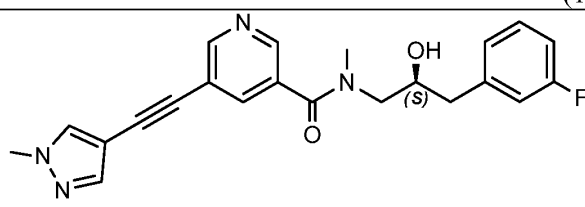
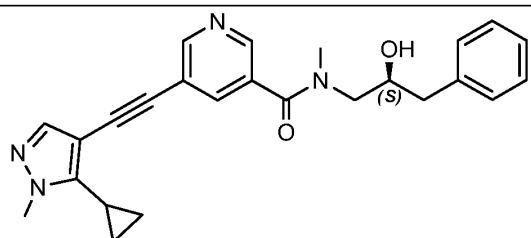
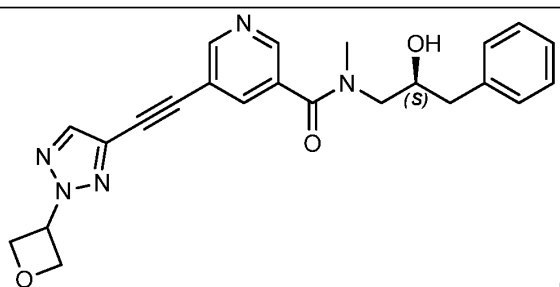
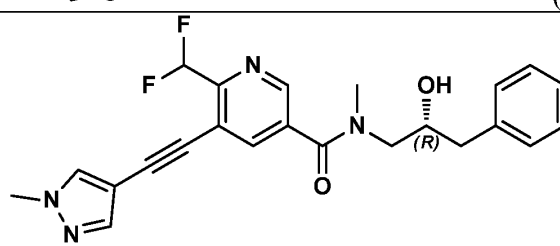
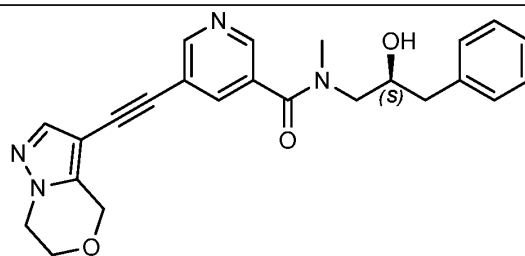
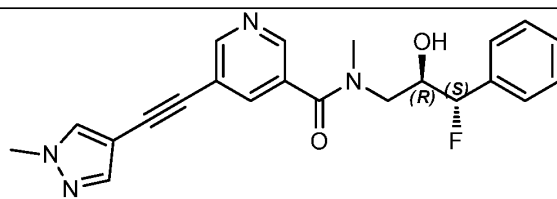
(*S*)-1-(*N*-methyl-5-((2-methyl-2*H*-1,2,3-triazol-4-yl)ethynyl)nicotinamido)-3-phenylpropan-2-yl glycinate; and

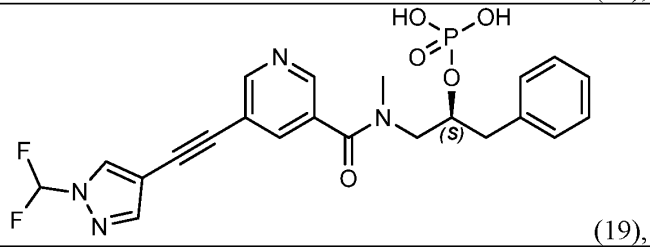
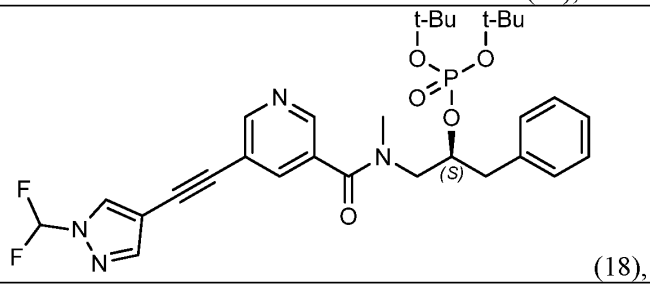
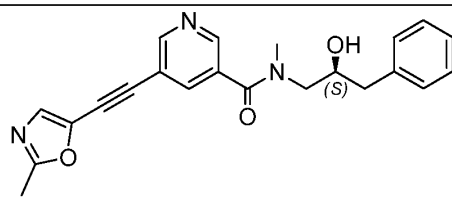
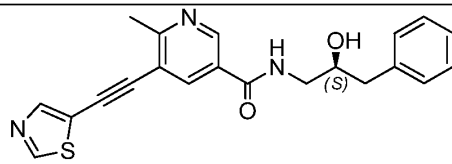
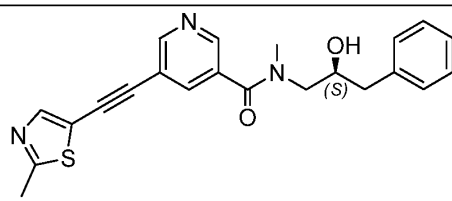
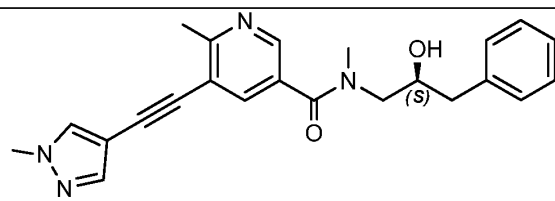
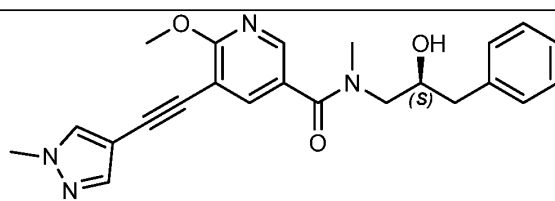
(*S*)-5-((1-(difluoromethyl)-5-methyl-1*H*-pyrazol-4-yl)ethynyl)-*N*-(2-hydroxy-3-phenylpropyl)-*N*-methylnicotinamide.

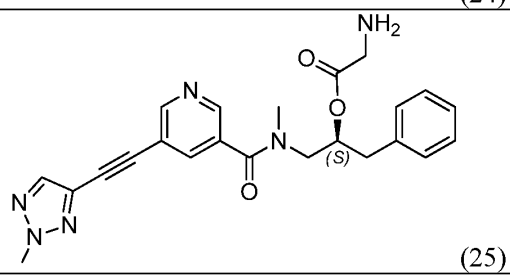
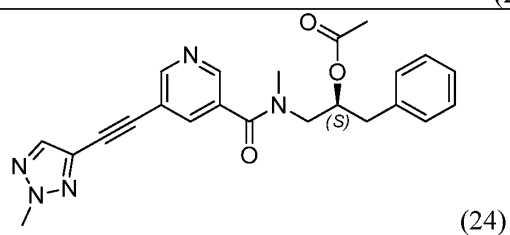
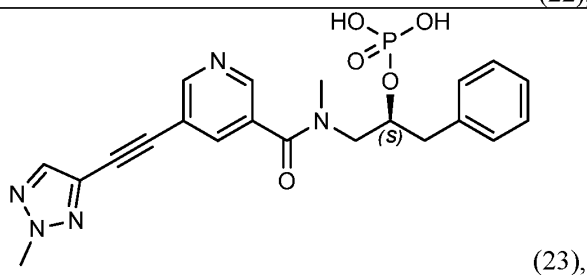
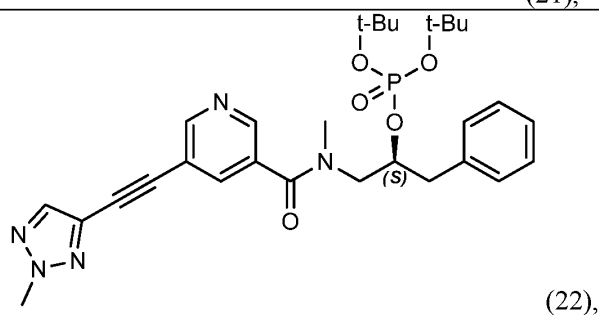
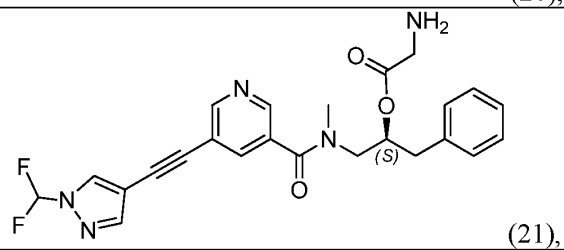
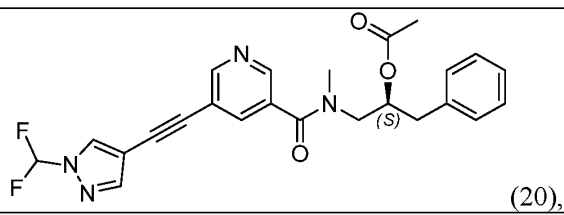
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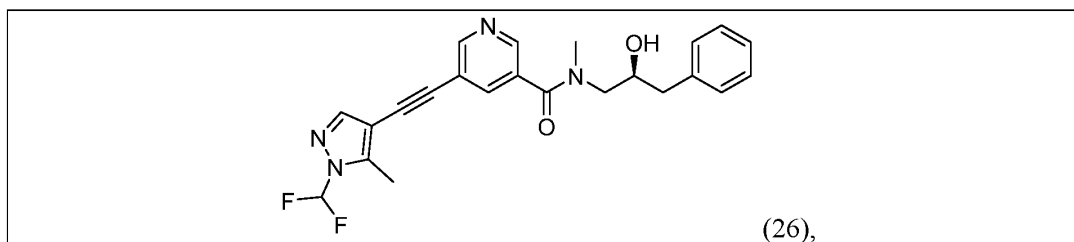
[0097] In certain embodiments, a compound of Formula (I) is selected from the group consisting of:











and pharmaceutically acceptable salts thereof.

(ii) Pharmaceutical Compositions and Methods of Use

[0098] In another aspect, the invention relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

[0099] Compounds of Formula (I), their pharmaceutically acceptable salts, and pharmaceutical compositions comprising same, may be useful in the treatment of subjects suffering from various diseases and conditions, *e.g.*, such as those associated with inhibition of RIPK1 activity. For example, in some embodiments, the compounds of the invention are useful for treating Ulcerative Colitis. Further provided are compounds of Formula (I), or pharmaceutically acceptable salts thereof, or compositions comprising same, for use in a medicament, *e.g.*, for use in treating Ulcerative Colitis.

(iii) Preparative Methods

[0100] Further provided herein are exemplary methods of preparing compounds of Formula (I), and salts thereof. See, *e.g.*, *Schemes 1–4* below, and the Examples.

[0101] In certain aspects, compounds of Formula (I), wherein R^1 is H, and salts thereof, may be made via a cross-coupling reaction between a heteroaryl group and a terminal alkyne (see, *e.g.*, *Schemes 1* and *2*).

[0102] Scheme 1 depicts a method of making a compound of Formula (I), wherein R^1 is H, or a salt thereof, by coupling a compound of formula (A), which comprises a terminal alkyne group, to a compound of Formula (B), which comprises a pyridinyl group substituted by a leaving group LG^1 under coupling conditions sufficient to generate a compound of Formula (I). In certain embodiments, the leaving group LG^1 is a halo (*e.g.*, chloro, bromo, iodo) or an activated hydroxyl group (*e.g.*, -OTf, -OTs, -OMs, or -OBs). In certain embodiments, the coupling conditions comprise a Pd(II) catalyst, optionally a ligand, and a base. For example, the Pd(II) catalyst may be bis(acetonitrile)dichloropalladium (II) ($Pd(MeCN)_2Cl_2$), Chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2),

the ligand may be 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos), and the base may be Cs_2CO_3 . In other embodiments, the coupling conditions comprise a Pd(0) catalyst, optionally a ligand, and a base. For example, the Pd(0) catalyst may be bis(tri-tert-butylphosphine)palladium(0) and the base may be potassium phosphate. In certain embodiments, the coupling conditions further comprise a copper salt, e.g., CuI.

[0103] Scheme 2 depicts a method of making a compound of Formula (I), wherein R^1 is H, or a salt thereof, by coupling a compound of formula (C), which comprises a leaving group LG^2 , to a compound of Formula (D), which comprises a pyridinyl group substituted by a terminal alkyne group under coupling conditions sufficient to generate a compound of Formula (I). In certain embodiments, the leaving group LG^2 is a halo (e.g., chloro, bromo, iodo) or an activated hydroxyl group (e.g., -OTf, -OTs, -OMs, or -OBs). In certain embodiments, the coupling conditions comprise a Pd(II) catalyst, optionally a ligand, and a base. For example, the Pd(II) catalyst may be bis(acetonitrile)dichloropalladium (II) ($\text{Pd}(\text{MeCN})_2\text{Cl}_2$), Chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2), the ligand may be 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos), and the base may be Cs_2CO_3 . In other embodiments, the coupling conditions comprise a Pd(0) catalyst, optionally a ligand, and a base. For example, the Pd(0) catalyst may be bis(tri-tert-butylphosphine)palladium(0) and the base may be potassium phosphate. In certain embodiments, the coupling conditions further comprise a copper salt, e.g., CuI.

[0104] In certain aspects, compounds of Formula (I), and salts thereof, may be made via an amide coupling reaction (see, e.g., Scheme 3).

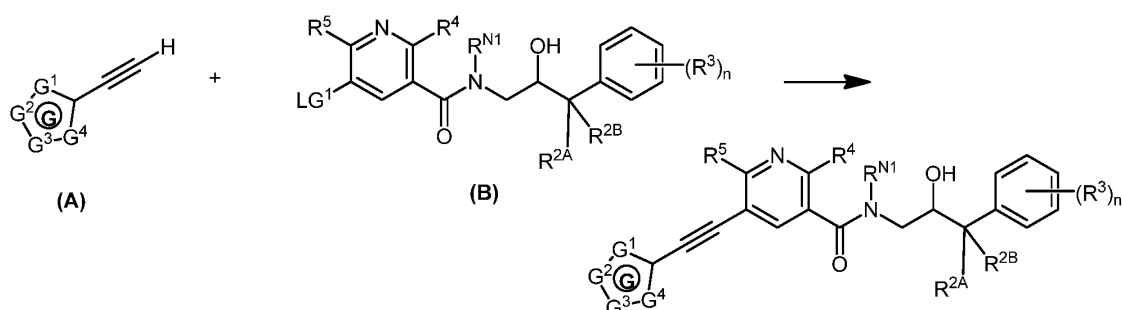
[0105] Scheme 3 depicts a method of making a compound of Formula (I), wherein R^1 is H, or a salt thereof, by coupling a compound of formula (E), which comprises a leaving group LG^3 bound to a carbonyl group, to a compound of Formula (F), which comprises an amino group - NHR^{N1} under coupling conditions sufficient to generate a compound of Formula (I). In certain embodiments, the leaving group LG^3 is a halo (e.g., chloro, bromo, iodo), a hydroxyl group, or an activated hydroxyl group (e.g., -OTf, -OTs, -OMs, or -OBs). In certain embodiments, the coupling conditions comprise an amide-coupling reagent and a base. In certain embodiments, the amide coupling reagent is 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), N,N'-carbonyldiimidazole (CDI), 2-(1H-

Benzotriazole-1-yl)-1,1,3,3-tetramethylammonium tetrafluoroborate (TBTU). In certain embodiments, the base is *N,N*-Diisopropylethylamine (DIEA) or trimethylamine (TEA).

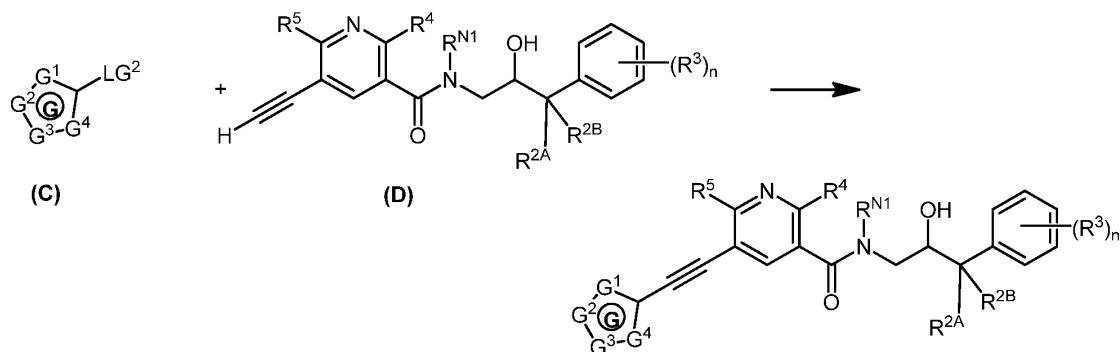
[0106] In certain embodiments, compounds of Formula (I) wherein R^1 is not H may be made by a reaction in which the $-OR^1$ hydroxyl group is substituted, e.g., by a phosphate group.

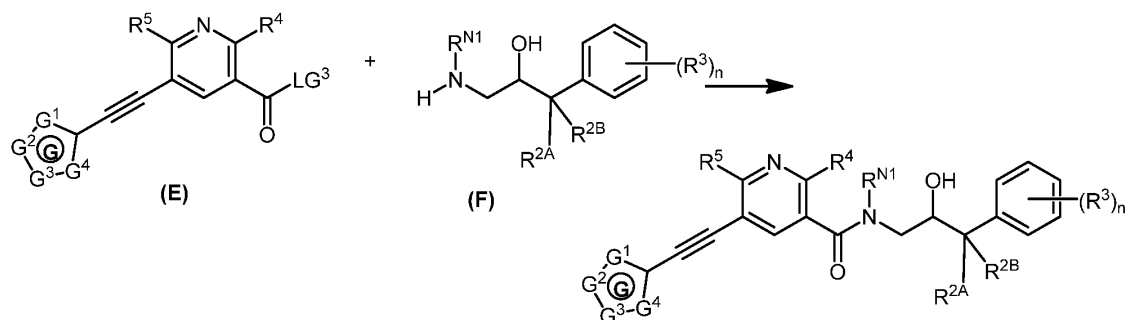
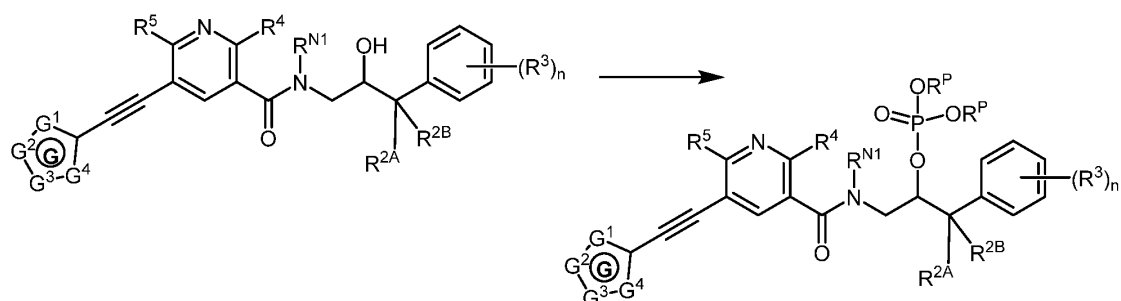
[0107] Scheme 4 depicts a method of making a compound of Formula (I) wherein R^1 is $-P(=O)(OR^P)_2$, or a salt thereof, by reacting the hydroxyl group with a phosphorus-containing agent under conditions sufficient to yield the compound wherein R^1 is $-P(=O)(OR^P)_2$. In some embodiments, the phosphorus-containing agent is a phosphoramidite (e.g., di-*tert*-butyl diethylphosphoramidite).

Scheme 1



Scheme 2



Scheme 3*Scheme 4***EXEMPLIFICATION**

[0108] In order that this disclosure may be more fully understood, the following Examples are set forth. It should be understood that these Examples are for illustrative purposes only and are not to be construed as limiting this disclosure in any manner.

[0109] Common abbreviations well known to those skilled in the art which are used throughout include those in Table A.

Table A. Abbreviations

Abbreviation	Definition
NMR	nuclear magnetic resonance
s	singlet
br s	broad singlet
d	doublet
br d	broad doublet

Abbreviation	Definition
t	triplet
br t	broad triplet
q	quartet
m	multiplet
br m	broad multiplet
dd	doublet of doublet
br dd	broad doublet of doublet
ddd	doublet of doublet of doublet
dt	doublet of triplet
dtd	doublet of triplet of doublet
tt	triplet of triplet
min	minute
h	hour
mL	milliliter
μ L	microliter
L	liter
g	gram
mg	milligram
mmol	millimoles
M	molarity (moles/liter)
μ M	micromolar
nM	nanomolar
ppm	parts per million
HPLC	high pressure liquid chromatography
UPLC® or UHPLC	ultra high performance liquid chromatography
LC/MS or LCMS	liquid chromatography- mass spectrometry
MS	mass spectrometry
ATP	adenosine triphosphate
BSA	bovine serum albumin
EDTA	ethylenediaminetetraacetic acid
DTT	dithiothreitol

Abbreviation	Definition
FRET	fluorescence energy transfer
HEPES	(4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid)
IC ₅₀	half maximal inhibitory concentration
Boc	<i>tert</i> -butoxycarboxyl
MOM	methoxymethyl
PMBM	<i>para</i> -methoxybenzylmethyl
THP	tetrahydropyranyl
XPhos	2-dicyclohexylphosphino-2,4,6-triisopropylbiphenyl
XPhos Pd G2	chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)
R _t	Retention time

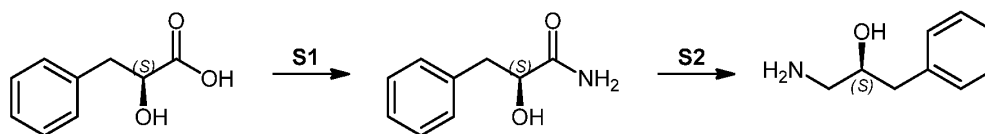
Analytical Methods

[0110] Unless otherwise stated, all ¹H NMR data were collected on a Varian 400 MHz Mercury Plus, Inova, or 400-MR instrument and chemical shifts are quoted in parts per million (ppm). HPLC (High pressure Liquid Chromatography), UPLC (ultra performance liquid chromatography, and LC/mass spectrometry (LC/MS) conditions are referenced using the Method letter as provided in Table B.

Table B.	
Method	Conditions
aa	LC/MS: The gradient was 5–60% mobile phase B in 1.6 minute then 60–95% mobile phase B to 2.2 minutes with a hold at 95% mobile phase B for 0.1 minute (1.0 mL/minute flow rate). Mobile phase A was 10mM ammonium acetate (NH ₄ OAc), mobile phase B was HPLC grade acetonitrile (MeCN). The column used for the chromatography is a 2.1x30 mm Waters Cortecs C18 column (1.6 μm particles). Detection methods are diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive/negative electrospray ionization in Mass Spectrometry.
bb	LC/MS: The gradient was 5–95% mobile phase B over 15 minutes (1.0 mL/minute flow rate). Mobile phase A was 0.1% formic acid in water, mobile phase B was HPLC grade acetonitrile (MeCN). The column used for the chromatography was 2.1 x 30

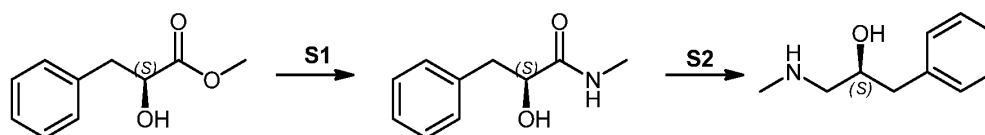
Table B.	
Method	Conditions
	mm Waters X–Select UPLC C18 (1.7 μ m particles). Detection methods were diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive/negative electrospray ionization.
cc	LC/MS: The gradient was 5–95% mobile phase B over 4 minute (1.0 mL/minute flow rate). Mobile phase A was 0.1% formic acid in water, mobile phase B was HPLC grade acetonitrile (MeCN). The column used for the chromatography was 4.6 x 30 mm Waters X–Select UPLC C18 (2.5 μ m particles). Detection methods were diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive/negative electrospray ionization.
dd	LC/MS: The gradient was 5–95% mobile phase B for 3 minutes (2.5 mL/minute flow rate). Mobile phase A was 0.1% ammonium in water, mobile phase B was HPLC grade acetonitrile (MeCN). The column used for the chromatography is a 4.6 x 30 mm Waters X–Bridge BEH C18 (2.5 μ m particles). Detection method is UV (254 nm) as well as positive/negative electrospray ionization.
ee	LC/MS: The gradient was 5–95% mobile phase B for 3 minutes (2.5 mL/minute flow rate). Mobile phase A was 0.1% formic acid, mobile phase B was HPLC grade acetonitrile (MeCN) with 0.1% formic acid. The column used for the chromatography is a 4.6 x 30 mm X–Select CSH C18 XP (2.5 μ m particles). Detection method is UV (254 nm) as well as positive/negative electrospray ionization.
ff	LC/MS (The gradient was 5% mobile phase B in 0.40 minutes and 5–95% mobile phase B at 0.40–3.00 minutes, hold on 95% mobile phase B for 1.00 minutes, and then 95–5% mobile phase B in 0.01 minute, the flow rate was 1.0 mL/minute. Mobile phase A was 0.037% Trifluoroacetic Acid in water, mobile phase B was 0.018% trifluoroacetic acid in acetonitrile. The column used for chromatography was a Kinetex C18 50*2.1mm column (5 μ m particles). Detection methods are diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive electrospray ionization. MS range was 100–1000.
a	UPLC: The gradient was 5–95% mobile phase B over 3 minutes (0.77 mL/minute flow rate). Mobile phase A was 0.1% ammonium in water, mobile phase B was HPLC grade acetonitrile (MeCN). The column used for chromatography is a 2.1 x 30 mm

Table B.	
Method	Conditions
	Waters Acquity BEH C18. Detection methods are diode array (DAD) and evaporative light scattering (ELSD) as well as positive/negative electrospray ionization.
b	UPLC: The gradient was 5–95% mobile phase B over 3 minutes (0.77 mL/minute flow rate). Mobile phase A was 0.1% formic acid in water, mobile phase B was HPLC grade acetonitrile (MeCN) with 0.1% formic acid. The column used for chromatography is a 2.1 x 30 mm Waters Acquity CSH C18. Detection methods are diode array (DAD) and evaporative light scattering (ELSD) as well as positive/negative electrospray ionization.
c	HPLC: The gradient was 5% mobile phase B in 0.40 minutes and 5-95% mobile phase B at 0.40-3.00 minutes, hold on 95% mobile phase B for 1 minute, and then 95-5% mobile phase B in 0.01 minutes ; the flow rate was 1.0 mL/minute. Mobile phase A was 0.037% trifluoroacetic acid in water, mobile phase B was 0.018% trifluoroacetic acid in acetonitrile. The column used for chromatography was a Kinetex C18 50*2.1mm column (5um particles). Detection methods are diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive electrospray ionization. MS range was 100-1000.
d	Reverse phase HPLC: The column used for chromatography was a Luna-C18 2.0*30mm, (3 um particles). Detection methods are diode array (DAD). MS mode was positive electrospray ionization. MS range was 100-1000. Mobile phase A was 0.037% trifluoroacetic acid (TFA) in water, and mobile phase B was 0.018% TFA in HPLC grade acetonitrile. The gradient was 5-95% mobile phase B in 2 minutes 0.5% mobile phase B in 0.01 minutes, 5-95% mobile phase B (0.01-1.00 minutes), 95-100% mobile phase B (1.00 -1.80 minutes), 5% mobile phase B in 1.81 minutes with a hold at 5% mobile phase B for 0.19 minutes. The flow rate was 1.0 mL/minutes (0.00-1.80 minutes) and 1.2 mL/minutes (1.81 -2.00 minutes).

Synthetic Intermediates**Preparation #1: (S)-1-Amino-3-phenylpropan-2-ol**

[0111] Step 1: (S)-2-Hydroxy-3-phenylpropanamide. Thionyl chloride (397 g, 3340 mmol) was added drop-wise to methanol (1.50 L) cooled to about -20°C . (S)-2-hydroxy-3-phenylpropanoic acid (150 g, 903 mmol) was added, and the mixture was stirred at room temperature for about 2 hours. The mixture was concentrated *in vacuo* and the resulting crude acid chloride was added to a 7 N solution of ammonia in methanol (1.50 L, 903 mmol). The mixture was stirred at room temperature for about 12 hours, after which the mixture was concentrated *in vacuo* to provide the title product (140 g, 93 % yield); ^1H NMR (400 MHz, chloroform-*d*) δ 2.44 (br d, $J=3.55$ Hz, 1H), 2.85 (dd, $J=13.94$, 8.68 Hz, 1H), 3.18 (dd, $J=13.94$, 4.16 Hz, 1H), 4.20–4.32 (m, 1H), 5.46 (br s, 1H), 6.31 (br s, 1H), 7.15–7.34 (m, 5H).

[0112] Step 2: (S)-1-Amino-3-phenylpropan-2-ol. To a solution of (S)-2-hydroxy-3-phenylpropanamide (140g, 848 mmol) in tetrahydrofuran (THF) (1.40 L) was added borane-dimethyl sulfide complex (424 mL, 4470 mmol) dropwise at room temperature. Once the addition was complete, the mixture was stirred at about 70°C for about 12 hours. The mixture was then cooled to room temperature, carefully quenched with methanol (20 mL), and concentrated *in vacuo* to provide the title compound (105 g, 81 % yield); ^1H NMR (400 MHz, chloroform-*d*) δ 2.61 (dd, $J=12.72$, 8.07 Hz, 1H), 2.75–2.79 (m, 2H), 2.87 (dd, $J=12.72$, 3.42 Hz, 1H), 3.73–3.82 (m, 1H), 7.18–7.40 (m, 5H).

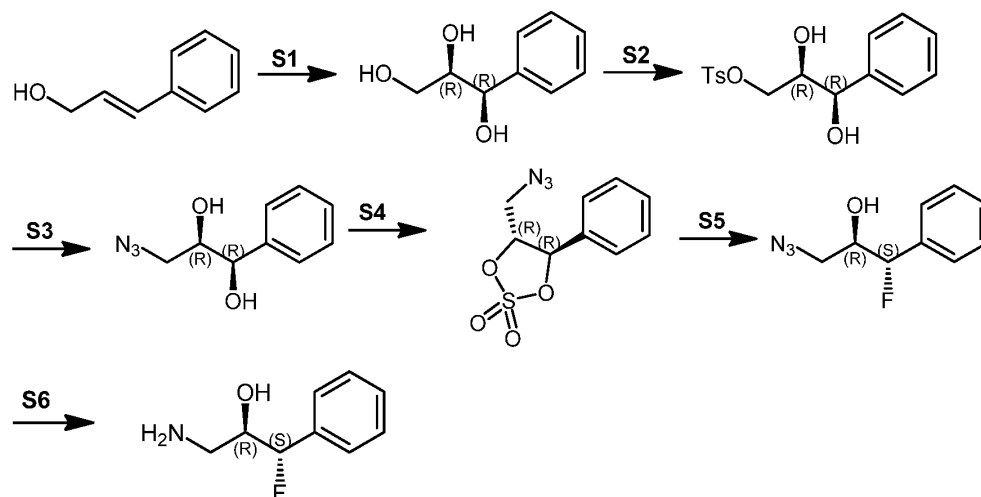
Preparation #2: (S)-1-(Methylamino)-3-phenylpropan-2-ol

[0113] Step 1: (S)-2-Hydroxy-3-phenylpropanamide. To a solution of (S)-methyl 2-hydroxy-3-phenylpropanoate (110 g, 549 mmol) in methanol (1.00 L) at room temperature was added methylamine (1373 mL, 2747 mmol) dropwise. Once the addition was complete, the mixture was stirred at room temperature for about 8 hours. The mixture was concentrated under reduced pressure to give a crude oil which was then triturated with a mixture of petroleum ether/ethyl acetate (10:1; 800 mL) for about 4 hours. The resulting product was recovered by

vacuum filtration and dried under vacuum to provide the title compound (80 g, 73%); ^1H NMR (400 MHz, chloroform- d) δ 2.81 (d, $J=5.01$ Hz, 3H), 2.83–2.91 (m, 1H), 3.24 (dd, $J=13.69$, 3.91 Hz, 1H), 4.29 (dd, $J=8.56$, 3.91 Hz, 1H), 6.58 (br s, 1H), 7.23–7.30 (m, 3H), 7.31–7.37 (m, 2H).

[0114] **Step 2: (*S*)-1-(Methylamino)-3-phenylpropan-2-ol.** To a solution of (*S*)-2-hydroxy-*N*-methyl-3-phenylpropanamide (70 g, 391 mmol) in tetrahydrofuran (THF) (700 mL) was added borane-dimethyl sulfide complex (117 mL, 1172 mmol) dropwise at about 5 °C. Once the addition was complete, the mixture was stirred at room temperature for about 1 hour, and then it was heated to about 70 °C and stirred for about 12 hours. The mixture was then cooled to about 10 °C, and methanol (500 mL) was added dropwise while maintaining an internal temperature between about 10 to 30 °C. Then a solution of HCl in methanol (4M, 2 L) was added dropwise and the resulting mixture was stirred at room temperature for about 12 hours. The mixture was concentrated, and the residue was partitioned between water (400 mL) and dichloromethane (DCM) (400 mL). The aqueous phase was washed with dichloromethane (DCM) (400 mL) and then neutralized to about pH = 12 by slow addition of 6 N Aq (aqueous) NaOH. The aqueous solution was extracted with 2-methyl tetrahydrofuran (2-MeTHF) (3 $\times$ 400 mL). The combined organic phases were dried over Na_2SO_4 , filtered and concentrated to give a residue, which was triturated with petroleum ether (120 mL) for 4 hours. The product was collected by filtration and concentrated to provide the title compound (54.9 g, 85%); ^1H NMR (400 MHz, methanol- d_4) δ 2.35 (s, 3H), 2.47–2.60 (m, 2H), 2.71–2.76 (m, 2H), 3.90 (dtd, $J=8.54$, 6.64, 3.53 Hz, 1H), 7.10–7.32 (m, 5H).

Preparation #3: (1*S*,2*R*)-3-amino-1-fluoro-1-phenylpropan-2-ol



[0115] Step 1: (1*R*,2*R*)-1-phenylpropane-1,2,3-triol. To a mixture of cinnamyl alcohol (5.58 mL, 43.2 mmol), water (94 mL), *tert*-butanol (94 mL) cooled to about 0 °C was added Sharpless Asymmetric Dihydroxylation AD-MIX-BETA (62.5 g, 43.2 mmol) and methanesulfonamide (6.17 g, 64.8 mmol) and the mixture was stirred for about 16 hours. Added 10% aq. sodium thiosulfate (150 mL) and ethyl acetate (EtOAc) (125 mL) and stirred for about 30 min. The aqueous phase was extracted with EtOAc (2 x 125 mL). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel eluting with 0–100% EtOAc/heptane to provide the title compound (4.5 g, 26.8 mmol, 61.9 % yield); ¹H NMR (400 MHz, chloroform-*d*) δ ppm 3.21 – 3.30 (m, 1 H) 3.37 – 3.55 (m, 2 H) 3.69 – 3.77 (m, 1 H) 3.79 – 4.05 (m, 2 H) 4.61 (dd, *J*=6.79, 3.36 Hz, 1 H) 7.27 (br s, 5 H).

[0116] Step 2: (2*R*,3*R*)-2,3-dihydroxy-3-phenylpropyl 4-methylbenzenesulfonate. To a mixture of (1*R*,2*R*)-1-phenylpropane-1,2,3-triol (4.5 g, 26.8 mmol), in toluene (80 mL) was added dibutyltin oxide (0.133 g, 0.535 mmol). The mixture was heated to reflux for 20 minutes and the mixture was cooled to room temperature. Upon cooling, the mixture was concentrated under reduced pressure. Dry dichloromethane (DCM) (53.5 mL), *p*-toluenesulfonyl chloride (5.10 g, 26.8 mmol) and triethylamine (TEA) (3.73 mL, 26.8 mmol) were added and reaction was stirred at room temperature under N₂ for about 16 hours. The mixture was quenched by adding water and the solution was extracted with DCM (3 x 75 mL). The combined organic phase was washed with water, dried (Na₂SO₄) and concentrated. The crude material was purified by flash column chromatography on silica gel eluting with 0–50% ethyl acetate (EtOAc)/heptane to provide the title compound (5.5 g, 17.06 mmol, 63.8 % yield). ¹H NMR (400 MHz, chloroform-*d*) δ 3.81–3.98 (m, 2H), 4.00–4.10 (m, 1H), 4.03–4.09 (m, 1H), 4.10–4.17 (m, 1H), 4.67 (br d, *J*=5.07 Hz, 1H), 7.16–7.35 (m, 8H), 7.76 (d, *J*=7.94 Hz, 2H)

[0117] Step 3: (1*R*,2*R*)-3-azido-1-phenylpropane-1,2-diol. A mixture of (2*R*,3*R*)-2,3-dihydroxy-3-phenylpropyl 4-methylbenzenesulfonate (5.5 g, 17.06 mmol) and sodium azide (2.218 g, 34.1 mmol) in *N,N*-dimethylformamide (DMF) (85 mL) was heated at about 80 °C for about 3 hours. The reaction mixture was cooled and then partitioned between EtOAc (250 mL) and water (200 mL). After separating the layers, the aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material purified by flash column chromatography on silica gel eluted with 0%–100% EtOAc/heptane to provide the title compound (2.98 g, 90%); ¹H NMR (400 MHz, dimethylsulfoxide-*d*₆) δ 7.37 – 7.21 (m, 5H), 5.37

(dd, $J = 4.7, 0.9$ Hz, 1H), 5.23 (d, $J = 5.6$ Hz, 1H), 4.50 (t, $J = 5.0$ Hz, 1H), 3.77 – 3.67 (m, 1H), 3.12 (dd, $J = 12.7, 3.3$ Hz, 1H), 2.98 (dd, $J = 12.7, 7.8$ Hz, 1H).

[0118] Step 4: (4*S*,5*S*)-4-(azidomethyl)-5-phenyl-1,3,2-dioxathiolane 2,2-dioxide.

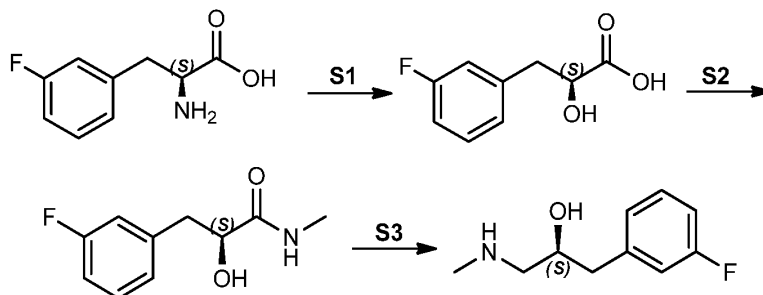
Thionyl chloride (2.252 mL, 30.8 mmol) was added to a solution of (1*R*,2*R*)-3-azido-1-phenylpropane-1,2-diol (2.98 g, 15.42 mmol) and pyridine (3.74 mL, 46.3 mmol) in dichloromethane (DCM) (154 mL) at about 0 °C, and the mixture was stirred at about 0 °C for 1 hour. Saturated aqueous CuSO₄ (75 mL) was added, and the mixture was extracted with DCM (3 × 75 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated. The resulting material was dissolved in acetonitrile (MeCN) (100 mL) and DCM (100 mL) and the solution was cooled to 0 °C. Sodium periodate (6.53 g, 30.5 mmol), ruthenium(III) chloride hydrate (0.069 g, 0.305 mmol) and water (150 mL) were added, and the mixture was stirred at 0 °C for 2 hours. Diethyl ether (120 mL) was added, and the mixture was washed with water (50 mL), saturated aqueous NaHCO₃ (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried (MgSO₄) and concentrated to provide the title compound (3.5 g, 90%); ¹H NMR (400 MHz, chloroform-*d*) δ 7.52 – 7.42 (m, 5H), 5.76 (d, $J = 8.9$ Hz, 1H), 4.91 (ddd, $J = 8.7, 4.4, 3.4$ Hz, 1H), 3.79 (dd, $J = 14.3, 3.3$ Hz, 1H), 3.54 (dd, $J = 14.3, 4.4$ Hz, 1H).

[0119] Step 5: (1*S*,2*R*)-3-azido-1-fluoro-1-phenylpropan-2-ol. A mixture of tetra-*N*-butylammonium fluoride (TBAF) (78 mL, 78 mmol) and acetonitrile (MeCN), (100 mL) that had been dried over 4Å molecular sieves was added to a solution of (4*S*,5*S*)-4-(azidomethyl)-5-phenyl-1,3,2-dioxathiolane 2,2-dioxide (10 g, 39.2 mmol) in MeCN (100 mL) at about 0 °C. The resulting mixture was stirred at 0 °C for 1 hour. The reaction mixture was concentrated, and the resulting crude product was dissolved in tetrahydrofuran (THF) (100 mL). H₂O (0.776 mL, 43.1 mmol) and H₂SO₄ (2.297 mL, 43.1 mmol) at 0 °C. The resulting mixture was stirred at room temperature for about 12 hours. The resulting mixture was extracted with ethyl acetate (EtOAc) (150 mL×2). The organic phase was washed with brine (75 mL), dried over Na₂SO₄ and concentrated. The crude material was purified by flash column chromatography on silica gel eluted with 0–100% EtOAc/petroleum ether to provide the title compound (50 g, 35%). ¹H NMR (400 MHz, chloroform-*d*) δ ppm: 2.00 (d, $J = 5.14$ Hz, 1 H) 3.53 (dd, $J = 5.01, 1.22$ Hz, 2 H) 4.02 – 4.11 (m, 1 H) 5.27 – 5.52 (m, 1 H) 7.37 – 7.46 (m, 5 H).

[0120] Step 6: (1*S*,2*R*)-3-amino-1-fluoro-1-phenylpropan-2-ol. A 100 mL round-bottomed flask equipped with 3-way gas-tight stopcock was charged with (1*S*,2*R*)-3-azido-1-fluoro-1-phenylpropan-2-ol (0.684 g, 3.50 mmol) and Lindlar Catalyst (palladium, 5 wt % on calcium carbonate, poisoned with lead) (0.373 g, 0.175 mmol) in methanol (20 mL)). The

resulting suspension was stirred under an atmosphere of hydrogen (balloon) at room temperature overnight. The suspension was filtered through a pad of Celite with methanol rinses and the filtrate was concentrated under reduced pressure to provide the title compound (0.55 g, 3.25 mmol, 93 % yield). ^1H NMR (400 MHz, chloroform-*d*) δ 7.46 – 7.26 (m, 5H), 5.40 (dd, J = 46.8, 5.6 Hz, 1H), 3.88 – 3.76 (m, 1H), 2.99 – 2.81 (m, 2H), 1.78 (br s, 3H).

Preparation #4: (S)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol



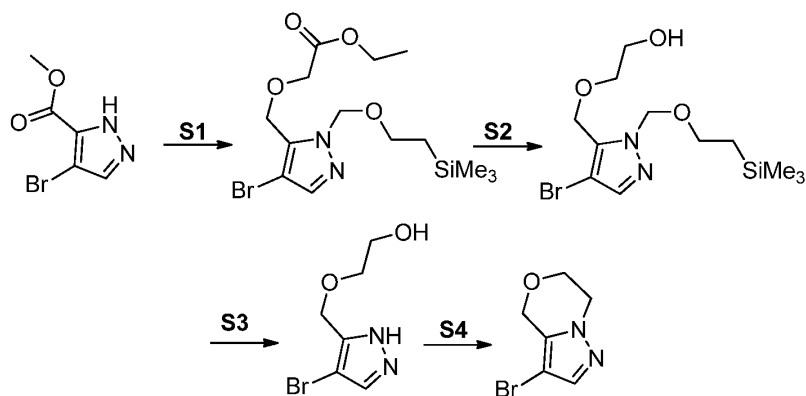
[0121] Step 1: (S)-3-(3-fluorophenyl)-2-hydroxypropanoic acid. A solution of NaNO_2 (2.26 g, 32.8 mmol) in H_2O (21.6 mL) was added dropwise to a stirred solution of (S)-2-amino-3-(3-fluorophenyl)propanoic acid (2.0 g, 10.92 mmol) in H_2O (50 mL) and acetic acid (AcOH) (15 mL) at about 0 °C. The mixture was warmed to room temperature and stirred for about 20 hours. Methylamine (2 M in tetrahydrofuran (THF), 22 mL, 43.7 mmol) was added dropwise and the mixture was stirred at room temperature for about 1 hour. The mixture was then concentrated *in vacuo* to remove the THF and the resulting aq mixture was extracted into ethyl acetate (EtOAc) (3 x 30 mL). The combined organic layers were washed with saturated aq NaCl (30 mL), dried over MgSO_4 and concentrated *in vacuo* to provide the title compound (20.11 g, 100 % yield); ^1H NMR (500 MHz, chloroform-*d*) δ 7.32 – 7.26 (m, 1H), 7.09 – 6.95 (m, 3H), 4.53 (dd, J = 7.1, 4.2 Hz, 1H), 3.21 (dd, J = 14.1, 4.2 Hz, 1H), 3.01 (dd, J = 14.1, 7.0 Hz, 1H).

[0122] Step 2: (S)-3-(3-fluorophenyl)-2-hydroxy-N-methylpropanamide. Thionyl chloride (2.87 mL, 39.3 mmol) was added dropwise to methanol (10 mL) at about -20 °C and a solution of (S)-3-(3-fluorophenyl)-2-hydroxypropanoic acid (2.01 g, 10.91 mmol) in methanol (5.00 mL) was added. The mixture was stirred at room temperature for about 2 hours. The mixture was concentrated *in vacuo* and the residue was taken up in methylamine (33% in ethanol, 14 mL, 109 mmol) and stirred at room temperature for about 2 hours. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (0–10% methanol

/DCM) to provide the title compound (1.67 g, 70 % yield); LC/MS (Table B, Method ee) R_t = 1.15 min; MS m/z 198 ($M+H$)⁺.

[0123] Step 3: (S)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol. A solution of (S)-3-(3-fluorophenyl)-2-hydroxy-N-methylpropanamide (1.67 g, 8.47 mmol) in tetrahydrofuran (THF) (45 mL) was heated to about 65 °C and borane dimethyl sulfide complex ($BH_3 \cdot SMe_2$) (2.4 mL, 25.4 mmol) was added. The resulting mixture was stirred for about 3 hours. The reaction mixture was cooled to room temperature and quenched via the dropwise addition of methanol (15 mL) and the solvents were removed *in vacuo*. The residue was loaded onto a column of Strong Cation Exchange (SCX) and washed with methanol (100 mL). The product was eluted with 0.7 M NH_3 in methanol (100 mL) and the solvent was removed *in vacuo* to provide the title compound (999 mg, 61%); LC/MS (Table B, Method ee) R_t = 0.32 min; MS m/z 184 ($M+H$)⁺.

Preparation #5: 3-bromo-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazine



[0124] Step 1: ethyl 2-((4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)methoxy)acetate. Methyl 4-bromo-1H-pyrazole-5-carboxylate (10.0 g, 48.8 mmol) was added in portions to a suspension of sodium hydride (60% in mineral oil) (2.05 g, 51.2 mmol) in *N,N*-dimethylformamide (DMF) (200 mL) stirring at about 0 °C. The resulting suspension was stirred at about 0 °C for about 15 minutes, at which point 2-(trimethylsilyl)ethoxymethyl chloride (10.4 mL, 58.5 mmol) was added dropwise (Me = methyl). The resulting solution was stirred at about 0 °C for about 1 hour. The reaction was quenched with ice water (250 mL) and extracted with ethyl acetate (EtOAc) (3 x 100 mL). The combined organic phases were washed with brine (250 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting product mixture was dissolved in tetrahydrofuran (THF) (50.0 mL) and added dropwise to a stirred mixture of lithium aluminum hydride (LAH) (1.37 g, 36.1 mmol) in THF (150 mL) cooled

at about 0 °C. The resulting suspension was stirred at about 0 °C for about 2 h. The reaction mixture was quenched at 0 °C by careful addition of water (1.5 mL), followed by 5 N aq. NaOH (1.5 mL) and more water (3 mL). The mixture was diluted with diethyl ether (100 mL), MgSO₄ (about 25 g) was added and the suspension was stirred for about 30 minutes. The reaction mixture was filtered through a pad of Celite, rinsed with EtOAc. The filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel eluted with 0–50% EtOAc/heptane to give a mixture of products (10.7 g). The mixture was dissolved in THF (174 mL), ethyl bromoacetate (6.11 g, 36.6 mmol) was added and the solution was cooled to about 0 °C. Sodium hydride (60% in mineral oil) (1.46 g, 36.6 mmol) was added and the resulting suspension was stirred at about 0 °C for about 3 hours. Stirring was continued for about 16 hours at room temperature, after which the reaction was cooled to about 0 °C and quenched with water (about 50 mL). The mixture was extracted with EtOAc (3 x 75 mL) and the combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel eluted with 0–50% EtOAc/heptane to provide the title compound (7.76 g, 56.7 % yield); ¹H NMR (400 MHz, chloroform-*d*) δ 7.48 (s, 1 H), 5.51 – 5.66 (m, 2 H), 4.76 (s, 2 H), 4.23 (q, *J*=7.21 Hz, 2 H), 4.03 – 4.12 (m, 2 H), 3.51 – 3.64 (m, 2 H), 1.30 (t, *J*=7.09 Hz, 3 H), 0.82 – 0.96 (m, 2 H), 0.02 (s, 9 H).

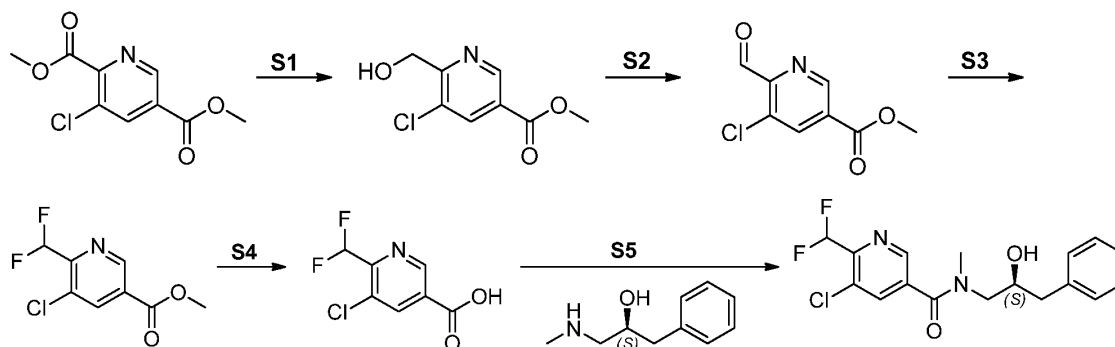
[0125] Step 2: 2-((4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)methoxy)ethanol. To a suspension of lithium aluminum hydride (LAH) (0.562 g, 14.8 mmol) in tetrahydrofuran (THF) (80 mL) cooled in ice bath was added a solution of ethyl 2-((4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)methoxy)acetate (7.76 g, 19.73 mmol) in THF (20 mL) and the resulting solution was stirred for about 20 minutes. Water (about 0.5 mL) was added, followed by 5 N aq. NaOH (0.5 mL), additional water (about 1 mL) and diethyl ether (50 mL). The mixture was stirred for about 10 minutes; MgSO₄ (about 20 g) was added and the suspension stirred for 30 minutes. The suspension was filtered through a pad of Celite which was washed with ethyl acetate (EtOAc). The combined filtrate was concentrated under reduced pressure to provide the title compound (6.83 g, 99 % yield); ¹H NMR (400 MHz, chloroform-*d*) δ 7.59 (s, 1 H), 5.37 (s, 2 H), 4.60 (s, 2 H), 3.71 – 3.77 (m, 2 H), 3.63 – 3.67 (m, 2 H), 3.52 – 3.60 (m, 2 H), 2.37 (br t, *J*=6.11 Hz, 1 H), 0.85 – 0.97 (m, 2 H), 0.03 – 0.01 (m, 9 H).

[0126] Step 3: 2-((4-bromo-1H-pyrazol-3-yl)methoxy)ethanol. A solution of 2-((4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)methoxy)ethanol (6.83 g, 19.4

mmol) in ethanol (100 mL) was treated with concentrated aq HCl (39 mL, 78 mmol) and the solution was heated at about 60 °C. After about 20 hours, the reaction was cooled to room temperature and was then concentrated under reduced pressure. Saturated aq NaHCO₃ solution (75 mL) was added and the mixture was stirred for about 20 minutes. The mixture was extracted with ethyl acetate (EtOAc) (3 x 50 mL) and the combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to provide the title compound (3.87 g, 90 % yield). ¹H NMR (400 MHz, chloroform-*d*) δ 7.52 (s, 1 H), 4.62 (s, 2 H), 3.77 – 3.81 (m, 2 H), 3.65 – 3.68 (m, 2 H).

[0127] Step 4: 3-bromo-6,7-dihydro-4H-pyrazolo[5,1-*c*][1,4]oxazine. A solution of 2-((4-bromo-1*H*-pyrazol-3-yl)methoxy)ethanol (0.250 g, 1.13 mmol) and tri-*N*-butylphosphine (0.558 mL, 2.26 mmol) in toluene (12 mL) at about 50 °C was treated with *N,N,N',N'*-tetramethylazodicarboxamide (0.389 g, 2.26 mmol) added dropwise via syringe. The resulting solution was stirred at room temperature for about 20 minutes, after which the reaction was quenched with water (1 mL). The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel eluted with 0–100% ethyl acetate (EtOAc)/heptane to provide the title compound (0.103 g, 45 % yield); ¹H NMR (400 MHz, chloroform-*d*) δ 7.46 (s, 1 H), 4.76 (s, 2 H), 4.14 – 4.20 (m, 2 H), 4.07 – 4.13 (m, 2 H).

Preparation #6: (S)-5-chloro-6-(difluoromethyl)-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide



[0128] Step 1: methyl 5-chloro-6-(hydroxymethyl)nicotinate. Dimethyl 3-chloropyridine-2,5-dicarboxylate (2.0 g, 8.71 mmol) was dissolved in tetrahydrofuran (THF) / methanol (1:2, 60 mL) and cooled to about 0 °C. CaCl₂ (7.8 g, 70 mmol) was added and the reaction mixture was stirred for about 30 minutes. Sodium borohydride (NaBH₄) (0.832 g, 22 mmol) was added portion wise and the reaction was stirred at about 0 °C for about 3 hours. The reaction was diluted with dichloromethane (DCM) (50 mL) and poured into ice cold H₂O (100

mL). Layers were separated and the aq layer was extracted into DCM (2 x 25 mL). The combined organic phase was washed with saturated aq NaCl (2 x 25 mL), dried over MgSO₄ and the solvents were removed *in vacuo* to provide the title compound (1.0 g, 54 % yield). ¹H NMR (500 MHz, dimethylsulfoxide-*d*₆) δ 9.00 (d, *J* = 1.8 Hz, 1H), 8.29 (d, *J* = 1.8 Hz, 1H), 5.42 (t, *J* = 6.0 Hz, 1H), 4.71 (d, *J* = 6.1 Hz, 2H), 3.91 (s, 3H).

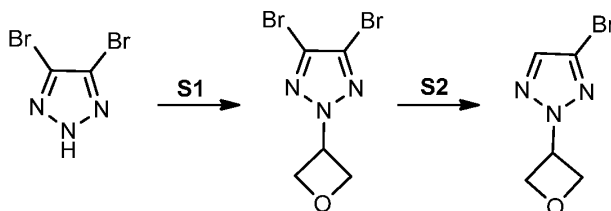
[0129] Step 2: Methyl 5-bromo-6-formylnicotinate. To a solution of methyl 5-bromo-6-(hydroxymethyl)nicotinate (0.723 g, 2.94 mmol) in dichloromethane (DCM) (10 mL) was added Dess–Martin periodinane (1.87 g, 4.41 mmol) and the reaction mixture stirred for about 18 hours at room temperature. To this was added a mixture of saturated aq NaHCO₃/1M aq Na₂S₂O₃ (1:1, 50 mL) and the biphasic mixture was stirred until clear. The phases were separated, and the aq phase was washed with dichloromethane (DCM) (2 x 50 mL). The combined organic phase was dried over MgSO₄ and the solvents were removed *in vacuo* to provide the title compound (0.623 g, 83 % yield). ¹H NMR (500 MHz, dimethylsulfoxide-*d*₆) δ 10.16 (s, 1H), 9.18 (d, *J* = 1.8 Hz, 1H), 8.48 (d, *J* = 1.5 Hz 1H), 3.95 (s, 3H).

[0130] Step 3: Methyl 5-chloro-6-(difluoromethyl)nicotinate. To a stirred solution of methyl 5-chloro-6-formylnicotinate (0.623 mg, 3.12 mmol) in chloroform (30 mL) was added Deoxo-Fluor[®] (50% in toluene, 2.9 mL, 7.80 mmol) and the mixture stirred at about 45 °C for about 24 hours. The reaction was quenched via the addition of saturated aq NaHCO₃ (10 mL), diluted with H₂O (10 mL) and extracted into dichloromethane (DCM) (3 x 10 mL). The combined organic layer was dried over MgSO₄, filtered and the solvents were removed *in vacuo*. The residue was purified via flash column chromatography on silica gel eluting with 0–60% ethyl acetate (EtOAc)/isohexane to provide the title compound (0.433 g, 60 % yield). ¹H NMR (500 MHz, dimethylsulfoxide-*d*₆) δ 9.10 (d, *J* = 1.8 Hz, 1H), 8.50 (d t, *J* = 1.7, 0.8 Hz, 1H), 7.28 (t, *J* = 52.9 Hz, 1H), 3.94 (s, 3H).

[0131] Step 4: 5-chloro-6-(difluoromethyl)nicotinic acid. Methyl 5-chloro-6-(difluoromethyl) nicotinate (0.200 g, 0.71 mmol) was suspended in methanol (2 mL) and 2M aq NaOH (1 mL, 2.00 mmol) was added. The reaction mixture was stirred at room temperature for about 3 hours. Aq 1M HCl was added dropwise until pH 2 and the mixture was extracted into ethyl acetate (EtOAc) (3 x 5 mL). The combined organic phase was dried over MgSO₄ and the solvents were removed *in vacuo* to provide the title compound (0.141 g, 91 % yield). ¹H NMR (500 MHz, dimethylsulfoxide-*d*₆) δ 14.03 (s, 1H), 9.08 (d, *J* = 1.7 Hz, 1H), 8.46 (d, *J* = 1.8 Hz, 1H), 7.27 (t, *J* = 53.0 Hz, 1H).

[0132] Step 5: (S)-5-chloro-6-(difluoromethyl)-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide. A mixture of 5-chloro-6-(difluoromethyl)nicotinic acid (0.141 g, 0.68 mmol), (S)-1-(methylamino)-3-phenylpropan-2-ol (0.123 mg, 0.75 mmol) (Preparation #2), 4-methylmorpholine (0.187 mL, 1.70 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl) (195 mg, 1.02 mmol) and 1-hydroxybenzotriazole (HOBt) hydrate (156 mg, 1.02 mmol) were dissolved in *N,N*-dimethylformamide (DMF) (5 mL) and stirred at room temperature for about 18 hours. The reaction mixture was diluted with ethyl acetate (EtOAc) (10 mL) and washed sequentially with saturated aq NH_4Cl (10 mL), saturated aq NaHCO_3 (10 mL) and saturated aq NaCl (3 x 10 mL). The organic phase was dried over MgSO_4 and the solvents were removed *in vacuo*. The crude residue was used without further purification. LC/MS (Table B, Method dd) $R_t = 1.89$ min; MS m/z : 355 ($\text{M}+\text{H}$) $^+$.

Preparation #7: 4-Bromo-2-(oxetan-3-yl)-2H-1,2,3-triazole

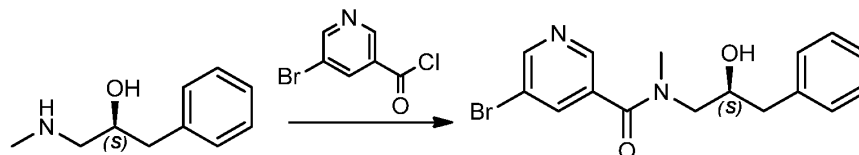


[0133] Step 1: 4,5-Dibromo-2-(oxetan-3-yl)-2H-1,2,3-triazole. To a mixture of 4,5-dibromo-2H-1,2,3-triazole (500 mg, 2.20 mmol) and 3-iodooxetane (0.213 mL, 2.42 mmol) in *N,N*-dimethylformamide (DMF) (20 mL) was added Cs_2CO_3 (2.1 g, 6.45 mmol). The mixture was stirred at about 120 °C for about 18 hours. The mixture was cooled to room temperature, diluted with ethyl acetate (EtOAc) (200 mL) and washed with H_2O (3 x 100 mL), saturated aq NaCl (2 x 200 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The material was purified by flash chromatography on silica gel (0–100% EtOAc/isohexane) to provide the title compound (529 mg, 81 % yield); ^1H NMR (500 MHz, dimethylsulfoxide- d_6) δ 5.90 – 5.81 (m, 1H), 4.97 (t, $J = 7.4$ Hz, 2H), 4.88 (t, $J = 6.5$ Hz, 2H).

[0134] Step 2: 4-Bromo-2-(oxetan-3-yl)-2H-1,2,3-triazole. To a vial was added 4,5-dibromo-2-(oxetan-3-yl)-2H-1,2,3-triazole (250 mg, 0.88 mmol) and tetrahydrofuran (THF) (4 mL). The mixture was cooled to about –30 °C. Isopropylmagnesium chloride (*i*PrMgCl) (2M in THF, 1.3 mL, 2.65 mmol) was added dropwise, and the mixture warmed to room temperature over about 3 hours. The mixture was quenched with saturated aq NH_4Cl (20 mL) and the aq layer was extracted into ethyl acetate (EtOAc) (3 x 20 mL). The organic layer was washed with saturated aq NaCl (2 x 50 mL), dried over MgSO_4 , filtered and the solvents were evaporated *in*

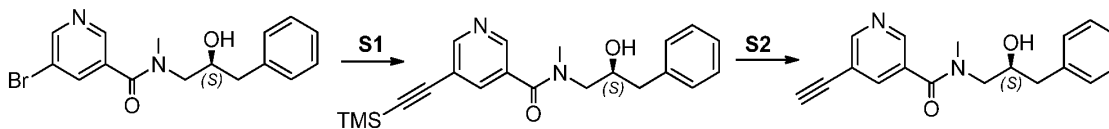
vacuo to provide the title compound (125 mg, 56% yield); ^1H NMR (500 MHz, dimethylsulfoxide- d_6) δ 8.11 (s, 1H), 5.90 – 5.82 (m, 1H), 5.01 – 4.95 (m, 2H), 4.91 – 4.86 (m, 2H).

Preparation #8: (S)-5-bromo-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide



[0135] To a stirred suspension of 5-bromonicotinic acid (7.52 g, 37.2 mmol) in dichloromethane (DCM) (130 mL) and *N,N*-dimethylformamide (DMF) (200 μL) was added a solution of oxalyl chloride in dichloromethane (DCM) (2M; 37.2 mL, 74.5 mmol). The mixture was stirred at room temperature for about 2 hours, after which it was concentrated under vacuum. The residue was dissolved in tetrahydrofuran (THF) (150 mL) and the resulting mixture was cooled in an ice bath before adding a mixture of (S)-1-(methylamino)-3-phenylpropan-2-ol (Preparation #2) (6.15 g, 37.2 mmol) and *N,N*-Diisopropylethylamine (DIEA) (19.5 mL, 112 mmol) in THF (20 mL). The reaction mixture was stirred at room temperature for about 1 hour, after which ethyl acetate (EtOAc) (50 mL), methyl *tert*-butyl ether (MTBE) (50 mL) and NaHCO_3 (100 mL) were added. The layers were separated, and the organics were concentrated under vacuum. The resulting crude material was purified by flash column chromatography on silica gel eluting with a gradient of 0–100% EtOAc/heptane to provide the title compound (11 g, 85% yield); ^1H NMR at 90 $^\circ\text{C}$ (500 MHz, dimethylsulfoxide- d_6) δ 8.70 (d, $J = 2.3$ Hz, 1H), 8.54 (d, $J = 1.9$ Hz, 1H), 8.01 (t, $J = 2.0$ Hz, 1H), 7.21 (d t, $J = 31.1, 7.5$ Hz, 5H), 4.76 (s, 1H), 4.02 (s, 1H), 3.27 (d, $J = 21.5$ Hz, 2H), 3.00 (s, 3H), 2.65 (s, 2H).

Preparation #9: (S)-5-ethynyl-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide



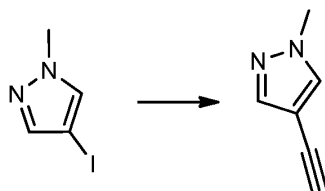
[0136] **Step 1: (S)-N-(2-hydroxy-3-phenylpropyl)-N-methyl-5-((trimethylsilyl)ethynyl) nicotinamide.** A mixture of (S)-5-bromo-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide (4.0 g, 8.93 mmol) (Preparation #8), ethynyltrimethylsilane (2.5 mL, 17.87 mmol), bis(triphenyl-phosphine)-palladium (II) dichloride ($\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$) (0.753 g, 1.07 mmol), CuI (0.340 g, 1.79 mmol) and Et_3N (8.7 mL, 62.5 mmol)

in *N,N*-dimethylformamide (DMF) (60 mL) were sparged with N₂ then heated to about 90 °C for about 2 hours. The mixture was cooled to room temperature, filtered through Celite and washed with ethyl acetate (EtOAc) (200 mL). The filtrate was diluted with EtOAc (200 mL) and H₂O (600 mL) and the layers were separated. The aq layer was extracted into EtOAc (2 x 300 mL) and the combined organic layer was washed with saturated aq NaCl (2 x 300 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The resulting material was purified by flash chromatography on silica gel (0–100% EtOAc/isohexane) to provide the title compound (3.3 g, 91 % yield); LC/MS (Table B, Method ee) R_t = 2.35 min; MS *m/z* 367 (M+H)⁺.

[0137] Step 2: (S)-5-ethynyl-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide.

To a stirred solution of (S)-N-(2-hydroxy-3-phenylpropyl)-N-methyl-5-((trimethylsilyl)ethynyl)nicotinamide (3.3 g, 9.00 mmol) in tetrahydrofuran (THF) (30 mL) was added tetra-*N*-butylammonium fluoride (TBAF) (1 M in THF) (11.70 mL, 11.70 mmol) and the mixture was stirred at room temperature for about 1 hour. The mixture was taken up in ethyl acetate (EtOAc) (150 mL) and washed with H₂O (150 mL) and saturated aq NaCl (150 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to give a brown oil which was purified by flash chromatography on silica gel (0–100% EtOAc/isohexane) to provide the title compound (2.3 g, 76 % yield); LC/MS (Table B, Method ee) R_t = 1.65 min; MS *m/z* 295 (M+H)⁺.

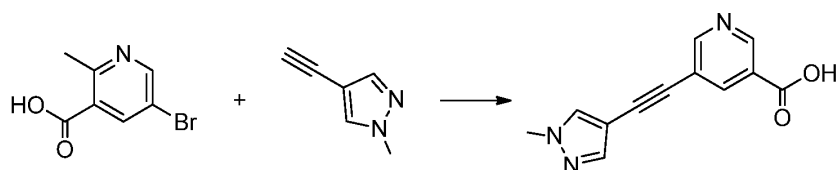
Preparation #10: 4-ethynyl-1-methyl-1*H*-pyrazole



[0138] To a solution of 4-iodo-1-methyl-1*H*-pyrazole (20 g, 96 mmol) in *N,N*-dimethylformamide (DMF) (120 mL) was added ethynyltrimethylsilane (13.2 g, 135 mmol), copper(I) iodide (1.282 g, 6.73 mmol), triphenylphosphine (PPh₃) (5.04 g, 19.23 mmol), diisopropylamine (12.6 g, 125 mmol) and Palladium(II) acetate (Pd(OAc)₂) (1.30 g, 5.77 mmol). The mixture was stirred under N₂ at about 60 °C for about 1 hour. After cooling to room temperature, the mixture was poured into water (200 mL) and extracted with ethyl acetate (EtOAc) (3 x 200 mL). The organic layer was combined and washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was triturated with methyl *tert*-butyl ether (MTBE) and the resulting suspension was filtered to remove solids. The solids were rinsed with methyl *tert*-butyl ether (MTBE) and the combined filtrate was

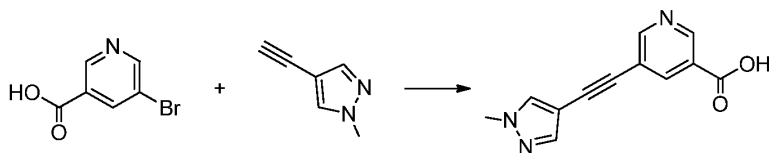
concentrated under vacuum. The resulting crude product was dissolved in methanol (200 mL), K_2CO_3 (1.55 g, 11.2 mmol) was added and the mixture was stirred at room temperature for about 1 hour. This mixture was poured into water (200 mL) and extracted with EtOAc (3 x 100 mL). The organic layer was combined and washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting crude material was purified by column chromatography on silica gel eluting with 0–25% EtOAc/petroleum ether to provide the title compound (5.0 g, 42% yield). 1H NMR (400 MHz, chloroform-*d*) δ 3.00 (s, 1H), 3.89 (s, 3H), 7.49–7.54 (m, 1H), 7.60 (s, 1H).

Preparation #11: 6-methyl-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)nicotinic acid



[0139] A mixture of 4-ethynyl-1-methyl-1H-pyrazole (Preparation #10) (1.175 g, 9.96 mmol), 5-bromo-6-methylnicotinic acid (2.080 g, 9.63 mmol), methanesulfonato(2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (XPhos Pd G3) (0.060 g, 0.071 mmol) and Cs_2CO_3 (3.760 g, 11.54 mmol) in *N,N*-dimethylformamide (DMF) (20 mL) was sparged with N_2 for about 5 minutes. The reaction mixture was stirred under N_2 at about 70 °C for about 3 hours. The reaction mixture was cooled to room temperature, water (40 mL) was added, and the mixture was acidified to pH ~2 with 1 M HCl (aq) (~20 mL). The precipitate was filtered, and the solids were then washed with water (30 mL) and dried in a vacuum oven to provide the title compound (2.18 g, 89% yield). 1H NMR (500 MHz, dimethylsulfoxide-*d*₆) δ 13.45 (s, 1H), 8.87 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 2.2 Hz, 1H), 8.15 (s, 1H), 7.75 (d, J = 0.7 Hz, 1H), 3.87 (s, 3H), 2.68 (s, 3H).

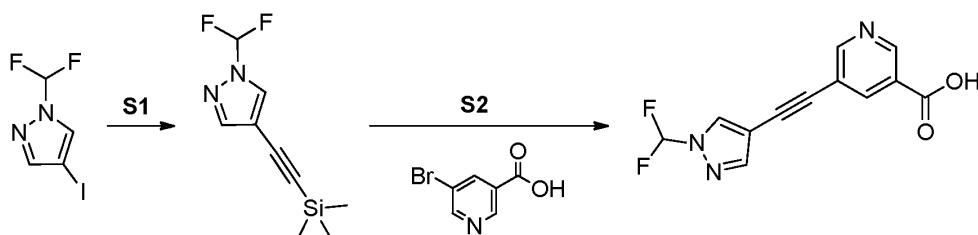
Preparation # 12: 5-((1-Methyl-1H-pyrazol-4-yl)ethynyl)nicotinic acid



[0140] 5-Bromonicotinic acid (1.59 g, 7.87 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos) (0.375 g, 0.79 mmol), bis(acetonitrile)dichloropalladium (II) ($Pd(MeCN)_2Cl_2$) (0.102 g, 0.39 mmol) and Cs_2CO_3 (3.1 g, 9.45 mmol) were added to a flask

and taken up in *N,N*-dimethylformamide (DMF) (30 mL). 4-Ethynyl-1-methyl-1*H*-pyrazole (Preparation #10) (1.0 g, 9.45 mmol) in DMF (5 mL) was added and the reaction mixture was stirred for about 3 hours at about 70 °C. The mixture was cooled to room temperature and the solvent removed *in vacuo*. The residue was diluted with H₂O (60 mL) and ethyl acetate (EtOAc) (60 mL). Layers were separated and the aq phase was acidified to pH 2 with 1M aq HCl. The resulting solid was filtered and dried to provide the title compound (1.66 g, 90 % yield); LC/MS (Table B, Method ee) *R*_t = 1.42 min; MS *m/z* 228 (M+H)⁺.

Preparation #13: 5-((1-(difluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)nicotinic acid

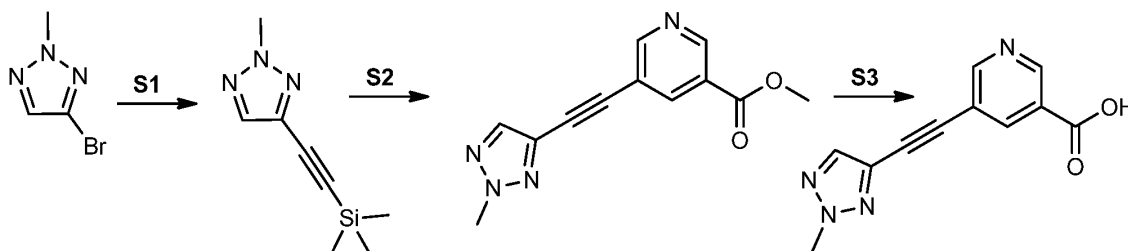


[0141] Step 1: 1-(difluoromethyl)-4-((trimethylsilyl)ethynyl)-1*H*-pyrazole. A suspension of 1-(difluoromethyl)-4-iodo-1*H*-pyrazole (10.0 g, 41.0 mmol), ethynyltrimethylsilane (6.04 g, 61.5 mmol) and methanesulfonato(2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (XPhos Pd G3) (0.173 g, 0.205 mmol) in tetrahydrofuran (THF) (100 mL) was sparged with N₂ for about 15 min. Diisopropylamine (11.68 mL, 82 mmol) and copper (I) iodide (0.020 g, 0.10 mmol) were added. The resulting mixture was stirred for about 12 h at about 65 °C. The mixture was diluted with methyl *tert*-butyl ether (MTBE) / Ethyl acetate (EtOAc) (1:1; 50 mL) and washed with water (100 mL) and sat. NaCl (100 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude material was distilled by vacuum distillation at about 160 °C to provide the title compound (4.0 g, 44% yield); ¹H NMR (400 MHz, chloroform-*d*) δ 0.21–0.28 (m, 9H), 6.94–7.36 (m, 1H), 7.69–7.77 (m, 1H), 7.95 (s, 1H).

[0142] Step 2: 5-((1-(difluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)nicotinic acid. A mixture of 1-(difluoromethyl)-4-((trimethylsilyl)ethynyl)-1*H*-pyrazole (73.8 g, 317 mmol), 5-bromonicotinic acid (40 g, 198 mmol), Cs₂CO₃ (77 g, 238 mmol) and methanesulfonato(2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (XPhos Pd G3) (1.676 g, 1.980 mmol) in *N,N*-dimethylformamide (DMF) (500 mL) were stirred under a N₂ sparge for about 10 min., after which tetrabutylammonium fluoride (218 mL, 218 mmol) was added and the mixture was stirred under N₂ at about 60 °C for about 12

h. The mixture was concentrated under reduced pressure and diluted with water (500 mL). The aqueous phase was extracted with methyl tertiary butyl ether (3 x 250 mL), and then the aqueous layer was adjusted to a pH of about 3 with 5N aq HCl. The resulting solids were collected via vacuum filtration and dried under vacuum to provide the title compound (47.5 g, 91% yield); ¹H NMR (400 MHz, dimethylsulfoxide-*d*₆) δ = 14.40 – 12.47 (m, 1H), 9.04 (d, *J* = 2.0 Hz, 1H), 8.92 (d, *J* = 2.5 Hz, 1H), 8.73 (s, 1H), 8.31 (t, *J* = 2.3 Hz, 1H), 8.12 (s, 1H), 8.02 – 7.70 (m, 1H).

Preparation #14: 5-((2-methyl-2H-1,2,3-triazol-4-yl)ethynyl)nicotinic acid



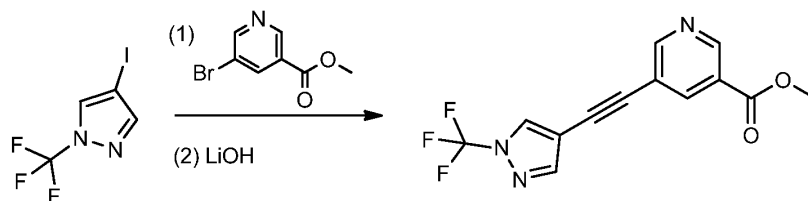
[0143] Step 1: 2-methyl-4-((trimethylsilyl)ethynyl)-2H-1,2,3-triazole. A mixture of 4-bromo-2-methyl-2H-1,2,3-triazole (500 mg, 3.09 mmol), ethynyltrimethylsilane (1.283 mL, 9.26 mmol), triethylamine (TEA) (0.860 mL, 6.17 mmol), Copper (I) iodide (29.4 mg, 0.154 mmol) and tetrakis(triphenylphosphine)palladium(0) (Pd(PPh₃)₄) (178 mg, 0.154 mmol) in *N,N*-dimethylformamide (DMF) (6 mL) was degassed with N₂ for 5 minutes, then heated to about 100 °C for about 1 hour. The mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel eluting with 0–50% yield ethyl acetate (EtOAc)/iso-hexane to provide the title compound (438 mg, 63% yield); ¹H NMR (500 MHz, chloroform-*d*) δ 7.63 (s, 1H), 4.17 (s, 3H), 0.25 (s, 9H).

[0144] Step 2: methyl 5-((2-methyl-2H-1,2,3-triazol-4-yl)ethynyl)nicotinate. To a vial containing methyl 5-bromonicotinate (1.142 g, 5.29 mmol), 2-methyl-4-((trimethylsilyl)ethynyl)-2H-1,2,3-triazole (1.517 g, 6.35 mmol), triethylamine (TEA) (5.16 mL, 37.0 mmol), Copper (I) iodide (0.101 g, 0.529 mmol) and bis(triphenylphosphine)palladium (II) dichloride (Pd(PPh₃)₂Cl₂) (0.371 g, 0.529 mmol) was added *N,N*-dimethylformamide (DMF) (15 mL) and the mixture degassed with nitrogen for 5 minutes, then tetra-*N*-butylammonium fluoride (TBAF) 1 M in tetrahydrofuran (THF) (7.93 mL, 7.93 mmol) was added and the mixture degassed for 30 seconds then heated to 100 °C for 1 hour. The mixture was concentrated, then taken into ethyl acetate (EtOAc) (100 mL) and washed with saturated sodium bicarbonate (aq) (100 mL). The aqueous layer was further extracted with EtOAc (2 x 50 mL), and the combined organic layers washed with water (100 mL). The organic layer was dried

using Na_2SO_4 , filtered and concentrated to give a brown oil, which was purified by flash column chromatography on silica gel eluting with 0–60% EtOAc/Isohexane to provide the title compound (0.978 g, 69% yield); ^1H NMR (500 MHz, chloroform-*d*) δ 9.17 (d, $J = 2.1$ Hz, 1H), 8.92 (d, $J = 2.1$ Hz, 1H), 8.43 (t, $J = 2.1$ Hz, 1H), 7.76 (s, 1H), 4.24 (s, 3H), 3.98 (s, 3H).

[0145] Step 3: 5-((2-methyl-2H-1,2,3-triazol-4-yl)ethynyl)nicotinic acid. To a flask containing methyl 5-((2-methyl-2H-1,2,3-triazol-4-yl)ethynyl)nicotinate (54 g, 223 mmol) in tetrahydrofuran (THF) (540 mL) and water (90 mL) was added NaOH (13.37 g, 334 mmol) and the mixture stirred at room temperature for 3 hours. The mixture was concentrated acidified to pH 2 with 1 M HCl (aq) (~10 mL). The resulting precipitate was filtered and dried overnight in the vacuum oven to provide the title compound (49 g, 91% yield); ^1H NMR (500 MHz, dimethylsulfoxide-*d*₆) δ 9.14 (s, 1H), 9.06 (s, 1H), 8.37 (s, 1H), 8.15 (s, 1H), 4.70 br (s, 1H), 4.21 (s, 3H).

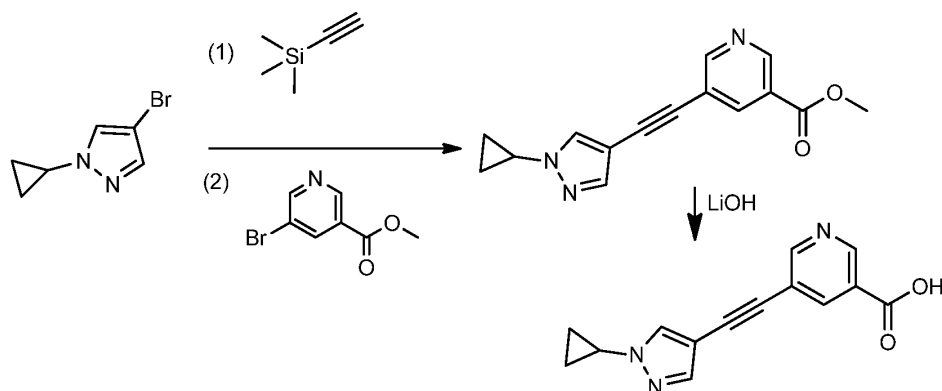
Preparation #15: 5-((1-(trifluoromethyl)-1H-pyrazol-4-yl)ethynyl)nicotinic acid



[0146] A mixture of triethylamine (TEA) (0.745 mL, 5.34 mmol), copper (I) iodide (0.051 g, 0.267 mmol), tetrakis(triphenylphosphine)palladium(0) ($\text{Pd}(\text{PPh}_3)_4$) (0.309 g, 0.267 mmol), 4-iodo-1-(trifluoromethyl)-1H-pyrazole (1 g, 2.67 mmol) and ethynyltrimethylsilane (1.110 mL, 8.02 mmol) in *N,N*-dimethylformamide (DMF) (8 mL) was sparged with N_2 for 5 minutes and then heated to about 100 °C for about 3 hours. The mixture was cooled to room temperature, concentrated *in vacuo* and filtered through a plug of silica gel using rinses of 50% ethyl acetate (EtOAc)/Isohexane. The filtrate was concentrated and the residue was taken up in acetonitrile (MeCN) (30 mL), and CsF (0.848 g, 5.58 mmol), methyl 5-bromonicotinate (1.005 g, 4.65 mmol), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (0.222 g, 0.465 mmol), bis(acetonitrile)dichloropalladium (II) ($\text{Pd}(\text{MeCN})_2\text{Cl}_2$) (0.060 g, 0.233 mmol) and Cs_2CO_3 (2.275 g, 6.98 mmol) were added. The mixture was sparged with N_2 and stirred under N_2 at about 70 °C for about 16 h. The reaction was cooled to room temperature and the mixture was adsorbed onto Celite (~25g) under reduced pressure prior to purification by flash column chromatography on silica gel eluting with 10–20% EtOAc/hexanes to obtain methyl 5-((1-(trifluoromethyl)-1H-pyrazol-4-yl)ethynyl)nicotinate (530 mg). This material was dissolved

in tetrahydrofuran (THF) (8.0 mL) to which a solution of LiOH (43 mg, 1.8 mmol) in water (2.0 mL) was added and the mixture was stirred at room temperature for about 16 hours. The reaction mixture was concentrated under reduced pressure and the remaining solution was acidified with 1 M hydrochloric acid. The resulting precipitate was collected by filtration and washed with water (5 mL) and hexanes (10 mL), and then dried under vacuum to obtain the title compound (479 mg, 94% yield). ^1H NMR (500 MHz, dimethylsulfoxide- d_6) δ 9.02 (s, 1H), 8.94 (d, J = 1.9 Hz, 1H), 8.61 (d, J = 2.2 Hz, 1H), 8.28 (t, J = 0.9 Hz, 1H), 8.20 (t, J = 2.1 Hz, 1H).

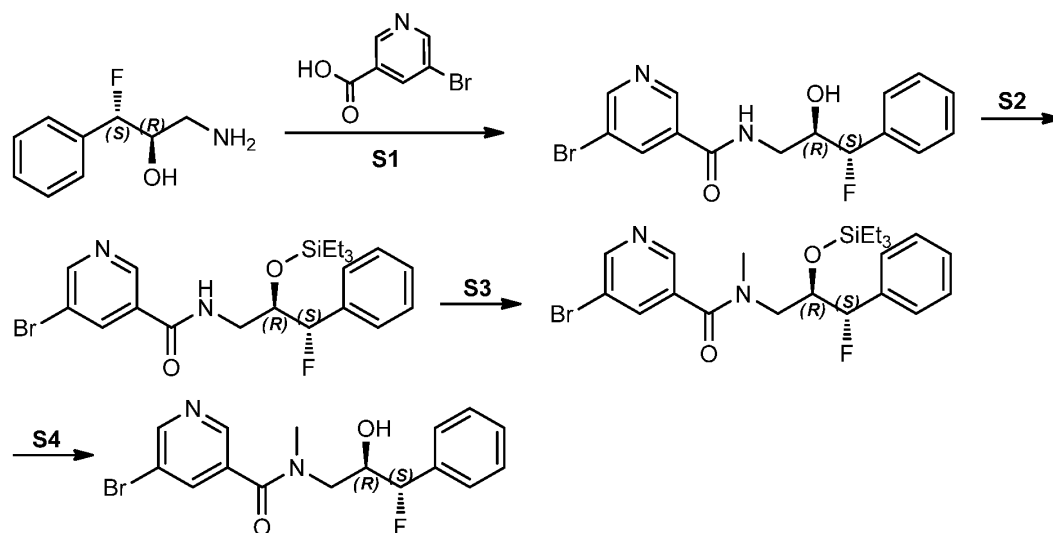
Preparation #16: 5-((1-cyclopropyl-1H-pyrazol-4-yl)ethynyl)nicotinic acid



[0147] A solution of 4-bromo-1-cyclopropyl-1H-pyrazole (660 mg, 3.53 mmol) and ethynyltrimethylsilane (1.8 mL, 12.99 mmol) in acetonitrile (MeCN) (4 mL) was added to a N_2 sparged solution of copper(I) iodide (16 mg, 0.084 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos) (205 mg, 0.430 mmol), $\text{PdCl}_2(\text{MeCN})_2$ (60 mg, 0.231 mmol) and *N,N*-Diisopropylethylamine (DIEA) (1.5 mL, 8.59 mmol) in acetonitrile (MeCN) (8 mL) and heated to 70 °C. After about 2 hours, a mixture of dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (XPhos) (205 mg, 0.430 mmol), $\text{PdCl}_2(\text{MeCN})_2$ (60 mg, 0.231 mmol) and Cs_2CO_3 (1150 mg, 3.53 mmol) in acetonitrile (MeCN) (3 mL) degassed by N_2 sparge was added followed by ethynyltrimethylsilane (1.8 mL, 12.99 mmol) and the mixture was heated at about 70 °C for about 16 h. The solution was cooled to room temperature and filtered through silica gel with washes of 1:1 hexanes/Ethyl acetate (EtOAc) (20 mL), and the filtrate was concentrated under reduced pressure. The crude material was dissolved in acetonitrile (MeCN) (12.5 mL) and CsF (536 mg, 3.53 mmol), methyl 5-bromonicotinate (635 mg, 2.94 mmol), X-Phos (140 mg, 0.294 mmol), $\text{PdCl}_2(\text{MeCN})_2$ (38.1 mg, 0.147 mmol) and Cs_2CO_3 (1437 mg, 4.41 mmol) were added. The reaction mixture was degassed with N_2 sparge and then heated at about 70 °C for about 4 hours. The reaction was concentrated under reduced pressure onto Celite (~15

mL) and purified by flash column chromatography on silica gel eluting with 20–70% EtOAc/hexanes to obtain the desired methyl ester (564 mg). LiOH (76 mg, 3.17 mmol) in water (4 mL) was added to a solution of the crude methyl ester (564 mg, 2.110 mmol) in tetrahydrofuran (THF) (12 mL) and allowed to stir at room temperature for 2 hours, then concentrated under reduced pressure to obtain the title compound (545 mg, 70% yield); ^1H NMR (500 MHz, dimethylsulfoxide- d_6) δ 8.87 (d, J = 1.9 Hz, 1H), 8.53 (d, J = 2.2 Hz, 1H), 8.22 (s, 1H), 8.12 (t, J = 2.0 Hz, 1H), 7.72 (s, 1H), 3.77 (t, J = 7.4, 3.9 Hz, 1H), 1.08 (t, J = 3.6 Hz, 2H), 0.98 (dd, J = 7.4, 2.5 Hz, 2H). Acid proton not observed.

Preparation #17: 5-bromo-*N*-((2*R*,3*S*)-3-fluoro-2-hydroxy-3-phenylpropyl)-*N*-methylnicotinamide



[0148] Step 1: 5-bromo-*N*-((2*R*,3*S*)-3-fluoro-2-hydroxy-3-phenylpropyl)nicotinamide. A 50 mL round-bottomed flask equipped with rubber septum and nitrogen inlet needle was charged with 5-bromonicotinic acid (0.322 g, 1.60 mmol), (1*S*,2*R*)-3-amino-1-fluoro-1-phenylpropan-2-ol (Preparation #3) (0.270 g, 1.60 mmol) (Preparation #5), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl) (0.459 g, 2.39 mmol), 1-hydroxybenzotriazole (HOBt) hydrate (0.367 g, 2.39 mmol), *N,N*-diisopropylethylamine (DIEA) (0.836 mL, 4.79 mmol) and *N,N*-dimethylformamide (DMF) (15 mL). The resulting solution was stirred at room temperature for about 16 hours. The reaction mixture was partitioned between ethyl acetate (50 mL) and sat NaHCO_3 (50 mL). After separating the layers, the aq layer was extracted with ethyl acetate (EtOAc) (2 x 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and concentrated

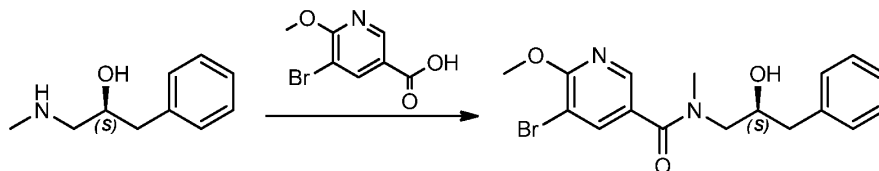
in vacuo. The crude residue was purified by flash chromatography on silica gel eluting with 0–100% EtOAc/heptane to provide the title compound (0.44 g, 78% yield); LC/MS (Table B, Method aa) R_t = 1.02 min; MS m/z : 353 and 355 (M+H)⁺.

[0149] Step 2: 5-bromo-*N*-((2*R*,3*S*)-3-fluoro-3-phenyl-2-((triethylsilyl)oxy)propyl)-nicotinamide. A round-bottomed flask was charged with 5-bromo-*N*-((2*R*,3*S*)-3-fluoro-2-hydroxy-3-phenylpropyl)nicotinamide (0.44 g, 1.25 mmol), 4-dimethylaminopyridine (DMAP) (0.076 g, 0.623 mmol), triethylamine (TEA) (1.04 mL, 7.47 mmol), triethylchlorosilane (SiEt₃-Cl) (0.316 mL, 1.87 mmol) and dichloromethane (DCM) (10 mL). The reaction was stirred at 0 °C for about 3 hours. The reaction was partitioned with saturated aq NaHCO₃ (10 mL) and water (10 mL) and ethyl acetate (EtOAc) (50 mL). The organic layer was separated and the aq layer was extracted with EtOAc (20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to provide the title compound (0.63 g, 100% yield); LC/MS (Table B, Method aa) R_t = 2.04 min; MS m/z : 467 and 469 (M+H)⁺.

[0150] Step 3: 5-bromo-*N*-((2*R*,3*S*)-3-fluoro-3-phenyl-2-((triethylsilyl)oxy)propyl)-*N*-methylnicotinamide. A solution of 5-bromo-*N*-((2*R*,3*S*)-3-fluoro-3-phenyl-2-((triethylsilyl)oxy)-propyl)nicotinamide (0.410 g, 0.807 mmol) and methyl iodide (MeI) (0.101 mL, 1.61 mmol) in *N,N*-dimethylformamide (DMF) (10 mL) at 0 °C was treated with 60% sodium hydride in mineral oil (0.032 g, 0.807 mmol). The resulting suspension was stirred at 0 °C for about 1 hour. The reaction was quenched with saturated NH₄Cl (20 mL), diluted with water and extracted with ethyl acetate (EtOAc) (3 x 30 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel eluting with 0–100% EtOAc/heptane to provide the title compound (0.32 g, 82% yield); LC/MS (Table B, Method aa) R_t = 2.05 min; MS m/z : 481 and 483 (M+H)⁺.

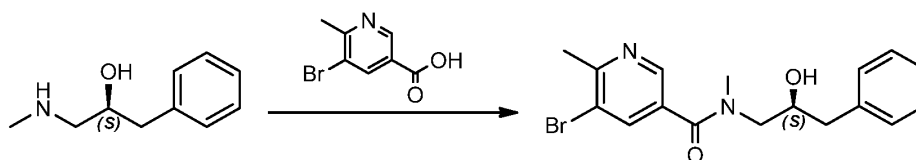
[0151] Step 4: 5-bromo-*N*-((2*R*,3*S*)-3-fluoro-2-hydroxy-3-phenylpropyl)-*N*-methylnicotinamide. A solution of 5-bromo-*N*-((2*R*,3*S*)-3-fluoro-3-phenyl-2-((triethylsilyl)oxy)-propyl)-*N*-methyl-nicotinamide (0.32 g, 0.66 mmol) and tetrahydrofuran (THF) (10 mL) at 0 °C was treated with 1 M tetra-*N*-butylammonium fluoride in THF (0.73 mL, 0.73 mmol). The reaction was stirred at 0 °C for about 2 hours. The reaction was quenched at 0 °C by the addition of sat NH₄Cl (20 mL). The mixture was extracted with ethyl acetate (EtOAc) (3 x 20 mL). The combined organic layers were washed with brine (75 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel eluting with 0–100% EtOAc/heptane to provide the title compound (0.29 g, 95% yield); LC/MS (Table B, Method aa) R_t = 1.07 min; MS m/z : 367 and 369 (M+H)⁺.

Preparation #18: (S)-5-bromo-N-(2-hydroxy-3-phenylpropyl)-6-methoxy-N-methylnicotinamide



[0152] To a stirred solution of 5-bromo-6-methoxynicotinic acid (0.300 g, 1.29 mmol) and (S)-1-(methylamino)-3-phenylpropan-2-ol (Preparation #2) (0.214 g, 1.29 mmol) in dichloromethane (DCM) (13 mL) was added *N,N*-Diisopropylethylamine (DIEA) (0.677 mL, 3.88 mmol) followed by 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) (0.737 g, 1.94 mmol) and the mixture stirred at room temperature for about 18 hours. The mixture was concentrated and purified by flash chromatography on silica gel (0–100% Ethyl acetate (EtOAc)/Isohexane) to provide the title compound (0.66 g, 94 % yield); LC/MS (Table B, Method b) $R_t = 1.99$ min; MS m/z 379 and 381 ($M+H$)⁺.

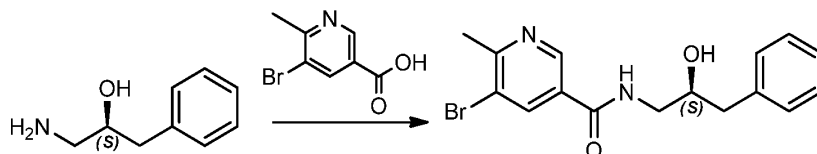
Preparation #19: (S)-5-bromo-N-(2-hydroxy-3-phenylpropyl)-N,6-dimethylnicotinamide



[0153] To a solution of 5-bromo-6-methylnicotinic acid (1.0 g, 4.66 mmol), 1-hydroxybenzotriazole (HOBt) hydrate (324 mg, 2.12 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl) (1.0 g, 5.51 mmol) in *N,N*-dimethylformamide (DMF) (10 mL) was added *N,N*-Diisopropylethylamine (DIEA) (0.740 mL, 4.24 mmol), the solution was stirred for about 5 minutes and then (S)-1-(methylamino)-3-phenylpropan-2-ol (Preparation #2) (700 mg, 4.24 mmol) was added. The reaction was stirred at room temperature for about 20 hours and the solvents were concentrated *in vacuo*. The residue was partitioned between ethyl acetate (EtOAc) (50 mL) and H₂O (50 mL), layers were separated, and the aq phase was extracted into EtOAc (2 x 50 mL). The combined organics were then washed with saturated aq NaCl (2 x 50 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude was purified by flash chromatography on silica gel (0–100% Ethyl acetate (EtOAc)/isohexane) to

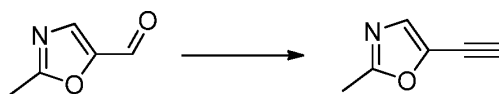
provide the title compound (411 mg, 24 % yield); LC/MS (Table B, Method a) $R_t = 1.79$ min; MS m/z 364 and 366 ($M+H$)⁺.

Preparation #20: (S)-5-bromo-N-(2-hydroxy-3-phenylpropyl)-6-methylnicotinamide



[0154] A mixture of 5-bromo-6-methylnicotinic acid (2.7 g, 13.2 mmol), (S)-1-amino-3-phenylpropan-2-ol (2 g, 13 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl) (3.3 g, 17.2 mmol), and 1-hydroxybenzotriazole (HOBt) hydrate (2.6 g, 17.2 mmol) was dissolved in *N,N*-dimethylformamide (DMF). *N,N*-Diisopropylethylamine (DIEA) (5.8 mL, 33.1 mmol) was added in one portion. The resulting solution was allowed to stir at room temperature for about 16 hours. Saturated aqueous NaHCO_3 (150 mL) and ethyl acetate (EtOAc) (150 mL) were added, and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with brine (2 x 100 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with 0–100% EtOAc/heptane to provide the title compound (2.3 g, 49 % yield). ^1H NMR (400 MHz, chloroform-*d*) δ 2.55 (s, 3H), 2.62–2.70 (m, 1H), 2.72–2.80 (m, 1H), 3.25 (ddd, $J = 13.63, 8.07, 5.20$ Hz, 1H), 3.45 (br s, 1H), 3.62 (ddd, $J = 13.82, 6.36, 3.18$ Hz, 1H), 3.93–4.00 (m, 1H), 7.02–7.12 (m, 3H), 7.16–7.23 (m, 2H), 8.08 (d, $J = 1.83$ Hz, 1H), 8.62 (d, $J = 1.71$ Hz, 1H).

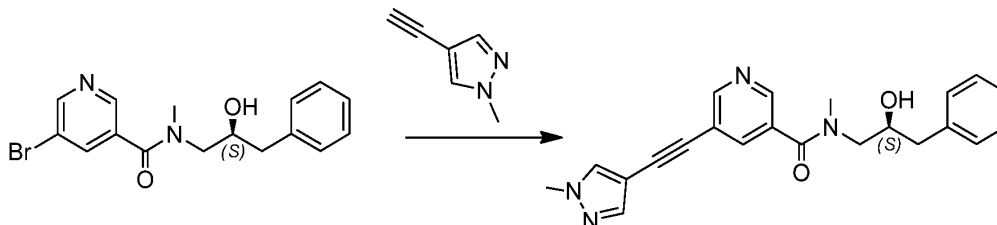
Preparation #21: 5-Ethynyl-2-methyloxazole



[0155] To a stirred solution of 2-methyloxazole-5-carbaldehyde (0.10 g, 0.94 mmol) and K_2CO_3 (0.26 g, 1.87 mmol) in methanol (MeOH) (3 mL) was added dimethyl(1-diazo-2-oxopropyl)phosphonate (0.21 g, 0.94 mmol) in MeOH (1 mL). The mixture was stirred for about 18 hours at room temperature and then filtered through celite rinsing with MeOH (10 mL). The solution was concentrated carefully *in vacuo* and the residue was purified by flash chromatography on silica gel (0–50% EtOAc/Isohexane) to give the title compound (0.17 g, 52 % yield); ^1H NMR (500 MHz, chloroform-*d*) δ 7.17 (s, 1H), 3.56 (s, 1H), 2.47 (s, 3H).

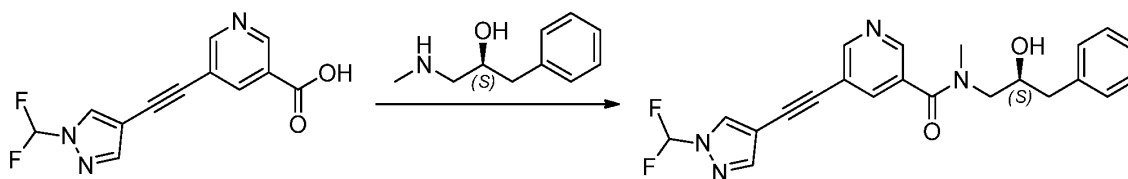
Synthetic Examples

Example #1: (S)-N-(2-hydroxy-3-phenylpropyl)-N-methyl-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)nicotinamide



[0156] (S)-5-bromo-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide (0.45 g, 1.29 mmol) (Preparation #8), 4-ethynyl-1-methyl-1H-pyrazole (Preparation #10) (0.31 g, 2.92 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos) (60 mg, 0.13 mmol), bis(acetonitrile)-dichloropalladium (II) ($\text{Pd}(\text{MeCN})_2\text{Cl}_2$) (20 mg, 0.08 mmol) and Cs_2CO_3 (0.51 g, 1.57 mmol) were taken up in acetonitrile (MeCN) (21 mL) and the mixture was sparged with N_2 for 10 minutes. The resulting mixture was then stirred at about 70 °C for about 3 hours. The mixture was cooled and filtered through Celite rinsing through with ethyl acetate (EtOAc) (60 mL). The solvents were removed *in vacuo* and the residue purified by flash chromatography on silica gel (0–10% methanol / EtOAc) to provide the title compound (0.25 g, 49 % yield). LC/MS (Table B, Method ee) R_t = 1.77 min; MS m/z 375 ($\text{M}+\text{H}^+$); ^1H NMR (500 MHz, dimethylsulfoxide- d_6 at 90 °C) δ 8.65 (d, J = 2.0 Hz, 1H), 8.50 (d, J = 2.0 Hz, 1H), 8.04 (s, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.29 – 7.12 (m, 5H), 4.75 (br s, 1H), 4.02 (br s, 1H), 3.88 (s, 3H), 3.36 – 3.26 (m, 2H), 3.00 (s, 3H), 2.70 – 2.61 (m, 2H).

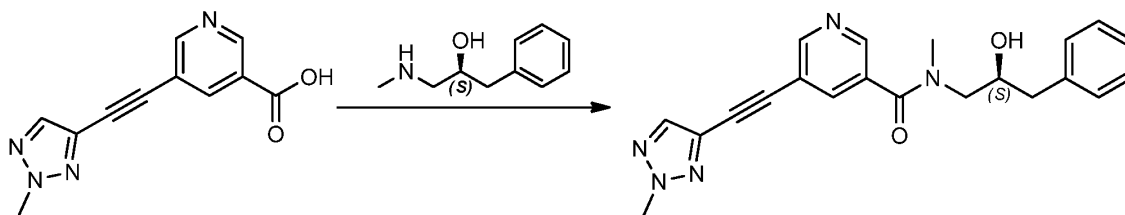
Example #2: (S)-5-((1-(difluoromethyl)-1H-pyrazol-4-yl)ethynyl)-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide



[0157] A mixture of 5-((1-(difluoromethyl)-1H-pyrazol-4-yl)ethynyl)nicotinic acid (Preparation #13) (95 g, 361 mmol), *N,N*-Diisopropylethylamine (DIEA) (189 mL, 1083 mmol) and 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) (151 g, 397 mmol) in *N,N*-dimethylformamide (DMF) (1.00 L) was stirred at room temperature for about 0.5 h. Then (S)-1-(methylamino)-3-phenylpropan-

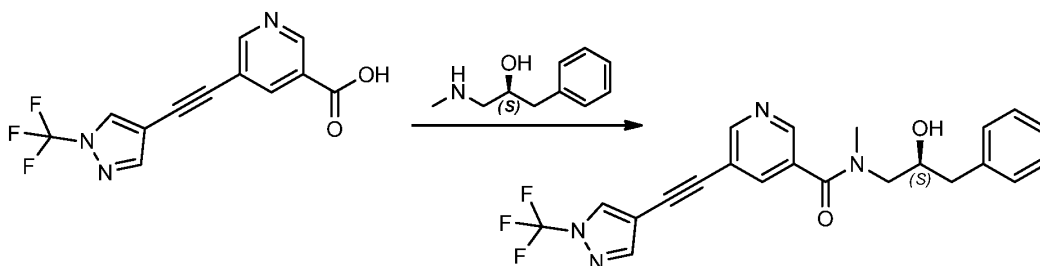
2-ol (Preparation #2) (59.6 g, 361 mmol) was added and the mixture was stirred at room temperature for about 12 hours. The mixture was poured into water (2.00 L) and extracted with ethyl acetate (EtOAc) (3 x 800 mL). The organic phase was washed with brine (1.50 L), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting material was purified by flash column chromatography on silica gel eluted with 0–100% EtOAc/petroleum ether to provide the title compound (98 g, 66% yield); LC/MS (Table B, Method aa) *R*_t = 1.21 min; MS *m/z*: 411 (M+H)⁺; ¹H NMR (400 MHz, dimethylsulfoxide-*d*₆) δ = 8.78 – 8.66 (m, 2H), 8.62 – 8.50 (m, 1H), 8.12 (d, *J* = 6.4 Hz, 1H), 8.03 – 7.69 (m, 2H), 7.30 – 7.07 (m, 5H), 5.17 – 4.95 (m, 1H), 4.06 (br d, *J* = 2.9 Hz, 1H), 3.89 (br d, *J* = 5.4 Hz, 1H), 3.58 (br dd, *J* = 3.9, 13.2 Hz, 1H), 3.41 – 3.35 (m, 1H), 3.20 – 3.11 (m, 1H), 2.98 (br d, *J* = 14.7 Hz, 3H), 2.81 – 2.72 (m, 1H), 2.71 – 2.63 (m, 1H).

Example #3: (*S*)-*N*-(2-hydroxy-3-phenylpropyl)-*N*-methyl-5-((2-methyl-2*H*-1,2,3-triazol-4-yl)ethynyl)nicotinamide



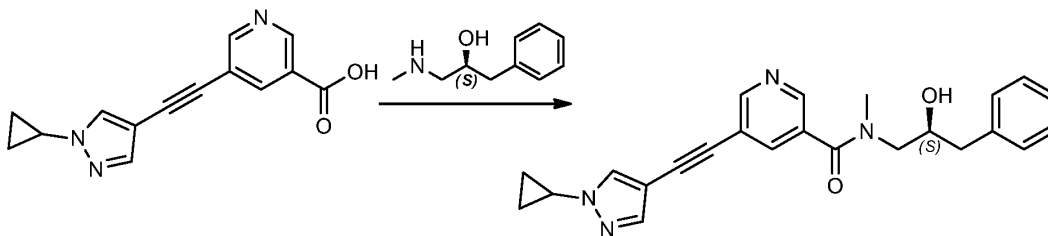
[0158] To a flask containing 5-((2-methyl-2*H*-1,2,3-triazol-4-yl)ethynyl)nicotinic acid (Preparation #14) (23 g, 101 mmol) in tetrahydrofuran (THF) (115 mL) was added *N,N'*-carbonyldiimidazole (CDI) (24.51 g, 151 mmol) and the mixture stirred at room temperature for about 5 hours. The reaction was added to a solution of (*S*)-1-(methylamino)-3-phenylpropan-2-ol (Preparation #2) (27.8 g, 151 mmol) and triethylamine (TEA) (28.1 mL, 202 mmol) in tetrahydrofuran (THF) (115 mL). The reaction was stirred at 25 °C for 2 hours. The reaction was completed by LC/MS. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (EtOAc) (300 mL). The organic layer was washed with 15% citric acid (300 mL), brine (500 mL), dried, filtered and concentrated to give a residue which was purified by flash chromatography on silica gel petroleum ether:EtOAc = 100:1~0:1 to give the title compound (70 g, 183 mmol, 91 % yield). (Table B, Method bb) *R*_t = 4.24 min; MS *m/z*: 376 (M+H)⁺; ¹H NMR (500 MHz dimethylsulfoxide-*d*₆ at 90 °C) δ 8.75 (s, 1H), 8.58 (s, 1H), 8.03 (s, 1H), 7.94 (s, 1H), 7.33 – 7.09 (m, 5H), 4.84 – 4.68 (broad m, 1H), 4.21 (s, 3H), 4.10 – 3.96 (broad m, 1H), 3.53 – 3.19 (broad m, 2H), 3.01 (s, 3H), 2.75 – 2.59 (broad m, 2H).

Example #4: (*S*)-*N*-(2-hydroxy-3-phenylpropyl)-*N*-methyl-5-((1-(trifluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)nicotinamide



[0159] 2-(3H-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium tetrafluoroborate (TBTU) (859 mg, 2.67 mmol) was added to a solution of (*S*)-1-(methylamino)-3-phenylpropan-2-ol (Preparation #2) (441 mg, 2.67 mmol), 5-((1-(trifluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)nicotinic acid (Preparation #15) (500 mg, 1.778 mmol) and *N,N*-Diisopropylethylamine (DIEA) (0.932 mL, 5.33 mmol) in *N,N*-dimethylformamide (DMF) (12.4 mL) was stirred at room temperature for about 36 h. Ethyl acetate (EtOAc) (10 mL) was added and the mixture was washed with water (2 x 10 mL) and brine (10 mL), dried over magnesium sulfate and then concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with 50–100% Ethyl acetate (EtOAc)/hexanes to provide the title compound (655 mg, 78% yield); (Table B, Method aa) R_t = 1.38 min; MS m/z : 429 ($M+H$)⁺; ¹H NMR (500 MHz, dimethylsulfoxide-*d*₆) δ 9.05 (d, J = 9.7 Hz, 1H), 8.87 – 8.50 (m, 2H), 8.30 (d, J = 8.0 Hz, 1H), 8.05 – 7.81 (m, 2H), 7.39 – 7.01 (m, 5H), 5.07 (dd, J = 76.1, 5.6 Hz, 1H), 4.07 (d, J = 8.9 Hz, 0.5H), 3.90 (d, J = 8.8 Hz, 0.5H), 3.58 (dd, J = 13.3, 4.1 Hz, 0.5H), 3.42 – 3.33 (m, 0.5H), 3.16 (dd, J = 6.3, 3.6 Hz, 1H), 2.99 (d, J = 18.2 Hz, 3H), 2.74 (s, 0.5H), 2.72 – 2.61 (m, 0.5H).

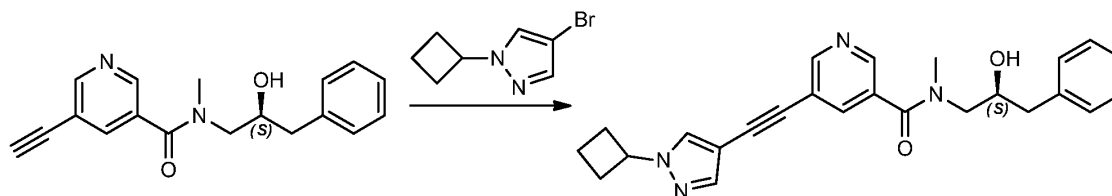
Example #5: (*S*)-*N*-(2-hydroxy-3-phenylpropyl)-*N*-methyl-5-((1-(trifluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)nicotinamide



[0160] A solution of 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) (882 mg, 2.319 mmol), 5-((1-cyclopropyl-

1*H*-pyrazol-4-yl)ethynyl)nicotinic acid (Preparation #16) (534 mg, 2.109 mmol), (*S*)-1-(methylamino)-3-phenylpropan-2-ol (Preparation #2) (383 mg, 2.319 mmol) and *N,N*-Diisopropylethylamine (DIEA) (1.105 mL, 6.33 mmol) in dichloromethane (DCM) (20 mL) and tetrahydrofuran (THF) (10 mL) and was stirred at room temperature for about 16 hours. Then, additional *N,N*-Diisopropylethylamine (DIEA) (1.105 mL, 6.33 mmol), (*S*)-1-(methylamino)-3-phenylpropan-2-ol (160 mg, 0.968 mmol) and HATU (882 mg, 2.319 mmol) were added and the mixture was stirred at room temperature for 2 hours. The reaction mixture was then diluted with DCM (50 mL) washed with saturated aq ammonium chloride (2 x 50 mL). The organic portion was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on a silica gel eluting with 0–6% methanol / dichloromethane (DCM) to obtain the title compound (460 mg, 52% yield). (Table B, Method cc) $R_t = 1.89$ min; MS m/z : 401 (M+H)⁺; ¹H NMR (500 MHz, dimethylsulfoxide-*d*₆) δ 8.67 (dd, $J = 31.1, 2.0$ Hz, 1H), 8.53 (dd, $J = 33.8, 2.0$ Hz, 1H), 8.25 (d, $J = 8.5$ Hz, 1H), 7.88 (dt, $J = 53.3, 2.1$ Hz, 1H), 7.74 (d, $J = 7.5$ Hz, 1H), 7.29 (d, $J = 4.5$ Hz, 2H), 7.23 – 7.08 (m, 2H), 5.06 (dd, $J = 70.9, 5.6$ Hz, 1H), 4.10 – 3.84 (m, 1H), 3.78 (dh, $J = 6.9, 3.3$ Hz, 1H), 3.69 – 3.51 (m, 1H), 3.43 – 3.33 (m, 1H), 3.21 – 3.09 (m, 2H), 2.98 (d, $J = 18.2$ Hz, 3H), 2.80 – 2.62 (m, 1H), 1.13 – 1.04 (m, 2H), 1.04 – 0.96 (m, 2H).

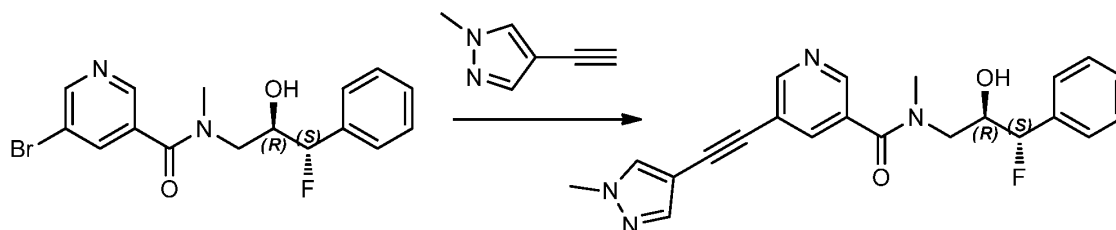
Example #6. (S)-5-((1-cyclobutyl-1*H*-pyrazol-4-yl)ethynyl)-*N*-(2-hydroxy-3-phenylpropyl)-*N*-methylnicotinamide



[0161] A 7 mL reaction vial equipped with septa cap outfitted with nitrogen inlet needle was charged with (*S*)-5-ethynyl-*N*-(2-hydroxy-3-phenylpropyl)-*N*-methylnicotinamide (Preparation #9) (0.140 g, 0.476 mmol), 4-bromo-1-cyclobutyl-1*H*-pyrazole (0.096 g, 0.476 mmol), potassium phosphate (0.121 g, 0.571 mmol), and bis(tri-*tert*-butylphosphine)palladium(0) (0.012 g, 0.024 mmol) in tetrahydrofuran (THF) (2 mL). The reaction mixture was sparged with nitrogen for about 20 minutes and then heated at about 50 °C for about 10 hours. The reaction was cooled to room temperature. The reaction was filtered through a pad of Celite then the filter cake was rinsed with ethyl acetate (EtOAc). The filtrate was concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica

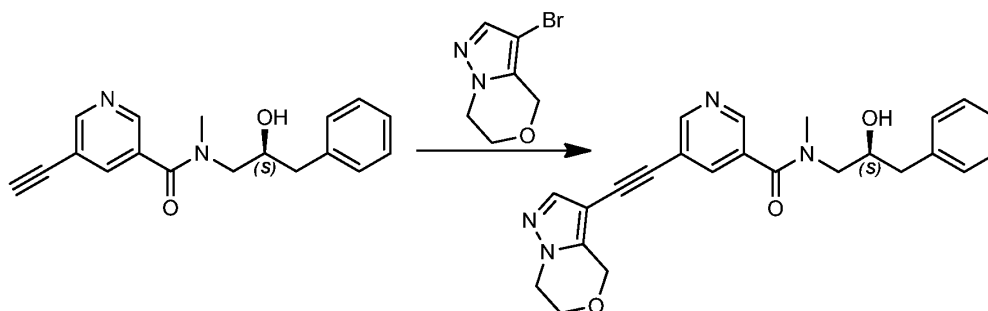
gel eluting with 0–100% EtOAc/heptane followed by 0–5% methanol /EtOAc. The eluent was concentrated *in vacuo* to provide the title compound (0.056 g, 28% yield); LC/MS (Table B, Method aa) R_t = 1.33 min; MS m/z : 415 (M+H)⁺; ¹H NMR (400 MHz, dimethylsulfoxide-*d*₆) δ 8.67 (d, J = 24.6 Hz, 1H), 8.52 (d, J = 26.4 Hz, 1H), 8.27 (d, J = 6.6 Hz, 1H), 7.96 – 7.71 (m, 2H), 7.34 – 7.05 (m, 5H), 5.16–4.92 (m, 1H), 4.11–3.83 (m, 1H), 3.23 – 3.07 (m, 1H), 2.98 (d, J = 14.1 Hz, 3H), 2.79 – 2.62 (m, 1H), 2.48–2.43 (m, 7H), 1.88 – 1.71 (m, 2H).

Example #7: *N*-((2*R*,3*S*)-3-fluoro-2-hydroxy-3-phenylpropyl)-*N*-methyl-5-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)nicotinamide



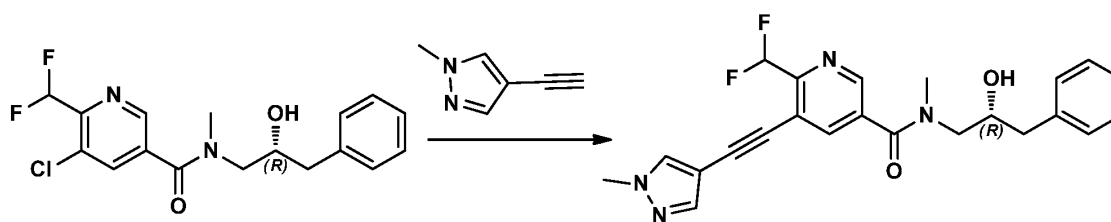
[0162] A 20 mL reaction vial equipped with septa cap and outfitted with nitrogen inlet needle was charged with 4-ethynyl-1-methyl-1*H*-pyrazole (Preparation #10) (0.105 g, 0.987 mmol), 5-bromo-*N*-((2*R*,3*S*)-3-fluoro-2-hydroxy-3-phenylpropyl)-*N*-methylnicotinamide (Preparation #17) (0.29 g, 0.79 mmol), Chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos Pd G2) (0.031 g, 0.039 mmol) and cesium carbonate (0.322 g, 0.987 mmol). The reaction was flushed with nitrogen. Acetonitrile (MeCN) (3.95 mL) was added and the mixture was sparged with nitrogen. The reaction mixture was heated at about 65 °C for about 3 hours. The reaction was cooled to room temperature. The reaction was filtered through a pad of Celite then the filter cake was rinsed with ethyl acetate (EtOAc). The filtrate was concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel eluting with 0–100% EtOAc/heptane. The material was dried under vacume to provide the title compound (0.139 g, 45% yield); LC/MS (Table B, Method aa) R_t = 1.04 min; MS m/z : 393 (M+H)⁺; ¹H NMR (400 MHz, dimethylsulfoxide-*d*₆) δ 8.66 (d, J = 35.0 Hz, 1H), 8.49 (d, J = 30.1 Hz, 1H), 8.13 (d, J = 5.5 Hz, 1H), 7.84 (d, J = 39.3 Hz, 1H), 7.73 (s, 1H), 7.48–7.23 (m, 5H), 5.67 – 5.16 (m, 2H), 4.31 – 4.00 (m, 1H), 3.87 (s, 3H), 3.39–3.19 (m, 2H), 2.98 (d, J = 20.7 Hz, 3H).

Example #8: (*S*)-5-((6,7-Dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-3-yl)ethynyl)-*N*-(2-hydroxy-3-phenylpropyl)-*N*-methylnicotinamide



[0163] A reaction vial was charged with (*S*)-5-ethynyl-*N*-(2-hydroxy-3-phenylpropyl)-*N*-methylnicotinamide (Preparation #9) (0.192 g, 0.652 mmol), 3-bromo-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazine (Preparation #5) (0.301 g, 0.652 mmol), K₃PO₄ (0.166 g, 0.783 mmol), bis(tri-*tert*-butylphosphine) palladium (0) (Pd(P-*t*Bu₃)₂) (0.017 g, 0.033 mmol) and tetrahydrofuran (THF) (2.2 mL). The reaction mixture was sparged with N₂ for about 20 minutes then heated to about 50 °C for about 20 hours. The reaction mixture was cooled to room temperature and filtered through a pad of Celite. The filter cake was rinsed with ethyl acetate (EtOAc), and the combined filtrate was concentrated *in vacuo*. The crude isolate was purified via flash chromatography (0%–100% Ethyl acetate (EtOAc) in heptane, then 0 to 5% methanol in EtOAc to furnish the title product (0.12 g, 44 % yield). LC/MS (Table B, Method aa) *R*_t = 1.04 min; MS *m/z*: 417 (M+H)⁺. ¹H NMR (400 MHz, dimethylsulfoxide-*d*₆) (rotamers present) δ: 8.74 – 8.61 (m, 1H), 8.60 – 8.46 (m, 1H), 7.97 – 7.81 (m, 1H), 7.81 – 7.73 (m, 1H), 7.33 – 7.25 (m, 2H), 7.25 – 7.06 (m, 3H), 5.16 – 4.88 (m, 3H), 4.18 – 3.83 (m, 5H), 3.62 – 3.33 (m, 1H), 3.21 – 3.10 (m, 1H), 3.03 – 2.93 (m, 3H), 2.81 – 2.52 (m, 2H).

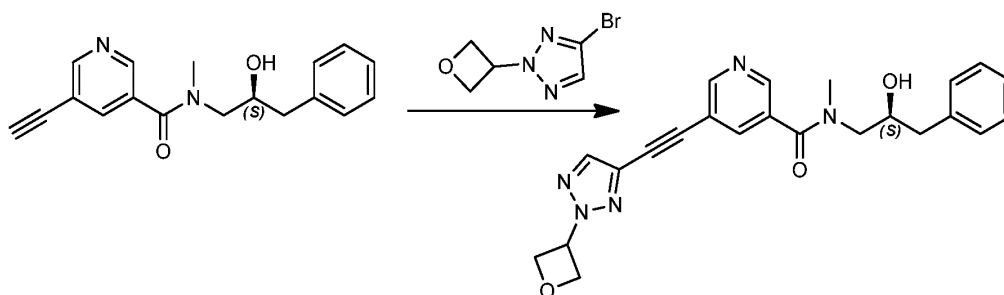
Example #9: (S)-6-(difluoromethyl)-N-(2-hydroxy-3-phenylpropyl)-N-methyl-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)nicotinamide



[0164] (*S*)-5-chloro-6-(difluoromethyl)-*N*-(2-hydroxy-3-phenylpropyl)-*N*-methylnicotinamide (100 mg, 0.28 mmol) (Preparation #6), 4-ethynyl-1-methyl-1*H*-pyrazole (Preparation #10) (30 mg, 0.28 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos) (27 mg, 0.06 mmol), bis(acetonitrile)dichloropalladium (II) (Pd(MeCN)₂Cl₂) (7.31 mg, 0.03 mmol) and Cs₂CO₃ (184 mg, 0.56 mmol) were taken up in acetonitrile (MeCN) (2 mL)

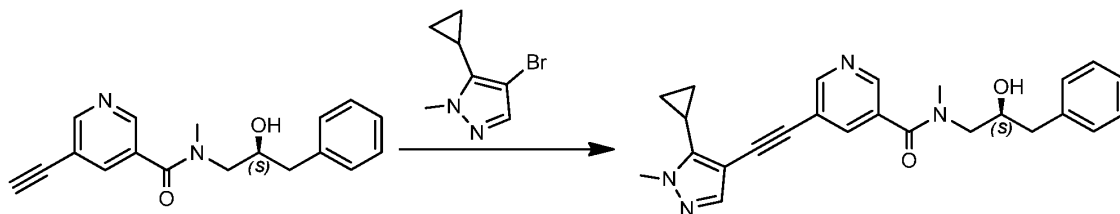
and the reaction mixture was sparged with N₂ for 10 minutes. The resulting mixture was then stirred at about 70 °C for about 3 hours. The reaction was cooled, and the solvents were removed *in vacuo*. The residue was subjected to flash column chromatography on silica gel eluting with 0–10% methanol / dichloromethane (DCM) to provide the title compound (54 mg, 43 % yield). LC/MS (Table B, Method dd) R_t = 1.85 min; MS *m/z*: 425 (M+H)⁺; ¹H NMR (500 MHz, 90 °C, dimethylsulfoxide-*d*₆) δ 8.59 (s, 1H), 8.09 (s, 1H), 7.98 (s, 1H), 7.72 (s, 1H), 7.36 – 6.97 (m, 6H), 4.80 (br s, 1H), 4.04 (s, 1H), 3.90 (br s, 3H), 3.30 (br s, 1H), 3.02 (br s, 4H) 2.71 (br s, 2H).

Example #10: (S)-N-(2-hydroxy-3-phenylpropyl)-N-methyl-5-((2-(oxetan-3-yl)-2H-1,2,3-triazol-4-yl)ethynyl)nicotinamide



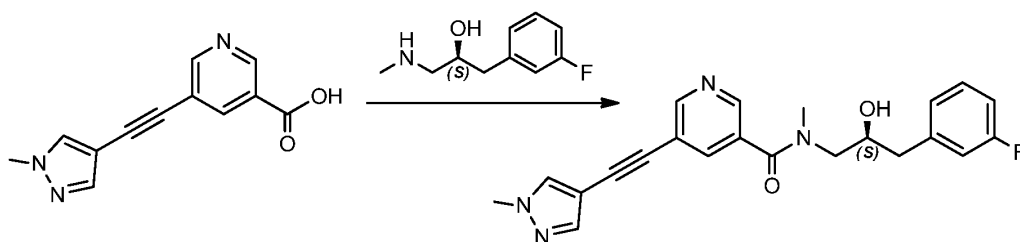
[0165] To a vial was added (S)-5-ethynyl-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide (Preparation #9) (0.120 g, 0.41 mmol), 4-bromo-2-(oxetan-3-yl)-2H-1,2,3-triazole (Preparation #7) (0.125 g, 0.61 mmol), Cs₂CO₃ (0.398 g, 1.22 mmol), bis(acetonitrile)dichloropalladium (II) (Pd(MeCN)₂Cl₂) (5 mg, 0.02 mmol), and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos) (19 mg, 0.04 mmol) and the vial was evacuated and back-filled with N₂ (x 3). To the vial was added acetonitrile (MeCN) (3.2 mL) and the mixture sparged with N₂ for about 5 minutes, then heated to about 70 °C for about 18 hours. The mixture was cooled to room temperature, filtered through Celite and washed with ethyl acetate (EtOAc) (40 mL). The solution was concentrated *in vacuo* and purified twice by flash chromatography on silica gel (0–5% methanol /dichloromethane (DCM)). The solid was triturated with methyl *tert*-butyl ether (MTBE) then dried to provide the title compound (13 mg, 7 % yield); LC/MS (Table B, Method ee) R_t = 1.77 min; MS *m/z* 418 (M+H)⁺; ¹H NMR (500 MHz, dimethylsulfoxide-*d*₆ at 90 °C) δ 8.78 (s, 1H), 8.61 (s, 1H), 8.20 (s, 1H), 7.98 (s, 1H), 7.30 – 7.11 (m, 5H), 5.93 – 5.86 (m, 1H), 5.08 – 5.03 (m, 2H), 5.00 – 4.96 (m, 2H), 4.83 – 4.71 (m, 1H), 4.11 – 3.97 (m, 1H), 3.45 – 3.24 (m, 2H), 3.02 (s, 3H), 2.76 – 2.60 (m, 2H).

Example #11: (S)-5-((5-cyclopropyl-1-methyl-1H-pyrazol-4-yl)ethynyl)-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide



[0166] To a vial was added (S)-5-ethynyl-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide (Preparation #9) (60 mg, 0.20 mmol), 4-bromo-5-cyclopropyl-1-methyl-1H-pyrazole (82 mg, 0.41 mmol), Cs_2CO_3 (199 mg, 0.61 mmol), bis(acetonitrile)dichloropalladium (II) ($\text{Pd}(\text{MeCN})_2\text{Cl}_2$) (5 mg, 0.019 mmol), and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos) (19 mg, 0.04 mmol) and the vial was evacuated and back-filled with N_2 (x 3). To the vial was added acetonitrile (MeCN) (2 mL) and the mixture sparged with N_2 for about 5 min, then heated to about 70 °C for about 4 h. The mixture was filtered through Celite rinsing with Ethyl acetate (EtOAc) (10 mL). The solution was concentrated *in vacuo* and purified via flash chromatography on silica gel (0–100% Ethyl acetate (EtOAc)/isohexane) to provide the title compound (16 mg, 18 % yield); LC/MS (Table B, Method b) R_t = 1.21 min; MS m/z 415 ($\text{M}+\text{H}^+$); ^1H NMR (500 MHz, dimethylsulfoxide- d_6 at 90 °C) δ 8.63 (d, J = 2.0 Hz, 1H), 8.50 (d, J = 2.0 Hz, 1H), 7.80 (d, J = 2.1 Hz, 1H), 7.53 (s, 1H), 7.27 – 7.13 (m, 5H), 4.76 (br s, 1H), 4.08 – 4.02 (m, 1H), 3.86 (s, 3H), 3.44 – 3.35 (m, 2H), 3.01 (s, 3H), 2.67 – 2.62 (m, 2H), 1.97 (ddd, J = 13.8, 8.1, 5.7 Hz, 1H), 1.13 – 1.04 (m, 4H).

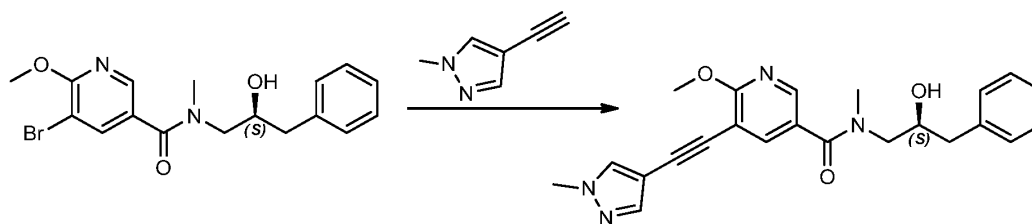
Example #12: (S)-N-(3-(3-fluorophenyl)-2-hydroxypropyl)-N-methyl-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)nicotinamide



[0167] 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouroniumtetrafluoro-borate (TBTU) (127 mg, 0.393 mmol) was added to a solution of (S)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol (Preparation #4) (60 mg, 0.327 mmol), 5-((1-methyl-1H-pyrazol-4-yl)ethynyl)nicotinic acid (Preparation #12) (74.4 mg,

0.327 mmol) and *N,N*-Diisopropylethylamine (DIEA) (0.172 mL, 0.982 mmol) in *N,N*-dimethylformamide (DMF) (2 mL) at room temperature and stirred for about 18 hours. The mixture was diluted with ethyl acetate (EtOAc) (10 mL) and saturated aq. NH_4Cl (10 mL) and the layers were separated. The organic layer was washed with saturated aq. NaCl (3 x 10 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel (0–10% methanol / dichloromethane (DCM)) followed by reverse phase chromatography (15–75% acetonitrile (MeCN) in H_2O (+ 0.1% ammonium bicarbonate)) to provide the title compound (72 mg, 53 % yield); LC/MS (Table B, Method ee) R_t = 1.74 min; MS m/z 393 ($\text{M}+\text{H}^+$). ^1H NMR (500 MHz, dimethylsulfoxide- d_6 at 90 °C) δ 8.66 (d, J = 2.0 Hz, 1H), 8.52 (d, J = 2.0 Hz, 1H), 8.04 (s, 1H), 7.84 (s, 1H), 7.68 (s, 1H), 7.28 (q, J = 7.5 Hz, 1H), 7.04 (s, 2H), 6.99 – 6.94 (m, 1H), 4.82 (br s, 1H), 4.04 (br s, 1H), 3.89 (s, 3H), 3.44 – 3.27 (m, 2H), 3.01 (s, 3H), 2.76 – 2.61 (m, 2H).

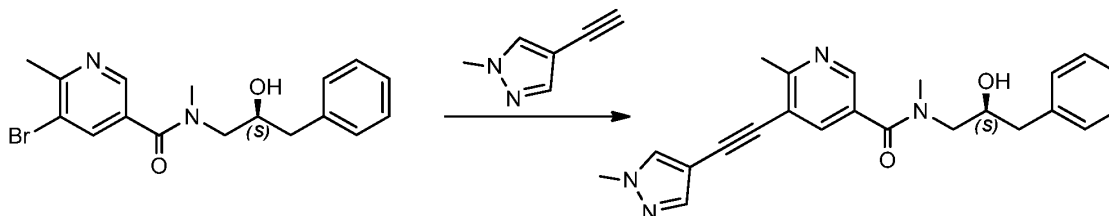
Example #13: (S)-N-(2-hydroxy-3-phenylpropyl)-6-methoxy-N-methyl-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)nicotinamide



[0168] To a flask was added (S)-5-bromo-N-(2-hydroxy-3-phenylpropyl)-6-methoxy-N-methylnicotinamide (Preparation #18) (0.220 g, 0.464 mmol), Cs_2CO_3 (0.189 g, 0.580 mmol), bis(acetonitrile)dichloropalladium (II) ($\text{Pd}(\text{MeCN})_2\text{Cl}_2$) (6 mg, 0.023 mmol), XPhos (0.022 g, 0.046 mmol) and acetonitrile (MeCN) (4 mL). The reaction was sparged with N_2 for 10 minutes and 4-ethynyl-1-methyl-1H-pyrazole (Preparation #10) (0.075 g, 0.707 mmol) in acetonitrile (MeCN) (1 mL) was added. The reaction was then heated to about 75 °C for about 30 minutes. The mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel (0–100% Ethyl acetate (EtOAc)/isohexane) to give a colorless oil. The oil was taken into methanol (1 mL) and acetic acid (AcOH) (0.2 mL) and loaded onto a pad of Strong Cation Exchange (SCX). The pad was washed with methanol (20 mL) followed by 0.7 M NH_3 in methanol (20 mL). The basic solution was concentrated and purified by flash chromatography on silica gel (0–10% methanol / dichloromethane (DCM)) to provide the title compound (25 mg, 13 % yield); LC/MS (Table B, Method b) R_t = 1.86 min; MS m/z 405 ($\text{M}+\text{H}^+$); ^1H NMR (500 MHz, dimethylsulfoxide- d_6 at 90 °C) δ 8.16 (d, J = 2.3 Hz, 1H), 8.00 (s, 1H), 7.78 (d, J = 2.3 Hz, 1H),

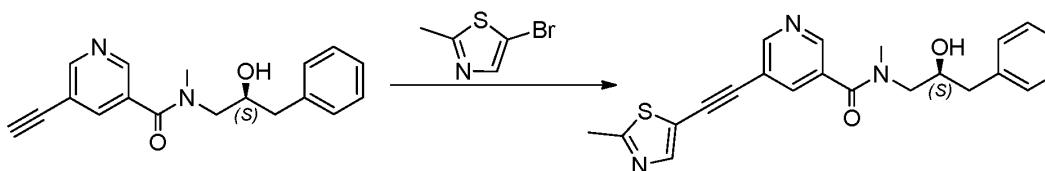
7.64 (s, 1H), 7.28 – 7.12 (m, 5H), 4.71 (d, $J = 5.6$ Hz, 1H), 3.99 (s, 3H), 3.87 (s, 3H), 3.39 (s, 1H), 3.32 (dd, $J = 13.8, 8.4$ Hz, 1H), 3.01 (s, 3H), 2.70 – 2.60 (m, 2H).

Example #14: (S)-N-(2-hydroxy-3-phenylpropyl)-N,6-dimethyl-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)nicotinamide



[0169] (S)-5-bromo-N-(2-hydroxy-3-phenylpropyl)-N,6-dimethylnicotinamide (Preparation #19) (130 mg, 0.358 mmol), 4-ethynyl-1-methyl-1H-pyrazole (Preparation #10) (76 mg, 0.716 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos) (17 mg, 0.036 mmol), bis(acetonitrile) dichloropalladium (II) ($\text{Pd}(\text{MeCN})_2\text{Cl}_2$) (5 mg, 0.018 mmol) and Cs_2CO_3 (140 mg, 0.429 mmol) were taken up in acetonitrile (MeCN) (6 mL) and the mixture was sparged with N_2 for about 10 minutes. The mixture was then stirred at about 70 °C for about 3 hours. The reaction was cooled and filtered through a pad of Celite rinsing with ethyl acetate (EtOAc) (20 mL). The solvents were removed *in vacuo* and the residue was pre-adsorbed onto Celite and purified by flash chromatography on silica gel (0–10% methanol / dichloromethane (DCM)) to provide the title compound (106 mg, 75 % yield); LC/MS (Table B, Method a) $R_t = 1.73$ min; MS m/z 389 ($\text{M}+\text{H}^+$). ^1H NMR (500 MHz, dimethylsulfoxide- d_6 at 90 °C) δ 8.38 (d, $J = 2.1$ Hz, 1H), 8.04 (s, 1H), 7.74 (d, $J = 2.1$ Hz, 1H), 7.67 (s, 1H), 7.27 – 7.13 (m, 5H), 4.81 – 4.61 (m, 1H), 4.08 – 3.97 (m, 1H), 3.88 (s, 3H), 3.49 – 3.23 (m, 2H), 3.00 (s, 3H), 2.71 – 2.66 (m, 2H), 2.64 (s, 3H).

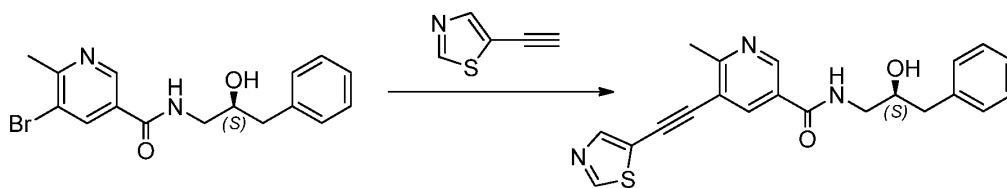
Example #15: (S)-N-(2-hydroxy-3-phenylpropyl)-N-methyl-5-((2-methylthiazol-5-yl)ethynyl) nicotinamide



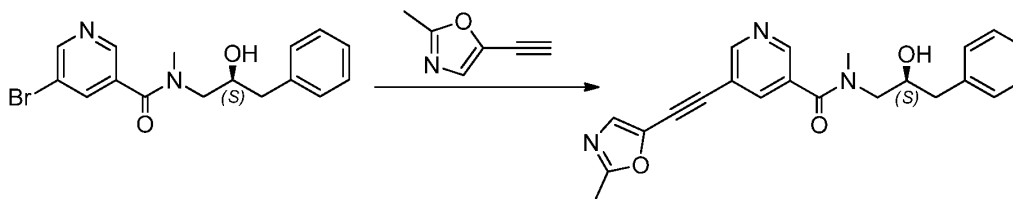
[0170] To a vial was added 5-bromo-2-methylthiazole (181 mg, 1.02 mmol), (S)-5-ethynyl-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide (Preparation # 9) (150 mg, 0.51 mmol)

Cs_2CO_3 (498 mg, 1.53 mmol), bis(acetonitrile)dichloropalladium (II) ($\text{Pd}(\text{MeCN})_2\text{Cl}_2$) (9.3 mg, 0.04 mmol) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos) (24.3 mg, 0.05 mmol) and the vial was evacuated and back-filled with N_2 (x 3). To the vial was added acetonitrile (5 mL) and the mixture sparged with N_2 for about 5 minutes, then heated to about 85 °C for about 3 hours. The mixture was filtered through Celite rinsing with ethyl acetate (EtOAc) (40 mL). The solution was concentrated *in vacuo* and purified by flash chromatography on silica gel (0–5% methanol/dichloromethane (DCM)) to provide a residue which was triturated with methyl *tert*-butyl ether (MTBE) and dried to provide the title compound (50 mg, 24 % yield); LC/MS (Table B, Method ee) R_t = 1.89 min; MS m/z 392 ($\text{M}+\text{H}$)⁺; ^1H NMR (500 MHz, dimethylsulfoxide- d_6 at 90 °C) δ 8.73 (s, 1H), 8.57 (s, 1H), 7.96 (s, 1H), 7.92 (s, 1H), 7.30 – 7.10 (m, 5H), 4.82 – 4.70 (broad m, 1H), 4.10 – 3.95 (broad m, 1H), 3.51 – 3.21 (broad m, 2H), 3.01 (s, 3H), 2.71 (s, 3H), 2.73 – 2.58 (broad m, 2H).

Example #16: (S)-N-(2-hydroxy-3-phenylpropyl)-6-methyl-5-(thiazol-5-ylethynyl)nicotinamide

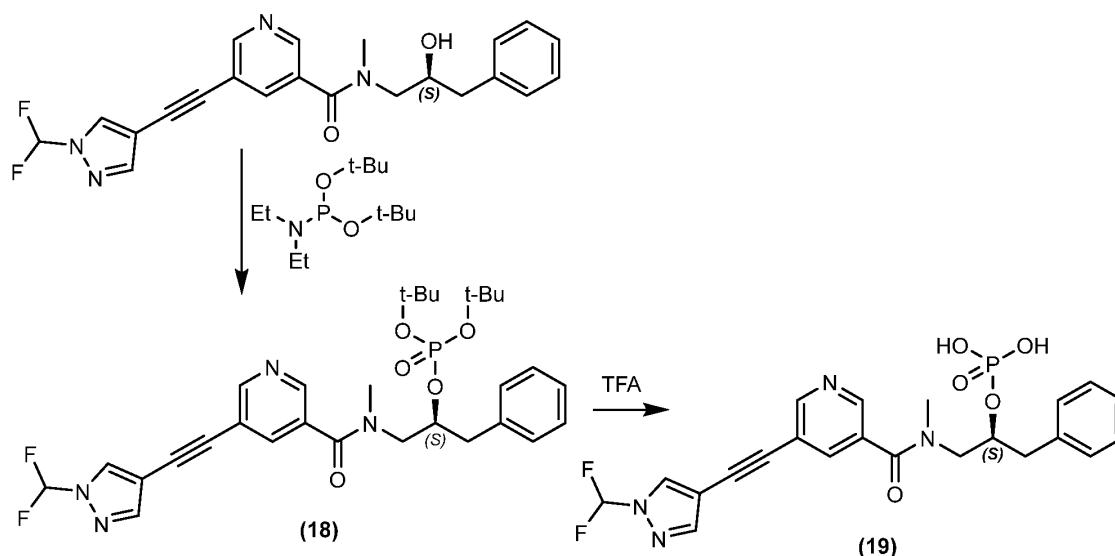


[0171] To a vial was charged 5-ethynylthiazole (30.6 mg, 0.28 mmol), (S)-5-bromo-N-(2-hydroxy-3-phenylpropyl)-6-methylnicotinamide (Preparation #20) (70 mg, 0.20 mmol) and CuI (7.6 mg, 0.04 mmol) and the vial was evacuated and back-filled with N_2 (x 3). *N,N*-Dimethylformamide (DMF) (3 mL) and Et_3N (498 mg, 1.53 mmol) were added and the reaction mixture was sparged with N_2 for about 15 minutes. Bis(triphenylphosphine)palladium (II) dichloride ($\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$) (16.9 mg, 0.02 mmol) was added and the reaction mixture was heated to about 90 °C for about 18 hours. The mixture was filtered through Celite rinsing with ethyl acetate (EtOAc) (10 mL). The solution was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (0–10% methanol/dichloromethane (DCM)) to provide the title compound (17 mg, 21 % yield); LC/MS (Table B, Method ee) R_t = 2.03 min; MS m/z 378 ($\text{M}+\text{H}$)⁺; ^1H NMR (500 MHz, dimethylsulfoxide- d_6) δ 9.23 (s, 1H), 8.88 (d, J = 2.3 Hz, 1H), 8.64 (t, J = 5.7 Hz, 1H), 8.33 (d, J = 2.3 Hz, 1H), 8.31 (s, 1H), 7.31 – 7.21 (m, 4H), 7.21 – 7.14 (m, 1H), 4.92 (d, J = 5.4 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.38 – 3.29 (m, 1H), 3.25 – 3.18 (m, 1H), 2.76 (dd, J = 13.6, 5.0 Hz, 1H), 2.69 (s, 3H), 2.65 (dd, J = 13.7, 7.6 Hz, 1H).

Example #17: (S)-N-(2-hydroxy-3-phenylpropyl)-N-methyl-5-((2-methyloxazol-5-yl)ethynyl)nicotinamide

[0172] (S)-5-bromo-N-(2-hydroxy-3-phenylpropyl)-6-methylnicotinamide (Preparation # 20) (318 mg, 0.91 mmol) Cs_2CO_3 (365 mg, 1.1 mmol), bis(acetonitrile)dichloropalladium (II) ($\text{Pd}(\text{MeCN})_2\text{Cl}_2$) (12 mg, 0.05 mmol) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos) (43 mg, 0.09 mmol) were taken up in MeCN (9 mL) and a solution of 5-ethynyl-2-methyloxazole (Preparation #21) (0.19 g, 0.91 mmol) in MeCN (1 mL) was added. The reaction mixture was sparged with N_2 for about 5 min and then heated to about 60 °C for about 3 hours. The mixture was filtered through Celite, solvents were concentrated *in vacuo* and the resulting residue was purified by flash chromatography on silica gel (0–10% MeOH/DCM) to provide the title compound (25 mg, 7 %); LC/MS (Table B, Method ee) R_t = 1.92 min; MS m/z 376 ($\text{M}+\text{H}^+$); ^1H NMR (500 MHz, dimethylsulfoxide- d_6 at 90 °C) δ 8.79 – 8.72 (m, 1H), 8.59 (d, J = 2.1 Hz, 1H), 7.94 (s, 1H), 7.49 (s, 1H), 7.21 (dt, J = 31.1, 7.3 Hz, 5H), 4.76 (br s, 1H), 4.02 (br s, 1H), 3.30 (br s, 2H), 3.01 (s, 3H), 2.64 (d, J = 9.1 Hz, 2H), 2.48 (s, 3H).

Examples #18 and 19: (S)-di-tert-butyl (1-(5-((1-(difluoromethyl)-1H-pyrazol-4-yl)ethynyl)-N-methylnicotinamido)-3-phenylpropan-2-yl) phosphate (Example #18) and (S)-1-(5-((1-(difluoromethyl)-1H-pyrazol-4-yl)ethynyl)-N-methylnicotinamido)-3-phenylpropan-2-yl dihydrogen phosphate (Example #19)

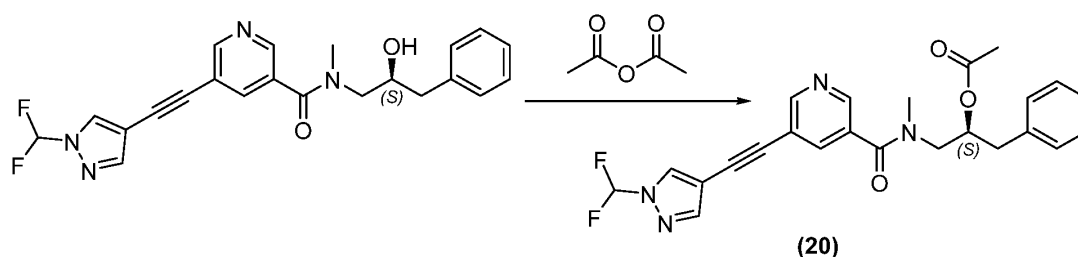


[0173] To a solution of (S)-5-((1-(difluoromethyl)-1H-pyrazol-4-yl)ethynyl)-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide (Example #2) (500 mg, 1.22 mmol) in *N*-Methyl-2-pyrrolidinone (1000 mL) was added di-tert-butyl diethylphosphoramidite (304 mg, 1.22 mmol) and 1*H*-tetrazole (10.8 mL, 4.87 mmol) in one portion at 20 °C under N₂. The mixture was stirred at 40 °C for 3 hours. Hydrogen peroxide (5.0 mL, 49 mmol) was added to the solution at 0 °C, and the mixture was stirred for an additional 2 hours. The mixture was poured into saturated Na₂SO₃ (75 mL) and extracted with ethyl acetate (EtOAc) (3 × 100 mL). The organic phase was washed with brine (100 mL), dried over Na₂SO₄, concentrated under reduced pressure to give the crude *t*-butyl phosphate ester, which was chromatographed on silica gel (petroleum ether: ethyl acetate=1:1-1:4) to provide (S)-di-tert-butyl (1-(5-((1-(difluoromethyl)-1H-pyrazol-4-yl)ethynyl)-N-methylnicotinamido)-3-phenylpropan-2-yl) phosphate (**Example #18**) (384 mg, 0.64 mmol, 52% yield). LC/MS (Table B, Method aa) *R*_t = 1.73 min; MS *m/z*: 545.20 (M-*t*Bu)⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.76 – 8.40 (m, 3H), 8.15 – 7.60 (m, 3H), 7.27-7.01 (m, 5H), 4.78-4.46 (br m, 1H), 3.75-2.72 (m, 7H), 1.50-1.18 (m, 18H). *t*Bu = *tert*-butyl; Et = ethyl.

[0174] A flask was charged with (S)-di-tert-butyl (1-(5-((1-(difluoromethyl)-1H-pyrazol-4-yl)ethynyl)-N-methylnicotinamido)-3-phenylpropan-2-yl) phosphate (**Example #18**) (381 mg, .632 mmol), dichloromethane (DCM) (5 mL) and trifluoroacetic acid (TFA) (0.61 mL, 7.9 mmol) and stirred at room temperature for approximately 19 hours. The mixture was concentrated under reduced pressure, then purified via reverse phase liquid chromatography (Atlantis® Prep T3 Phenomenex 5 μm 19 x 50 mm column, 5 to 95 acetonitrile (MeCN):water (formic acid buffer) at 1 mL/minute) to provide the title compound, **Example #19** (230 mg, 0.47 mmol, 74% yield). LC/MS (Table B, Method ff) *R*_t = 1.96 min; MS *m/z*: 491.0 (M+H)⁺; ¹H NMR (400 MHz,

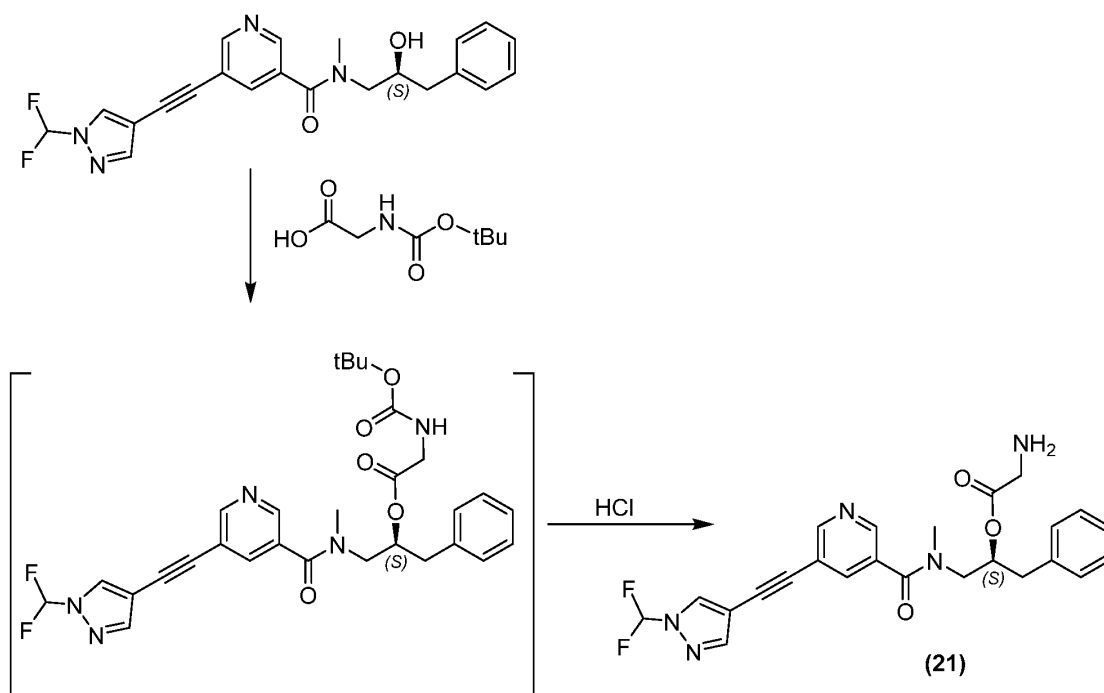
DMSO-*d*₆) δ 8.78 – 8.69 (m, 1H), 8.65 – 8.57 (m, 1H), 8.44 (d, *J* = 1.0 Hz, 1H), 8.14 – 8.08 (m, 1H), 8.03 – 7.99 (m, 1H), 7.97 (s, 1H), 7.88 – 7.84 (m, 1H), 7.76 (s, 1H), 7.73 – 7.69 (m, 1H), 7.35 – 7.28 (m, 2H), 7.27 – 7.21 (m, 1H), 7.19 – 7.12 (m, 1H), 7.03 (br d, *J* = 7.5 Hz, 1H), 4.80 – 4.73 (m, 1H), 4.52 – 4.45 (m, 1H), 3.84 – 3.76 (m, 1H), 3.66 (br d, *J* = 13.5 Hz, 1H), 3.33 (br dd, *J* = 9.5, 13.5 Hz, 1H), 3.27 – 3.11 (m, 1H), 3.08 – 3.00 (m, 1H), 2.97 (s, 1H), 2.95 (br s, 1H), 2.92 (s, 2H), 2.90 – 2.85 (m, 1H), 2.79 – 2.69 (m, 1H), 2.07 (s, 1H), 1.78 (s, 1H), 1.74 (s, 1H).

Example #20: **(*S*)-1-(5-((1-(difluoromethyl)-1H-pyrazol-4-yl)ethynyl)-N-methylnicotinamido)-3-phenylpropan-2-yl acetate**



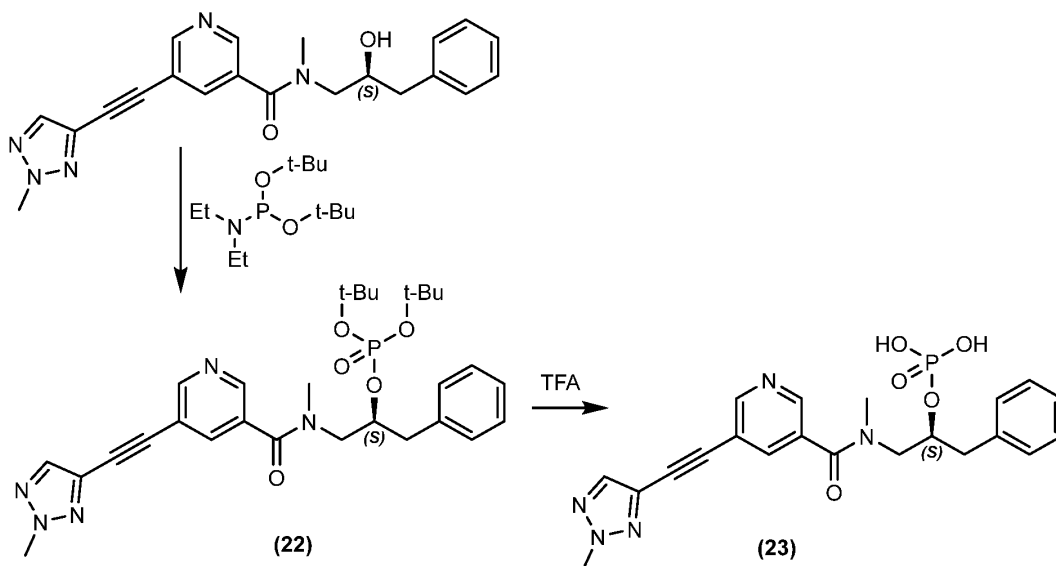
[0175] To a solution of (*S*)-5-((1-(difluoromethyl)-1H-pyrazol-4-yl)ethynyl)-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide (Example #2) (2.00 g, 4.87 mmol) in 20 mL of dichloromethane was added triethylamine (2.38 mL, 17.1 mmol), acetic anhydride (1.0 mL, 11 mmol) and 4-dimethylaminopyridine (0.095 g, 0.78 mmol). The mixture was stirred at 20 °C for 2 hours. After this time, the mixture was poured into saturated ammonium chloride. The organic phase was extracted with brine (50 mL), dried over sodium sulfate, and concentrated. The resultant residue was purified by preparative HPLC (Table B, Method c) to provide the title compound (1.0 g, 2.1 mmol, 44% yield). ¹H NMR (400 MHz, chloroform-*d*) δ = 8.74 (br s, 1H), 8.54 (s, 1H), 8.06 (s, 1H), 7.82 (s, 1H), 7.75 (br s, 1H), 7.38 – 7.28 (m, 2H), 7.24 – 7.03 (m, 3H), 5.58 – 5.21 (m, 1H), 4.02 – 3.89 (m, 1H), 3.64 – 3.55 (m, 1H), 3.54 – 3.45 (m, 1H), 3.40 – 3.26 (m, 1H), 3.13 – 2.93 (m, 5H), 2.89 – 2.78 (m, 1H), 2.69 – 2.53 (m, 1H), 2.14 – 1.99 (m, 3H).

Example #21: **(*S*)-1-(5-((1-(difluoromethyl)-1H-pyrazol-4-yl)ethynyl)-N-methylnicotinamido)-3-phenylpropan-2-yl 2-aminoacetate, hydrochloric acid**



[0176] To a solution of 2-((tert-butoxycarbonyl)amino)acetic acid (0.854 g, 4.87 mmol) in 5.0 mL of acetonitrile was added (S)-5-((1-(difluoromethyl)-1H-pyrazol-3-yl)ethynyl)-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide (Example #2) (2.0 g, 4.9 mmol), *N,N*-dicyclohexylcarbodiimide (DCC) (1.05 g, 5.08 mmol) and 4-dimethylaminopyridine (DMAP) (0.015 g, 0.12 mmol). The mixture was stirred at 20 °C for 12 hours. After this time, the reaction mixture was filtered and the filtrate was concentrated in vacuo to give a crude intermediate, (S)-1-(5-((1-(difluoromethyl)-1H-pyrazol-4-yl)ethynyl)-N-methylnicotinamido)-3-phenylpropan-2-yl (tert-butoxycarbonyl)glycinate (2.4 g, 4.2 mmol), which was then dissolved in ethyl acetate (15 mL). Hydrogen chloride solution in ethyl acetate (4M, 20 mL) was added, and the reaction mixture was stirred at 20°C for 30 minutes. After this time, the mixture was concentrated under pressure to give a residue, which was purified by preparative HPLC (Table B, Method c; R_t = 2,13 min) to provide the title compound (1.2 g, 2.3 mmol, 54% yield). ^1H NMR (400 MHz, dimethylsulfoxide- d_6) δ = 8.88 – 8.70 (m, 2H), 8.61 (d, J = 1.5 Hz, 1H), 8.57 – 8.42 (m, 3H), 8.19 – 8.09 (m, 1H), 8.09 – 7.74 (m, 2H), 7.37 – 7.29 (m, 3H), 7.28 – 7.15 (m, 2H), 7.08 (br d, J = 6.5 Hz, 1H), 5.54 – 5.17 (m, 1H), 3.86 – 3.62 (m, 2H), 3.70 – 3.62 (m, 1H), 3.52 – 3.38 (m, 1H), 3.09 – 3.00 (m, 1H), 2.99 (s, 1H), 2.96 (s, 2H), 2.95 – 2.89 (m, 1H), 2.82 – 2.66 (m, 1H). tBu = tert-butyl.

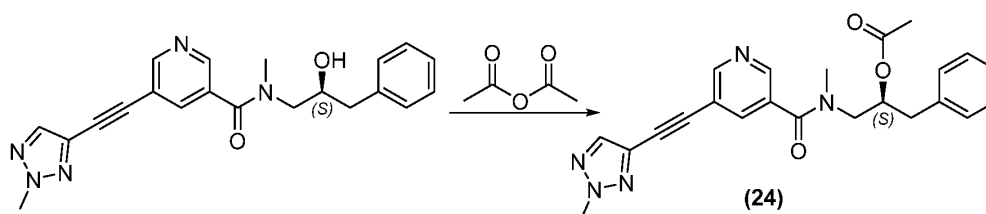
Examples #22 and #23: (*S*)-di-*tert*-butyl (1-(*N*-methyl-5-((2-methyl-5-*2H*-1,2,3-triazol-4-yl)ethynyl)nicotinamido)-3-phenylpropan-2-yl) phosphate (Example #22) and (*S*) (1-(*N*-methyl-5-((2-methyl-2*H*-1,2,3-triazol-4-yl)ethynyl)nicotinamido)-3-phenylpropan-2-yl) dihydrogen phosphate (Example #23)



[0177] To a solution of (*S*)-*N*-(2-hydroxy-3-phenylpropyl)-*N*-methyl-5-((2-methyl-2*H*-1,2,3-triazol-4-yl)ethynyl)nicotinamide (Example #3) (2.00 g, 5.33 mmol) in 40 mL of *N*-methylpyrrolidine was added di-*tert*-butyl diethylphosphoramidite (20.0 mL, 5.33 mmol) and 1*H*-tetrazole (1.493 g, 21.31 mmol) in one portion at 20 °C under nitrogen, and stirred for 2 hours. After this time, hydrogen peroxide (20.0 mL, 555 mmol) was added to the solution at 0°C. The mixture was stirred at 20 °C for 1 hour, and an aliquot was removed and analyzed by LC-MS. LC-MS showed that the starting material was completely consumed and the desired product (phosphate ester) was detected. The resulting mixture was quenched by addition of 20 mL of sodium sulfite at 10°C, and then stirred for 30 minutes. The mixture was poured into ice water, then saturated sodium sulfite solution was added until pH=7. Ethyl acetate (200 mL) was added to the mixture, the mixture was agitated, and the layers were separated. This process was repeated three times. The organic layer was concentrated and the crude (*S*)-di-*tert*-butyl (1-(*N*-methyl-5-((2-methyl-2*H*-1,2,3-triazol-4-yl)ethynyl)nicotinamido)-3-phenylpropan-2-yl) phosphate (**Example #22**) was used in the next step without further purification. tBu = *tert*-butyl; Et = ethyl.

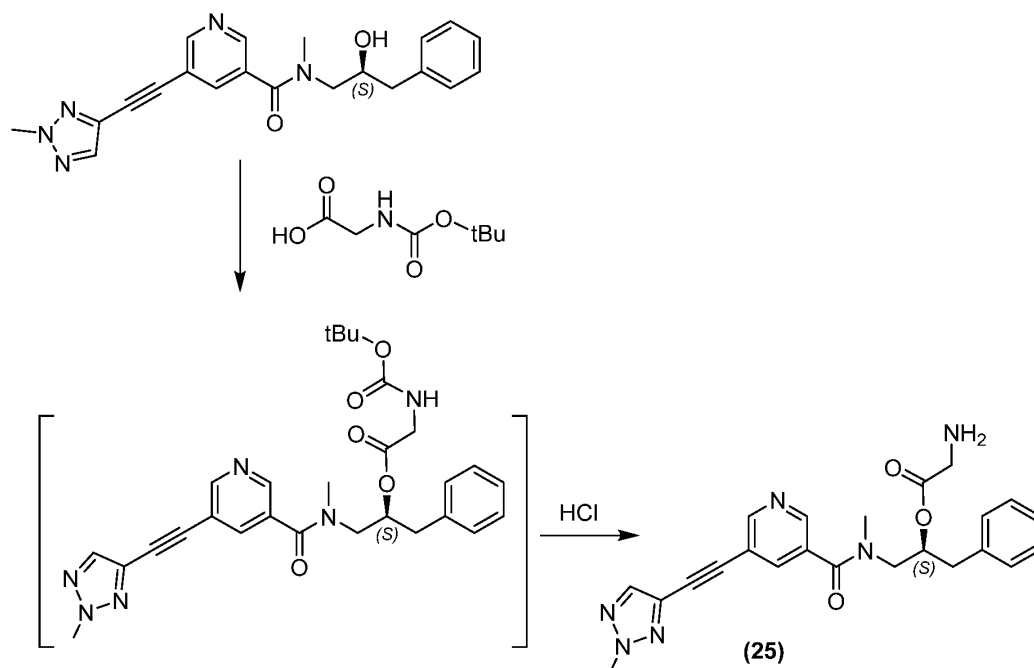
[0178] To a solution of (*S*)-di-*tert*-butyl (1-(*N*-methyl-5-((2-methyl-2*H*-1,2,3-triazol-4-yl)ethynyl)nicotinamido)-3-phenylpropan-2-yl) phosphate (**Example #22**) (2 g, 3.52 mmol) in 15 mL of dichloromethane was added trifluoroacetic acid (TFA) (5 mL, 64.9 mmol) at 20 °C under nitrogen. The mixture was stirred for 2 hours. After this time, the reaction was concentrated and purified by reverse phase column chromatography (Table B, Method d) to provide the title compound (**Example #23**) (930 mg, 2.00 mmol, 56.8% yield). ¹H NMR (400 MHz, dimethylsulfoxide-*d*₆) δ 8.45–8.83 (m, 2H), 7.80–8.17 (m, 2H), 7.21–7.35 (m, 3H), 7.00–7.19 (m, 2H), 4.43–4.82 (m, 1H), 4.17–4.29 (m, 3H), 3.31–3.70 (m, 1H), 2.72–3.26 (m, 6H).

Example #24: (*S*)-1-(*N*-methyl-5-((2-methyl-2*H*-1,2,3-triazol-4-yl)ethynyl)nicotinamido)-3-phenylpropan-2-yl acetate



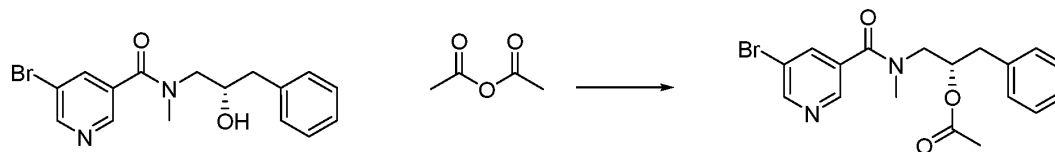
[0179] To a solution of (*S*)-*N*-(2-hydroxy-3-phenylpropyl)-*N*-methyl-5-((2-methyl-2*H*-1,2,3-triazol-4-yl)ethynyl)nicotinamide (**Example #3**) (1.50 g, 4.00 mmol) in 30 mL of dichloromethane was added triethylamine (1.89 mL, 13.6 mmol) and acetic anhydride (0.857 g, 8.39 mmol) in one portion at 20 °C under nitrogen. The mixture was stirred at 20 °C for 12 hours. After this time, the reaction was quenched with 50 mL of water. The organic and aqueous layers were separated, and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated and the product was isolated by flash chromatography (20-50% EtOAc/hexanes) to provide the title compound (1.20 g, 2.86 mmol, 71.6 % yield). ¹H NMR (400 MHz, dimethylsulfoxide-*d*₆) δ 8.79 (s, 1H), 8.55 (d, *J*=1.75 Hz, 1H), 8.06 (s, 1H), 7.90 (s, 1H), 7.10–7.34 (m, 5H), 5.24–5.42 (m, 1H), 4.21 (s, 3H), 3.47–3.70 (m, 2H), 2.97 (s, 3H), 2.76–2.95 (m, 2H), 1.96 (s, 3H).

Example #25: **(S)-1-(N-methyl-5-((2-methyl-2H-1,2,3-triazol-4-yl)ethynyl)nicotinamido)-3-phenylpropan-2-yl 2-aminoacetate, hydrochloric acid**

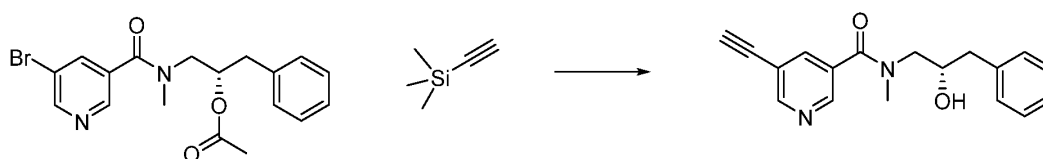


[0180] To a stirring solution of 2-((tert-butoxycarbonyl)amino)acetic acid (0.933 g, 5.33 mmol) in 5.0 mL of acetonitrile at 25 °C was added ((S)-N-(2-hydroxy-3-phenylpropyl)-N-methyl-5-((2-methyl-2H-1,2,3-triazol-4-yl)ethynyl)nicotinamide (Example #3) (2.00 g, 5.33 mmol). *N,N'*-dicyclohexylcarbodiimide (DCC) (1.37 g, 6.66 mmol) was added, followed by slow addition of a 5.3 mL acetonitrile solution of 4-dimethylaminopyridine (DMAP) (0.020 g, 0.16 mmol), keeping the reaction temperature between 20–25 °C. The suspension was stirred for 2 hours at 25 °C. After this time, the reaction mixture was filtered. The filtrate was concentrated and the resulting residue was purified by flash chromatography on silica gel (petroleum ether: ethyl acetate = 4:1~1:1) to give the crude intermediate, (S)-1-(N-methyl-5-((2-methyl-2H-1,2,3-triazol-4-yl)ethynyl)nicotinamido)-3-phenylpropan-2-yl 2-((tert-butoxycarbonyl)amino)acetate (2.2 g, 3.9 mmol, 74% yield), which was then dissolved in ethyl acetate (10 mL). Hydrogen chloride solution in ethyl acetate (4M, 20 mL, 80 mmol) was added to the solution, and the mixture was stirred for 1 hour at 25 °C. The resulting suspension was dried under vacuum to provide the title compound (1.38 g, 2.85 mmol, 69.1 % yield). ¹H NMR (400 MHz, dimethylsulfoxide-*d*₆) δ 8.80 (s, 1H), 8.60 (br s, 1H), 8.47 (br s, 3H), 8.08 (s, 1H), 7.97 (br s, 1H), 7.16–7.35 (m, 5H), 5.25–5.57 (m, 1H), 4.63 (br s, 6H), 4.21 (s, 3H), 3.65–3.79 (m, 3H), 2.80–3.06 (m, 5H). tBu = tert-butyl.

[0181] Example #26: (S)-5-((1-(difluoromethyl)-5-methyl-1H-pyrazol-4-yl)ethynyl)-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide

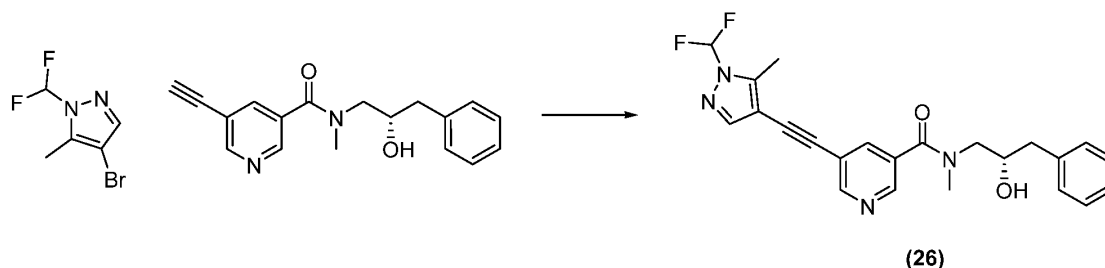


[0182] (S)-5-Bromo-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide (15 g, 43.0 mmol) (preparation #8), N,N-dimethylpyridin-4-amine (0.525 g, 4.30 mmol) and pyridine (17.37 mL, 215 mmol) were combined in dichloromethane (DCM) (150 mL) at about room temperature. Acetic anhydride (5.26 g, 51.5 mmol) was added dropwise. After about 4h methyl tertbutyl ether (MTBE) (300 mL) and saturated copper sulfate (200 mL) were added, the organics were separated and washed with water (2 x 100mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to provide (S)-1-(5-bromo-N-methylnicotinamido)-3-phenylpropan-2-yl acetate (16.8 g, 43.0 mmol, 100% yield) as an oil. LC/MS (Method aa) *R_t* = 1.31 min.; MS *m/z*: 391.18, 393.16 (M+H)⁺.



[0183] (S)-1-(5-bromo-N-methylnicotinamido)-3-phenylpropan-2-yl acetate (12.8 g, 32.7 mmol), ethynyltrimethylsilane (9.64 g, 98 mmol), diisopropylamine (9.33 mL, 65.4 mmol) were combined in dimethyl formamide (DMF) (60 mL) at about room temperature. 3A mole sieves were added. After about 2h copper(I) iodide (0.062 g, 0.327 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.230 g, 0.327 mmol) were added. The reaction mixture was warmed to about 80°C. After about 6h, the mixture was cooled to room temperature. Saturated NaHCO₃ (100 mL) and methyl tertbutyl ether (MTBE) (100 mL) and cysteine (2g) were added and the reaction mixture was stirred at about room temperature. After about 4h the mixture was filtered through celite, and the organics were separated, washed with brine (50 mL) and concentrated *in vacuo*. The crude alkyne was dissolved in methanol (MeOH) (100 mL) at about room temperature, and potassium carbonate (9.04 g, 65.4 mmol) was added. After about 4h the mixture was partially concentrated *in vacuo*. Methyltertbutyl ether and ethyl acetate (MTBE/EtOAc) (1:1) (100 mL) and water (50 mL) were added. The organics were separated, concentrated *in vacuo* and purified by flash chromatography on silica gel (SiO₂) (EtOAc/Hep) to provide (S)-5-ethynyl-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide

(6.8 g, 23.10 mmol, 70.6 % yield) as an oil. HPLC method aa: R_t = 0.94 min.; MS m/z : 295.3 (M+H)⁺.



[0184] (S)-5-ethynyl-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide (6.8 g, 23.10 mmol), 4-bromo-1-(difluoromethyl)-5-methyl-1H-pyrazole (5.36 g, 25.4 mmol), diisopropylamine (6.59 mL, 46.2 mmol), copper(I) iodide (0.044 g, 0.231 mmol) and methanesulfonato(2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (0.196 g, 0.231 mmol) were combined in dimethyl formamide (DMF) (70 mL). The reaction mixture was sparged with nitrogen. After 10 min the rxn mixture was heated to 80°C. After 4h cooled to room temperature. The mixture was diluted with methyltertbutyl ether and ethyl acetate (MTBE/EtOAc) (1:1) (20 mL) and water (20 mL), and cysteine (500 mg) was added. After stirring for 4h, the organics were filtered and separated, washed with brine (10 mL), concentrated *in vacuo* and purified by flash chromatography on silica gel (SiO₂) (EtOAc/Hep). The product fractions were combined and concentrated *in vacuo*. The residue was dissolved in methyltertbutyl ether MTBE (20 mL) and heptane was added until the solution was cloudy. After stirring for 20h, the solids were collected and dried *in vacuo* to provide (S)-5-((1-(difluoromethyl)-5-methyl-1H-pyrazol-4-yl)ethynyl)-N-(2-hydroxy-3-phenylpropyl)-N-methylnicotinamide (5.8 g, 13.66 mmol, 59.2 % yield) as a white solid. HPLC method aa: R_t = 1.28 min.; MS m/z : 425.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.77 – 8.65 (m, 1H), 8.58 – 8.47 (m, 1H), 8.01 – 7.67 (m, 2H), 7.30 – 7.04 (m, 6H), 5.10 – 4.90 (m, 1H), 4.09 – 3.81 (m, 1H), 3.59 – 3.29 (m, 1H), 3.16 – 3.07 (m, 1H), 2.99 – 2.91 (m, 4H), 2.78 – 2.59 (m, 1H), 2.56 – 2.51 (m, 3H).

Assays and Activity Data

RIPK1 Binding Assay

[0185] Compounds were tested for their ability to displace a fluorescent probe from recombinant human RIPK1. Test compound RIPK1 binding (IC₅₀) data is provided in Table C.

[0186] Recombinant human RIPK1 (1–375) was prepared as described in Harris *et al.*, *ACS Med. Chem. Letters* (2013) 4:1238–1243 (Supplementary Information), with the following

exceptions: (i) instead of using the gene sequence from NM_003804.3, the gene was synthesized with codon optimization for BEV expression system, and (ii) the gene was cloned into the vector pFastBac1, not pDEST8.

[0187] A fluorescent probe containing an Oregon green fluorophore was synthesized from a compound known to bind to RIPK1.

[0188] The assay was performed in a buffer containing 50 mM *N*-2-Hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid (HEPES) (pH 7.5), 10 mM MgCl₂, 1 mM ethylene diamine tetraacetic acid (EDTA), and 0.01% BRIJ-35 (Polyoxyethylene (23) lauryl ether). Test compounds were solvated in dimethyl sulfoxide (DMSO) at final concentrations 4-fold serially diluted from 100 to 0.000095 uM in technical duplicates into an empty 384 well plate. Recombinant RIPK1 (final concentration of 2.5 nM) was added to the wells and incubated with test compound for 1 hour at room temperature. A solution containing the fluorescent probe (final concentration 5 nM) and an LanthaScreen Tb-anti-GST antibody (ThermoFisher Scientific; final concentration of 5 nM) was then added to each well, with the Tb-anti-GST antibody binding to the GST portion of the recombinant RIPK1 and providing the corresponding FRET pair to the fluorescent probe. The plate was incubated for 1 hour at room temperature and read on an Envision plate reader using a time resolved FRET protocol. Data was normalized and analyzed using Studies from Dotmatics.

U937 TNF/zVAD Cytotoxicity Cell Assay

[0189] Compounds were tested for their ability to prevent TNF induced necroptosis in U937 cells. Treatment with TNF and the caspase inhibitor zVAD-FMK results in the activation and phosphorylation of RIPK1 and subsequent phosphorylation of RIPK3 and MLKL (Mixed Lineage Kinase Domain Like Pseudokinase), leading to induction of necroptotic cell death that is measured as a reduction in cell viability. U937 TNF/zVAD induced cytotoxicity (IC₅₀) data, indicative of a test compound's ability to inhibit RIPK1, is provided in Table C. Similar U937 assay protocols have been previously described; see, *e.g.*, Harris *et al.*, *ACS Med. Chem. Letters* (2013) 4:1238–1243 and Supplementary Information.

[0190] Test compounds were solvated in dimethyl sulfoxide (DMSO) and 3-fold serially diluted from 10 uM to 0.0005 uM with technical duplicates into an empty 384 well plate. U937 cells were resuspended at a concentration of 500,000 cells/mL in fresh RPMI (Roswell Park Memorial Institute) 1640 growth medium containing 10% heat inactivated fetal bovine serum (FBS) and seeded into a 384 well plate containing compounds and incubated for 1 hour at 37 °C.

Following incubation, the cells were challenged with TNF α (final concentration of 10 ng/mL) and Z-VAD FMK (N-Benzyloxycarbonyl-Val-Ala-Asp(O-Me) fluoromethyl ketone; final concentration of 20 μ M) for 16–20 hours at 37 °C. Following the incubation with TNF α /Z-VAD, cells were lysed with Cell Titer-Glo and incubated for 5–10 minutes. The plate was then read on an Envision plate reader. Data was normalized and analyzed with Studies from Dotmatics.

Table C.		
Example	RIPK1 Binding IC₅₀ (μM)	U937 TNF/zVAD Induced Cytotoxicity IC₅₀ (μM)
1	0.011	0.034
2	0.004	0.011
3	0.036	0.196
4	0.030	0.199
5	0.014	0.049
6	0.003	0.006
7	0.007	0.009
8	0.006	0.013
9	0.018	0.029
10	0.043	0.380
11	0.002	0.005
12	0.013	0.020
13	0.095	0.382
14	0.008	0.018
15	25	--
16	0.515	2.580
17	0.032	0.146
26	0.0018	0.003

Selectivity Data

[0191] Compounds were tested in a screening platform for their ability to bind to hundreds of human kinases and disease-relevant mutant variants thereof. Binding affinities are provided in Table D.

[0192] **The Method.** The screening method uses an immobilized ligand on a solid support, a DNA-tagged kinase, and a test compound. Test compounds that bind the kinase active site and directly (sterically) or indirectly (allosterically) prevent kinase binding to an immobilized ligand on a solid support will reduce the amount of kinase captured on the solid support. Conversely, test compound that do not bind the kinase have no effect on the amount of kinase captured on the solid support. Screening "hits" are identified by measuring the amount of kinase captured in test compound versus control samples by using a quantitative, precise and ultra-sensitive qPCR method that detects the DNA label associated with the kinase. In a similar manner, dissociation constants (K_d) for test compound-kinase interactions are calculated by measuring the amount of kinase captured on the solid support as a function of the test compound concentration.

[0193] **Kinase assays.** For most assays, kinase-tagged T7 phage strains were grown in parallel in 24-well blocks in an *E. coli* host derived from the BL21 strain. *E. coli* were grown to log-phase and infected with T7 phage from a frozen stock (multiplicity of infection = 0.4) and incubated with shaking at 32°C until lysis (90-150 minutes). The lysates were centrifuged (6,000 x g) and filtered (0.2µm) to remove cell debris. The remaining kinases were produced in HEK-293 cells and subsequently tagged with DNA for qPCR detection. Streptavidin-coated magnetic beads were treated with biotinylated small molecule ligands for 30 minutes at room temperature to generate affinity resins for kinase assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1 % BSA, 0.05 % Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific phage binding. Binding reactions were assembled by combining kinases, liganded affinity beads, and test compounds in 1x binding buffer (20 % SeaBlock, 0.17x PBS, 0.05 % Tween 20, 6 mM DTT). Test compounds were prepared as 40x stocks in 100% DMSO and directly diluted into the assay. All reactions were performed in polypropylene 384-well plates in a final volume of 0.02 mL. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05 % Tween 20). The beads were then re-suspended in elution buffer (1x PBS, 0.05 % Tween 20, 0.5 µM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The kinase concentration in the eluates was measured by qPCR.

[0194] **Percent Control calculation.** The compounds were screened at 100 nM concentration, and results for the binding interactions are shown below in Table D as percent control, where lower numbers indicate stronger hits. The calculation for percent control is shown

below. The negative control was DMSO (100% control), and a control compound was used as positive control (0% control).

$$\left(\frac{\text{test compound signal} - \text{positive control signal}}{\text{negative control signal} - \text{positive control signal}} \right) \times 100$$

Table D.

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
AAK1	96	100
ABL1(E255K)-phosphorylated	86	91
ABL1(F317I)-nonphosphorylated	100	100
ABL1(F317I)-phosphorylated	100	98
ABL1(F317L)-nonphosphorylated	100	100
ABL1(F317L)-phosphorylated	82	88
ABL1(H396P)-nonphosphorylated	88	96
ABL1(H396P)-phosphorylated	94	93
ABL1(M351T)-phosphorylated	86	97
ABL1(Q252H)-nonphosphorylated	92	100
ABL1(Q252H)-phosphorylated	99	99
ABL1(T315I)-nonphosphorylated	100	97
ABL1(T315I)-phosphorylated	80	92
ABL1(Y253F)-phosphorylated	100	100
ABL1-nonphosphorylated	72	96
ABL1-phosphorylated	79	78
ABL2	100	98
ACVR1	100	100
ACVR1B	100	100
ACVR2A	94	100
ACVR2B	91	99
ACVRL1	100	100

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
ADCK3	100	100
ADCK4	100	100
AKT1	100	100
AKT2	99	90
AKT3	100	100
ALK	100	100
ALK(C1156Y)	100	100
ALK(L1196M)	100	100
AMPK-alpha1	100	100
AMPK-alpha2	89	100
ANKK1	100	100
ARK5	100	100
ASK1	88	100
ASK2	100	98
AURKA	100	100
AURKB	100	90
AURKC	100	100
AXL	100	96
BIKE	100	100
BLK	85	96
BMPR1A	86	94
BMPR1B	98	99
BMPR2	100	89
BMX	100	100
BRAF	100	100
BRAF(V600E)	97	97
BRK	100	100
BRSK1	99	99

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
BRSK2	96	95
BTK	100	96
BUB1	93	85
CAMK1	100	62
CAMK1B	82	83
CAMK1D	100	74
CAMK1G	93	100
CAMK2A	97	100
CAMK2B	100	92
CAMK2D	100	100
CAMK2G	94	100
CAMK4	100	100
CAMKK1	100	100
CAMKK2	99	100
CASK	99	94
CDC2L1	100	100
CDC2L2	100	100
CDC2L5	100	100
CDK11	4.8	92
CDK2	100	100
CDK3	100	100
CDK4	100	93
CDK4-cyclinD1	100	97
CDK4-cyclinD3	100	100
CDK5	100	100
CDK7	100	100
CDK8	10	98
CDK9	100	100

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
CDKL1	100	100
CDKL2	100	95
CDKL3	100	97
CDKL5	93	86
CHEK1	100	100
CHEK2	100	100
CIT	98	95
CLK1	100	100
CLK2	95	100
CLK3	97	93
CLK4	92	100
CSF1R	100	100
CSF1R-autoinhibited	99	99
CSK	98	93
CSNK1A1	100	92
CSNK1A1L	100	97
CSNK1D	100	100
CSNK1E	67	74
CSNK1G1	100	100
CSNK1G2	100	95
CSNK1G3	99	100
CSNK2A1	98	98
CSNK2A2	100	100
CTK	100	90
DAPK1	100	100
DAPK2	100	90
DAPK3	100	97
DCAMKL1	100	100

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
DCAMKL2	100	100
DCAMKL3	100	100
DDR1	100	100
DDR2	100	100
DLK	100	100
DMPK	100	100
DMPK2	97	96
DRAK1	95	100
DRAK2	100	100
DYRK1A	90	85
DYRK1B	97	79
DYRK2	100	97
EGFR	93	100
EGFR(E746-A750del)	100	94
EGFR(G719C)	100	77
EGFR(G719S)	100	72
EGFR(L747-E749del, A750P)	100	84
EGFR(L747-S752del, P753S)	100	97
EGFR(L747-T751del,Sins)	100	79
EGFR(L858R)	100	94
EGFR(L858R,T790M)	83	94
EGFR(L861Q)	100	86
EGFR(S752-I759del)	100	100
EGFR(T790M)	100	100
EIF2AK1	100	96
EPHA1	100	100
EPHA2	100	100
EPHA3	100	100

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
EPHA4	97	96
EPHA5	100	100
EPHA6	100	100
EPHA7	97	96
EPHA8	99	100
EPHB1	100	100
EPHB2	100	100
EPHB3	100	100
EPHB4	100	100
EPHB6	100	100
ERBB2	70	65
ERBB3	100	100
ERBB4	94	93
ERK1	97	95
ERK2	100	100
ERK3	100	100
ERK4	100	100
ERK5	100	100
ERK8	100	100
ERN1	100	93
FAK	100	100
FER	100	96
FES	100	100
FGFR1	94	95
FGFR2	100	100
FGFR3	100	100
FGFR3(G697C)	100	100
FGFR4	100	100

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
FGR	100	99
FLT1	100	100
FLT3	100	100
FLT3(D835H)	100	100
FLT3(D835V)	100	100
FLT3(D835Y)	100	100
FLT3(ITD)	100	100
FLT3(ITD,D835V)	100	100
FLT3(ITD,F691L)	98	97
FLT3(K663Q)	100	100
FLT3(N841I)	99	96
FLT3(R834Q)	100	100
FLT3-autoinhibited	95	96
FLT4	100	100
FRK	100	100
FYN	100	100
GAK	100	100
GCN2(Kin.Dom.2,S808G)	95	97
GRK1	100	98
GRK2	96	79
GRK3	82	81
GRK4	100	100
GRK7	100	100
GSK3A	100	100
GSK3B	100	98
HASPIN	86	83
HCK	100	100
HIPK1	72	82

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
HIPK2	99	79
HIPK3	100	88
HIPK4	100	100
HPK1	78	92
HUNK	82	96
ICK	100	93
IGF1R	100	98
IKK-alpha	100	99
IKK-beta	96	96
IKK-epsilon	100	94
INSR	100	100
INSRR	100	100
IRAK1	91	86
IRAK3	96	92
IRAK4	91	83
ITK	99	100
JAK1(JH1domain-catalytic)	100	100
JAK1(JH2domain-pseudokinase)	93	86
JAK2(JH1domain-catalytic)	100	100
JAK3(JH1domain-catalytic)	100	100
JNK1	92	87
JNK2	91	92
JNK3	83	86
KIT	100	99
KIT(A829P)	100	99
KIT(D816H)	100	98
KIT(D816V)	100	100
KIT(L576P)	100	98

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
KIT(V559D)	100	96
KIT(V559D,T670I)	97	100
KIT(V559D,V654A)	94	100
KIT-autoinhibited	94	94
LATS1	100	88
LATS2	98	100
LCK	100	95
LIMK1	100	100
LIMK2	95	93
LKB1	70	79
LOK	100	100
LRRK2	100	81
LRRK2(G2019S)	100	93
LTK	100	100
LYN	71	80
LZK	99	99
MAK	100	100
MAP3K1	100	100
MAP3K15	100	97
MAP3K2	99	95
MAP3K3	96	92
MAP3K4	100	100
MAP4K2	88	83
MAP4K3	100	100
MAP4K4	92	95
MAP4K5	87	95
MAPKAPK2	100	100
MAPKAPK5	94	96

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
MARK1	100	96
MARK2	96	100
MARK3	98	97
MARK4	91	94
MAST1	100	97
MEK1	98	99
MEK2	99	98
MEK3	94	79
MEK4	100	100
MEK5	89	87
MEK6	100	96
MELK	77	83
MERTK	100	100
MET	100	100
MET(M1250T)	100	100
MET(Y1235D)	98	99
MINK	100	100
MKK7	98	96
MKNK1	96	91
MKNK2	82	79
MLCK	100	100
MLK1	100	96
MLK2	66	69
MLK3	95	89
MRCKA	100	100
MRCKB	95	100
MST1	100	100
MST1R	98	92

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
MST2	100	99
MST3	100	100
MST4	97	84
MTOR	73	67
MUSK	100	100
MYLK	87	86
MYLK2	100	96
MYLK4	99	100
MYO3A	99	93
MYO3B	95	79
NDR1	100	100
NDR2	94	84
NEK1	100	100
NEK10	91	100
NEK11	100	95
NEK2	100	100
NEK3	96	96
NEK4	100	100
NEK5	100	94
NEK6	100	100
NEK7	100	99
NEK9	100	100
NIK	84	88
NIM1	89	89
NLK	100	100
OSR1	88	89
p38-alpha	100	100
p38-beta	100	97

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
p38-delta	100	100
p38-gamma	100	88
PAK1	100	100
PAK2	97	92
PAK3	71	100
PAK4	98	98
PAK6	85	80
PAK7	100	100
PCTK1	91	84
PCTK2	100	100
PCTK3	100	100
PDGFRA	73	85
PDGFRB	100	100
PDPK1	99	100
PFCDPK1(P.falciparum)	95	96
PFPK5(P.falciparum)	90	100
PFTAIRE2	100	100
PFTK1	100	100
PHKG1	100	100
PHKG2	100	100
PIK3C2B	100	100
PIK3C2G	85	78
PIK3CA	100	100
PIK3CA(C420R)	83	86
PIK3CA(E542K)	89	81
PIK3CA(E545A)	89	94
PIK3CA(E545K)	91	85
PIK3CA(H1047L)	85	71

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
PIK3CA(H1047Y)	71	72
PIK3CA(I800L)	96	87
PIK3CA(M1043I)	92	85
PIK3CA(Q546K)	96	88
PIK3CB	100	95
PIK3CD	99	85
PIK3CG	100	100
PIK4CB	100	98
PIKFYVE	57	57
PIM1	98	100
PIM2	95	100
PIM3	100	100
PIP5K1A	100	92
PIP5K1C	100	85
PIP5K2B	100	95
PIP5K2C	63	74
PKAC-alpha	94	94
PKAC-beta	92	100
PKMYT1	99	100
PKN1	91	100
PKN2	97	100
PKNB(M.tuberculosis)	100	100
PLK1	87	87
PLK2	98	91
PLK3	97	92
PLK4	100	100
PRKCD	98	94
PRKCE	72	68

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
PRKCH	100	91
PRKCI	96	92
PRKCQ	94	98
PRKD1	100	100
PRKD2	79	100
PRKD3	100	100
PRKG1	92	100
PRKG2	100	97
PRKR	100	97
PRKX	100	100
PRP4	89	82
PYK2	100	100
QSK	88	85
RAF1	100	100
RET	100	100
RET(M918T)	100	100
RET(V804L)	100	100
RET(V804M)	100	100
RIOK1	100	100
RIOK2	95	95
RIOK3	100	100
RIPK1	26	91
RIPK2	100	100
RIPK4	100	100
RIPK5	100	96
ROCK1	100	100
ROCK2	100	100
ROS1	100	91

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
RPS6KA4(Kin.Dom.1-N-terminal)	97	100
RPS6KA4(Kin.Dom.2-C-terminal)	97	100
RPS6KA5(Kin.Dom.1-N-terminal)	91	100
RPS6KA5(Kin.Dom.2-C-terminal)	95	90
RSK1(Kin.Dom.1-N-terminal)	96	100
RSK1(Kin.Dom.2-C-terminal)	100	100
RSK2(Kin.Dom.1-N-terminal)	100	94
RSK2(Kin.Dom.2-C-terminal)	100	100
RSK3(Kin.Dom.1-N-terminal)	97	100
RSK3(Kin.Dom.2-C-terminal)	100	100
RSK4(Kin.Dom.1-N-terminal)	100	93
RSK4(Kin.Dom.2-C-terminal)	100	100
S6K1	95	95
SBK1	97	95
SGK	96	90
SgK110	81	77
SGK2	100	93
SGK3	100	100
SIK	100	100
SIK2	89	96
SLK	99	97
SNARK	99	99
SNRK	100	100
SRC	97	100
SRMS	100	96
SRPK1	100	100
SRPK2	93	100
SRPK3	90	100

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
STK16	98	92
STK33	88	100
STK35	99	100
STK36	100	100
STK39	100	100
SYK	97	93
TAK1	97	95
TAOK1	100	100
TAOK2	84	77
TAOK3	92	85
TBK1	79	84
TEC	99	93
TESK1	100	100
TGFBR1	100	100
TGFBR2	100	100
TIE1	100	100
TIE2	100	88
TLK1	100	100
TLK2	100	100
TNIK	100	100
TNK1	100	100
TNK2	100	100
TNNI3K	100	100
TRKA	100	81
TRKB	100	94
TRKC	100	68
TRPM6	99	95
TSSK1B	88	76

	Compound #2	Compound #19
DiscoverX Gene Symbol	Percent Control at 100 nM Compound Concentration	Percent Control at 100 nM Compound Concentration
TSSK3	82	100
TTK	100	82
TXK	100	100
TYK2(JH1 domain-catalytic)	100	100
TYK2(JH2 domain-pseudokinase)	100	90
TYRO3	99	100
ULK1	100	100
ULK2	100	94
ULK3	97	96
VEGFR2	96	97
VPS34	87	90
VRK2	91	95
WEE1	92	100
WEE2	100	100
WNK1	93	94
WNK2	100	100
WNK3	100	100
WNK4	84	81
YANK1	100	100
YANK2	100	95
YANK3	67	54
YES	100	100
YSK1	100	97
YSK4	99	90
ZAK	100	100
ZAP70	98	98

[0195] Based on the binding affinities in Table D, a selectivity score (S-score) was calculated for each compound as a quantitative measure of compound selectivity. The S-score is calculated

by dividing the number of kinases that a compound binds to by the total number of distinct kinases tested, excluding mutant variants. The selectivity score value can be calculated using %Ctrl as a potency threshold, as shown below, and provides a quantitative method of describing compound selectivity to facilitate comparison of different compounds.

[0196] $S(10) = (\text{number of non-mutant kinases with \%Ctrl} < 35) / (\text{number of non-mutant kinases tested})$.

[0197] $S(35) = (\text{number of non-mutant kinases with \%Ctrl} < 10) / (\text{number of non-mutant kinases tested})$.

[0198] $S(35) = (\text{number of non-mutant kinases with \%Ctrl} < 1) / (\text{number of non-mutant kinases tested})$.

[0199] Results are shown in Table E.

Table E.

Compound	Selectivity Score Type	Number of Hits	Number of Non-Mutant Kinases	Screening Concentration (nM)	Selectivity Score
Compound #2	S(35)	3	403	100	0.007
Compound #2	S(10)	1	403	100	0.002
Compound #2	S(1)	0	403	100	0
Compound #19	S(35)	0	403	100	0
Compound #19	S(10)	0	403	100	0
Compound #19	S(1)	0	403	100	0

Prodrug Bioconversion

[0200] Phosphatase enzymes are ambiguously expressed with unique tissue specific isoforms and are key catalysts in the conversion of phosphate-containing prodrugs. To determine if exemplary phosphate prodrug compounds of the invention are enzymatically converted to the parent molecule across relevant species, the prodrug compounds were incubated with intestinal S9 cell fractions obtained from mouse, rat, dog, monkey, and human.

[0201] Phosphate prodrugs were incubated (1 μ M) for up to 2 hours in Tris-Cl buffer (pH 7.4) containing 3 mM magnesium chloride, intestinal S9 protein (0.01 and 25 mg/mL (ms, rat, hu, Table F) from mouse, rat, dog, monkey or human. Incubations were conducted in the absence and presence of 1 mM sodium orthovanadate, a phosphatase inhibitor. Prodrug depletion and parent formation were monitored by LC-MS/MS and normalized to internal standard as the analyte peak area ratio.

Table F. In vitro intrinsic clearance as measured by prodrug disappearance in intestinal S9 cell fractions.

Example	Clint (μ L/min/mg intestinal S9 protein) (0.25 mg/mL)			Clint (μ L/min/mg intestinal S9 protein) (0.01 mg/mL)		
	Human	Rat	Mouse	Human	Rat	Mouse
19	296	42.4	54.7	1608.5	< 137**	116.8
21	592.9	901.6	> 4166.5*	815.9	2599.5	11160
23	243.4	36.7	23.3	1180.2	< 137**	< 137**
25	410	393.8	> 1640.7*	378.1	1087.6	6821.9

* – Values were qualified because Clint was generated from a 2 time point curve

** – The qualified value was estimated based on 15% remaining after 2 hour incubation

Table G. In vitro intrinsic clearance as measured by Example #19 disappearance in intestinal S9 cell fractions.

Clint (μ L/min/mg intestinal S9 protein) (0.25 mg/mL)					
Experiment	Human	Monkey	Dog	Rat	Mouse
1	246	87.5	331	25.6	43.1
2	228	60.3	387	16.9	74.6
3	235	60.7	397	50.6	42.2
Mean	236.3	69.5	371.7	31	53.3
SD	9.1	15.6	35.6	17.5	18.5

Values are presented as Clint in units of μ L/min/mg intestinal S9 protein.

Table H. In vitro intrinsic clearance as measured by Example #21 disappearance in intestinal S9 cell fractions.

Clint ($\mu\text{L}/\text{min}/\text{mg}$ intestinal S9 protein) 0.25 mg/mL)					
Experiment	Human	Monkey	Dog	Rat	Mouse
1	391	89.6	5.62	396	> 480*
2	400	91.3	16.1	719	> 480*
3	355	90.7	14.3	750	> 480*
Mean	382	90.5	12.0	622	> 480*
SD	24.3	0.861	5.62	196	

Values are presented as Clint in units of $\mu\text{L}/\text{min}/\text{mg}$ intestinal S9 protein.

* - Values were qualified because CLint was generated from a 2 time-point curve

Table I. In vitro intrinsic clearance as measured by Example #23 disappearance in intestinal S9 cell fractions.

Clint ($\mu\text{L}/\text{min}/\text{mg}$ intestinal S9 protein) 0.25 mg/mL)					
Experiment	Human	Monkey	Dog	Rat	Mouse
1	199	55.4	354	29.1	26.2
2	241	47.7	369	33.8	34.3
3	203	48.1	345	28.2	31.3
Mean	214	50.4	356	30.4	30.6
SD	23.3	4.35	12.4	3.04	4.07

Values are presented as Clint in units of $\mu\text{L}/\text{min}/\text{mg}$ intestinal S9 protein.

* - Values were qualified because CLint was generated from a 2 time-point curve

Table J. In vitro intrinsic clearance as measured by Example #25 disappearance in intestinal S9 cell fractions.

Clint ($\mu\text{L}/\text{min}/\text{mg}$ intestinal S9 protein) 0.25 mg/mL)					
Experiment	Human	Monkey	Dog	Rat	Mouse
1	272	38.1	10.2	217	> 480*

2	294	49.0	14.4	318	> 480*
3	293	40.7	11.5	299	> 480*
Mean	286	42.6	12.0	278	> 480*
SD	12.7	5.66	2.14	53.8	

Values are presented as Clint in units of $\mu\text{L}/\text{min}/\text{mg}$ intestinal S9 protein.

* - Values were qualified because CLint was generated from a 2 time-point curve

OTHER EMBODIMENTS

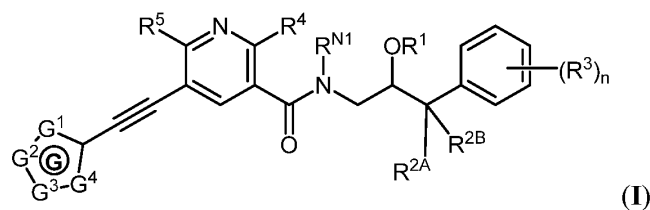
[0202] This application refers to various issued patents, published patent applications, journal articles, and other publications, each of which is incorporated herein by reference.

[0203] The foregoing has been described of certain non-limiting embodiments of the present disclosure. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present disclosure, as defined in the following claims.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is hydrogen, or

R^1 is $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2OR^{P1}$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$, wherein each instance of R^{P1} is independently selected from the group consisting of hydrogen and substituted or unsubstituted C_{1-4} alkyl, and R^{P2} is substituted or unsubstituted C_{1-4} alkyl;

R^{2A} and R^{2B} are each independently hydrogen or halo;

each R^3 is independently selected from the group consisting of halo and substituted or unsubstituted C_{1-4} alkyl, wherein n is 0, 1, or 2;

R^{N1} is hydrogen or substituted or unsubstituted C_{1-4} alkyl;

R^4 is independently selected from the group consisting of hydrogen, $-OR^{4A}$, and substituted or unsubstituted C_{1-4} alkyl, wherein R^{4A} is hydrogen or substituted or unsubstituted C_{1-4} alkyl;

R^5 is independently selected from the group consisting of hydrogen, $-OR^{5A}$, and substituted or unsubstituted C_{1-4} alkyl, wherein R^{5A} is hydrogen or substituted or unsubstituted C_{1-4} alkyl;

Ring G is a 5-membered heteroaryl ring, wherein each G^1 , G^2 , G^3 , and G^4 is, independently, CH, CR^{G1} , N, NR^{N2} , O, or S, provided at least one of G^1 , G^2 , G^3 , and G^4 is N, NR^{N2} , O, or S, and wherein no more than two of G^1 , G^2 , G^3 , and G^4 is O or S;

each instance of R^{G1} is independently selected from the group consisting of halo, $-OR^{G2}$, $-NR^7$, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted 3-4-membered carbocyclyl, or substituted or unsubstituted 4-membered heterocyclyl, wherein R^{G2} is hydrogen or substituted or unsubstituted C_{1-4} alkyl;

or two vicinal R^{G1} groups, taken together with the atoms to which they are attached, form a fused substituted or unsubstituted 5–6 membered carbocyclyl or fused substituted or unsubstituted 5–6 membered heterocyclyl;

or a vicinal R^{G1} group and R^{N2} group, taken together with the atoms to which they are attached, form a fused substituted or unsubstituted 5–6 membered heterocyclyl;

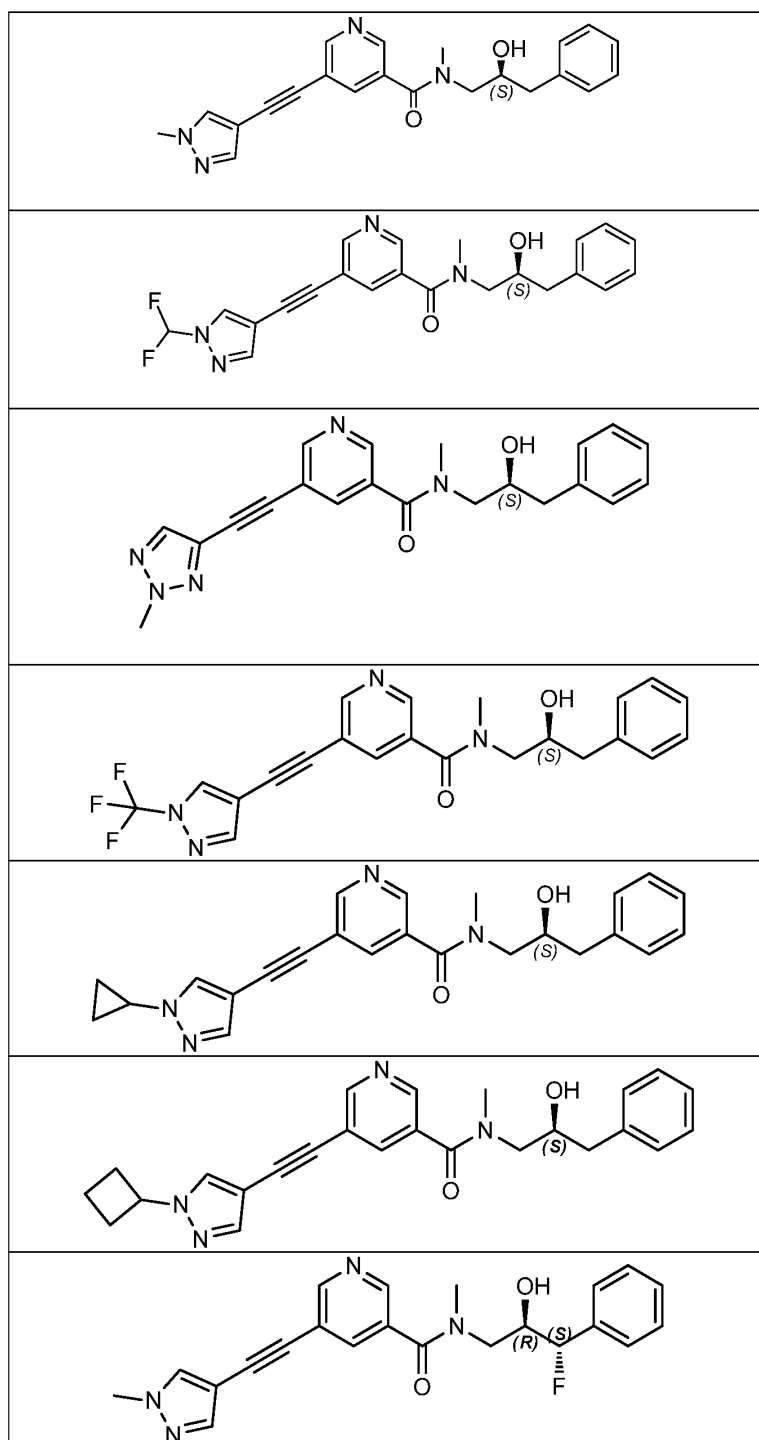
each R^{N2} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted 3–4–membered carbocyclyl, and substituted or unsubstituted 4–membered heterocyclyl;

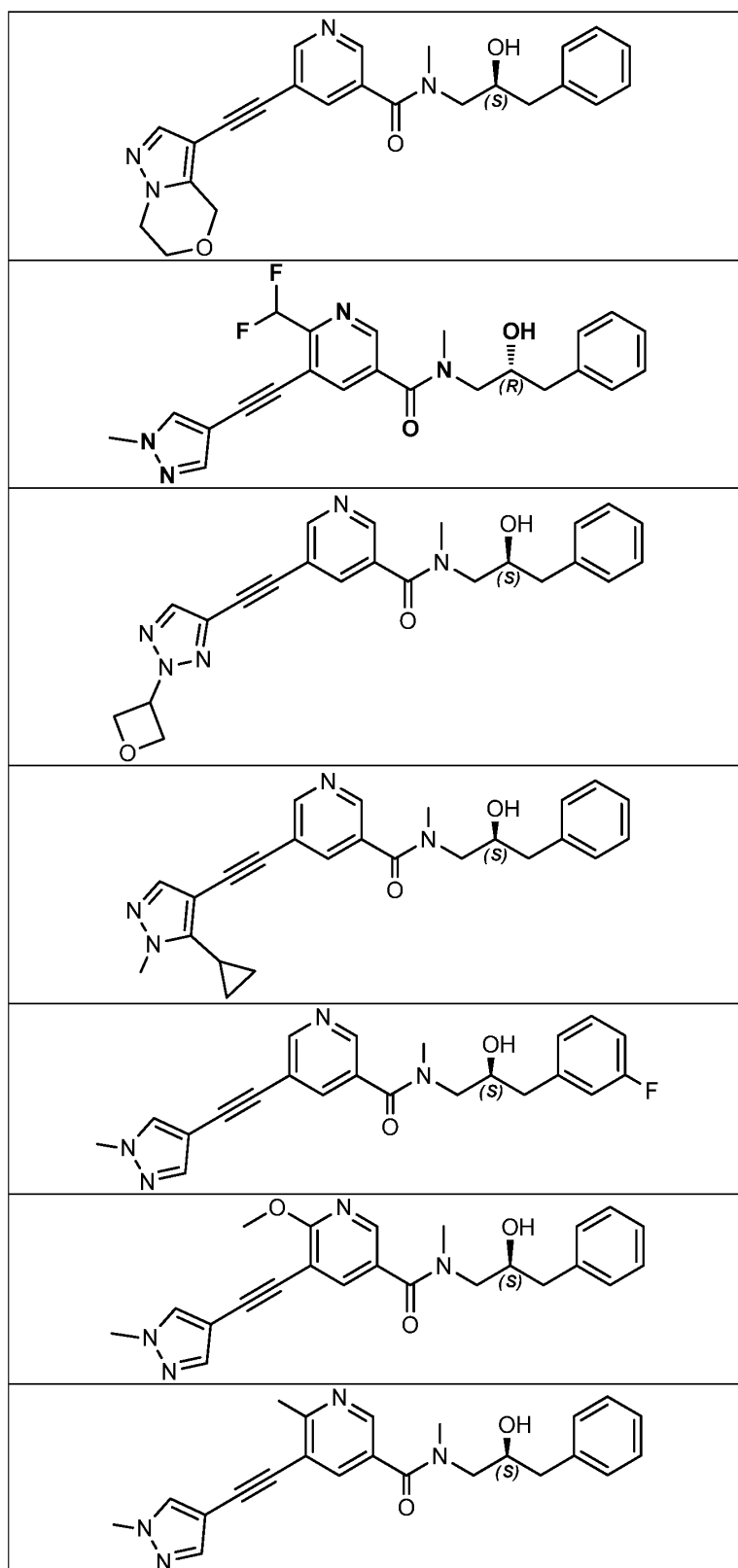
each R^7 is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted 3–4–membered carbocyclyl, and substituted or unsubstituted 4–membered heterocyclyl; and

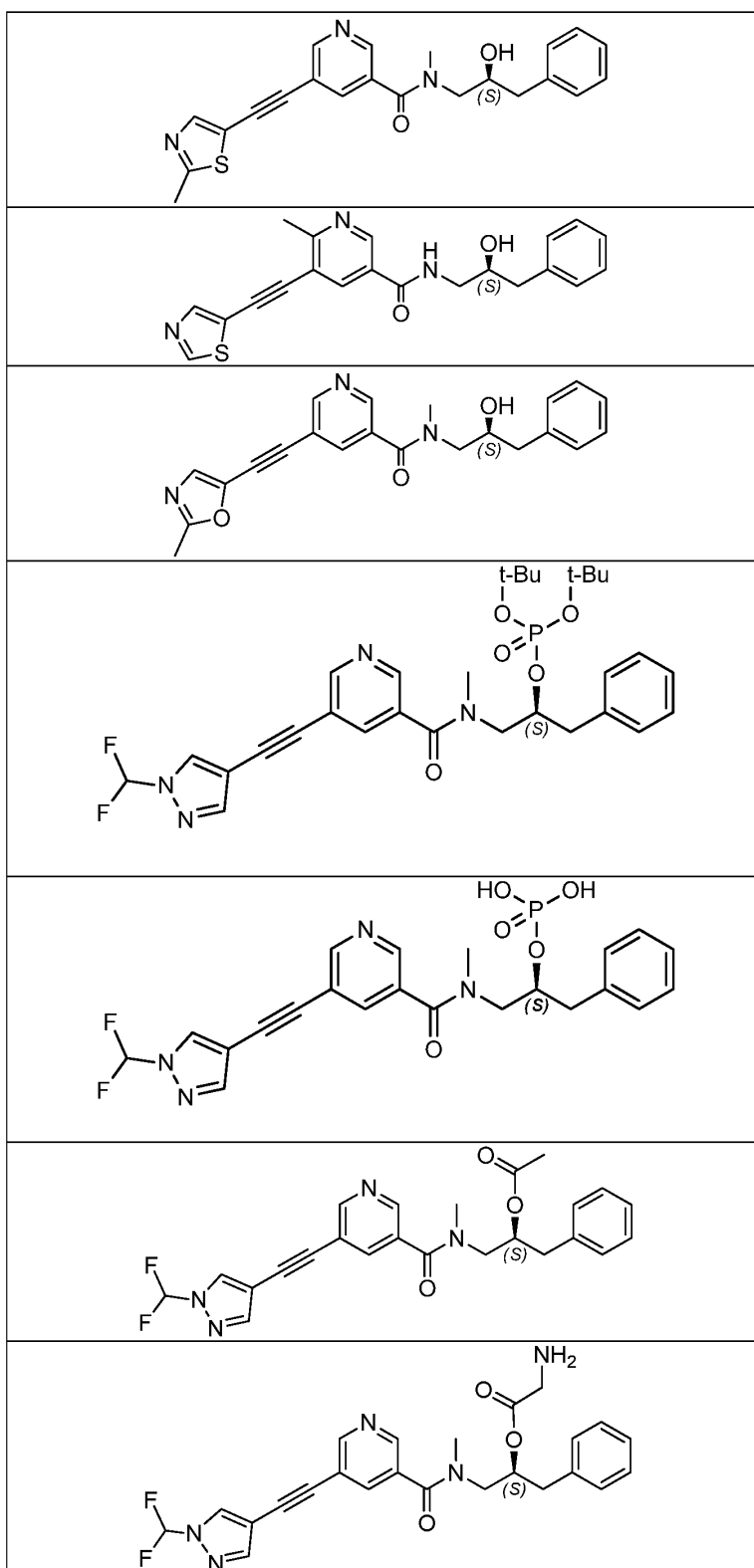
each instance of substituted or unsubstituted is optionally and independently substituted by 0, 1, 2, or 3 substituents selected from the group consisting of halo, $-OH$, $-O(C_{1-4}alkyl)$, and $-O(C_{1-4}haloalkyl)$.

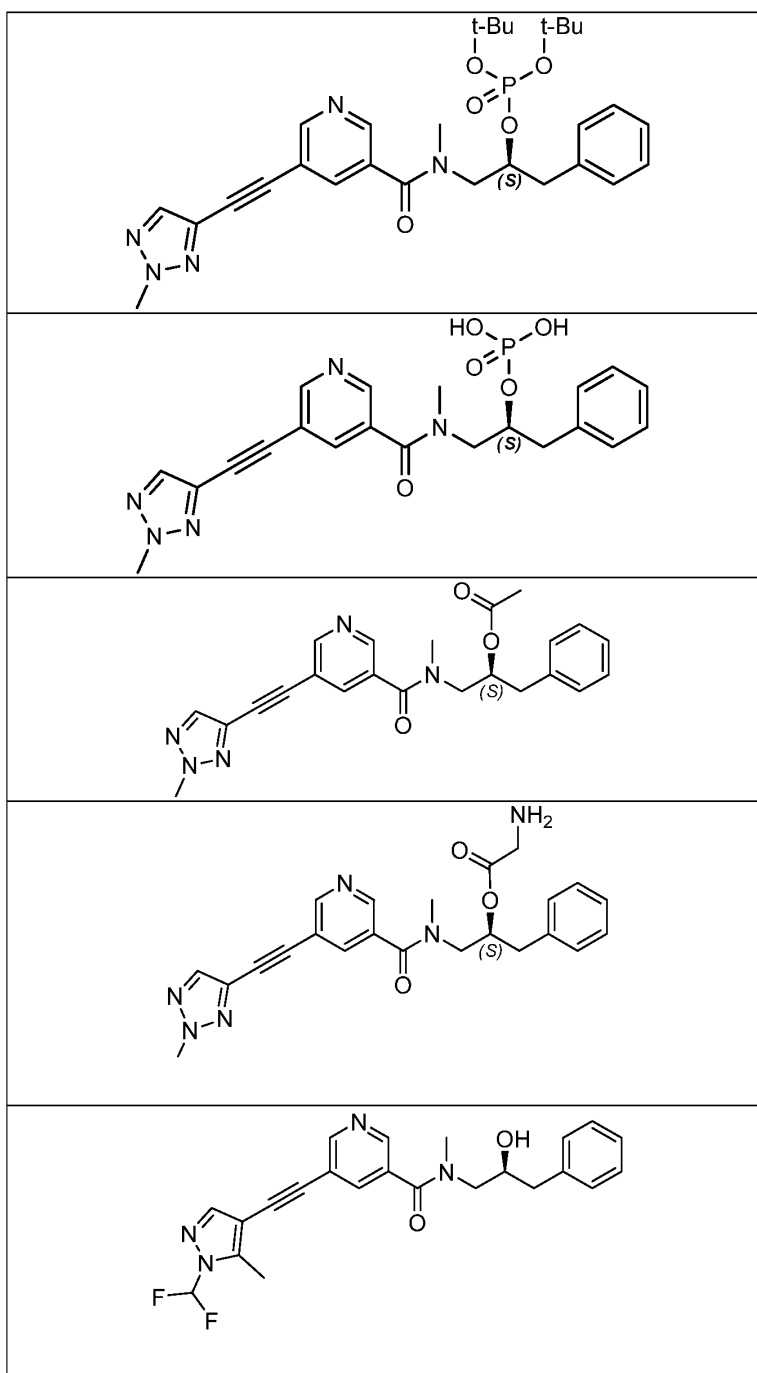
2. The compound of claim 1, wherein in Ring G, at least one of G^1 , G^2 , G^3 , and G^4 is N or NR^{N2} .
3. The compound of claim 2, wherein in Ring G, at least one of G^2 or G^3 is N or NR^{N2} .
4. The compound of claim 1 or 2, wherein in Ring G, at least two of G^1 , G^2 , G^3 , and G^4 is N or NR^{N2} .
5. The compound of any one of claims 1-4, wherein Ring G is a diazole.
6. The compound of claim 5, wherein G^2 and G^3 are each independently N or NR^{N2} .
7. The compound of any one of claims 1-4, wherein Ring G is a triazole.
8. The compound of claim 7, wherein G^2 , G^3 , and G^4 are each independently N or NR^{N2} .
9. The compound of any one of claims 1-8, wherein R^{N2} is alkyl or haloalkyl.
10. The compound of any one of claims 1-6, wherein one of G^1 and G^2 is CR^{G1} .
11. The compound of claim 10, wherein R^{G1} is methyl or cyclopropyl.
12. The compound of any one of claims 1-11, wherein R^4 is hydrogen.

13. The compound of any one of claims 1-12, wherein R^5 is hydrogen, alkoxy, or haloalkyl.
14. The compound of any one of claims 1-12, wherein R^5 is hydrogen, methyl, methoxy, or difluoromethyl.
15. The compound of claim 14, wherein R^5 is hydrogen.
16. The compound of any one of claims 1-15, wherein R^{N1} is hydrogen or methyl.
17. The compound of claim 16, wherein R^{N1} is hydrogen.
18. The compound of claim 16, wherein R^{N1} is methyl.
19. The compound of any one of claims 1-18, wherein R^{2A} and R^{2B} are each hydrogen.
20. The compound of any one of claims 1-18, wherein one of R^{2A} and R^{2B} is hydrogen and the other is fluoro.
21. The compound of any one of claims 1-20, wherein n is 0 or 1.
22. The compound of claim 21, wherein n is 1.
23. The compound of claim 22, wherein R^3 is halo.
24. The compound of claim 21, wherein n is 0.
25. The compound of any one of claims 1-24, wherein R^1 is hydrogen.
26. The compound of any one of claims 1-24, wherein R^1 is $-P(=O)(OR^{P1})_2$, $-C(=O)CH_2N(R^{P1})_2$, or $-C(=O)R^{P2}$.
27. The compound of claim 26, wherein R^1 is $-P(=O)(OR^{P1})_2$.
28. The compound of claim 27, wherein each R^{P1} is independently selected from the group consisting of hydrogen and unsubstituted C_{1-4} alkyl.
29. The compound of claim 28, wherein each R^{P1} is hydrogen.
30. The compound of claim 28, wherein each R^{P1} is unsubstituted C_{1-4} alkyl.
31. The compound of claim 1, selected from the following table:









or a pharmaceutically acceptable salt thereof.

32. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.