

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

28 March 2019 (28.03.2019)



(10) International Publication Number

WO 2019/057946 A1

(51) International Patent Classification:

C07D 263/56 (2006.01) C07D 235/08 (2006.01)

C07D 401/14 (2006.01) C07D 263/58 (2006.01)

C07D 231/56 (2006.01) A61P 27/02 (2006.01)

C07D 401/04 (2006.01)

Published:

— with international search report (Art. 21(3))

(21) International Application Number:

PCT/EP2018/075712

(22) International Filing Date:

21 September 2018 (21.09.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/562,843 25 September 2017 (25.09.2017) US

(71) Applicant (for all designated States except US): **F. HOFF-MANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, 4070 Basel (CH).

(71) Applicant (for US only): **GENENTECH, INC.** [US/US]; 1 DNA Way, South San Francisco, California 94080 (US).

(72) Inventors: **STIVALA, Craig**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, California 94080 (US). **HEFFRON, Timothy**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, California 94080 (US).

(74) Agent: **BERNARD, Guillaume**; Grenzacherstrasse 124, 4070 Basel (CH).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

(54) Title: MULTI-CYCLIC AROMATIC COMPOUNDS AS FACTOR D INHIBITORS

(57) Abstract: Multi-cyclic aromatic compounds and methods of use as Factor D modulators are described herein.

WO 2019/057946 A1

MULTI-CYCLIC AROMATIC COMPOUNDS AS FACTOR D INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. Provisional Application Serial No. 62/562,843, filed September 25, 2017, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to inhibitors of the complement alternative pathway, and more particularly to inhibitors of Factor D.

BACKGROUND OF THE INVENTION

The complement system plays a central role in the clearance of immune complexes and the immune response to infectious agents, foreign antigens, virus-infected cells, and tumor cells. However, complement is also involved in pathological inflammation and in autoimmune diseases. Therefore, inhibition of excessive or uncontrolled activation of the complement cascade could provide clinical benefit to patients with such diseases and conditions.

The complement system encompasses three distinct activation pathways, designated the classical, mannose-binding lectin, and the alternative pathways. V.M. Holers In Clinical Immunology: Principles and Practice, ed. R.R. Rich, Mosby Press; 1996, 363-391. The classical pathway is a calcium/magnesium-dependent cascade which is normally activated by the formation of antigen-antibody complexes. The mannose-binding lectin (MBL) pathway is initiated by the binding of MBL to carbohydrate structures on pathogens, resulting in the activation of MBL protease (MASP) that cleaves C2 and C4 to form active C2a, C2b, C4a and C4b. The alternative pathway is a magnesium-dependent cascade which is activated by deposition and activation of C3 on certain susceptible surfaces (e.g., cell wall polysaccharides of yeast and bacteria, and certain biopolymer materials). Activation of the complement pathway generates biologically active fragments of complement proteins, e.g., C3a, C4a and C5a anaphylatoxins and C5b-9 membrane attack complexes (MAC), which mediate inflammatory activities involving leukocyte chemotaxis, activation of macrophages, neutrophils, platelets, mast cells and endothelial cells, vascular permeability, cytolysis, and tissue injury.

Factor D is a highly specific serine protease essential for activation of the alternative complement pathway. It cleaves factor B bound to C3b, generating the C3b/Bb enzyme which is the active component of the alternative pathway C3/C5 convertases. Factor D may be a suitable target for inhibition, since its plasma concentration in humans is very low (1.8 µg/ml), and it has been shown to be the limiting enzyme for activation of the alternative complement pathway. P.H. Lesavre and H.J. Müller-Eberhard. (1978) J. Exp. Med. 148: 1498-1510; J.E. Volanakis et al. (1985) New Eng. J. Med. 312: 395-401.

The down-regulation of complement activation has been demonstrated to be effective in treating several disease indications in animal models and in ex vivo studies, e.g., systemic lupus erythematosus and glomerulonephritis, rheumatoid arthritis, cardiopulmonary bypass and hemodialysis, hyperacute rejection in organ transplantation, myocardial infarction, reperfusion injury, and adult respiratory distress syndrome. In addition, other inflammatory conditions and autoimmune/immune complex diseases are also closely associated with complement activation, including thermal injury, severe asthma, anaphylactic shock, bowel inflammation, urticaria, angioedema, vasculitis, multiple sclerosis, myasthenia gravis, membranoproliferative glomerulonephritis, and Sjögren's syndrome.

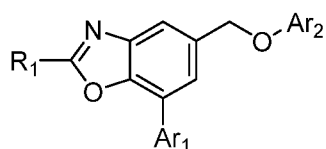
Age-related macular degeneration (AMD) is a progressive chronic disease of the central retina with significant consequences for visual acuity. Lim et al. (2012) Lancet 379:1728. Late forms of the disease are the leading cause of vision loss in industrialized countries. For the Caucasian population ≥ 40 years of age the prevalence of early AMD is estimated at 6.8% and advanced AMD at 1.5%. See de Jong (2006) N. Engl. J. Med. 355: 1474. The prevalence of late AMD increases dramatically with age rising to 11.8% after 80 years of age. Two types of AMD exist, non-exudative (dry) and exudative (wet) AMD. The more common dry form AMD involves atrophic and hypertrophic changes in the retinal pigment epithelium (RPE) underlying the central retina (macula) as well as deposits (drusen) on the RPE. Advanced dry AMD can result in significant retinal damage, including geographic atrophy (GA), with irreversible vision loss. Moreover, patients with dry AMD can progress to the wet form, in which abnormal blood vessels called choroidal neovascular membranes (CNVMs) develop under the retina, leak fluid and blood, and ultimately cause a blinding disciform scar in and under the retina.

Drugs targeting new blood vessel formation (neovascularization) have been the mainstay for treating wet AMD. Ranibizumab, which is an anti-VEGFA antibody fragment, has proven to be highly effective in improving vision for patients afflicted with wet AMD.

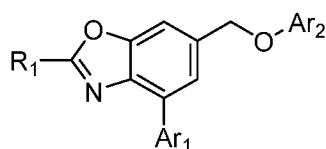
Recent studies have implicated an association between AMD and key proteins in the complement cascade and a number of therapies targeting specific complement components are being developed to treat dry AMD. A humanized anti-Factor D Fab fragment (aFD.WT; lampalizumab; FCFD4514S) that potently inhibits Factor D and the alternative complement pathway, through binding to an exosite on Factor D is currently in clinical development for the treatment of GA associated with dry AMD. Katschke et al. (2012) J. Biol. Chem. 287:12886. A recent phase II clinical trial has shown that monthly intravitreal injection of lampalizumab effectively slowed the progression of GA lesions in patients with advanced dry AMD.

SUMMARY OF THE INVENTION

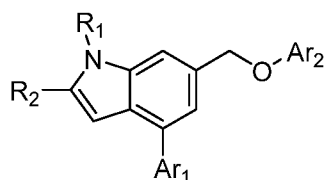
One aspect of the invention includes a compound having a structure selected from the group consisting of:



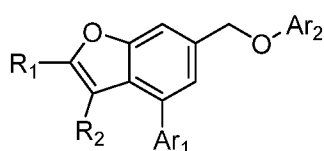
(I-A),



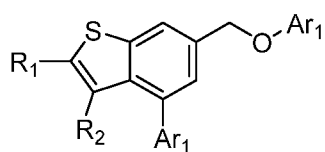
(II-A),



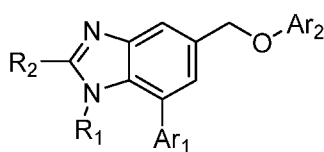
(III-A),



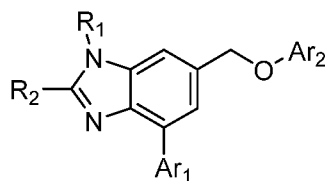
(IV-A),



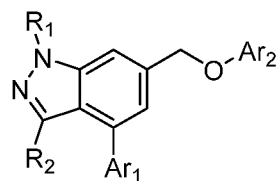
(V-A),



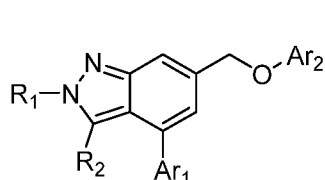
(VI-A),



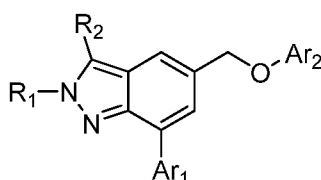
(VII-A),



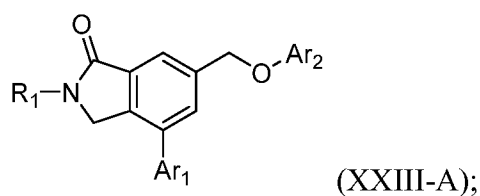
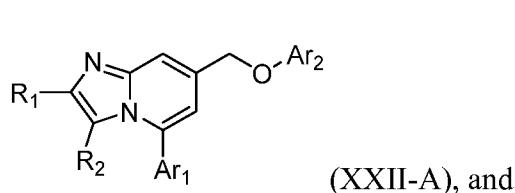
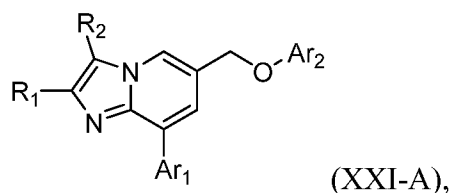
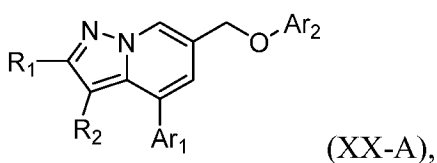
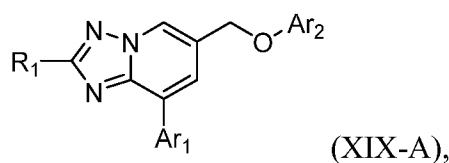
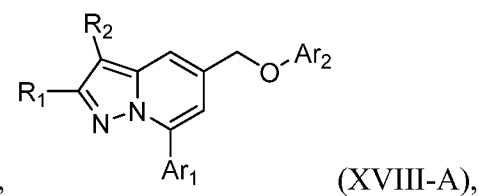
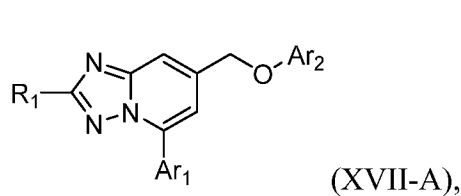
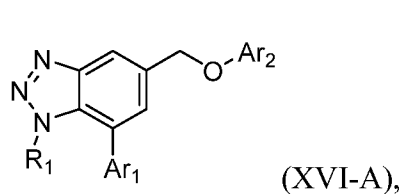
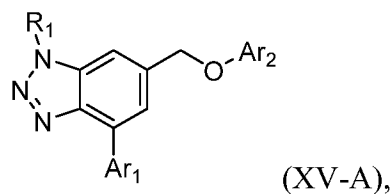
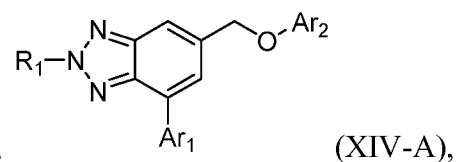
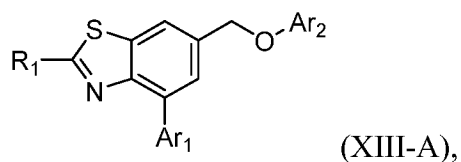
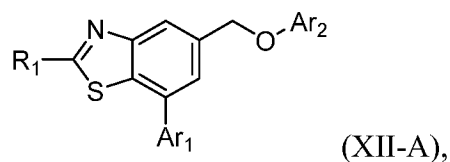
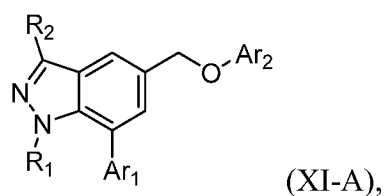
(VIII-A),



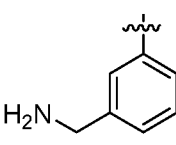
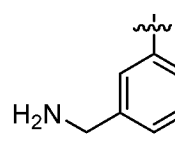
(IX-A),

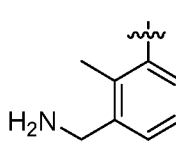
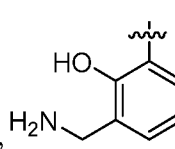
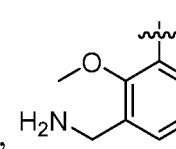
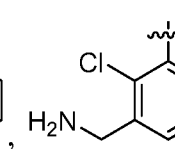
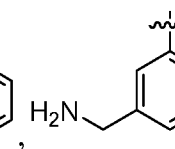


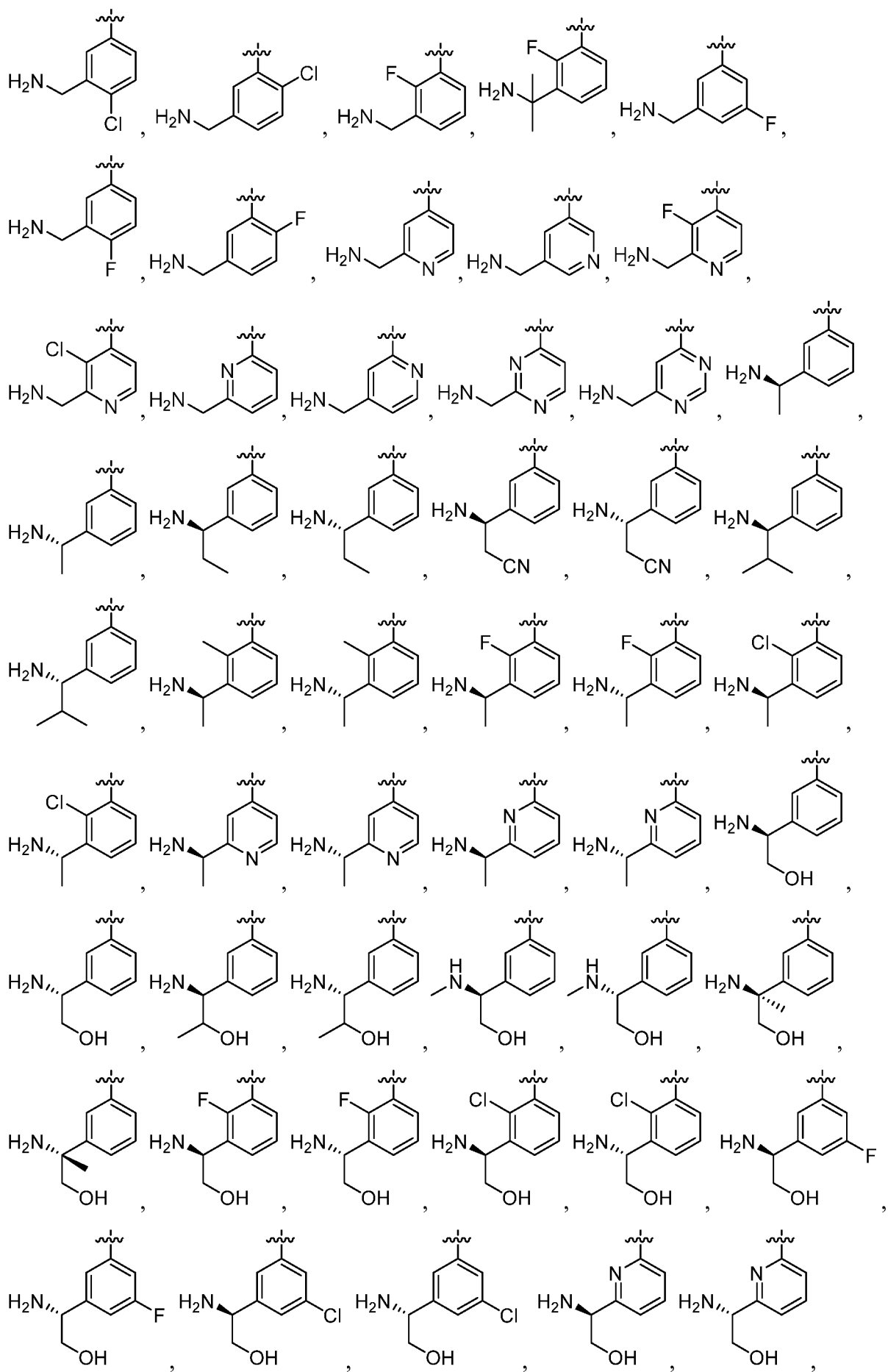
(X-A),

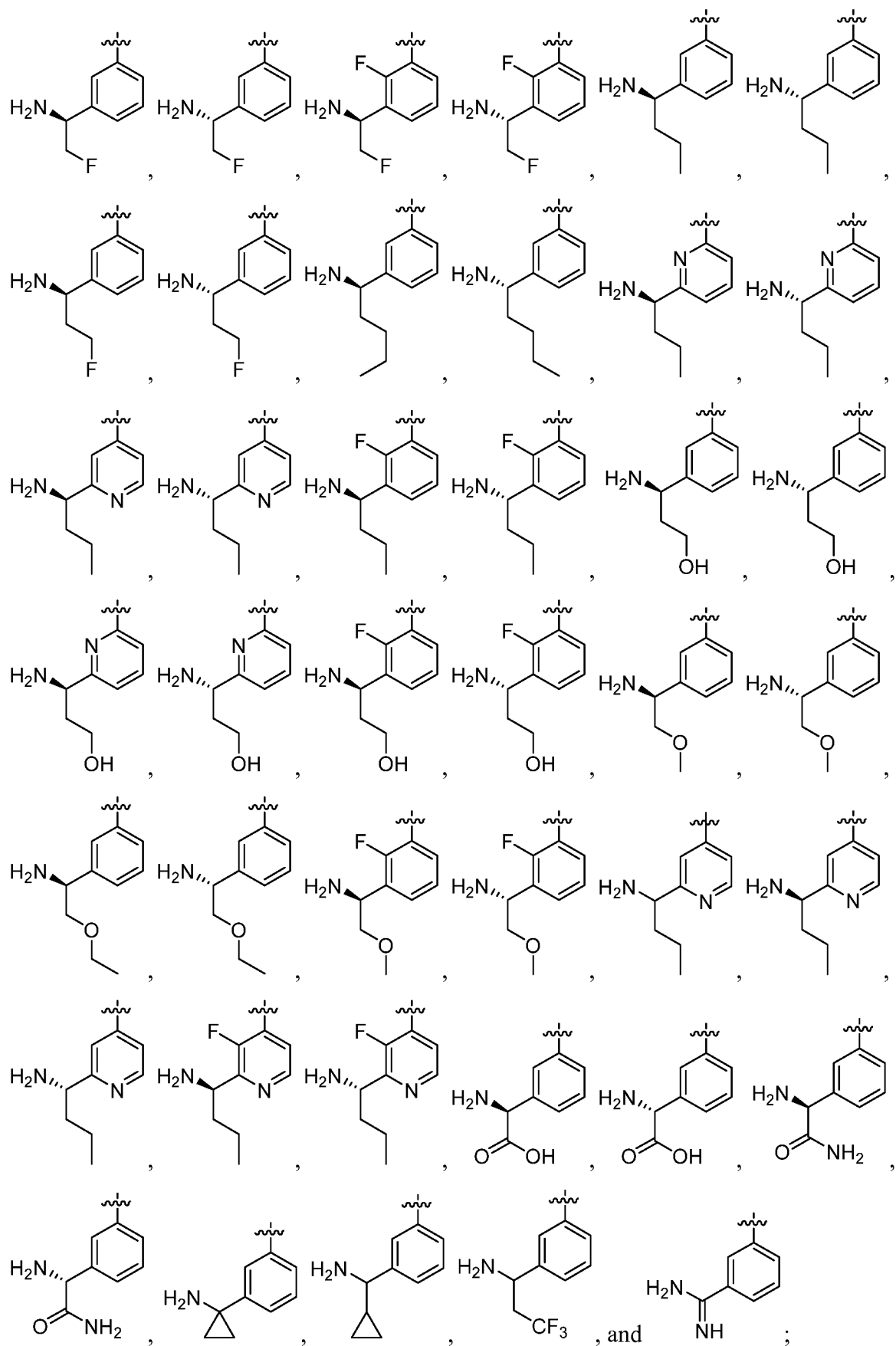


or a stereoisomer or a pharmaceutically acceptable salt thereof, wherein:

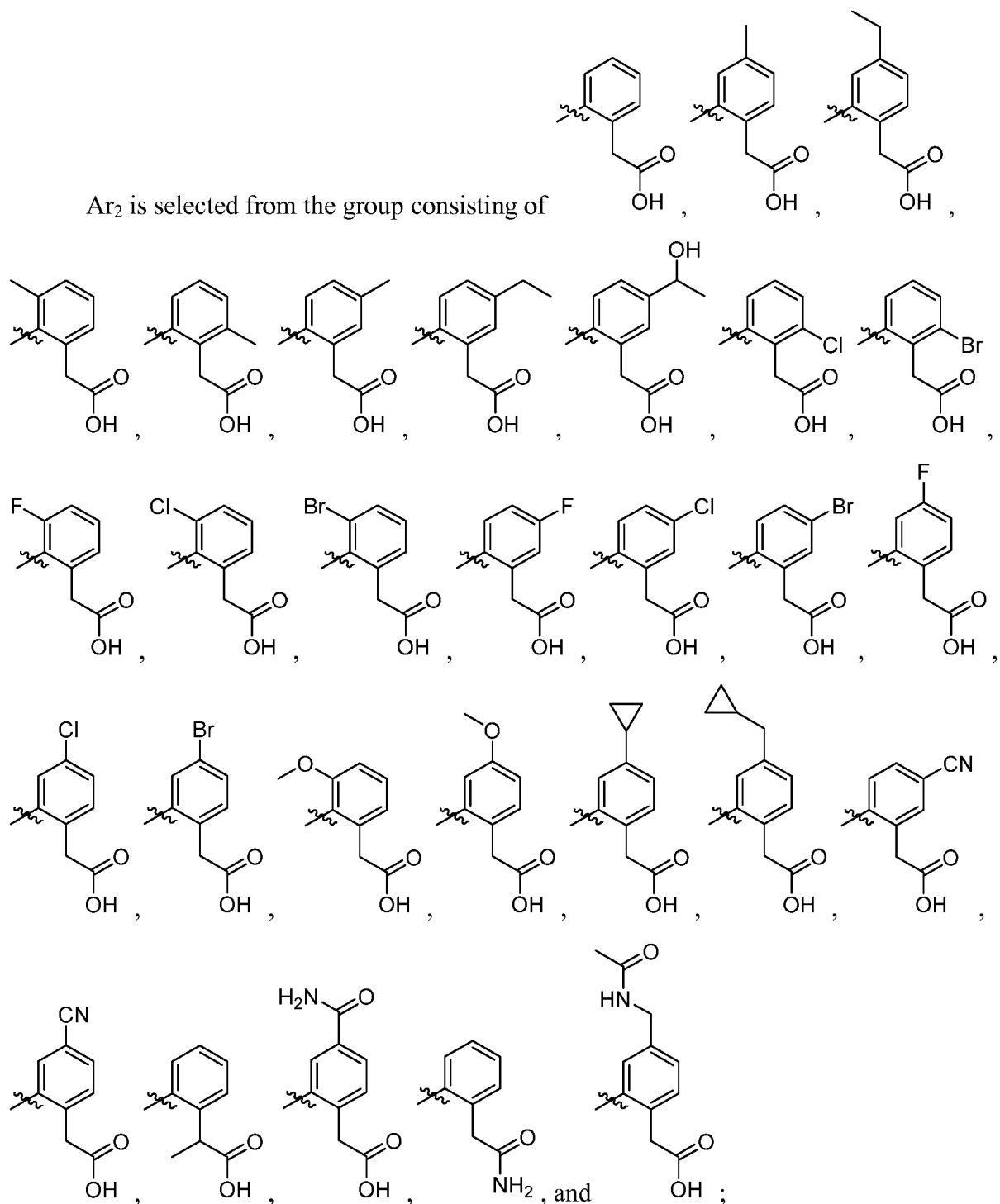
Ar₁ is selected from the group consisting of , ,

, , , , ,





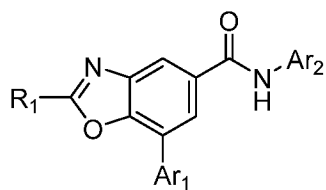
Ar₂ is selected from the group consisting of



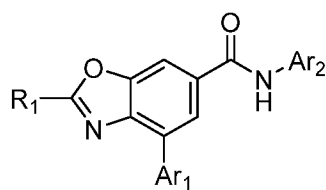
each R₁ and R₂ are independently selected from the group consisting of hydrogen, halo, cyano, -OR₃, -SR₃, -NR₃R₄, -C(O)R₃, -C(O)OR₃, -C(O)NR₃R₄, -S(O)₂R₃, C₁-C₆ alkyl optionally substituted with R₃, C₆-C₁₄ aryl optionally substituted with R₃, and C₅-C₁₄ heteroaryl optionally substituted with R₃; and

10 each R₃ and R₄ are independently selected from the group consisting of hydrogen, -NH₂, C₁-C₆ alkyl, C₆-C₁₂ aryl, and C₅-C₁₄ heteroaryl.

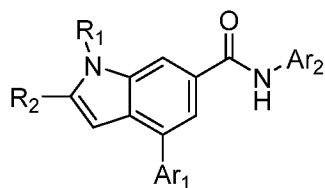
Another aspect of the invention includes a compound having a structure selected from the group consisting of:



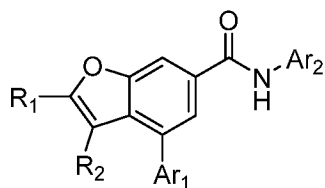
(I-B),



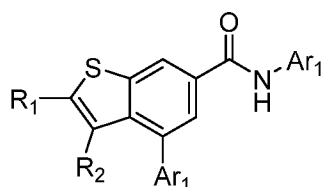
(II-B),



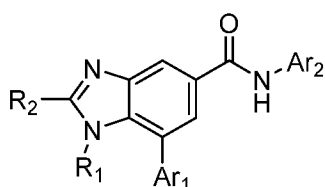
(III-B),



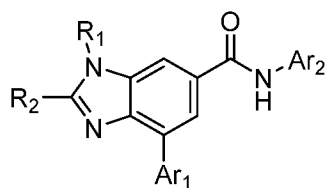
(IV-B),



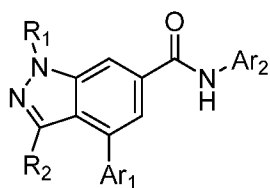
(V-B),



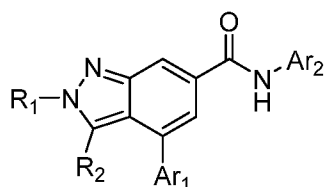
(VI-B),



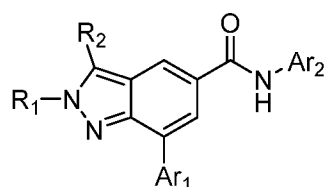
(VII-B),



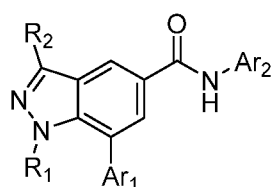
(VIII-B),



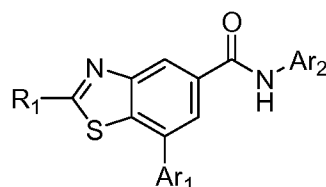
(IX-B),



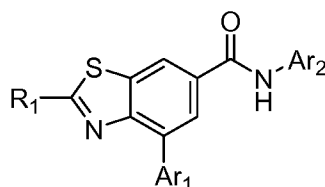
(X-B),



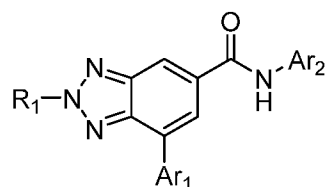
(XI-B),



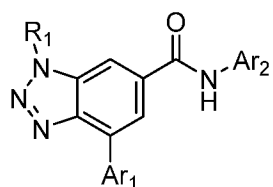
(XII-B),



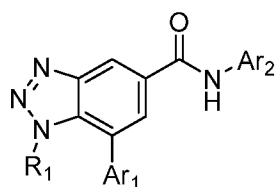
(XIII-B),



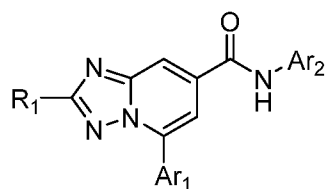
(XIV-B),



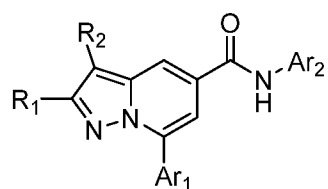
(XV-B),



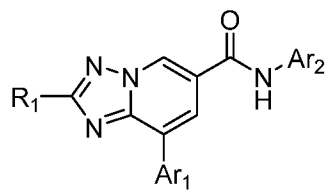
(XVI-B),



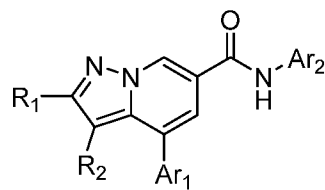
(XVII-B),



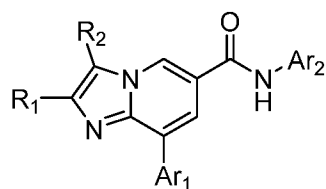
(XVIII-B),



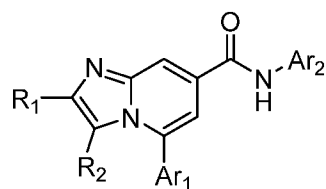
(XIX-B),



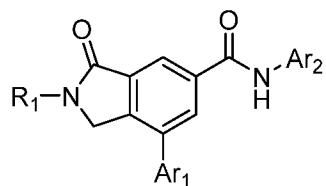
(XX-B),



(XXI-B),

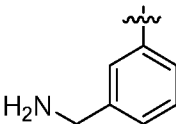
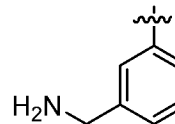


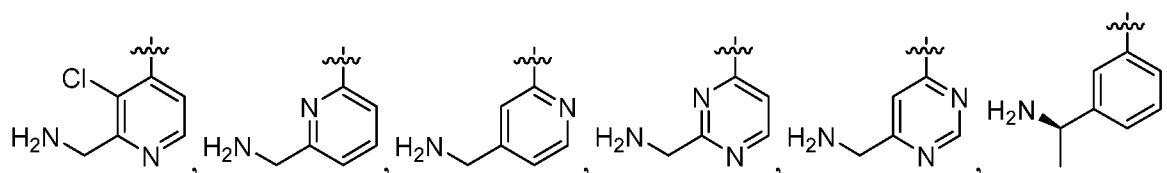
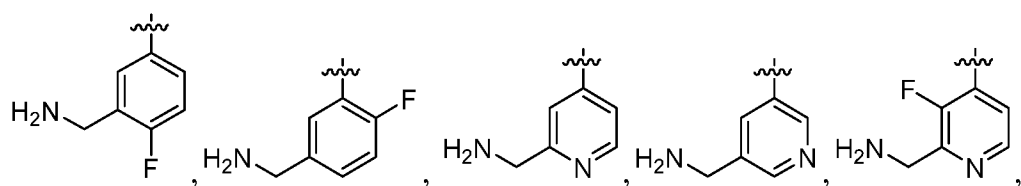
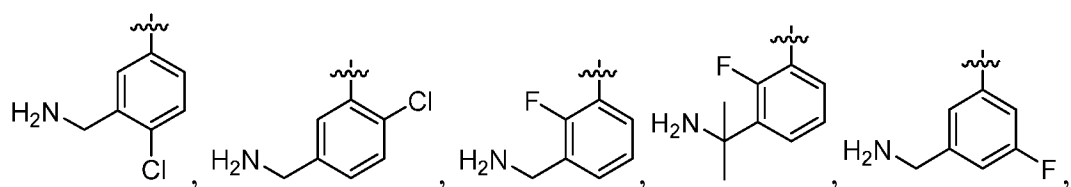
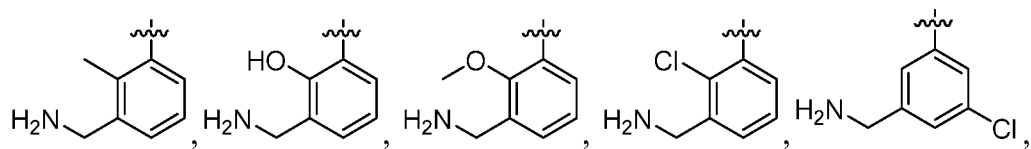
(XXII-B), and



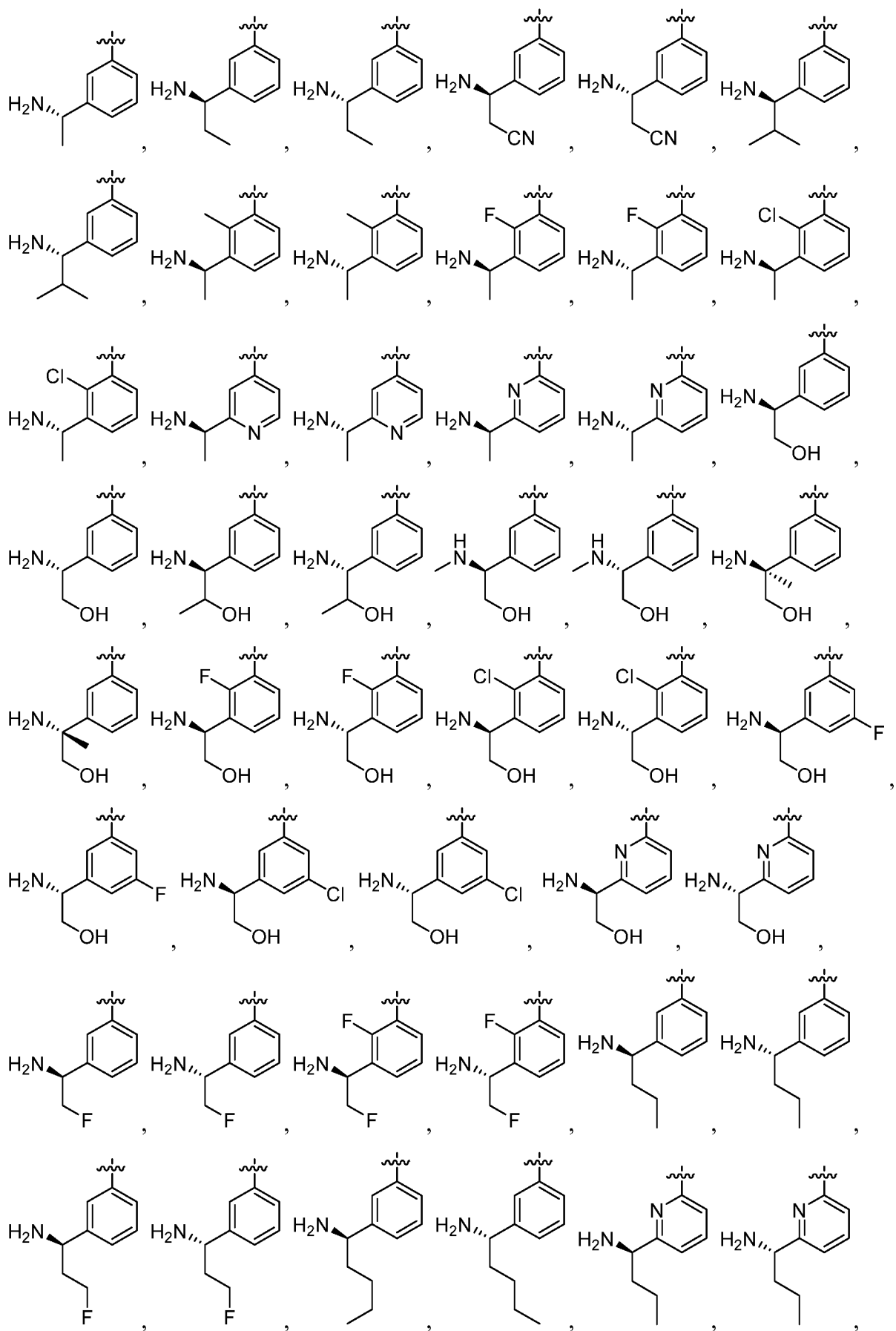
(XXIII-B);

5 or a stereoisomer or a pharmaceutically acceptable salt thereof, wherein:


Ar₁ is selected from the group consisting of , ,

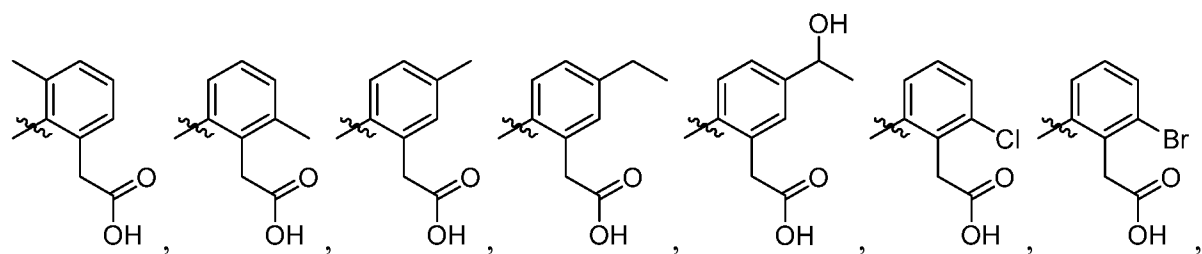


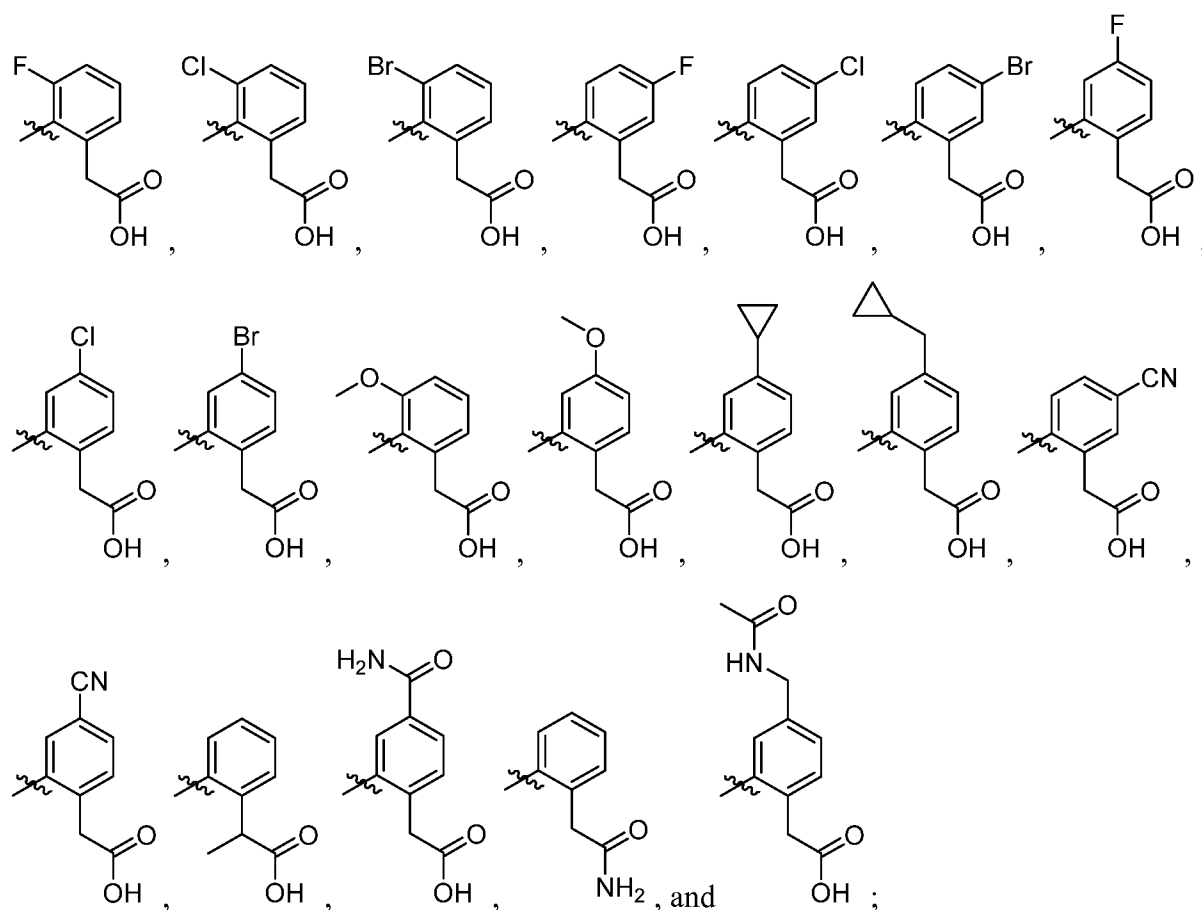
10











each R_1 and R_2 are independently selected from the group consisting of hydrogen, halo, cyano, $-OR_3$, $-SR_3$, $-NR_3R_4$, $-C(O)R_3$, $-C(O)OR_3$, $-C(O)NR_3R_4$, $-S(O)_2R_3$, C_1 - C_6 alkyl optionally substituted with R_3 , C_6 - C_{14} aryl optionally substituted with R_3 , and C_5 - C_{14} heteroaryl optionally substituted with R_3 ; and

each R_3 and R_4 are independently selected from the group consisting of hydrogen, $-NH_2$, C_1 - C_6 alkyl, C_6 - C_{12} aryl, and C_5 - C_{14} heteroaryl.

Also provided is a pharmaceutical formulation that comprises a compound of the invention or a stereoisomer or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, carrier or diluent.

Another aspect includes a delivery device for ocular delivery comprising the pharmaceutical formulation and a means for delivering the formulation intravitreally to a patient.

Another aspect includes a method of modulating complement alternative pathway activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of the invention, or a stereoisomer or a

pharmaceutically acceptable salt thereof.

Another aspect includes a method of treating a disease or disorder in a subject mediated by complement activation, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of the invention, or a

5 stereoisomer or a pharmaceutically acceptable salt thereof.

Another aspect includes a method of preventing, treating or lessening the severity of a disease or condition responsive to the inhibition of Factor D, in a patient. The method can comprise administering to the patient a therapeutically effective amount of a compound of the invention, or a stereoisomer or a pharmaceutically acceptable salt thereof.

10 Another aspect includes the use of a compound of the invention, or a stereoisomer or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease responsive to the inhibition of Factor D.

Another aspect includes the use of a compound of the invention, or a stereoisomer or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating a
15 complement-mediated disorder in a subject.

Another aspect includes a kit for treating a disease or disorder responsive to the inhibition of Factor D. The kit can comprise a first pharmaceutical formulation comprising a compound of the invention, or a stereoisomer or a pharmaceutically acceptable salt thereof, and instructions for use.

20 Another aspect includes a combination comprising a therapeutically effective amount of any one of a compound of the present invention, or a stereoisomer or a pharmaceutically acceptable salt thereof, and a second therapeutically active agent.

DETAILED DESCRIPTION OF THE INVENTION

25 DEFINITIONS

“Halogen” or “halo” refers to F, Cl, Br or I. Additionally, terms such as “haloalkyl,” are meant to include monohaloalkyl and polyhaloalkyl.

The term “alkyl” refers to a saturated linear or branched-chain monovalent hydrocarbon radical, wherein the alkyl radical may be optionally substituted. In one
30 example, the alkyl radical is one to eighteen carbon atoms (C₁-C₁₈). In other examples, the

alkyl radical is C₀-C₆, C₀-C₅, C₀-C₃, C₁-C₁₂, C₁-C₁₀, C₁-C₈, C₁-C₆, C₁-C₅, C₁-C₄, or C₁-C₃. C₀ alkyl refers to a bond. Examples of alkyl groups include methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (n-Pr, n-propyl, -CH₂CH₂CH₃), 2-propyl (i-Pr, i-propyl, -CH(CH₃)₂), 1-butyl (n-Bu, n-butyl, -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (i-Bu, i-butyl, -CH₂CH(CH₃)₂), 2-butyl (s-Bu, s-butyl, -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (t-Bu, t-butyl, -C(CH₃)₃), 1-pentyl (n-pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), 1-heptyl and 1-octyl. In some embodiments, substituents for “optionally substituted alkyls” include one to four instances of F, Cl, Br, I, OH, SH, CN, NH₂, NHCH₃, N(CH₃)₂, NO₂, N₃, C(O)CH₃, COOH, CO₂CH₃, methyl, ethyl, propyl, iso-propyl, butyl, isobutyl, cyclopropyl, methoxy, ethoxy, propoxy, oxo, trifluoromethyl, difluoromethyl, sulfonylamino, methanesulfonylamino, SO, SO₂, phenyl, piperidinyl, piperizinyl, and pyrimidinyl, wherein the alkyl, phenyl and heterocyclic portions thereof may be optionally substituted, such as by one to four instances of substituents selected from this same list.

“Aryl” refers to a carbocyclic aromatic group, whether or not fused to one or more groups, having the number of carbon atoms designated, or if no number is designated, up to 14 carbon atoms. One example includes aryl groups having 6-14 carbon atoms. Another example includes aryl groups having 6-10 carbon atoms. Examples of aryl groups include phenyl, naphthyl, biphenyl, phenanthrenyl, naphthacenyl, 1,2,3,4-tetrahydronaphthalenyl, 1H-indenyl, 2,3-dihydro-1H-indenyl, and the like (see, e.g., Lang’s Handbook of Chemistry (Dean, J. A., ed.) 13th ed. Table 7-2 [1985]). A particular aryl is phenyl. Substituted phenyl or substituted aryl means a phenyl group or aryl group substituted with one, two, three, four or five substituents, for example, 1-2, 1-3 or 1-4 substituents, such as chosen from groups specified herein (see “optionally substituted” definition), such as F, Cl, Br, I, OH, SH, CN, NH₂, NHCH₃, N(CH₃)₂, NO₂, N₃, C(O)CH₃, COOH, CO₂CH₃, methyl, ethyl, propyl, iso-propyl, butyl, isobutyl, cyclopropyl, methoxy, ethoxy, propoxy, oxo, trifluoromethyl, difluoromethyl, sulfonylamino, methanesulfonylamino, SO, SO₂, phenyl, piperidinyl,

piperizinyl, and pyrimidinyl, wherein the alkyl, phenyl and heterocyclic portions thereof may be optionally substituted, such as by one to four instances of substituents selected from this same list. Examples of the term “substituted phenyl” include a mono- or di(halo)phenyl group such as 2-chlorophenyl, 2-bromophenyl, 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl, 2,4-difluorophenyl and the like; a mono- or di(hydroxy)phenyl group such as 4-hydroxyphenyl, 3-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 3- or 4-nitrophenyl; a cyanophenyl group, for example, 4-cyanophenyl; a mono- or di(alkyl)phenyl group such as 4-methylphenyl, 2,4-dimethylphenyl, 2-methylphenyl, 4-(isopropyl)phenyl, 4-ethylphenyl, 3-(n-propyl)phenyl and the like; a mono or di(alkoxy)phenyl group, for example, 3,4-dimethoxyphenyl, 3-methoxy-4-benzyloxyphenyl, 3-ethoxyphenyl, 4-(isopropoxy)phenyl, 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 3- or 4- trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such 4-carboxyphenyl, a mono- or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 3-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 3-(N-methylsulfonylamino))phenyl. Also, the term “substituted phenyl” represents disubstituted phenyl groups where the substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy-4-chlorophenyl, 2-chloro-5-difluoromethoxy and the like, as well as trisubstituted phenyl groups where the substituents are different, for example 3-methoxy-4-benzyloxy-6-methyl sulfonylamino, 3-methoxy-4-benzyloxy-6-phenyl sulfonylamino, and tetrasubstituted phenyl groups where the substituents are different such as 3-methoxy-4-benzyloxy-5-methyl-6-phenyl sulfonylamino.

The terms “compound(s) of the invention,” and “compound(s) of the present invention” and the like, unless otherwise indicated, include compounds falling within the scope of the structural formulae recited herein and the compounds of Tables 1 and 2 herein, including stereoisomers (including atropisomers), geometric isomers, tautomers, solvates, metabolites, isotopes, salts (e.g., pharmaceutically acceptable salts), and prodrugs thereof. In

some embodiments, solvates, metabolites, isotopes or prodrugs are excluded, or any combination thereof.

“Cycloalkyl” refers to a non-aromatic, saturated or partially unsaturated hydrocarbon ring group wherein the cycloalkyl group may be optionally substituted independently with one or more substituents described herein. In one example, the cycloalkyl group is 3 to 12 carbon atoms (C₃-C₁₂). In other examples, cycloalkyl is C₃-C₈, C₃-C₁₀ or C₅-C₁₀. In other examples, the cycloalkyl group, as a monocycle, is C₃-C₈, C₃-C₆ or C₅-C₆. In another example, the cycloalkyl group, as a bicycle, is C₇-C₁₂. In another example, the cycloalkyl group, as a spiro system, is C₅-C₁₂. Examples of monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, perdeuteriocyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl and cyclododecyl. Exemplary arrangements of bicyclic cycloalkyls having 7 to 12 ring atoms include, but are not limited to, [4,4], [4,5], [5,5], [5,6] or [6,6] ring systems. Exemplary bridged bicyclic cycloalkyls include, but are not limited to, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. Examples of spiro cycloalkyl include, spiro[2.2]pentane, spiro[2.3]hexane, spiro[2.4]heptane, spiro[2.5]octane and spiro[4.5]decane. In some embodiments, substituents for “optionally substituted cycloalkyls” include one to four instances of F, Cl, Br, I, OH, SH, CN, NH₂, NHCH₃, N(CH₃)₂, NO₂, N₃, C(O)CH₃, COOH, CO₂CH₃, methyl, ethyl, propyl, iso-propyl, butyl, isobutyl, cyclopropyl, methoxy, ethoxy, propoxy, oxo, trifluoromethyl, difluoromethyl, sulfonylamino, methanesulfonylamino, SO, SO₂, phenyl, piperidinyl, piperizinyl, and pyrimidinyl, wherein the alkyl, aryl and heterocyclic portions thereof may be optionally substituted, such as by one to four instances of substituents selected from this same list.

“Heterocyclic group”, “heterocyclic”, “heterocycle”, “heterocyclyl”, or “heterocyclo” are used interchangeably and refer to any mono-, bi-, tricyclic or spiro, saturated, partially saturated or unsaturated, aromatic (heteroaryl) or non-aromatic (e.g., heterocycloalkyl), ring system, having 3 to 20 ring atoms, where the ring atoms are carbon, and at least one atom in the ring or ring system is a heteroatom selected from nitrogen, sulfur or oxygen. If any ring atom of a cyclic system is a heteroatom, that system is a heterocycle, regardless of the point of attachment of the cyclic system to the rest of the molecule. In one example, heterocyclyl includes 3-11 ring atoms (“members”) and includes monocycles, bicycles, tricycles and spiro ring systems, wherein the ring atoms are carbon, where at least one atom in the ring or ring

system is a heteroatom selected from nitrogen, sulfur or oxygen. In one example, heterocyclyl includes 1 to 4 heteroatoms. In one example, heterocyclyl includes 1 to 3 heteroatoms. In another example, heterocyclyl includes 3- to 7-membered monocycles having 1-2, 1-3 or 1-4 heteroatoms selected from nitrogen, sulfur or oxygen. In another example, heterocyclyl includes 4- to 6-membered monocycles having 1-2, 1-3 or 1-4 heteroatoms selected from nitrogen, sulfur or oxygen. In another example, heterocyclyl includes 3-membered monocycles. In another example, heterocyclyl includes 4-membered monocycles. In another example, heterocyclyl includes 5-6 membered monocycles, e.g., 5-6 membered heteroaryl. In another example, heterocyclyl includes 3-11 membered heterocycloalkyls, such as 4-11 membered heterocycloalkyls. In some embodiments, a heterocycloalkyl includes at least one nitrogen. In one example, the heterocyclyl group includes 0 to 3 double bonds. Any nitrogen or sulfur heteroatom may optionally be oxidized (e.g., NO, SO, SO₂), and any nitrogen heteroatom may optionally be quaternized (e.g., [NR₄]⁺Cl⁻, [NR₄]⁺OH⁻). Example heterocycles are oxiranyl, aziridinyl, thiranyl, azetidiny, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, pyrrolidinyl, dihydro-1H-pyrrolyl, dihydrofuranyl, tetrahydrofuranyl, dihydrothienyl, tetrahydrothienyl, imidazolidinyl, piperidinyl, piperazinyl, isoquinolinyl, tetrahydroisoquinolinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, dihydropyranyl, tetrahydropyranyl, hexahydrothiopyranyl, hexahydropyrimidinyl, oxazinanyl, thiazinanyl, thioxanyl, homopiperazinyl, homopiperidinyl, azepanyl, oxepanyl, thiepanyl, oxazepinyl, oxazepanyl, diazepanyl, 1,4-diazepanyl, diazepinyl, thiazepinyl, thiazepanyl, tetrahydrothiopyranyl, oxazolidinyl, thiazolidinyl, isothiazolidinyl, 1,1-dioxoisothiazolidinonyl, oxazolidinonyl, imidazolidinonyl, 4,5,6,7-tetrahydro[2H]indazolyl, tetrahydrobenzimidazolyl, 4,5,6,7-tetrahydrobenzo[d]imidazolyl, 1,6-dihydroimidazol[4,5-d]pyrrolo[2,3-b]pyridinyl, thiazinyl, oxazinyl, thiadiazinyl, oxadiazinyl, dithiazinyl, dioxazinyl, oxathiazinyl, thiatiazinyl, oxatriazinyl, dithiadiazinyl, imidazolinyl, dihydropyrimidyl, tetrahydropyrimidyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, thiapyranyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrimidinonyl, pyrimidindionyl, pyrimidin-2,4-dionyl, piperazinonyl, piperazindionyl, pyrazolidinylimidazolinyl, 3-azabicyclo[3.1.0]hexanyl, 3,6-diazabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 2-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, 2-azabicyclo[2.2.2]octanyl, 8-azabicyclo[2.2.2]octanyl, 7-oxabicyclo[2.2.1]heptane, azaspiro[3.5]nonanyl, azaspiro[2.5]octanyl, azaspiro[4.5]decanyl, 1-azaspiro[4.5]decan-2-onyl, azaspiro[5.5]undecanyl, tetrahydroindolyl, octahydroindolyl,

tetrahydroisindolyl, tetrahydroindazolyl, 1,1-dioxohexahydrothiopyranyl. Examples of 5-membered heterocycles containing a sulfur or oxygen atom and one to three nitrogen atoms are thiazolyl, including thiazol-2-yl and thiazol-2-yl N-oxide, thiadiazolyl, including 1,3,4-thiadiazol-5-yl and 1,2,4-thiadiazol-5-yl, oxazolyl, for example oxazol-2-yl, and oxadiazolyl, such as 1,3,4-oxadiazol-5-yl, and 1,2,4-oxadiazol-5-yl. Example 5-membered ring heterocycles containing 2 to 4 nitrogen atoms include imidazolyl, such as imidazol-2-yl; triazolyl, such as 1,3,4-triazol-5-yl; 1,2,3-triazol-5-yl, 1,2,4-triazol-5-yl, and tetrazolyl, such as 1H-tetrazol-5-yl. Example benzo-fused 5-membered heterocycles are benzoxazol-2-yl, benzthiazol-2-yl and benzimidazol-2-yl. Example 6-membered heterocycles contain one to three nitrogen atoms and optionally a sulfur or oxygen atom, for example pyridyl, such as pyrid-2-yl, pyrid-3-yl, and pyrid-4-yl; pyrimidyl, such as pyrimid-2-yl and pyrimid-4-yl; triazinyl, such as 1,3,4-triazin-2-yl and 1,3,5-triazin-4-yl; pyridazinyl, in particular pyridazin-3-yl, and pyrazinyl. The pyridine N-oxides and pyridazine N-oxides and the pyridyl, pyrimid-2-yl, pyrimid-4-yl, pyridazinyl and the 1,3,4-triazin-2-yl groups, are other example heterocycle groups. Heterocycles may be optionally substituted. For example, substituents for “optionally substituted heterocycles” include one to four instances of F, Cl, Br, I, OH, SH, CN, NH₂, NHCH₃, N(CH₃)₂, NO₂, N₃, C(O)CH₃, COOH, CO₂CH₃, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, cyclopropyl, methoxy, ethoxy, propoxy, oxo, trifluoromethyl, difluoromethyl, sulfonylamino, methanesulfonylamino, SO, SO₂, phenyl, piperidinyl, piperizinyl, and pyrimidinyl, wherein the alkyl, aryl and heterocyclic portions thereof may be optionally substituted, such as by one to four instances of substituents selected from this same list.

“Heteroaryl” refers to any mono-, bi-, or tricyclic ring system where at least one ring is a 5- or 6-membered aromatic ring containing from 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur, and in an example embodiment, at least one heteroatom is nitrogen. See, for example, Lang’s Handbook of Chemistry (Dean, J. A., ed.) 13th ed. Table 7-2 [1985]. Included in the definition are any bicyclic groups where any of the above heteroaryl rings are fused to an aryl ring, wherein the aryl ring or the heteroaryl ring is joined to the remainder of the molecule. In one embodiment, heteroaryl includes 5-6 membered monocyclic aromatic groups where one or more ring atoms is nitrogen, sulfur or oxygen. Example heteroaryl groups include thienyl, furyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, tetrazinyl, tetrazolo[1,5-

b]pyridazinyl, imidazol[1,2-a]pyrimidinyl and purinyl, as well as benzo-fused derivatives, for example benzoxazolyl, benzofuryl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl, benzoimidazolyl and indolyl. Heteroaryl groups can be optionally substituted. In some embodiments, substituents for “optionally substituted heteroaryls” include one to four instances of F, Cl, Br, I, OH, SH, CN, NH₂, NHCH₃, N(CH₃)₂, NO₂, N₃, C(O)CH₃, COOH, CO₂CH₃, methyl, ethyl, propyl, iso-propyl, butyl, isobutyl, cyclopropyl, methoxy, ethoxy, propoxy, trifluoromethyl, difluoromethyl, sulfonylamino, methanesulfonylamino, SO, SO₂, phenyl, piperidinyl, piperizinyl, and pyrimidinyl, wherein the alkyl, phenyl and heterocyclic portions thereof may be optionally substituted, such as by one to four instances of substituents selected from this same list.

In particular embodiments, a heterocyclyl group is attached at a carbon atom of the heterocyclyl group. By way of example, carbon bonded heterocyclyl groups include bonding arrangements at position 2, 3, 4, 5, or 6 of a pyridine ring, position 3, 4, 5, or 6 of a pyridazine ring, position 2, 4, 5, or 6 of a pyrimidine ring, position 2, 3, 5, or 6 of a pyrazine ring, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole ring, position 2, 4, or 5 of an oxazole, imidazole or thiazole ring, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole ring, position 2 or 3 of an aziridine ring, position 2, 3, or 4 of an azetidine ring, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline ring or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline ring.

In certain embodiments, the heterocyclyl group is N-attached. By way of example, nitrogen bonded heterocyclyl or heteroaryl groups include bonding arrangements at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β -carboline.

The term “alkoxy” refers to a linear or branched monovalent radical represented by the formula -OR in which R is alkyl, as defined herein. Alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, mono-, di- and tri-fluoromethoxy and cyclopropoxy. “Haloalkoxy” refers to a haloalkyl group, as that term is defined herein, as R.

The term "alkanoyl" refers to group (alkyl)-C(=O)-, wherein alkyl is as defined herein. For example, C₁-C₆alkanoyl refers to a group of formula (C₁-C₅alkyl)-C(=O)-.

Alkanoyl groups include, formyl, acetyl, propanoyl, isopropanoyl, butanoyl, isobutanoyl, pentanoyl, 3-methylpentanoyl, and hexanoyl.

“Optionally substituted” unless otherwise specified means that a group may be unsubstituted or substituted by one or more (e.g., 0, 1, 2, 3, 4, or 5 or more, or any range derivable therein) of the substituents listed for that group in which said substituents may be the same or different. In an embodiment, an optionally substituted group has 1 substituent. In another embodiment an optionally substituted group has 2 substituents. In another embodiment an optionally substituted group has 3 substituents. In another embodiment an optionally substituted group has 4 substituents. In another embodiment an optionally substituted group has 5 substituents.

As used herein a wavy line “~” that intersects a bond in a chemical structure indicate the point of attachment of the atom to which the wavy bond is connected in the chemical structure to the remainder of a molecule, or to the remainder of a fragment of a molecule. In some embodiments, an arrow together with an asterisk is used in the manner of a wavy line to indicate a point of attachment.

In certain embodiments, divalent groups are described generically without specific bonding configurations. It is understood that the generic description is meant to include both bonding configurations, unless specified otherwise. For example, in the group $R^1-R^2-R^3$, if the group R^2 is described as $-CH_2C(O)-$, then it is understood that this group can be bonded both as $R^1-CH_2C(O)-R^3$, and as $R^1-C(O)CH_2-R^3$, unless specified otherwise.

The phrase “pharmaceutically acceptable” refers to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, such as, for example, a human, as appropriate.

Compounds of the invention may be in the form of a salt, such as a pharmaceutically acceptable salt. “Pharmaceutically acceptable salts” include both acid and base addition salts. “Pharmaceutically acceptable acid addition salt” refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid and the like, and organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, malonic

acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

5 “Pharmaceutically acceptable base addition salts” include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particular base addition salts are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from
10 pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, tromethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine,
15 piperidine, N-ethylpiperidine, polyamine resins and the like. Particular organic non-toxic bases include isopropylamine, diethylamine, ethanolamine, tromethamine, dicyclohexylamine, choline, and caffeine.

In some embodiments, a salt is selected from a hydrochloride, hydrobromide, trifluoroacetate, sulphate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate,
20 pyruvate, succinate, oxalate, methanesulphonate, p-toluenesulphonate, bisulphate, benzenesulphonate, ethanesulphonate, malonate, xinafoate, ascorbate, oleate, nicotinate, saccharinate, adipate, formate, glycolate, palmitate, L-lactate, D-lactate, aspartate, malate, L-tartrate, D-tartrate, stearate, furoate (e.g., 2-furoate or 3-furoate), napadisylate (naphthalene-1,5-disulfonate or naphthalene-1-(sulfonic acid)-5-sulfonate), edisylate (ethane-1,2-
25 disulfonate or ethane-1-(sulfonic acid)-2-sulfonate), isothionate (2-hydroxyethylsulfonate), 2-mesitylenesulphonate, 2-naphthalenesulphonate, 2,5-dichlorobenzenesulphonate, D-mandelate, L-mandelate, cinnamate, benzoate, adipate, esylate, malonate, mesitylate (2-mesitylenesulphonate), napsylate (2-naphthalenesulfonate), camsylate (camphor-10-sulphonate, for example (1S)-(+)-10-camphorsulfonic acid salt), glutamate, glutarate,
30 hippurate (2-(benzoylamino)acetate), orotate, xylate (p-xylene-2-sulphonate), and pamoic (2,2'-dihydroxy-1,1'-dinaphthylmethane-3,3'-dicarboxylate).

A “sterile” formulation is aseptic or free from all living microorganisms and their spores.

“Stereoisomers” refer to compounds that have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. Stereoisomers include diastereomers, enantiomers, conformers and the like.

5 “Chiral” refers to molecules which have the property of non-superimposability of the mirror image partner, while the term “achiral” refers to molecules which are superimposable on their mirror image partner.

“Diastereomer” refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g., melting points, boiling points, spectral properties or biological
10 activities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography such as HPLC.

“Enantiomers” refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker,
15 Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., “Stereochemistry of Organic Compounds”, John Wiley & Sons, Inc., New York, 1994. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S*, are used to denote the absolute
20 configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an
25 enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms “racemic mixture” and “racemate” refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

30 The term “tautomer” or “tautomeric form” refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton,

such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

Certain compounds of the invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. A "solvate" refers to an association or complex of one or more solvent molecules and a compound of the present invention. Examples of solvents that form solvates include water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine. Certain compounds of the invention can exist in multiple crystalline or amorphous forms. In general, all physical forms are intended to be within the scope of the present invention. The term "hydrate" refers to the complex where the solvent molecule is water.

A "metabolite" refers to a product produced through metabolism in the body of a specified compound or salt thereof. Such products can result, for example, from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound.

Metabolite products typically are identified by preparing a radiolabelled (e.g., ^{14}C or ^3H) isotope of a compound of the invention, administering it in a detectable dose (e.g., greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to a human, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS, LC/MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well known to those skilled in the art. The metabolite products, so long as they are not otherwise found in vivo, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention.

"Amino-protecting group" as used herein refers to a derivative of the groups commonly employed to block or protect an amino group while reactions are carried out on other functional groups on the compound. Examples of such protecting groups include carbamates, amides, alkyl and aryl groups, and imines, as well as many N-heteroatom derivatives which can be removed to regenerate the desired amine group. Particular amino protecting groups are Pmb (p-Methoxybenzyl), Boc (tert-Butyloxycarbonyl), Fmoc (9-

Fluorenylmethyloxycarbonyl) and Cbz (Carbobenzyloxy). Further examples of these groups are found in T. W. Greene and P. G. M. Wuts, "Protecting Groups in Organic Synthesis, 3rd ed., John Wiley & Sons, Inc., 1999. The term "protected amino" refers to an amino group substituted with one of the above amino-protecting groups.

5 "Carboxy-protecting group" as used herein refers to those groups that are stable to the conditions of subsequent reaction(s) at other positions of the molecule, which may be removed at the appropriate point without disrupting the remainder of the molecule, to give the unprotected carboxy-group. Examples of carboxy protecting groups include, ester groups and heterocyclyl groups. Ester derivatives of the carboxylic acid group may be employed to
10 block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such ester groups include substituted arylalkyl, including substituted benzyls, such as 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxybenzhydryl, 2,2',4,4'-
15 tetramethoxybenzhydryl, alkyl or substituted alkyl esters such as methyl, ethyl, t-butyl allyl or t-amyl, triphenylmethyl (trityl), 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4''-trimethoxytrityl, 2-phenylprop-2-yl, thioesters such as t-butyl thioester, silyl esters such as trimethylsilyl, t-butyldimethylsilyl esters, phenacyl, 2,2,2-trichloroethyl, beta-(trimethylsilyl)ethyl, beta-(di(n-butyl)methylsilyl)ethyl, p-toluenesulfonyl, 4-
20 nitrobenzylsulfonyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)prop-1-en-3-yl, and like moieties. Another example of carboxy-protecting groups are heterocyclyl groups such as 1,3-oxazoliny. Further examples of these groups are found in T. W. Greene and P. G. M. Wuts, "Protecting Groups in Organic Synthesis, 3rd ed., John Wiley & Sons, Inc., 1999. The term "protected carboxy" refers to a carboxy group substituted with one of the above carboxy-
25 protecting groups.

"Hydroxy-protecting group" as used herein refers to a derivative of the hydroxy group commonly employed to block or protect the hydroxy group while reactions are carried out on other functional groups on the compound. Examples of such protecting groups include tetrahydropyranyloxy, benzoyl, acetoxy, carbamoyloxy, benzyl, and silylethers (e.g., TBS,
30 TBDPS) groups. Further examples of these groups are found in T. W. Greene and P. G. M. Wuts, "Protecting Groups in Organic Synthesis, 3rd ed., John Wiley & Sons, Inc., 1999. The term "protected hydroxy" refers to a hydroxy group substituted with one of the above hydroxy-protecting groups.

Compounds of the invention may contain one or more asymmetric carbon atoms. Accordingly, the compounds may exist as diastereomers, enantiomers or mixtures thereof. The syntheses of the compounds may employ racemates, diastereomers or enantiomers as starting materials or as intermediates. Mixtures of particular diastereomeric compounds may
5 be separated, or enriched in one or more particular diastereomers, by chromatographic or crystallization methods. Similarly, enantiomeric mixtures may be separated, or enantiomerically enriched, using the same techniques or others known in the art. Each of the asymmetric carbon or nitrogen atoms may be in the R or S configuration and both of these configurations are within the scope of the invention.

10 In the structures shown herein, where the stereochemistry of any particular chiral atom is not specified, then all stereoisomers are contemplated and included as the compounds of the invention. Where stereochemistry is specified by a solid wedge or dashed line representing a particular configuration, then that stereoisomer is so specified and defined. Unless otherwise specified, if solid wedges or dashed lines are used, relative stereochemistry
15 is intended.

Another aspect includes prodrugs of the compounds of the invention including known amino-protecting and carboxy-protecting groups which are released, for example hydrolyzed, to yield the compound of the present invention under physiologic conditions.

The term "prodrug" refers to a precursor or derivative form of a pharmaceutically
20 active substance that is less efficacious to the patient compared to the parent drug and is capable of being enzymatically or hydrolytically activated or converted into the more active parent form. See, e.g., Wilman, "Prodrugs in Cancer Chemotherapy" Biochemical Society Transactions, 14, pp. 375-382, 615th Meeting Belfast (1986) and Stella et al., "Prodrugs: A Chemical Approach to Targeted Drug Delivery," Directed Drug Delivery, Borchardt et al.,
25 (ed.), pp. 247-267, Humana Press (1985). Prodrugs include, but are not limited to, phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, D-amino acid-modified prodrugs, glycosylated prodrugs, β -lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs or optionally substituted phenylacetamide-containing prodrugs, and 5-
30 fluorocytosine and 5-fluorouridine prodrugs.

A particular class of prodrugs are compounds in which a nitrogen atom in an amino, amidino, aminoalkyleneamino, iminoalkyleneamino or guanidino group is substituted with a

hydroxy group, an alkylcarbonyl (-CO-R) group, an alkoxycarbonyl (-CO-OR), or an acyloxyalkyl-alkoxycarbonyl (-CO-O-R-O-CO-R) group where R is a monovalent or divalent group, for example alkyl, alkylene or aryl, or a group having the Formula -C(O)-O-CP1P2-haloalkyl, where P1 and P2 are the same or different and are hydrogen, alkyl, alkoxy, cyano, halogen, alkyl or aryl. In a particular embodiment, the nitrogen atom is one of the nitrogen atoms of the amidino group of the compounds of the invention. Prodrugs may be prepared by reacting a compound of the present invention with an activated group, such as acyl groups, to bond, for example, a nitrogen atom in the compound to the exemplary carbonyl of the activated acyl group. Examples of activated carbonyl compounds are those containing a leaving group bonded to the carbonyl group, and include, for example, acyl halides, acyl amines, acyl pyridinium salts, acyl alkoxides, acyl phenoxides such as p-nitrophenoxy acyl, dinitrophenoxy acyl, fluorophenoxy acyl, and difluorophenoxy acyl. The reactions are generally carried out in inert solvents at reduced temperatures such as -78 to about 50°C. The reactions may also be carried out in the presence of an inorganic base, for example potassium carbonate or sodium bicarbonate, or an organic base such as an amine, including pyridine, trimethylamine, triethylamine, triethanolamine, or the like.

Additional types of prodrugs are also encompassed. For instance, a free carboxyl group of a compound of the invention can be derivatized as an amide or alkyl ester. As another example, compounds of the invention comprising free hydroxy groups can be derivatized as prodrugs by converting the hydroxy group into a group such as, but not limited to, a phosphate ester, hemisuccinate, dimethylaminoacetate, or phosphoryloxymethyloxycarbonyl group, as outlined in Fleisher, D. et al., (1996) Improved oral drug delivery: solubility limitations overcome by the use of prodrugs *Advanced Drug Delivery Reviews*, 19:115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers, wherein the acyl group can be an alkyl ester optionally substituted with groups including, but not limited to, ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in J. Med. Chem., (1996), 39:10. More specific examples include replacement of the hydrogen atom of the alcohol group with a group such as (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-C₆)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁-

C₆)alkanoyl, alpha-amino(C₁-C₄)alkanoyl, arylacyl and alpha-aminoacyl, or alpha-aminoacyl-alpha-aminoacyl, where each alpha-aminoacyl group is independently selected from the naturally occurring L-amino acids, P(O)(OH)₂, -P(O)(O(C₁-C₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

5 “Leaving group” refers to a portion of a first reactant in a chemical reaction that is displaced from the first reactant in the chemical reaction. Examples of leaving groups include, but are not limited to, halogen atoms, alkoxy and sulfonyloxy groups. Example sulfonyloxy groups include, but are not limited to, alkylsulfonyloxy groups (for example methyl sulfonyloxy (mesylate group) and trifluoromethylsulfonyloxy (triflate group)) and
10 arylsulfonyloxy groups (for example p-toluenesulfonyloxy (tosylate group) and p-nitrosulfonyloxy (nosylate group)).

A “subject,” “individual,” or “patient” is a vertebrate. In certain embodiments, the vertebrate is a mammal. Mammals include, but are not limited to, farm animals (such as cows), sport animals, pets (such as guinea pigs, cats, dogs, rabbits and horses), primates, mice
15 and rats. In certain embodiments, a mammal is a human. In embodiments comprising administration of a compound of to a patient, the patient is typically in need thereof.

The terms “inhibiting” and “reducing,” or any variation of these terms, includes any measurable decrease or complete inhibition to achieve a desired result. For example, there may be a decrease of about, at most about, or at least about 5%, 10%, 15%, 20%, 25%, 30%,
20 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more, or any range derivable therein, reduction of activity (e.g., Factor D activity) compared to normal.

A “therapeutically effective amount” means an amount of a compound of the present invention, such as a compound falling within the scope of the various structural formulae
25 disclosed herein (e.g., a compound of Tables 1 and 2), that (i) treats or prevents the particular disease, condition or disorder, or (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease, condition, or disorder, and optionally (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition or disorder described herein. In some embodiments, the therapeutically effective amount is an amount
30 sufficient to decrease or alleviate the symptoms of a complement-associated disorder or complement-associated eye condition. In some embodiments, a therapeutically effective

amount is an amount of a chemical entity described herein sufficient to significantly decrease the activity of Factor D.

“Treatment” (and variations such as “treat” or “treating”) refers to clinical intervention in an attempt to alter the natural course of the individual or cell being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, stabilized (i.e., not worsening) state of disease, decreasing the rate of disease progression, amelioration or palliation of the disease state, prolonging survival as compared to expected survival if not receiving treatment and remission or improved prognosis. In some embodiments, compounds of the invention, are used to delay development of a disease or disorder or to slow the progression of a disease or disorder. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder, (for example, through a genetic mutation) or those in which the condition or disorder is to be prevented. In yet another embodiment, “treat”, “treating” or “treatment” refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, “treat”, “treating” or “treatment” refers to preventing or delaying the onset or development or progression of the disease or disorder.

The term “complement-associated disorder” is used in the broadest sense and includes disorders associated with excessive or uncontrolled complement activation. They include complement activation during cardiopulmonary bypass operations; complement activation due to ischemia-reperfusion following acute myocardial infarction, aneurysm, stroke, hemorrhagic shock, crush injury, multiple organ failure, hypobolemic shock, intestinal ischemia or other events causing ischemia. Complement activation has also been shown to be associated with inflammatory conditions such as severe burns, endotoxemia, septic shock, adult respiratory distress syndrome, hemodialysis; anaphylactic shock, severe asthma, angioedema, Crohn’s disease, sickle cell anemia, poststreptococcal glomerulonephritis and pancreatitis. The disorder may be the result of an adverse drug reaction, drug allergy, IL-2 induced vascular leakage syndrome or radiographic contrast media allergy. It also includes autoimmune disease such as systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, Alzheimer’s disease and multiple sclerosis. Complement activation is also associated with transplant rejection. Complement activation is also associated with ocular

diseases such as age-related macular degeneration, diabetic retinopathy and other ischemia-related retinopathies, choroidal neovascularization (CNV), uveitis, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization.

5 The term “complement-associated eye condition” is used in the broadest sense and includes all eye conditions the pathology of which involves complement, including the classical and the alternative pathways, and in particular the alternative pathway of complement. Complement-associated eye conditions include, without limitation, macular degenerative diseases, such as all stages of age-related macular degeneration (AMD),
10 including dry and wet (non-exudative and exudative) forms, choroidal neovascularization (CNV), uveitis, open-angle and angle-closure glaucoma, diabetic and other ischemia-related retinopathies, and other intraocular neovascular diseases, such as diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization. In one
15 example, complement-associated eye conditions includes age-related macular degeneration (AMD), including non-exudative (e.g., intermediate dry AMD or geographic atrophy (GA)) and exudative (e.g., wet AMD (choroidal neovascularization (CNV)) AMD, diabetic retinopathy (DR), endophthalmitis and uveitis. In a further example, nonexudative AMD may include the presence of hard drusen, soft drusen, geographic atrophy and/or pigment
20 clumping. In one example, complement-associated eye conditions include age-related macular degeneration (AMD), including early AMD (e.g., includes multiple small to one or more non-extensive medium sized drusen), intermediate AMD (e.g., includes extensive medium drusen to one or more large drusen) and advanced AMD (e.g., includes geographic atrophy or advanced wet AMD (CNV). (Ferris et al., AREDS Report No. 18; Sallo et al.,
25 Eye Res., 34(3): 238-40 (2009); Jager et al., *New Engl. J. Med.*, 359(1): 1735 (2008)). In a further example, intermediate dry AMD may include large confluent drusen. In a further example, geographic atrophy may include photoreceptor and/or Retinal Pigmented Epithelial (RPE) loss. In a further example, the area of geographic atrophy may be small or large and/or may be in the macula area or in the peripheral retina. In one example, complement-
30 associated eye condition is intermediate dry AMD. In one example, complement-associated eye condition is geographic atrophy. In one example, complement-associated eye condition is wet AMD (choroidal neovascularization (CNV)).

The terms “Factor D” and “fD” and “FD,” as used herein, refers to any native, mature Factor D which results from processing of a Factor D precursor protein in a cell. The term includes Factor D from any vertebrate source, including mammals such as primates (e.g., humans and cynomolgus monkeys) and rodents (e.g., mice and rats), unless otherwise indicated. The term also includes naturally occurring variants of Factor D, e.g., splice variants or allelic variants.

The term “pharmaceutical formulation” refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered.

A “pharmaceutically acceptable carrier” refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

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. Exemplary isotopes that can be incorporated into compounds of the invention, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I , respectively. Isotopically-labeled compounds (e.g., those labeled with ^3H and ^{14}C) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., ^3H) and carbon-14 (i.e., ^{14}C) isotopes can be useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). In some embodiments, in compounds of the invention, one or more carbon atoms are replaced by ^{13}C - or ^{14}C -enriched carbon. Positron emitting isotopes such as ^{15}O , ^{13}N , ^{11}C , and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds can generally be prepared by following procedures analogous to those disclosed in the Schemes or in the Examples herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

It is specifically contemplated that any limitation discussed with respect to one embodiment of the invention may apply to any other embodiment of the invention. Furthermore, any compound or composition of the invention may be used in any method of the invention, and any method of the invention may be used to produce or to utilize any compound or composition of the invention.

The use of the term “or” is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternative are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and “and/or.”

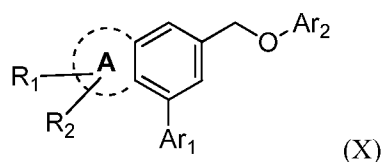
Throughout this application, the term “about” is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value.

As used herein, “a” or “an” means one or more, unless clearly indicated otherwise. As used herein, “another” means at least a second or more.

Headings used herein are intended only for organizational purposes.

FACTOR D INHIBITORS

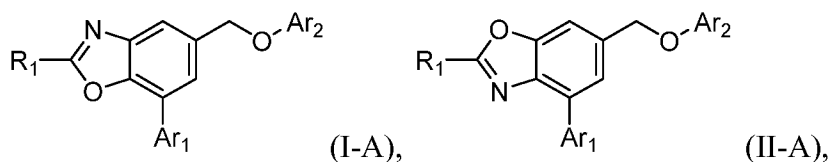
In some embodiments, a compound of the invention is a compound of structure (X):

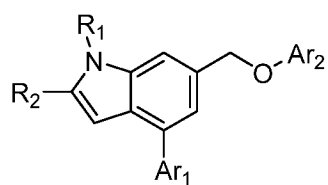


wherein R_1 , Ar_1 , Ar_2 , and, if present, R_2 , are as defined herein, and ring A is a monocyclic heterocycle,

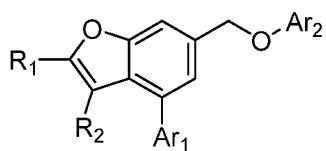
or a stereoisomer or a pharmaceutically acceptable salt thereof.

Another aspect of the invention includes a compound having a structure selected from among structures (I-A) through (XXIII-A). These structures are set forth below:

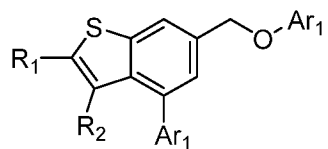




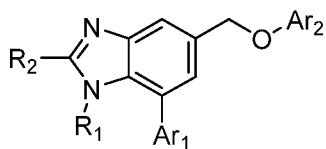
(III-A),



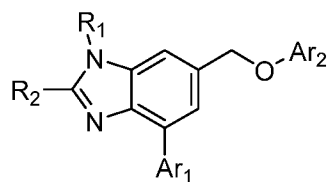
(IV-A),



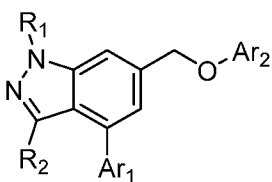
(V-A),



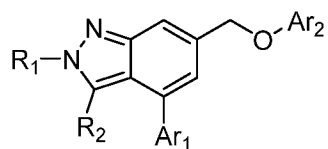
(VI-A),



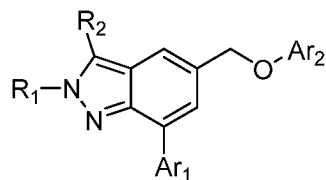
(VII-A),



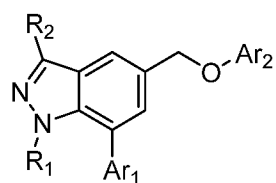
(VIII-A),



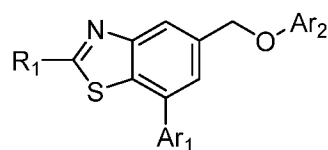
(IX-A),



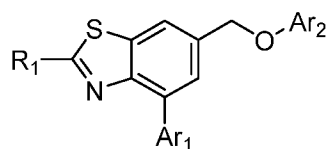
(X-A),



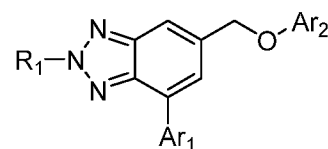
(XI-A),



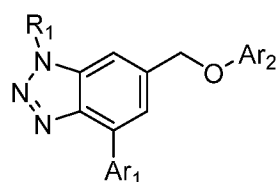
(XII-A),



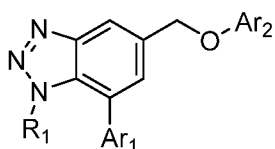
(XIII-A),



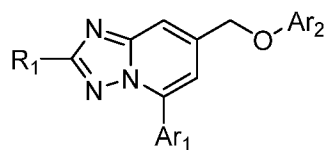
(XIV-A),



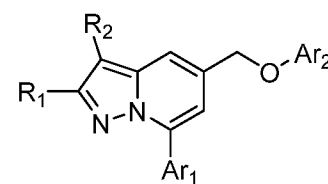
(XV-A),



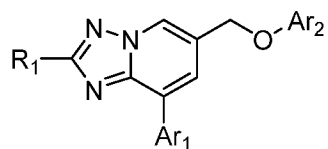
(XVI-A),



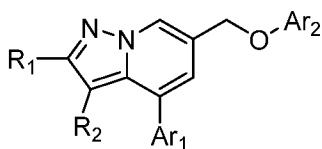
(XVII-A),



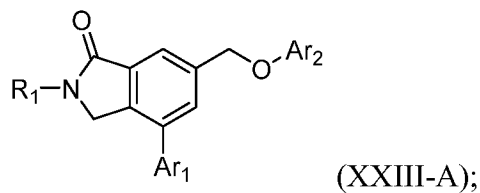
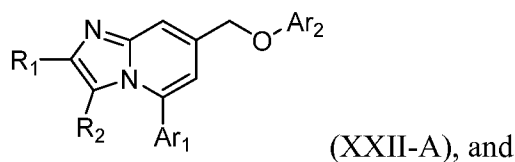
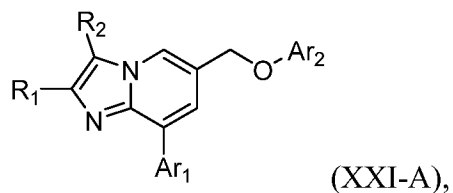
(XVIII-A),



(XIX-A),



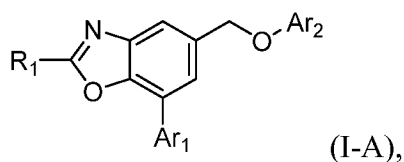
(XX-A),



or a stereoisomer or a pharmaceutically acceptable salt thereof.

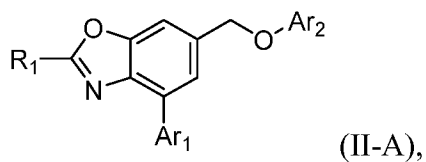
In the above structures (I-A) through (XXIII-A), R₁, R₂, Ar₁, and Ar₂ are as further
 5 detailed herein below.

According to some embodiments, the compound of the invention has the structure:



or a stereoisomer or a pharmaceutically acceptable salt thereof.

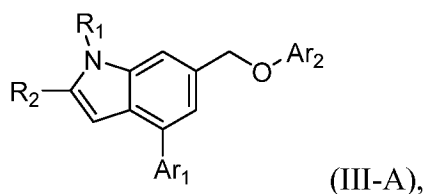
According to some embodiments, the compound of the invention has the structure:



10

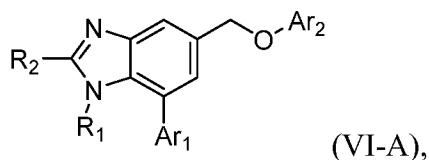
or a stereoisomer or a pharmaceutically acceptable salt thereof.

According to some embodiments, the compound of the invention has the structure:



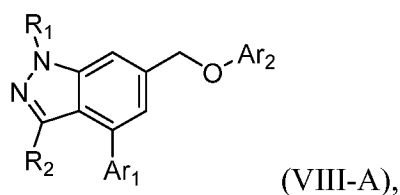
or a stereoisomer or a pharmaceutically acceptable salt thereof.

15 According to some embodiments, the compound of the invention has the structure:



or a stereoisomer or a pharmaceutically acceptable salt thereof.

According to some embodiments, the compound of the invention has the structure:

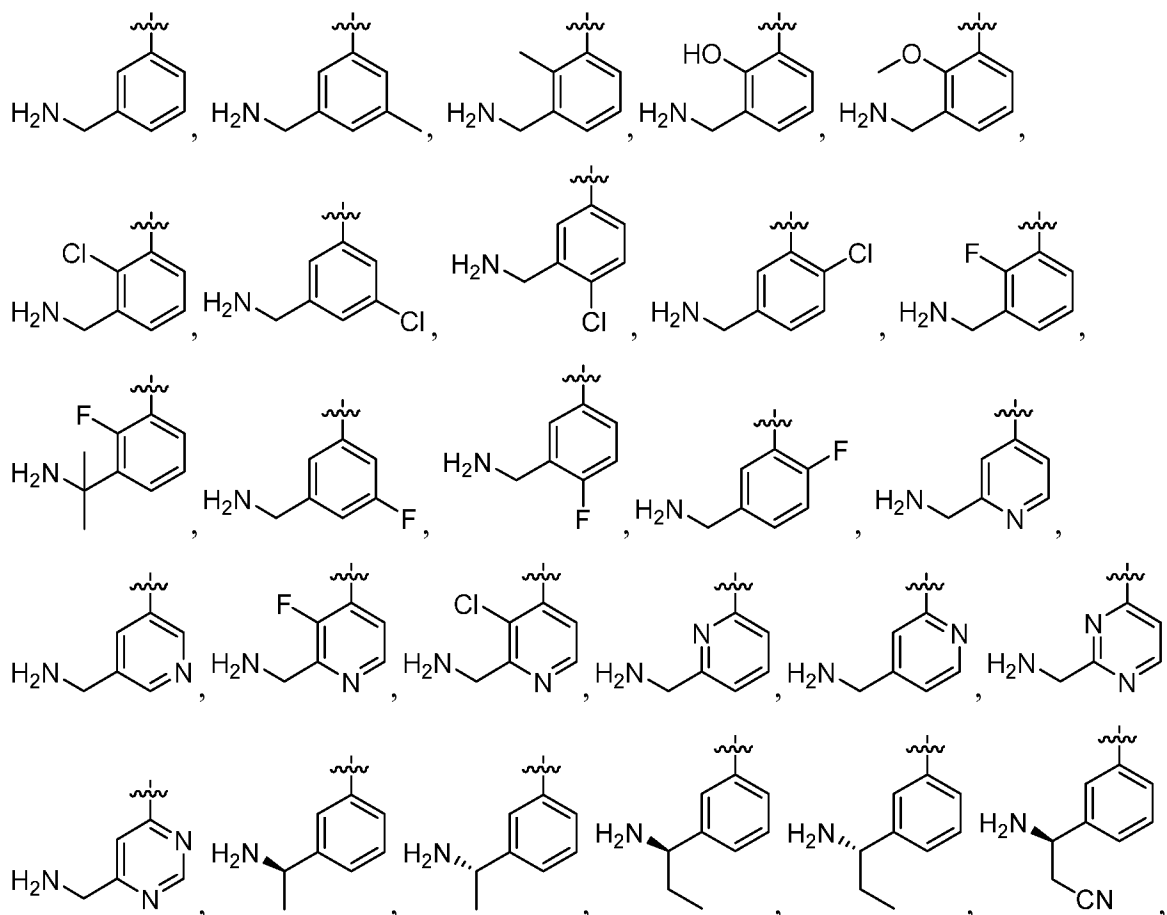


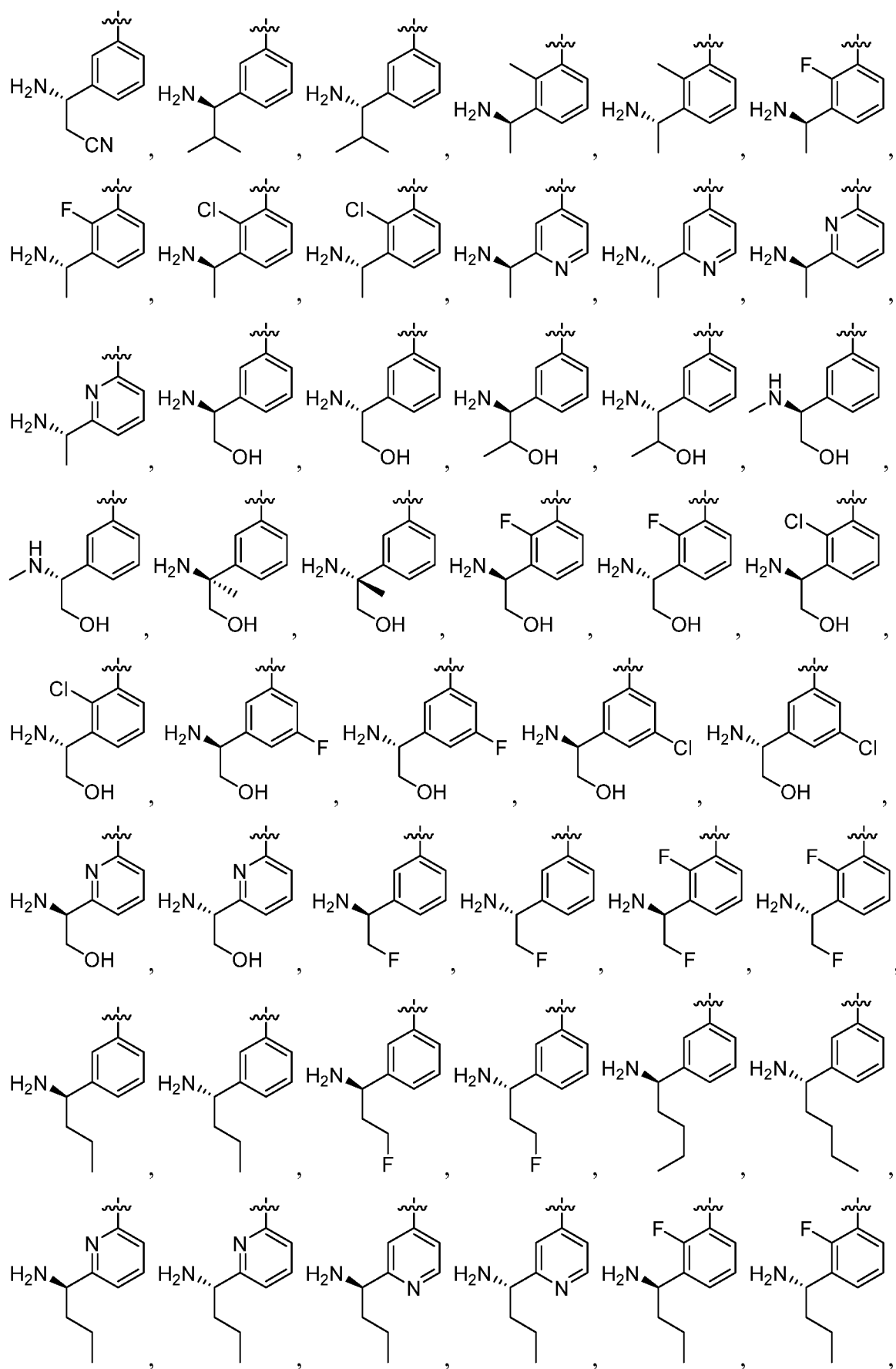
5 or a stereoisomer or a pharmaceutically acceptable salt thereof.

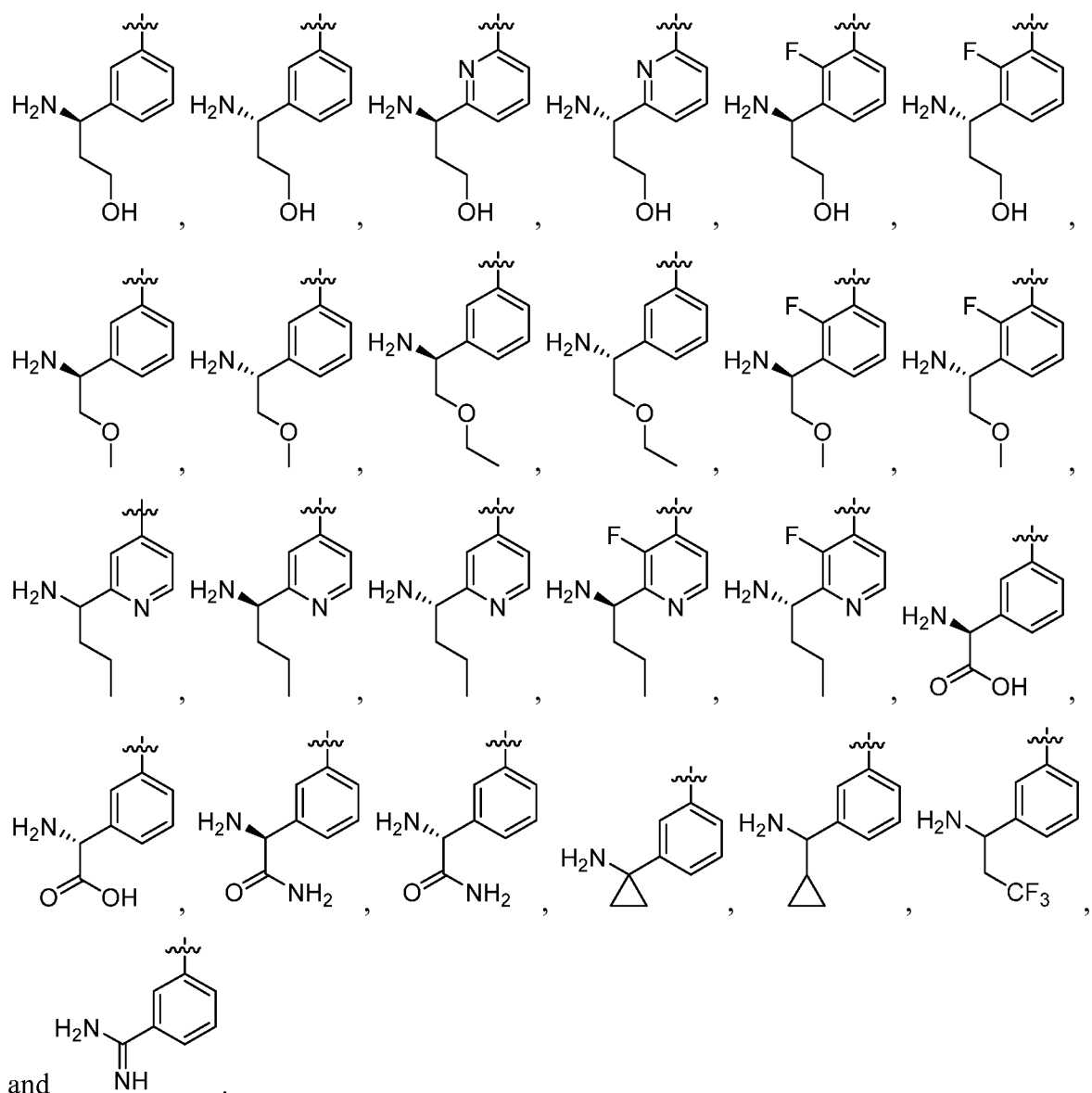
In the above structures (I-A), (II-A), (III-A), (VI-A), and (VIII-A), R₁, R₂, Ar₁, and Ar₂ are as further detailed herein below.

According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a

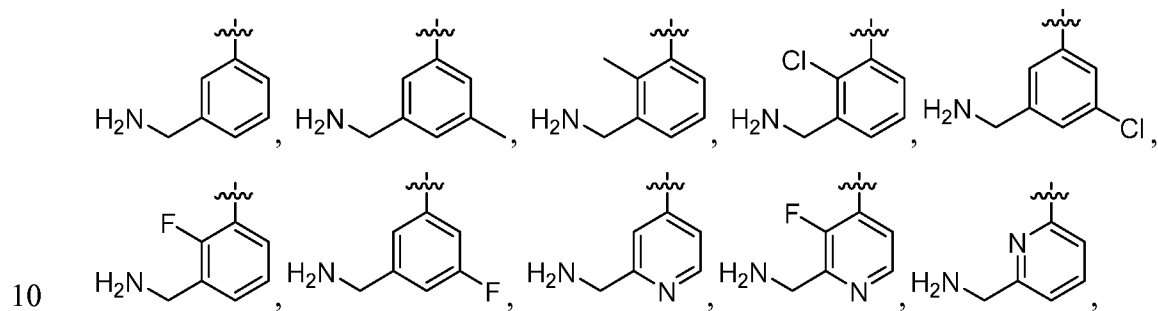
10 pharmaceutically acceptable salt thereof, Ar₁ is selected from the group consisting of

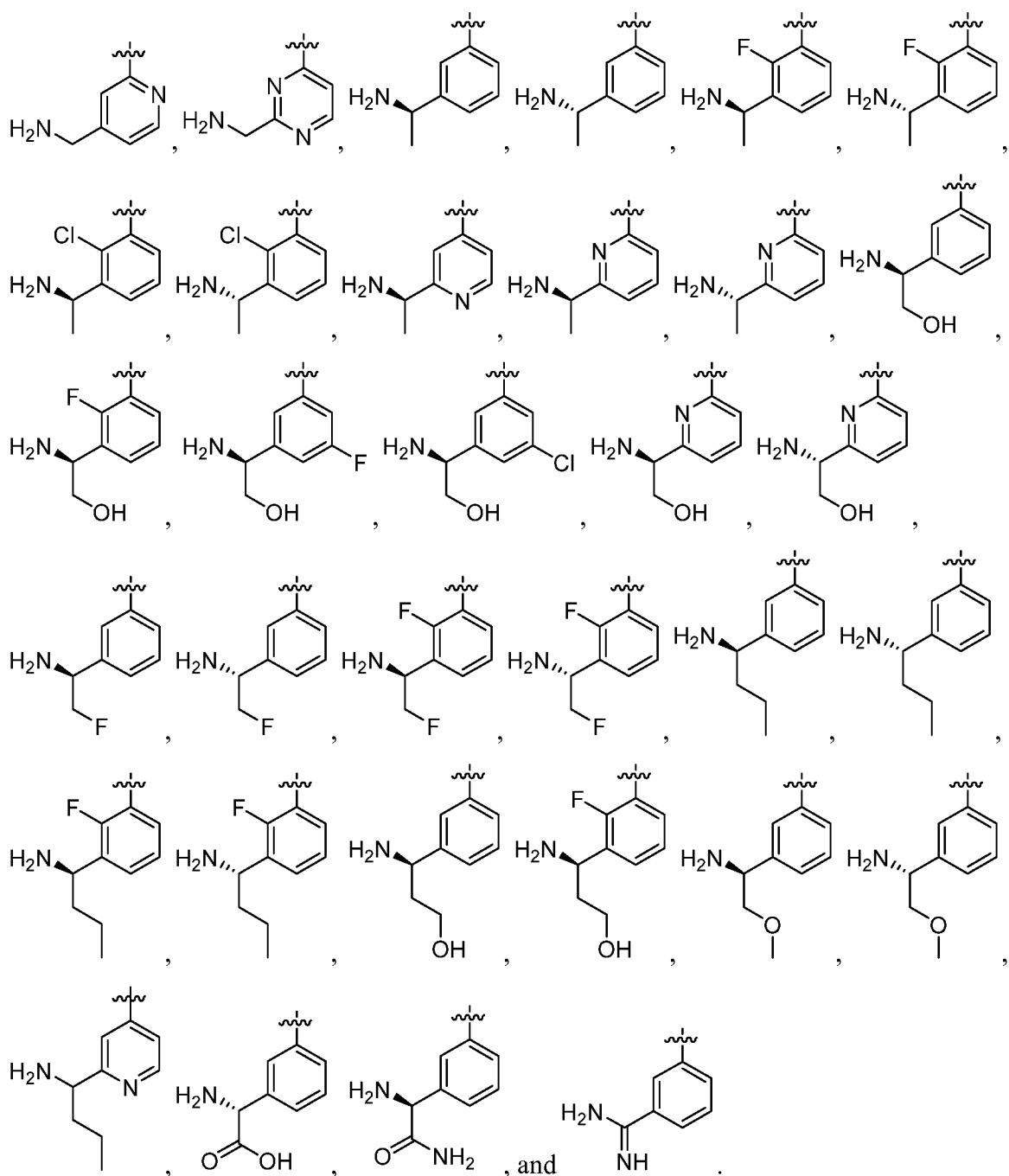




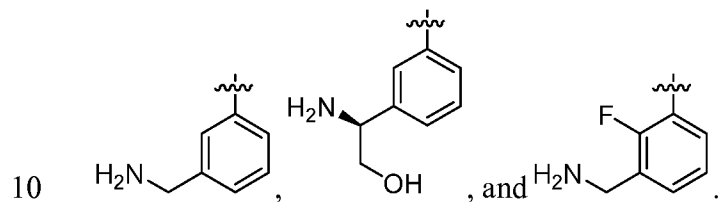


According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a pharmaceutically acceptable salt thereof, Ar₁ is selected from the group consisting of






According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a pharmaceutically acceptable salt thereof, Ar₁ is selected from the group consisting of



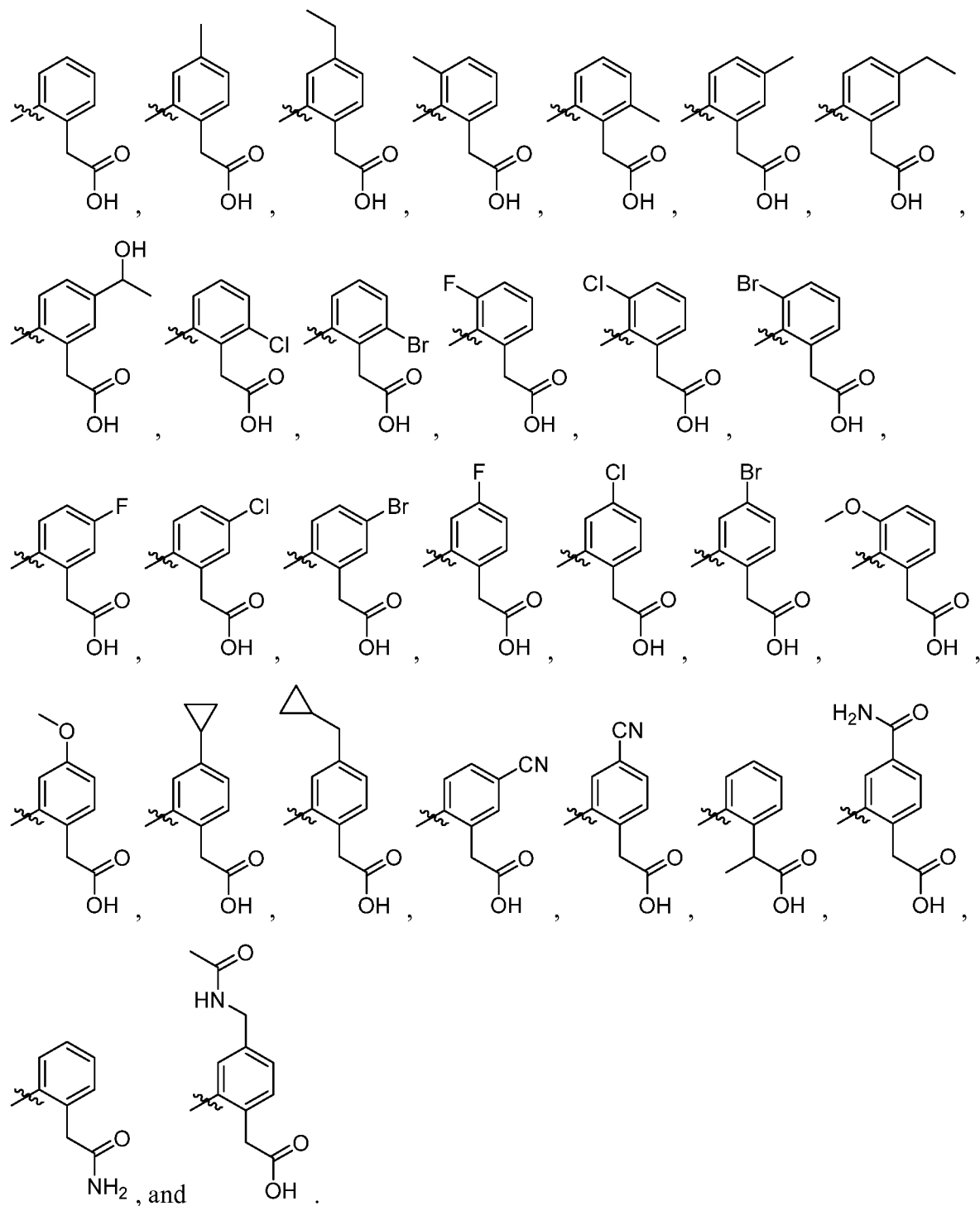
According to some embodiments of the compound of the invention having a structure

selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a

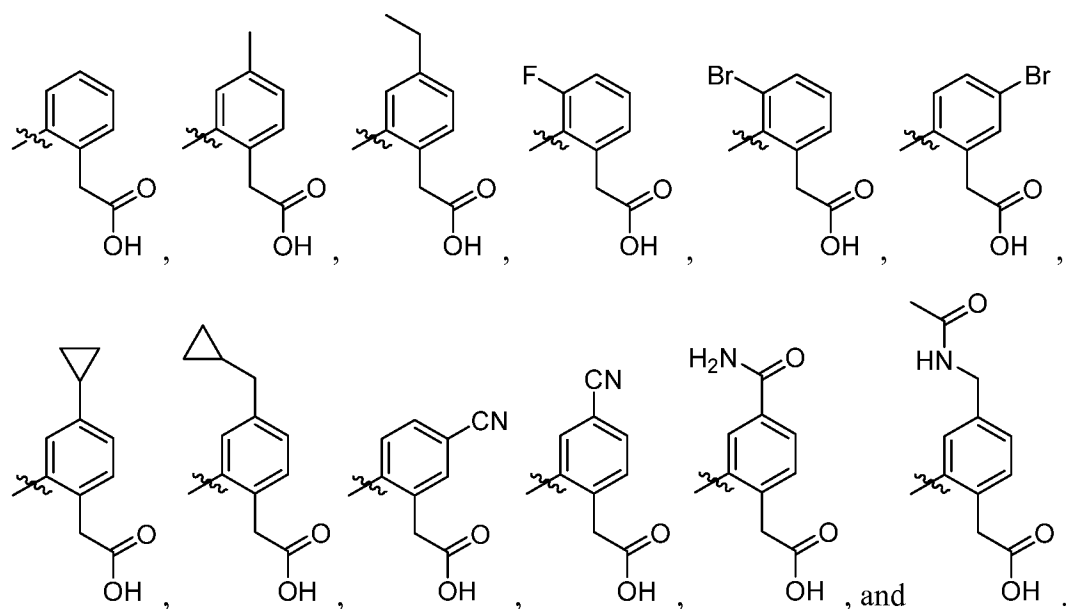
pharmaceutically acceptable salt thereof, Ar₁ is .

According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a

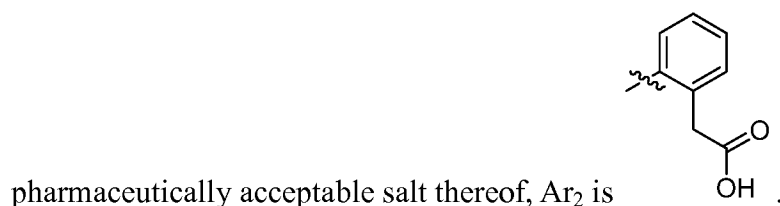
5 pharmaceutically acceptable salt thereof, Ar₂ is selected from the group consisting of



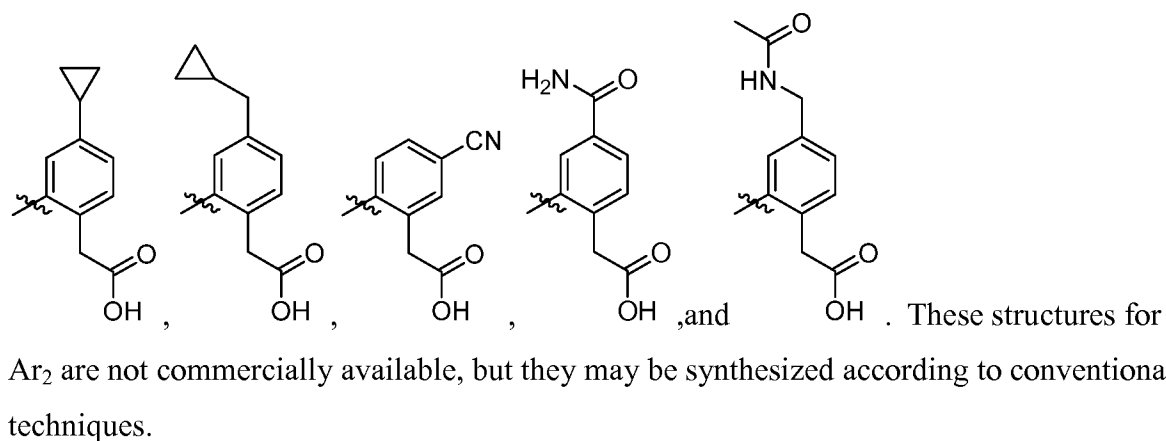
According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a pharmaceutically acceptable salt thereof, Ar₂ is selected from the group consisting of



According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a



10 According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a pharmaceutically acceptable salt thereof, Ar₂ is selected from the group consisting of



15 According to some embodiments of the compound of the invention having a structure

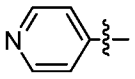
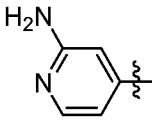
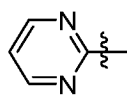
selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a pharmaceutically acceptable salt thereof, each R_1 and R_2 are independently selected from the group consisting of hydrogen, halo, cyano, $-OR_3$, $-SR_3$, $-NR_3R_4$, $-C(O)R_3$, $-C(O)OR_3$, $-C(O)NR_3R_4$, $-S(O)_2R_3$, C_1 - C_6 alkyl optionally substituted with R_3 , C_6 - C_{14} aryl optionally substituted with R_3 , and C_5 - C_{14} heteroaryl optionally substituted with R_3 .

According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a pharmaceutically acceptable salt thereof, each R_3 and R_4 are independently selected from the group consisting of hydrogen, $-NH_2$, C_1 - C_6 alkyl, C_6 - C_{12} aryl, and C_5 - C_{14} heteroaryl.

According to some embodiments of the compound of the invention, the alkyl, aryl, and heteroaryl may be optionally substituted.

According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a pharmaceutically acceptable salt thereof, each R_3 and R_4 are independently selected from the group consisting of hydrogen and C_1 - C_6 alkyl. According to some embodiments of the compound of the invention, the alkyl may be optionally substituted.

According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a pharmaceutically acceptable salt thereof, each R_1 and R_2 are independently selected from the

group consisting of hydrogen, $-NH_2$, $-CH_3$, , , and .

Structural information gleaned from the Protein Data Bank (PDB) (5FCK and 5NB7) along with an internal crystal structure allowed for molecular modeling that suggests R_1 , R_2 , R_3 , and R_4 should extend out into a solvent exposed region of the Factor D protein. Based on this molecular modeling but without being bound by theory, it is believed that a wide variety of functional groups may be incorporated into these positions and may contribute to modulation of properties of each molecule such as solubility and permeability as well as to some extent, potency. According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a pharmaceutically acceptable salt thereof, each R_1 , R_2 , R_3 , and R_4 may be optionally further substituted. Suitable additional substituent groups include functional groups known in the art such as amides, amino acids, ureas, ketones, guanidines, alkanes, alkenes, alkynes,

aryls, heterocycllys (e.g., heteroaryls), amines, alcohols, carboxylates, carboxylic acids, esters, cyano, cycloalkyls, halo, thiols, thioethers, thioureas, thioamides, polyethers including pegylation, and any combination thereof. These groups can be introduced using standard reactions for the formations of C-C, C-N, C-O, or C-S bonds. Such groups may be optionally substituted with other functional groups. Amino acids include any amino acid currently known, including L and D stereoisomers. The amino acids may be bonded to the structures according to the present invention at the carboxylate moiety or the amino moiety. The pegylation group may comprise a polyethylene glycol having weight average molecular weight of from about 100 Da to about 300,000 Da, such as from about 500 Da to about 300,000 Da, or from about 20,000 Da to about 60,000 Da. The pegylation group may be linear, branched, or dendritic.

According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a pharmaceutically acceptable salt thereof, each R_1 and R_2 are independently selected from the group consisting of hydrogen, halo, cyano, $-OH$, $-O-C_1-C_6$ alkyl, $-SH$, $-S-C_1-C_6$ alkyl, $-NH_2$, $-NHC_1-C_6$ alkyl, $-N(C_1-C_6$ alkyl) $_2$, $-C(O)H$, $C(O)C_1-C_6$ alkyl, $-C(O)OH$, $-C(O)OC_1-C_6$ alkyl, $-C(O)ONH_2$, $-C(O)ONHC_1-C_6$ alkyl, $-C(O)ON(C_1-C_6$ alkyl) $_2$, $-S(O)_2H$, $-S(O)_2C_1-C_6$ alkyl, C_1-C_6 alkyl, C_6-C_{14} aryl, and C_5-C_{14} heteroaryl. According to some embodiments of the compound of the invention, the alkyl, aryl, and heteroaryl may be optionally substituted, for example, with additional substituent groups including functional groups known in the art such as amides, amino acids, ureas, ketones, guanidines, alkanes, alkenes, alkynes, aryls, heterocycllys (e.g., heteroaryls), amines, alcohols, carboxylates, carboxylic acids, esters, cyano, cycloalkyls, halo, thiols, thioethers, thioureas, thioamides, polyethers including pegylation, and any combination thereof. Amino acids include any amino acid currently known, including L and D stereoisomers. The amino acids may be bonded to the structures according to the present invention at the carboxylate moiety or the amino moiety. The pegylation group may comprise a polyethylene glycol having weight average molecular weight of from about 100 Da to about 300,000 Da, such as from about 500 Da to about 300,000 Da, or from about 20,000 Da to about 60,000 Da. The pegylation group may be linear, branched, or dendritic.

According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a pharmaceutically acceptable salt thereof, the total molecular weight of R_1 , R_2 , R_3 , and R_4 and

any substituents thereon is less than about 500 Da, such as less than about 400 Da, less than about 300 Da, less than about 200 Da, or even less than about 100 Da, such as between about 1 Da and about 500 Da, or between about 2 Da and about 500 Da, or between about 10 Da and about 500 Da, or between about 20 Da and about 400 Da.

5 According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a pharmaceutically acceptable salt thereof, the total molecular weight of R₁, R₂, R₃, and R₄ and any substituents thereon is greater than about 500 Da, such as greater than about 1000 Da, or even greater than about 10,000 Da, such as between about 500 Da and about 300,000 Da, 10 between about 500 Da and about 60,000 Da, between about 500 Da and about 10,000 Da, or between about 500 Da and about 1000 Da.

 According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a pharmaceutically acceptable salt thereof, the R₁, R₂, R₃, and R₄ and any substituents thereon 15 may increase the total polar surface area (TPSA) and/or hydrogen bond donor count in order to maximize solubility and/or reduce permeability. Methods of measuring TPSA and hydrogen bond donor count are known in the art.

 According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a 20 pharmaceutically acceptable salt thereof, the R₁, R₂, R₃, and R₄ and any substituents thereon may affect the permeability of the compound of the present invention. In some embodiments, such a structure has an increased solubility compared to a reference Factor D inhibitor. In some embodiments, such a structure has a reduced permeability compared to a reference Factor D inhibitor. In some embodiments, such a structure has an increased solubility and a 25 decreased permeability compared to a reference Factor D inhibitor. In some embodiments, as measured by the MDCK Permeability Assay described below, the R₁, R₂, R₃, and R₄ and any substituents thereon may reduce the permeability to a value less than 1. In some embodiments, as measured by the MDCK Permeability Assay described below, the R₁, R₂, R₃, and R₄ and any substituents thereon may reduce the permeability to a value greater than 30 or equal to 1.

MDCK Permeability Assay

 Madin-Darby Kidney cells (MDCKI) can be obtained from the National Institutes of

Health, (Bethesda, MD). Cells are maintained in Dulbecco's Modified Eagle Medium supplemented with 10% fetal bovine serum and 5 $\mu\text{g/mL}$ plasmocin before seeding on Millipore Millicell-24 well plates at 2.5×10^5 cells/mL and allowed to grow for 5 days. Prior to the permeability experiment cell monolayers are equilibrated in transport buffer (Hank's

5 Balanced Salt Solution with 10 mM Hepes, pH 7.4) for 20 minutes at 37°C with 5% CO₂ and 95% relative humidity. Test compound dose solutions are prepared at 10 μM in transport buffer containing the monolayer integrity marker lucifer yellow (100 μM). The dose solutions are added to the donor chambers and transport buffer is added to all receiver chambers. The permeability is examined in the apical to basolateral (A:B) and basolateral to

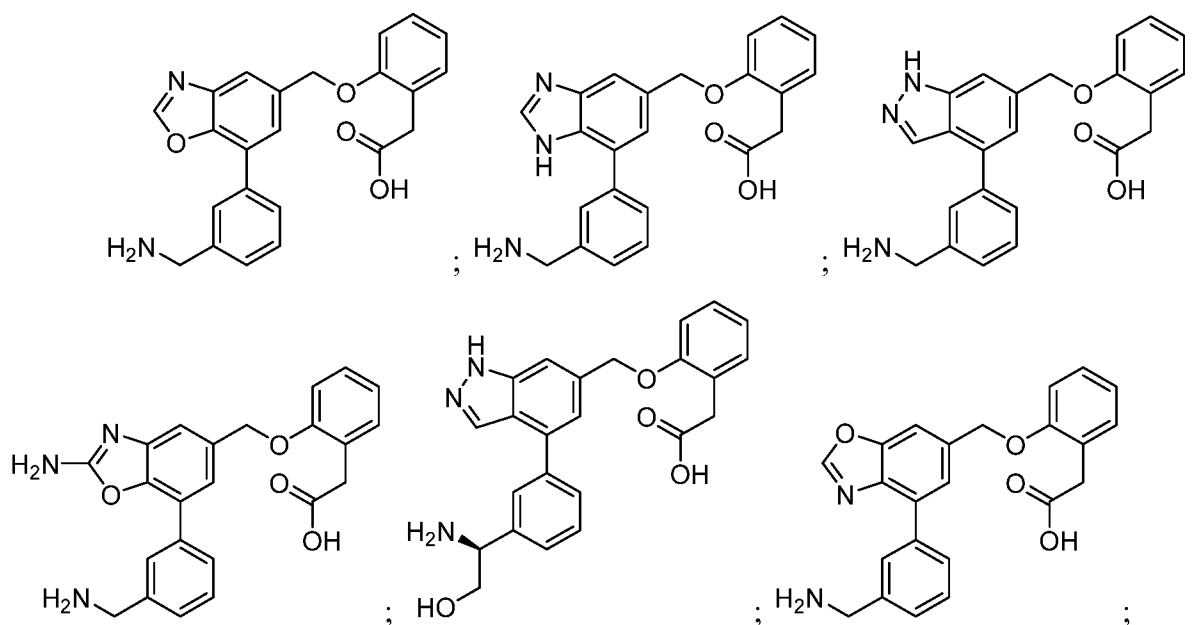
10 apical (B:A) directions. The receiver chambers are sampled at 60, 120, and 180 min and are replenished with fresh transport buffer. Lucifer yellow is measured using a fluorescence plate reader (ex: 425 nm; em: 530 nm) and compound concentrations in the donor and receiving compartments are determined by LC-MS/MS analysis. The apparent permeability (P_{app}) in the A:B and B:A directions is calculated as follows:

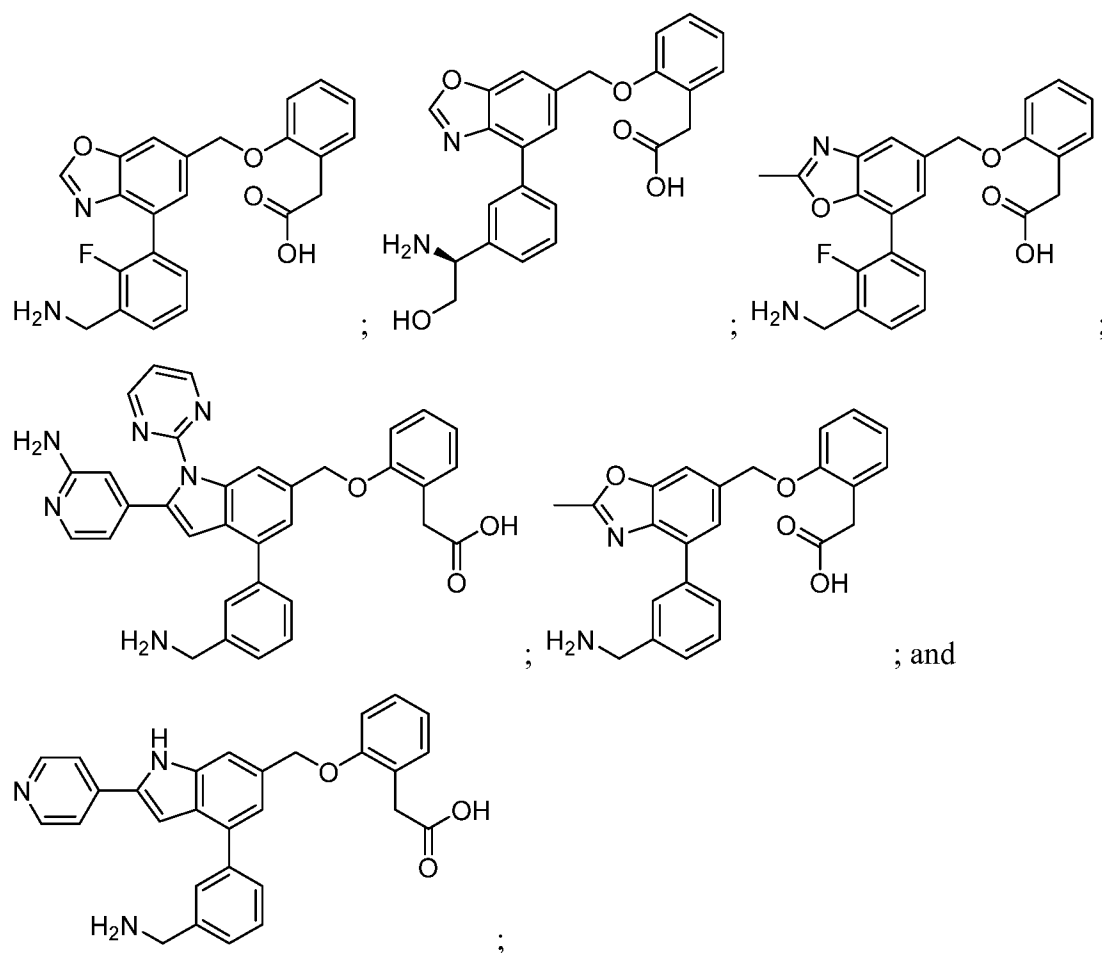
$$15 \quad P_{\text{app}} = (dQ/dt) \cdot (1/AC_0),$$

where: dQ/dt = rate of compound appearance in the receiver compartment; A = surface area of the insert; and C_0 = initial substrate concentration at time 0 min.

According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a

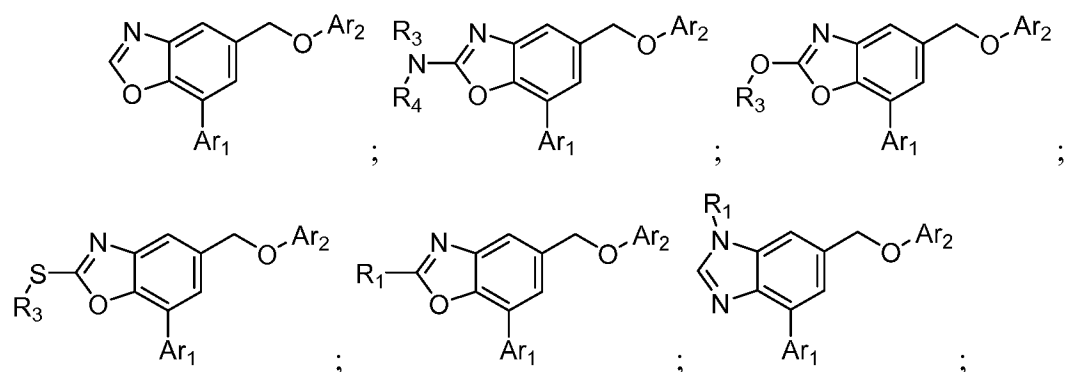
20 pharmaceutically acceptable salt thereof, the compound may be selected from the group consisting of:



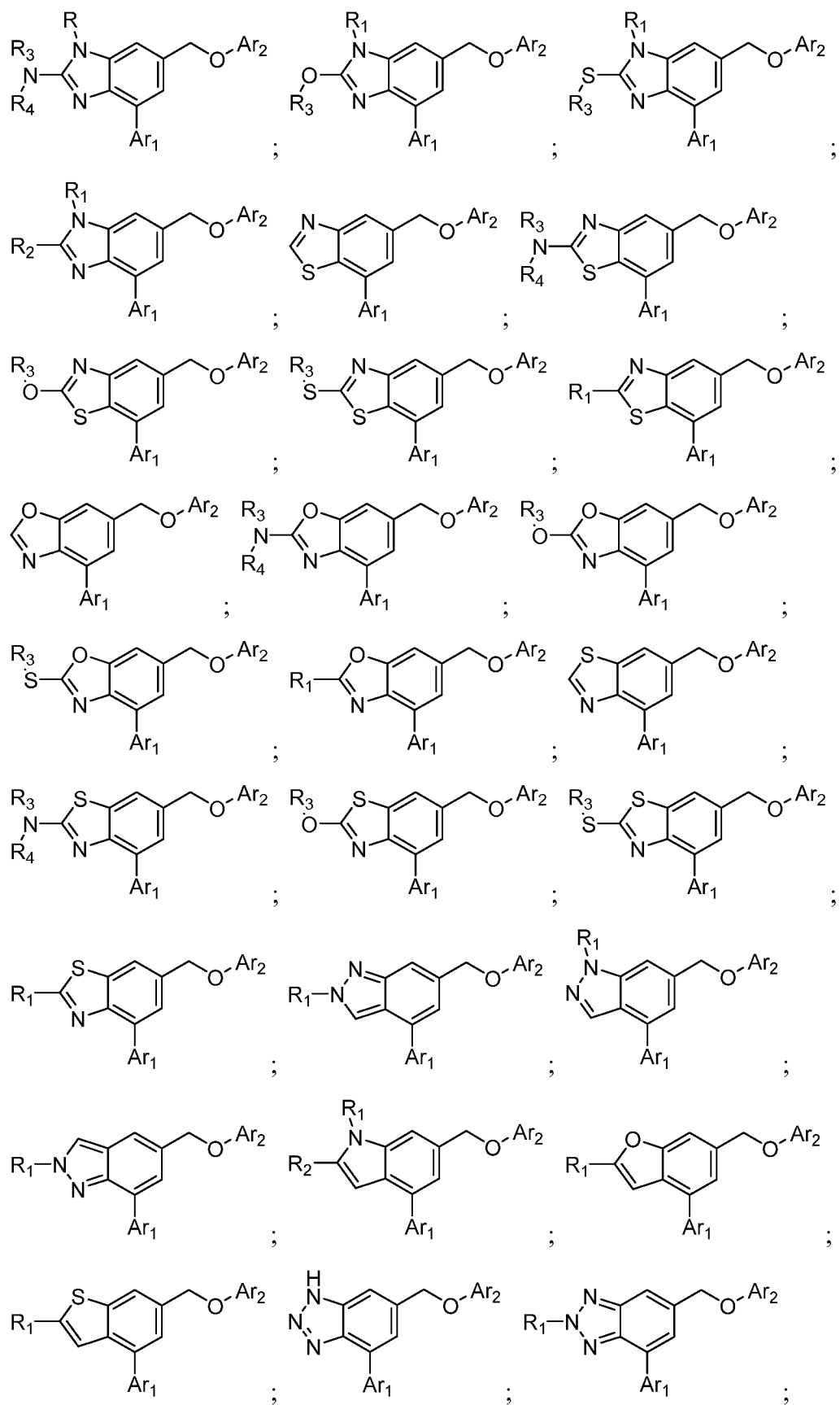


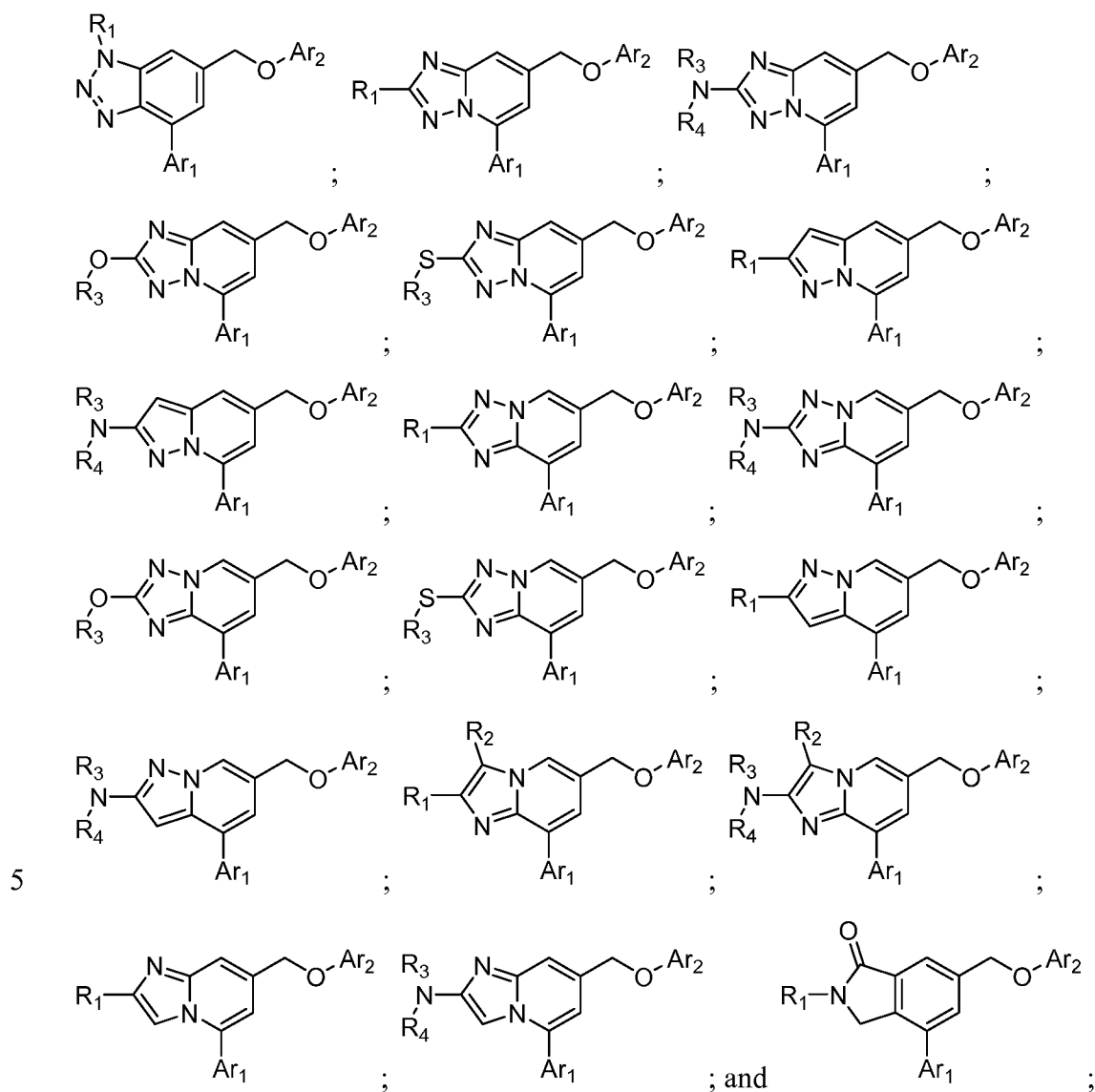
or a stereoisomer or a pharmaceutically acceptable salt thereof.

- 5 According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a pharmaceutically acceptable salt thereof, the compound may be selected from the group consisting of:



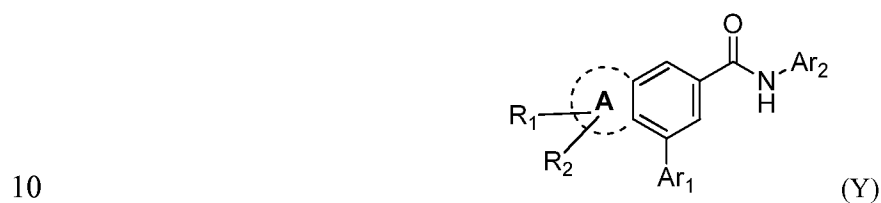
10





or a stereoisomer or a pharmaceutically acceptable salt thereof. In the above structures, R₁, R₂, R₃, R₄, Ar₁, and Ar₂ are as defined herein.

In some embodiments, a compound of the invention is a compound of structure (Y):

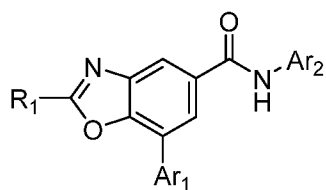


wherein R₁, Ar₁, Ar₂, and, if present, R₂, are as defined herein, and ring A is a monocyclic heterocycle,

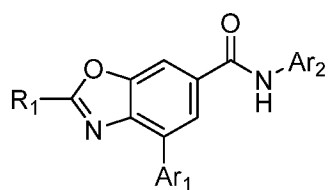
or a stereoisomer or a pharmaceutically acceptable salt thereof.

A further aspect of the invention includes a compound having a structure selected

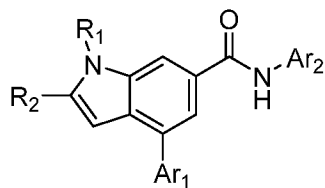
from among structures (I-B) through (XXIII-B). These structures are set forth below:



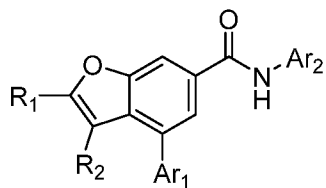
(I-B),



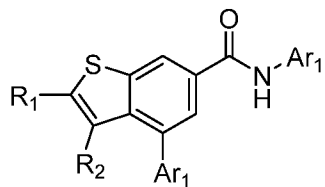
(II-B),



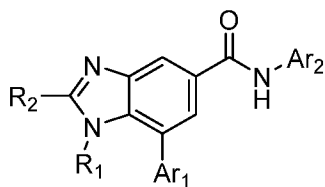
(III-B),



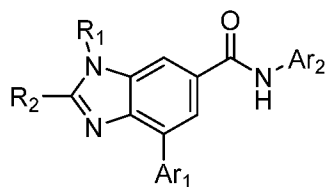
(IV-B),



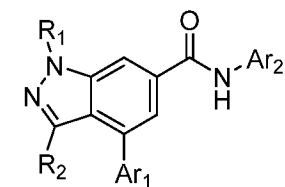
(V-B),



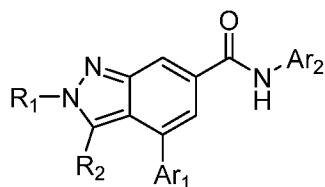
(VI-B),



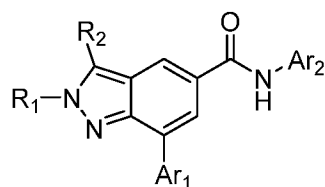
(VII-B),



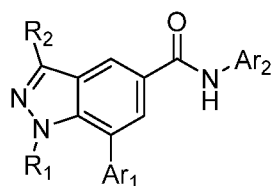
(VIII-B),



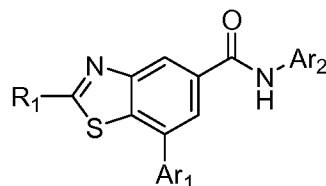
(IX-B),



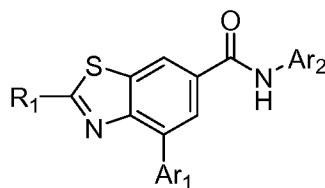
(X-B),



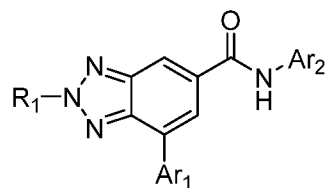
(XI-B),



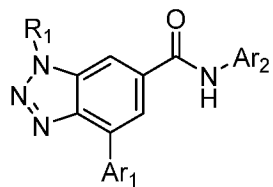
(XII-B),



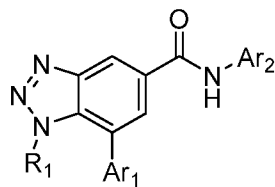
(XIII-B),



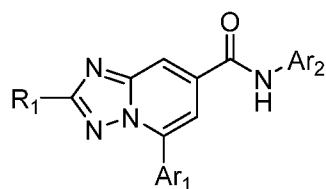
(XIV-B),



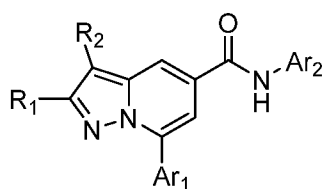
(XV-B),



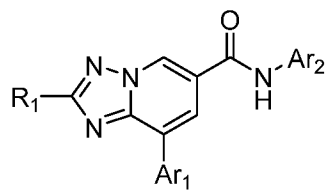
(XVI-B),



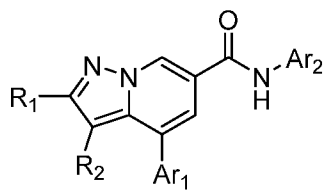
(XVII-B),



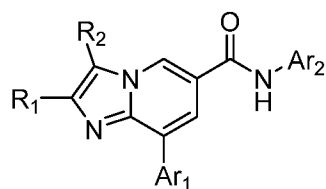
(XVIII-B),



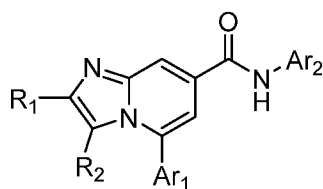
(XIX-B),



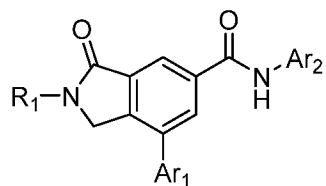
(XX-B),



(XXI-B),



(XXII-B), and

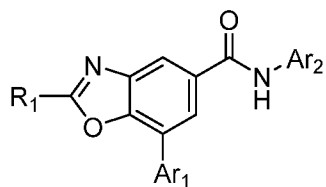


(XXIII-B);

5 or a stereoisomer or a pharmaceutically acceptable salt thereof.

In the above structures (I-B) through (XXIII-B), R₁, R₂, Ar₁, and Ar₂ are as further detailed herein below.

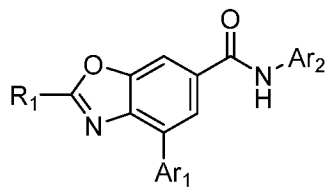
According to some embodiments, the compound of the invention has the structure:



(I-B),

10 or a stereoisomer or a pharmaceutically acceptable salt thereof.

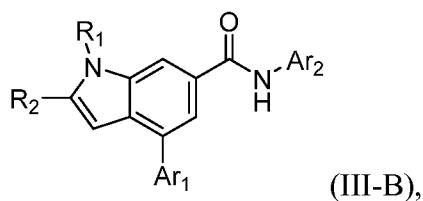
According to some embodiments, the compound of the invention has the structure:



(II-B),

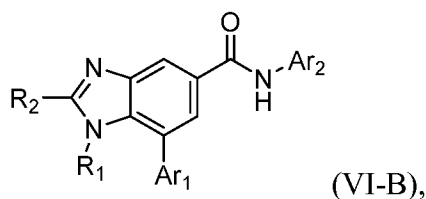
or a stereoisomer or a pharmaceutically acceptable salt thereof.

According to some embodiments, the compound of the invention has the structure:



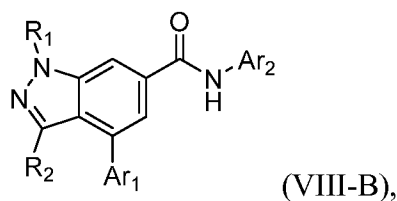
or a stereoisomer or a pharmaceutically acceptable salt thereof.

According to some embodiments, the compound of the invention has the structure:



or a stereoisomer or a pharmaceutically acceptable salt thereof.

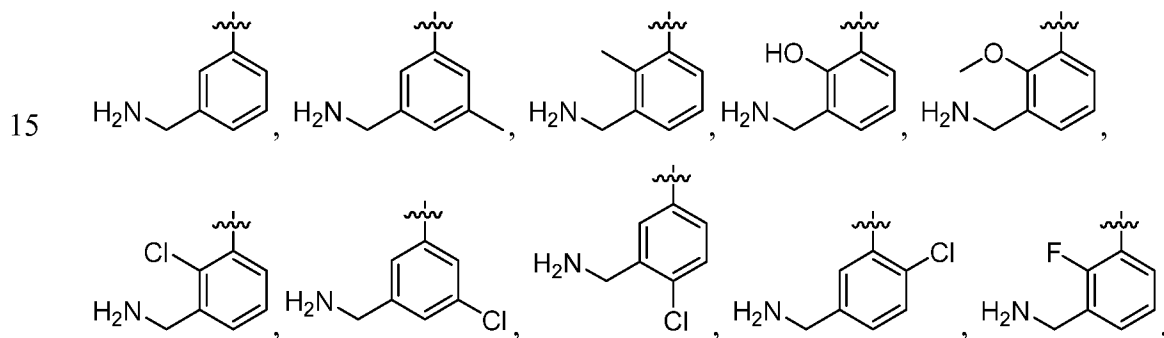
According to some embodiments, the compound of the invention has the structure:

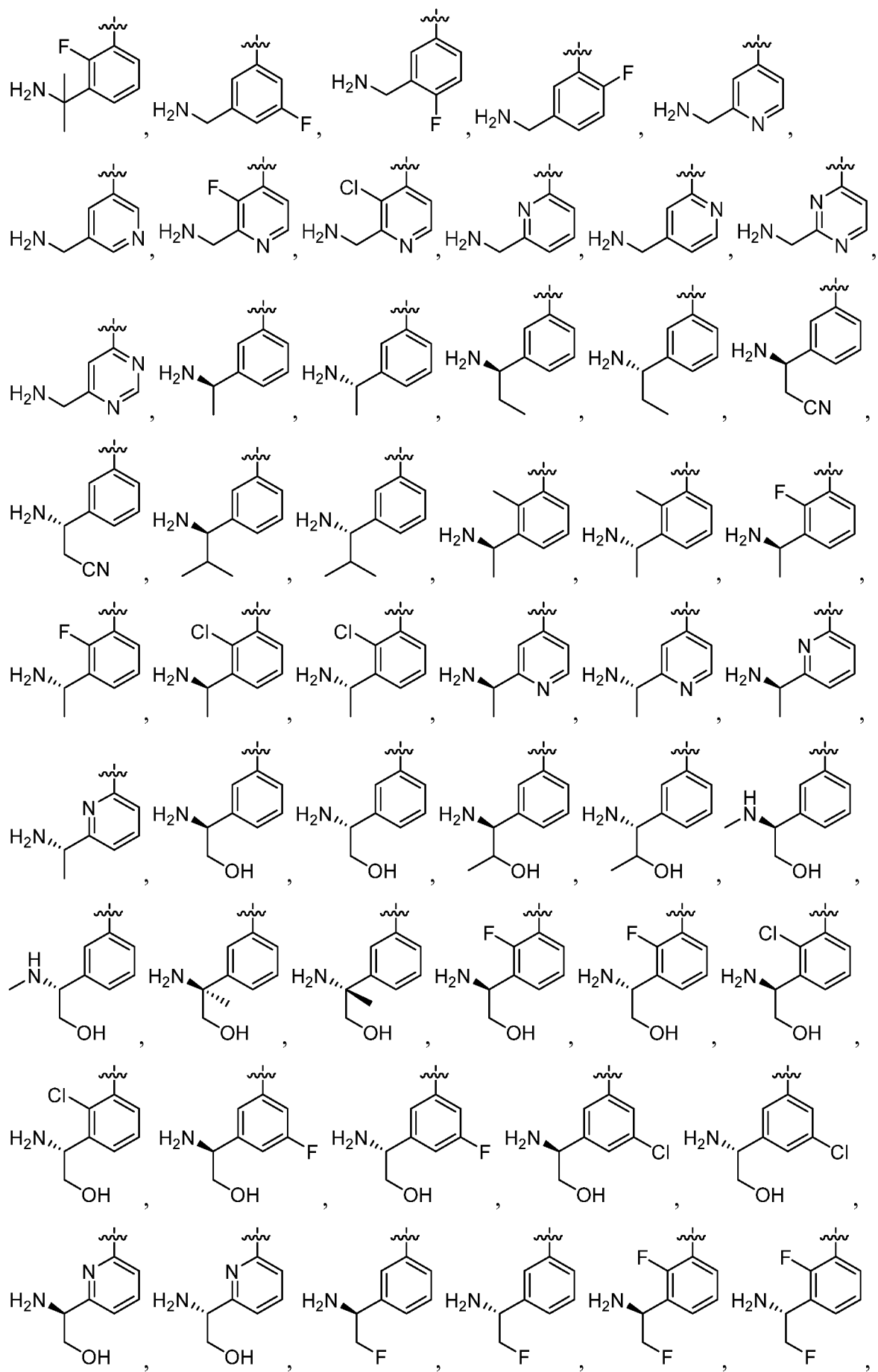


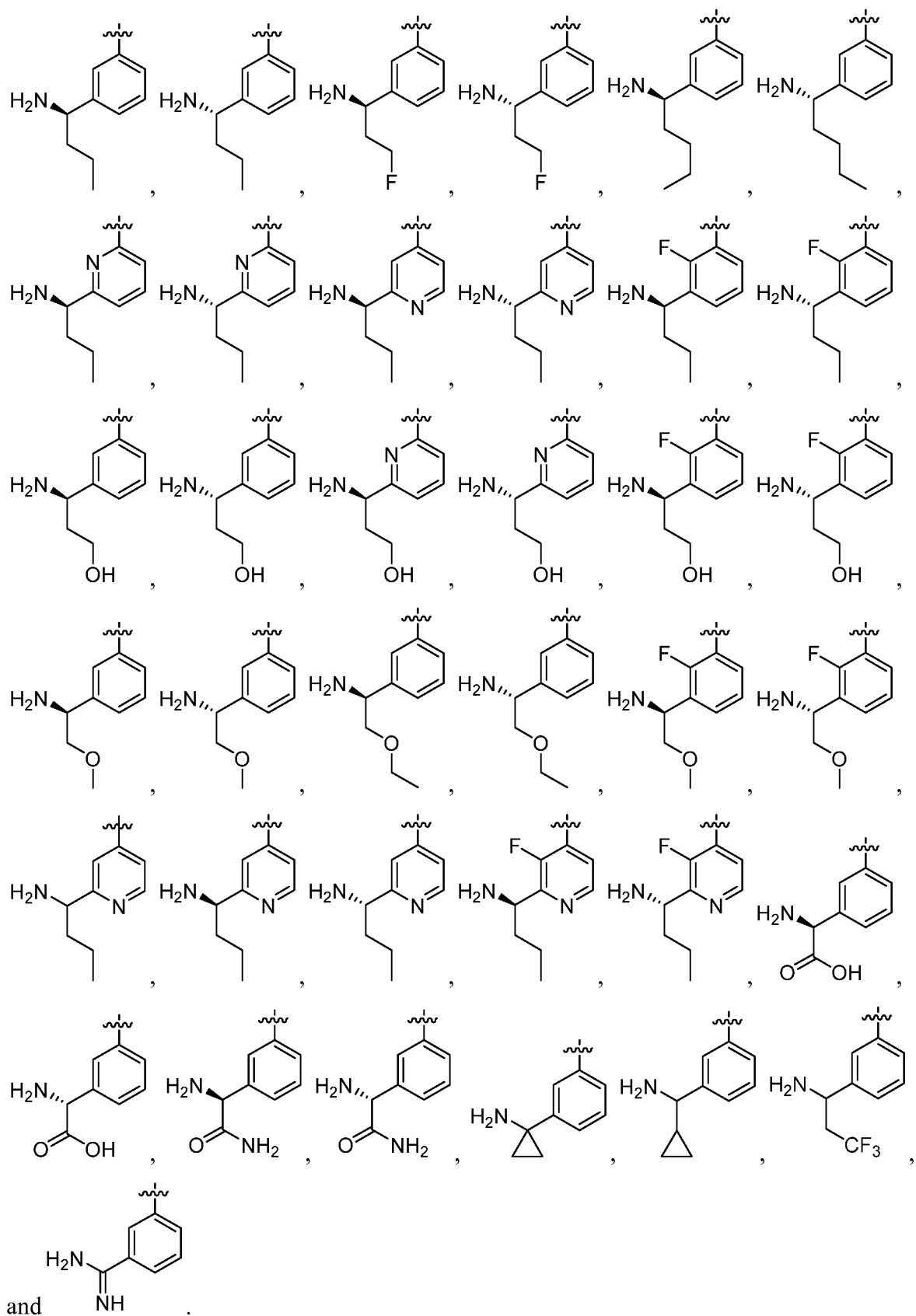
or a stereoisomer or a pharmaceutically acceptable salt thereof.

In the above structures (I-B), (II-B), (III-B), (VI-B), and (VIII-B), R₁, R₂, Ar₁, and Ar₂ are as further detailed herein below.

According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a pharmaceutically acceptable salt thereof, Ar₁ is selected from the group consisting of

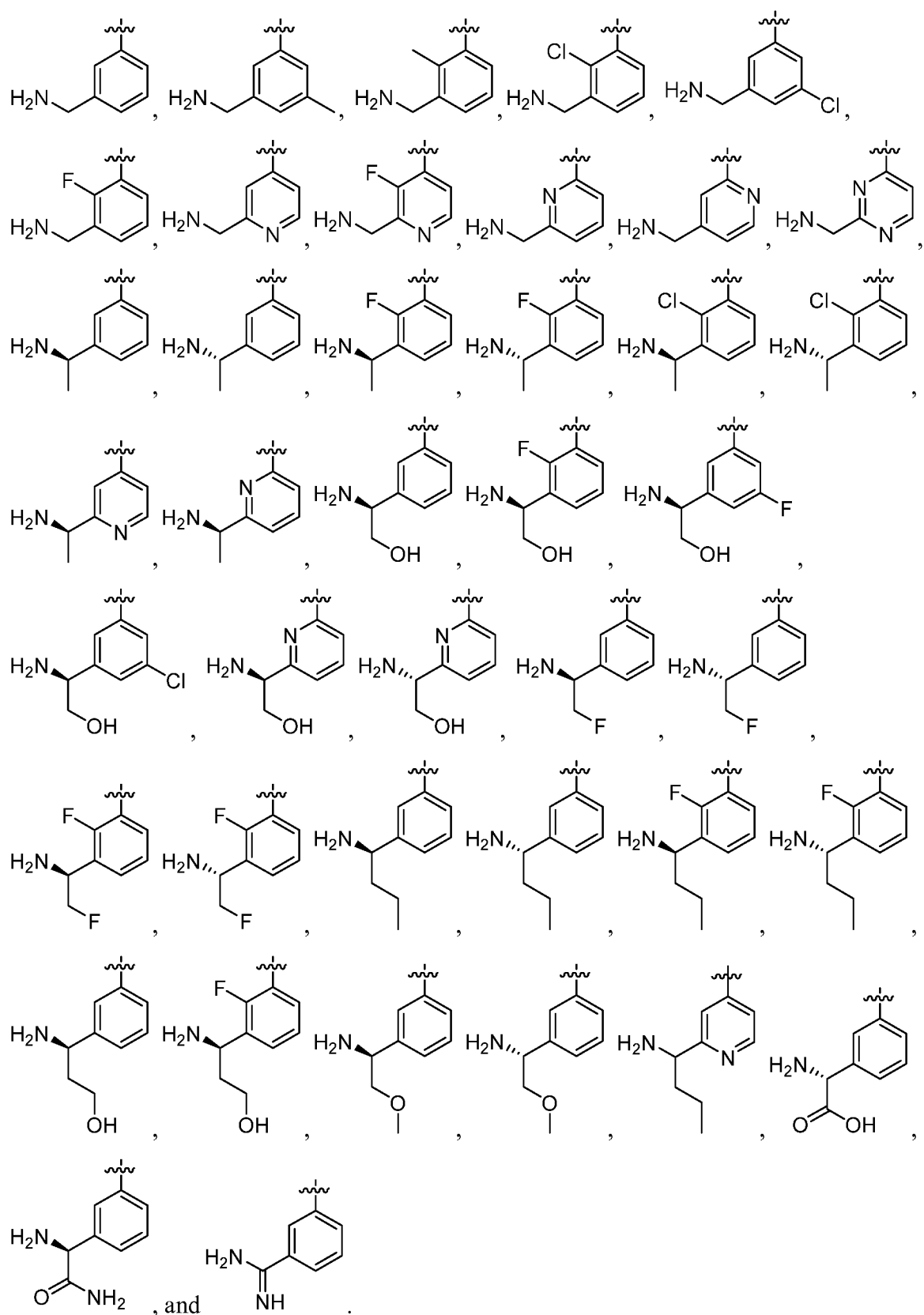






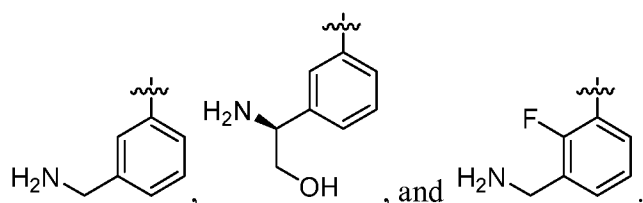
According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a

pharmaceutically acceptable salt thereof, Ar₁ is selected from the group consisting of

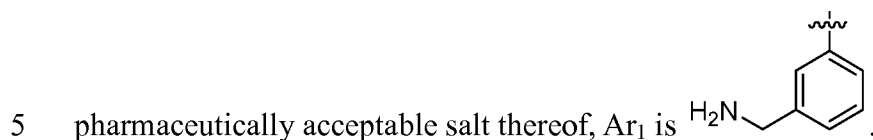


According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a

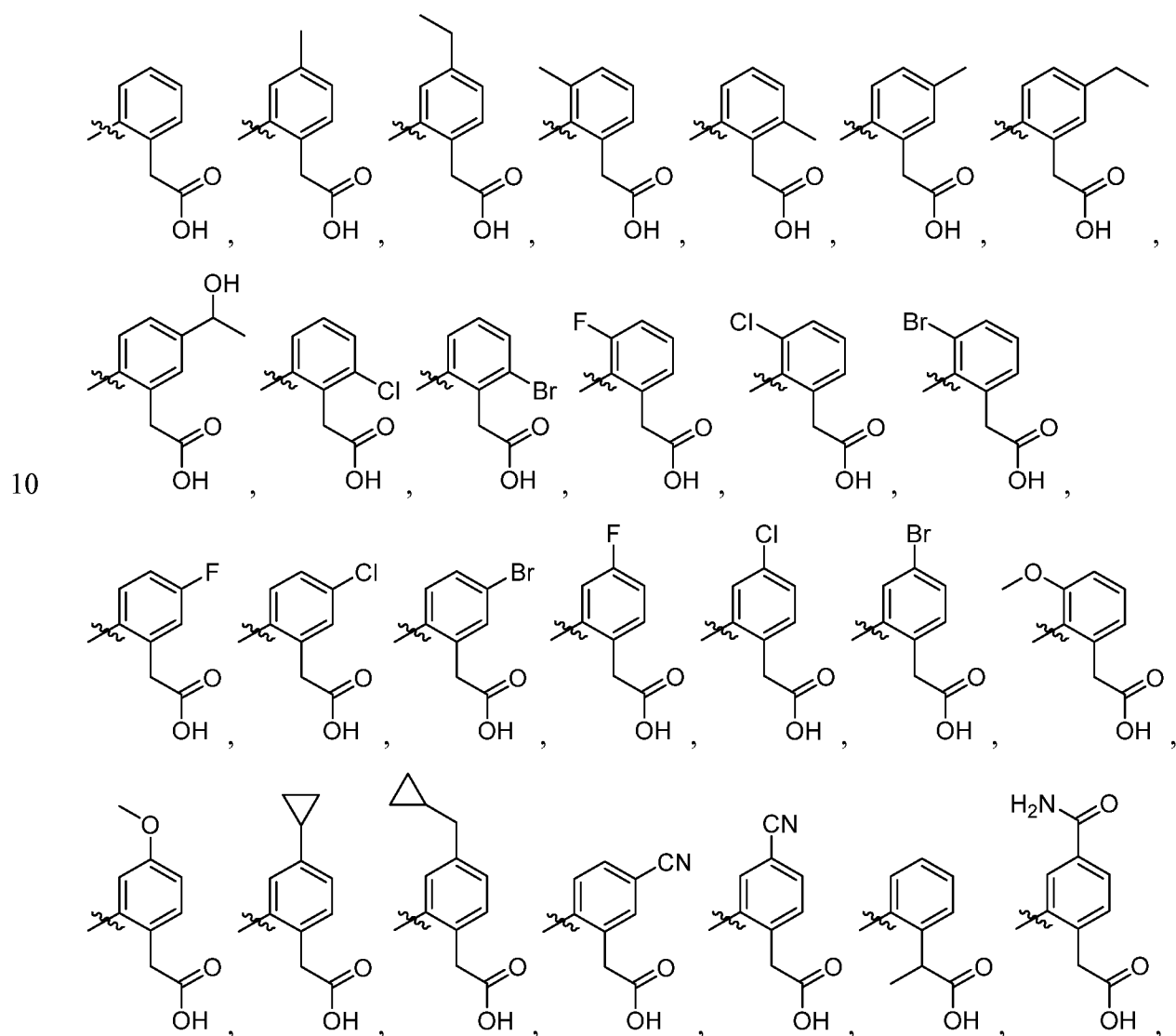
pharmaceutically acceptable salt thereof, Ar₁ is selected from the group consisting of

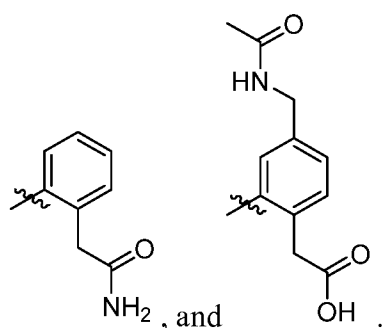


According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a

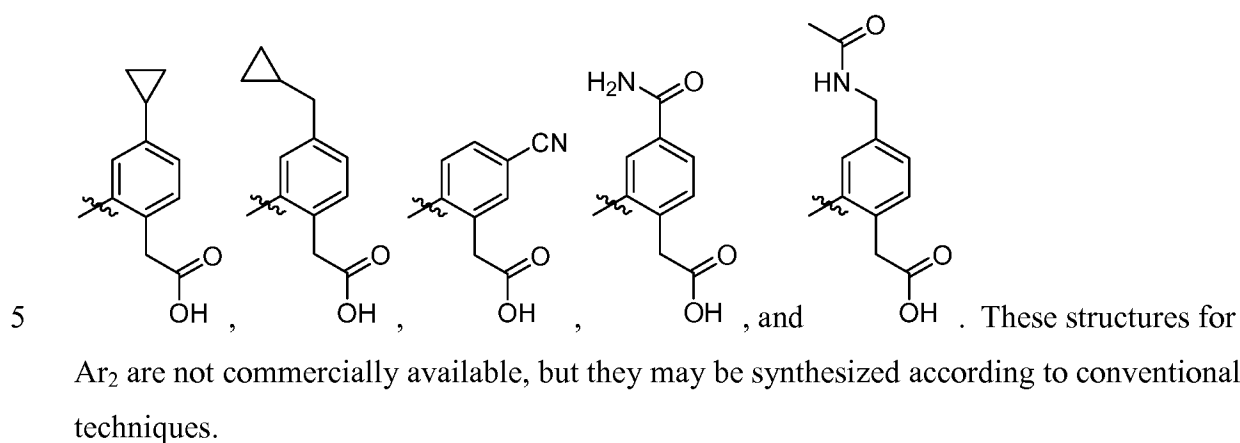


According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a pharmaceutically acceptable salt thereof, Ar₂ is selected from the group consisting of

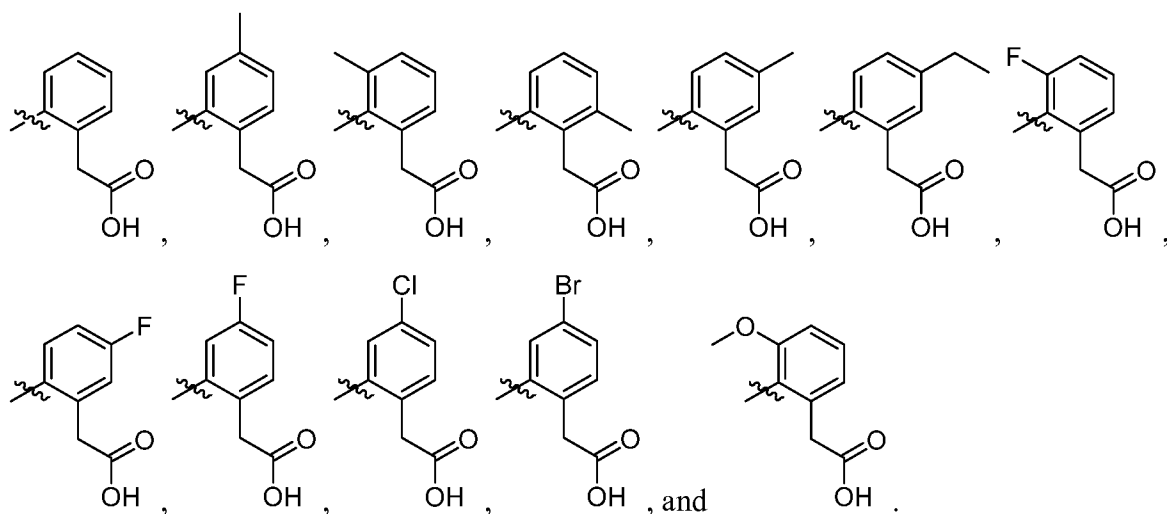




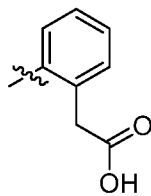
According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a pharmaceutically acceptable salt thereof, Ar₂ is selected from the group consisting of



10 According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a pharmaceutically acceptable salt thereof, Ar₂ is selected from the group consisting of



According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a



pharmaceutically acceptable salt thereof, Ar₂ is

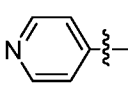
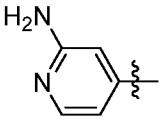
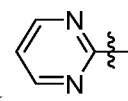
According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a pharmaceutically acceptable salt thereof, each R₁ and R₂ are independently selected from the group consisting of hydrogen, halo, cyano, -OR₃, -SR₃, -NR₃R₄, -C(O)R₃, -C(O)OR₃, -C(O)NR₃R₄, -S(O)₂R₃, C₁-C₆ alkyl optionally substituted with R₃, C₆-C₁₄ aryl optionally substituted with R₃, and C₅-C₁₄ heteroaryl optionally substituted with R₃.

According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a pharmaceutically acceptable salt thereof, each R₃ and R₄ are independently selected from the group consisting of hydrogen, -NH₂, C₁-C₆ alkyl, C₆-C₁₂ aryl, and C₅-C₁₄ heteroaryl. According to some embodiments of the compound of the invention, the alkyl, aryl, and heteroaryl may be optionally substituted.

According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a pharmaceutically acceptable salt thereof, each R₃ and R₄ are independently selected from the group consisting of hydrogen and C₁-C₆ alkyl. According to some embodiments of the compound of the invention, the alkyl may be optionally substituted.

According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a pharmaceutically acceptable salt thereof, each R₁ and R₂ are independently selected from the group consisting of hydrogen, -OR₃, -SR₃, -NR₃R₄, C₆-C₁₄ aryl, C₅-C₁₄ heteroaryl optionally substituted with -NR₃R₄, and C₁-C₆ alkyl optionally substituted with C₆-C₁₄ aryl.

According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a pharmaceutically acceptable salt thereof, each R₁ and R₂ are independently selected from the

group consisting of hydrogen, -NH₂, -CH₃, , , and .

As noted above, structural information gleaned from the Protein Data Bank (PDB) (5FCK and 5NB7) along with an internal crystal structure allowed for molecular modeling that suggests R₁, R₂, R₃, and R₄ should extend out into a solvent exposed region of the Factor D protein. Based on this molecular modeling but without being bound by theory, it is

believed that a wide variety of functional groups may be incorporated into these positions and may contribute to modulation of properties of each molecule such as solubility and permeability as well as to some extent, potency. According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a pharmaceutically acceptable salt thereof, each R₁, R₂, R₃, and R₄ may be optionally further substituted. Suitable additional substituent groups include functional groups known in the art such as amides, amino acids, ureas, ketones, guanidines, alkanes, alkenes, alkynes, aryls, heterocyclyls (e.g., heteroaryls), amines, alcohols, carboxylates, carboxylic acids, esters, cyano, cycloalkyls, halo, thiols, thioethers, thioureas, thioamides, polyethers including pegylation and any combination thereof. These groups can be introduced using standard reactions for the formations of C-C, C-N, C-O, or C-S bonds. Such groups may be optionally substituted with other functional groups. Amino acids include any amino acid currently known, including L and D stereoisomers. The amino acids may be bonded to the structures according to the present invention at the carboxylate moiety or the amino moiety. The pegylation group may comprise a polyethylene glycol having weight average molecular weight of from about 100 Da to about 300,000 Da, such as from about 500 D to about 300,000 Da, or from about 20,000 Da to about 60,000 Da. The pegylation group may be linear, branched, or dendritic.

According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a pharmaceutically acceptable salt thereof, each R₁ and R₂ are independently selected from the group consisting of hydrogen, halo, cyano, -OH, -O-C₁-C₆ alkyl, -SH, -S-C₁-C₆ alkyl, -NH₂, -NHC₁-C₆ alkyl, -N(C₁-C₆ alkyl)₂, -C(O)H, C(O)C₁-C₆ alkyl, -C(O)OH, -C(O)OC₁-C₆ alkyl, -C(O)ONH₂, -C(O)ONHC₁-C₆ alkyl, -C(O)ON(C₁-C₆ alkyl)₂, -S(O)₂H, -S(O)₂C₁-C₆ alkyl, C₁-C₆ alkyl, C₆-C₁₄ aryl, and C₅-C₁₄ heteroaryl. According to some embodiments of the compound of the invention, the alkyl, aryl, and heteroaryl may be optionally substituted, for example, with additional substituent groups including functional groups known in the art such as amides, amino acids, ureas, ketones, guanidines, alkanes, alkenes, alkynes, aryl, heteroaryl, amines, alcohols, carboxylates, carboxylic acids, esters, cyano, cycloalkyls, halo,

thiols, thioethers, thioureas, thioamides, polyethers including pegylation and any combination thereof. Amino acids include any amino acid currently known, including L and D stereoisomers. The amino acids may be bonded to the structures according to the present invention at the carboxylate moiety or the amino moiety. The pegylation group may
5 comprise a polyethylene glycol having weight average molecular weight of from about 100 Da to about 300,000 Da, such as from about 500 Da to about 300,000 Da, or from about 20,000 Da to about 60,000 Da. The pegylation group may be linear, branched, or dendritic.

According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a
10 pharmaceutically acceptable salt thereof, the total molecular weight of R₁, R₂, R₃, and R₄ and any substituents thereon is less than about 500 Da, such as less than about 400 Da, less than about 300 Da, less than about 200 Da, or even less than about 100 Da, such as between about 1 Da and about 500 Da, or between about 2 Da and about 500 Da, or between about 10 Da and about 500 Da, or between about 20 Da and about 400 Da.

According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a
15 pharmaceutically acceptable salt thereof, the total molecular weight of R₁, R₂, R₃, and R₄ and any substituents thereon is greater than about 500 Da, such as greater than about 1000 Da, or even greater than about 10,000 Da, such as between about 500 Da and about 300,000 Da,
20 between about 500 Da and about 60,000 Da, between about 500 Da and about 10,000 Da, or between about 500 Da and about 1000 Da.

According to some embodiments of the compound of the invention having a structure selected from among structures (I-A) through (XXIII-A), or a stereoisomer or a
25 pharmaceutically acceptable salt thereof, the R₁, R₂, R₃, and R₄ and any substituents thereon may increase TPSA and/or hydrogen bond donor count in order to maximize solubility and/or reduce permeability. Methods of measuring TPSA and hydrogen bond donor count are known in the art.

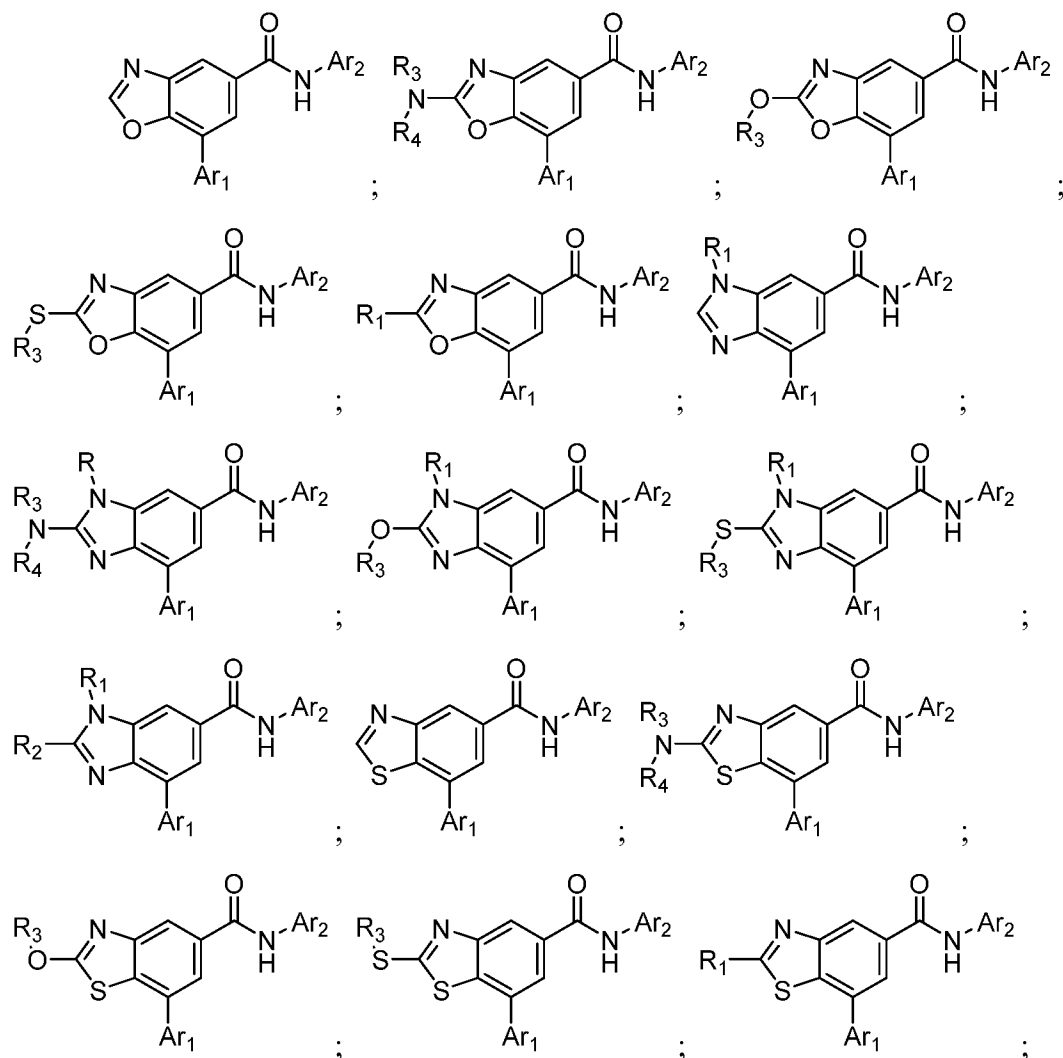
According to some embodiments of the compound of the invention having a structure selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a
30 pharmaceutically acceptable salt thereof, the R₁, R₂, R₃, and R₄ and any substituents thereon may affect the permeability of the compound of the present invention. In some embodiments, such a structure has an increased solubility compared to a reference Factor D inhibitor. In

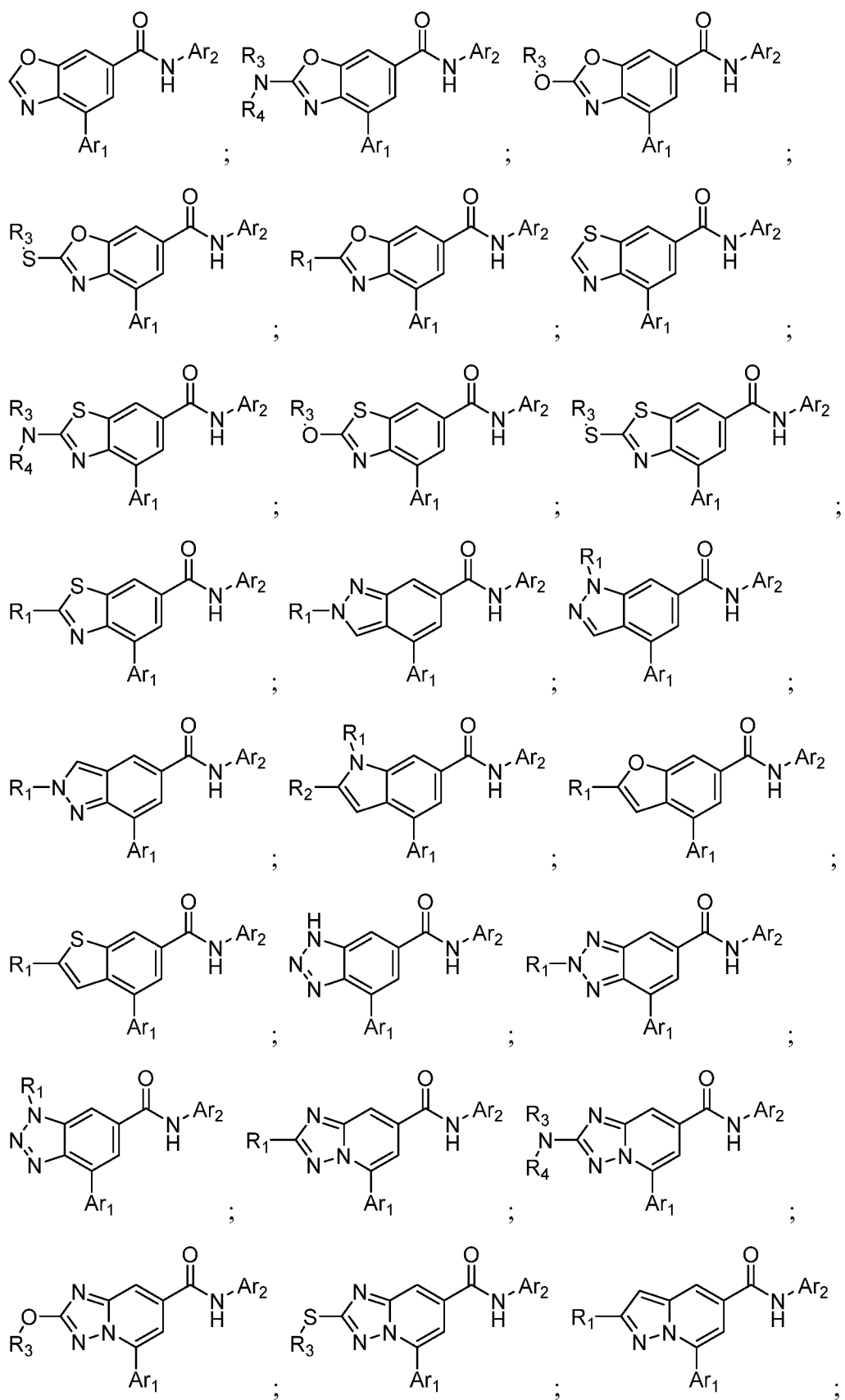
some embodiments, such a structure has a reduced permeability compared to a reference Factor D inhibitor. In some embodiments, such a structure has an increased solubility and a decreased permeability compared to a reference Factor D inhibitor. In some embodiments, as measured by the MDCK Permeability Assay described above the R_1 , R_2 , R_3 , and R_4 and any substituents thereon may reduce the permeability to a value less than 1. In some

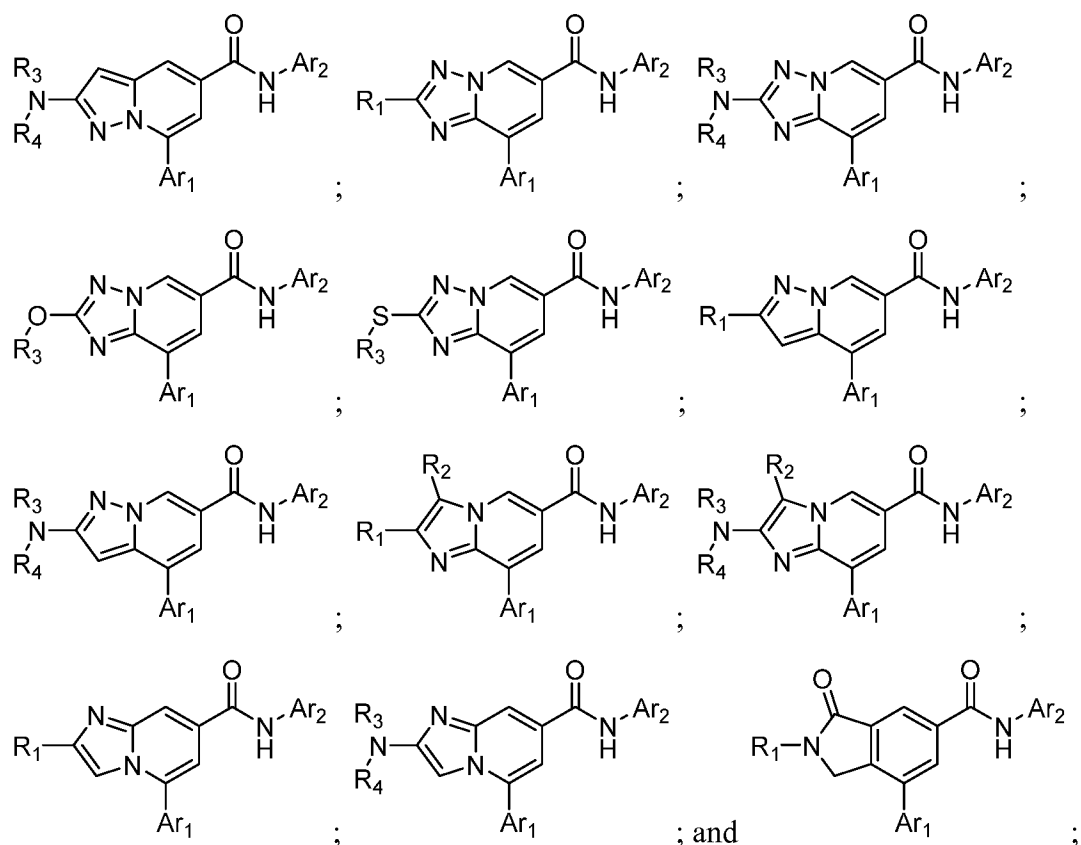
5 embodiments, as measured by the MDCK Permeability Assay described above the R_1 , R_2 , R_3 , and R_4 and any substituents thereon may reduce the permeability to a value greater than or equal to 1.

According to some embodiments of the compound of the invention having a structure

10 selected from among structures (I-B) through (XXIII-B), or a stereoisomer or a pharmaceutically acceptable salt thereof, the compound may be selected from the group consisting of:







5 or a stereoisomer or a pharmaceutically acceptable salt thereof.

In the above structures, R₁, R₂, R₃, R₄, Ar₁, and Ar₂ are as defined herein.

In some embodiments, a compound is selected from the group consisting of the compounds of Tables 1 and 2, shown below, or a stereoisomer or pharmaceutically acceptable salt thereof.

10

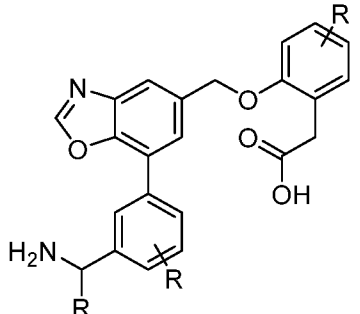
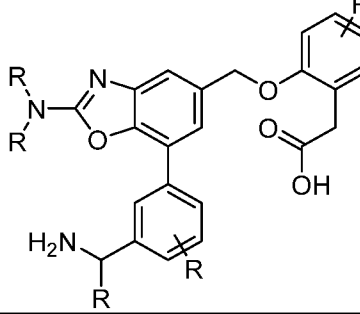
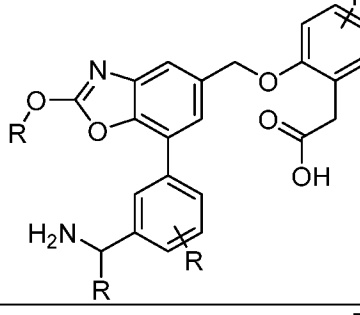
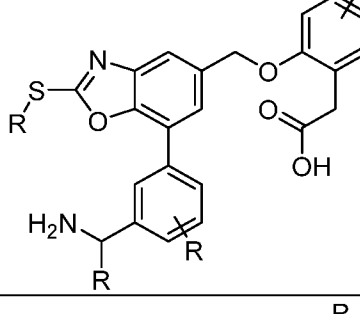
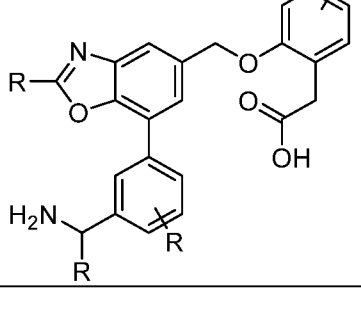
Table 1. Exemplary compounds of the present invention. Salts of such compounds are also contemplated.

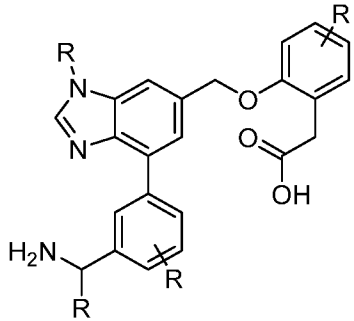
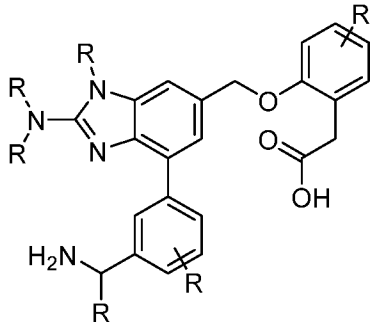
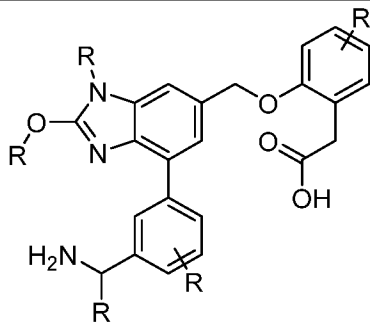
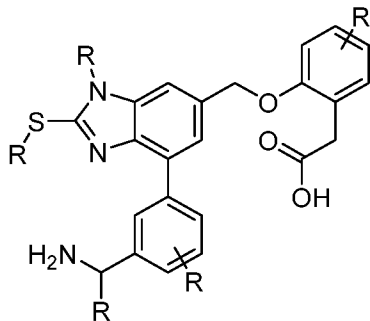
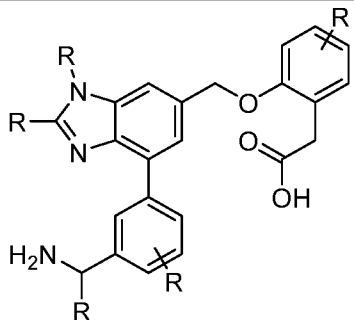
Example	Structure	Compound Name
1		2-(2-((7-(3-(aminomethyl)phenyl)benzo[d]oxazol-5-yl)methoxy)phenyl)acetic acid

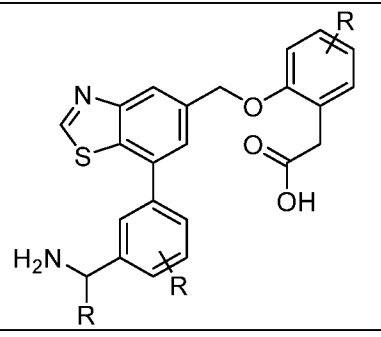
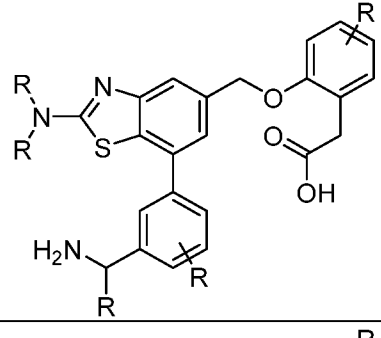
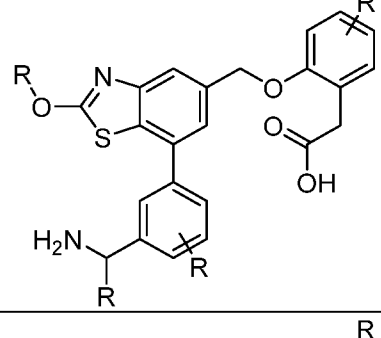
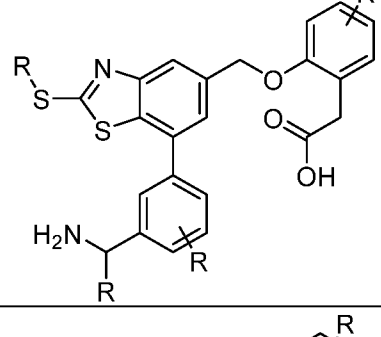
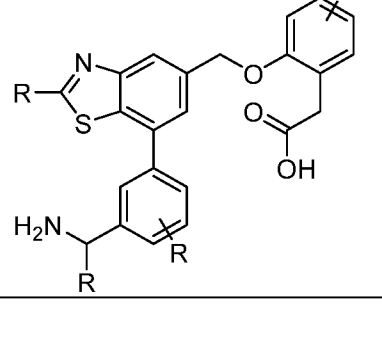
2		2-(2-((7-(3-(aminomethyl)phenyl)-1H-benzo[d]imidazol-5-yl)methoxy)phenyl)acetic acid
3		2-(2-((4-(3-(aminomethyl)phenyl)-1H-indazol-6-yl)methoxy)phenyl)acetic acid
4		2-(2-((2-amino-7-(3-(aminomethyl)phenyl)benzo[d]oxazol-5-yl)methoxy)phenyl)acetic acid
5		(S)-2-(2-((4-(3-(1-amino-2-hydroxyethyl)phenyl)-1H-indazol-6-yl)methoxy)phenyl)acetic acid
6		2-(2-((4-(3-(aminomethyl)phenyl)benzo[d]oxazol-6-yl)methoxy)phenyl)acetic acid
7		2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzo[d]oxazol-6-yl)methoxy)phenyl)acetic acid

8		(S)-2-(2-((4-(3-(1-amino-2-hydroxyethyl)phenyl)benzo[d]oxazol-6-yl)methoxy)phenyl)acetic acid
9		2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)acetic acid
10		2-(2-((4-(3-(aminomethyl)phenyl)-2-(2-aminopyridin-4-yl)-1-(pyrimidin-2-yl)-1H-indol-6-yl)methoxy)phenyl)acetic acid
11		2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)acetic acid
12		2-(2-((4-(3-(aminomethyl)phenyl)-2-(pyridin-4-yl)-1H-indol-6-yl)methoxy)phenyl)acetic acid

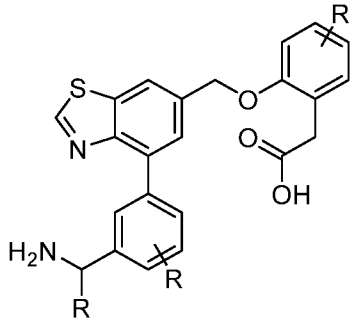
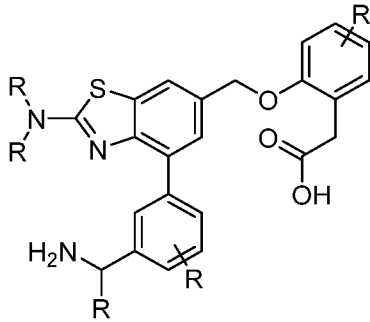
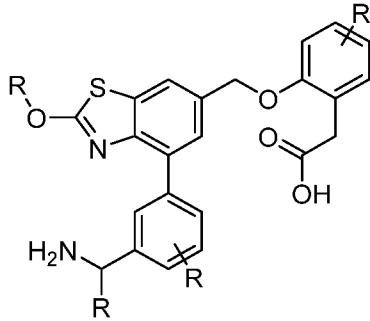
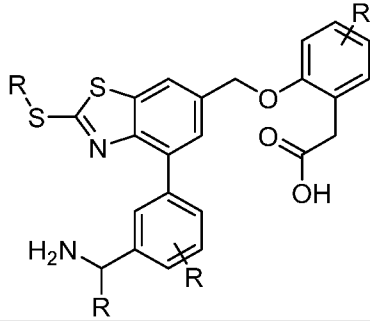
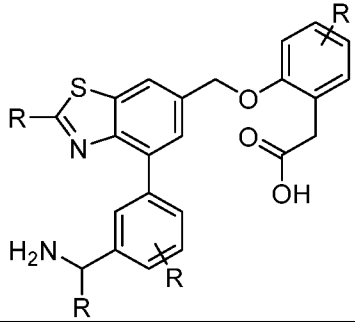
Table 2. Additional compounds of the present invention that are contemplated. Salts of such compounds are also contemplated. In some embodiments of the compounds presented in Table 2, the R groups provided on each structure denote substituents consistent with the definitions of R₁, R₂, R₃, Ar₁, and Ar₂ as provided in detail herein, where it is understood that each R group may be the same or different.

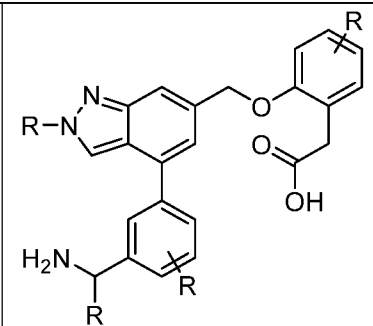
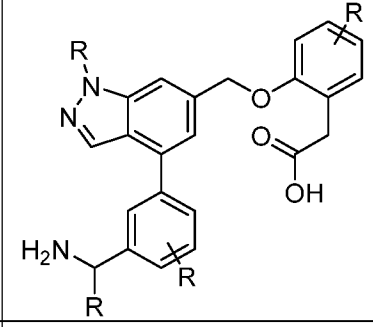
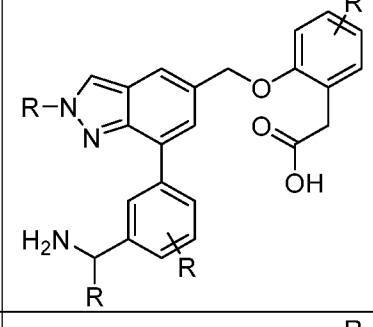
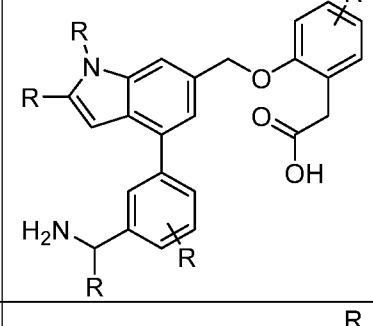
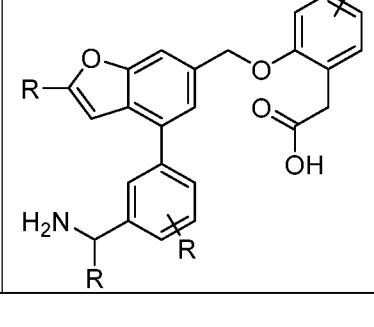
Prophetic Scaffold	Structure
1	
2	
3	
4	
5	

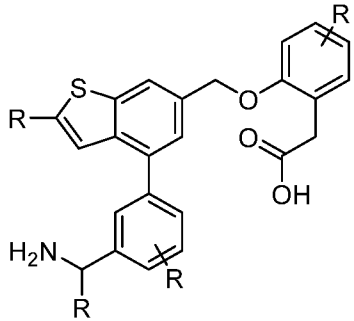
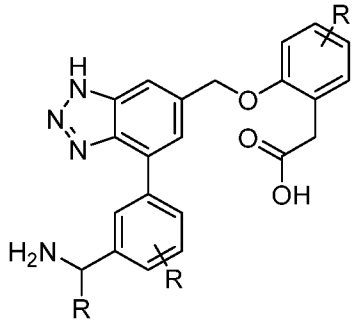
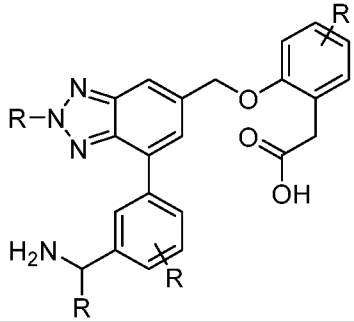
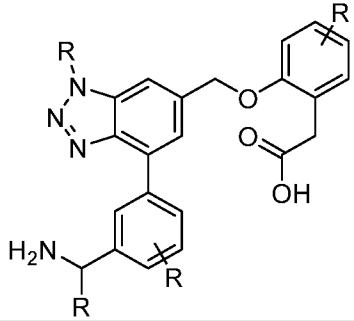
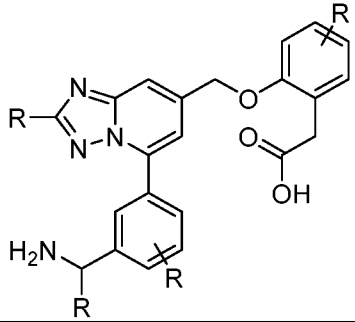
6	
7	
8	
9	
10	

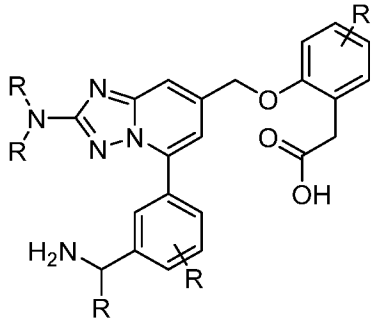
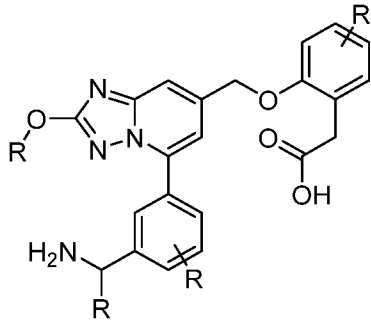
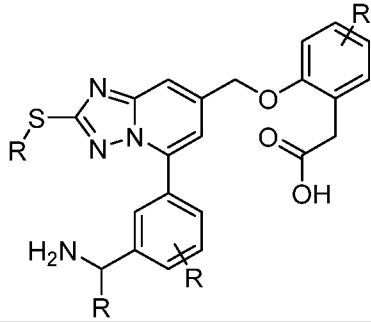
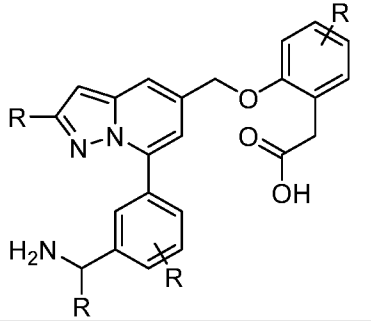
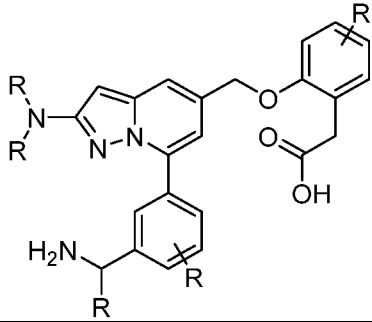
11	
12	
13	
14	
15	

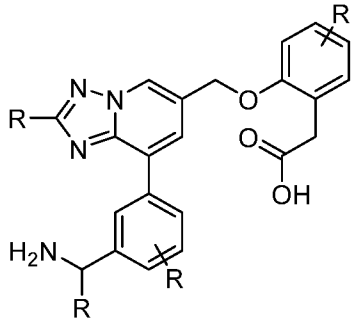
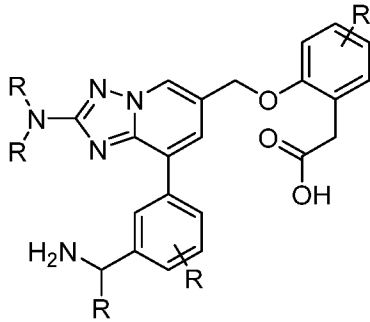
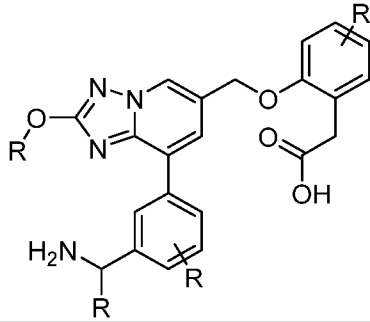
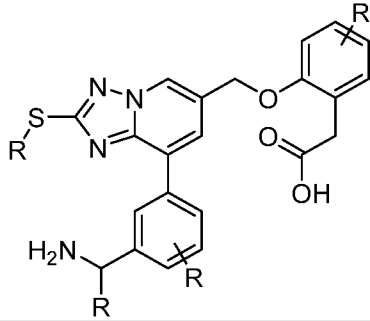
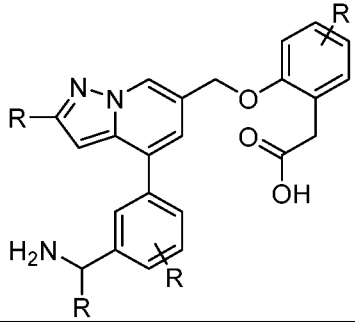
16	
17	
18	
19	
20	

21	
22	
23	
24	
25	

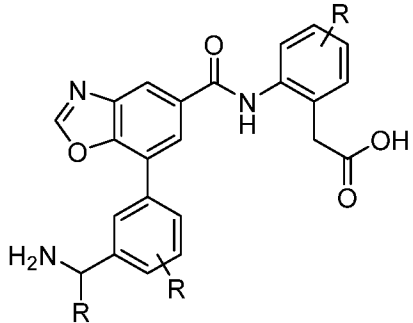
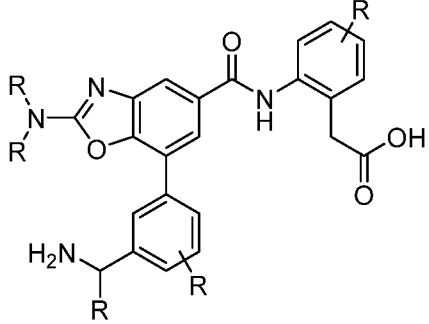
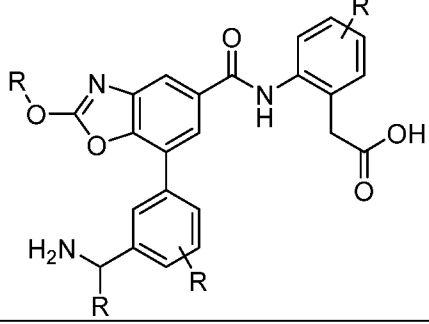
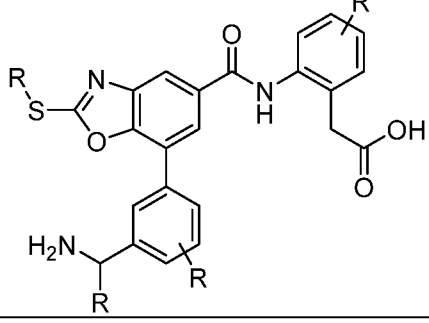
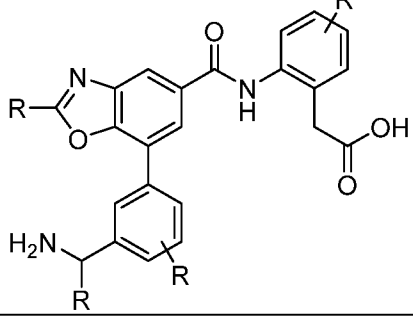
26	
27	
28	
29	
30	

31	
32	
33	
34	
35	

36	
37	
38	
39	
40	

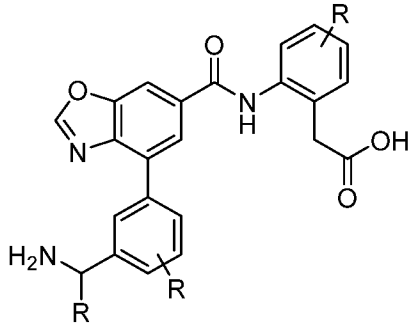
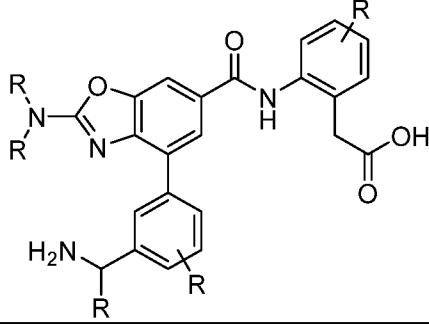
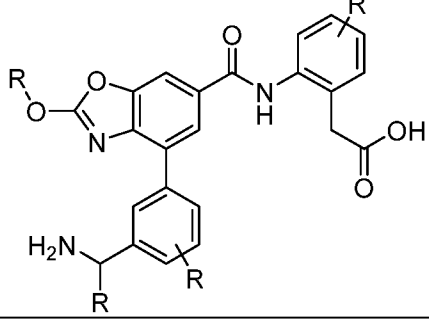
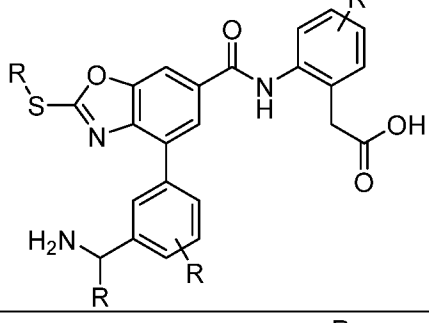
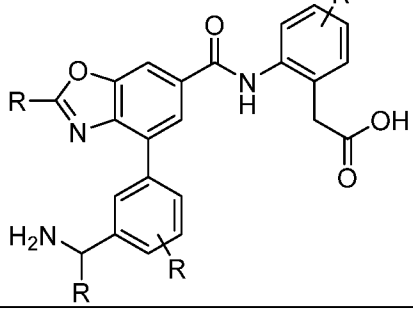
41	
42	
43	
44	
45	

46	
47	
48	
49	
50	

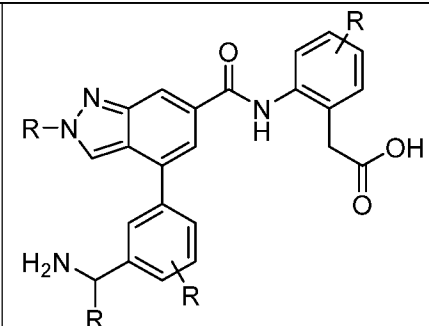
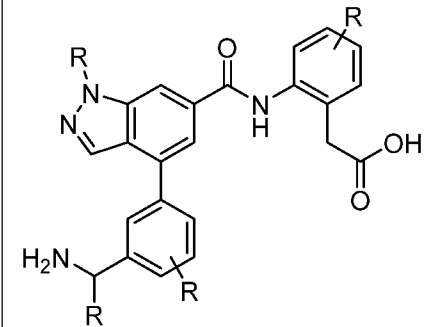
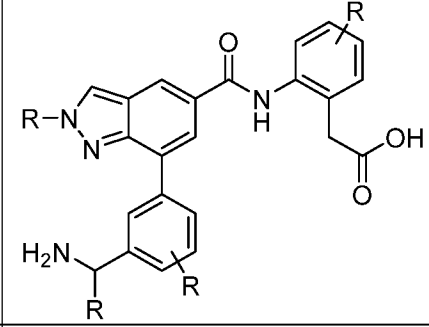
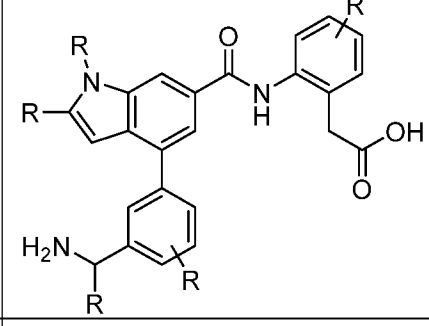
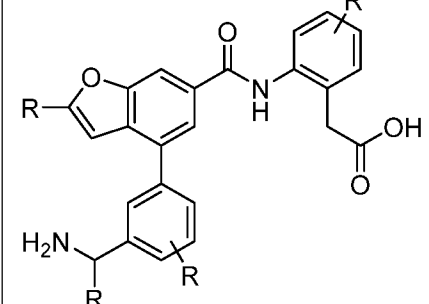
51	
52	
53	
54	
55	

56	
57	
58	
59	
60	

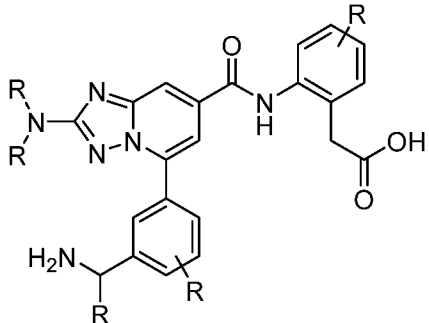
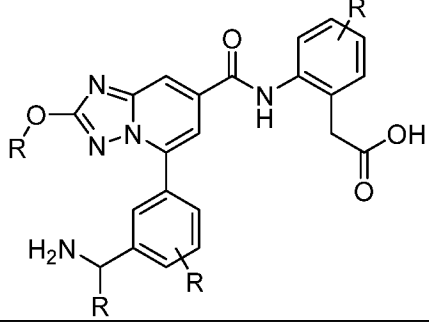
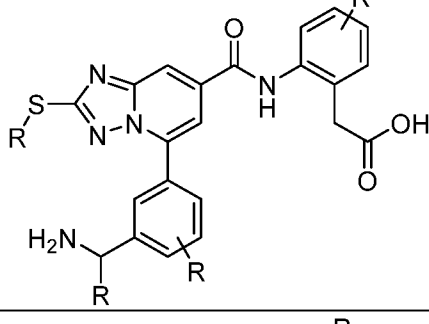
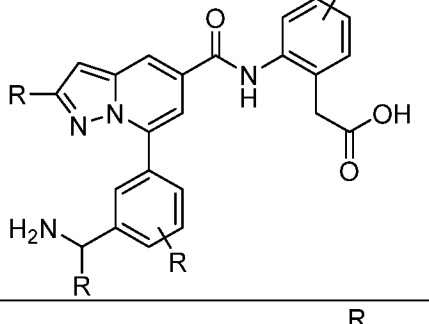
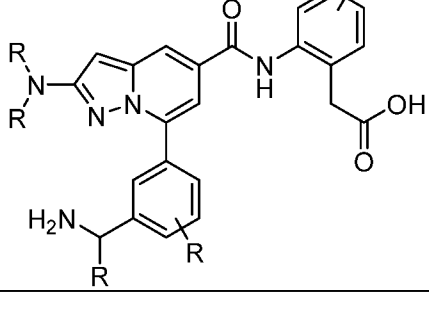
61	
62	
63	
64	
65	

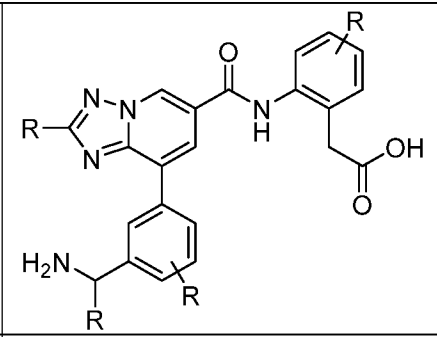
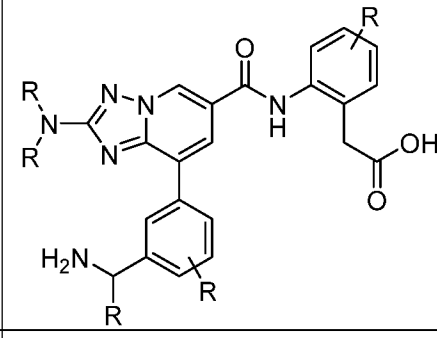
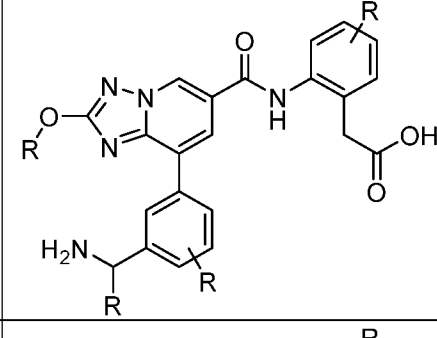
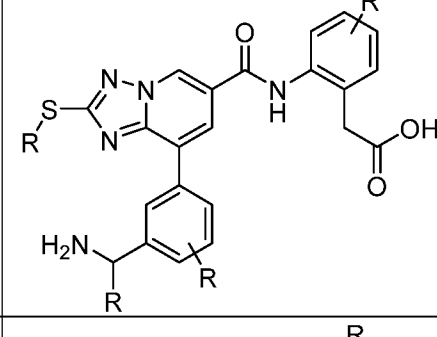
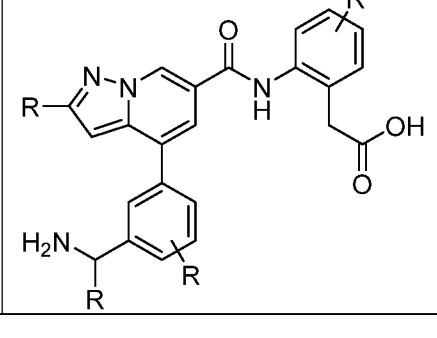
66	
67	
68	
69	
70	

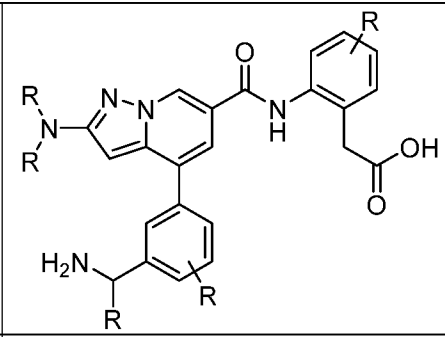
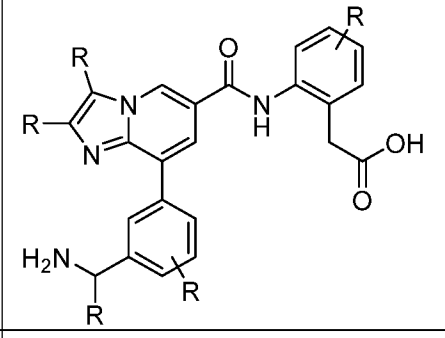
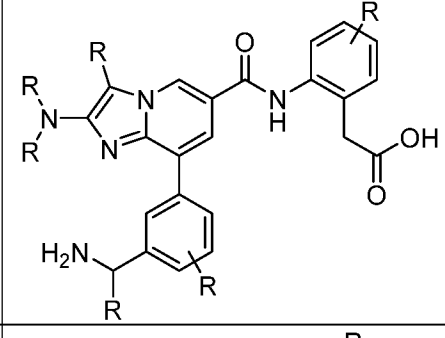
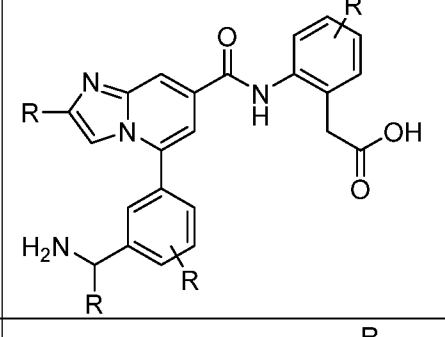
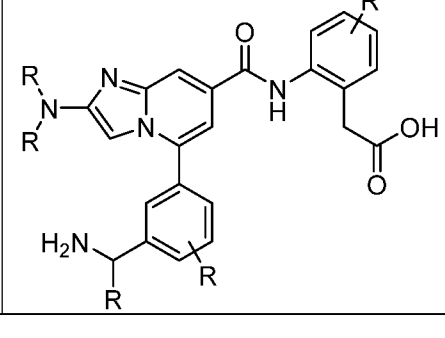
71	
72	
73	
74	
75	

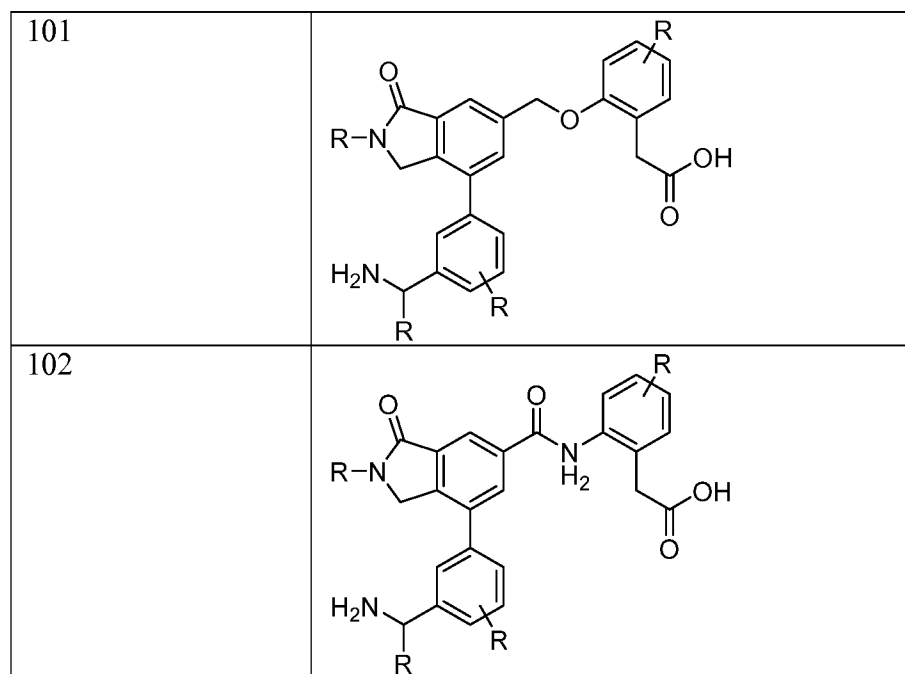
76	
77	
78	
79	
80	

81	
82	
83	
84	
85	

86	
87	
88	
89	
90	

91	
92	
93	
94	
95	

96	
97	
98	
99	
100	



SYNTHESIS OF FACTOR D INHIBITORS

Compounds of the present invention can be made by a variety of methods depicted in the illustrative synthetic reaction schemes shown and described below. The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as

US2004/0006104 A1, US2005/0250820 A1, US2010/0190994 A1, US2011/0190269 A1, US2012/0088750 A1, US2016/0108039 A1, US2016/0168138 A1, WO2004/29050 A1, WO2005/16876 A2, WO2006/76415 A2, WO2008/81399 A2, WO2010/111483 A1, WO2011/140325 A1, WO2013/6792 A1, WO2014/113303 A1, WO2014/159224 A1, WO2015/105779 A1, WO2015/114452 A2, WO2015/38503 A1, WO2016/119700 A1, WO2016/144351 A1, WO2016/207785 A1, WO2017/36404 A1, WO2017/69980 A1,

Angewandte Chemie - International Edition, **2008**, vol. 47, # 8 p. 1473 – 1476, Arkivoc, **2013**, vol. 2013, # 4 p. 405 – 412, Bioorganic and Medicinal Chemistry Letters, **2009**, vol. 19, # 3 p. 894 – 899, Bioorganic and Medicinal Chemistry Letters, **2012**, vol. 22, # 23 p. 7227 – 7231, Bioorganic and Medicinal Chemistry, **2014**, vol. 22, # 13 p. 3498 – 3507, Bioorganic and Medicinal Chemistry, **2017**, vol. 25, # 9 p. 2635 – 2642, Bulletin of the Chemical Society of Japan, **2012**, vol. 85, # 5 p. 613 – 623, Journal of the American Chemical Society, **2012**, vol. 134, # 30 p. 12466 –

12469, Journal of Medicinal Chemistry, **1986**, vol. 29, # 9 p. 1637 – 1643, Journal of Medicinal Chemistry, **2006**, vol. 49, # 12 p. 3719 – 3742, Journal of Organic Chemistry, **2001**, vol. 66, # 20 p. 6576 – 6584, Journal of Organic Chemistry, **2012**, vol. 77, # 9 p. 4473 – 4478, European Journal of Medicinal Chemistry, **2011**, vol. 46, # 1 p. 417 – 422, Tetrahedron, **2013**, vol. 69, # 34 p. 7082 – 7089, and Tetrahedron, **2017**, vol. 73, # 2 p. 172 – 178. The following synthetic reaction schemes are merely illustrative of some methods by which the compounds of the present invention can be synthesized, and various modifications to these synthetic reaction schemes can be made and will be suggested to one skilled in the art having referred to the disclosure contained in this Application.

For illustrative purposes, reaction Schemes below provide routes for synthesizing the compounds of the invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used. Although some specific starting materials and reagents are depicted in the Schemes and discussed below, other starting materials and reagents can be substituted to provide a variety of derivatives or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

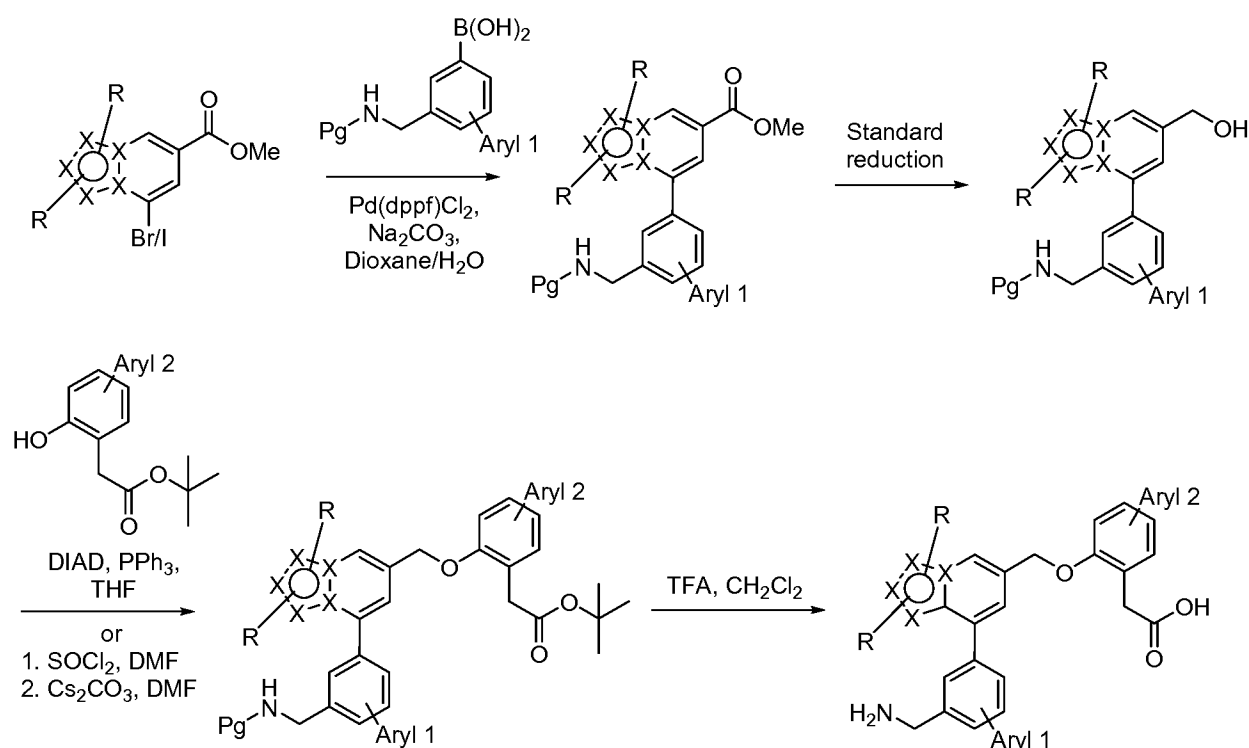
Unless specified to the contrary, the reactions described herein preferably are conducted under an inert atmosphere at atmospheric pressure at a reaction temperature range of from about -78°C to about 150°C, more preferably from about 0°C to about 125°C, and most preferably and conveniently at about room (or ambient) temperature, or, about 20°C.

Some compounds in following schemes are depicted with generalized substituents; however, one skilled in the art will immediately appreciate that the nature of the R groups can varied to afford the various compounds contemplated in this invention. Moreover, the reaction conditions are exemplary and alternative conditions are well known. The reaction

sequences in the following examples are not meant to limit the scope of the invention as set forth in the claims.

In the General Reaction Sequences, the following abbreviations are used: DMF is N,N-dimethylformamide; TFA is trifluoroacetic acid; HATU is N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate; DIAD is diisopropyl azodicarboxylate; THF is tetrahydrofuran; and Pd(dppf)Cl₂ is [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride.

General Reaction Sequence 1



10

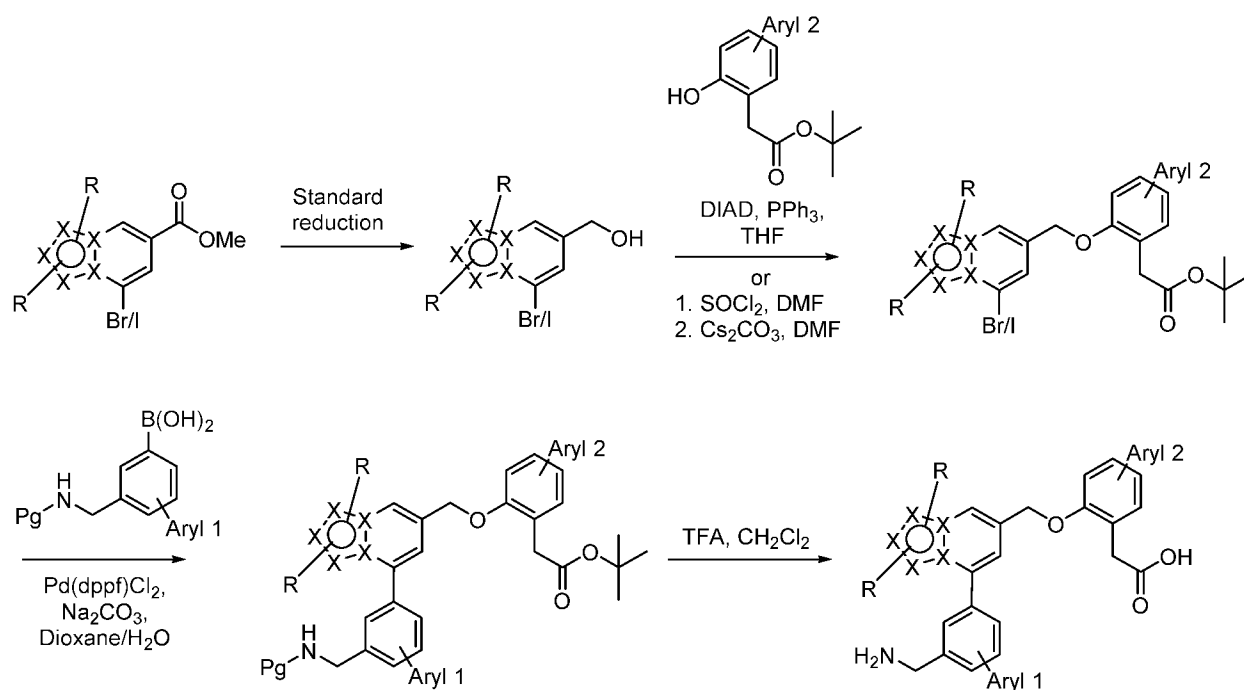
The bromo/iodo group can be coupled with a boronic ester/acid under metal-catalyzed conditions, e.g., Pd(dppf)Cl_2 , sodium carbonate, in Dioxane/ H_2O at elevated temperatures (80°C to 100°C) to provide the corresponding biaryl after purification. The methyl ester can be reduced under standard conditions. Exemplary reductants which can be used include lithium aluminum hydride (LAH or LiAlH_4) at temperatures ranging from -78°C to room temperature, sodium borohydride (NaBH_4) at temperatures ranging from -78°C to room temperature, and diisobutylaluminum hydride (DIBAL) at temperatures ranging from -78°C

15

to room temperature. See General Reduction Procedure herein) to provide the benzylic alcohol. Coupling of the benzylic alcohol with a phenol can be accomplished via Mitsunobu reaction (DIAD, and triphenylphosphine in THF), or by a two-step procedure which involves conversion of the benzylic alcohol to a benzylic chloride (thionyl chloride (SOCl_2) in DMF at 0°C to room temperature) followed by displacement of the benzylic chloride with a phenol (cesium carbonate in DMF at room temperature to 40°C) to afford the desired benzylic ether. Deprotection of the acid-labile protecting groups (trifluoroacetic acid (TFA)) in dichloromethane at temperatures ranging from 0°C to 40°C) should provide the desired amino acids.

10

General Reaction Sequence 2

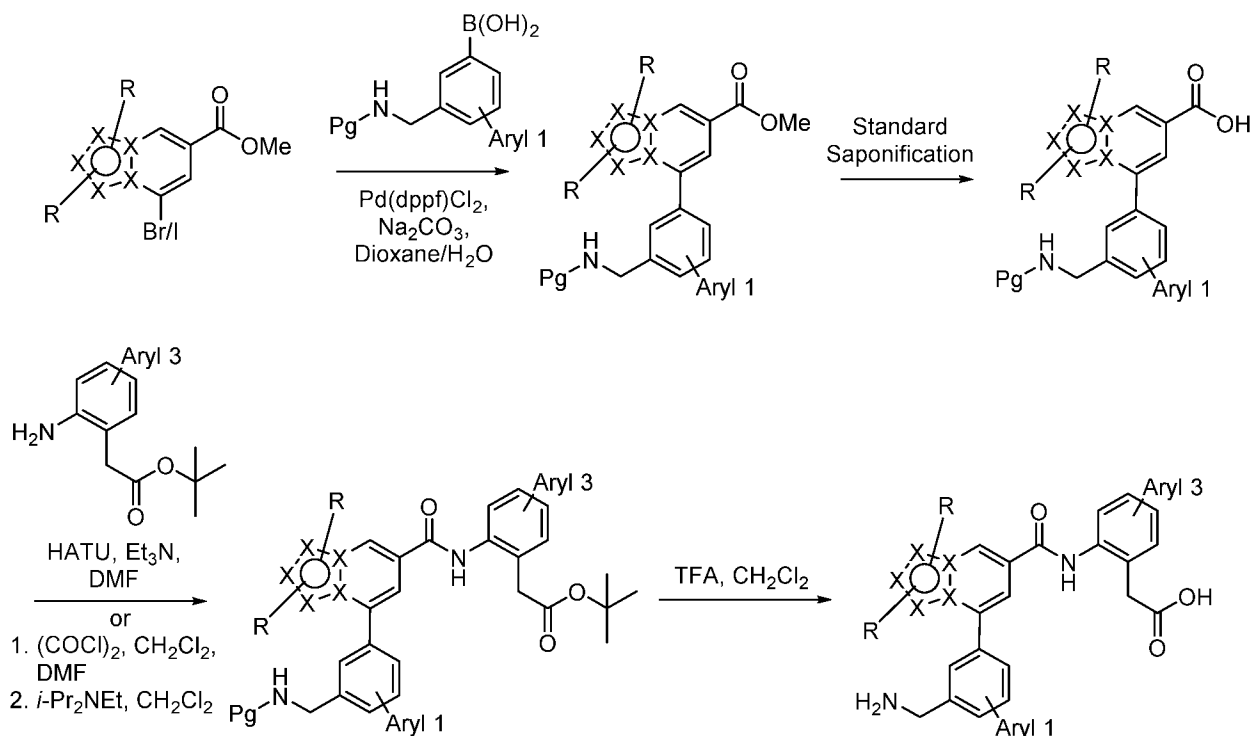


The methyl ester can be reduced under standard conditions. Exemplary reductants which can be used include lithium aluminum hydride (LAH or LiAlH_4) at temperatures ranging from -78°C to room temperature, sodium borohydride (NaBH_4) at temperatures ranging from -78°C to room temperature, and diisobutylaluminum hydride (DIBAL) at temperatures ranging from -78°C to room temperature. See General Reduction Procedure herein. Reduction reactions provide the benzylic alcohol. Coupling of the benzylic alcohol with a phenol can be accomplished via Mitsunobu reaction (DIAD, and triphenylphosphine in THF), or by a two-step procedure which involves conversion of the benzylic alcohol to a

20

benzylic chloride (thionyl chloride (SOCl_2) in DMF at 0°C to room temperature) followed by displacement of the benzylic chloride with a phenol (cesium carbonate in DMF at room temperature to 40°C) to afford the desired benzylic ether. The bromo/iodo group can be coupled with a boronic ester/acid under metal-catalyzed conditions (Pd(dppf)Cl_2 , sodium carbonate, in Dioxane/ H_2O at elevated temperatures (80°C to 100°C)) to provide the corresponding biaryl after purification. Deprotection of the acid-labile protecting groups (trifluoroacetic acid (TFA)) in dichloromethane at temperatures ranging from 0°C to 40°C) should provide the desired amino acids.

10

General Reaction Sequence 3

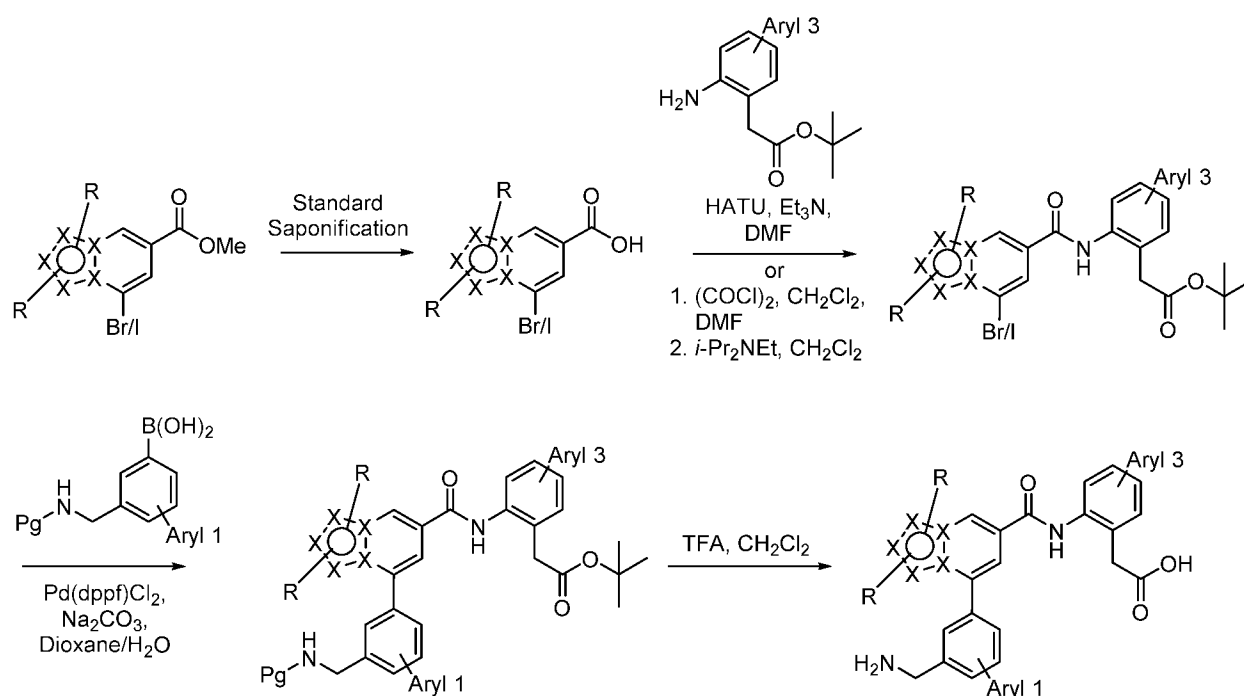
The bromo/iodo group can be coupled with a boronic ester/acid under metal-catalyzed conditions (e.g., Pd(dppf)Cl_2 , sodium carbonate, in Dioxane/ H_2O at elevated temperatures (80°C to 100°C)) to provide the corresponding biaryl after purification. The methyl ester can be saponified under standard conditions (examples of bases which can be used include lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, potassium trimethylsilanoate, and trimethyltin hydroxide). See General Saponification Procedure herein. Saponification provides the benzoic acid. Coupling of the benzoic acid with an aniline can be accomplished under standard peptide coupling conditions (peptide

coupling reagents can include HATU, PyAOP, DCC, EDCI, etc, with triethylamine or N,N-diisopropylethylamine in DMF or dichloromethane at temperatures ranging from 0°C to 80 °C), or by a two-step procedure which involves conversion of the benzoic acid to a benzoyl chloride (oxalyl chloride in dichloromethane with DMF at 0°C to room temperature)

- 5 followed by coupling of the aniline (triethylamine or N,N-diisopropylethylamine in dichloromethane at room temperature to 40°C) to afford the desired amide. Deprotection of the acid-labile protecting groups (trifluoroacetic acid (TFA)) in dichloromethane at temperatures ranging from 0°C to 40°C) should provide the desired amino acids.

10

General Reaction Sequence 4



The methyl ester can be saponified under standard conditions (examples of bases which can be used include lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, potassium trimethylsilanoate, and trimethyltin hydroxide). See General Saponification Procedure herein. Saponification provides the benzoic acid. Coupling of the benzoic acid with an aniline can be accomplished under standard peptide coupling conditions (peptide coupling reagents can include HATU, PyAOP, DCC, EDCI, etc, with triethylamine or N,N-diisopropylethylamine in DMF or dichloromethane at temperatures ranging from 0°C to 80°C), or by a two-step procedure which involves conversion of the benzoic acid to a

20

benzoyl chloride (oxalyl chloride in dichloromethane with DMF at 0°C to room temperature) followed by coupling of the aniline (triethylamine or N,N-diisopropylethylamine in dichloromethane at rt to 40°C) to afford the desired amide. The bromo/iodo group can be coupled with a boronic ester/acid under metal-catalyzed conditions (Pd(dppf)Cl₂, sodium carbonate, in Dioxane/H₂O at elevated temperatures (80°C to 100°C)) to provide the corresponding biaryl after purification. Deprotection of the acid-labile protecting groups (trifluoroacetic acid (TFA)) in dichloromethane at temperatures ranging from 0°C to 40 °C) should provide the desired amino acids.

Examples of General Reduction Procedures for each of the above General Reactions Sequences are provided below.

DIBAL Reduction

Diisobutylaluminum hydride can be added to a solution of the ester in dichloromethane at -78°C over 10 min. After, the reaction should be allowed to stir at this temperature for an additional 1-2 hours. If needed the reaction can be warmed slowly to 0°C over 1 hour. Saturated aqueous Rochelle's salts can be added at -78°C or at 0°C. After the reaction is quenched, it can be warmed to room temperature and stirred vigorously until the emulsion separates. The reaction can be diluted with isopropyl acetate and water. The aqueous layer can be extracted with isopropyl acetate. The combined organic layers can be dried with sodium sulfate, concentrated, and the crude residue can be purified by flash column chromatography or carried through to the next reaction without further purification.

NaBH₄ Reduction

A solution of calcium chloride in ethanol can be added to a solution of the ester in THF. The solution can be cooled to 0°C and NaBH₄ can be added. The mixture can be allowed to warm to 20°C and stirred until complete. After, the reaction mixture can be quenched with water. The aqueous layer can be extracted with isopropyl acetate. The combined organic layers can be dried with sodium sulfate, concentrated, and the crude residue can be purified by flash column chromatography or carried through to the next reaction without further purification.

LiAlH₄ Reduction

LiAlH₄ can be added to a solution of the ester in THF at temperatures ranging from -78°C to 0°C. The reaction can be warmed to temperatures ranging from 25°C to reflux and stirred until complete. Upon completion, the mixture can be cooled to 0°C quenched with

H₂O, 15% NaOH, then H₂O. The solution can be stirred at 25°C until a precipitate forms. The mixture can be filtered through a pad of celite. The filtrate can be concentrated under reduced pressure and the crude residue can be purified by flash column chromatography or carried through to the next reaction without further purification.

- 5 Example of General Saponification Procedure for each of the above General Reactions Sequences are provided below.

 Lithium hydroxide can be added to a solution of the ester in a mixture of THF/Water/Methanol (1:1:1) at 0°C. The reaction was be warmed to temeratures ranging from 25°C to relax. Upon completion, the pH of the reaction can be adjusted to pH 1 by
10 using 1 M HCl. The reaction mixture can be further diluted with isopropyl acetate and water. The aqueous layer can be extracted with isopropyl acetate. The combined organic layers can be dried with sodium sulfate, concentrated, and the crude residue can be purified by flash column chromatography or carried through to the next reaction without further purification.

15 METHODS OF TREATMENT WITH AND USES OF FACTOR D INHIBITORS

 Compounds of the present invention are useful as Factor D inhibitors. Accordingly, in one embodiment is provided a method of inhibiting Factor D in a patient in need of therapy, comprising administering to the patient a compound of the present invention. An “individual,” “patient,” or “subject” according to any of the embodiments herein may be a
20 human. For the prevention or treatment of disease, the appropriate dosage of the compound of the present invention will depend on the type of disease to be treated, the severity and course of the disease, whether the compound of the present invention is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the compound of the present invention and the discretion of the attending
25 physician.

 In some embodiments, a compound of the present invention may be used to treat a mammal. In some embodiments, a compound of the present invention is administered to a nonhuman mammal for the purposes of obtaining preclinical data, for example. Exemplary nonhuman mammals to be treated include nonhuman primates, dogs, cats, rodents and other
30 mammals in which preclinical studies are performed. Such mammals may be established animal models for a disease to be treated with the a compound of the present invention, or

may be used to study toxicity of the a compound of the present invention. In each of these embodiments, dose escalation studies may be performed on the mammal.

In another embodiment is provided a method of contacting a cell, such as an *ex vivo* cell, with a compound of the present invention to inhibit Factor D activity in the cell.

5 The compound of the present invention may be formulated, dosed and administered in a manner consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to
10 medical practitioners. The "therapeutically effective amount" of the compound of the present invention to be administered will be governed by such considerations, and is the minimum amount necessary to prevent, ameliorate, or treat a disease or disorder. The compound of the present invention need not be, but is optionally formulated with one or more agents currently used to prevent or treat the disorder in question. The effective amount of such other agents
15 depends on the amount of compound of the present invention present in the formulation, the type of disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as used hereinbefore or about from 1 to 99% of the heretofore employed dosages.

 Also provided is a pharmaceutical formulation comprising a compound falling within
20 the scope of the various structural formulae disclosed herein, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, carrier or diluent. Compounds of the invention, including pharmaceutical formulations comprising such compounds, may be used in the methods described herein.

 Further provided is a method of preventing, treating, or lessening the severity of a
25 disease or condition responsive to the inhibition of Factor D in a patient, comprising administering to the patient a therapeutically effective amount of a compound of the present invention, or a stereoisomer or pharmaceutically acceptable salt thereof.

 A compound of the present invention may be used to treat complement-mediated disorders. These disorders are associated with excessive or uncontrolled complement
30 activation. They include: complement activation during cardiopulmonary bypass operations; complement activation due to ischemia-reperfusion following acute myocardial infarction, aneurysm, stroke, hemorrhagic shock, crush injury, multiple organ failure, hypobolemic

shock and intestinal ischemia. These disorders can also include disease or condition is an inflammatory condition such as severe burns, endotoxemia, septic shock, acute respiratory distress syndrome, hemodialysis, anaphylactic shock, severe asthma, angioedema, Crohn's disease, ulcerative colitis, sickle cell anemia, poststreptococcal glomerulonephritis and pancreatitis. The disorder may be the result of an adverse drug reaction, drug allergy, IL-2 induced vascular leakage syndrome or radiographic contrast media allergy. It also includes autoimmune disease such as systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, Alzheimer's disease, amyotrophic lateral sclerosis and multiple sclerosis.

Complement activation is also associated with transplant rejection. Recently there has been a strong correlation shown between complement activation and ocular diseases such as age-related macular degeneration, diabetic retinopathy and other ischemia-related retinopathies, choroidal neovascularization (CNV), uveitis, diabetic macular edema, various glaucoma indications including open- and angle-closure glaucoma, normal tension glaucoma, congenital glaucoma, secondary glaucoma, pigmentary glaucoma, uveitic glaucoma, neovascular glaucoma and traumatic glaucoma, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization. A compound of the present invention may be used to treat any one or more of these conditions.

DOSAGE & ADMINISTRATION

The present invention provides pharmaceutical formulations or medicaments containing the compounds of the invention and at least one therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments. In one example, compound falling within the scope of the various structural formulae disclosed herein, or a stereoisomer or pharmaceutically acceptable salt thereof, with the desired degree of purity may be formulated by mixing with physiologically acceptable carriers, *i.e.*, carriers that are non-toxic to recipients at the dosages and concentrations employed into a dosage form at ambient temperature and at the appropriate pH. The pH of the formulation depends mainly on the particular use and the concentration of compound, but typically ranges anywhere from about 3 to about 8. In one example, a compound falling within the scope of the various structural formulae disclosed herein is formulated in an acetate buffer, at pH 5. In another embodiment, the compound falling within the scope of the various structural formulae disclosed herein is sterile. The

compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the severity of the disorder, the particular patient being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The “effective amount” of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to inhibit Factor D activity. Typically such amount may be below the amount that is toxic to normal cells, or the patient as a whole.

The pharmaceutical formulation (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well-known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing a compound falling within the scope of the various structural formulae disclosed herein, or a stereoisomer or pharmaceutically acceptable salt thereof, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides, copolymers of L-glutamic acid and gamma-ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

A dose to treat human patients may range from about 0.1 µg to about 1000 mg of a compound falling within the scope of the various structural formulae disclosed herein, or a

stereoisomer or pharmaceutically acceptable salt thereof. A typical dose may be about 1 mg to about 300 mg of the compound. A dose may be administered once a day (QD), twice per day (BID), or more frequently, depending on the pharmacokinetic and pharmacodynamic properties, including absorption, distribution, metabolism, and excretion of the particular compound. In addition, toxicity factors may influence the dosage and administration regimen. When administered orally, the pill, capsule, or tablet may be ingested daily or less frequently for a specified period of time. The regimen may be repeated for a number of cycles of therapy.

The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal, epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The compounds of the present invention may be administered in any convenient administrative form, *e.g.*, tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, *e.g.*, diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, *e.g.*, Ansel, H. C., *et al.*, *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*. Philadelphia: Lippincott, Williams & Wilkins, **2004**; Gennaro, Alfonso R., *et al.* *Remington: The Science and Practice of Pharmacy*. Philadelphia: Lippincott, Williams & Wilkins, **2000**; and Rowe, R. C., *Handbook of Pharmaceutical Excipients*, Chicago, Pharmaceutical Press, **2005**. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (*i.e.*, a compound of the present invention or pharmaceutical formulation thereof) or aid in the manufacturing of the pharmaceutical product (*i.e.*, medicament).

For oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefore, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

An example of a suitable oral dosage form is a tablet containing about 25 mg, 50 mg, 100 mg, 250 mg or 500 mg of the compound of the invention compounded with about 90-30 mg anhydrous lactose, about 5-40 mg sodium croscarmellose, about 5-30 mg polyvinylpyrrolidone (PVP) K30, and about 1-10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving the compound, for example 5-400 mg, of the invention in a suitable buffer solution, e.g., a phosphate buffer, adding a tonicifier, e.g., a salt such as sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

In some embodiments, the compounds of the present invention are suitable for prevention or treatment of an ocular disease or condition. In some embodiments, pharmaceutical formulations may be administered by ocular, intraocular, and/or intravitreal injection, and/or juxtasceral injection, and/or subtenon injection, and/or superchoroidal injection and/or topical administration in the form of eye drops and/or ointment. Such compounds of the invention may be delivered by a variety of methods, e.g., intravitreally as a device and/or a depot that allows for slow release of the compound into the vitreous, including those described in references such as *Intraocular Drug Delivery*, Jaffe, Jaffe, Ashton, and Pearson, editors, Taylor & Francis (March 2006). In one example, a device may be in the form of a min pump and/or a matrix and/or a passive diffusion system and/or encapsulated cells that release the compound for a prolonged period of time (*Intraocular Drug*

Delivery, Jaffe, Jaffe, Ashton, and Pearson, editors, Taylor & Francis (March 2006). Other methods of administration may also be used, which includes but is not limited to, topical, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intranasal, and intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

Formulations for ocular, intraocular or intravitreal administration can be prepared by methods and using ingredients known in the art. A main requirement for efficient treatment is proper penetration through the eye. Unlike diseases of the front of the eye, where drugs can be delivered topically, retinal diseases require a more site-specific approach. Eye drops and ointments rarely penetrate the back of the eye, and the blood-ocular barrier hinders penetration of systemically administered drugs into ocular tissue. Accordingly, usually the method of choice for drug delivery to treat retinal disease, such as AMD and CNV, is direct intravitreal injection. Intravitreal injections are usually repeated at intervals which depend on the patient's condition, and the properties and half-life of the drug delivered. For intraocular (e.g., intravitreal) penetration, usually molecules of smaller size are preferred.

In one embodiment, the pharmaceutical formulation also includes at least one additional anti-proliferative agent.

An embodiment, therefore, includes a pharmaceutical formulation comprising a compound falling within the scope of the various structural formulae disclosed herein, or a stereoisomer or pharmaceutically acceptable salt thereof. A further embodiment includes a pharmaceutical formulation comprising a compound falling within the scope of the various structural formulae disclosed herein, or a stereoisomer or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefore. Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered parenterally, orally or by any other desired route.

Combination Therapy

The compound falling within the scope of the various structural formulae disclosed herein may be employed alone or in combination with other therapeutic agents for the

treatment of a disease or disorder described herein. The second compound of the pharmaceutical combination formulation or dosing regimen preferably has complementary activities to the compound falling within the scope of the various structural formulae disclosed herein such that they do not adversely affect each other. The combination therapy may provide "synergy" and prove "synergistic", *i.e.*, the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately.

The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. The combined administration includes co-administration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities.

Combination therapies according to the present invention thus comprise the administration of at least one compound falling within the scope of the various structural formulae disclosed herein, or a stereoisomer or pharmaceutically acceptable salt thereof, and the use of at least one other treatment method. The amounts of the compound falling within the scope of the various structural formulae disclosed herein and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

In some embodiments, the second therapeutic compound is selected from an HTRA1 antagonist, an ANG2 antagonist (such as anti-ANG2 antibodies as disclosed, for example, in US20090304694 A1), a TIE2 antagonist (such as anti-TIE2 antibodies as disclosed, for example, in US Patent No. 6,376,653), a VEGF antagonist (such as VEGF antagonists as disclosed, for example, in US Patent No. 6,884,879 issued Feb. 26, 2015 and WO98/45331 (bevacizumab and other humanized anti-VEGF antibodies); WO2005/012359 and WO2005/044853 (G6 or B20 series antibodies (e.g., G6-31, B20-4.1); WO98/45331 (ranabizumab), and a second complement component antagonist. In some embodiments, the HTRA1 antagonist is an anti-HTRA1 antibody. In some embodiments, the ANG2 antagonist is an anti-ANG2 antibody. In some embodiments, the TIE2 antagonist is an anti-TIE2 antibody. In some embodiments, a VEGF antagonist is selected from a VEGF trap (such as aflibercept (Eylea®) and an anti-VEGF antibody (such as bevacizumab (Avastin®) or ranabizumab (Lucentis®)). In some embodiments, the second complement component

antagonist inhibits various members of the classical or alternative complement pathway (complement inhibitors), selected from C1, C2, C3, C4, C5, C6, C7, C8, C9 complement components.

In some embodiments, the treatment of the present disclosure for complement-mediated disorders in a human subject with a complement-mediated disorder comprises administering to the subject an effective amount of a therapeutic compound and further comprising administering to the subject an effective amount of a second therapeutic compound. In some embodiments, the second therapeutic compound is an HTRA1 antagonist. In some embodiments, the second therapeutic compound is an ANG2 antagonist. In some embodiments, the second therapeutic compound is a TIE2 antagonist. In some embodiments, the second therapeutic compound is a VEGF antagonist. In some embodiments, the second therapeutic compound is a second complement component antagonist. In some embodiments, the complement-mediated disorder is a complement-associated eye condition. In some embodiments, the ocular disorder is age-related macular degeneration (AMD), including non-exudative (e.g., intermediate dry AMD or geographic atrophy (GA)) and exudative (e.g., wet AMD (choroidal neovascularization (CNV)) AMD, diabetic retinopathy (DR), endophthalmitis and uveitis. In one example, the complement-associated eye condition is intermediate dry AMD. In some embodiments, the complement-associated eye condition is geographic atrophy. In some embodiments, the complement-associated eye condition is wet AMD (choroidal neovascularization (CNV)).

Combined administration herein includes co-administration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein generally there is a time period while both (or all) active agents simultaneously exert their biological activities.

ARTICLES OF MANUFACTURE

In another embodiment of the invention, an article of manufacture, or "kit", containing materials useful for the treatment of the diseases and disorders described above is provided. In one embodiment, the kit comprises a container comprising a compound falling within the scope of the various structural formulae disclosed herein, or a stereoisomer or pharmaceutically acceptable salt thereof. The kit may further comprise a label or package insert on or associated with the container. The term "package insert" is used to refer to

instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products. Suitable containers include, for example, bottles, vials, syringes, blister pack, etc. The container may be formed from a variety of materials such as glass or plastic. The container may hold a compound falling within the scope of the various structural formulae disclosed herein or a formulation thereof which is effective for treating the condition and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is a compound falling within the scope of the various structural formulae disclosed herein. Alternatively, or additionally, the article of manufacture may further comprise a second container comprising a pharmaceutical diluent, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

In another embodiment, the kits are suitable for the delivery of solid oral forms of a compound falling within the scope of the various structural formulae disclosed herein, such as tablets or capsules. Such a kit can include a number of unit dosages. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms.

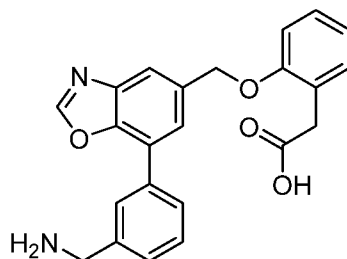
EXAMPLES

The following examples illustrate the preparation and biological evaluation of compounds within the scope of the invention. These examples and preparations which follow are provided to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

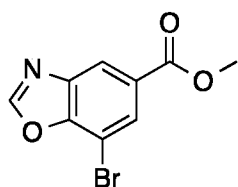
The following provides non-limiting examples of compounds according to the present invention.

Example 1. 2-(2-((7-(3-(aminomethyl)phenyl)benzo[d]oxazol-5-yl)methoxy)phenyl)acetic acid

Using General Reaction Sequence 1

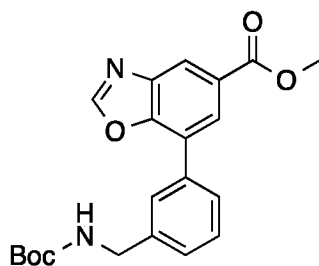


5 Step 1 – Synthesis of methyl 7-bromobenzo[d]oxazole-5-carboxylate (1-a):



Triethylorthoformate (40.6 mL, 244 mmol) was added to methyl 3-amino-5-bromo-4-hydroxybenzoate (4.0 g, 16.3 mmol) and the reaction was heated at 100°C for 2 hours. The reaction was cooled to room temperature and 10% NaOH (30 mL) was added. The aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic layers were concentrated under reduced pressure and the crude residue was purified by flash column chromatography (silica, petroleum ether/EtOAc 30/1 to 2/1) to give methyl 7-bromobenzo[d]oxazole-5-carboxylate (0.800 g, 19 % Yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 1.4 Hz, 1H), 8.31 (d, *J* = 1.4 Hz, 1H), 8.21 (s, 1H), 3.98 (s, 3H). LCMS: *m/z* = + 255.8 (M+H⁺)

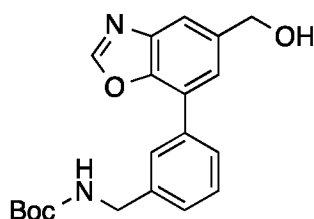
Step 2 – Synthesis of methyl 7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)benzo[d]oxazole-5-carboxylate (1-b):



To a solution of methyl 7-bromobenzo[d]oxazole-5-carboxylate (0.780 g, 3.05 mmol) in

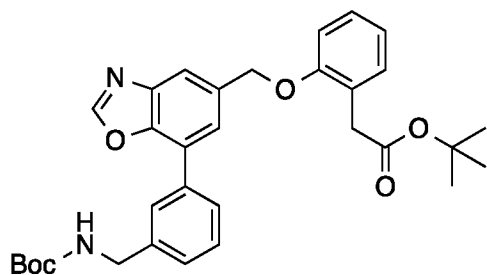
dioxane (5 mL) was added *tert*-butyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)carbamate (1.22 g, 3.66 mmol) followed by Na₂CO₃ (0.646 g, 6.09 mmol dissolved in H₂O (3 mL)). The reaction mixture was degassed and purged with nitrogen (3x). Then Pd(dppf)Cl₂ (0.446 g, 0.609 mmol) was added under N₂, and the mixture was heated at 80°C for 2 hours. After cooling to room temperature, water (8 mL) was added. The aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were concentrated under reduced pressure and the crude residue was purified by flash column chromatography (silica, petroleum ether/EtOAc 30/1 to 1/1) to give methyl 7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)benzo[*d*]oxazole-5-carboxylate (1.0 g, 2.61 mmol, 86% Yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.47 (s, 1H), 8.34 (s, 1H), 8.22 (s, 1H), 7.78 (s, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 7.7 Hz, 1H), 4.93 (s, 1H), 4.44 (d, *J* = 6.0 Hz, 2H), 4.00 (s, 3H), 1.48 (s, 9H). LCMS: *m/z* = + 765.1 (2M+H⁺)

Step 3 – Synthesis of *tert*-butyl (3-(5-(hydroxymethyl)benzo[*d*]oxazol-7-yl)benzyl)carbamate (1-c):



A mixture of methyl 7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)benzo[*d*]oxazole-5-carboxylate (1.0 g, 2.61 mmol) in THF (10 mL) was cooled to 0°C, then a mixture of CaCl₂ (0.579 g, 5.22 mmol dissolved in EtOH (10 mL)) was added followed by NaBH₄ (0.395 g, 10.4 mmol) and the mixture was stirred at 20°C. After 2 h, the reaction mixture was quenched with water (30 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers were concentrated under reduced pressure and the crude residue was purified by prep-TLC (petroleum ether/EtOAc = 1:1) to give *tert*-butyl (3-(5-(hydroxymethyl)benzo[*d*]oxazol-7-yl)benzyl)carbamate (0.400 g, 43% Yield) as a yellow solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.16 (s, 1H), 7.80 – 7.74 (m, 3H), 7.65 – 7.60 (m, 1H), 7.55 – 7.45 (m, 1H), 7.35 – 7.29 (m, 1H), 4.88 (d, *J* = 5.0 Hz, 2H), 4.42 (d, *J* = 6.1 Hz, 2H), 1.48 (s, 9H). LCMS: *m/z* = + 355.0 (M+H⁺)

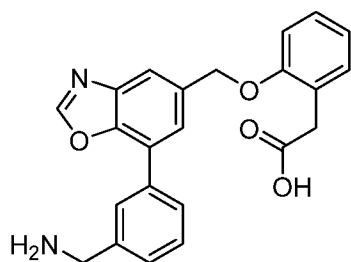
Step 4 – Synthesis of *tert*-butyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)benzo[*d*]oxazol-5-yl)methoxy)phenyl)acetate (**1-d**):



Twelve reactions were carried out in parallel.

- 5 To a solution of *tert*-butyl (3-(5-(hydroxymethyl)benzo[*d*]oxazol-7-yl)benzyl)carbamate (20 mg, 56.4 μ mol) and *tert*-butyl 2-(2-hydroxyphenyl)acetate (14.1 mg, 67.7 μ mol) in THF (1 mL) was added DIAD (17.1 mg, 84.6 μ mol, 16.5 μ L) followed by PPh₃ (29.6 mg, 0.113 mmol) under N₂. The mixture was stirred at 80°C for 2 hours. After cooling to room temperature, the 12 reactions were combined, and the reaction mixture was quenched with
- 10 water (8 mL). The aqueous layer was extracted with EtOAc (3 x 4 mL). The combined organic layers were concentrated under reduced pressure and the crude residue was purified by prep-TLC (petroleum ether/EtOAc = 1:1) to give *tert*-butyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)benzo[*d*]oxazol-5-yl)methoxy)phenyl)acetate (0.100 g, 27% Yield) as a yellow solid. ¹H NMR (400 MHz, MeOD) δ 8.54 (s, 1H), 7.79-7.85 (m, 4H), 7.46-7.48 (t, 1H), 7.35 (d, *J* = 8 Hz, 1H), 7.25 (t, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.92-6.94 (m, 1H), 5.28 (s, 2H), 4.34 (br s, 2H), 3.61 (s, 2H), 1.45 (s, 9H), 1.28 (s, 9H). LCMS: *m/z* = + 545.1 (M+H⁺)
- 15

- Step 5 – Synthesis of 2-(2-((7-(3-(aminomethyl)phenyl)benzo[*d*]oxazol-5-yl)methoxy)phenyl)acetic acid (**1**)
- 20



A mixture of *tert*-butyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)benzo[*d*]oxazol-5-yl)methoxy)phenyl)acetate (0.100 g, 0.184 mmol) in DCM (1 mL) was

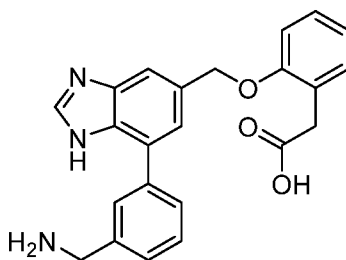
added TFA (0.628 g, 5.51 mmol, 0.408 mL) and stirred at 20°C for 12 hours. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by prep-HPLC (neutral condition, column: Agela Durashell C18 150*25 5 μ ; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 20%-50%, 10.5 min) to give 2-(2-((7-(3-

- 5 (aminomethyl)phenyl)benzo[d]oxazol-5-yl)methoxy)phenyl)acetic acid (15.3 mg, 21% Yield) as a white solid. ¹H NMR (400 MHz, MeOD) δ 8.57 (s, 1H), 8.31 (s, 1H), 8.14-8.16 (m, 2H), 7.76 (s, 1H), 7.50-7.54 (m, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.16-7.20 (m, 2H), 6.99 (d, *J* = 8 Hz, 1H), 6.89-6.91 (m, 1H), 5.31 (s, 2H), 4.19 (s, 2H), 3.60 (s, 2H). LCMS: *m/z* = + 389.1 (M+H⁺), 3.37 minutes.

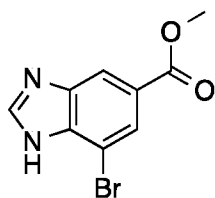
10

Example 2. 2-(2-((7-(3-(aminomethyl)phenyl)-1*H*-benzo[d]imidazol-5-yl)methoxy)phenyl)acetic acid

Using General Reaction Sequence 1

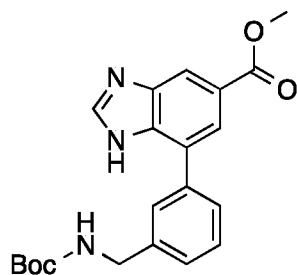


- 15 Step 1 – Synthesis of methyl 7-bromo-1*H*-benzo[d]imidazole-5-carboxylate (**2-a**)



- 20 TsOH•H₂O (0.388 g, 2.04 mmol) was added to a mixture of triethylorthoformate (6.8 mL, 40.8 mmol) and methyl 3,4-diamino-5-bromobenzoate (5.0 g, 20.4 mmol) in THF (150 mL). The mixture was stirred at 20°C for 5 hours. After cooling to room temperature, the mixture was concentrated under reduced pressure. EtOAc (20 mL) was added to the crude residue and the mixture was filtered. The filter cake was collected to give methyl 7-bromo-1*H*-benzo[d]imidazole-5-carboxylate (4.0 g, 77% Yield) as a pink solid. ¹H NMR (400 MHz, DMSO) δ 13.10 (br s, 1H), 8.51 (s, 1H), 8.17 (s, 1H), 7.96 (s, 1H), 3.87 (s, 2H).

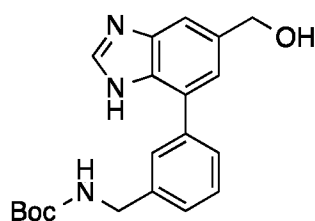
Step 2 – Synthesis of methyl 7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1*H*-benzo[*d*]imidazole-5-carboxylate (**2-b**)



To a mixture of methyl 7-bromo-1*H*-benzo[*d*]imidazole-5-carboxylate (1.0 g, 3.92 mmol) and
 5 *tert*-butyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)carbamate (2.74 g, 8.23 mmol) in 1,4-dioxane (30 mL) was added the solution of Na₂CO₃ (1.25 g, 11.8 mmol dissolved in H₂O (6 mL)) and Pd(dppf)Cl₂ (0.746 g, 1.02 mmol) in one portion at 25°C under N₂. The mixture was stirred at 80 °C for 3 h. After cooling to room temperature, the reaction was concentrated under reduced pressure. The crude residue was purified by flash column
 10 chromatography (silica, Petroleum ether: EtOAc = 50:1 to 0:1) to give methyl 7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1*H*-benzo[*d*]imidazole-5-carboxylate (1.07 g, 66% Yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.30 (s, 1H), 8.0 (s, 1H), 7.87 (s, 1H), 7.68 (s, 1H), 7.59 (s, 1H), 7.36-7.38 (m, 1H), 7.22-7.24 (m, 1H), 5.21 (s, 1H), 4.31 (br s, 2H), 3.93 (s, 3H), 1.42 (s, 9H).

15

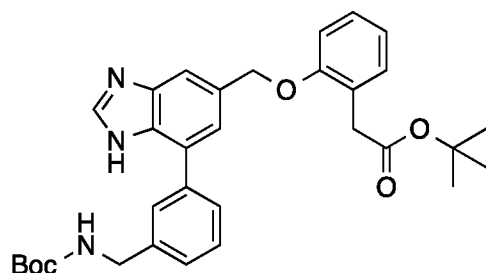
Step 3 – *tert*-butyl (3-(5-(hydroxymethyl)-1*H*-benzo[*d*]imidazol-7-yl)benzyl)carbamate (**2-c**)



To a mixture of methyl 7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1*H*-benzo[*d*]imidazole-5-carboxylate (1.0 g, 2.62 mmol) in THF (20 mL) was added LiAlH₄
 20 (0.497 g, 13.1 mmol) in one portion at 0°C under N₂. The mixture was then warmed to 25°C. After 1 h, the mixture was cooled to 0°C and quenched with 0.6 mL H₂O, 0.6 mL 15% NaOH then 1.2 mL H₂O. The solution was stirred at 25°C for 0.5 hr, then the mixture was filtered through a pad of celite. The filtrate was collected and concentrated under reduced pressure to give *tert*-butyl (3-(5-(hydroxymethyl)-1*H*-benzo[*d*]imidazol-7-yl)benzyl)carbamate (0.780 g,

84% Yield) as a yellow solid, which was used directly in the next step without further purification.

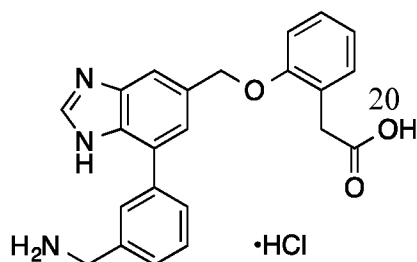
Step 4 – Synthesis of *tert*-butyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1*H*-benzo[*d*]imidazol-5-yl)methoxy)phenyl)acetate (**2-d**):



Two reactions were carried out in parallel.

To a mixture of *tert*-butyl (3-(5-(hydroxymethyl)-1*H*-benzo[*d*]imidazol-7-yl)benzyl)carbamate (0.100 g, 0.283 mmol) and *tert*-butyl 2-(2-hydroxyphenyl)acetate (0.300 g, 1.44 mmol) in THF (3 mL) was added PPh₃ (0.125 g, 0.475 mmol) and DIAD (0.100 g, 0.495 mmol) in one portion at 0°C under N₂. The mixture was stirred at 40°C for 1 hr. The two batches were combined and the mixture was concentrated under reduced pressure. The crude residue was purified by prep-TLC (Dichloromethane: Methanol = 20:1) to give *tert*-butyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino) methyl)phenyl)-1*H*-benzo[*d*]imidazol-5-yl)methoxy)phenyl)acetate (12 mg, 17.4 μmol, 3% Yield) as colorless oil.

Step 5 – Synthesis of 2-(2-((7-(3-(aminomethyl)phenyl)-1*H*-benzo[*d*]imidazol-5-yl)methoxy)phenyl)acetic acid (**2**):



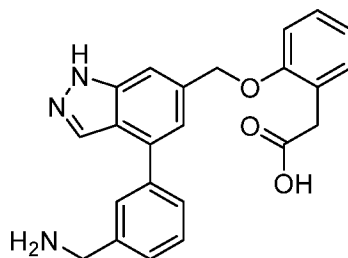
To a mixture of *tert*-butyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1*H*-benzo[*d*]imidazol-5-yl)methoxy)phenyl)acetate (0.03 g, 55.18 μmol) in 1,4-dioxane (2 mL) was added HCl/dioxane (4 M, 1.5 mL) in one portion. The mixture was stirred at 40°C for 3 h. The mixture was concentrated under vacuum to give 2-(2-((7-(3-(aminomethyl)phenyl)-

1*H*-benzo[*d*]imidazol-5-yl)methoxy)phenyl)acetic acid (14 mg, 57% Yield, HCl salt) as a white solid. ¹H NMR (400 MHz, MeOD) δ 9.34 (s, 1H), 7.96 (s, 1H), 7.89 (s, 1H), 7.81-7.83 (m, 2H), 7.63-7.67 (m, 2H), 7.24-7.26 (m, 2H), 6.95-7.07 (m, 2H), 5.40 (s, 2H), 4.28 (s, 2H), 3.60 (s, 2H). LCMS: *m/z* = + 388.1 (M+H⁺), 2.77 minutes.

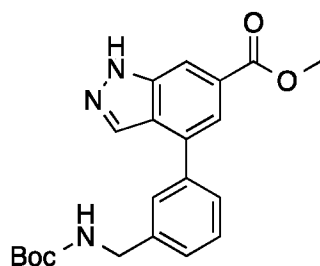
5

Example 3. 2-(2-((4-(3-(aminomethyl)phenyl)-1*H*-indazol-6-yl)methoxy)phenyl)acetic acid

Using General Reaction Sequence 1

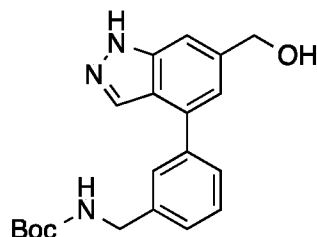


10 **Step 1** – Synthesis of methyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1*H*-indazole-6-carboxylate (**3-a**):



To the solution of methyl 4-bromo-1*H*-indazole-6-carboxylate (1.74 g, 6.82 mmol) and *tert*-butyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)carbamate (4.32 g, 13 mmol) in 1,4-dioxane (30 mL) was added Na₂CO₃ (2.32 g, 21.9 mmol dissolved in H₂O (6 mL)). Pd(dppf)Cl₂ (1.15 g, 1.57 mmol) was added in one portion at 25°C under N₂, then the reaction was heated to 90°C. After 5 h, the mixture was cooled to room temperature and was filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography (silica, Petroleum ether: EtOAc = 50 : 1 to 1 : 1) to give methyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl) phenyl)-1*H*-indazole-6-carboxylate (1.0 g, 37% Yield) as a white solid. ¹H NMR: (400 MHz, CDCl₃) δ 8.21 (s, 2H), 7.86 (s, 1H), 7.59 - 7.65 (m, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 4.45 (bs, 2H), 3.95 (s, 3H), 1.47 (s, 9H).

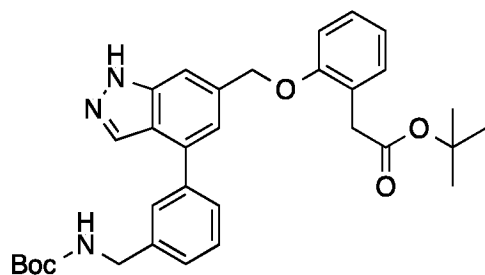
Step 2 – Synthesis of *tert*-butyl (3-(6-(hydroxymethyl)-1*H*-indazol-4-yl)benzyl) carbamate (**3-b**):



- 5 To a mixture of methyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1*H*-indazole-6-carboxylate (1.0 g, 2.62 mmol) in THF (20 mL) was added LiAlH₄ (0.249 g, 6.55 mmol) in one portion at 0°C under N₂, then was warmed to 25°C. After 2 h, the mixture was cooled to 0°C and 0.3 mL H₂O was added, 0.3 mL 15% NaOH was added, then 0.6 mL H₂O was added. The solution was stirred at 25°C for 0.5 hr. The mixture was filtered through a pad of
10 celite. The filtrate was collected and concentrated under reduced pressure to give *tert*-butyl (3-(6-(hydroxymethyl)-1*H*-indazol-4-yl)benzyl)carbamate (0.700 g, 76% yield) as a white solid, which was used in the next step without further purification. ¹H NMR (400 MHz, MeOD) δ 7.67 - 8.14 (m, 1H), 7.64 (s, 1H), 7.54 - 7.61 (m, 1H), 7.51 (s, 1H), 7.41 - 7.48 (m, 1H), 7.31 (br.s, 1H), 7.21 - 7.25 (m, 1H), 4.78 (s, 2H), 4.31 (s, 2H), 1.47 (s, 9H).

15

Step 3 – Synthesis of *tert*-butyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl) - 1*H*-indazol-6-yl)methoxy)phenyl)acetate (**3-c**):

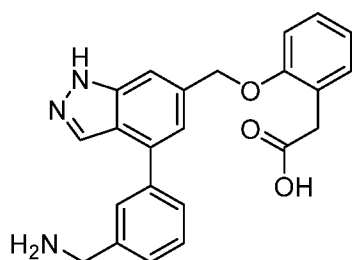


15 reactions were carried out in parallel.

- 20 To a mixture of *tert*-butyl (3-(6-(hydroxymethyl)-1*H*-indazol-4-yl)benzyl)carbamate (20 mg, 56.6 μmol) and *tert*-butyl 2-(2-hydroxyphenyl)acetate (60 mg, 0.288 mmol) in THF (0.600 mL) was added PPh₃ (24.9 mg, 95.1 μmol) and DIAD (20 mg, 99 μmol, 19.3 μL). The mixture was stirred at 40°C for 1 hr. The 15 reactions were combined and the mixture was

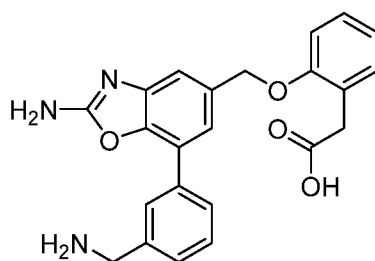
concentrated under reduced pressure. The crude residue was purified by prep-TLC (Petroleum ether: EtOAc = 1 : 1) to give *tert*-butyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1*H*-indazol-6-yl)methoxy)phenyl)acetate (30 mg, 7% Yield) as colorless oil. ¹H NMR: (400 MHz, CDCl₃) δ 8.12 (s, 1H), 7.58 - 7.69 (m, 3H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.20 - 7.29 (m, 4H), 6.91 - 6.99 (m, 2H), 5.22 (s, 2H), 4.36 (br. s., 2H), 3.58 (s, 2H), 1.40 (s, 9H), 1.28 (s, 9H).

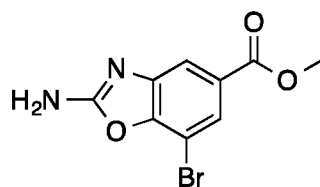
Step 4 – Synthesis of 2-(2-((4-(3-(aminomethyl)phenyl)-1*H*-indazol-6-yl)methoxy)phenyl)acetic acid (3):



To a mixture of *tert*-butyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1*H*-indazol-6-yl)methoxy)phenyl)acetate (30 mg, 55.2 μmol) in 1,4-dioxane (2 mL) was added HCl/dioxane (4 M, 2.76 mL) in one portion at 25°C under N₂. The mixture was stirred at 40°C for 4 hr. The mixture was concentrated under vacuum to give 2-(2-((4-(3-(aminomethyl)phenyl)-1*H*-indazol-6-yl)methoxy)phenyl)acetic acid (20 mg, 82% Yield, HCl salt) as a white solid. ¹H NMR (400 MHz, MeOD) δ 7.76 - 8.13 (m, 1H), 7.58 - 7.74 (m, 2H), 7.55 (s, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.43 (s, 1H), 6.98-7.15 (m, 2H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.83 (t, *J* = 7.6 Hz, 1H), 5.24 (s, 2H), 4.15 (s, 2H), 3.62 (s, 2H). LCMS: *m/z* = + 388.1 (M+H⁺), 3.31 minutes.

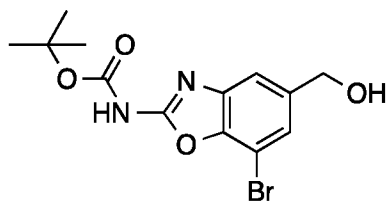
Example 4. 2-(2-((2-amino-7-(3-(aminomethyl)phenyl)benzo[d]oxazol-5-yl)methoxy)phenyl)acetic acid



Step 1 – Synthesis of methyl 2-amino-7-bromobenzo[d]oxazole-5-carboxylate (**4-a**):

Cyanogen bromide ((3.0 M in dichloromethane, 7.0 mL, 21.1 mmol) was added to a solution of the methyl 3-amino-5-bromo-4-hydroxy-benzoate (4.00 g, 16.3 mmol) in water (7.4 mL).

- 5 The reaction was heated at reflux for 1 h. After cooling to room temperature, the reaction was carefully quenched with saturated aqueous sodium bicarbonate. The reaction was further diluted with water and the precipitate was filtered off. The filter cake was rinsed with water and dried under vacuum to afford methyl 2-amino-7-bromo-1,3-benzoxazole-5-carboxylate (4.0 g, 15 mmol, 91% Yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.95 (s, 2H), 7.74 (d, *J* = 1.4
- 10 Hz, 1H), 7.69 (d, *J* = 1.5 Hz, 1H), 3.85 (s, 3H). LCMS: *m/z* = + 272 (M+H⁺)

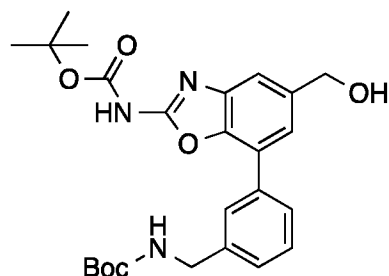
Step 2 – Synthesis of *tert*-butyl (7-bromo-5-(hydroxymethyl)benzo[d]oxazol-2-yl)carbamate (**4-b**):

- 15 Di-*tert*-butyl dicarbonate (9.6 g, 44 mmol) was added to a solution of the methyl 2-amino-7-bromo-1,3-benzoxazole-5-carboxylate (4.0 g, 15 mmol) and N,N-diisopropylethylamine (7.7 mL, 44 mmol) and 4-dimethylaminopyridine (0.366 g, 3.0 mmol) in N,N-dimethylformamide (30 mL) at room temperature. After 18 h, the reaction was diluted with water and isopropyl acetate. The aqueous layer was extracted with isopropyl acetate (3 x 100 mL). The combined
- 20 organic layers were dried with sodium sulfate, concentrated, and the residue was purified by flash column chromatography (silica, 0% to 100% isopropyl acetate - heptane) to give an inseparable mixture of the mono boc and the diboc products (5.39 g). This mixture was directly submitted to the next reaction without any further purification.

- Diisobutylaluminum hydride (1.0 M in toluene, 44 mL, 44 mmol) was added to a solution of
- 25 methyl 7-bromo-2-(*tert*-butoxycarbonylamino)-1,3-benzoxazole-5-carboxylate (5.39 g, 14.5 mmol) in dichloromethane (73 mL) over 15 minutes at -78°C. After the addition was

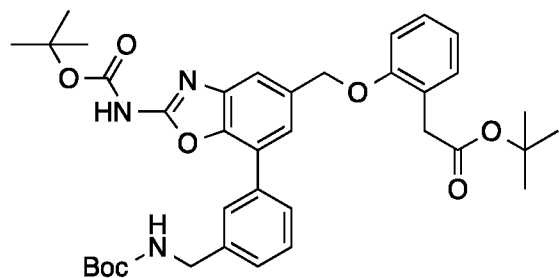
complete, the reaction was allowed to stir at this temperature for an additional 1h 20 min. A saturated aqueous solution of Rochelle's salts were added to the reaction at -78°C. The reaction was warmed to room temperature and stirred vigorously for 4 h. The reaction was diluted with water and isopropyl acetate. The aqueous layer was extracted with isopropyl acetate (4 x 100 mL). The combined organic layers were dried with sodium sulfate, concentrated, and the crude residue was purified by flash column chromatography (silica 0% to 100% isopropyl acetate - heptane) to give *tert*-butyl N-[7-bromo-5-(hydroxymethyl)-1,3-benzoxazol-2-yl]carbamate (0.230 g, 0.670 mmol, 4.6% Yield).

10 **Step 3 – Synthesis of *tert*-butyl (7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-5-(hydroxymethyl)benzo[d]oxazol-2-yl)carbamate (4-c):**



[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (98 mg, 0.134 mmol) was added to a solution of *tert*-butyl N-[7-bromo-5-(hydroxymethyl)-1,3-benzoxazol-2-yl]carbamate (0.230 g, 0.670 mmol) and 3-(N-Boc-aminomethyl)phenylboronic acid (0.202 g, 0.804 mmol) in a solution of 1,4-dioxane (1.3 mL) and aqueous sodium carbonate (0.142 g, 1.34 mmol, dissolved in 0.67 mL of water). The reaction was degassed with nitrogen for 5 min. The flask was sealed and heated at 100°C for 45 min. After cooling, the reaction was diluted with isopropyl acetate and water. The aqueous layer was extracted with isopropyl acetate (3 x 30 mL). The combined organic layers were dried with sodium sulfate, concentrated, and the crude residue was purified by flash column chromatography (silica, 0% to 100% isopropyl acetate - heptane) to give *tert*-butyl N-[[3-[2-(*tert*-butoxycarbonylamino)-5-(hydroxymethyl)-1,3-benzoxazol-7-yl]phenyl]methyl] carbamate (0.230 g, 0.490 mmol, 73% Yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 9.05 (bs, 1H), 7.73 – 7.63 (m, 2H), 7.49 – 7.42 (m, 1H), 7.45 – 7.35 (m, 2H), 7.30 – 7.23 (m, 1H), 5.22 (bs, 1H), 4.76 (s, 2H), 4.40 – 4.33 (m, 2H), 1.61 (s, 9H), 1.44 (s, 9H). LCMS: *m/z* = + 470 (M+H⁺)

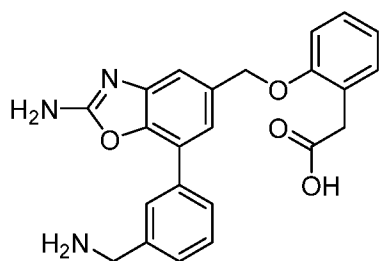
Step 4 – Synthesis of *tert*-butyl (7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-5-(chloromethyl)benzo[*d*] oxazol-2-yl)carbamate (**4-d**):



Thionyl chloride (70 μ L 0.980 mmol) was added to a solution of *tert*-butyl N-[[3-[2-(*tert*-butoxycarbonylamino)-5-(hydroxymethyl)-1,3-benzoxazol-7-yl]phenyl]methyl] carbamate (0.230 g, 0.490 mmol) in N,N-dimethylformamide (4.9 mL) at 0°C over 10 min. After stirring for an additional 1 h, saturated aqueous sodium bicarbonate and isopropyl acetate were added. The aqueous layer was extracted with isopropyl acetate (3 x 30 mL). The combined organic layers were dried with sodium sulfate, concentrated, and the crude residue was submitted to the next step without further purification.

tert-Butyl 2-(2-hydroxyphenyl)acetate (0.306 g 1.47 mmol), cesium carbonate (0.480 g, 1.47 mmol) and the crude residue (0.490 mmol) were dissolved in N,N-dimethylformamide (4.9 mL) and heated at 40 °C for 4 h. After cooling to room temperature, the reaction was diluted with isopropyl acetate and water. The aqueous layer was extracted with isopropyl acetate (3 x 30 mL). The combined organic layers were dried with sodium sulfate, concentrated, and the crude residue was purified by flash column chromatography (silica, 0% to 100% isopropyl acetate - heptane) to give *tert*-butyl 2-[2-[[2-(*tert*-butoxycarbonylamino)-7-[3-[[*tert*-butoxycarbonylamino)methyl]phenyl]-1,3-benzoxazol-5-yl]methoxy]phenyl]acetate (0.135 g, 0.205 mmol, 41.8% Yield). LCMS: $m/z = + 660$ ($M+H^+$)

Step 5 – Synthesis of 2-(2-((2-amino-7-(3-(aminomethyl)phenyl)benzo[*d*]oxazol-5-yl)methoxy)phenyl)acetic acid (**4**)



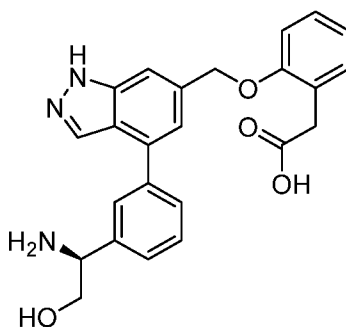
Trifluoroacetic acid (0.5 mL) was added to a solution of tert-butyl 2-[2-[[2-(*tert*-butoxycarbonylamino)-7-[3-[(*tert*-butoxycarbonylamino)methyl]phenyl]-1,3-benzoxazol-5-yl]methoxy]phenyl]acetate (0.125 g, 0.190 mmol) in dichloromethane (3.8 mL) at 0 °C.

After 10 minutes, the reaction was warmed to room temperature and stirred for an additional

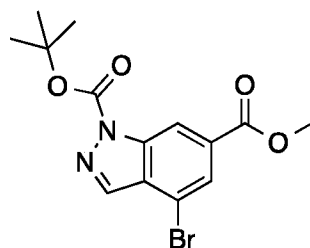
- 5 1h. The solvent was evaporated under reduced pressure and the crude residue was purified by SFC to give 2-[2-[[2-amino-7-[3-(aminomethyl)phenyl]-1,3-benzoxazol-5-yl]methoxy]phenyl] acetic acid (16.9 mg, 41.9 μ mol, 22.1% Yield). ^1H NMR (400 MHz, DMSO- d_6) δ 8.23 (bs, 1H), 7.94 (dt, J = 7.9, 1.4 Hz, 1H), 7.58 (d, J = 1.6 Hz, 1H), 7.52 – 7.41 (m, 3H), 7.35 (dt, J = 7.8, 1.3 Hz, 1H), 7.25 (d, J = 1.5 Hz, 1H), 7.16 – 7.05 (m, 2H), 6.98 – 6.90 (m, 10 1H), 6.81 (td, J = 7.4, 1.1 Hz, 1H), 5.19 (s, 2H), 4.02 (s, 2H), 3.43 (s, 2H). LCMS: m/z = + 404.2 ($\text{M}+\text{H}^+$), 3.09 minutes.

Example 5. (S)-2-(2-((4-(3-(1-amino-2-hydroxyethyl)phenyl)-1H-indazol-6-yl)methoxy)phenyl) acetic acid

15 **Using General Reaction Sequence 1**



Step 1 – Synthesis of 1-(*tert*-butyl) 6-methyl 4-bromo-1*H*-indazole-1,6-dicarboxylate (**5-a**):

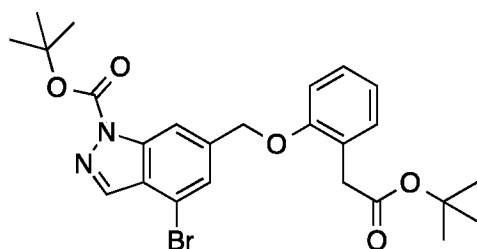


- 20 Methyl 4-bromo-1*H*-indazole-6-carboxylate (1.5 g, 5.9 mmol) and di-*tert*-butyl carbonate (1.6 g, 7.1 mmol) were dissolved in THF (20 mL). DMAP (73 mg, 0.59 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by flash column

chromatography (silica, 0-50% iPrOAc/heptane) to give 1-(*tert*-butyl) 6-methyl 4-bromo-1*H*-indazole-1,6-dicarboxylate (1.57 g, 4.42 mmol, 75% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.86 (t, *J* = 1.0 Hz, 1H), 8.23 (d, *J* = 0.9 Hz, 1H), 8.15 (d, *J* = 1.1 Hz, 1H), 3.98 (s, 3H), 1.75 (s, 9H). LCMS: *m/z* = + 296 (M-CO₂Me)⁺.

5

Step 2 – Synthesis of *tert*-butyl 4-bromo-6-((2-(2-(*tert*-butoxy)-2-oxoethyl)phenoxy)methyl)-1*H*-indazole-1-carboxylate (**5-b**):



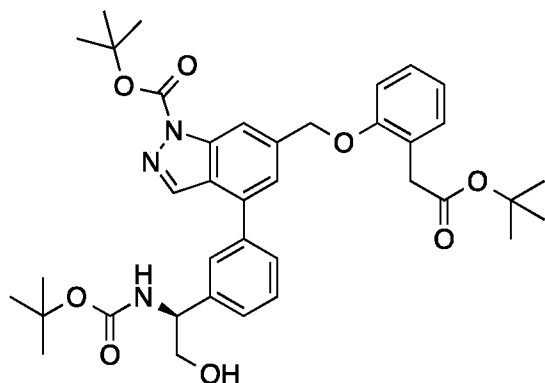
10 *tert*-Butyl 6-methyl 4-bromo-1*H*-indazole-1,6-dicarboxylate (0.400 g, 1.13 mmol) was dissolved in dichloromethane (11 mL) and the reaction mixture was cooled to -78°C. DIBAL (1.0 M in toluene, 3.4 mL, 3.4 mmol) was added dropwise and the reaction was warmed to 0°C. The reaction mixture was quenched with a saturated aqueous solution of Rochelle's salts and was allowed to warm to room temperature and stir overnight. The organic layer was separated, dried with sodium sulfate, and concentrated under reduced pressure to give *tert*-butyl 4-bromo-6-(hydroxymethyl)-1*H*-indazole-1-carboxylate (0.270 g, 0.83 mmol, 73% yield), which was used in the next reaction without further purification. LCMS: *m/z* = +327 (M+H⁺).

20 *tert*-Butyl 4-bromo-6-(hydroxymethyl)-1*H*-indazole-1-carboxylate (0.270 g, 0.83 mmol) and *tert*-butyl 2-(2-hydroxyphenyl)acetate (0.206 g, 0.99 mmol) were dissolved in THF (16.5 mL) under a nitrogen atmosphere. DIAD (0.25 mL, 1.24 mmol) and then PPh₃ (0.442 g, 1.65 mmol) were added. The vial was sealed and heated to 80°C until complete consumption of starting material. After cooling to room temperature, water was added to the reaction mixture. The aqueous layer was extracted with isopropyl acetate. The combined organic layers were dried with sodium sulfate, concentrated, and the crude residue was purified by flash column chromatography (silica, 0-100% iPrOAc/heptane) to give *tert*-butyl 4-bromo-6-((2-(2-(*tert*-butoxy)-2-oxoethyl)phenoxy)methyl)-1*H*-indazole-1-carboxylate (0.150 g, 0.29 mmol, 35% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.23 – 8.19 (m, 1H), 8.17 (d, *J* = 0.8 Hz, 1H), 7.62 (dd, *J* = 1.2, 0.6 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 2H), 6.96 (td, *J* = 7.5, 1.1 Hz, 1H), 6.93 –

25

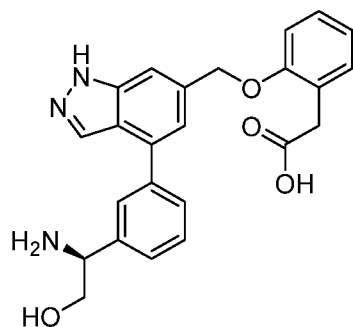
6.87 (m, 1H), 5.20 (s, 2H), 3.62 (s, 2H), 1.71 (s, 9H), 1.39 (s, 9H). LCMS: $m/z = +539$ (M+Na)⁺.

Step 3 – Synthesis of *tert*-butyl (*S*)-6-((2-(2-(*tert*-butoxy)-2-oxoethyl)phenoxy)methyl)-4-(3-(1-((*tert*-butoxycarbonyl)amino)-2-hydroxyethyl)phenyl)-1*H*-indazole-1-carboxylate (**5-c**):



tert-Butyl 4-bromo-6-((2-(2-(*tert*-butoxy)-2-oxoethyl)phenoxy)methyl)-1*H*-indazole-1-carboxylate (0.150 g, 0.29 mmol, 1.0 equiv.) and *tert*-butyl (*S*)-(2-hydroxy-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)carbamate (0.126 g, 0.35 mmol) were dissolved in dioxane (0.5 mL). Sodium carbonate (61 mg, 0.58 mmol, dissolved in water (0.3 mL)) was added and the reaction mixture was degassed with nitrogen. Pd(dppf)Cl₂ (43 mg, 0.058 mmol) was added and the vial was sealed and heated to 100°C for 1 hour. After cooling to room temperature, the reaction mixture was diluted with water and filtered over celite. The filtrate was diluted with water and isopropyl acetate. The aqueous layer was extracted with isopropyl acetate. The combined organic layers were dried with sodium sulfate, concentrated, and the crude residue was purified by flash column chromatography (silica, 0-100% iPrOAc/heptane) to give *tert*-butyl (*S*)-6-((2-(2-(*tert*-butoxy)-2-oxoethyl)phenoxy)methyl)-4-(3-(1-((*tert*-butoxycarbonyl)amino)-2-hydroxyethyl)phenyl)-1*H*-indazole-1-carboxylate (0.104 g, 0.15 mmol, 53% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.31 – 8.21 (m, 2H), 7.71 – 7.54 (m, 3H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.22 (td, *J* = 7.6, 1.8 Hz, 3H), 6.99 – 6.91 (m, 2H), 6.83 – 6.69 (m, 1H), 5.53 (s, 1H), 5.30 (s, 2H), 4.88 (s, 1H), 1.74 (s, 9H), 1.28 (s, 10H), 1.24 (s, 6H). LCMS $m/z = +696$ (M+Na)⁺.

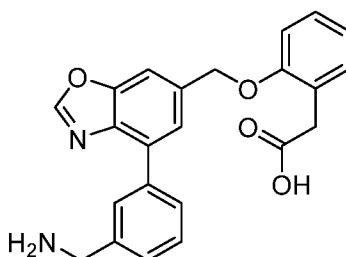
Step 4 – Synthesis of (*S*)-2-(2-((4-(3-(1-amino-2-hydroxyethyl)phenyl)-1*H*-indazol-6-yl)methoxy)phenyl)acetic acid (**5**):



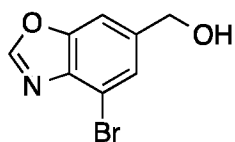
tert-Butyl (*S*)-6-((2-(2-(*tert*-butoxy)-2-oxoethyl)phenoxy)methyl)-4-(3-(1-((*tert*-
5 butoxycarbonyl)amino)-2-hydroxyethyl)phenyl)-1*H*-indazole-1-carboxylate (0.104 g, 0.15
mmol) was dissolved in dichloromethane (3 mL) and the reaction mixture was cooled to
0 °C. TFA (1 mL) was added and the reaction was allowed to warm to room temperature with
stirring. Upon completion, the reaction mixture was concentrated and the crude residue was
purified by prep-HPLC (Gemini-NX C18, 50 x 30 mm, 5µm; mobile phase 0.1% Ammonium
10 Hydroxide in Water – Acetonitrile; B% 2%-60% 10 min; detection at 240 nm) to give (*S*)-2-
(2-((4-(3-(1-amino-2-hydroxyethyl)phenyl)-1*H*-indazol-6-yl)methoxy) phenyl)acetic acid (32
mg, 76 µmol, 50% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.27 (s, 1H), 8.23 (dd, *J* = 2.7,
1.3 Hz, 2H), 7.84 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.64 (d, *J* = 1.1 Hz, 1H), 7.57 (d, *J* = 1.2 Hz, 1H),
7.49 (t, *J* = 7.6 Hz, 1H), 7.41 – 7.33 (m, 1H), 7.10 (t, *J* = 7.4 Hz, 2H), 7.05 – 6.97 (m, 1H),
15 6.81 (td, *J* = 7.3, 1.1 Hz, 1H), 5.28 (s, 2H), 4.20 (dd, *J* = 6.8, 4.3 Hz, 1H), 3.81 – 3.66 (m,
2H), 3.52 – 3.27 (m, 2H). LCMS *m/z* = +418.2 (*M*+*H*⁺), 3.11 minutes.

Example 6. 2-(2-((4-(3-(aminomethyl)phenyl)benzo[d]oxazol-6-yl)methoxy)phenyl)acetic acid

20 **Using General Reaction Sequence 2**



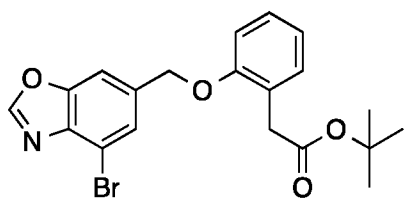
Step 1 – Synthesis of (4-bromobenzo[d]oxazol-6-yl)methanol (**6-b**):



Trimethylorthoformate (2.2 mL, 20 mmol) was added to a suspension of methyl 4-amino-3-bromo-5-hydroxy-benzoate (2.5 g, 10 mmol) in toluene (10 mL). The reaction was heated at 100°C for 1 h. After cooling to room temperature, the solvent was removed under reduced pressure and the crude residue was submitted to the next reaction without further purification.

Diisobutylaluminum hydride (1.0 M in toluene, 25 mL, 25 mmol) was added to a solution of the crude residue in dichloromethane (51 mL) at -78°C over 10 min. After, the reaction was allowed to stir at this temperature for an additional 2 h. Saturated aqueous Rochelle's salts were added at -78°C and the reaction was warmed to room temperature. After 4 h, the reaction was diluted with isopropyl acetate and water. The aqueous layer was extracted with isopropyl acetate (3 x 200 mL). The combined organic layers were dried with sodium sulfate, concentrated, and the crude residue was purified by flash column chromatography (silica, 0% to 100% isopropyl acetate - heptane) to give (4-bromo-1,3-benzoxazol-6-yl)methanol (0.80 g, 3.5 mmol, 35% yield over 2 steps). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.14 (s, 1H), 7.59 – 7.55 (m, 2H), 4.82 (s, 2H). LCMS *m/z* = +227.7 (M+H⁺).

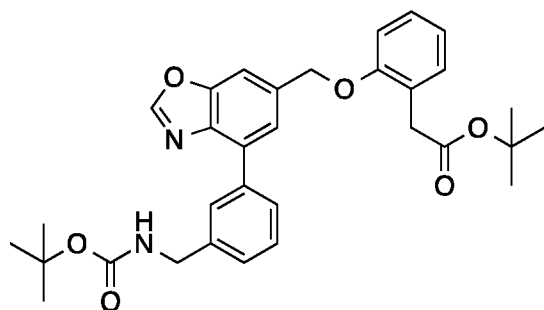
Step 2 – Synthesis of *tert*-butyl 2-(2-((4-bromobenzo[d]oxazol-6-yl)methoxy)phenyl) acetate (**6-b**)



Diisopropyl azodicarboxylate (0.910 mL, 4.60 mmol) was added to a solution of (4-bromo-1,3-benzoxazol-6-yl)methanol (0.700 g, 3.07 mmol), *tert*-butyl 2-(2-hydroxyphenyl)acetate (0.528 g, 3.38 mmol) and triphenylphosphine (1.21 g, 4.60 mmol) in THF (20.5 mL) at room temperature. After 10 min, the reaction was concentrated under reduced pressure and the crude residue was purified by flash column chromatography (silica, 0% to 30% isopropyl acetate - heptane) to give *tert*-butyl 2-[2-[(4-bromo-1,3-benzoxazol-6-yl)methoxy]phenyl] acetate (0.528 g, 1.26 mmol, 41.1% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.15 (s,

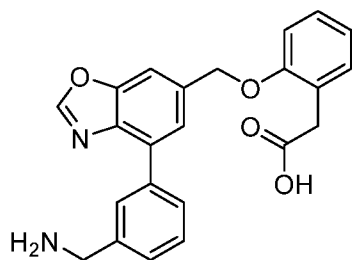
1H), 7.71-7.68 (m, 1H), 7.65-7.62 (m, 1H), 7.26-7.20 (m, 2H), 6.96 (td, $J = 7.4, 1.1$ Hz, 1H), 6.93 – 6.86 (m, 1H), 5.20 (s, 2H), 3.62 (s, 2H), 1.41 (s, 9H). LCMS $m/z = +361.8$ (M-(C₄H₈)+H)⁺.

- 5 Step 3 – Synthesis of *tert*-butyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)benzo[d]oxazol-6-yl)methoxy)phenyl)acetate (**6-c**)



- tert*-Butyl 2-[2-[(4-bromo-1,3-benzoxazol-6-yl)methoxy]phenyl]acetate (0.176 g, 0.421 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (63 mg, 84.2 μ mol),
 10 *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylcarbamate (0.186 g, 0.547 mmol), and sodium carbonate (89.2 mg, 0.842 mmol, dissolved in water (0.420 mL)) were dissolved in 1,4-dioxane (1.4 mL). The solution was degassed with nitrogen for 5 min. The reaction was sealed and heated at 100°C. After 30 min, the reaction cooled to room temperature and the reaction was filtered through a plug of celite using isopropyl acetate. The
 15 filtrate was concentrated and the crude residue was purified by flash column chromatography (silica, 0% to 100% isopropyl acetate - heptane) to give *tert*-butyl 2-[2-[[4-[3-[(*tert*-butoxycarbonylamino)methyl]phenyl]-1,3-benzoxazol-6-yl]methoxy]phenyl] acetate (0.150 g, 0.275 mmol, 65.5% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.14 (s, 1H), 7.92 – 7.82 (m, 2H), 7.73 – 7.70 (m, 1H), 7.60 – 7.58 (m, 1H), 7.48 (t, $J = 7.7$ Hz, 1H), 7.44 – 7.31 (m,
 20 1H), 7.25 – 7.20 (m, 2H), 6.98 – 6.92 (m, 2H), 5.28 (s, 2H), 4.98 (bs, 1H), 4.42 (d, $J = 5.9$ Hz, 2H), 3.64 (s, 2H), 1.47 (s, 9H), 1.37 (s, 9H). LCMS $m/z = +433$ (M-2(C₄H₈)+H)⁺.

Step 4 – Synthesis of 2-(2-((4-(3-(aminomethyl)phenyl)benzo[d]oxazol-6-yl)methoxy)phenyl)acetic acid (6)



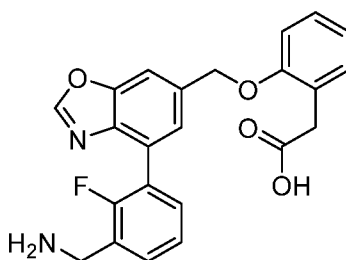
Trifluoroacetic acid (1.4 mL) was added to a solution of *tert*-butyl 2-[2-[[4-[3-[(*tert*-

- 5 butoxycarbonylamino)methyl]phenyl]-1,3-benzoxazol-6-yl]methoxy]phenyl]acetate (0.150 g, 0.275 mmol) in dichloromethane (2.8 mL) at room temperature. After 30 min, the reaction was concentrated under reduced pressure. The crude residue was purified by prep-HPLC (Gemini-NX C18, 50 x 30 mm, 5μm; mobile phase 0.1% Ammonium Hydroxide in Water – Acetonitrile; B% 5%-50% 10 min; detection at 210 nm) to give 2-[2-[[4-[3-
- 10 (aminomethyl)phenyl]-1,3-benzoxazol-6 yl] methoxy]phenyl]acetic acid (94.2 mg, 0.243 mmol, 88% Yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.82 (s, 1H), 8.41 - 8.35 (m, 2H), 8.05 (d, *J* = 1.4 Hz, 1H), 7.83 (d, *J* = 1.3 Hz, 1H), 7.55 – 7.43 (m, 1H), 7.36-7.33 (m, 1H), 7.14 - 7.06 (m, 2H), 6.96 - 6.92 (m, 1H), 6.84 - 6.78 (m, 1H), 5.32 (s, 2H), 4.01 (s, 2H) 3.41 (s, 2H). LCMS *m/z* = +389.2 (M+H⁺), 3.30 minutes.

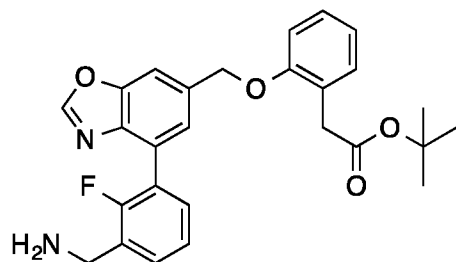
15

Example 7. 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzo[d]oxazol-6-yl)methoxy)phenyl)acetic acid

Using General Reaction Sequence 2

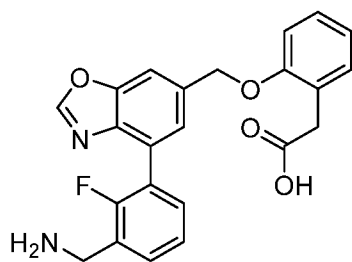


Step 1 – Synthesis of *tert*-butyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzo[d]oxazol-6-yl)methoxy)phenyl)acetate (8-a):



tert-Butyl 2-[2-[(4-bromo-1,3-benzoxazol-6-yl)methoxy]phenyl]acetate (0.176 g, 0.421 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (63 mg, 0.0842 mmol), 3-(aminomethyl)-2-fluorophenylboronic acid, HCl (0.116 g, 0.547 mmol), and sodium carbonate (89.2 mg, 0.842 mmol dissolved in water (0.42 mL)) were dissolved in 1,4-dioxane (1.4 mL). The solution was degassed with nitrogen for 5 minutes. The reaction was sealed and heated at 100°C for 30 min. After cooling to room temperature, the reaction was filtered through a plug of celite using methanol. The filtrate was concentrated and the crude residue was purified by flash column chromatography (silica, 0% to 100% isopropyl acetate - heptane) to give *tert*-butyl 2-[2-[[4-[3-(aminomethyl)-2-fluoro-phenyl]-1,3-benzoxazol-6-yl]methoxy]phenyl]acetate (0.190 g, 0.411 mmol, 98% Yield) ¹H NMR (400 MHz, Chloroform-*d*) δ 8.20 (s, 1H), 7.80 – 7.77 (m, 1H), 7.62 – 7.51 (m, 2H), 7.50 – 7.38 (m, 1H), 7.30 - 7.19 (m, 3H), 7.00 – 6.91 (m, 2H), 5.28 (s, 2H), 4.06 (s, 2H), 3.63 (s, 2H), 1.37 (s, 9H). LCMS *m/z* = +463.1 (M+H⁺).

Step 2 – Synthesis of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzo[d]oxazol-6-yl)methoxy)phenyl)acetic acid (8):

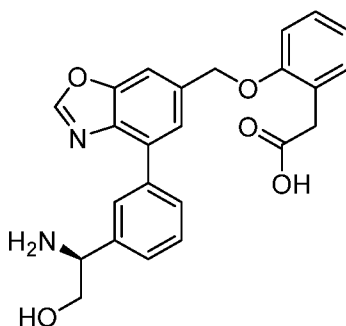


Trifluoroacetic acid (2.05 mL) was added to a solution of *tert*-butyl 2-[2-[[4-[3-(aminomethyl)-2-fluoro-phenyl]-1,3-benzoxazol-6-yl]methoxy]phenyl]acetate (0.190 g, 0.411 mmol) in dichloromethane (4.1 mL) at 0°C. After 10 min, the reaction was warmed to room temperature and stirred for an additional 1h. The solvent was removed under reduced

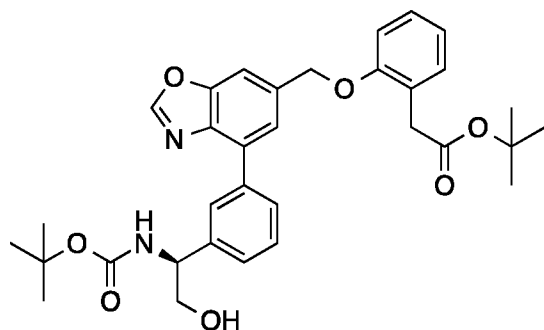
pressure. The crude residue was purified by SFC to give 2-[2-[[4-[3-(aminomethyl)-2-fluoro-phenyl]-1,3-benzoxazol-6-yl]methoxy]phenyl]acetic acid (7.7 mg). ^1H NMR (400 MHz, DMSO- d_6) δ 9.21 (s, 0.6H), 8.79 (d, J = 11.5 Hz, 0.4H), 7.94 (s, 0.6 H), 7.87 (d, J = 10.3 Hz, 0.4H), 7.50 – 7.37 (m, 1H), 7.25 – 7.11 (m, 4H), 7.10 – 6.96 (m, 2H), 6.95 – 6.82 (m, 2H), 5.09 – 5.06 (m, 2H), 3.82 (s, 2H), 3.53 – 3.50 (m, 2H). LCMS m/z = +425.2 ($\text{M}+\text{H}^+$), 2.91 minutes.

Example 8. (*S*)-2-(2-((4-(3-(1-amino-2-hydroxyethyl)phenyl)benzo[*d*]oxazol-6-yl)methoxy)phenyl) acetic acid

10 Using General Reaction Sequence 2



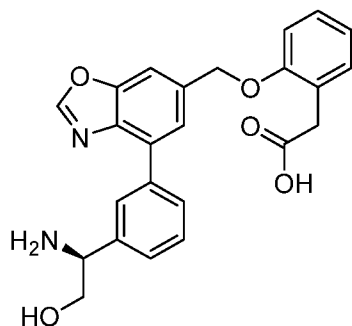
Step 1 – Synthesis of *tert*-butyl (*S*)-2-(2-((4-(3-(1-((*tert*-butoxycarbonyl)amino)-2-hydroxyethyl)phenyl) benzo[*d*]oxazol-6-yl)methoxy)phenyl)acetate (**7-a**):



- 15 *tert*-Butyl 2-[2-[(4-bromo-1,3-benzoxazol-6-yl)methoxy]phenyl]acetate (0.176 g, 0.421 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (62.8 mg, 84.2 μmol), [3-[(1*S*)-1-(*tert*-butoxycarbonylamino)-2-hydroxy-ethyl]phenyl]boronic acid (0.166 g, 0.463 mmol), and sodium carbonate (89.2 mg, 0.842 mmol dissolved in water (0.42 mL)) were dissolved in 1,4-dioxane (1.4 mL). The solution was degassed with nitrogen for 5 minutes.
- 20 The reaction was then sealed and heated at 100°C for 30 min. After cooling to room temperature, the reaction was filtered through a plug of celite using methanol. The filtrate was concentrated and the crude residue was purified by flash column chromatography (silica,

0% to 100% isopropyl acetate - heptane) to give *tert*-butyl 2-[2-[[4-[3-[(1*S*)-1-(*tert*-butoxycarbonylamino)-2-hydroxy-ethyl]phenyl]-1,3-benzoxazol-6-yl]methoxy]phenyl]acetate (0.166 g, 0.288 mmol, 68.7% Yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.14 (s, 1H), 7.97 – 7.91 (m, 1H) 7.91-7.86 (m, 1H), 7.72 - 7.68 (m, 1H), 7.64 - 7.60 (m, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.38 - 7.32 (m, 1H), 7.29 – 7.19 (m, 2H), 7.01 – 6.91 (m, 2H), 5.45 (bs, 1H), 5.29 (s, 2H), 4.89 (bs, 1H), 3.93 (t, *J* = 5.7 Hz, 2H), 3.65 (s, 2H), 2.48 (bs, 1H), 1.44 (s, 9H), 1.36 (s, 9H). LCMS *m/z* = +463.0 (M-2(C₄H₈)+H)⁺.

Step 2 – Synthesis of (*S*)-2-(2-((4-(3-(1-amino-2-hydroxyethyl)phenyl)benzo[*d*]oxazol-6-yl)methoxy)phenyl) acetic acid (**7**)

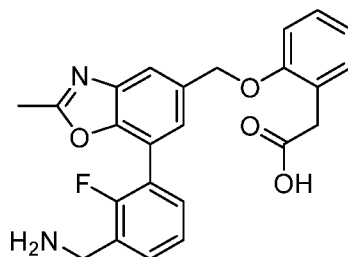


Trifluoroacetic acid (1.44 mL) was added to a solution of *tert*-butyl 2-[2-[[4-[3-[(1*S*)-1-(*tert*-butoxycarbonylamino)-2-hydroxy-ethyl]phenyl]-1,3-benzoxazol-6-yl]methoxy]phenyl]acetate (0.166 g, 0.289 mmol) in dichloromethane (2.89 mL) at room temperature.

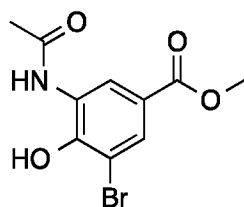
After 30 min, the reaction was concentrated under reduced pressure and the crude residue was purified by prep-HPLC (Gemini-NX C18, 50 x 30 mm, 5μm; mobile phase 0.1% Ammonium Hydroxide in Water – Acetonitrile; B% 2%-40% 10 min, 210 nm) to give (*S*)-2-(2-((4-(3-(1-amino-2-hydroxyethyl)phenyl)benzo[*d*]oxazol-6-yl)methoxy)phenyl) acetic acid (64 mg, 0.154 mmol, 54% Yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.82 (s, 1H), 8.41-8.36 (m, 2H), 8.02-7.99 (m, 1H), 7.90-7.86 (m, 1H), 7.52 – 7.41 (m, 1H), 7.38-7.33 (m, 1H), 7.14-7.04 (m, 2H), 7.01 – 6.93 (m, 1H), 6.85-6.78 (m, 1H), 5.31 (s, 2H), 4.21 (dd, *J* = 6.9, 4.3 Hz, 1H), 3.74 (qd, *J* = 11.6, 5.6 Hz, 2H), 3.48 (d, *J* = 15.3 Hz, 1H), 3.36 (d, *J* = 15.3 Hz, 1H). LCMS *m/z* = +419.2 (M+H⁺), 3.31 minutes.

Example 9. 2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)acetic acid

Using General Reaction Sequence 1

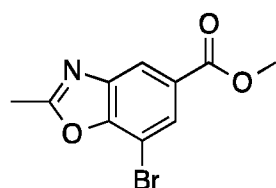


5 Step 1 – Synthesis of methyl 3-acetamido-5-bromo-4-hydroxybenzoate (9-a):



Methyl 3-amino-5-bromo-4-hydroxybenzoate (4.00 g, 16.3 mmol) in pyridine (160 mL) and dichloromethane (40.0 mL) was cooled to 0°C under N₂, then acetyl chloride (1.28 g, 16.3 mmol, 1.16 mL) was added dropwise slowly. The mixture was warmed to 25°C and stirred for 12 h. The reaction mixture was concentrated under vacuum. Water (30.0 mL) was added to the crude residue at 25 °C and the mixture was allowed to stir for 10 min. The mixture was filtered and the filtrate cake was collected and dried under reduced pressure to give methyl 3-acetamido-5-bromo-4-hydroxybenzoate (3.70 g, 12.8 mmol, 55.1% yield, 70% purity) as a black solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1 H), 8.02 (m, 1 H), 7.79 (s, 1 H), 7.39 (br s, 2 H), 3.88 (s, 1 H), 2.26 (s, 3 H). LCMS *m/z* = +287.9 (M+H⁺).

Step 2 – Synthesis of methyl 7-bromo-2-methylbenzo[d]oxazole-5-carboxylate (9-b):

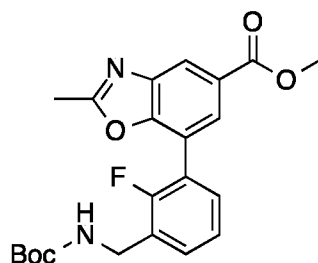


To a mixture of methyl 3-acetamido-5-bromo-4-hydroxybenzoate (3.26 g, 11.3 mmol) in *p*-xylene (30 mL) was added PPTS (0.569 g, 2.26 mmol) in one portion at 25°C under N₂. The mixture was stirred at 145°C for 7 h. The mixture was cooled to 25°C and the reaction was

poured into water (50 mL) and stirred for 10 min. The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers was washed with brine (30 mL), dried with sodium sulfate, concentrated and the crude residue was purified by flash column chromatography (silica, petroleum ether / ethyl acetate = 30/1 to 1/1) to give methyl 7-

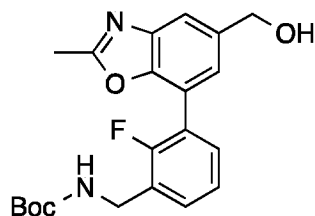
- 5 bromo-2-methylbenzo[*d*]oxazole-5-carboxylate (1.63 g, 6.03 mmol, 53% Yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.28 (s, 1 H), 8.21 (s, 1 H), 3.96 (s, 3 H), 2.72 (s, 3 H). LCMS *m/z* = +270.0 (M+H⁺).

Step 3 – Synthesis of methyl 7-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)-2-methylbenzo[*d*]oxazole-5-carboxylate (**9-c**):



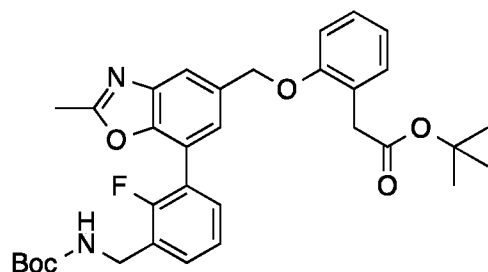
- To a mixture of methyl 7-bromo-2-methylbenzo[*d*]oxazole-5-carboxylate (0.70 g, 2.59 mmol) and *tert*-butyl (2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)carbamate (1.09 g, 3.11 mmol) in 1,4-dioxane (7 mL) was added Na₂CO₃ (0.549 g, 5.18 mmol dissolved in H₂O (2 mL)) and Pd(dppf)Cl₂•CH₂Cl₂ (0.423 g, 0.518 mmol) in one portion at 25°C under N₂. The mixture was stirred at 80°C for 2 h. After cooling to room temperature, the residue was poured into water (20 mL) and stirred for 5 min. The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried with sodium sulfate, concentrated and the crude residue was purified by flash column chromatography (silica, petroleum ether / ethyl acetate = 30/1 to 3/1) to give methyl 7-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)-2-methylbenzo[*d*]oxazole-5-carboxylate (1.00 g, 2.36 mmol, 91.2% yield) as a red oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.35 (s, 1 H), 8.14 (s, 1 H), 7.43-7.51 (m, 2 H), 7.25 (t, *J* = 8.0 Hz, 1 H), 4.46 (d, *J* = 5.6 Hz, 2 H), 3.96 (s, 3 H), 2.66 (s, 3 H), 1.46 (s, 9H). LCMS *m/z* = +415.0 (M+H⁺).

Step 4 – Synthesis of *tert*-butyl (2-fluoro-3-(5-(hydroxymethyl)-2-methylbenzo[*d*]oxazol-7-yl)benzyl)carbamate (**9-d**):



A mixture of methyl 7-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)-2-methylbenzo[*d*]oxazole-5-carboxylate (0.700 g, 1.69 mmol) in THF (3 mL) and EtOH (3 mL) was cooled to 0°C, then CaCl₂ (0.375 g, 3.38 mmol) was added followed by NaBH₄ (0.256 g, 6.76 mmol), the mixture was warmed to 25°C. After 2 h, the reaction mixture was quenched with water (10 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were concentrated and the crude residue was purified by flash column chromatography (silica, petroleum ether/EtOAc = 30/1 to 1/1) to give *tert*-butyl (2-fluoro-3-(5-(hydroxymethyl)-2-methylbenzo[*d*]oxazol-7-yl)benzyl)carbamate (0.280 g, 0.725 mmol, 43% yield) as a brown oil.

Step 5 – Synthesis of *tert*-butyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)-2-methylbenzo[*d*]oxazol-5-yl)methoxy)phenyl)acetate (**9-e**):

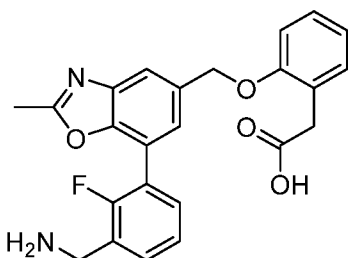


Sixteen reactions were carried out in parallel.

To a solution of *tert*-butyl 2-(2-hydroxyphenyl)acetate (43.1 mg, 0.207 mmol) in THF (1.00 mL) was added DIAD (31.4 mg, 0.155 mmol, 30.2 μ L) followed by PPh₃ (54.3 mg, 0.207 mmol) under N₂ at 0°C. *tert*-Butyl (2-fluoro-3-(5-(hydroxymethyl)-2-methylbenzo[*d*]oxazol-7-yl)benzyl)carbamate (20.0 mg, 51.8 μ mol) was added and the mixture was stirred at 80°C under N₂ for 2 h. The sixteen reactions were combined and poured into water (10 mL). The aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were concentrated and the crude residue was purified by prep-TLC (silica, petroleum ether / ethyl

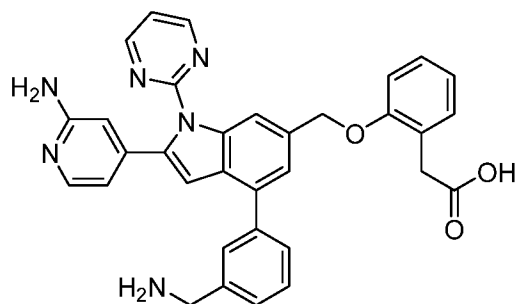
acetate = 3/1) to give *tert*-butyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)-2-methylbenzo[*d*]oxazol-5-yl)methoxy)phenyl)acetate (56.0 mg, 97.1 μ mol, 11.2% yield) as a pale yellow oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.74 (s, 1 H), 7.42-7.50 (m, 3 H), 7.21-7.26 (m, 3 H), 6.94-6.97 (m, 2 H), 6.27-6.32 (m, 1 H), 5.21 (s, 2 H), 4.46 (d, J = 6 Hz, 2 H), 3.60 (s, 2 H), 2.65 (s, 3 H), 1.46 (s, 9 H), 1.33 (s, 9 H). LCMS m/z = +421.2 ($\text{M}-2(\text{C}_4\text{H}_8)-\text{CO}_2+\text{H}$) $^+$.

Step 6 – Synthesis of 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-methylbenzo[*d*] oxazol-5-yl)methoxy)phenyl)acetic acid (9**):**

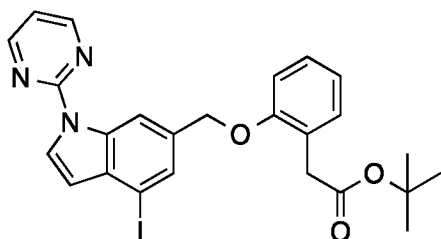


To a solution of *tert*-butyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)-2-methylbenzo[*d*]oxazol-5-yl)methoxy)phenyl)acetate (56.0 mg, 97.1 μ mol) in dichloromethane (1.00 mL) was added TFA (36.0 μ L) at 25°C. The reaction was allowed to stir at 25°C for 12 hours. Na_2CO_3 (0.100 g, 0.972 mmol) was added and the reaction stirred at 25°C for 10 min. The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by prep-HPLC (neutral condition, column: Xtimate C18 150*25mm*5 μ m; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 15%-45%, 10.5 min) to give 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-methylbenzo[*d*]oxazol-5-yl)methoxy)phenyl)acetic acid (5.10 mg, 12.1 μ mol 12.5% yield) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.90 (s, 1 H), 7.81 (m, 1 H), 7.69 (s, 1 H), 7.36-7.38 (m, 1 H), 7.20 - 7.21 (m, 1 H), 7.18 (d, J = 2 Hz, 1 H), 7.14 (d, J = 9.6 Hz, 1 H), 6.99 (d, J = 7.6 Hz, 1 H), 6.87-6.97 (m, 1 H), 5.39 (s, 2 H), 4.22 (s, 2 H), 3.58 (s, 2 H), 2.65 (s, 3 H). LCMS m/z = +421.1 ($\text{M}+\text{H}^+$), 3.29 minutes.

Example 10. 2-(2-((4-(3-(aminomethyl)phenyl)-2-(2-aminopyridin-4-yl)-1-(pyrimidin-2-yl)-1H-indol-6-yl)methoxy)phenyl)acetic acid



- 5 Step 1 – Synthesis of *tert*-butyl 2-(2-((4-iodo-1-(pyrimidin-2-yl)-1H-indol-6-yl)methoxy)phenyl)acetate (**10-a**):



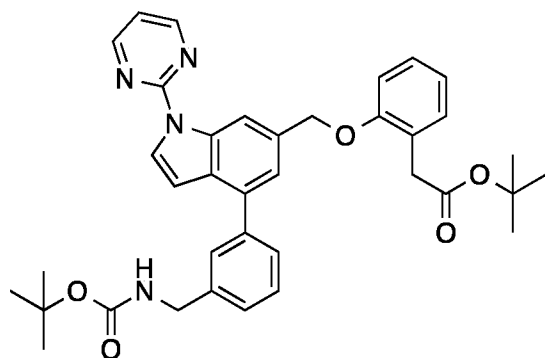
- Sodium hydride (60 mass% in mineral oil, 0.160 g, 4.0 mmol) was added to a solution of methyl 4-iodo-1H-indole-6-carboxylate (1.0 g, 3.3 mmol) in N,N-dimethylformamide (11 mL) at rt. After 10 min, 2-chloropyrimidine (0.480 g, 4.0 mmol) was added and the reaction was heated at 140°C for 4 h. After cooling to rt the reaction was diluted with water and dichloromethane. The aqueous layer was extracted with dichloromethane (6 x 50 mL). The combined organic layers were dried with sodium sulfate, concentrated and the crude residue was submitted to the next step without further purification.
- 15 Diisobutylaluminum hydride (1.2 M in toluene, 8.3 mL, 10.0 mmol) was added to a solution of the crude residue in dichloromethane (17 mL) at -78°C. The reaction was warmed from -78°C to 0°C over 30 min. A saturated aqueous solution of Rochelle's salts were added and the reaction was allowed to stir at rt for 12 h. The reaction was diluted with isopropyl acetate and water. The aqueous layer was extracted with isopropyl acetate (2 x 100 mL). The combined organic layers were dried with sodium sulfate, concentrated and the crude residue was submitted to the next step without further purification.
- 20

Thionyl chloride (0.49 mL, 6.6 mmol) was added to a solution of the crude residue in N,N-dimethylformamide (33 mL) at 0°C over 10 min. The reaction was allowed to stir at this

temperature for 1 h. Saturated aqueous sodium bicarbonate and isopropyl acetate were added. The aqueous layer was extracted with isopropyl acetate (3 x 100 mL). The combined organic layers were dried with sodium sulfate, concentrated and the crude residue was submitted to the next step without further purification.

- 5 *tert*-Butyl 2-(2-(hydroxyphenyl)acetate (0.80 g, 3.70 mmol), cesium carbonate (3.20 g, 10.0 mmol) and the crude residue were dissolved in N,N-dimethylformamide (33 mL) and heated at 40°C for 4 h. After cooling to rt, the reaction was diluted with isopropyl acetate and water. The aqueous layer was extracted with isopropyl acetate (3 x 100 mL). The combined organic layers were dried with sodium sulfate, concentrated and the crude residue was purified by
- 10 flash column chromatography (silica, 0% to 100% isopropyl acetate - heptane) to give *tert*-butyl 2-[2-[(4-iodo-1-pyrimidin-2-yl-indol-6-yl)methoxy]phenyl]acetate (0.50 g, 0.92 mmol, 28% Yield over 4 steps). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.91 (s, 1H), 8.73 (d, *J* = 4.8 Hz, 2H), 8.40 – 8.32 (m, 1H), 7.74 (d, *J* = 1.3 Hz, 1H), 7.25 – 7.17 (m, 2H), 7.10 (t, *J* = 4.8 Hz, 1H), 7.02 – 6.89 (m, 2H), 6.65 (dd, *J* = 3.6, 0.8 Hz, 1H), 5.19 (s, 2H), 3.64 (s, 2H), 1.36
- 15 (s, 9H). LCMS *m/z* = + 564.0 (M+Na⁺).

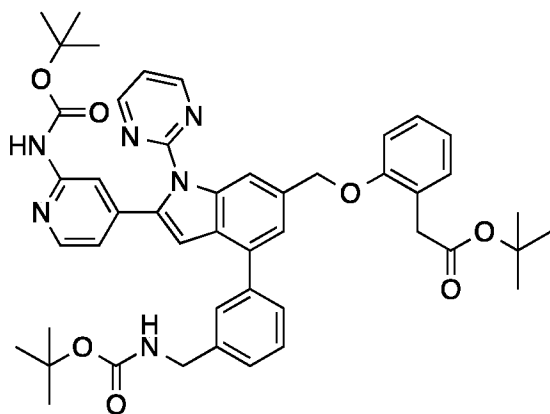
Step 2 – Synthesis of *tert*-butyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1-(pyrimidin-2-yl)-1*H*-indol-6-yl)methoxy)phenyl)acetate (**10-b**):



- 20 [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.140 g, 0.18 mmol) was added to a solution of *tert*-butyl 2-[2-[(4-iodo-1-pyrimidin-2-yl-indol-6-yl)methoxy]phenyl]acetate (0.50 g, 0.92 mmol), and 3-(N-Boc-aminomethyl)phenylboronic acid (0.290 g, 1.10 mmol) in a solution of 1,4-dioxane (3.1 mL) and a solution of sodium carbonate (0.20 g, 1.80 mmol in water (0.92 mL)). The reaction was degassed with nitrogen
- 25 for 5 min. The flask was sealed and heated at 100°C for 45 min. After cooling, the reaction was diluted with isopropyl acetate and water. The aqueous layer was extracted with isopropyl

acetate (3 x 30 mL). The combined organic layers were dried with sodium sulfate, concentrated, and the crude residue was purified by flash column chromatography (silica, 0% to 100% isopropyl acetate - heptane) to give *tert*-butyl 2-[2-[[4-[3-[(*tert*-butoxycarbonylamino)methyl]phenyl]-1-pyrimidin-2-yl-indol-6-yl]methoxy]phenyl]acetate (0.500 g, 0.806 mmol, 87% Yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.98 – 8.92 (m, 1H), 8.74 (d, *J* = 4.8 Hz, 2H), 8.32 (d, *J* = 3.7 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.50 – 7.42 (m, 1H), 7.40 (d, *J* = 1.5 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.27 – 7.17 (m, 2H), 7.09 (t, *J* = 4.8 Hz, 1H), 7.06 – 6.98 (m, 1H), 6.93 (td, *J* = 7.4, 1.1 Hz, 1H), 6.84 (dd, *J* = 3.7, 0.8 Hz, 1H), 5.29 (s, 2H), 4.97 (s, 1H), 4.42 (d, *J* = 5.9 Hz, 2H), 3.65 (s, 2H), 1.47 (s, 9H), 1.27 (s, 9H). LCMS *m/z* = + 643.2 (M+Na⁺).

Step 3 – Synthesis of *tert*-butyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-(2-((*tert*-butoxycarbonyl)amino)pyridin-4-yl)-1-(pyrimidin-2-yl)-1*H*-indol-6-yl)methoxy)phenyl)acetate (**10-c**):

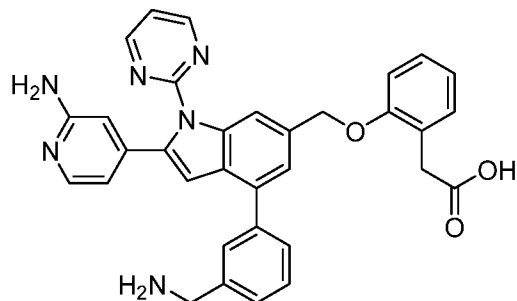


Dichloro(pentamethylcyclopentadienyl)rhodium(III) dimer (8.2 mg, 0.01289 mmol), silver trifluoroacetate (0.569 g, 2.58 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-ylcarbamate (0.434 g, 1.29 mmol), and *tert*-butyl 2-[2-[[4-[3-[(*tert*-butoxycarbonylamino)methyl]phenyl]-1-pyrimidin-2-yl-indol-6-yl]methoxy]phenyl]acetate (0.400 g, 0.644 mmol) were dissolved in methanol (3.2 mL) and the reaction was heated at 60°C for 12 h. After cooling to rt, the reaction was filtered through celite using isopropyl acetate. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography (silica, 0% to 100% isopropyl acetate - heptane) to give *tert*-butyl 2-[2-[[4-[3-[(*tert*-butoxycarbonylamino)methyl]phenyl]-2-[2-(*tert*-butoxycarbonylamino)-4-pyridyl]-1-pyrimidin-2-yl-indol-6-yl]methoxy]phenyl]acetate (0.270 g, 0.332 mmol, 52% Yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.74 (d, *J* = 4.8 Hz,

2H), 8.32 (s, 1H), 8.21 (s, 1H), 7.98 – 7.91 (m, 2H), 7.61 – 7.51 (m, 2H), 7.46 (t, $J = 7.8$ Hz, 1H), 7.41 – 7.31 (m, 2H), 7.26 – 7.17 (m, 3H), 7.12 (s, 1H), 7.01 – 6.89 (m, 2H), 6.83 – 6.77 (m, 1H), 5.25 (s, 2H), 5.05 (dd, $J = 12.0, 7.5$ Hz, 1H), 4.41 (d, $J = 5.8$ Hz, 2H), 3.61 (s, 2H), 1.46 (s, 9H), 1.44 (s, 9H), 1.27 (s, 9H). LCMS $m/z = + 813.3$ ($M+Na^+$).

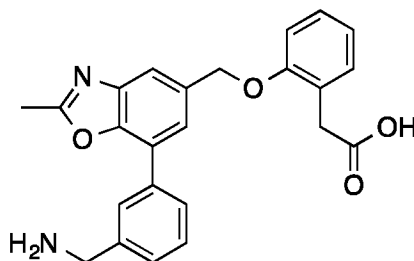
5

Step 4 – Synthesis of 2-(2-((4-(3-(aminomethyl)phenyl)-2-(2-aminopyridin-4-yl)-1-(pyrimidin-2-yl)-1H-indol-6-yl)methoxy)phenyl)acetic acid (**10**):

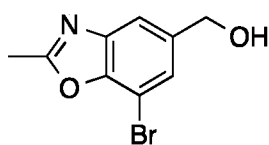


Trifluoroacetic acid (0.59 mL) was added to a solution of *tert*-butyl 2-[2-[[4-[3-[(*tert*-butoxycarbonylamino)methyl]phenyl]-2-[2-(*tert*-butoxycarbonylamino)-4-pyridyl]-1-pyrimidin-2-yl-indol-6-yl]methoxy]phenyl]acetate (0.240 g, 0.295 mmol) in dichloromethane (2.59 mL) at 0°C. After 10 min, the reaction was warmed to rt and stirred for an additional 2 h. The solvent was evaporated under reduced pressure and the crude residue was purified by prep-HPLC (Gemini-NX C18, 50 x 30 mm, 5 μ m; mobile phase 0.1% Ammonium Hydroxide in Water – Acetonitrile; B% 5%-50% 10 min; detection at 230 nm) to give 2-(2-((4-(3-(aminomethyl)phenyl)-2-(2-aminopyridin-4-yl)-1-(pyrimidin-2-yl)-1H-indol-6-yl)methoxy)phenyl)acetic acid (56 mg). 1H NMR (400 MHz, DMSO- d_6) δ 8.99 – 8.89 (m, 2H), 8.16 (s, 1H), 7.98 (s, 1H), 7.88 – 7.81 (m, 1H), 7.81 - 7.75 (m, 1H), 7.70 (d, $J = 1.4$ Hz, 1H), 7.69 – 7.37 (m, 2H), 7.38 - 7.29 (m, 1H), 7.14 – 6.98 (m, 3H), 6.96 - 6.91 (m, 1H), 6.83 - 6.76 (m, 1H), 6.36 - 6.32 (m, 1H), 6.32 – 6.22 (m, 1H), 5.87 (s, 2H), 5.27 (s, 2H), 4.01 (s, 2H), 3.40 (s, 2H). LCMS $m/z = +557.3$ ($M+H^+$), 3.04 minutes.

Example 11. 2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)acetic acid



5 Step 1 – Synthesis of (7-bromo-2-methylbenzo[d]oxazol-5-yl)methanol (11-a):

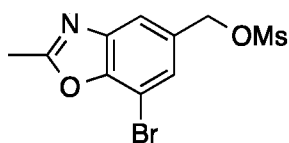


Two reactions were carried out in parallel.

A solution of methyl 7-bromo-2-methylbenzo[d]oxazole-5-carboxylate (1.00 g, 3.52 mmol) in THF (7.00 mL) was cooled to 0°C, then LAH (0.200 g, 5.28 mmol) was added at 0°C.

10 After 1 h, the reaction mixture was quenched with water (15.0 mL) at 0°C, then NaOH (15.0%, 15.0 mL) was added. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were concentrated under reduced pressure. The crude residues of the two reactions were combined and purified by prep-TLC (Petroleum ether / Ethyl acetate = 1/1) to give (7-bromo-2-methylbenzo[d]oxazol-5-yl)methanol (0.350 g, 1.45 mmol, 44% yield) as a yellow solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.56 (s, 1 H), 7.49 (s, 1 H), 4.77 (d, *J* = 5.6 Hz, 2 H), 2.67 (s, 3 H), 1.90 (t, *J* = 6 Hz, 1 H).

Step 2 – Synthesis of (7-bromo-2-methylbenzo[d]oxazol-5-yl)methyl methanesulfonate (11-b):



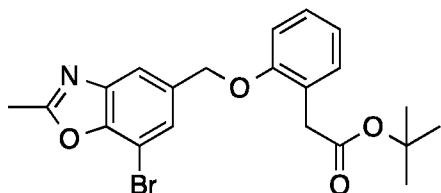
20

A mixture of (7-bromo-2-methylbenzo[d]oxazol-5-yl)methanol (0.350 g, 1.45 mmol) in DCM (2.00 mL) was added TEA (0.80 mL, 5.78 mmol,) followed by MsCl (0.20 mL, 2.62 mmol), the mixture was stirred at 25°C for 2 h. The reaction mixture was washed with water (3.00 mL) and extrated with DCM (3 x 1.00 mL). The combined organic layers were concentrated

under reduced pressure to give (7-bromo-2-methylbenzo[*d*]oxazol-5-yl)methyl methanesulfonate (0.320 g, 69% yield) as a pale pink solid which was used to next step directly without further purification. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.59 (s, 1 H), 7.50 (s, 1 H), 4.65 (s, 2 H), 3.68 (s, 1 H), 2.69 (s, 3 H).

5

Step 3 – Synthesis of *tert*-butyl 2-(2-((7-bromo-2-methylbenzo[*d*]oxazol-5-yl)methoxy)phenyl)acetate (11-c):

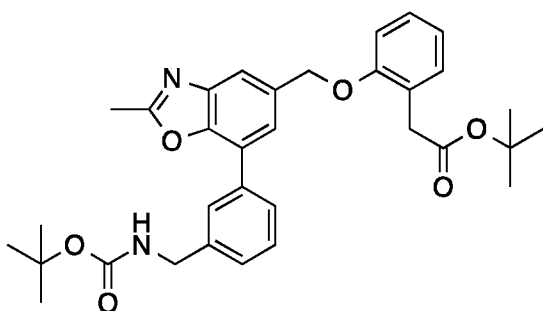


To a solution of *tert*-butyl 2-(2-hydroxyphenyl)acetate (0.156 g, 0.750 mmol) in DMF (2.00 mL) was added NaH (60% in mineral oil, 37.5 mg, 0.937 mmol,) at 0°C, then *tert*-butyl 2-(2-((7-bromo-2-methylbenzo[*d*]oxazol-5-yl)methoxy)phenyl)acetate (0.200 g, 0.625 mmol) was added and the mixture was stirred at 25°C for 1 h. The reaction mixture was poured into ice water (5.00 mL) and extracted with EtOAc (2 x 2.00 mL). The combined organic layers were dried over Na₂SO₄, concentrated and the crude residue was purified by prep-TLC (Petroleum ether / Ethyl acetate = 5/1, R_f = 0.6) to give *tert*-butyl 2-(2-((7-bromo-2-methylbenzo[*d*]oxazol-5-yl)methoxy)phenyl)acetate (90.0 mg, 33% yield) as colorless oil. LCMS *m/z* = +376.0 (M+H⁺).

15

20

Step 4 – Synthesis of *tert*-butyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-methylbenzo[*d*]oxazol-5-yl)methoxy)phenyl)acetate (11-d):

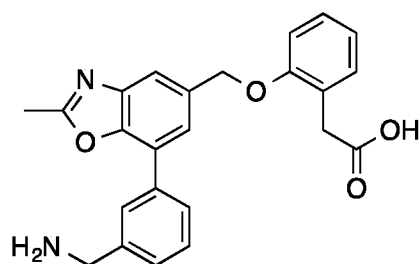


To a solution of *tert*-butyl 2-(2-((7-bromo-2-methylbenzo[*d*]oxazol-5-yl)methoxy)phenyl)acetate (90.0 mg, 0.208 mmol) and *tert*-butyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)carbamate (83.3 mg, 0.250 mmol) in dioxane (1.00 mL) was

added Na₂CO₃ (44.1 mg, 0.416 mmol) in H₂O (0.100 mL) followed by Pd(dppf)Cl₂•CH₂Cl₂ (34.0 mg, 41.6 μmol) under N₂. The mixture was heated at 80°C for 0.5 h. The reaction mixture was concentrated under reduced pressure, and the crude residue was purified by prep-TLC (Petroleum ether / Ethyl acetate = 5/1) to give *tert*-butyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-methylbenzo[*d*]oxazol-5-yl)methoxy)phenyl)acetate (33% yield) as yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.75-7.77 (m, 2 H), 7.68 (s, 1 H), 7.58 (s, 2 H), 7.47-4.58 (m, 1 H), 7.31-7.32 (m, 1 H), 7.20-7.22 (m, 2 H), 6.94-6.97 (m, 2 H), 5.22 (s, 1 H), 4.42 (d, *J* = 5.6 Hz, 2 H), 3.62 (s, 2 H), 2.68 (s, 3 H), 1.46 (s, 9 H), 1.34 (s, 9 H). LCMS *m/z* = +403.1 (M-2(C₄H₈)-CO₂+H⁺).

10

Step 5 – Synthesis of 2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzo[*d*]oxazol-5-yl)methoxy)phenyl)acetic acid (11):

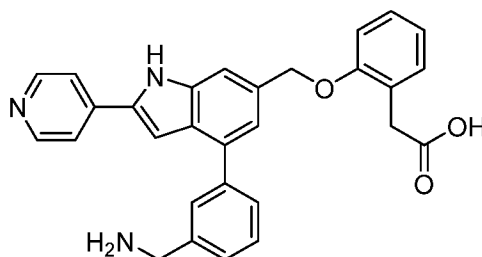


A solution of of *tert*-butyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-methylbenzo[*d*]oxazol-5-yl)methoxy)phenyl)acetate (54.0 mg, 96.7 μmol) in DCM (1.00 mL) was added TFA (55.1 mg, 0.483 mmol) and stirred at 25°C for 12 h. Na₂CO₃ (0.100 g, 0.972 mmol) was added and the reaction mixture was stirred at 25°C for 10 min. The mixture was filtered and the filtrate was concentrated in vacuum. The crude residue was purified by prep-HPLC (neutral condition, column: Xtimate C18 150*25mm*5μm; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 12%-42%, 10.5min) to give 2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzo[*d*]oxazol-5-yl)methoxy)phenyl)acetic acid (5.6 mg, 14.3% yield) as a white solid.

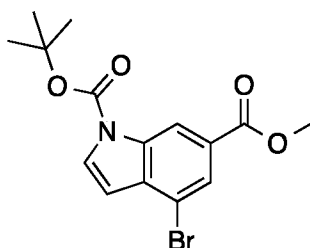
¹H NMR: (MeOD 400 MHz) δ 8.29 (s, 1 H), 8.12-8.14 (m, 1 H), 8.06 (s, 1 H), 7.62 (s, 1 H), 7.52 (t, *J* = 4 Hz, 1 H), 7.45 (d, *J* = 3.6 Hz, 1 H), 7.17-7.20 (m, 2 H), 6.97-6.99 (m, 1 H), 6.88-6.97 (m, 1 H), 5.29 (s, 2 H), 4.21 (s, 2 H), 3.61 (s, 2 H), 2.70 (s, 3 H). LCMS *m/z* = +403.1 (M+H⁺)

25

Example 12. 2-((2-((4-(3-(aminomethyl)phenyl)-2-(pyridin-4-yl)-1H-indol-6-yl)methoxy)phenyl)acetic acid

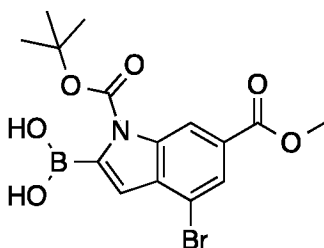


5 Step 1 – Synthesis of 1-(tert-butyl) 6-methyl 4-bromo-1H-indole-1,6-dicarboxylate (12-a):



To a mixture of methyl 4-bromo-1H-indole-6-carboxylate (10.0 g, 39.4 mmol) in THF (100 mL) was added DMAP (0.962 g, 7.87 mmol) and (Boc)₂O (9.45 g, 43.3 mmol, 9.95 mL) in one portion at 0°C under N₂. The mixture was stirred at 25°C for 0.5 hr. The reaction mixture was concentrated under vacuum. The crude residue was purified by flash column chromatography (silica, Petroleum ether / Ethyl acetate = 30/1 to 5/1) to give 1-(tert-butyl) 6-methyl 4-bromo-1H-indole-1,6-dicarboxylate (13.1 g, 93% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.83 (s, 1H), 8.11 (d, *J* = 1.6 Hz, 1H), 7.79 (d, *J* = 4.0 Hz, 1H), 6.69 (d, *J* = 3.2 Hz, 1H), 3.95 (s, 3H), 1.71 (s, 9H).

15 Step 2 – Synthesis of (4-bromo-1-(tert-butoxycarbonyl)-6-(methoxycarbonyl)-1H-indol-2-yl)boronic acid (12-b):

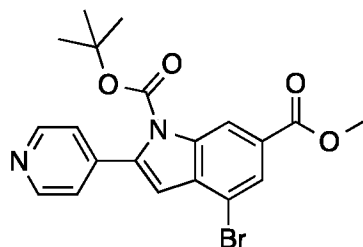


To a mixture of 1-(tert-butyl) 6-methyl 4-bromo-1H-indole-1,6-dicarboxylate (3.00 g, 8.47 mmol) in THF (30.0 mL) was added triisopropyl borate (2.42 g, 12.9 mmol) and LDA (2 M

in THF, 5.51 mL) in one portion at 0°C under N₂. The mixture was stirred at 0°C for 2 hours. The reaction mixture was quenched with 2N HCl (20.0 mL) to adjust the pH to 7. Water (20.0 mL) was added and the mixture was extracted with ethyl acetate (3 x 20.0 mL). The combined organic layers were concentrated and the crude residue was washed with CH₃CN (10.0 mL). The precipitate was filtered, collected and dried under vacuum to give (4-bromo-1-(*tert*-butoxycarbonyl)-6-(methoxycarbonyl)-1*H*-indol-2-yl)boronic acid (1.57 g, 44.7% yield) as a yellow solid.

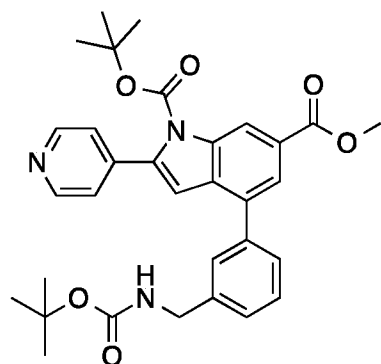
¹H NMR (400 MHz, Chloroform-*d*) δ 8.77 (s, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 12.8 Hz, 1H), 6.93 (s, 2H), 3.96 (s, 3H), 1.79 (s, 9H).

Step 3 – Synthesis of 1-(*tert*-butyl) 6-methyl 4-bromo-2-(pyridin-4-yl)-1*H*-indole-1,6-dicarboxylate (**12-c**):



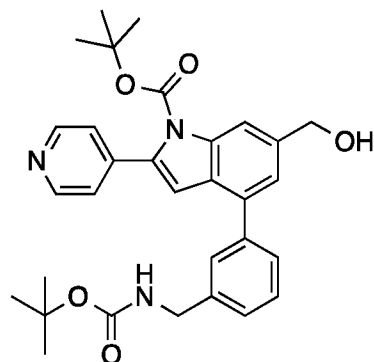
To a mixture of (4-bromo-1-(*tert*-butoxycarbonyl)-6-(methoxycarbonyl)-1*H*-indol-2-yl)boronic acid (1.50 g, 3.77 mmol) and 4-bromopyridine (1.19 g, 7.54 mmol) in 1,4-dioxane (15.0 mL) was added Na₂CO₃ (1.20 g, 11.3 mmol) in H₂O (3.00 mL) and Pd(dppf)Cl₂.CH₂Cl₂ (0.308 g, 0.377 mmol) in one portion at 25°C under N₂. The mixture was heated at 80°C for 2 hours. The residue was poured into water (20.0 mL) and stirred for 5 min. The aqueous layer was extracted with ethyl acetate (3 x 20.0 mL). The combined organic layers were washed with brine (20.0 mL), dried with anhydrous Na₂SO₄, filtered, concentrated, and the crude residue was purified by flash column chromatography (silica, Petroleum ether / Ethyl acetate = 30/1 to 3/1) to give 1-(*tert*-butyl) 6-methyl 4-bromo-2-(pyridin-4-yl)-1*H*-indole-1,6-dicarboxylate (0.600 g, 35% yield) as a yellow solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.89 (d, *J* = 0.8 Hz, 1H), 8.71 (d, *J* = 6.0 Hz, 2H), 8.16 (d, *J* = 6.0 Hz, 1H), 7.38-7.39 (m, 2H), 6.78 (d, *J* = 4.8 Hz, 1H), 3.98 (s, 3H), 1.40 (s, 9H).

Step 4 – Synthesis of 1-(*tert*-butyl) 6-methyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-(pyridin-4-yl)-1*H*-indole-1,6-dicarboxylate (**12-d**):



To a mixture of 1-(*tert*-butyl) 6-methyl 4-bromo-2-(pyridin-4-yl)-1*H*-indole-1,6-dicarboxylate (0.450 g, 1.04 mmol) and *tert*-butyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)carbamate (0.695 g, 2.09 mmol) in 1,4-dioxane (10.0 mL) was added Na₂CO₃ (0.332 g, 3.13 mmol) in H₂O (2.00 mL) and Pd(dppf)Cl₂.CH₂Cl₂ (85.2 mg, 0.104 mmol) in one portion at 25°C under N₂. The mixture was heated at 80°C for 2 hours. The residue was poured into water (20.0 mL) and stirred for 5 min. The aqueous layer was extracted with ethyl acetate (3 x 20.0 mL). The combined organic layers were washed with brine (20.0 mL), dried with anhydrous Na₂SO₄, filtered, concentrated and the crude residue was purified by prep-TLC (Petroleum ether / Ethyl acetate = 3/1) to give 1-(*tert*-butyl) 6-methyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-(pyridin-4-yl)-1*H*-indole-1,6-dicarboxylate (0.450 g, 75% yield) as colourless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.95 (s, 1H), 8.66-8.67 (m, 2H), 8.04 (d, *J* = 1.2 Hz, 1H), 7.53 (d, *J* = 12.4 Hz, 2H), 7.45-7.48 (m, 1H), 7.36-7.38 (m, 2H), 7.34 (d, *J* = 7.6 Hz, 1H), 6.84 (s, 1H), 4.93 (s, 1H), 4.41 (d, *J* = 5.2 Hz, 2H), 3.99 (s, 3H), 1.43 (s, 9H), 1.42 (s, 9H)

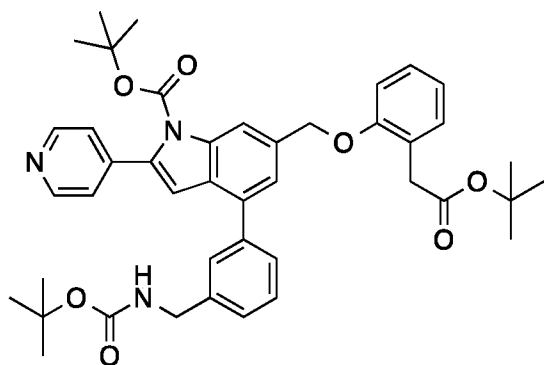
Step 5 – Synthesis of *tert*-butyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-6-(hydroxymethyl)-2-(pyridin-4-yl)-1*H*-indole-1-carboxylate (**12-e**):



To a mixture of 1-(*tert*-butyl) 6-methyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-(pyridin-4-yl)-1*H*-indole-1,6-dicarboxylate (0.450 g, 0.807 mmol) in THF (10.0 mL) was

added LiAlH₄ (0.123 g, 3.23 mmol) in one portion at 0°C under N₂. The mixture was stirred at 25°C for 1 hour. The mixture was cooled to 0°C, 0.30 mL H₂O was added, 0.30 mL 15% NaOH was added, then 0.60 mL H₂O was added, the solution was stirred at 25°C for 0.5 hr. The precipitate was filtered through a pad of celite. The filtrate was collected and concentrated under vacuum. The crude residue was purified by prep-TLC (Petroleum ether / Ethyl acetate = 1/1) to give *tert*-butyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-6-(hydroxymethyl)-2-(pyridin-4-yl)-1*H*-indole-1-carboxylate (0.160 g, 46% yield) as a yellow solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.75 (s, 1H), 8.64 (d, *J* = 6.4 Hz, 2H), 7.62 (d, *J* = 9.2 Hz, 2H), 7.53-7.55 (m, 2H), 7.46-7.50 (m, 2H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.21 (s, 1H), 7.17 (s, 1H), 4.96 (s, 1H), 4.87 (s, 2H), 4.44 (d, *J* = 5.6 Hz, 2H), 1.47 (s, 9H)

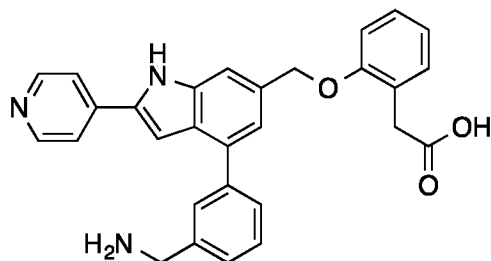
Step 6 – Synthesis of *tert*-butyl 6-((2-(2-(*tert*-butoxy)-2-oxoethyl)phenoxy)methyl)-4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-(pyridin-4-yl)-1*H*-indole-1-carboxylate (**12-f**):



To a mixture of *tert*-butyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-6-(hydroxymethyl)-2-(pyridin-4-yl)-1*H*-indole-1-carboxylate (0.110 g, 0.256 mmol) and *tert*-butyl 2-(2-hydroxyphenyl)acetate (0.107 g, 0.512 mmol) in THF (5.00 mL) was added DIAD (77.7 mg, 0.384 mmol) and PPh₃ (0.134 g, 0.512 mmol) in one portion at 25°C under N₂. The mixture was heated at 40°C for 2 hours. The mixture was concentrated under vacuum. The crude residue was purified by prep-TLC (Petroleum ether / Ethyl acetate = 1/1). The material that was collected from the prep-TLC was then purified by prep-HPLC (column: Nano-micro Kromasil C18 100 * 30mm 5um; mobile phase : [water(0.1%TFA)-ACN]; B%: 45%-70%, 10min) to give *tert*-butyl 6-((2-(2-(*tert*-butoxy)-2-oxoethyl)phenoxy)methyl)-4-(3-(((*tert*-butoxycarbonyl) amino)methyl)phenyl)-2-(pyridin-4-yl)-1*H*-indole-1-carboxylate (10.0 mg, 6.30% yield) as a yellow solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 6.8 Hz, 2H), 8.19 (d, *J* = 6.8 Hz, 2H), 7.68 (s, 1H), 7.58-7.62 (m, 3H), 7.49 (t, *J* = 7.6 Hz,

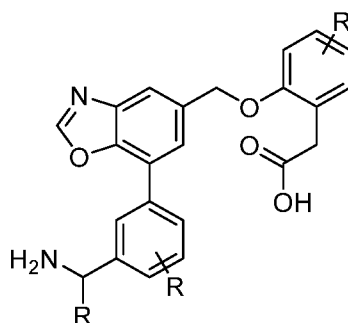
1H), 7.32-7.35 (m, 2H), 7.24-7.27 (m, 1H), 7.19 (d, $J = 8$ Hz, 1H), 7.09 (d, $J = 8.8$ Hz, 1H), 6.92 (t, $J = 6.8$ Hz, 1H), 5.28 (s, 2H), 4.36 (s, 2H), 3.61 (s, 2H), 1.43 (s, 9H), 1.25 (s, 9H)

Step 7 – Synthesis of 2-((4-(3-(aminomethyl)phenyl)-2-(pyridin-4-yl)-1*H*-indol-6-yl)methoxy)phenyl)acetic acid (**12**):

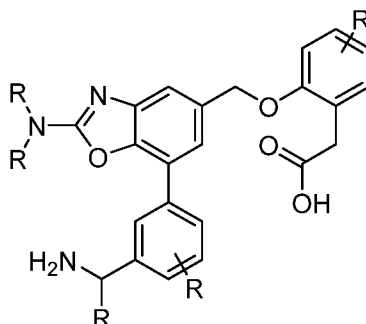


To a mixture of *tert*-butyl 6-((2-(2-(*tert*-butoxy)-2-oxoethyl)phenoxy)methyl)-4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-(pyridin-4-yl)-1*H*-indole-1-carboxylate (13.0 mg, 21.0 μ mol) in EtOAc (1.00 mL) was added HCl/EtOAc (4 M, 0.867 mL) in one portion at 25°C under N₂. The mixture was stirred at 25°C for 4 hrs. The mixture was concentrated under vacuum and the crude residue was purified by prep-HPLC (column : Waters Xbridge 150 * 25 5 μ ; mobile phase : [water (0.05% HCl) - ACN]; B% : 15% - 30%, 12 min) to give 2-((4-(3-(aminomethyl)phenyl)-2-(pyridin-4-yl)-1*H*-indol-6-yl)methoxy)phenyl)acetic acid (2.50 mg, 24% yield, HCl salt) as a yellow solid. ¹H NMR: (MeOD 400MHz) δ ppm 8.69 (d, $J = 5.6$ Hz, 2H), 8.37 (d, $J = 6$ Hz, 2H), 7.84-7.87 (m, 2H), 7.76 (s, 1H), 7.62-7.66 (m, 2H), 7.53 (d, $J = 7.6$ Hz, 1H), 7.38 (s, 1H), 7.23-7.27 (m, 2H), 7.07 (d, $J = 8.4$ Hz, 1H), 6.92-6.95 (m, 1H), 5.33 (s, 2H), 4.27 (s, 2H), 3.73 (s, 2H). LCMS $m/z = +464.2$ (M+H⁺), 2.92 minutes.

The following provides non-limiting examples of additional contemplated compounds according to the present invention.

Prophetic Scaffold 1

Prophetic Scaffold 1 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. Compounds of Prophetic Scaffold 1 can be accessed via General Reaction Sequence 1 or General Reaction Sequence 2 by following the procedures described for the preparation of Example 1 and/or Example 6.

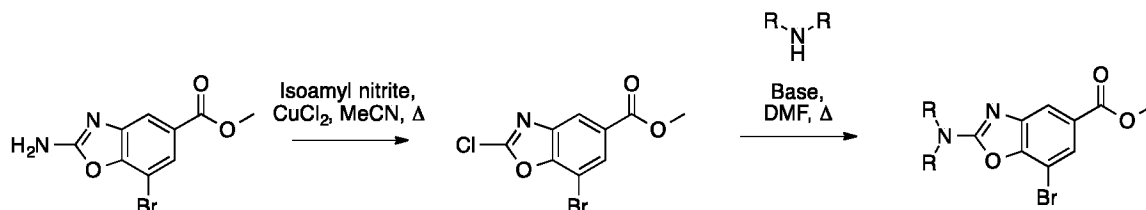
Prophetic Scaffold 2

Prophetic Scaffold 2 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R_1 position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. Scheme 1 provides details of the reactions available for the preparation of compounds useful for the preparation of compounds of Prophetic Scaffold 2. Methyl 2-amino-7-bromobenzo[d]oxazole-5-carboxylate may undergo a Sandmeyer reaction using reagents such as isoamyl nitrite and copper(II) chloride (first reaction) to deliver methyl 7-bromo-2-chlorobenzo[d]oxazole-5-carboxylate. Methyl 7-bromo-2-chlorobenzo[d]oxazole-5-carboxylate may undergo an S_NAr with an amine and a base such as cesium carbonate, triethylamine, or diisopropylethylamine (second reaction) to generate products as shown in

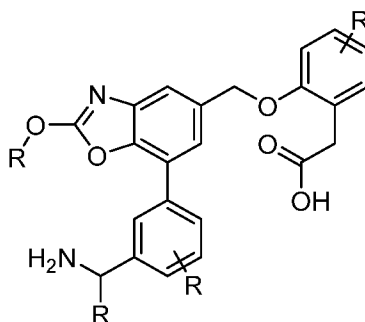
Scheme 1. Compounds of Prophetic Scaffold 2 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2 by following the procedures described for the preparation of Example 4.

5

Scheme 1- Preparation of Amino Group for Prophetic Scaffold 2

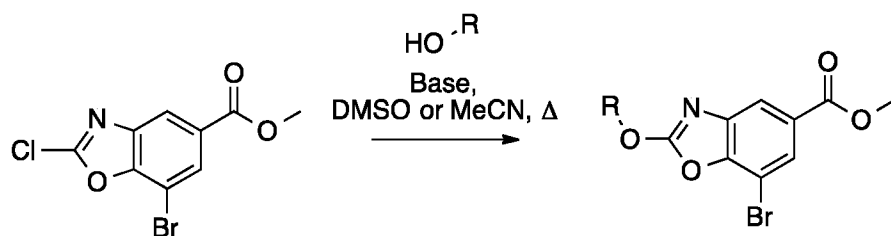


Prophetic Scaffold 3

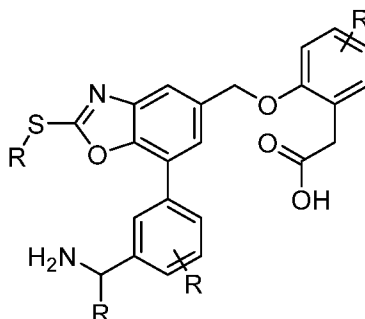


- 10 Prophetic Scaffold 3 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The ether group at the R_1 position can be derived from any commercially available alcohol or phenol that may or may not be amenable for further functionalization.
- 15 Scheme 2 provides details of the reactions available for the preparation of compounds useful for the preparation of compounds of Prophetic Scaffold 3. Methyl 7-bromo-2-chlorobenzo[d]oxazole-5-carboxylate may undergo an S_NAr with an alcohol and a base such as cesium carbonate, triethylamine, diisopropylethylamine, or sodium hydride to generate products as shown in Scheme 2. Compounds of Prophetic Scaffold 3 can be prepared
- 20 following General Reaction Sequence 1 or General Reaction Sequence 2. For representative literature procedures see - WO2016/207785 A1, **2016** and US2004/6104 A1, **2004**.

Scheme 2 - Preparation of Ether Group for Prophetic Scaffold 3



Prophetic Scaffold 4



5

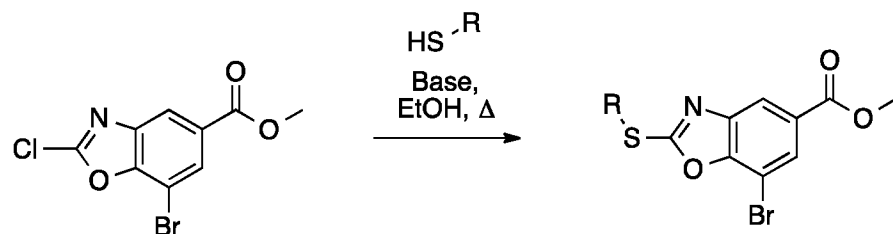
Prophetic Scaffold 4 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The thioether group at the R_1 position can be derived from any commercially available thiol, alkyl or aromatic, that may or may not be amenable for further functionalization.

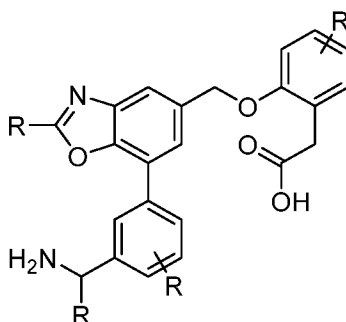
10

Scheme 3 provides details of the reactions available for the preparation of compounds useful for the preparation of compounds of Prophetic Scaffold 4. Methyl 7-bromo-2-chlorobenzo[d]oxazole-5-carboxylate may undergo an S_NAr with a thiol and a base such as cesium carbonate, triethylamine, diisopropylethylamine, or sodium hydride to generate products of as shown in Scheme 3. Compounds of Prophetic Scaffold 4 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

15

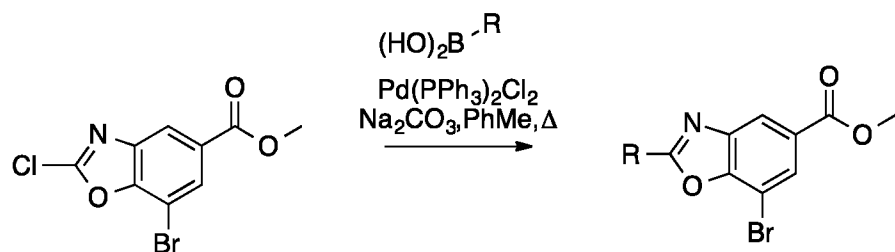
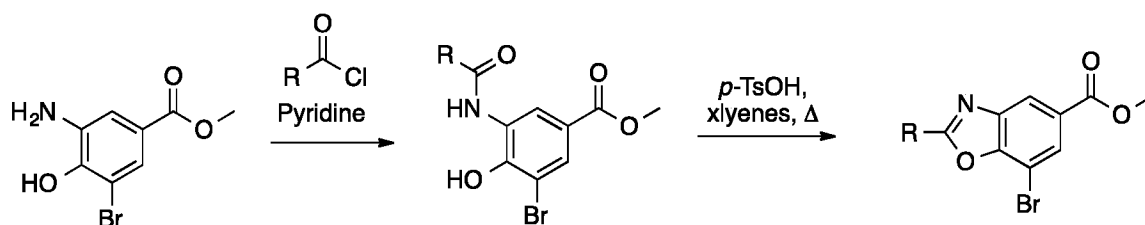
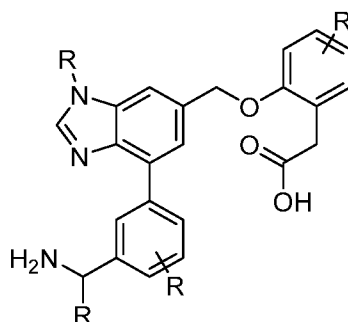
Scheme 3 - Preparation of Thioether Group for Prophetic Scaffold 4



Prophetic Scaffold 5

Prophetic Scaffold 5 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituent at the R_1 position can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further functionalization. See Scheme 4. Alternatively, the substituent at the R_1 position can be derived from any commercially carboxylic acid or acyl chloride that may or may not be amenable for further functionalization. See Scheme 5. Scheme 4 provides details of the reactions available for the preparation of compounds useful for the preparation of compounds of Prophetic Scaffold 5. Methyl 7-bromo-2-chlorobenzo[d]oxazole-5-carboxylate may undergo a palladium catalyzed Suzuki cross-coupling with a boronic acid using a catalyst such as bis(triphenylphosphine)palladium(II) dichloride ($Pd(PPh_3)_2Cl_2$), and a base such as sodium carbonate to deliver products as shown in Scheme 4. Compounds of Prophetic Scaffold 5 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

Scheme 5 provides an alternative synthetic route for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 5. Methyl 3-amino-5-bromo-4-hydroxybenzoate may undergo an acylation with an acid chloride and a base such as pyridine (first step) to deliver the intermediate as shown in Scheme 5. The intermediate compound as shown in Scheme 5 may undergo a dehydrative cyclization using an acid such as *p*-toluenesulfonic acid (second step) to provide products as shown in Scheme 5. Compounds of Prophetic Scaffold 5 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

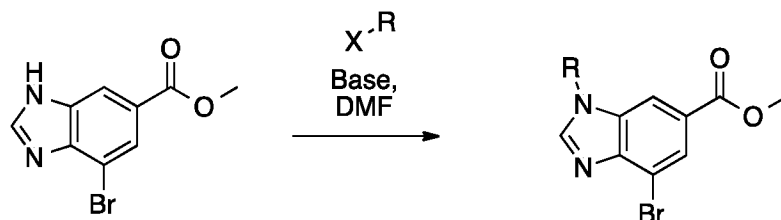
Scheme 4 - Preparation of Substituent Moiety for Prophetic Scaffold 5**Scheme 5 - Preparation of Substituent Moiety for Prophetic Scaffold 5****Prophetic Scaffold 6**

Prophetic Scaffold 6 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituent at the R_1 position can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization.

Scheme 6 provides details of the reactions available for the preparation of compounds useful for the preparation of compounds of Prophetic Scaffold 6. Methyl 4-bromo-1H-benzo[d]imidazole-6-carboxylate may undergo alkylation with an electrophile and a base such as sodium hydride or cesium carbonate to deliver products as shown in Scheme 6. Compounds of Prophetic Scaffold 6 can be prepared following General Reaction Sequence 1

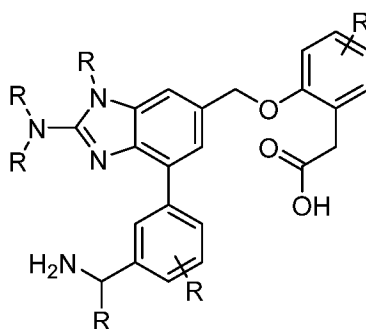
or General Reaction Sequence 2.

Scheme 6 - Preparation of Substituent Moiety for Prophetic Scaffold 6



5

Prophetic Scaffold 7



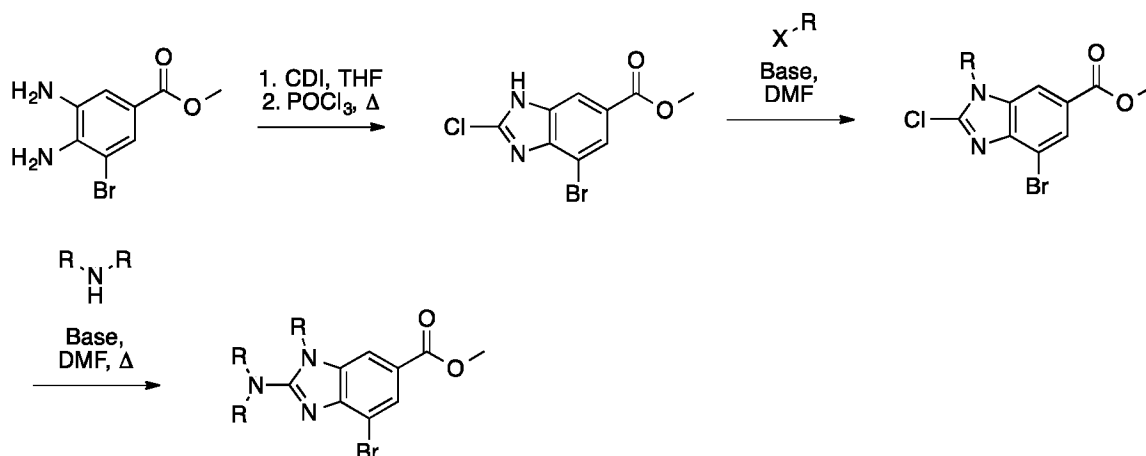
Prophetic Scaffold 7 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituent at the R_1 position can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization. The amino group at the R_2 position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization.

- 15 Scheme 7 provides details of the reactions available for the preparation of compounds useful for the preparation of compounds of Prophetic Scaffold 7. Methyl 3,4-diamino-5-bromobenzoate may undergo a reaction with carbonyldiimidazole (CDI) then phosphoryl chloride (first step) to deliver methyl 4-bromo-2-chloro-1*H*-benzo[*d*]imidazole-6-carboxylate. Methyl 4-bromo-2-chloro-1*H*-benzo[*d*]imidazole-6-carboxylate may undergo
- 20 alkylation with an electrophile and a base such as sodium hydride or cesium carbonate (second step) to deliver intermediate compounds as shown in Scheme 7. The intermediate compounds may undergo an S_NAr with an amine and a base such as cesium carbonate, triethylamine, or diisopropylethylamine (third step) to generate products as shown in Scheme

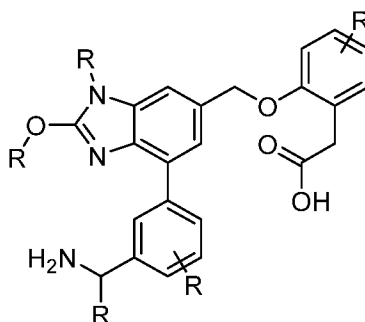
7. Compounds of Prophetic Scaffold 7 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2. For representative literature procedures see – Journal of Medicinal Chemistry, **2006**, vol. 49, # 12 p. 3719 – 3742, European Journal of Medicinal Chemistry, **2011**, vol. 46, # 1 p. 417 – 422

5

Scheme 7 - Preparation of Substituent Groups for Prophetic Scaffold 7



Prophetic Scaffold 8



10

Prophetic Scaffold 8 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituent at the R₁ position can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization. The ether group at the R₂ position can be derived from any commercially available alcohol or phenol that may or may not be amenable for further functionalization.

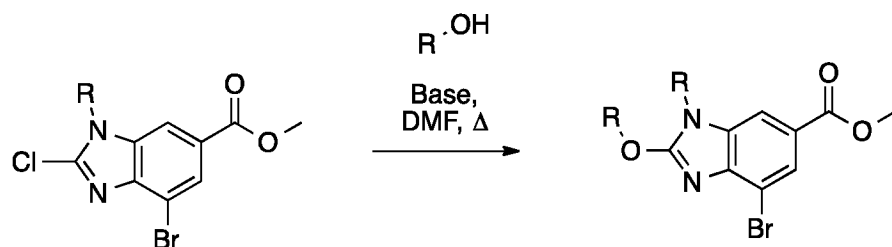
15

Scheme 8 provides details of the reactions available for the preparation of compounds that

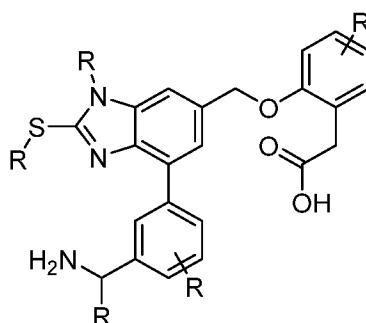
can be used to prepare compounds of Prophetic Scaffold 8. Reactants may undergo an S_NAr with an alcohol and a base such as cesium carbonate, triethylamine, diisopropylethylamine, or sodium hydride to generate products as shown in Scheme 8. Compounds of Prophetic Scaffold 8 can be prepared following General Reaction Sequence 1 or General Reaction

5 Sequence 2.

Scheme 8 - Preparation of Substituent Groups for Prophetic Scaffold 8



10 Prophetic Scaffold 9

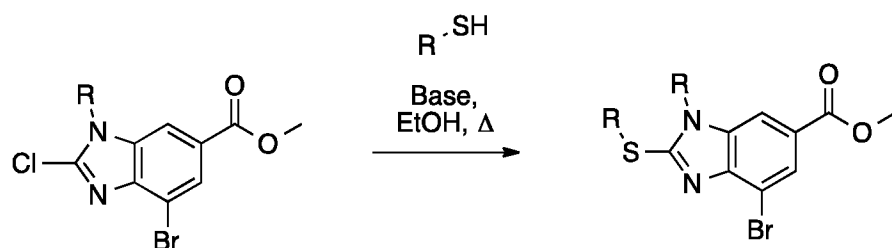


Prophetic Scaffold 9 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituent at the R_1 position can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization. The thioether group at the R_2 position can be derived from any commercially available thiol, alkyl or aromatic, that may or may not be amenable for further functionalization.

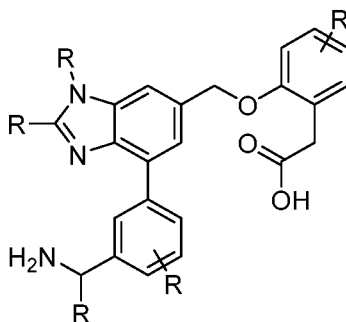
Scheme 9 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 9. Reactants may undergo an S_NAr with an alcohol and a base such as cesium carbonate, triethylamine, diisopropylethylamine, pyridine, or sodium hydride to generate products as shown in Scheme 9. Compounds of

Prophetic Scaffold 9 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

Scheme 9 - Preparation of Substituent Groups for Prophetic Scaffold 9



Prophetic Scaffold 10

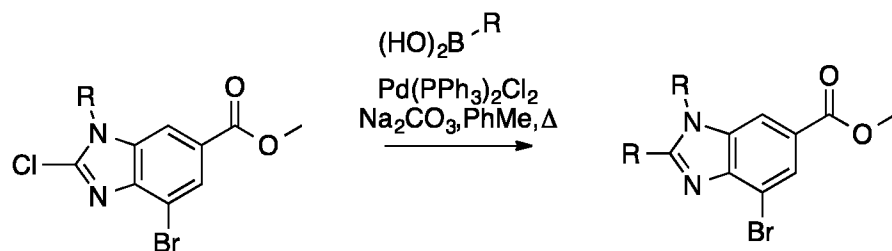


Prophetic Scaffold 10 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituent groups at the R_1 and R_2 positions can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further functionalization (Scheme 10). Alternatively, the groups at the R_1 and R_2 positions can be derived from any commercially carboxylic acid or acyl chloride that may or may not be amenable for further functionalization (Scheme 11). Additionally, the groups at the R_1 and R_2 positions can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization. Scheme 10 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 10. Compounds may undergo a palladium catalyzed Suzuki cross-coupling with a boronic acid using a catalyst such as bis(triphenylphosphine)palladium(II) dichloride ($Pd(PPh_3)_2Cl_2$), and a base such as sodium carbonate to deliver products as shown in Scheme 10. Compounds of Prophetic Scaffold 10

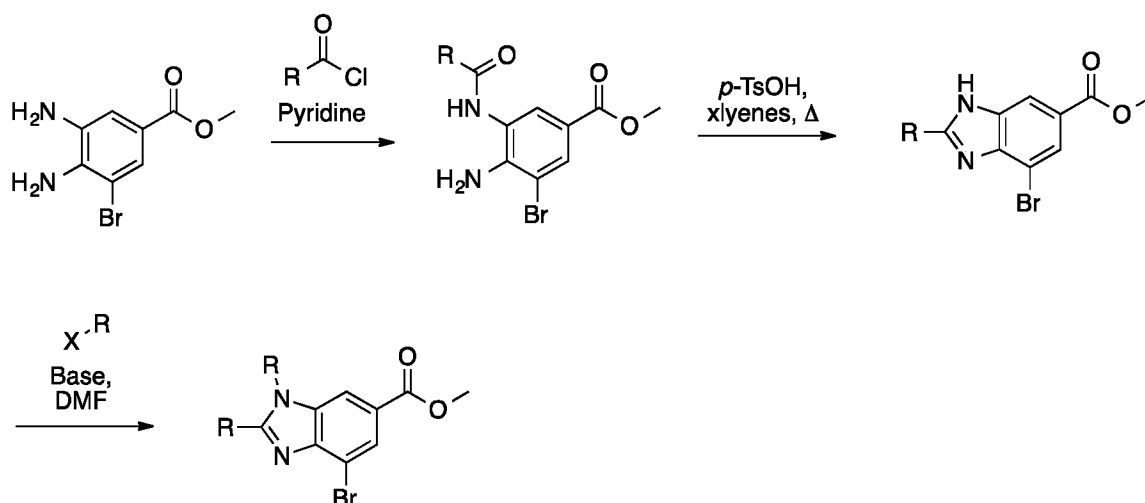
can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

Scheme 11 provides an alternative synthetic route to for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 10. Methyl 3,4-diamino-5-bromobenzoate may undergo an acylation with an acid chloride and a base such as pyridine (first step) to deliver intermediate compounds as shown in Scheme 11. Intermediate compounds may undergo a dehydrative cyclization using an acid such as *p*-toluenesulfonic acid (second step) to provide intermediate compounds as shown in Scheme 11. Intermediate compounds may undergo alkylation with an electrophile and a base such as sodium hydride or cesium carbonate (third step) to deliver products as shown in Scheme 11. Compounds of Prophetic Scaffold 10 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

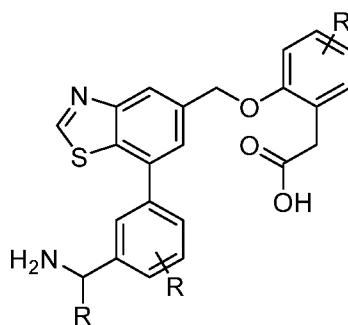
Scheme 10 - Preparation of Substituent Groups for Prophetic Scaffold 10



Scheme 11 - Preparation of Substituent Groups for Prophetic Scaffold 10



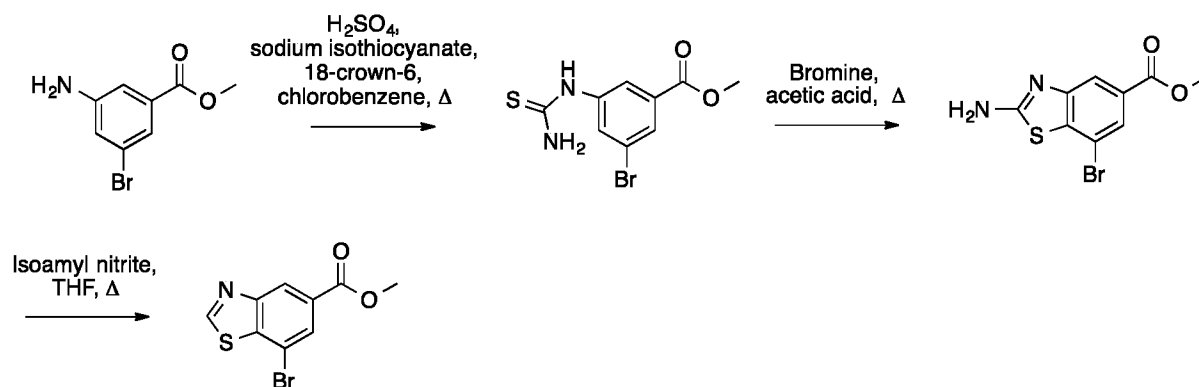
Prophetic Scaffold 11



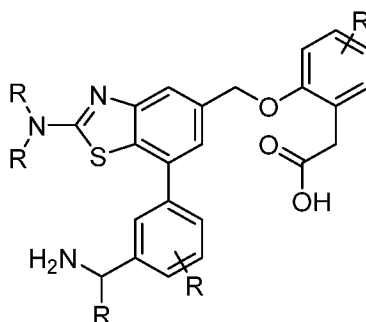
Prophetic Scaffold 11 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein.

Scheme 12 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 11. Methyl 3-amino-5-bromobenzoate may undergo a reaction with an isothiocyanate such as sodium isothiocyanate, an acid such as sulfuric acid, and a cation scavenger such as 18-crown-6 (first step) to deliver methyl 3-bromo-5-thioureidobenzoate. Methyl 3-bromo-5-thioureidobenzoate may cyclize upon exposure to bromine and acetic acid (second step) to deliver methyl 2-amino-7-bromobenzo[*d*]thiazole-5-carboxylate. Methyl 2-amino-7-bromobenzo[*d*]thiazole-5-carboxylate may be reduced with isoamyl nitrile (third step) to deliver methyl 7-bromobenzo[*d*]thiazole-5-carboxylate. Compounds of Prophetic Scaffold 11 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2. For representative literature procedures see - WO2008/81399 A2, **2008**, WO2015/38503 A1, **2015**, and WO2004/29050 A1, **2004**

Scheme 12 - Preparation of Substituent Groups for Prophetic Scaffold 11



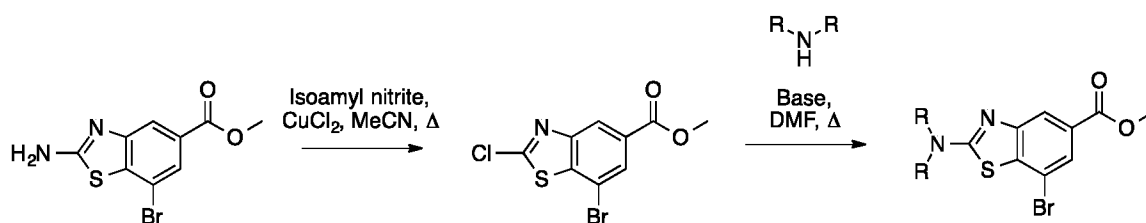
Prophetic Scaffold 12



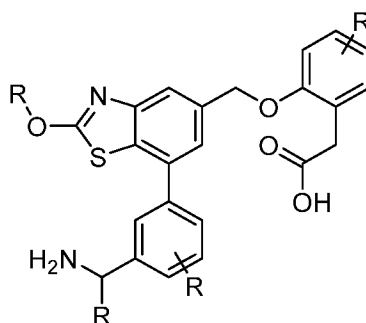
Prophetic Scaffold 12 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R₁ position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization.

Scheme 13 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 12. Methyl 2-amino-7-bromobenzo[d]thiazole-5-carboxylate may undergo a Sandmeyer reaction using reagents such as isoamyl nitrite and copper(II) chloride (first step) to deliver methyl 7-bromo-2-chlorobenzo[d]thiazole-5-carboxylate. Methyl 7-bromo-2-chlorobenzo[d]thiazole-5-carboxylate may undergo an S_NAr with an amine and a base such as cesium carbonate, triethylamine, or diisopropylethylamine (second step) to generate products as shown in Scheme 13. Compounds of Prophetic Scaffold 12 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2 by following the procedures described for the preparation of Example 4. For representative literature procedures see - WO2016/144351 A1, **2016**, and US2016/168138 A1, **2016**.

Scheme 13 - Preparation of Substituent Groups for Prophetic Scaffold 12



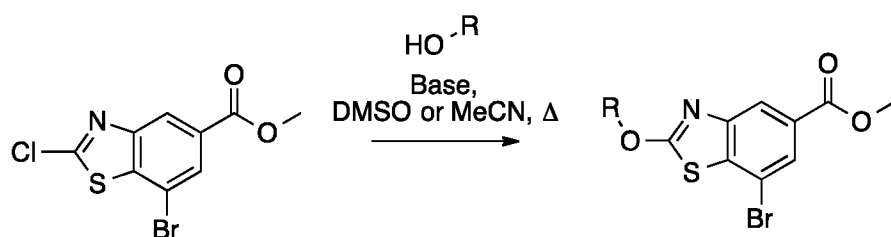
Prophetic Scaffold 13



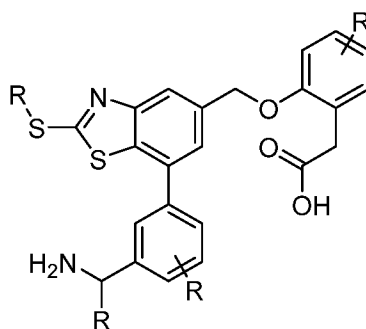
Prophetic Scaffold 13 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The ether group at the R_1 position can be derived from any commercially available alcohol or phenol that may or may not be amenable for further functionalization.

Scheme 14 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 13. Methyl 7-bromo-2-chlorobenzo[d]thiazole-5-carboxylate may undergo an S_NAr with an alcohol and a base such as cesium carbonate, triethylamine, diisopropylethylamine, or sodium hydride to generate products as shown in Scheme 14. Compounds of Prophetic Scaffold 13 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2. For a representative literature procedure see - WO2014/113303 A1, 2014

Scheme 14 - Preparation of Substituent Groups for Prophetic Scaffold 13



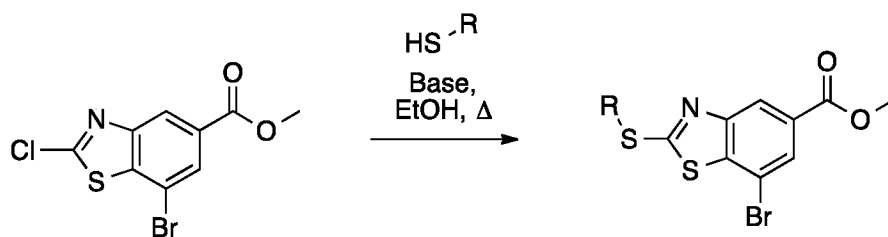
Prophetic Scaffold 14



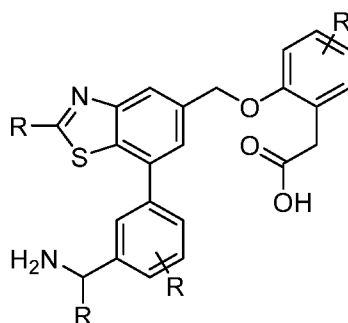
Prophetic Scaffold 14 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The thioether group at the R_1 position can be derived from any commercially available thiol, alkyl or aromatic, that may or may not be amenable for further functionalization.

Scheme 15 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 14. Methyl 7-bromo-2-chlorobenzo[d]thiazole-5-carboxylate may undergo an S_NAr with a thiol and a base such as cesium carbonate, triethylamine, diisopropylethylamine, or sodium hydride to generate products as shown in Scheme 15. Compounds of Prophetic Scaffold 14 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2. For a representative literature procedure see – US2005/250820 A1, 2005

Scheme 15 - Preparation of Substituent Groups for Prophetic Scaffold 14



Prophetic Scaffold 15

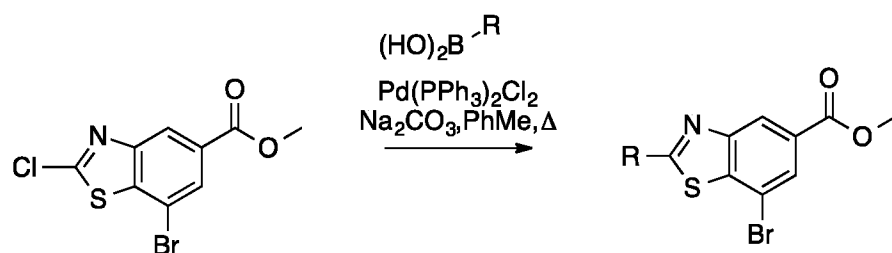


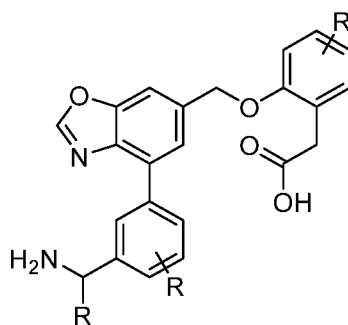
Prophetic Scaffold 15 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 position can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further functionalization. See Scheme 16. Scheme 16 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold

15. Methyl 7-bromo-2-chlorobenzo[*d*]thiazole-5-carboxylate may undergo a palladium catalyzed Suzuki cross-coupling with a boronic acid using a catalyst such as bis(triphenylphosphine)palladium(II) dichloride ($Pd(PPh_3)_2Cl_2$), and a base such as sodium carbonate to deliver products as shown in Scheme 16. Compounds of Prophetic Scaffold 15 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

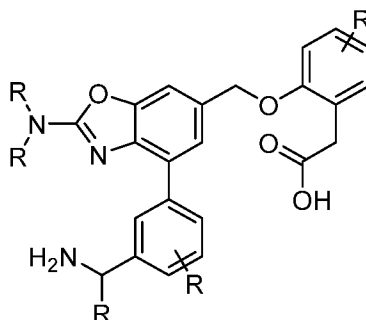
For representative literature procedure see – US2010/190994 A1, **2010**, WO2014/159224 A1, **2014**, and WO2006/76415 A2, **2006**

Scheme 16 - Preparation of Substituent Groups for Prophetic Scaffold 15



Prophetic Scaffold 16

Prophetic Scaffold 16 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. Compounds of Prophetic Scaffold 16 can be accessed via General Reaction Sequence 1 or General Reaction Sequence 2 by following the procedures described for the preparation of Example 1 and/or Example 6.

Prophetic Scaffold 17

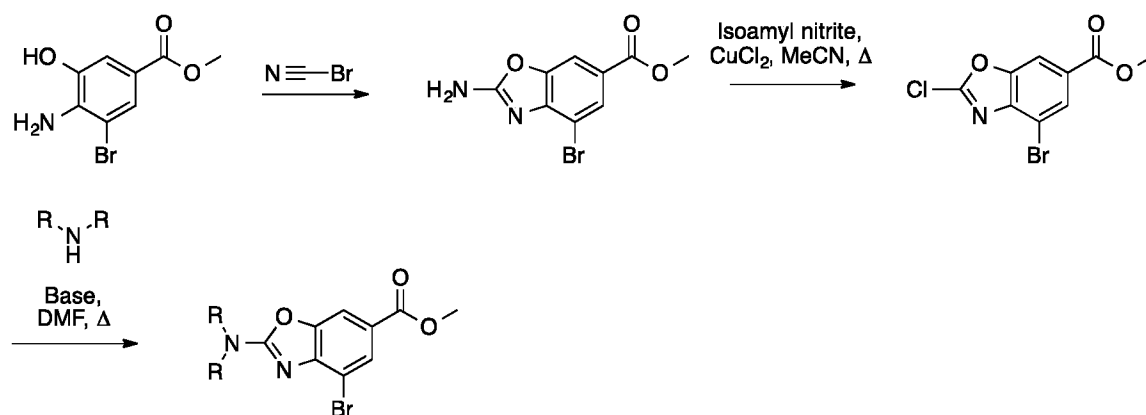
Prophetic Scaffold 17 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R_1 position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization.

Scheme 17 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 17. Methyl 4-amino-3-bromo-5-hydroxybenzoate may undergo a reaction cyanogen bromide (first step) to deliver methyl 2-amino-4-bromobenzo[d]oxazole-6-carboxylate. Methyl 2-amino-4-bromobenzo[d]oxazole-6-carboxylate may undergo a Sandmeyer reaction using reagents such as isoamyl nitrite and copper(II) chloride (second step) to deliver methyl 4-bromo-2-chlorobenzo[d]oxazole-6-

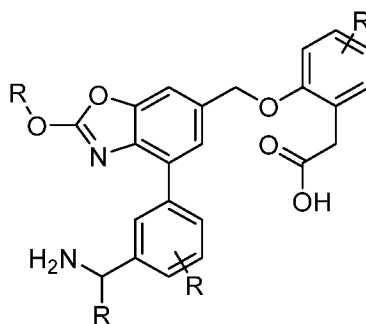
carboxylate. Methyl 4-bromo-2-chlorobenzo[d]oxazole-6-carboxylate may undergo an S_NAr with an amine and a base such as cesium carbonate, triethylamine, or diisopropylethylamine (third step) to generate products as shown in Scheme 17. Compounds of Prophetic Scaffold 17 can be accessed via General Reaction Sequence 1 or General Reaction Sequence 2 by

5 following the procedures described for the preparation of Example 4.

Scheme 17 - Preparation of Substituent Groups for Prophetic Scaffold 17



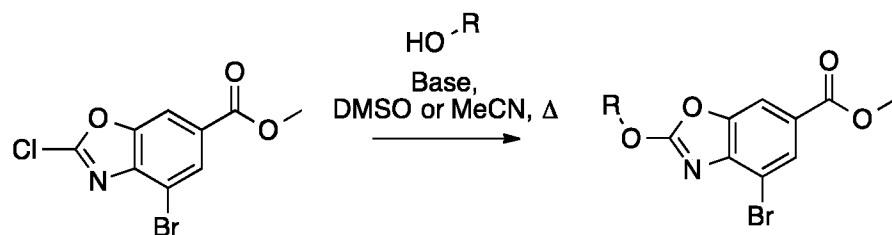
10 Prophetic Scaffold 18



Prophetic Scaffold 18 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The ether group at the R_1 position can be derived from any commercially available alcohol or phenol that may or may not be amenable for further functionalization. Scheme 18 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 18. Methyl 4-bromo-2-chlorobenzo[d]oxazole-6-carboxylate may undergo an S_NAr with an alcohol and a base such as cesium carbonate, triethylamine, diisopropylethylamine, or sodium hydride to generate products as shown in Scheme 18. Compounds of Prophetic Scaffold 18 can be

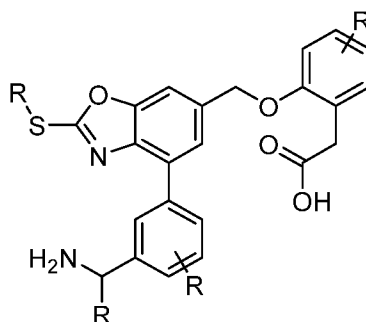
prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

Scheme 18 - Preparation of Substituent Groups for Prophetic Scaffold 18



5

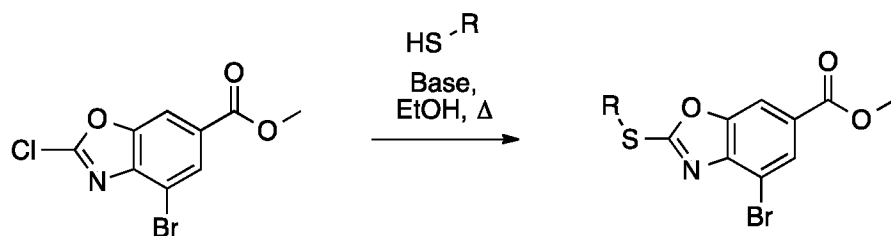
Prophetic Scaffold 19



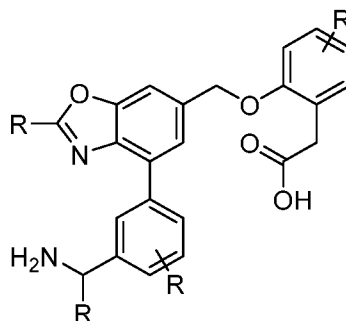
Prophetic Scaffold 19 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The thioether group at the R₁ position can be derived from any commercially available thiol, alkyl or aromatic, that may or may not be amenable for further functionalization.

Scheme 19 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 19. Methyl 4-bromo-2-chlorobenzo[d]oxazole-6-carboxylate may undergo an S_NAr with a thiol and a base such as cesium carbonate, triethylamine, diisopropylethylamine, or sodium hydride to generate products as shown in Scheme 19. Compounds of Prophetic Scaffold 19 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

Scheme 19 - Preparation of Substituent Groups for Prophetic Scaffold 19



Prophetic Scaffold 20



5

Prophetic Scaffold 20 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituent at the R_1 position can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further functionalization. See Scheme 20. Alternatively, the substituent at the R_1 position can be derived from any commercially carboxylic acid or acyl chloride that may or may not be amenable for further functionalization. See Scheme 21. Scheme 20 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 20. Methyl 4-bromo-2-chlorobenzo[d]oxazole-6-carboxylate may undergo a palladium catalyzed Suzuki cross-coupling with a boronic acid using a catalyst such as bis(triphenylphosphine)palladium(II) dichloride ($\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$), and a base such as sodium carbonate to deliver products as shown in Scheme 20. Compounds of Prophetic Scaffold 20 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

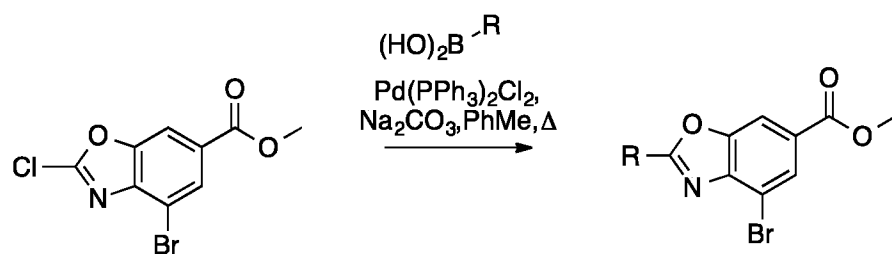
20

Scheme 21 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 20. Methyl 4-amino-3-bromo-5-hydroxybenzoate may undergo an acylation with an acid chloride and a base such as pyridine

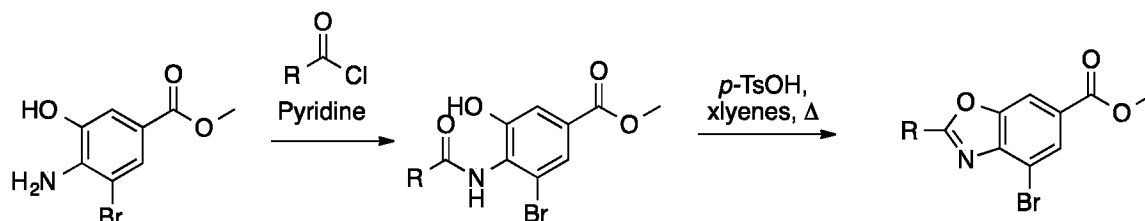
(first step) to deliver intermediate compounds as shown in Scheme 21. Intermediate compounds as shown in Scheme 21 may undergo a dehydrative cyclization using an acid such as *p*-toluenesulfonic acid to provide products as shown in Scheme 21. Compounds of Prophetic Scaffold 20 can be prepared following General Reaction Sequence 1 or General

5 Reaction Sequence 2.

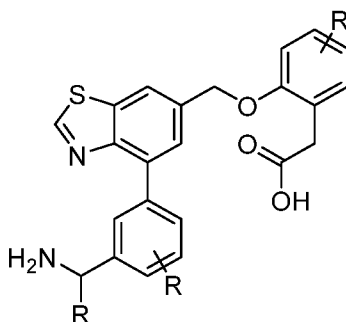
Scheme 20 - Preparation of Substituent Groups for Prophetic Scaffold 20



10 Scheme 21 - Preparation of Substituent Groups for Prophetic Scaffold 20



Prophetic Scaffold 21

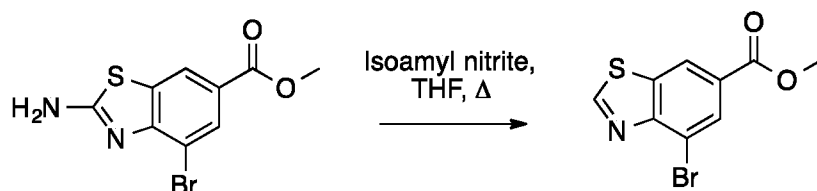


15 Prophetic Scaffold 21 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. Scheme 22 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 21.

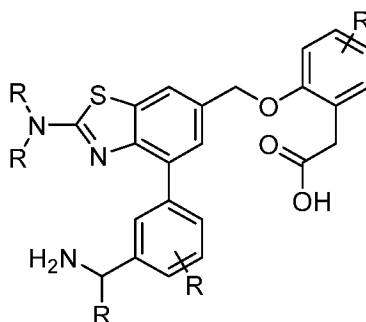
Methyl 2-amino-4-bromobenzo[d]thiazole-6-carboxylate may be reduced with a reagent such as isoamyl nitrile to deliver methyl 4-bromobenzo[d]thiazole-6-carboxylate. Compounds of Prophetic Scaffold 21 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

5

Scheme 22 - Preparation of Substituent Groups for Prophetic Scaffold 21



Prophetic Scaffold 22



10

Prophetic Scaffold 22 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amine groups at the R₁ position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. Scheme 23 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 22.

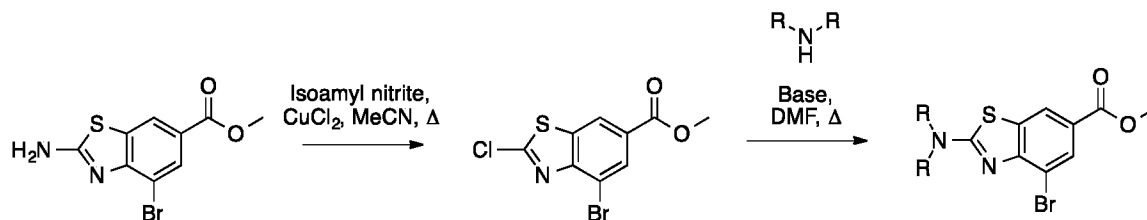
15

Methyl 2-amino-4-bromobenzo[d]thiazole-6-carboxylate may undergo a Sandmeyer reaction using reagents such as isoamyl nitrite and copper(II) chloride (first step) to deliver methyl 4-bromo-2-chlorobenzo[d]thiazole-6-carboxylate. Methyl 4-bromo-2-chlorobenzo[d]thiazole-6-carboxylate may undergo an S_NAr with an amine and a base such as cesium carbonate, triethylamine, or diisopropylethylamine (second step) to generate products as shown in Scheme 23. Compounds of Prophetic Scaffold 22 can be accessed via General Reaction Sequence 1 or General Reaction Sequence 2 by following the procedures described for the

20

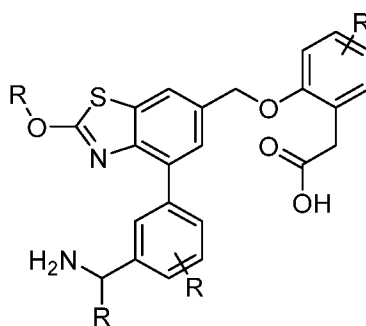
preparation of Example 4.

Scheme 23 - Preparation of Substituent Groups for Prophetic Scaffold 22



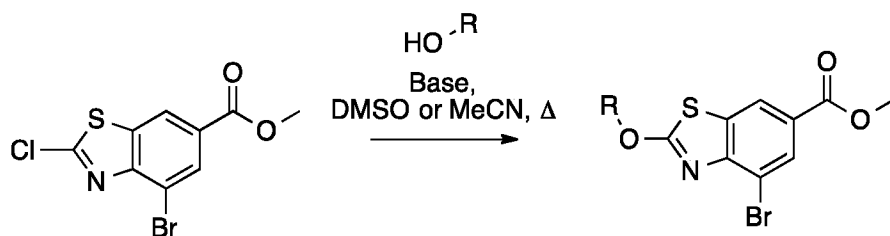
5

Prophetic Scaffold 23

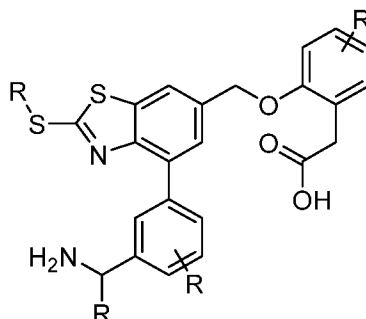


Prophetic Scaffold 23 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The ether groups at the R_1 position can be derived from any commercially available alcohol or phenol that may or may not be amenable for further functionalization. Scheme 24 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 23. Methyl 4-bromo-2-chlorobenzo[d]thiazole-6-carboxylate may undergo an S_NAr with an alcohol and a base such as cesium carbonate, triethylamine, diisopropylethylamine, or sodium hydride to generate products as shown in Scheme 24. Compounds of Prophetic Scaffold 23 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

Scheme 24 - Preparation of Substituent Groups for Prophetic Scaffold 23



Prophetic Scaffold 24

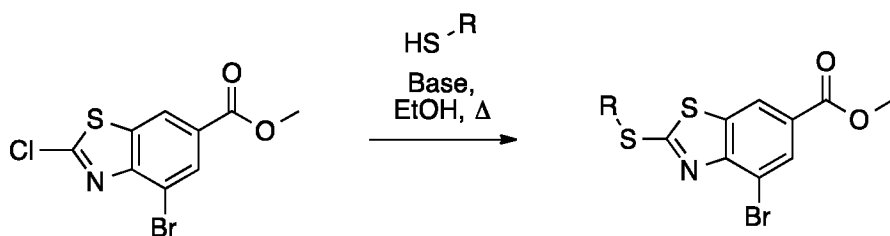


5

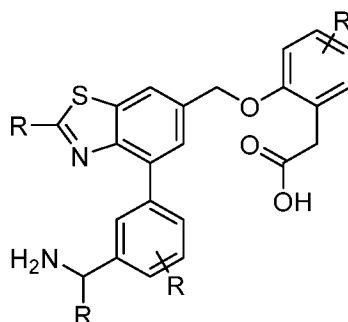
Prophetic Scaffold 24 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The thioether groups at the R_1 position can be derived from any commercially available thiol, alkyl or aromatic, that may or may not be amenable for further functionalization. Scheme 25 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 24. Methyl 4-bromo-2-chlorobenzo[d]thiazole-6-carboxylate may undergo an $\text{S}_{\text{N}}\text{Ar}$ with a thiol and a base such as cesium carbonate, triethylamine, diisopropylethylamine, or sodium hydride to generate products as shown in Scheme 25. Compounds of Prophetic Scaffold 24 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

15

Scheme 25 - Preparation of Substituent Groups for Prophetic Scaffold 24

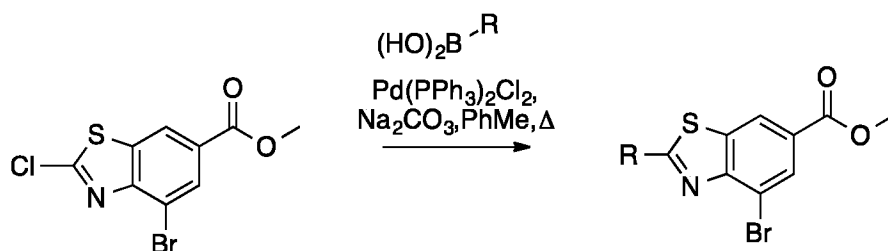


Prophetic Scaffold 25

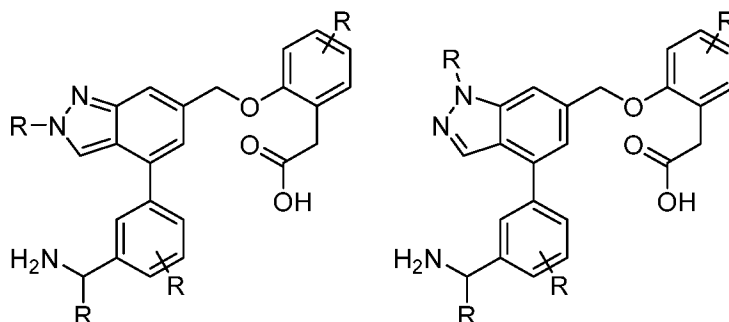


Prophetic Scaffold 25 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and
 5 Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the
 structures disclosed herein. The substituents at the R_1 position can be derived from any
 commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic
 acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further
 functionalization. Scheme 26 provides details of the reactions available for the preparation of
 10 compounds that can be used to prepare compounds of Prophetic Scaffold 25. Methyl 4-
 bromo-2-chlorobenzo[d]thiazole-6-carboxylate may undergo a palladium catalyzed Suzuki
 cross-coupling with a boronic acid using a catalyst such as
 bis(triphenylphosphine)palladium(II) dichloride ($Pd(PPh_3)_2Cl_2$), and a base such as sodium
 carbonate to deliver products as shown in Scheme 26. Compounds of Prophetic Scaffold 25
 15 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

Scheme 26 - Preparation of Substituent Groups for Prophetic Scaffold 25



Prophetic Scaffolds 26 and 27

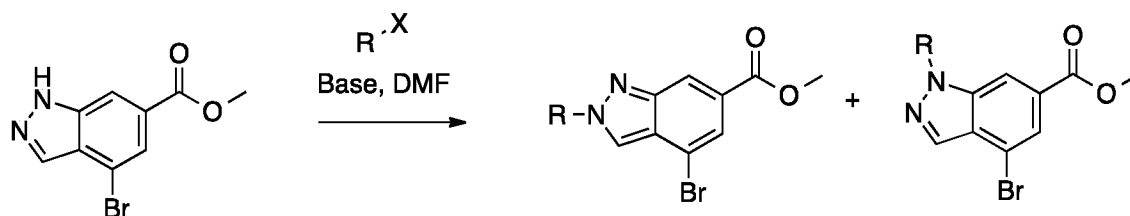


Prophetic Scaffolds 26 and 27 may consist of any combination of benzylic amines Aryl 1

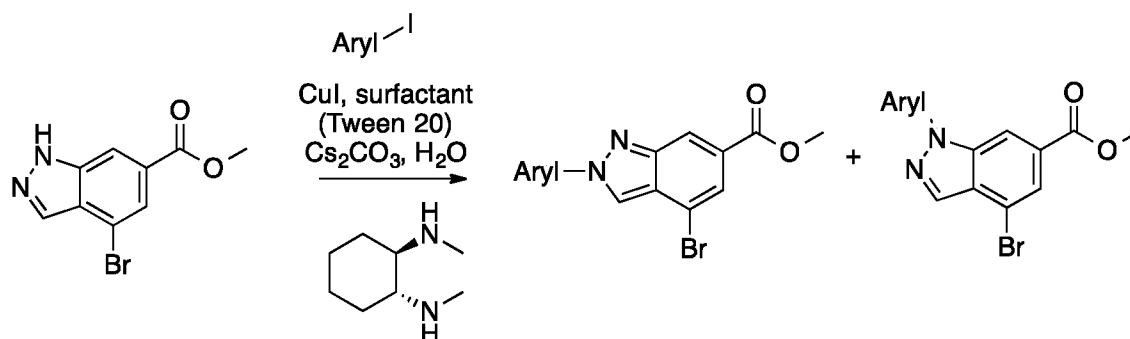
(Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R₁ and R₂ positions can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization. Scheme 27 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffolds 26 and 27. Methyl 4-bromo-1*H*-indazole-6-carboxylate may undergo alkylation with an electrophile and a base such as sodium hydride or cesium carbonate to deliver a mixture of products as shown in Scheme 27. Compounds of Prophetic Scaffold 26 or of Prophetic Scaffold 27 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

Scheme 28 provides an alternative synthetic route to for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 26 and Prophetic Scaffold 27. Methyl 4-bromo-1*H*-indazole-6-carboxylate may undergo an Ullman coupling with an aryl halide, a copper source such as copper iodide, a surfactant such as Tween 20, and a base such as cesium carbonate to deliver a mixture of products as shown in Scheme 27. Compounds of Prophetic Scaffold 26 or of Prophetic Scaffold 27 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2. For representative literature procedures see - WO2011/140325 A1, **2011**, and Tetrahedron, **2017**, vol. 73, # 2 p. 172 – 178

Scheme 27 - Preparation of Substituent Groups for Prophetic Scaffolds 26 and 27

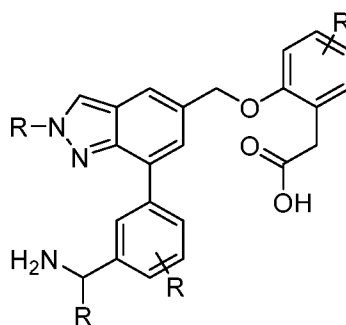


Scheme 28 - Preparation of Substituent Groups for Prophetic Scaffolds 26 and 27



5

Prophetic Scaffold 28



Prophetic Scaffold 28 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R₁ position can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization.

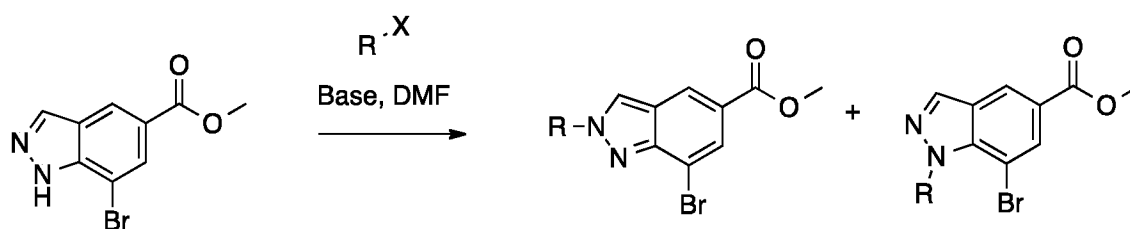
Scheme 29 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 28. Methyl 7-bromo-1H-indazole-5-carboxylate may undergo alkylation with an electrophile and a base such as sodium hydride or cesium carbonate to deliver a mixture of products as shown in Scheme 29. Compounds of Prophetic Scaffold 28 can be prepared following General Reaction Sequence 1 or General

15

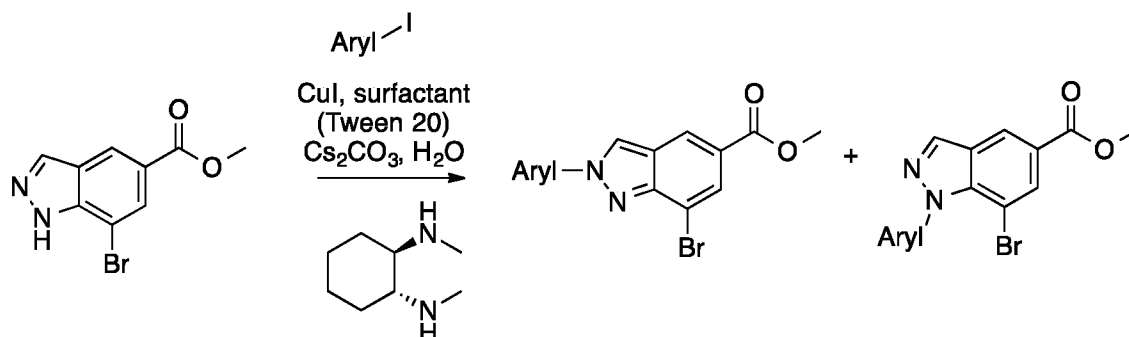
Reaction Sequence 2.

Scheme 30 provides an alternative synthetic route to for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 28. Methyl 7-bromo-1*H*-indazole-5-carboxylate may undergo an Ullman coupling with an aryl halide, a copper source such as copper iodide, a surfactant such as Tween 20, and a base such as cesium carbonate to deliver a mixture of products as shown in Scheme 30. Compounds of Prophetic Scaffold 28 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

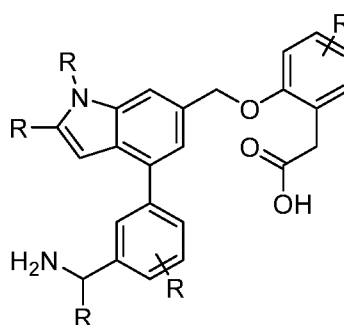
Scheme 29 - Preparation of Substituent Groups for Prophetic Scaffold 28



Scheme 30 - Preparation of Substituent Groups for Prophetic Scaffold 28



Prophetic Scaffold 29



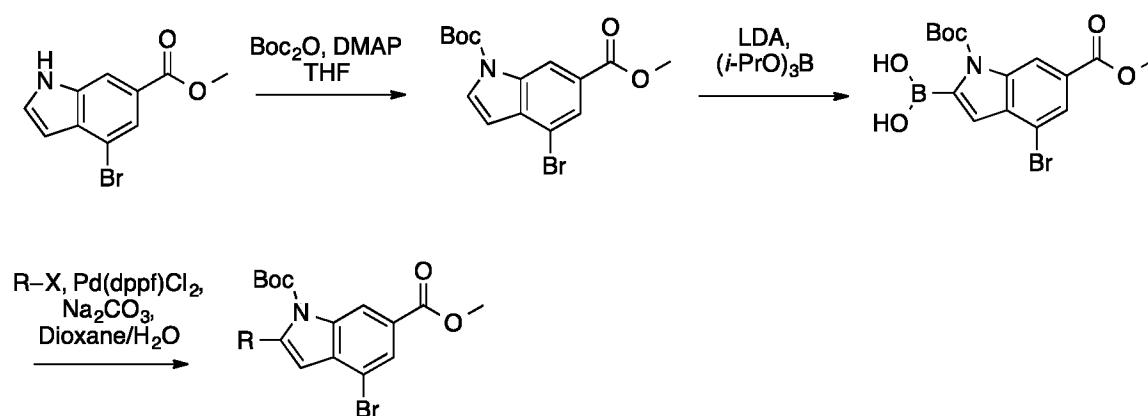
Prophetic Scaffold 29 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and

Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R₁ and R₂ positions can be derived from any commercially available alkyl halide, aryl halide, heteroaryl halide, alkenyl halide, or alkyne that may or may not be amenable for further functionalization.

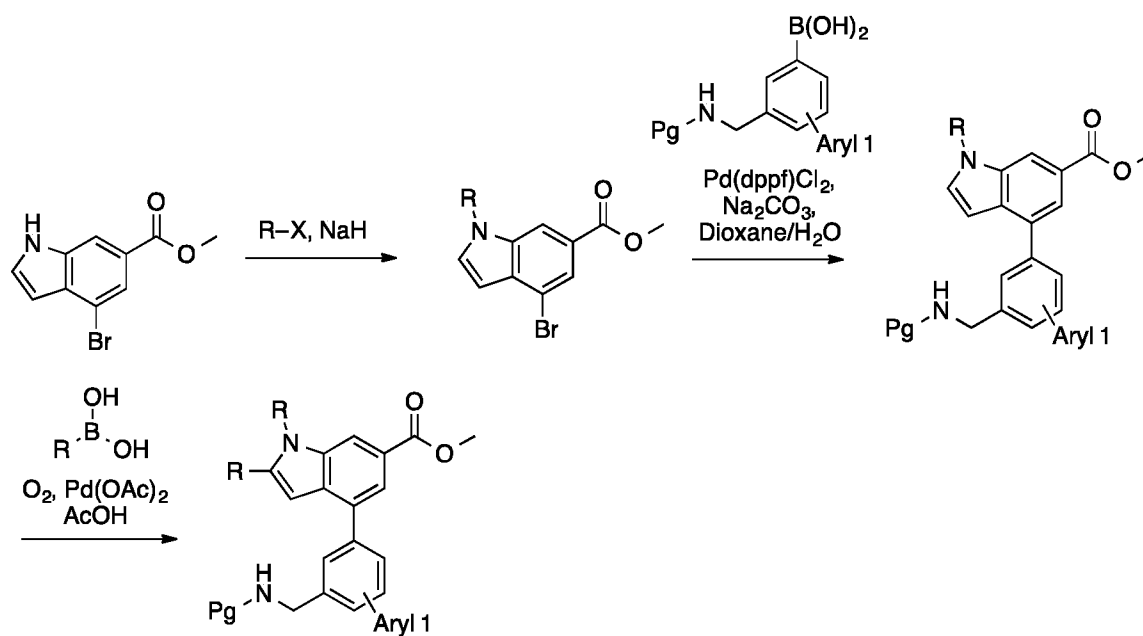
5 Scheme 31 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 29. Methyl 4-bromo-1*H*-indole-6-carboxylate may be protected with a protecting group, such as Boc, using di-*tert*-butyl-dicarbonate, and DMAP in THF (first step) to generate 1-(*tert*-butyl) 6-methyl 4-bromo-1*H*-indole-1,6-dicarboxylate. 1-(*tert*-Butyl) 6-methyl 4-bromo-1*H*-indole-1,6-dicarboxylate may
10 be deprotonated using a base such as LDA, and quenched with a borate, such as triisopropyl borate (second step) to deliver (4-bromo-1-(*tert*-butoxycarbonyl)-6-(methoxycarbonyl)-1*H*-indol-2-yl)boronic acid. (4-Bromo-1-(*tert*-butoxycarbonyl)-6-(methoxycarbonyl)-1*H*-indol-2-yl)boronic acid may undergo a Suzuki cross coupling with a palladium catalyst such as Pd(dppf)Cl₂, a base such as sodium carbonate, and a halide (third step) to deliver products as
15 shown in Scheme 31. Compounds of Prophetic Scaffold 29 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

Scheme 32 provides an alternative synthetic route to for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 29. Methyl 4-bromo-1*H*-indole-6-carboxylate may undergo an alkylation with an electrophile (first step) to deliver intermediate
20 compounds as shown in Scheme 32. Intermediate compounds may undergo a Suzuki cross coupling with a palladium catalyst such as Pd(dppf)Cl₂, a base such as sodium carbonate, and a boronic acid (second step) to deliver intermediate compounds as shown in Scheme 32. The intermediate compounds may undergo a cross coupling with a palladium source such as palladium acetate, an oxidant such as oxygen, an acid such as acetic acid, with a boronic acid
25 (third step) to deliver products as shown in Scheme 32. Compounds of Prophetic Scaffold 29 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2. For a representative literature procedure see - Angewandte Chemie - International Edition, **2008**, vol. 47, # 8 p. 1473 – 1476.

Scheme 31 - Preparation of Substituent Groups for Prophetic Scaffold 29

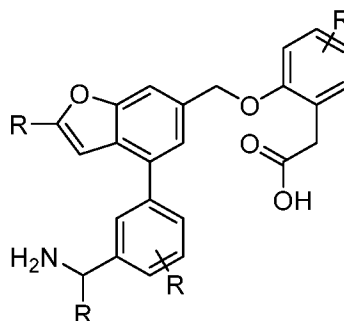


Scheme 32 - Preparation of Substituent Groups for Prophetic Scaffold 29



5

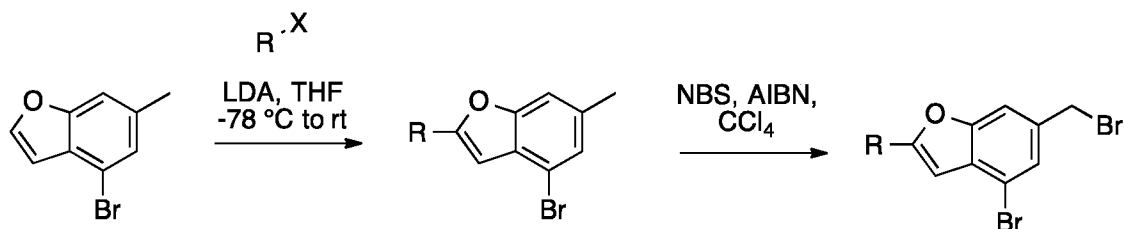
Prophetic Scaffold 30



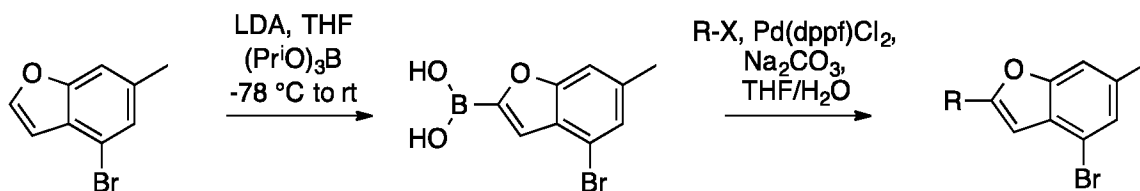
Prophetic Scaffold 30 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 position can be derived from any commercially available alkyl halide, aryl halide, heteroaryl halide, alkenyl halide, or alkyne that may or may not be amenable for further functionalization. Scheme 33 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 30. 4-bromo-6-methylbenzofuran may be deprotonated with a base such as LDA, and quenched with an electrophile (first step) to deliver intermediate compounds as shown in Scheme 33. Intermediate compounds may undergo benzylic halogenation using a halide source such as N-bromosuccinimide, and a radical initiator such as AIBN (second step) to deliver products as shown in Scheme 33. Compounds of Prophetic Scaffold 30 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.

Scheme 34 provides an alternative synthetic route to for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 30. 4-Bromo-6-methylbenzofuran may be deprotonated with a base such as LDA, and quenched with a borate, such as triisopropyl borate (first step) to deliver (4-bromo-6-methylbenzofuran-2-yl)boronic acid. (4-Bromo-6-methylbenzofuran-2-yl)boronic acid may undergo a Suzuki cross coupling with a palladium catalyst such as $Pd(dppf)Cl_2$, a base such as sodium carbonate, and a halide (second step) to deliver products as shown in Scheme 34. Compounds of Prophetic Scaffold 30 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2. For representative literature procedures see - Journal of the American Chemical Society, **2012**, vol. 134, # 30 p. 12466 – 12469, WO2017/69980 A1, **2017**, WO2010/111483 A1, **2010**, WO2010/111483 A1, **2010**, Bioorganic and Medicinal Chemistry Letters, **2012**, vol. 22, # 23 p. 7227 – 7231, and Arkivoc, **2013**, vol. 2013, # 4 p. 405 – 412.

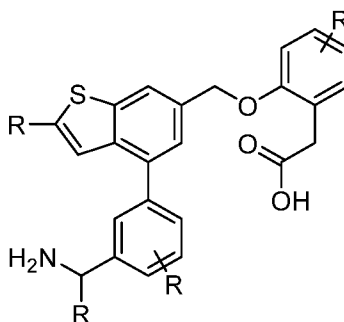
Scheme 33 - Preparation of Substituent Groups for Prophetic Scaffold 30



Scheme 34 - Preparation of Substituent Groups for Prophetic Scaffold 30



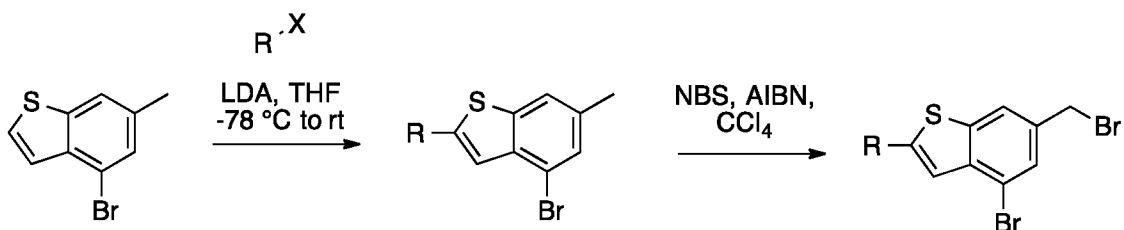
5 Prophetic Scaffold 31



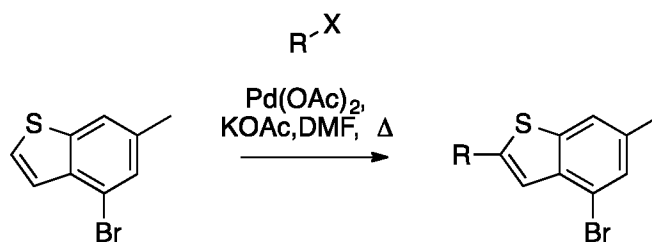
- Prophetic Scaffold 31 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 position can be derived from any commercially available alkyl halide, aryl halide, heteroaryl halide, alkenyl halide, or alkyne that may or may not be amenable for further functionalization. Scheme 35 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 31. 4-Bromo-6-methylbenzo[*b*]thiophene may be deprotonated with a base such as LDA, and quenched with an electrophile (first step) to deliver intermediate compounds as shown in Scheme 35. Intermediate compounds may undergo benzylic halogenation using a halide source such as N-bromosuccinimide, and a radical initiator such as AIBN (second step) to deliver products as shown in Scheme 35. Compounds of Prophetic Scaffold 31 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2.
- Scheme 36 provides an alternative synthetic route to for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 31. 4-Bromo-6-methylbenzo[*b*]thiophene may undergo a Suzuki cross coupling with a palladium catalyst such as palladium acetate, a base such as potassium acetate, and a halide to deliver products as shown in Scheme 36. Compounds of Prophetic Scaffold 31 can be prepared following

General Reaction Sequence 1 or General Reaction Sequence 2. For representative literature procedures see - WO2017/36404 A1, **2017**, Bulletin of the Chemical Society of Japan, **2012**, vol. 85, # 5 p. 613 – 623, Tetrahedron, **2013**, vol. 69, # 34 p. 7082 – 7089, Journal of Medicinal Chemistry, **1986**, vol. 29, # 9 p. 1637 – 1643, and Bioorganic and Medicinal Chemistry, **2014**, vol. 22, # 13 p. 3498 - 3507

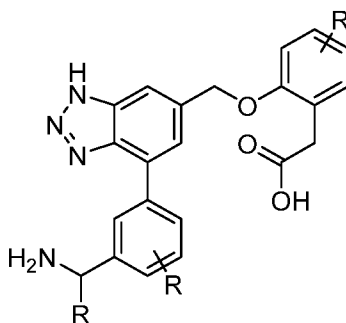
Scheme 35 - Preparation of Substituent Groups for Prophetic Scaffold 31



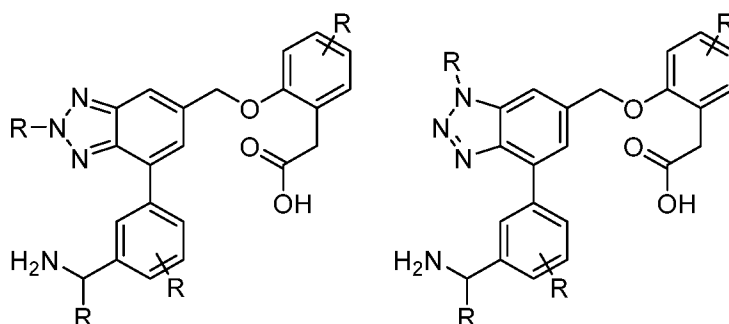
Scheme 36 - Preparation of Substituent Groups for Prophetic Scaffold 31



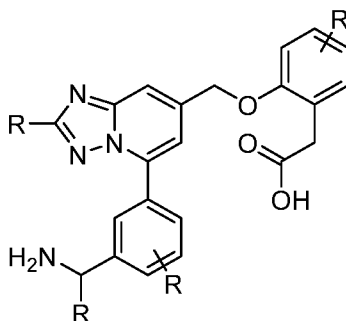
Prophetic Scaffold 32



- 15 Prophetic Scaffold 32 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. Compounds of Prophetic Scaffold 32 can be accessed via General Reaction Sequence 1 or General Reaction Sequence 2 by following the procedures described for the preparation of Example 2, and/or Example 3, and/or Example 5.

Prophetic Scaffold 33 and 34

Prophetic Scaffolds 33 and 34 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R₁ and R₂ positions can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffolds 33 and 34 may be prepared by using analogues approaches to the ones described for the preparation of Prophetic Scaffolds 26 and 27 and by following General Reaction Sequence 1 or General Reaction Sequence 2. In this case methyl 4-bromo-1*H*-benzo[*d*][1,2,3]triazole-6-carboxylate should be used as the starting material.

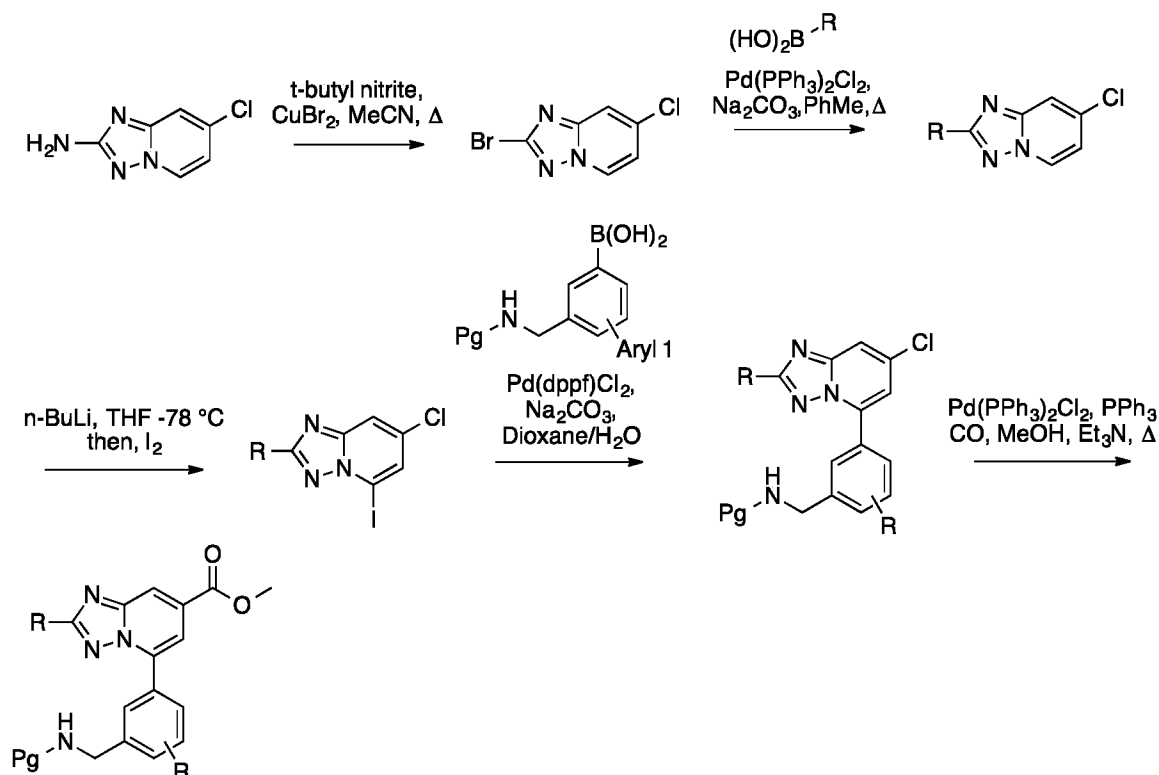
Prophetic Scaffold 35

Prophetic Scaffold 35 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R₁ position can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further functionalization.

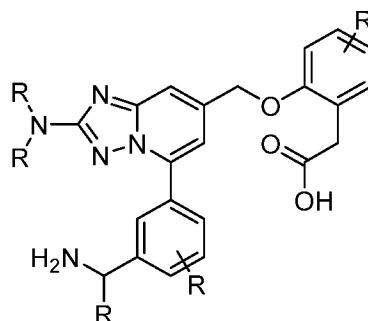
Scheme 37 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 35. 7-Chloro-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine undergo a Sandmeyer reaction using reagents such as *t*-butyl nitrite and copper(II) bromide (first step) to deliver 2-bromo-7-chloro-[1,2,4]triazolo[1,5-*a*]pyridine. 2-Bromo-7-chloro-[1,2,4]triazolo[1,5-*a*]pyridine may undergo a palladium catalyzed Suzuki cross-coupling with a boronic acid using a catalyst such as bis(triphenylphosphine)palladium(II) dichloride ($\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$), and a base such as sodium carbonate (second step) to deliver intermediate compounds as shown in Scheme 37.

Intermediate compounds may be deprotonated using a base such as *n*-butyllithium and quenched with iodine (third step) to deliver intermediate compounds as shown in Scheme 37. Intermediate compounds may undergo a Suzuki cross coupling with a palladium catalyst such as $\text{Pd}(\text{dppf})\text{Cl}_2$, a base such as sodium carbonate, and a boronic acid (fourth step) to deliver intermediate compounds as shown in Scheme 37. Intermediate compounds may undergo alkoxycarbonylation with a palladium catalyst such as $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, a ligand such a triphenylphosphine, a source of carbon monoxide such as carbon monoxide gas, an alcohol such as methanol, and a base such as triethylamine to generate products as shown in Scheme 37. Compounds of Prophetic Scaffold 35 can be prepared following General Reaction Sequence 1. For representative literature procedures see - Bioorganic and Medicinal Chemistry Letters, **2009** , vol. 19, # 3 p. 894 – 899 and WO2005/16876 A2, **2005**.

Scheme 37 - Preparation of Substituent Groups for Prophetic Scaffold 35



Prophetic Scaffold 36



5

Prophetic Scaffold 36 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R₁ position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization.

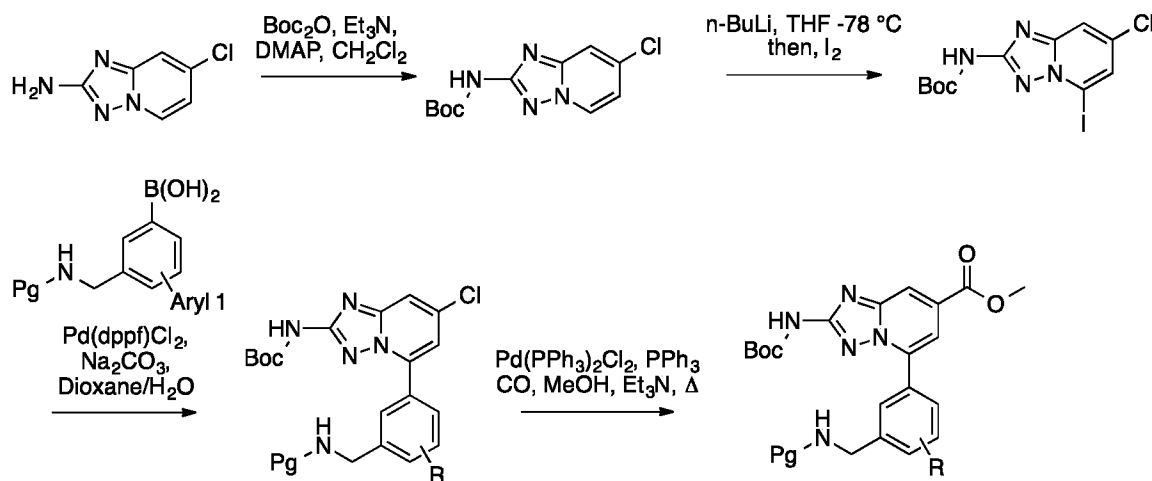
10

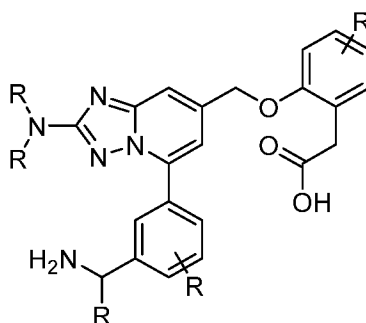
Scheme 38 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 36. 7-Chloro-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine may be protected with a protecting group, such as Boc, using di-*tert*-butyl-

dicarbonate, and a base such as triethylamine and DMAP (first step) to generate *tert*-butyl (7-chloro-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate. *tert*-Butyl (7-chloro-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate may be deprotonated using a base such as *n*-butyllithium and then quenched with iodine (second step) to deliver *tert*-butyl (7-chloro-5-iodo-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate. *tert*-Butyl (7-chloro-5-iodo-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate may undergo a Suzuki cross coupling with a palladium catalyst such as Pd(dppf)Cl₂, a base such as sodium carbonate, and a boronic acid (third step) to deliver intermediate compounds as shown in Scheme 38. Intermediate compounds may undergo a alkoxy carbonylation with a palladium catalyst such as Pd(PPh₃)₂Cl₂, a ligand such a triphenylphosphine, a source of carbon monoxide such as carbon monoxide gas, an alcohol such as methanol, and a base such as triethylamine to generate products as shown in Scheme 38. Compounds of Prophetic Scaffold 36 can be prepared following General Reaction Sequence 1.

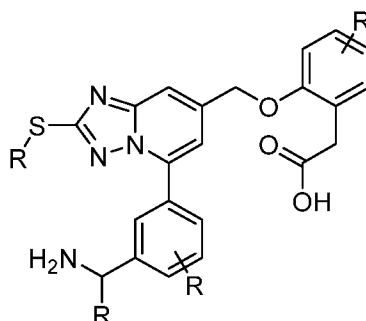
Compounds of Prophetic Scaffold 36 may also be prepared from 2-bromo-7-chloro-[1,2,4]triazolo[1,5-*a*]pyridine using analogues approaches and reaction conditions to the ones described for the preparation of Prophetic Scaffold 2 and General Reaction Sequence 1.

Scheme 38 - Preparation of Substituent Groups for Prophetic Scaffold 36



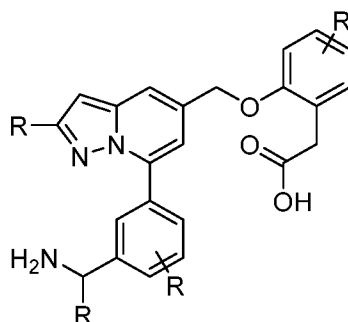
Prophetic Scaffold 37

Prophetic Scaffold 37 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R₁ position can be derived from any commercially available alcohol or phenol that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 37 may be prepared by using analogues approaches to the ones described for the preparation of Prophetic Scaffold 8, Prophetic Scaffold 35, and General Reaction Sequence 1 by using 2-bromo-7-chloro-[1,2,4]triazolo[1,5-*a*]pyridine as the starting material.

Prophetic Scaffold 38

Prophetic Scaffold 38 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The thioether group at the R₁ position can be derived from any commercially available thiol, alkyl or aromatic, that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 38 may be prepared by using analogues approaches to the ones described for the preparation of Prophetic Scaffold 9, Prophetic Scaffold 35, and General Reaction Sequence 1 using 2-bromo-7-chloro-[1,2,4]triazolo[1,5-*a*]pyridine as the starting material.

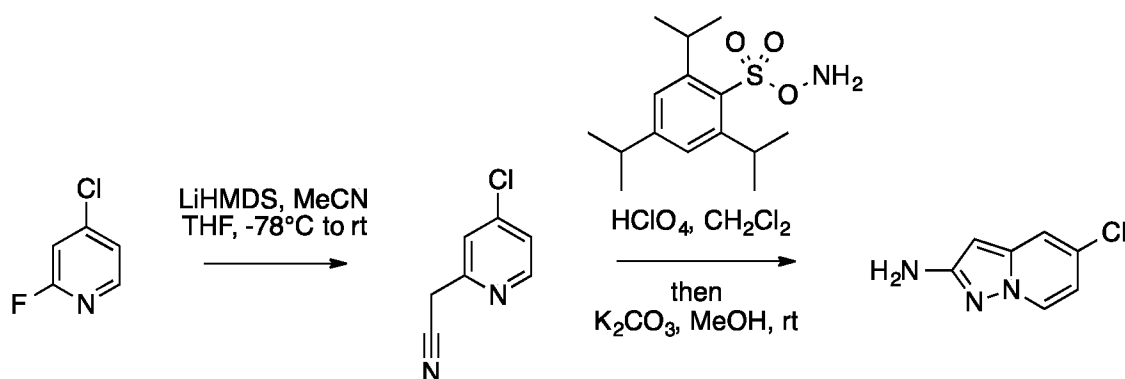
Prophetic Scaffold 39



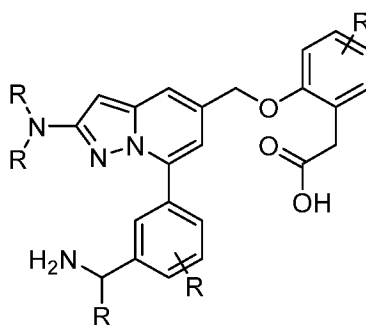
Prophetic Scaffold 39 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 position can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further functionalization.

Scheme 39 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 39. 4-Chloro-2-fluoropyridine may undergo an S_NAr with acetonitrile using a base such as LiHMDS to give 2-(4-chloropyridin-2-yl)acetonitrile. Ethyl o-mesitylsulfonylacetohydroxamic acid can initially be reacted with $HClO_4$; the resulting precipitate can be added to a solution of 2-(4-Chloropyridin-2-yl)acetonitrile and a base such as potassium carbonate to generate 5-chloropyrazolo[1,5-*a*]pyridin-2-amine. Compounds of Prophetic Scaffold 39 may be prepared using analogous approaches and reaction conditions to the ones described for the preparation of Prophetic Scaffold 35 and General Reaction Sequence 1. For representative literature procedures see - WO2013/6792 A1, **2013**, and Bioorganic and Medicinal Chemistry, **2017**, vol. 25, # 9 p. 2635 – 2642.

Scheme 39 - Preparation of Substituent Groups for Prophetic Scaffold 39



Prophetic Scaffold 40

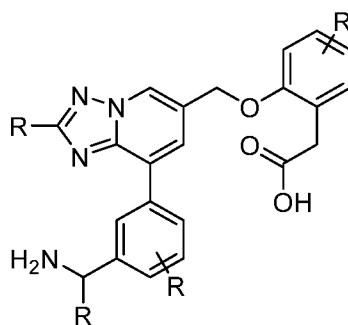


5

Prophetic Scaffold 40 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R₁ position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 40 may be prepared by using analogues approaches to the ones described for the preparation of Prophetic Scaffold 36, Prophetic Scaffold 39, and General Reaction Sequence 1 using 5-chloropyrazolo[1,5-*a*]pyridin-2-amine as the starting material.

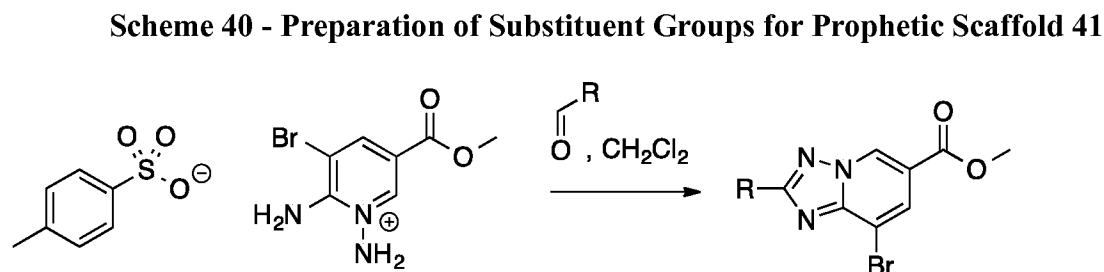
10

15

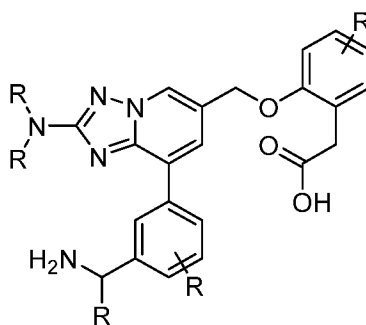
Prophetic Scaffold 41

Prophetic Scaffold 41 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 position can be derived from any commercially available aldehyde that may or may not be amenable for further functionalization.

Scheme 40 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 41. 1,2-Diamino-3-bromo-5-(methoxycarbonyl)pyridin-1-ium 4-methylbenzenesulfonate may be condensed with a base an aldehyde to deliver products as shown in Scheme 40. Compounds of Prophetic Scaffold 41 can be prepared following General Reaction Sequence 1 or General Reaction Sequence 2. For a representative literature procedure see - WO2015/105779 A1, 2015



Prophetic Scaffold 42

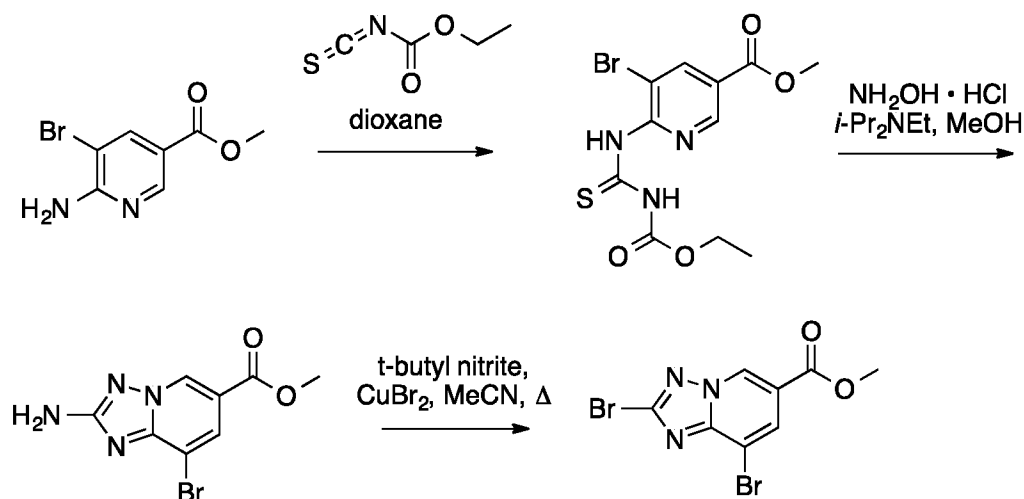


Prophetic Scaffold 42 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R₁ position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization.

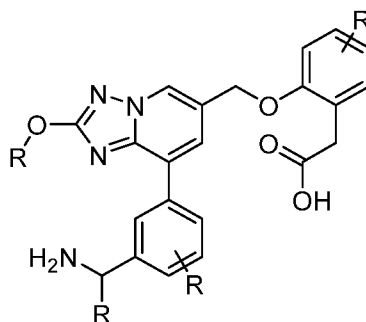
Scheme 41 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 42. Methyl 6-amino-5-

bromonicotinate may reacted with an isothiocyanate such as *O*-ethyl carbonisothiocyanatidate to deliver methyl 5-bromo-6-(3-(ethoxycarbonyl)thioureido)nicotinate. Methyl 5-bromo-6-(3-(ethoxycarbonyl)thioureido)nicotinate may reacted with hydroxylamine hydrochloride and a base such as N,N-diisopropylethylamine to deliver methyl 2-amino-8-bromo-[1,2,4]triazolo[1,5-*a*]pyridine-6-carboxylate. Methyl 2-amino-8-bromo-[1,2,4]triazolo[1,5-*a*]pyridine-6-carboxylate may undergo a Sandmeyer reaction using reagents such as *t*-butyl nitrite and copper(II) bromide to deliver methyl 2,8-dibromo-[1,2,4]triazolo[1,5-*a*]pyridine-6-carboxylate. Compounds of Prophetic Scaffold 42 may be prepared by using analogues approaches to the ones described for the preparation of Prophetic Scaffold 2. Compounds of Prophetic Scaffold 42 may also be prepared following General Reaction Sequence 1 or General Reaction Sequence 2 by using Methyl 2,8-dibromo-[1,2,4]triazolo[1,5-*a*]pyridine-6-carboxylate or methyl 2-amino-8-bromo-[1,2,4]triazolo[1,5-*a*]pyridine-6-carboxylate as the starting material. For representative literature procedures see - US2011/190269 A1, **2011**, and US2016/108039 A1, **2016**

Scheme 41 - Preparation of Substituent Groups for Prophetic Scaffold 42



Prophetic Scaffold 43

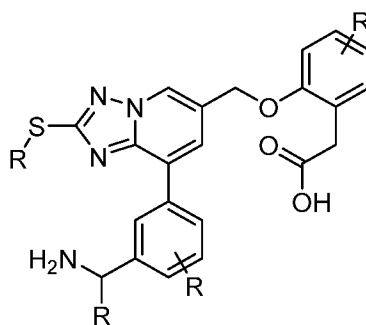


5

Prophetic Scaffold 43 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The ether group at the R_1 position can be derived from any commercially available alcohol or phenol that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 43 may be prepared by using analogues approaches to the ones described for the preparation of Prophetic Scaffold 8. Compounds of Prophetic Scaffold 43 may also be prepared following General Reaction Sequence 1 or General Reaction Sequence 2 by using methyl 2,8-dibromo-[1,2,4]triazolo[1,5-*a*]pyridine-6-carboxylate as the starting material.

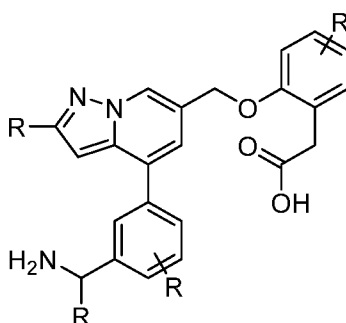
10

Prophetic Scaffold 44



Prophetic Scaffold 44 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The thioether group at the R₁ position can be derived from any commercially available thiol, alkyl or aromatic, that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 44 may be prepared by using analogues approaches to the ones described for the preparation of Prophetic Scaffold 9. Compounds of Prophetic Scaffold 44 may also be prepared following General Reaction Sequence 1 or General Reaction Sequence 2 by using methyl 2,8-dibromo-[1,2,4]triazolo[1,5-*a*]pyridine-6-carboxylate as the starting material.

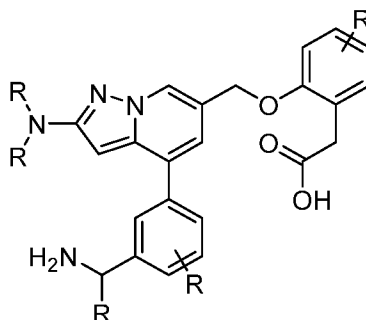
Prophetic Scaffold 45



Prophetic Scaffold 45 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R₁ position can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 45 may be prepared by using analogues approaches to the ones described for the preparation of Prophetic Scaffold 35, and General

Reaction Sequence 1 using 4,6-dibromopyrazolo[1,5-*a*]pyridin-2-amine as the starting material. For a representative literature procedure see - WO2015/114452 A2, 2015

Prophetic Scaffold 46

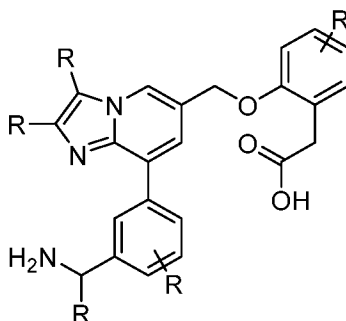


5

Prophetic Scaffold 46 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R₁ position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 46 and may be prepared by using analogues approaches to the ones described for the preparation of Prophetic Scaffold 35, Prophetic Scaffold 36, and General Reaction Sequence 1 using 4,6-dibromopyrazolo[1,5-*a*]pyridin-2-amine as the starting material.

10

15 Prophetic Scaffold 47



Prophetic Scaffold 47 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R₁ and R₂ positions can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for

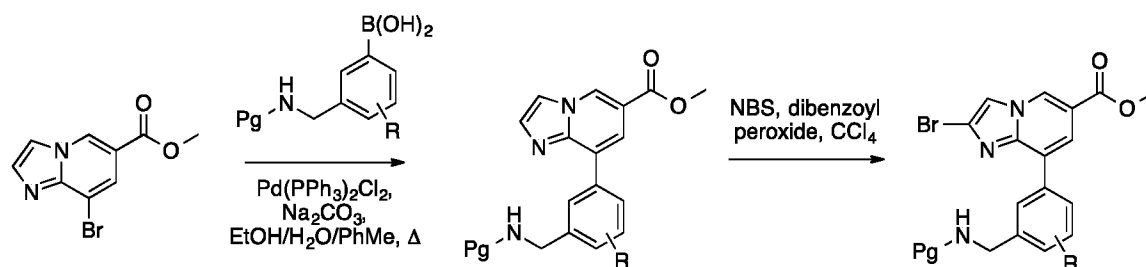
20

further functionalization (Scheme 42). Additionally, The substituents at the R₁ and R₂ positions can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization (Scheme 43).

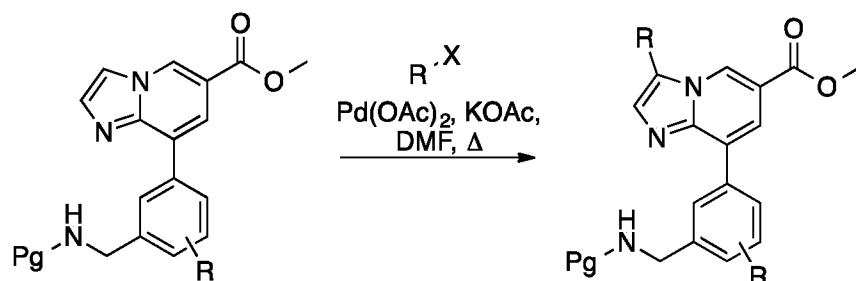
Scheme 42 provides details of the reactions available for the preparation of compounds useful for the preparation of compounds of Prophetic Scaffold 47. Methyl 8-bromoimidazo[1,2-*a*]pyridine-6-carboxylate may undergo a palladium catalyzed Suzuki cross-coupling with a boronic acid using a catalyst such as bis(triphenylphosphine)palladium(II) dichloride (Pd(PPh₃)₂Cl₂), and a base such as sodium carbonate (first step) to deliver intermediate compounds as shown in Scheme 42. Intermediate compounds may undergo a radical bromination with a bromine source such as N-bromosuccinimide and a radical initiator such as dibenzoyl peroxide to deliver products as shown in Scheme 42. Compounds of Prophetic Scaffold 47 may be prepared using analogues approaches and reaction conditions to the ones described for the preparation of Prophetic Scaffold 5 and General Reaction Sequence 1.

Scheme 43 provides an alternative synthetic route to for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 47. Compounds may undergo a direct cross coupling using a palladium catalyst such as palladium acetate, a base such as potassium acetate, and halide to generate products as shown in Scheme 43. Compounds of Prophetic Scaffold 47 may be prepared using analogues approaches and reaction conditions to the ones described for the preparation of Prophetic Scaffold 5 and General Reaction Sequence 1. For representative literature procedures see - Journal of Organic Chemistry, **2001**, vol. 66, # 20 p. 6576 – 6584, Journal of Organic Chemistry, **2012**, vol. 77, # 9 p. 4473 - 4478

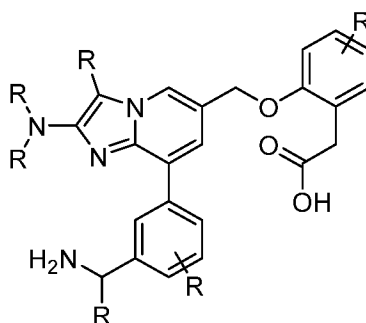
Scheme 42 - Preparation of Substituent Groups for Prophetic Scaffold 47



Scheme 43 - Preparation of Substituent Groups for Prophetic Scaffold 47



Prophetic Scaffold 48

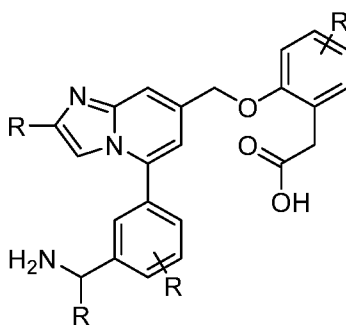


5

Prophetic Scaffold 48 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R_1 position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. The substituents at the R_2 position can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 48 where may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 2, Prophetic Scaffold 47 and General Reaction Sequence 1.

15

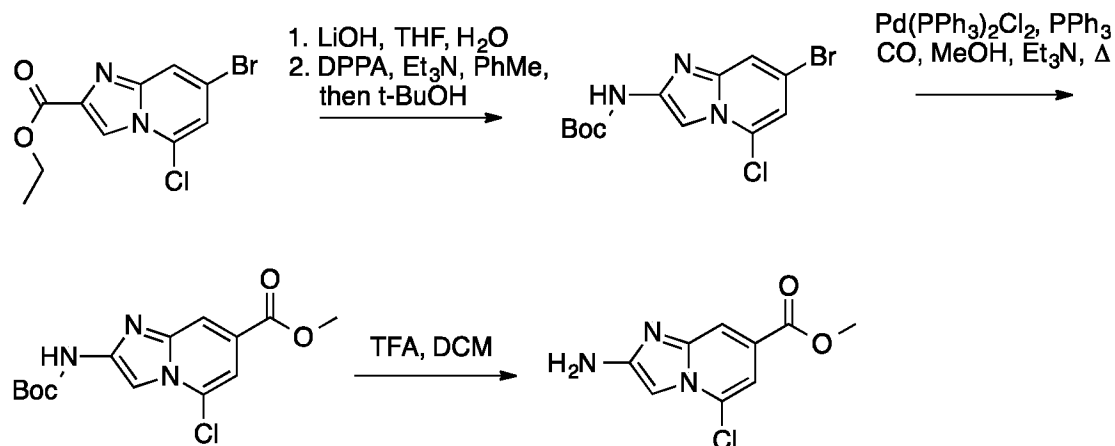
Prophetic Scaffold 49



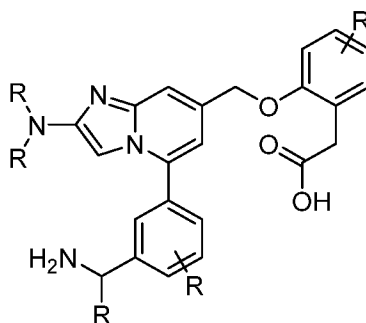
Prophetic Scaffold 49 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 position can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further functionalization.

Scheme 44 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 49. Ethyl 7-bromo-5-chloroimidazo[1,2-*a*]pyridine-2-carboxylate may undergo a saponification with a base such as lithium hydroxide. The resulting carboxylic acid may undergo a Curtius rearrangement with using reagents such as DPPA, a base such as triethylamine, and an alcohol such as *t*-butanol to generate *tert*-butyl (7-bromo-5-chloroimidazo[1,2-*a*]pyridin-2-yl)carbamate. *tert*-Butyl (7-bromo-5-chloroimidazo[1,2-*a*]pyridin-2-yl)carbamate may undergo a palladium catalyzed Suzuki cross-coupling with a boronic acid using a catalyst such as bis(triphenylphosphine)palladium(II) dichloride ($Pd(PPh_3)_2Cl_2$), and a base such as sodium carbonate to deliver intermediate compounds as shown in Scheme 44. Intermediate compounds may undergo Boc-deprotection using an acid such as trifluoroacetic acid to deliver products as shown in Scheme 44. Compounds of Prophetic Scaffold 48 may be prepared using analogous approaches and reaction conditions to the ones described for the preparation of Prophetic Scaffold 35, Prophetic Scaffold 36, General Reaction Sequence 1 and General Reaction Sequence 2. For representative literature procedures see - US2012/88750 A1, 2012, and WO2016/119700 A1, 2016

Scheme 44 - Preparation of Substituent Groups for Prophetic Scaffold 49



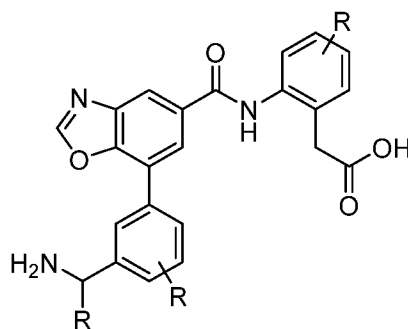
Prophetic Scaffold 50



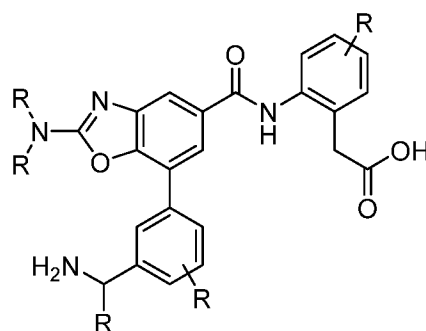
5

Prophetic Scaffold 50 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R₁ position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 50 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 2, Prophetic Scaffold 35, Prophetic Scaffold 36, General Reaction Sequence 1, and General Reaction Sequence 2 using methyl 2-((*tert*-butoxycarbonyl)amino)-5-chloroimidazo[1,2-*a*]pyridine-7-carboxylate or methyl 2-amino-5-chloroimidazo[1,2-*a*]pyridine-7-carboxylate as the starting material.

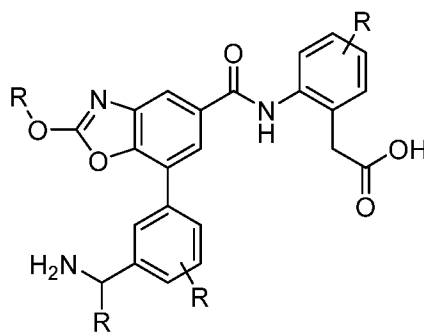
15

Prophetic Scaffold 51

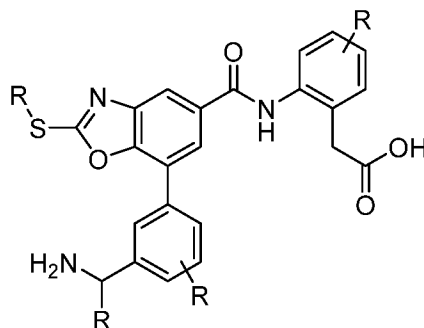
Prophetic Scaffold 51 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. Compounds of Prophetic Scaffold 51 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 1, Prophetic Scaffold 16, General Reaction Sequence 3, and General Reaction Sequence 4.

10 Prophetic Scaffold 52

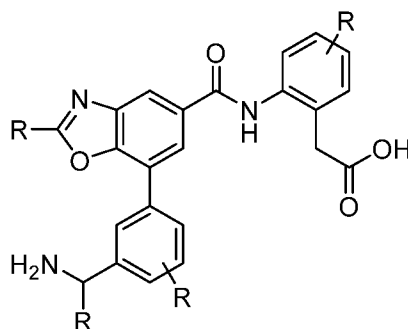
Prophetic Scaffold 52 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R_1 position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 52 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 2, Prophetic Scaffold 17, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 53

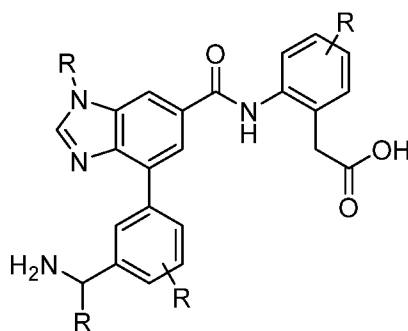
Prophetic Scaffold 53 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The ether group at the R_1 position can be derived from any commercially available alcohol or phenol that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 53 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 3, Prophetic Scaffold 18, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 54

Prophetic Scaffold 54 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The thioether group at the R_1 position can be derived from any commercially available thiol, alkyl or aromatic, that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 54 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 4, Prophetic Scaffold 19, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 55

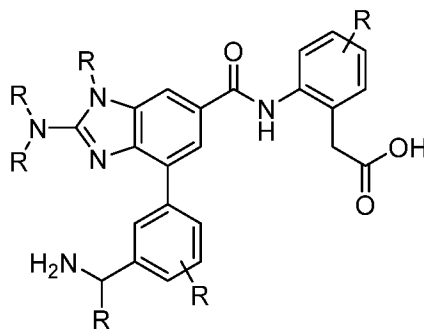
Prophetic Scaffold 55 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and
 5 Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the
 structures disclosed herein. The substituents at the R_1 position can be derived from any
 commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic
 acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further
 functionalization. Compounds of Prophetic Scaffold 55 may be prepared by using analogues
 10 approaches and reaction procedures to the ones described for the preparation of Prophetic
 Scaffold 5, Prophetic Scaffold 20, General Reaction Sequence 3, and General Reaction
 Sequence 4.

Prophetic Scaffold 56

Prophetic Scaffold 56 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and
 15 Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the
 structures disclosed herein. The substituents at the R_1 position can be derived from any
 commercially available alkyl halide, aryl halide, or heteroaryl halide that that may or may not
 20 be amenable for further functionalization. Compounds of Prophetic Scaffold 56 may be
 prepared by using analogues approaches and reaction procedures to the ones described for the

preparation of Prophetic Scaffold 6, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 57



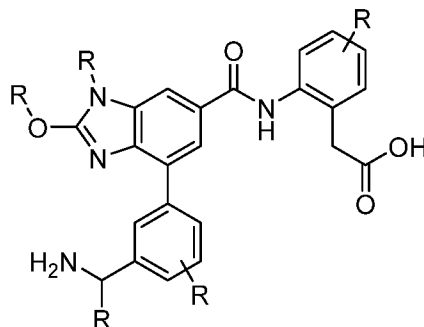
5

Prophetic Scaffold 57 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R_2 position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. Additionally, the substituents at the R_1 position can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 57 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 7, General Reaction Sequence 3, and General Reaction Sequence 4.

10

15

Prophetic Scaffold 58

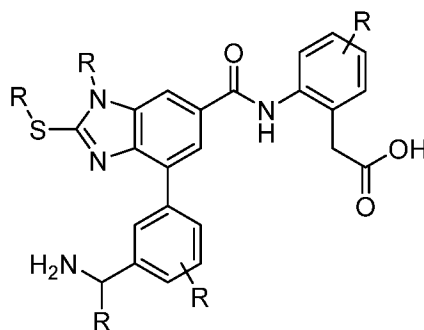


Prophetic Scaffold 58 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The ether group at the R_2 position can be derived from any

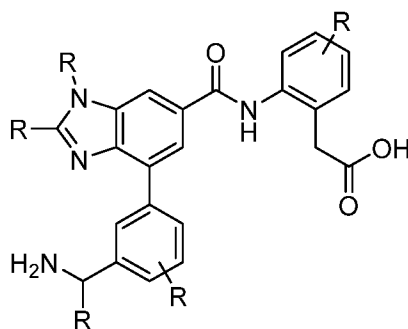
20

commercially available alcohol or phenol that may or may not be amenable for further functionalization. Additionally, the substituents at the R₁ position can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 58 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 8, General Reaction Sequence 3, and General Reaction Sequence 4.

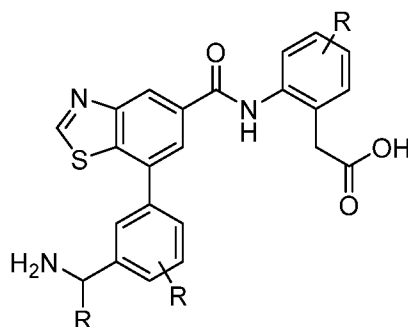
Prophetic Scaffold 59



Prophetic Scaffold 59 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The thioether group at the R₂ position can be derived from any commercially thiol, alkyl or aromatic, that may or may not be amenable for further functionalization. Additionally, the substituents at the R₁ position can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 59 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 9, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 60

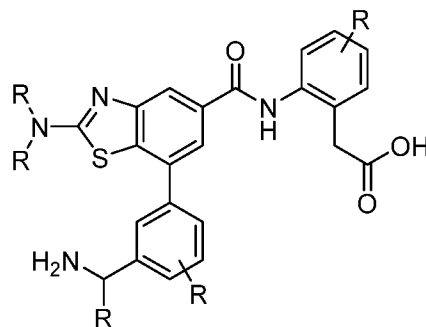
Prophetic Scaffold 60 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 and R_2 positions can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further functionalization. Alternatively, the substituents at the R_1 and R_2 positions can be derived from any commercially carboxylic acid or acyl chloride that may or may not be amenable for further functionalization. Additionally, the substituents at the R_1 and R_2 positions can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 60 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 10, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 61

Prophetic Scaffold 61 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. Compounds of Prophetic Scaffold 61 where may be prepared by

using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 11, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 62

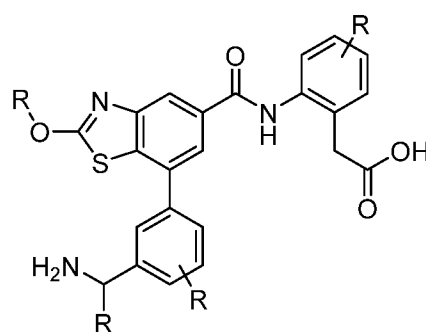


5

Prophetic Scaffold 62 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R₁ position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 62 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 12, General Reaction Sequence 3, and General Reaction Sequence 4.

10

Prophetic Scaffold 63



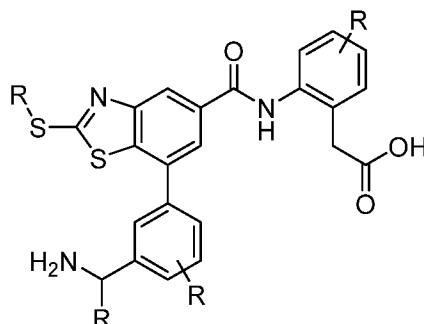
15

Prophetic Scaffold 63 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The ether group at the R₁ position can be derived from any commercially available alcohol or phenol that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 63 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic

20

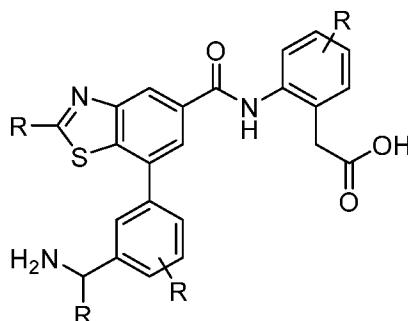
Scaffold 13, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 64



- 5 Prophetic Scaffold 64 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The thioether group at the R₁ position can be derived from any commercially available thiol, alkyl or aromatic, that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 64 may be prepared by using analogues
- 10 approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 14, General Reaction Sequence 3, and General Reaction Sequence 4.

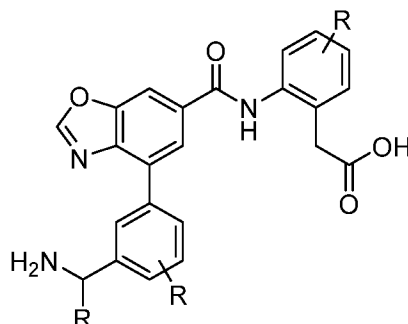
Prophetic Scaffold 65



- 15 Prophetic Scaffold 65 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R₁ position can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further
- 20 functionalization. Compounds of Prophetic Scaffold 65 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic

Scaffold 15, General Reaction Sequence 3, and General Reaction Sequence 4.

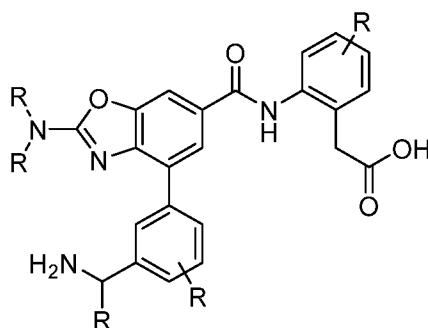
Prophetic Scaffold 66



- 5 Prophetic Scaffold 66 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. Compounds of Prophetic Scaffold 66 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 16, General Reaction Sequence 3, and General Reaction Sequence 4.

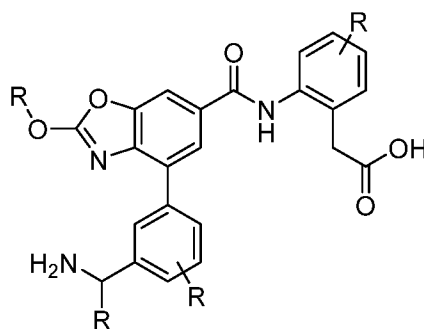
10

Prophetic Scaffold 67

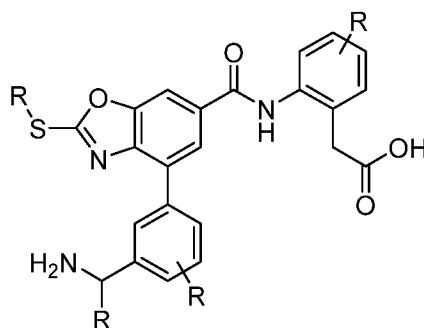


- 15 Prophetic Scaffold 67 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R_1 position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 67 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 17, General Reaction Sequence 3, and General Reaction Sequence 4.

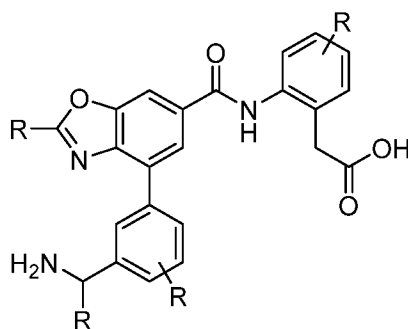
20

Prophetic Scaffold 68

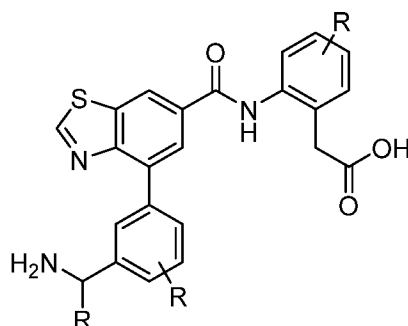
Prophetic Scaffold 68 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The ether group at the R_1 position can be derived from any commercially available alcohol or phenol that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 68 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 18, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 69

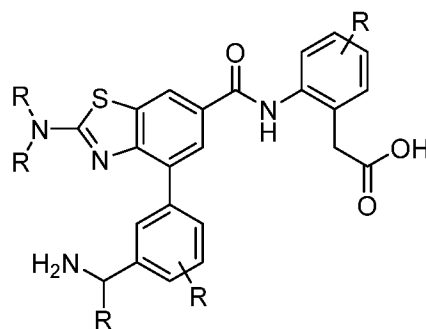
Prophetic Scaffold 69 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The thioether group at the R_1 position can be derived from any commercially available thiol, alkyl or aromatic, that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 69 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 19, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 70

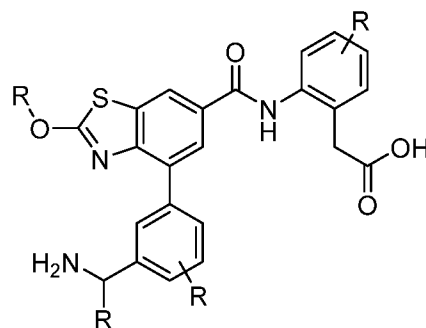
Prophetic Scaffold 70 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 position can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further functionalization. Alternatively, The substituents at the R_1 position can be derived from any commercially carboxylic acid or acyl chloride that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 70 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 20, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 71

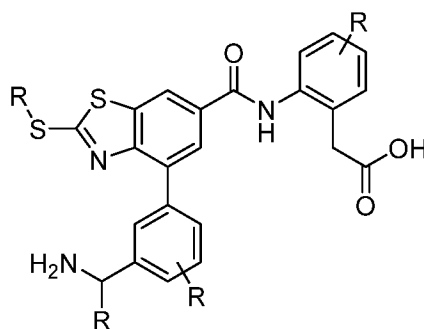
Prophetic Scaffold 71 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. Compounds of Prophetic Scaffold 71 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 21, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 72

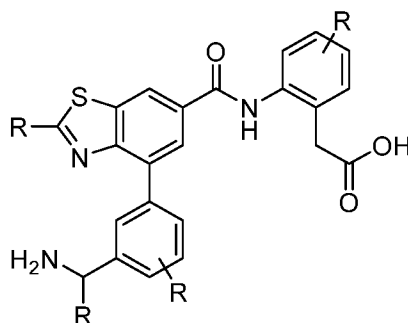
Prophetic Scaffold 72 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R_1 position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 72 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 22, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 73

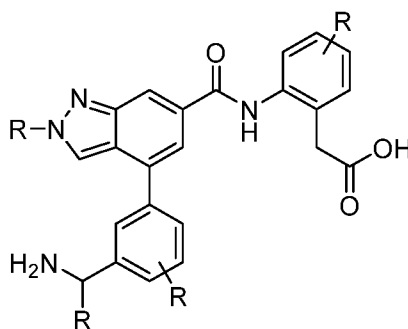
Prophetic Scaffold 73 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The ether group at the R_1 position can be derived from any commercially available alcohol or phenol that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 73 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 23, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 74

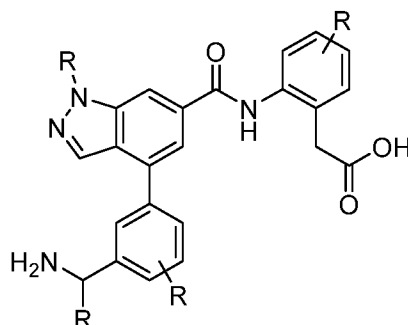
Prophetic Scaffold 74 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The thioether group at the R₁ position can be derived from any commercially available thiol, alkyl or aromatic, that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 74 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 24, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 75

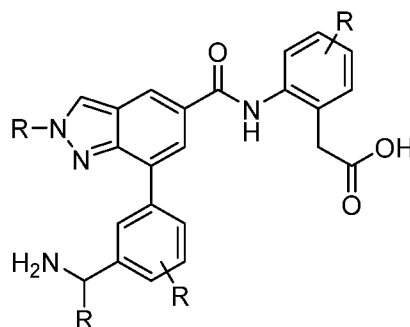
Prophetic Scaffold 75 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R₁ position can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 75 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 25, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 76

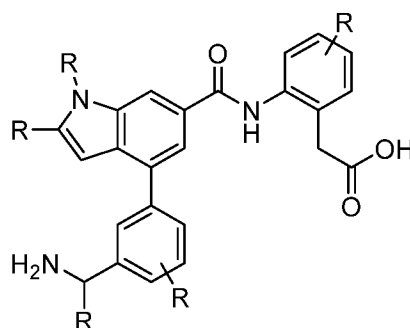
Prophetic Scaffold 76 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 position can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 76 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 26, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 77

Prophetic Scaffold 77 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_2 position can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 77 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 27, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 78

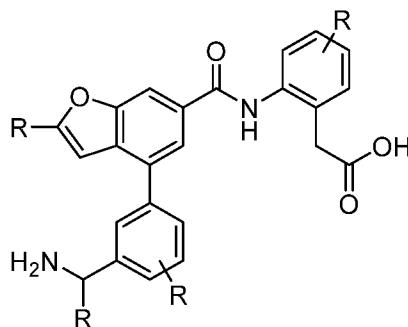
Prophetic Scaffold 78 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 position can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 78 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 28, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 79

Prophetic Scaffold 79 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 and R_2 positions can be derived from any commercially available alkyl halide, aryl halide, heteroaryl halide, alkenyl halide, or alkyne that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 79 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 29, General

Reaction Sequence 3, and General Reaction Sequence 4.

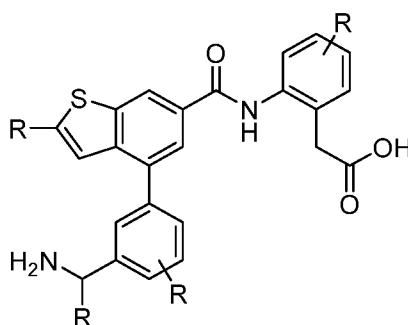
Prophetic Scaffold 80



- 5 Prophetic Scaffold 80 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R₁ position can be derived from any commercially available alkyl halide, aryl halide, heteroaryl halide, alkenyl halide, or alkyne that may or may not be amenable for further functionalization. Compounds of Prophetic
- 10 Scaffold 80 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 30, General Reaction Sequence 3, and General Reaction Sequence 4. In these cases, the benzylic halogenation (Scheme XX) should be substituted with a benzylic oxidation, which can be accomplished using oxidant, such as potassium permanganate or chromium (VI) oxide.

15

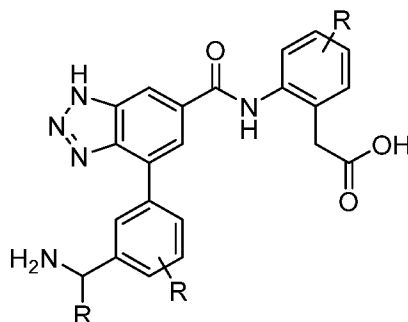
Prophetic Scaffold 81



- Prophetic Scaffold 81 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R₁ position can be derived from any commercially available alkyl halide, aryl halide, heteroaryl halide, alkenyl halide, or alkyne
- 20

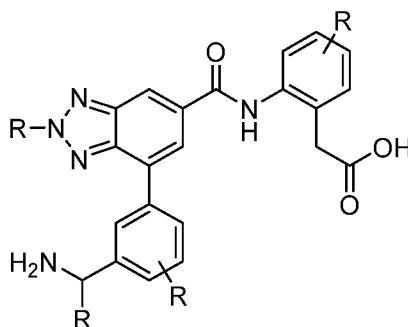
that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 81 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 31, General Reaction Sequence 3, and General Reaction Sequence 4. In these cases, the benzylic halogenation (Scheme XX) should be substituted with a benzylic oxidation, which can be accomplished using oxidant, such as potassium permanganate or chromium (VI) oxide.

Prophetic Scaffold 82



Prophetic Scaffold 82 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. Compounds of Prophetic Scaffold 82 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 32, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 83

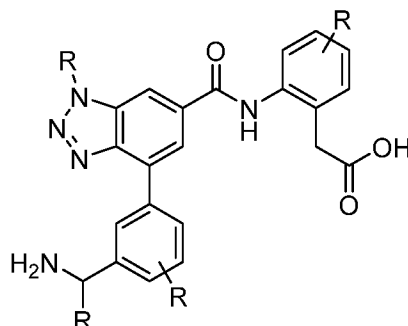


Prophetic Scaffold 83 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 position can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be

amenable for further functionalization. Compounds of Prophetic Scaffold 83 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 33, General Reaction Sequence 3, and General Reaction Sequence 4.

5

Prophetic Scaffold 84

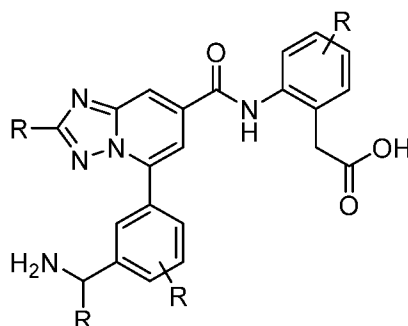


Prophetic Scaffold 84 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 position can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 84 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 34, General Reaction Sequence 3, and General Reaction Sequence 4.

10

15

Prophetic Scaffold 85



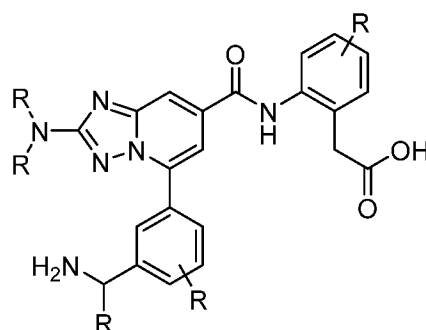
Prophetic Scaffold 85 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 position can be derived from any

20

commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 85 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic

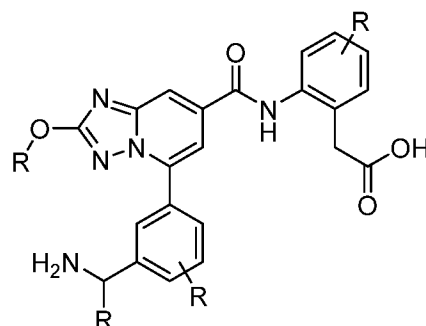
5 Scaffold 35, General Reaction Sequence 3, and General Reaction Sequence 2.

Prophetic Scaffold 86



Prophetic Scaffold 86 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and
 10 Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R₁ position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 86 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of
 15 Prophetic Scaffold 36, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 87

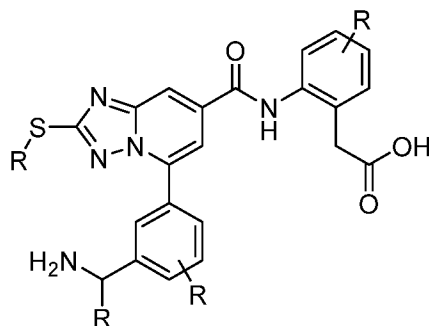


Prophetic Scaffold 87 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and
 20 Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The ether group at the R₁ position can be derived from any

commercially available alcohol or phenol that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 87 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 37, General Reaction Sequence 3, and General Reaction Sequence 4.

5

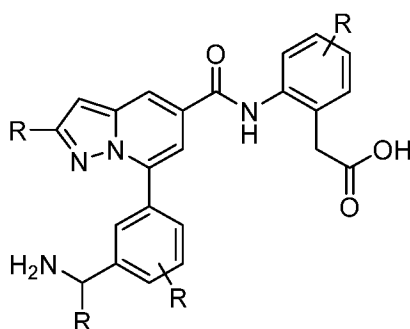
Prophetic Scaffold 88



Prophetic Scaffold 88 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The thioether group at the R_1 position can be derived from any commercially available thiol, alkyl or aromatic, that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 88 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 38, General Reaction Sequence 3, and General Reaction Sequence 4.

15

Prophetic Scaffold 89



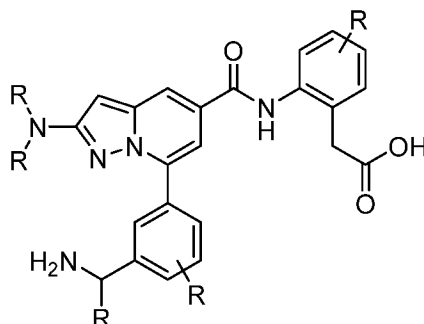
Prophetic Scaffold 89 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 position can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic

20

acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 89 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 39, General Reaction Sequence 3, and General Reaction Sequence 4.

5

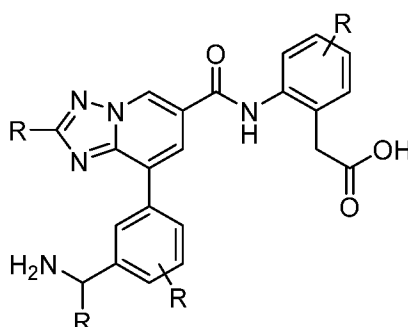
Prophetic Scaffold 90



Prophetic Scaffold 90 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R_1 position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 90 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 40, General Reaction Sequence 3, and General Reaction Sequence 4.

15

Prophetic Scaffold 91

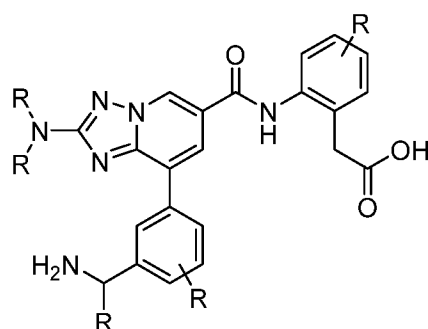


Prophetic Scaffold 91 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 position can be derived from any commercially available aldehyde that may or may not be amenable for further

20

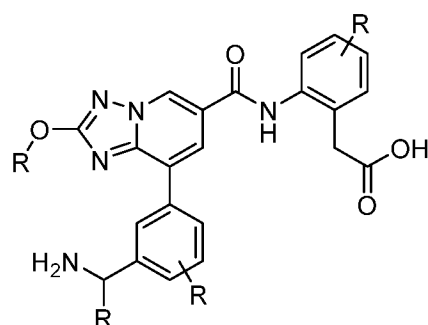
functionalization. Compounds of Prophetic Scaffold 91 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 41, General Reaction Sequence 3, and General Reaction Sequence 4.

5 Prophetic Scaffold 92



Prophetic Scaffold 92 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R₁ position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 92 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 42, General Reaction Sequence 3, and General Reaction Sequence 4.

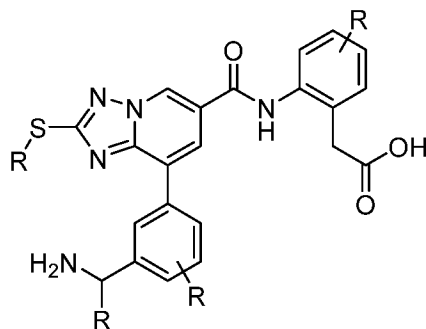
15 Prophetic Scaffold 93



Prophetic Scaffold 93 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The ether group at the R₁ position can be derived from any commercially available alcohol or phenol that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 93 may be prepared by using analogues

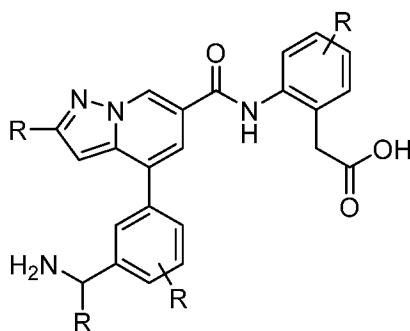
approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 43, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 94



Prophetic Scaffold 94 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The thioether group at the R₁ position can be derived from any commercially available thiol, alkyl or aromatic, that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 94 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 44, General Reaction Sequence 3, and General Reaction Sequence 4.

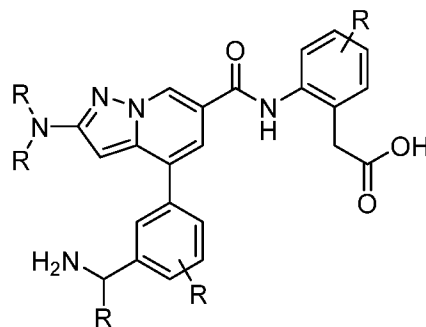
Prophetic Scaffold 95



Prophetic Scaffold 95 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R₁ position can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 95 may be prepared by using analogues

approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 45, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 96

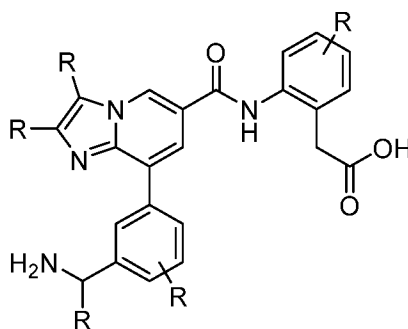


5

Prophetic Scaffold 96 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R_1 position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 96 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 46, General Reaction Sequence 3, and General Reaction Sequence 4.

10

Prophetic Scaffold 97



15

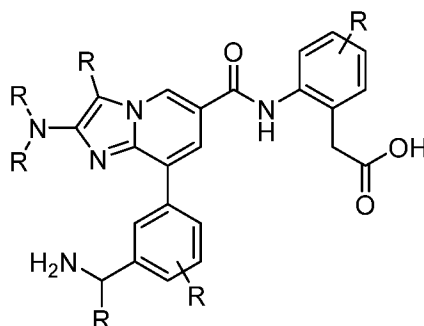
Prophetic Scaffold 97 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 and R_2 positions can be derived from any commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further functionalization. Additionally, The substituents at the R_1 and R_2 positions can be

20

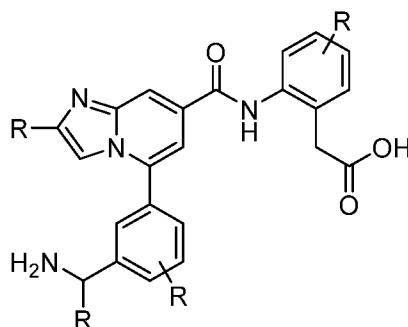
derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 97 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 47, General Reaction Sequence 3, and

5 General Reaction Sequence 4.

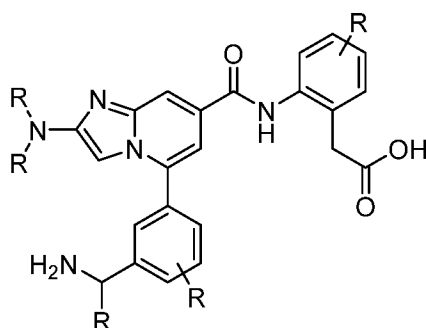
Prophetic Scaffold 98



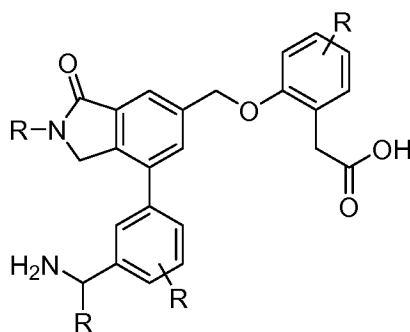
Prophetic Scaffold 98 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and
10 Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The amino group at the R₁ position can be derived from any commercially available primary or secondary amine that may or may not be amenable for further functionalization. Additionally, the substituent at the R₂ position can be derived from
15 any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 98 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 48, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 99

Prophetic Scaffold 99 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and
5 Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the
structures disclosed herein. The substituents at the R_1 position can be derived from any
commercially available alkyl boronic acid/ester, aryl boronic acid/ester, heteroaryl boronic
acid/ester, alkenyl boronic acid/ester, or alkyne that may or may not be amenable for further
functionalization. Compounds of Prophetic Scaffold 99 may be prepared by using analogues
10 approaches and reaction procedures to the ones described for the preparation of Prophetic
Scaffold 49, General Reaction Sequence 3, and General Reaction Sequence 4.

Prophetic Scaffold 100

Prophetic Scaffold 100 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and
15 Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the
structures disclosed herein. The amino group at the R_1 position can be derived from any
commercially available primary or secondary amine that may or may not be amenable for
further functionalization. Compounds of Prophetic Scaffold 100 may be prepared by using
analogues approaches and reaction procedures to the ones described for the preparation of
20 Prophetic Scaffold 50, General Reaction Sequence 3, and General Reaction Sequence 4.

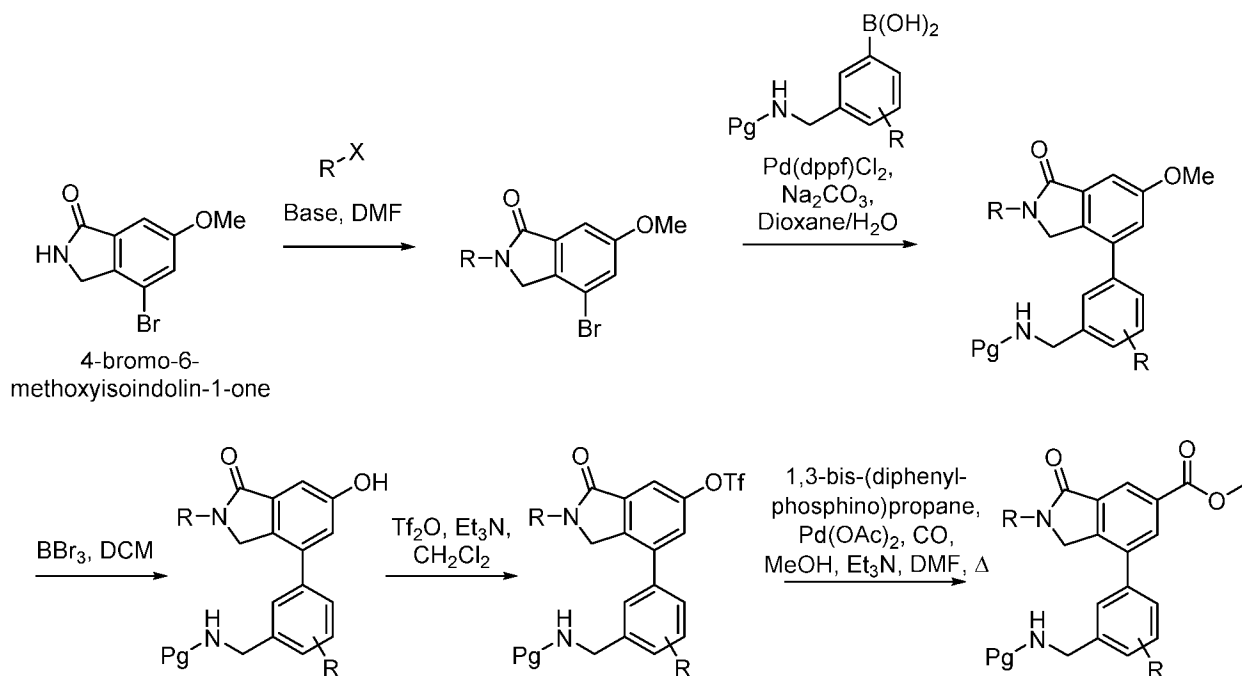
Prophetic Scaffold 101

Prophetic Scaffold 101 may consist of any combination of benzylic amines Aryl 1 (Ar₁) and Aryl 2 (Ar₂) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R₁ position can be derived from any commercially available alkyl halide, aryl halide, or heteroaryl halide that may or may not be amenable for further functionalization.

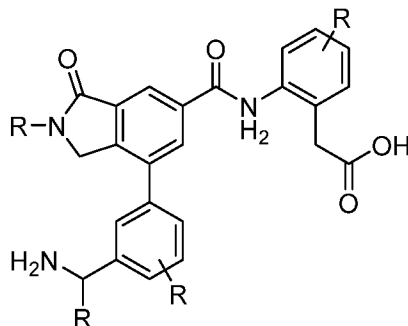
Scheme 45 provides details of the reactions available for the preparation of compounds that can be used to prepare compounds of Prophetic Scaffold 101. 4-Bromo-6-methoxyisoindolin-1-one may undergo alkylation with an electrophile and a base such as sodium hydride or cesium carbonate (first step) to deliver intermediate compounds as shown in Scheme 45. Intermediate compounds may undergo a palladium catalyzed Suzuki cross-coupling with a boronic acid using a catalyst such as Pd(dppf)Cl₂, and a base such as sodium carbonate (second step) to deliver intermediate compounds as shown in Scheme 45.

Intermediate compounds may be dealkylated using boron tribromide (third step) to deliver intermediate compounds as shown in Scheme 45. Intermediate compounds may be reacted with triflic anhydride and a base such as trimethylamine (fourth step) to deliver intermediate compounds as shown in Scheme 45. Intermediate compounds may undergo alkoxycarbonylation with a palladium catalyst such as palladium acetate (Pd(OAc)₂), a ligand such as 1,3-bis-(diphenylphosphino)propane, a source of carbon monoxide such as carbon monoxide gas, an alcohol such as methanol, and a base such as trimethylamine (fifth step) to generate products as shown in Scheme 45. Compounds of Prophetic Scaffold 101 can be prepared following General Reaction Sequence 1. For representative literature procedures see - WO2004/108672 A1, **2004**, WO2011/163610 A2, **2011**, and WO2005/58301 A1, **2005**

Scheme 45- Preparation of Substituent Groups for Prophetic Scaffold 101



5 Prophetic Scaffold 102



Prophetic Scaffold 102 may consist of any combination of benzylic amines Aryl 1 (Ar_1) and Aryl 2 (Ar_2) as described above. The R groups shown in the structure are consistent with the structures disclosed herein. The substituents at the R_1 position can be derived from any commercially available thiol, alkyl or aromatic, that may or may not be amenable for further functionalization. Compounds of Prophetic Scaffold 102 may be prepared by using analogues approaches and reaction procedures to the ones described for the preparation of Prophetic Scaffold 102, and General Reaction Sequence 3.

Biological Examples

Factor D cleavage of factor B TR-FRET assay

Serial dilutions of small molecule inhibitors (SMI's) were prepared in DMSO at 200x their final concentration in the assay. 2 μ L of these curves were then transferred into 98 μ L New Enzymatic Reaction Buffer (ERB; 75 mM NaCl, 1 mM MgCl₂, 25 mM Tris, 0.005% polysorbate 20, pH 7.3) to achieve a 4X concentration in 2% DMSO. After thoroughly mixing, the diluted compound curves were combined in equal volumes with 12.5 ng/mL (0.5 nM) Factor D (fD, Complement Technology; Tyler, TX) or ERB (no enzyme control) and incubated at room temperature, shaking, for 1 hour. The fD/SMI mixtures (7 μ L/well) were added to 384-well Proxypate F plus black plates (Perkin Elmer Health Sciences; Waltham, MA) followed by 7 μ L/well of substrate; the final in-well fD concentration was 125 pM. The substrate consisted of a mixture of C3b (Complement Technology) at 7 μ g/mL (39.7 nM) and factor B (Complement Technology) at 1 μ g/mL (10.8 nM). The SMI's, enzyme, and substrate were incubated for 45 min at room temperature with gentle agitation. The reaction was stopped with 7 μ L/well of a detection reagent cocktail mixture consisting of biotinylated anti-factor Bb (2F12, GNE PRO282909) at 8 nM, Europium-conjugated anti-factor Ba (custom conjugation of 1C3, GNE PRO282908 by Life Technologies; Madison, WI) at 4 nM, and streptavidin-Alexa 647 at 25 nM. The plate was incubated at room temperature in the dark for 60 min. Time-resolved fluorescence energy transfer was detected with a PHERAstar FS or CLARIOstar microplate reader (BMG LabTech; Cary, NC) by exciting at 337 nm and detecting Europium emission at 620 nm and Alexa fluor emission at 665 nm. The inhibitor concentrations causing half-maximal inhibition (IC₅₀) were determined by nonlinear regression analysis using a four-parameter fit model (KaleidaGraph Synergy Software; Reading, PA or GraphPad Prism). Table 3 below provides Factor D IC₅₀ values for representative compounds of the present invention.

Table 3. Factor D IC₅₀ (μ M) values for representative compounds of the present invention.

Example	IC ₅₀ (μ M)
1	0.024
2	0.144
3	0.037

4	0.0025
5	0.015
6	0.0321
7	
8	0.0298
9	0.0052
10	0.0053
11	
12	

Blank = not determined

The features disclosed in the foregoing description, or the following claims, expressed in their specific forms or in terms of a means for performing the disclosed function, or a method or process for attaining the disclosed result, as appropriate, may, separately, or in any combination of such features, be utilized for realizing the invention in diverse forms thereof.

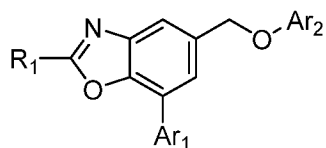
The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

The patents, published applications, and scientific literature referred to herein establish the knowledge of those skilled in the art and are hereby incorporated by reference in their entirety to the same extent as if each was specifically and individually recited herein.

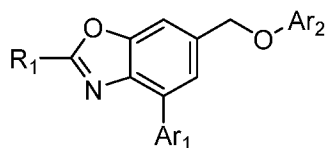
* * * * *

What is claimed is:

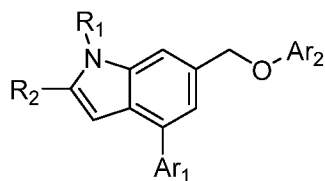
1. A compound having a structure selected from the group consisting of:



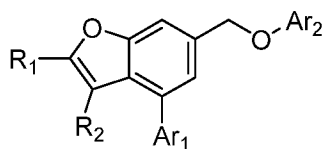
(I-A),



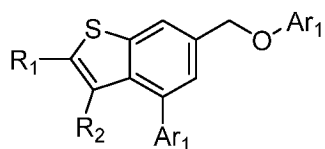
(II-A),



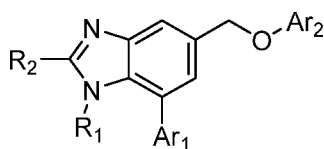
(III-A),



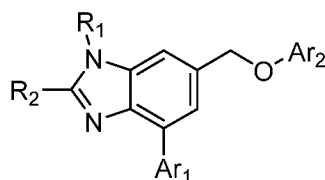
(IV-A),



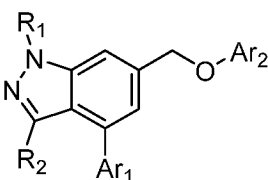
(V-A),



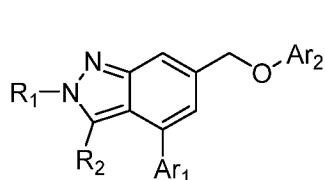
(VI-A),



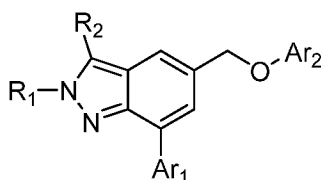
(VII-A),



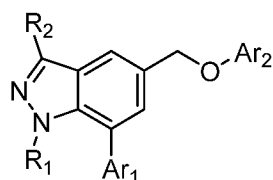
(VIII-A),



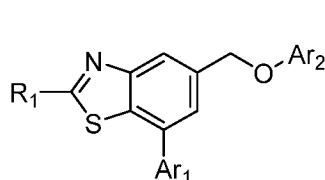
(IX-A),



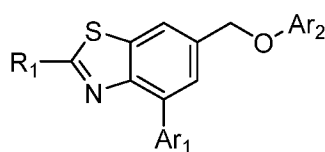
(X-A),



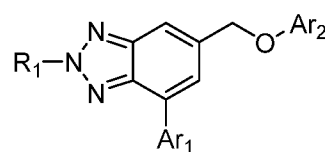
(XI-A),



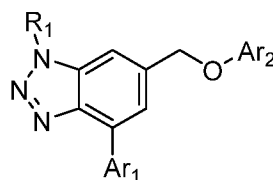
(XII-A),



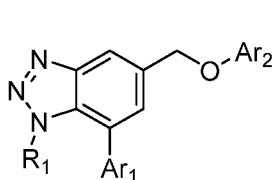
(XIII-A),



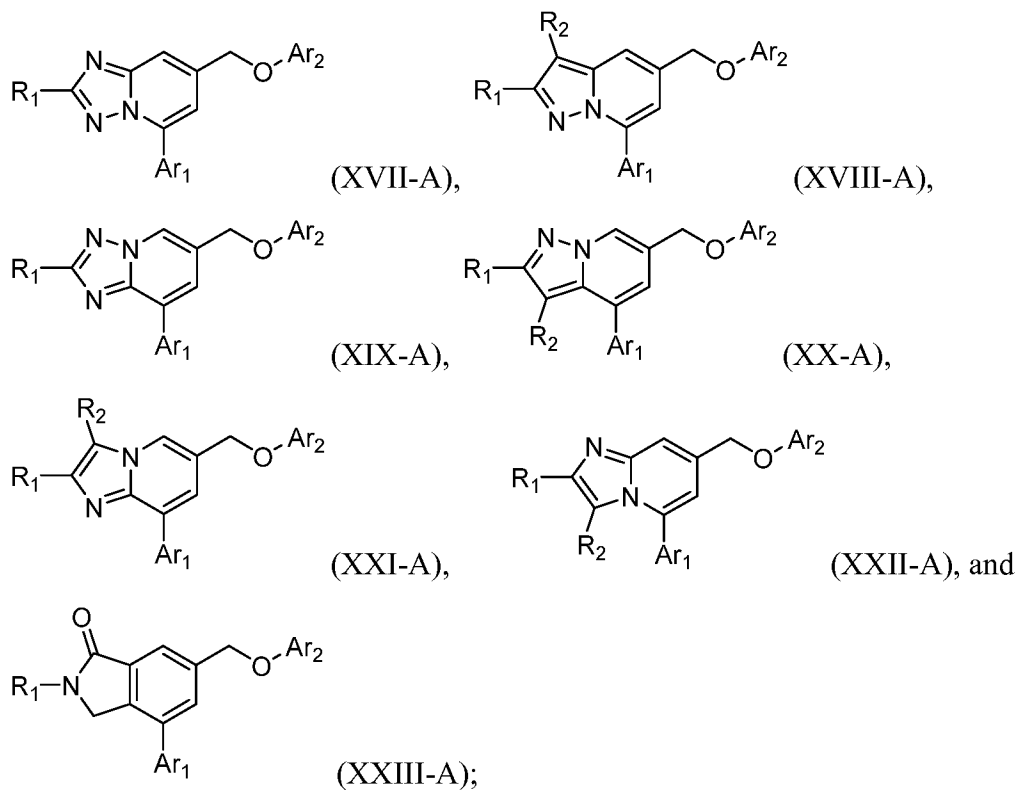
(XIV-A),



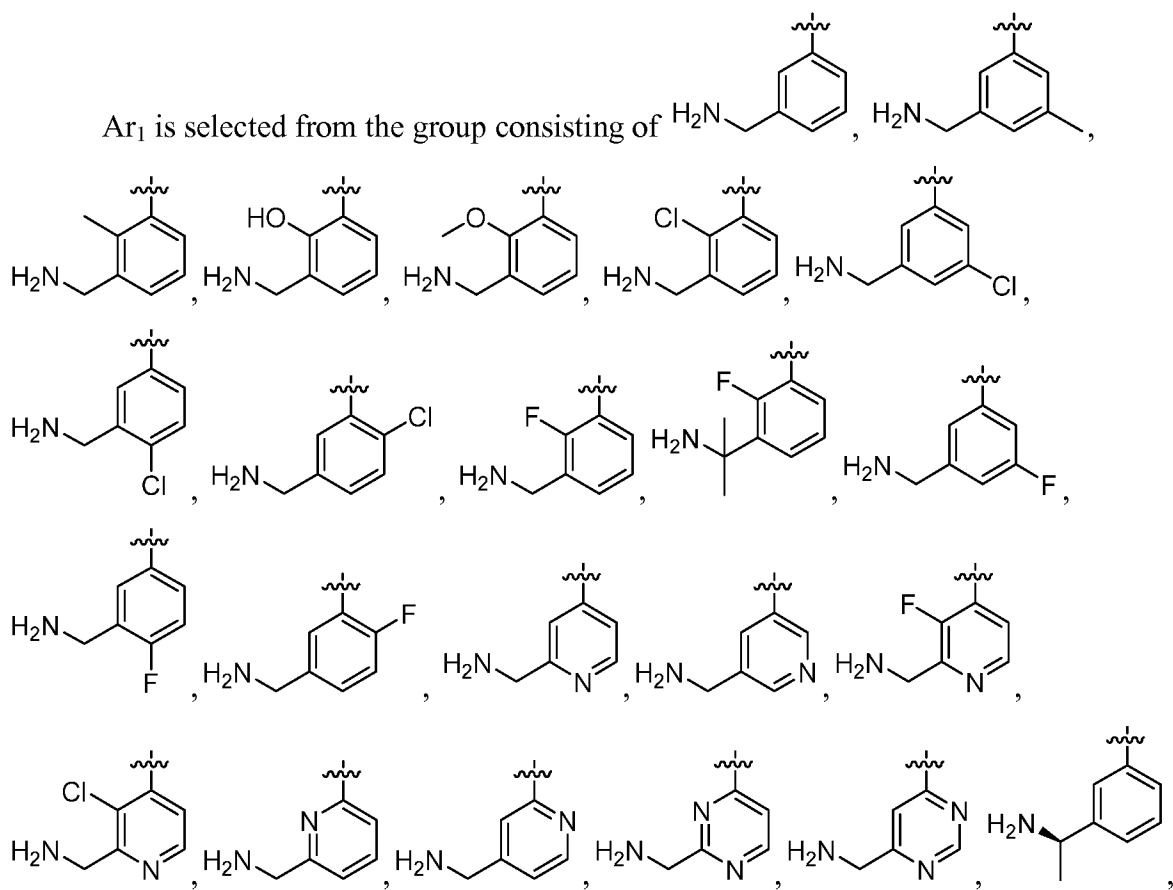
(XV-A),

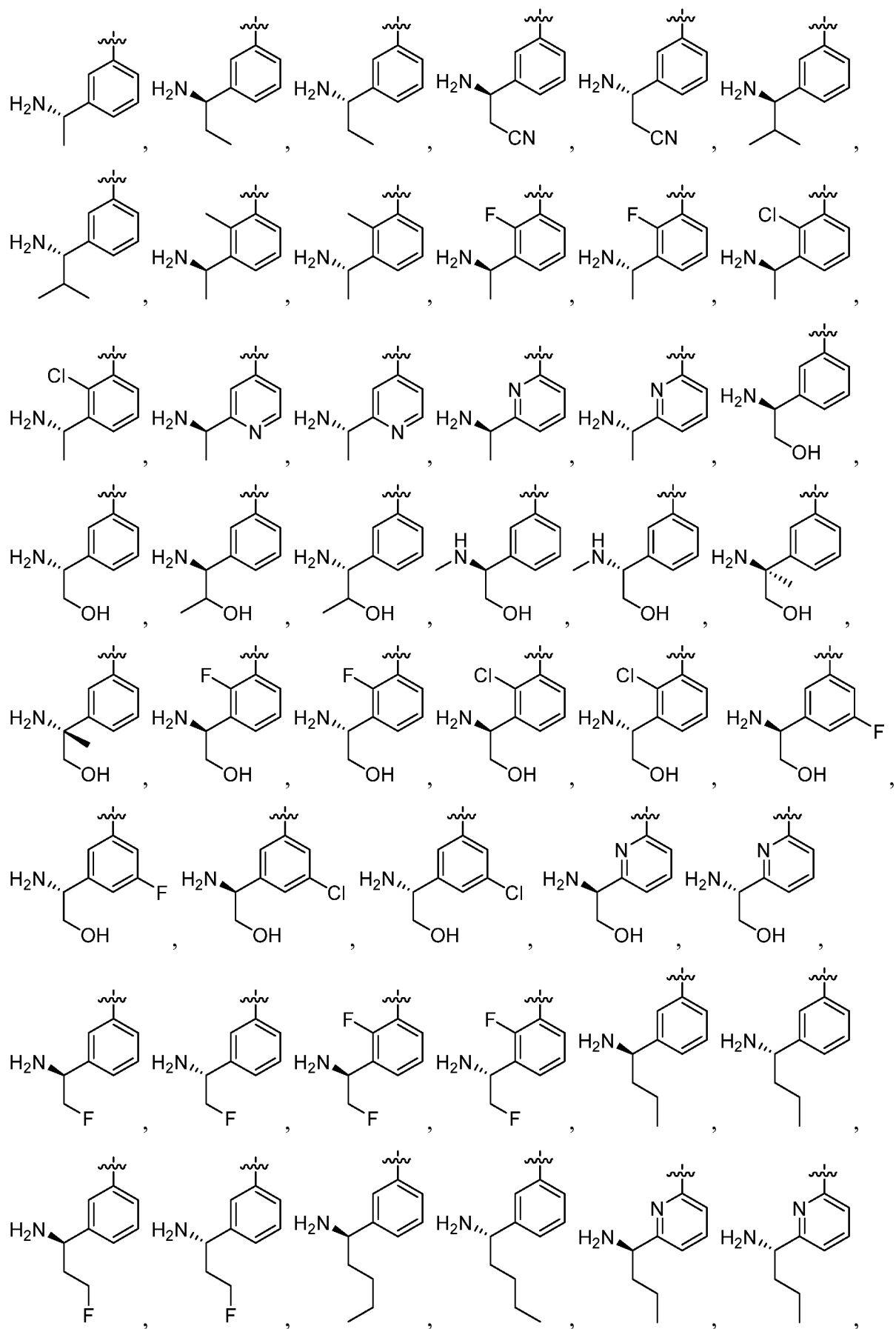


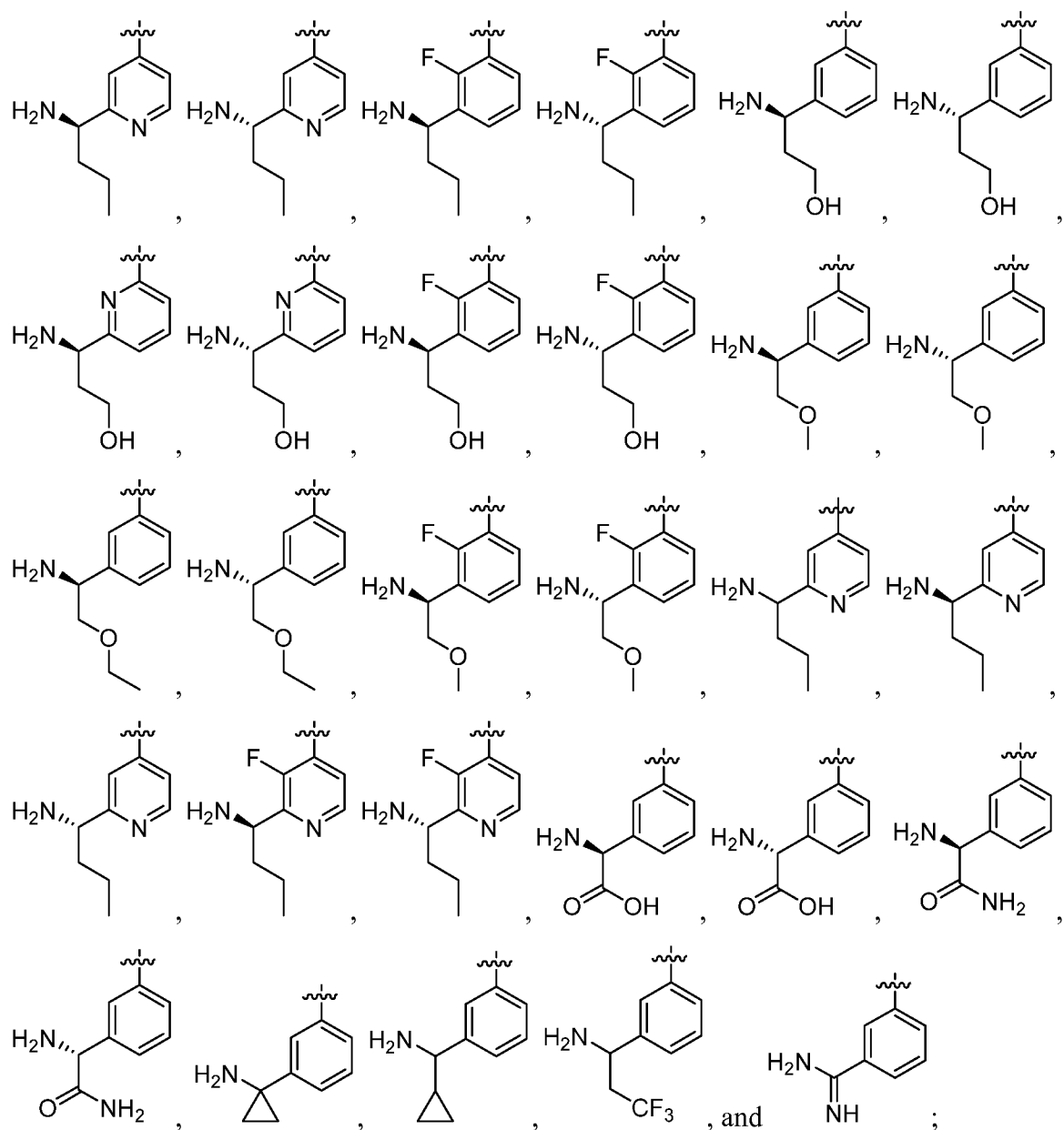
(XVI-A),



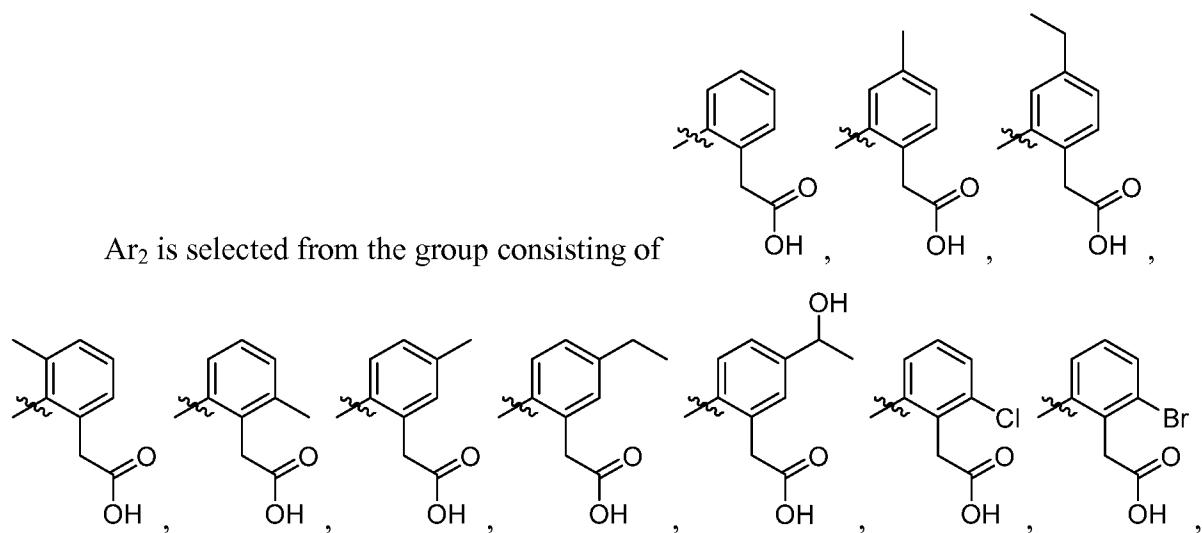
or a stereoisomer or a pharmaceutically acceptable salt thereof, wherein:

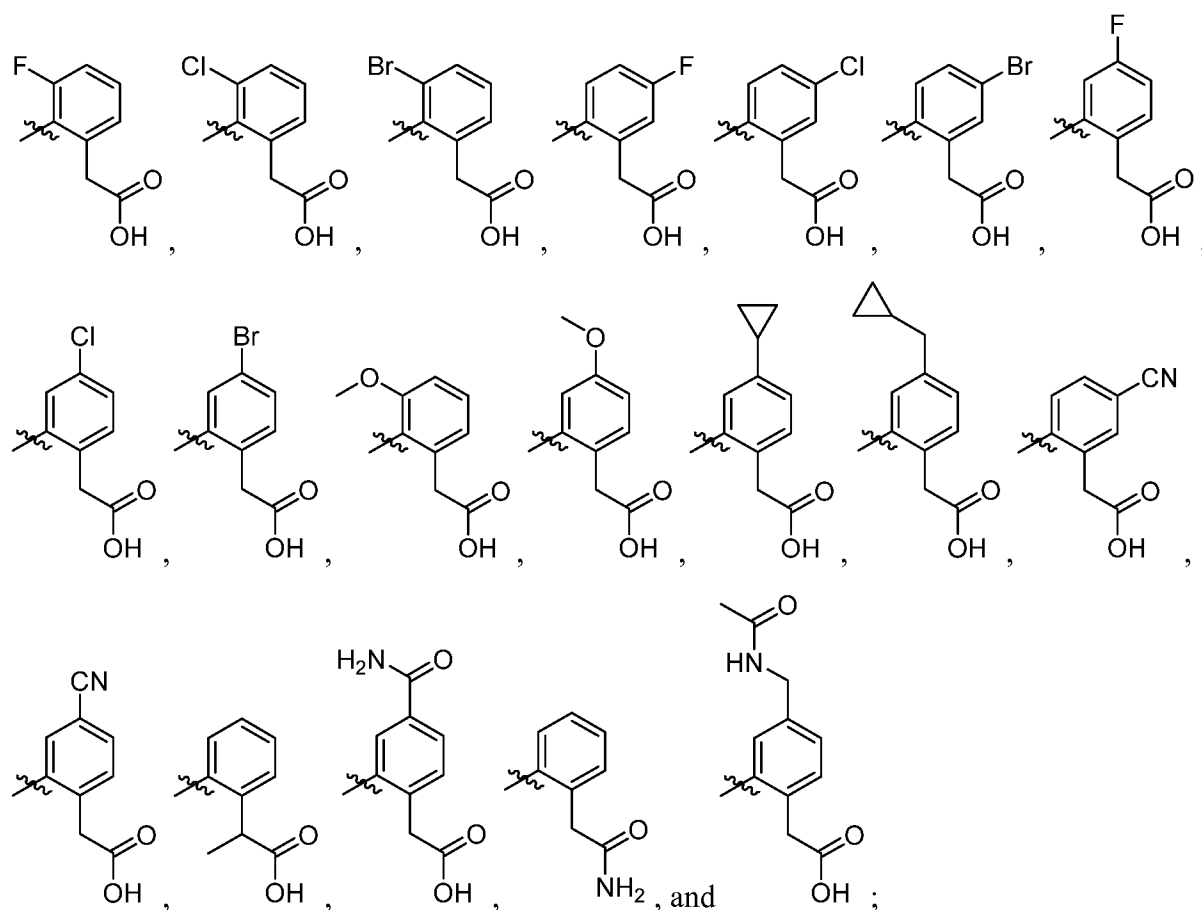






Ar₂ is selected from the group consisting of

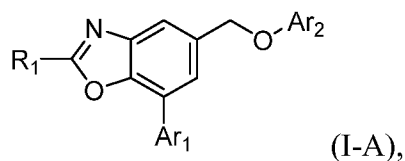




each R_1 and R_2 are independently selected from the group consisting of hydrogen, halo, cyano, $-OR_3$, $-SR_3$, $-NR_3R_4$, $-C(O)R_3$, $-C(O)OR_3$, $-C(O)NR_3R_4$, $-S(O)_2R_3$, C_1 - C_6 alkyl optionally substituted with R_3 , C_6 - C_{14} aryl optionally substituted with R_3 , and C_5 - C_{14} heteroaryl optionally substituted with R_3 ; and

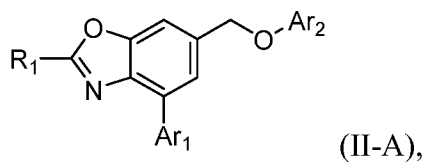
each R_3 and R_4 are independently selected from the group consisting of hydrogen, $-NH_2$, C_1 - C_6 alkyl, C_6 - C_{12} aryl, and C_5 - C_{14} heteroaryl.

2. The compound of claim 1 having the structure



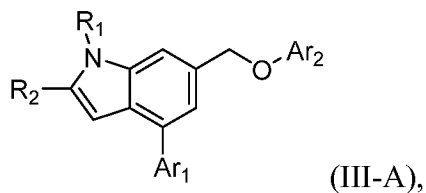
or a stereoisomer or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 having the structure



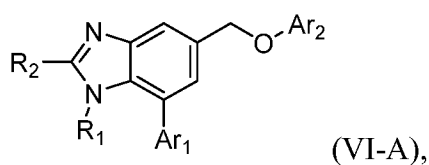
or a stereoisomer or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1 having the structure



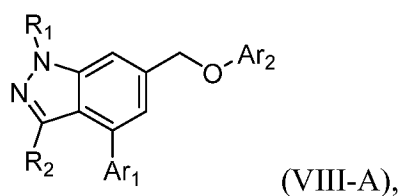
or a stereoisomer or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1 having the structure



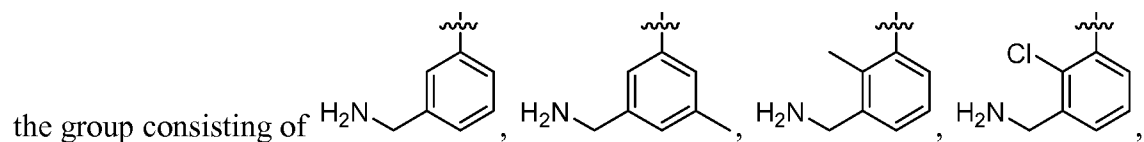
or a stereoisomer or a pharmaceutically acceptable salt thereof.

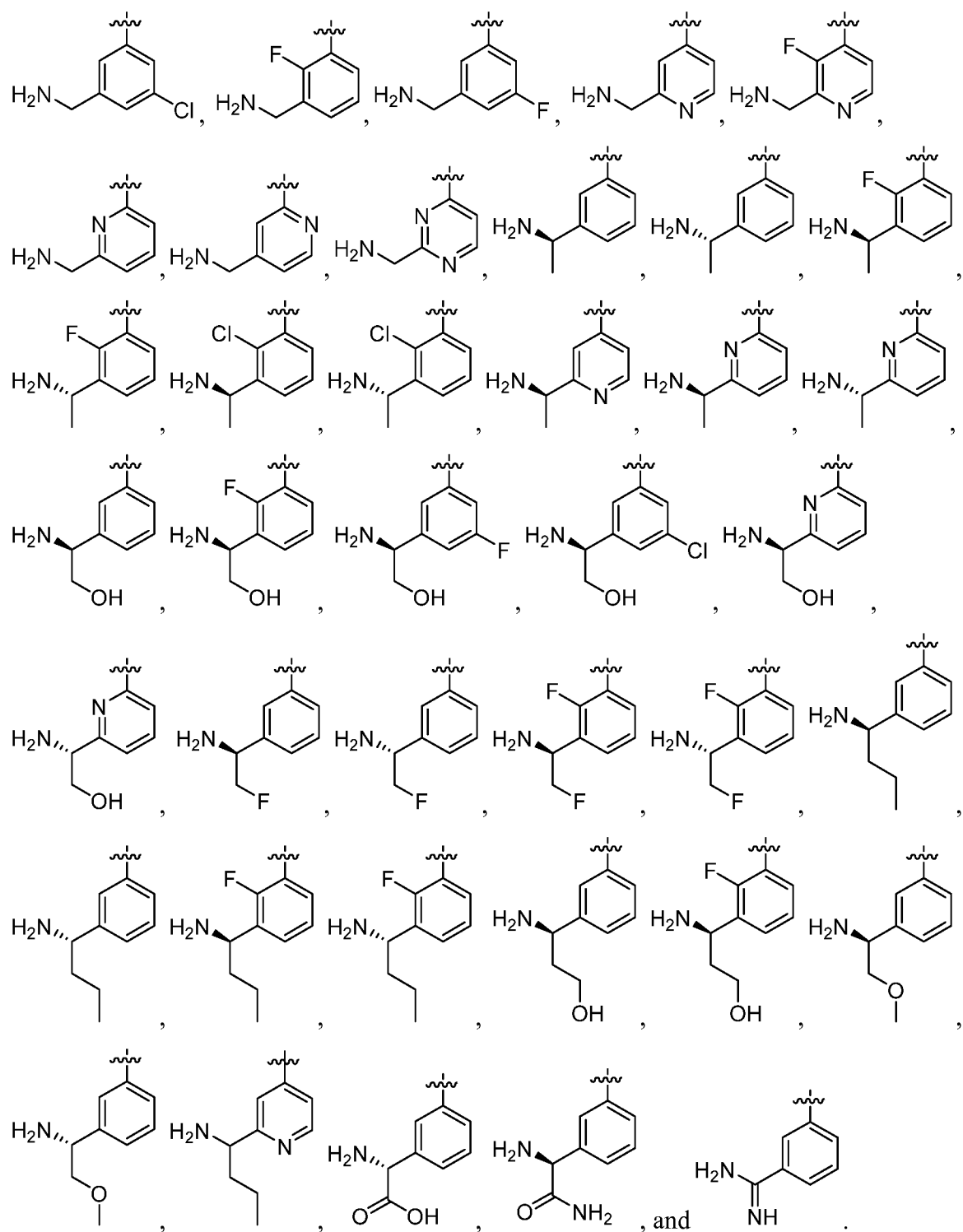
6. The compound of claim 1 having the structure



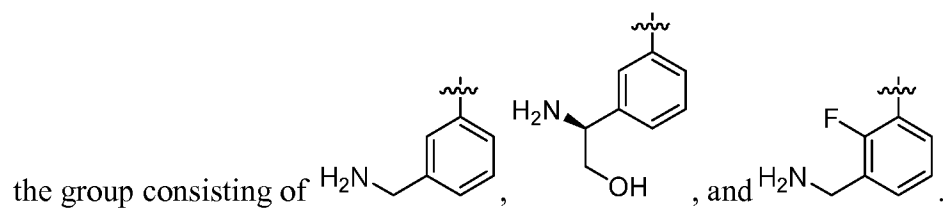
or a stereoisomer or a pharmaceutically acceptable salt thereof.

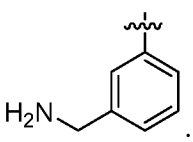
7. The compound of any one of claims 1 through 6 wherein Ar₁ is selected from



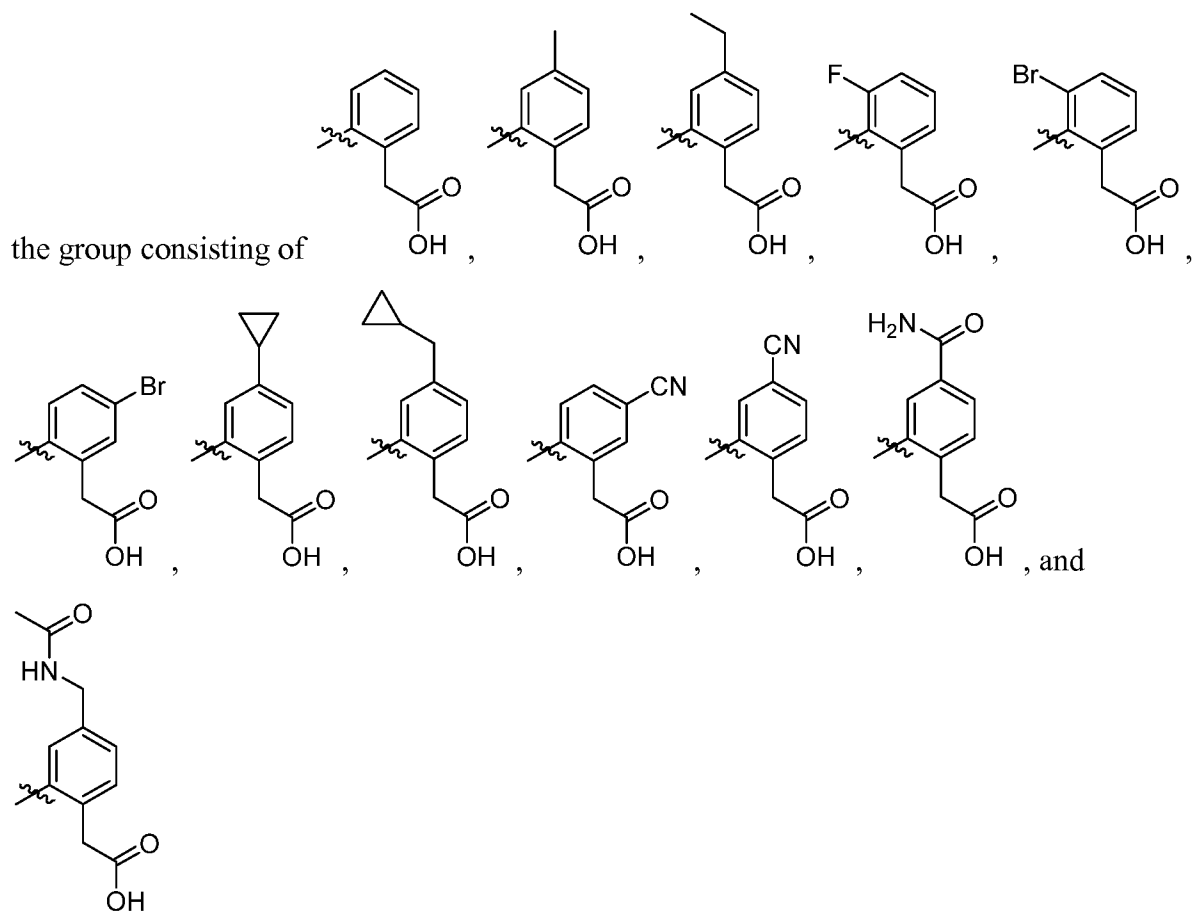


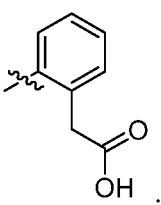
8. The compound of any one of claims 1 through 6 wherein Ar₁ is selected from



9. The compound of any one of claims 1 through 6 wherein Ar₁ is .

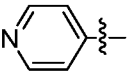
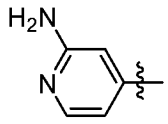
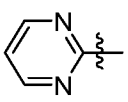
10. The compound of any one of claims 1 through 9 wherein Ar₂ is selected from



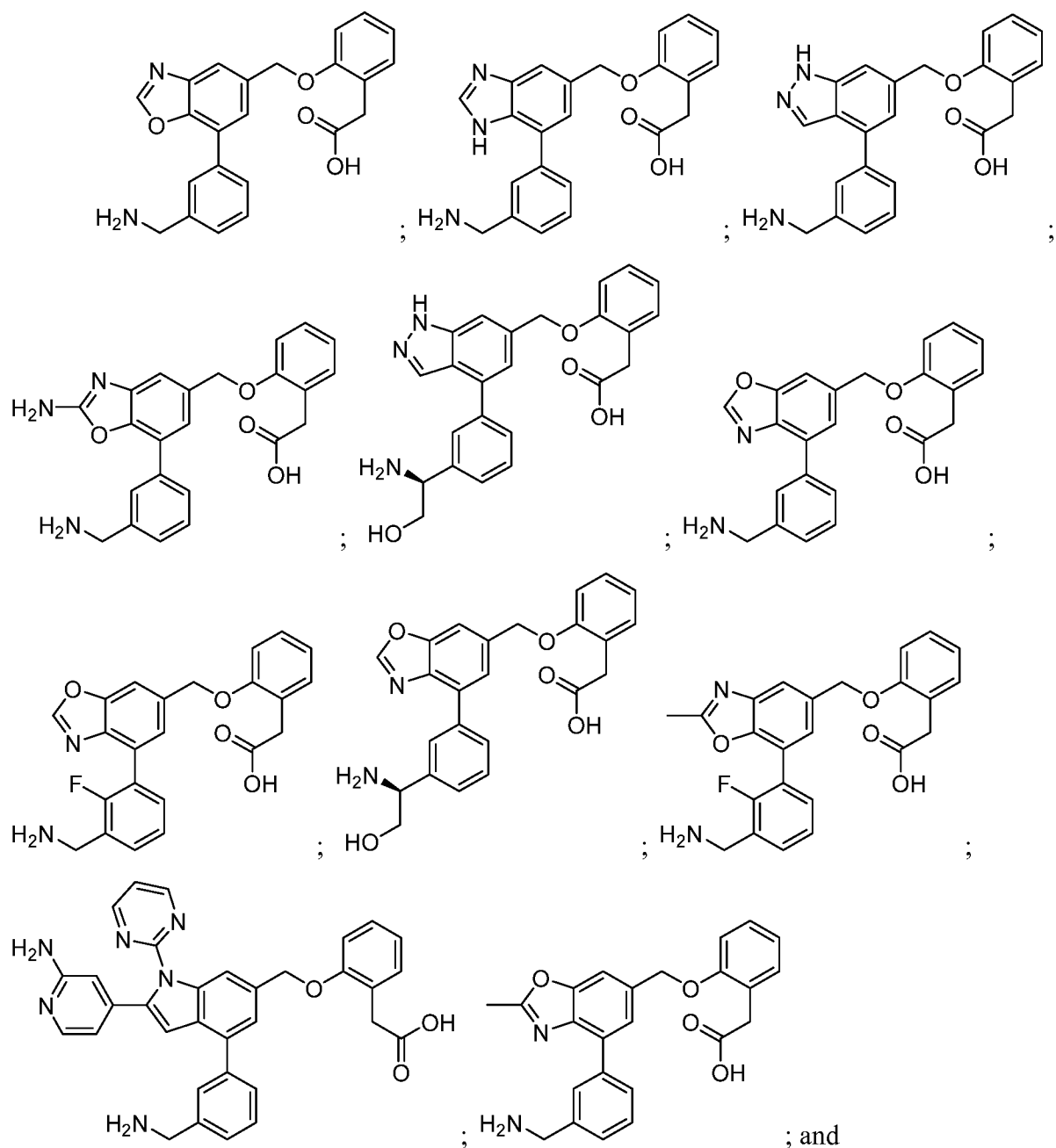
11. The compound of any one of claims 1 through 9 wherein Ar₂ is .

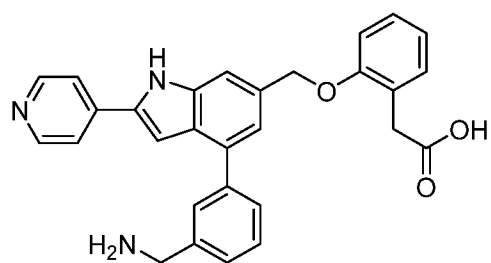
12. The compound of any one of claims 1 through 11 wherein each R₁ and R₂ are independently selected from the group consisting of hydrogen, -OR₃, -SR₃, -NR₃R₄, C₆-C₁₄ aryl, C₅-C₁₄ heteroaryl optionally substituted with -NR₃R₄, and C₁-C₆ alkyl optionally substituted with C₆-C₁₄ aryl; and wherein each R₃ and R₄ are as defined in claim 1.

13. The compound of any one of claims 1 through 12 wherein each R₃ and R₄ are independently selected from the group consisting of hydrogen and C₁-C₆ alkyl.

14. The compound of any one of claims 1 through 11 wherein each R_1 and R_2 are independently selected from the group consisting of hydrogen, $-NH_2$, $-CH_3$, , , and .

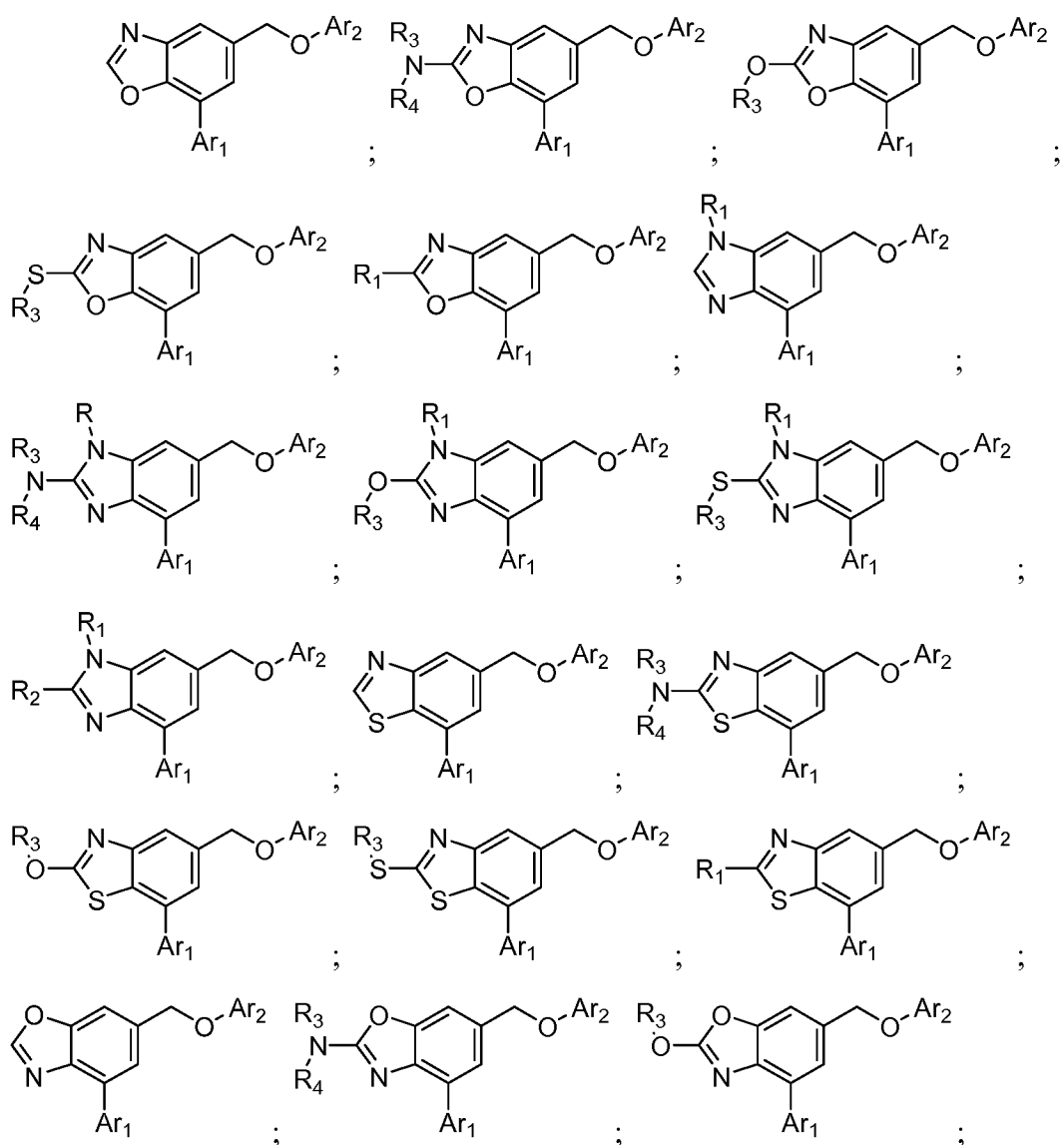
15. The compound of any one of claims 1 through 14 selected from the group consisting of:

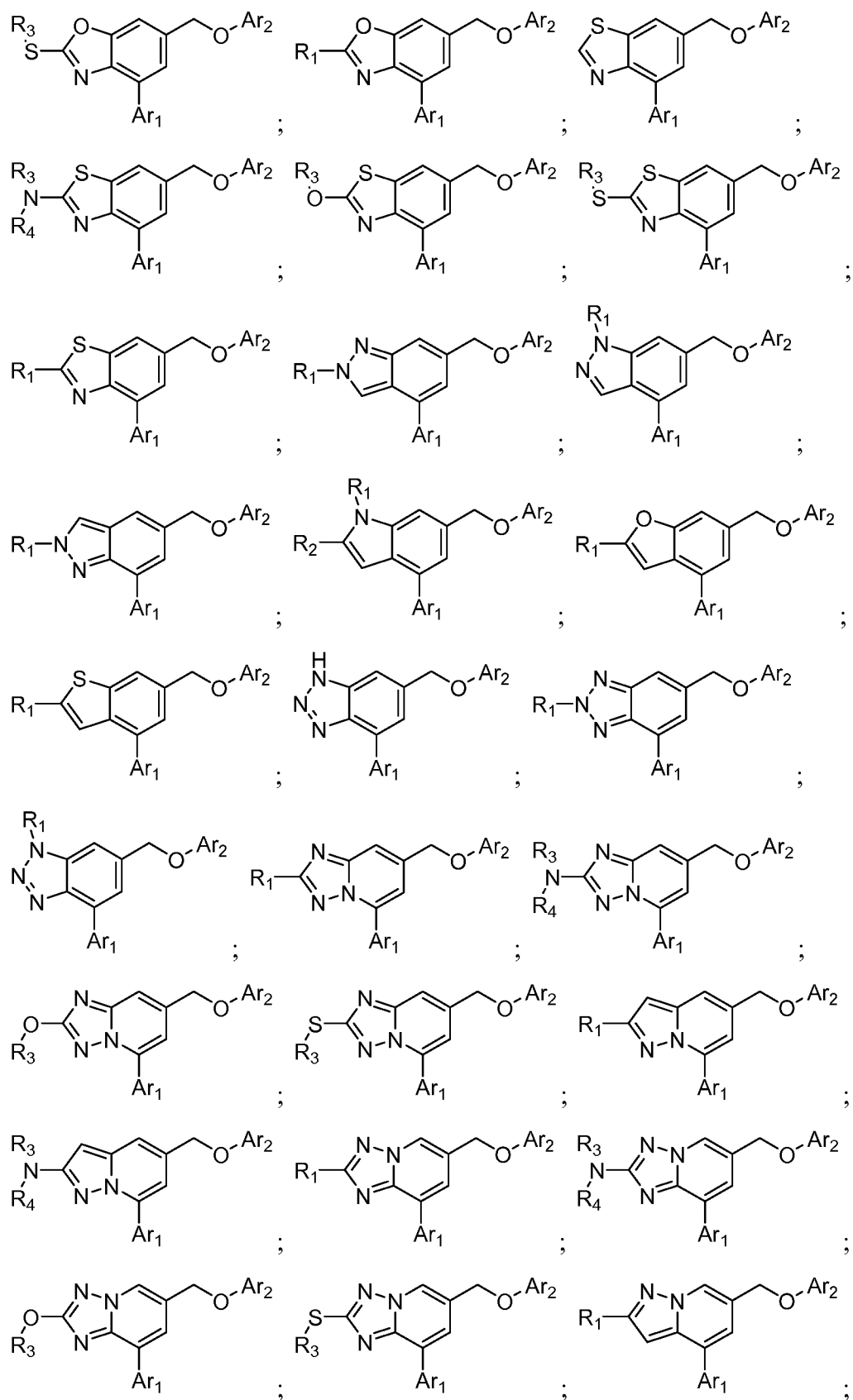


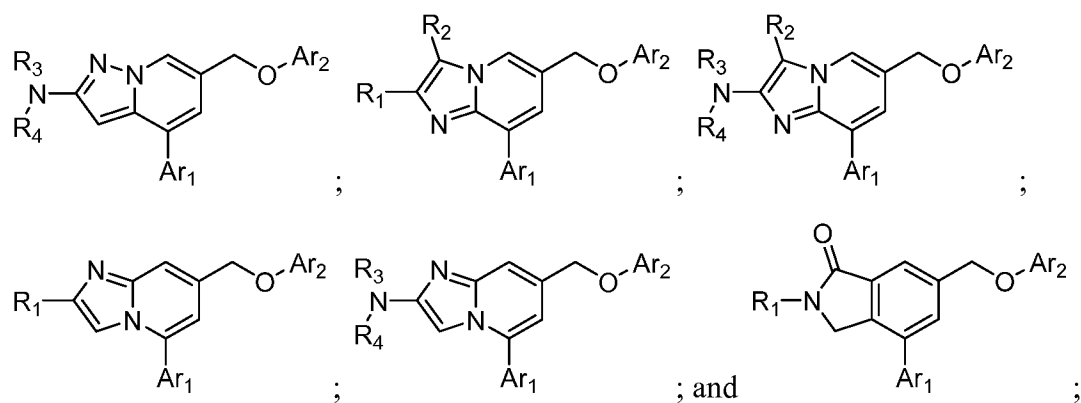


or a stereoisomer or a pharmaceutically acceptable salt thereof.

16. The compound of any one of claims 1 through 14 selected from the group consisting of:



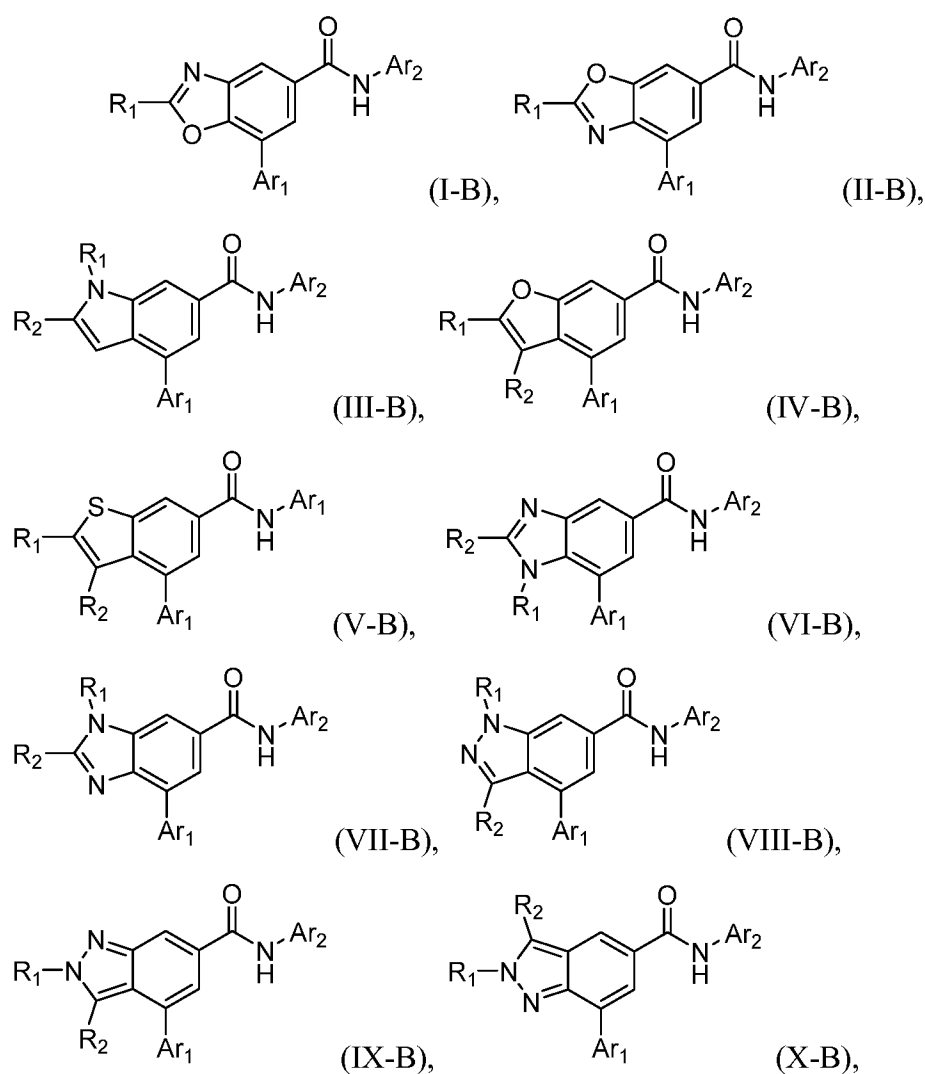


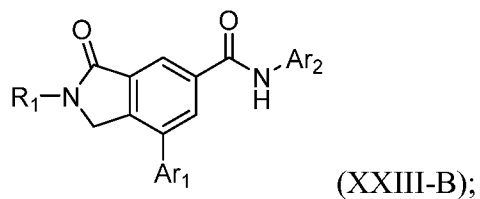
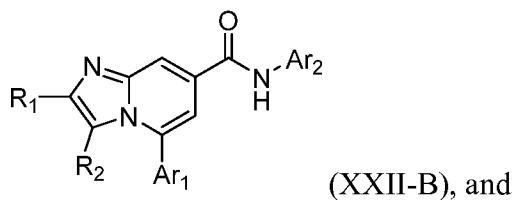
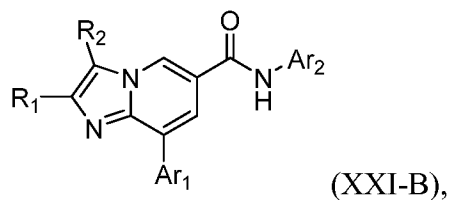
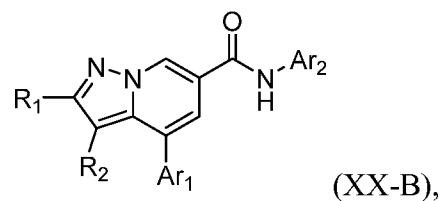
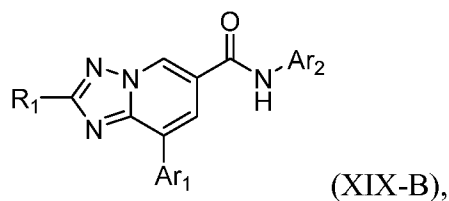
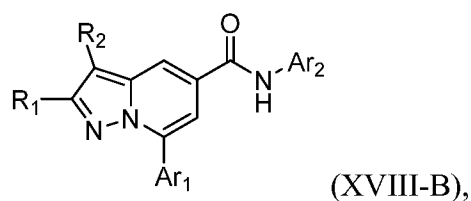
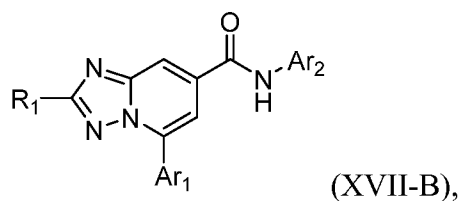
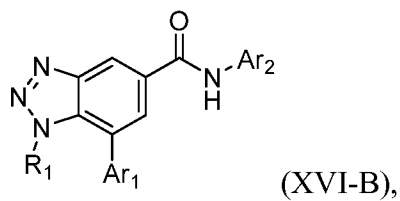
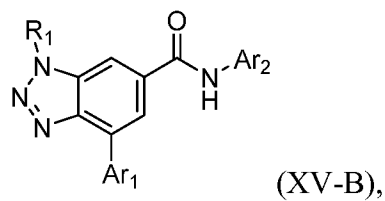
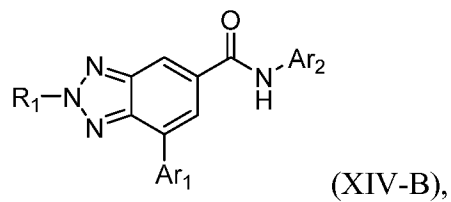
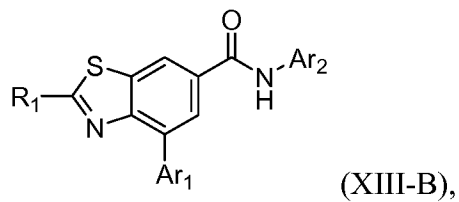
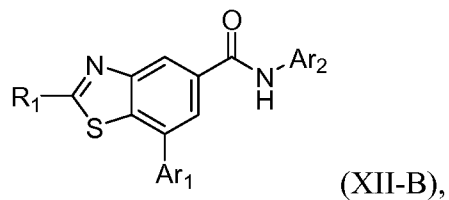
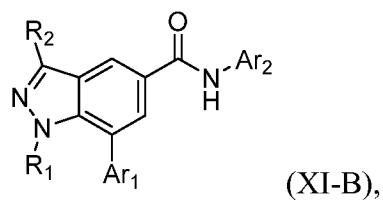


or a stereoisomer or a pharmaceutically acceptable salt thereof,

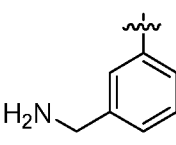
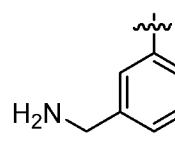
wherein R_1 , R_2 , R_3 , R_4 , Ar_1 , and Ar_2 are as defined in claim 1.

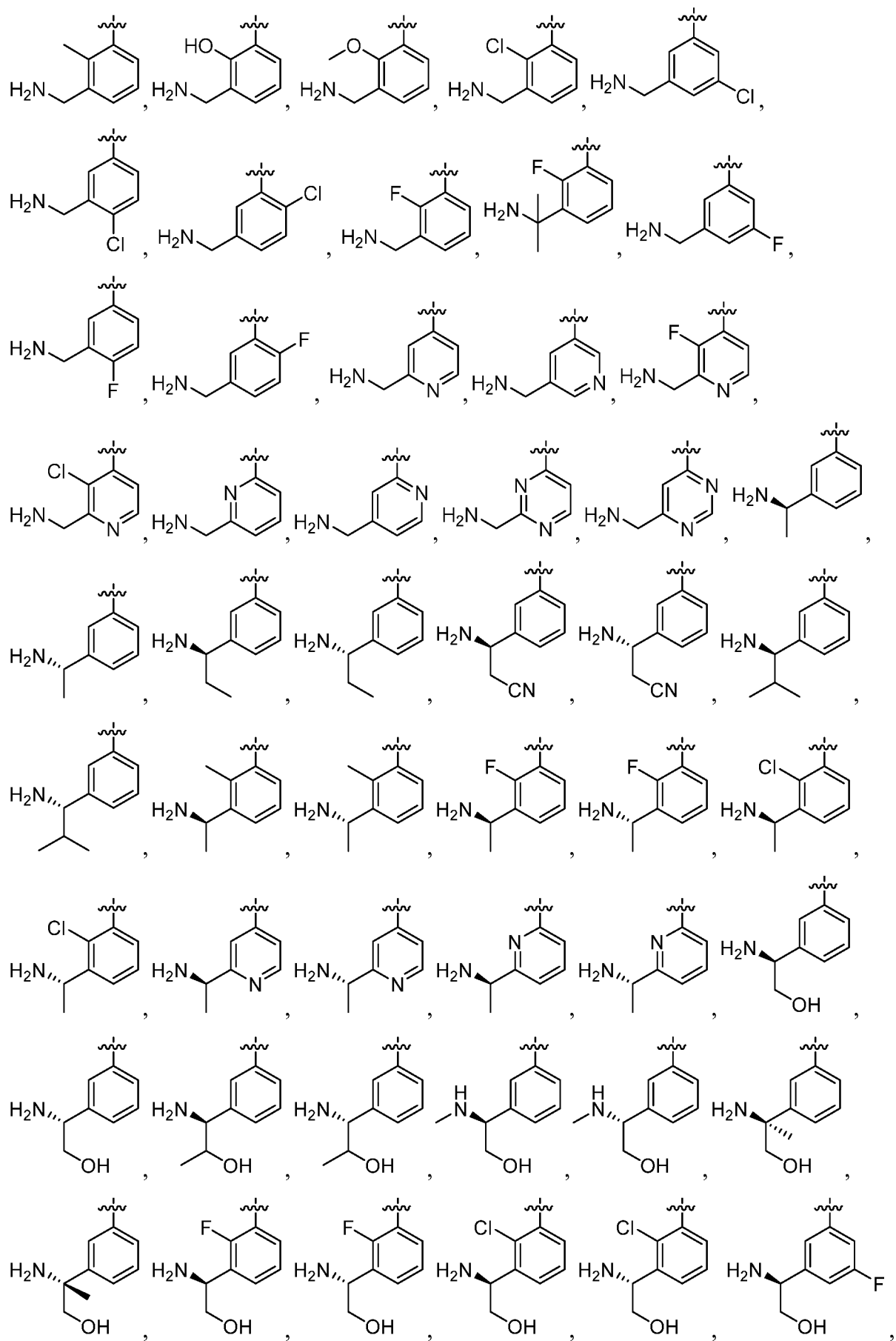
17. A compound having a structure selected from the group consisting of:



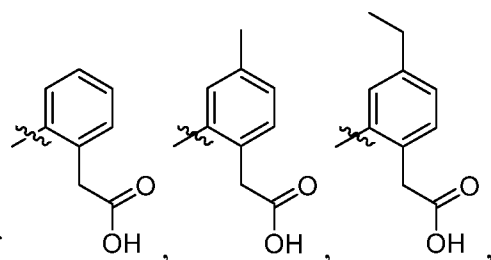
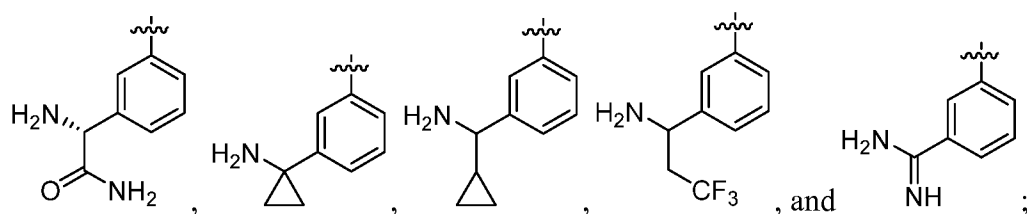


or a stereoisomer or a pharmaceutically acceptable salt thereof, wherein:

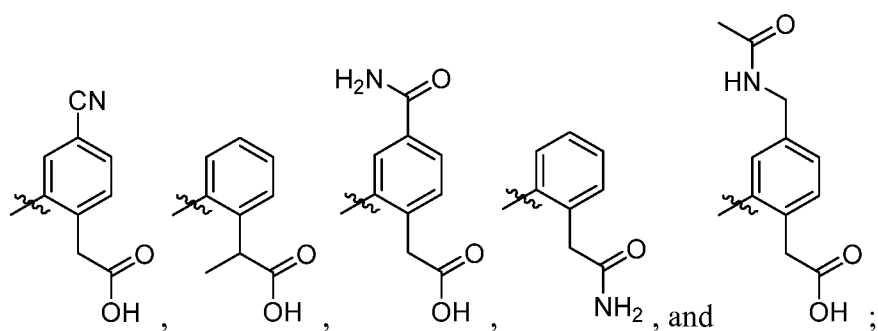
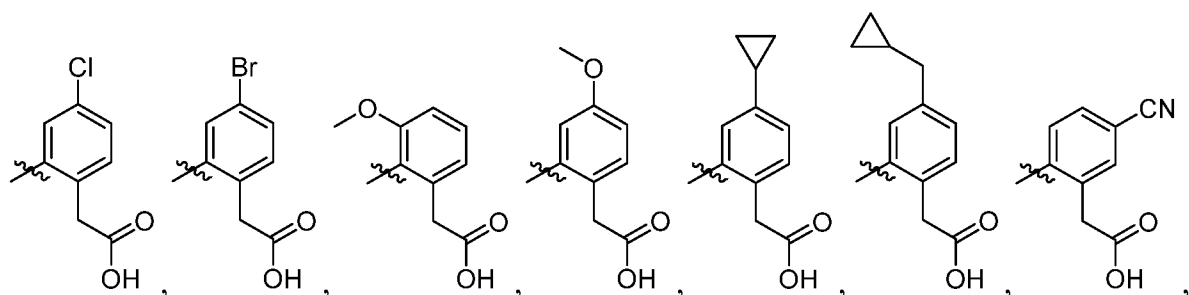
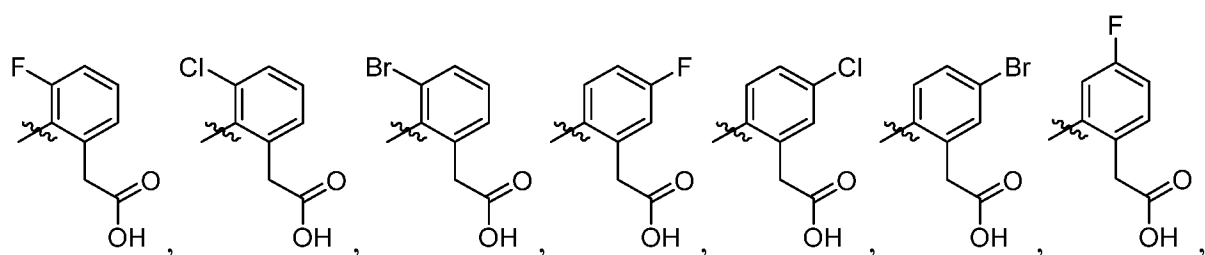
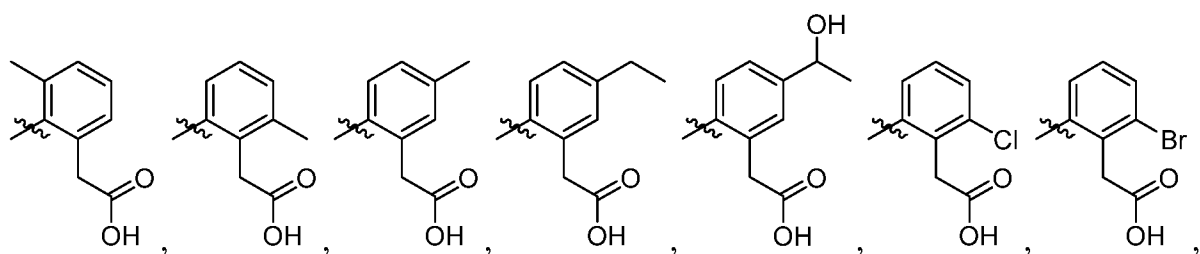
Ar₁ is selected from the group consisting of , ,







Ar₂ is selected from the group consisting of

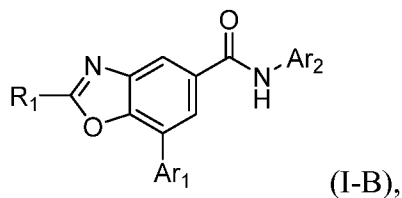


each R₁ and R₂ are independently selected from the group consisting of hydrogen, halo, cyano, -OR₃, -SR₃, -NR₃R₄, -C(O)R₃, -C(O)OR₃, -C(O)NR₃R₄, -S(O)₂R₃, C₁-C₆ alkyl

optionally substituted with R_3 , C_6 - C_{14} aryl optionally substituted with R_3 , and C_5 - C_{14} heteroaryl optionally substituted with R_3 ; and

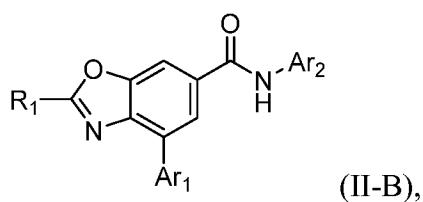
each R_3 and R_4 are independently selected from the group consisting of hydrogen, - NH_2 , C_1 - C_6 alkyl, C_6 - C_{12} aryl, and C_5 - C_{14} heteroaryl.

18. The compound of claim 17 having the structure



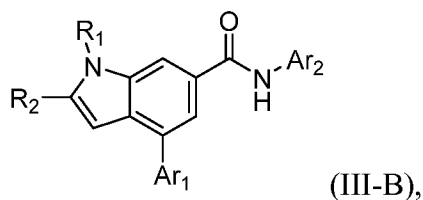
or a stereoisomer or a pharmaceutically acceptable salt thereof.

19. The compound of claim 17 having the structure



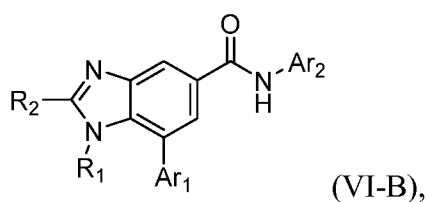
or a stereoisomer or a pharmaceutically acceptable salt thereof.

20. The compound of claim 17 having the structure



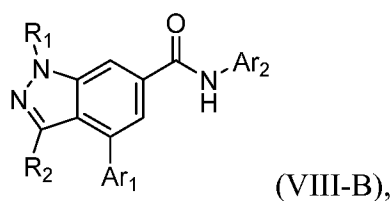
or a stereoisomer or a pharmaceutically acceptable salt thereof.

21. The compound of claim 17 having the structure



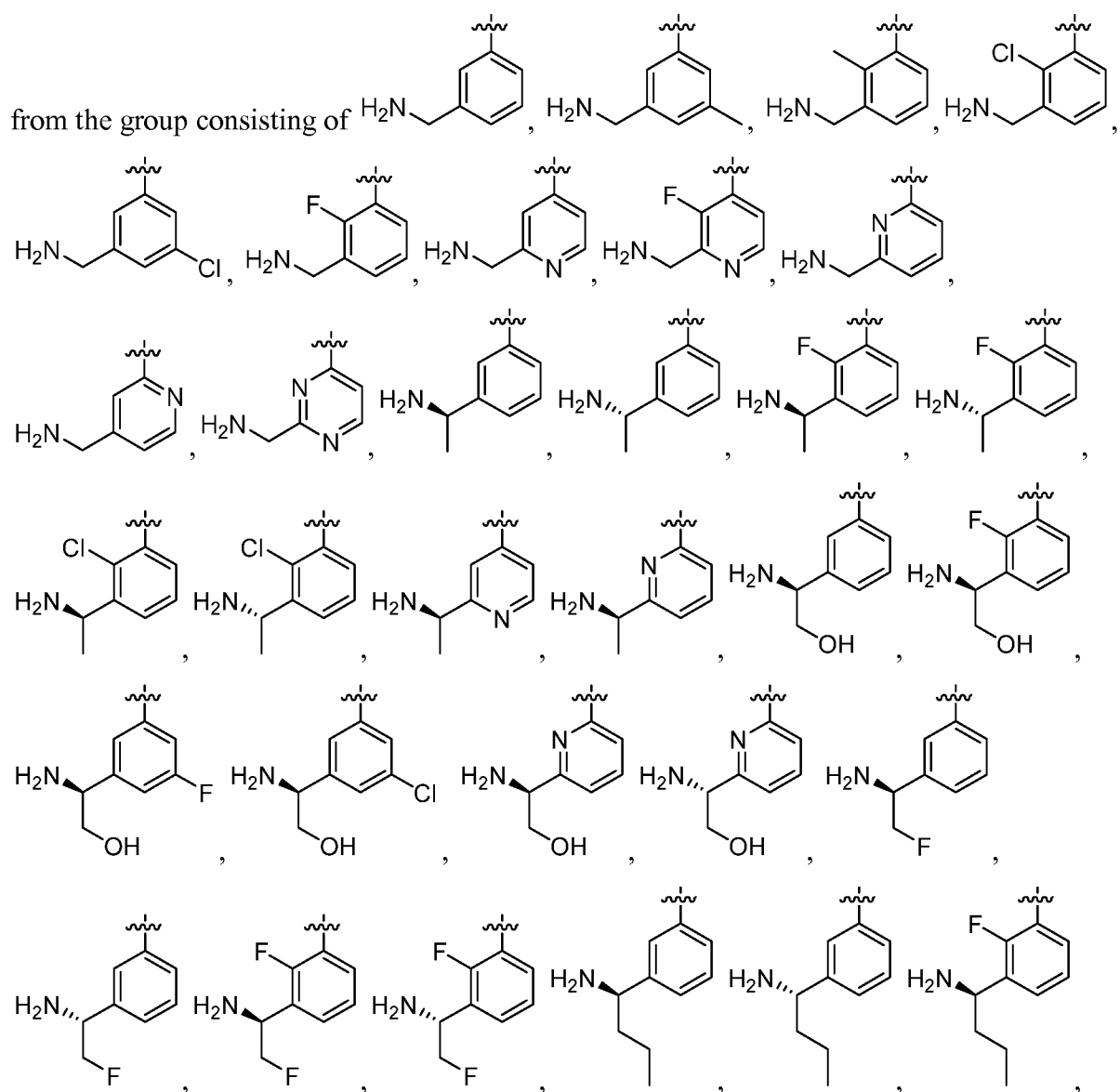
or a stereoisomer or a pharmaceutically acceptable salt thereof.

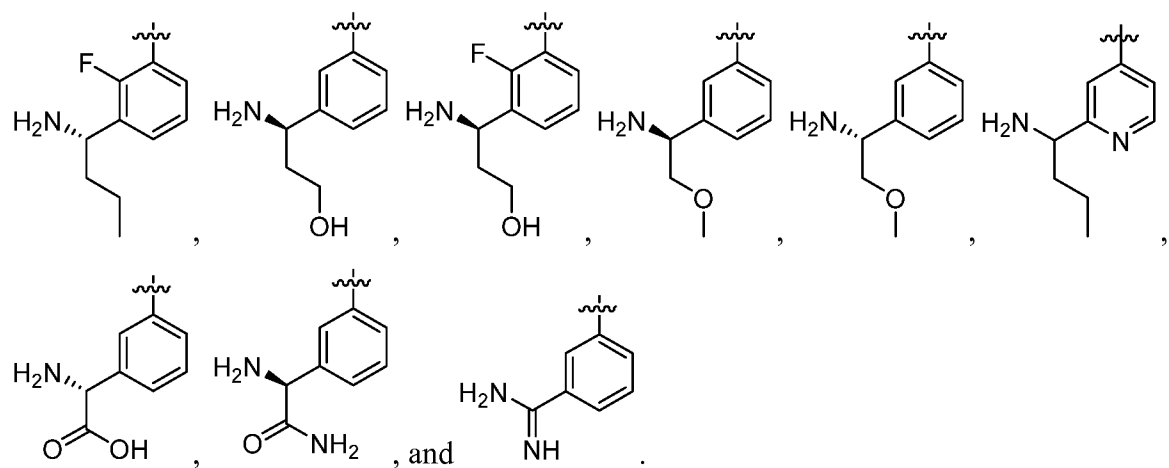
22. The compound of claim 17 having the structure



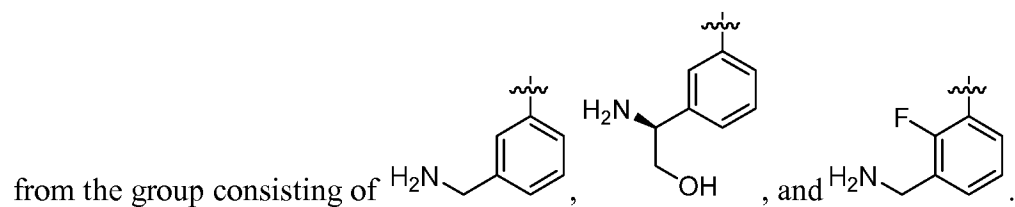
or a stereoisomer or a pharmaceutically acceptable salt thereof.

23. The compound of any one of claims 17 through 22 wherein Ar₁ is selected

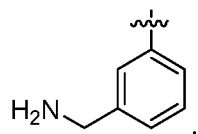




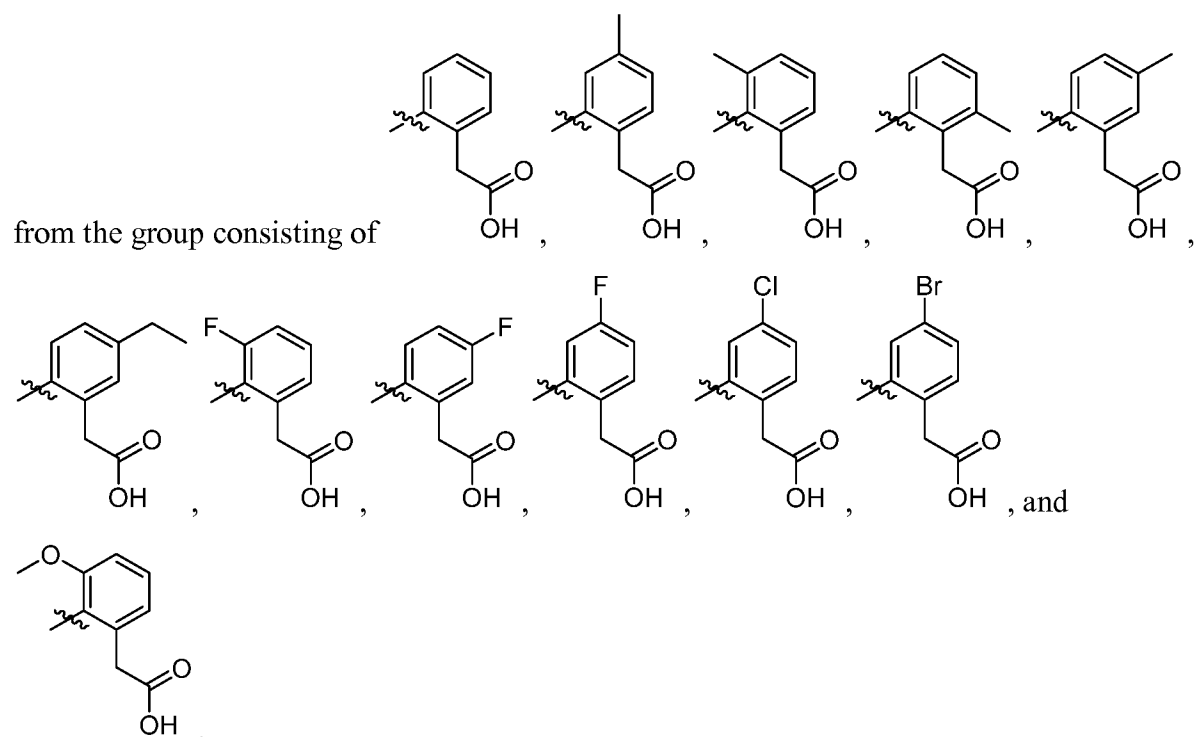
24. The compound of any one of claims 17 through 22 wherein Ar₁ is selected



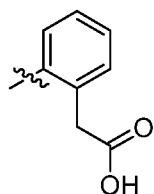
25. The compound of any one of claims 17 through 22 wherein Ar₁ is



26. The compound of any one of claims 17 through 25 wherein Ar₂ is selected

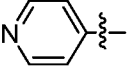


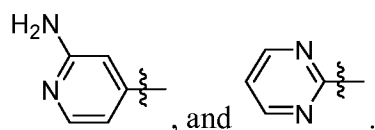
27. The compound of any one of claims 17 through 25 wherein Ar₂ is



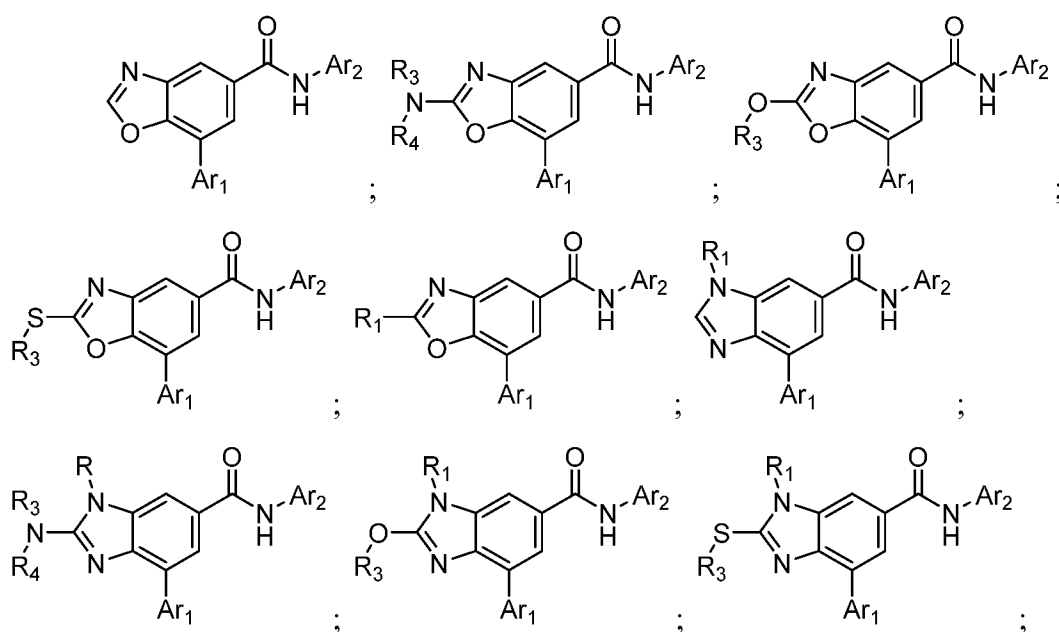
28. The compound of any one of claims 17 through 27 wherein each R₁ and R₂ are independently selected from the group consisting of hydrogen, -OR₃, -SR₃, -NR₃R₄, C₆-C₁₄ aryl, C₅-C₁₄ heteroaryl optionally substituted with -NR₃R₄, and C₁-C₆ alkyl optionally substituted with C₆-C₁₄ aryl.

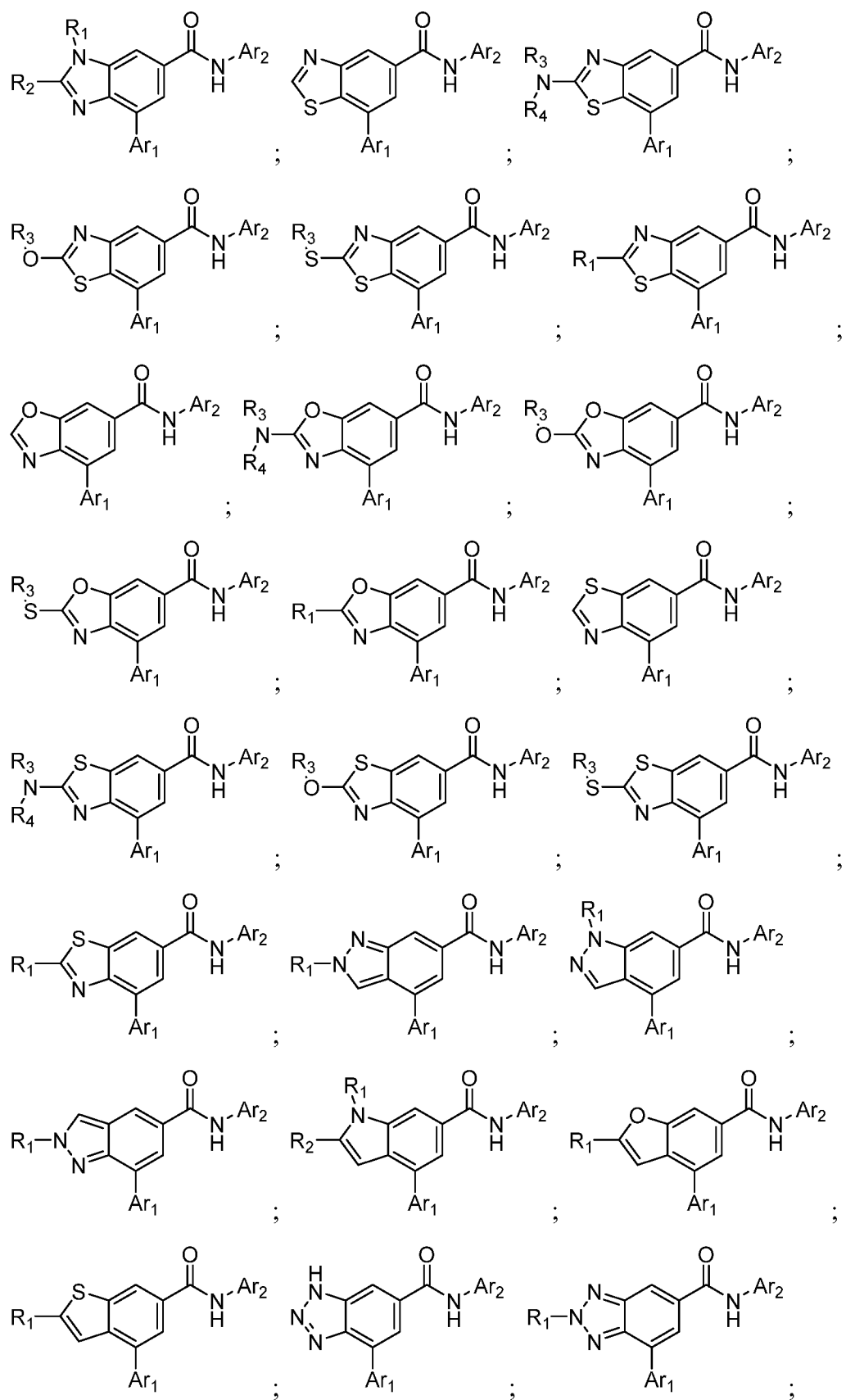
29. The compound of any one of claims 17 through 28 wherein each R₃ and R₄ are independently selected from the group consisting of hydrogen and C₁-C₆ alkyl.

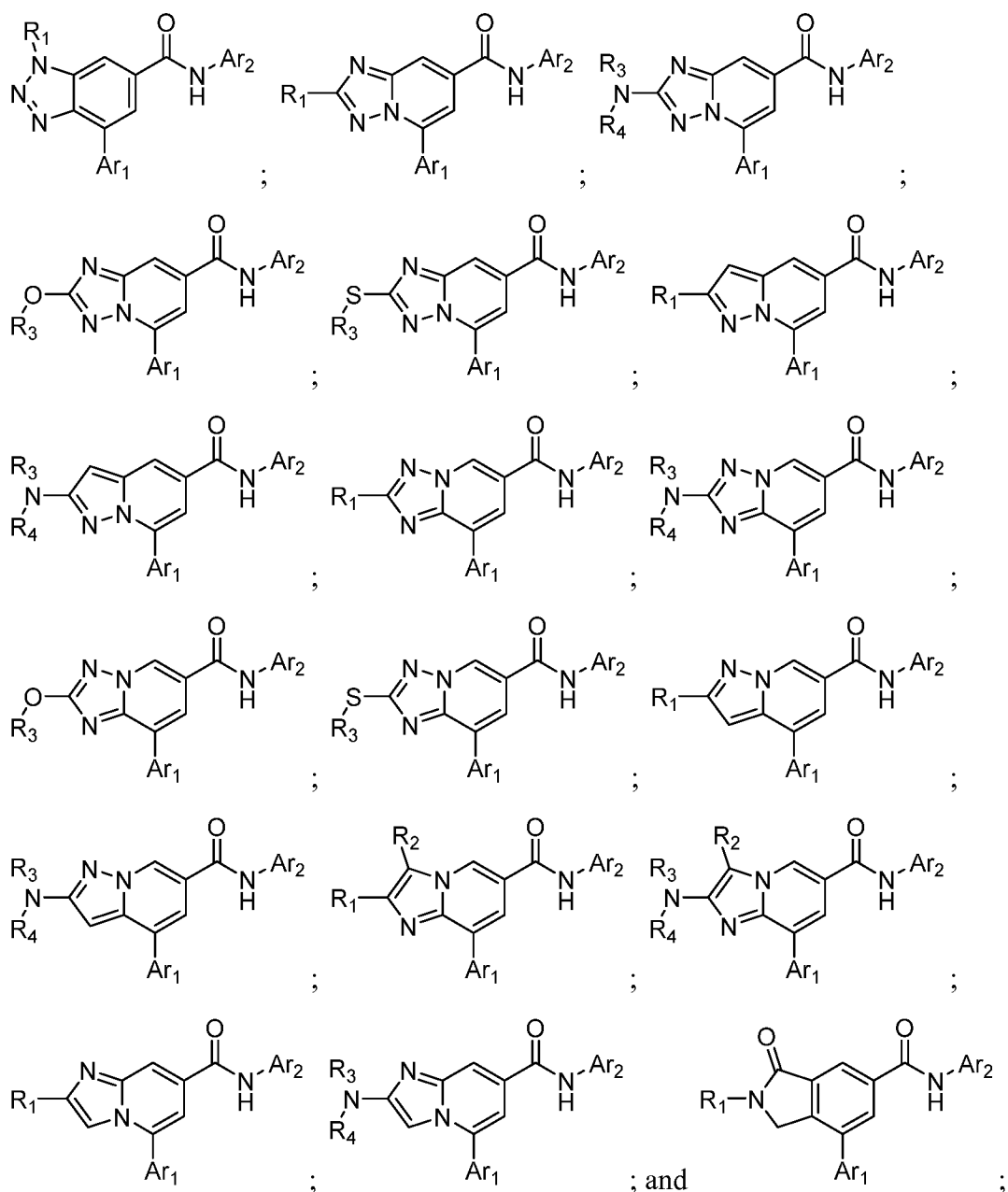
30. The compound of any one of claims 17 through 27 wherein each R₁ and R₂ are independently selected from the group consisting of hydrogen, -NH₂, -CH₃, ,



31. The compound of any one of claims 17 through 30 selected from the group consisting of:







or a stereoisomer or a pharmaceutically acceptable salt thereof,

wherein R_1 , R_2 , R_3 , R_4 , Ar_1 , and Ar_2 are as defined in claim 17.

32. A pharmaceutical formulation comprising a compound of any one of claims 1-31, or a stereoisomer or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, carrier or diluent.

33. A delivery device for ocular delivery comprising the pharmaceutical formulation of claim 32 and a means for delivering the formulation intravitreally to a patient.

34. A method of modulating complement alternative pathway activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of any one of claims 1-31, or a stereoisomer or a pharmaceutically acceptable salt thereof.

35. A method of treating a disease or disorder in a subject mediated by complement activation, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of any one of claims 1-31, or a stereoisomer or a pharmaceutically acceptable salt thereof.

36. The method of claim 35, wherein the complement-mediated disorder is systemic.

37. The method of claim 35, wherein the complement-mediated disorder is a complement-associated eye condition.

38. The method of claim 37, wherein the complement-associated eye condition is selected from age-related macular degeneration (AMD), including dry and wet (non-exudative and exudative) forms, choroidal neovascularization (CNV), uveitis, diabetic retinopathy, ischemia-related retinopathy, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization.

39. The method of claim 37, wherein the complement-associated eye condition is selected from intermediate dry form AMD or geographic atrophy (GA).

40. A method of preventing, treating, or lessening the severity of a disease or condition responsive to the inhibition of Factor D in a patient, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-31, or a stereoisomer or a pharmaceutically acceptable salt thereof.

41. Use of a compound of any one of claims 1-31, or a stereoisomer or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating a complement-mediated disorder in a subject.

42. The use of claim 41, wherein the complement-mediated disorder is a complement-associated eye condition.

43. The use of claim 41, wherein the complement-mediated disorder is systemic.
44. The use of claim 42, wherein the complement-associated eye condition is selected from age-related macular degeneration (AMD), including dry and wet (non-exudative and exudative) forms, choroidal neovascularization (CNV), uveitis, diabetic retinopathy, ischemia-related retinopathy, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization.
45. The use of claim 42, wherein the complement-associated eye condition is selected from intermediate dry form AMD or geographic atrophy (GA).
46. A method of inhibiting Factor D in a cell, *ex vivo*, comprising contacting the cell with a compound according to any of claims 1-31, or a stereoisomer or a pharmaceutically acceptable salt thereof.
47. A method of inhibiting Factor D in a patient in need of therapy, comprising administering to the patient a compound of any one of claims 1-31, or a stereoisomer or a pharmaceutically acceptable salt thereof.
48. A combination comprising a therapeutically effective amount of a compound of any one of claims 1-31, or a stereoisomer or a pharmaceutically acceptable salt thereof, and a second therapeutically active agent.
49. The combination of claim 48, wherein the additional therapeutic agent is selected from an ANG2 antagonist, a TIE2 antagonist, a VEGF antagonist, and a second complement component antagonist.
50. The combination of claim 48, wherein the additional therapeutic agent is an anti-ANG2 antibody.
51. The combination of claim 48, wherein the additional therapeutic agent is an anti-TIE2 antibody.
52. The combination of claim 48, wherein the additional therapeutic agent is selected from a VEGF trap and an anti-VEGF antibody.
53. The compound of any one of claims 1-31, or a stereoisomer or a

pharmaceutically acceptable salt thereof, for use in therapy.

54. The compound of any one of claims 1-31, or a stereoisomer or a pharmaceutically acceptable salt thereof, for use in a method of treating a complement-mediated disorder in a subject.

55. The compound of any one of claims 1-31, or a stereoisomer or a pharmaceutically acceptable salt thereof, for use in a method of treating a systemic complement-mediated disorder in a subject.

56. The compound of claim 55, wherein the complement-mediated disorder is a complement-associated eye condition.

57. The compound of claim 56, wherein the complement-associated eye condition is selected from age-related macular degeneration (AMD), including dry and wet (non-exudative and exudative) forms, choroidal neovascularization (CNV), uveitis, diabetic retinopathy, ischemia-related retinopathy, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, and retinal neovascularization.

58. The compound of claim 56, wherein the complement-associated eye condition is selected from intermediate dry form AMD or geographic atrophy (GA).

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/075712

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D263/56 C07D401/14 C07D231/56 C07D401/04 C07D235/08
C07D263/58 A61P27/02

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/009977 A1 (NOVARTIS AG [CH]; BELANGER DAVID B [US]; FLOHR STEFANIE [CH]; GELIN CH) 22 January 2015 (2015-01-22)	1-14, 16-58
A	page 497; claim 1 page 505; claims 33-34 -----	15
A	WO 2016/088082 A1 (NOVARTIS AG [CH]; BELANGER DAVID [US]; FLOHR STEFANIE [DE]; GELIN CHRI) 9 June 2016 (2016-06-09) page 92; claim 1 -----	1-58



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

25 October 2018

Date of mailing of the international search report

15/11/2018

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Jeanjean, Fabien

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2018/075712

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015009977 A1	22-01-2015	AU 2014290498 A1	04-02-2016
		CA 2917614 A1	22-01-2015
		CN 105555766 A	04-05-2016
		EA 201690247 A1	30-06-2016
		EP 3022182 A1	25-05-2016
		JP 2016529238 A	23-09-2016
		KR 20160036568 A	04-04-2016
		TW 201546030 A	16-12-2015
		US 2016145247 A1	26-05-2016
		WO 2015009977 A1	22-01-2015

WO 2016088082 A1	09-06-2016	NONE	
