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(54) Title: HTRA1 INHIBITORS AND USES THEREOF

(57) Abstract: Disclosed herein are compounds that act as inhibitors of the serine protease HTRA1, compositions comprising the compounds, and uses of the compounds, e.g., in treatment of HTRA1 associated disorders, including age-related macular degeneration.



WO 2025/006856 A1

HTRA1 INHIBITORS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to and the benefit of U.S. Provisional Patent Application No. 63/510,797, filed on June 28, 2023, which is incorporated herein by reference in its entirety.

SEQUENCE LISTING STATEMENT

The contents of the electronic sequence listing titled STDU2_41633_601_SequenceListing.xml (Size: 2,310 bytes; and Date of Creation: June 25, 2024) is incorporated herein by reference in its entirety.

FIELD

The present disclosure is directed to compounds that act as inhibitors of the serine protease HTRA1, compositions comprising the compounds, and uses of the compounds, e.g., in treatment of HTRA1 associated disorders, including age-related macular degeneration.

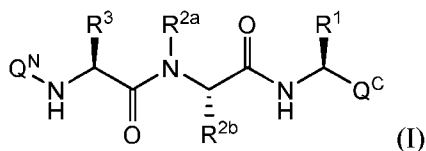
BACKGROUND

Age-related macular degeneration (AMD) is the leading cause of vision loss in people 65 and older, with two different disease forms: dry and wet. There are currently no effective therapeutics for dry-AMD, the more common and earlier form of disease.

Genome-wide association studies with AMD patients identified a genetic promoter mutation resulting in overexpression of the serine protease, HTRA1, increasing disease-risk by up to eight-fold (Klein *et al. Science* 2005, 308 (5720), 385–389.). Increased HTRA1 activity results in abnormal proteolysis of Thrombospondin-1, which activates a monocyte-accumulation pathway, causing inflammation and retinal pigment epithelial degeneration characteristic of both genetic and age-related dry-AMD. Accordingly, inhibition of HTRA1 may provide a treatment for AMD, including dry AMD, along with other disorders associated with HTRA1.

SUMMARY

In one aspect, disclosed herein is a compound of formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

Q^N is $-X-R^N$, wherein: X is selected from $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-S(O)_2-$, and a bond; R^N is selected from C_1-C_6 alkyl, aryl, and $-(CR^aR^b)_p-Z$; p is 1, 2, or 3; R^a and R^b are each independently selected from hydrogen and C_1-C_4 alkyl, wherein one R^a and one R^b , together with the carbon atom to which they are attached, are optionally taken together to form a 3- to 6-membered cycloalkyl; and Z is selected from aryl and heterocyclyl; wherein each R^N is optionally substituted with 1 or 2 substituents independently selected from halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, $-OH$, and $-COOH$;

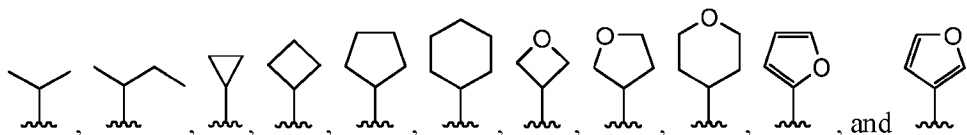
Q^C is selected from $-B(OR^{C1})_2$ and $-C(O)R^{C2}$, wherein each R^{C1} is independently selected from hydrogen, C_1-C_6 alkyl, and aryl, or two R^{C1} , together with the atoms to which they are attached, form an optionally substituted ring, and R^{C2} is selected from C_1-C_4 alkyl and C_1-C_4 haloalkyl;

R^1 is selected from C_3-C_8 alkyl, hydroxy- C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, and monocyclic heteroaryl;

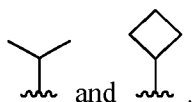
R^{2a} is hydrogen or C_1-C_4 -alkyl, and R^{2b} is selected from C_1-C_8 alkyl, aryl- C_1-C_4 -alkyl, heteroaryl- C_1-C_4 -alkyl, hydroxy, and $-(CH_2)_mNH-R^{2c}$, wherein m is 1, 2, 3, 4, 5, or 6, R^{2c} is selected from H and $-COO(C_1-C_6\text{-alkyl})$, and the aryl is unsubstituted or substituted with 1 or 2 substituents independently selected from hydroxy and C_1-C_6 -alkoxy; or R^{2a} and R^{2b} , together with the atoms to which they are attached, form an optionally substituted ring; and

R^3 is selected from C_1-C_8 alkyl and $-(CH_2)_n-Y$, wherein n is 0, 1, 2, or 3, and Y is selected from aryl, heteroaryl, cycloalkyl, and heterocyclyl, wherein the alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl are each independently unsubstituted or substituted with 1 or 2 substituents independently selected from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, halo, cyano, C_1-C_4 haloalkyl, hydroxy, amino, and C_1-C_4 alkoxy, and wherein the aryl or the heteroaryl is optionally substituted with a group that is taken together with R^{C2} to form an optionally substituted ring.

In some embodiments, R^1 is selected from C_3-C_4 alkyl and C_3-C_5 cycloalkyl. In some embodiments, R^1 is selected from:

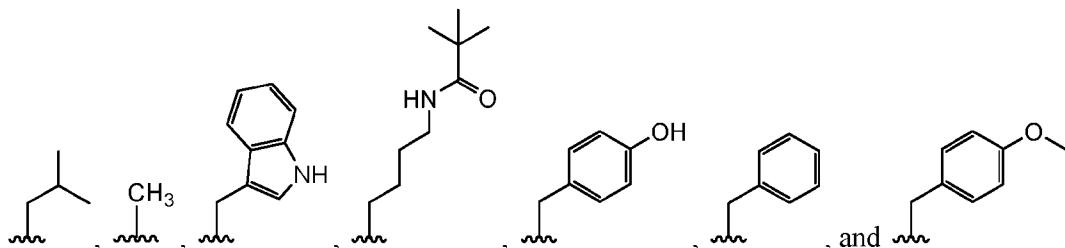


In some embodiments, R^1 is selected from:

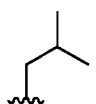


In some embodiments, R^{2a} is hydrogen, and R^{2b} is selected from C₁-C₄ alkyl, -CH₂-phenyl, -CH₂-indolyl, and -(CH₂)₄NH- R^{2c} , wherein R^{2c} is selected from H and -COO(tBu), and the phenyl is unsubstituted or substituted with one substituent selected from hydroxy and

5 C₁-C₄-alkoxy. In some embodiments, R^{2a} is hydrogen or methyl, and R^{2b} is selected from:



In some embodiments, R^{2a} is hydrogen, and R^{2b} is:

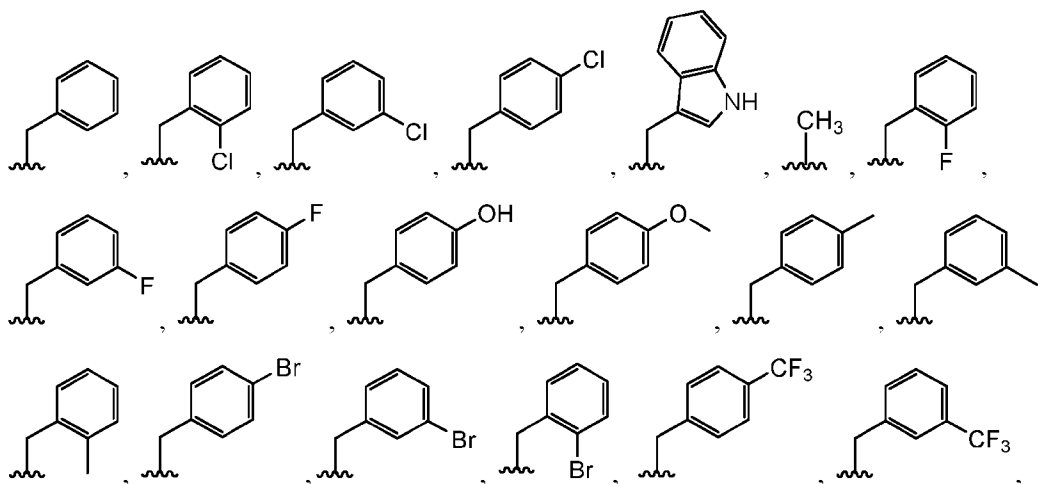


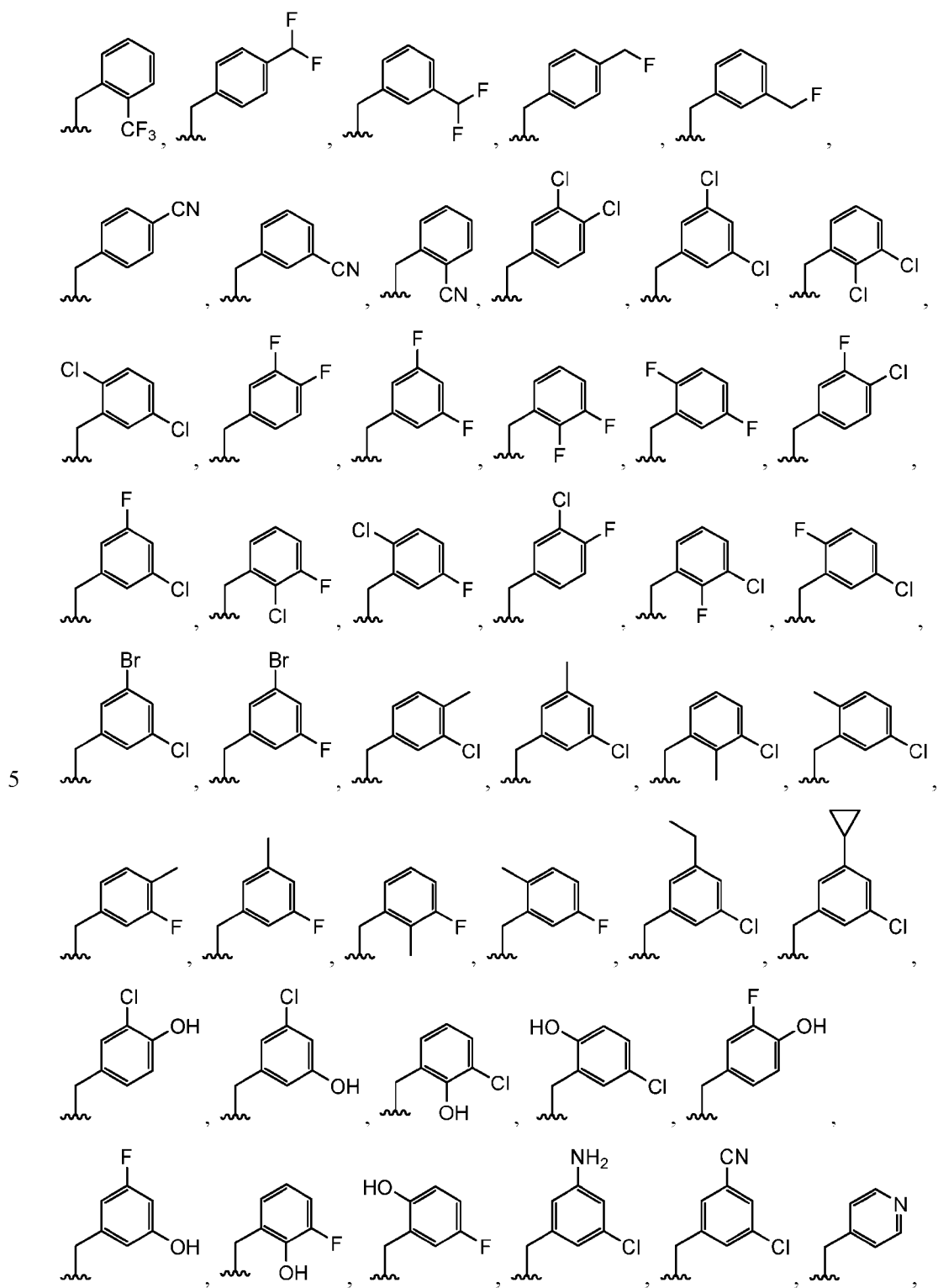
In some embodiments, R^{2a} and R^{2b} , together with the atoms to which they are attached, form an optionally substituted five-membered saturated ring.

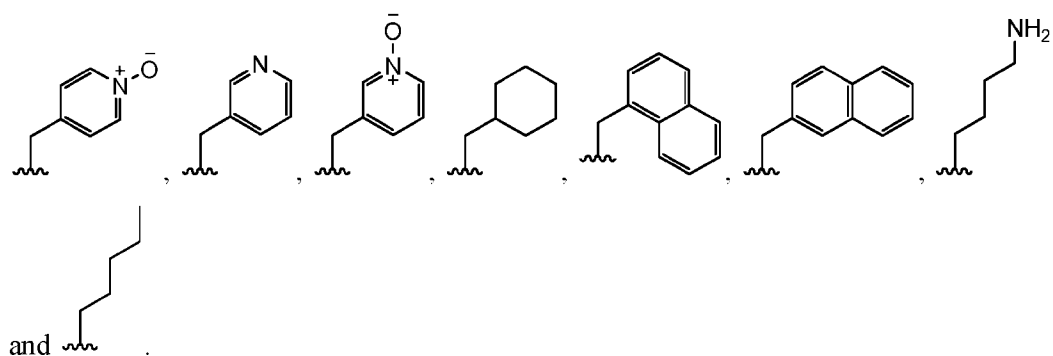
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In some embodiments, R^3 is selected from C₁-C₆ alkyl, -CH₂-phenyl, -CH₂-naphthyl, -CH₂-indolyl, -CH₂-pyridyl, and -CH₂-cyclohexyl, wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from methyl, ethyl, fluoro, chloro, bromo, hydroxy, methoxy, cyano, fluoromethyl, difluoromethyl, and trifluoromethyl, and

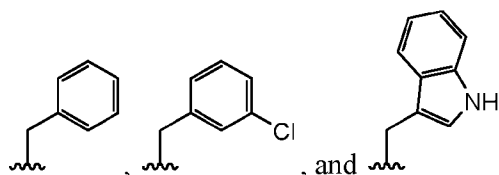
15 wherein the pyridyl is unsubstituted or substituted with one oxo group. In some embodiments, R^3 is selected from:



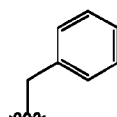




In some embodiments, R^3 is selected from:

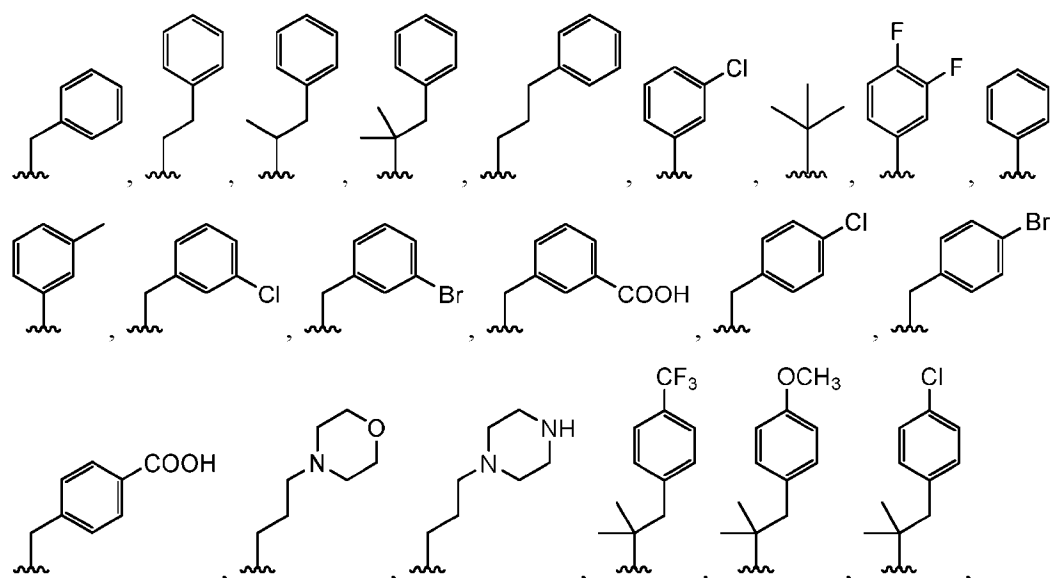


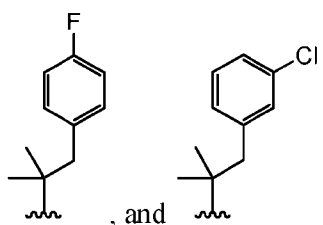
5 In some embodiments, R^3 is:



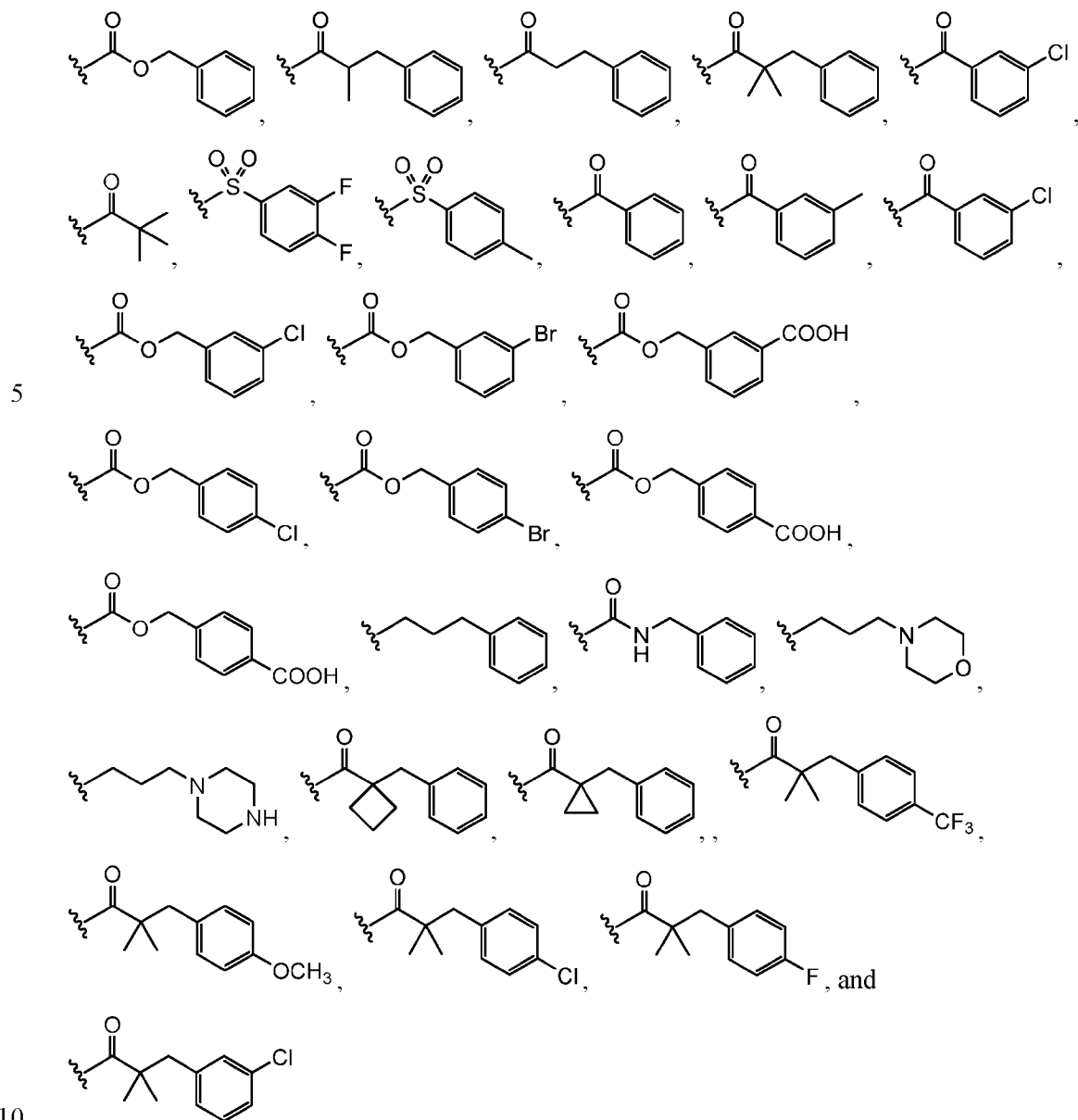
In some embodiments, R^N is selected from C₃-C₄ alkyl, phenyl, phenyl-C₁-C₃-alkyl, and heterocyclyl-C₁-C₃-alkyl, wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from halo, methyl, and -COOH. In some embodiments,

10 R^N is selected from:





In some embodiments, Q^N is selected from:



In some embodiments, Q^C is $-B(OR^{C1})_2$, and each R^{C1} is independently selected from hydrogen, C_1 - C_4 alkyl, and phenyl, or two R^{C1} , together with the atoms to which they are

attached, form an optionally substituted saturated 5- to 6-membered ring. In some embodiments, each R^{C1} is hydrogen.

In some embodiments, Q^C is $-C(O)R^{C2}$, and R^{C2} is C_1 - C_4 haloalkyl.

In some embodiments, the compound is selected from a compound shown in FIG. 1.

5 In another aspect, disclosed herein is a pharmaceutical composition comprising a compound disclosed herein (e.g., a compound of formula (I)), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another aspect, disclosed herein is a method of treating a disorder associated with HTRA1 in a subject in need thereof, comprising administering to the subject a therapeutically
10 effective amount of a compound disclosed herein (e.g., a compound of formula (I)). or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein (e.g., a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof). In some embodiments, the disorder is selected from macular degeneration, Alzheimer's disease, arthritis, bladder cancer, intervertebral disc
15 degeneration, Lyme disease, osteoarthritis, preeclampsia, rheumatoid arthritis, and TGFBI-associated corneal dystrophies. In some embodiments, the disorder is age-related macular degeneration. In some embodiments, the age-related macular degeneration is dry age-related macular degeneration.

In another aspect, disclosed herein is a method of inhibiting HTRA1 in a sample,
20 comprising contacting the sample with an effective amount of a compound disclosed herein (e.g., a compound of formula (I)). or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein (e.g., a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof).

In another aspect, disclosed herein is a use of a compound disclosed herein (e.g., a
25 compound of formula (I))., or a pharmaceutically acceptable salt thereof, as a medicament.

In another aspect, disclosed herein is a use of a compound disclosed herein (e.g., a compound of formula (I))., or a pharmaceutically acceptable salt thereof, for treating a disorder associated with HTRA1. In some embodiments, the disorder is selected from age-related macular degeneration, Alzheimer's disease, arthritis, bladder cancer, intervertebral
30 disc degeneration, Lyme disease, osteoarthritis, preeclampsia, rheumatoid arthritis, and TGFBI-associated corneal dystrophies. In some embodiments, the disorder is age-related macular degeneration. In some embodiments, the age-related macular degeneration is dry age-related macular degeneration.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows structures of compounds of the present disclosure.

FIG. 2 shows structures of additional compounds falling in the scope of Formula (I).

DETAILED DESCRIPTION

5 Provided herein are compounds that act as inhibitors of the serine protease HTRA1. Also provided herein are compositions comprising the compounds, and uses of the compounds, e.g., in treatment of HTRA1 associated disorders, including age-related macular degeneration.

Definitions

10 Unless otherwise defined herein, scientific and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. For example, any nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics, and protein and nucleic acid chemistry and hybridization described herein are those
15 that are well known and commonly used in the art. The meaning and scope of the terms should be clear; in the event, however of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

 As used herein and in the appended claims, the singular forms “a”, “an”, and “the”
20 include plural reference unless the context clearly dictates otherwise.

 For the recitation of numeric ranges herein, each intervening number there between with the same degree of precision is explicitly contemplated. For example, for the range of 6-9, the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0-7.0, the numbers 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, and 7.0 are explicitly contemplated.

25 Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific
30 functional moieties and reactivity, are described in Sorrell, Organic Chemistry, 2nd edition, University Science Books, Sausalito, 2006; Smith, March's Advanced Organic Chemistry: Reactions, Mechanism, and Structure, 7th Edition, John Wiley & Sons, Inc., New York, 2013;

Larock, Comprehensive Organic Transformations, 3rd Edition, John Wiley & Sons, Inc., New York, 2018; and Carruthers, Some Modern Methods of Organic Synthesis, 3rd Edition, Cambridge University Press, Cambridge, 1987; the entire contents of each of which are incorporated herein by reference.

5 As used herein, the term “alkyl” refers to a radical of a straight or branched saturated hydrocarbon chain. The alkyl chain can include, e.g., from 1 to 24 carbon atoms (C₁-C₂₄ alkyl), 1 to 16 carbon atoms (C₁-C₁₆ alkyl), 1 to 14 carbon atoms (C₁-C₁₄ alkyl), 1 to 12 carbon atoms (C₁-C₁₂ alkyl), 1 to 10 carbon atoms (C₁-C₁₀ alkyl), 1 to 8 carbon atoms (C₁-C₈ alkyl), 1 to 6 carbon atoms (C₁-C₆ alkyl), 1 to 4 carbon atoms (C₁-C₄ alkyl), 1 to 3 carbon
10 atoms (C₁-C₃ alkyl), or 1 to 2 carbon atoms (C₁-C₂ alkyl). Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, and n-dodecyl.

 As used herein, the term “aryl” refers to a radical of a monocyclic, bicyclic, or
15 tricyclic 4n+2 aromatic ring system (e.g., having 6, 10, or 14 π electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms (“C₆-C₁₄ aryl”). In some embodiments, an aryl group has six ring carbon atoms (“C₆ aryl,” i.e., phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C₁₀ aryl,” e.g., naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon
20 atoms (“C₁₄ aryl,” e.g., anthracenyl and phenanthrenyl).

 As used herein, the term “arylalkyl” refers to an alkyl group, as defined herein, in which at least one hydrogen atom is replaced with an aryl group, as defined herein. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, and 3-phenylpropyl.

25 As used herein, the term “cycloalkyl” refers to a radical of a saturated carbocyclic ring system containing three to ten carbon atoms and zero heteroatoms. The cycloalkyl may be monocyclic, bicyclic, bridged, fused, or spirocyclic. Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, adamantyl, bicyclo[2.2.1]heptanyl,
30 bicyclo[3.2.1]octanyl, and bicyclo[5.2.0]nonanyl.

 As used herein, the term “cyano” refers to a -CN group.

 As used herein, the term “halogen” or “halo” refers to F, Cl, Br, or I.

 As used herein, the term “haloalkyl” refers to an alkyl group, as defined herein, in which at least one hydrogen atom (e.g., one, two, three, four, five, six, seven or eight

hydrogen atoms) is replaced with a halogen. In some embodiments, each hydrogen atom of the alkyl group is replaced with a halogen ("perhaloalkyl"). Representative examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, and 3,3,3-trifluoropropyl.

- 5 As used herein, the term "heterocyclyl" refers to a radical of a 3- to 10-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("3-10 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits.
- 10 A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more cycloalkyl groups wherein
- 15 the point of attachment is either on the cycloalkyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. A heterocyclyl group may be described as, e.g., a 3-7-membered
- 20 heterocyclyl, wherein the term "membered" refers to the non-hydrogen ring atoms, i.e., carbon, nitrogen, oxygen, sulfur, boron, phosphorus, and silicon, within the moiety. Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, and thiorenly. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, oxetanyl, and thietanyl.
- 25 Exemplary 5-membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing
- 30 three heteroatoms include, without limitation, triazoliny, oxadiazoliny, and thiadiazoliny. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl (e.g., 2,2,6,6-tetramethylpiperidinyl), tetrahydropyranyl, dihydropyridinyl, pyridinonyl (e.g., 1-methylpyridin-2-onyl), and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation,

piperazinyl, morpholinyl, pyridazinonyl (2-methylpyridazin-3-onyl), pyrimidinonyl (e.g., 1-methylpyrimidin-2-onyl, 3-methylpyrimidin-4-onyl), dithianyl, dioxanyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C₆ aryl ring (also referred to herein as a 5,6-bicyclic heterocyclyl ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothieryl, benzoxazolinonyl, and the like.

Exemplary 5-membered heterocyclyl groups fused to a heterocyclyl ring (also referred to herein as a 5,5-bicyclic heterocyclyl ring) include, without limitation, octahydropyrrolopyrrolyl (e.g., octahydropyrrolo[3,4-c]pyrrolyl), and the like. Exemplary 6-membered heterocyclyl groups fused to a heterocyclyl ring (also referred to as a 4,6-membered heterocyclyl ring) include, without limitation, diazaspirononanyl (e.g., 2,7-diazaspiro[3.5]nonanyl). Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclyl ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like. Exemplary 6-membered heterocyclyl groups fused to a cycloalkyl ring (also referred to herein as a 6,7-bicyclic heterocyclyl ring) include, without limitation, azabicyclooctanyl (e.g., (1,5)-8-azabicyclo[3.2.1]octanyl). Exemplary 6-membered heterocyclyl groups fused to a cycloalkyl ring (also referred to herein as a 6,8-bicyclic heterocyclyl ring) include, without limitation, azabicyclononanyl (e.g., 9-azabicyclo[3.3.1]nonanyl).

As used herein, the term “nitro” refers to an -NO₂ group.

When a group or moiety can be substituted, the term “substituted” indicates that one or more (e.g., 1, 2, 3, 4, 5, or 6; in some embodiments 1, 2, or 3; and in other embodiments 1 or 2) hydrogens on the group indicated in the expression using “substituted” can be replaced with a selection of recited indicated groups or with a suitable substituent group known to those of skill in the art (e.g., one or more of the groups recited below), provided that the designated atom’s normal valence is not exceeded. Substituent groups include, but are not limited to, alkyl, alkenyl, alkynyl, alkoxy, acyl, amino, amido, amidino, aryl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, cycloalkyl, cycloalkenyl, guanidino, halo, haloalkyl, haloalkoxy, heteroalkyl, heteroaryl, heterocyclyl, hydroxy, hydrazino, imino, oxo, nitro, phosphate, phosphonate, sulfonic acid, thiol, thione, or combinations thereof.

As used herein, in chemical structures the indication:



represents a point of attachment of one moiety to another moiety (e.g., a substituent group to the rest of the compound).

For compounds described herein, groups and substituents thereof may be selected in accordance with permitted valence of the atoms and the substituents, such that the selections and substitutions result in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

When substituent groups are specified by their conventional chemical formulae, written from left to right, such indication also encompass substituent groups resulting from writing the structure from right to left. For example, if a bivalent group is shown as $\text{-CH}_2\text{O-}$, such indication also encompasses $\text{-OCH}_2\text{-}$; similarly, -OC(O)NH- also encompasses -NHC(O)O- .

The terms “administer,” “administering,” or “administration,” as used herein refer to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing a compound or a pharmaceutical composition.

As used herein, the terms “condition,” “disease,” and “disorder” are used interchangeably.

An “effective amount” of a compound or composition refers to an amount sufficient to elicit a desired biological response (e.g., treating a condition). As will be appreciated by those skilled in the art, the effective amount of a compound may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment. For example, in treating cancer, an effective amount of a compound or composition may reduce tumor burden or stop the growth or spread of a tumor.

A “therapeutically effective amount” of a compound or composition is an amount sufficient to provide a therapeutic benefit in the treatment of a condition, or to delay or minimize one or more symptoms associated with the condition. In some embodiments, a therapeutically effective amount is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, that provides a therapeutic benefit in the treatment of the condition. The term “therapeutically effective amount” can encompass an

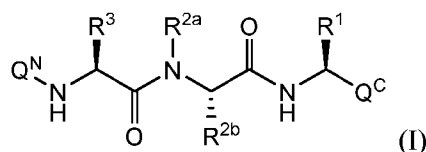
amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, or enhances the therapeutic efficacy of another therapeutic agent.

A “subject” to which administration is contemplated includes, but is not limited to, a human (i.e., a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult, or senior adult)) and/or other non-human animals, for example, mammals (e.g., primates (e.g., cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs) and birds (e.g., commercially relevant birds such as chickens, ducks, geese, and/or turkeys).

As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or condition, or one or more signs or symptoms thereof. In some embodiments, “treatment,” “treat,” and “treating” require that signs or symptoms of the disease disorder or condition have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease or condition. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

Compounds

Disclosed herein is a compound of formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

Q^{N} is $-\text{X-R}^{\text{N}}$, wherein: X is selected from $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{S}(\text{O})_2-$, and a bond; R^{N} is selected from C_1 - C_6 alkyl, aryl, and $-(\text{CR}^{\text{a}}\text{R}^{\text{b}})_p\text{-Z}$; p is 1, 2, or 3; R^{a} and R^{b} are each independently selected from hydrogen and C_1 - C_4 alkyl, wherein one R^{a} and one R^{b} , together with the carbon atom to which they are attached, are optionally taken together to form a 3- to 6-membered cycloalkyl; and Z is selected from aryl and heterocyclyl; wherein each R^{N} is optionally substituted with 1 or 2 substituents independently selected from halo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, $-\text{OH}$, and $-\text{COOH}$;

Q^{C} is selected from $-\text{B}(\text{OR}^{\text{C}1})_2$ and $-\text{C}(\text{O})\text{R}^{\text{C}2}$, wherein each $\text{R}^{\text{C}1}$ is independently selected from hydrogen, C_1 - C_6 alkyl, and aryl, or two $\text{R}^{\text{C}1}$, together with the atoms to which

they are attached, form an optionally substituted ring, and R^{C2} is selected from C₁-C₄ alkyl and C₁-C₄ haloalkyl;

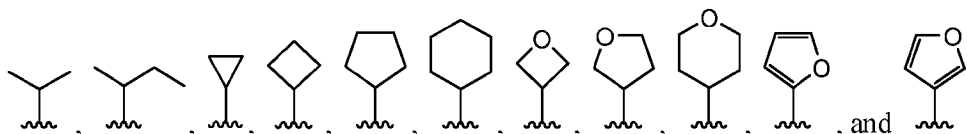
R^1 is selected from C₃-C₈ alkyl, hydroxy-C₁-C₆ alkyl, C₃-C₆ cycloalkyl, and 3- to 6-membered heterocyclyl;

5 R^{2a} is hydrogen or C₁-C₄-alkyl, and R^{2b} is selected from C₁-C₈ alkyl, aryl-C₁-C₄-alkyl, heteroaryl-C₁-C₄-alkyl, hydroxy, and $-(CH_2)_mNH-R^{2c}$, wherein m is 1, 2, 3, 4, 5, or 6, R^{2c} is selected from H and $-COO(C_1-C_6\text{-alkyl})$, and the aryl is unsubstituted or substituted with 1 or 2 substituents independently selected from hydroxy and C₁-C₆-alkoxy; or R^{2a} and R^{2b} , together with the atoms to which they are attached, form an optionally substituted ring; and

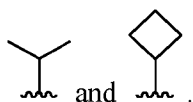
10 R^3 is selected from C₁-C₈ alkyl and $-(CH_2)_n-Y$, wherein n is 0, 1, 2, or 3, and Y is selected from aryl, heteroaryl, cycloalkyl, and heterocyclyl, wherein the alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl are each independently unsubstituted or substituted with 1 or 2 substituents independently selected from C₁-C₄ alkyl, C₃-C₆ cycloalkyl, halo, cyano, C₁-C₄ haloalkyl, hydroxy, amino, and C₁-C₄ alkoxy, and wherein the aryl or the
15 heteroaryl is optionally substituted with a group that is taken together with R^{C2} to form an optionally substituted ring.

In some embodiments, R^1 is selected from C₃-C₈ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, and 5- to 6-membered monocyclic heteroaryl. In some embodiments, R^1 is selected from C₃-C₆ alkyl, C₃-C₆ cycloalkyl, a 3- to 6-membered monocyclic
20 heterocyclyl having one heteroatom selected from O and N, and a 5-membered heteroaryl having one heteroatom selected from O and N. In some embodiments, R^1 is selected from C₃-C₅ alkyl, C₃-C₅ cycloalkyl, a 4- to 6-membered monocyclic heterocyclyl having one oxygen atom, and a 5-membered heteroaryl having one oxygen atom. In some embodiments, R^1 is selected from C₃-C₄ alkyl and C₃-C₅ cycloalkyl.

25 In some embodiments, R^1 is selected from:

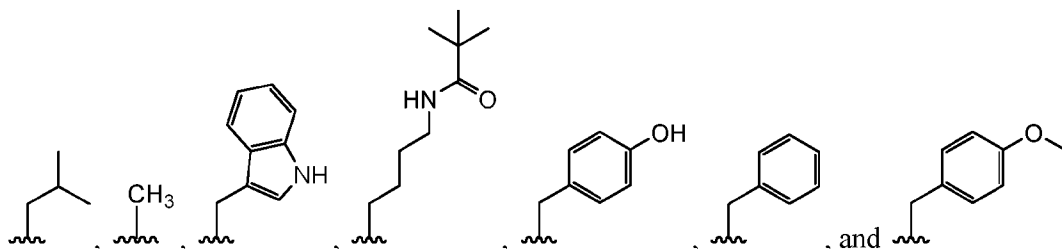


In some embodiments, R^1 is selected from:

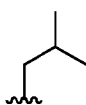


30 In some embodiments, R^{2a} is hydrogen or C₁-C₄-alkyl, and R^{2b} is selected from C₁-C₈ alkyl, aryl-C₁-C₄-alkyl, heteroaryl-C₁-C₄-alkyl, hydroxy, and $-(CH_2)_mNH-R^{2c}$, wherein m is

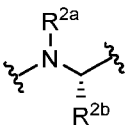
- 1, 2, 3, 4, 5, or 6, R^{2c} is selected from H and $-\text{COO}(\text{C}_1\text{-C}_6\text{-alkyl})$, and the aryl is unsubstituted or substituted with 1 or 2 substituents independently selected from hydroxy and $\text{C}_1\text{-C}_6\text{-alkoxy}$. In some embodiments, R^{2a} is hydrogen or $\text{C}_1\text{-C}_2$ alkyl, and R^{2b} is $\text{C}_1\text{-C}_6$ alkyl, aryl- $\text{C}_1\text{-C}_2\text{-alkyl}$, heteroaryl- $\text{C}_1\text{-C}_2\text{-alkyl}$, and $-(\text{CH}_2)_m\text{NH-}R^{2c}$, wherein m is 2, 3, or 4, R^{2c} is
- 5 selected from H and $-\text{COO}(\text{C}_1\text{-C}_4\text{-alkyl})$, and the aryl is unsubstituted or substituted with 1 or 2 substituents independently selected from hydroxy and $\text{C}_1\text{-C}_4\text{-alkoxy}$. In some embodiments, R^{2a} is hydrogen, and R^{2b} is selected from $\text{C}_1\text{-C}_4$ alkyl, $-\text{CH}_2\text{-phenyl}$, $-\text{CH}_2\text{-indolyl}$, and $-(\text{CH}_2)_4\text{NH-}R^{2c}$, wherein R^{2c} is selected from H and $-\text{COO}(\text{tBu})$, and the phenyl is unsubstituted or substituted with one substituent selected from hydroxy and $\text{C}_1\text{-C}_4\text{-alkoxy}$. In
- 10 some embodiments, R^{2a} is hydrogen or methyl, and R^{2b} is selected from:

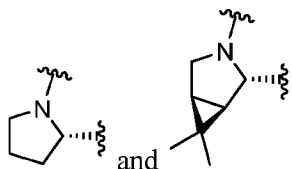


In some embodiments, R^{2a} is hydrogen, and R^{2b} is:



- In some embodiments, R^{2a} and R^{2b} , together with the atoms to which they are
- 15 attached, form an optionally substituted five-membered saturated ring. In some embodiments, R^{2a} and R^{2b} , together with the atoms to which they are attached, form an unsubstituted five-membered saturated ring. In some embodiments, R^{2a} and R^{2b} , together with the atoms to which they are attached, form a five-membered saturated ring fused with a second 3- to 6-membered ring that is optionally further substituted with 1 or 2 substituents selected from $\text{C}_1\text{-}$

- 20 C_4 alkyl. In some embodiments, the group  in Formula (I) has a formula selected from:

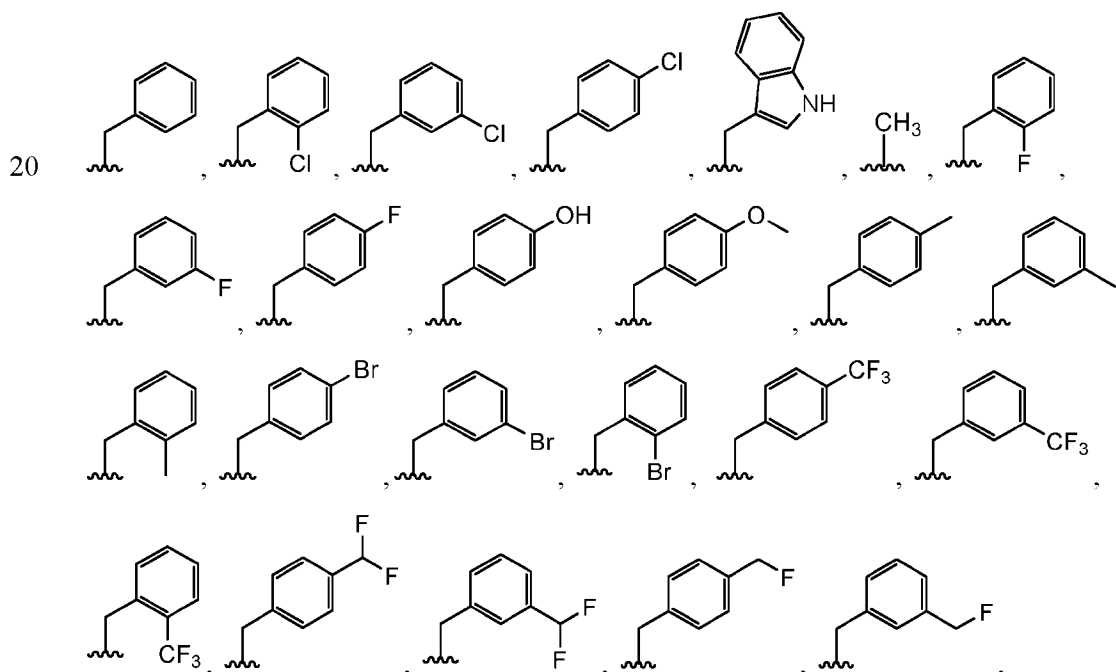


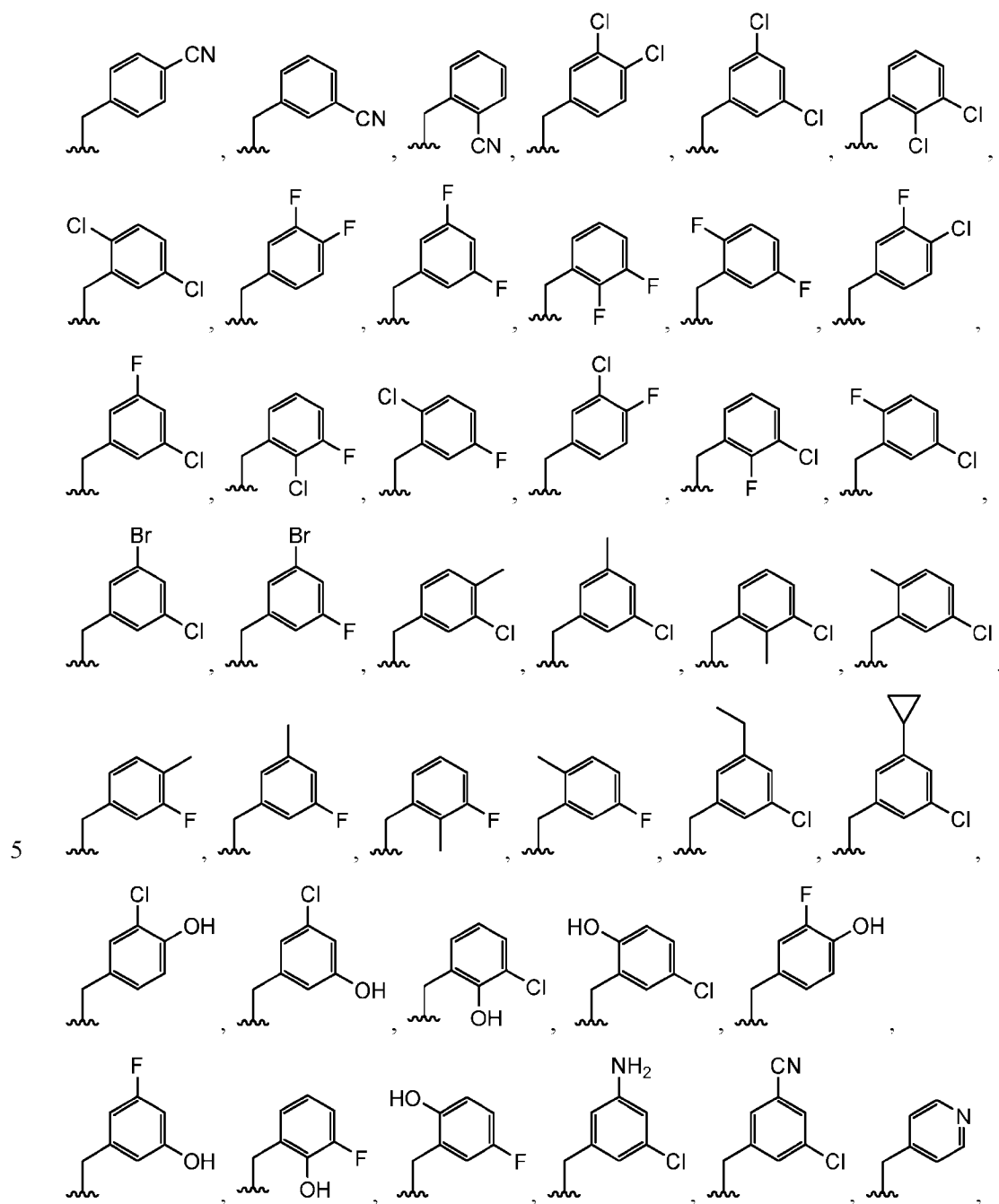
In some embodiments, R³ is selected from C₁-C₈ alkyl and -(CH₂)_n-Y, wherein n is 0, 1, 2, or 3, and Y is selected from aryl, heteroaryl, cycloalkyl, and heterocyclyl, wherein the alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl are each independently unsubstituted or substituted with 1 or 2 substituents independently selected from C₁-C₄ alkyl, C₃-C₆ cycloalkyl, halo, cyano, C₁-C₄ haloalkyl, hydroxy, amino, and C₁-C₄ alkoxy.

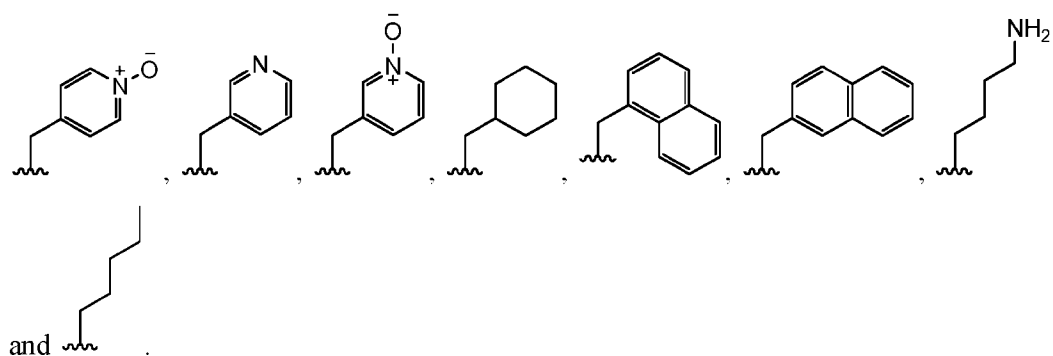
In some embodiments, R^3 is selected from C_1 - C_6 alkyl and $-(CH_2)_n-Y$, wherein n is 1 or 2, and Y is selected from aryl, a monocyclic or bicyclic heteroaryl having 1 or 2 heteroatoms independently selected from N, O, and S, and C_3 - C_6 -cycloalkyl, wherein the alkyl, aryl, and heteroaryl are independently unsubstituted or substituted with 1 or 2 substituents independently selected from C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, halo, cyano, C_1 - C_4 haloalkyl, hydroxy, amino, and C_1 - C_4 alkoxy. In some embodiments, R^3 is selected from C_1 - C_6 alkyl, $-CH_2$ -phenyl, $-CH_2$ -naphthyl, $-CH_2$ -indolyl, $-CH_2$ -pyridyl, and $-CH_2$ -cyclohexyl, wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from methyl, ethyl, fluoro, chloro, bromo, hydroxy, methoxy, cyano, fluoromethyl, difluoromethyl, and trifluoromethyl, and wherein the pyridyl is unsubstituted or substituted with one oxo group.

In some embodiments, R³ is aryl or heteroaryl that is optionally substituted with a group that is taken together with R^{C2} to form an optionally substituted ring

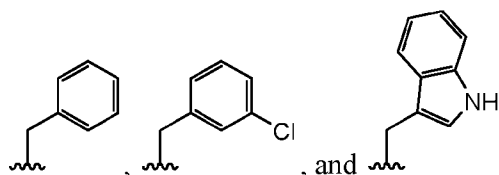
In some embodiments, R^3 is selected from:



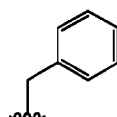




In some embodiments, R^3 is selected from:



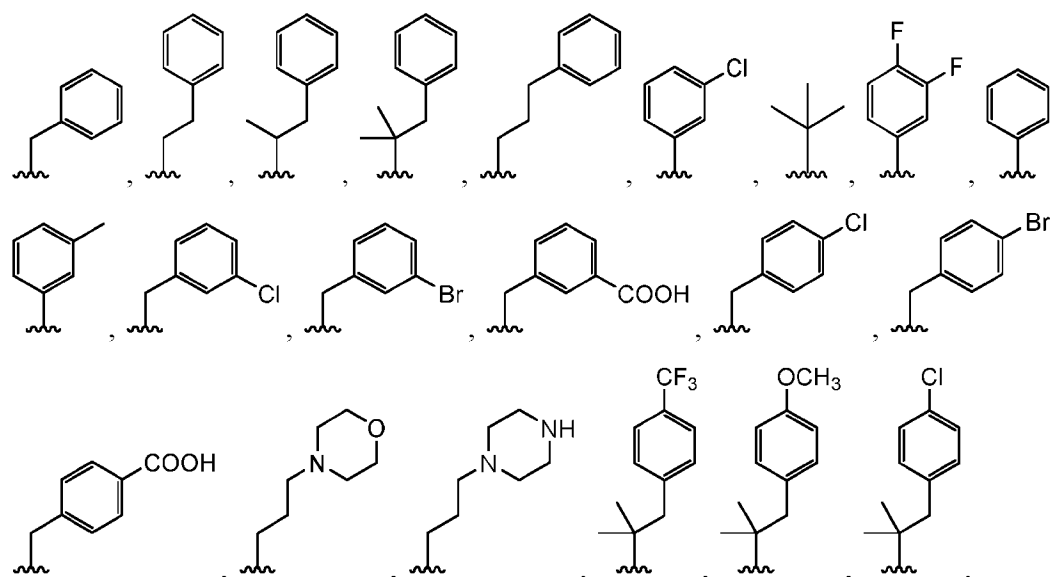
5 In some embodiments, R^3 is:

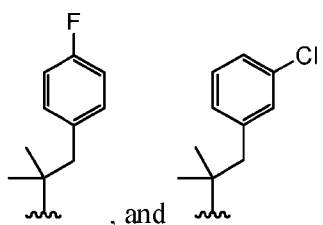


In some embodiments, X is -C(O)-. In some embodiments, -C(O)O-. In some embodiments, -C(O)NH-. In some embodiments, -S(O)₂-. In some embodiments, X is a bond.

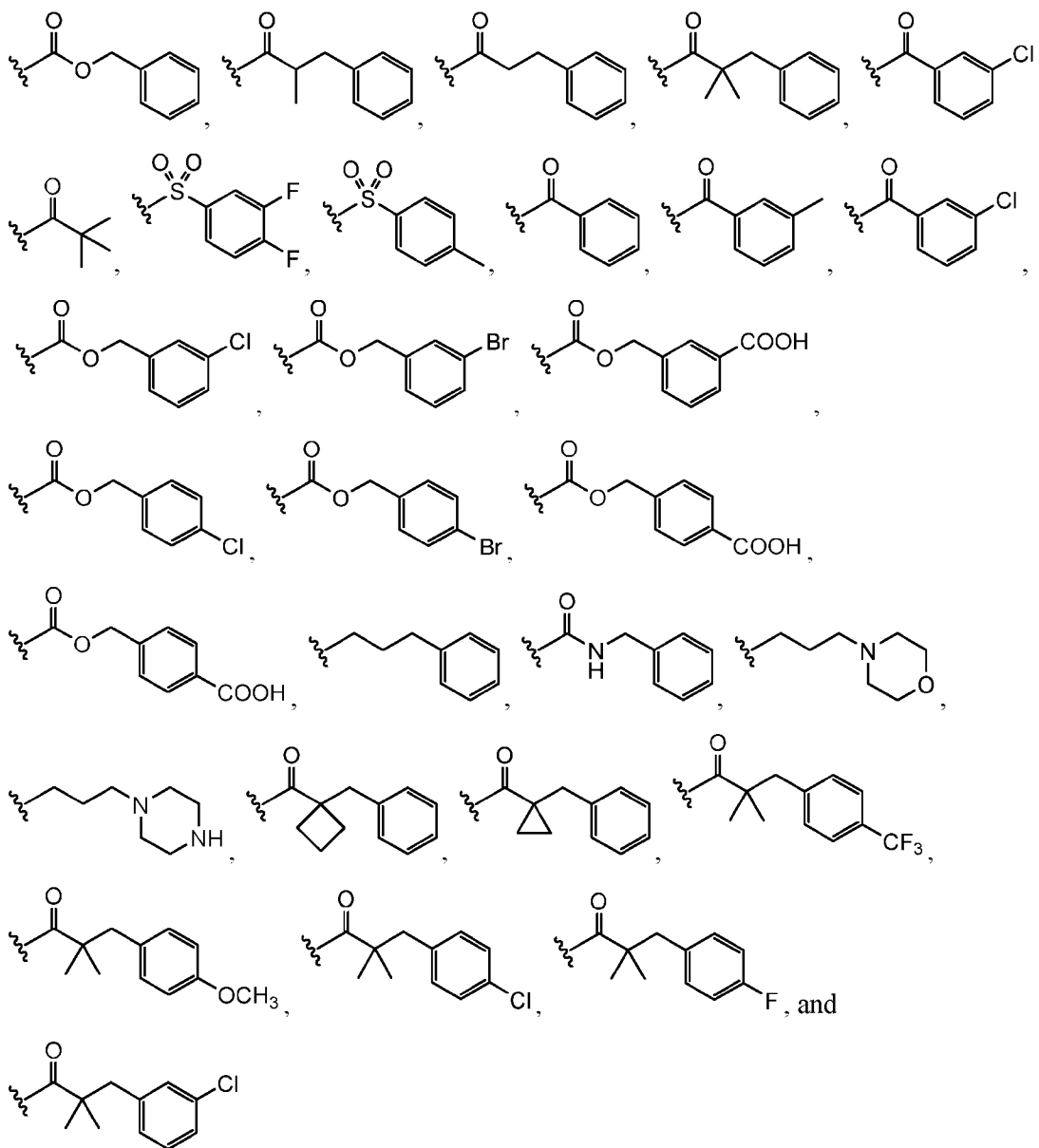
In some embodiments, R^N is selected from C₃-C₄ alkyl, phenyl, phenyl-C₁-C₃-alkyl, 10 and heterocyclyl-C₁-C₃-alkyl, wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from halo, methyl, and -COOH.

In some embodiments, R^N is selected from:





In some embodiments, Q^N is selected from:



In some embodiments, Q^C is $-B(OR^{C1})_2$, and each R^{C1} is independently selected from hydrogen, C_1 - C_4 alkyl, and phenyl, or two R^{C1} , together with the atoms to which they are attached, form an optionally substituted saturated 5- to 6-membered ring. In some

embodiments, each R^{C1} is hydrogen. In some embodiments, Q^C is $-C(O)R^{C2}$, and R^{C2} is C_1-C_4 haloalkyl.

In some embodiments, the compound of formula (I) is a compound illustrated in FIG. 1, or a pharmaceutically acceptable salt thereof.

5 Additional compounds of formula (I) are illustrated in FIG. 2.

The compounds of the present disclosure have at least one asymmetric center. Compounds with asymmetric centers give rise to enantiomers (optical isomers), diastereomers (configurational isomers) or both, and it is intended that all of the possible enantiomers and diastereomers in mixtures and as pure or partially purified compounds are
10 included within the scope of this disclosure.

The independent syntheses of the enantiomerically or diastereomerically enriched compounds, or their chromatographic separations, may be achieved as known in the art by appropriate modification of the methodology disclosed herein. The absolute stereochemistry of a compound may be determined by using X-ray crystallography to determine the crystal
15 structure of crystalline products or crystalline intermediates that are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well-known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure
20 compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to pure enantiomers by cleavage of the added chiral residue. Racemic mixtures of compounds can also be separated directly by
25 chromatographic methods using chiral stationary phases, which methods are well known in the art. Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

The compound (e.g., a compound of formula (I)) may possess tautomeric forms, and
30 tautomers also constitute embodiments of the disclosure.

The present disclosure also includes isotopically-labeled compounds (e.g., an isotopically-labeled compound of formula (I)), which are identical to those recited in formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the disclosure are hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine, such as, but not limited to ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{31}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Substitution with heavier isotopes such as deuterium, i.e. ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. The compound may incorporate positron-emitting isotopes for medical imaging and positron-emitting tomography (PET) studies for determining the distribution of receptors. Suitable positron-emitting isotopes that can be incorporated in compounds of formula (I) are ^{11}C , ^{13}N , ^{15}O , and ^{18}F .

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein using an appropriate isotopically-labeled reagent in place of a non-isotopically-labeled reagent.

Compounds of formula (I) can be synthesized by a variety of methods, including those illustrated in the Examples. Compounds and intermediates may be isolated and purified by methods well-known to those skilled in the art of organic synthesis. Examples of conventional methods for isolating and purifying compounds can include, but are not limited to, chromatography on solid supports such as silica gel, alumina, or silica derivatized with alkylsilane groups, by recrystallization at high or low temperature with an optional pretreatment with activated carbon, thin-layer chromatography, distillation at various pressures, sublimation under vacuum, and trituration, as described for instance in "Vogel's Textbook of Practical Organic Chemistry," 5th edition (1989), by Furniss, Hannaford, Smith, and Tatchell, pub. Longman Scientific & Technical, Essex CM20 2JE, England.

Reaction conditions and reaction times for each individual step can vary depending on the particular reactants employed and substituents present in the reactants used. Reactions can be worked up in a conventional manner, e.g., by eliminating the solvent from the residue and further purified according to methodologies generally known in the art such as, but not limited to, crystallization, distillation, extraction, trituration and chromatography. Unless otherwise described, the starting materials and reagents are either commercially available or can be prepared by one skilled in the art from commercially available materials using methods described in the chemical literature.

Standard experimentation, including appropriate manipulation of the reaction conditions, reagents and sequence of the synthetic route, protection of any chemical functionality that cannot be compatible with the reaction conditions, and deprotection at a

suitable point in the reaction sequence of the method are included in the scope of the disclosure. Suitable protecting groups and the methods for protecting and deprotecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which can be found in PGM Wuts and TW Greene, in Greene's book
5 titled Protective Groups in Organic Synthesis (4th ed.), John Wiley & Sons, NY (2006).

When an optically active form of a disclosed compound is required, it can be obtained by carrying out one of the procedures described herein using an optically active starting material (prepared, for example, by asymmetric induction of a suitable reaction step), or by resolution of a mixture of the stereoisomers of the compound or intermediates using a
10 standard procedure (such as chromatographic separation, recrystallization or enzymatic resolution).

Similarly, when a pure geometric isomer of a compound is required, it can be obtained by carrying out one of the procedures described herein using a pure geometric isomer as a starting material, or by resolution of a mixture of the geometric isomers of the
15 compound or intermediates using a standard procedure such as chromatographic separation.

The synthetic schemes and specific examples as described are illustrative and are not to be read as limiting the scope of the disclosure or the claims. Alternatives, modifications, and equivalents of the synthetic methods and specific examples are contemplated.

The disclosed compounds may exist as pharmaceutically acceptable salts. The term
20 "pharmaceutically acceptable salt" refers to salts or zwitterions of the compounds which are water or oil-soluble or dispersible, suitable for treatment of disorders without undue toxicity, irritation, or allergic response, commensurate with a reasonable benefit/risk ratio and effective for their intended use. The salts may be prepared during the final isolation and purification of the compounds or separately by reacting an amino group of the compounds
25 with a suitable acid. For example, a compound may be dissolved in a suitable solvent, such as but not limited to methanol and water and treated with at least one equivalent of an acid, like hydrochloric acid. The resulting salt may precipitate out and be isolated by filtration and dried under reduced pressure. Alternatively, the solvent and excess acid may be removed under reduced pressure to provide a salt. Representative salts include acetate, adipate,
30 alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, isethionate, fumarate, lactate, maleate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, oxalate, maleate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, glutamate,

para-toluenesulfonate, undecanoate, hydrochloric, hydrobromic, sulfuric, phosphoric and the like. The amino groups of the compounds may also be quaternized with alkyl chlorides, bromides and iodides such as methyl, ethyl, propyl, isopropyl, butyl, lauryl, myristyl, stearyl, and the like. In one embodiment, the compound is in the form of a trifluoroacetate salt.

5 Basic addition salts may be prepared during the final isolation and purification of the disclosed compounds by reaction of a phosphate, phosphonate or carboxyl group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation such as lithium, sodium, potassium, calcium, magnesium, or aluminum, or an organic primary, secondary, or tertiary amine. Quaternary amine salts can be prepared, such as those derived
10 from methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, 1-phenamine and N,N'-dibenzylethylenediamine, ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine, and the like.

15 Compounds disclosed herein can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present disclosure. Certain compounds of the disclosure may also exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to
20 be within the scope of the present disclosure.

Pharmaceutical Compositions

 The disclosed compounds may be incorporated into pharmaceutical compositions suitable for administration to a subject (such as a patient, which may be a human or non-human). The pharmaceutical compositions may include a “therapeutically effective amount”
25 or a “prophylactically effective amount” of the agent. A “therapeutically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the composition may be determined by a person skilled in the art and may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the composition to
30 elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of a compound of the disclosure are outweighed by the therapeutically beneficial effects. A “prophylactically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic

result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease or condition, the prophylactically effective amount will be less than the therapeutically effective amount.

The pharmaceutical compositions may include pharmaceutically acceptable carriers.

5 The term “pharmaceutically acceptable carrier,” as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as, but not limited to, lactose, glucose and sucrose; starches such as, but not limited to, corn starch and potato starch; cellulose and its derivatives such as, but not limited to, sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered
10 tragacanth; malt; gelatin; talc; excipients such as, but not limited to, cocoa butter and suppository waxes; oils such as, but not limited to, peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such as propylene glycol; esters such as, but not limited to, ethyl oleate and ethyl laurate; agar; buffering agents such as, but not limited to, magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water;
15 isotonic saline; Ringer’s solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as, but not limited to, sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the
20 composition, according to the judgment of the formulator.

Thus, the compounds and their pharmaceutically acceptable salts may be formulated for administration by, for example, solid dosing, eye drop, in a topical oil-based formulation, injection, inhalation (either through the mouth or the nose), implants, or oral, buccal, parenteral, or rectal administration. Techniques and formulations may generally be found in
25 “Remington’s Pharmaceutical Sciences,” (Meade Publishing Co., Easton, Pa.). Therapeutic compositions must typically be sterile and stable under the conditions of manufacture and storage.

The route by which the disclosed compounds are administered and the form of the composition will dictate the type of carrier to be used. The composition may be in a variety of
30 forms, suitable, for example, for systemic administration (e.g., oral, rectal, nasal, sublingual, buccal, implants, or parenteral) or topical administration (e.g., dermal, pulmonary, nasal, aural, ocular, liposome delivery systems, or iontophoresis). In some embodiments, the composition is in a form suitable for parenteral administration, e.g., intravenous,

intramuscular, or subcutaneous administration. In some embodiments, the composition is in a form suitable for an implant, e.g., an ocular implant.

In some embodiments, the composition is in a form suitable for ocular administration, such as an ophthalmic formulation. Such compositions may include components such as
5 surfactants, tonicity agents, buffers, preservatives, co-solvents, and viscosity building agents.

In some embodiments, disclosed herein is an ophthalmic formulation comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an ophthalmically acceptable carrier. Such a composition may be suitable for topical ophthalmic administration to a subject in need thereof.

10 The ophthalmic formulations, which can be administered topically, periocularly, or intraocularly, comprise an effective amount of one or more compounds of formula (I), or pharmaceutically acceptable salts thereof. In some embodiments, for formulations intended to be administered topically to the eye in the form of eye drops or eye ointments, the amount of the compound of formula (I) will be 0.001 to 1.0% (w/w). When applied as eye drops, in
15 some embodiments, one to two drops of such formulations will be administered from once to several times per day.

The compounds of the present disclosure can be administered as solutions, suspensions, or emulsions (dispersions) in an ophthalmically acceptable vehicle. An “ophthalmically acceptable” component, as used herein, refers to a component which will not
20 cause any significant ocular damage or ocular discomfort at the intended concentration and over the time of intended use. Solubilizers and stabilizers should be non-reactive. An “ophthalmically acceptable vehicle” refers to any substance or combination of substances which are non-reactive with the compounds and suitable for administration to a patient. Suitable vehicles may be non-aqueous liquid media including the physiologically acceptable
25 oils such as silicone oil, USP mineral oil, white oil, polyethylene glycol, polyethoxylated castor oil and vegetable oils, for example corn oil, peanut oil, or the like. Other suitable vehicles may be aqueous or oil-in-water solutions suitable for topical application to the eye. These vehicles may be preferred based on ease of formulation, as well as a subject’s ability to easily administer such formulations by means of instilling drops of the compositions in the
30 affected eyes. The formulations may also be suspensions, viscous or semi-viscous gels, or other types of solid or semi-solid formulations. In some embodiments, the formulations comprise one or more fat bases, such as natural wax e.g. white bees wax, carnauba wax, wool wax (wool fat), purified lanolin, anhydrous lanolin; petroleum wax, e.g. solid paraffin, microcrystalline wax; hydrocarbons, e.g., liquid paraffin, white petrolatum, yellow

petrolatum; or combinations thereof. The formulations may be applied by use of the hands or an applicator such as a wipe, a contact lens, a dropper or a spray.

Various tonicity agents may be employed to adjust the tonicity of the composition, e.g., to that of natural tears. For example, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, dextrose, and/or mannitol may be added to the composition to approximate physiological tonicity. Such an amount of tonicity agent will vary, depending on the particular agent to be added. In some embodiments, the formulations will have a tonicity agent in an amount sufficient to cause the final composition to have an ophthalmically acceptable osmolality (e.g., about 200-400 mOsm/kg).

An appropriate buffer system (e.g., sodium phosphate, sodium acetate, sodium citrate, sodium borate, or boric acid) may be added to the formulations to prevent pH drift under storage conditions. The particular concentration will vary, depending on the agent employed. In some embodiments, the buffer will be selected to maintain a target pH within the range of pH 6-7.5.

Topical ophthalmic formulations may also comprise aqueous carriers. Such carriers can be formulated as a phospholipid carrier or an artificial tears carrier, or mixtures of both. As used herein, "phospholipid carrier" and "artificial tears carrier" refer to aqueous formulations which: (i) comprise one or more phospholipids (in the case of phospholipid carriers) or other compounds, which lubricate, or "wet," approximate the consistency of endogenous tears, aid in natural tear build-up, or otherwise provide temporary relief of dry eye symptoms and conditions upon ocular administration; (ii) are safe; and (iii) provide the appropriate delivery vehicle for the topical administration of an effective amount of one or more compounds disclosed herein.

Other compounds designed to lubricate, approximate the consistency of endogenous tears, aid in natural tear build-up, or otherwise provide temporary relief of dry eye symptoms and conditions upon ocular administration the eye are known in the art. Such compounds may enhance the viscosity of the composition, and include, but are not limited to: monomeric polyols, such as glycerol, propylene glycol, ethylene glycol; polymeric polyols, such as polyethylene glycol, hydroxypropylmethyl cellulose, carboxy methyl cellulose sodium, hydroxypropyl cellulose; dextrans, such as dextran 70; water soluble proteins, such as gelatin; and vinyl polymers, such as polyvinyl alcohol, polyvinylpyrrolidone, povidone and carbomers; and the like.

Other compounds may also be added to the ophthalmic formulations of the present disclosure to increase the viscosity of the compositions. Examples of viscosity enhancing

agents include, but are not limited to: polysaccharides, such as hyaluronic acid and its salts, chondroitin sulfate and its salts, dextrans, various polymers of the cellulose family; vinyl polymers; and acrylic acid polymers. In general, the phospholipid carrier or artificial tears carrier compositions will exhibit a viscosity of 1 to 400 centipoise.

5 Preservatives may be required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, chlorobutanol, benzododecinium bromide, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, polyquaternium- 1, or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from 0.001 to 1.0% w/v. Compositions of the present
10 invention may be sterile but unpreserved, and such compositions generally will not contain preservatives.

 In other embodiments, compounds of formula (I) are formulated for systemic administration. Carriers for systemic administration typically include at least one of diluents, lubricants, binders, disintegrants, colorants, flavors, sweeteners, antioxidants, preservatives,
15 glidants, solvents, suspending agents, wetting agents, surfactants, combinations thereof, and others.

 Suitable diluents include sugars such as glucose, lactose, dextrose, and sucrose; diols such as propylene glycol; calcium carbonate; sodium carbonate; sugar alcohols, such as glycerin; mannitol; and sorbitol. The amount of diluent(s) in a systemic or topical
20 composition is typically about 50 to about 90% by weight of the composition.

 Suitable lubricants include silica, talc, stearic acid and its magnesium salts and calcium salts, calcium sulfate; and liquid lubricants such as polyethylene glycol and vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma. The amount of lubricant(s) in a systemic or topical composition is typically about
25 5 to about 10% by weight of the composition.

 Suitable binders include polyvinyl pyrrolidone; magnesium aluminum silicate; starches such as corn starch and potato starch; gelatin; tragacanth; and cellulose and its derivatives, such as sodium carboxymethylcellulose, ethyl cellulose, methylcellulose, microcrystalline cellulose, and sodium carboxymethylcellulose. The amount of binder(s) in a
30 systemic composition is typically about 5 to about 50% by weight of the composition.

 Suitable disintegrants include agar, alginic acid and the sodium salt thereof, effervescent mixtures, croscarmellose, crospovidone, sodium carboxymethyl starch, sodium starch glycolate, clays, and ion exchange resins. The amount of disintegrant(s) in a systemic or topical composition is typically about 0.1 to about 10% by weight of the composition.

Suitable colorants include a colorant such as an FD&C dye. When used, the amount of colorant in a systemic or topical composition is typically about 0.005 to about 0.1% by weight of the composition.

5 Suitable flavors include menthol, peppermint, and fruit flavors. The amount of flavor(s), when used, in a systemic or topical composition is typically about 0.1 to about 1.0%.

Suitable sweeteners include aspartame and saccharin. The amount of sweetener(s), when used, in a systemic or topical composition is typically about 0.001 to about 1% by weight of the composition.

10 Suitable antioxidants include butylated hydroxyanisole ("BHA"), butylated hydroxytoluene ("BHT"), and vitamin E. The amount of antioxidant(s) in a systemic or topical composition is typically about 0.1 to about 5% by weight of the composition.

Suitable preservatives include benzalkonium chloride, methyl paraben, and sodium benzoate. The amount of preservative(s) in a systemic or topical composition is typically
15 about 0.01 to about 5% by weight of the composition.

Suitable glidants include silicon dioxide. The amount of glidant(s) in a systemic or topical composition is typically about 1 to about 5% by weight of the composition.

Suitable solvents include water, isotonic saline, ethyl oleate, glycerin, hydroxylated castor oils, alcohols such as ethanol, and aqueous buffer solutions, such as phosphate buffer
20 solutions. In some embodiments, the solvent is an aqueous buffer solution, such as phosphate-buffered saline. The amount of solvent(s) in a systemic or topical composition is typically from about 0 to about 100% by weight of the composition.

Suitable suspending agents include AVICEL RC-591 (from FMC Corporation of Philadelphia, PA) and sodium alginate. The amount of suspending agent(s) in a systemic or
25 topical composition is typically about 1 to about 8% by weight of the composition.

Suitable surfactants include lecithin, Polysorbate 80, and sodium lauryl sulfate, and the TWEENS from Atlas Powder Company of Wilmington, Delaware. Suitable surfactants include those disclosed in the C.T.F.A. Cosmetic Ingredient Handbook, 1992, pp.587-592; Remington's Pharmaceutical Sciences, 15th Ed. 1975, pp. 335-337; and McCutcheon's
30 Volume 1, Emulsifiers & Detergents, 1994, North American Edition, pp. 236-239. The amount of surfactant(s) in the systemic or topical composition is typically about 0.1% to about 5% by weight of the composition.

Although the amounts of components in the systemic compositions may vary depending on the type of systemic composition prepared, in general, systemic compositions

include 0.01% to 50% by weight of an active compound and 50% to 99.99% by weight of one or more carriers. Compositions for parenteral administration typically include 0.1% to 10% by weight of actives and 90% to 99.9% by weight of a carrier including a diluent and a solvent.

5 Compositions for oral administration can have various dosage forms. For example, solid forms include tablets, capsules, granules, and bulk powders. These oral dosage forms include a safe and effective amount, usually at least about 5% by weight, and more particularly from about 25% to about 50% by weight of actives. The oral dosage compositions include about 50% to about 95% by weight of carriers, and more particularly,
10 from about 50% to about 75% by weight.

 Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed. Tablets typically include an active component, and a carrier comprising ingredients selected from diluents, lubricants, binders, disintegrants, colorants, flavors, sweeteners, glidants, and combinations thereof. Specific diluents include calcium
15 carbonate, sodium carbonate, mannitol, lactose and cellulose. Specific binders include starch, gelatin, and sucrose. Specific disintegrants include alginic acid and croscarmellose. Specific lubricants include magnesium stearate, stearic acid, and talc. Specific colorants are the FD&C dyes, which can be added for appearance. Chewable tablets preferably contain sweeteners such as aspartame and saccharin, or flavors such as menthol, peppermint, fruit flavors, or a
20 combination thereof.

 Capsules (including implants, time release and sustained release formulations) typically include an active compound and a carrier including one or more diluents disclosed above in a capsule comprising gelatin. Granules typically comprise a disclosed compound, and preferably glidants such as silicon dioxide to improve flow characteristics. Implants can
25 be of the biodegradable or the non-biodegradable type.

 The selection of ingredients in the carrier for oral compositions depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of this disclosure.

 Solid compositions may be coated by conventional methods, typically with pH or
30 time-dependent coatings, such that a disclosed compound is released in the gastrointestinal tract in the vicinity of the desired application, or at various points and times to extend the desired action. The coatings typically include one or more components selected from the group consisting of cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl

methyl cellulose phthalate, ethyl cellulose, EUDRAGIT® coatings (available from Evonik Industries of Essen, Germany), waxes and shellac.

Compositions for oral administration can have liquid forms. For example, suitable liquid forms include aqueous solutions, emulsions, suspensions, solutions reconstituted from non-effervescent granules, suspensions reconstituted from non-effervescent granules, effervescent preparations reconstituted from effervescent granules, elixirs, tinctures, syrups, and the like. Liquid orally administered compositions typically include a disclosed compound and a carrier, namely, a carrier selected from diluents, colorants, flavors, sweeteners, preservatives, solvents, suspending agents, and surfactants. Peroral liquid compositions preferably include one or more ingredients selected from colorants, flavors, and sweeteners.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically include one or more of soluble filler substances such as diluents including sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose, and hydroxypropyl methylcellulose. Such compositions may further include lubricants, colorants, flavors, sweeteners, antioxidants, and glidants.

The disclosed compounds can be topically administered. Topical compositions that can be applied locally to the skin may be in any form including solids, solutions, oils, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, skin patches, and the like. Topical compositions include: a disclosed compound (e.g., a compound disclosed herein, or a pharmaceutically acceptable salt thereof) and a carrier. The carrier of the topical composition preferably aids penetration of the compounds into the skin. The carrier may further include one or more optional components.

The amount of the carrier employed in conjunction with a disclosed compound is sufficient to provide a practical quantity of composition for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this disclosure are described in the following references: Modern Pharmaceutics, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms, 2nd Ed., (1976).

A carrier may include a single ingredient or a combination of two or more ingredients. In the topical compositions, the carrier includes a topical carrier. Suitable topical carriers include one or more ingredients selected from phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, symmetrical alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate,

dimethyl isosorbide, castor oil, combinations thereof, and the like. More particularly, carriers for skin applications include propylene glycol, dimethyl isosorbide, and water, and even more particularly, phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, and symmetrical alcohols.

5 The carrier of a topical composition may further include one or more ingredients selected from emollients, propellants, solvents, humectants, thickeners, powders, fragrances, pigments, and preservatives, all of which are optional.

 Suitable emollients include stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, isopropyl
10 isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic
15 acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate, and combinations thereof. Specific emollients for skin include stearyl alcohol and polydimethylsiloxane. The amount of emollient(s) in a skin-based topical composition is typically about 5% to about 95% by weight of the composition.

 Suitable propellants include propane, butane, isobutane, dimethyl ether, carbon
20 dioxide, nitrous oxide, and combinations thereof. The amount of propellant(s) in a topical composition is typically about 0% to about 95% by weight of the composition.

 Suitable solvents include water, ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethylsulfoxide, dimethyl formamide, tetrahydrofuran, and combinations
25 thereof. Specific solvents include ethyl alcohol and homotopic alcohols. The amount of solvent(s) in a topical composition is typically about 0% to about 95% by weight of the composition.

 Suitable humectants include glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin, and combinations thereof. Specific humectants
30 include glycerin. The amount of humectant(s) in a topical composition is typically 0% to 95% by weight of the composition.

 The amount of thickener(s) in a topical composition is typically about 0% to about 95% by weight of the composition.

Suitable powders include beta-cyclodextrins, hydroxypropyl cyclodextrins, chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically-modified magnesium aluminum silicate, organically-modified montmorillonite clay, hydrated
 5 aluminum silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate, and combinations thereof. The amount of powder(s) in a topical composition is typically 0% to 95% by weight of the composition.

The amount of fragrance in a topical composition is typically about 0% to about 0.5%, particularly, about 0.001% to about 0.1% by weight of the composition.

10 Suitable pH adjusting additives include HCl or NaOH in amounts sufficient to adjust the pH of a topical pharmaceutical composition.

Methods of Use

Compounds of formula (I) can be used for treatment of a variety of disorders that are associated with HTRA1. Accordingly, disclosed herein is a method of treating a disorder
 15 associated with HTRA1 in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein (e.g., a compound of formula (I), or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition disclosed herein (e.g., a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof).

20 HTRA1 has been implicated in a number of disorders. Examples include, but are not limited to, macular degeneration (*see, e.g., Yang et al. (2006) Science 314(5801), 992–993; Lin et al. (2018) Aging Cell, 17(4), e12710; Jones et al. (2011) Proc. Natl. Acad. Sci. USA, 108(35), 14578–14583; Vierkotten et al. (2011) PloS One, 6(8), e22959; Alzheimer's Disease (see, e.g., Grau et al. (2005) Proc. Natl. Acad. Sci. USA, 102(17), 6021–6026;*

25 Tennstaedt et al. (2012) J. Biol. Chem. 287(25), 20931–20941; Xiao et al. (2021) CNS Neurosci. Ther. 27(12), 1531–1539), bladder cancer (*see, e.g., Lorenzi et al. (2013) Int. J. Cancer 133(11), 2650–2661; intervertebral disc degeneration (see, e.g., Tiaden, et al. (2012) J. Biol. Chem. 287(25), 21335–21345; Akhatib et al. (2013) J. Biol. Chem. 288(26), 19280–19287; Lyme disease (see, e.g., Russell et al. (2016) Mol. Microbiol. 99(3), 586–596;*

30 Russell et al. (2013) Mol. Microbiol. 90(2), 241–251; Russell et al. (2013) Mol. Microbiol. 90(2), 228–240; and Ye et al. (2016) Infect. Immun. 84(8), 2372–2381); osteoarthritis (*see, e.g., Holt et al. (2012) Osteoarthr. Cartilage, 20(5), 430–439; Chen et al. (2019) Am. J. Pathol. 189(7), 1423–1434; Bhutada et al. (2022) Osteoarthr. Cartilage, 30(8),*

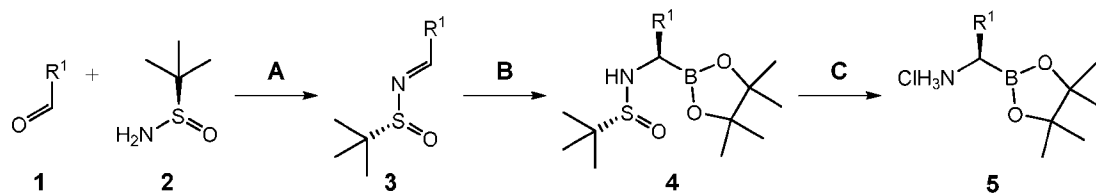
1091–1102; Tossetta *et al.* (2022) *Bone*, 157(116350), 116350; Tsuchiya *et al.* (2005) *Bone*, 37(3), 323–336; Polur *et al.* (2010) *Histol. Histopathol.* 25(5), 599–608); preeclampsia (see, e.g., Gesuita *et al.* (2019) *Pregnancy Hypertens.* 18, 58–62; Liu *et al.* (2018) *Mol. Med. Rep.* 18(3), 2937–2944; Teoh *et al.* (2015) *Placenta* 36(9), 990–995; Ajayi *et al.* (2008) *Am. J. Obstet. Gynecol.* 199(5), 557.e1-10); rheumatoid arthritis (see, e.g., Grau *et al.* (2006) *J. Biol. Chem.* 281(10), 6124–6129); and TGFBI-associated corneal dystrophies (see, e.g., Venkatraman *et al.* (2017) *J. Proteome Res.* 16(8), 2899–2913; Poulsen *et al.* (2019) *J. Biol. Chem.* 294(31), 11817–11828).

Accordingly, disclosed herein is a method of treating a disorder in a subject in need thereof, wherein the disorder is selected from macular degeneration, Alzheimer's disease, arthritis, bladder cancer, intervertebral disc degeneration, Lyme disease, osteoarthritis, preeclampsia, rheumatoid arthritis, and TGFBI-associated corneal dystrophies, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein (e.g., a compound of formula (I), or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition disclosed herein (e.g., a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof). In some embodiments, the disorder is macular degeneration. In some embodiments, the disorder is age-related macular degeneration. In some embodiments, the disorder is dry age-related macular degeneration.

Examples

Abbreviations used in the Examples include the following: CBz is carboxybenzyl; DCM is dichloromethane; DIPEA is *N,N*-diisopropylethylamine; DMF is *N,N*-dimethylformamide; DMSO is dimethylsulfoxide; and HBTU is 3-[bis(dimethylamino)methyl]-1,2,3,4-tetrahydro-1H-benzotriazin-4-yl hexafluorophosphate.

Example 1: Synthesis of R¹ α-borylated amines



See, e.g., Buesking *et al.* *J. Org. Chem.* **2014**, 79 (8), 3671–3677.

Step A. To a solution of the aldehydes **1** and (R)-2-methylpropane-2-sulfinamide **2** in tetrahydrofuran, was added tetraethoxytitanium. The resulting mixture was stirred for 12–48

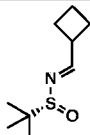
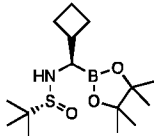
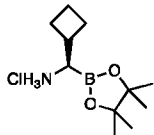
hours at ambient temperature. The reaction mixture was then added to a mixture of saturated sodium chloride aqueous solution and ethyl acetate. The resulting suspension was filtered through a pad of Celite and washed with ethyl acetate. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give the desired compound as a colorless oil which was used without further purification (50–85% yield).

Step B. Tricyclohexylphosphine tetrafluoroborate (1.2 mol%) was stirred in toluene before a solution of aqueous copper II sulfate (1.2 mol%) was added. Then, benzylamine (5 mol%) was added in a dropwise fashion and the blue biphasic solution became a pale blue emulsion. This was stirred for 10–30 min before a solution of (*R*)-*N*-sulfinamides **3** were added as a solution of toluene. Then, 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane was added as a single, solid portion and the reaction was allowed to stir for 12–36 hours. The reaction was filtered over a pad of Celite and concentrated under reduced pressure. It was purified by column chromatography to give 20–60% yields of α -borylated sulfinamides **4** typically as white solids.

Step C. α -borylated sulfinamides **4** were dissolved in 1,4-dioxane before the addition of 4M HCl in 1,4-dioxane. After 3–12 hours, the formed precipitate was filtered and washed with a hexanes:diethyl ether mixture to give α -borylated amines **5** as an HCl salt, typically as white solids in 20–60% yields.

Table 1 below shows structures and characterization data for compounds made according to the above general methods.

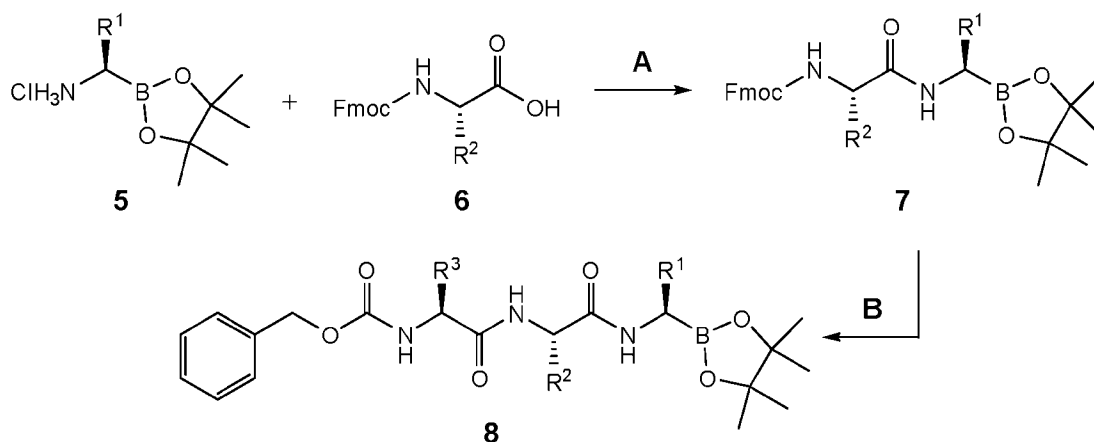
Table 1. Structures and Characterization Data

Structure	¹ H NMR / MS
	¹ H NMR (500 MHz, CDCl ₃) δ 8.11 (d, <i>J</i> = 4.7 Hz, 1H), 3.37 (pdd, <i>J</i> = 8.1, 4.8, 1.1 Hz, 1H), 2.25–2.15 (m, 4H), 2.09–2.06 (m, 1H), 1.98–1.9 (m, 1H), 1.20 (s, 9H).
	¹ H NMR (500 MHz, CDCl ₃) δ 2.97 (d, <i>J</i> = 9 Hz, 1H), 2.60–2.52 (m, 1H), 2.13–2.10 (m, 1H), 1.98–1.95 (m, 1H), 1.87–1.79 (m, 4H), 1.25 (s, 6H), 1.26 (s, 6H), 1.23 (s, 3H), 1.18 (s, 6H). C ₁₅ H ₃₁ BNO ₃ S [M+H] ⁺ calc., 316.2; found, 316.1
	¹ H NMR (500 MHz, CDCl ₃) δ 3.68 (s, 1H), 2.77 (d, <i>J</i> = 9.3, 1H), 2.70–2.58 (m, 1H), 2.17–2.09 (m, 2H), 2.01–1.65 (m, 4H), 1.33 (s, 6H), 1.33 (s, 6H), 1.27 (s, 1H), 1.22 (s, 1H). C ₁₁ H ₂₃ BNO ₂ [M+H] ⁺ calc. 212.1; found 212.1

	$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 0.91-0.97 (m, 2H), 1.04-1.11 (m, 2H), 1.17 (s, 9H), 1.92-2.02 (m, 1H), 7.44 (d, 1H).
	$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 0.26-0.36 (m, 2H), 0.45-0.62 (m, 2H), 1.20 (s, 9H), 1.22-1.29 (m, 12H), 2.38 (dd, 1H), 3.26 (brd, 1H).
	$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 0.37-0.42 (m, 1H), 0.59-0.73 (m, 3H), 1.17-1.31 (m, 13H), 2.49-2.59 (m, 1H), 8.25 (br s, 3H).
	$^1\text{H NMR}$ (400 MHz, DMSO-d_6) δ = 7.83 (br s, 3H), 2.87-2.69 (m, 1H), 1.29-1.22 (s, 12H), 1.20 (d, J = 7.6 Hz, 3H).
	$^1\text{H NMR}$ (400 MHz, DMSO-d_6) δ = 7.82 (s, 3H), 2.76-2.63 (m, 1H), 1.79-1.59 (m, 1H), 1.54-1.37 (m, 2H), 1.25 (s, 12H), 0.87 (d, J = 6.5 Hz, 6H).
	$^1\text{H NMR}$ (400 MHz, DMSO-d_6) δ = 7.84 (s, 3H), 2.62 (br s, 1H), 2.12 - 2.01 (m, 1H), 1.73 (br s, 2H), 1.62 - 1.45 (m, 4H), 1.25 (m, 12H).

Example 2: Synthesis of Boronic Ester Compounds

Method 1

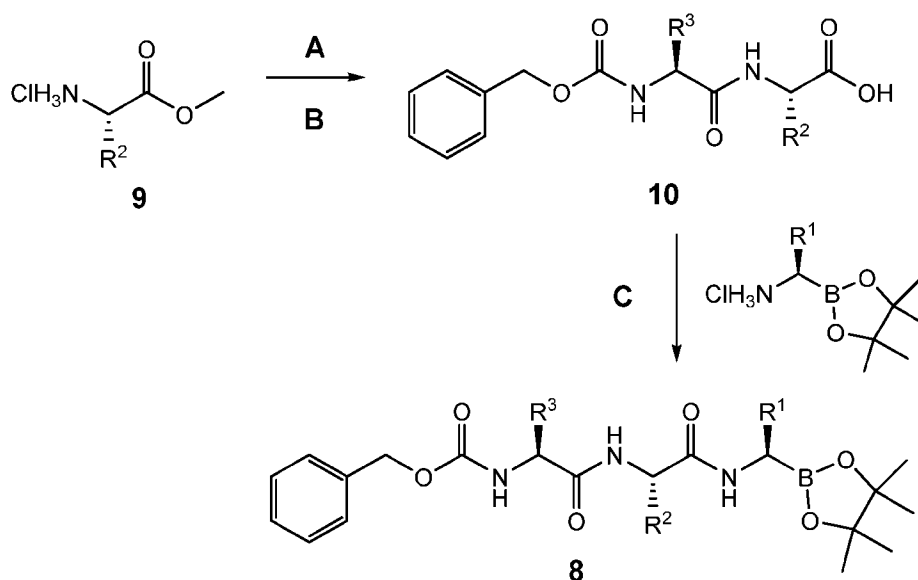


- 5 Step A. To a stirred solution of Fmoc-amino acids **6** in dichloromethane were added the HCl salts of α -borylated amines **5**. The mixture was cooled to 0 °C and HBTU was added followed by DIPEA. The reaction mixture was stirred for 12–36 hours at ambient temperature. The mixture was diluted with saturated aqueous sodium chloride and ethyl

acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate three times. The combined ethyl acetate extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue is purified by chromatography to give compounds **7** in 80–95% yields, typically as white solids.

5 Step B. Compounds **7** were treated with a solution of piperidine in DMF (20%) for 15 minutes before the mixture was evaporated to dryness. This residue was then taken up in DCM and a CBz-protected amino acid was added. The solution was cooled to 0 °C and HBTU followed by DIPEA were added sequentially. The reaction mixture was stirred for 12–36 hours at room temperature. The mixture was diluted with saturated aqueous sodium
10 chloride and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate three times. The combined ethyl acetate extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give crude compounds **8** which were used in subsequent chemistry without further purification.

15 **Method 2**



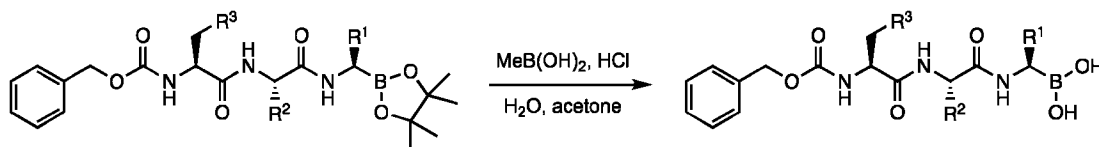
Step A. HCl salt / methyl esters of amino acids **9** and Z-amino acids were combined under an atmosphere of nitrogen before the addition of DCM (0.1–0.3 M). The solution was cooled to 0 °C and HBTU followed by DIPEA were added sequentially. The reaction mixture
20 was stirred for 12–36 hours at room temperature. The mixture was diluted with saturated aqueous sodium chloride and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate three times. The combined ethyl acetate extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give crude

penultimate compounds **8** which were used in subsequent chemistry without further purification.

Step B. Methyl esters were dissolved in a mixture of THF and water before the addition of LiOH and stirred overnight at ambient temperature. The mixture was brought to pH = 1 with 1M HCl and extracted three times with ethyl acetate. The combined organic fractions were washed with brine, dried over magnesium sulfate, concentrated under reduced pressure, and purified by reverse phase chromatography to give free acids **10** in 40–99% yield.

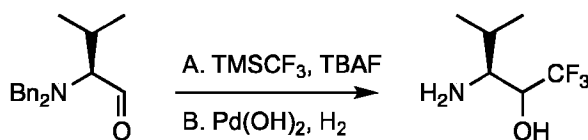
Step C. HCl salts of boronic acids were combined under an atmosphere of nitrogen before the addition of DCM (0.1–0.3 M). The solution was cooled to 0 °C and HBTU followed by DIPEA were added sequentially. The reaction mixture was stirred for 12–36 hours at room temperature. The mixture was diluted with saturated aqueous sodium chloride and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate three times. The combined ethyl acetate extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give crude boronic esters **8** which were used in subsequent chemistry without further purification.

Example 3: Synthesis of Boronic Acid Compounds of Formula (I)



To a stirred solution of boronic ester (1.0 eq) in acetone and water (0.1M overall) was added methylboronic acid (10 eq) and 1M hydrochloric acid aqueous solution. The reaction mixture was stirred for 12–48 hours days at ambient temperature. After the reaction was complete, the mixture was concentrated under reduced pressure and purified by chromatography using a Biotage Sfar C18 D column with Water/Acetonitrile gradient (100% water to 0% over 40 column volumes) to give boronic acids as white solids (17–90% yield) after drying by lyophilization.

Example 4: Synthesis of trifluoro-amino alcohols



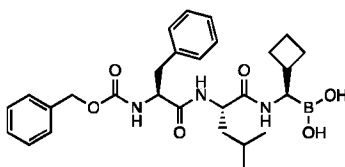
Step-A: (3S)-3-(dibenzylamino)-1,1,1-trifluoro-4-methylpentan-2-ol

To a solution mixture of aldehyde (1eq) in THF was added catalytic amount of TBAF at 0°C and stirred for 5 mins. Then TMSCF₃ (2 eq) was added and stirring continued for 15 mins. Then, TBAF (another catalytic amount) was added and continued for 4h at rt. Reaction mixture was evaporated under vacuum, crude was diluted with EtOAc and washed with water and organic layer was dried over Na₂SO₄ and concentrated under vacuo. Crude was purified by column chromatography to afford dibenzyl amino alcohols.

Step-B: (3S)-3-amino-1,1,1-trifluoro-4-methylpentan-2-ol

To a solution mixture of dibenzyl amino alcohol (1 eq) in MeOH was added catalytic Pd(OH)₂ at rt under H₂-gas atmosphere and continued for 16h at rt. Reaction mixture was filtered through celite bed and the organic layer was concentrated under vacuum. Crude was purified by column chromatography to afford trifluoro-amino alcohol.

The trifluoro amino alcohol was coupled using the same methods as either Method 1 or Method 2. Following the procedure listed in WO 2016/135070, a standard Des-Martin oxidation was used to reveal the trifluoro ketone after amide formation.

Example 5: Synthesis of Compounds of Formula (I)**Compound 1**

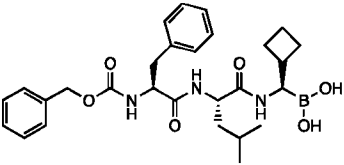
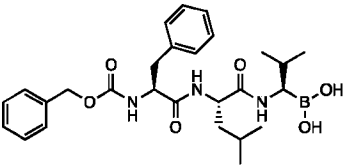
To a stirred solution of benzyl N-[(1S)-1-benzyl-2-[[[(1S)-1-[(R)-cyclobutyl-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]carbamoyl]-3-methyl-butyl]amino]-2-oxoethyl]carbamate **11** (264 mg, 0.44 mmol, 1.0 eq) in acetone (2.4 mL) was added methylboronic acid (261 mg, 4.4 mmol, 10 eq) and 0.2 M aqueous hydrochloric acid solution (2.4 mL). The reaction mixture was stirred for 3 days at room temperature. The mixture was concentrated under reduced pressure and purified on a Biotage Sfar C18 D column with Water/MeOH gradient (100% water to 0% over 40 column volumes) to give 122 mg (0.23 mmol, 70%) of desired product as a white solid. ¹H NMR (500 MHz, MeOD) δ 7.38–7.20 (m, 10H), 5.03 (s, 2H), 4.59 (dd, *J* = 9.9, 4.4 Hz, 1H), 4.37 (dd, *J* = 9.4, 5.2 Hz, 1H), 3.10 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.87 (dd, *J* = 14.1, 9.2 Hz, 1H), 2.56 (d, *J* = 9.1 Hz, 1H), 2.43 (p, *J* = 8.1 Hz, 1H), 2.09–2.0 (m, 2H), 1.87 (h, *J* = 8.9 Hz, 1H), 1.82–1.70 (m, 4H), 1.62–1.55 (m,

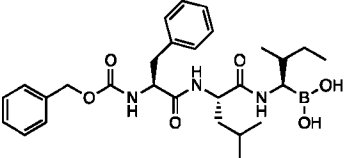
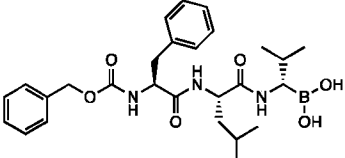
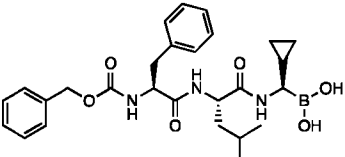
2H), 0.94 (d, $J = 5.9$ Hz, 3H), 0.90 (d, $J = 5.8$ Hz, 3H), 0.19 (s, 1H). Calculated for $C_{28}H_{38}BN_3O_6$ $[M-OH]^+$: 506.3; found: 506.3.

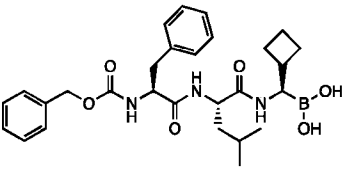
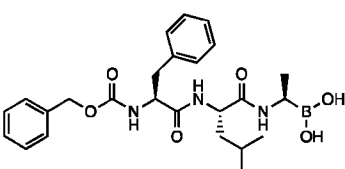
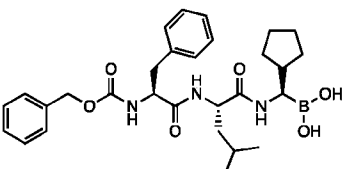
Additional Compounds and Characterization Data

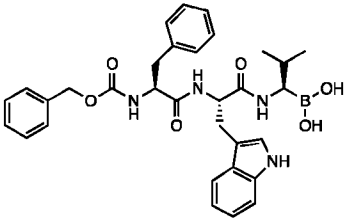
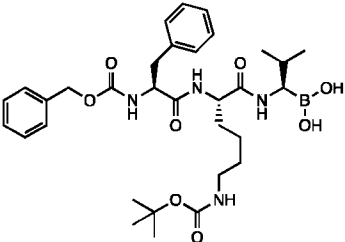
- 5 Additional compounds were prepared according to the general procedures outlined above, using appropriate starting materials. Structures and characterization data are provided in Table 2.

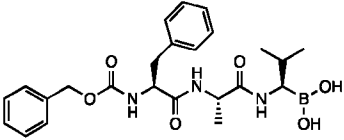
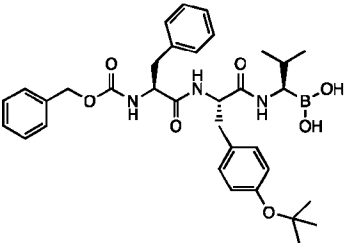
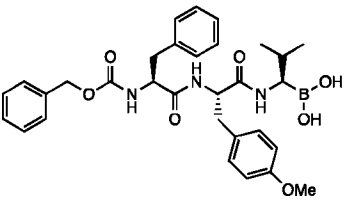
Table 2. Compound structures and data

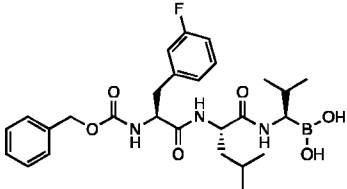
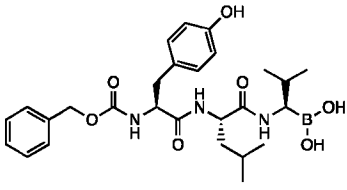
Cpd	HTRA1 IC ₅₀ ^a	Structure	¹ H NMR / MS
P1 Variation			
1	A		¹ H NMR (500 MHz, MeOD) δ 7.38–7.20 (m, 10H), 5.03 (s, 2H), 4.59 (dd, $J = 9.9, 4.4$ Hz, 1H), 4.37 (dd, $J = 9.4, 5.2$ Hz, 1H), 3.10 (dd, $J = 14.0, 5.3$ Hz, 1H), 2.87 (dd, $J = 14.1, 9.2$ Hz, 1H), 2.56 (d, $J = 9.1$ Hz, 1H), 2.43 (p, $J = 8.1$ Hz, 1H), 2.09–2.0 (m, 2H), 1.87 (h, $J = 8.9$ Hz, 1H), 1.82–1.70 (m, 4H), 1.62–1.55 (m, 2H), 0.94 (d, $J = 5.9$ Hz, 3H), 0.90 (d, $J = 5.8$ Hz, 3H), 0.19 (s, 1H). Calculated for $C_{28}H_{38}BN_3O_6$ $[M-OH]^+$: 506.3; found: 506.3
2	B		¹ H NMR (500 MHz, MeOD) δ 7.16–6.98 (m, 10H), 4.83 (d, $J = 2.6$ Hz, 2H), 4.42 (dd, $J = 10.0, 4.5$ Hz, 1H), 4.19 (dd, $J = 9.2, 5.2$ Hz, 1H), 2.91 (dd, $J = 14.0, 5.3$ Hz, 1H), 2.67 (dd, $J = 14.0, 9.2$ Hz, 1H), 2.09 (d, $J = 8.4$ Hz, 1H), 1.63–1.48 (m, 2H), 1.44–1.38 (m, 2H), 1.04 (s, 1H), 1.00 (s, 1H), 0.78–0.69 (m, 12H).

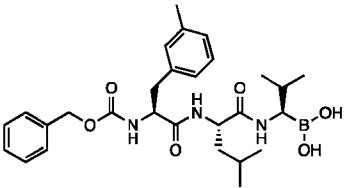
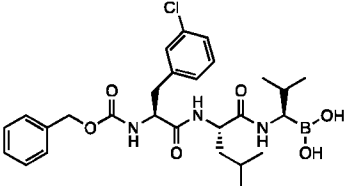
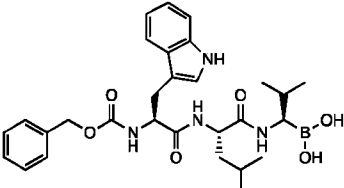
			$C_{27}H_{37}BN_3O_5$ [M-OH] ⁺ = calc. 494.2; found, 494.2
3	B		¹ H NMR (500 MHz, MeOD) δ 7.35–7.17 (m, 10H), 5.07–4.98 (m, 2H), 4.62 (dt, <i>J</i> = 9.8, 4.5 Hz, 1H), 4.38 (dd, <i>J</i> = 9.4, 5.2 Hz, 1H), 3.11 (dd, <i>J</i> = 14.0, 5.2 Hz, 1H), 2.91–2.83 (m, 1H), 2.45–2.38 (m, 1H), 1.72 (t, <i>J</i> = 10.0 Hz, 1H), 1.66–1.43 (m, 4H), 1.29 (d, <i>J</i> = 6.6 Hz, 1H), 0.97–0.83 (m, 12H). $C_{28}H_{39}BN_3O_5$ [M-OH] ⁺ = calc. 508.3; found, 508.3
4	D		¹ H NMR (500 MHz, MeOD) δ 7.36–7.17 (m, 10H), 5.02 (q, <i>J</i> = 12.5 Hz, 2H), 4.66 (dd, <i>J</i> = 10.2, 4.7 Hz, 1H), 4.38 (dd, <i>J</i> = 9.2, 5.1 Hz, 1H), 3.10 (dd, <i>J</i> = 14.0, 5.2 Hz, 1H), 2.86 (dd, <i>J</i> = 14.0, 9.2 Hz, 1H), 2.27 (d, <i>J</i> = 8.4 Hz, 1H), 1.85–1.67 (m, 2H), 1.67–1.53 (m, 2H), 1.00–0.84 (m, 12H). $C_{27}H_{37}BN_3O_5$ [M-OH] ⁺ = calc. 494.2; found, 494.2
5	C		¹ H NMR (500 MHz, MeOD) δ 7.35–7.17 (m, 10H), 5.09–4.96 (m, 2H), 4.61 (dd, <i>J</i> = 10.1, 4.7 Hz, 1H), 4.38 (dd, <i>J</i> = 9.3, 5.2 Hz, 1H), 3.11 (dd, <i>J</i> = 14.0, 5.2 Hz, 1H), 2.87 (dd, <i>J</i> = 14.0, 9.4 Hz, 1H), 1.77 (d, <i>J</i> = 10.3 Hz, 1H), 1.73 (d, <i>J</i> = 9.2 Hz, 1H), 1.66–1.54 (m,

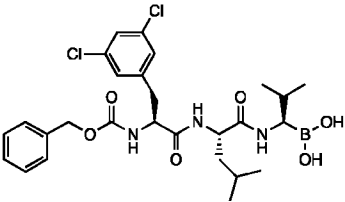
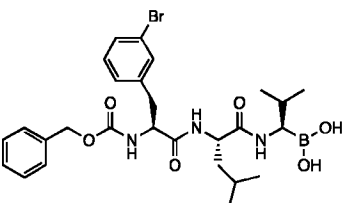
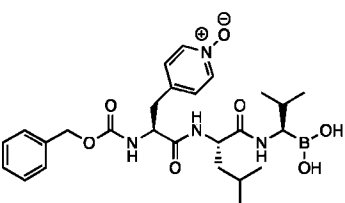
			3H), 1.33–1.27 (m, 1H), 0.95 (d, J = 5.9 Hz, 3H), 0.90 (d, J = 5.9 Hz, 3H), 0.81 (dddd, J = 13.0, 10.1, 8.0, 4.9 Hz, 1H), 0.51 (dd, J = 8.0, 1.9 Hz, 2H), 0.24–0.14 (m, 2H). $C_{27}H_{35}BN_3O_5$ [M-OH]⁺ = calc. 492.3; found, 492.3
6	C		¹H NMR (500 MHz, MeOD) δ 7.38–7.20 (m, 10H), 5.03 (s, 2H), 4.59 (dd, J = 9.9, 4.4 Hz, 1H), 4.37 (dd, J = 9.4, 5.2 Hz, 1H), 3.10 (dd, J = 14.0, 5.3 Hz, 1H), 2.87 (dd, J = 14.1, 9.2 Hz, 1H), 2.56 (d, J = 9.1 Hz, 1H), 2.43 (p, J = 8.1 Hz, 1H), 2.09–2.0 (m, 2H), 1.87 (h, J = 8.9 Hz, 1H), 1.82–1.70 (m, 4H), 1.62–1.55 (m, 2H), 0.94 (d, J = 5.9 Hz, 3H), 0.90 (d, J = 5.8 Hz, 3H), 0.19 (s, 1H). Calculated for $C_{28}H_{38}BN_3O_6$ [M-OH]⁺: 506.3; found: 506.3
7	NA		¹H NMR (400 MHz, DMSO-d₆) δ = 7.61 - 7.38 (m, 1H), 7.37 - 6.94 (m, 10H), 4.93 - 4.90 (m, 2H), 4.41 - 4.35 (m, 2H), 3.02 - 2.99 (m, 1H), 2.76 - 2.68 (m, 1H), 1.59 - 1.46 (m, 3H), 1.23 - 1.16 (m, 1H), 0.89 - 0.82 (m, 9H). $C_{25}H_{34}BN_3O_6$ [M-OH]⁺ = calc. 465.2; found 466.23
8	NA		¹H NMR (400 MHz, DMSO-d₆) δ = 8.50 (s, 1H), 8.29 - 8.27 (m, 1H), 8.16 - 8.13 (m, 1H), 7.57 (s, 1H), 7.50 - 7.48 (m, 1H), 7.31 - 7.18 (m, 10H), 4.92 - 4.88 (m, 2H), 4.44 (br s, 1H),

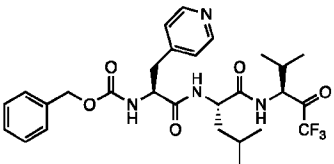
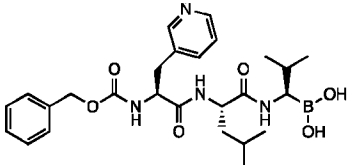
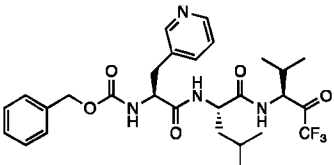
			4.29 - 4.25 (m, 1H), 3.00 - 2.95 (m, 1H), 2.75 - 2.67 (m, 1H), 2.43 (br d, $J = 10.2$ Hz, 1H), 1.90-1.83 (m, 1H), 1.57 - 1.10 (m, 11H), 0.90 - 0.77 (m, 6H). $C_{29}H_{40}BN_3O_6$ [M- OH]$^+$ = calc. 519.3; found 520.2
P2 Variation			
9	A		^1H NMR (500 MHz, MeOD) δ 7.60 (d, J = 7.8 Hz, 1H), 7.38– 7.01 (m, 14H), 5.04 (d, $J = 12.5$ Hz, 1H), 4.98 (d, $J = 12.5$ Hz, 1H), 4.92–4.89 (m, 1H) 4.35 (dd, $J =$ 9.1, 5.4 Hz, 1H), 3.29 (t, $J = 7.3$ Hz, 1H), 3.03 (dd, $J =$ 14.0, 5.5 Hz, 1H), 2.81 (dd, $J = 13.9$, 9.2 Hz, 1H), 2.19 (d, $J = 8.9$ Hz, 1H), 1.68–1.57 (m, 1H), 1.32 (d, $J = 6.6$ Hz, 1H), 0.86 (d, $J = 6.7$ Hz, 3H), 0.69 (d, $J =$ 6.6 Hz, 3H). Calculated for $C_{32}H_{36}BN_4O_5$ [M- OH]$^+$: 567.2; found: 567.3
10	B		^1H NMR (500 MHz, MeOD) δ 7.35–7.18 (m, 10H), 5.03 (d, $J = 2.3$ Hz, 2H), 4.56–4.49 (m, 1H), 4.38 (dd, $J = 9.3$, 5.1 Hz, 1H), 3.11 (dd, $J = 14.0$, 5.2 Hz, 1H), 3.02 (t, $J =$ 6.9 Hz, 2H), 2.86 (dd, $J = 14.0$, 9.3 Hz, 1H), 2.29 (d, $J =$ 8.6 Hz, 1H), 1.85– 1.72 (m, 2H), 1.47 (t, $J = 7.3$ Hz, 2H), 1.42 (s, 9H), 1.39– 1.25 (m, 4H), 0.94 (dd, $J = 12.2$, 6.6 Hz, 6H).

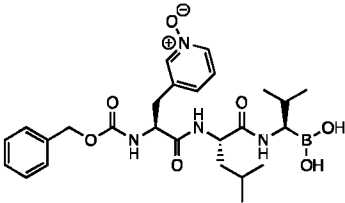
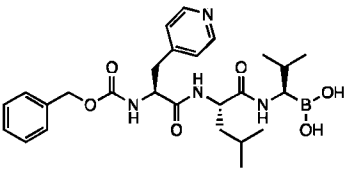
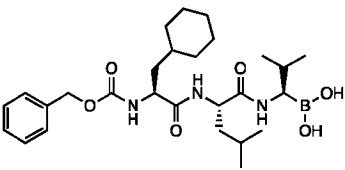
			Calculated for $C_{32}H_{46}BN_4O_7$ [M-OH]⁺: 609.3; found: 609.3
11	C		¹H NMR (400 MHz, DMSO-d₆) δ = 8.50 - 8.33 (m, 1H), 7.66 (s, 1H), 7.53 (br d, J = 8.5 Hz, 1H), 7.38 - 7.07 (m, 10H), 5.00 - 4.77 (m, 2H), 4.51 - 4.36 (m, 1H), 4.36 - 4.20 (m, 1H), 3.08 - 2.94 (m, 1H), 2.78 - 2.64 (m, 1H), 2.33 (s, 1H), 1.78 - 1.64 (m, 1H), 1.29 - 1.14 (m, 3H), 0.88 - 0.71 (m, 6H). Calculated for $C_{24}H_{32}BN_3O_6$ [M-OH]⁺: 451.3; found: 452.2
12	A		¹H NMR (500 MHz, MeOD) δ 7.35-7.22 (m, 8H), 7.22-7.13 (m, 4H), 6.95-6.89 (m, 2H), 5.05-4.97 (m, 2H), 4.77 (t, J = 7.7 Hz, 1H), 4.34 (dd, J = 9.5, 5.2 Hz, 1H), 3.12-2.98 (m, 3H), 2.77 (dd, J = 14.0, 9.5 Hz, 1H), 2.20 (d, J = 9.0 Hz, 1H), 1.63 (q, J = 6.9 Hz, 1H), 1.30 (s, 9H), 0.86 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H). Calculated for $C_{34}H_{43}BN_3O_6$ [M-OH]⁺: 600.3; found: 600.3
13	A		¹H NMR (400 MHz, DMSO-d₆) δ = 8.56 - 8.08 (m, 1H), 7.65 (s, 1H), 7.47 (br dd, J = 5.2, 8.6 Hz, 1H), 7.35 - 7.03 (m, 13H), 6.83 - 6.68 (m, 2H), 5.01 - 4.81 (m, 2H), 4.66 - 4.44 (m, 1H), 4.35 - 4.13 (m, 1H), 3.72 - 3.57 (m, 3H), 3.02 - 2.63 (m, 5H),

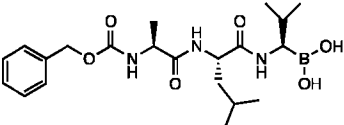
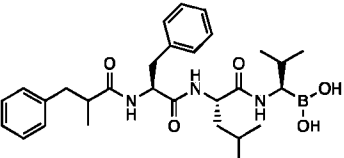
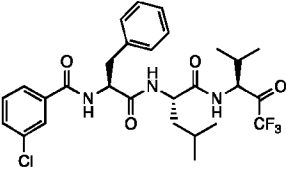
			1.84 - 1.66 (m, 1H), 0.91 - 0.63 (m, 6H). Calculated for C₃₁H₃₈BN₃O₇ [M- H₂O]⁺: 557.38; found: 558.38
P3 Variation			
14	A		¹H NMR (500 MHz, MeOD) δ 7.15–7.05 (m, 6H), 6.87 (d, <i>J</i> = 7.6 Hz, 1H), 6.83 (dt, <i>J</i> = 10.1, 2.1 Hz, 1H), 6.75 (td, <i>J</i> = 8.6, 2.7 Hz, 1H), 4.89–4.77 (m, 2H), 4.43 (dd, <i>J</i> = 10.0, 4.5 Hz, 1H), 4.20 (dd, <i>J</i> = 9.4, 5.1 Hz, 1H), 2.92 (dd, <i>J</i> = 14.0, 5.1 Hz, 1H), 2.68 (dd, <i>J</i> = 14.0, 9.4 Hz, 1H), 2.10 (d, <i>J</i> = 8.4 Hz, 1H), 1.63–1.50 (m, 2fH), 1.41 (dq, <i>J</i> = 10.3, 6.1 Hz, 2H), 1.14–1.07 (m, 1H), 0.78–0.67 (m, 12H). Calculated for C₂₇H₃₆BFN₃O₅ [M- H₂O]⁺: 512.3 ; found: 512.3
15	B		¹H NMR (500 MHz, MeOD) δ 7.17–7.05 (m, 5H), 6.86 (d, <i>J</i> = 8.5 Hz, 2H), 6.53–6.47 (m, 2H), 4.85 (q, <i>J</i> = 12.5 Hz, 2H), 4.41 (dd, <i>J</i> = 10.1, 4.6 Hz, 1H), 4.11 (dd, <i>J</i> = 8.7, 5.6 Hz, 1H), 2.81 (dd, <i>J</i> = 14.0, 5.6 Hz, 1H), 2.60 (dd, <i>J</i> = 14.1, 8.8 Hz, 1H), 2.09 (d, <i>J</i> = 8.5 Hz, 1H), 1.63–1.48 (m, 2H), 1.44–1.34 (m, 2H), 1.10 (d, <i>J</i> = 6.6 Hz, 1H), 0.77–0.72 (m, 9H), 0.70 (d, <i>J</i> = 6.0 Hz, 3H). Calculated for C₂₇H₃₇BN₃O₆ [M- OH]⁺: 510.3; found: 510.2

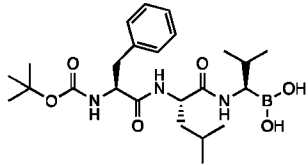
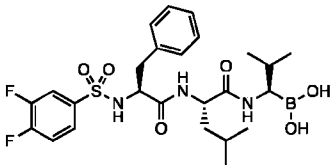
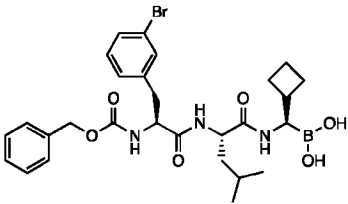
16	A		¹H NMR (500 MHz, MeOD) δ 7.16–7.05 (m, 5H), 6.95 (t, <i>J</i> = 7.5 Hz, 1H), 6.90–6.81 (m, 3H), 4.89–4.78 (m, 2H), 4.42 (dd, <i>J</i> = 9.9, 4.5 Hz, 1H), 4.17 (dd, <i>J</i> = 9.3, 5.2 Hz, 1H), 2.87 (dd, <i>J</i> = 14.0, 5.3 Hz, 1H), 2.63 (dd, <i>J</i> = 14.0, 9.3 Hz, 1H), 2.10 (s, 3H), 1.63–1.47 (m, 2H), 1.40 (qd, <i>J</i> = 9.3, 6.1 Hz, 2H), 1.10 (d, <i>J</i> = 6.6 Hz, 1H), 0.78–0.67 (m, 12H). Calculated for C₂₈H₃₉BN₃O₅ [M–OH]⁺: 508.3; found: 508.3
17	A		¹H NMR (500 MHz, MeOD) δ 7.16–6.97 (m, 9H), 4.88–4.80 (m, 2H), 4.43 (dd, <i>J</i> = 10.0, 4.5 Hz, 1H), 4.19 (dd, <i>J</i> = 9.5, 5.2 Hz, 1H), 2.91 (dd, <i>J</i> = 14.0, 5.1 Hz, 1H), 2.66 (dd, <i>J</i> = 14.0, 9.4 Hz, 1H), 2.10 (d, <i>J</i> = 8.4 Hz, 1H), 1.63–1.49 (m, 2H), 1.41 (ddd, <i>J</i> = 12.3, 8.1, 3.9 Hz, 2H), 1.10 (d, <i>J</i> = 6.6 Hz, 1H), 0.78–0.69 (m, 12H). Calculated for C₂₇H₃₆BClN₃O₅ [M–OH]⁺: 528.2; found: 528.2
18	A		¹H NMR (500 MHz, MeOD) δ 7.60 (dd, <i>J</i> = 8.0, 3.4 Hz, 1H), 7.36–7.28 (m, 6H), 7.16–7.08 (m, 2H), 7.02 (ddd, <i>J</i> = 8.0, 7.0, 1.1 Hz, 1H), 5.11–5.02 (m, 2H), 4.60 (dd, <i>J</i> = 9.9, 5.5 Hz, 1H), 4.45 (dd, <i>J</i> = 7.7, 5.9 Hz, 1H), 3.27 (dd, <i>J</i> = 14.7, 5.7 Hz, 1H), 3.14 (dd, <i>J</i> = 14.8, 7.7

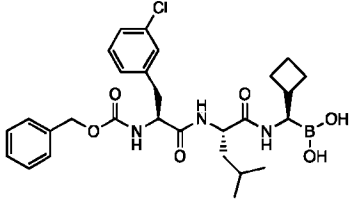
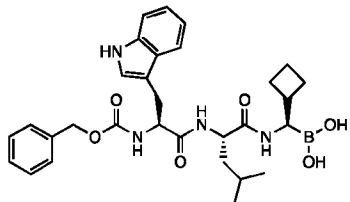
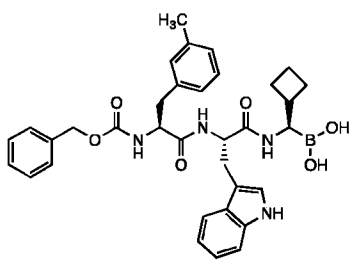
			Hz, 1H), 2.26 (d, J= 8.4 Hz, 1H), 1.78 (dp, J= 8.5, 6.6 Hz, 1H), 1.65–1.52 (m, 3H), 1.46 (dt, J= 14.1, 6.4 Hz, 1H), 0.95 (t, J= 6.4 Hz, 6H), 0.90 (d, J= 6.7 Hz, 3H), 0.83 (d, J= 6.5 Hz, 3H). Calculated for $C_{29}H_{38}BN_4O_5$ [M–OH]⁺: 533.3; found: 533.2
19	A		¹H NMR (400 MHz, DMSO-d_6) δ = 8.46 - 8.11 (m, 1H), 7.76 - 7.05 (m, 10H), 5.15 - 4.75 (m, 2H), 4.63 - 4.15 (m, 2H), 3.08 - 2.86 (m, 1H), 2.76 - 2.60 (m, 1H), 2.31 - 2.09 (m, 1H), 1.86 - 1.33 (m, 3H), 1.27 - 1.01 (m, 1H), 0.98 - 0.55 (m, 12H). Calculated for $C_{27}H_{36}BCl_2N_3O_6$ [M–H₂O]⁺: 561.2; found: 562.15
20	A		¹H NMR (400 MHz, DMSO-d_6) δ = 8.58 - 8.18 (m, 1H), 7.62-7.56 (m, 2H), 7.39-7.16 (m, 9H), 4.93-4.92 (m, 2H), 4.45-4.43 (m, 1H), 4.26 (brs, 2H), 3.00-2.94 (m, 2H), 2.72-2.67 (m, 2H), 2.32-2.28 (m, 1H), 1.69-1.49 (m, 5H), 1.06-0.76 (m, 12H). Calculated for $C_{27}H_{37}BBrN_3O_6$; [M–H₂O]⁺: 571.; found: 572.27
21	C		¹H NMR (400 MHz, DMSO-d_6) δ = 8.63 - 8.25 (m, 1H), 8.23 - 7.98 (m, 2H), 7.65 - 7.45 (m, 1H), 7.41 - 7.06 (m, 5H), 5.06 - 4.72 (m, 2H), 4.50 - 4.20 (m, 2H), 3.03 - 2.84 (m, 1H), 2.79 -

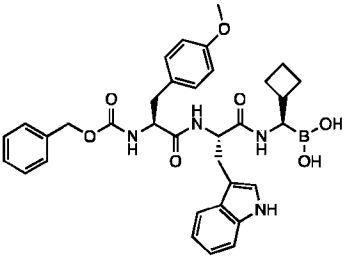
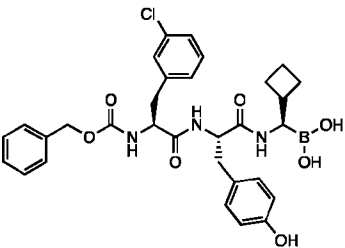
			2.69 (m, 1H), 1.85 - 1.32 (m, 4H), 1.14 - 1.01 (m, 1H), 0.98 - 0.70 (m, 12H). Calculated for $C_{26}H_{37}BN_4O_7$; $[M-H_2O]^+$: 510.2.; found: 511.21.
22	C		^1H NMR (400 MHz, DMSO-d_6) δ = 8.93 - 8.53 (m, 2H), 8.46 - 8.28 (m, 1H), 7.88 (s, 1H), 7.70 - 7.58 (m, 1H), 7.40 - 7.16 (m, 6H), 5.01 - 4.82 (m, 2H), 4.65 - 4.51 (m, 1H), 4.61 - 4.50 (m, 1H), 4.51 (s, 1H), 4.38 (s, 1H), 4.52 - 4.31 (m, 1H), 4.12 - 3.95 (m, 1H), 3.29 - 3.11 (m, 1H), 3.02 - 2.85 (m, 1H), 2.30 - 2.09 (m, 1H), 1.73 - 1.34 (m, 3H), 1.03 - 0.82 (m, 12H). Calculated for $C_{28}H_{35}F_3N_4O_5$ $[M/Z]^+$: 564.6.; found: 565.2
23	C		^1HNMR (400 MHz, DMSO-d_6) δ = 8.52 - 8.48 (m, 1H), 8.81 - 8.48 (m, 1H), 8.48 - 8.47 (m, 1H), 8.39 - 8.10 (m, 2H), 7.93 - 7.76 (m, 1H), 7.72 - 7.56 (m, 1H), 7.42 - 7.11 (m, 6H), 5.00 - 4.80 (m, 2H), 4.51 - 4.16 (m, 2H), 3.05 - 2.80 (m, 3H), 1.90 - 1.31 (m, 6H), 1.02 - 0.68 (m, 12H). Calculated for $C_{26}H_{37}BN_4O_6$ $[M-H_2O]^+$: 494.; found: 495.1
24	C		^1H NMR (400 MHz, DMSO-d_6) δ = 8.85 - 8.64 (m, 2H), 8.41 - 8.21 (m, 2H), 7.88 - 6.78 (m, 8H), 5.08 - 4.75 (m, 2H), 4.62 - 3.93 (m, 3H), 3.18 - 3.11 (m, 1H), 2.96 - 2.80 (m, 1H), 2.28 -

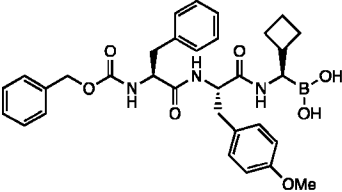
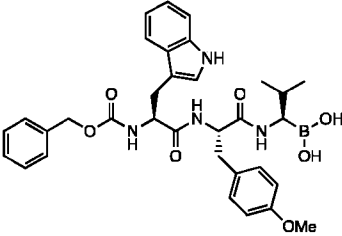
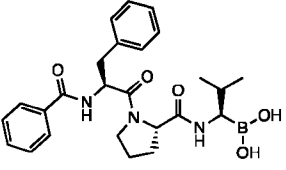
			2.12 (m, 1H), 1.68 - 1.11 (m, 4H), 0.99 - 0.75 (m, 12H). Calculated for $C_{28}H_{35}F_3N_4O_5$ [M/z]⁺: 564.2.; found: 565.2
25	C		¹H NMR (400 MHz, DMSO-d₆) δ = 8.29 - 7.98 (m, 2H), 7.76 - 7.41 (m, 2H), 7.41 - 7.07 (m, 8H), 5.07 - 4.82 (m, 2H), 4.29 (br d, J = 4.5 Hz, 2H), 3.06 - 2.85 (m, 2H), 2.76 - 2.62 (m, 1H), 1.89 - 1.32 (m, 6H), 1.30 - 1.30 (m, 1H), 0.98 - 0.80 (m, 12H). Calculated for $C_{26}H_{37}BN_4O_7$ [M-H₂O]⁺: 510.4.; found: 511.1
26	C		¹H NMR (400 MHz, DMSO-d₆) δ = 8.67 (s, 2H), 7.80 (s, 2H), 7.45 - 7.12 (m, 7H), 4.95 (br s, 2H), 4.54 - 4.39 (m, 1H), 4.34 - 4.18 (m, 1H), 3.28 - 2.90 (m, 4H), 1.88 - 1.40 (m, 5H), 1.32 - 1.19 (m, 3H), 1.01 - 0.83 (m, 12H). Calculated for $C_{26}H_{37}BN_4O_6$ [M-H₂O]⁺: 494.4.; found: 495.2
27	B		¹H NMR (400 MHz, DMSO-d₆) δ = 8.67 (s, 2H), 7.80 (s, 2H), 7.45 - 7.12 (m, 7H), 4.95 (br s, 2H), 4.54 - 4.39 (m, 1H), 4.34 - 4.18 (m, 1H), 3.28 - 2.90 (m, 4H), 1.88 - 1.40 (m, 5H), 1.32 - 1.19 (m, 3H), 1.01 - 0.83 (m, 12H). Calculated for $C_{27}H_{43}BN_3O_5$ [M-OH]⁺: 500.3.; found: 500.2

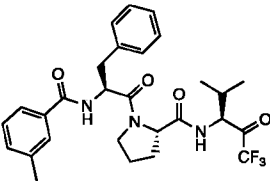
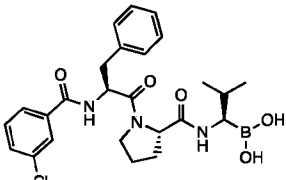
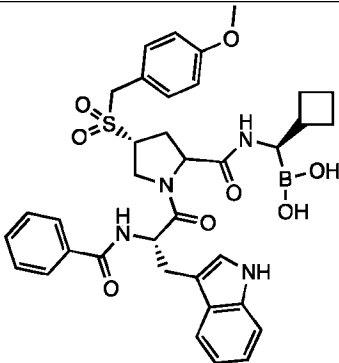
28	D		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.22 - 8.04 (m, 1H), 7.66 (s, 1H), 7.52 - 7.42 (m, 1H), 7.38 - 7.09 (m, 5H), 5.12 - 4.83 (m, 2H), 4.54 - 4.16 (m, 1H), 4.13 - 3.97 (m, 1H), 3.04 - 2.96 (m, 1H), 2.33 - 2.22 (m, 1H), 1.83 - 1.34 (m, 4H), 1.29 - 1.12 (m, 3H), 1.00 - 0.68 (m, 12H). Calculated for C ₂₁ H ₃₄ BN ₃ O ₆ [M-H ₂ O] ⁺ : 417.3.; found: 418.2
P4 variation			
29	B		Mixture of diastereomers precludes analysis by NMR. Calculated for C ₂₉ H ₄₁ BN ₃ O ₄ [M-OH] ⁺ : 506.3.; found: 418.2
30	C		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.75 - 8.62 (m, 2H), 8.40 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H), 7.83 (brs, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.2 Hz, 1H), 7.49-7.45 (m, 1H), 7.37-7.34 (m, 2H), 7.27-7.14 (m, 4H), 6.95-6.88 (m, 1H), 4.75-4.70 (m, 1H), 4.58-4.36 (m, 2H), 4.06-4.03 (m, 1H), 3.11-2.93 (m, 2H), 2.32-2.17 (m, 1H), 1.65-1.42 (m, 3H), 0.93-0.74 (m, 12H). Calculated for C ₂₈ H ₃₃ ClF ₃ N ₃ O ₄ [M/z] ⁺ : 567.2.; found: 567.94.

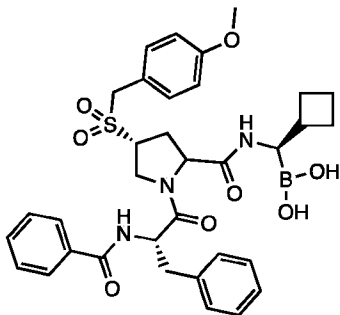
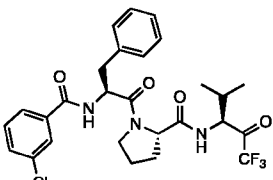
31	C		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.19 - 7.89 (m, 1H), 7.76 - 7.52 (m, 1H), 7.36 - 7.12 (m, 6H), 6.95 (br d, <i>J</i> = 8.8 Hz, 1H), 4.54 - 4.25 (m, 1H), 4.22 - 4.05 (m, 1H), 3.03 - 2.87 (m, 1H), 2.78 - 2.63 (m, 1H), 1.86 - 1.56 (m, 2H), 1.47 (s, 1H), 1.35 - 1.19 (m, 9H), 0.94 - 0.71 (m, 12H). Calculated for C ₂₄ H ₄₀ BN ₃ O ₆ [M-H ₂ O] ⁺ : 459.4.; found: 460.2.
32	C		¹ H NMR (500 MHz, MeOD) δ 7.23 (dddd, <i>J</i> = 12.1, 9.7, 6.5, 2.6 Hz, 2H), 7.08 (dt, <i>J</i> = 10.3, 8.0 Hz, 1H), 6.96 (dt, <i>J</i> = 6.0, 2.6 Hz, 3H), 6.92 (dd, <i>J</i> = 6.7, 2.9 Hz, 2H), 4.35 (dd, <i>J</i> = 9.4, 5.3 Hz, 1H), 3.83 (dd, <i>J</i> = 10.4, 4.1 Hz, 1H), 2.81 (dd, <i>J</i> = 14.1, 4.1 Hz, 1H), 2.48 (dd, <i>J</i> = 14.0, 10.4 Hz, 1H), 2.11 (d, <i>J</i> = 8.5 Hz, 1H), 1.58 (dp, <i>J</i> = 8.5, 6.6 Hz, 1H), 1.50-1.33 (m, 2H), 0.81-0.71 (m, 12H). Calculated for C ₂₅ H ₃₃ BF ₂ N ₃ O ₅ S [M-OH] ⁺ : 536.2.; found: 536.2.
Multiple Variations			
33	A		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.43 - 8.36 (m, 1H), 7.58 (brs, 2H), 7.41-7.22 (m, 9H), 4.92-4.89 (brs, 2H), 4.45 (brs, 1H), 4.27 (brs, 1H), 3.02-2.99 (m, 1H), 2.72-2.66 (m, 1H), 2.29-2.33 (m, 2H), 1.71-1.49 (m, 10H), 1.03-0.84 (m, 6H).

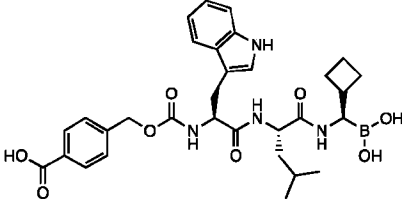
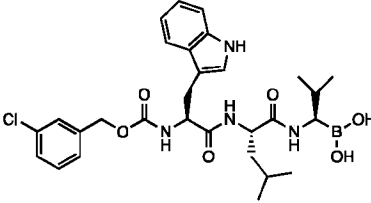
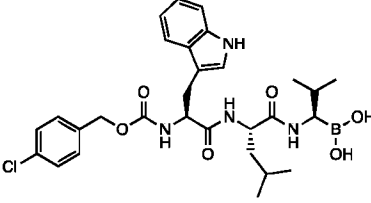
			Calculated for $C_{28}H_{37}BBrN_3O_6$ [M-OH]⁺: 584.2.; found: 584.1.
34	A		¹H NMR (400 MHz, DMSO-d₆) δ = 8.71 - 8.59 (m, 1H), 8.46 - 8.25 (m, 1H), 7.68 - 7.07 (m, 11H), 5.01 - 4.81 (m, 2H), 4.55 - 4.20 (m, 2H), 3.09 - 2.94 (m, 1H), 2.92 - 2.81 (m, 1H), 2.80 - 2.66 (m, 1H), 2.29 (s, 1H), 1.91 - 1.38 (m, 9H), 1.05 - 0.72 (m, 6H). Calculated for $C_{28}H_{37}BClN_3O_6$ [M-H₂O]⁺: 539.2.; found: 540.17.
35	A		¹H NMR (400 MHz, DMSO-d₆) δ = 10.93 - 10.67 (m, 1H), 8.72 - 8.19 (m, 1H), 7.82 - 6.80 (m, 11H), 5.10 - 4.75 (m, 2H), 4.58 - 4.23 (m, 1H), 3.15 - 3.03 (m, 1H), 2.98 - 2.84 (m, 1H), 2.40 - 2.24 (m, 1H), 1.95 - 1.36 (m, 8H), 0.98 - 0.70 (m, 6H). Calculated for $C_{30}H_{39}BN_4O_6$ [M-H₂O]⁺: 544.4.; found: 545.4.
36	A		¹H NMR (500 MHz, MeOD) δ 10.47 (d, J = 17.8 Hz, 1H), 7.58 (t, J = 6.9 Hz, 1H), 7.39-7.35 (m, 1H), 7.33-7.25 (m, 4H), 7.22-7.17 (m, 1H), 7.17-6.99 (m, 6H), 6.96 (t, J = 6.2 Hz, 1H), 5.04 (d, J = 12.7, 1H), 4.97 (J = 12.5 Hz, 1H), 4.36-4.33 (m, 1H), 3.29 (d, J = 7.8 Hz, 1H), 3.01 (dt, J = 14.0, 4.5 Hz, 1H), 2.78 (dt, J = 13.9, 9.2 Hz, 1H),

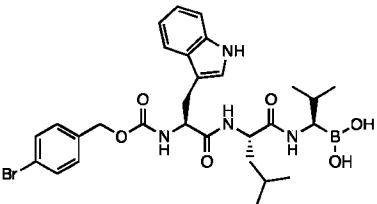
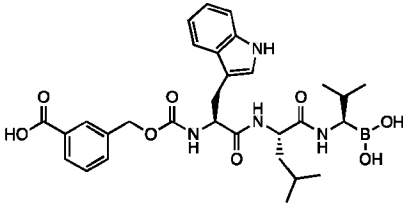
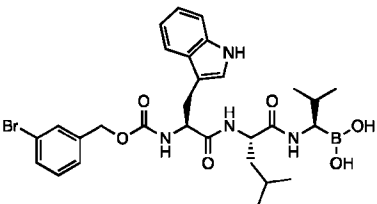
			2.47 (d, J= 9.2 Hz, 1H), 2.40 (t, J= 9.3 Hz, 1H), 2.29 (s, 3H), 2.27–2.09 (m, 2H), 2.01–1.88 (m, 1H), 1.83–1.70 (m, 2H), 1.64 (m, 2H), 1.45 (m, 1H). [M–H₂O]⁺ calc. for C₃₄H₃₈BClN₄O₅: 593.3; found: 593.3
37	A		¹H NMR (500 MHz, MeOD) δ 10.49–10.41 (s, 1H), 7.57–7.53 (m, 1H), 7.37 (dd, J= 8.1, 1.0 Hz, 1H), 7.33–7.23 (m, 5H), 7.16–7.10 (m, 2H), 7.07–7.03 (m, 3H), 6.76 (m, 2H), 5.03 (d, J= 12.5 Hz, 1H), 4.95 (d, J= 12.5 Hz, 1H), 4.90 (m, 2H), 4.33 (dd, J= 8.9, 5.3 Hz, 1H), 3.37 (s, 3H), 3.33 (dt, J= 3.3, 1.6 Hz, 1H), 3.29 (m, 1H), 2.97 (dd, J= 13.9, 5.7 Hz, 1H), 2.84–2.74 (m, 1H), 2.41 (t, J= 9.3 Hz, 1H), 2.19–2.03 (m, 1H), 1.98–1.90 (m, 1H), 1.82–1.58 (m, 4H), 1.51–1.37 (m, 1H). [M–H₂O]⁺ calc. for C₃₄H₃₈BClN₄O₆: 609.3; found: 609.3
38	A		¹H NMR (500 MHz, MeOD) δ 7.38–7.21 (m, 9H), 7.15–7.11 (m, 1H), 7.10–7.04 (m, 2H), 6.77–6.74 (m, 2H), 5.07 (d, J= 12.4 Hz, 1H), 5.01 (d, J= 12.6 Hz, 1H), 4.75–4.71 (m, 1H), 4.40–4.35 (m, 1H), 3.06–2.97 (m, 3H), 2.84–2.78 (m, 1H), 2.53–2.43 (m, 1H), 2.31–2.37 (m, 1H), 2.05–1.93 (m, 1H), 1.91–1.62 (m, 5H),

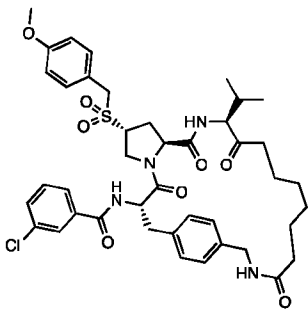
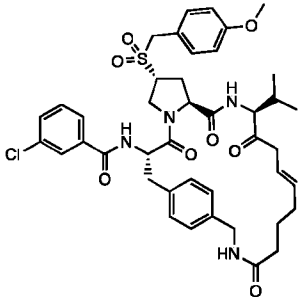
			1.53 (q, $J = 8.8$ Hz, 1H) [M-H₂O]⁺ calc. for C₃₁H₃₄BClN₃O₆: 590.2; found: 590.2
39	A		¹H NMR (400 MHz, DMSO-d₆) δ = 8.64 - 8.08 (m, 2H), 7.57 (s, 1H), 7.49 - 7.40 (m, 1H), 7.35 - 7.10 (m, 12H), 6.86 - 6.84 (m, 1H), 6.86 - 6.70 (m, 2H), 4.97 - 4.82 (m, 2H), 4.65 - 4.43 (m, 1H), 4.30 - 4.17 (m, 1H), 3.72 - 3.56 (m, 3H), 3.03 - 2.63 (m, 6H), 1.87 - 1.46 (m, 6H). Calculated for C₃₂H₃₈BN₃O₇ [M-H₂O]⁺: 569.2.; found: 570.35.
40	A		¹H NMR (400 MHz, DMSO-d₆) δ = 10.79 (s, 1H), 7.59 (br d, $J = 7.9$ Hz, 1H), 7.45 - 6.88 (m, 13H), 6.84 - 6.66 (m, 2H), 5.02 - 4.79 (m, 2H), 4.72 - 4.58 (m, 1H), 4.39 - 4.21 (m, 1H), 3.70 - 3.58 (m, 3H), 3.03 - 2.78 (m, 4H), 1.80 - 1.65 (m, 1H), 0.94 - 0.68 (m, 6H). Calculated for C₃₃H₃₉BN₄O₇ [M-H₂O]⁺: 596.2.; found: 597.4.
Miscellaneous			
41	C		¹H NMR (400 MHz, DMSO-d₆) δ = 8.85 - 8.53 (m, 1H), 7.62 - 7.58 (m, 2H), 7.38 - 7.17 (m, 8H), 4.85 (d, $J = 8.0$ Hz, 1H), 4.70 - 4.60 (m, 1H), 3.03 - 3.01 (m, 2H), 2.32 - 2.25 (m, 4H), 1.96 - 1.82 (m, 4H), 0.88 - 0.79 (m, 6H). Calculated for C₂₆H₃₄BN₃O₅ [M-

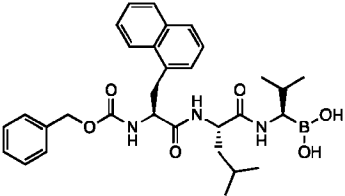
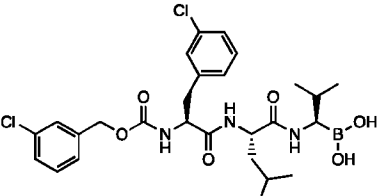
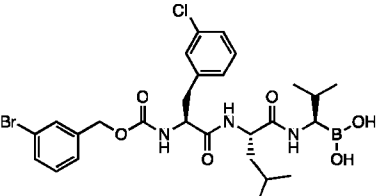
			H ₂ O] ⁺ : 461.; found: 462.2
42	C		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.65 (m, 2H), 7.65-7.59 (m, 3H), 7.47-7.45 (m, 1H), 7.39-7.37 (m, 3H), 7.36-7.23 (m, 7H), 7.19-7.15 (m, 2H), 6.89 (s, 1H), 6.83 (s, 1H), 4.85-4.83 (m, 1H), 4.58-4.45 (m, 2H), 4.07-4.03 (m, 1H), 3.77-3.63 (m, 3H), 3.05-2.99 (m, 3H), 2.33 (s, 5H), 2.27-2.18 (m, 2H), 1.98-1.78 (m, 6H), 0.97-0.86 (m, 6H), 0.82-0.78 (m, 4H). Calculated for C ₂₈ H ₃₂ F ₃ N ₃ O ₄ [M/z] ⁺ : 531.23.; found: 532.4
43	C		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.94 - 8.92 (m, 1H), 7.86 - 7.74 (m, 1H), 7.65 - 7.57 (m, 2H), 7.51 - 7.45 (m, 1H), 7.38 - 7.31 (m, 2H), 7.29 - 7.15 (m, 4H), 4.85 - 4.84 (m, 1H), 4.38 - 4.36 (m, 1H), 3.74 - 3.70 (m, 2H), 3.32 - 2.91 (m, 3H), 2.32 - 2.25 (m, 1H), 1.99 - 1.67 (m, 5H), 0.88 - 0.71 (m, 6H). Calculated for C ₂₅ H ₃₁ BClN ₃ O ₅ [M-H ₂ O] ⁺ : 481.2.; found: 482.1
44	A		¹ H NMR (400 MHz, DMSO-d ₆) δ = 10.95-10.86 (m, 1H), 8.95-8.62 (m, 2H), 7.92-7.72 (m, 3H), 7.52-7.15 (m, 14H), 7.04-6.88 (m, 6H), 4.80-4.77 (m, 2H), 4.51-4.39 (m, 3H), 4.28-4.14 (m, 2H), 4.01-3.92 (m, 2H), 3.78-3.70 (m, 5H), 3.58-3.43 (m, 2H),

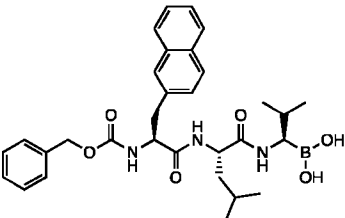
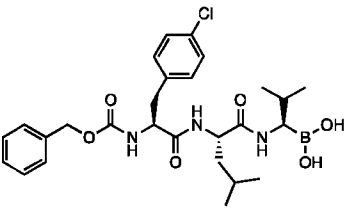
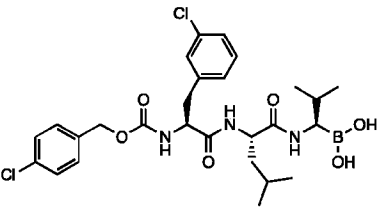
			3.26-3.22 (m, 2H), 3.05-3.01 (m, 1H), 2.88-2.67 (m, 1H), 2.49-2.32 (m, 1H), 1.83-1.51 (m, 8H). Calculated for C₃₆H₄₁BN₄O₈S [M- H₂O]⁺: 682.3.; found: 683.16
45	A		¹H NMR (400 MHz, DMSO-d₆) δ = 8.95 - 8.69 (m, 1H), 8.04 - 7.70 (m, 2H), 7.67 - 7.07 (m, 10H), 7.01 - 6.86 (m, 2H), 4.95 - 4.60 (m, 1H), 4.59 - 4.32 (m, 2H), 4.20 - 3.84 (m, 1H), 3.81 - 3.64 (m, 3H), 3.10 - 2.76 (m, 3H), 1.97 - 1.47 (m, 6H). Calculated for C₃₄H₄₀BN₃O₈S [M- H₂O]⁺: 643.2.; found: 644.3
46	C		¹H NMR (500 MHz, MeOD) δ 7.76 (q, J = 1.7 Hz, 1H), 7.67 (dq, J = 7.8, 1.5 Hz, 1H), 7.54 (ddd, J = 8.1, 2.1, 1.0 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.37-7.27 (m, 4H), 7.26-7.20 (m, 1H), 5.10-5.05 (m, 1H), 4.64-4.56 (m, 1H), 4.26 (dd, J = 27.7, 3.0 Hz, 1H), 3.92 (dt, J = 9.8, 6.5 Hz, 1H), 3.72-3.64 (m, 1H), 3.27 (dd, J = 14.2, 4.8 Hz, 1H), 3.05 (ddd, J = 14.0, 9.2, 4.6 Hz, 1H), 2.36 (dq, J = 23.6, 6.9, 3.0 Hz, 1H), 2.22-2.08 (m, 1H), 2.07-1.96 (m, 2H), 1.11-1.05 (m, 2H), 1.05-0.97 (m, 5H), 0.93-0.86 (m, 1H).

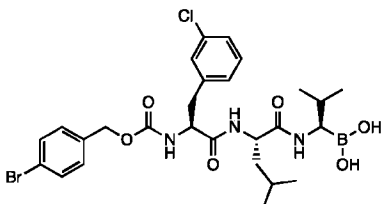
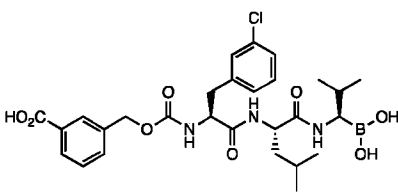
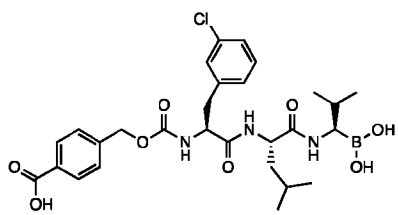
47	C		¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.94 (br s, 1H), 10.83 (br d, <i>J</i> = 5.1 Hz, 1H), 7.95 - 7.56 (m, 4H), 7.41 - 6.88 (m, 7H), 5.13 - 4.82 (m, 2H), 4.54 - 4.25 (m, 2H), 3.16 - 2.99 (m, 2H), 2.96 - 2.83 (m, 1H), 2.38 - 2.30 (m, 1H), 1.86 - 1.66 (m, 1H), 1.64 - 1.38 (m, 3H), 0.95 - 0.69 (m, 12H). Calculated for C ₃₀ H ₃₉ BN ₄ O ₈ [M-H ₂ O] ⁺ : 576.2.; found: [M-H] ⁺ 575.5
48	A		¹ H NMR (400 MHz, DMSO-d ₆) δ = 10.80 (d, <i>J</i> = 6.0 Hz, 1H), 8.23-8.21 (m, 1H), 7.67-7.64 (m, 2H), 7.51-7.47 (m, 1H), 7.35-7.15 (m, 6H), 7.07-6.93 (m, 2H), 4.99-4.87 (m, 2H), 4.47 (d, <i>J</i> = 7.2 Hz, 1H), 4.32 (d, <i>J</i> = 6.8 Hz, 2H), 3.11-2.99 (m, 2H), 2.92-2.86 (m, 1H), 2.33 (brs, 1H), 1.82-1.72 (m, 1H), 1.59-1.49 (m, 1H), 0.89-0.79 (m, 3H), 0.89-0.79 (m, 12H). Calculated C ₂₉ H ₃₈ BClN ₄ O ₆ [M-H ₂ O] ⁺ : 566.3.; found: 567.2
49	A		¹ H NMR (400 MHz, DMSO-d ₆) δ = 10.92 - 10.72 (m, 1H), 8.36 - 8.09 (m, 1H), 7.77 - 7.59 (m, 2H), 7.50 - 6.87 (m, 8H), 5.13 - 4.73 (m, 2H), 4.56 - 4.21 (m, 2H), 3.17 - 2.96 (m, 1H), 2.96 - 2.81 (m, 1H), 2.34 (s, 1H), 1.87 - 1.66 (m, 1H), 1.65 - 1.36 (m, 3H), 0.94 - 0.72 (m, 12H). Calculated C ₂₉ H ₃₈ BClN ₄ O ₆ [M-

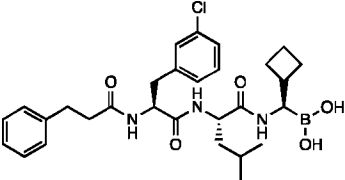
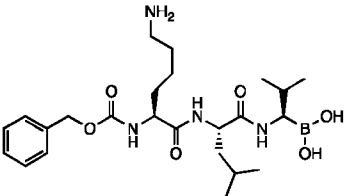
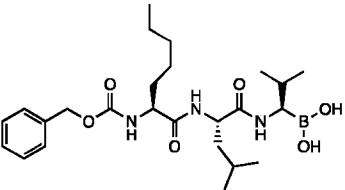
			$\text{H}_2\text{O}]^+$: 566.2.; found: 567.2.
50	A		^1H NMR (400 MHz, DMSO-d_6) δ = 10.98 - 10.61 (m, 1H), 7.75 - 7.27 (m, 6H), 7.24 - 6.91 (m, 6H), 5.01 - 4.70 (m, 2H), 4.63 - 4.18 (m, 2H), 3.15 - 2.97 (m, 1H), 2.95 - 2.78 (m, 1H), 2.37 - 2.02 (m, 1H), 1.88 - 1.71 (m, 1H), 1.98 - 1.36 (m, 2H), 0.96 - 0.72 (m, 12H). Calculated for $\text{C}_{29}\text{H}_{38}\text{BBrN}_4\text{O}_6$ $[\text{M}-\text{H}_2\text{O}]^+$: 611.3.; found: 613.0.
51	C		^1H NMR (400 MHz, DMSO-d_6) δ = 13.02 (s, 1H), 11.01 - 10.67 (m, 1H), 8.53 - 8.08 (m, 1H), 7.94 - 6.86 (m, 11H), 5.13 - 4.74 (m, 2H), 4.55 - 4.16 (m, 2H), 3.16 - 2.79 (m, 2H), 2.43 - 2.29 (m, 1H), 1.92 - 1.38 (m, 4H), 1.04 - 0.67 (m, 12H). Calculated for $\text{C}_{30}\text{H}_{39}\text{BN}_4\text{O}_8$ $[\text{M}-\text{H}_2\text{O}]^+$: 576.2.; found: 575.4. $[\text{M}-\text{H}]$.
52	A		^1H NMR (400 MHz, DMSO-d_6) δ = 10.80 (br d, J = 7.1 Hz, 1H), 8.35 - 8.17 (m, 1H), 7.74 - 7.58 (m, 2H), 7.73 - 7.37 (m, 2H), 7.35 - 6.90 (m, 7H), 5.12 - 4.77 (m, 2H), 4.50 - 4.16 (m, 2H), 3.15 - 2.97 (m, 1H), 2.96 - 2.82 (m, 1H), 1.86 - 1.38 (m, 4H), 0.98 - 0.66 (m, 12H). Calculated for $\text{C}_{29}\text{H}_{38}\text{BBrN}_4\text{O}_6$ $[\text{M}-\text{H}_2\text{O}]^+$: 611.3.; found: 613.0

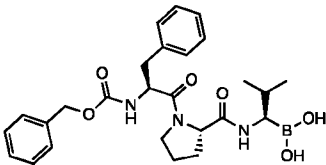
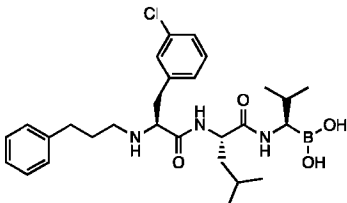
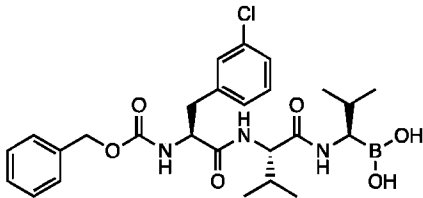
53	C		¹H NMR (400 MHz, DMSO-d₆) δ = 9.14 - 8.91 (m, 1H), 8.50 - 8.08 (m, 2H), 7.99 - 7.99 (m, 1H), 8.08 - 7.82 (m, 1H), 7.68 - 7.45 (m, 2H), 7.41 - 7.07 (m, 5H), 6.91 (br d, <i>J</i> = 8.1 Hz, 1H), 4.74 - 4.43 (m, 3H), 4.40 - 4.14 (m, 4H), 3.84 - 3.57 (m, 5H), 3.19 (br d, <i>J</i> = 13.5 Hz, 1H), 2.88 (br d, <i>J</i> = 13.1 Hz, 1H), 2.73 - 2.62 (m, 1H), 2.44 - 2.34 (m, 1H), 2.32 - 1.97 (m, 5H), 1.91 - 1.78 (m, 1H), 1.69 - 1.46 (m, 4H), 1.38 - 1.13 (m, 4H), 0.99 - 0.72 (m, 6H). Calculated for C₄₂H₅₁ClN₄O₈S [M/z] : 806.3; found: 807.7
54	C		¹H NMR (500 MHz, MeOD) δ 8.75 (d, <i>J</i> = 6.9 Hz, 1H), 8.14 (d, <i>J</i> = 8.6 Hz, 1H), 7.92 (t, <i>J</i> = 1.9 Hz, 1H), 7.82 (dt, <i>J</i> = 7.8, 1.3 Hz, 1H), 7.59 (ddd, <i>J</i> = 8.1, 2.2, 1.0 Hz, 1H), 7.49 (t, <i>J</i> = 7.9 Hz, 1H), 7.40-7.29 (m, 2H), 7.25 (q, <i>J</i> = 8.1 Hz, 2H), 7.01-6.91 (m, 2H), 5.69 (dt, <i>J</i> = 13.9, 6.7 Hz, 1H), 5.58 (dt, <i>J</i> = 14.9, 7.1 Hz, 1H), 4.68 (ddd, <i>J</i> = 10.6, 8.6, 4.5 Hz, 2H), 4.49-4.27 (m, 5H), 4.09 (dd, <i>J</i> = 11.1, 6.3 Hz, 1H), 3.84-3.80 (m, 2H), 3.70 (p, <i>J</i> = 7.6 Hz, 1H), 3.31-3.18 (m, 1H), 3.10 (dd, <i>J</i> = 12.6, 4.2 Hz, 1H), 3.06-2.99 (m, 2H), 2.51 (dt, <i>J</i> = 13.7, 8.4 Hz, 1H), 2.34 (dt, <i>J</i> = 13.0, 6.5 Hz, 1H), 2.27-2.18 (m, 2H), 2.15

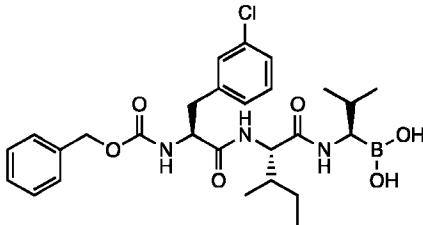
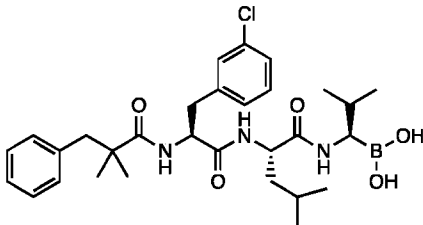
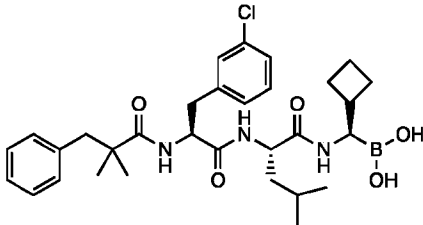
			(q, $J = 7.0$ Hz, 2H), 2.06–1.93 (m, 2H), 1.80 (dtq, $J = 28.8$, 14.7, 7.2 Hz, 2H), 1.47–1.38 (m, 1H), 1.31 (s, 1H), 1.13–1.00 (m, 4H), 0.98–0.80 (m, 4H). Calculated for $C_{42}H_{49}ClN_4O_8S$ [M/z]: 804.3.; found: 804.6
55	A		^1H NMR (400 MHz, DMSO-d_6) δ = 8.61 - 8.08 (m, 2H), 7.98 - 7.73 (m, 2H), 7.73 - 7.01 (m, 11H), 5.02 - 4.63 (m, 2H), 4.60 - 4.23 (m, 2H), 3.62 - 3.47 (m, 1H), 3.22 - 3.06 (m, 1H), 3.02 (t, $J = 7.2$ Hz, 1H), 2.33 (br s, 1H), 1.87 - 1.42 (m, 4H), 0.97 - 0.69 (m, 12H). Calculated for $C_{31}H_{40}BN_3O_8$ [M-H_2O]$^+$: 543.3.; found: 544.4
56	A		^1H NMR (400 MHz, DMSO-d_6) δ = 8.62 - 8.00 (m, 1H), 7.76 - 7.52 (m, 1H), 7.49 - 7.01 (m, 8H), 5.03 - 4.81 (m, 2H), 4.52 - 4.18 (m, 2H), 3.10 - 2.61 (m, 3H), 2.27 (s, 1H), 1.91 - 1.27 (m, 4H), 0.95 - 0.68 (m, 12H). Calculated for $C_{27}H_{36}BCl_2N_3O_8$ [M-H_2O]$^+$: 561.2.; found: 561.78 and 563.77
57	A		^1H NMR (400 MHz, DMSO-d_6) δ = 8.68 - 8.12 (m, 1H), 7.72 - 7.57 (m, 2H), 7.45 (br d, $J = 23.1$ Hz, 3H), 7.36 - 7.08 (m, 6H), 5.04 - 4.79 (m, 2H), 4.51 - 4.15 (m, 2H), 3.09 - 2.89 (m, 1H), 2.70 (br t, $J = 12.5$ Hz, 1H), 2.27

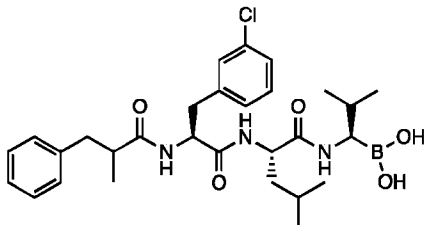
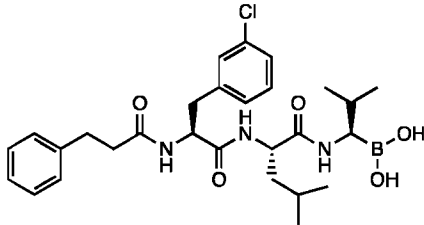
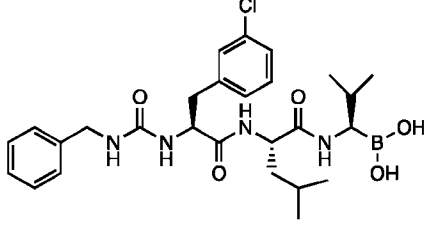
			(s, 1H), 1.95 - 1.33 (m, 4H), 0.99 - 0.67 (m, 12H). Calculated for $C_{27}H_{36}BBrClN_3O_6$ $[M-H_2O]^+$: 605.2.; found: 607.9
58	A		^1H NMR (400 MHz, DMSO-d_6) δ = 8.65 - 8.10 (m, 2H), 7.92 - 7.36 (m, 9H), 7.31 - 6.96 (m, 6H), 5.01 - 4.71 (m, 2H), 4.55 - 4.25 (m, 2H), 3.23 - 3.07 (m, 1H), 3.03 - 2.79 (m, 1H), 2.32 (br s, 1H), 1.88 - 1.39 (m, 4H), 0.95 - 0.68 (m, 12H). Calculated for $C_{31}H_{40}BN_3O_6$ $[M-H_2O]^+$: 543.3.; found: 544.2
59	A		^1H NMR (400 MHz, DMSO-d_6) δ = 8.49 (s, 1H), 8.31 (d, J = 7.2 Hz, 1H), 7.53 - 7.48 (m, 1H), 7.35 - 7.15 (m, 9H), 4.96 - 4.88 (m, 2H), 4.45 - 4.26 (m, 2H), 3.01 - 2.94 (m, 1H), 2.73 - 2.67 (m, 1H), 2.28 (brs, 1H), 1.72 - 1.67 (m, 1H), 1.60 - 1.45 (m, 3H), 0.90 - 0.75 (m, 12H). Calculated for $C_{27}H_{37}BClN_3O_6$ $[M-H_2O]^+$: 527.2.; found: 528.4
60	A		^1H NMR (400 MHz, DMSO-d_6) δ = 8.62 - 8.09 (m, 1H), 7.72 - 7.51 (m, 2H), 7.49 - 7.11 (m, 8H), 5.00 - 4.76 (m, 2H), 4.52 - 4.11 (m, 2H), 3.07 - 2.89 (m, 1H), 2.70 (br t, J = 12.4 Hz, 1H), 2.27 (s, 1H), 1.88 - 1.31 (m, 4H), 0.99 - 0.65 (m, 12H). Calculated for $C_{27}H_{36}BCl_2N_3O_6$ $[M-$

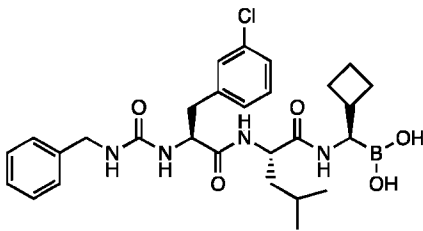
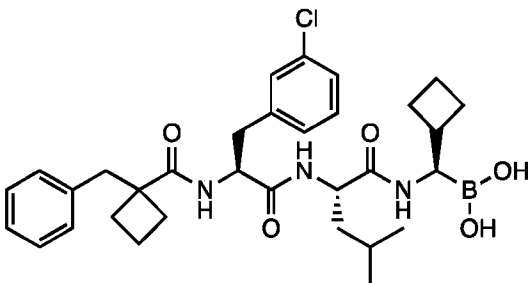
			$\text{H}_2\text{O}]^+$: 561.2.; found: 562.1 and 563.98
61	A		^1H NMR (400 MHz, DMSO-d_6) δ = 8.52 (s, 1H), 8.37 - 8.11 (m, 1H), 7.70 - 7.32 (m, 5H), 7.34 - 7.25 (m, 3H), 7.25 - 7.06 (m, 3H), 4.90 (br d, J = 6.1 Hz, 2H), 4.50 - 4.17 (m, 2H), 3.07 - 2.90 (m, 1H), 2.70 (br t, J = 12.5 Hz, 1H), 2.28 (s, 1H), 1.87 - 1.35 (m, 4H), 0.94 - 0.66 (m, 12H). Calculated for $\text{C}_{27}\text{H}_{36}\text{BBrClN}_3\text{O}_6$ $[\text{M}-\text{H}_2\text{O}]^+$: 605.2.; found: 607.7
62	B		^1H NMR (500 MHz, MeOD) δ 8.02 (s, 1H), 8.00-7.95 (m, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.48 (q, J = 7.6 Hz, 2H), 7.32 (s, 1H), 7.31-7.17 (m, 3H), 5.16 - 5.07 (m, 2H), 4.64 (dd, J = 9.9, 5.2 Hz, 1H), 4.40 (dt, J = 9.7, 5.4 Hz, 1H), 3.16-3.08 (m, 2H), 2.89 (dd, J = 14.0, 9.3 Hz, 1H), 2.30 (d, J = 8.4 Hz, 1H), 1.84-1.70 (m, 2H), 1.61 (q, J = 4.1 Hz, 3H), 0.99-0.88 (m, 16H). Calculated for $\text{C}_{30}\text{H}_{38}\text{BClNO}_7$ $[\text{M}-\text{H}_2\text{O}]^+$: 570.2.; found: 570.3
63	B		^1H NMR (400 MHz, DMSO-d_6) δ = 12.96 (s, 1H), 8.62 - 8.10 (m, 2H), 7.88 (br dd, J = 4.6, 8.0 Hz, 2H), 7.74 - 7.59 (m, 2H), 7.52 - 7.15 (m, 7H), 5.11 - 4.87 (m, 2H), 4.53 - 4.19 (m, 2H), 3.07 - 2.88 (m, 1H), 2.78 - 2.63 (m, 1H), 2.28 (s, 1H), 1.85 - 1.34 (m, 4H), 0.96 - 0.65 (m, 12H).

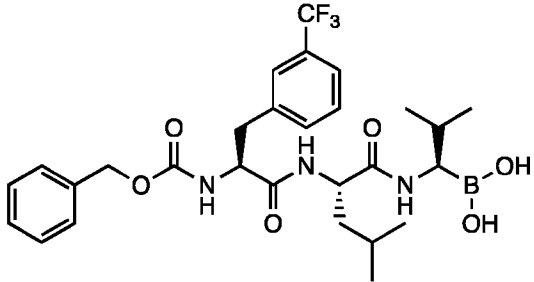
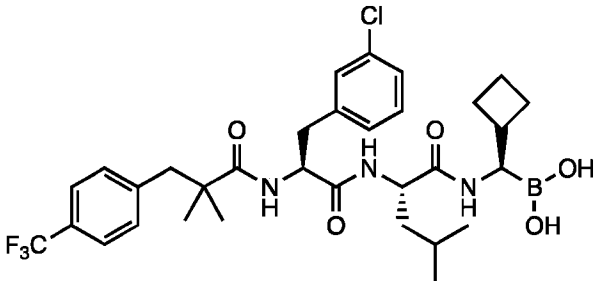
			Calculated for $C_{28}H_{37}BClN_3O_8$ [M-H₂O]⁺: 571.2.; found: 572.1
64	B		¹H NMR (500 MHz, MeOD) δ 7.29–7.19 (m, 5H), 7.16–7.09 (m, 4H), 4.59 (ddd, <i>J</i> = 9.3, 5.2, 3.6 Hz, 1H), 3.08 (ddd, <i>J</i> = 14.1, 5.2, 2.3 Hz, 1H), 2.88–2.76 (m, 3H), 2.61–2.35 (m, 5H), 2.13–1.96 (m, 2H), 1.94–1.67 (m, 5H), 1.67–1.54 (m, 2H), 0.97 (dd, <i>J</i> = 6.4, 2.1 Hz, 3H), 0.92 (dd, <i>J</i> = 6.2, 1.8 Hz, 3H). Calculated for $C_{29}H_{38}BClN_3O_4$ [M-H₂O]⁺: 538.3; found: 538.3
65	D		¹H NMR (500 MHz, MeOD) δ 7.39–7.27 (m, 5H), 5.15–5.04 (m, 2H), 4.65 (dd, <i>J</i> = 9.8, 5.5 Hz, 1H), 4.10 (dd, <i>J</i> = 8.1, 5.8 Hz, 1H), 2.91 (t, <i>J</i> = 7.7 Hz, 2H), 2.30 (d, <i>J</i> = 8.4 Hz, 1H), 1.84–1.57 (m, 8H), 1.54–1.39 (m, 3H), 1.20 (s, 1H), 1.04–0.87 (m, 10H). Calculated for $C_{24}H_{40}BN_4O_5$ [M-H₂O]⁺: 475.3.; found: 475.3
66	C		¹H NMR (500 MHz, MeOD) δ 7.39–7.25 (m, 4H), 5.14–5.02 (m, 2H), 4.66 (dd, <i>J</i> = 9.9, 5.2 Hz, 1H), 4.04 (dd, <i>J</i> = 8.4, 5.7 Hz, 1H), 2.27 (d, <i>J</i> = 8.5 Hz, 1H), 1.82–1.69 (m, 4H), 1.67–1.56 (m, 3H), 1.46–1.25 (m, 6H), 1.00–0.87 (m, 15H). Calculated for $C_{25}H_{41}BN_3O_5$ [M-

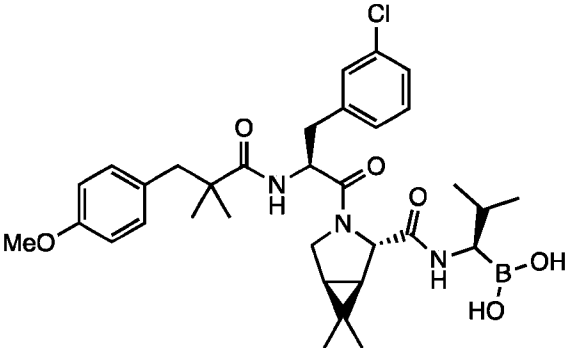
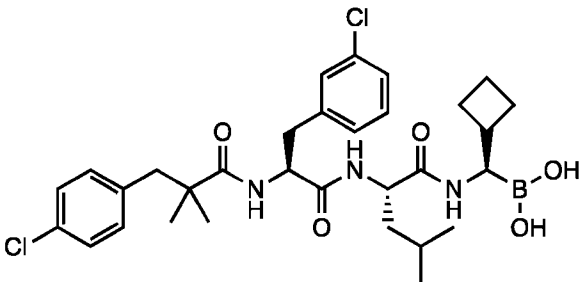
			$\text{H}_2\text{O}]^+$: 474.3.; found: 474.4
67	C		^1H NMR (500 MHz, MeOD) δ 7.38–7.13 (m, 8H), 5.04–4.96 (m, 2H), 4.60 (td, J = 6.2, 3.2 Hz, 1H), 3.75 (dt, J = 9.7, 6.5 Hz, 1H), 3.47–3.35 (m, 1H), 3.08 (dd, J = 14.0, 5.7 Hz, 1H), 2.86 (dd, J = 14.0, 8.7 Hz, 1H), 2.35 (d, J = 8.8 Hz, 1H), 2.25 (ddd, J = 13.8, 9.6, 5.5 Hz, 1H), 2.10–1.91 (m, 4H), 1.88–1.68 (m, 2H), 0.94 (m, 6H), 0.85 (ddt, J = 9.6, 7.0, 3.2 Hz, 2H). Calculated for $\text{C}_{26}\text{H}_{33}\text{BN}_3\text{O}_5$ $[\text{M}-\text{H}_2\text{O}]^+$: 478.3.; found: 478.2
68	C		^1H NMR (500 MHz, MeOD) δ 7.30–7.19 (m, 5H), 7.18–7.08 (m, 4H), 4.66 (dd, J = 9.4, 5.6 Hz, 1H), 3.45–3.39 (m, 1H), 2.96 (dd, J = 13.7, 6.2 Hz, 1H), 2.83 (dd, J = 13.7, 7.3 Hz, 1H), 2.58 (qq, J = 6.4, 3.0 Hz, 3H), 2.48 (dt, J = 11.2, 7.2 Hz, 1H), 2.30 (d, J = 8.8 Hz, 1H), 1.83–1.70 (m, 3H), 1.68–1.48 (m, 4H), 0.97–0.89 (m, 11H). Calculated for $\text{C}_{24}\text{H}_{40}\text{BClN}_3\text{O}_3$ $[\text{M}-\text{H}_2\text{O}]^+$: 512.3.; found: 512.2
69	NA		^1H NMR (500 MHz, MeOD) δ 7.36–7.17 (m, 9H), 5.10–4.97 (m, 2H), 4.46 (dd, J = 9.6, 5.1 Hz, 1H), 4.41 (t, J = 7.5 Hz, 1H), 3.12 (dt, J = 13.9, 5.1 Hz, 1H), 2.84 (ddd, J = 13.8, 9.8, 2.8 Hz, 1H), 2.28 (m, 1H), 2.12 (dq, J = 14.1, 7.0

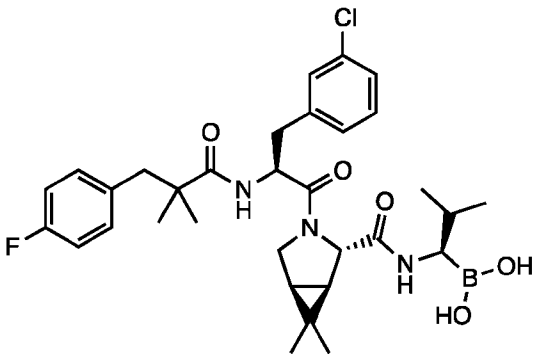
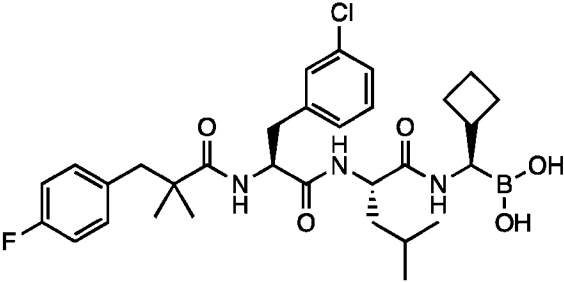
			Hz, 1H), 1.78 (tdt, $J = 12.5, 8.3, 6.4$ Hz, 1H), 1.05–0.90 (m, 12H). Calculated for $C_{26}H_{34}BClN_3O_5$ [M–OH]⁺: 514.2; found, 514.2.
70	B		¹H NMR (500 MHz, MeOD) δ 7.39–7.15 (m, 9H), 5.04 (s, 2H), 4.51–4.40 (m, 2H), 3.11 (dt, $J = 14.0, 4.7$ Hz, 1H), 2.84 (ddd, $J = 13.2, 9.5, 2.9$ Hz, 1H), 2.33–2.22 (m, 1H), 1.92 (s, 1H), 1.78 (dddd, $J = 19.8, 15.2, 11.1, 6.7$ Hz, 1H), 1.64–1.55 (m, 2H), 1.30–1.19 (m, 1H), 0.95 (m, 12H). Calculated for $C_{28}H_{37}BClN_2O_5$ [M–OH]⁺: 528.2; found: 528.2
71	A		¹H NMR (500 MHz, MeOD) δ 7.31–7.09 (m, 7H), 7.04–6.99 (m, 2H), 4.67 (dddd, $J = 12.9, 9.7, 6.5, 4.7$ Hz, 2H), 3.11 (ddd, $J = 14.0, 5.1, 2.8$ Hz, 1H), 2.91 (ddd, $J = 13.8, 9.4, 4.3$ Hz, 1H), 2.82–2.71 (m, 2H), 2.37–2.25 (m, 1H), 1.87–1.58 (m, 3H), 1.09 (d, $J = 1.5$ Hz, 6H), 1.03–0.92 (m, 12H). Calculated for $C_{30}H_{42}BClN_3O_4$ [M–OH]⁺: 554.3; found, 554.4
72	A		¹H NMR (500 MHz, MeOD) δ 7.31–7.10 (m, 8H), 7.01 (dt, $J = 7.4, 2.0$ Hz, 2H), 4.71–4.59 (m, 2H), 3.10 (ddd, $J = 13.9, 5.2, 3.5$ Hz, 1H), 2.91 (ddd, $J = 13.6, 9.3, 3.9$ Hz, 1H), 2.79 (dd, $J = 13.3, 2.4$

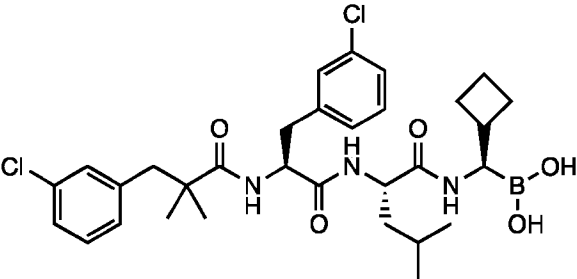
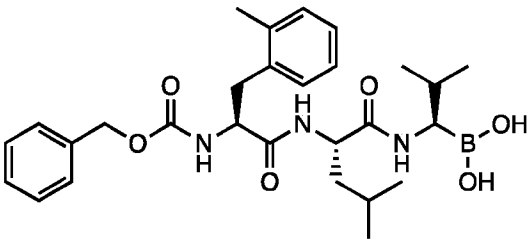
			Hz, 1H), 2.74 (d, J= 13.2 Hz, 1H), 2.65–2.55 (m, 1H), 2.44 (dq, J= 15.9, 8.1 Hz, 1H), 2.16–2.00 (m, 1H), 1.95–1.57 (m, 8H), 1.09 (t, J= 2.3 Hz, 6H), 1.01 (dd, J= 6.4, 2.0 Hz, 3H), 0.96 (dd, J= 6.3, 1.7 Hz, 3H). Calculate for $C_{31}H_{42}BClN_3O_4$ [M-OH]⁺, 566.3; found, 566.3
73	A		Mix of diastereomers precluded NMR analysis. Calculated for $C_{29}H_{40}BClN_3O_4$ [M-OH], 540.3; found, 540.3
74	NA		¹H NMR (500 MHz, MeOD) δ 7.31–7.22 (m, 5H), 7.19–7.12 (m, 4H), 4.69–4.59 (m, 2H), 3.11 (ddd, J= 14.0, 5.1, 1.6 Hz, 1H), 2.89–2.78 (m, 3H), 2.48 (ddd, J= 8.9, 6.6, 1.2 Hz, 2H), 2.35–2.23 (m, 1H), 1.85–1.56 (m, 4H), 1.01–0.93 (m, 12H). Calculated for $C_{28}H_{38}BClN_3O_4$ [M-OH]⁺, 526.3; found, 526.2
75	B		¹H NMR (500 MHz, MeOD) δ 7.34–7.17 (m, 9H), 4.68 (ddd, J= 14.2, 10.0, 4.8 Hz, 1H), 4.53–4.43 (m, 1H), 4.35–4.22 (m, 2H), 3.12 (dd, J= 14.0, 5.2 Hz, 1H), 2.89 (ddd, J= 14.1, 8.8, 5.8 Hz, 1H), 2.26 (dd, J= 27.8, 9.1 Hz, 1H), 1.84–1.57 (m, 4H), 0.99–0.92 (m, 12H).

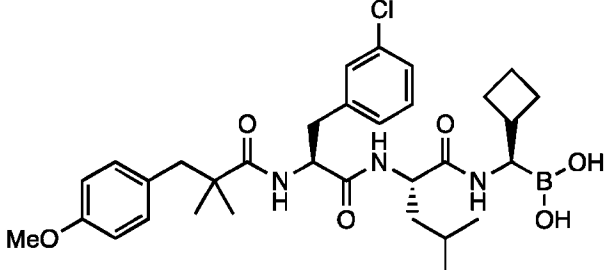
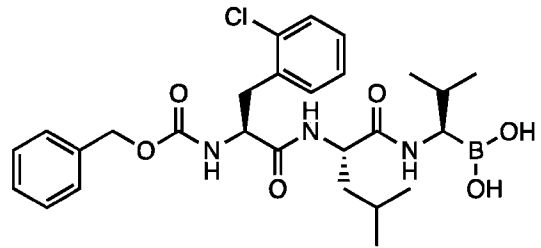
			Calculated for $C_{27}H_{37}BClN_4O_4$ [M-OH]⁺ 527.3; found, 527.3 Exact Mass: 527.2591
76	A		¹H NMR (500 MHz, MeOD) δ 7.33–7.27 (m, 5H), 7.25–7.18 (m, 4H), 4.64 (dd, <i>J</i> = 10.1, 4.9 Hz, 1H), 4.51–4.45 (m, 1H), 4.30 (dd, <i>J</i> = 5.0, 1.9 Hz, 3H), 3.12 (dd, <i>J</i> = 14.1, 5.2 Hz, 1H), 2.90 (dd, <i>J</i> = 14.1, 8.8 Hz, 1H), 2.56 (d, <i>J</i> = 9.0 Hz, 1H), 2.42 (dq, <i>J</i> = 9.1, 7.7 Hz, 1H), 2.14–1.99 (m, 2H), 1.92–1.83 (m, 1H), 1.83–1.70 (m, 4H), 1.71–1.58 (m, 2H), 0.97 (d, <i>J</i> = 6.3 Hz, 3H), 0.93 (d, <i>J</i> = 6.2 Hz, 3H). Calculated for $C_{28}H_{37}BClN_4O_4$ [M-OH], 539.3; found, 539.2
Additional Compounds			
77	A		¹H NMR (500 MHz, MeOD) δ 7.35–7.17 (m, 4H), 7.17–7.09 (m, 3H), 6.96–6.89 (m, 2H), 4.67–4.53 (m, 2H), 3.10 (dd, <i>J</i> = 13.9, 4.9 Hz, 1H), 2.95 (d, <i>J</i> = 7.7 Hz, 1H), 2.86 (dd, <i>J</i> = 14.0, 10.0 Hz, 1H), 2.60 (d, <i>J</i> = 9.0 Hz, 1H), 2.47–2.35 (m, 2H), 2.26–2.12 (m, 2H), 2.03 (dddd, <i>J</i> = 24.8, 17.6, 9.5, 4.7 Hz, 4H), 1.94–1.51 (m, 9H), 0.98 (d, <i>J</i> = 6.3 Hz, 3H), 0.94 (d, <i>J</i> = 6.4 Hz, 3H). Calc for $C_{32}H_{42}BClN_3O_4$ [M-OH]⁺ 578.2951 Found: 578.3

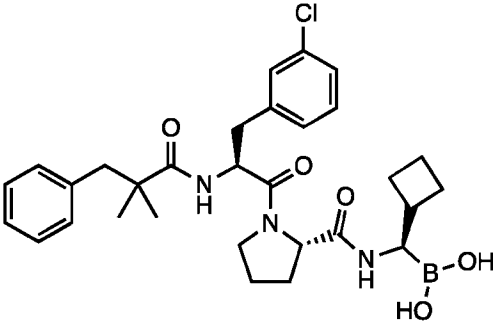
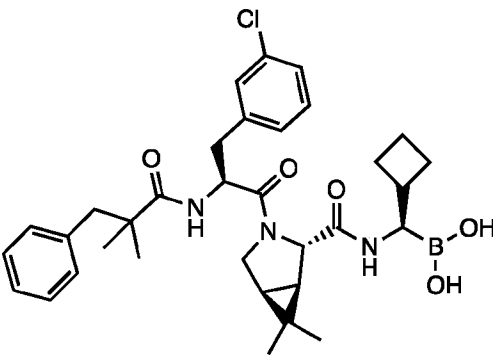
78	B		¹H NMR (500 MHz, MeOD) δ 8.59 (dd, <i>J</i> = 15.0, 7.4 Hz, 1H), 7.65–7.41 (m, 5H), 7.36–7.22 (m, 4H), 5.11–4.96 (m, 2H), 4.67 (qd, <i>J</i> = 7.2, 4.4 Hz, 1H), 4.41 (dt, <i>J</i> = 9.0, 4.7 Hz, 1H), 3.25–3.13 (m, 1H), 2.95 (ddd, <i>J</i> = 14.1, 9.6, 7.5 Hz, 1H), 2.35–2.20 (m, 1H), 1.74 (dq, <i>J</i> = 13.1, 6.3 Hz, 2H), 1.61 (pd, <i>J</i> = 6.9, 2.6 Hz, 2H), 1.00–0.87 (m, 12H). Calc. for C₂₈H₃₆BF₃N₃O₅ [M–OH]⁺: 562.2695 Found: 562.3
79	A		¹H NMR (500 MHz, MeOD) δ 7.47 (d, <i>J</i> = 8.1 Hz, 2H), 7.32–7.15 (m, 5H), 7.15–7.10 (m, 1H), 4.72 (dd, <i>J</i> = 9.4, 5.0 Hz, 1H), 4.39 (dd, <i>J</i> = 9.1, 5.9 Hz, 1H), 3.27 (dd, <i>J</i> = 13.4, 7.2 Hz, 1H), 3.21–3.09 (m, 2H), 2.97–2.88 (m, 2H), 2.82 (d, <i>J</i> = 13.2 Hz, 1H), 2.51 (dt, <i>J</i> = 15.2, 7.6 Hz, 1H), 2.11–2.00 (m, 2H), 1.99–1.82 (m, 2H), 1.79–1.52 (m, 5H), 1.31 (s, 1H), 1.11 (s, 3H), 1.10 (s, 3H), 0.97 (d, <i>J</i> = 6.5 Hz, 3H), 0.94 (d, <i>J</i> = 6.5 Hz, 3H). Calc for C₃₂H₄₁BClF₃N₃O₅ [M–OH]⁺: 634.2825; found, 634.2

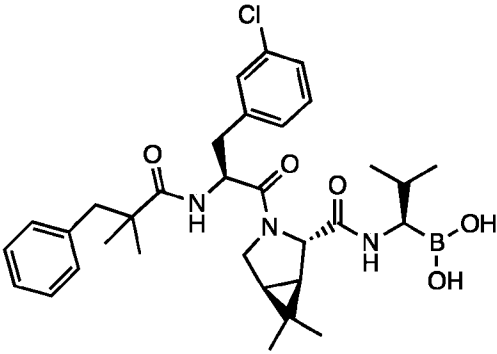
80	A		¹H NMR (500 MHz, MeOD) δ 7.51–7.44 (m, 1H), 7.32–7.16 (m, 4H), 6.91–6.84 (m, 2H), 6.69 (d, <i>J</i> = 8.8 Hz, 2H), 4.79 (ddd, <i>J</i> = 9.7, 8.0, 4.7 Hz, 1H), 3.94 (dd, <i>J</i> = 10.4, 5.5 Hz, 1H), 3.84 (d, <i>J</i> = 10.4 Hz, 1H), 3.73 (s, 3H), 3.23 (q, <i>J</i> = 7.4 Hz, 1H), 3.10–2.95 (m, 1H), 2.85 (ddd, <i>J</i> = 13.2, 9.6, 3.2 Hz, 1H), 2.70 (d, <i>J</i> = 13.3 Hz, 1H), 2.65 (s, 1H), 2.61 (d, <i>J</i> = 13.4 Hz, 1H), 2.30 (dd, <i>J</i> = 10.0, 8.2 Hz, 1H), 1.90–1.64 (m, 2H), 1.45 (d, <i>J</i> = 7.6 Hz, 1H), 1.37 (dd, <i>J</i> = 6.9, 4.3 Hz, 6H), 1.09 (d, <i>J</i> = 4.8 Hz, 3H), 1.02 (d, <i>J</i> = 3.7 Hz, 3H), 0.98–0.95 (m, 3H), 0.95–0.90 (m, 3H). Calculated for: C₃₃H₄₄BClN₃O₅ [M–OH]⁺ 608.3057 Found: 608.3
81	B		¹H NMR (500 MHz, MeOD) δ 7.15–7.06 (m, 3H), 7.03–7.00 (m, 2H), 6.95 (td, <i>J</i> = 4.6, 1.9 Hz, 1H), 6.84 (d, <i>J</i> = 8.4 Hz, 2H), 4.54 (dd, <i>J</i> = 9.3, 5.1 Hz, 1H), 4.27–4.20 (m, 1H), 3.51 (d, <i>J</i> = 0.8 Hz, 1H), 3.16–3.09 (m, 1H), 3.07–3.00 (m, 1H), 2.97 (dd, <i>J</i> = 13.9, 5.0 Hz, 1H), 2.77 (dd, <i>J</i> = 13.9, 9.4 Hz, 1H), 2.65 (d, <i>J</i> = 13.3 Hz, 1H), 2.57 (d, <i>J</i> = 13.3 Hz, 1H), 2.37 (p, <i>J</i> = 7.5 Hz, 1H), 1.91 (dddd, <i>J</i> = 10.4, 6.9, 4.7, 3.5 Hz, 2H), 1.81–1.71 (m, 2H), 1.63–1.55 (m, 2H), 1.55–1.39 (m, 3H), 1.16 (s, 2H), 1.06–

			1.01 (m, 2H), 0.94 (d, $J = 3.0$ Hz, 6H), 0.83 (d, $J = 6.5$ Hz, 3H), 0.80 (d, $J = 6.5$ Hz, 3H). $C_{31}H_{41}BCl_2N_3O_5$ [M-OH]⁻ 600.2562; found: 600.3
82	A		^1H NMR (500 MHz, MeOD) δ 7.50 (d, $J = 8.1$ Hz, 1H), 7.36–7.16 (m, 4H), 7.01–6.92 (m, 2H), 6.85 (t, $J = 8.8$ Hz, 2H), 4.78 (ddd, $J = 10.0, 4.8, 3.1$ Hz, 1H), 3.96 (dd, $J = 10.3, 5.5$ Hz, 1H), 3.85 (d, $J = 10.3$ Hz, 1H), 3.07 (dd, $J = 14.2, 4.5$ Hz, 1H), 2.89–2.82 (m, 1H), 2.74 (d, $J = 13.4$ Hz, 1H), 2.68 (d, $J = 13.4$ Hz, 1H), 2.38 (d, $J = 8.7$ Hz, 1H), 1.81 (dt, $J = 8.7, 6.6$ Hz, 1H), 1.68 (dd, $J = 7.5, 5.3$ Hz, 1H), 1.47 (d, $J = 7.6$ Hz, 1H), 1.09 (s, 3H), 1.03 (d, $J = 4.5$ Hz, 6H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.93 (d, $J = 6.6$ Hz, 3H), 0.91 (s, 3H). Calculated for $C_{32}H_{41}BClFN_3O_4^+$ [M-OH]⁺ 596.2857; Found: 596.2
83	A		^1H NMR (500 MHz, MeOD) δ 7.31–7.19 (m, 3H), 7.13 (dq, $J = 6.3, 2.2$ Hz, 1H), 6.96 (dt, $J = 7.7, 5.5$ Hz, 2H), 6.86 (dd, $J = 9.0, 7.9$ Hz, 2H), 4.61 (ddd, $J = 15.1, 9.7, 5.3$ Hz, 2H), 3.09 (dd, $J = 13.9, 4.7$ Hz, 1H), 2.88 (dd, $J = 13.9, 10.1$ Hz, 1H), 2.76 (d, $J = 13.1$ Hz, 1H), 2.69 (d, $J = 13.4$ Hz, 1H), 2.61 (d, $J = 9.1$ Hz, 1H), 2.43 (dt, $J = 15.8, 7.9$ Hz, 1H), 2.14–1.97 (m,

			2H), 1.95–1.55 (m, 6jH), 1.15 (d, $J=19.3$ Hz, 1H), 1.06 (d, $J=1.6$ Hz, 6H), 0.99 (dd, $J=6.4, 2.2$ Hz, 3H), 0.94 (dd, $J=6.4, 1.9$ Hz, 3H). Calc for $C_{31}H_{41}BClFN_3O_4^+$ [M–OH]$^+$: 584.2857; found: 584.3
84	A		^1H NMR (500 MHz, MeOD) δ 7.34–6.99 (m, 7H), 6.92 (ddd, $J=6.7, 3.7, 1.7$ Hz, 1H), 4.63 (ddd, $J=9.3, 4.8, 2.4$ Hz, 2H), 3.08 (dt, $J=13.9, 4.3$ Hz, 1H), 2.94–2.85 (m, 1H), 2.80 (d, $J=13.5$ Hz, 1H), 2.74–2.67 (m, 1H), 2.63–2.52 (m, 1H), 2.42 (dq, $J=16.1, 8.1$ Hz, 1H), 2.12–1.99 (m, 2fH), 1.93–1.53 (m, 7H), 1.07 (dd, $J=10.4, 1.9$ Hz, 6H), 0.98 (dd, $J=6.4, 2.4$ Hz, 3H), 0.94 (dd, $J=6.3, 2.3$ Hz, 3H). Calc: $C_{31}H_{41}BCl_2N_3O_4^+$ [M–OH]$^+$: 600.2562 found: 600.3
85	B		^1H NMR (500 MHz, MeOD) δ 7.35–7.23 (m, 5H), 7.19–7.01 (m, 4H), 5.03 (s, 2H), 4.63 (dd, $J=10.2, 4.6$ Hz, 1H), 4.50–4.30 (m, 1H), 3.12 (dd, $J=14.7, 5.7$ Hz, 1H), 2.90 (dd, $J=14.4, 8.7$ Hz, 1H), 2.34 (s, 3H), 2.22 (t, $J=9.0$ Hz, 1H), 1.73 (d, $J=13.7$ Hz, 2H), 1.66–1.51 (m, 2H), 1.05–0.79 (m, 12H). Calculated for $C_{28}H_{39}BN_3O_5^+$

			[M-OH]⁺: 508.2977; Found: 508.2
86	A		¹H NMR (500 MHz, MeOD) δ 7.30–7.17 (m, 3H), 7.11 (dt, <i>J</i> = 6.9, 1.8 Hz, 1H), 6.89 (d, <i>J</i> = 8.7 Hz, 2H), 6.75–6.68 (m, 2H), 4.69–4.54 (m, 2H), 3.73 (s, 3H), 3.08 (dd, <i>J</i> = 14.0, 5.0 Hz, 1H), 2.89 (dd, <i>J</i> = 13.9, 9.5 Hz, 1H), 2.71 (d, <i>J</i> = 13.4 Hz, 1H), 2.65 (d, <i>J</i> = 1.3 Hz, 1H), 2.64–2.60 (m, 1H), 2.43 (dq, <i>J</i> = 16.0, 7.9 Hz, 1H), 2.13–1.99 (m, 1H), 1.96–1.54 (m, 8H), 1.05 (d, <i>J</i> = 1.9 Hz, 6H), 0.98 (d, <i>J</i> = 6.4 Hz, 3H), 0.94 (d, <i>J</i> = 6.2 Hz, 3H). Calculated for: C₃₂H₄₄BClN₃O₅⁺ [M-OH]⁺: 596.3057 Found: 596.3
87	A		¹H NMR (500 MHz, MeOD) δ 7.34–7.24 (m, 6H), 7.21 (tdd, <i>J</i> = 8.8, 4.5, 1.9 Hz, 2H), 7.07 (t, <i>J</i> = 7.1 Hz, 1H), 5.02 (d, <i>J</i> = 3.4 Hz, 2H), 4.63 (ddt, <i>J</i> = 14.3, 9.6, 5.2 Hz, 1H), 4.57–4.41 (m, 1H), 4.37 (dt, <i>J</i> = 7.9, 3.8 Hz, 1H), 3.27 (ddd, <i>J</i> = 14.2, 5.6, 1.7 Hz, 1H), 3.18–3.10 (m, 1H), 3.07–2.98 (m, 1H), 2.98–2.83 (m, 1H), 2.27–2.18 (m, 1H), 1.81–1.70 (m, 2H), 1.62 (ddd, <i>J</i> = 18.1, 12.4, 5.8 Hz, 2H), 1.00–0.86 (m, 12H). Calculated for: C₂₇H₃₆BClN₃O₅⁺ [M-OH]⁺: 528.2431 Found: 528.2

88	C		¹H NMR (500 MHz, MeOD) δ 7.35–7.09 (m, 8H), 7.04–7.00 (m, 1H), 4.95–4.88 (m, 1H), 4.41 (dd, <i>J</i> = 8.2, 4.5 Hz, 1H), 3.82 (dt, <i>J</i> = 10.1, 6.7 Hz, 1H), 3.72–3.63 (m, 1H), 3.25 (dtdd, <i>J</i> = 14.0, 13.0, 7.0, 5.6 Hz, 2H), 3.13 (dd, <i>J</i> = 14.0, 5.0 Hz, 1H), 2.94 (dd, <i>J</i> = 14.0, 8.9 Hz, 1H), 2.78 (d, <i>J</i> = 13.2 Hz, 1H), 2.74 (d, <i>J</i> = 13.2 Hz, 1H), 2.53 (hept, <i>J</i> = 7.8 Hz, 1H), 2.26–2.14 (m, 1H), 2.14–1.87 (m, 8H), 1.82–1.70 (m, 2H), 1.08 (s, 3H), 1.07 (s, 3H). For C₂₉H₃₈BClN₃O₄ [M–OH]⁺: 550.3, found: 550.3
89	NA		¹H NMR (500 MHz, MeOD) δ 7.32–7.20 (m, 3H), 7.20–7.13 (m, 4H), 7.02–6.98 (m, 2H), 3.98 (dd, <i>J</i> = 10.3, 5.5 Hz, 1H), 3.86 (d, <i>J</i> = 10.3 Hz, 1H), 3.32–3.26 (m, 1H), 3.26–3.19 (m, 1H), 3.11 (dd, <i>J</i> = 14.1, 4.7 Hz, 1H), 2.88 (dd, <i>J</i> = 14.1, 9.1 Hz, 1H), 2.78 (d, <i>J</i> = 13.2 Hz, 1H), 2.71 (d, <i>J</i> = 13.2 Hz, 1H), 2.55 (dq, <i>J</i> = 15.1, 7.0 Hz, 1H), 2.13–2.04 (m, 2H), 1.97–1.86 (m, 3H), 1.81–1.72 (m, 2H), 1.61 (dd, <i>J</i> = 7.6, 5.3 Hz, 1H), 1.38 (d, <i>J</i> = 7.5 Hz, 1H), 1.08 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 0.92 (s, 3H). Calc. for C₃₃H₄₂BClN₃O₄ [M–OH]⁺ 590.2951, found: 590.2

90	A		¹ H NMR (500 MHz, MeOD) δ 7.33–7.20 (m, 4H), 7.16 (dd, <i>J</i> = 5.1, 2.0 Hz, 3H), 7.02–6.96 (m, 2H), 4.86–4.80 (m, 1H), 4.54 (s, 1H), 3.97 (dd, <i>J</i> = 10.3, 5.4 Hz, 1H), 3.88 (d, <i>J</i> = 10.3 Hz, 1H), 3.09 (dd, <i>J</i> = 14.1, 4.8 Hz, 1H), 2.88 (dd, <i>J</i> = 14.1, 9.7 Hz, 1H), 2.79 (d, <i>J</i> = 13.3 Hz, 1H), 2.70 (d, <i>J</i> = 13.3 Hz, 1H), 2.41 (d, <i>J</i> = 8.6 Hz, 1H), 1.83 (dh, <i>J</i> = 8.6, 6.7 Hz, 1H), 1.69 (dd, <i>J</i> = 7.5, 5.3 Hz, 1H), 1.55–1.47 (m, 1H), 1.11 (s, 3H), 1.05 (d, <i>J</i> = 3.4 Hz, 6H), 0.99 (d, <i>J</i> = 6.6 Hz, 3H), 0.97–0.94 (m, 6H). Calc. for C ₃₂ H ₄₁ BClN ₃ O ₄ [M–OH] ⁺ 578.3; found, 578.3
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^a IC₅₀ key: A = <100nM; B = 100nM–500nM; C: 500nM–10,000nM; D = >10000 nM; NA = data not available

Example 6: RBC Protease Assay

- 5 Reaction Buffer: 50 mM Tris, pH 8.0, 200 mM NaCl, 0.25% CHAPS, 0.75% DMSO (final). HTRA1 Enzyme: R&D Systems cat# 2916-SE-020; *E. coli*-derived human HTRA1/PRSS11 protein Gly156-Pro480, with an N-terminal Met and C-terminal 6-His tag, MW=36 kDa. Substrate: H2-optimal substrate, Ex/Em=320/405 nm, Mca-IRRVSYSF(K-Dnp)K (SEQ ID NO: 1). Control compound: Compound 18. Reaction Conditions: Substrate
- 10 Final concentration in the assay = 2.5 μM; HTRA1, 6.5 nM.

- Reaction Procedure: solutions of the enzyme and substrate were prepared in fresh Reaction Buffer. The enzyme solution was delivered to the reaction well, and then the compounds in DMSO were delivered to the reaction mixture by using Acoustic Technology (Echo 550, LabCyte Inc. Sunnyvale, CA) in nanoliter range. After 20 min incubation, the
- 15 substrate solution was into the reaction well to initiate the reaction. The enzyme activities were monitored every 5 min as a time-course measurement of the increase in fluorescence signal from fluorescently labeled peptide substrate for 120 min at room temperature. Data was

analyzed by taking slope (signal/time) of the linear portion of the measurement. (Note: time periods taken for sole are different for each protease, as some are linear for 0-120 min, some for 0-30 min, etc.) Slopes were calculated using Excel, and curve fits were performed using GraphPad Prism software.

5 IC₅₀ values obtained from this assay are presented in Table 2.

Example 7: Cytotoxicity Assay

ARPE19 cells were cultured by growing ARPE19 cells to 95% confluency, seeding 20,000 cells per well (2×10^4 cells per well) at a final volume of 100 μ L per well in lanes 2-12 of a 96 well plate, and incubating the cells at 37°C for 24 hours. Cell media was aspirated carefully so as not to touch the cells at the bottom of the plate, and 100 μ L of PBS per well was immediately added to wash the cells. The PBS was aspirated, followed by addition of 50 μ L of serum-free media to every well.

Drug solutions were prepared for desired final concentrations of 0.0005 μ M, 0.005 μ M, 0.5 μ M, 5 μ M, and 50 μ M in quadruplicates. The required intermediate concentrations were determined for 5 μ L of drug to be double the desired final concentration when added to 245 μ L serum-free media. For example, for cells treated with 50 μ M drug, 5 μ L of 5 mM drug stock must be added to 245 μ L serum-free media for an intermediate dilution of 100 μ M. The drug was first diluted into DMSO, then 5 μ L of each drug was added into 245 μ L serum-free media per previous calculations, and then a 2% DMSO in serum-free media dilution for the 8 wells of control cells was prepared.

For conducting drug treatment assays in the ARPE19 cells, 50 μ L of intermediate drug dilution was added to 4 designated wells, and the plate was incubated at 37°C for 5 hours. The drug treatment media was aspirated from the cells and tips were changed for each half of the plate. Cells were replenished with 150 μ L complete media per well, followed by incubating the plate at 37°C for 72 hours.

For performing CCK8 reading, 10 mL of 10% CCK8 solution was prepared (Dojindo, CK04) per plate by diluting CCK8 reagent into serum-free media. Media was aspirated from cells, followed by addition of 100 μ L of 10% CCK8 solution per well, including lane 1 which contains no cells (serves as blank). The plate was incubated at 37°C for 1 hour. Any noticeable bubbles were popped with a syringe needle. Absorbance values were acquired at 450 nM using a Tecan plate reader.

To determine CC₅₀ values from absorbance readings, the values from the blank wells were averaged to calculate blank/baseline signal. The blank was subtracted from all other

data points. The values from the control wells were averaged to calculate the maximum signal. All values were divided by the maximum signal and multiply by 100 to calculate percent metabolic activity. Data points were fit on a non-linear regression curve using Prism to determine the cytotoxic concentration at which each drug causes 50% cell death (CC₅₀).

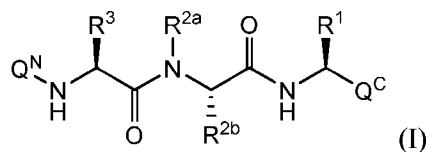
5 Data are shown in Table 3.

Table 3. CC50 data

Compound	CC50
1	2.6 μ M
2	0.173 μ M

CLAIMS

1. A compound of formula (I):



5 or a pharmaceutically acceptable salt thereof, wherein:

Q^N is $-X-R^N$, wherein: X is selected from $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-S(O)_2-$, and a bond; R^N is selected from C_1-C_6 alkyl, aryl, and $-(CR^aR^b)_p-Z$; p is 1, 2, or 3; R^a and R^b are each independently selected from hydrogen and C_1-C_4 alkyl, wherein one R^a and one R^b , together with the carbon atom to which they are attached, are optionally taken together to form a 3- to 6-membered cycloalkyl; and Z is selected from aryl and heterocyclyl; wherein each R^N is optionally substituted with 1 or 2 substituents independently selected from halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, $-OH$, and $-COOH$;

Q^C is selected from $-B(OR^{C1})_2$ and $-C(O)R^{C2}$, wherein each R^{C1} is independently selected from hydrogen, C_1-C_6 alkyl, and aryl, or two R^{C1} , together with the atoms to which they are attached, form an optionally substituted ring, and R^{C2} is selected from C_1-C_4 alkyl and C_1-C_4 haloalkyl;

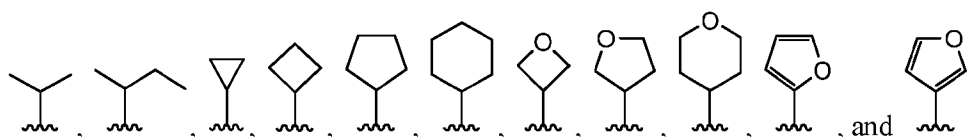
R^1 is selected from C_3-C_8 alkyl, hydroxy- C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, and monocyclic heteroaryl;

R^{2a} is hydrogen or C_1-C_4 -alkyl, and R^{2b} is selected from C_1-C_8 alkyl, aryl- C_1-C_4 -alkyl, heteroaryl- C_1-C_4 -alkyl, hydroxy, and $-(CH_2)_mNH-R^{2c}$, wherein m is 1, 2, 3, 4, 5, or 6, R^{2c} is selected from H and $-COO(C_1-C_6\text{-alkyl})$, and the aryl is unsubstituted or substituted with 1 or 2 substituents independently selected from hydroxy and C_1-C_6 -alkoxy; or R^{2a} and R^{2b} , together with the atoms to which they are attached, form an optionally substituted ring; and

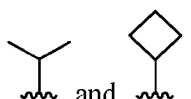
R^3 is selected from C_1-C_8 alkyl and $-(CH_2)_n-Y$, wherein n is 0, 1, 2, or 3, and Y is selected from aryl, heteroaryl, cycloalkyl, and heterocyclyl, wherein the alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl are each independently unsubstituted or substituted with 1 or 2 substituents independently selected from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, halo, cyano, C_1-C_4 haloalkyl, hydroxy, amino, and C_1-C_4 alkoxy, and wherein the aryl or the heteroaryl is optionally substituted with a group that is taken together with R^{C2} to form an optionally substituted ring.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from C₃-C₄ alkyl and C₃-C₅ cycloalkyl.

3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof,
5 wherein R^1 is selected from:

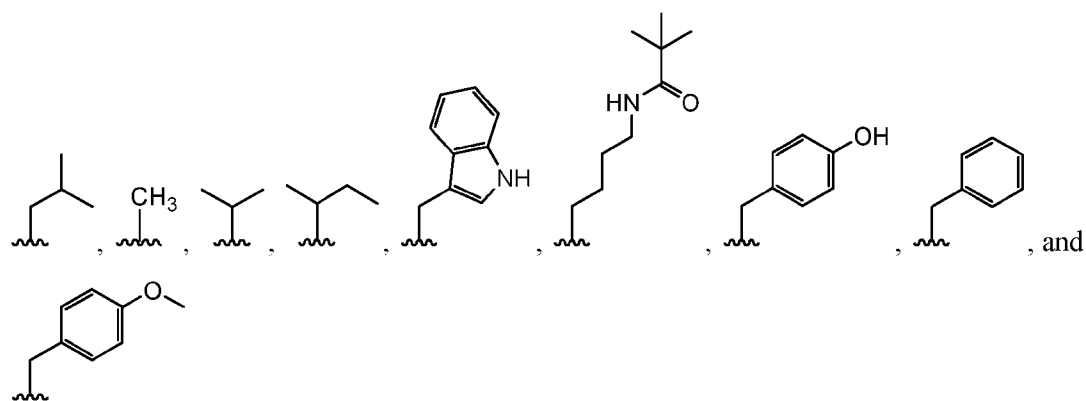


4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from:

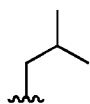


5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is hydrogen, and R^{2b} is selected from C₁-C₄ alkyl, -CH₂-phenyl, -CH₂-indolyl, and -(CH₂)₄NH- R^{2c} , wherein R^{2c} is selected from H and -COO(tBu), and the phenyl
15 is unsubstituted or substituted with one substituent selected from hydroxy and C₁-C₄-alkoxy.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is hydrogen or methyl, and R^{2b} is selected from:



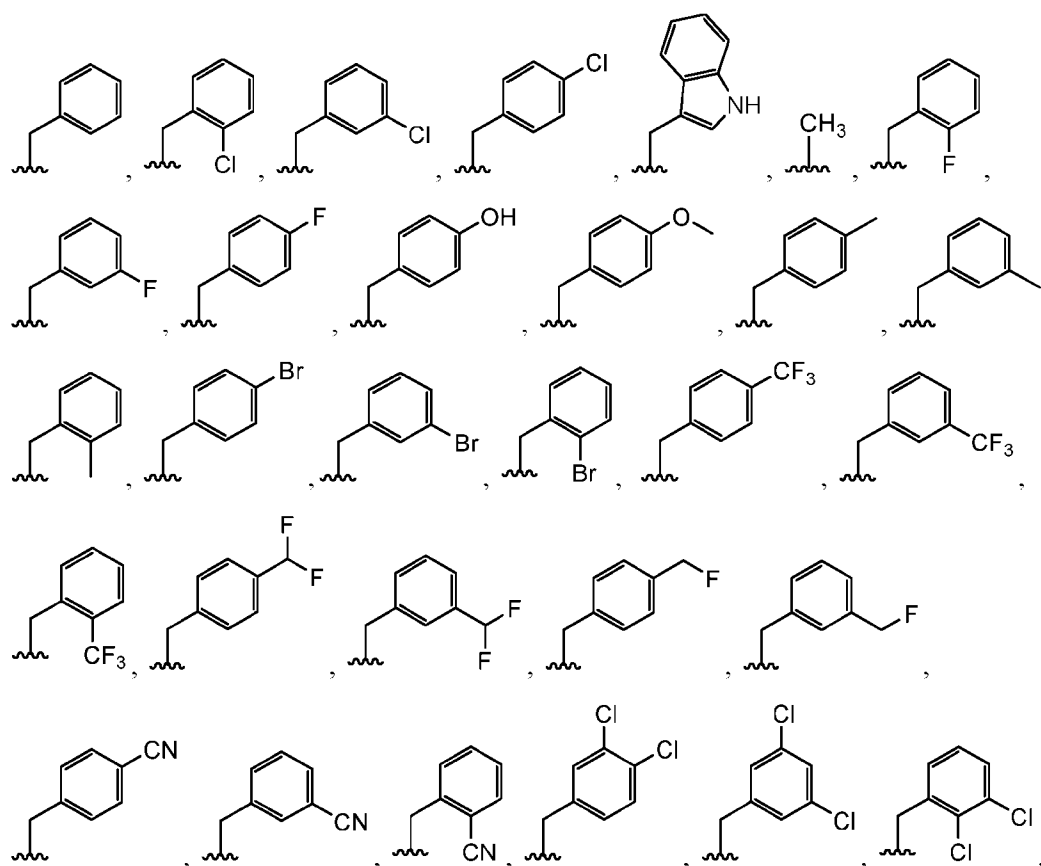
7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is hydrogen, and R^{2b} is:

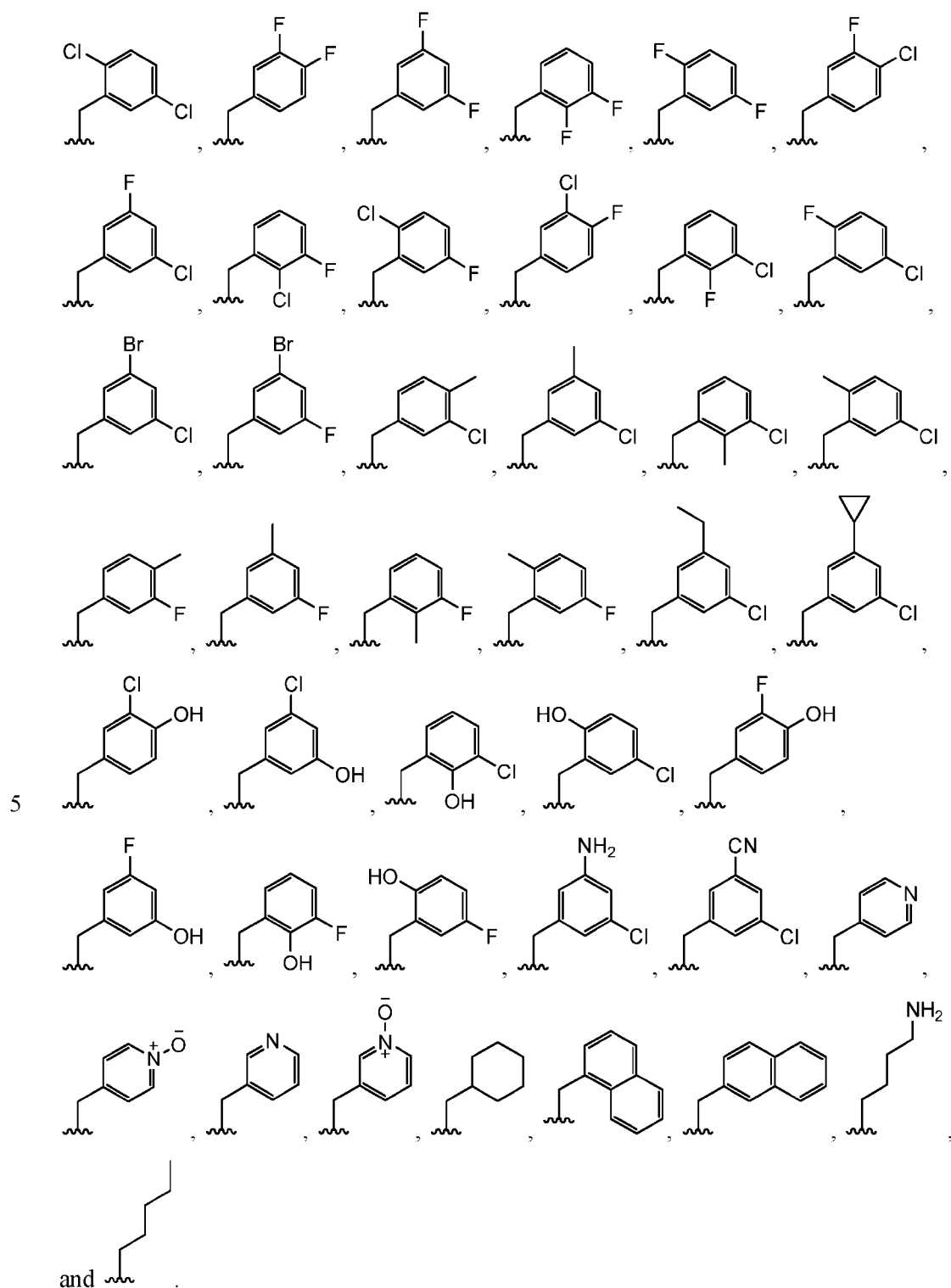


8. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} , together with the atoms to which they are attached, form an optionally substituted five-membered saturated ring.

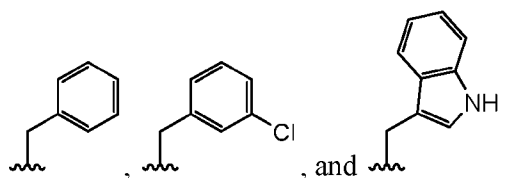
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from C_1 - C_6 alkyl, $-CH_2$ -phenyl, $-CH_2$ -naphthyl, $-CH_2$ -indolyl, $-CH_2$ -pyridyl, and $-CH_2$ -cyclohexyl, wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from methyl, ethyl, fluoro, chloro, bromo, hydroxy, methoxy, cyano, fluoromethyl, difluoromethyl, and trifluoromethyl, and wherein the pyridyl is unsubstituted or substituted with one oxo group.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from:

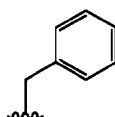




- 10 11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from:



12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^3 is:



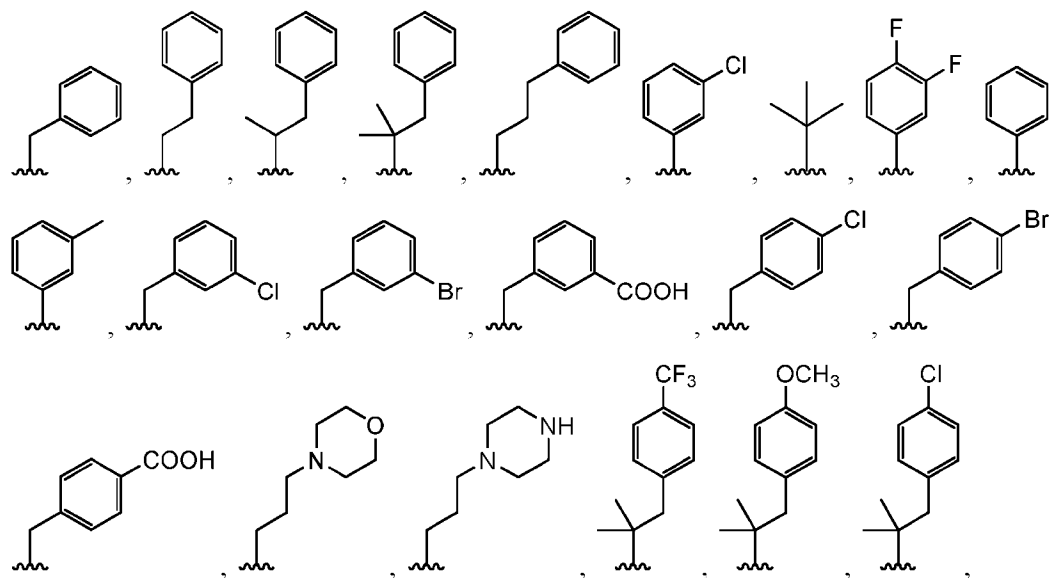
5

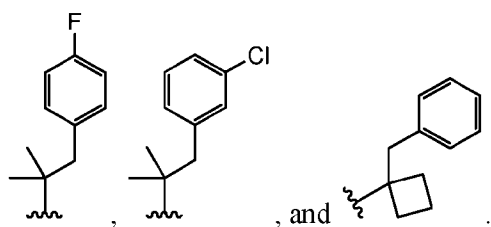
13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^N is selected from C_3 - C_4 alkyl, phenyl, phenyl- C_1 - C_3 -alkyl, and heterocyclyl- C_1 - C_3 -alkyl, wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from halo, methyl, trifluoromethyl, methoxy, and -COOH.

10

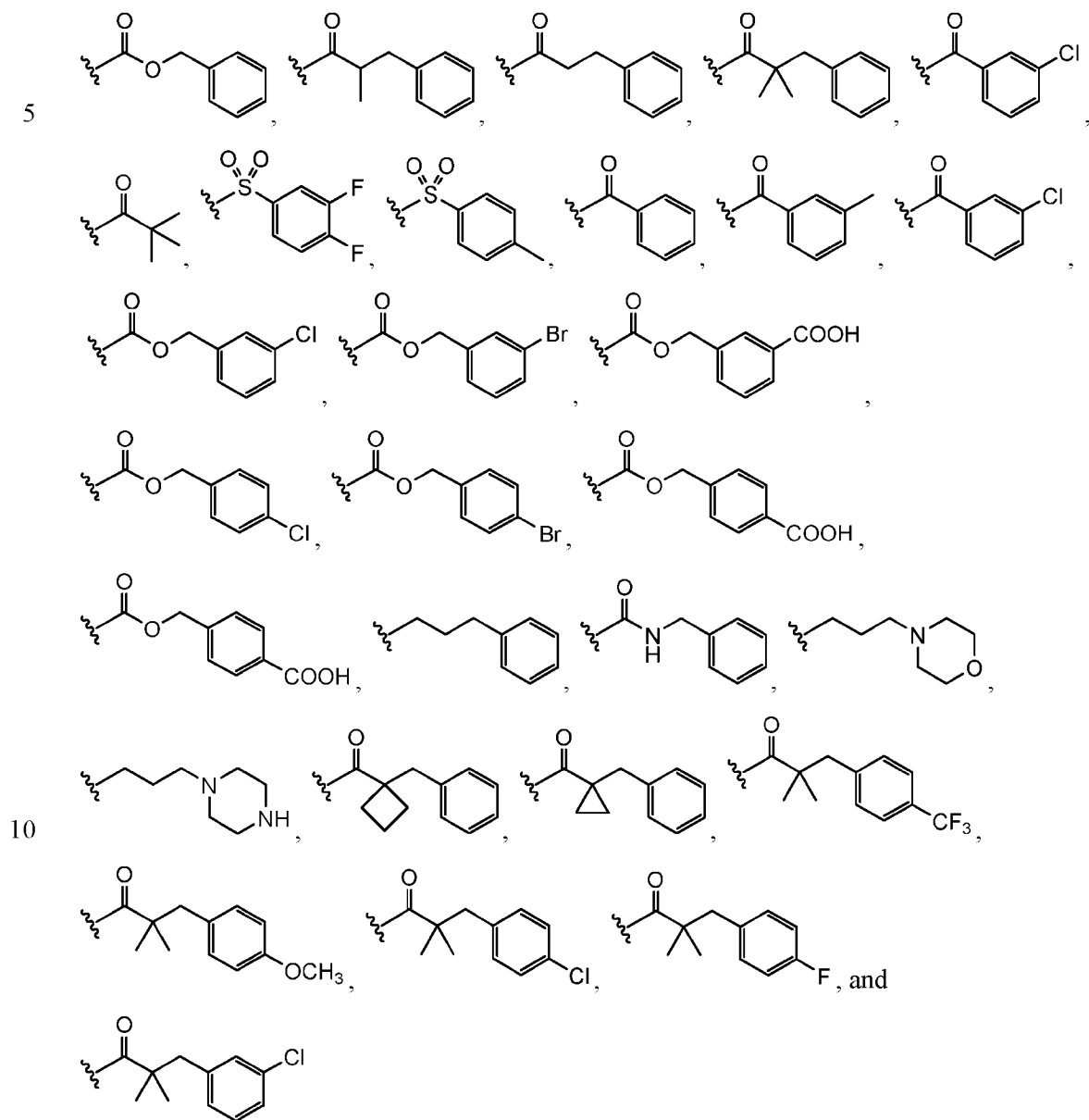
14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein R^N is selected from:

15





15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein Q^N is selected from:



16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein Q^C is $-B(OR^{C1})_2$, and each R^{C1} is independently selected from hydrogen, C₁-C₄ alkyl, and phenyl, or two R^{C1} , together with the atoms to which they are attached, form an optionally substituted saturated 5- to 6-membered ring.
- 5
17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein each R^{C1} is hydrogen.
18. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein Q^C is $-C(O)R^{C2}$, and R^{C2} is C₁-C₄ haloalkyl.
- 10
19. The compound of claim 1, selected from compounds illustrated in FIG. 1, or pharmaceutically acceptable salts thereof.
- 15
20. A pharmaceutical composition comprising a compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
21. A method of treating a disorder associated with HTRA1 in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-19 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 20.
- 20
22. The method of claim 21, wherein the disorder is selected from macular degeneration, Alzheimer's disease, arthritis, bladder cancer, intervertebral disc degeneration, Lyme disease, osteoarthritis, preeclampsia, rheumatoid arthritis, and TGFBI-associated corneal dystrophies.
- 25
23. The method of claim 21, wherein the disorder is age-related macular degeneration.
24. The method of claim 23, wherein the age-related macular degeneration is dry age-related macular degeneration.
- 30
25. A method of inhibiting HTRA1 in a sample, comprising contacting the sample with an effective amount of a compound of any one of claims 1-19 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 20.

26. Use of a compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, as a medicament.
- 5 27. Use of a compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, for treating a disorder associated with HTRA1.
28. The use of claim 27, wherein the disorder is selected from age-related macular degeneration, Alzheimer's disease, arthritis, bladder cancer, intervertebral disc degeneration, 10 Lyme disease, osteoarthritis, preeclampsia, rheumatoid arthritis, and TGFBI-associated corneal dystrophies.
29. The use of claim 27, wherein the disorder is age-related macular degeneration.
- 15 30. The use of claim 29, wherein the age-related macular degeneration is dry age-related macular degeneration.

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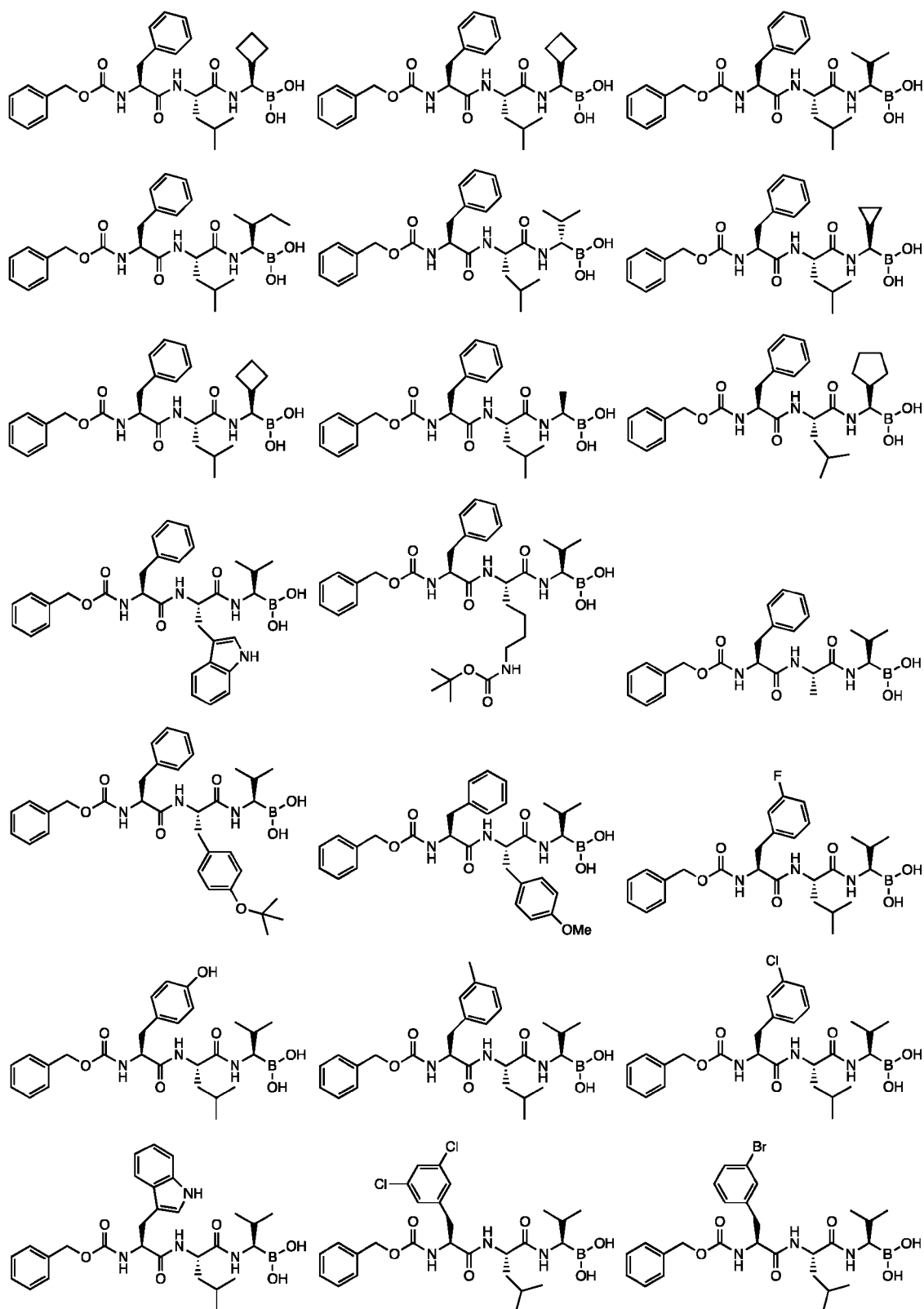


FIG. 1

2/22

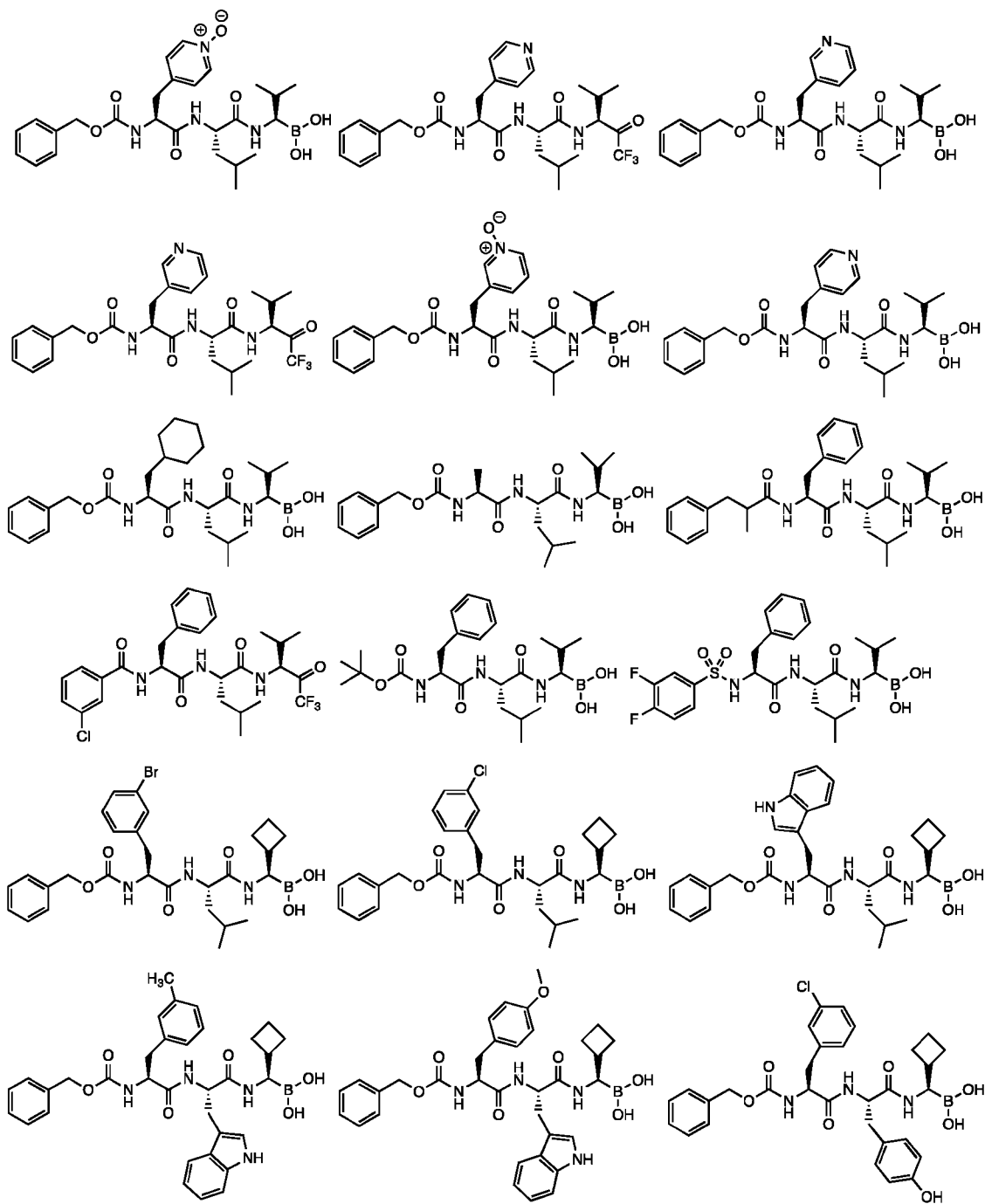


FIG. 1 (cont'd)

3/22

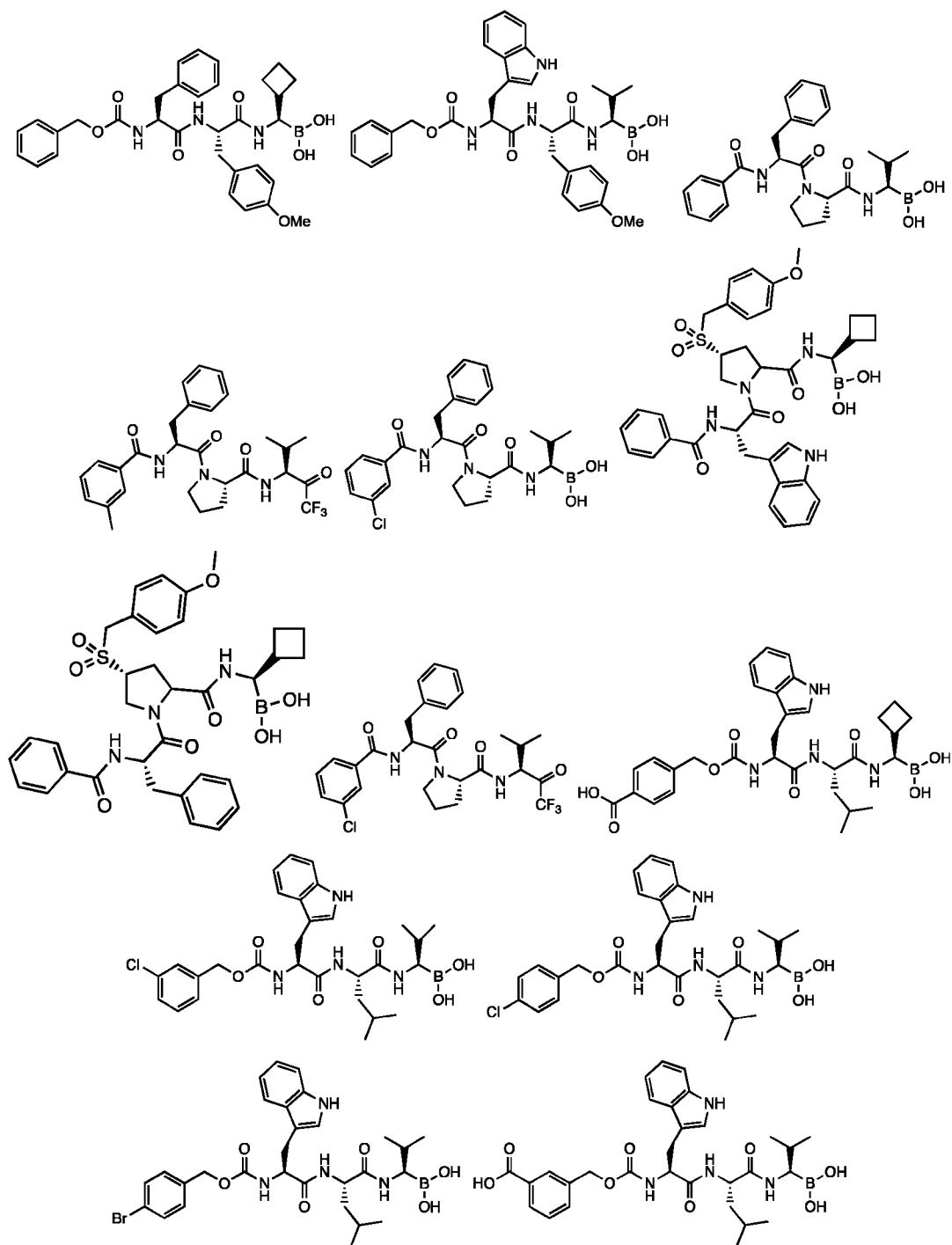


FIG. 1 (cont'd)

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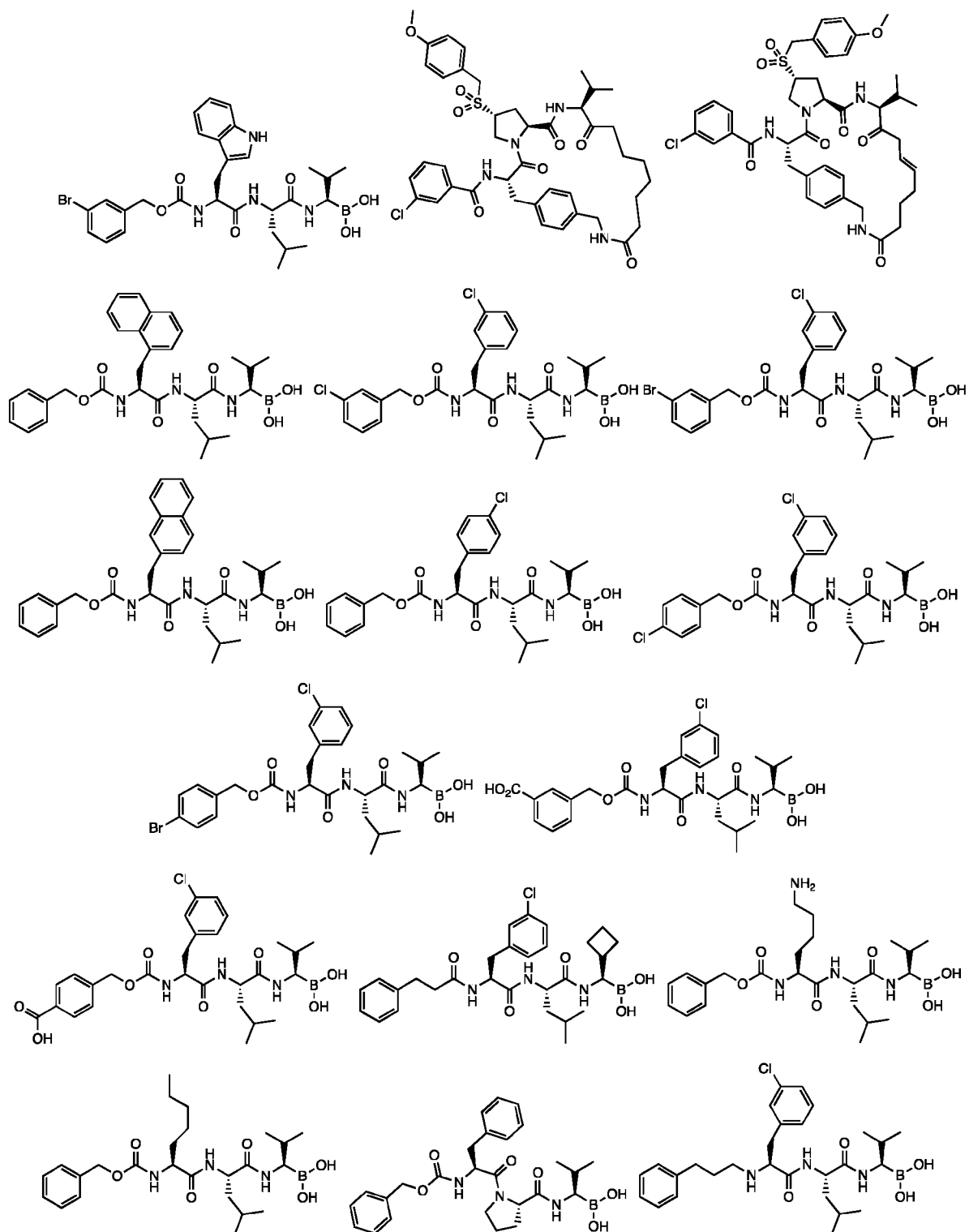


FIG. 1 (cont'd)

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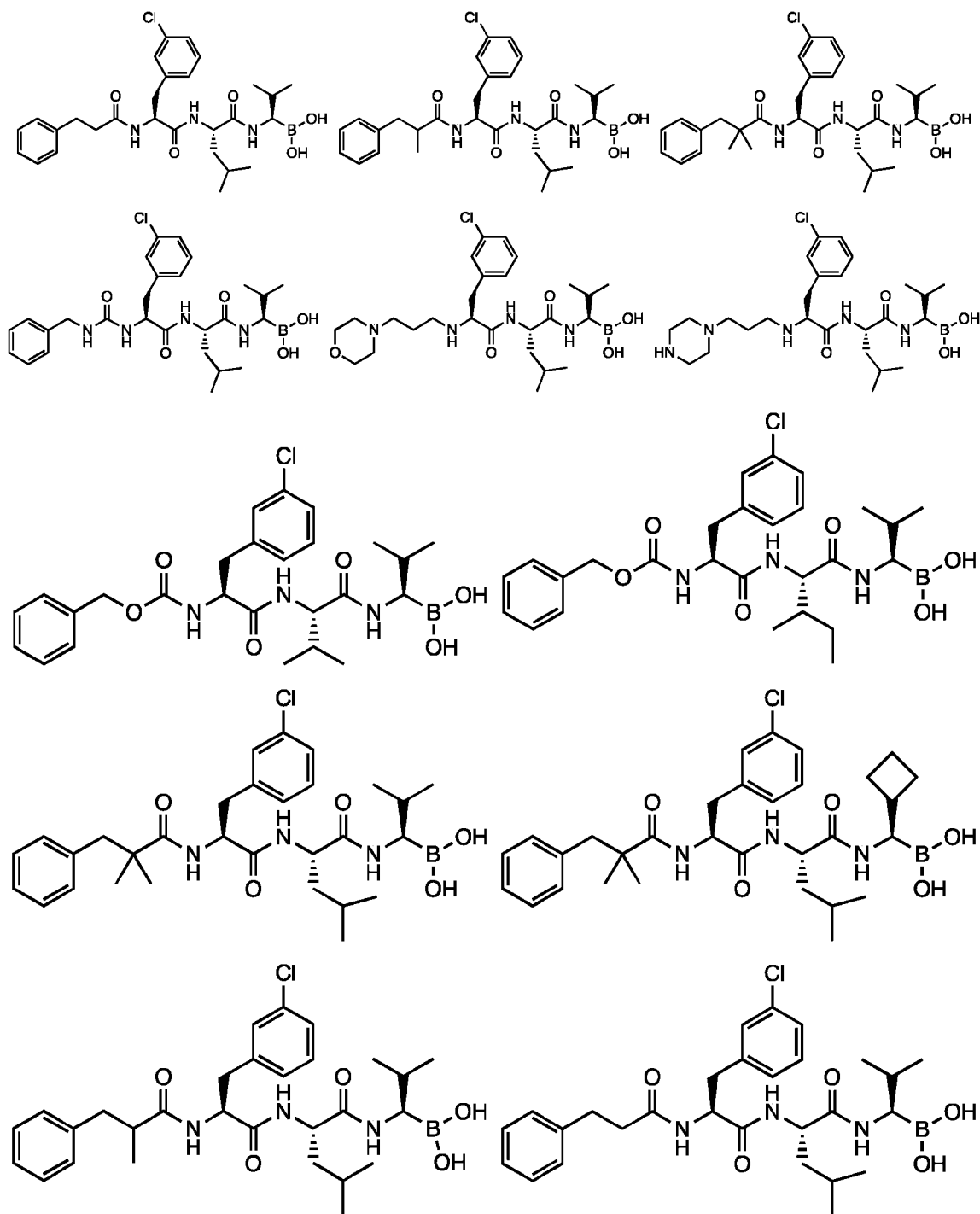


FIG. 1 (cont'd)

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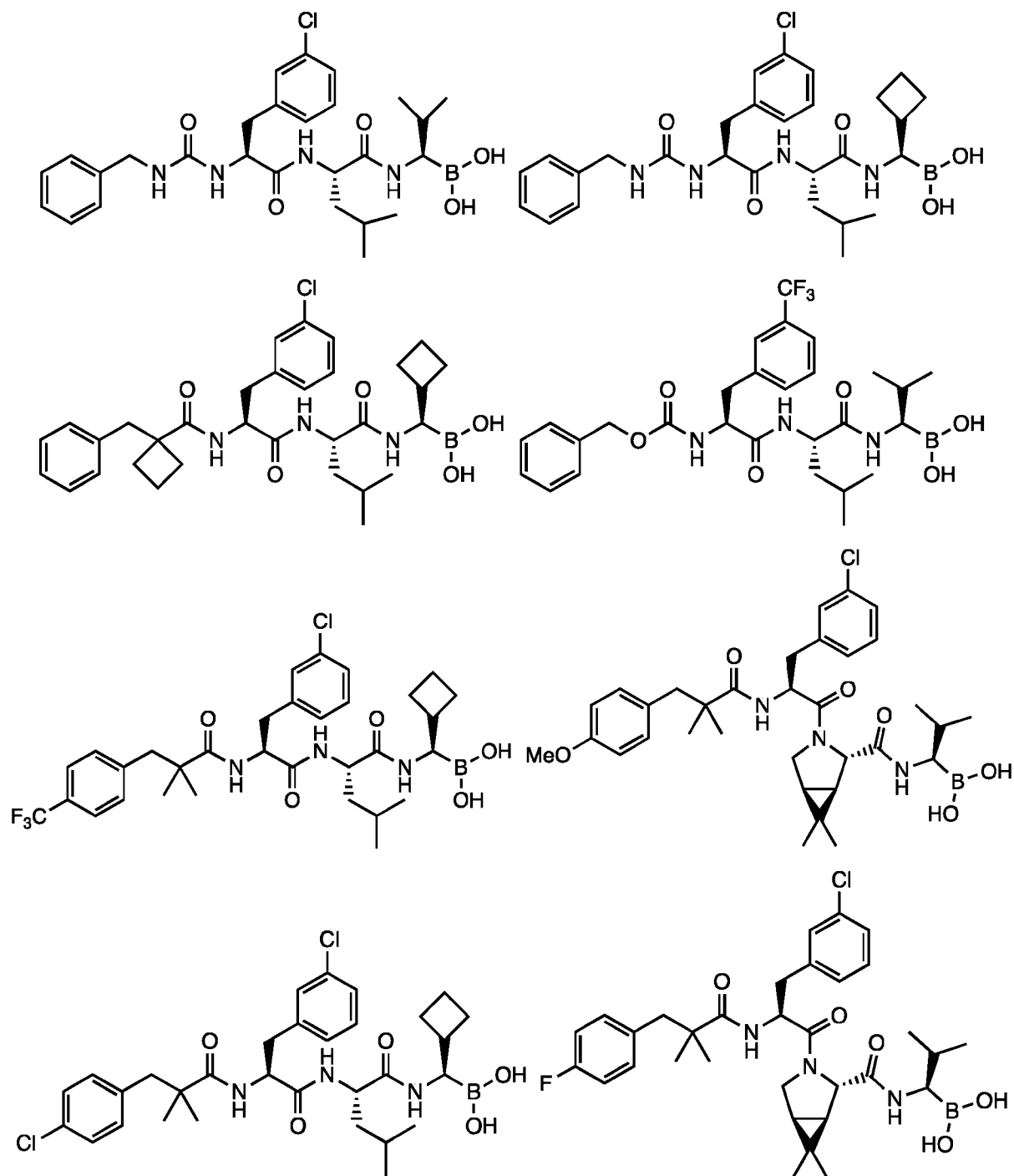


FIG. 1 (cont'd)

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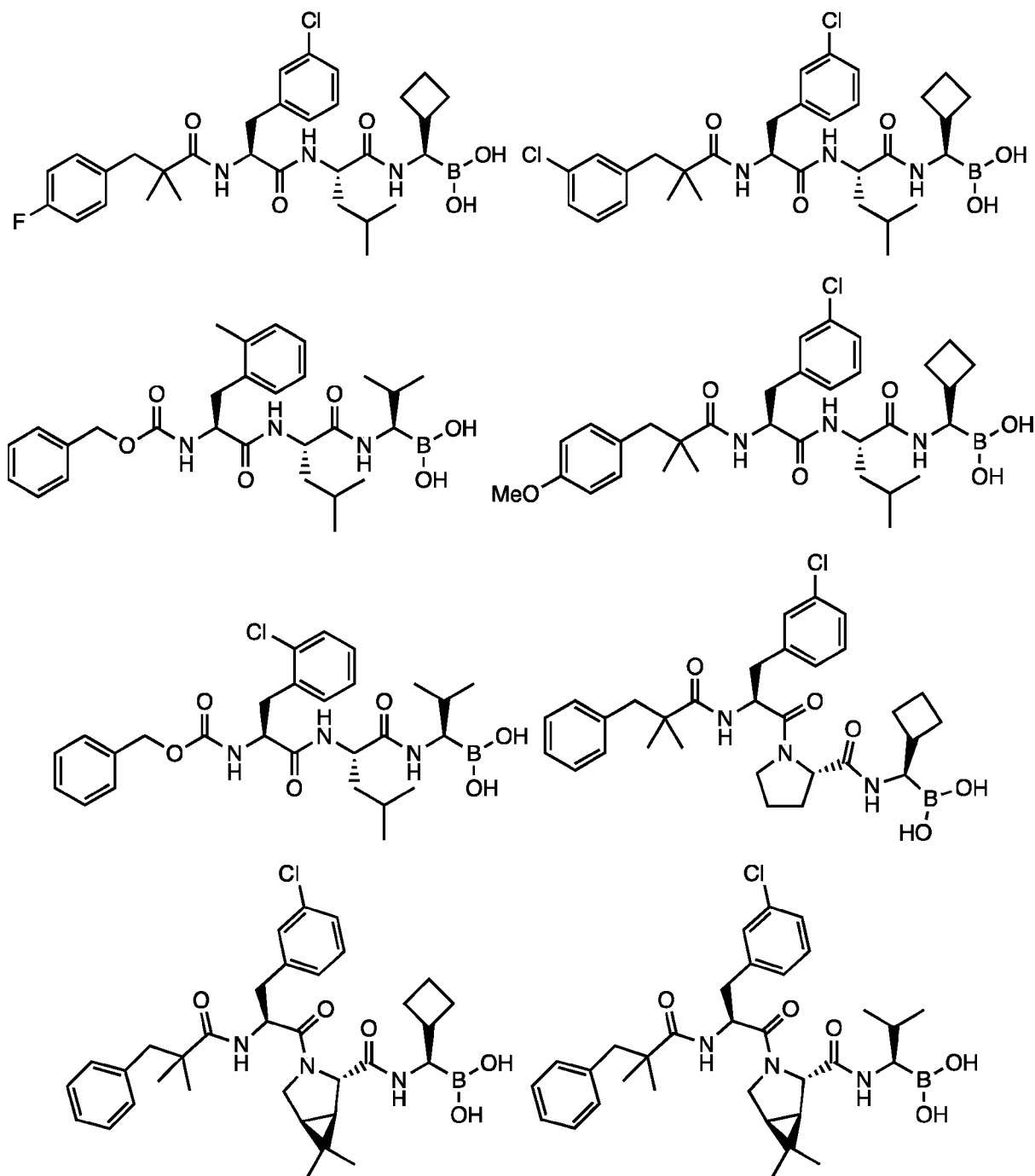


FIG. 1 (cont'd)

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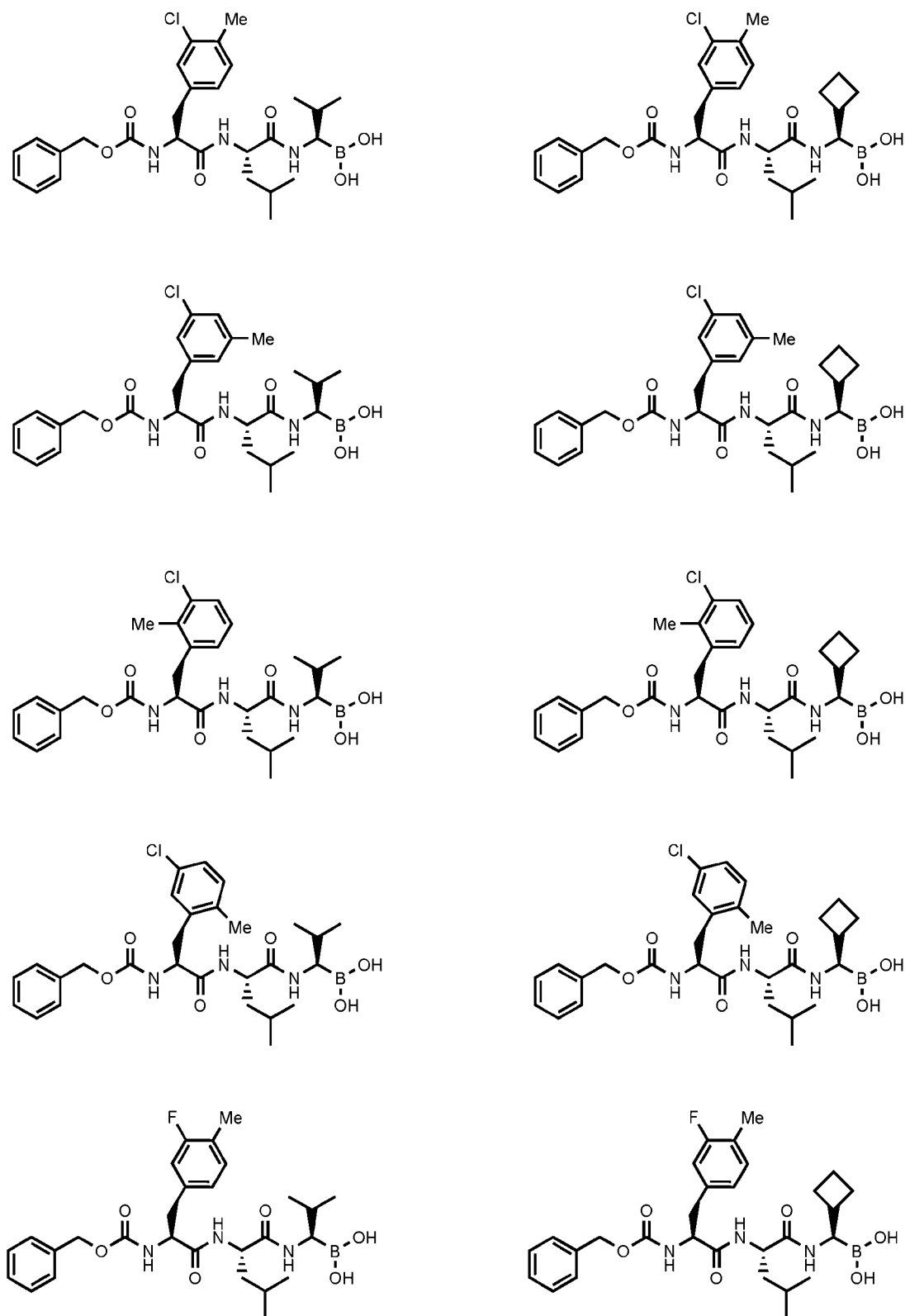


FIG. 2

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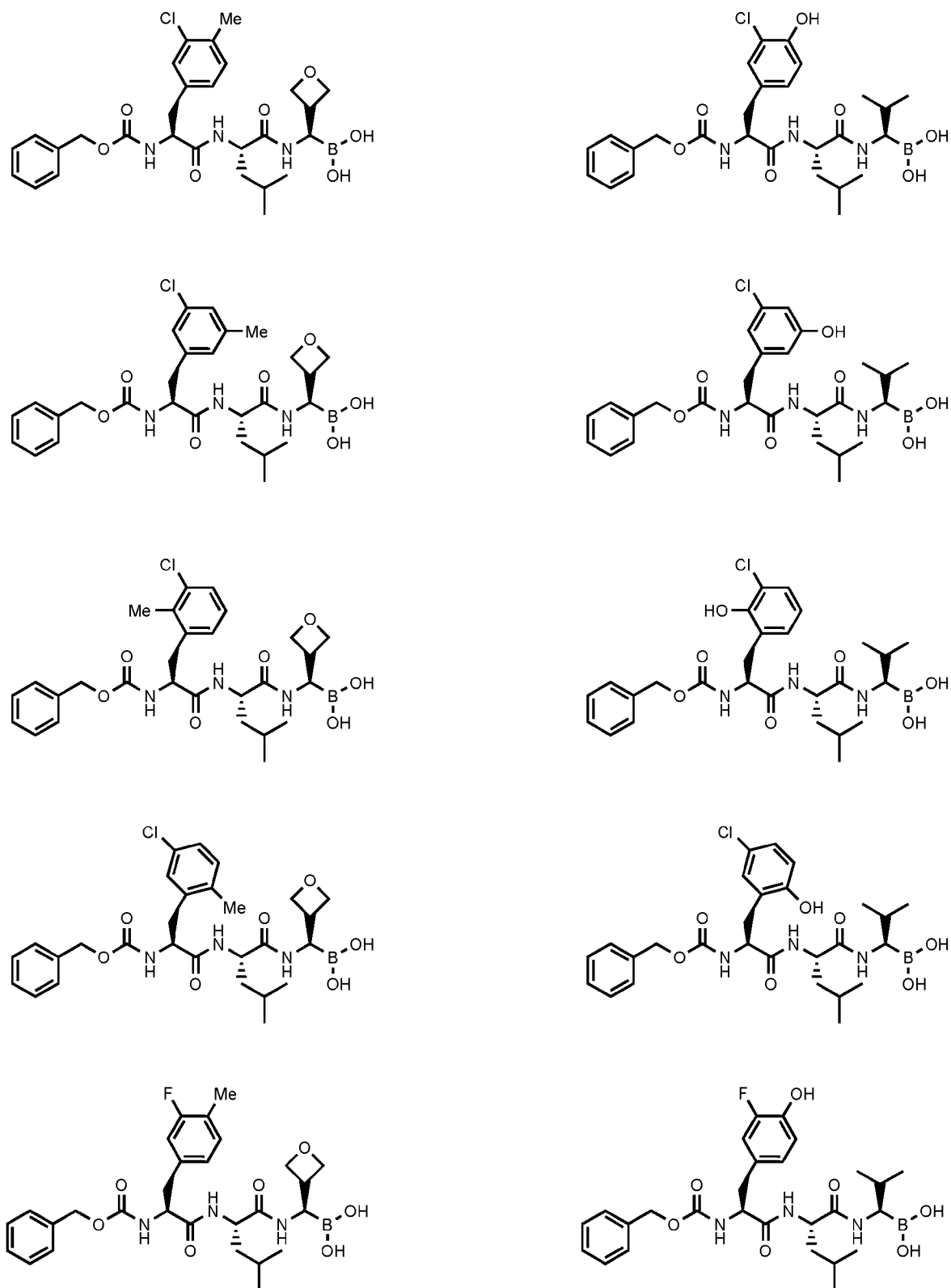


FIG. 2 (cont'd)

10/22

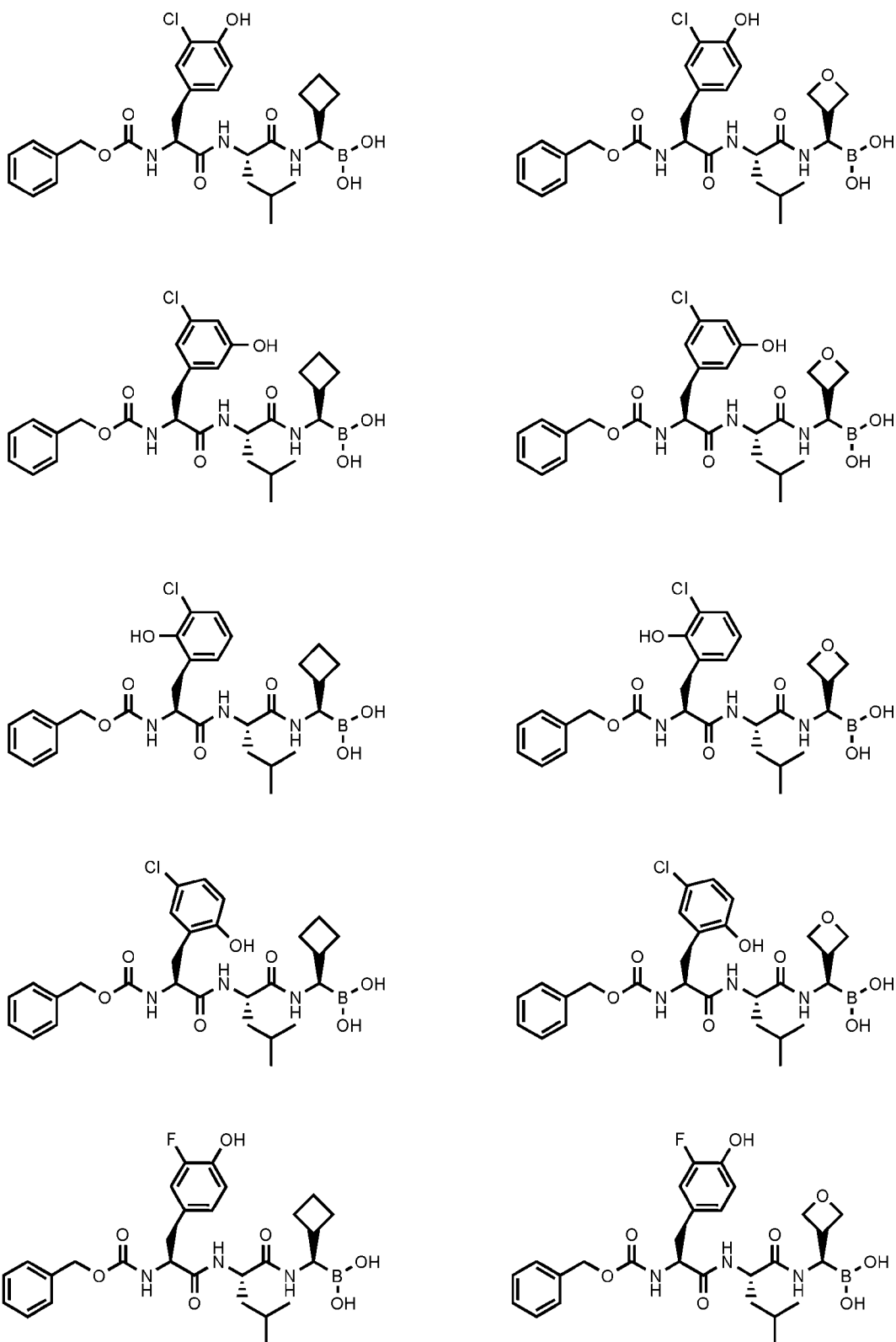


FIG. 2 (cont'd)

11/22

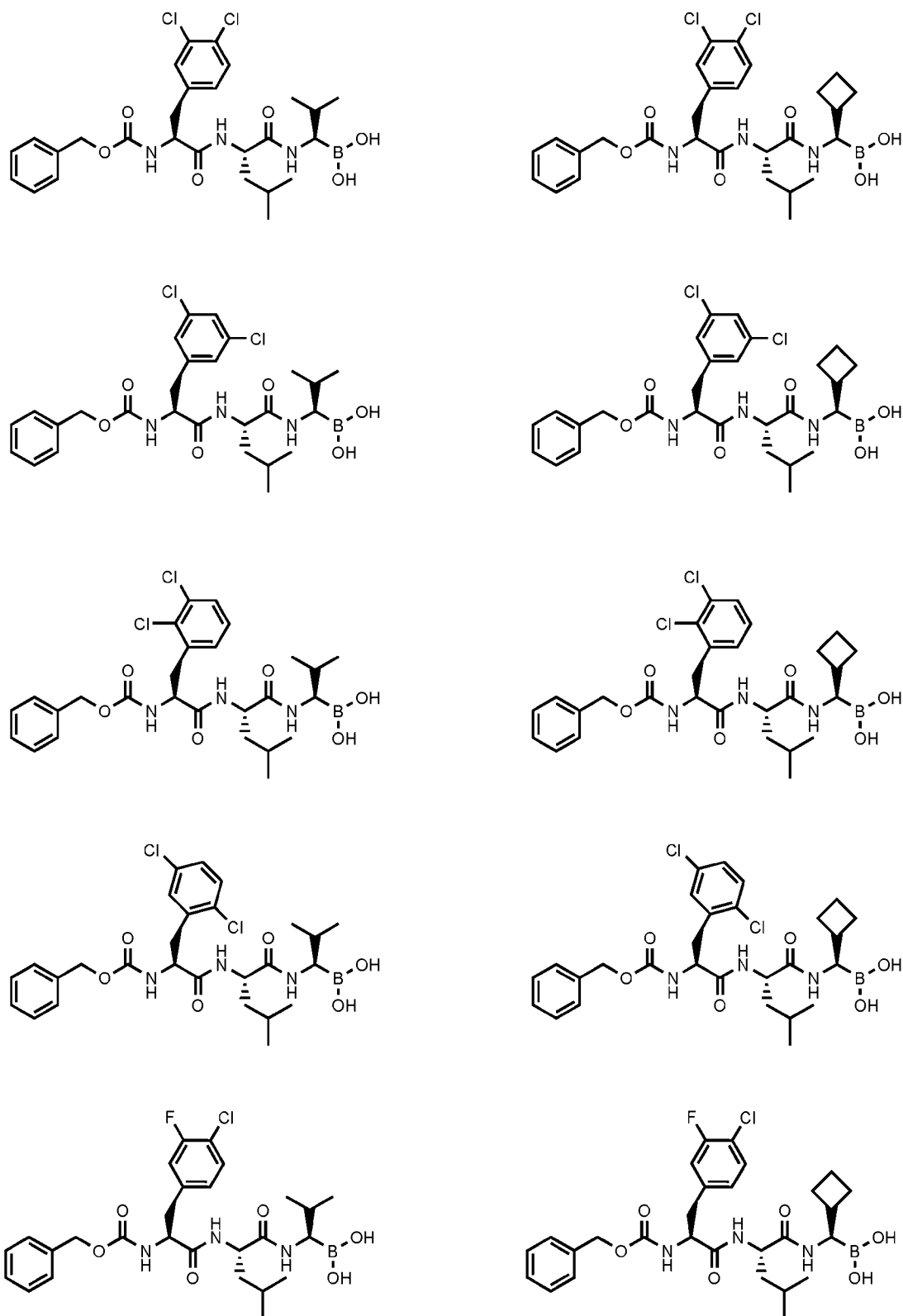


FIG. 2 (cont'd)

12/22

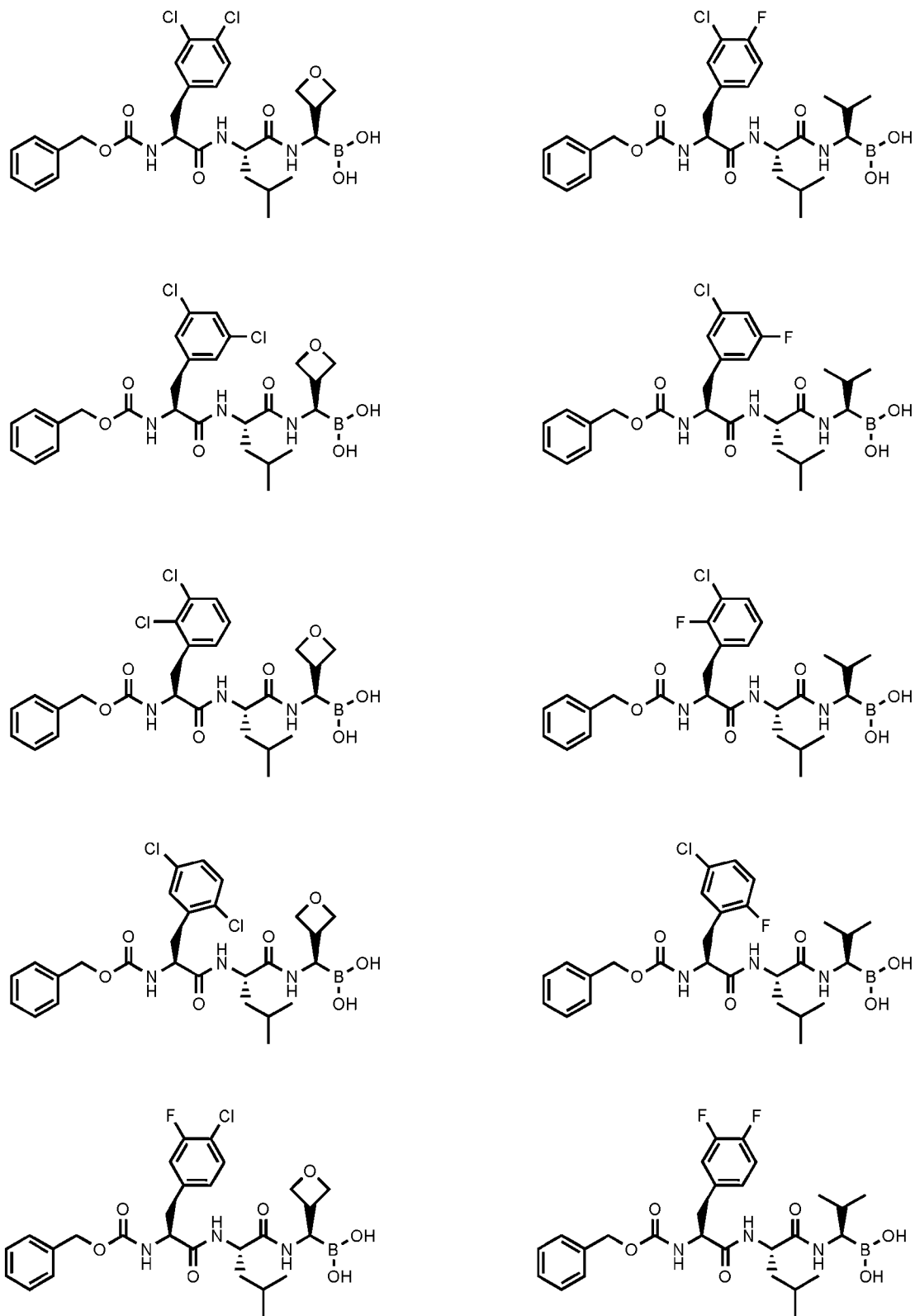


FIG. 2 (cont'd)

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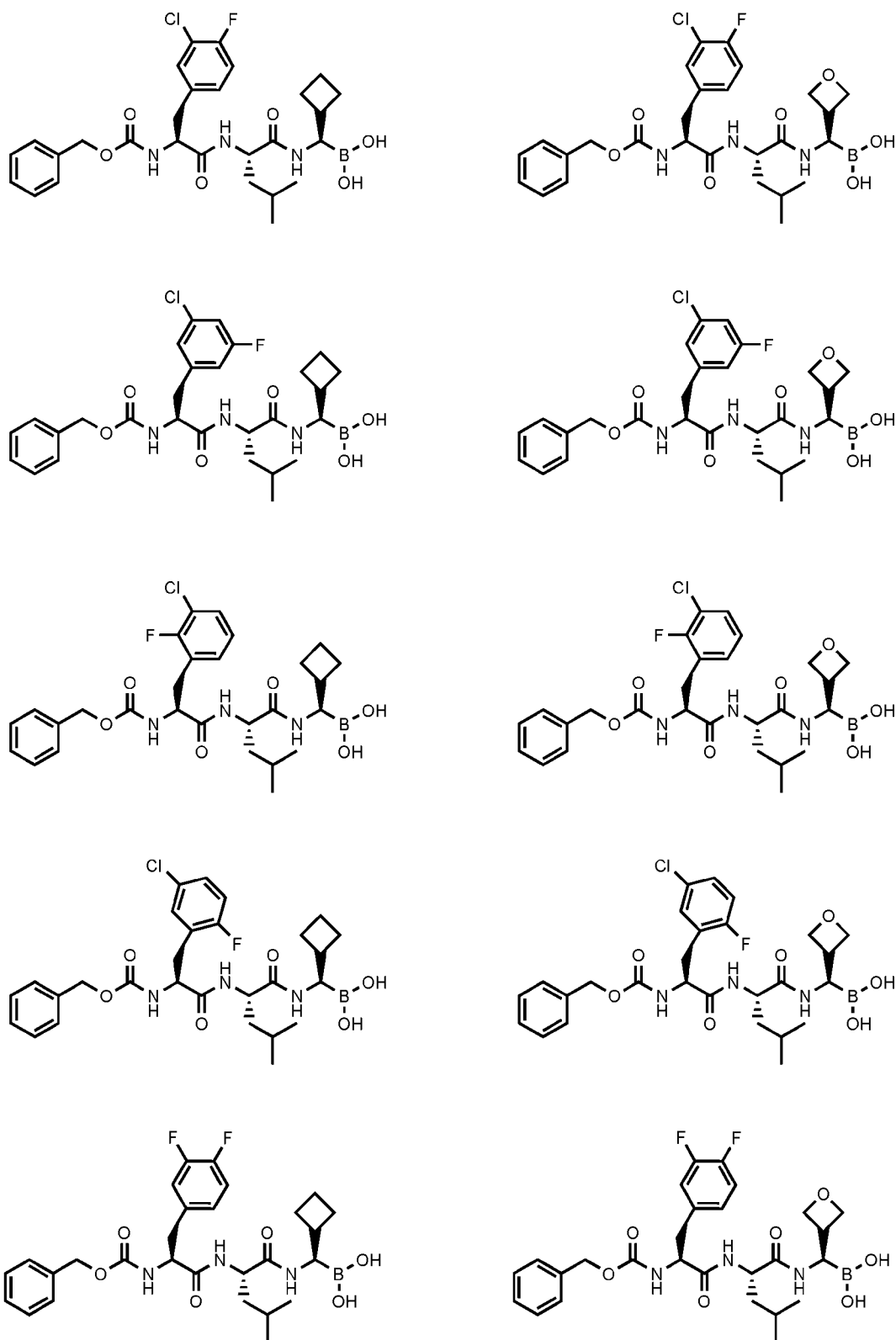


FIG. 2 (cont'd)

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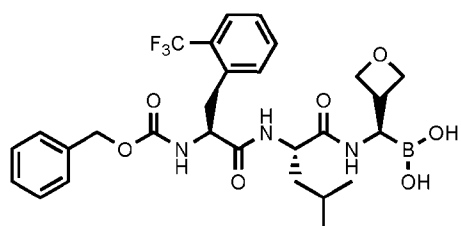
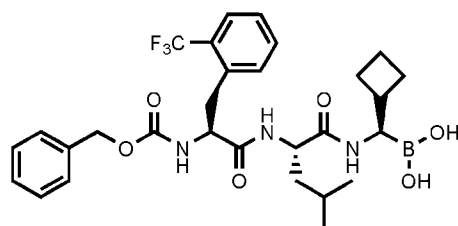
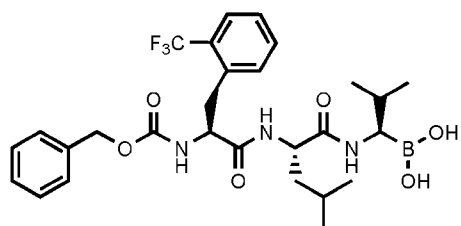
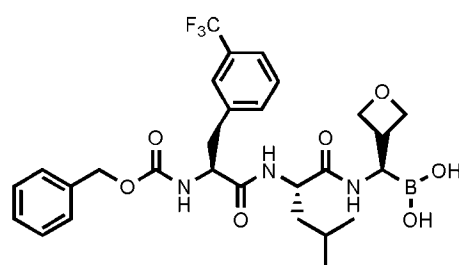
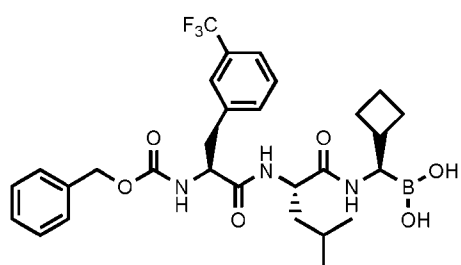
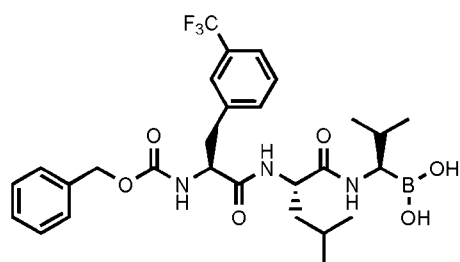
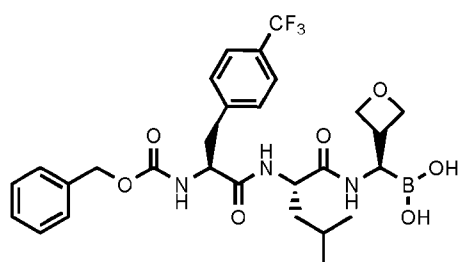
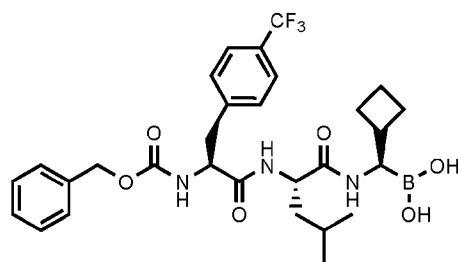
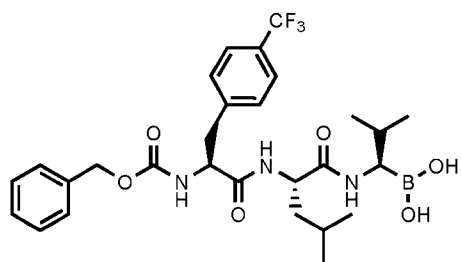


FIG. 2 (cont'd)

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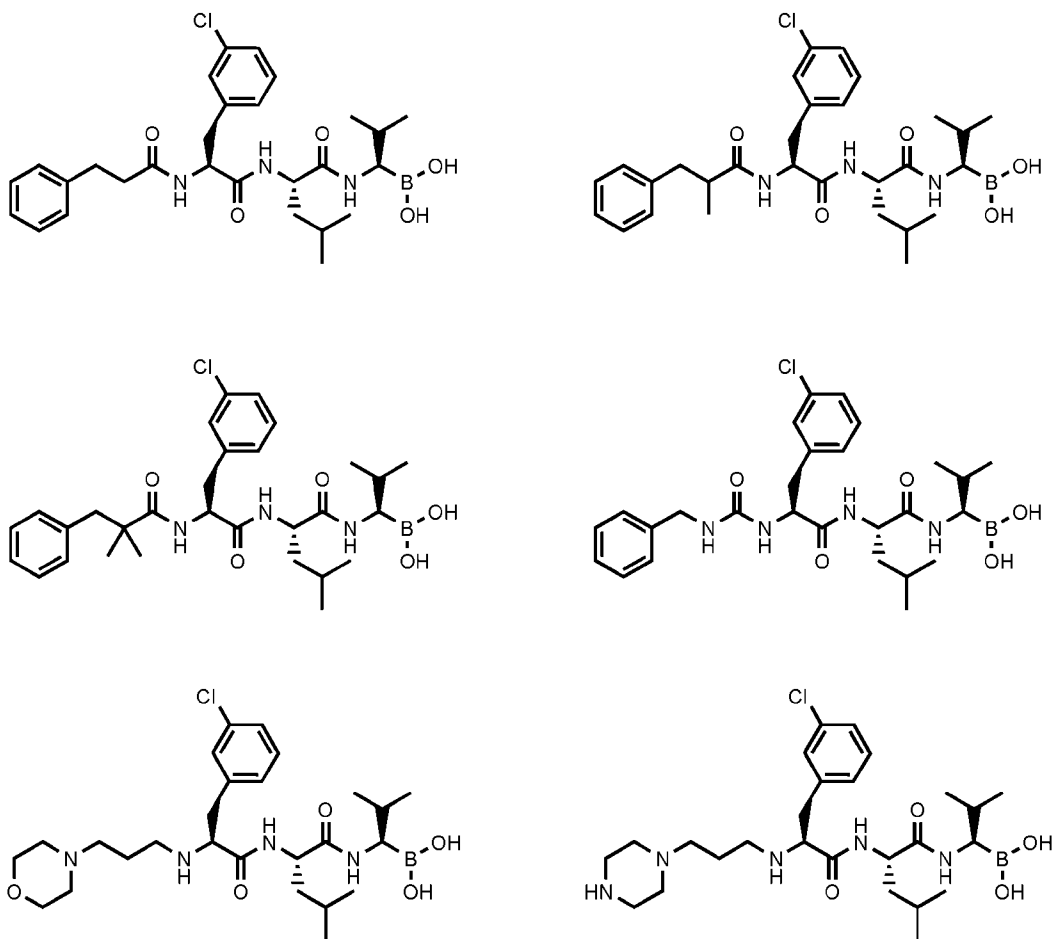


FIG. 2 (cont'd)

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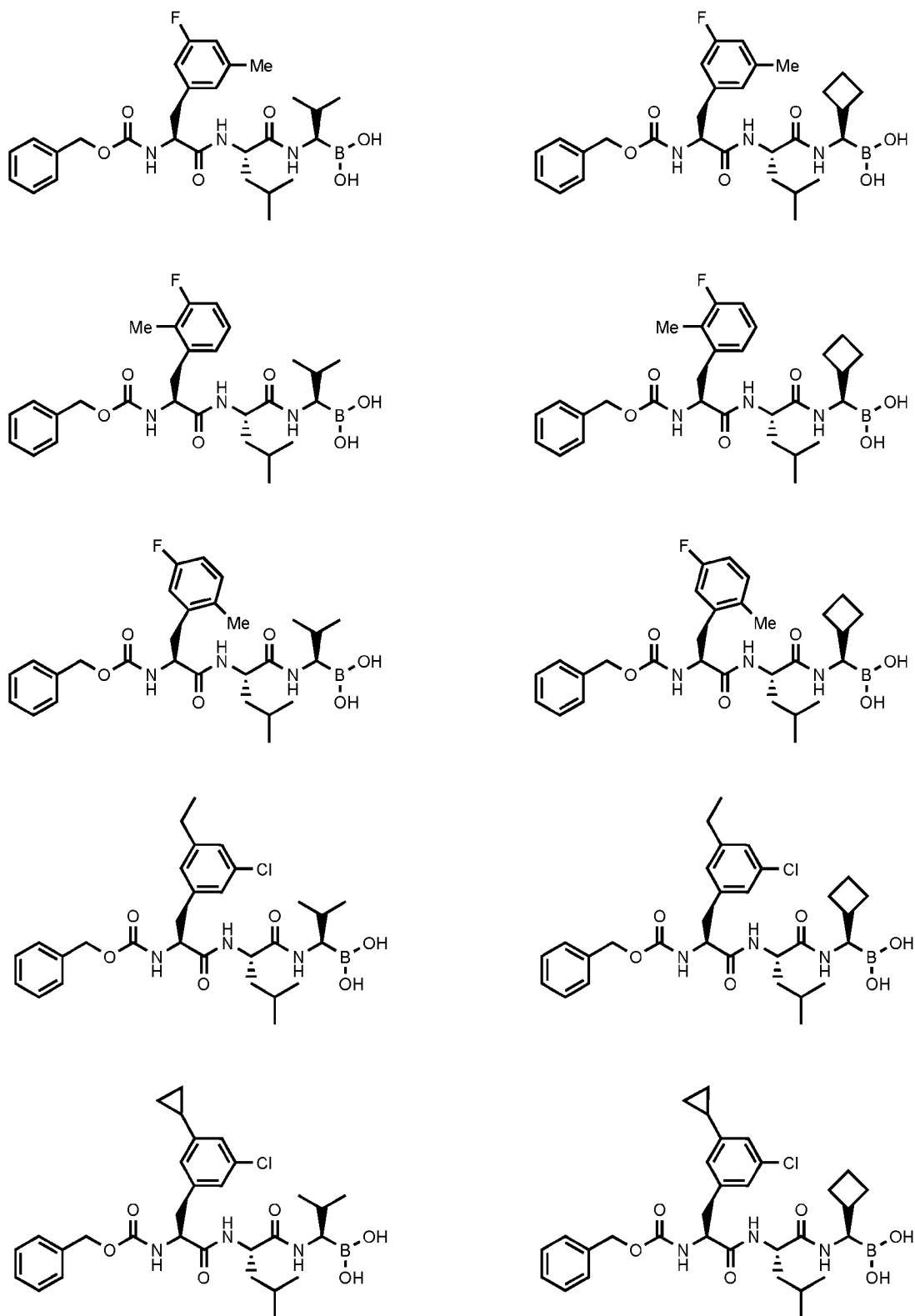


FIG. 2 (cont'd)

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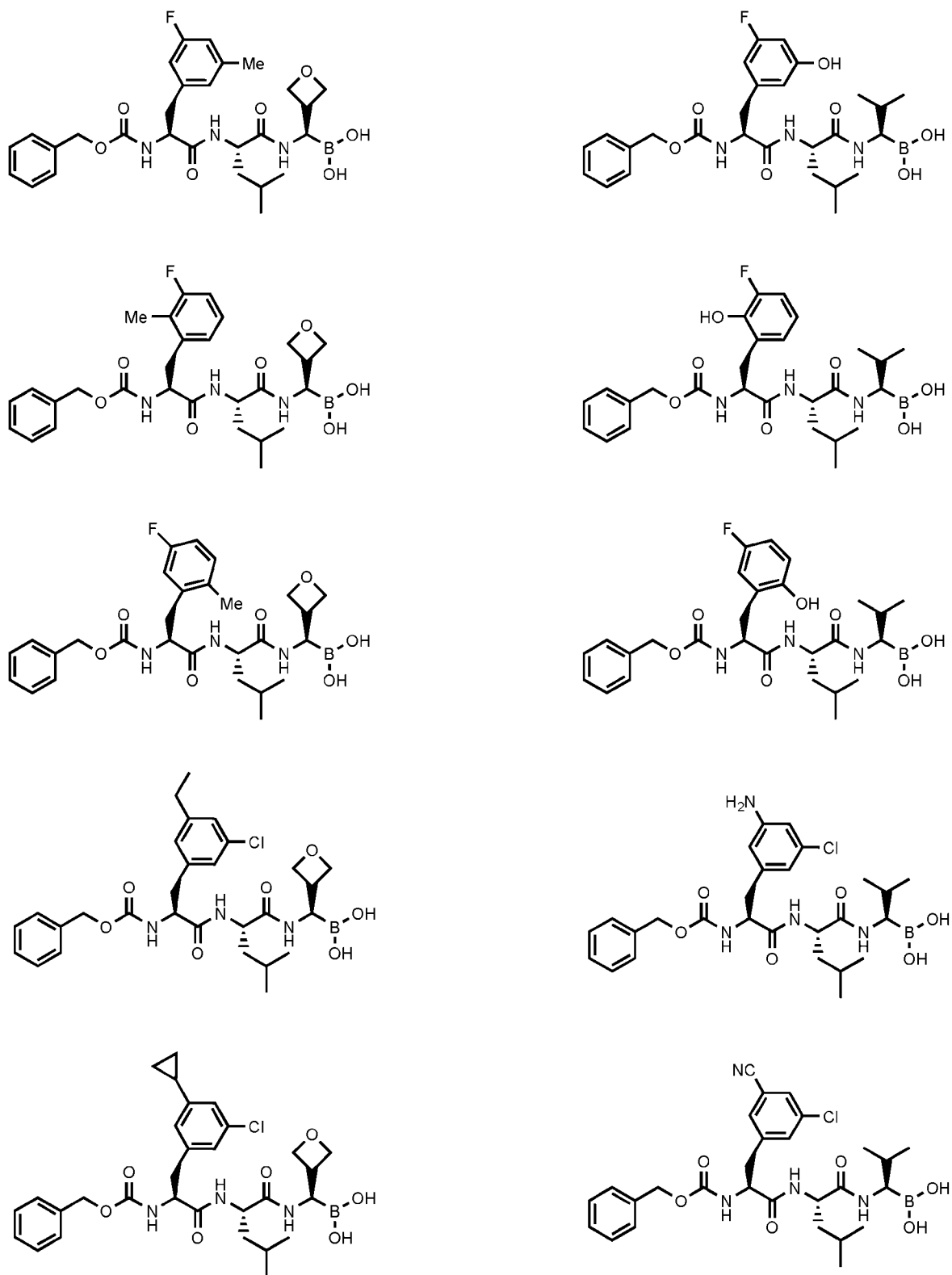


FIG. 2 (cont'd)

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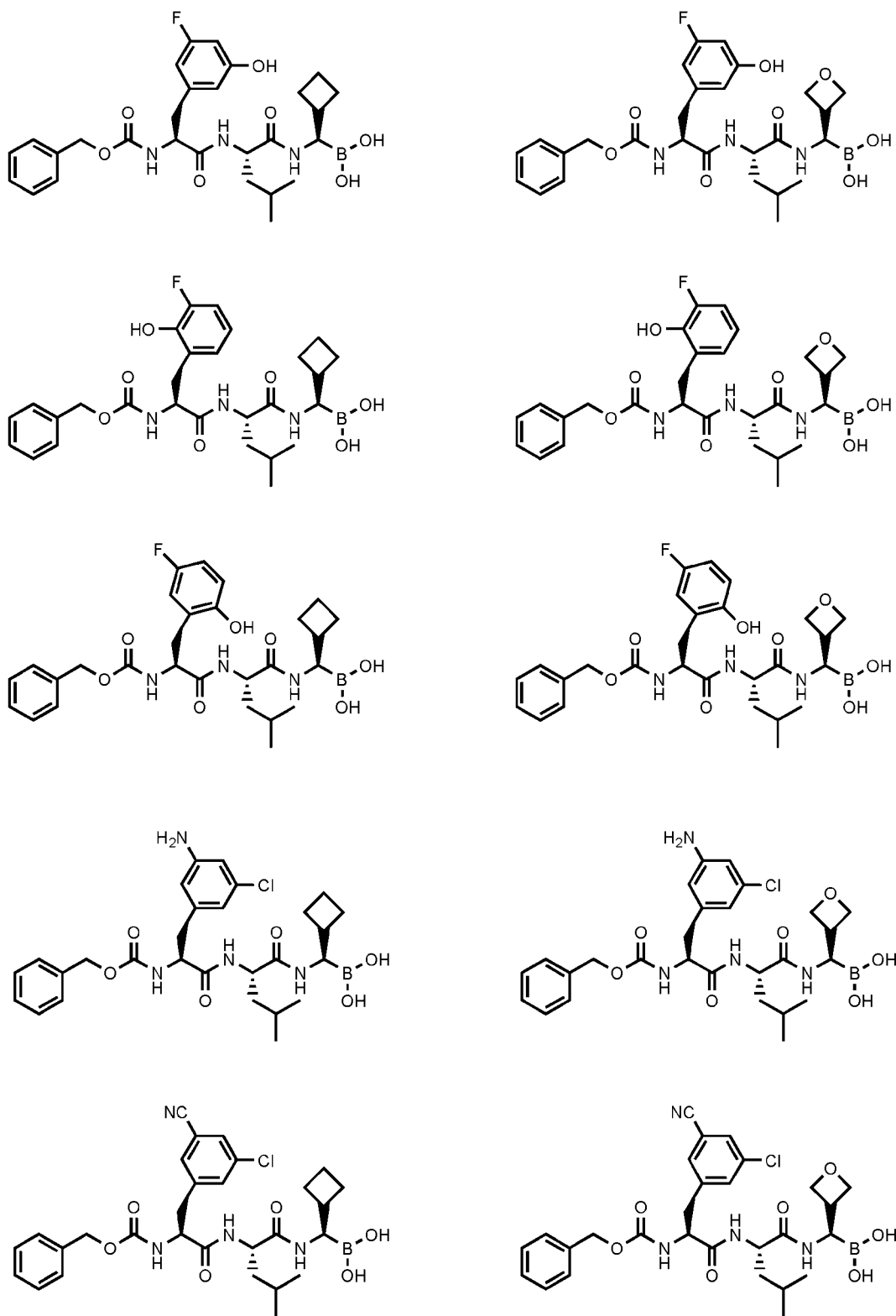


FIG. 2 (cont'd)

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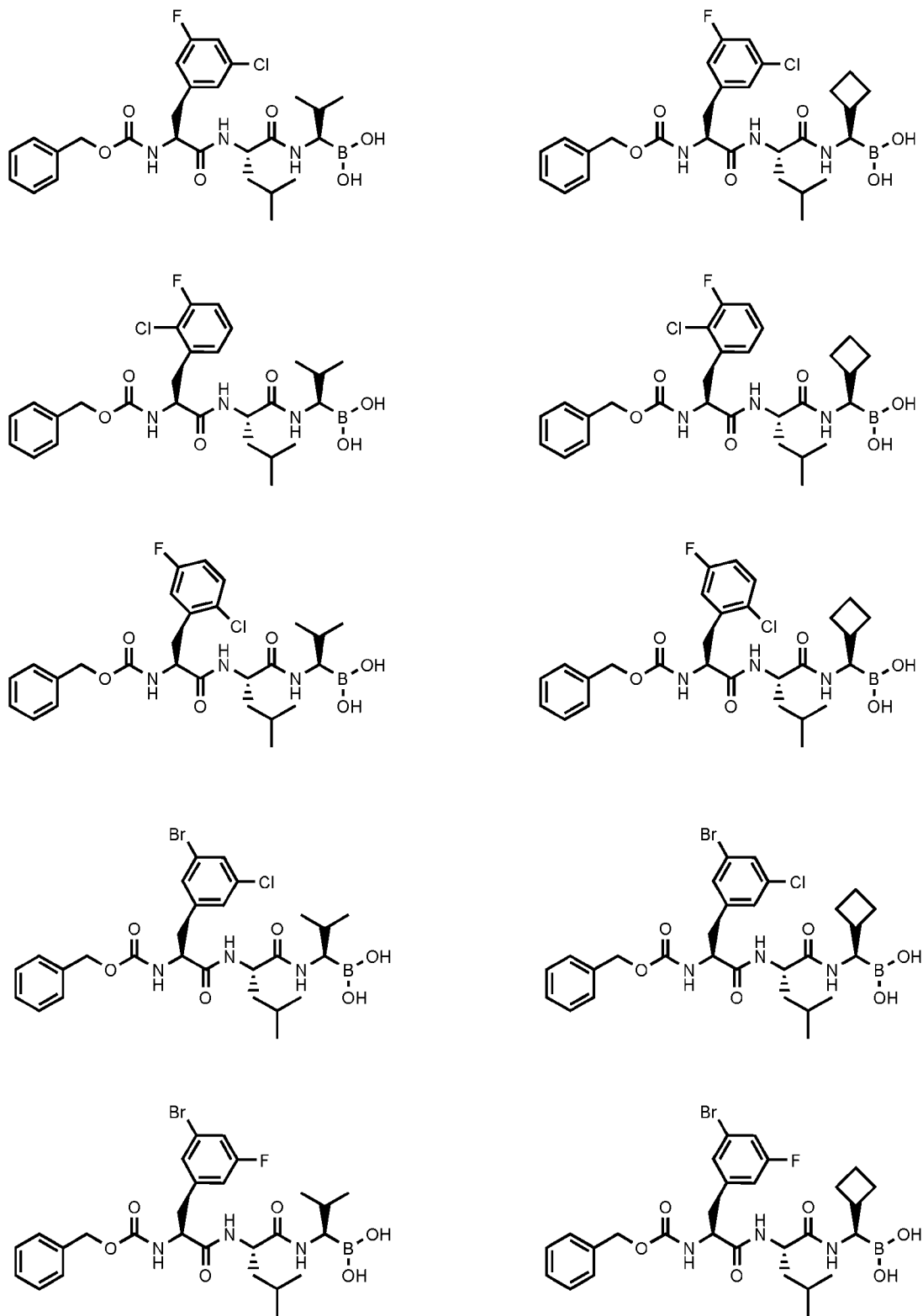


FIG. 2 (cont'd)

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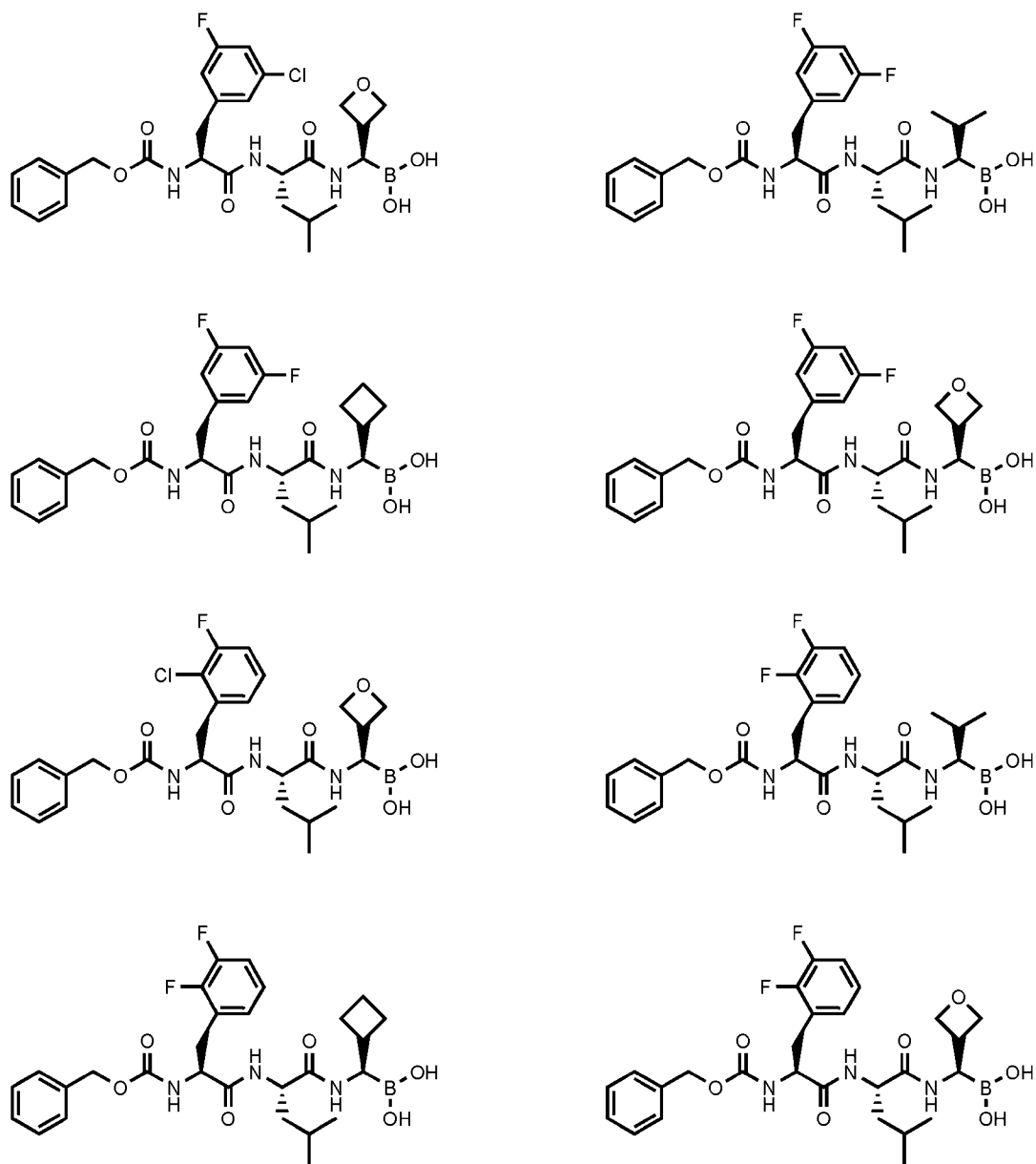


FIG. 2 (cont'd)

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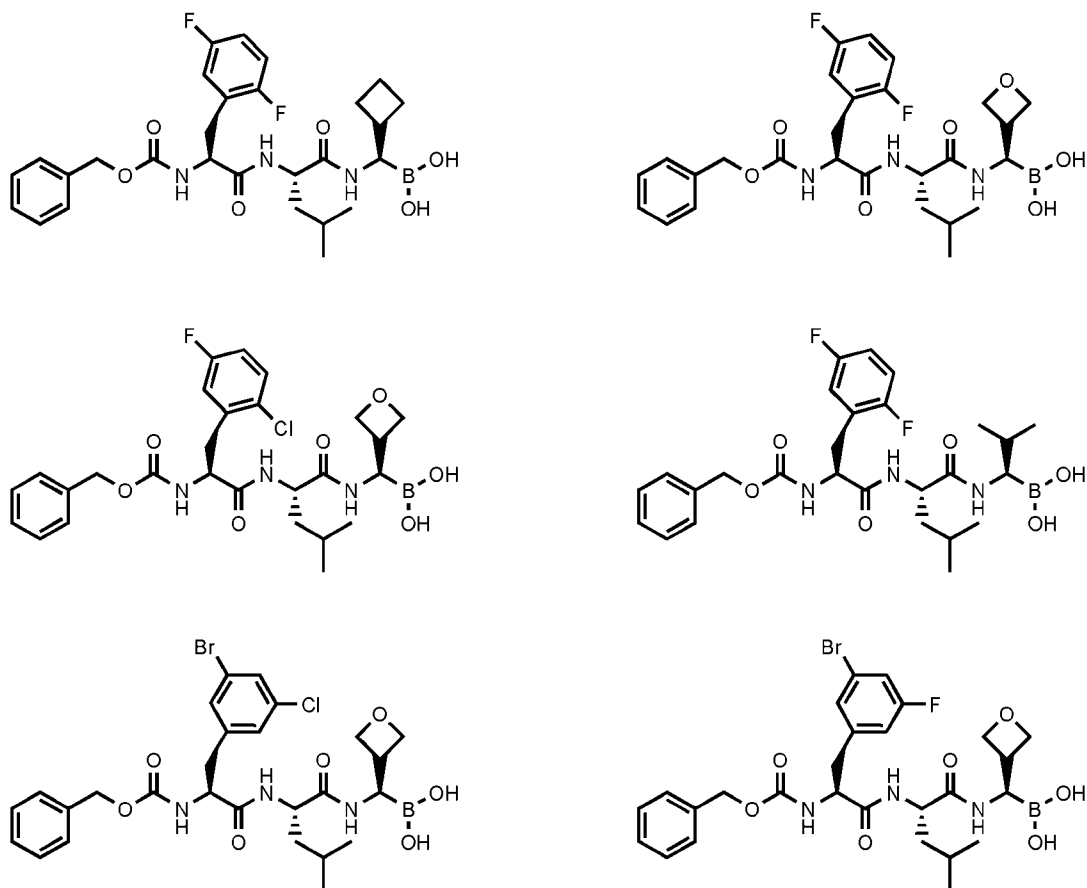


FIG. 2 (cont'd)

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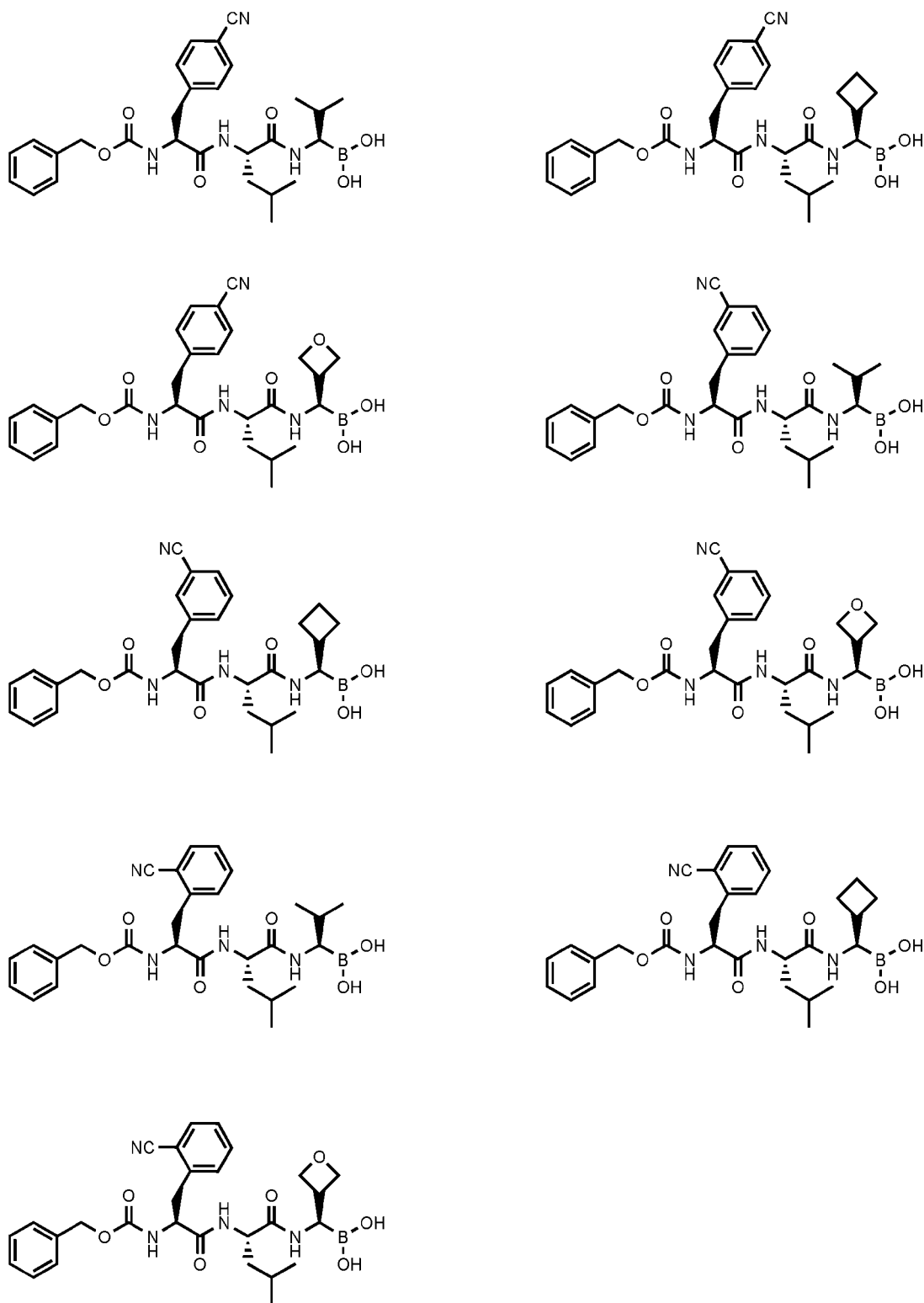


FIG. 2 (cont'd)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/035982

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **C07K 5/08** (2024.01); **A61K 38/06** (2024.01); A61P 25/28 (2024.01); A61P 27/02 (2024.01); A61P 35/00 (2024.01)
CPC: **C07K 5/08**; **A61K 38/06**; A61P 25/28; A61P 27/02; A61P 35/00

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)

See Search History Document

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

See Search History Document

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

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2019/0152895 A1 (HOFFMANN-LA ROCHE INC.) 23 May 2019 (23.05.2019) entire document	1-3, 19
A	US 2018/0371016 A1 (HOFFMANN-LA ROCHE INC.) 27 December 2018 (27.12.2018) entire document	1-3, 19
A	PUBCHEM, SID 242582261, Modify Date: 17 February 2021 [retrieved on 18 August 2024], Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/substance/242582261 > entire document	1-3, 19



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
“D” document cited by the applicant in the international application
“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

05 September 2024 (05.09.2024)

Date of mailing of the international search report

25 October 2024 (25.10.2024)

Name and mailing address of the ISA/US

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Telephone No. **571-272-4300**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/035982

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: **4-18, 20-30**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-3 and 19 are drawn to compounds of formula (I), or a pharmaceutically acceptable salt thereof.

The first invention of Group I+ is restricted to a compound of formula (I), or a pharmaceutically acceptable salt thereof, specifically the first shown compound in FIG. 1. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed compound species presented in the claims (see claim 19; see also FIG. 1). It is believed that claims 1-3 and 19 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of formula (I), or a pharmaceutically acceptable salt thereof, specifically the second shown compound in FIG. 1. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables, QN, R1, R2a, R2b, R3, QC, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound having the core structure of formula (I), or a pharmaceutically acceptable salt thereof, these shared technical features do not

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

represent a contribution over the prior art as disclosed by Substance Record for SID 242582261 to PubChem (hereinafter, "PubChem").

PubChem teaches a compound having the core structure of formula (I), or a pharmaceutically acceptable salt thereof (Pg. 2, compound as shown).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-3, 19**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.