

USP30 INHIBITORS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to United States Provisional Patent Application serial number 63/159,258, filed March 10, 2021, the contents of which are hereby incorporated by reference in their entirety.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates to compounds and methods useful for inhibiting ubiquitin carboxyl-terminal hydrolase 30 ("USP30"), also known as deubiquitinating enzyme 30, ubiquitin thioesterase 30, or ubiquitin-specific-processing protease 30. The invention also provides pharmaceutically acceptable compositions comprising compounds of the present invention and methods of using said compositions in the treatment of various disorders.

BACKGROUND OF THE INVENTION

[0003] Parkinson's disease (PD), an age-associated neurodegenerative disorder second only to Alzheimer's disease (AD) in prevalence, affects nearly 1 million Americans with an estimated financial cost of \$15 billion (Marras et al. Parkinson's Foundation PG: Prevalence of Parkinson's disease across North America. NPJ Parkinsons Dis 2018, 4:21. PMC6039505; Gooch et al. The burden of neurological disease in the United States: A summary report and call to action. Ann Neurol 2017, 81:479-484). Those numbers are anticipated to grow as the aged population world-wide increases. Although it is becoming increasingly evident that PD is a systemic disease involving a number of peripheral tissues as well as multiple brains regions and neuronal populations beyond dopaminergic neurons (Obeso et al. Past, present, and future of Parkinson's disease: A special essay on the 200th Anniversary of the Shaking Palsy. Mov Disord 2017, 32:1264-1310. PMC5685546.), existing treatments for PD primarily augment dopaminergic neurotransmission to provide symptomatic benefit. The efficacy of such treatments diminish with disease progression and intolerable motor complications emerge in a significant proportion of patients. Moreover, non-motor symptoms, including cognitive deficits reflecting non-dopaminergic pathology, remain a major source of disability. Given the strengths in the rigor of prior research implicating mitochondrial deficits in PD and AD, targeting the Parkin-USP30

pathway to restore mitochondrial homeostasis as a means of slowing disease progression holds great promise for the treatment of PD and AD.

[0004] Convergent evidence – specifically, human pharmacology, genetics, and tissue pathology as well as animal model data – indicate that restoration of mitochondrial quality control, including induction of mitophagy (clearance of damaged mitochondria) and bioenergetics, holds the promise of slowing the progression of both PD (Park et al. Mitochondrial Dysfunction in Parkinson's Disease: New Mechanistic Insights and Therapeutic Perspectives. *Curr Neurol Neurosci Rep* 2018, 18:21. PMC5882770.) as well as AD (Fang et al. Mitophagy inhibits amyloid-beta and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. *Nat Neurosci* 2019, 22:401-412.). The first evidence of mitochondrial dysfunction in PD emerged from the observation that exposure to the mitochondrial complex I inhibitor, 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP), causes rapid parkinsonism and dopamine neuronal death (Langston et al. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 1983, 219:979-980.). Genetic studies of monogenic PD show that pathogenic mutations in genes encoding proteins participating in mitochondrial quality control, such as *PINK1*, *PRKN*, *FBXO7*, *DJ-1*, *VPS13C*, and *CHCHD2* cause autosomal recessive, early onset parkinsonism (Canet-Aviles et al. The Parkinson's disease protein DJ-1 is neuroprotective due to cysteine-sulfinic acid-driven mitochondrial localization. *Proc Natl Acad Sci U S A* 2004, 101:9103-9108. PMC428480; Funayama et al. CHCHD2 mutations in autosomal dominant late-onset Parkinson's disease: a genome-wide linkage and sequencing study. *Lancet Neurol* 2015, 14:274-282; Burchell et al. The Parkinson's disease-linked proteins Fbxo7 and Parkin interact to mediate mitophagy. *Nat Neurosci* 2013, 16:1257-1265. PMC3827746; Lesage et al. French Parkinson's Disease Genetics S, International Parkinson's Disease Genomics C: Loss of VPS13C Function in Autosomal-Recessive Parkinsonism Causes Mitochondrial Dysfunction and Increases PINK1/Parkin-Dependent Mitophagy. *Am J Hum Genet* 2016, 98:500-513. PMC4800038; Paisan-Ruiz et al. Early-onset L-dopa-responsive parkinsonism with pyramidal signs due to ATP13A2, PLA2G6, FBXO7 and spatacsin mutations. *Mov Disord* 2010, 25:1791-1800. PMC6005705.). Importantly, Genome-Wide Association (GWA) studies of sporadic PD show that mitochondrial-function-associated genes are risk factors for sporadic, late-onset PD (Billingsley et al. International Parkinson's Disease Genomics C, Ryten M, Koks S: Mitochondria function associated genes contribute to Parkinson's Disease risk and later age at onset. *NPJ Parkinsons Dis* 2019, 5:8. PMC6531455.).

Moreover, a decrease in respiratory capacity of mitochondria has been shown in autopsied brain tissue from sporadic PD cases (Schapira et al. Mitochondrial complex I deficiency in Parkinson's disease. *J Neurochem* 1990, 54:823-827.). Recent evidence from peripheral blood cells of early/prodromal PD cases also demonstrates mitochondrial dysfunction (Smith et al. Mitochondrial dysfunction and increased glycolysis in prodromal and early Parkinson's blood cells. *Mov Disord* 2018, 33:1580-1590. PMC6221131.). Finally, mitochondrial complex I inhibitors such as MPTP or Rotenone cause retrograde degeneration of nigrostriatal dopamine neurons in animal models highlighting that these neurons with the most severe and prototypical degeneration in PD are particularly sensitive to mitochondrial dysfunction.

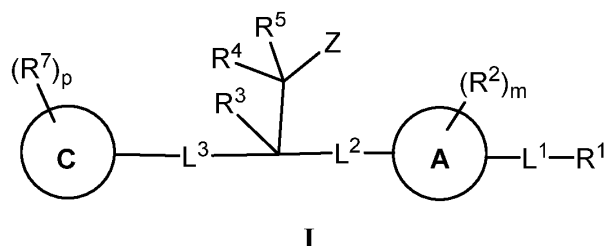
[0005] Abnormal mitochondrial accumulation and mitophagy deficits have been observed in other age-related diseases such as AD and with aging itself (Fang et al. 2019; Ridge and Kauwe, Mitochondria and Alzheimer's Disease: the Role of Mitochondrial Genetic Variation. *Curr Genet Med Rep* 2018, 6:1-10. PMC5842281.). Recent work by Fang et al., demonstrates that mitophagy is reduced in the hippocampus of AD patients and that increased mitophagy is able to rescue cognitive impairment and prevent both A β plaques and tau hyperphosphorylation in induced pluripotent stem cells (iPSC) and multiple animal models of AD (Fang et al. 2019). Positron Emission Tomography (PET) imaging of AD patients have suggested reduced oxidative phosphorylation and TCA cycle, while post-mortem analysis suggests a reduction in PGC1 α , a transcriptional regulator of mitochondrial biogenesis and an essential part of the mitochondrial quality control cycle (Kapogiannis and Mattson, Disrupted energy metabolism and neuronal circuit dysfunction in cognitive impairment and Alzheimer's disease. *Lancet Neurol* 2011, 10:187-198. PMC3026092; Katsouri et al. PPARgamma-coactivator-1alpha gene transfer reduces neuronal loss and amyloid-beta generation by reducing beta-secretase in an Alzheimer's disease model. *Proc Natl Acad Sci U S A* 2016, 113:12292-12297. PMC5087021.). Transmission Electron Microscopy (TEM) analysis of mitochondrial structures in the hippocampus of post-mortem AD patients demonstrates abnormal mitochondrial morphology, altered mitophagy, and a reduction in parkin levels, which was exacerbated with disease progression (Ye et al., Parkin-mediated mitophagy in mutant hAPP neurons and Alzheimer's disease patient brains. *Hum Mol Genet* 2015, 24:2938-2951. PMC4406302.).

[0006] Modulating mitochondrial pathways, including increasing expression of Parkin or depletion of USP30, has been shown to be protective in a variety of genetic and toxin-based animal

models of PD in multiple species (Bingol et al., The mitochondrial deubiquitinase USP30 opposes parkin-mediated mitophagy. *Nature* 2014, 510:370-375; Bian et al., Overexpression of parkin ameliorates dopaminergic neurodegeneration induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice. *PLoS One* 2012, 7:e39953. PMC3390003; Hou et al., Parkin represses 6-hydroxydopamine-induced apoptosis via stabilizing scaffold protein p62 in PC12 cells. *Acta Pharmacol Sin* 2015, 36:1300-1307. PMC4635325; Lo Bianco et al., Lentiviral vector delivery of parkin prevents dopaminergic degeneration in an alpha-synuclein rat model of Parkinson's disease. *Proc Natl Acad Sci USA* 2004, 101:17510-17515. PMC536019; Paterna et al., DJ-1 and Parkin modulate dopamine-dependent behavior and inhibit MPTP-induced nigral dopamine neuron loss in mice. *Mol Ther* 2007, 15:698-704; Vercammen et al., Parkin protects against neurotoxicity in the 6-hydroxydopamine rat model for Parkinson's disease. *Mol Ther* 2006, 14:716-723; Yasuda et al., Parkin-mediated protection of dopaminergic neurons in a chronic MPTP-minipump mouse model of Parkinson disease. *J Neuropathol Exp Neurol* 2011, 70:686-697; Yasuda et al., Neuronal specificity of alpha-synuclein toxicity and effect of Parkin co-expression in primates. *Neuroscience* 2007, 144:743-753; Liang et al., USP30 deubiquitylates mitochondrial Parkin substrates and restricts apoptotic cell death. *EMBO Rep* 2015, 16:618-627. PMC4428036.). PINK1/Parkin-dependent linear ubiquitination of proteins on the outer mitochondrial membrane (OMM) leads to removal of damaged protein and mitochondria through fission of mitochondrial derived vesicles (MDVs) or recruitment of phagophores to begin the mitophagy process. The deubiquitinating (DUB) enzyme, USP30, is present specifically on the OMM (unlike other DUBs such as USP8, 15 and 35 implicated in mitochondrial quality control), and acts as a counterbalance to this process by specifically removing ubiquitin chains on parkin substrates. Involvement of USP30 in regulating mitophagy has been well established through functional genomic studies in mammalian, including human, cells and flies, further validating it as a promising target (Bingol et al., 2014). Without wishing to be bound by any particular theory, it is believed that USP30 inhibitors will promote the clearance of damaged mitochondria to restore mitochondrial homeostasis, attenuating the pathogenic cascade associated with PD pathogenesis.

SUMMARY OF THE INVENTION

[0007] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of USP30. Such compounds have the general formula **I**:



or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0008] Compounds of the present invention, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with mitochondrial homeostasis implicating USP30. Such diseases, disorders, or conditions include those described herein.

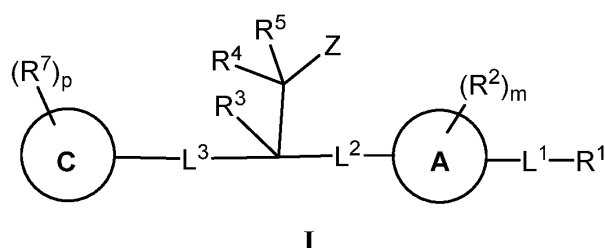
[0009] Compounds provided by this invention are also useful for the study of USP30 in biological and pathological phenomena; the study of mitochondrial homeostasis occurring in bodily tissues; and the comparative evaluation of new USP30 inhibitors or other regulators of mitochondrial homeostasis *in vitro* or *in vivo*.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Certain Embodiments of the Invention:

[0010] Compounds of the present invention, and compositions thereof, are useful as inhibitors of USP30.

[0011] In certain embodiments, the present invention provides a compound of formula **I**:



or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered

saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

L^1 is a covalent bond or a C_{1-3} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-C(CF_3)H-$, $-N(R)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-C(O)N(R)-$, $-N(R)C(O)-$, $-S(O)-$, $-S(O)_2-$, $-S(O)N(R)-$, $-S(O)_2N(R)-$, or $-S(O)(R)=N-$;

each R is independently hydrogen or an optionally substituted C_{1-3} aliphatic group; or:

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur; or

an R group and R^1 on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;

R^1 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^2 is independently halogen, $-CF_3$, $-CN$, $-C(O)NHR$, $-NO_2$, $-NHR$, $-NHC(O)R$, $-NHS(O)_2R$, $-N(R)_2$, or $-OR$, or an optionally substituted C_{1-6} aliphatic group; or

two R^2 on the same carbon are optionally taken together to form $=O$;

L^2 is selected from the group consisting of $-C(O)N(R')$, $-CH_2O-$, $-CH_2N(R')$, $-C(OH)(H)CH_2N(R')$, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R' is hydrogen or a C_{1-3} aliphatic group;

L^3 is selected from the group consisting of $-C(O)N(R'')$, $-OC(O)N(R'')$, $-CH_2O-$, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R'' is hydrogen or a C_{1-3} aliphatic group;

R^3 is hydrogen or C_{1-3} aliphatic; or:

R^3 and R^4 are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring; or

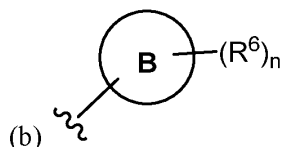
R^3 and R^5 are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring;

R^4 is hydrogen or C_{1-3} aliphatic;

R^5 is hydrogen or C_{1-3} aliphatic;

Z is:

(a) selected from an optionally substituted C_{1-6} aliphatic group, and $-OR$;



(c) taken together with R^4 and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 ;

(d) taken together with R^5 and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 ; or

(e) taken together with R'' and their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the nitrogen of L^3 , independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 ;

Ring B is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially

unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R⁶ is independently halogen, phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -CN, -NO₂, -NHR, -N(R)₂, -OR, -C(O)R, -C(O)OR, or an optionally substituted C₁₋₆ aliphatic group; or:

two R⁶ on the same carbon are optionally taken together to form =O;

an R⁶ group and R' group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur;

an R⁶ group and R³ group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated spiro-fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen or sulfur; or

an R⁶ group and R'' group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur;

Ring C is phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R⁷ is independently halogen, -CN, -NO₂, -NHR, -N(R)₂, -OR, or an optionally substituted C₁₋₆ aliphatic group; or

two R⁷ on the same carbon are optionally taken together to form =O;

each of m, n, and p is independently 0, 1, 2, 3 or 4.

2. Compounds and Definitions:

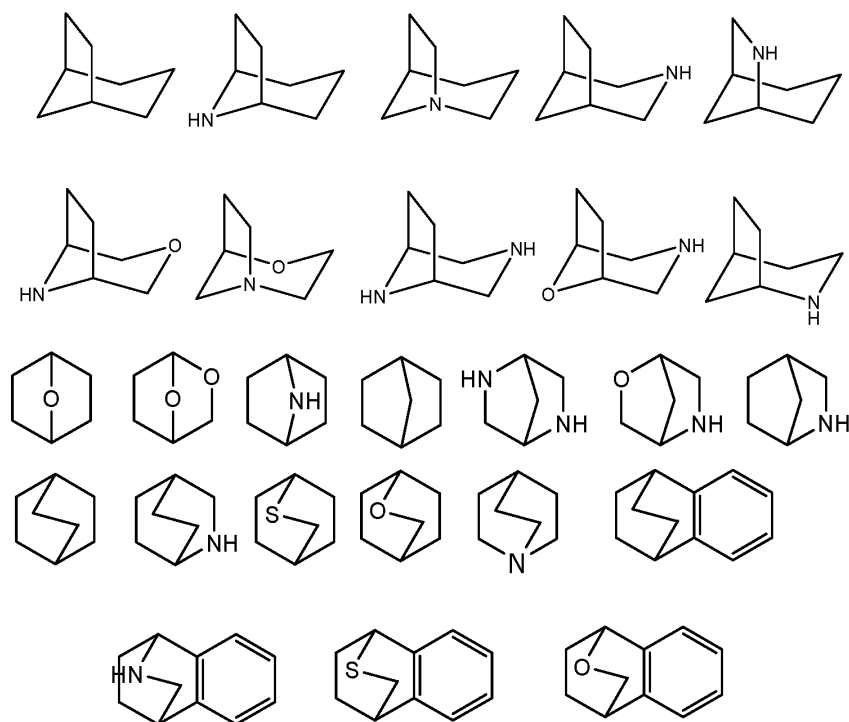
[0012] Compounds of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the

following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0013] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle," "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C₃-C₆ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0014] As used herein, the term "bridged bicyclic" refers to any bicyclic ring system, i.e. carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a "bridge" is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a "bridgehead" is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon

or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bridged bicyclics include:



[0015] The term “lower alkyl” refers to a C₁₋₄ straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[0016] The term “lower haloalkyl” refers to a C₁₋₄ straight or branched alkyl group that is substituted with one or more halogen atoms.

[0017] The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl)).

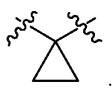
[0018] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

[0019] As used herein, the term “bivalent C₁₋₈ (or C₁₋₆) saturated or unsaturated, straight or branched, hydrocarbon chain”, refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0020] The term “alkylene” refers to a bivalent alkyl group. An “alkylene chain” is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0021] The term “alkenylene” refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0022] As used herein, the term “cyclopropylenyl” refers to a bivalent cyclopropyl group of

the following structure: .

[0023] The term “halogen” means F, Cl, Br, or I.

[0024] The term “aryl” used alone or as part of a larger moiety as in “aralkyl,” “aralkoxy,” or “aryloxyalkyl,” refers to monocyclic or bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term “aryl” may be used interchangeably with the term “aryl ring.” In certain embodiments of the present invention, “aryl” refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term “aryl,” as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0025] The terms “heteroaryl” and “heteroar-,” used alone or as part of a larger moiety, e.g., “heteroaralkyl,” or “heteroaralkoxy,” refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term “heteroatom” refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl,

pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms “heteroaryl” and “heteroar-”, as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolyl, phthalazinyl, quinazolinyl, quinoxalyl, 4*H*-quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, and pyrido[2,3-*b*]-1,4-oxazin-3(4*H*)-one. A heteroaryl group may be mono- or bicyclic. The term “heteroaryl” may be used interchangeably with the terms “heteroaryl ring,” “heteroaryl group,” or “heteroaromatic,” any of which terms include rings that are optionally substituted. The term “heteroalkyl” refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0026] As used herein, the terms “heterocycle,” “heterocyclyl,” “heterocyclic radical,” and “heterocyclic ring” are used interchangeably and refer to a stable 5- to 7-membered monocyclic or 7-10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term “nitrogen” includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl), or ⁺NR (as in *N*-substituted pyrrolidinyl).

[0027] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholyl, 2-oxa-6-azaspiro[3.3]heptane, and quinuclidinyl. The terms “heterocycle,” “heterocyclyl,” “heterocyclyl ring,” “heterocyclic group,” “heterocyclic moiety,” and “heterocyclic radical,” are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolyl, 3*H*-indolyl, chromanyl,

phenanthridinyl, or tetrahydroquinolinyl. A heterocyclyl group may be mono- or bicyclic. The term “heterocyclylalkyl” refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0028] As used herein, the term “partially unsaturated” refers to a ring moiety that includes at least one double or triple bond. The term “partially unsaturated” is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0029] As described herein, compounds of the invention may contain “optionally substituted” moieties. In general, the term “substituted,” whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0030] Suitable monovalent substituents on a substitutable carbon atom of an “optionally substituted” group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$; $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R° ; $-CH=CHPh$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}$ -pyridyl which may be substituted with R° ; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$;

$-\text{N}(\text{R}^\circ)\text{S}(\text{O})_2\text{NR}^\circ_2$; $-\text{N}(\text{R}^\circ)\text{S}(\text{O})_2\text{R}^\circ$; $-\text{N}(\text{OR}^\circ)\text{R}^\circ$; $-\text{C}(\text{NH})\text{NR}^\circ_2$; $-\text{P}(\text{O})_2\text{R}^\circ$; $-\text{P}(\text{O})\text{R}^\circ_2$; $-\text{OP}(\text{O})\text{R}^\circ_2$; $-\text{OP}(\text{O})(\text{OR}^\circ)_2$; $-\text{SiR}^\circ_3$; $-(\text{C}_{1-4} \text{ straight or branched alkylene})\text{O}-\text{N}(\text{R}^\circ)_2$; or $-(\text{C}_{1-4} \text{ straight or branched alkylene})\text{C}(\text{O})\text{O}-\text{N}(\text{R}^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, $-\text{CH}_2$ -(5-6 membered heteroaryl ring), or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R° , taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0031] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(\text{CH}_2)_{0-2}\text{R}^\bullet$, $-(\text{haloR}^\bullet)$, $-(\text{CH}_2)_{0-2}\text{OH}$, $-(\text{CH}_2)_{0-2}\text{OR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{CH}(\text{OR}^\bullet)_2$, $-\text{O}(\text{haloR}^\bullet)$, $-\text{CN}$, $-\text{N}_3$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{R}^\bullet$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{OR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{SR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{SH}$, $-(\text{CH}_2)_{0-2}\text{NH}_2$, $-(\text{CH}_2)_{0-2}\text{NHR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{NR}^\bullet_2$, $-\text{NO}_2$, $-\text{SiR}^\bullet_3$, $-\text{OSiR}^\bullet_3$, $-\text{C}(\text{O})\text{SR}^\bullet$, $-(\text{C}_{1-4} \text{ straight or branched alkylene})\text{C}(\text{O})\text{OR}^\bullet$, or $-\text{SSR}^\bullet$ wherein each $\text{R}^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include $=\text{O}$ and $=\text{S}$.

[0032] Suitable divalent substituents on a saturated carbon atom of an “optionally substituted” group include the following: $=\text{O}$, $=\text{S}$, $=\text{NNR}^*_2$, $=\text{NNHC}(\text{O})\text{R}^*$, $=\text{NNHC}(\text{O})\text{OR}^*$, $=\text{NNHS}(\text{O})_2\text{R}^*$, $=\text{NR}^*$, $=\text{NOR}^*$, $-\text{O}(\text{C}(\text{R}^*_2))_{2-3}\text{O}-$, or $-\text{S}(\text{C}(\text{R}^*_2))_{2-3}\text{S}-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an “optionally substituted” group include: $-\text{O}(\text{CR}^*_2)_{2-3}\text{O}-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0033] Suitable substituents on the aliphatic group of R^* include halogen, $-R^\bullet$, $-(\text{halo}R^\bullet)$, $-\text{OH}$, $-\text{OR}^\bullet$, $-\text{O}(\text{halo}R^\bullet)$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^\bullet$, $-\text{NH}_2$, $-\text{NHR}^\bullet$, $-\text{NR}^\bullet_2$, or $-\text{NO}_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0034] Suitable substituents on a substitutable nitrogen of an “optionally substituted” group include $-R^\dagger$, $-\text{NR}^\dagger_2$, $-\text{C}(\text{O})R^\dagger$, $-\text{C}(\text{O})\text{OR}^\dagger$, $-\text{C}(\text{O})\text{C}(\text{O})R^\dagger$, $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})R^\dagger$, $-\text{S}(\text{O})_2R^\dagger$, $-\text{S}(\text{O})_2\text{NR}^\dagger_2$, $-\text{C}(\text{S})\text{NR}^\dagger_2$, $-\text{C}(\text{NH})\text{NR}^\dagger_2$, or $-\text{N}(R^\dagger)\text{S}(\text{O})_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted $-\text{OPh}$, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0035] Suitable substituents on the aliphatic group of $R^\dagger$ are independently halogen, $-R^\bullet$, $-(\text{halo}R^\bullet)$, $-\text{OH}$, $-\text{OR}^\bullet$, $-\text{O}(\text{halo}R^\bullet)$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^\bullet$, $-\text{NH}_2$, $-\text{NHR}^\bullet$, $-\text{NR}^\bullet_2$, or $-\text{NO}_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0036] As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with

organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[0037] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0038] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention. In certain embodiments, a warhead moiety, R^1 , of a provided compound comprises one or more deuterium atoms. In certain

embodiments, Ring B of a provided compound may be substituted with one or more deuterium atoms.

[0039] As used herein, the term “inhibitor” is defined as a compound that binds to and /or inhibits USP30 with measurable affinity. In certain embodiments, an inhibitor has an IC₅₀ and/or binding constant of less than about 50 μM, less than about 1 μM, less than about 500 nM, less than about 100 nM, less than about 10 nM, or less than about 1 nM.

[0040] A compound of the present invention may be tethered to a detectable moiety. It will be appreciated that such compounds are useful as imaging agents. One of ordinary skill in the art will recognize that a detectable moiety may be attached to a provided compound *via* a suitable substituent. As used herein, the term “suitable substituent” refers to a moiety that is capable of covalent attachment to a detectable moiety. Such moieties are well known to one of ordinary skill in the art and include groups containing, e.g., a carboxylate moiety, an amino moiety, a thiol moiety, or a hydroxyl moiety, to name but a few. It will be appreciated that such moieties may be directly attached to a provided compound or *via* a tethering group, such as a bivalent saturated or unsaturated hydrocarbon chain. In some embodiments, such moieties may be attached via click chemistry. In some embodiments, such moieties may be attached via a 1,3-cycloaddition of an azide with an alkyne, optionally in the presence of a copper catalyst. Methods of using click chemistry are known in the art and include those described by Rostovtsev *et al.*, *Angew. Chem. Int. Ed.* 2002, 41, 2596-99 and Sun *et al.*, *Bioconjugate Chem.*, 2006, 17, 52-57.

[0041] As used herein, the term “detectable moiety” is used interchangeably with the term “label” and relates to any moiety capable of being detected, e.g., primary labels and secondary labels. Primary labels, such as radioisotopes (e.g., tritium, ³²P, ³³P, ³⁵S, or ¹⁴C), mass-tags, and fluorescent labels are signal generating reporter groups which can be detected without further modifications. Detectable moieties also include luminescent and phosphorescent groups.

[0042] The term “secondary label” as used herein refers to moieties such as biotin and various protein antigens that require the presence of a second intermediate for production of a detectable signal. For biotin, the secondary intermediate may include streptavidin-enzyme conjugates. For antigen labels, secondary intermediates may include antibody-enzyme conjugates. Some fluorescent groups act as secondary labels because they transfer energy to another group in the process of nonradiative fluorescent resonance energy transfer (FRET), and the second group produces the detected signal.

[0043] The terms “fluorescent label”, “fluorescent dye”, and “fluorophore” as used herein refer to moieties that absorb light energy at a defined excitation wavelength and emit light energy at a different wavelength. Examples of fluorescent labels include, but are not limited to: Alexa Fluor dyes (Alexa Fluor 350, Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 633, Alexa Fluor 660 and Alexa Fluor 680), AMCA, AMCA-S, BODIPY dyes (BODIPY FL, BODIPY R6G, BODIPY TMR, BODIPY TR, BODIPY 530/550, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY 630/650, BODIPY 650/665), Carboxyrhodamine 6G, carboxy-X-rhodamine (ROX), Cascade Blue, Cascade Yellow, Coumarin 343, Cyanine dyes (Cy3, Cy5, Cy3.5, Cy5.5), Dansyl, Dapoxyl, Dialkylaminocoumarin, 4',5'-Dichloro-2',7'-dimethoxy-fluorescein, DM-NERF, Eosin, Erythrosin, Fluorescein, FAM, Hydroxycoumarin, IRDyes (IRD40, IRD 700, IRD 800), JOE, Lissamine rhodamine B, Marina Blue, Methoxycoumarin, Naphthofluorescein, Oregon Green 488, Oregon Green 500, Oregon Green 514, Pacific Blue, PyMPO, Pyrene, Rhodamine B, Rhodamine 6G, Rhodamine Green, Rhodamine Red, Rhodol Green, 2',4',5',7'-Tetra-bromosulfone-fluorescein, Tetramethyl-rhodamine (TMR), Carboxytetramethylrhodamine (TAMRA), Texas Red, Texas Red-X.

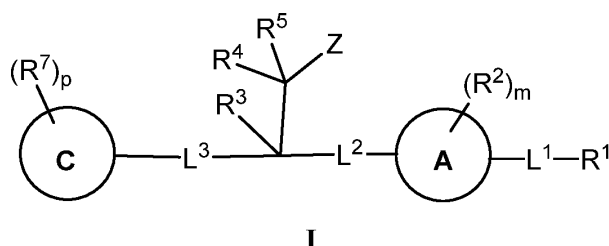
[0044] The term “mass-tag” as used herein refers to any moiety that is capable of being uniquely detected by virtue of its mass using mass spectrometry (MS) detection techniques. Examples of mass-tags include electrophore release tags such as N-[3-[4'-[(p-Methoxytetrafluorobenzyl)oxy]phenyl]-3-methylglyceronyl]isonipecotic Acid, 4'-[2,3,5,6-Tetrafluoro-4-(pentafluorophenoxy)]methyl acetophenone, and their derivatives. The synthesis and utility of these mass-tags is described in United States Patents 4,650,750, 4,709,016, 5,360,8191, 5,516,931, 5,602,273, 5,604,104, 5,610,020, and 5,650,270. Other examples of mass-tags include, but are not limited to, nucleotides, dideoxynucleotides, oligonucleotides of varying length and base composition, oligopeptides, oligosaccharides, and other synthetic polymers of varying length and monomer composition. A large variety of organic molecules, both neutral and charged (biomolecules or synthetic compounds) of an appropriate mass range (100-2000 Daltons) may also be used as mass-tags.

[0045] The terms “measurable affinity” and “measurably inhibit,” as used herein, means a measurable change in USP30 activity between a sample comprising a compound of the present

invention, or composition thereof, and USP30, and an equivalent sample comprising USP30, in the absence of said compound, or composition thereof.

3. Description of Exemplary Embodiments:

[0046] As described above, in certain embodiments, the present invention provides a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

L¹ is a covalent bond or a C₁₋₃ bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -C(CF₃)H-, -N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)N(R)-, -N(R)C(O)-, -S(O)-, -S(O)₂-, -S(O)N(R)-, -S(O)₂N(R)-, or -S(O)(R)=N-;

each R is independently hydrogen or an optionally substituted C₁₋₃ aliphatic group; or:

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur; or

an R group and R¹ on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;

R^1 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^2 is independently halogen, $-CF_3$, $-CN$, $-C(O)NHR$, $-NO_2$, $-NHR$, $-NHC(O)R$, $-NHS(O)_2R$, $-N(R)_2$, or $-OR$, or an optionally substituted C_{1-6} aliphatic group; or
two R^2 on the same carbon are optionally taken together to form $=O$;

L^2 is selected from the group consisting of $-C(O)N(R')$ -, $-CH_2O$ -, $-CH_2N(R')$ -, $-C(OH)(H)CH_2N(R')$ -, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R' is hydrogen or a C_{1-3} aliphatic group;

L^3 is selected from the group consisting of $-C(O)N(R'')$ -, $-OC(O)N(R'')$ -, $-CH_2O$ -, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R'' is hydrogen or a C_{1-3} aliphatic group;

R^3 is hydrogen or C_{1-3} aliphatic; or:

R^3 and R^4 are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring; or

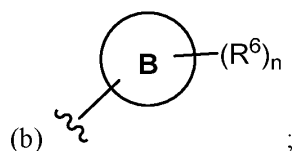
R^3 and R^5 are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring;

R^4 is hydrogen or C_{1-3} aliphatic;

R^5 is hydrogen or C_{1-3} aliphatic;

Z is:

(a) selected from an optionally substituted C_{1-6} aliphatic group, and $-OR$;



- (c) taken together with R⁴ and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R⁶;
- (d) taken together with R⁵ and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R⁶; or
- (e) taken together with R'' and their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the nitrogen of L³, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R⁶;

Ring B is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R⁶ is independently halogen, phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -CN, -NO₂, -NHR, -N(R)₂, -OR, -C(O)R, -C(O)OR, or an optionally substituted C₁₋₆ aliphatic group; or:

two R⁶ on the same carbon are optionally taken together to form =O;

an R⁶ group and R' group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur;

an R⁶ group and R³ group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated spiro-fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen or sulfur; or

an R⁶ group and R⁷ group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur;

Ring C is phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

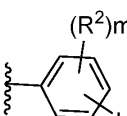
each R⁷ is independently halogen, -CN, -NO₂, -NHR, -N(R)₂, -OR, or an optionally substituted C₁₋₆ aliphatic group; or

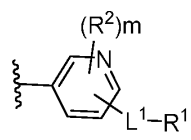
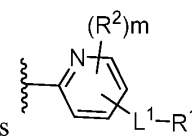
two R⁷ on the same carbon are optionally taken together to form =O;

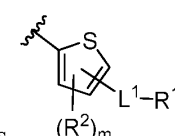
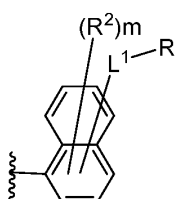
each of m, n, and p is independently 0, 1, 2, 3 or 4.

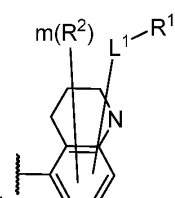
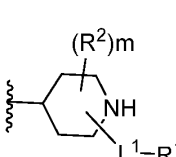
[0047] As defined generally above, Ring A is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0048] In some embodiments, Ring A is phenyl. In some embodiments, Ring A is a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring. In some embodiments, Ring A is a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0049] In some embodiments, Ring A is . In some embodiments, Ring A is

. In some embodiments, Ring A is . In some embodiments, Ring

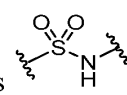
A is . In some embodiments, Ring A is . In some embodiments,

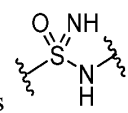
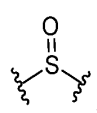
Ring A is . In some embodiments, Ring A is .

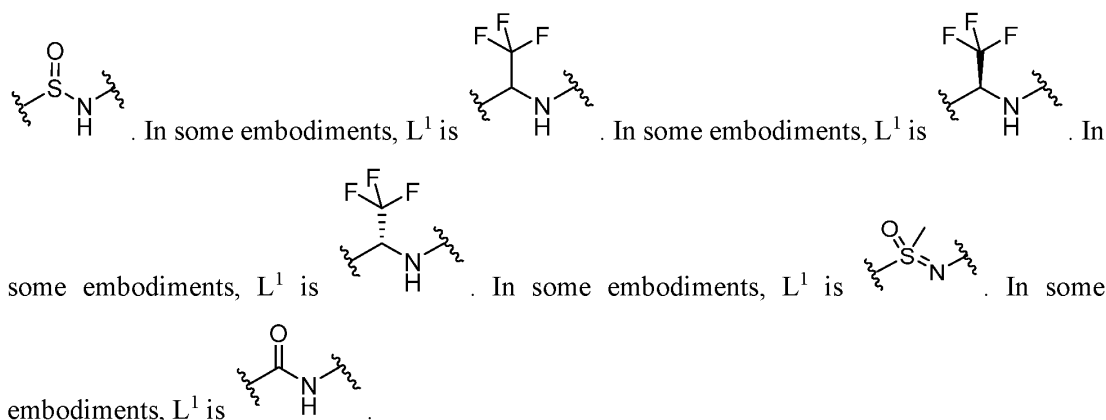
[0050] In some embodiments, Ring A is selected from those depicted in **Table 1** below. In some embodiments, Ring A is selected from those depicted in **Table 11** below.

[0051] As defined generally above, L¹ is a covalent bond or a C₁₋₃ bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -C(CF₃)H-, -N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)N(R)-, -N(R)C(O)-, -S(O)-, -S(O)₂-, -S(O)N(R)-, -S(O)₂N(R)-, or -S(O)(R)=N-.

[0052] In some embodiments, L¹ is a covalent bond. In some embodiments, L¹ is a C₁₋₃ bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -C(CF₃)H-, -N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)N(R)-, -N(R)C(O)-, -S(O)-, -S(O)₂-, -S(O)N(R)-, -S(O)₂N(R)-, or -S(O)(R)=N-.

[0053] In some embodiments, L¹ is . In some embodiments, L¹ is . In some

embodiments, L¹ is . In some embodiments, L¹ is . In some embodiments, L¹ is



[0054] In some embodiments, when L¹ is $-\text{S}(\text{O})_2\text{N}(\text{R})-$, R¹ is other than hydrogen, isopropyl, t-butyl, 1-methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 1-trifluoromethylcyclopropyl, or 3-methyl-3-oxetanyl. In some embodiments, when L¹ is $-\text{S}(\text{O})_2\text{N}(\text{R})-$, and R¹ is hydrogen, isopropyl, t-butyl, 1-methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 1-trifluoromethylcyclopropyl, or 3-methyl-3-oxetanyl, then Ring A is not unsubstituted phenyl or naphthyl.

[0055] In some embodiments, L¹ is selected from those depicted in **Table 1** below. In some embodiments, L¹ is selected from those depicted in **Table 11** below.

[0056] As defined generally above, each R is independently hydrogen or an optionally substituted C₁₋₃ aliphatic group; two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur; or an R group and R¹ on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur.

[0057] In some embodiments, R is hydrogen. In some embodiments, R is an optionally substituted C₁₋₃ aliphatic group. In some embodiments, two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur. In some embodiments, an R group and R¹ on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated,

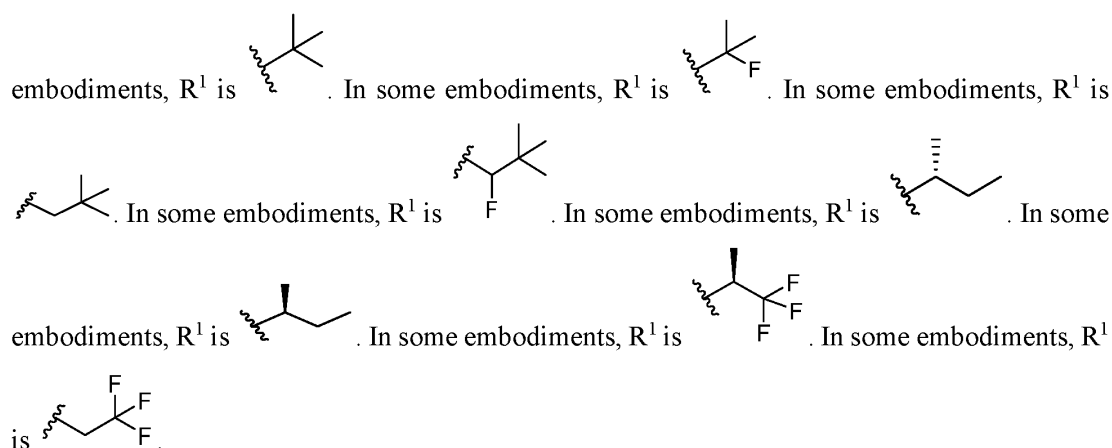
partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur.

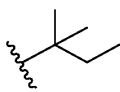
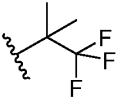
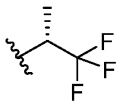
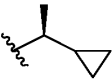
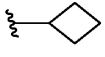
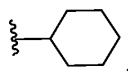
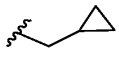
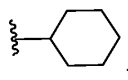
[0058] In some embodiments, R is selected from those depicted in **Table 1** below. In some embodiments, R is selected from those depicted in **Table 11** below.

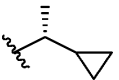
[0059] As defined generally above, R¹ is hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

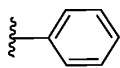
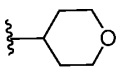
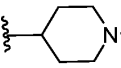
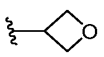
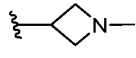
[0060] In some embodiments, R¹ is hydrogen. In some embodiments, R¹ is an optionally substituted group selected from C₁₋₆ aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

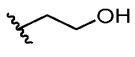
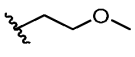
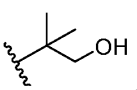
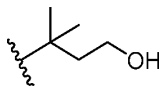
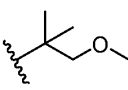
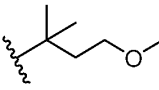
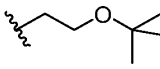
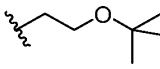
[0061] In some embodiments, R¹ is methyl. In some embodiments, R¹ is ethyl. In some

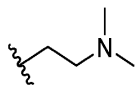
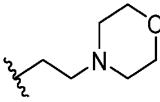
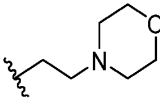
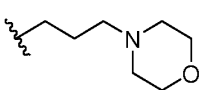
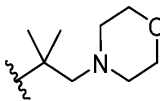
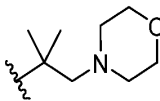


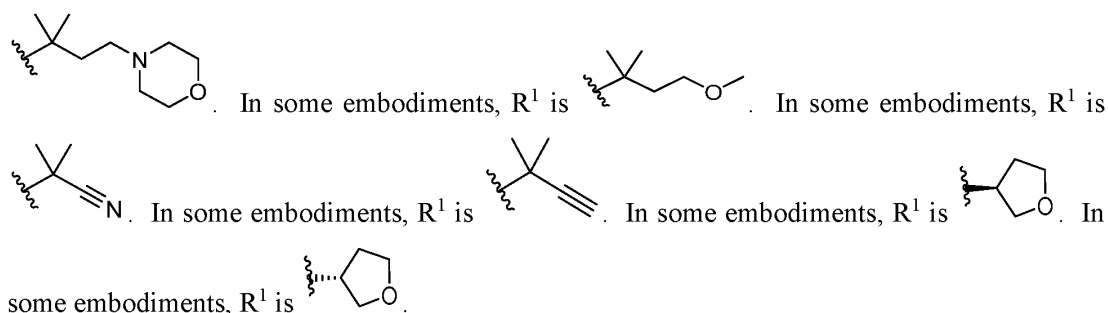
[0062] In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is .

[0063] In some embodiments, R¹ is .

[0064] In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is .

[0065] In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is .

R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is . In some embodiments, R¹ is .



[0066] In some embodiments, R¹ is other than hydrogen, isopropyl, t-butyl, 1-methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 1-trifluoromethylcyclopropyl, or 3-methyl-3-oxetanyl when L¹ is –S(O)₂N(R)–.

[0067] In some embodiments, R¹ is other than hydrogen or ethyl when L¹ is –S(O)₂N(R)– and Ring A is naphthyl.

[0068] In some embodiments, R¹ is selected from those depicted in **Table 1** below. In some embodiments, R¹ is selected from those depicted in **Table 11** below.

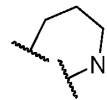
[0069] As defined generally above, each R² is independently halogen, –CF₃, –CN, –C(O)NHR, –NO₂, –NHR, –NHC(O)R, –NHS(O)₂R, –N(R)₂, or –OR, or an optionally substituted C₁₋₆ aliphatic group; or two R² on the same carbon are optionally taken together to form =O; or two R² groups are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen or sulfur.

[0070] In some embodiments, R² is halogen, –CF₃, –CN, –C(O)NHR, –NO₂, –NHR, –NHC(O)R, –NHS(O)₂R, –N(R)₂, or –OR. In some embodiments, R² is an optionally substituted C₁₋₆ aliphatic group. In some embodiments, two R² on the same carbon are optionally taken together to form =O. In some embodiments, two R² groups are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen or sulfur.

[0071] In some embodiments, R² is methyl.

[0072] In some embodiments, R² is methoxy. In some embodiments, R² is fluoro. In some embodiments, R² is chloro. In some embodiments, R² is cyano. In some embodiments, R² is hydroxy. In some embodiments, R² is trifluoromethyl.

[0073] In some embodiments, two R^2 groups are taken together with their intervening atoms to form a 6 membered partially unsaturated fused ring having 1 nitrogen. In some embodiments,

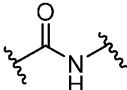
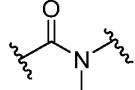
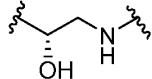
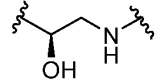
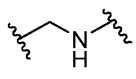
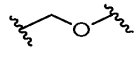


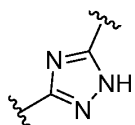
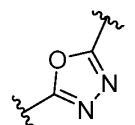
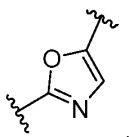
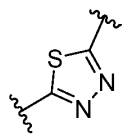
two R^1 groups are taken together with their intervening atoms to form

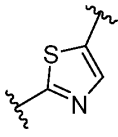
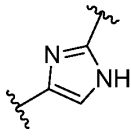
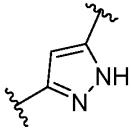
[0074] In some embodiments, R^2 is selected from those depicted in **Table 1** below. In some embodiments, R^2 is selected from those depicted in **Table 11** below.

[0075] As defined generally above, L^2 is selected from the group consisting of $-C(O)N(R')$ -, $-CH_2O-$, $-CH_2N(R')$ -, $-C(OH)(H)CH_2N(R')$ -, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0076] In some embodiments, L^2 is $-C(O)N(R')$ -. In some embodiments, L^2 is $-CH_2O-$. In some embodiments, L^2 is $-CH_2N(R')$ -. In some embodiments, L^2 is $-C(OH)(H)CH_2N(R')$ -. In some embodiments, L^2 is a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0077] In some embodiments, L^2 is . In some embodiments, L^2 is . In some embodiments, L^2 is . In some embodiments, L^2 is . In some embodiments, L^2 is . In some embodiments, L^2 is .

[0078] In some embodiments, L^2 is . In some embodiments, L^2 is . In some embodiments, L^2 is . In some embodiments, L^2 is . In some

embodiments, L^2 is . In some embodiments, L^2 is . In some embodiments, L^2 is .

[0079] In some embodiments, L^2 is selected from those depicted in **Table 1** below. In some embodiments, L^2 is selected from those depicted in **Table 11** below.

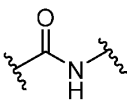
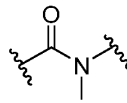
[0080] As defined generally above, R' is hydrogen or a C_{1-3} aliphatic group.

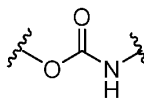
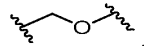
[0081] In some embodiments, R' is hydrogen. In some embodiments, R' is a C_{1-3} aliphatic group. In some embodiments, R' is methyl. In some embodiments, R' is ethyl. In some embodiments, R' is n-propyl.

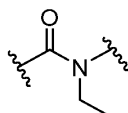
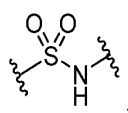
[0082] In some embodiments, R' is selected from those depicted in **Table 1** below. In some embodiments, R' is selected from those depicted in **Table 11** below.

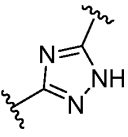
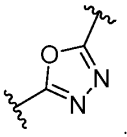
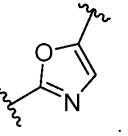
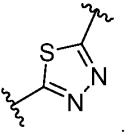
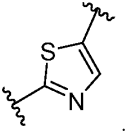
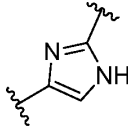
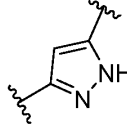
[0083] As defined generally above, L^3 is selected from the group consisting of $-C(O)N(R'')$ -, $-OC(O)N(R'')$ -, $-CH_2O-$, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0084] In some embodiments, L^3 is $-C(O)N(R'')$ -. In some embodiments, L^3 is $-OC(O)N(R'')$ -. In some embodiments, L^3 is $-CH_2O-$. In some embodiments, L^3 is $-C(O)NH-$. In some embodiments, L^3 is $-OC(O)NH-$. In some embodiments, L^3 is a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0085] In some embodiments, L^3 is . In some embodiments, L^3 is . In

some embodiments, L^3 is . In some embodiments, L^3 is . In some

embodiments, L^3 is . In some embodiments, L^3 is .

[0086] In some embodiments, L^3 is . In some embodiments, L^3 is . In some embodiments, L^3 is . In some embodiments, L^3 is . In some embodiments, L^3 is . In some embodiments, L^3 is . In some embodiments, L^3 is .

[0087] In some embodiments, L^3 is selected from those depicted in **Table 1** below. In some embodiments, L^3 is selected from those depicted in **Table 11** below.

[0088] In some embodiments, at least one of L^2 and L^3 is a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

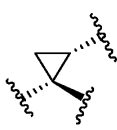
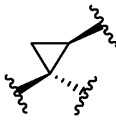
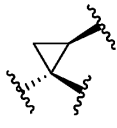
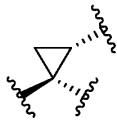
[0089] As defined generally above, R'' is hydrogen or a C_{1-3} aliphatic group.

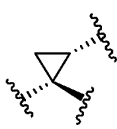
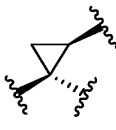
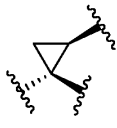
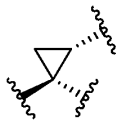
[0090] In some embodiments, R'' is hydrogen. In some embodiments, R'' is a C_{1-3} aliphatic group. In some embodiments, R'' is methyl. In some embodiments, R'' is ethyl. In some embodiments, R'' is n-propyl.

[0091] In some embodiments, R'' is selected from those depicted in **Table 1** below. In some embodiments, R'' is selected from those depicted in **Table 11** below.

[0092] As defined generally above, R^3 is hydrogen or C_{1-3} aliphatic, or: R^3 and R^4 are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring, or R^3 and R^5 are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring.

[0093] In some embodiments, R^3 is hydrogen. In some embodiments, R^3 is C_{1-3} aliphatic. In some embodiments, R^3 and R^4 are taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring. In some embodiments, R^3 and R^5 are taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring.

[0094] In some embodiments, R^3 and R^4 are taken together to form . In some embodiments, R^3 and R^4 are taken together to form . In some embodiments, R^3 and R^4 are taken together to form . In some embodiments, R^3 and R^4 are taken together to form .

[0095] In some embodiments, R^3 and R^5 are taken together to form . In some embodiments, R^3 and R^5 are taken together to form . In some embodiments, R^3 and R^5 are taken together to form . In some embodiments, R^3 and R^5 are taken together to form .

[0096] In some embodiments, R^3 is selected from those depicted in **Table 1** below. In some embodiments, R^3 is selected from those depicted in **Table 11** below.

[0097] As defined generally above, R^4 is hydrogen or C_{1-3} aliphatic.

[0098] In some embodiments, R^4 is hydrogen. In some embodiments, R^4 is C_{1-3} aliphatic. In some embodiments, R^4 is methyl.

[0099] In some embodiments, R^4 is selected from those depicted in **Table 1** below. In some embodiments, R^4 is selected from those depicted in **Table 11** below.

[00100] As defined generally above, R^5 is hydrogen or C_{1-3} aliphatic. In some embodiments, R^5 is methyl.

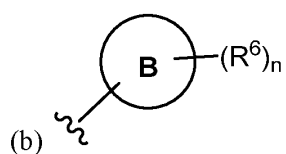
[00101] In some embodiments, R^5 is hydrogen. In some embodiments, R^5 is C_{1-3} aliphatic.

[00102] In some embodiments, R^5 is selected from those depicted in **Table 1** below. In some embodiments, R^5 is selected from those depicted in **Table 11** below.

[00103] In some embodiments, both R^4 and R^5 are methyl.

[00104] As defined generally above, Z is:

(a) selected from an optionally substituted C_{1-6} aliphatic group, and $-OR$;



(c) taken together with R^4 and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 ;

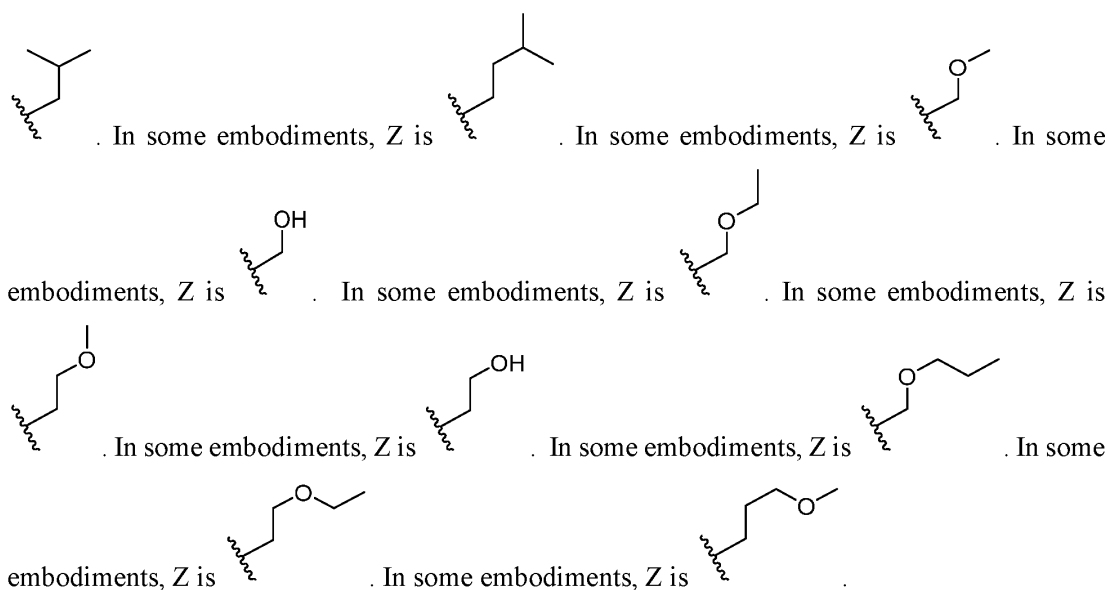
(d) taken together with R^5 and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 ; or

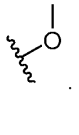
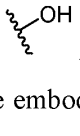
(e) taken together with R'' and their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the nitrogen of L^3 , independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 .

[00105] In some embodiments, Z is selected from an optionally substituted C_{1-6} aliphatic group, and $-OR$.

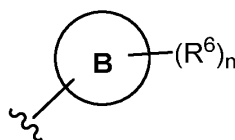
[00106] In some embodiments, Z is an optionally substituted C_{1-6} aliphatic group. In some embodiments, Z is optionally substituted ethyl. In some embodiments, Z is optionally substituted n-propyl. In some embodiments, Z is optionally substituted n-butyl. In some embodiments, Z is

optionally substituted n-pentyl. In some embodiments, Z is . In some embodiments, Z is



[00107] In some embodiments, Z is $-OR$. In some embodiments, Z is  . In some
 embodiments, Z is  .

[00108] In some embodiments, Z is selected from those depicted in **Table 1** below. In some
 embodiments, Z is selected from those depicted in **Table 11** below.



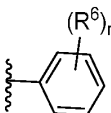
[00109] In some embodiments, Z is  .

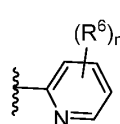
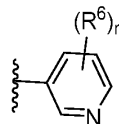
[00110] As defined generally above, Ring B is phenyl, a 5-6 membered heteroaryl ring having
 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered
 bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-
 8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered
 saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected
 from nitrogen, oxygen, or sulfur.

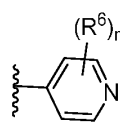
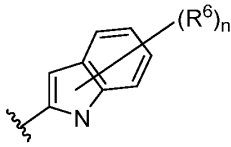
[00111] In some embodiments, Ring B is phenyl. In some embodiments, Ring B is a 5-6
 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen,
 or sulfur. In some embodiments, Ring B is an 8-10 membered bicyclic aryl or heteroaryl ring

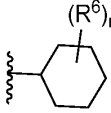
having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring B is a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring. In some embodiments, Ring B is a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring B is a 5-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring B is a 4 membered saturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

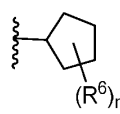
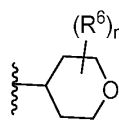
[00112]

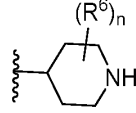
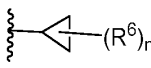
[00113] In some embodiments, Ring B is . In some embodiments, Ring B is

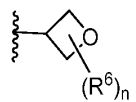
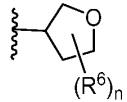
. In some embodiments, Ring B is . In some embodiments, Ring B is

. In some embodiments, Ring B is .

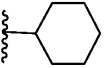
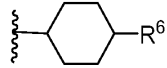
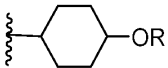
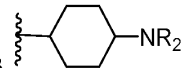
[00114] In some embodiments, Ring B is . In some embodiments, Ring B is

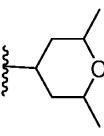
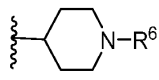
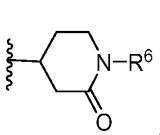
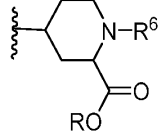
. In some embodiments, Ring B is . In some embodiments, Ring B is

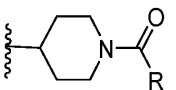
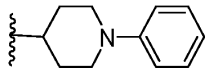
. In some embodiments, Ring B is . In some embodiments, Ring B is

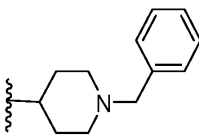
. In some embodiments, Ring B is .

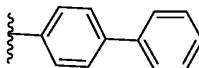
[00115] In some embodiments, Ring B is . In some embodiments, Ring B is .

In some embodiments, Ring B is . In some embodiments, Ring B is . In some embodiments, Ring B is . In some embodiments, Ring B is .

In some embodiments, Ring B is . In some embodiments, Ring B is . In some embodiments, Ring B is . In some embodiments, Ring B is .

In some embodiments, Ring B is . In some embodiments, Ring B is .

In some embodiments, Ring B is .

[00116] In some embodiments, Ring B is .

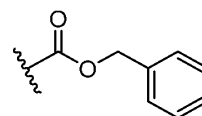
[00117] In some embodiments, Ring B is selected from those depicted in **Table 1** below. In some embodiments, Ring B is selected from those depicted in **Table 11** below.

[00118] As defined generally above, each R^6 is independently halogen, phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, $-CN$, $-NO_2$, $-NHR$, $-N(R)_2$, $-OR$, $-C(O)R$, $-C(O)OR$, or an optionally substituted C_{1-6} aliphatic group, or: two R^6 on the same carbon are optionally taken together to form $=O$; an R^6 group and R^7 group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur; an R^6 group and R^3 group

are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated spiro-fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen or sulfur; or an R⁶ group and R⁷ group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur.

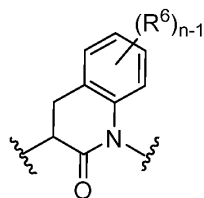
[00119] In some embodiments, each R⁶ is independently halogen, phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -CN, -NO₂, -NHR, -N(R)₂, -OR, -C(O)R, -C(O)OR, or an optionally substituted C₁₋₆ aliphatic group. In some embodiments, R⁶ is halogen, -CN, -NO₂, -NHR, -N(R)₂, -OR, or an optionally substituted C₁₋₆ aliphatic group. In some embodiments, two R⁶ on the same carbon are taken together to form =O. In some embodiments, an R⁶ group and R⁷ group are taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur. In some embodiments, an R⁶ group and R³ group are taken together with their intervening atoms to form a 5-8 membered partially unsaturated spiro-fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen or sulfur. In some embodiments, an R⁶ group and R⁷ group are taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur.

[00120] In some embodiments, R⁶ is methyl. In some embodiments, R⁶ is methoxy. In some embodiments, R⁶ is fluoro. In some embodiments, R⁶ is ethyl. In some embodiments, R⁶ is phenyl.

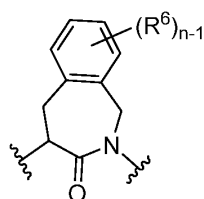


In some embodiments, R⁶ is -C(O)OR. In some embodiments, R⁶ is

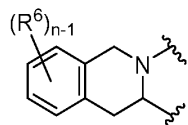
[00121] In some embodiments, an R^6 group and R^7 group are taken together to form



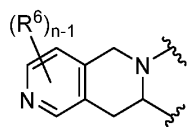
. In some embodiments, an R^6 group and R^7 group are taken together to form



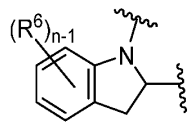
[00122] In some embodiments, an R^6 group and $R^{7'}$ group are taken together to form



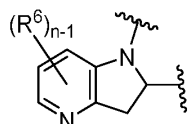
. In some embodiments, an R^6 group and $R^{7'}$ group are taken together to form



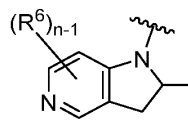
. In some embodiments, an R^6 group and $R^{7'}$ group are taken together to form



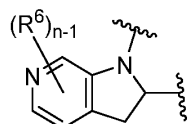
. In some embodiments, an R^6 group and $R^{7'}$ group are taken together to form



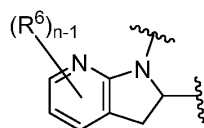
. In some embodiments, an R^6 group and $R^{7'}$ group are taken together to form

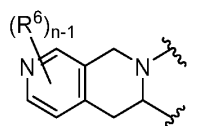


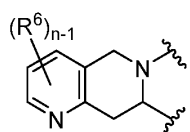
. In some embodiments, an R^6 group and $R^{7'}$ group are taken together to form



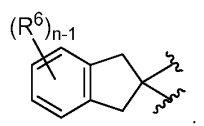
. In some embodiments, an R^6 group and $R^{7'}$ group are taken together to form

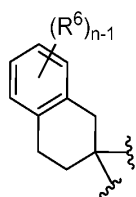
. In some embodiments, an R⁶ group and Rⁿ group are taken together to form

. In some embodiments, an R⁶ group and Rⁿ group are taken together to form



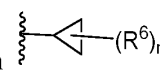
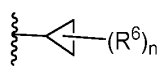
[00123] In some embodiments, an R⁶ group and R³ group are taken together to form

. In some embodiments, an R⁶ group and R³ group are taken together to form

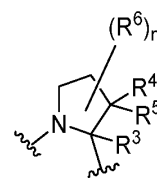


[00124] In some embodiments, R⁶ is selected from those depicted in **Table 1** below. In some embodiments, R⁶ is selected from those depicted in **Table 11** below.

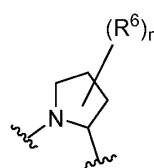
[00125] In some embodiments, Z is taken together with R⁴ and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R⁶. In some embodiments, Z is taken together with R⁵ and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R⁶.

[00126] In some embodiments, Z and R⁴ are taken together to form . In some embodiments, Z and R⁵ are taken together to form .

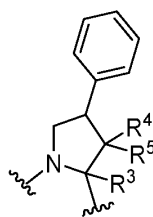
[00127] In some embodiments, Z is taken together with R'' and their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the nitrogen of L³, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R⁶.



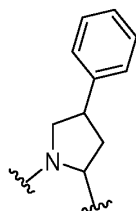
[00128] In some embodiments, Z and R'' are taken together to form



embodiments, Z and R'' are taken together to form



R'' are taken together to form

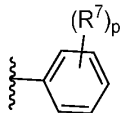


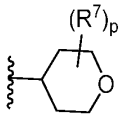
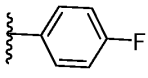
to form

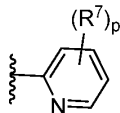
[00129] As defined generally above, Ring C is phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

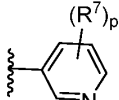
[00130] In some embodiments, Ring C is phenyl. In some embodiments, Ring C is a 3-8 membered saturated or partially unsaturated carbocyclic ring. In some embodiments, Ring C is a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms

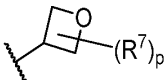
independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring C is a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring C is an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

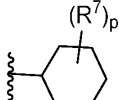
[00131] In some embodiments, Ring C is . In some embodiments, Ring C is

. In some embodiments, Ring C is .

[00132] In some embodiments, Ring C is . In some embodiments, Ring C is

.

[00133] In some embodiments, Ring C is . In some embodiments, Ring C is

.

[00134] In some embodiments, Ring C is selected from those depicted in **Table 1** below. In some embodiments, Ring C is selected from those depicted in **Table 11** below.

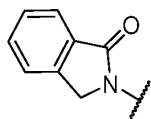
[00135] As defined generally above, R^7 is independently halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{NHR}$, $-\text{N}(\text{R})_2$, $-\text{OR}$, or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same carbon are optionally taken together to form $=\text{O}$.

[00136] As defined generally above, an R^7 group and R'' group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur.

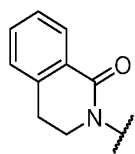
[00137] In some embodiments, R^7 is halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{NHR}$, $-\text{N(R)}_2$, $-\text{OR}$, or an optionally substituted C_{1-6} aliphatic group. In some embodiments, two R^7 on the same carbon are optionally taken together to form $=\text{O}$.

[00138] In some embodiments, R^7 is fluoro.

[00139] In some embodiments, an R^7 group and R'' group are taken together with their



intervening atoms to form



taken together with their intervening atoms to form

[00140] In some embodiments, R^7 is selected from those depicted in **Table 1** below. In some embodiments, R^7 is selected from those depicted in **Table 11** below.

[00141] As defined generally above, each of m , n , and p is independently 0, 1, 2, 3 or 4.

[00142] In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4.

[00143] In some embodiments, m is selected from those depicted in **Table 1** below. In some embodiments, m is selected from those depicted in **Table 11** below.

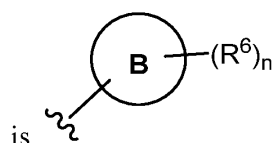
[00144] In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

[00145] In some embodiments, n is selected from those depicted in **Table 1** below. In some embodiments, n is selected from those depicted in **Table 11** below.

[00146] In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4.

[00147] In some embodiments, p is selected from those depicted in **Table 1** below. In some embodiments, p is selected from those depicted in **Table 11** below.

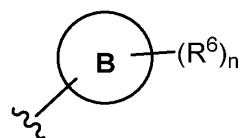
[00148] In certain embodiments, Ring A is phenyl; L^1 is $-\text{S(O)}_2\text{N(H)}-$; R is a C_1 aliphatic group; R^1 is C_4 aliphatic or a 4-membered saturated heterocyclic ring having 1 oxygen atom; R^2 is $-\text{OR}$; L^2 is $-\text{C(O)N(H)}-$; L^3 is $-\text{C(O)N(H)}-$; R^3 is hydrogen; R^4 is hydrogen; R^5 is hydrogen; Z



is ; Ring B is a 6-membered saturated heterocyclic ring having 1 oxygen atom; Ring C is phenyl; R^7 is halogen; m is 1; p is 1; and n is 0.

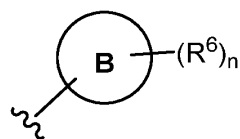
[00149] In certain embodiments, Ring A is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; L^1 is $-\text{S}(\text{O})_2\text{N}(\text{H})-$; R^1 is C_4 aliphatic; L^2 is $-\text{C}(\text{O})\text{N}(\text{H})-$; L^3 is $-\text{C}(\text{O})\text{N}(\text{H})-$; R^3 is hydrogen; R^4 is hydrogen; R^5 is hydrogen; Z is a C_3 aliphatic group; Ring C is phenyl; R^7 is halogen; m is 0; and p is 1.

[00150] In certain embodiments, Ring A is phenyl; L^1 is $-\text{S}(\text{O})_2\text{N}(\text{H})-$; R is a C_1 aliphatic group; R^1 is an optionally substituted 3-membered saturated monocyclic carbocyclic ring; R^2 is $-\text{OR}$; L^2 is $-\text{C}(\text{O})\text{N}(\text{H})-$; L^3 is $-\text{C}(\text{O})\text{N}(\text{H})-$; R^3 is hydrogen; R^4 is hydrogen; R^5 is hydrogen; Z is



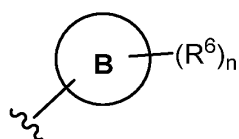
; Ring B is phenyl; Ring C is phenyl; R^7 is halogen; m is 0 or 1; p is 1; and n is 0.

[00151] In certain embodiments, Ring A is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; L^1 is $-\text{S}(\text{O})_2\text{N}(\text{H})-$; R is a C_1 aliphatic group; R^1 is a C_4 aliphatic or 4-membered heterocyclic ring with 1 oxygen atom; R^2 is $-\text{OR}$; L^2 is $-\text{C}(\text{O})\text{N}(\text{H})-$; L^3 is $-\text{C}(\text{O})\text{N}(\text{H})-$; R^3 is



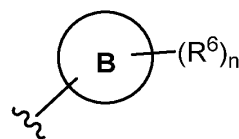
hydrogen; R^4 is hydrogen; R^5 is hydrogen; Z is ; Ring B is a 6-membered saturated heterocyclic ring having 1 nitrogen atom; R^6 is a C_1 aliphatic group; Ring C is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; R^7 is halogen; m is 0 or 1; p is 1; and n is 0 or 1.

[00152] In certain embodiments, Ring A is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; L^1 is $-\text{S}(\text{O})_2\text{N}(\text{H})-$; R is a C_1 aliphatic group; R^1 is an optionally substituted group selected from 3-membered saturated monocyclic carbocyclic ring or C_{3-4} aliphatic; R^2 is $-\text{OR}$; L^2 is $-\text{C}(\text{O})\text{N}(\text{H})-$; L^3 is $-\text{C}(\text{O})\text{N}(\text{H})-$; R^3 is hydrogen; R^4 is hydrogen; R^5 is hydrogen; Z is



; Ring B is phenyl; Ring C is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; R^7 is halogen; m is 0 or 1; p is 1; and n is 0.

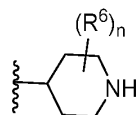
[00153] In certain embodiments, Ring A is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; L^1 is $-S(O)_2N(H)-$; R is a C_1 aliphatic group; R^1 is an optionally substituted C_4 aliphatic or a 4-5 membered saturated monocyclic carbocyclic ring; R^2 is $-OR$; L^2 is $-C(O)N(H)-$



; L^3 is $-C(O)N(H)-$; R^3 is hydrogen; R^4 is hydrogen; R^5 is hydrogen; Z is ; Ring B is a 6-membered saturated heterocyclic ring having 1 oxygen atom; Ring C is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; R^7 is halogen; m is 0 or 1; p is 1; and n is 0.

[00154] In certain embodiments, Z is , , , or . In

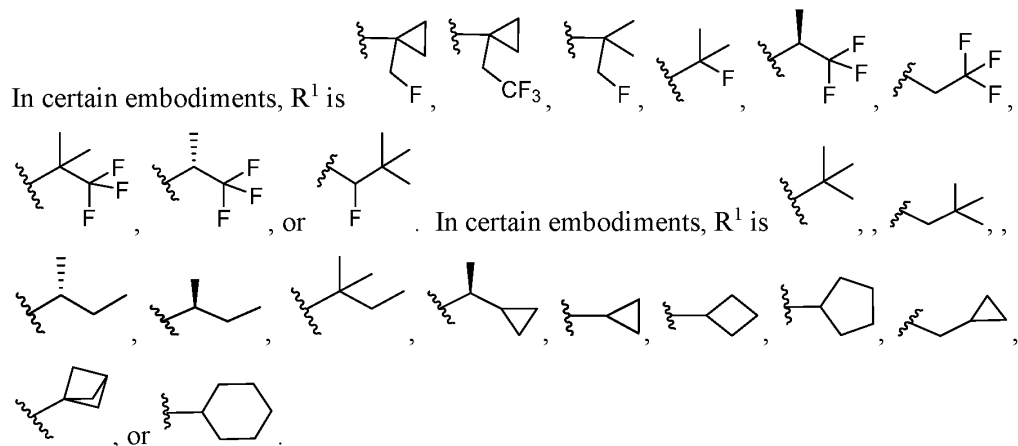
certain embodiments, Z is or . In certain embodiments, Z is or



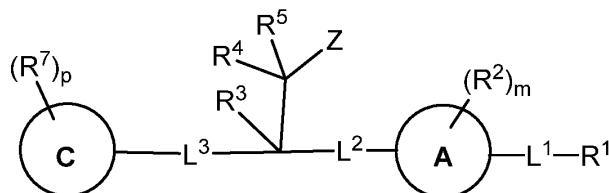
[00155] In certain embodiments, Ring C is , L^1 is , L^2 is ,

and L^3 is .

[00156] In certain embodiments, R^1 is , , , , , , , , , , , , , , or .



[00157] In some embodiments, the compound of formula **I** is a compound of formula **I-a**:



I-a

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

L¹ is a covalent bond or a C₁₋₃ bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -C(CF₃)H-, -N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)N(R)-, -N(R)C(O)-, -S(O)-, -S(O)₂-, -S(O)N(R)-, -S(O)₂N(R)-, or -S(O)(R)=N-;

each R is independently hydrogen or an optionally substituted C₁₋₃ aliphatic group; or:

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring

having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur; or

an R group and R¹ on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;

R¹ is hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R² is independently halogen, -CF₃, -CN, -C(O)NHR, -NO₂, -NHR, -NHC(O)R, -NHS(O)₂R, -N(R)₂, or -OR, or an optionally substituted C₁₋₆ aliphatic group; or

two R² on the same carbon are optionally taken together to form =O;

L² is selected from the group consisting of -C(O)N(R')-, -CH₂O-, -CH₂N(R')-, -C(OH)(H)CH₂N(R')-, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R' is hydrogen or a C₁₋₃ aliphatic group;

L³ is selected from the group consisting of -C(O)N(R'')-, -OC(O)N(R'')-, -CH₂O-, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R'' is hydrogen or a C₁₋₃ aliphatic group;

R³ is hydrogen or C₁₋₃ aliphatic; or:

R³ and R⁴ are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring; or

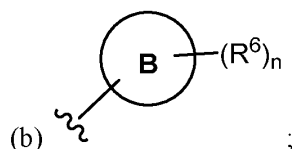
R³ and R⁵ are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring;

R⁴ is hydrogen or C₁₋₃ aliphatic;

R⁵ is hydrogen or C₁₋₃ aliphatic;

Z is:

(a) an optionally substituted C₁₋₆ aliphatic group; or



Ring B is a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 5-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R⁶ is independently halogen, phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -CN, -NO₂, -NHR, -N(R)₂, -OR, -C(O)R, -C(O)OR, or an optionally substituted C₁₋₆ aliphatic group, or two R⁶ on the same carbon are optionally taken together to form =O;

Ring C is phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

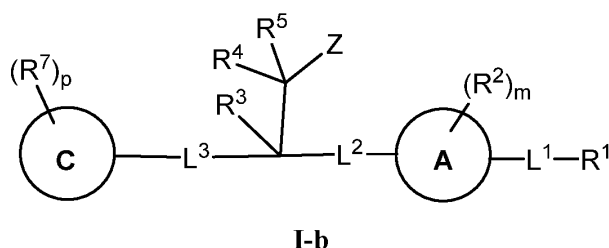
each R⁷ is independently halogen, -CN, -NO₂, -NHR, -N(R)₂, -OR, or an optionally substituted C₁₋₆ aliphatic group; or

two R⁷ on the same carbon are optionally taken together to form =O;

each of m, n, and p is independently 0, 1, 2, 3 or 4;

wherein when Ring A is phenyl or naphthyl, L¹ is -S(O)₂N(H)-, and R¹ is isopropyl, t-butyl, 1-methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 1-trifluoromethylcyclopropyl or 3-methyl-3-oxetanyl, then m is not 0.

[00158] In some embodiments, the compound of formula **I** is a compound of formula **I-b**:



or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

L^1 is a covalent bond or a C_{1-3} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-C(CF_3)H-$, $-N(R)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-C(O)N(R)-$, $-N(R)C(O)-$, $-S(O)-$, $-S(O)_2-$, $-S(O)N(R)-$, $-S(O)_2N(R)-$, or $-S(O)(R)=N-$;

each R is independently hydrogen or an optionally substituted C_{1-3} aliphatic group; or:

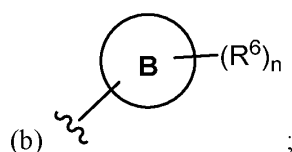
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur; or

an R group and R^1 on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;

R^1 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from

- nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;
- each R^2 is independently halogen, $-CF_3$, $-CN$, $-C(O)NHR$, $-NO_2$, $-NHR$, $-NHC(O)R$, $-NHS(O)_2R$, $-N(R)_2$, or $-OR$, or an optionally substituted C_{1-6} aliphatic group; or
- two R^2 on the same carbon are optionally taken together to form $=O$;
- L^2 is selected from the group consisting of $-C(O)N(R')$, $-CH_2O-$, $-CH_2N(R')$, $-C(OH)(H)CH_2N(R')$, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;
- R' is hydrogen or a C_{1-3} aliphatic group;
- L^3 is selected from the group consisting of $-C(O)N(R'')$, $-OC(O)N(R'')$, $-CH_2O-$, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;
- R'' is hydrogen or a C_{1-3} aliphatic group;
- R^3 is hydrogen or C_{1-3} aliphatic; or:
- R^3 and R^4 are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring; or
- R^3 and R^5 are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring;
- R^4 is hydrogen or C_{1-3} aliphatic;
- R^5 is hydrogen or C_{1-3} aliphatic;
- Z is:

(a) $-OR$; or



- Ring B is a 4 membered saturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;
- each R^6 is independently halogen, phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated

heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, $-\text{CN}$, $-\text{NO}_2$, $-\text{NHR}$, $-\text{N(R)}_2$, $-\text{OR}$, $-\text{C(O)R}$, $-\text{C(O)OR}$, or an optionally substituted C_{1-6} aliphatic group, or two R^6 on the same carbon are optionally taken together to form $=\text{O}$;

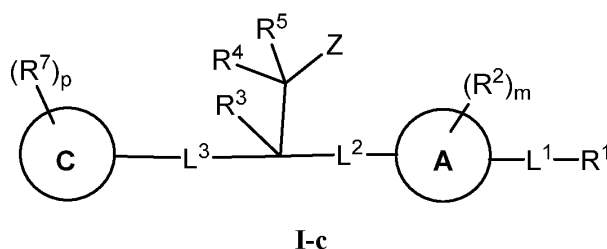
Ring C is phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^7 is independently halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{NHR}$, $-\text{N(R)}_2$, $-\text{OR}$, or an optionally substituted C_{1-6} aliphatic group; or

two R^7 on the same carbon are optionally taken together to form $=\text{O}$;

each of m, n, and p is independently 0, 1, 2, 3 or 4.

[00159] In some embodiments, the compound of formula I is a compound of formula I-c:



or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

L^1 is a covalent bond or a C_{1-3} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-\text{C}(\text{CF}_3)\text{H}-$, $-\text{N(R)}-$, $-\text{O}-$, $-\text{C(O)}-$, $-\text{OC(O)}-$, $-\text{C(O)O}-$, $-\text{C(O)N(R)}-$, $-\text{N(R)C(O)}-$, $-\text{S(O)}-$, $-\text{S(O)}_2-$, $-\text{S(O)N(R)}-$, $-\text{S(O)}_2\text{N(R)}-$, or $-\text{S(O)(R)=N}-$;

each R is independently hydrogen or an optionally substituted C_{1-3} aliphatic group; or:

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur; or

an R group and R¹ on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;

R¹ is hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R² is independently halogen, -CF₃, -CN, -C(O)NHR, -NO₂, -NHR, -NHC(O)R, -NHS(O)₂R, -N(R)₂, or -OR, or an optionally substituted C₁₋₆ aliphatic group; or

two R² on the same carbon are optionally taken together to form =O;

L² is selected from the group consisting of -C(O)N(R')-, -CH₂O-, -CH₂N(R')-, -C(OH)(H)CH₂N(R')-, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R' is hydrogen or a C₁₋₃ aliphatic group;

L³ is selected from the group consisting of -C(O)N(R'')-, -OC(O)N(R'')-, -CH₂O-, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R'' is hydrogen or a C₁₋₃ aliphatic group;

R³ is hydrogen or C₁₋₃ aliphatic;

R⁴ is hydrogen or C₁₋₃ aliphatic;

R⁵ is hydrogen or C₁₋₃ aliphatic;

Z is:

- (a) taken together with R^4 and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 ;
- (b) taken together with R^5 and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 ; or
- (c) taken together with R'' and their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the nitrogen of L^3 , independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 .

each R^6 is independently halogen, phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, $-CN$, $-NO_2$, $-NHR$, $-N(R)_2$, $-OR$, $-C(O)R$, $-C(O)OR$, or an optionally substituted C_{1-6} aliphatic group; or two R^6 on the same carbon are optionally taken together to form $=O$;

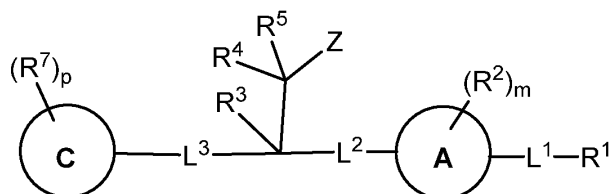
Ring C is phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^7 is independently halogen, $-CN$, $-NO_2$, $-NHR$, $-N(R)_2$, $-OR$, or an optionally substituted C_{1-6} aliphatic group; or

two R^7 on the same carbon are optionally taken together to form $=O$;

each of m , n , and p is independently 0, 1, 2, 3 or 4.

[00160] In some embodiments, the compound of formula **I** is a compound of formula **I-d**:



I-d

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

L¹ is a covalent bond or a C₁₋₃ bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -C(CF₃)H-, -N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)N(R)-, -N(R)C(O)-, -S(O)-, -S(O)₂-, -S(O)N(R)-, -S(O)₂N(R)-, or -S(O)(R)=N-;

each R is independently hydrogen or an optionally substituted C₁₋₃ aliphatic group; or:

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur; or

an R group and R¹ on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;

R¹ is hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R² is independently halogen, -CF₃, -CN, -C(O)NHR, -NO₂, -NHR, -NHC(O)R, -NHS(O)₂R, -N(R)₂, or -OR, or an optionally substituted C₁₋₆ aliphatic group; or

two R² on the same carbon are optionally taken together to form =O;

L^2 is selected from the group consisting of $-C(O)N(R')$ -, $-CH_2O$ -, $-CH_2N(R')$ -, $-C(OH)(H)CH_2N(R')$ -, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R' is hydrogen or a C_{1-3} aliphatic group;

L^3 is selected from the group consisting of $-C(O)N(R'')$ -, $-OC(O)N(R'')$ -, $-CH_2O$ -, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R'' is hydrogen or a C_{1-3} aliphatic group;

R^3 is hydrogen or C_{1-3} aliphatic; or:

R^3 and R^4 are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring; or

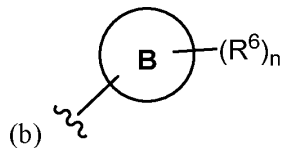
R^3 and R^5 are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring;

R^4 is hydrogen or C_{1-3} aliphatic;

R^5 is hydrogen or C_{1-3} aliphatic;

Z is:

(a) selected from an optionally substituted C_{1-6} aliphatic group, and $-OR$;



(c) taken together with R^4 and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 ;

(d) taken together with R^5 and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 ; or

(e) taken together with R'' and their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the nitrogen of L^3 , independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 .

Ring B is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R⁶ is independently halogen, phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -CN, -NO₂, -NHR, -N(R)₂, -OR, -C(O)R, -C(O)OR, or an optionally substituted C₁₋₆ aliphatic group; or:

two R⁶ on the same carbon are optionally taken together to form =O;

an R⁶ group and R' group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur;

an R⁶ group and R³ group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated spiro-fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen or sulfur; or

an R⁶ group and R'' group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur;

Ring C is phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

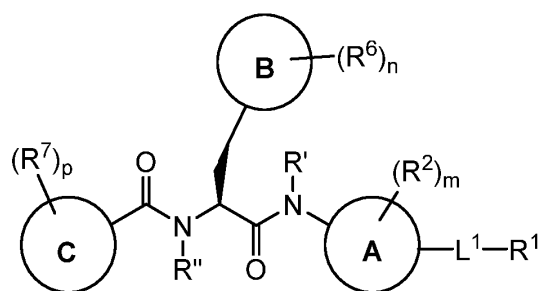
each R⁷ is independently halogen, -CN, -NO₂, -NHR, -N(R)₂, -OR, or an optionally substituted C₁₋₆ aliphatic group; or

two R⁷ on the same carbon are optionally taken together to form =O;

each of m, n, and p is independently 0, 1, 2, 3 or 4;

wherein at least one of L^2 and L^3 is a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

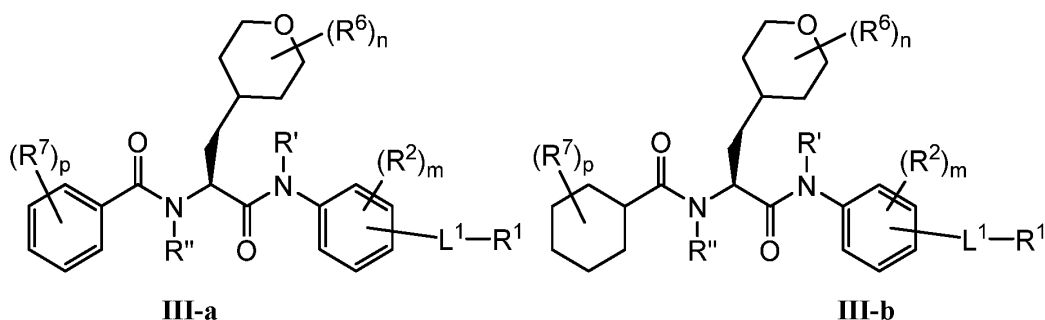
[00161] In certain embodiments, the present invention provides a compound of formula **I**, wherein L^2 is $-C(O)N(R')$, L^3 is $-C(O)N(R'')$, Z is $-\text{Ring B}-(R^6)_n$ and R^3 , R^4 , and R^5 are each hydrogen, thereby forming a compound of formula **II**:

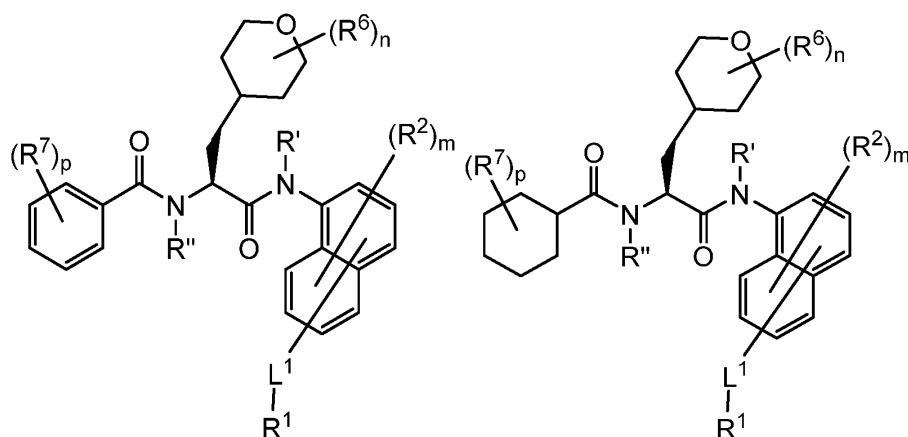


II

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, Ring B, Ring C, L^1 , R^1 , R^2 , R^6 , R^7 , R' , R'' , m, n, and p, is as defined above and described in embodiments herein, both singly and in combination.

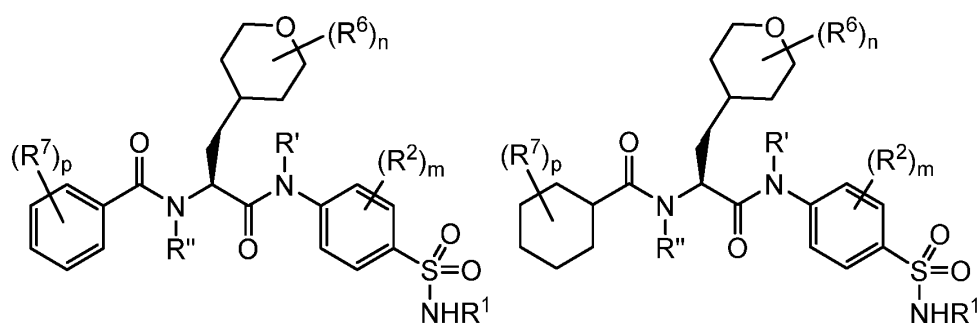
[00162] In certain embodiments, the present invention provides a compound of formula **II**, wherein Ring A is phenyl, Ring B is tetrahydropyran, and Ring C is phenyl; Ring A is phenyl, Ring B is tetrahydropyran, and Ring C is cyclohexyl; Ring A is naphthyl, Ring B is tetrahydropyran, and Ring C is phenyl; or Ring A is naphthyl, Ring B is tetrahydropyran, and Ring C is cyclohexyl; thereby forming a compound of formula **III-a**, **III-b**, **III-c**, or **III-d** respectively:

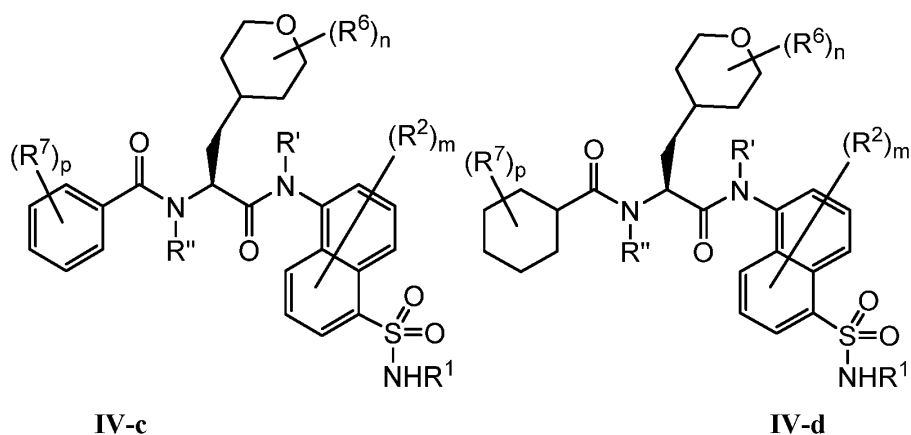


**III-c****III-d**

or a pharmaceutically acceptable salt thereof, wherein each of L^1 , R^1 , R^2 , R^6 , R^7 , R' , R'' , m , n , and p , is as defined above and described in embodiments herein, both singly and in combination.

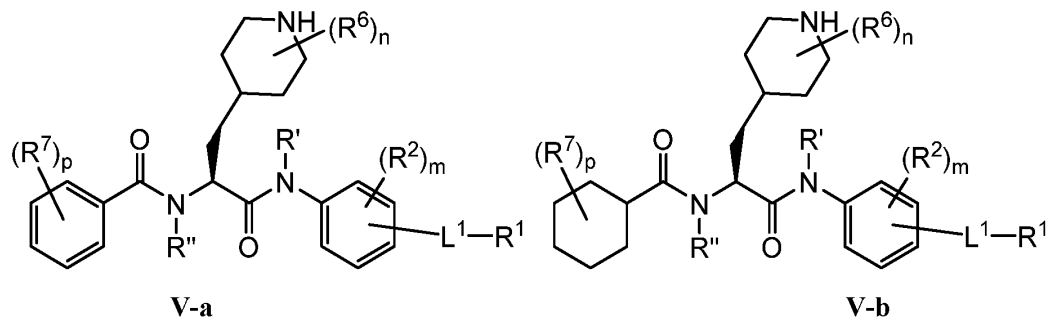
[00163] In certain embodiments, the present invention provides a compound of formulae **III-a**, **III-b**, **III-c**, or **III-d** wherein L^1 are each $-S(O)_2N(R)-$, wherein the R of $-S(O)_2N(R)-$ is hydrogen, thereby forming a compound of formulae **IV-a**, **IV-b**, **IV-c**, and **IV-d** respectively:

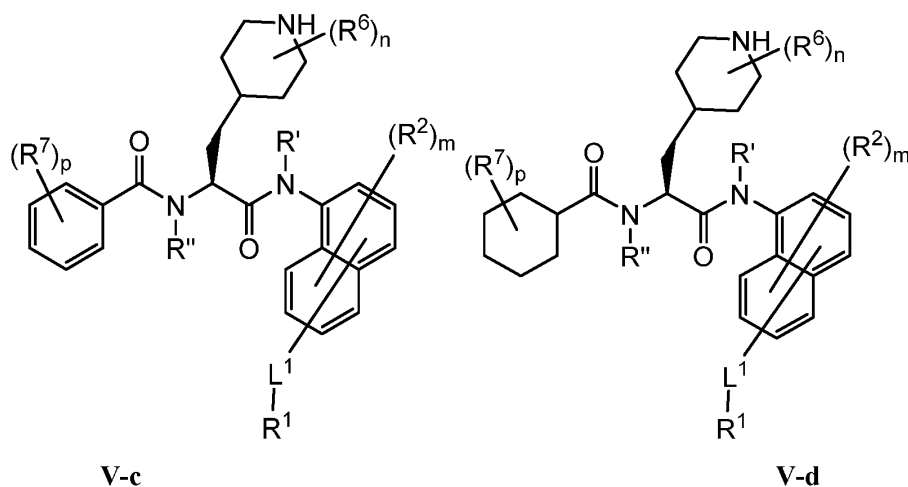
**IV-a****IV-b**



or a pharmaceutically acceptable salt thereof, wherein each of R^1 , R^2 , R^6 , R^7 , R' , R'' , m , n , and p , is as defined above and described in embodiments herein, both singly and in combination.

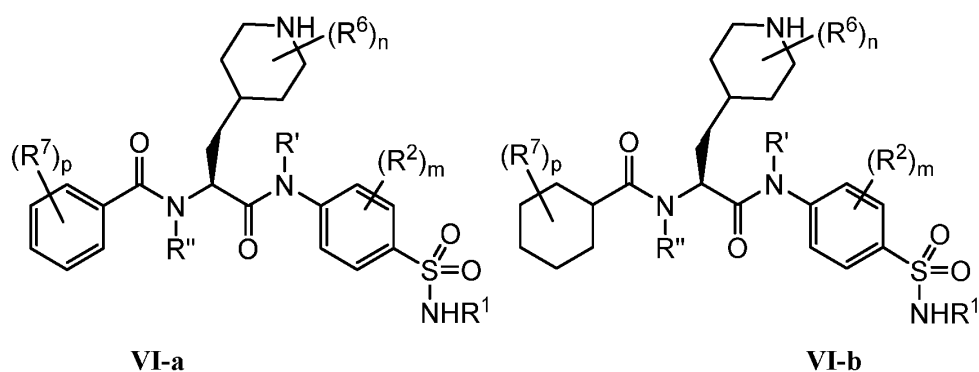
[00164] In certain embodiments, the present invention provides a compound of formula **II**, wherein Ring A is phenyl, Ring B is piperidine, and Ring C is phenyl; Ring A is phenyl, Ring B is piperidine, and Ring C is cyclohexyl; Ring A is naphthyl, Ring B is piperidine, and Ring C is phenyl; or Ring A is naphthyl, Ring B is piperidine, and Ring C is cyclohexyl; thereby forming a compound of formula **V-a**, **V-b**, **V-c**, or **V-d** respectively:

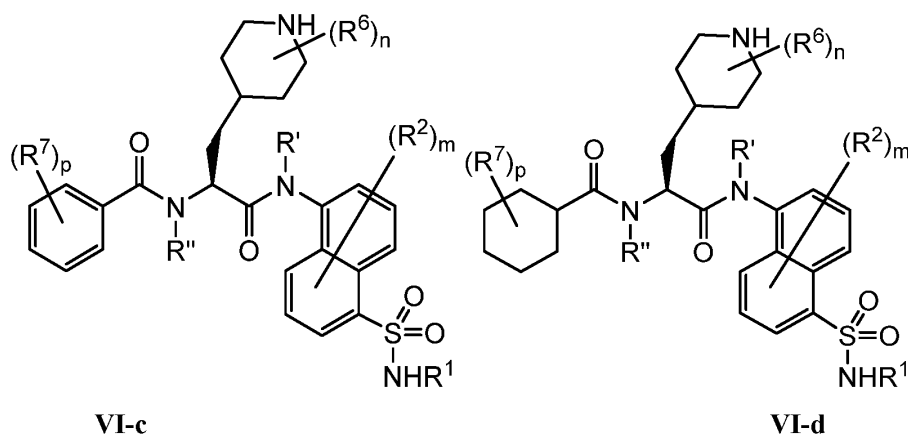




or a pharmaceutically acceptable salt thereof, wherein each of L^1 , R^1 , R^2 , R^6 , R^7 , R' , R'' , m , n , and p , is as defined above and described in embodiments herein, both singly and in combination.

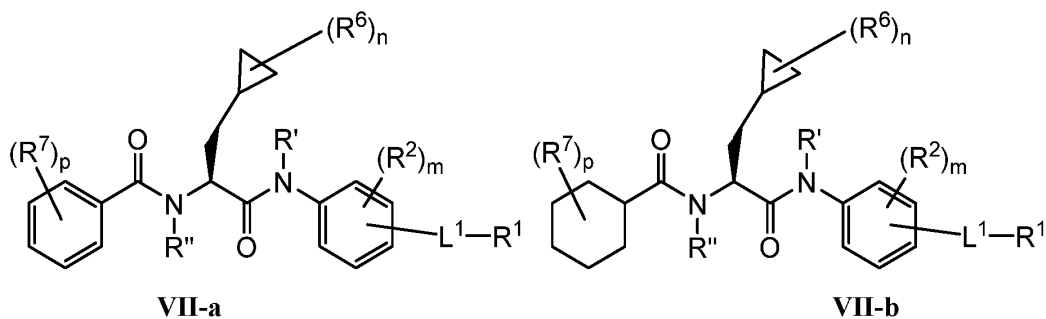
[00165] In certain embodiments, the present invention provides a compound of formulae **V-a**, **V-b**, **V-c**, or **V-d** wherein L^1 are each $-S(O)_2N(R)-$, wherein the R of $-S(O)_2N(R)-$ is hydrogen, thereby forming a compound of formulae **VI-a**, **VI-b**, **VI-c**, and **VI-d** respectively:

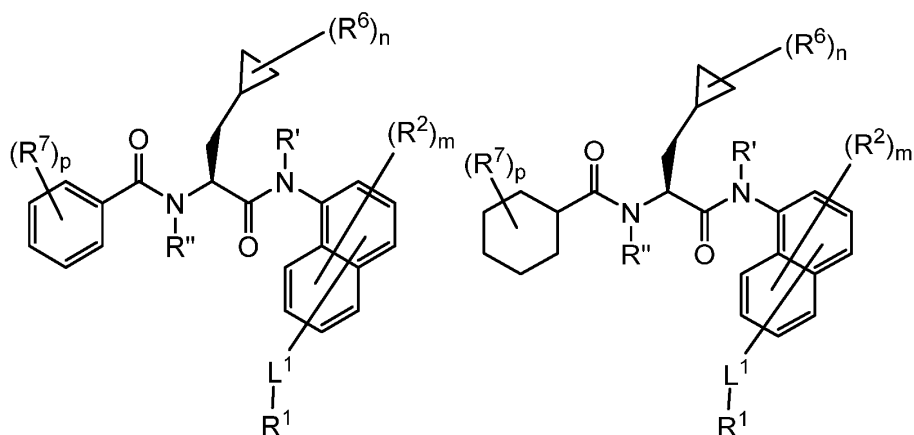




or a pharmaceutically acceptable salt thereof, wherein each of R^1 , R^2 , R^6 , R^7 , R' , R'' , m , n , and p , is as defined above and described in embodiments herein, both singly and in combination.

[00166] In certain embodiments, the present invention provides a compound of formula **II**, wherein Ring A is phenyl, Ring B is cyclopropyl, and Ring C is phenyl; Ring A is phenyl, Ring B is cyclopropyl, and Ring C is cyclohexyl; Ring A is naphthyl, Ring B is cyclopropyl, and Ring C is phenyl; or Ring A is naphthyl, Ring B is cyclopropyl, and Ring C is cyclohexyl; thereby forming a compound of formula **VII-a**, **VII-b**, **VII-c**, or **VII-d** respectively:



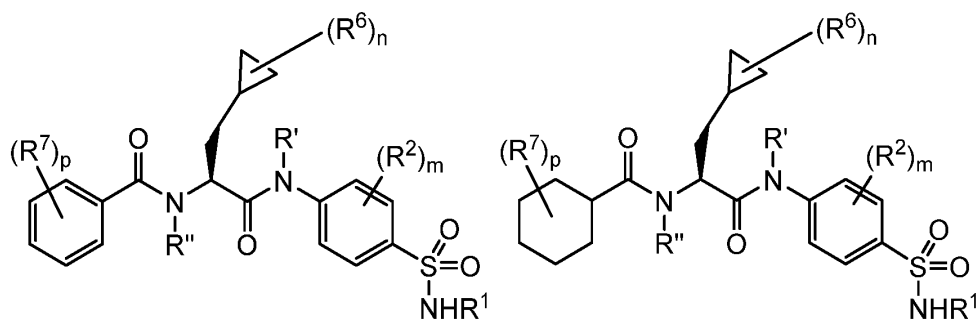


VII-c

VII-d

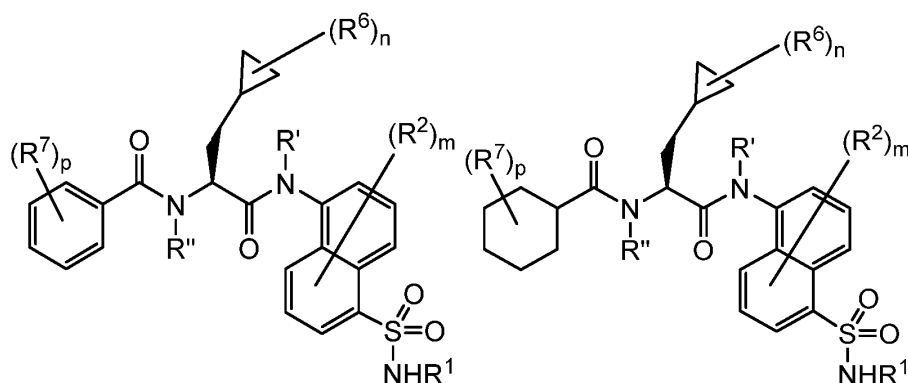
or a pharmaceutically acceptable salt thereof, wherein each of L^1 , R^1 , R^2 , R^6 , R^7 , R' , R'' , m , n , and p , is as defined above and described in embodiments herein, both singly and in combination.

[00167] In certain embodiments, the present invention provides a compound of formulae **VII-a**, **VII-b**, **VII-c**, or **VII-d** wherein L^1 are each $-S(O)_2N(R)-$, wherein the R of $-S(O)_2N(R)-$ is hydrogen, thereby forming a compound of formulae **VIII-a**, **VIII-b**, **VIII-c**, and **VIII-d** respectively:



VIII-a

VIII-b

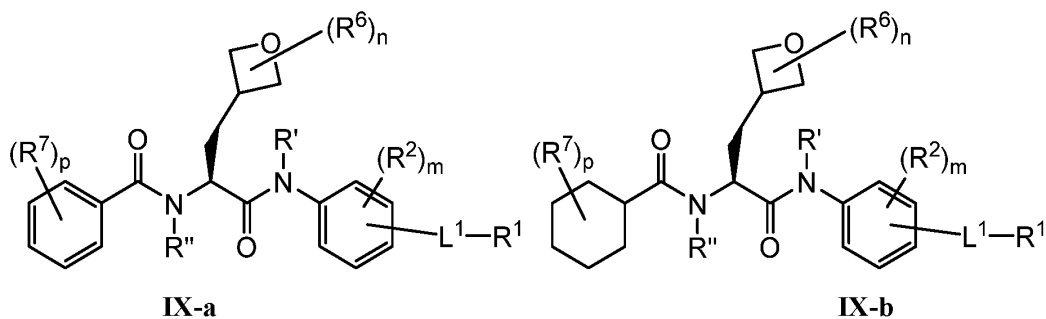


VIII-c

VIII-d

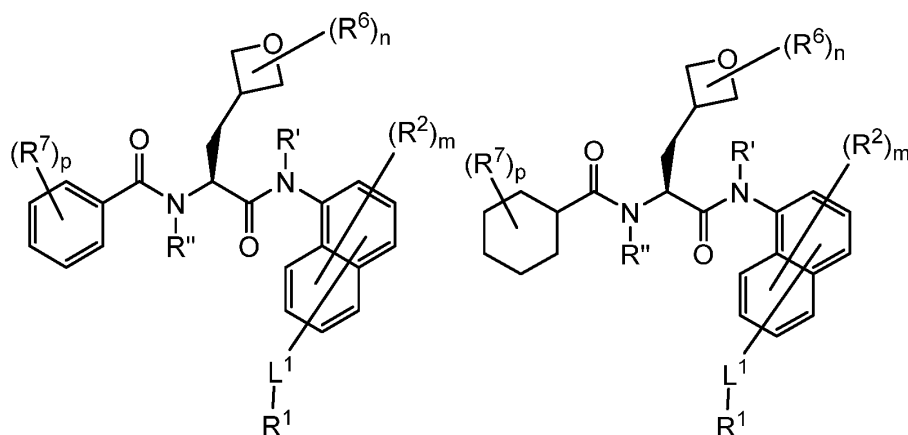
or a pharmaceutically acceptable salt thereof, wherein each of R^1 , R^2 , R^6 , R^7 , R' , R'' , m , n , and p , is as defined above and described in embodiments herein, both singly and in combination.

[00168] In certain embodiments, the present invention provides a compound of formula **II**, wherein Ring A is phenyl, Ring B is oxetanyl, and Ring C is phenyl; Ring A is phenyl, Ring B is oxetanyl, and Ring C is cyclohexyl; Ring A is naphthyl, Ring B is oxetanyl, and Ring C is phenyl; or Ring A is naphthyl, Ring B is oxetanyl, and Ring C is cyclohexyl; thereby forming a compound of formula **IX-a**, **IX-b**, **IX-c**, or **IX-d** respectively:



IX-a

IX-b

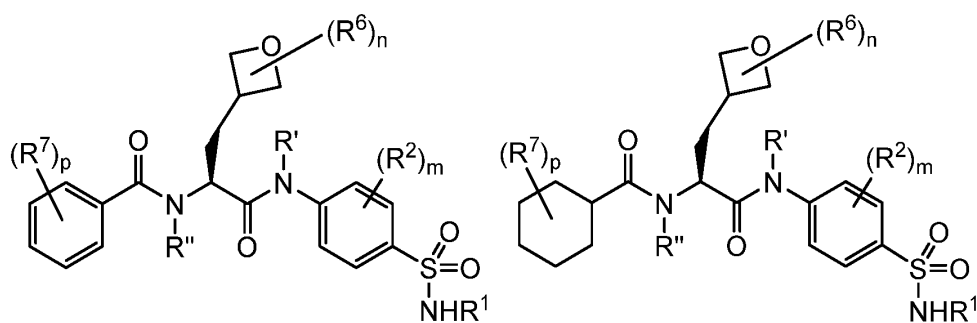


IX-c

IX-d

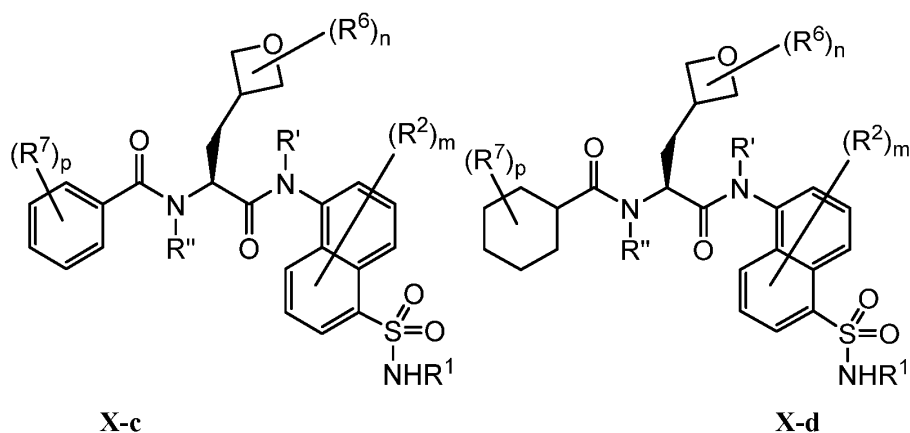
or a pharmaceutically acceptable salt thereof, wherein each of L^1 , R^1 , R^2 , R^6 , R^7 , R' , R'' , m , n , and p , is as defined above and described in embodiments herein, both singly and in combination.

[00169] In certain embodiments, the present invention provides a compound of formulae **IX-a**, **IX-b**, **IX-c**, or **IX-d** wherein L^1 are each $-S(O)_2N(R)-$, wherein the R of $-S(O)_2N(R)-$ is hydrogen, thereby forming a compound of formulae **X-a**, **X-b**, **X-c**, and **X-d** respectively:



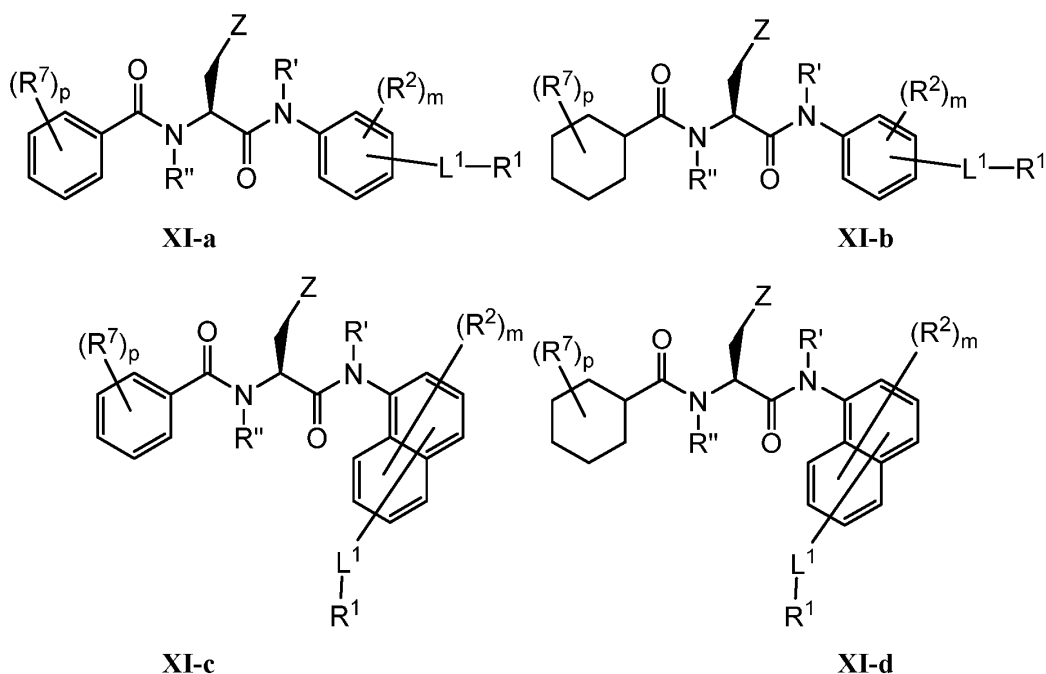
X-a

X-b



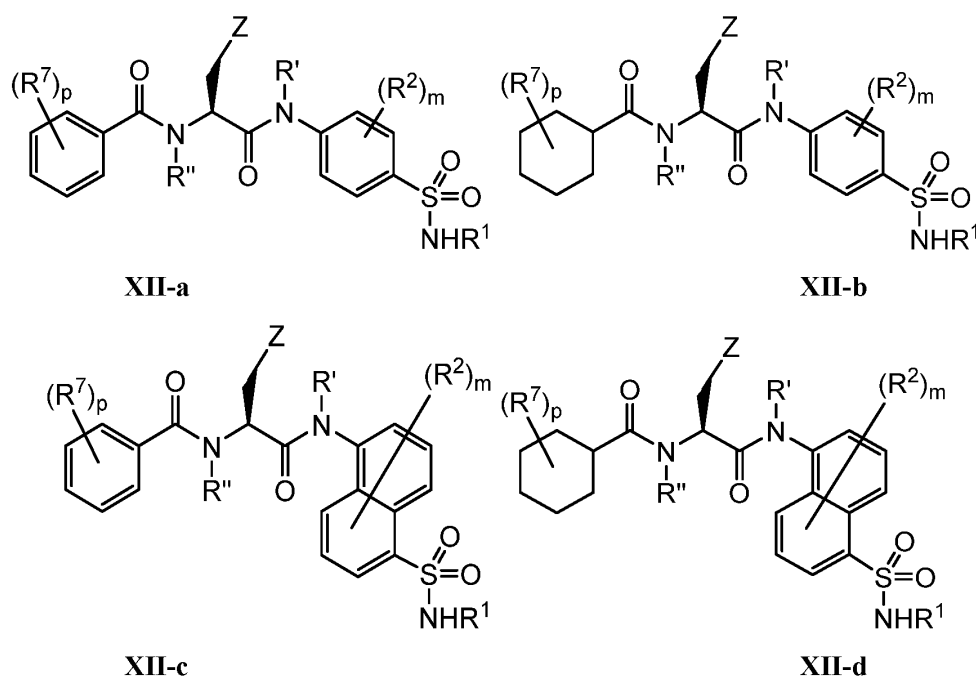
or a pharmaceutically acceptable salt thereof, wherein each of R^1 , R^2 , R^6 , R^7 , R' , R'' , m , n , and p , is as defined above and described in embodiments herein, both singly and in combination.

[00170] In certain embodiments, the present invention provides a compound of formula **I**, wherein L^2 is $-C(O)N(R')$, L^3 is $-C(O)N(R'')$, R^3 , R^4 , and R^5 are each hydrogen, and: Ring A is phenyl, and Ring C is phenyl; Ring A is phenyl, and Ring C is cyclohexyl; Ring A is naphthyl, and Ring C is phenyl; or Ring A is naphthyl, and Ring C is cyclohexyl; thereby forming a compound of formula **XI-a**, **XI-b**, **XI-c**, or **XI-d** respectively:



or a pharmaceutically acceptable salt thereof, wherein each of Z, L^1 , R^1 , R^2 , R^6 , R^7 , R' , R'' , m, n and p, is as defined above and described in embodiments herein, both singly and in combination.

[00171] In certain embodiments, the present invention provides a compound of formulae **XI-a**, **XI-b**, **XI-c**, or **XI-d** wherein L^1 are each $-S(O)_2N(R)-$, wherein the R of $-S(O)_2N(R)-$ is hydrogen, thereby forming a compound of formulae **XII-a**, **XII-b**, **XII-c**, and **XII-d** respectively:

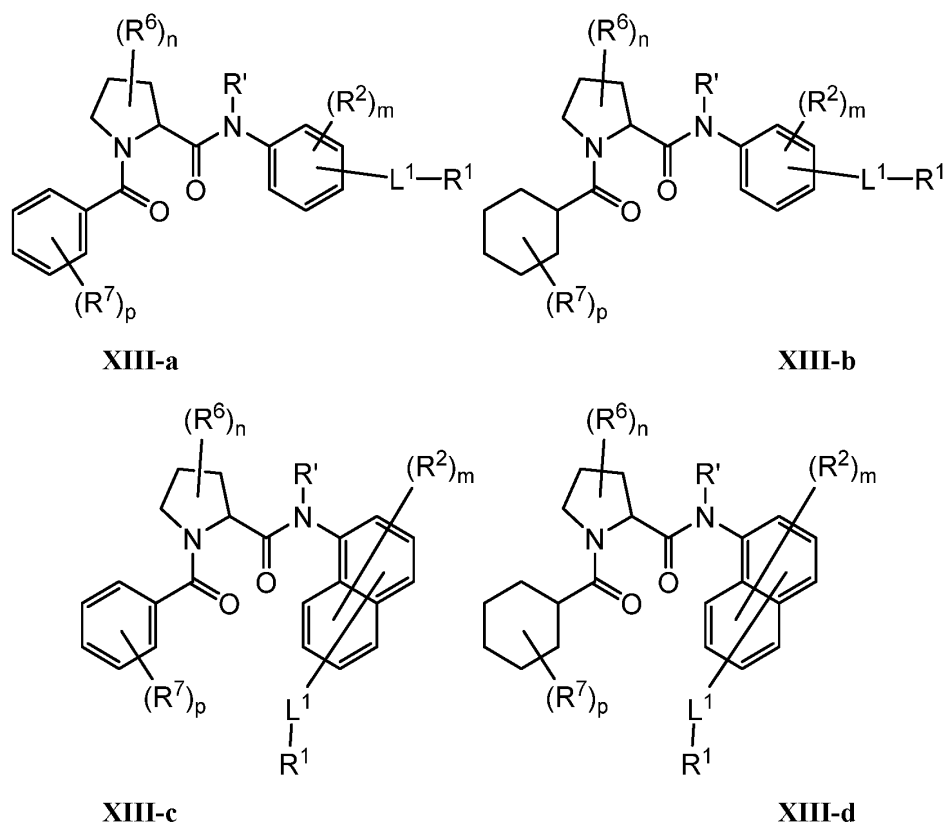


or a pharmaceutically acceptable salt thereof, wherein each of Z, R^1 , R^2 , R^6 , R^7 , R' , R'' , m, n, and p, is as defined above and described in embodiments herein, both singly and in combination.

[00172] In certain embodiments, the invention provides a compound of any one of formulae **XI-a**, **XI-b**, **XI-c**, **XI-d**, **XII-a**, **XII-b**, **XII-c**, and **XII-d**, wherein Z is $-OR$. In certain embodiments, the invention provides a compound of any one of formulae **XI-a**, **XI-b**, **XI-c**, **XI-d**, **XII-a**, **XII-b**, **XII-c**, and **XII-d**, wherein Z is an optionally substituted C_{1-6} aliphatic group.

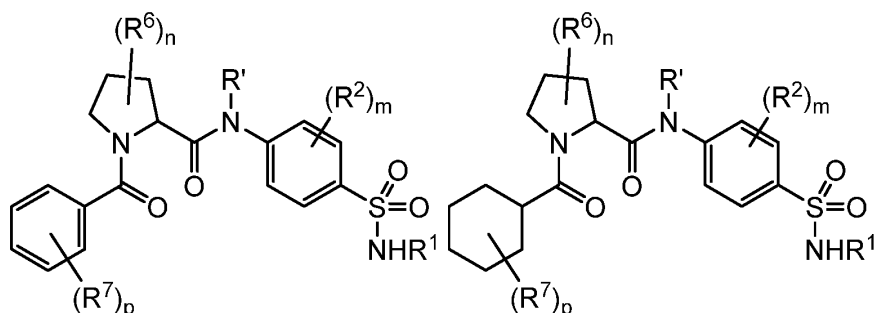
[00173] In certain embodiments, the present invention provides a compound of formula **I**, wherein L^2 is $-C(O)N(R')$, L^3 is $-C(O)N(R'')$, R^3 , R^4 , and R^5 are each hydrogen, Z is taken together with R'' and their intervening atoms to form a 5 membered saturated ring, optionally substituted with n instances of R^6 , and: Ring A is phenyl, and Ring C is phenyl; Ring A is

phenyl, and Ring C is cyclohexyl; Ring A is naphthyl, and Ring C is phenyl; or Ring A is naphthyl, and Ring C is cyclohexyl; thereby forming a compound of formula **XIII-a**, **XIII-b**, **XIII-c**, or **XIII-d** respectively:



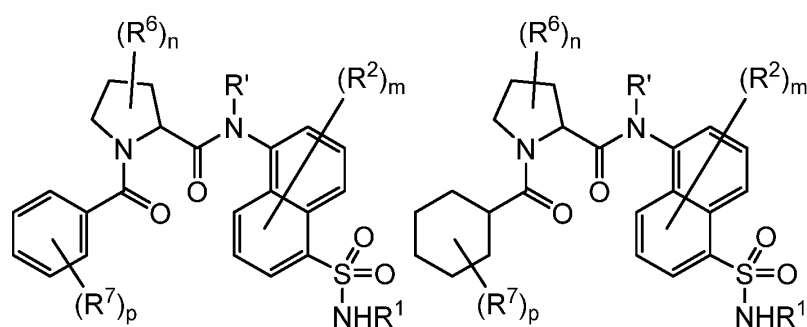
or a pharmaceutically acceptable salt thereof, wherein each of Z, L¹, R¹, R², R⁶, R⁷, R', m, n and p, is as defined above and described in embodiments herein, both singly and in combination.

[00174] In certain embodiments, the present invention provides a compound of formulae **XIII-a**, **XIII-b**, **XIII-c**, or **XIII-d** wherein L¹ are each –S(O)₂N(R)–, wherein the R of –S(O)₂N(R)– is hydrogen, thereby forming a compound of formulae **XIV-a**, **XIV-b**, **XIV-c**, and **XIV-d** respectively:



XIV-a

XIV-b

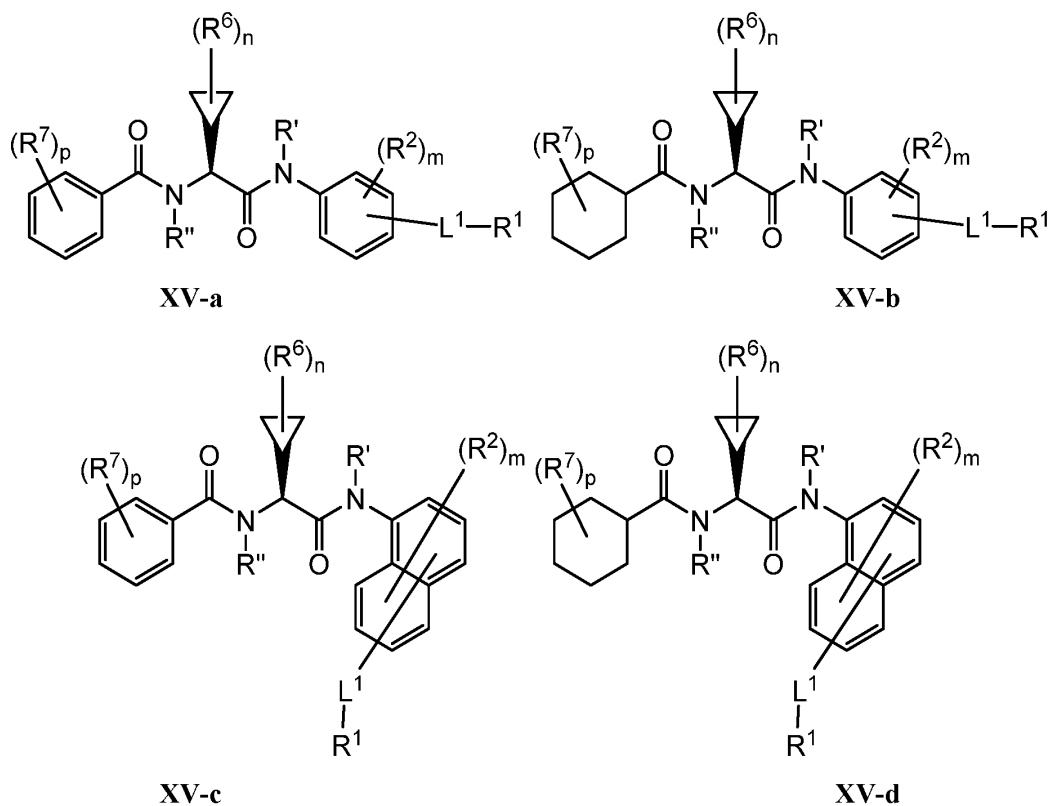


XIV-c

XIV-d

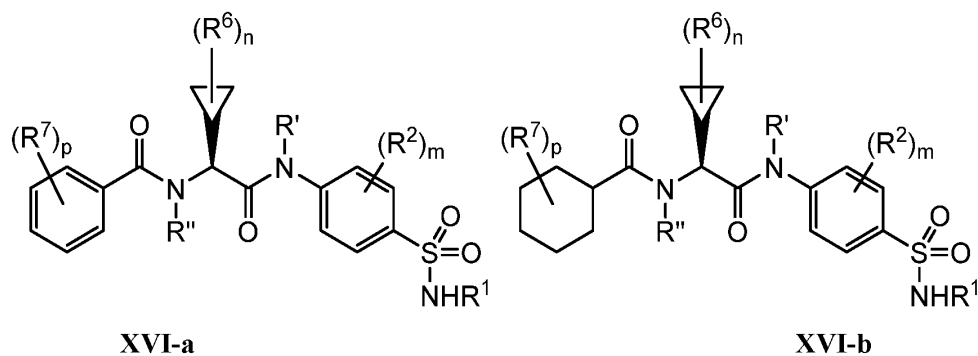
or a pharmaceutically acceptable salt thereof, wherein each of R^1 , R^2 , R^6 , R^7 , R' , m , n , and p , is as defined above and described in embodiments herein, both singly and in combination.

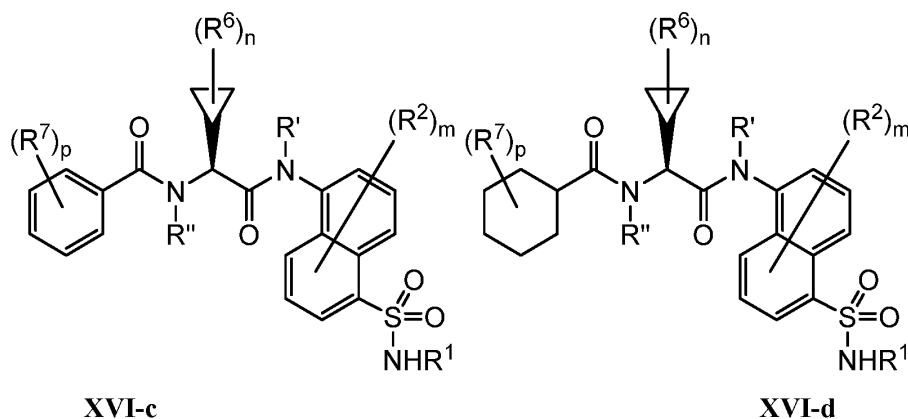
[00175] In certain embodiments, the present invention provides a compound of formula **I**, wherein L^2 is $-C(O)N(R')$, L^3 is $-C(O)N(R'')$, R^3 is hydrogen, one of R^4 and R^5 is hydrogen, and the other is taken together with Z and the intervening carbon atom to form a cyclopropyl group optionally substituted with n instances of R^6 , and: Ring A is phenyl, and Ring C is phenyl; Ring A is phenyl, and Ring C is cyclohexyl; Ring A is naphthyl, and Ring C is phenyl; or Ring A is naphthyl, and Ring C is cyclohexyl; thereby forming a compound of formula **XV-a**, **XV-b**, **XV-c**, or **XV-d** respectively:



or a pharmaceutically acceptable salt thereof, wherein each of L^1 , R^1 , R^2 , R^6 , R^7 , R' , R'' , m , n and p , is as defined above and described in embodiments herein, both singly and in combination.

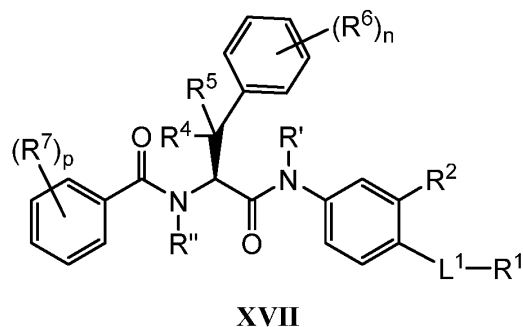
[00176] In certain embodiments, the present invention provides a compound of formulae **XV-a**, **XV-b**, **XV-c**, or **XV-d** wherein L^1 are each $-S(O)_2N(R)-$, wherein the R of $-S(O)_2N(R)-$ is hydrogen, thereby forming a compound of formulae **XVI-a**, **XVI-b**, **XVI-c**, and **XVI-d** respectively:





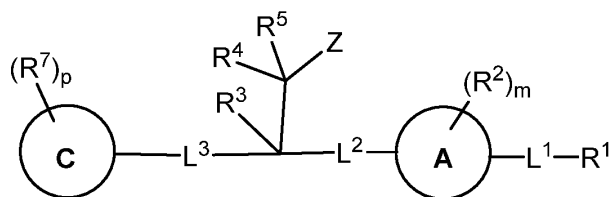
or a pharmaceutically acceptable salt thereof, wherein each of R^1 , R^2 , R^6 , R^7 , R' , R'' , m , n , and p , is as defined above and described in embodiments herein, both singly and in combination.

[00177] In certain embodiments, the present invention provides a compound of formula **I**, wherein L^2 is $-C(O)N(R')$, L^3 is $-C(O)N(R'')$, Z is $-\text{Ring B}-(R^6)_n$, wherein Ring B is phenyl, R^3 is hydrogen, Ring A is phenyl and Ring C is phenyl substituted at the 3-position by R^2 and substituted at the 4-position by L^1-R^1 thereby forming a compound of formula **XVII**:



or a pharmaceutically acceptable salt thereof, wherein each of L^1 , R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R' , R'' , n , and p , is as defined above and described in embodiments herein, both singly and in combination.

[00178] In certain embodiments, the present invention provides a compound of formula XVIII:



XVIII

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

L¹ is a covalent bond or a C₁₋₃ bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -C(CF₃)H-, -N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)N(R)-, -N(R)C(O)-, -S(O)-, -S(O)₂-, -S(O)N(R)-, -S(O)₂N(R)-, or -S(O)(R)=N-;

each R is independently hydrogen or an optionally substituted C₁₋₃ aliphatic group; or:

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur; or

an R group and R¹ on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;

R¹ is hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from

nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^2 is independently halogen, $-CF_3$, $-CN$, $-C(O)NHR$, $-NO_2$, $-NHR$, $-NHC(O)R$, $-NHS(O)_2R$, $-N(R)_2$, or $-OR$, or an optionally substituted C_{1-6} aliphatic group; or

two R^2 on the same carbon are optionally taken together to form $=O$;

L^2 is selected from the group consisting of $-C(O)N(R')$, $-CH_2O-$, $-CH_2N(R')$, $-C(OH)(H)CH_2N(R')$, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R' is hydrogen or a C_{1-3} aliphatic group;

L^3 is selected from the group consisting of $-C(O)N(R'')$, $-OC(O)N(R'')$, $-CH_2O-$, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R'' is hydrogen or a C_{1-3} aliphatic group;

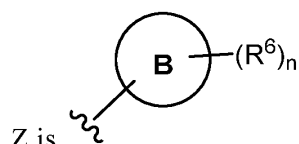
R^3 is hydrogen or C_{1-3} aliphatic; or:

R^3 and R^4 are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring; or

R^3 and R^5 are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring;

R^4 is hydrogen or C_{1-3} aliphatic;

R^5 is hydrogen or C_{1-3} aliphatic;



, wherein Ring B is a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein Ring B is substituted with one occurrence of R^z , wherein R^z is a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein the 5-6 membered heteroaryl ring is substituted with 1 or 2 substituents independently select from halogen, $-CN$, $-NHR$, $-N(R)_2$, $-OR$, or a C_{1-6} aliphatic group;

each R^6 is independently halogen, $-CN$, $-NO_2$, $-NHR$, $-N(R)_2$, $-OR$, $-C(O)R$, $-C(O)OR$, or an optionally substituted C_{1-6} aliphatic group; or:

two R^6 on the same carbon are optionally taken together to form $=O$;

an R^6 group and R^7 group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur;

an R^6 group and R^3 group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated spiro-fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen or sulfur; or

an R^6 group and R^8 group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur;

Ring C is phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

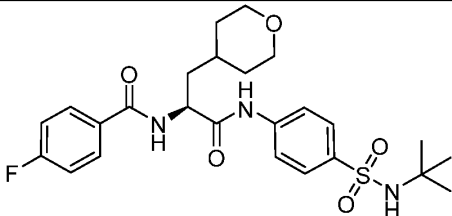
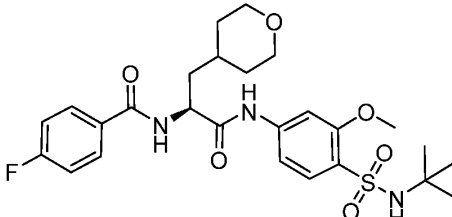
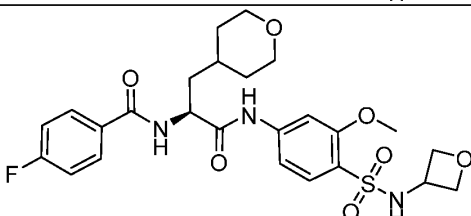
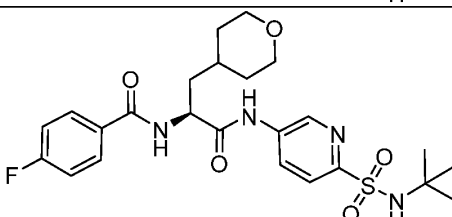
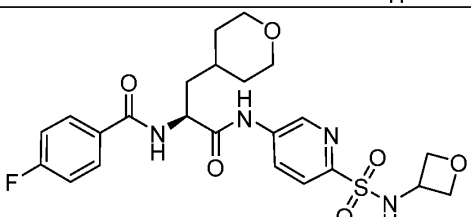
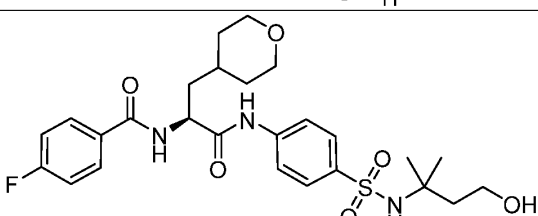
each R^7 is independently halogen, $-CN$, $-NO_2$, $-NHR$, $-N(R)_2$, $-OR$, or an optionally substituted C_{1-6} aliphatic group; or

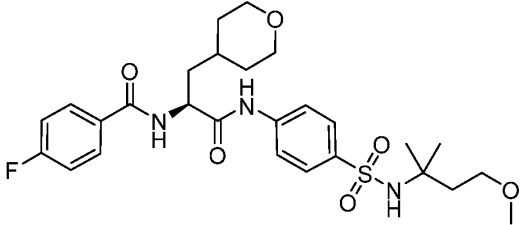
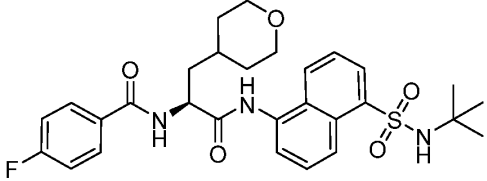
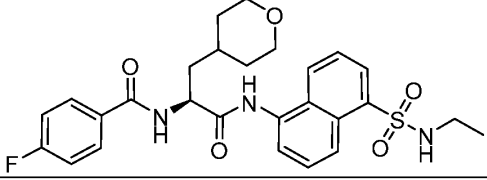
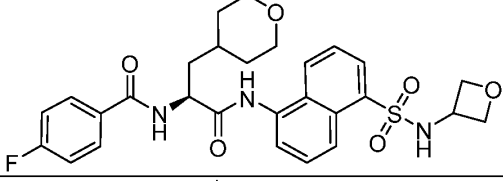
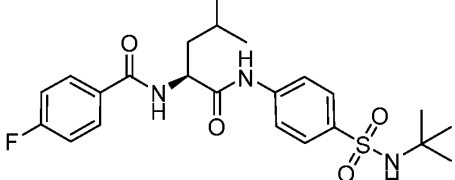
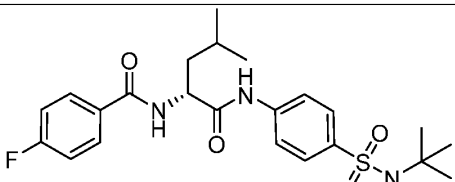
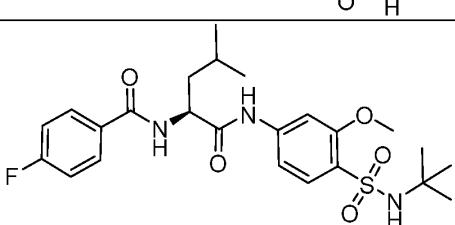
two R^7 on the same carbon are optionally taken together to form $=O$;

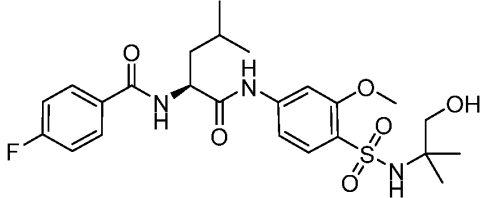
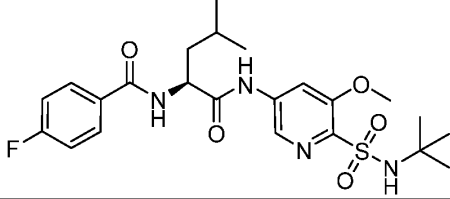
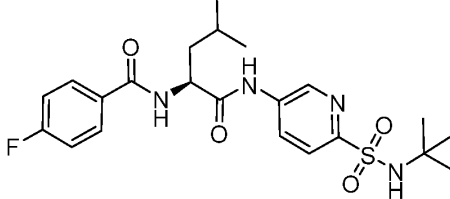
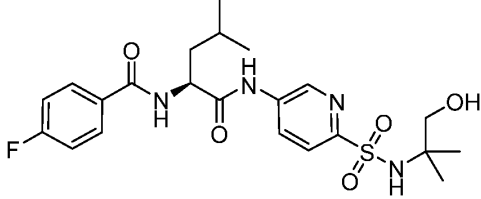
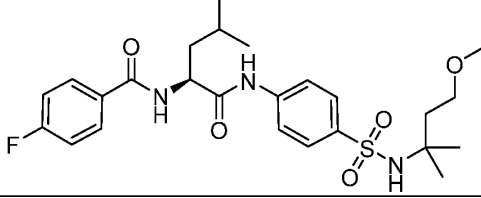
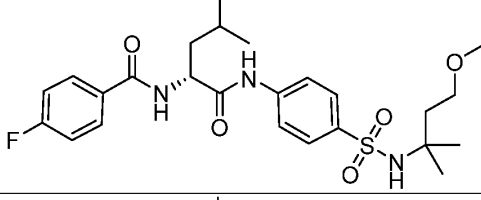
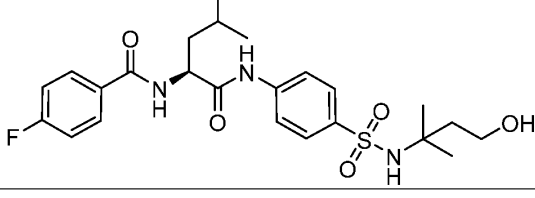
each of m, n, and p is independently 0, 1, 2, 3 or 4.

[00179] Exemplary compounds of the invention are set forth in **Table 1**, below. Additionally exemplary compounds of the invention are set forth in **Table 11** and **Table 12** below in the Examples.

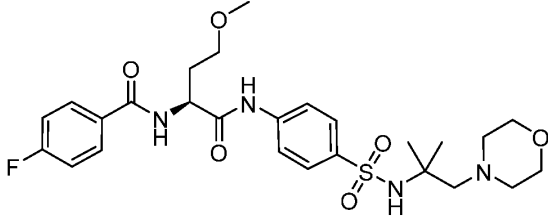
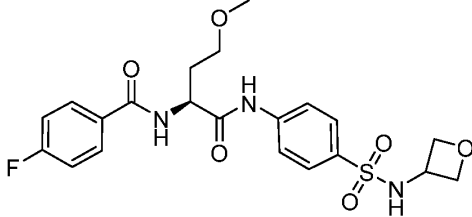
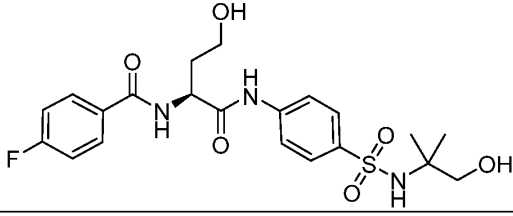
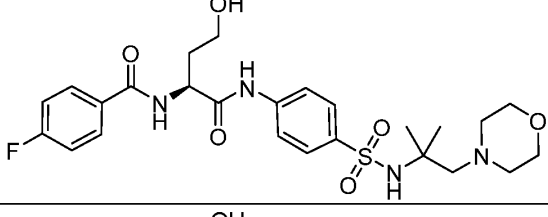
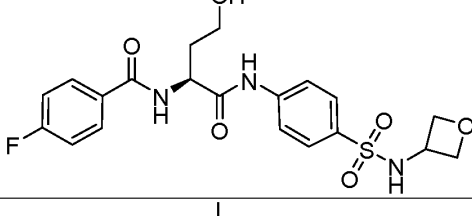
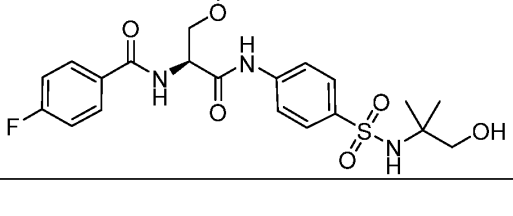
Table 1. Exemplary Compounds

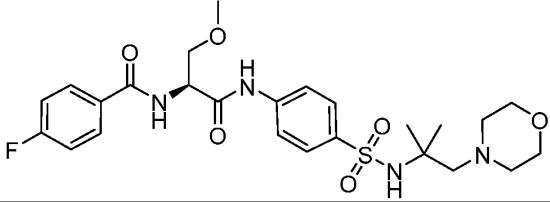
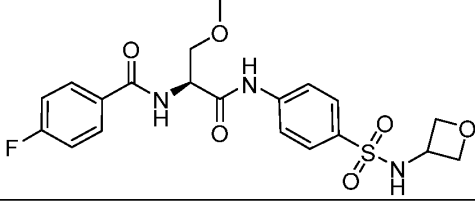
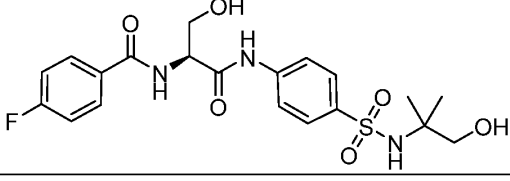
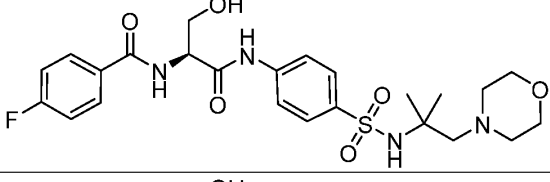
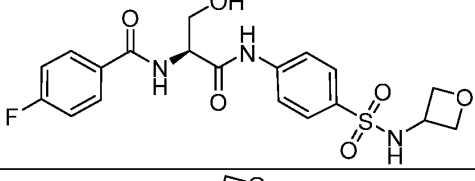
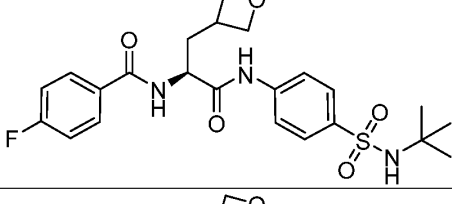
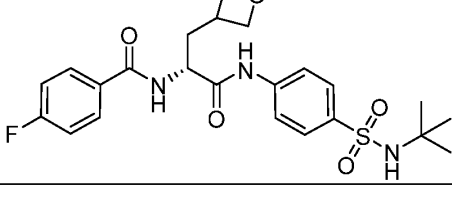
Compound No.	Structure
I-1	
I-2	
I-3	
I-4	
I-5	
I-6	

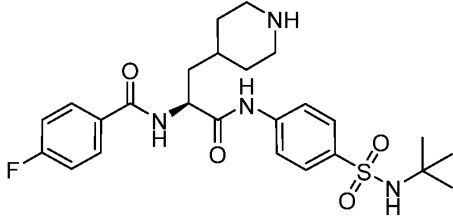
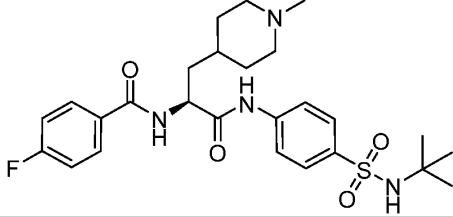
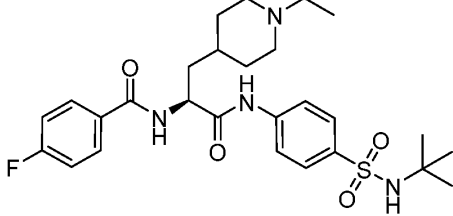
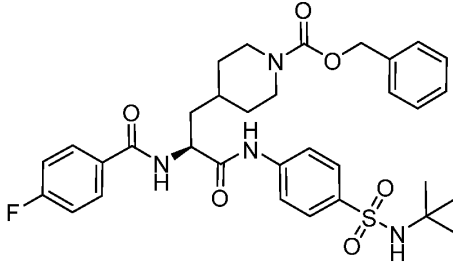
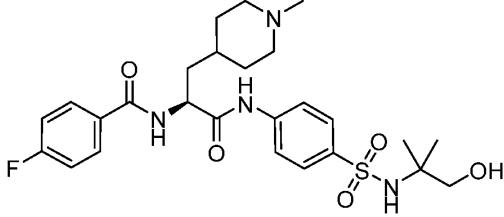
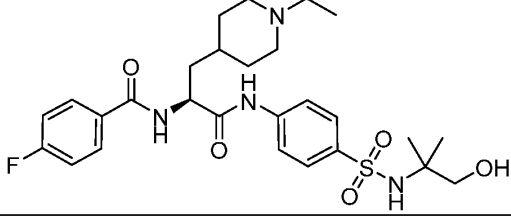
Compound No.	Structure
I-7	
I-8	
I-9	
I-10	
I-11	
I-12	
I-13	

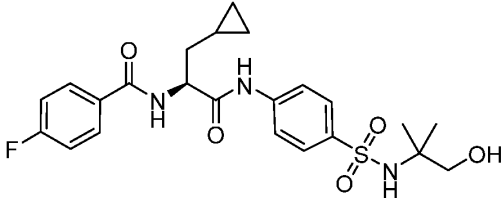
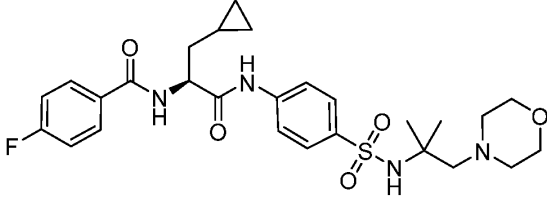
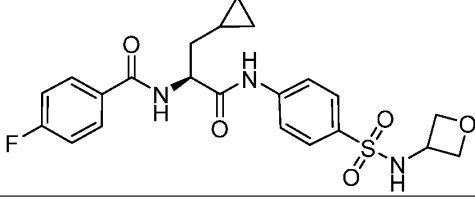
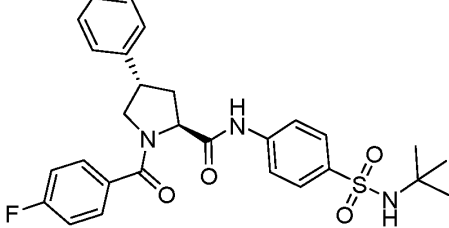
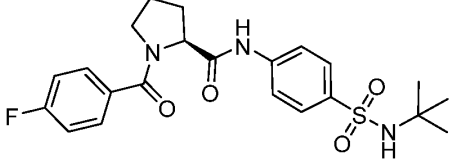
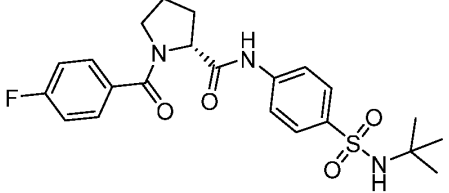
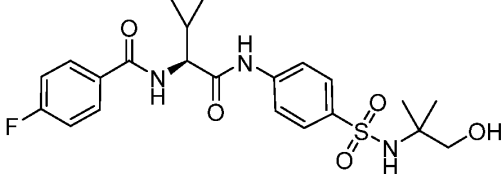
Compound No.	Structure
I-14	
I-15	
I-16	
I-17	
I-18	
I-19	
I-20	

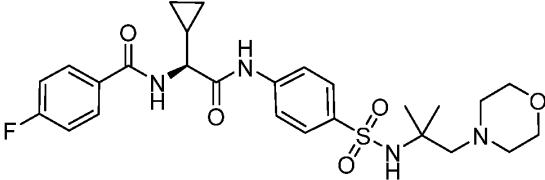
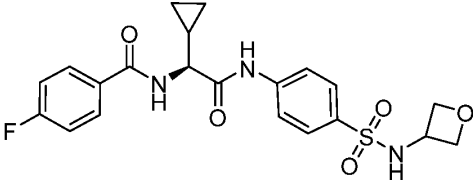
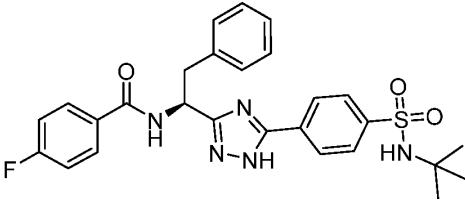
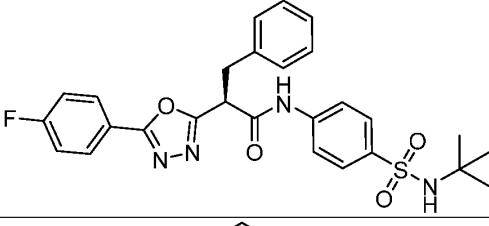
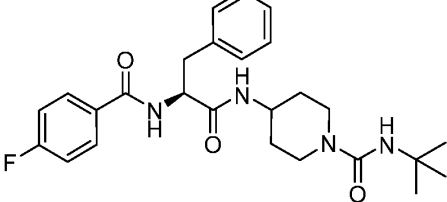
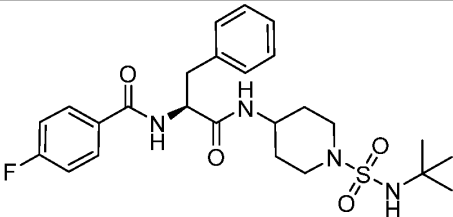
Compound No.	Structure
I-21	 <chem>CC1(C)CC(C(=O)N1C(=O)N[C@@H](C)C(=O)Nc2ccc(S(=O)(=O)N[C@@H](C)(C)CO)cc2)c3ccc(F)cc3</chem>
I-22	 <chem>CC1(C)CC(C(=O)N1C(=O)N[C@@H](C)C(=O)Nc2ccc(S(=O)(=O)N[C@@H]3CCOC3)cc2)c3ccc(F)cc3</chem>
I-23	 <chem>CC(C)(C)N[C@@H](C(=O)N[C@@H](C)C(=O)Nc1ccc(S(=O)(=O)N(C)(C)C(C)(C)C)cc1)C(=O)Nc2ccc(F)cc2</chem>
I-24	 <chem>CC(C)(C)N[C@@H](C(=O)N[C@@H](C)C(=O)Nc1ccc(S(=O)(=O)N[C@@H]2CCOC2)cc1)C(=O)Nc3ccc(F)cc3</chem>
I-25	 <chem>CC(C)(C)N[C@@H](C(=O)N[C@@H](C)C(=O)Nc1ccc(S(=O)(=O)N(C)(C)C(C)(C)C)cc1)C(=O)Nc2ccc(F)cc2</chem>
I-26	 <chem>CC(C)(C)N[C@@H](C(=O)N[C@@H](C)C(=O)Nc1ccc(S(=O)(=O)N[C@@H](C)(C)CO)cc1)C(=O)Nc2ccc(F)cc2</chem>

Compound No.	Structure
I-27	
I-28	
I-29	
I-30	
I-31	
I-32	

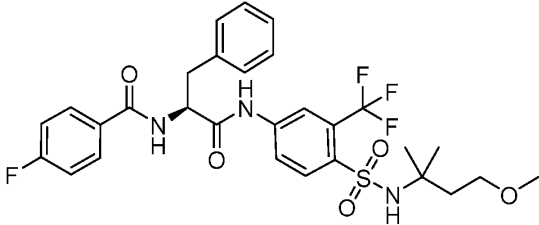
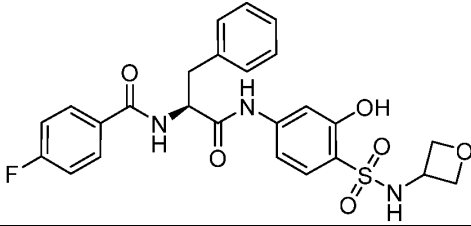
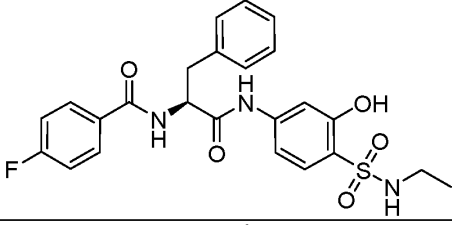
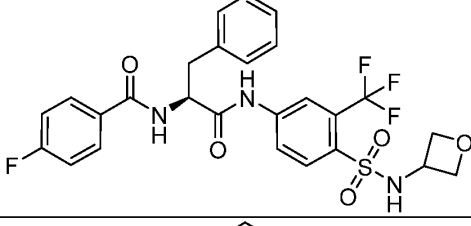
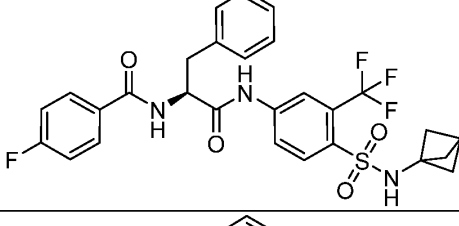
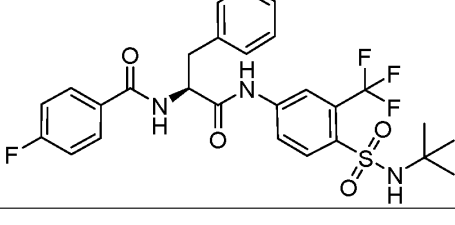
Compound No.	Structure
I-33	
I-34	
I-35	
I-36	
I-37	
I-38	
I-39	

Compound No.	Structure
I-40	
I-41	
I-42	
I-43	
I-44	
I-45	

Compound No.	Structure
I-46	
I-47	
I-48	
I-49	
I-50	
I-51	
I-52	

Compound No.	Structure
I-53	
I-54	
I-55	
I-56	
I-57	
I-58	

Compound No.	Structure
I-59	
I-60	
I-61	
I-62	
I-63	
I-64	

Compound No.	Structure
I-65	
I-66	
I-67	
I-68	
I-69	
I-70	

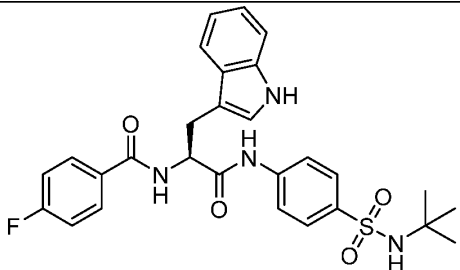
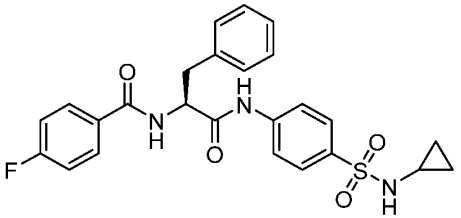
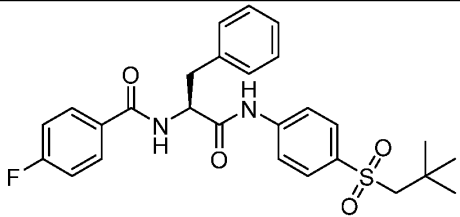
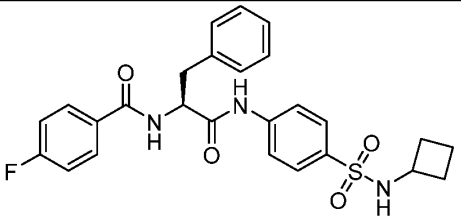
[00180] In some embodiments, the method employs a compound set forth in **Table 1**, above, or a pharmaceutically acceptable salt thereof. In some embodiments, the method employs a compound set forth in **Table 11**, below, or a pharmaceutically acceptable salt thereof. In some embodiments, the method employs a compound set forth in **Table 12**, below, or a pharmaceutically acceptable salt thereof.

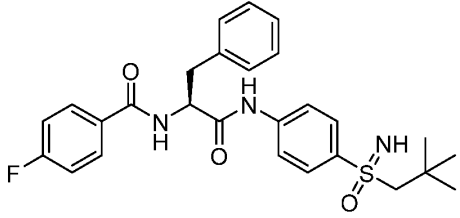
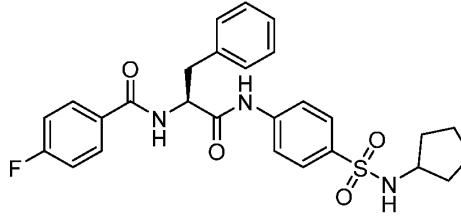
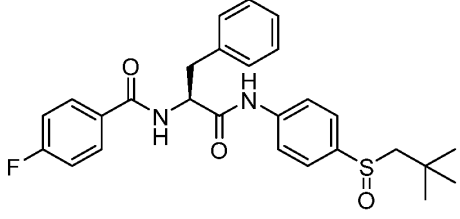
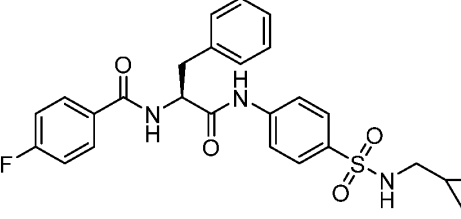
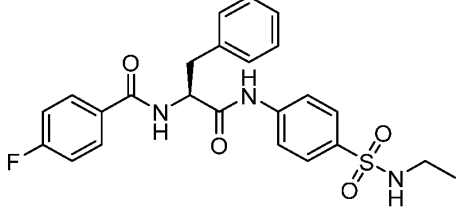
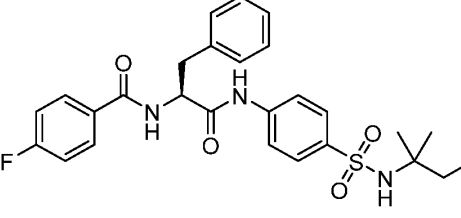
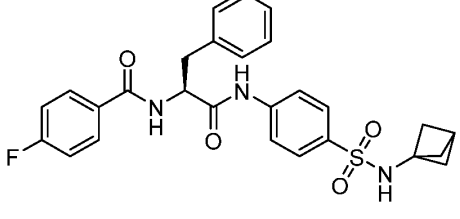
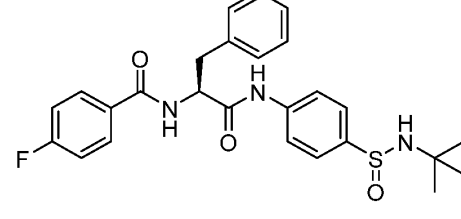
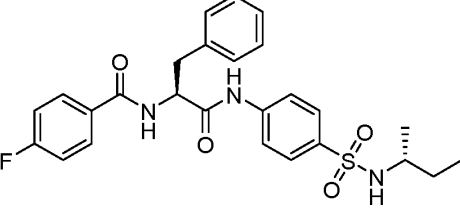
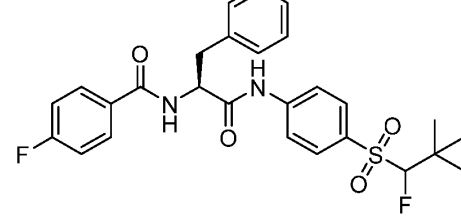
[00181] In certain embodiments, the present invention provides a compound set forth in **Table 11** below. In certain embodiments, the present invention provides a compound set forth in **Table 12** below.

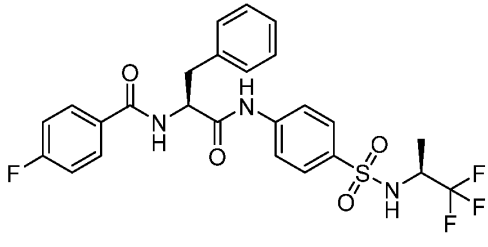
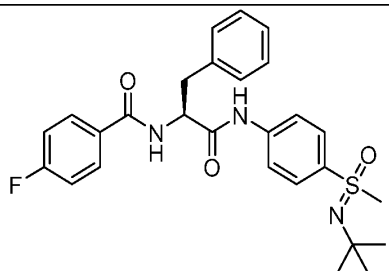
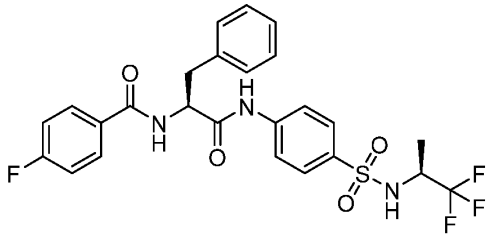
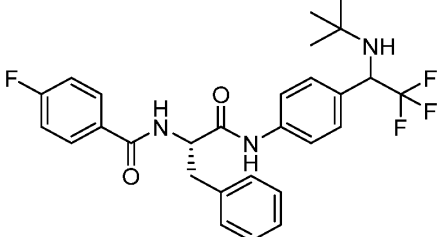
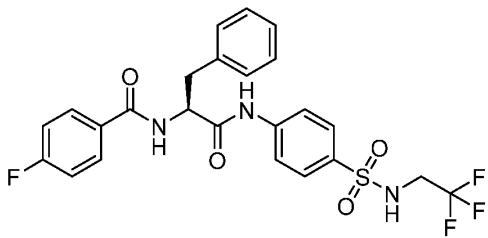
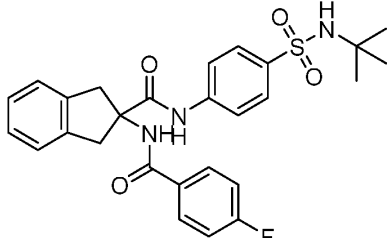
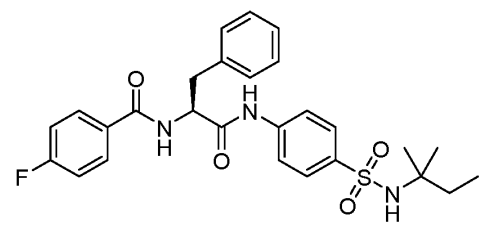
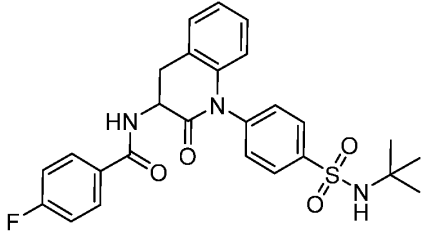
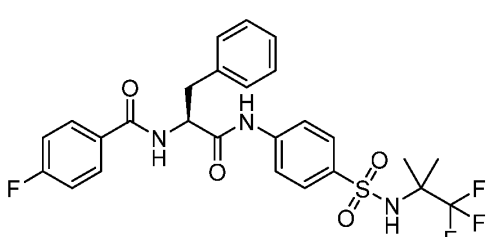
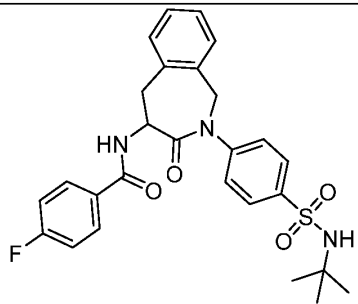
[00182] In certain embodiments, the present invention provides a compound set forth in **Table 1** or a pharmaceutically acceptable salt thereof. In certain embodiments, the present invention provides a compound set forth in **Table 11** or a pharmaceutically acceptable salt thereof. In certain embodiments, the present invention provides a compound set forth in **Table 12** or a pharmaceutically acceptable salt thereof.

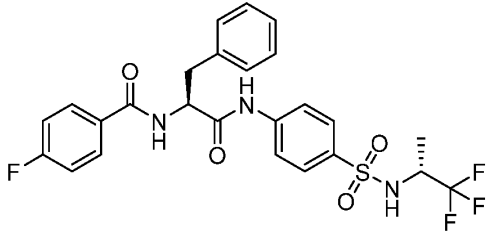
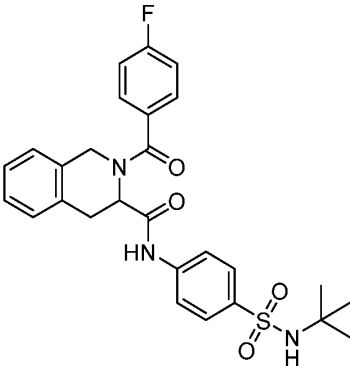
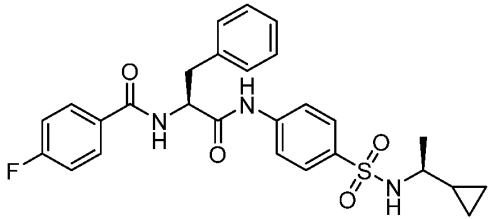
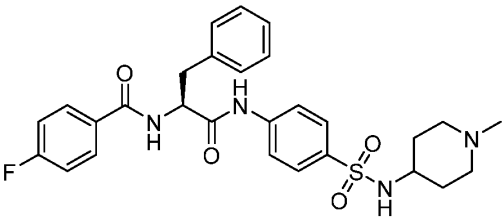
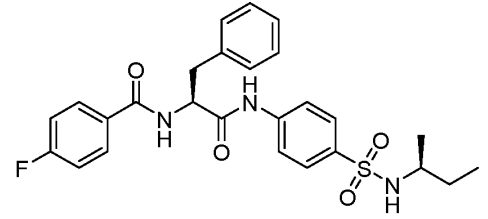
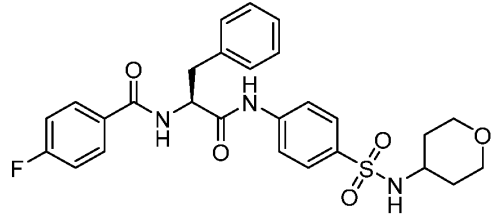
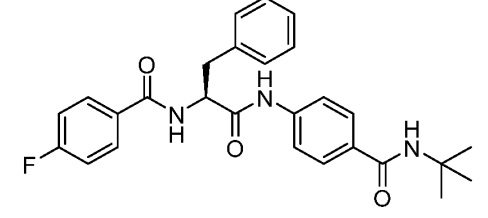
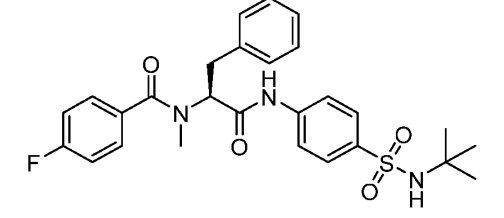
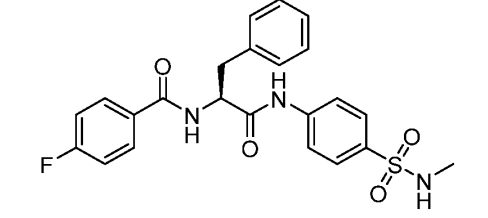
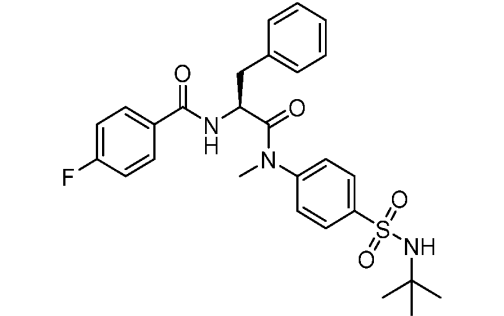
[00183] In certain embodiments, the present invention provides a compound other than one selected from those depicted in **Table 1-X**, below, or a pharmaceutically acceptable salt thereof.

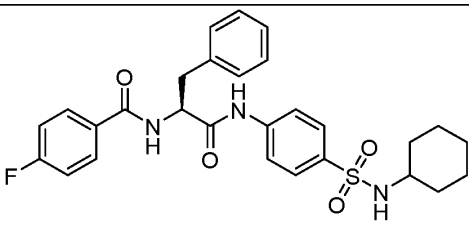
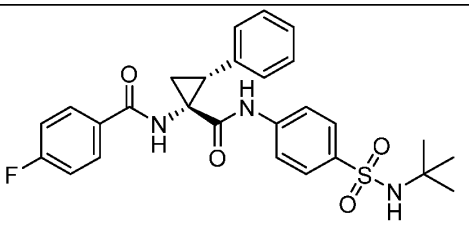
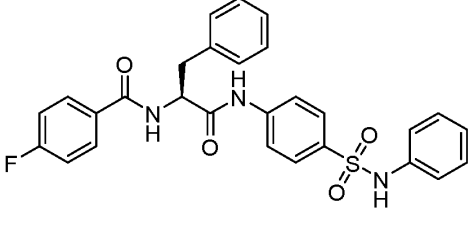
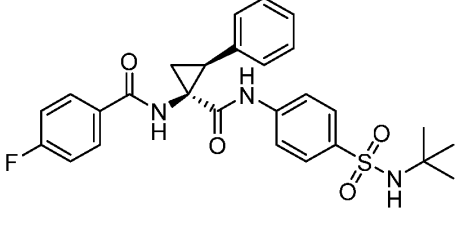
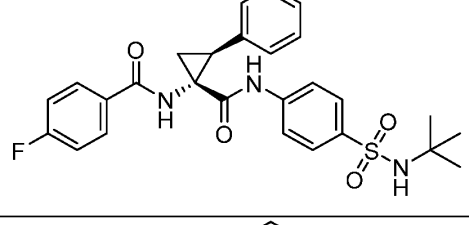
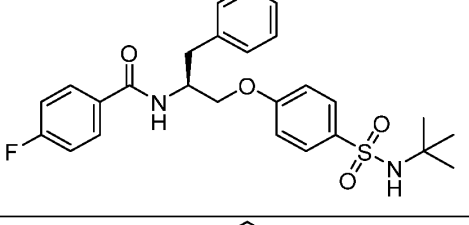
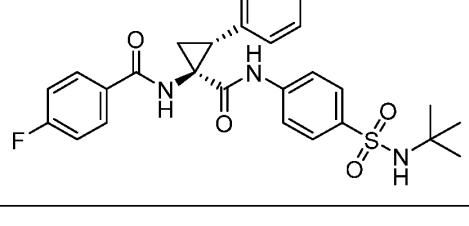
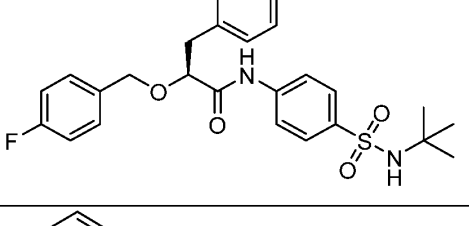
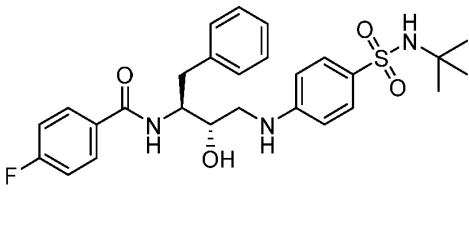
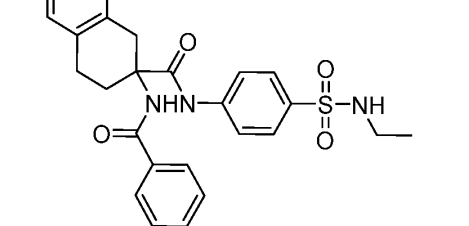
Table 1-X. Excluded Compounds

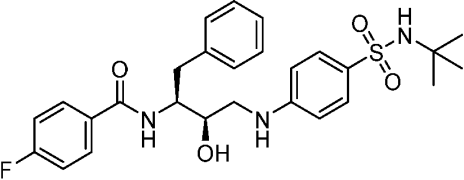
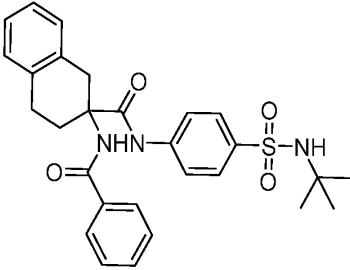
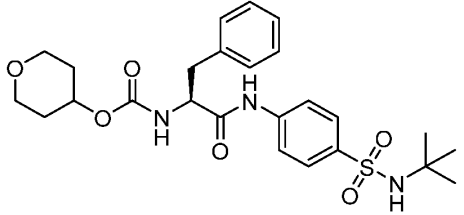
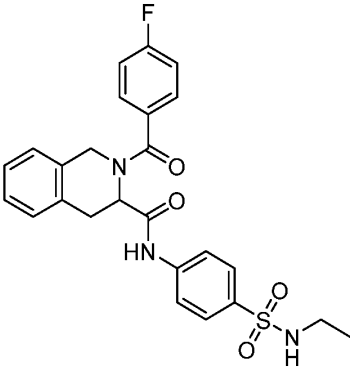
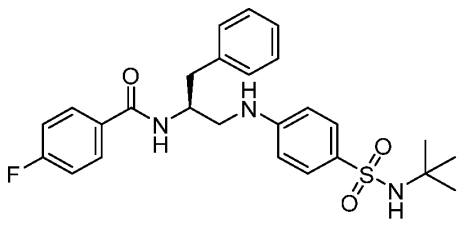
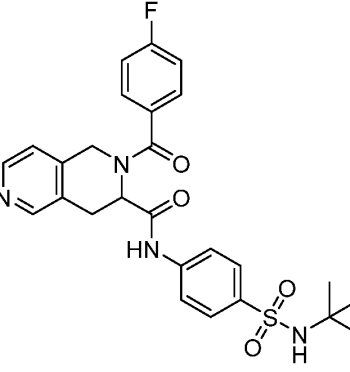
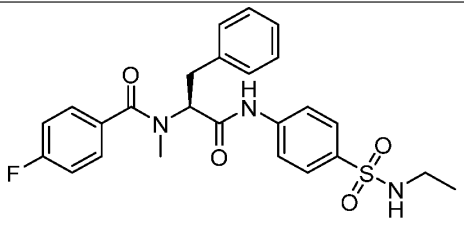
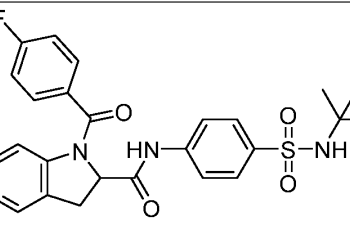
Structure	
	
	

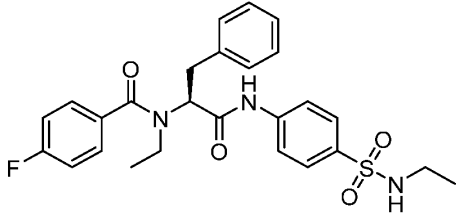
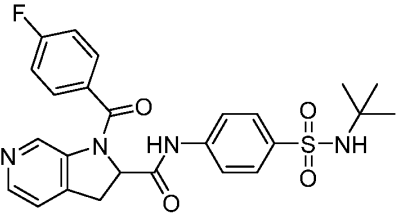
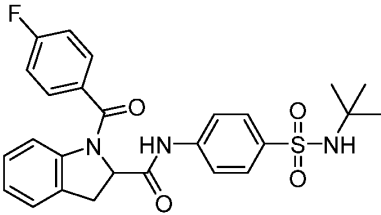
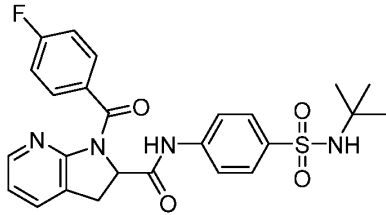
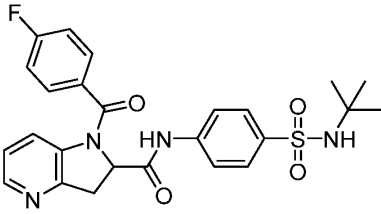
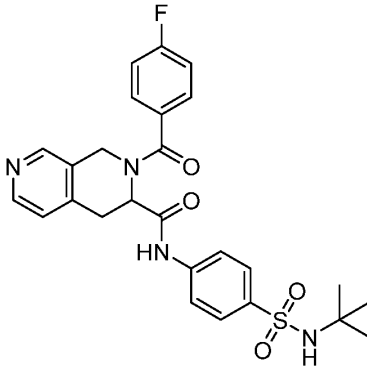
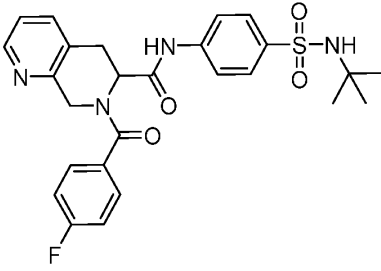
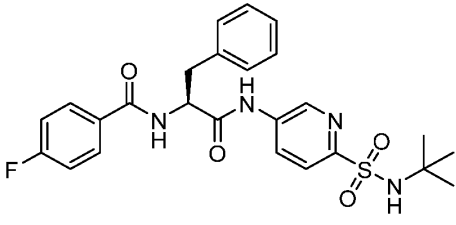
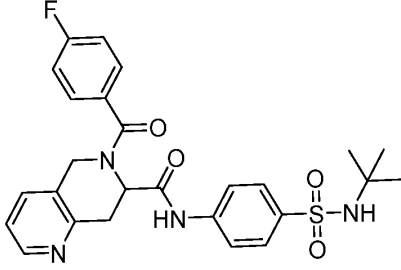
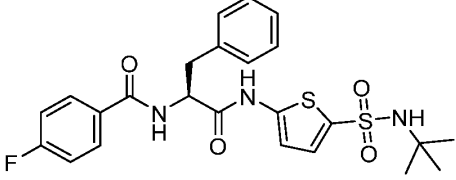
Structure	
	
	
	
	
	

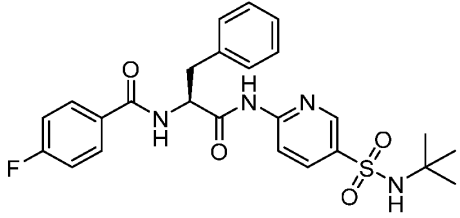
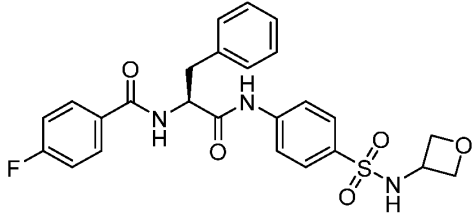
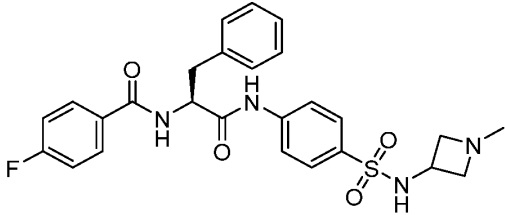
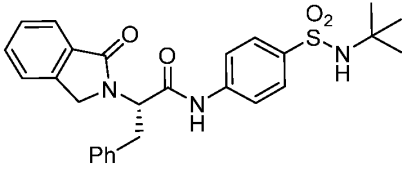
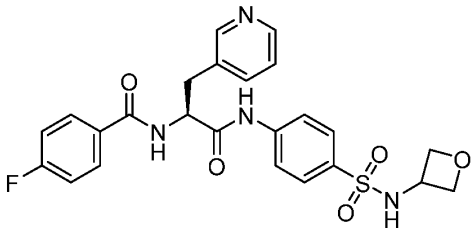
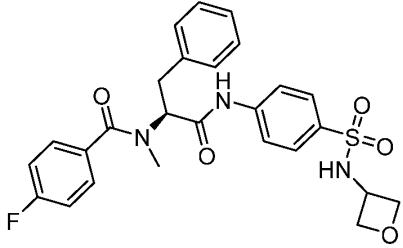
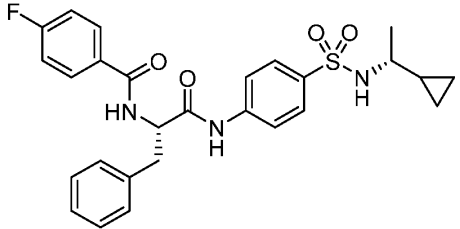
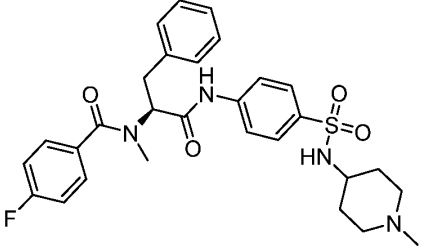
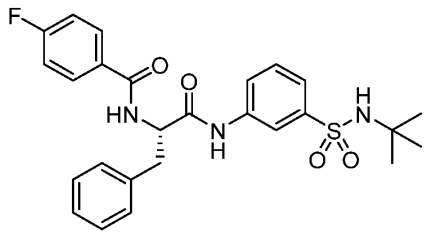
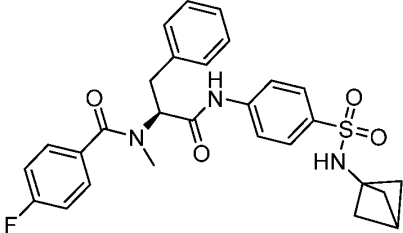
Structure	
	
	
	
	
	

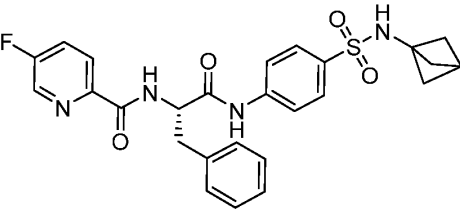
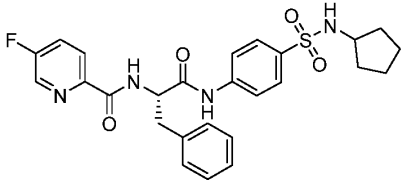
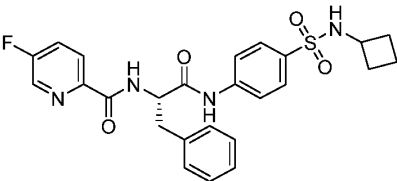
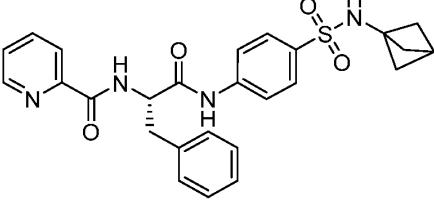
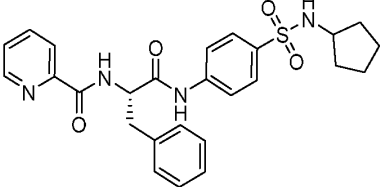
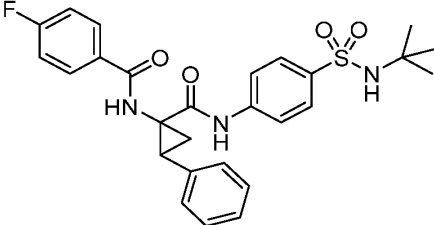
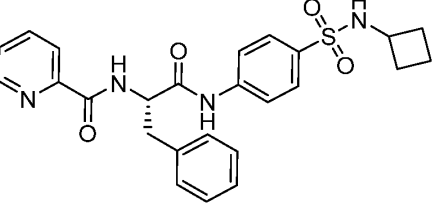
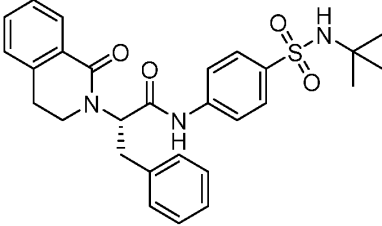
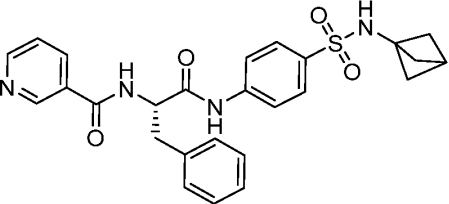
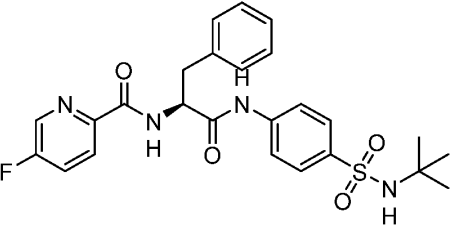
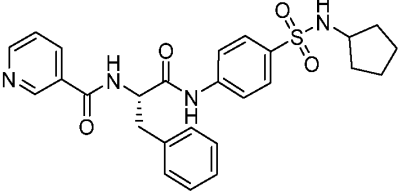
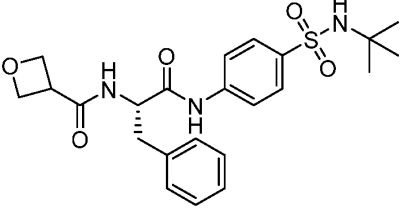
Structure	
	
	
	
	
	

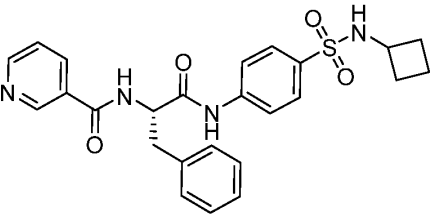
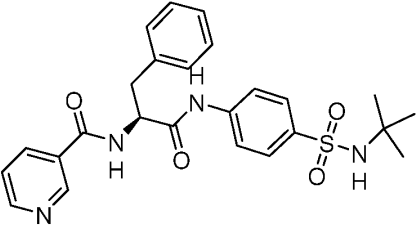
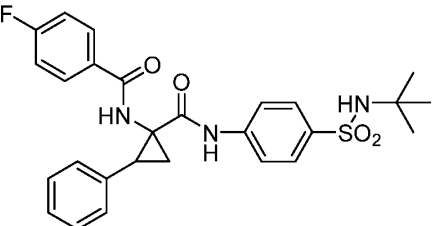
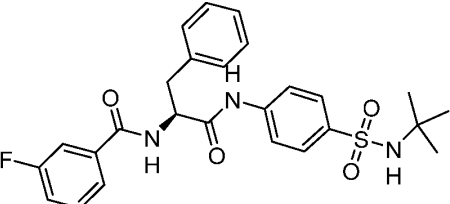
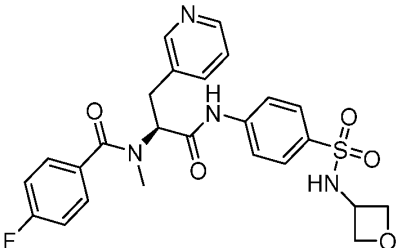
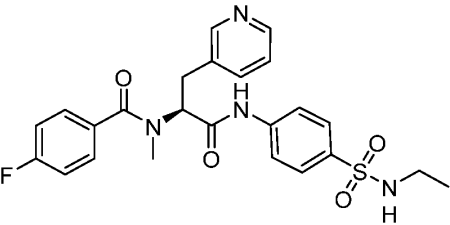
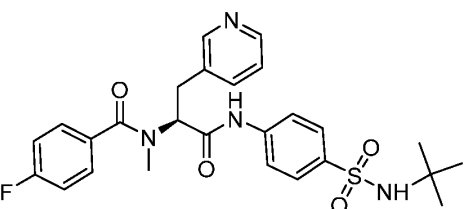
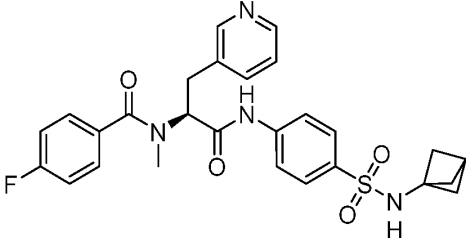
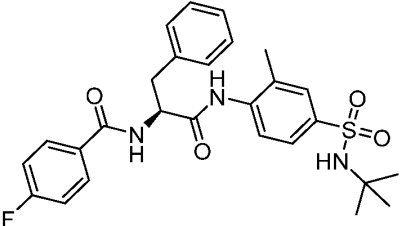
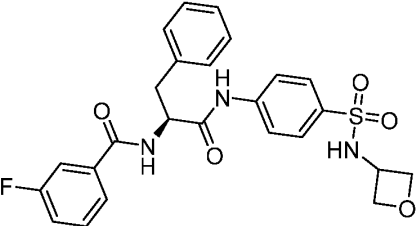
Structure	
	
	
	
	
	

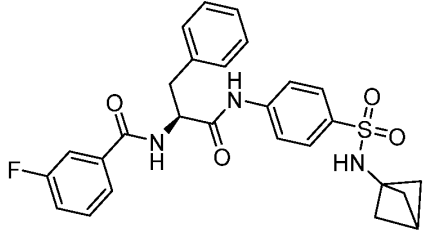
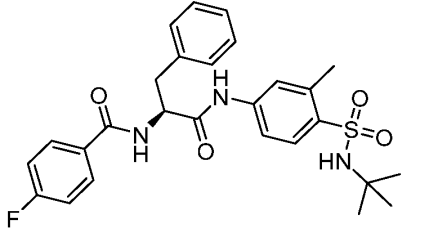
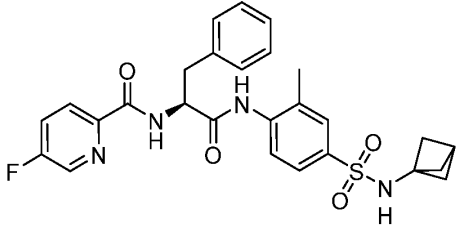
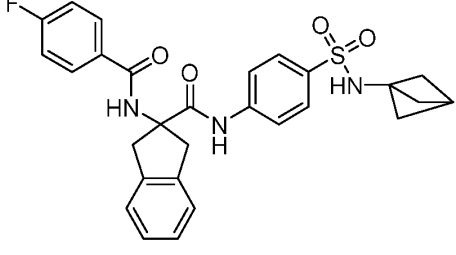
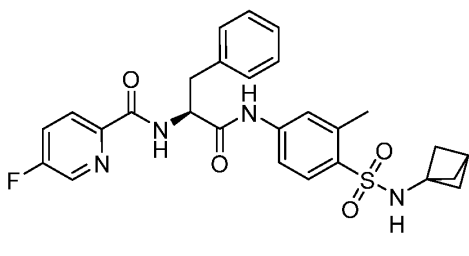
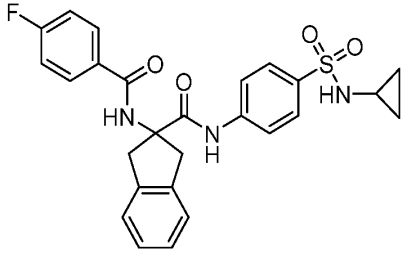
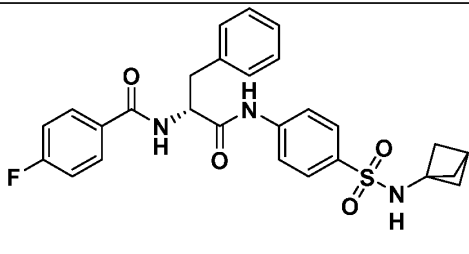
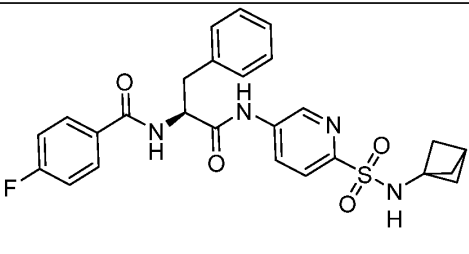
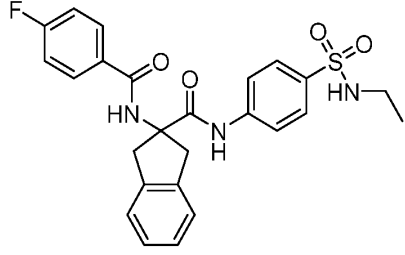
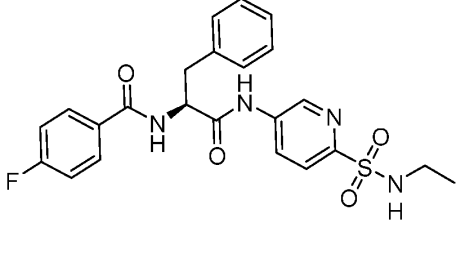
Structure	
	
	
	
	

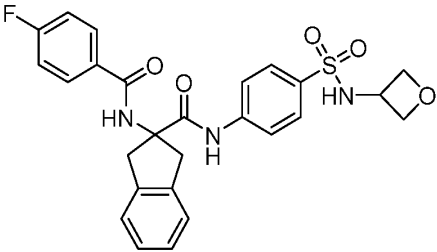
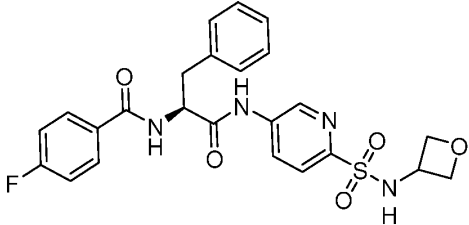
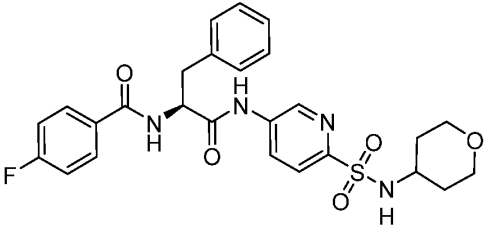
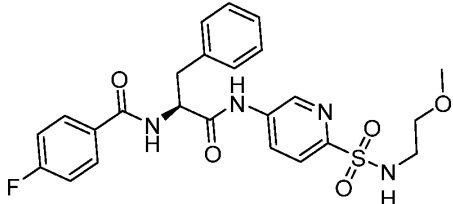
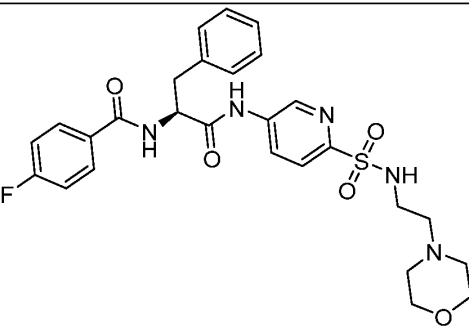
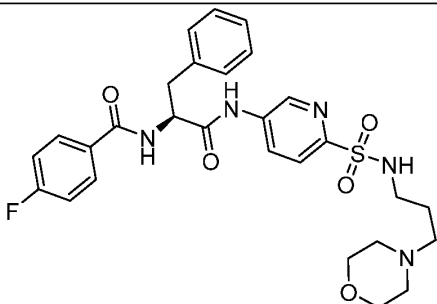
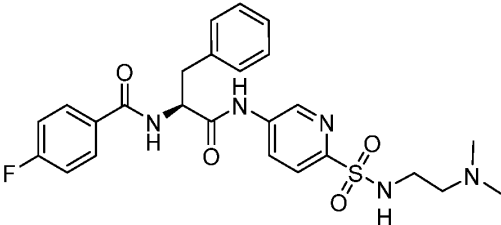
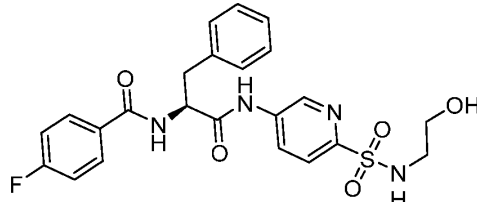
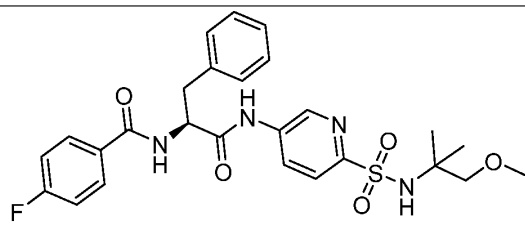
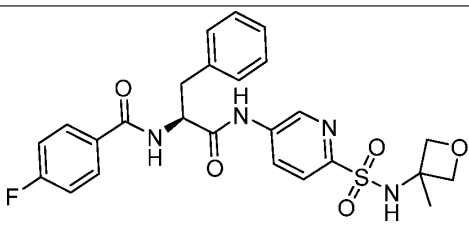
Structure	
	
	
	
	
	

Structure	
	
	
	
	
	

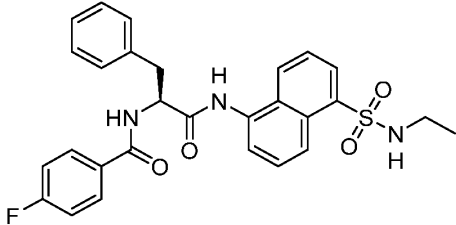
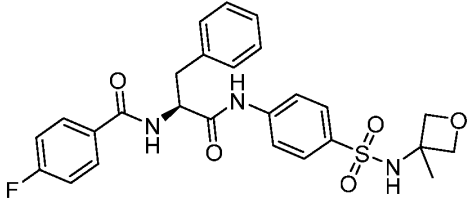
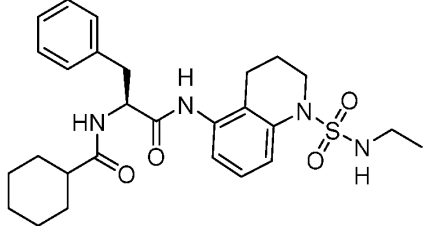
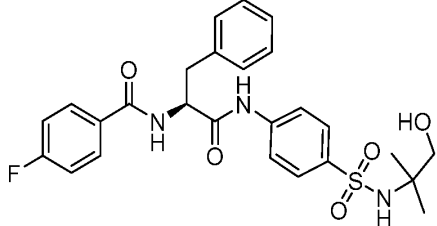
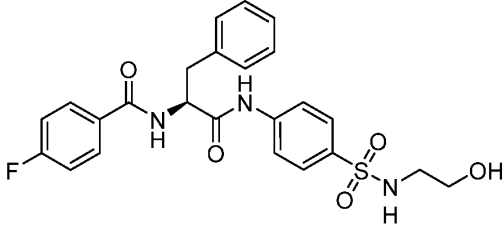
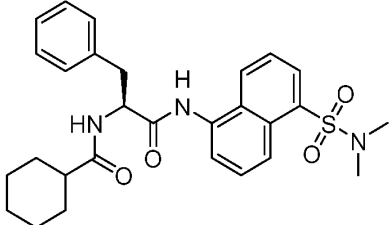
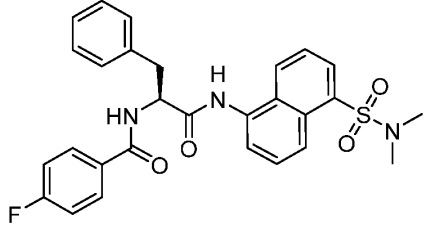
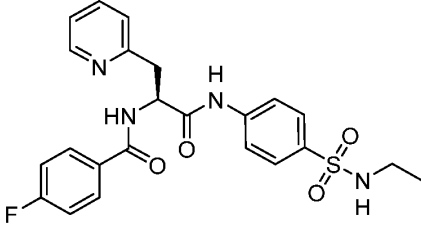
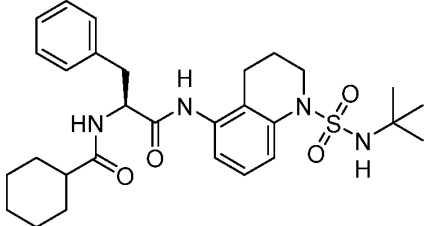
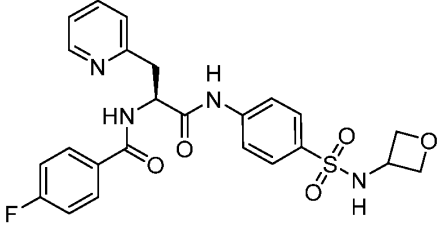
Structure	
	
	
	
	
	
	

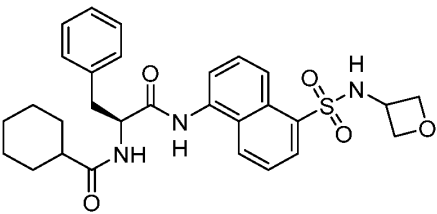
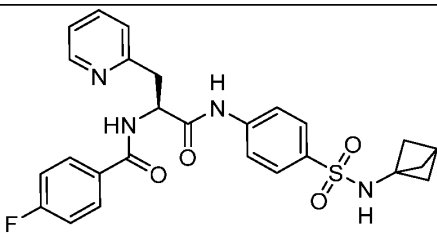
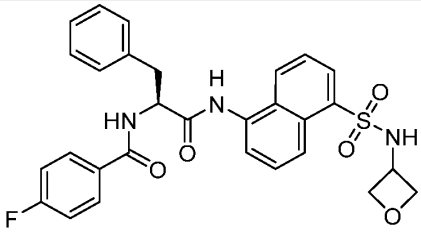
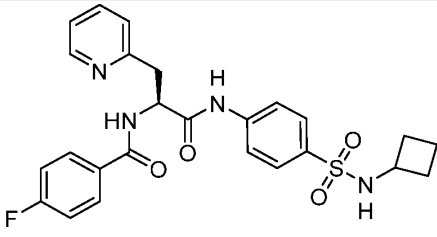
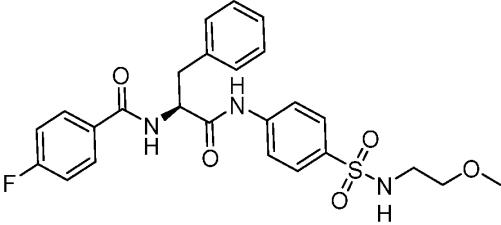
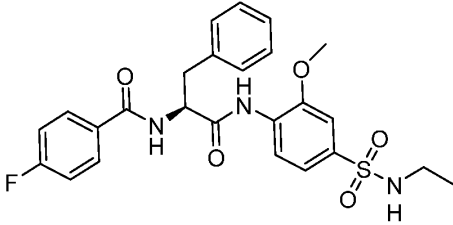
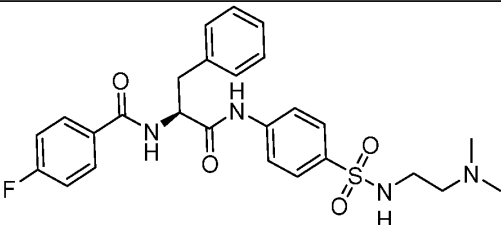
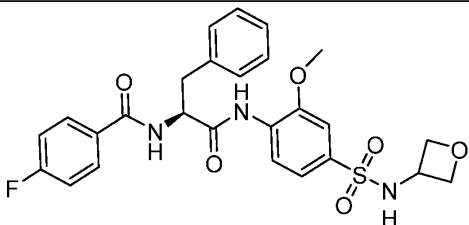
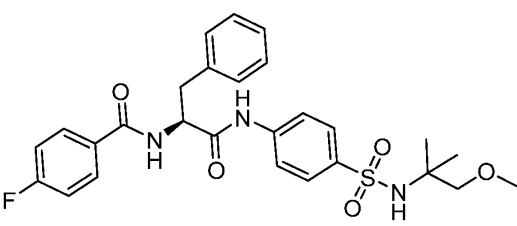
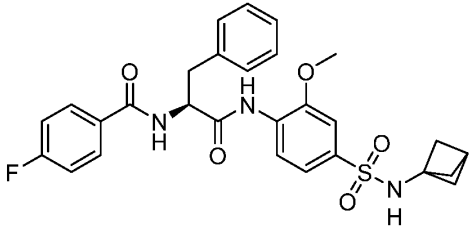
Structure	
	
	
	
	
	

Structure	
	
	
	
	
	

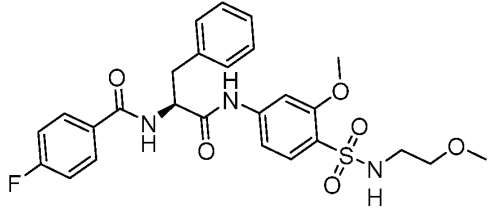
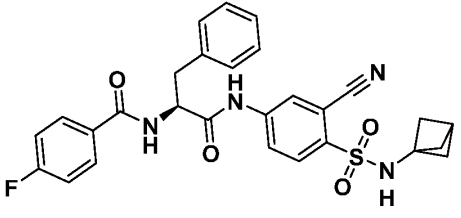
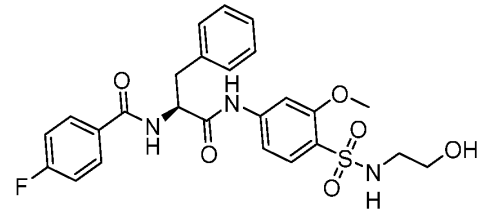
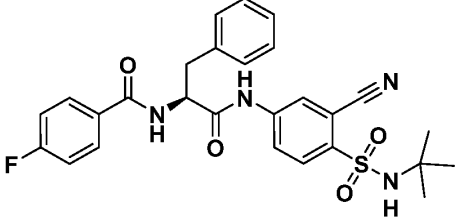
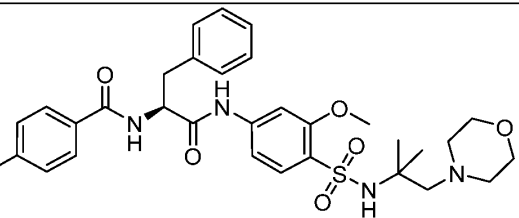
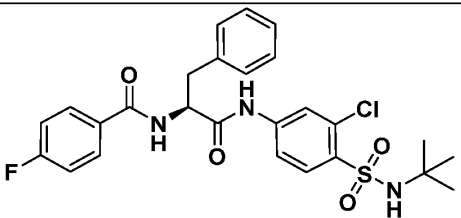
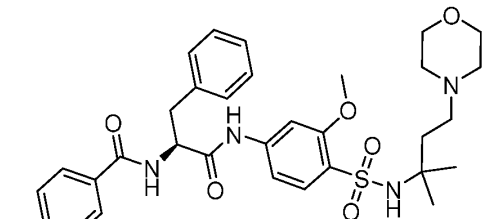
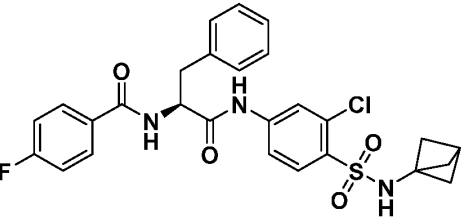
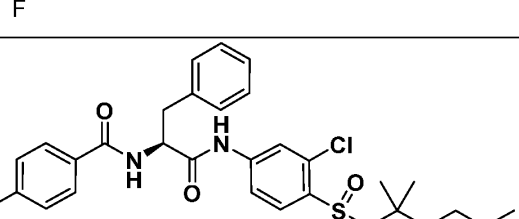
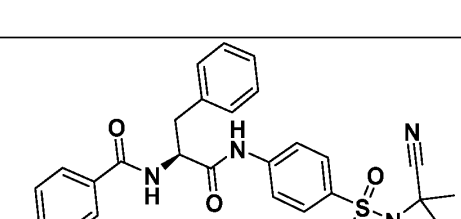
Structure	
	
	
	
	
	

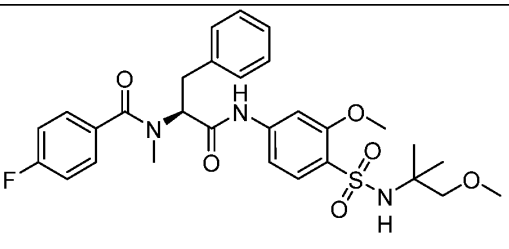
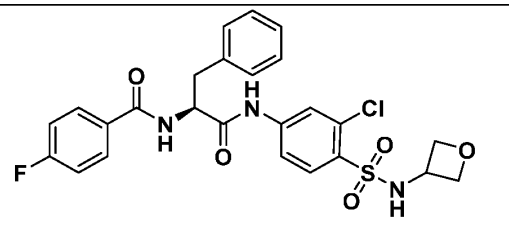
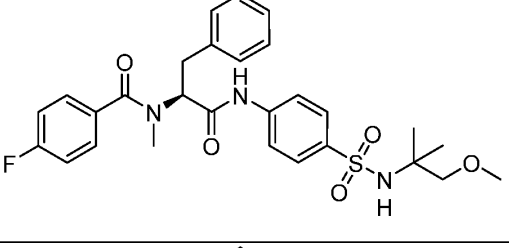
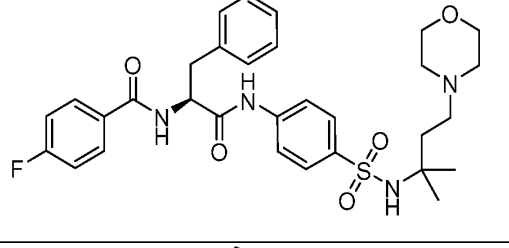
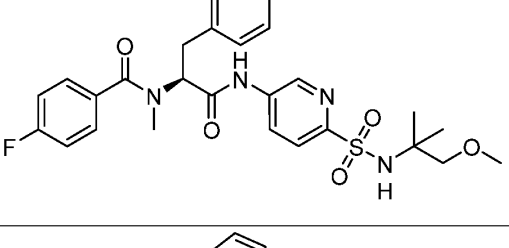
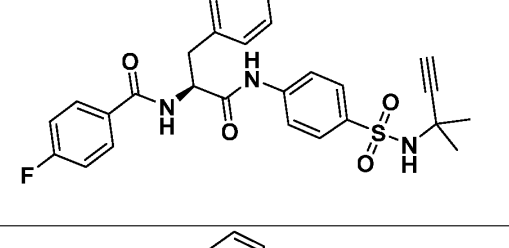
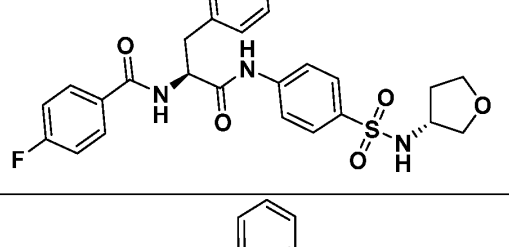
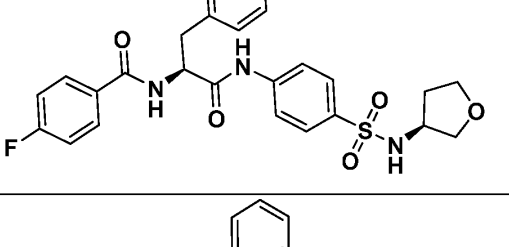
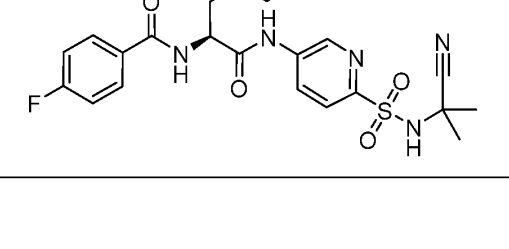
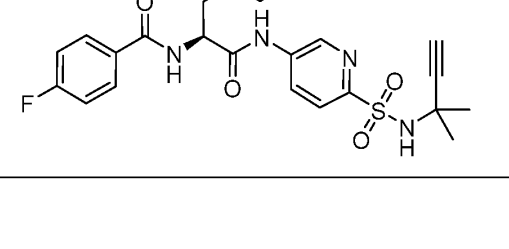
Structure	

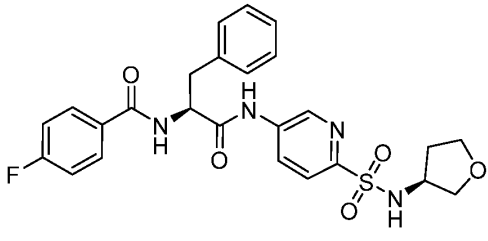
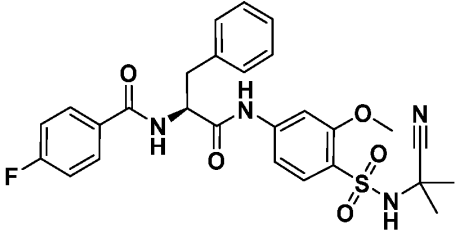
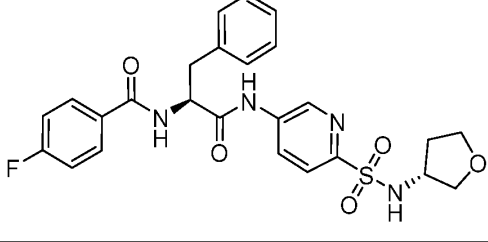
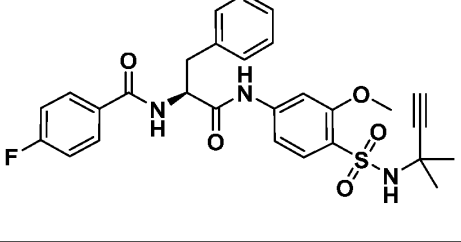
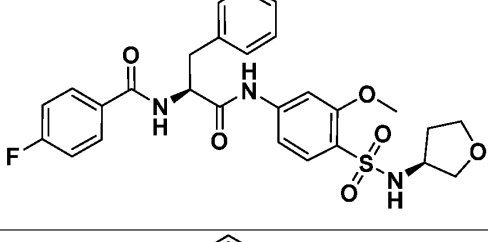
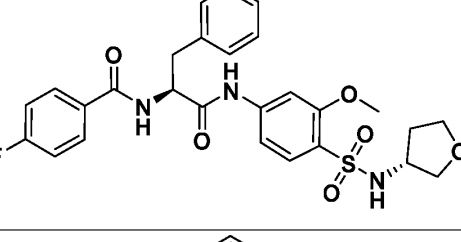
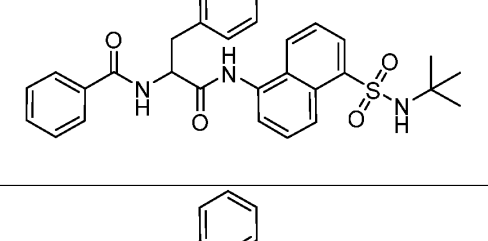
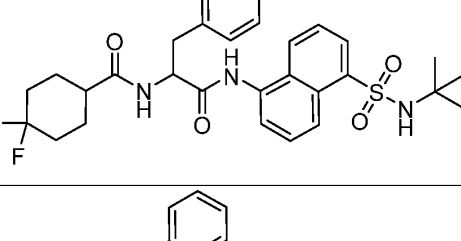
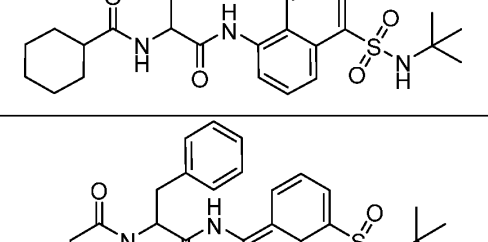
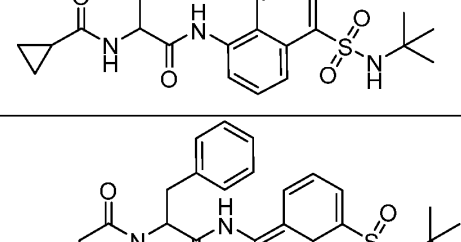
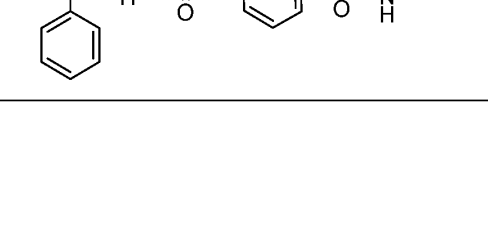
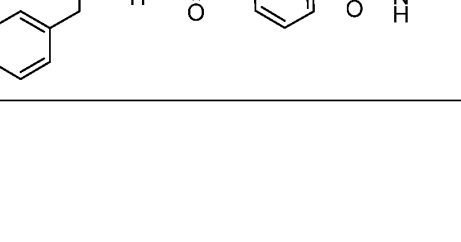
Structure	
	
	
	
	
	

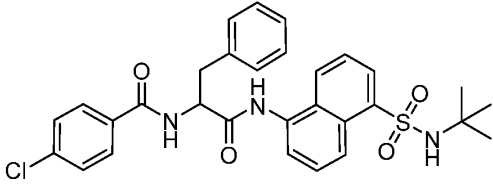
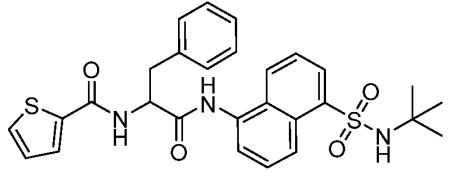
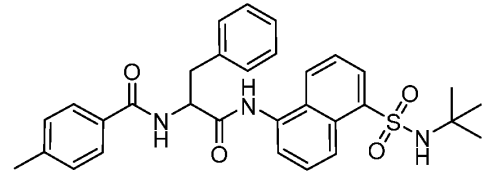
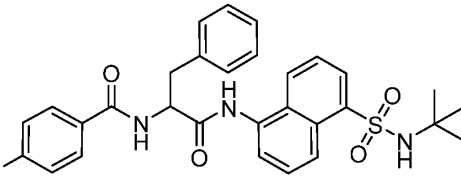
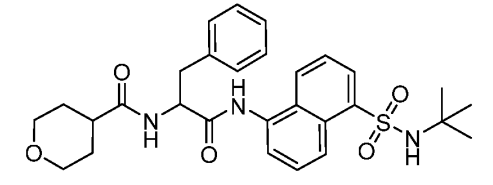
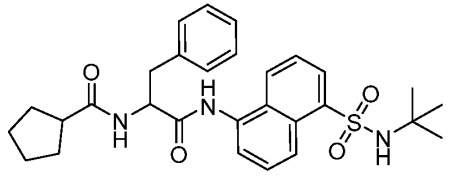
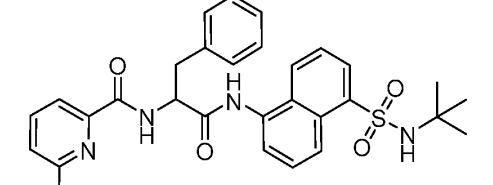
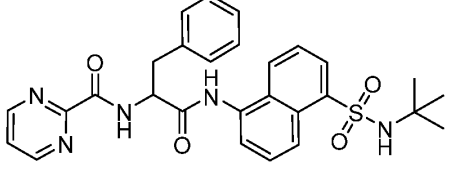
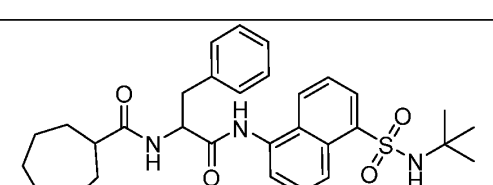
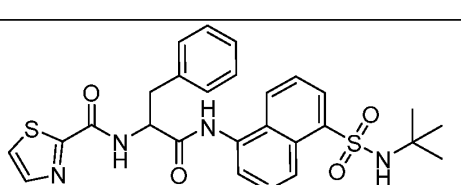
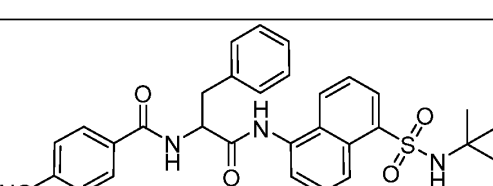
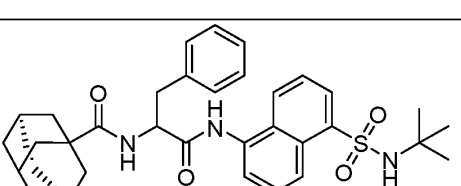
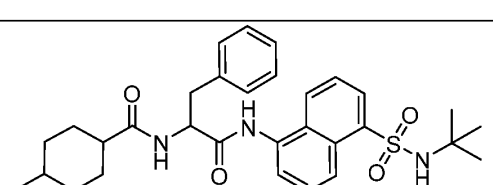
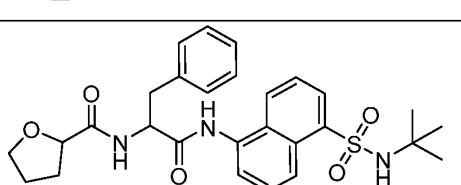
Structure	
	
	
	
	
	

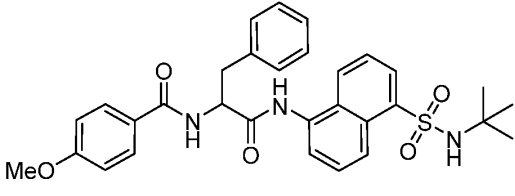
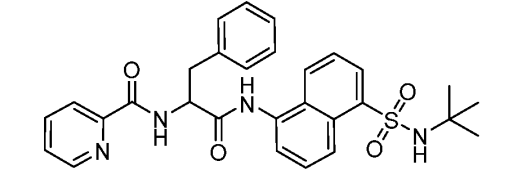
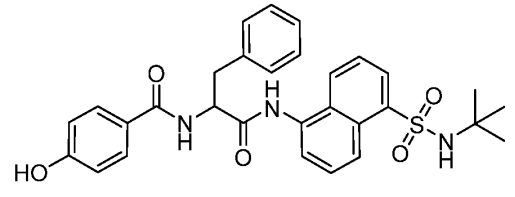
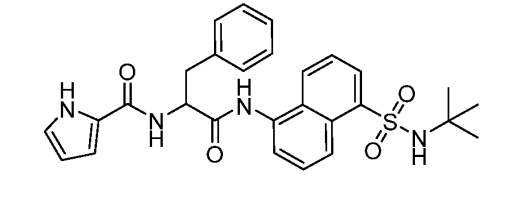
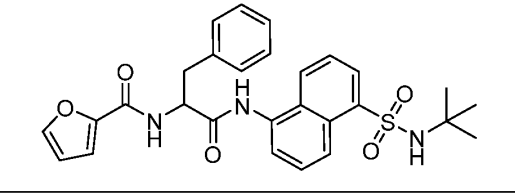
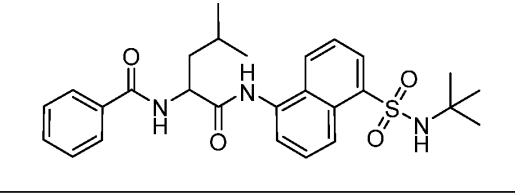
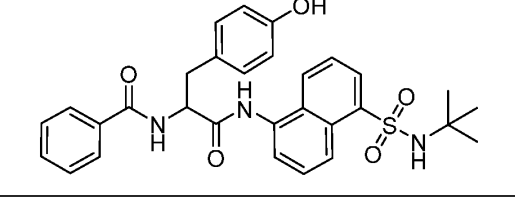
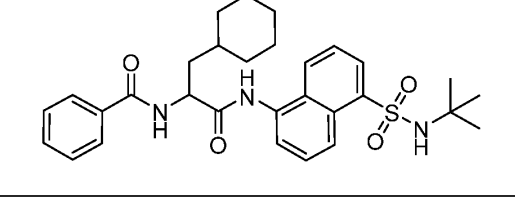
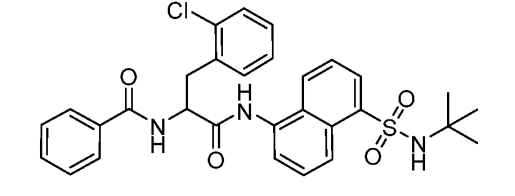
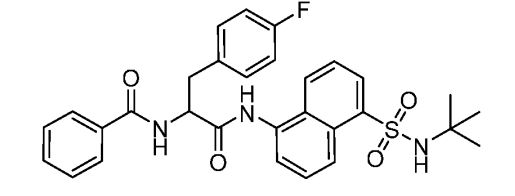
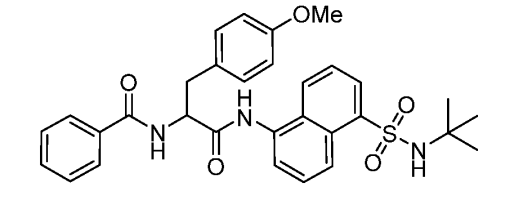
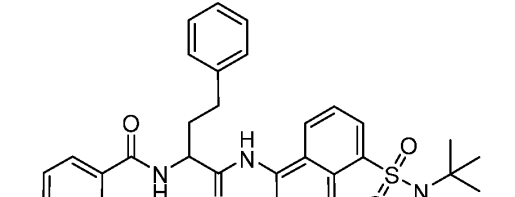
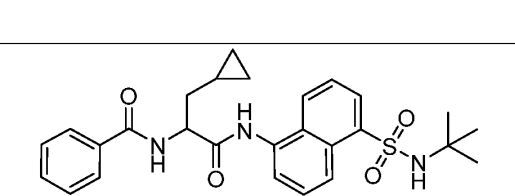
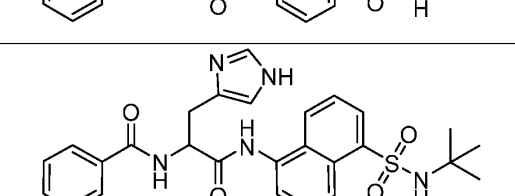
Structure	

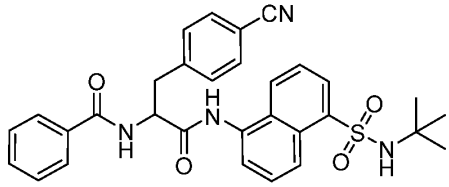
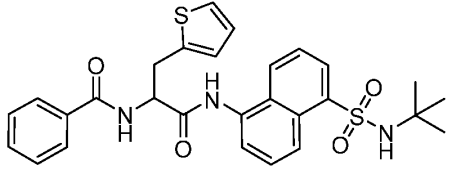
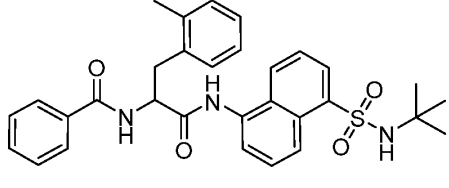
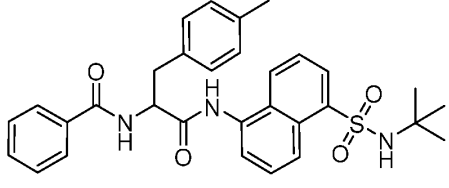
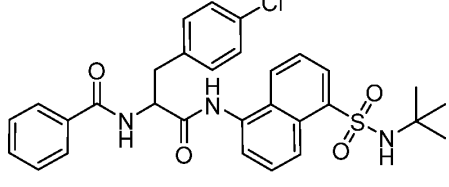
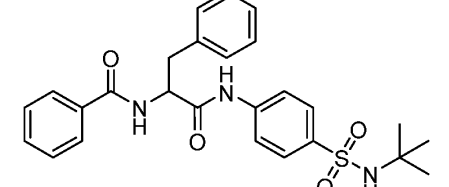
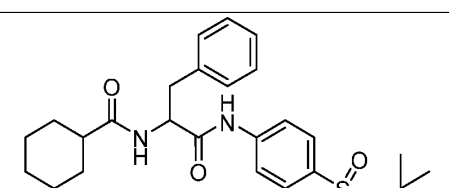
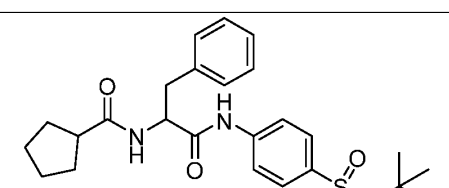
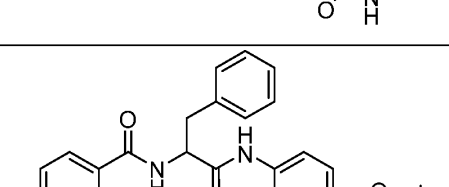
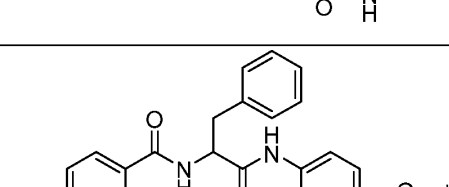
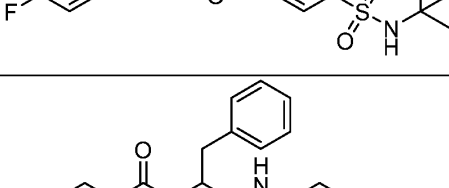
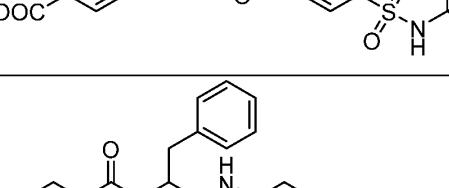
Structure	
	
	
	
	
	

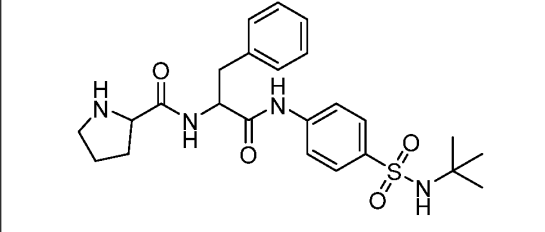
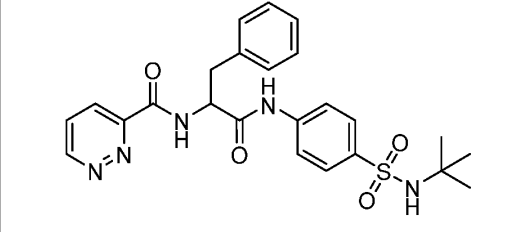
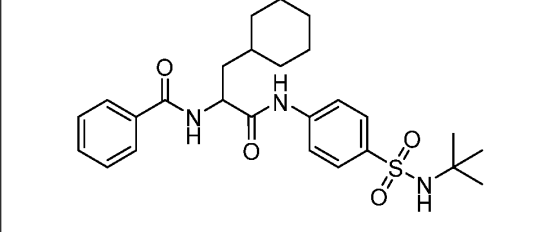
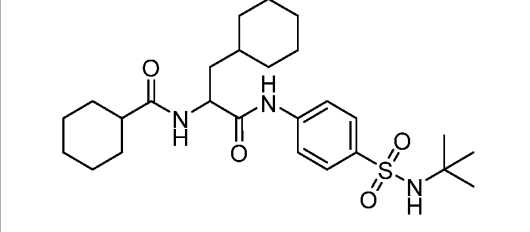
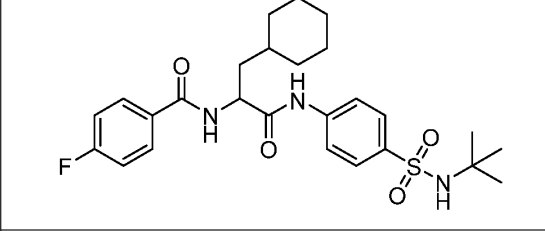
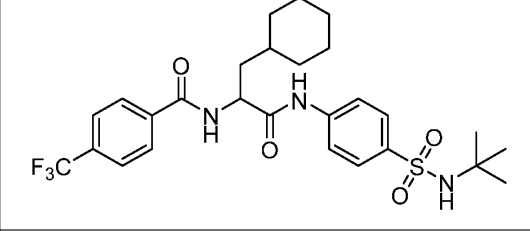
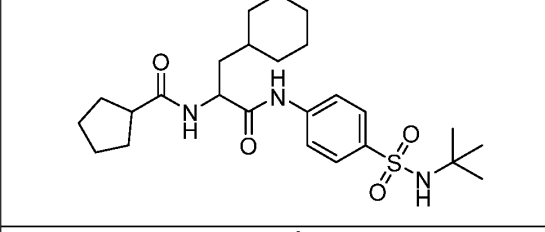
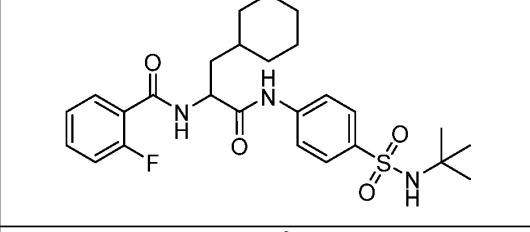
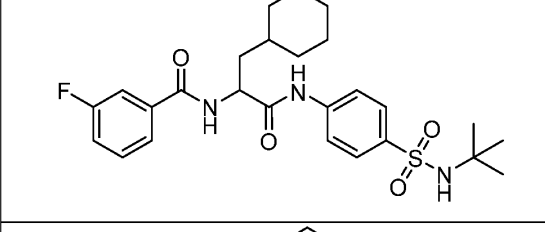
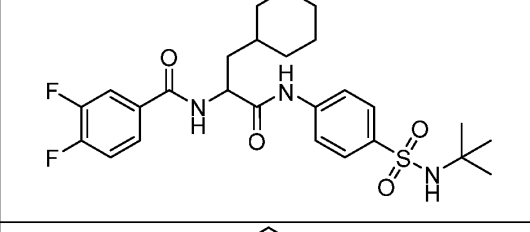
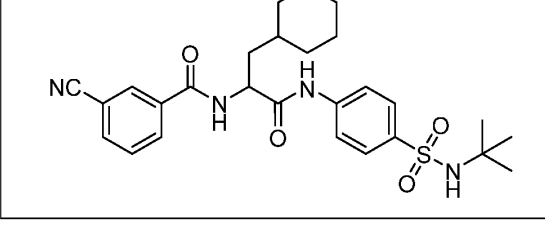
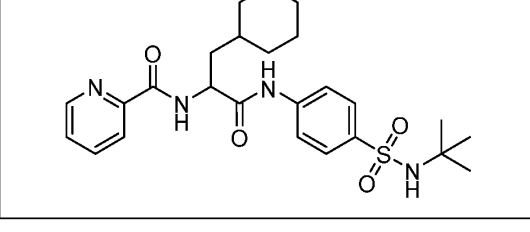
Structure	
	
	
	
	
	

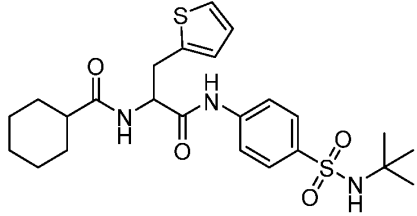
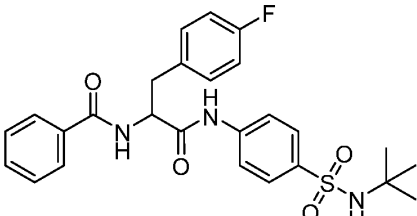
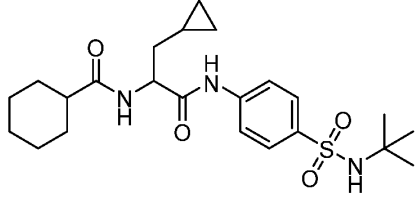
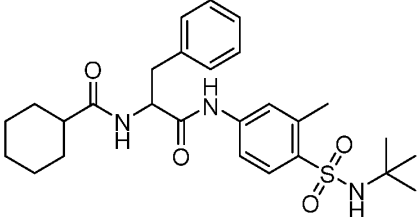
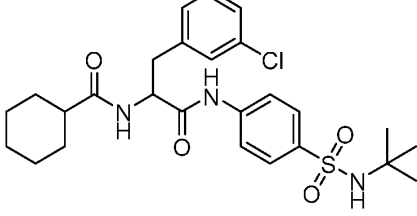
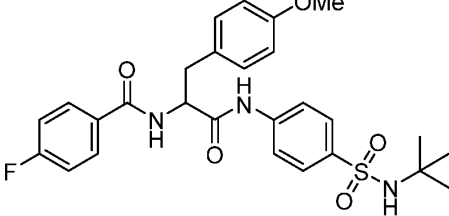
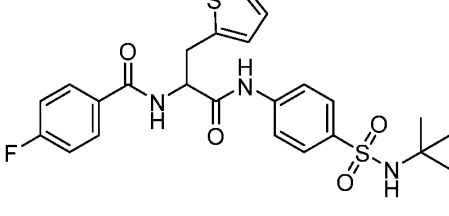
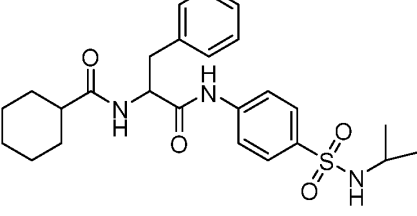
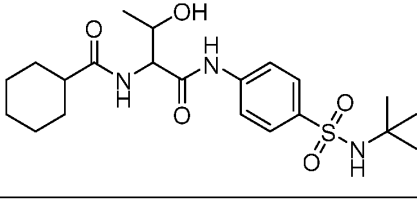
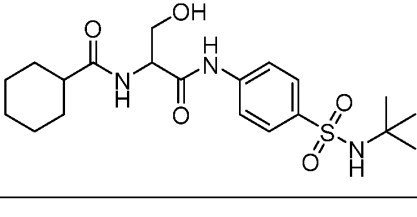
Structure	
	
	
	
	
	
	

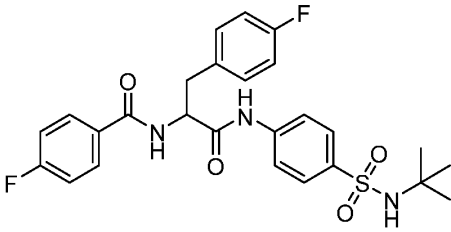
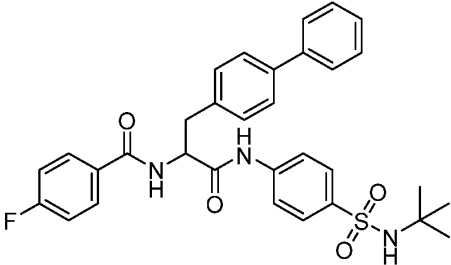
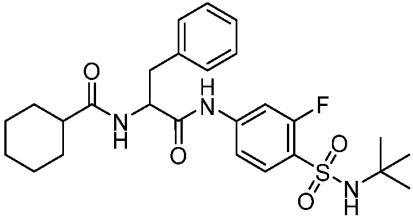
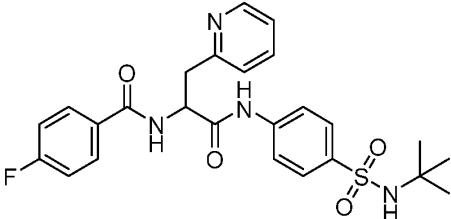
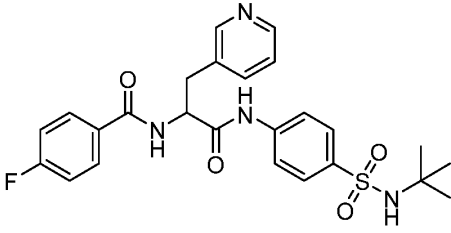
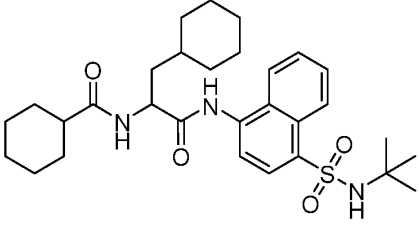
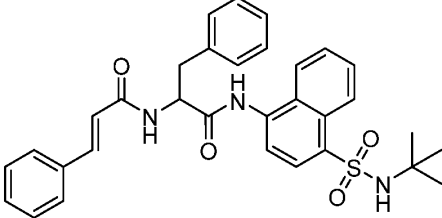
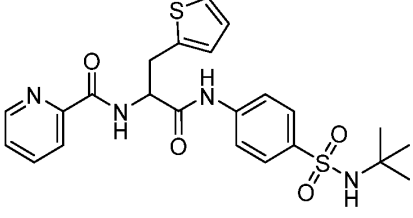
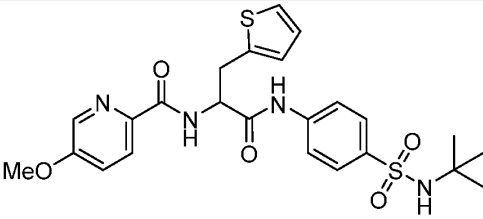
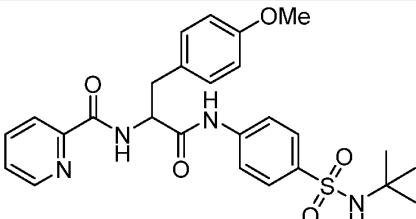
Structure	
	
	
	
	
	
	
	

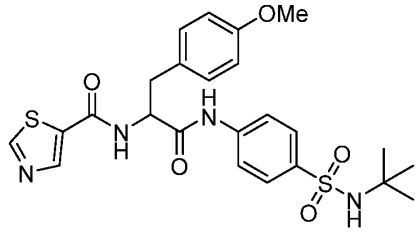
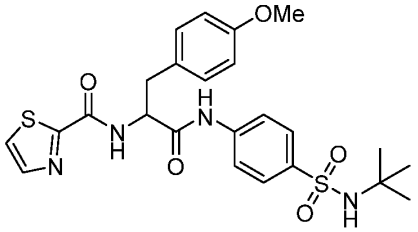
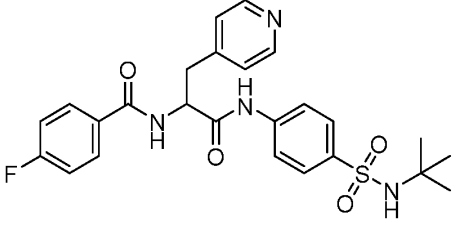
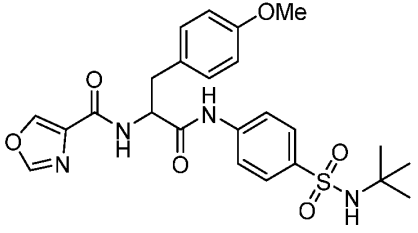
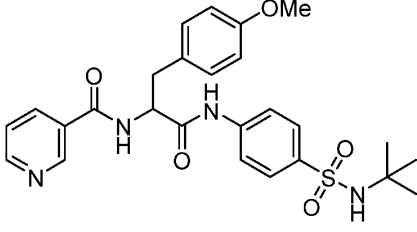
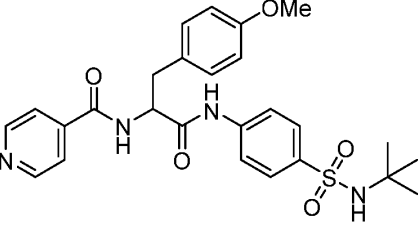
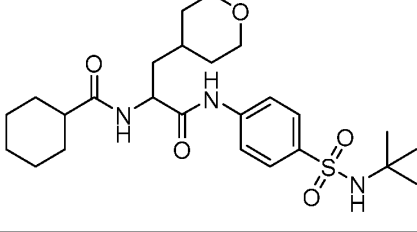
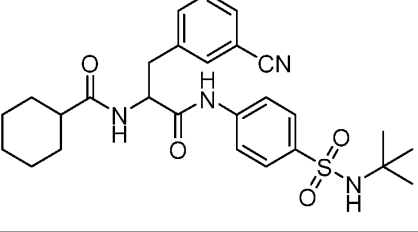
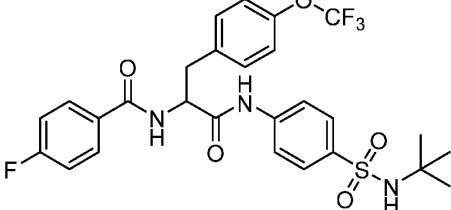
Structure	
	
	
	
	
	
	
	

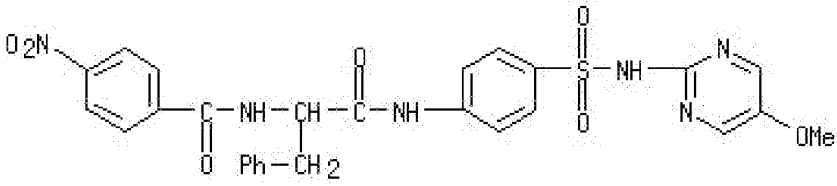
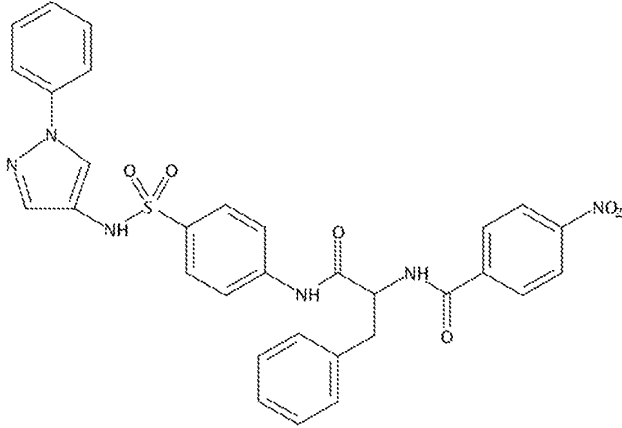
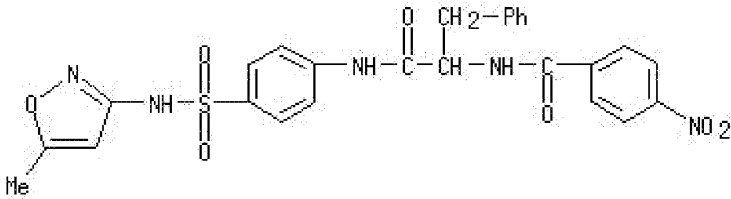
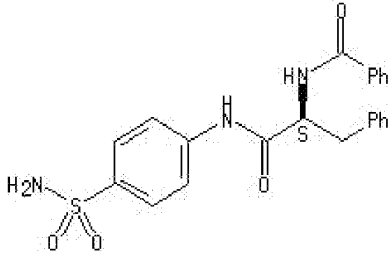
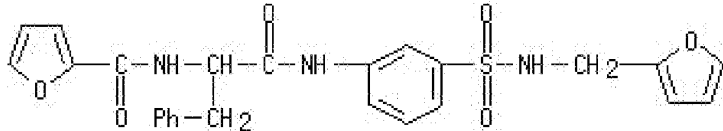
Structure	
	
	
	
	
	
	

Structure	
	
	
	
	
	
	

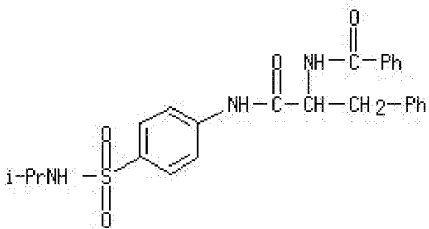
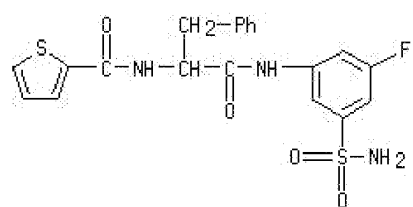
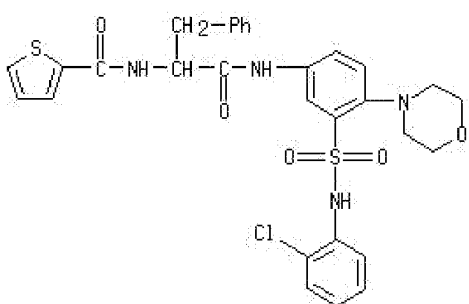
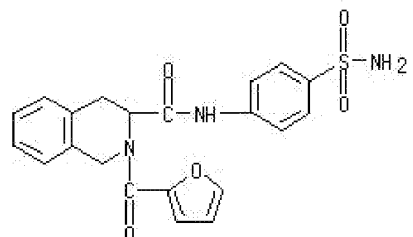
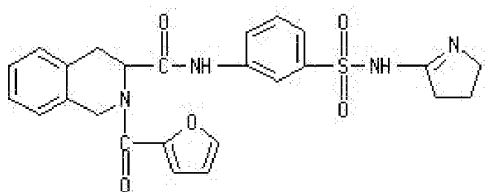
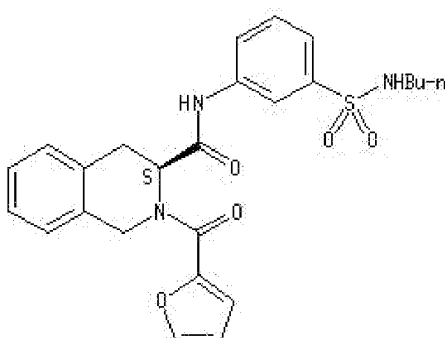
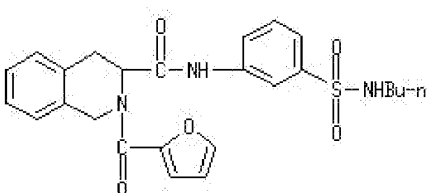
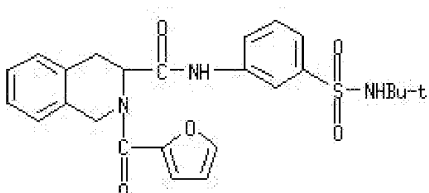
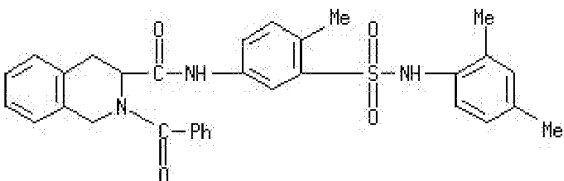
Structure	
	
	
	
	
	

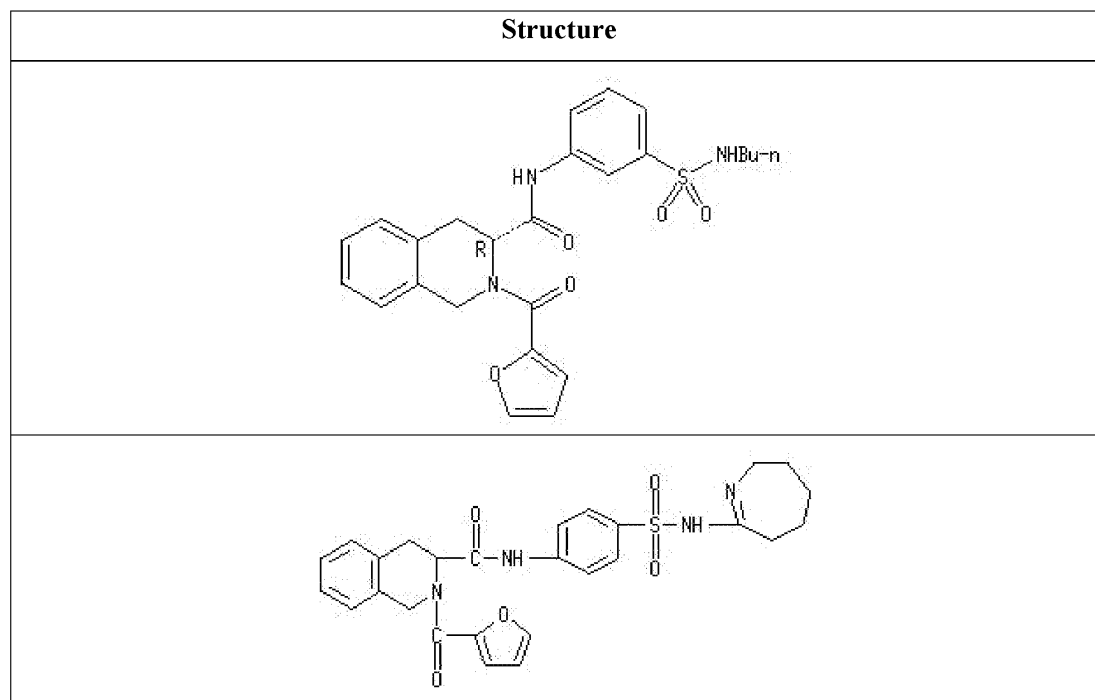
Structure	
	
	
	
	
	

Structure	
	
	
	
	
	

Structure






Structure	

Structure	
	
	
	
	
	



4. Uses, Formulation and Administration

Pharmaceutically acceptable compositions

[00184] According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in compositions of this invention is such that is effective to measurably inhibit USP30 in a biological sample or in a patient. In certain embodiments, the amount of compound in compositions of this invention is such that is effective to measurably inhibit USP30 in a biological sample or in a patient. In certain embodiments, a composition of this invention is formulated for administration to a patient in need of such composition. In some embodiments, a composition of this invention is formulated for oral administration to a patient.

[00185] The term “patient,” as used herein, means an animal, preferably a mammal, and most preferably a human.

[00186] The term “pharmaceutically acceptable carrier, adjuvant, or vehicle” refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles

that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[00187] A “pharmaceutically acceptable derivative” means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof.

[00188] As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of USP30.

[00189] Compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[00190] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may

also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00191] Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[00192] Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[00193] Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[00194] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[00195] For topical applications, provided pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively,

provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[00196] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[00197] Pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[00198] Most preferably, pharmaceutically acceptable compositions of this invention are formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions of this invention are administered without food. In other embodiments, pharmaceutically acceptable compositions of this invention are administered with food.

[00199] The amount of compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, provided compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[00200] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[00201] Compounds and compositions described herein are generally useful for the inhibition of USP30.

[00202] USP30, a deubiquitinase (DUB) localized to mitochondria and peroxisomes is an antagonist of Parkin- mediated mitophagy and of PEX2-mediated pexophagy. USP30, through its deubiquitinase activity, counteracts ubiquitination and degradation of damaged mitochondria, and inhibition of USP30 rescues mitophagy defects caused by mutant Parkin. Further, inhibition of USP30 decreases oxidative stress and provides protection against the mitochondrial toxin, rotenone. Since damaged mitochondria are more likely to accumulate Parkin, USP30 inhibition should preferentially clear unhealthy mitochondria. USP30 inhibition may beneficially increase rates of basal mitophagy, increase production of mitochondrial derived vesicles, arrest mitochondrial fission and trafficking, and generally improve mitochondrial quality control mechanisms. In addition to neurons (such as substantia nigra neurons, which are especially vulnerable to mitochondria dysfunction in Parkinson's disease), long-lived metabolically active cells such as cardiomyocytes also rely on an efficient mitochondria quality control system. In this context, Parkin has been shown to protect cardiomyocytes against ischemia/reperfusion injury through activating mitophagy and clearing damaged mitochondria in response to ischemic stress. Thus, inhibitors of USP30 are provided for use in treating a conditions involving mitochondrial defects, including neurological conditions, cardiac conditions, and systemic conditions. Deubiquinating enzymes function to oppose the action of the ubiquitinating enzymes in post-translational modification of cellular proteins. These conditions collectively represent examples of age related disorders and symptoms of natural aging suggesting further utility of USP30 inhibition to slow the process of aging and occurrence of age related disease. USP30 is a deubiquitinase that is localized to mitochondria and has been shown in expression studies to oppose the action of Parkin- mediated ubiquitination and clearance of damaged mitochondria while also opposing basal ubiquitination by ligases such as MUL1 and MARCH5. USP30 that is localized to peroxisomes has been shown to oppose ubiquitination by PEX E3 ligases and induction of selective autophagy.

[00203] In particular, disclosed herein are methods for modulating the activity of USP30 for the treatment of diseases, developmental delays, and symptoms related to mitochondrial dysfunction. For example, the disclosed compounds and compositions are useful in the treatment of

mitochondrial diseases, such as Alpers's Disease, CPEO-Chronic progressive external ophthalmoplegia, Kearns-Sayra Syndrome (KSS), Leber Hereditary Optic Neuropathy (LHON), MELAS -Mitochondrial myopathy, encephalomyopathy, lactic acidosis, and strokelike episodes, MERRF-Myoclonic epilepsy and ragged-red fiber disease, NARP-neurogenic muscle weakness, ataxia, retinitis pigmentosa, and Pearson Syndrome. Additionally, the disclosed compounds and compositions are useful in the treatment of other USP30-related diseases, such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) (Tsubouchi K, Araya J, Kuwano K. PINK1-PARK2-mediated mitophagy in COPD and IPF pathogenesis. *Inflamm Regen*. 2018;38:18. Published 2018 Oct 24. doi:10.1186/s41232-018-0077-6; Kobayashi K, Araya J, Minagawa S, et al. Involvement of PARK2-Mediated Mitophagy in Idiopathic Pulmonary Fibrosis Pathogenesis. *J Immunol*. 2016;197(2):504–516. doi:10.4049/jimmunol.1600265; Ryter SW, Rosas IO, Owen CA, et al. Mitochondrial Dysfunction as a Pathogenic Mediator of Chronic Obstructive Pulmonary Disease and Idiopathic Pulmonary Fibrosis. *Am J Respir Cell Mol Biol*. 2018;15(Suppl 4):S266–S272. doi:10.1163/AnnalsATS.201808-585MG; and Ito S, Araya J, Kurita Y, et al. PARK2-mediated mitophagy is involved in regulation of HBEC senescence in COPD pathogenesis. *Autophagy*. 2015;11(3):547–559. doi:10.1080/15548627.2015.1017190). Alternatively, the disclosed compounds and compositions are useful in the treatment of other USP30-related diseases, such as cardiovascular disease, kidney disease, pulmonary fibrosis, ophthalmic conditions, cancer, cognitive disease, and other related conditions (Lin Q, Li S, Jiang N, et al. PINK1-parkin pathway of mitophagy protects against contrast-induced acute kidney injury via decreasing mitochondrial ROS and NLRP3 inflammasome activation. *Redox Biol*. 2019;26:101254. doi:10.1016/j.redox.2019.101254; Wang Y, Cai J, Tang C, Dong Z. Mitophagy in Acute Kidney Injury and Kidney Repair. *Cells*. 2020;9(2):338. Published 2020 Feb 1. doi:10.3390/cells9020338; Wang Y, Tang C, Cai J, et al. PINK1/Parkin-mediated mitophagy is activated in cisplatin nephrotoxicity to protect against kidney injury. *Cell Death Dis*. 2018;9(11):1113. Published 2018 Nov 1. doi:10.1038/s41419-018-1152-2; and Tang C, Han H, Yan M, et al. PINK1-PRKN/PARK2 pathway of mitophagy is activated to protect against renal ischemia-reperfusion injury. *Autophagy*. 2018;14(5):880–897. doi:10.1080/15548627.2017.1405880). Disclosed compounds are useful in the treatment of peroxisome related diseases such as Ataxia-telangiectasia mutated, Heimler syndrome, Infantile refsum disease, Neonatal adrenoleukodystrophy, Rhizomelic chondrodysplasia punctate, White

matter dementia, Zellweger syndrome, and Zellweger spectrum disorders (Riccio et al. Deubiquitinating enzyme USP30 maintains basal peroxisome abundance by regulating pexophagy. *J Cell Biol.* 2019;218(3):798–807. doi:10.1083/jcb.201804172; Marcassa et al. Dual role of USP30 in controlling basal pexophagy and mitophagy. *EMBO Rep.* 2018;19(7):e45595. doi:10.15252/embr.201745595; and Nazarko TY. Pexophagy is responsible for 65% of cases of peroxisome biogenesis disorders. *Autophagy.* 2017;13(5):991–994. doi:10.1080/15548627.2017.1291480).

[00204] Methods of treating a USP30-related disease or condition in a subject are disclosed. The methods can include administering to the subject an effective amount of one or more compounds or compositions provided herein. In one embodiment, the USP30-related disease is a mitochondrial disease. Examples of mitochondrial diseases include, but are not limited to, Alpers' s Disease, CPEO-Chronic progressive external ophthalmoplegia , Kearns-Sayra Syndrome (KSS), Leber Hereditary Optic Neuropathy (LHON), MELAS -Mitochondrial myopathy, encephalomyopathy, lactic acidosis, and stroke-like episodes, MERRF-Myoclonic epilepsy and ragged-red fiber disease, NARP-neurogenic muscle weakness, ataxia, and retinitis pigmentosa, and Pearson Syndrome. In other embodiments, the USP30-related disease is a vascular disease (such as a cardiovascular disease or any disease that would benefit from increasing vascularization in tissues exhibiting impaired or inadequate blood flow). In other embodiments, the USP30- related disease is a muscular disease, such as a muscular dystrophy. Examples of muscular dystrophy include but are not limited to Duchenne muscular dystrophy, Becker muscular dystrophy, limb-girdle muscular dystrophy, congenital muscular dystrophy, facioscapulohumeral muscular dystrophy, myotonic muscular dystrophy, oculopharyngeal muscular dystrophy, distal muscular dystrophy, and Emery- Dreifuss muscular dystrophy. In other embodiments, the USP30-related disease is a form of pulmonary fibrosis. In other embodiments, the USP30-related disease is natural aging or an age-related disease (Sun N, Youle RJ, Finkel T. The Mitochondrial Basis of Aging. *Mol Cell.* 2016;61(5):654–666. doi:10.1016/j.molcel.2016.01.028; .Cornelissen T, Vilain S, Vints K, Goukko N, Verstreken P, Vandenberghe W. Deficiency of parkin and PINK1 impairs age-dependent mitophagy in *Drosophila*. *Elife.* 2018;7:e35878. Published 2018 May 29. doi:10.7554/eLife.35878; Ryu D, Mouchiroud L, Andreux PA, et al. Urolithin A induces mitophagy and prolongs lifespan in *C. elegans* and increases muscle function in rodents. *Nat Med.* 2016;22(8):879–888. doi:10.1038/nm.4132; Brown EE, Lewin AS, Ash JD. Mitochondria:

Potential Targets for Protection in Age-Related Macular Degeneration. *Adv Exp Med Biol.* 2018;1074:11–17. doi:10.1007/978-3-319-75402-4_2; and Ito et al. 2015).

[00205] In some embodiments, the USP30-related disease or condition is a demyelinating disease, such as multiple sclerosis, Charcot-Marie-Tooth disease, Pelizaeus-Merzbacher disease, encephalomyelitis, neuromyelitis optica, adrenoleukodystrophy, or Guillian-Barre syndrome.

[00206] In other embodiments, the USP30-related disease is a metabolic disease. Examples of metabolic diseases include but are not limited to obesity, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia, hypercholesterolemia, dyslipidemia, Syndrome X, and Type II diabetes mellitus.

[00207] In yet other embodiments, the USP30-related disease is a muscle structure disorder. Examples of a muscle structure disorders include, but are not limited to, Bethlem myopathy, central core disease, congenital fiber type disproportion, distal muscular dystrophy (MD), Duchenne & Becker MD, Emery-Dreifuss MD, facioscapulohumeral MD, hyaline body myopathy, limb-girdle MD, a muscle sodium channel disorders, myotonic chondrodystrophy, myotonic dystrophy, myotubular myopathy, nemaline body disease, oculopharyngeal MD, and stress urinary incontinence.

[00208] In still other embodiments, the USP30-related disease is a neuronal activation disorder, Examples of neuronal activation disorders include, but are not limited to, amyotrophic lateral sclerosis, Charcot-Marie-Tooth disease, Guillain-Barre syndrome, Lambert-Eaton syndrome, multiple sclerosis, myasthenia gravis, nerve lesion, peripheral neuropathy, spinal muscular atrophy, tardy ulnar nerve palsy, and toxic myoneural disorder. In other embodiments, the USP30-related disease is a muscle fatigue disorder.

[00209] Examples of muscle fatigue disorders include, but are not limited to chronic fatigue syndrome, diabetes (type I or II), glycogen storage disease, fibromyalgia, Friedreich's ataxia, intermittent claudication, lipid storage myopathy, MELAS, mucopolysaccharidosis, Pompe disease, and thyrotoxic myopathy.

[00210] In some embodiments, the USP30-related disease is a muscle mass disorder.

[00211] Examples of muscle mass disorders include, but are not limited to, cachexia, cartilage degeneration, cerebral palsy, compartment syndrome, critical illness myopathy, inclusion body myositis, muscular atrophy (disuse), sarcopenia, steroid myopathy, and systemic lupus erythematosus.

[00212] In other embodiments, the USP30-related disease is a beta oxidation disease.

[00213] Examples of beta oxidation diseases include, but are not limited to, systemic carnitine transporter, carnitine palmitoyltransferase (CPT) II deficiency, very long- chain acyl- CoA dehydrogenase (LCHAD or VLCAD) deficiency, trifunctional enzyme deficiency, medium - chain acyl - CoA dehydrogenase (MCAD) deficiency, short - chain acyl- CoA dehydrogenase (SCAD) deficiency, and riboflavin - responsive disorders of β -oxidation (RR -MADD).

[00214] In some embodiments, the USP30-related disease is a vascular disease. Examples of vascular diseases include, but are not limited to, peripheral vascular insufficiency, peripheral vascular disease, intermittent claudication, peripheral vascular disease (PVD), peripheral artery disease (PAD), peripheral artery occlusive disease (PAOD), and peripheral obliterative arteriopathy.

[00215] In other embodiments, the USP30-related disease is an ocular vascular disease.

[00216] Examples of ocular vascular diseases include, but are not limited to, age-related macular degeneration (AMD), stargardt disease, hypertensive retinopathy, diabetic retinopathy, retinopathy, macular degeneration, retinal haemorrhage, and glaucoma.

[00217] In yet other embodiments, the USP30-related disease is a muscular eye disease.

[00218] Examples of muscular eye diseases include, but are not limited to, strabismus (crossed eye/wandering eye/walleye ophthalmoparesis), progressive external ophthalmoplegia, esotropia, exotropia, a disorder of refraction and accommodation, hypermetropia, myopia, astigmatism, anisometropia, presbyopia, a disorders of accommodation, or internal ophthalmoplegia. In yet other embodiments, the USP30-related disease is a metabolic disease.

[00219] Examples of metabolic disorders include, but are not limited to, hyperlipidemia, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, HDL hypocholesterolemia, LDL hypercholesterolemia and/or HLD non-cholesterolemia, VLDL hyperproteinemia, dyslipoproteinemia, apolipoprotein A-I hypoproteinemia, atherosclerosis, disease of arterial sclerosis, disease of cardiovascular systems, cerebrovascular disease, peripheral circulatory disease, metabolic syndrome, syndrome X, obesity, diabetes (type I or II), hyperglycemia, insulin resistance, impaired glucose tolerance, hyperinsulinism, diabetic complication, cardiac insufficiency, cardiac infarction, cardiomyopathy, hypertension, non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), thrombus, Parkinson's disease, Alzheimer's disease, neurodegenerative disease, demyelinating disease, multiple sclerosis, adrenal

leukodystrophy, dermatitis, psoriasis, acne, skin aging, trichosis, inflammation, arthritis, asthma, hypersensitive intestine syndrome, ulcerative colitis, Crohn's disease, and pancreatitis.

[00220] In still other embodiments, the USP30-related disease is cancer. Examples of cancer include, but are not limited to, cancers of the colon, large intestine, skin, breast, prostate, ovary, and/or lung.

[00221] In other embodiments, the USP30-related disease is an ischemic injury. Examples of ischemic injuries include, but are not limited to, cardiac ischemia, such as myocardial infarction; brain ischemia (e.g., acute ischemic stroke; chronic ischemic of the brain, such as vascular dementia; and transient ischemic attack (TIA); bowel ischemia, such as ischemic colitis; limb ischemia, such as acute arm or leg ischemia; subcutaneous ischemia, such as cyanosis or gangrene; and ischemic organ injury, such as ischemic renal injury (IRI).

[00222] In still other embodiments, the USP30-related disease is a renal disease. Examples of renal diseases include, but are not limited to, glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, acute nephritis, recurrent hematuria, persistent hematuria, chronic nephritis, rapidly progressive nephritis, acute kidney injury (also known as acute renal failure), chronic renal failure, diabetic nephropathy, or Bartter's syndrome.

[00223] Even though USP30 inhibitors are known in the art, there is a continuing need to provide novel inhibitors having more effective or advantageous pharmaceutically relevant properties. For example, compounds with increased activity, selectivity over other deubiquitinating enzymes (DUBs) such as USP8, USP15, and USP16, and ADMET (absorption, distribution, metabolism, excretion, and/or toxicity) properties. Thus, in some embodiments, the present invention provides inhibitors of USP30 which show selectivity over other DUBs.

[00224] USP8 is a DUB within the same phylogenetic tree as USP30, localizes to mitochondria and mediates K6-linked deubiquitination (Kemp M: Recent Advances in the Discovery of Deubiquitinating Enzyme Inhibitors. *Prog Med Chem* 2016, 55:149-192). USP8 can also deubiquitinate parkin, thus it may impact the mitophagy pathway. Furthermore, embryonic lethality resulting from USP8 knockout (Niendorf et al., Essential role of ubiquitin-specific protease 8 for receptor tyrosine kinase stability and endocytic trafficking in vivo. *Mol Cell Biol* 2007, 27:5029-5039. PMC1951504.) suggests USP8 inhibition may have detrimental toxicity. USP15 also localizes to mitochondria and can alter parkin-mediated mitophagy (Coyne and Wing, The business of deubiquitination - location, location, location. *F1000Res* 2016, 5. PMC4755399.).

USP16 is similar to USP30 in that they both lack an aspartate as part of their catalytic triad (Gersch et al, Mechanism and regulation of the Lys6-selective deubiquitinase USP30. Nat Struct Mol Biol 2017, 24:920-930. PMC5757785; Nijman et al., A genomic and functional inventory of deubiquitinating enzymes. Cell 2005, 123:773-786; Mevissen and Komander, Mechanisms of Deubiquitinase Specificity and Regulation. Annu Rev Biochem 2017, 86:159-192.) and knockout of this gene is embryonic lethal.

[00225] 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 disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. 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 prevent or delay their recurrence.

[00226] Provided compounds are inhibitors of USP30 and are therefore useful for treating one or more disorders associated with activity of USP30. Thus, in certain embodiments, the present invention provides a method for treating a USP30-mediated disorder comprising the step of administering to a patient in need thereof a compound of the present invention, or pharmaceutically acceptable composition thereof.

[00227] As used herein, the term “USP30-mediated” disorders, diseases, and/or conditions as used herein means any disease or other deleterious condition in which USP30 is known to play a role. Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which USP30 is known to play a role.

[00228] Furthermore, the invention provides the use of a compound according to the definitions herein, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof for the preparation of a medicament for the treatment of a USP30-mediated disorder.

Combination Therapies

[00229] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents, which are normally administered to treat that condition, may be administered in combination with compounds and compositions of this invention. As used herein, additional

therapeutic agents that are normally administered to treat a particular disease, or condition, are known as “appropriate for the disease, or condition, being treated.”

[00230] In certain embodiments, a provided combination, or composition thereof, is administered in combination with another therapeutic agent.

[00231] Examples of agents the combinations of this invention may also be combined with include, without limitation: treatments for Alzheimer’s Disease such as Aricept[®] and Exelon[®]; treatments for HIV such as ritonavir; treatments for Parkinson’s Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex[®] and Rebif[®]), Copaxone[®], and mitoxantrone; treatments for asthma such as albuterol and Singulair[®]; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; agents that prolong or improve pharmacokinetics such as cytochrome P450 inhibitors (i.e., inhibitors of metabolic breakdown) and CYP3A4 inhibitors (e.g., ketokenazole and ritonavir), and agents for treating immunodeficiency disorders such as gamma globulin.

[00232] In certain embodiments, combination therapies of the present invention, or a pharmaceutically acceptable composition thereof, are administered in combination with a monoclonal antibody or an siRNA therapeutic.

[00233] Those additional agents may be administered separately from a provided combination therapy, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted

simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[00234] As used herein, the term “combination,” “combined,” and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a combination of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form.

[00235] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00236] In one embodiment, the present invention provides a composition comprising a compound of formula **I** and one or more additional therapeutic agents. The therapeutic agent may be administered together with a compound of formula **I**, or may be administered prior to or following administration of a compound of formula **I**. Suitable therapeutic agents are described in further detail below. In certain embodiments, a compound of formula **I** may be administered up to 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5, hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, or 18 hours before the therapeutic agent. In other embodiments, a compound of formula **I** may be administered up to 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5, hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, or 18 hours following the therapeutic agent.

[00237] In another embodiment, the present invention provides a method of treating an inflammatory disease, disorder or condition by administering to a patient in need thereof a compound of formula **I** and one or more additional therapeutic agents. Such additional therapeutic agents may be small molecules or recombinant biologic agents and include, for example, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, colchicine (Colcrys®), corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, probenecid,

allopurinol, febuxostat (Uloric®), sulfasalazine (Azulfidine®), antimalarials such as hydroxychloroquine (Plaquenil®) and chloroquine (Aralen®), methotrexate (Rheumatrex®), gold salts such as gold thioglucose (Solganal®), gold thiomalate (Myochrysine®) and auranofin (Ridaura®), D-penicillamine (Depen® or Cuprimine®), azathioprine (Imuran®), cyclophosphamide (Cytoxan®), chlorambucil (Leukeran®), cyclosporine (Sandimmune®), leflunomide (Arava®) and “anti-TNF” agents such as etanercept (Enbrel®), infliximab (Remicade®), golimumab (Simponi®), certolizumab pegol (Cimzia®) and adalimumab (Humira®), “anti-IL-1” agents such as anakinra (Kineret®) and rilonacept (Arcalyst®), canakinumab (Ilaris®), anti-Jak inhibitors such as tofacitinib, antibodies such as rituximab (Rituxan®), “anti-T-cell” agents such as abatacept (Orencia®), “anti-IL-6” agents such as tocilizumab (Actemra®), diclofenac, cortisone, hyaluronic acid (Synvisc® or Hyalgan®), monoclonal antibodies such as tanezumab, anticoagulants such as heparin (Calcinparine® or Liquaemin®) and warfarin (Coumadin®), antidiarrheals such as diphenoxylate (Lomotil®) and loperamide (Imodium®), bile acid binding agents such as cholestyramine, alosetron (Lotronex®), lubiprostone (Amitiza®), laxatives such as Milk of Magnesia, polyethylene glycol (MiraLax®), Dulcolax®, Correctol® and Senokot®, anticholinergics or antispasmodics such as dicyclomine (Bentyl®), Singulair®, beta-2 agonists such as albuterol (Ventolin® HFA, Proventil® HFA), levalbuterol (Xopenex®), metaproterenol (Alupent®), pirbuterol acetate (Maxair®), terbutaline sulfate (Brethaire®), salmeterol xinafoate (Serevent®) and formoterol (Foradil®), anticholinergic agents such as ipratropium bromide (Atrovent®) and tiotropium (Spiriva®), inhaled corticosteroids such as beclomethasone dipropionate (Beclovent®, Qvar®, and Vanceril®), triamcinolone acetonide (Azmecort®), mometasone (Asthmanex®), budesonide (Pulmocort®), and flunisolide (Aerobid®), Afviar®, Symbicort®, Dulera®, cromolyn sodium (Intal®), methylxanthines such as theophylline (Theo-Dur®, Theolair®, Slo-bid®, Uniphyll®, Theo-24®) and aminophylline, IgE antibodies such as omalizumab (Xolair®), nucleoside reverse transcriptase inhibitors such as zidovudine (Retrovir®), abacavir (Ziagen®), abacavir/lamivudine (Epzicom®), abacavir/lamivudine/zidovudine (Trizivir®), didanosine (Videx®), emtricitabine (Emtriva®), lamivudine (Epivir®), lamivudine/zidovudine (Combivir®), stavudine (Zerit®), and zalcitabine (Hivid®), non-nucleoside reverse transcriptase inhibitors such as delavirdine (Rescriptor®), efavirenz (Sustiva®), nevirapine (Viramune®) and etravirine (Intelence®), nucleotide reverse transcriptase inhibitors such as tenofovir (Viread®), protease inhibitors such as amprenavir

(Agenerase®), atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Lexiva®), indinavir (Crixivan®), lopinavir and ritonavir (Kaletra®), nelfinavir (Viracept®), ritonavir (Norvir®), saquinavir (Fortovase® or Invirase®), and tipranavir (Aptivus®), entry inhibitors such as enfuvirtide (Fuzeon®) and maraviroc (Selzentry®), integrase inhibitors such as raltegravir (Isentress®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), bortezomib (Velcade®), and dexamethasone (Decadron®) in combination with lenalidomide (Revlimid®), or any combination(s) thereof.

[00238] In another embodiment, the present invention provides a method of treating rheumatoid arthritis comprising administering to a patient in need thereof a compound of formula **I** and one or more additional therapeutic agents selected from non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, sulfasalazine (Azulfidine®), antimalarials such as hydroxychloroquine (Plaquenil®) and chloroquine (Aralen®), methotrexate (Rheumatrex®), gold salts such as gold thioglucose (Solganal®), gold thiomalate (Myochrysine®) and auranofin (Ridaura®), D-penicillamine (Depen® or Cuprimine®), azathioprine (Imuran®), cyclophosphamide (Cytosan®), chlorambucil (Leukeran®), cyclosporine (Sandimmune®), leflunomide (Arava®) and “anti-TNF” agents such as etanercept (Enbrel®), infliximab (Remicade®), golimumab (Simponi®), certolizumab pegol (Cimzia®) and adalimumab (Humira®), “anti-IL-1” agents such as anakinra (Kineret®) and rilonacept (Arcalyst®), antibodies such as rituximab (Rituxan®), “anti-T-cell” agents such as abatacept (Orencia®) and “anti-IL-6” agents such as tocilizumab (Actemra®).

[00239] In some embodiments, the present invention provides a method of treating osteoarthritis comprising administering to a patient in need thereof a compound of formula **I** and one or more additional therapeutic agents selected from acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, diclofenac, cortisone, hyaluronic acid (Synvisc® or Hyalgan®) and monoclonal antibodies such as tanezumab.

[00240] In some embodiments, the present invention provides a method of treating systemic lupus erythematosus comprising administering to a patient in need thereof a compound of formula **I** and one or more additional therapeutic agents selected from acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and

celecoxib, corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, antimalarials such as hydroxychloroquine (Plaquenil®) and chloroquine (Aralen®), cyclophosphamide (Cytosan®), methotrexate (Rheumatrex®), azathioprine (Imuran®) and anticoagulants such as heparin (Calcinarine® or Liquaemin®) and warfarin (Coumadin®).

[00241] In some embodiments, the present invention provides a method of treating Crohn's disease, ulcerative colitis, or inflammatory bowel disease comprising administering to a patient in need thereof a compound of formula I and one or more additional therapeutic agents selected from mesalamine (Asacol®) sulfasalazine (Azulfidine®), antidiarrheals such as diphenoxylate (Lomotil®) and loperamide (Imodium®), bile acid binding agents such as cholestyramine, alosetron (Lotronex®), lubiprostone (Amitiza®), laxatives such as Milk of Magnesia, polyethylene glycol (MiraLax®), Dulcolax®, Correctol® and Senokot® and anticholinergics or antispasmodics such as dicyclomine (Bentyl®), anti-TNF therapies, steroids, and antibiotics such as Flagyl or ciprofloxacin.

[00242] In some embodiments, the present invention provides a method of treating asthma comprising administering to a patient in need thereof a compound of formula I and one or more additional therapeutic agents selected from Singulair®, beta-2 agonists such as albuterol (Ventolin® HFA, Proventil® HFA), levalbuterol (Xopenex®), metaproterenol (Alupent®), pirbuterol acetate (Maxair®), terbutaline sulfate (Brethaire®), salmeterol xinafoate (Serevent®) and formoterol (Foradil®), anticholinergic agents such as ipratropium bromide (Atrovent®) and tiotropium (Spiriva®), inhaled corticosteroids such as prednisone, prednisolone, beclomethasone dipropionate (Beclovent®, Qvar®, and Vanceril®), triamcinolone acetonide (Azmecort®), mometasone (Asthmanex®), budesonide (Pulmocort®), flunisolide (Aerobid®), Afviar®, Symbicort®, and Dulera®, cromolyn sodium (Intal®), methylxanthines such as theophylline (Theo-Dur®, Theolair®, Slo-bid®, Uniphyll®, Theo-24®) and aminophylline, and IgE antibodies such as omalizumab (Xolair®).

[00243] In some embodiments, the present invention provides a method of treating COPD comprising administering to a patient in need thereof a compound of formula I and one or more additional therapeutic agents selected from beta-2 agonists such as albuterol (Ventolin® HFA, Proventil® HFA), levalbuterol (Xopenex®), metaproterenol (Alupent®), pirbuterol acetate (Maxair®), terbutaline sulfate (Brethaire®), salmeterol xinafoate (Serevent®) and formoterol (Foradil®), anticholinergic agents such as ipratropium bromide (Atrovent®) and tiotropium

(Spiriva®), methylxanthines such as theophylline (Theo-Dur®, Theolair®, Slo-bid®, Uniphyll®, Theo-24®) and aminophylline, inhaled corticosteroids such as prednisone, prednisolone, beclomethasone dipropionate (Beclovent®, Qvar®, and Vanceril®), triamcinolone acetonide (Azmacort®), mometasone (Asthmanex®), budesonide (Pulmocort®), flunisolide (Aerobid®), Afviar®, Symbicort®, and Dulera®,

[00244] In another embodiment, the present invention provides a method of treating a hematological malignancy comprising administering to a patient in need thereof a compound of formula **I** and one or more additional therapeutic agents selected from rituximab (Rituxan®), cyclophosphamide (Cytoxan®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), prednisone, a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a PI3K inhibitor, a SYK inhibitor, and combinations thereof.

[00245] In another embodiment, the present invention provides a method of treating a solid tumor comprising administering to a patient in need thereof a compound of formula **I** and one or more additional therapeutic agents selected from rituximab (Rituxan®), cyclophosphamide (Cytoxan®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), prednisone, a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a PI3K inhibitor, a SYK inhibitor, and combinations thereof.

[00246] In another embodiment, the present invention provides a method of treating a hematological malignancy comprising administering to a patient in need thereof a compound of formula **I** and a Hedgehog (Hh) signaling pathway inhibitor. In some embodiments, the hematological malignancy is DLBCL (Ramirez *et al* “Defining causative factors contributing in the activation of hedgehog signaling in diffuse large B-cell lymphoma” Leuk. Res. (2012), published online July 17, and incorporated herein by reference in its entirety).

[00247] In another embodiment, the present invention provides a method of treating diffuse large B-cell lymphoma (DLBCL) comprising administering to a patient in need thereof a compound of formula **I** and one or more additional therapeutic agents selected from rituximab (Rituxan®), cyclophosphamide (Cytoxan®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), prednisone, a hedgehog signaling inhibitor, and combinations thereof.

[00248] In another embodiment, the present invention provides a method of treating multiple myeloma comprising administering to a patient in need thereof a compound of formula **I** and one or more additional therapeutic agents selected from bortezomib (Velcade®), and dexamethasone

(Decadron®), a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, a SYK inhibitor in combination with lenalidomide (Revlimid®).

[00249] In another embodiment, the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a compound of formula **I** and a BTK inhibitor, wherein the disease is selected from inflammatory bowel disease, arthritis, systemic lupus erythematosus (SLE), vasculitis, idiopathic thrombocytopenic purpura (ITP), rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease, autoimmune thyroiditis, Sjogren's syndrome, multiple sclerosis, systemic sclerosis, Lyme neuroborreliosis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, Addison's disease, opsoclonus-myoclonus syndrome, ankylosing spondylosis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, autoimmune gastritis, pernicious anemia, celiac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behcet's disease, chronic fatigue, dysautonomia, membranous glomerulonephropathy, endometriosis, interstitial cystitis, pemphigus vulgaris, bullous pemphigoid, neuromyotonia, scleroderma, vulvodynia, a hyperproliferative disease, rejection of transplanted organs or tissues, Acquired Immunodeficiency Syndrome (AIDS, also known as HIV), type 1 diabetes, graft versus host disease, transplantation, transfusion, anaphylaxis, allergies (e.g., allergies to plant pollens, latex, drugs, foods, insect poisons, animal hair, animal dander, dust mites, or cockroach calyx), type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, and atopic dermatitis, asthma, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, Crohn's disease, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, uveitis,

vaginitis, vasculitis, or vulvitis, B-cell proliferative disorder, e.g., diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, multiple myeloma (also known as plasma cell myeloma), non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, or lymphomatoid granulomatosis, breast cancer, prostate cancer, or cancer of the mast cells (e.g., mastocytoma, mast cell leukemia, mast cell sarcoma, systemic mastocytosis), bone cancer, colorectal cancer, pancreatic cancer, diseases of the bone and joints including, without limitation, rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome, systemic sclerosis, osteoporosis, bone cancer, bone metastasis, a thromboembolic disorder, (e.g., myocardial infarct, angina pectoris, reocclusion after angioplasty, restenosis after angioplasty, reocclusion after aortocoronary bypass, restenosis after aortocoronary bypass, stroke, transitory ischemia, a peripheral arterial occlusive disorder, pulmonary embolism, deep venous thrombosis), inflammatory pelvic disease, urethritis, skin sunburn, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, cholecystitis, agammaglobulinemia, psoriasis, allergy, Crohn's disease, irritable bowel syndrome, ulcerative colitis, Sjogren's disease, tissue graft rejection, hyperacute rejection of transplanted organs, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), autoimmune alopecia, pernicious anemia, glomerulonephritis, dermatomyositis, multiple sclerosis, scleroderma, vasculitis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome, atherosclerosis, Addison's disease, Parkinson's disease, Alzheimer's disease, diabetes, septic shock, systemic lupus erythematosus (SLE), rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, osteoarthritis, chronic idiopathic thrombocytopenic purpura, Waldenstrom macroglobulinemia, myasthenia gravis, Hashimoto's thyroiditis, atopic dermatitis, degenerative joint disease, vitiligo, autoimmune hypopituitarism, Guillain-Barre syndrome, Behcet's disease, scleroderma, mycosis fungoides, acute inflammatory

responses (such as acute respiratory distress syndrome and ischemia/reperfusion injury), and Graves' disease.

[00250] In another embodiment, the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a compound of formula **I** and a PI3K inhibitor, wherein the disease is selected from a cancer, a neurodegenerative disorder, an angiogenic disorder, a viral disease, an autoimmune disease, an inflammatory disorder, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), liver disease, pathologic immune conditions involving T cell activation, a cardiovascular disorder, and a CNS disorder.

[00251] In another embodiment, the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a compound of formula **I** and a PI3K inhibitor, wherein the disease is selected from benign or malignant tumor, carcinoma or solid tumor of the brain, kidney (e.g., renal cell carcinoma (RCC)), liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, endometrium, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastomas, neuroblastomas, multiple myeloma or gastrointestinal cancer, especially colon carcinoma or colorectal adenoma or a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphomas, (including, for example, non-Hodgkin's Lymphoma (NHL) and Hodgkin's lymphoma (also termed Hodgkin's or Hodgkin's disease)), a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, or a leukemia, diseases include Cowden syndrome, Lhermitte-Duclos disease and Bannayan-Zonana syndrome, or diseases in which the PI3K/PKB pathway is aberrantly activated, asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection, acute lung injury (ALI), adult/acute respiratory distress syndrome (ARDS), chronic

obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy, bronchitis of whatever type or genesis including, but not limited to, acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis, pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis, Loffler's syndrome, eosinophilic, pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction, psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphigus, epidermolysis bullosa acquisita, conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or etiology, including autoimmune hematological disorders (e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy, restenosis, cardiomegaly, atherosclerosis, myocardial infarction, ischemic stroke and congestive heart failure, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and cerebral ischemia, and neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity and hypoxia.

[00252] In some embodiments the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a compound of formula **I** and a Bcl-2 inhibitor, wherein the disease is an inflammatory disorder, an autoimmune disorder, a proliferative disorder, an endocrine disorder, a neurological disorder, or a disorder associated with transplantation. In some embodiments, the disorder is a proliferative disorder, lupus, or lupus nephritis. In some embodiments, the proliferative disorder is chronic lymphocytic leukemia, diffuse large B-cell lymphoma, Hodgkin's disease, small-cell lung cancer, non-small-cell lung cancer, myelodysplastic syndrome, lymphoma, a hematological neoplasm, or solid tumor.

[00253] In some embodiments the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a compound of formula **I** and a parkin activator, wherein the disease is an inflammatory disorder, an autoimmune disorder, a proliferative disorder, an endocrine disorder, a neurological disorder, or a disorder associated with transplantation. In some embodiments, the disorder is a neurological disorder. In some embodiments, the disorder is Parkinson's disease. In some embodiments, the disorder is Alzheimer's disease.

[00254] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of an autoimmune disorder, an inflammatory disorder, a proliferative disorder, an endocrine disorder, a neurological disorder, or a disorder associated with transplantation. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. Compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the

treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term “patient”, as used herein, means an animal, preferably a mammal, and most preferably a human.

[00255] Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00256] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00257] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00258] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00259] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microcapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00260] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00261] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i)

lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00262] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00263] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00264] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention.

Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00265] According to one embodiment, the invention relates to a method of inhibiting USP30 activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00266] According to another embodiment, the invention relates to a method of inhibiting USP30 activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound. In certain embodiments, the invention relates to a method of irreversibly inhibiting USP30, or a mutant thereof, activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00267] In another embodiment, the invention provides a method of selectively inhibiting USP30 over one or more DUBs. In some embodiments, a compound of the present invention is more than 2-fold selective over USP8, USP15, and/or USP16. In some embodiments, a compound of the present invention is more than 5-fold selective over USP8, USP15, and/or USP16. In some embodiments, a compound of the present invention is more than 10-fold selective over USP8, USP15, and/or USP16. In some embodiments, a compound of the present invention is more than 50-fold selective over USP8, USP15, and/or USP16. In some embodiments, a compound of the present invention is more than 100-fold selective over USP8, USP15, and/or USP16.

[00268] The term “biological sample”, as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00269] Inhibition of USP30 activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to biological assays.

[00270] Another embodiment of the present invention relates to a method of inhibiting USP30 activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound.

[00271] According to another embodiment, the invention relates to a method of inhibiting activity of USP30 in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. According to certain embodiments, the invention relates to a method of reversibly or irreversibly inhibiting USP30 activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. In other embodiments, the present invention provides a method for treating a disorder mediated by USP30 in a patient in need thereof, comprising the step of administering to said patient a compound according to the present invention or pharmaceutically acceptable composition thereof. Such disorders are described in detail herein.

[00272] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents that are normally administered to treat that condition, may also be present in the compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as “appropriate for the disease, or condition, being treated.”

[00273] A compound of the current invention may also be used to advantage in combination with other therapeutic compounds. In some embodiments, the other therapeutic compounds are antiproliferative compounds. Such antiproliferative compounds include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; matrix metalloproteinase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors such as 17-AAG (17-allylaminogeldanamycin,

NSC330507), 17-DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 from Conforma Therapeutics; temozolomide (Temodal[®]); kinesin spindle protein inhibitors, such as SB715992 or SB743921 from GlaxoSmithKline, or pentamidine/chlorpromazine from CombinatoRx; MEK inhibitors such as ARRY142886 from Array BioPharma, AZD6244 from AstraZeneca, PD181461 from Pfizer and leucovorin. The term "aromatase inhibitor" as used herein relates to a compound which inhibits estrogen production, for instance, the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane is marketed under the trade name Aromasin[™]. Formestane is marketed under the trade name Lentaron[™]. Fadrozole is marketed under the trade name Afema[™]. Anastrozole is marketed under the trade name Arimidex[™]. Letrozole is marketed under the trade names Femara[™] or Femar[™]. Aminoglutethimide is marketed under the trade name Orimeten[™]. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, such as breast tumors.

[00274] The term "antiestrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen is marketed under the trade name Nolvadex[™]. Raloxifene hydrochloride is marketed under the trade name Evista[™]. Fulvestrant can be administered under the trade name Faslodex[™]. A combination of the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, such as breast tumors.

[00275] The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (Casodex[™]). The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate. Goserelin can be administered under the trade name Zoladex[™].

[00276] The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, gimatecan, irinotecan, camptothecin and its analogues, 9-nitrocamptothecin and the

macromolecular camptothecin conjugate PNU-166148. Irinotecan can be administered, e.g. in the form as it is marketed, e.g. under the trademark Camptosar™. Topotecan is marketed under the trade name Hycamptin™.

[00277] The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin (including liposomal formulation, such as Caelyx™), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophyllotoxines etoposide and teniposide. Etoposide is marketed under the trade name Etopophos™. Teniposide is marketed under the trade name VM 26-Bristol. Doxorubicin is marketed under the trade name Acriblastin™ or Adriamycin™. Epirubicin is marketed under the trade name Farmorubicin™. Idarubicin is marketed under the trade name Zavedos™. Mitoxantrone is marketed under the trade name Novantron.

[00278] The term "microtubule active agent" relates to microtubule stabilizing, microtubule destabilizing compounds and microtubulin polymerization inhibitors including, but not limited to taxanes, such as paclitaxel and docetaxel; vinca alkaloids, such as vinblastine or vinblastine sulfate, vincristine or vincristine sulfate, and vinorelbine; discodermolides; cochicine and epothilones and derivatives thereof. Paclitaxel is marketed under the trade name Taxol™. Docetaxel is marketed under the trade name Taxotere™. Vinblastine sulfate is marketed under the trade name Vinblastin R.P™. Vincristine sulfate is marketed under the trade name Farmistin™.

[00279] The term "alkylating agent" as used herein includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide is marketed under the trade name Cyclostin™. Ifosfamide is marketed under the trade name Holoxan™.

[00280] The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes, but is not limited to, suberoylanilide hydroxamic acid (SAHA).

[00281] The term "antineoplastic antimetabolite" includes, but is not limited to, 5-fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists such as pemetrexed. Capecitabine is marketed under the trade name Xeloda™. Gemcitabine is marketed under the trade name Gemzar™.

[00282] The term "platin compound" as used herein includes, but is not limited to, carboplatin, cis-platin, cisplatin and oxaliplatin. Carboplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark Carboplat™. Oxaliplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark Eloxatin™.

[00283] The term "compounds targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or further anti-angiogenic compounds" as used herein includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, such as a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib, SU101, SU6668 and GFB-111; b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR); c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the kinase activity of IGF-I receptor, or antibodies that target the extracellular domain of IGF-I receptor or its growth factors; d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors; e) compounds targeting, decreasing or inhibiting the activity of the Axl receptor tyrosine kinase family; f) compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase; g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, such as imatinib; h) compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases, which are part of the PDGFR family, such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, such as imatinib; i) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. BCR-Abl kinase) and mutants, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib or nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 from ParkeDavis; or dasatinib (BMS-354825); j) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK/pan-JAK, FAK, PDK1,

PKB/Akt, Ras/MAPK, PI3K, SYK, BTK and TEC family, and/or members of the cyclin-dependent kinase family (CDK) including staurosporine derivatives, such as midostaurin; examples of further compounds include UCN-01, safinol, BAY 43-9006, Bryostatin 1, Perifosine, Ilmofofosine, RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds; FTIs; PD184352 or QAN697 (a PI3K inhibitor) or AT7519 (CDK inhibitor); k) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (Gleevec™) or tyrphostin such as Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5- dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin); l) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR₁ ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, such as EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, CP 358774, ZD 1839, ZM 105180; trastuzumab (Herceptin™), cetuximab (Erbix™), Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives; m) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor, such as compounds which target, decrease or inhibit the activity of c-Met, especially compounds which inhibit the kinase activity of c-Met receptor, or antibodies that target the extracellular domain of c-Met or bind to HGF, n) compounds targeting, decreasing or inhibiting the kinase activity of one or more JAK family members (JAK1/JAK2/JAK3/TYK2 and/or pan-JAK), including but not limited to PRT-062070, SB-1578, baricitinib, pacritinib, momelotinib, VX-509, AZD-1480, TG-101348, tofacitinib, and ruxolitinib; o) compounds targeting, decreasing or inhibiting the kinase activity of PI3 kinase (PI3K) including but not limited to ATU-027, SF-1126, DS-7423, PBI-05204, GSK-2126458, ZSTK-474, buparlisib, pictrelisib, PF-4691502, BYL-719, dactolisib, XL-147, XL-765, and idelalisib; and; and q) compounds targeting, decreasing or inhibiting the signaling effects of hedgehog protein (Hh) or smoothened receptor (SMO) pathways,

including but not limited to cyclopamine, vismodegib, itraconazole, erismodegib, and IPI-926 (saridegib).

[00284] The term “PI3K inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against one or more enzymes in the phosphatidylinositol-3-kinase family, including, but not limited to PI3K α , PI3K γ , PI3K δ , PI3K β , PI3K-C2 α , PI3K-C2 β , PI3K-C2 γ , Vps34, p110- α , p110- β , p110- γ , p110- δ , p85- α , p85- β , p55- γ , p150, p101, and p87. Examples of PI3K inhibitors useful in this invention include but are not limited to ATU-027, SF-1126, DS-7423, PBI-05204, GSK-2126458, ZSTK-474, buparlisib, pictrelisib, PF-4691502, BYL-719, dactolisib, XL-147, XL-765, and idelalisib.

[00285] The term “BTK inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against Bruton’s Tyrosine Kinase (BTK), including, but not limited to AVL-292 and ibrutinib.

[00286] The term “SYK inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against spleen tyrosine kinase (SYK), including but not limited to PRT-062070, R-343, R-333, Excellair, PRT-062607, and fostamatinib.

[00287] The term “Bcl-2 inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against B-cell lymphoma 2 protein (Bcl-2), including but not limited to ABT-199, ABT-731, ABT-737, apogossypol, Ascenta’s pan-Bcl-2 inhibitors, curcumin (and analogs thereof), dual Bcl-2/Bcl-xL inhibitors (Infinity Pharmaceuticals/Novartis Pharmaceuticals), Genasense (G3139), HA14-1 (and analogs thereof; see WO2008118802), navitoclax (and analogs thereof, see US7390799), NH-1 (Shenayng Pharmaceutical University), obatoclax (and analogs thereof, see WO2004106328), S-001 (Gloria Pharmaceuticals), TW series compounds (Univ. of Michigan), and venetoclax. In some embodiments the Bcl-2 inhibitor is a small molecule therapeutic. In some embodiments the Bcl-2 inhibitor is a peptidomimetic.

[00288] Further examples of BTK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2008039218 and WO2011090760, the entirety of which are incorporated herein by reference.

[00289] Further examples of SYK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2003063794, WO2005007623, and WO2006078846, the entirety of which are incorporated herein by reference.

[00290] Further examples of PI3K inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2004019973, WO2004089925, WO2007016176, US8138347, WO2002088112, WO2007084786, WO2007129161, WO2006122806, WO2005113554, and WO2007044729 the entirety of which are incorporated herein by reference.

[00291] Further examples of JAK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2009114512, WO2008109943, WO2007053452, WO2000142246, and WO2007070514, the entirety of which are incorporated herein by reference.

[00292] Further anti-angiogenic compounds include compounds having another mechanism for their activity, e.g. unrelated to protein or lipid kinase inhibition e.g. thalidomide (Thalomid™) and TNP-470.

[00293] Examples of proteasome inhibitors useful for use in combination with compounds of the invention include, but are not limited to bortezomib, disulfiram, epigallocatechin-3-gallate (EGCG), salinosporamide A, carfilzomib, ONX-0912, CEP-18770, and MLN9708.

[00294] Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are e.g. inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[00295] Compounds which induce cell differentiation processes include, but are not limited to, retinoic acid, α - γ - or δ - tocopherol or α - γ - or δ -tocotrienol.

[00296] The term cyclooxygenase inhibitor as used herein includes, but is not limited to, Cox-2 inhibitors, 5-alkyl substituted 2-arylamino phenylacetic acid and derivatives, such as celecoxib (Celebrex™), rofecoxib (Vioxx™), etoricoxib, valdecoxib or a 5-alkyl-2- arylamino phenylacetic acid, such as 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib.

[00297] The term "bisphosphonates" as used herein includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. Etridonic acid is marketed under the trade name Didronel™. Clodronic acid is marketed under the trade name Bonafos™. Tiludronic acid is marketed under the trade name Skelid™. Pamidronic acid is marketed under the trade name Aredia™. Alendronic acid is marketed under the trade name Fosamax™. Ibandronic acid is marketed under the trade name Bondranat™. Risedronic acid is marketed under the trade name Actonel™. Zoledronic acid is marketed under the trade name

Zometa™. The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (Rapamune®), everolimus (Certican™), CCI-779 and ABT578.

[00298] The term "heparanase inhibitor" as used herein refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88. The term "biological response modifier" as used herein refers to a lymphokine or interferons.

[00299] The term "inhibitor of Ras oncogenic isoforms", such as H-Ras, K-Ras, or N-Ras, as used herein refers to compounds which target, decrease or inhibit the oncogenic activity of Ras; for example, a "farnesyl transferase inhibitor" such as L-744832, DK8G557 or R115777 (Zarnestra™). The term "telomerase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, such as telomestatin.

[00300] The term "methionine aminopeptidase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase include, but are not limited to, bengamide or a derivative thereof.

[00301] The term "proteasome inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include, but are not limited to, Bortezomib (Velcade™) and MLN 341.

[00302] The term "matrix metalloproteinase inhibitor" or ("MMP" inhibitor) as used herein includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, e.g. hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B or AAJ996.

[00303] The term "compounds used in the treatment of hematologic malignancies" as used herein includes, but is not limited to, FMS-like tyrosine kinase inhibitors, which are compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1-β-D-arabinofuransylcytosine (ara-c) and bisulfan; ALK inhibitors, which are compounds which target, decrease or inhibit anaplastic lymphoma kinase, and Bcl-2 inhibitors.

[00304] Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, such as PKC412, midostaurin, a staurosporine derivative, SU11248 and MLN518.

[00305] The term "HSP90 inhibitors" as used herein includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteasome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90, such as 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

[00306] The term "antiproliferative antibodies" as used herein includes, but is not limited to, trastuzumab (Herceptin™), Trastuzumab-DM1, erbitux, bevacizumab (Avastin™), rituximab (Rituxan®), PRO64553 (anti-CD40) and 2C4 Antibody. By antibodies is meant intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

[00307] For the treatment of acute myeloid leukemia (AML), compounds of the current invention can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of the current invention can be administered in combination with, for example, farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412. In some embodiments, the present invention provides a method of treating AML associated with an ITD and/or D835Y mutation, comprising administering a compound of the present invention together with a one or more FLT3 inhibitors. In some embodiments, the FLT3 inhibitors are selected from quizartinib (AC220), a staurosporine derivative (*e.g.* midostaurin or lestaurtinib), sorafenib, tandutinib, LY-2401401, LS-104, EB-10, famitinib, NOV-110302, NMS-P948, AST-487, G-749, SB-1317, S-209, SC-110219, AKN-028, fedratinib, tozasertib, and sunitinib. In some embodiments, the FLT3 inhibitors are selected from quizartinib, midostaurin, lestaurtinib, sorafenib, and sunitinib.

[00308] Other anti-leukemic compounds include, for example, Ara-C, a pyrimidine analog, which is the 2'-alpha-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is

the purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate. Compounds which target, decrease or inhibit activity of histone deacetylase (HDAC) inhibitors such as sodium butyrate and suberoylanilide hydroxamic acid (SAHA) inhibit the activity of the enzymes known as histone deacetylases. Specific HDAC inhibitors include MS275, SAHA, FK228 (formerly FR901228), Trichostatin A and compounds disclosed in US 6,552,065 including, but not limited to, N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof and N-hydroxy-3-[4-[(2-hydroxyethyl){2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof, especially the lactate salt. Somatostatin receptor antagonists as used herein refer to compounds which target, treat or inhibit the somatostatin receptor such as octreotide, and SOM230. Tumor cell damaging approaches refer to approaches such as ionizing radiation. The term "ionizing radiation" referred to above and hereinafter means ionizing radiation that occurs as either electromagnetic rays (such as X-rays and gamma rays) or particles (such as alpha and beta particles). Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. See Hellman, Principles of Radiation Therapy, Cancer, in Principles and Practice of Oncology, Devita et al., Eds., 4th Edition, Vol. 1, pp. 248-275 (1993).

[00309] Also included are EDG binders and ribonucleotide reductase inhibitors. The term "EDG binders" as used herein refers to a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720. The term "ribonucleotide reductase inhibitors" refers to pyrimidine or purine nucleoside analogs including, but not limited to, fludarabine and/or cytosine arabinoside (ara-C), 6-thioguanine, 5-fluorouracil, cladribine, 6-mercaptopurine (especially in combination with ara-C against ALL) and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1H-isoindole-1,3-dione derivatives.

[00310] Also included are in particular those compounds, proteins or monoclonal antibodies of VEGF such as 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine succinate; AngiostatinTM; EndostatinTM; anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor antibodies, such as rhuMAb and RHUFab, VEGF aptamer such as Macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgGI antibody, Angiozyme (RPI 4610) and Bevacizumab (AvastinTM).

[00311] Photodynamic therapy as used herein refers to therapy which uses certain chemicals known as photosensitizing compounds to treat or prevent cancers. Examples of photodynamic therapy include treatment with compounds, such as Visudyne™ and porfimer sodium.

[00312] Angiostatic steroids as used herein refers to compounds which block or inhibit angiogenesis, such as, e.g., anecortave, triamcinolone, hydrocortisone, 11- α -epihydrocortisol, cortexolone, 17 α -hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

[00313] Implants containing corticosteroids refers to compounds, such as fluocinolone and dexamethasone.

[00314] Other chemotherapeutic compounds include, but are not limited to, plant alkaloids, hormonal compounds and antagonists; biological response modifiers, preferably lymphokines or interferons; antisense oligonucleotides or oligonucleotide derivatives; shRNA or siRNA; or miscellaneous compounds or compounds with other or unknown mechanism of action.

[00315] The compounds of the invention are also useful as co-therapeutic compounds for use in combination with other drug substances such as anti-inflammatory, bronchodilatory or antihistamine drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. A compound of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Accordingly the invention includes a combination of a compound of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said compound of the invention and said drug substance being in the same or different pharmaceutical composition.

[00316] Suitable anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate; non-steroidal glucocorticoid receptor agonists; LTB₄ antagonists such LY293111, CGS025019C, CP-195543, SC-53228, BIIL 284, ONO 4057, SB 209247; LTD₄ antagonists such as montelukast and zafirlukast; PDE4 inhibitors such cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden), V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering- Plough), Arofylline (Almirall Prodesfarma), PD189659 / PD168787 (Parke-

Davis), AWD-12- 281 (Asta Medica), CDC-801 (Celgene), SeICID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo); A2a agonists; A2b antagonists; and beta-2 adrenoceptor agonists such as albuterol (salbutamol), metaproterenol, terbutaline, salmeterol fenoterol, procaterol, and especially, formoterol and pharmaceutically acceptable salts thereof. Suitable bronchodilatory drugs include anticholinergic or antimuscarinic compounds, in particular ipratropium bromide, oxitropium bromide, tiotropium salts and CHF 4226 (Chiesi), and glycopyrrolate.

[00317] Suitable antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, ebastine, epinastine, mizolastine and tefenadine.

[00318] Other useful combinations of compounds of the invention with anti-inflammatory drugs are those with antagonists of chemokine receptors, e.g. CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists such as Schering-Plough antagonists SC-351125, SCH-55700 and SCH-D, and Takeda antagonists such as N-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5H-benzo-cyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-N,N-dimethyl-2H-pyran-4-aminium chloride (TAK-770).

[00319] The structure of the active compounds identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications).

[00320] A compound of the current invention may also be used in combination with known therapeutic processes, for example, the administration of hormones or radiation. In certain embodiments, a provided compound is used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

[00321] A compound of the current invention can be administered alone or in combination with one or more other therapeutic compounds, possible combination therapy taking the form of fixed combinations or the administration of a compound of the invention and one or more other therapeutic compounds being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic compounds. A compound of the current invention can besides or in addition be administered especially for tumor therapy in

combination with chemotherapy, radiotherapy, immunotherapy, phototherapy, surgical intervention, or a combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumor regression, or even chemopreventive therapy, for example in patients at risk.

[00322] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[00323] As used herein, the term “combination,” “combined,” and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of the current invention, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[00324] The amount of both an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive compound can be administered.

[00325] In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 – 1,000 µg/kg body weight/day of the additional therapeutic agent can be administered.

[00326] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition

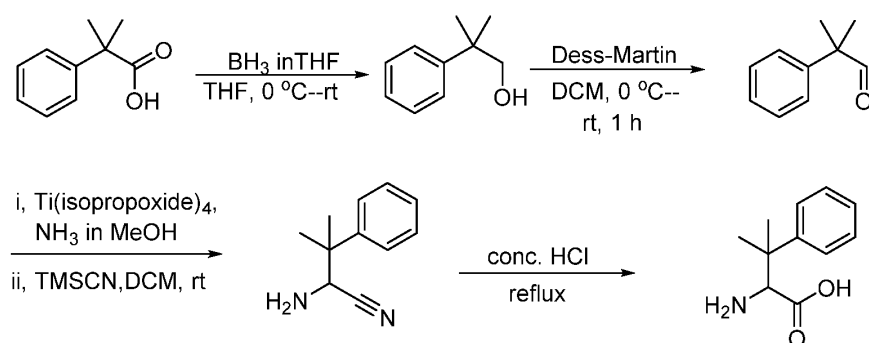
comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

EXEMPLIFICATION

[00327] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present invention, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

Example 1: Synthesis of Intermediates

Preparation of 2-amino-3-methyl-3-phenylbutanoic acid



[00328] Step 1: 2-methyl-2-phenylpropan-1-ol

[00329] BH_3 in THF (1N, 200 mL, 0.2 mol, 2.00 equiv) was added dropwise to a solution of 16.4 g 2-methyl-2-phenylpropanoic acid (0.1mol, 1.00 equiv) in 150 mL THF at 0 °C. The resulting mixture was stirred for 17 hours at room temperature. MeOH (150 mL) was added dropwise at 0 °C to quench the reaction. The resulting mixture was concentrated and purified by column chromatography (silica gel, petroleum ether:ethyl acetate (1:1)) to afford 14 g 2-methyl-2-phenylpropan-1-ol as a colorless oil (95% yield). MS (ESI^+) m/z 151.1 $[\text{M}+\text{H}]^+$.

[00330] Step 2: 2-methyl-2-phenylpropanal

[00331] Dess-Martin reagent (59.4g, 140 mmol, 1.5 equiv) was added in portion to a solution

of 14 g 2-methyl-2-phenylpropan-1-ol (93.3 mmol, 1.00 equiv) in DCM (1L). The resulting mixture was stirred for 2 hours at room temperature. Sat. NaHSO₃ (1L) was added dropwise to the reaction mixture to quench the reaction, and the resulting mixture was extracted with DCM (2 x 500 mL). The combined organic layers were washed with brine (2 X 100 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (10:1)) afforded 12 g 2-methyl-2-phenylpropanal as a colorless oil (85.7% yield). MS (ESI⁺) m/z 149.1[M+H]⁺.

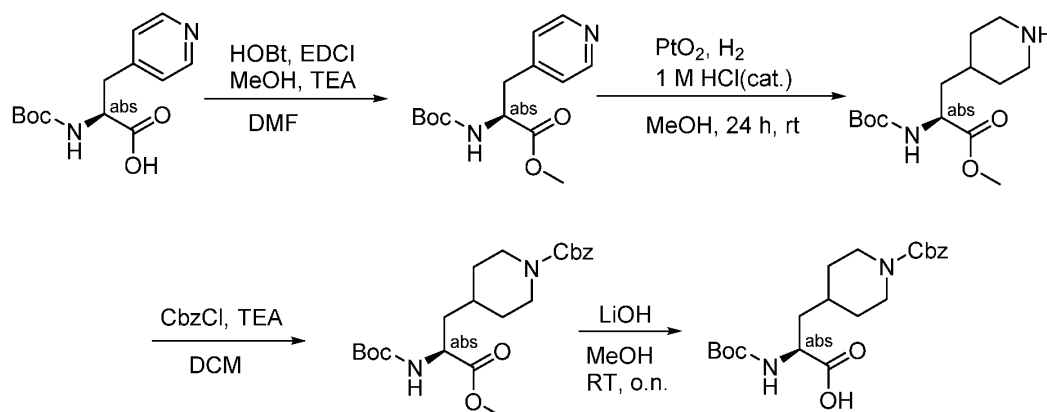
[00332] Preparation of 2-amino-3-methyl-3-phenylbutanenitrile

[00333] NH₃ in MeOH (7N, 70 mL) was added to a solution of 2-methyl-2-phenylpropanal (8 g, 54 mmol, 1.00 equiv) at 0 °C, followed by Ti(OiPr)₄ (18.4 g, 65 mmol, 1.2 equiv). After 1 hour, TMSCN (21 g, 210 mmol, 3.95 equiv) was added dropwise at 0 °C. The resulting mixture was stirred for 17 hours at room temperature. The mixture was diluted with 200 mL water and extracted with DCM (3 x 200 mL). The combined organic layers were washed with brine (3x100 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (4:1 to 1:1)) provided 2.8 g 2-amino-3-methyl-3-phenylbutanenitrile as a yellow solid (35% yield). MS (ESI⁺) m/z 175.1 [M+H]⁺.

[00334] Step 3: 2-amino-3-methyl-3-phenylbutanoic acid

[00335] A mixture of 2.8 g 2-amino-3-methyl-3-phenylbutanenitrile (16 mmol, 1.00 equiv) in 50 mL conc.HCl was refluxed for 17 h. The reaction mixture was extracted with DCM (2 x 50 mL), then the water phase was adjusted to PH=6-7 and concentrated to give crude 2-amino-3-methyl-3-phenylbutanoic acid (1 g, 50% yield). MS (ESI⁺) m/z 194.1 [M+H]⁺.

Preparation of (S)-3-(1-((benzyloxy)carbonyl)piperidin-4-yl)-2-((tert-butoxy carbonyl)amino)propanoic acid



[00336] Step 1: methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(pyridin-4-yl) propanoate

[00337] To a solution of 10 g (S)-2-((tert-butoxycarbonyl)amino)-3-(pyridin-4-yl)propanoic acid (37.55 mmol, 1.00 equiv), 13 g 1-Hydroxybenzotriazole (93.88 mmol, 2.50 equiv), 18 g *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (93.88 mmol, 2.50 equiv) and 11 g triethylamine (112.65 mmol, 3.00 equiv) in 80 mL *N,N*-dimethylformamide was added dropwise 4.8 g of methanol (150.21 mmol, 4.00 equiv) at room temperature. The resulting mixture was stirred for 6 hours at room temperature. The mixture was diluted with 100 mL water and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (1:1)) afforded 9.6 g methyl (S)-2-((tert-butoxy carbonyl)amino)-3-(pyridin-4-yl)propanoate as a yellow solid (91 % yield). MS (ESI+) *m/z* 281 [M+H]⁺.

[00338] Step 2: methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(piperidin-4-yl) propanoate

[00339] A mixture of 9.6 g methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(pyridin-4-yl)propanoate (34.25 mmol, 1.00 equiv) and 1.9 g Platinum dioxide (8.56 mmol, 0.25 equiv) in 10 mL 1M Hydrochloric acid and 100 mL methanol was stirred for 5 hours at room temperature under hydrogen. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, methylene chloride: methanol (20:1)) to afford 3.6 g methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(piperidin-4-yl)propanoate as a colorless oil (37% yield). MS (ESI+) *m/z* 287 [M+H]⁺.

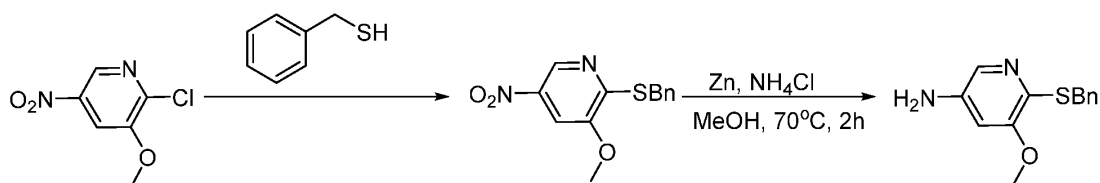
[00340] Step 3: benzyl (S)-4-(2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)piperidine-1-carboxylate

[00341] To a solution of 2.8 g methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(piperidin-4-yl)propanoate (9.80 mmol, 1.00 equiv) and 1.98 g triethylamine (19.56 mmol, 2.00 equiv) in 30 mL methylene chloride at 0 °C was added dropwise 2.00 g carbobenzoxy chloride (11.70 mmol, 1.20 equiv). The resulting mixture was stirred for 3 hours at room temperature. The mixture was diluted with 20 mL water and extracted with methylene chloride (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (5:1)) provided 2.6 g benzyl (S)-4-(2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)piperidine-1-carboxylate as a yellow solid (65% yield). MS (ESI⁺) m/z 421 [M+H]⁺.

[00342] Step 4: (S)-3-(1-((benzyloxy)carbonyl)piperidin-4-yl)-2-((tert-butoxy carbonyl)amino)propanoic acid

[00343] A mixture of 2.6 g benzyl (S)-4-(2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)piperidine-1-carboxylate (6.18 mmol, 1.00 equiv) and 742 mg Lithium hydroxide monohydrate (30.91 mmol, 5.00 equiv) in 20 mL water and 100 mL methanol was stirred at room temperature for 12 hours. The mixture was concentrated in vacuo and the residue was diluted with 5 mL water. The pH value of the solution was adjusted to 6-5 with 1N hydrochloric acid. The crude product was precipitated out, filtered and dried under vacuum to afford 2.2 g (S)-3-(1-((benzyloxy)carbonyl)piperidin-4-yl)-2-((tert-butoxycarbonyl)amino)propanoic acid as a white solid (88 % yield). MS (ESI⁺) m/z 407 [M+H]⁺.

Preparation of 6-(benzylthio)-5-methoxypyridin-3-amine



[00344] Step 1: 2-(benzylthio)-3-methoxy-5-nitropyridine

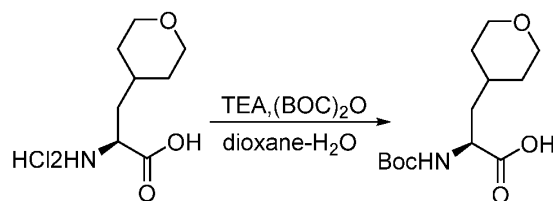
[00345] To a solution of 2-chloro-3-methoxy-5-nitropyridine (9.00 g, 47.80 mmol, 1.00 equiv) and potassium carbonate (13.23 g, 95.70 mmol, 2.00 equiv) in 300 mL anhydrous N,N-

dimethylformamide was added dropwise phenylmethanethiol (7.12 g, 57.40 mmol, 1.20 equiv) at room temperature. The resulting mixture was stirred for 12 hours at 60 °C. The mixture was cooled to room temperature, diluted with 500 mL water and extracted with ethyl acetate (3 x 500 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (5:1)) afforded 2-(benzylthio)-3-methoxy-5-nitropyridine as a yellow solid (10.50 g, 79 % yield). MS (ESI⁺) m/z 277 [M+H]⁺.

[00346] Step 2: 6-(benzylthio)-5-methoxypyridin-3-amine

[00347] To a solution of 2-(benzylthio)-3-methoxy-5-nitropyridine (10 g, 36.23 mmol, 1.00 equiv) in 200 mL methanol was added ammonium chloride (9.68 g, 181.15 mmol, 5.00 equiv) and zinc (9.47 g, 144.92 mmol, 4.00 equiv) at room temperature. The resulting mixture was stirred for 2 hours at 70 °C under nitrogen atmosphere. The mixture was cooled to room temperature, filtered and the filtrate was concentrated in vacuo. The residue was diluted with 50 mL water, then adjusted to pH=9 with sodium bicarbonate (aq.), extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (2 X 100 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (2:1)) afforded 6-(benzylthio)-5-methoxypyridin-3-amine as an orange oil (5.7 g, 64% yield). MS (ESI⁺) m/z 247 [M+H]⁺.

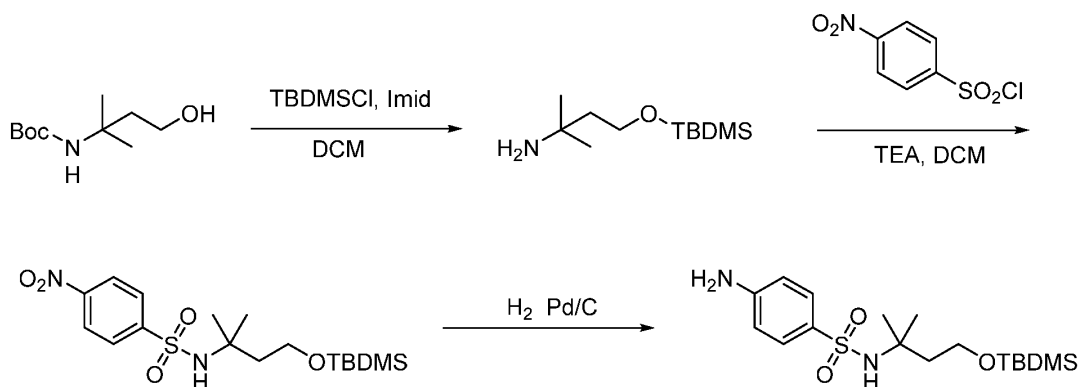
Preparation of (S)-2-((tert-butoxycarbonyl)amino)-3-(tetrahydro-2H-pyran-4-yl)propanoic acid



[00348] To a solution of 10.0g (S)-2-amino-3-(tetrahydro-2H-pyran-4-yl)propanoic acid hydrochloride (47.85 mmol, 1.00 equiv) and 33 ml (BOC)₂O (143.54 mmol, 3.00 equiv) in 50 mL H₂O and 50mL dioxane was added 21 mL TEA (143.54 mmol, 3.00 equiv) at 0 °C. The resulting mixture was stirred for 5 hours at room temperature. The resulting mixture was adjusted to pH=2 with citric acid, diluted with 200 mL water and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (1x200 mL), The mixture was concentrated to

afford 10.5 g (*S*)-2-((tert-butoxycarbonyl)amino)-3-(tetrahydro-2*H*-pyran-4-yl)propanoic acid as a white solid (81 % yield). MS (ESI⁺) *m/z* 274.2 [M+H]⁺.

Preparation of 4-amino-N-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)benzenesulfonamide



[00349] Step 1: 4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-amine

[00350] To a solution of 1.0 g 3-amino-3-methylbutan-1-ol (9.71 mmol, 1.00 equiv) in 30 mL dichloromethane was added 1.3 g imidazole (19.42 mmol, 2.00 equiv) and 1.7 g tert-Butyldimethylsilyl chloride (11.65 mmol, 1.20 equiv) at 0 °C. The resulting mixture was stirred at room temperature overnight. The mixture was diluted with 50 mL water and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo to afford 2 g 4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-amine as a colorless oil (95% yield). MS (ESI⁺) *m/z* 218 [M+H]⁺.

[00351] Step 2: N-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-4-nitrobenzenesulfonamide

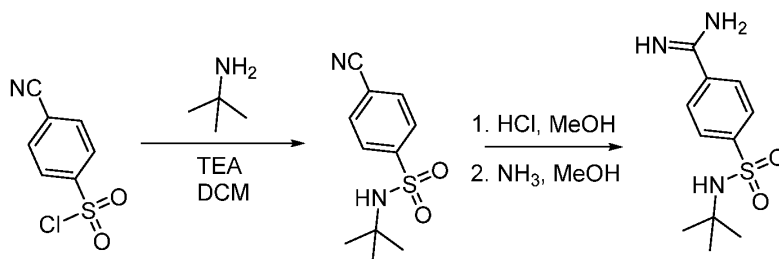
[00352] To a solution of 1.4 g 4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-amine (6.5 mmol, 1.50 equiv) and 0.9 mL triethylamine (6.5 mmol, 1.50 equiv) in 10 mL dichloromethane was added dropwise a solution 0.95 g 4-nitrobenzenesulfonyl chloride (4.3 mmol, 1.00 equiv) at 0 °C. The resulting mixture was stirred for 4 hours at room temperature. The mixture was diluted with 10 mL water and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate

was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (8:1)) provided 1.5 g N-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-4-nitrobenzenesulfonamide as a white solid (88% yield). MS (ESI⁺) *m/z* 403 [M+H]⁺.

[00353] Step 3: 4-amino-N-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)benzenesulfonamide

[00354] A mixture of 1.3 g N-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-4-nitrobenzenesulfonamide (3.22 mmol, 1.00 equiv) and 100 mg Pd/C in 30 mL methanol was stirred at room temperature under H₂ overnight. The mixture was filtered and the filtrate was concentrated in vacuo to afford 1.2 g 4-amino-N-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)benzenesulfonamide as a white solid (100 % yield). MS (ESI⁺) *m/z* 373 [M+H]⁺.

Preparation of 4-(N-(tert-butyl)sulfamoyl)benzimidamide



[00355] Step 1: N-(tert-butyl)-4-cyanobenzenesulfonamide

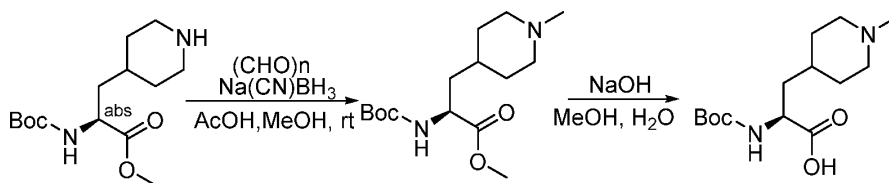
[00356] A mixture of 4-cyanobenzenesulfonyl chloride (3.0 g, 14.88 mmol, 1.0 equiv), triethylamine (3.01 g, 29.76 mmol, 2.0 equiv), 2-methylpropan-2-amine (1.09 g, 14.88 mmol, 1.0 equiv) in DCM (50 mL) was stirred at 0 °C for 1 hour. The mixture was diluted with DCM (100 mL) and washed with water (100 mL x 2). The organic phase was concentrated and the residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate (5/1, v/v)) to yield N-(tert-butyl)-4-cyanobenzenesulfonamide (2.0 g, 56.4 % yield) as a yellow solid. MS (ESI⁺) *m/z* 239.2 [M+H]⁺.

[00357] Step 2: 4-(N-(tert-butyl)sulfamoyl)benzimidamide

[00358] NaOMe (6.05 g, 30% in MeOH, 33.57 mmol, 4.00 equiv) was added to a solution N-(tert-butyl)-4-cyanobenzenesulfonamide (2.0 g, 8.39 mmol, 1.0 equiv) in MeOH (30 mL). The mixture was stirred at 80 °C for 16 hours. The mixture was concentrated and then was dissolved

in MeOH (30 mL). NH_4Cl (897.82 mg, 16.79 mmol, 2.00 equiv) was added to the mixture, and the resulting mixture was stirred at 80 °C for 3 hours. The mixture was diluted with DCM (100 mL x 3) and washed with water (100 mL x 2). The organic phase was concentrated and the residue was purified by column chromatography on silica gel 4-(N-(tert-butyl)sulfamoyl)benzimidamide (1.2 g, 56 % yield) as a yellow solid. MS (ESI^+) m/z 256.1 $[\text{M}+\text{H}]^+$.

Preparation of (S)-2-((tert-butoxycarbonyl)amino)-3- (1-methylpiperidin-4-yl) propanoic acid



[00359] Step 1: methyl (S)-2-((tert-butoxycarbonyl)amino)-3- (1-methylpiperidin-4-yl)propanoate

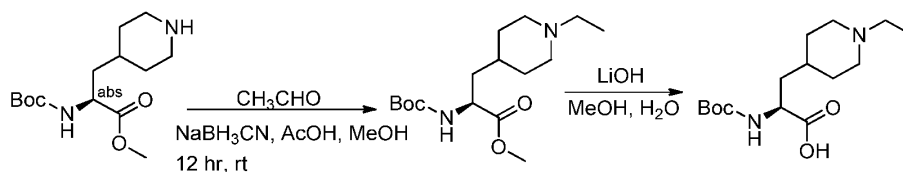
[00360] To a solution of 1.2 g methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(piperidin-4-yl)propanoate (4.19 mmol, 1.00 equiv) and 1.3 g paraformaldehyde (14.67 mmol, 3.5 equiv) was added 790 mg $\text{Na}(\text{CN})\text{CH}_3$ (12.57 mmol, 3.00 equiv) and 503 mg AcOH (8.38 mmol, 2.00 equiv) in 30 mL MeOH at 0 °C. The mixture was stirred at room temperature for 17 hours. The mixture was concentrated in vacuo. The residue was diluted with 20 mL water and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, DCM:MeOH (20:1)) afforded methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(1-methylpiperidin-4-yl)propanoate as a white oil (600 mg, 48 % yield). MS (ESI^+) m/z 301.2 $[\text{M}+\text{H}]^+$.

[00361] Step 2: (S)-2-((tert-butoxycarbonyl)amino)-3- (1-methylpiperidin-4-yl) propanoic acid

[00362] A mixture of 1.1 g (S)-2-((tert-butoxycarbonyl)amino)-3- (1-methylpiperidin-4-yl)propanoate (3.66 mmol, 1.00 equiv) and 585 mg NaOH (14.63 mmol, 4.00 equiv) in 10 mL water and 40 mL methanol was stirred at room temperature for 18 hours. The mixture was concentrated in vacuo and the residue was diluted with 5 mL water. The pH value of the solution was adjusted to 6-5 with 1N hydrochloric acid. The crude product was concentrated under

vacuum to afford crude 900 mg (S)-2-((tert-butoxycarbonyl)amino)-3-(1-methylpiperidin-4-yl)propanoic acid as a white solid (90 % yield). MS (ESI⁻) m/z 285.2 [M-H]⁻.

Preparation of (S)-2-((tert-butoxycarbonyl)amino)-3-(1-ethylpiperidin-4-yl) propanoic acid



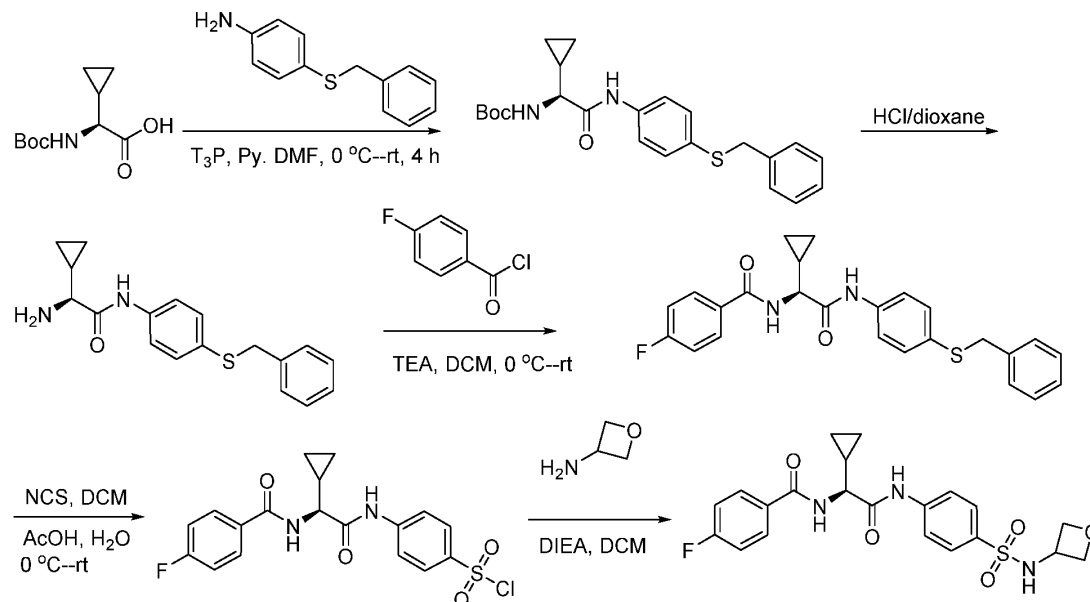
[00363] Step 1: methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(1-ethylpiperidin-4-yl)propanoate

[00364] To a solution of 2.5 g methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(1-methylpiperidin-4-yl)propanoate (8.73 mmol, 1.00 equiv) and 3.49 mL acetaldehyde in THF (5N, 17.45 mmol, 2.0 equiv) was added 1.6 g Na(CN)CH₃ (26.19 mmol, 3.00 equiv) and 1.0 g AcOH (17.45 mmol, 2.00 equiv) in 40 mL MeOH at 0 °C. The mixture was stirred at room temperature for 17 hours. The mixture was concentrated in vacuo. The residue was diluted with 20 mL water and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, DCM:MeOH (30:1)) afforded methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(1-ethylpiperidin-4-yl)propanoate as a yellow oil (1.7 g, 67 % yield). MS (ESI⁺) m/z 315.2 [M+H]⁺.

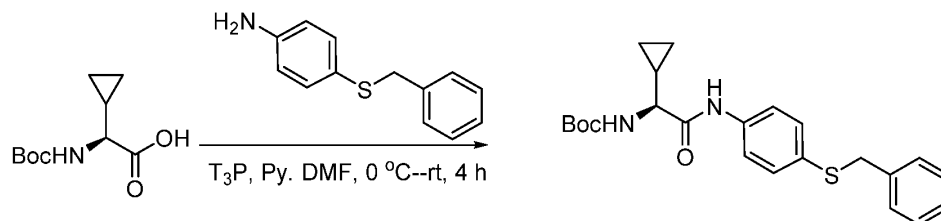
[00365] Step 2: (S)-2-((tert-butoxycarbonyl)amino)-3-(1-ethylpiperidin-4-yl) propanoic acid

[00366] A mixture of 1.5 g methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(1-ethylpiperidin-4-yl)propanoate (4.77 mmol, 1.00 equiv) and 572 mg LiOH (14.63 mmol, 5.00 equiv) in 15 mL water and 100 mL methanol was stirred at room temperature for 18 hours. The mixture was concentrated in vacuo and the residue was diluted with 5 mL water. The pH value of the solution was adjusted to 6-5 with 1N hydrochloric acid. The crude product was concentrated under vacuum to afford crude 1.4 g (S)-2-((tert-butoxycarbonyl)amino)-3-(1-ethylpiperidin-4-yl)propanoic acid as a white solid (100 % yield). MS (ESI⁻) m/z 299.2 [M-H]⁻.

Example 2: Synthesis of (S)-N-(1-cyclopropyl-2-((4-(N-(oxetan-3-yl)sulfamoyl)phenyl)amino)-2-oxoethyl)-4-fluorobenzamide (I-54)



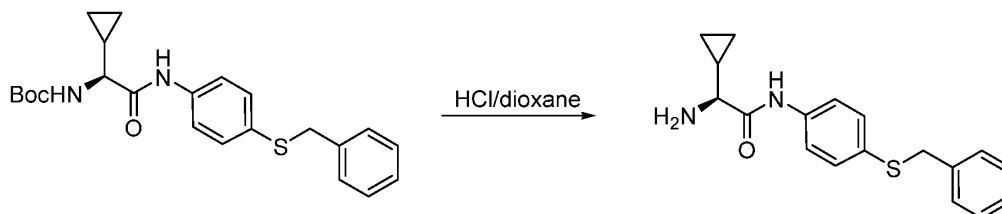
[00367] Step 1: tert-butyl (S)-2-((4-(benzylthio)phenyl)amino)-1-cyclopropyl-2-oxoethylcarbamate



[00368] To a solution of 1.7 g 4-(benzylthio)aniline (7.9 mmol, 1.00 equiv), 1.7 g (S)-2-((tert-butoxycarbonyl)amino)-2-cyclopropylacetic acid (7.9 mmol, 1.00 equiv) and 6.24 g pyridine (79 mmol, 10.00 equiv) in 30 mL N,N-dimethylformamide was added dropwise a solution of 25.8 g propanephosphonic acid cyclic anhydride in DMF (50%, 39.5 mmol, 5.00 equiv) at 0 °C. The resulting mixture was stirred for 4 hours at 0 °C. The mixture was diluted with 100 mL water and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (3x100 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (2:1)) provided 2.67 g tert-butyl (S)-2-((4-(benzylthio)phenyl)amino)-1-cyclopropyl-2-

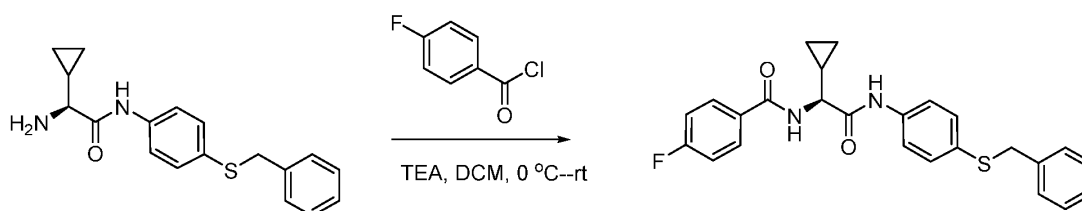
oxoethyl)carbamate as a yellow solid (82.2% yield). MS (ESI⁺) m/z 357.2 [M-56+H]⁺.

[00369] Step 2: (S)-2-amino-N-(4-(benzylthio)phenyl)-2-cyclopropylacetamide hydrochloride



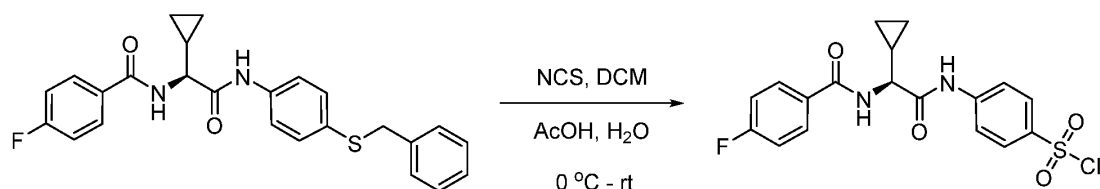
[00370] A mixture of 2.67 g tert-butyl (S)-2-((4-(benzylthio)phenyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (6.5 mmol, 1.00 equiv) in 30 mL hydrochloric acid in 1,4-dioxane (4.0 M) was stirred at room temperature for 3 hours. The mixture was concentrated to afford 2.0 g crude (S)-2-amino-N-(4-(benzylthio)phenyl)-2-cyclopropylacetamide hydrochloride as a light yellow solid (100 % yield). MS (ESI⁺) m/z 412.1 [M+H]⁺.

[00371] Step 3: (S)-N-(2-((4-(benzylthio)phenyl)amino)-1-cyclopropyl-2-oxoethyl)-4-fluorobenzamide



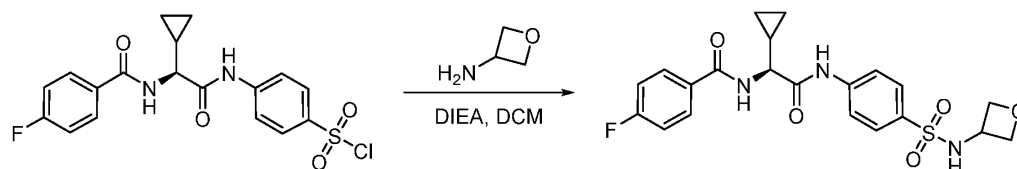
[00372] To a solution of 2.0 g (S)-2-amino-N-(4-(benzylthio)phenyl)-2-cyclopropylacetamide hydrochloride (6.4 mmol, 1.00 equiv.) and 2.94 g TEA (38.5 mmol, 6.00 equiv) in 40 mL dichloromethane was added dropwise 1.01 g 4-fluorobenzoyl chloride (6.4 mmol, 1.00 equiv) at 0 °C. The resulting mixture was stirred for 2 hours at 0 °C. The resulting mixture was diluted with 20 mL water and extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine (1x30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (1:1)) afforded 2.43 g (S)-N-(2-((4-(benzylthio)phenyl)amino)-1-cyclopropyl-2-oxoethyl)-4-fluorobenzamide as a yellow solid (87.7 % yield). MS (ESI⁺) m/z 515 [M+H]⁺.

[00373] Step 4: (S)-4-(2-cyclopropyl-2-(4-fluorobenzamido)acetamido) benzenesulfonyl chloride



[00374] To a solution of 1.97 g (S)-N-(2-((4-(benzylthio)phenyl)amino)-1-cyclopropyl-2-oxoethyl)-4-fluorobenzamide (4.5 mmol, 1.00 equiv) in 18 mL acetic acid and 6 mL water was added 2.39 g N-chlorosuccinimide (17.9 mmol, 4.00 equiv) at 0 °C. The resulting mixture was stirred at 0 °C for 1 hour. The mixture was diluted with 10 mL water and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (1x30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (1:1)) afforded 1.3 g (S)-4-(2-cyclopropyl-2-(4-fluorobenzamido)acetamido)benzenesulfonyl chloride as a yellow solid (70.7 % yield). MS (ESI⁺) m/z 411.1 [M+H]⁺.

[00375] Step 5: (S)-N-(1-cyclopropyl-2-((4-(N-(oxetan-3-yl)sulfamoyl)phenyl) amino)-2-oxoethyl)-4-fluorobenzamide (I-54)



[00376] To a mixture of 133.5 mg oxetan-3-amine (1.83 mmol, 5.0 equiv) and 236.1 mg N,N-diisopropylethylamine (1.83 mmol, 5.00 equiv) in 15 mL dichloromethane was added 150 mg (S)-6-(2-(4-fluorobenzamido)-3-phenylpropanamido) pyridine-3-sulfonyl chloride (0.36 mmol, 1.00 equiv). The mixture was stirred at room temperature for 1 hour. The mixture was diluted with 10 mL water and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions: Column, Xbridge Prep C18 19*250mm 5um; Mobile Phase, A: 0.1%NH₃H₂O/H₂O B:CAN; *Gradient : 30% B to 40%B within 15min.UV detection at 254/220

nm. The product-containing fractions were combined and concentrated in vacuo and lyophilized overnight to afford 100 mg (S)-N-(1-cyclopropyl-2-((4-(N-(oxetan-3-yl)sulfamoyl)phenyl)amino)-2-oxoethyl)-4-fluorobenzamide (I-54) as a white solid.

[00377] The compounds in **Table 2** were made by a method analogous to the method used to make **I-54**, substituting the appropriate Boc protected amino acid in step 1 and the appropriate amine in step 5.

Table 2. Compounds made by a method analogous to I-54

Cmpd #	MS [M+H] ⁺	¹ H NMR
I-54	448.2	¹ H NMR (400 MHz, DMSO) δ 10.45 (s, 1H), 8.98 (d, J = 6.7 Hz, 1H), 8.43 (d, J = 8.2 Hz, 1H), 8.06-7.96 (m, 2H), 7.83 (d, J = 8.9 Hz, 2H), 7.72 (d, J = 8.9 Hz, 2H), 7.33-7.29 (m, 2H), 4.55-4.44 (m, 2H), 4.36-4.32 (m, 1H), 4.28-4.23 (m, 2H), 3.86-3.82 (m, 1H), 1.35-1.21 (m, 1H), 0.70-0.66 (m, 1H), 0.64-0.51 (m, 2H), 0.38-0.36 (m, 1H).
I-6	536	¹ H NMR (400 MHz, DMSO) δ 10.49 (s, 1H), 8.73 (d, J = 7.6 Hz, 1H), 8.02-7.98 (m, 2H), 7.79-7.73 (m, 4H), 7.35-7.29 (m, 3H), 4.70-4.65 (m, 1H), 4.41 (t, J = 4.9 Hz, 1H), 3.85-3.81 (m, 2H), 3.46-3.41 (m, 2H), 3.29-3.19 (m, 2H), 1.88-1.80 (m, 1H), 1.70-1.60 (m, 6H), 1.30-1.18 (m, 3H), 1.05 (s, 6H).
I-7	550.2	¹ H NMR (400 MHz, DMSO) δ 10.49 (s, 1H), 8.72 (d, J = 7.5 Hz, 1H), 8.01-7.98 (m, 2H), 7.77 (q, J = 9.0 Hz, 4H), 7.33-7.29 (m, 3H), 4.70-4.65 (m, 1H), 3.84-3.81 (m, 2H), 3.30-3.19 (m, 4H), 3.15 (s, 3H), 1.84 (t, J = 9.4 Hz, 1H), 1.69-1.60 (m, 6H), 1.29-1.17 (m, 2H), 1.05 (s, 6H).
I-13	494	¹ H NMR (400 MHz, DMSO) δ 10.45 (s, 1H), 8.67 (d, J = 7.6 Hz, 1H), 8.17-7.88 (m, 2H), 7.66 (d, J = 8.6 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.31-7.29 (m, 3H), 6.84 (s, 1H), 4.65-4.60 (m, 1H), 3.87 (s, 3H), 1.86-1.69 (m, 2H), 1.62-1.51 (m, 1H), 1.10-1.01 (m, 9H), 0.97-0.87 (m, 6H).
I-14	510	¹ H NMR (400 MHz, DMSO) δ 10.48 (s, 1H), 8.69 (d, J = 7.5 Hz, 1H), 8.11-7.87 (m, 2H), 7.66 (d, J = 8.6 Hz, 1H), 7.57 (d, J = 1.8 Hz, 1H),

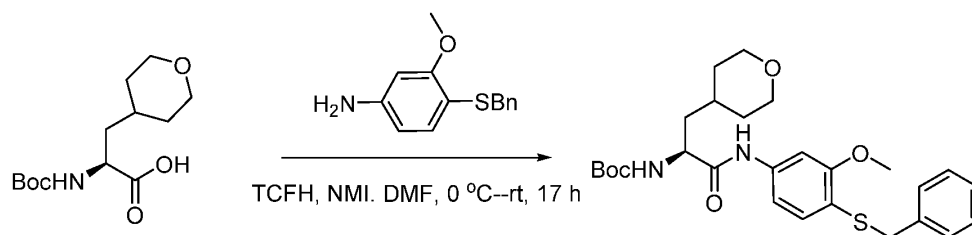
		7.37-7.23 (m, 3H), 6.42 (s, 1H), 4.87 (s, 1H), 4.71-4.52 (m, 1H), 3.86 (d, $J = 8.4$ Hz, 3H), 3.14 (s, 2H), 1.91-1.69 (m, 2H), 1.66-1.51 (m, 1H), 1.05-0.85 (m, 12H).
I-22	464	^1H NMR (400 MHz, DMSO) δ 10.53 (s, 1H), 8.70 (d, $J = 7.5$ Hz, 1H), 8.42 (d, $J = 8.3$ Hz, 1H), 8.02-7.97 (m, 2H), 7.84-7.80 (m, 2H), 7.74-7.69 (m, 2H), 7.34-7.28 (m, 2H), 4.67-4.61 (m, 1H), 4.51-4.47 (m, 2H), 4.39-4.30 (m, 1H), 4.24 (t, $J = 6.2$ Hz, 2H), 1.85-1.71 (m, 2H), 1.60-1.53 (m, 1H), 0.93 (dd, $J = 11.7, 6.4$ Hz, 6H).
I-23	478	^1H NMR (400 MHz, DMSO) δ 10.48 (s, 1H), 8.69 (d, $J = 7.4$ Hz, 1H), 8.02-7.97 (m, 2H), 7.80-7.74 (m, 4H), 7.39 (s, 1H), 7.34-7.28 (m, 2H), 4.52 (d, $J = 7.2$ Hz, 1H), 1.86-1.77 (m, 2H), 1.57-1.55 (m, 1H), 1.43-1.33 (m, 1H), 1.28-1.18 (m, 1H), 1.08 (s, 9H), 0.90-0.86 (m, 6H).
I-24	478	^1H NMR (400 MHz, DMSO) δ 10.53 (s, 1H), 8.70 (d, $J = 7.3$ Hz, 1H), 8.42 (d, $J = 8.0$ Hz, 1H), 8.01-7.89 (m, 2H), 7.81 (d, $J = 8.9$ Hz, 2H), 7.72 (d, $J = 8.9$ Hz, 2H), 7.37-7.25 (m, 2H), 4.54-4.49 (m, 3H), 4.41-4.29 (m, 1H), 4.25-4.22 (m, 2H), 1.91-1.73 (m, 2H), 1.59-1.55 (m, 1H), 1.47-1.29 (m, 1H), 1.25-1.20 (m, 1H), 0.91-0.86 (m, 6H).
I-26	482	^1H NMR (400 MHz, DMSO) δ 10.51 (s, 1H), 8.73 (d, $J = 7.3$ Hz, 1H), 8.02-7.97 (m, 2H), 7.80-7.74 (m, 4H), 7.32 (t, $J = 8.8$ Hz, 2H), 7.18 (s, 1H), 4.73 (t, $J = 5.8$ Hz, 1H), 4.67-4.61 (m, 1H), 3.49-3.45 (m, 2H), 3.24 (s, 3H), 3.17 (d, $J = 5.8$ Hz, 2H), 2.12-2.01 (m, 2H), 0.99 (s, 6H).
I-27	551	^1H NMR (400 MHz, DMSO) δ 10.48 (s, 1H), 8.71 (d, $J = 7.4$ Hz, 1H), 8.01-7.97 (m, 2H), 7.76 (t, $J = 6.4$ Hz, 4H), 7.32 (t, $J = 8.8$ Hz, 2H), 7.20 (s, 1H), 4.66-4.61 (m, 1H), 3.54-3.51 (m, 4H), 3.46 (t, $J = 5.7$ Hz, 2H), 3.23 (s, 3H), 2.48-2.45 (m, 4H), 2.28 (s, 2H), 2.10-2.01 (m, 2H), 1.02 (s, 6H).
I-28	466	^1H NMR (400 MHz, DMSO) δ 10.54 (s, 1H), 8.73 (d, $J = 7.3$ Hz, 1H), 8.42 (d, $J = 8.0$ Hz, 1H), 8.01-7.97 (m, 2H), 7.82 (d, $J = 8.9$ Hz, 2H), 7.71 (d, $J = 8.9$ Hz, 2H), 7.32 (t, $J = 8.9$ Hz, 2H), 4.66-4.61 (m, 1H),

		4.49 (t, $J = 6.7$ Hz, 2H), 4.37-4.32 (m, 1H), 4.24 (t, $J = 6.3$ Hz, 2H), 3.47 (m, 2H), 3.23 (s, 3H), 2.10-2.00 (m, 2H).
I-31	452.2	^1H NMR (400 MHz, DMSO) δ 10.49 (s, 1H), 8.70 (d, $J = 8.0$ Hz, 1H), 8.41 (d, $J = 8.0$ Hz, 1H), 8.00-7.96 (m, 2H), 7.82 (d, $J = 8.0$ Hz, 2H), 7.71 (d, $J = 8.0$ Hz, 2H), 7.32 (t, $J = 8.0$ Hz, 2H), 4.69-4.61 (m, 2H), 4.451-4.47 (m, 2H), 4.34 (s, 1H), 4.25-4.22 (m, 2H), 3.58-3.55 (m, 2H), 2.00-1.96 (m, 2H).
I-32	468	^1H NMR (400 MHz, DMSO) δ 10.56 (s, 1H), 8.76 (d, $J = 7.3$ Hz, 1H), 8.12-7.90 (m, 2H), 7.86-7.69 (m, 4H), 7.32 (t, $J = 8.9$ Hz, 2H), 7.18 (s, 1H), 4.83 (d, $J = 6.4$ Hz, 1H), 4.72 (t, $J = 5.8$ Hz, 1H), 3.82-3.63 (m, 2H), 3.29 (s, 2H), 3.17 (d, $J = 5.8$ Hz, 2H), 0.99 (s, 6H).
I-33	537	^1H NMR (400 MHz, DMSO) δ 10.55 (s, 1H), 8.75 (d, $J = 7.3$ Hz, 1H), 8.08-7.92 (m, 2H), 7.78 (s, 4H), 7.39-7.25 (m, 2H), 7.21 (s, 1H), 4.89-4.74 (m, 1H), 3.78-3.68 (m, 2H), 3.59-3.46 (m, 4H), 3.30 (s, 3H), 2.48-2.43 (m, 4H), 2.29 (s, 2H), 1.02 (s, 6H).
I-34	452	^1H NMR (400 MHz, DMSO) δ 10.60 (s, 1H), 8.76 (d, $J = 7.2$ Hz, 1H), 8.43 (d, $J = 8.3$ Hz, 1H), 8.08 – 7.91 (m, 2H), 7.82 (d, $J = 8.9$ Hz, 2H), 7.72 (d, $J = 8.9$ Hz, 2H), 7.38-7.26 (m, 2H), 4.83 (q, $J = 6.9$ Hz, 1H), 4.49 (t, $J = 6.8$ Hz, 2H), 4.43-4.30 (m, 1H), 4.24 (t, $J = 6.2$ Hz, 2H), 3.82-3.64 (m, 2H), 3.31 (d, $J = 6.9$ Hz, 3H).
I-37	438.2	^1H NMR (400 MHz, DMSO) δ 10.49 (s, 1H), 8.53 (d, $J = 4.0$ Hz, 1H), 8.41 (s, 1H), 8.03-7.96 (m, 2H), 7.85-7.79 (m, 2H), 7.74-7.69 (m, 2H), 7.36-7.29 (m, 2H), 5.11 (t, $J = 4.0$ Hz, 1H), 4.67-4.63 (m, 1H), 4.51-4.47 (m, 2H), 4.35-4.30 (m, 2H), 4.25-4.22 (m, 1H), 4.23 (t, 2H), 3.84-3.78 (m, 2H).
I-46	478	^1H NMR (400 MHz, DMSO) δ 10.51 (s, 1H), 8.76 (d, $J = 7.1$ Hz, 1H), 8.03-7.98 (m, 2H), 7.77 (s, 4H), 7.32 (t, $J = 8.6$ Hz, 2H), 7.17 (s, 1H), 4.72 (t, $J = 5.6$ Hz, 1H), 4.67-4.62 (m, 1H), 3.17 (d, $J = 5.6$ Hz, 2H),

		2.50 (s, 4H), 1.95-1.88 (m, 1H), 1.58-1.51 (m, 1H), 0.99 (s, 6H), 0.87 (s, 1H), 0.46-0.35 (m, 2H), 0.23-0.20 (m, 1H), 0.17-0.11 (m, 1H).
I-47	547	¹ H NMR (400 MHz, DMSO) δ 10.49 (s, 1H), 8.73 (d, J = 7.3 Hz, 1H), 8.02-7.98 (m, 2H), 7.77 (s, 4H), 7.31 (t, J = 12.0 Hz, 2H), 7.20 (s, 1H), 4.67-4.62 (m, 1H), 3.53-3.51 (m, 4H), 2.47-2.44 (m, 4H), 2.28 (s, 2H), 1.94-1.88 (m, 1H), 1.57-1.51 (m, 1H), 1.02 (s, 6H), 0.88-0.84 (m, 1H), 0.46-0.36 (m, 2H), 0.24-0.18 (m, 1H), 0.16-0.10 (m, 1H).
I-48	462	¹ H NMR (400 MHz, DMSO) δ 10.54 (s, 1H), 8.74 (d, J = 7.1 Hz, 1H), 8.41 (d, J = 7.5 Hz, 1H), 8.02-7.98 (m, 2H), 7.81 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 8.7 Hz, 2H), 7.32 (t, J = 8.8 Hz, 2H), 4.67-4.62 (m, 1H), 4.49 (t, J = 6.6 Hz, 2H), 4.37-4.32 (m, 1H), 4.23 (t, J = 6.2 Hz, 2H), 1.97-1.86 (m, 1H), 1.59-1.48 (m, 1H), 0.87 (s, 1H), 0.45-0.36 (m, 2H), 0.23-0.11 (m, 2H).
I-52	464	¹ H NMR (400 MHz, DMSO) δ 10.40 (s, 1H), 8.97 (d, J = 6.7 Hz, 1H), 8.07-7.98 (m, 2H), 7.84-7.74 (m, 4H), 7.31 (t, J = 8.9 Hz, 2H), 7.18 (s, 1H), 4.72 (t, J = 5.8 Hz, 1H), 3.90-3.80 (m, 1H), 3.17 (d, J = 5.8 Hz, 2H), 1.39-1.23 (m, 1H), 1.00 (s, 6H), 0.73-0.52 (m, 3H), 0.43-0.31 (m, 1H).
I-53	533	¹ H NMR (400 MHz, DMSO) δ 10.40 (s, 1H), 8.97 (d, J = 6.7 Hz, 1H), 8.03-7.88 (m, 2H), 7.90-7.65 (m, 4H), 7.31 (t, J = 8.8 Hz, 2H), 7.21 (s, 1H), 4.02-3.72 (m, 1H), 3.72- 3.40 (m, 4H), 2.49-2.41 (m, 4H), 2.29 (s, 2H), 1.30 (dt, J = 8.2, 6.3 Hz, 1H), 1.02 (s, 6H), 0.79-0.49 (m, 3H), 0.46-0.28 (m, 1H).
I-59	604	¹ H NMR (400 MHz, DMSO) δ 10.63 (s, 1H), 8.92 (d, J = 7.9 Hz, 1H), 7.98-7.86 (m, 2H), 7.89-7.68 (m, 4H), 7.68-7.55 (m, 4H), 7.51 (d, J = 8.3 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.38-7.24 (m, 4H), 4.97-4.79 (m, 1H), 4.41 (t, J = 4.9 Hz, 1H), 3.54-3.37 (m, 2H), 3.19-3.18 (m, 2H), 1.62 (t, J = 7.1 Hz, 2H), 1.06 (s, 6H).

I-60	574	¹ H NMR (400 MHz, DMSO) δ 10.64 (s, 1H), 8.94 (d, J = 7.7 Hz, 1H), 7.97-7.88 (m, 2H), 7.82-7.75 (m, 4H), 7.65-7.58 (m, 4H), 7.51 (d, J = 8.2 Hz, 2H), 7.47-7.39 (m, 3H), 7.32 (dt, J = 13.5, 8.1 Hz, 3H), 5.01-4.71 (m, 1H), 3.22-3.12 (m, 2H), 1.08 (s, 9H).
I-61	526.4	¹ H NMR (400 MHz, DMSO) δ 10.45 (s, 1H), 8.12 (d, J = 7.4 Hz, 1H), 7.77-7.68 (m, 8H), 7.50-7.49 (m, 1H), 7.40 (m, 2H), 7.31-7.15 (m, 5H), 4.66-4.61 (m, 1H), 5.07 (d, J = 8.0 Hz 1H), 1.53-1.48 (m, 6H), 1.08 (s, 9H).
I-62	542.5	¹ H NMR (400 MHz, DMSO) δ 10.45 (s, 1H), 8.11 (d, J = 8.8 Hz, 1H), 7.77-7.68 (m, 6H), 7.50 (d, J = 7.6 Hz, 2H), 7.31-7.14 (m, 6H), 5.07 (d, J = 8.8 Hz, 1H), 4.75 (t, J = 5.7 Hz, 1H), 3.18 (d, J = 5.7 Hz, 2H), 1.50 (d, J = 20.7 Hz, 6H), 1.00 (s, 6H).

[00378] Alternative Step 1: tert-butyl (S)-(1-((4-(benzylthio)-3-methoxyphenyl)amino)-1-oxo-3-(tetrahydro-2H-pyran-4-yl)propan-2-yl)carbamate



[00379] A mixture of 4-(benzylthio)-3-methoxyaniline (1.0 g, 4.08 mmol, 1.0 equiv), (S)-2-((tert-butoxycarbonyl)amino)-3-(tetrahydro-2H-pyran-4-yl)propanoic acid (1.11 g, 4.08 mmol, 1.0 equiv), TCFH (2.56 g, 9.16 mmol, 2.0 equiv) and NMI (1.34 g, 16.32 mmol, 4.0 equiv) in N,N-dimethylformamide (20 mL) was stirred at room temperature overnight. The mixture was diluted with ethyl acetate (50 mL) and washed with water (50 mL x 3). The organic phase was concentrated and the residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate (5/1, v/v)) to give tert-butyl (S)-(1-((4-(benzylthio)-3-methoxyphenyl) amino)-1-oxo-3-(tetrahydro-2H-pyran-4-yl)propan-2-yl)carbamate as a white solid (1.1 g, 53.9 % yield). MS (ESI⁺) m/z 501.2 [M+H]⁺

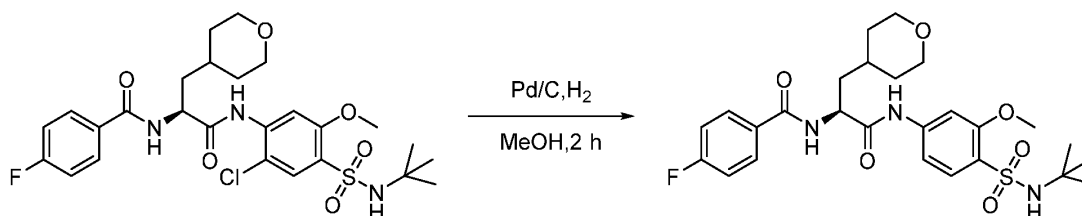
[00380] The compounds in **Table 3** were made by a method analogous to the method used to make I-54, using the alternative step 1 amide coupling conditions, substituting the appropriate Boc protected amino acid in step 1 and the appropriate amine in step 5.

Table 3. Compounds made by a method analogous to I-54, using Alternative Step 1

Cmpd #	MS [M+H] ⁺	¹ H NMR
I-4	507	¹ H NMR (400 MHz, DMSO) δ 10.71 (s, 1H), 8.89 (d, J = 2.1 Hz, 1H), 8.77 (d, J = 7.5 Hz, 1H), 8.33-8.24 (m, 1H), 8.06-7.96 (m, 2H), 7.93 (d, J = 8.6 Hz, 1H), 7.58 (s, 1H), 7.40-7.27 (m, 2H), 4.69 (s, 1H), 3.89-3.77 (m, 2H), 3.30-3.23 (m, 2H), 1.90-1.78 (m, 1H), 1.71-1.59 (m, 4H), 1.24 (s, 2H), 1.08 (s, 9H).
I-5	507	¹ H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 8.86 (d, J = 2.1 Hz, 1H), 8.78 (d, J = 7.4 Hz, 1H), 8.66 (s, 1H), 8.35-8.24 (m, 1H), 8.06-7.95 (m, 2H), 7.90 (d, J = 8.6 Hz, 1H), 7.37-7.27 (m, 2H), 4.69 (s, 1H), 4.56 (t, J = 4.6 Hz, 3H), 4.34 (d, J = 5.3 Hz, 2H), 3.90-3.77 (m, 2H), 3.29-3.16 (m, 2H), 1.85 (d, J = 10.4 Hz, 1H), 1.72-1.56 (m, 4H), 1.24 (s, 2H).
I-15	495	¹ H NMR (400 MHz, DMSO) δ 10.70 (s, 1H), 8.72 (d, J = 8.0 Hz, 1H), 8.40 (s, 1H), 8.03-7.98 (m, 3H), 8.35-7.29 (m, 2H), 7.12 (s, 1H), 4.68-4.63 (m, 1H), 3.91 (s, 3H), 1.82-1.80 (m, 2H), 1.62-1.58 (m, 1H), 1.08 (s, 9H), 0.97-0.93 (m, 6H).
I-16	465	¹ H NMR (400 MHz, DMSO) δ 10.72 (s, 1H), 8.89 (d, J = 2.4 Hz, 1H), 8.74 (d, J = 7.5 Hz, 1H), 8.29-8.26 (m, 1H), 8.04-7.90 (m, 3H), 7.58 (s, 1H), 7.34-7.29 (m, 2H), 4.68-4.63 (m, 1H), 1.82-1.78 (m, 2H), 1.65-1.55 (m, 1H), 1.08 (s, 9H), 0.97 – 0.92 (m, 6H).
I-17	481	¹ H NMR (400 MHz, DMSO) δ 10.73 (s, 1H), 8.89 (d, J = 2.4 Hz, 1H), 8.74 (d, J = 7.5 Hz, 1H), 8.29-8.27 (m, 1H), 8.00-7.92 (m, 3H), 7.34-7.28 (m, 3H), 4.74 (t, J = 5.9 Hz, 1H), 4.67-4.65 (m, 1H), 3.18 (d, J =

		5.9 Hz, 2H), 1.82-1.80 (m, 2H), 1.61 (s, 1H), 1.00 (s, 6H), 0.97-0.92 (m, 6H).
I-41	519	¹ H NMR (400 MHz, DMSO) δ 10.48 (s, 1H), 8.72 (d, J = 7.3 Hz, 1H), 8.01-7.96 (m, 2H), 7.79-7.74 (m, 4H), 7.39 (s, 1H), 7.34-7.28 (m, 2H), 4.66-4.64 (m, 1H), 2.73-2.70 (m, 2H), 2.10 (s, 3H), 1.78-1.63 (m, 6H), 1.44-1.32 (m, 1H), 1.27-1.14 (m, 2H), 1.07 (s, 9H).
I-42	533	¹ H NMR (400 MHz, DMSO) δ 10.47 (s, 1H), 8.70 (d, J = 7.5 Hz, 1H), 8.00-7.97 (m, 2H), 7.79-7.74 (m, 4H), 7.39 (s, 1H), 7.31 (t, J = 8.8 Hz, 2H), 4.68-4.62 (m, 1H), 2.82 (d, J = 10.8 Hz, 2H), 2.27-2.25 (m, 2H), 1.86-1.61 (m, 6H), 1.46-1.36 (m, 1H), 1.41 (s, 1H) 1.23-1.16 (m, 2H), 1.07 (s, 9H), 0.96 (t, J = 7.2 Hz, 3H).
I-44	535	¹ H NMR (400 MHz, DMSO) δ 10.47 (s, 1H), 8.70 (d, J = 7.6 Hz, 1H), 8.00-7.97 (m, 2H), 7.79-7.74 (m, 4H), 7.35-7.29 (m, 2H), 7.17 (s, 1H), 4.72 (t, J = 5.8 Hz, 1H), 4.68-4.62 (m, 1H), 3.17 (d, J = 5.8 Hz, 2H), 2.74-2.70 (m, 2H), 2.11 (s, 3H), 1.85-1.60 (m, 7H), 1.41-1.34 (m, 1H), 1.24-1.18 (m, 2H), 0.99 (s, 6H).
I-45	549	¹ H NMR (400 MHz, DMSO) δ 10.48 (s, 1H), 8.70 (d, J = 7.5 Hz, 1H), 8.00-7.97 (m, 2H), 7.79-7.75 (m, 4H), 7.34-7.29 (m, 2H), 7.17 (s, 1H), 4.72 (t, J = 5.8 Hz, 1H), 4.68-4.62 (m, 1H), 3.17 (d, J = 5.8 Hz, 2H), 2.82 (d, J = 10.9 Hz, 2H), 2.26 (q, J = 7.1 Hz, 2H), 1.86-1.61 (m, 6H), 1.47-1.35 (m, 1H), 1.25-1.13 (m, 2H), 0.99 (s, 6H), 0.96 (t, J = 7.2 Hz, 3H).

[00381] Synthesis of (S)-N-(1-((4-(N-(tert-butyl)sulfamoyl)-3-methoxyphenyl)amino)-1-oxo-3-(tetrahydro-2H-pyran-4-yl)propan-2-yl)-4-fluorobenzamide (I-2)



[00382] A solution of (S)-N-(1-((4-(N-(tert-butyl)sulfamoyl)-2-chloro-5-methoxyphenyl)amino)-1-oxo-3-(tetrahydro-2H-pyran-4-yl)propan-2-yl)-4-fluorobenzamide (obtained via an analogous method to **I-54**) (130 mg, 0.23 mmol, 1.00 equiv) and Pd/C (65 mg) in MeOH (6 mL) was stirred at 65 °C for 16 hours under hydrogen. The mixture was filtered and the filtrate was purified by Prep-HPLC with the following conditions: Column, Xtimate C18, 21.2*250 mm, 10 um; Mobile Phase, water (0.1% NH₃-H₂O) and ACN; UV detection at 254/214 nm. The product-containing fractions were combined and concentrated in vacuo and lyophilized overnight to give (S)-N-(1-((4-(N-(tert-butyl)sulfamoyl)-3-methoxyphenyl)amino)-1-oxo-3-(tetrahydro-2H-pyran-4-yl)propan-2-yl)-4-fluorobenzamide (**I-2**) as a white solid (58.5 mg, 48% yield).

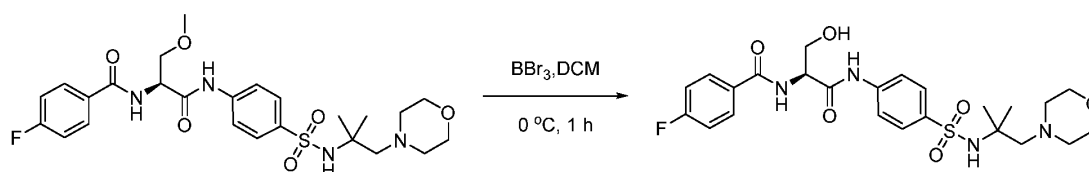
[00383] The compounds in **Table 4** were made by a method analogous to the method used to make **I-2**, via the method used to make **I-54**, substituting the appropriate Boc protected amino acid in step 1 and the appropriate amine in step 5.

Table 4. Compounds made by a method analogous to I-2

Cmpd #	MS [M+H] ⁺	¹ H NMR
I-2	536	¹ H NMR (400 MHz, DMSO) δ 10.45 (s, 1H), 8.71 (d, <i>J</i> = 7.5 Hz, 1H), 8.01-7.94 (m, 2H), 7.66 (d, <i>J</i> = 8.6 Hz, 1H), 7.55 (d, <i>J</i> = 1.8 Hz, 1H), 7.37-7.26 (m, 3H), 6.84 (s, 1H), 4.67 (s, 1H), 3.88-3.76 (m, 5H), 3.27-3.14 (m, 2H), 1.85 (s, 1H), 1.72-1.56 (m, 4H), 1.24 (t, <i>J</i> = 9.2 Hz, 2H), 1.05 (s, 9H).

I-3	536	¹ H NMR (400 MHz, DMSO) δ 10.49 (s, 1H), 8.71 (d, J = 7.5 Hz, 1H), 8.16 (d, J = 7.7 Hz, 1H), 8.03-7.95 (m, 2H), 7.64 (d, J = 8.6 Hz, 1H), 7.55 (d, J = 1.8 Hz, 1H), 7.35-7.24 (m, 3H), 4.66 (s, 1H), 4.47 (d, J = 2.3 Hz, 2H), 4.38-4.31 (m, 3H), 3.92-3.77 (m, 5H), 3.27- 3.17 (m, 2H), 1.84 (s, 1H), 1.71-1.54 (m, 4H), 1.24 (s, 2H).
-----	-----	---

[00384] Synthesis of (S)-4-fluoro-N-(3-hydroxy-1-((4-(N-(2-methyl-1-morpholinopropan-2-yl)sulfamoyl)phenyl)amino)-1-oxopropan-2-yl)benzamide (I-36)



[00385] To a solution of (S)-4-fluoro-N-(4-methoxy-1-((4-(N-(2-methyl-1-morpholinopropan-2-yl)sulfamoyl)phenyl)amino)-1-oxobutan-2-yl)benzamide (obtained via an analogous method to **I-54**) (160 mg, 0.298 mmol, 1.00 equiv) in 10 mL dichloromethane was added dropwise of BBr₃ (373 mg, 1.49 mmol, 5.0 equiv) at 0 °C. The resulting mixture was stirred for 1 hour at 0 °C. The resulting mixture was diluted with 1 mL methanol and 20 mL water and extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine (1x30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, DCM: methanol (10:1)) afforded (S)-4-fluoro-N-(3-hydroxy-1-((4-(N-(2-methyl-1-morpholinopropan-2-yl)sulfamoyl)phenyl)amino)-1-oxopropan-2-yl)benzamide (**I-36**) as a white solid (47 mg, 30.3 % yield).

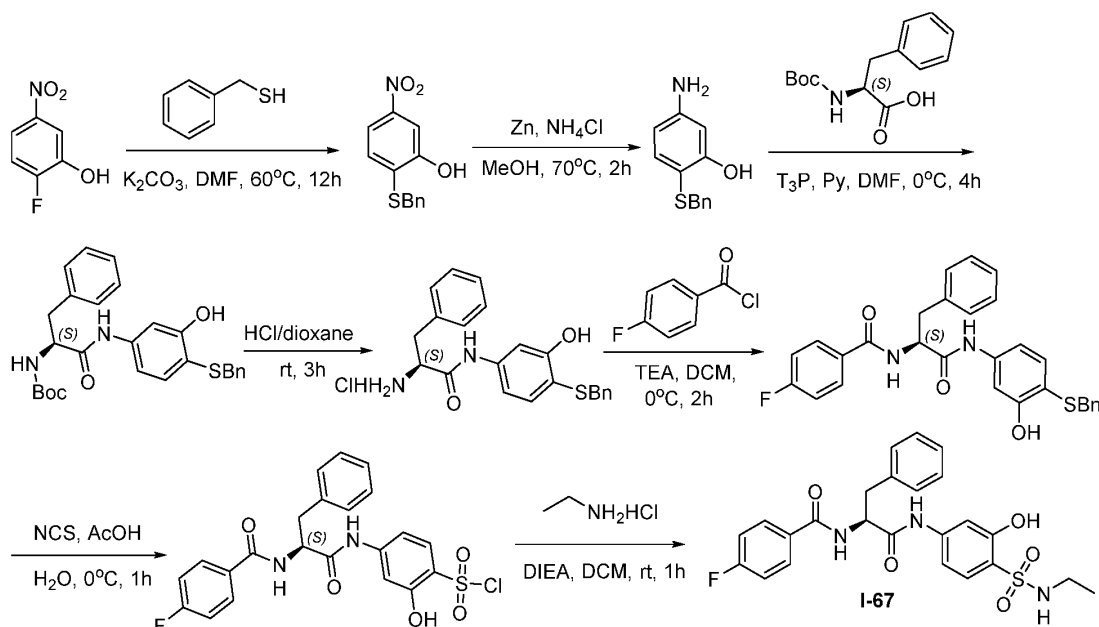
[00386] The compounds in **Table 5** were made by a method analogous to the method used to make **I-36**, via the method used to make **I-54**, substituting the appropriate Boc protected amino acid in step 1 and the appropriate amine in step 5.

Table 5. Compounds made by a method analogous to I-36

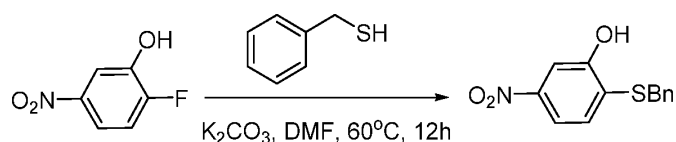
Cmpd #	MS [M+H] ⁺	¹ H NMR
--------	--------------------------	--------------------

I-36	523	¹ H NMR (400 MHz, DMSO) δ 10.45 (s, 1H), 8.52 (d, J = 4.0 Hz, 1H), 8.00-7.99 (m, 1H), 7.78-7.77 (m, 2H), 7.35-7.30 (m, 2H), 7.20 (s, 1H), 5.11 (t, J = 5.5 Hz, 1H), 4.71-4.55 (m, 1H), 3.91-3.71 (m, 2H), 3.58-3.45 (m, 4H), 2.48-2.42 (m, 4H), 2.29 (s, 2H), 1.01 (s, 6H).
I-29	468	¹ H NMR (400 MHz, DMSO) δ 10.45 (s, 1H), 8.70 (d, J = 7.1 Hz, 1H), 8.05-7.91 (m, 2H), 7.84-7.69 (m, 4H), 7.38-7.26 (m, 2H), 7.17 (s, 1H), 4.78-4.63 (m, 3H), 3.59-3.54 (m, 2H), 3.17 (d, J = 5.8 Hz, 2H), 2.01-1.96 (m, 2H), 0.99 (s, 6H).
I-30	537	¹ H NMR (400 MHz, DMSO) δ 10.44 (s, 1H), 8.69 (d, J = 7.1 Hz, 1H), 8.05-7.91 (m, 2H), 7.84-7.72 (m, 4H), 7.38-7.26 (m, 2H), 7.20 (s, 1H), 4.69-4.63 (m, 2H), 3.60-3.50 (m, 6H), 2.51-2.45 (m, 4H), 2.29 (s, 2H), 1.99 (t, J = 6.4 Hz, 2H), 1.02 (s, 6H).
I-35	454	¹ H NMR (400 MHz, DMSO) δ 10.45 (s, 1H), 8.52 (d, J = 7.3 Hz, 1H), 8.04-7.96 (m, 2H), 7.81-7.74 (m, 4H), 7.33 (t, J = 8.9 Hz, 2H), 7.17 (s, 1H), 5.10 (t, J = 5.7 Hz, 1H), 4.83-4.51 (m, 2H), 3.81 (d, J = 3.4 Hz, 2H), 3.16 (d, J = 5.7 Hz, 2H), 0.99 (s, 6H).

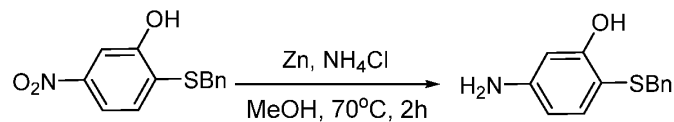
Example 3: Synthesis of (S)-N-(1-(4-(N-ethylsulfamoyl)-3-hydroxyphenylamino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide (I-67)



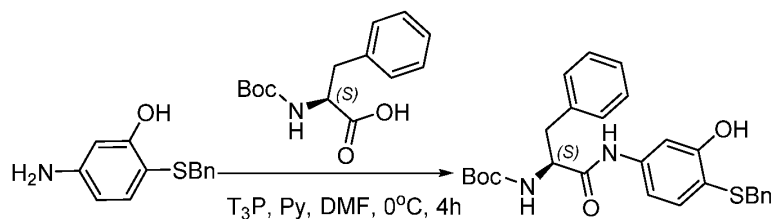
[00387] Step 1: 2-(benzylthio)-5-nitrophenol



[00388] To a solution of 7.85 g 2-fluoro-5-nitrophenol (50 mmol, 1.00 equiv) and 13.8 g potassium carbonate (100 mmol, 2.00 equiv) in 300 mL anhydrous N,N-dimethylformamide was added dropwise 7.44 g of phenylmethanethiol (60 mmol, 1.20 equiv) at room temperature. The resulting mixture was stirred for 12 h at 60°C. The mixture was cooled to room temperature, diluted with 500 mL water and extracted with ethyl acetate (3 x 500 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (2:1)) afforded 7.6 g 2-(benzylthio)-5-nitrophenol as a yellow solid (58 % yield). MS (ESI⁺) m/z 262 [M+H]⁺.

[00389] Step 2: 5-amino-2-(benzylthio)phenol

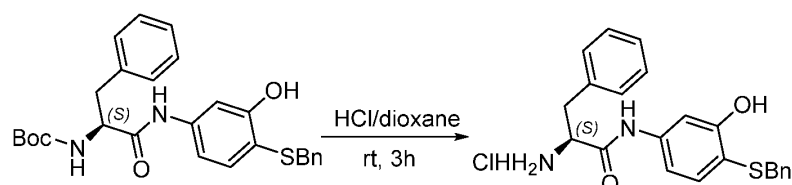
[00390] To a solution of 7.6 g 2-(benzylthio)-5-nitrophenol (29 mmol, 1.00 equiv) in 200 mL methanol was added 7.76 g ammonium chloride (145 mmol, 5.00 equiv) and 7.54 g zinc (116 mmol, 4.00 equiv) at room temperature. The resulting mixture was stirred for 2 h at 70°C under nitrogen atmosphere. The mixture was cooled to room temperature, filtered and the filtrate concentrated *in vacuo*. The residue was diluted with 50 mL water, then adjusted to pH 9 with sodium bicarbonate (aq.). The mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (2 X 100 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, petroleum ether/ethyl acetate (1:1)) afforded 3.5 g 5-amino-2-(benzylthio)phenol as an orange oil (52% yield). MS (ESI⁺) *m/z* 232 [M+H]⁺.

[00391] Step 3: (S)-tert-butyl 1-(4-(benzylthio)-3-hydroxyphenylamino)-1-oxo-3-phenylpropan-2-ylcarbamate

[00392] To a solution of 1.9 g (S)-2-(tert-butoxycarbonylamino)-3-phenylpropanoic acid (7.14 mmol, 1.00 equiv), 1.66 g 5-amino-2-(benzylthio)phenol (7.14 mmol, 1 equiv) and 5.64 g pyridine (71.40 mmol, 10.00 equiv) in 40 mL N,N-dimethylformamide was added dropwise a solution 18.42 g propanephosphonic acid cyclic anhydride in ethyl acetate (50%, 35.70 mmol, 5.00 equiv) at 0°C. The resulting mixture was stirred for 4 h at 0°C. The mixture was diluted with 100 mL water and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (3x100 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, petroleum ether:ethyl

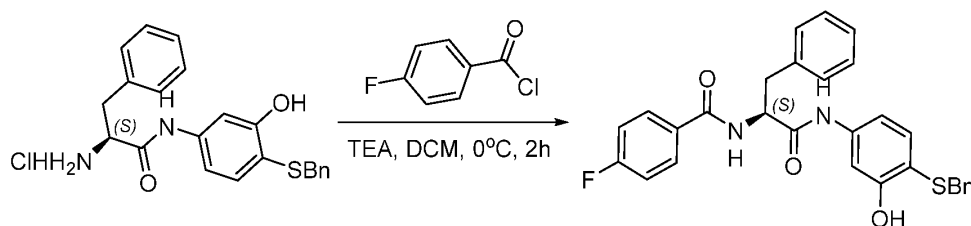
acetate (1:1)) provided 2 g (S)-tert-butyl 1-(4-(benzylthio)-3-hydroxyphenylamino)-1-oxo-3-phenylpropan-2-ylcarbamate as a yellow solid (59% yield). MS (ESI⁺) m/z 423 [M-56+H]⁺.

[00393] Step 4: (S)-2-amino-N-(4-(benzylthio)-3-hydroxyphenyl)-3-phenylpropanamide hydrochloride



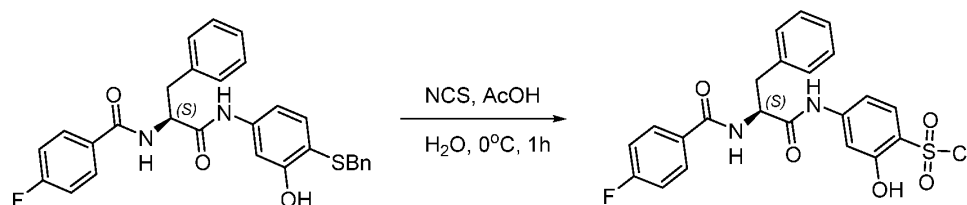
[00394] A mixture of 2 g (S)-tert-butyl 1-(4-(benzylthio)-3-hydroxyphenylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (4.18 mmol, 1.00 equiv) in 20 mL hydrochloric acid in 1,4-dioxane (4.0 M) was stirred at room temperature for 3 h. The mixture was concentrated to afford 1.74 g (S)-2-amino-N-(4-(benzylthio)-3-hydroxyphenyl)-3-phenylpropanamide hydrochloride as a light yellow solid (100 % yield). MS (ESI⁺) m/z 379 [M+H]⁺.

[00395] Step 5: (S)-N-(1-(4-(benzylthio)-3-hydroxyphenylamino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide



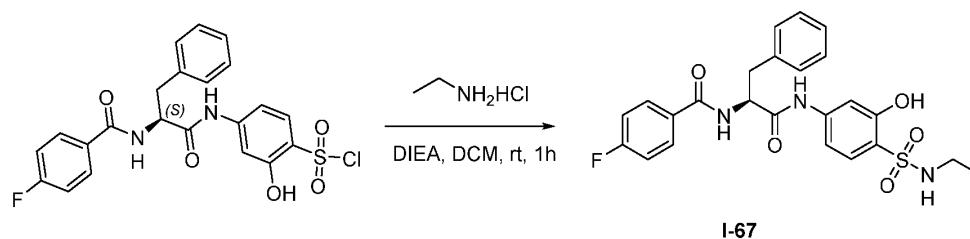
[00396] To a solution of 1.74 g (S)-2-amino-N-(4-(benzylthio)-3-hydroxyphenyl)-3-phenylpropanamide hydrochloride (4.2 mmol, 1.00 equiv) and 2.55 g triethylamine (25.2 mmol, 6.00 equiv) in 20 mL dichloromethane was added dropwise 796.3 mg 4-fluorobenzoyl chloride (5.04 mmol, 1.20 equiv) at 0°C. The resulting mixture was stirred for 2 h at 0°C. The resulting mixture was diluted with 20 mL water and extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine (1x30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (1:1)) afforded 1.1 g (S)-N-(1-(4-(benzylthio)-3-hydroxyphenylamino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide as a yellow solid (52 % yield). MS (ESI⁺) m/z 501 [M+H]⁺.

[00397] Step 6: (S)-4-(2-(4-fluorobenzamido)-3-phenylpropanamido)-2-hydroxybenzene-1-sulfonyl chloride



[00398] To a solution of 1.1 g (S)-N-(1-(4-(benzylthio)-3-hydroxyphenylamino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide (2.2 mmol, 1.00 equiv) in 12 mL acetic acid and 4 mL water was added 1.17 g N-chlorosuccinimide (8.8 mmol, 4.00 equiv) at 0°C. The resulting mixture was stirred at 0°C for 2 h. The mixture was diluted with 30 mL water and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (1x50 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated to give 0.43 g (S)-4-(2-(4-fluorobenzamido)-3-phenylpropanamido)-2-hydroxybenzene-1-sulfonyl chloride as a white solid (41 % yield). MS (ESI⁺) m/z 477 [M+H]⁺.

[00399] Step 7: (S)-N-(1-(4-(N-ethylsulfamoyl)-3-hydroxyphenylamino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide



[00400] To a mixture of 170.1 mg ethanamine hydrochloride (2.1 mmol, 5.0 equiv) and 270.9 mg N,N-diisopropylethylamine (2.1 mmol, 5.00 equiv) in 10 mL dichloromethane was added 200 mg (S)-4-(2-(4-fluorobenzamido)-3-phenylpropanamido)-2-hydroxybenzene-1-sulfonyl chloride (0.42 mmol, 1.00 equiv). The mixture was stirred at room temperature for 1 h. The mixture was diluted with 10 mL water and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions: Column, YMC-Actus Triart C18, 30*250 mm, 5 um; Mobile Phase,

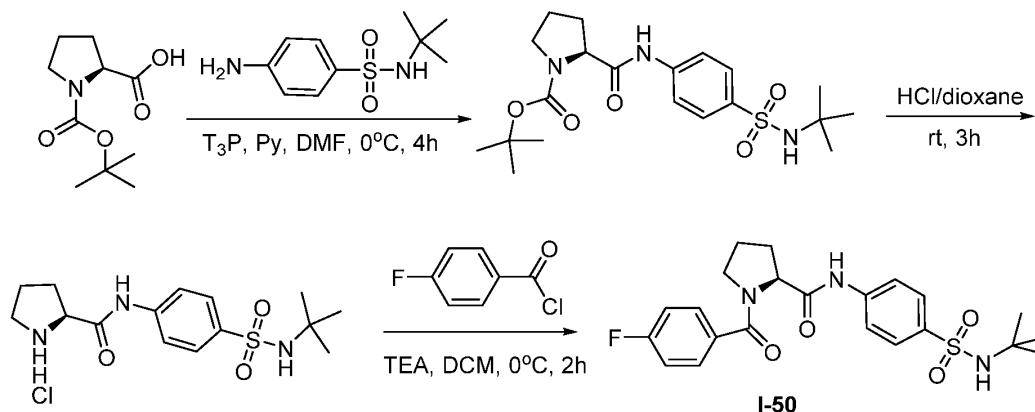
water (10% NH_4HCO_3 +0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$) and ACN (21% ACN up to 34% in 7 min); UV detection at 254/220 nm. The product-containing fractions were combined and evaporated partially in vacuo and lyophilized overnight to afford 42.4 mg (S)-N-(1-(4-(N-ethylsulfamoyl)-3-hydroxyphenylamino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide (**I-67**) as a white solid.

[00401] The compounds in **Table 6** were made by a method analogous to the method used to make **I-67**, substituting the appropriate amine in step 7.

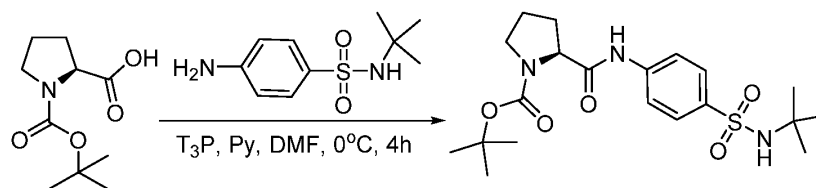
Table 6. Compounds made by a method analogous to I-67

Cmpd #	yield	MS [M+H] ⁺	¹ H NMR
I-67	21%	486	¹ H NMR (300 MHz, CD_3OD) δ 7.86-7.82 (m, 2H), 7.61 (d, 1H), 7.48 (s, 1H), 7.34-7.15 (m, 7H), 6.99-6.96 (m, 1H), 4.94-4.89 (m, 1H), 3.31-3.08 (m, 2H), 2.99 (q, 2H), 1.09 (t, 3H).
I-66	18%	514	¹ H NMR (400 MHz, CD_3OD) δ 7.86-7.83 (m, 2H), 7.62 (d, 1H), 7.52 (s, 1H), 7.35-7.16 (m, 7H), 6.96 (dd, 1H), 4.94-4.90 (m, 1H), 4.64-4.62 (m, 2H), 4.54-4.52 (m, 3H), 3.31-3.16 (m, 2H).
I-64	20%	524	¹ H NMR (400 MHz, CD_3OD) δ 7.88-7.83 (m, 2H), 7.63 (d, 1H), 7.52 (s, 1H), 7.35-7.16 (m, 7H), 7.01-6.99 (m, 1H), 4.94-4.90 (m, 1H), 3.31-3.14 (m, 2H), 2.27 (s, 1H), 1.78 (s, 6H).
I-63	22%	514	¹ H NMR (400 MHz, CD_3OD) δ 7.87-7.83 (m, 2H), 7.64 (d, 1H), 7.49 (s, 1H), 7.35-7.17 (m, 7H), 7.01-6.99 (m, 1H), 4.94-4.90 (m, 1H), 3.31-3.14 (m, 2H), 1.19 (s, 9H).

Example 4: Synthesis of (S)-N-(4-(N-tert-butylsulfamoyl)phenyl)-1-(4-fluorobenzoyl)pyrrolidine-2-carboxamide (I-50)

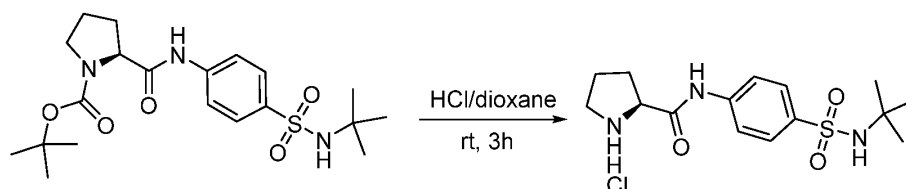


[00402] Step 1: (S)-tert-butyl 2-(4-(N-tert-butylsulfamoyl)phenylcarbamoyl)pyrrolidine-1-carboxylate



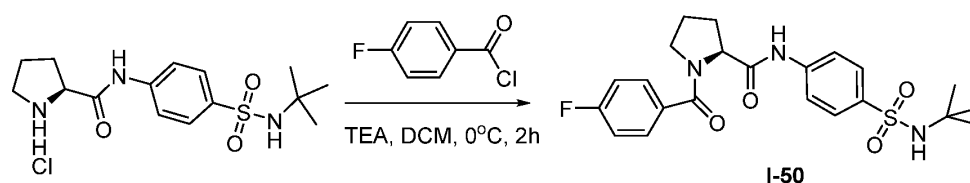
[00403] To a solution of 456 mg 4-amino-N-tert-butylbenzenesulfonamide (2 mmol, 1.00 equiv), 430 mg (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (2 mmol, 1.00 equiv) and 1.58 g pyridine (20 mmol, 10.00 equiv) in 10 mL N,N-dimethylformamide was added dropwise a solution 5.16 g propanephosphonic acid cyclic anhydride in ethyl acetate (50%, 10 mmol, 5.00 equiv) at 0°C. The resulting mixture was stirred for 4 h at 0°C. The mixture was diluted with 100 mL water and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (3x50 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (3:1)) provided 518.5 mg (S)-tert-butyl 2-(4-(N-tert-butylsulfamoyl)phenylcarbamoyl)pyrrolidine-1-carboxylate as a yellow solid (61% yield). MS (ESI⁺) m/z 424 [M-H]⁺.

[00404] Step 2: (S)-N-(4-(N-tert-butylsulfamoyl)phenyl)pyrrolidine-2-carboxamide hydrochloride



[00405] A mixture of 518.5 mg (S)-tert-butyl 2-(4-(N-tert-butylsulfamoyl)phenylcarbamoyl)pyrrolidine-1-carboxylate (1.22 mmol, 1.00 equiv) in 10 mL hydrochloric acid in 1,4-dioxane (4.0 M) was stirred at room temperature for 3 h. The mixture was concentrated to afford 443 mg (S)-N-(4-(N-tert-butylsulfamoyl)phenyl)pyrrolidine-2-carboxamide hydrochloride as a light yellow solid (100 % yield). MS (ESI⁺) m/z 326 [M+H]⁺.

[00406] Step 3: (S)-N-(4-(N-tert-butylsulfamoyl)phenyl)-1-(4-fluorobenzoyl)pyrrolidine-2-carboxamide



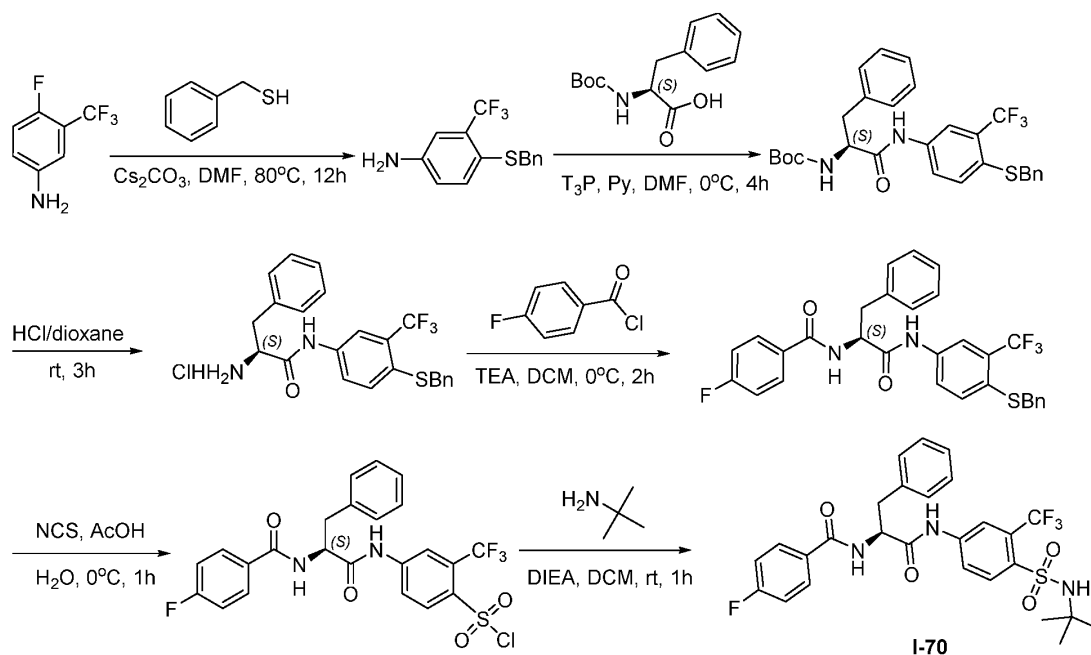
[00407] To a solution of 97.88 mg (S)-N-(4-(N-tert-butylsulfamoyl)phenyl)pyrrolidine-2-carboxamide hydrochloride (0.27 mmol, 1.00 equiv) and 163.62 mg triethylamine (1.62 mmol, 6.00 equiv) in 10 mL dichloromethane was added dropwise 51.2 mg 4-fluorobenzoyl chloride (0.324 mmol, 1.20 equiv) at 0°C. The resulting mixture was stirred for 2 h at 0°C. The resulting mixture was diluted with 20 mL water and extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine (1x30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated in vacuo. The crude product was purified by Prep-HPLC with the following conditions: Column, YMC-Actus Triart C18, 30*250 mm, 5 um; Mobile Phase, water (10% NH₄HCO₃+0.1% NH₃-H₂O) and ACN (31% ACN up to 55% in 7 min); UV detection at 254/220 nm. The product-containing fractions were combined and evaporated partially in vacuo and lyophilized overnight to afford 33 mg (S)-N-(4-(N-tert-butylsulfamoyl)phenyl)-1-(4-fluorobenzoyl)pyrrolidine-2-carboxamide (**I-50**) as a white solid (27% yield). MS (ESI, m/z) 448

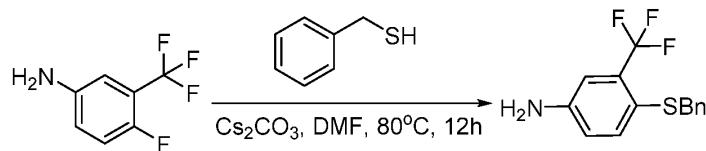
$[M+H]^+$; ^1H NMR (300 MHz, d_6 -DMSO) δ 10.45 (s, 1H), 7.85-7.50 (m, 6H), 7.45-7.08 (m, 3H), 4.66-4.40 (m, 1H), 3.64-3.54 (m, 2H), 2.36-2.28 (m, 1H), 2.05-1.84 (m, 3H), 1.09 (s, 9H).

[00408] Compound **I-51** was made by a method analogous to the method used to make **I-50**, substituting (R)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid for (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid in Step 1.

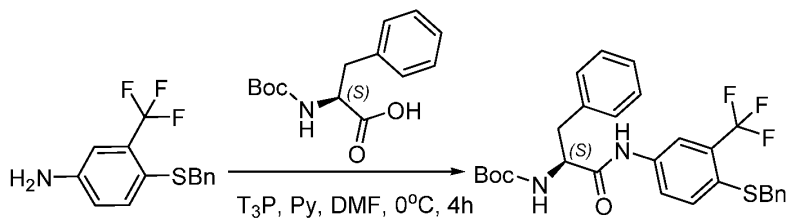
Cmpd #	yield	MS	^1H NMR
I-51	34%	446 $[M-H]^-$	^1H NMR (400 MHz, d_6 -DMSO) δ 10.45 (s, 1H), 7.85-7.62 (m, 5H), 7.60-7.10 (m, 4H), 4.65-4.40 (m, 1H), 3.64-3.54 (m, 2H), 2.36-2.28 (m, 1H), 2.05-1.84 (m, 3H), 1.09 (s, 9H).

Example 5: Synthesis of (S)-N-(1-(4-(N-tert-butylsulfamoyl)-3-(trifluoromethyl)phenylamino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide (I-70)



[00409] Step 1: 4-(benzylthio)-3-(trifluoromethyl)benzenamine

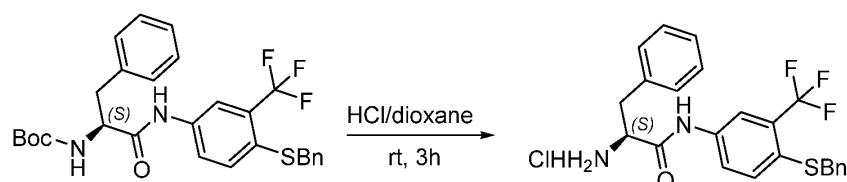
[00410] To a solution of 9 g 4-fluoro-3-(trifluoromethyl)benzenamine (50 mmol, 1.00 equiv) and 32.6 g cesium carbonate (100 mmol, 2.00 equiv) in 300 mL anhydrous N,N-dimethylformamide was added dropwise 7.44 g of phenylmethanethiol (60 mmol, 1.20 equiv) at room temperature. The resulting mixture was stirred for 12 h at 80°C. The mixture was cooled to room temperature, diluted with 500 mL water and extracted with ethyl acetate (3 x 500 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (2:1)) afforded 3.7 g 4-(benzylthio)-3-(trifluoromethyl)benzenamine as a yellow solid (26 % yield). MS (ESI⁺) m/z 284 [M+H]⁺.

[00411] Step 2: (S)-tert-butyl 1-(4-(benzylthio)-3-(trifluoromethyl)phenylamino)-1-oxo-3-phenylpropan-2-ylcarbamate

[00412] To a solution of 1.9 g (S)-2-(tert-butoxycarbonylamino)-3-phenylpropanoic acid (7.14 mmol, 1.00 equiv), 2.03 g 4-(benzylthio)-3-(trifluoromethyl)benzenamine (7.14 mmol, 1 equiv) and 5.64 g pyridine (71.40 mmol, 10.00 equiv) in 40 mL N,N-dimethylformamide was added dropwise a solution 18.42 g propanephosphonic acid cyclic anhydride in ethyl acetate (50%, 35.70 mmol, 5.00 equiv) at 0°C. The resulting mixture was stirred for 4 h at 0°C. The mixture was diluted with 100 mL water and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (3x100 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (1:1)) provided 2.5 g (S)-tert-butyl 1-(4-(benzylthio)-3-

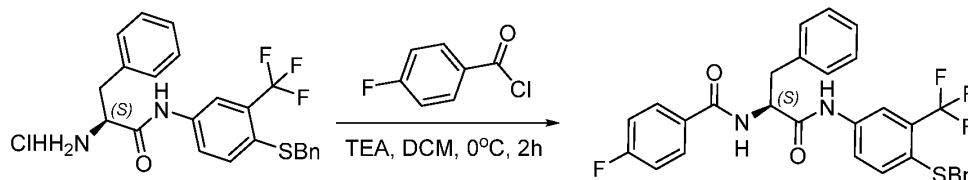
(trifluoromethyl)phenylamino)-1-oxo-3-phenylpropan-2-ylcarbamate as a yellow solid (66% yield). MS (ESI⁺) m/z 475 [M-56+H]⁺.

[00413] Step 3: (S)-2-amino-N-(4-(benzylthio)-3-(trifluoromethyl)phenyl)-3-phenylpropanamide hydrochloride



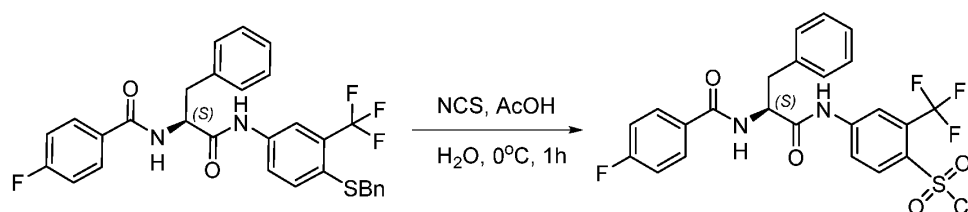
[00414] A mixture of 2.5 g (S)-tert-butyl 1-(4-(benzylthio)-3-(trifluoromethyl)phenylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (4.72 mmol, 1.00 equiv) in 20 mL hydrochloric acid in 1,4-dioxane (4.0 M) was stirred at room temperature for 3 h. The mixture was concentrated to afford 2.2 g (S)-2-amino-N-(4-(benzylthio)-3-(trifluoromethyl)phenyl)-3-phenylpropanamide hydrochloride as a light yellow solid (100 % yield). MS (ESI⁺) m/z 431 [M+H]⁺.

[00415] Step 4: (S)-N-(1-(4-(benzylthio)-3-(trifluoromethyl)phenylamino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide



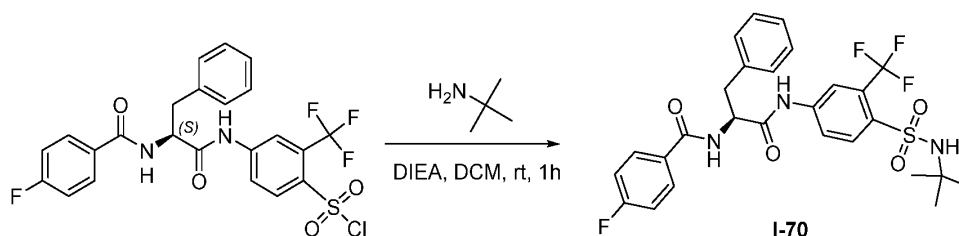
[00416] To a solution of 2.2 g (S)-2-amino-N-(4-(benzylthio)-3-(trifluoromethyl)phenyl)-3-phenylpropanamide hydrochloride (4.72 mmol, 1.00 equiv) and 2.86 g triethylamine (28.32 mmol, 6.00 equiv) in 20 mL dichloromethane was added dropwise 895 mg 4-fluorobenzoyl chloride (5.66 mmol, 1.20 equiv) at 0°C. The resulting mixture was stirred for 2 h at 0°C. The resulting mixture was diluted with 20 mL water and extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine (1x30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (1:1)) afforded 1.5 g (S)-N-(1-(4-(benzylthio)-3-(trifluoromethyl)phenylamino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide as a yellow solid (57 % yield). MS (ESI⁺) m/z 553 [M+H]⁺.

[00417] Step 5: (S)-4-(2-(4-fluorobenzamido)-3-phenylpropanamido)-2-(trifluoromethyl)benzene-1-sulfonyl chloride



[00418] To a solution of 1.5 g (S)-N-(1-(4-(benzylthio)-3-(trifluoromethyl)phenylamino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide (2.72 mmol, 1.00 equiv) in 12 mL acetic acid and 4 mL water was added 1.45 g N-chlorosuccinimide (10.88 mmol, 4.00 equiv) at 0°C. The resulting mixture was stirred at 0°C for 2 h. The mixture was diluted with 30 mL water and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (1x50 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated to give 0.62 g (S)-4-(2-(4-fluorobenzamido)-3-phenylpropanamido)-2-(trifluoromethyl)benzene-1-sulfonyl chloride as a white solid (43 % yield). MS (ESI⁺) m/z 529 [M+H]⁺.

[00419] Step 6: (S)-N-(1-(4-(N-tert-butylsulfamoyl)-3-(trifluoromethyl)phenylamino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide



[00420] To a mixture of 138.3 mg 2-methylpropan-2-amine (1.895 mmol, 5.0 equiv) and 244.5 mg N,N-diisopropylethylamine (1.895 mmol, 5.00 equiv) in 10 mL dichloromethane was added 200 mg (S)-4-(2-(4-fluorobenzamido)-3-phenylpropanamido)-2-(trifluoromethyl)benzene-1-sulfonyl chloride (0.379 mmol, 1.00 equiv). The mixture was stirred at room temperature for 1 h. The mixture was diluted with 10 mL water and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions: Column, YMC-Actus Triart C18, 30*250

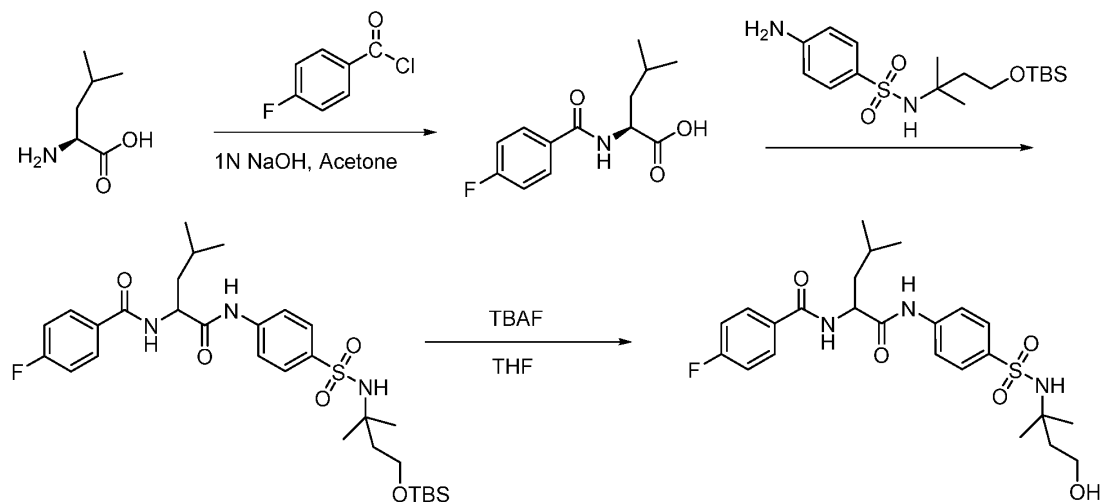
mm, 5 μ m; Mobile Phase, water (10% NH_4HCO_3 +0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$) and ACN (33% ACN up to 45% in 7 min); UV detection at 254/220 nm. The product-containing fractions were combined and evaporated partially in vacuo and lyophilized overnight to afford 35.9 mg (S)-N-(1-(4-(N-tert-butylsulfamoyl)-3-(trifluoromethyl)phenylamino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide as a white solid.

[00421] The compounds in **Table 7** were made by a method analogous to the method used to make **I-70**, substituting the appropriate amine in step 6.

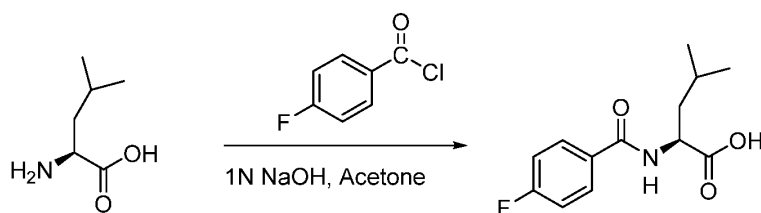
Table 7. Compounds made by a method analogous to I-70

Cmpd #	yield	MS [M+H] ⁺	¹ H NMR
I-70	17%	566	¹ H NMR (400 MHz, CD_3OD) δ 8.18 (d, 1H), 8.11 (s, 1H), 7.94 (dd, 1H), 7.88-7.85 (m, 2H), 7.36-7.17 (m, 7H), 4.94-4.90 (m, 1H), 3.31-3.17 (m, 2H), 1.24 (s, 9H).
I-69	18%	576	¹ H NMR (400 MHz, CD_3OD) δ 8.15-8.13 (m, 2H), 7.97 (dd, 1H), 7.89-7.85 (m, 2H), 7.36-7.18 (m, 7H), 4.94-4.90 (m, 1H), 3.31-3.15 (m, 2H), 2.32 (s, 1H), 1.86 (s, 6H).
I-68	16%	566	¹ H NMR (400 MHz, CD_3OD) δ 8.10-8.08 (m, 2H), 7.98 (dd, 1H), 7.89-7.85 (m, 2H), 7.35-7.18 (m, 7H), 4.94-4.90 (m, 1H), 4.71-4.68 (m, 2H), 4.57-4.49 (m, 3H), 3.31-3.15 (m, 2H).
I-65	19%	610	¹ H NMR (400 MHz, CD_3OD) δ 8.17-8.13 (m, 2H), 7.95 (dd, 1H), 7.89-7.85 (m, 2H), 7.36-7.18 (m, 7H), 4.94-4.90 (m, 1H), 3.53 (t, 2H), 3.32 (s, 3H), 3.31-3.17 (m, 2H), 1.82 (t, 2H), 1.23 (s, 6H).

Example 6: Synthesis of 4-fluoro-N-(1-((4-(N-(4-hydroxy-2-methylbutan-2-yl)sulfamoyl)phenyl)amino)-4-methyl-1-oxopentan-2-yl)benzamide (I-70)

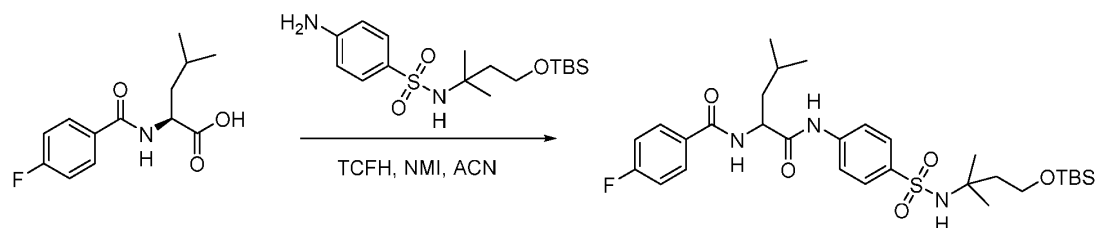


[00422] Step 1: (4-fluorobenzoyl)-L-leucine



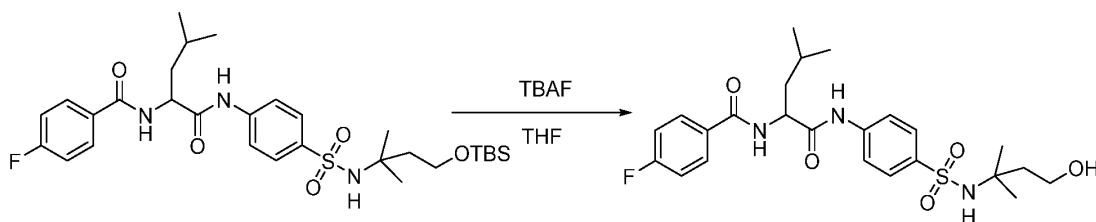
[00423] To a solution of 992 mg L-leucine (7.57 mmol, 1.00 equiv) in 10 mL acetone and 16 mL 1N NaOH was added dropwise 1.20 g of 4-fluorobenzoyl chloride (7.57 mmol, 1.00 equiv) at 0 °C. The resulting mixture was stirred for 2 hours at room temperature. The mixture was adjusted to PH=4 with 1N HCl and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (2:1)) afforded 1.6 g (4-fluorobenzoyl)-L-leucine as a white solid (84 % yield). MS (ESI⁺) m/z 254 [M+H]⁺.

[00424] Step 2: N-(1-((4-(N-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)sulfamoyl)phenyl)amino)-4-methyl-1-oxopentan-2-yl)-4-fluorobenzamide



[00425] A solution of 1.2 g 4-amino-N-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)benzenesulfonamide (3.2 mmol, 1.00 equiv), 1.6 g (4-fluorobenzoyl)-L-leucine (6.4 mmol, 2.00 equiv), 792 mg 1-Methylimidazole (9.6 mmol, 3.00 equiv) and 913 mg N,N,N',N'-Tetramethylchloroformamidinium hexafluorophosphate (6.8 mmol, 2.10 equiv) in 20 mL acetonitrile were stirred for 12 hours at room temperature. The resulting mixture was diluted with 20 mL water and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (3:1)) afforded 450 mg N-(1-((4-(N-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)sulfamoyl)phenyl)amino)-4-methyl-1-oxopentan-2-yl)-4-fluorobenzamide as a white solid (23 % yield). MS (ESI⁺) m/z 608 [M+H]⁺.

[00426] Step 3: 4-fluoro-N-(1-((4-(N-(4-hydroxy-2-methylbutan-2-yl)sulfamoyl)phenyl)amino)-4-methyl-1-oxopentan-2-yl)benzamide (I-20 and I-21)



[00427] To a solution of 450 mg N-(1-((4-(N-(4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)sulfamoyl)phenyl)amino)-4-methyl-1-oxopentan-2-yl)-4-fluorobenzamide (0.74 mmol, 1.00 equiv) in 10 mL tetrahydrofuran was added 0.7 mL (1M in tetrahydrofuran) TBAF (0.74 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred at room temperature for 12 hours. The mixture was diluted with 10 mL water and extracted with ethyl acetate (3 x 20 mL).

The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (1:1)) afforded 0.24 g 4-fluoro-N-(1-((4-(N-(4-hydroxy-2-methylbutan-2-yl)sulfamoyl)phenyl)amino)-4-methyl-1-oxopentan-2-yl)benzamide as a white solid (66 % yield). MS (ESI⁺) m/z 494 [M+H]⁺.

[00428] The racemates were separated via chiral Prep-HPLC with the following conditions: Column, OD-H, 0.46 cm I.D. *15 cm L; Mobile Phase, CO₂:EtOH (0.1%DEA)=70:30; Flow rate: 2.5 ml, Wave length UV 254 nm. to give 59 mg (R)-4-fluoro-N-(1-((4-(N-(4-hydroxy-2-methylbutan-2-yl)sulfamoyl)phenyl)amino)-4-methyl-1-oxopentan-2-yl)benzamide (**I-21**) and 74.9 mg (S)-4-fluoro-N-(1-((4-(N-(4-hydroxy-2-methylbutan-2-yl)sulfamoyl)phenyl)amino)-4-methyl-1-oxopentan-2-yl)benzamide (**I-20**).

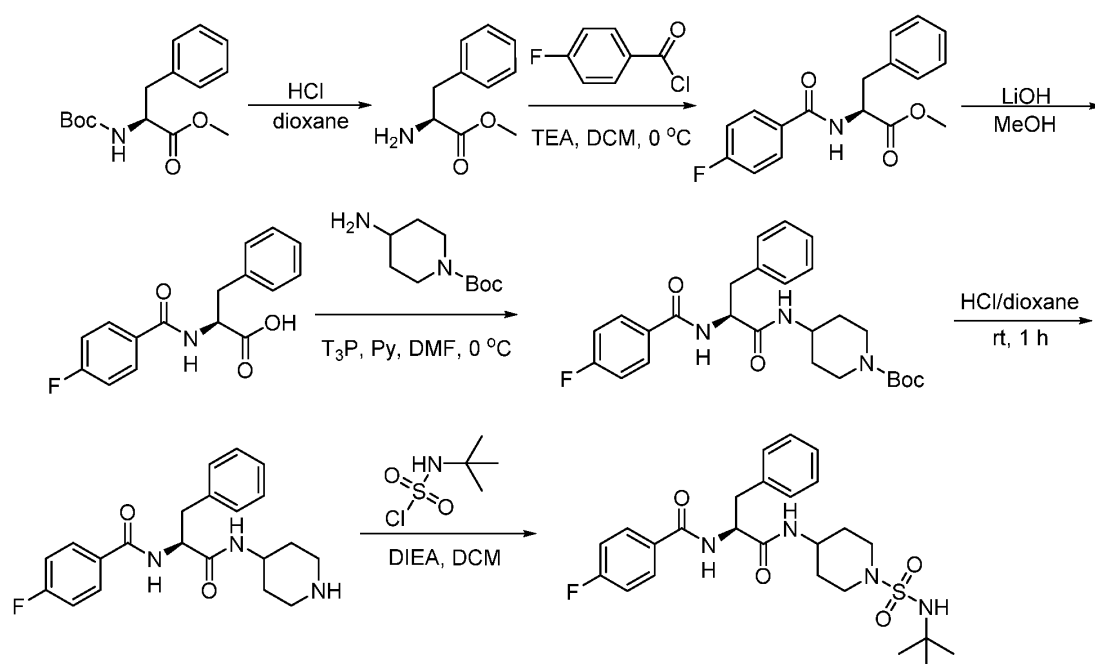
[00429] **I-18** and **I-19** were made by an analogous method to the method described for **I-20** and **I-21**. The characterization information for **I-18**, **I-19**, **I-20** and **I-21** are reported below in Table 8.

Table 8. Compounds made by a method analogous to I-20 and I-21

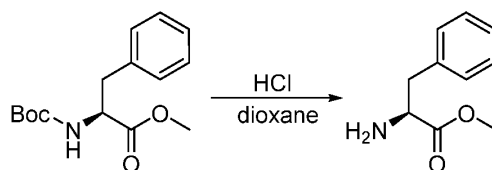
Cmpd #	MS [M+H] ⁺	¹ H NMR
I-18	508.2	¹ H NMR (400 MHz, DMSO) δ 10.49 (s, 1H), 8.69 (d, <i>J</i> = 7.1 Hz, 1H), 8.00-7.97 (m, 2H), 7.78-7.76 (m, 4H), 7.33-7.29 (m, 3H), 4.67-4.61 (m, 1H), 3.34-3.30 (m, 2H), 3.15 (s, 3H), 1.80-1.58 (m, 5H), 1.05 (s, 6H), 0.96-0.91 (m, 6H).
I-19	508.2	¹ H NMR (400 MHz, DMSO) δ 10.49 (s, 1H), 8.69 (d, <i>J</i> = 7.1 Hz, 1H), 8.00-7.97 (m, 2H), 7.78-7.76 (m, 4H), 7.33-7.29 (m, 3H), 4.67-4.61 (m, 1H), 3.34-3.30 (m, 2H), 3.15 (s, 3H), 1.80-1.58 (m, 5H), 1.05 (s, 6H), 0.96-0.91 (m, 6H).
I-20	494.2	¹ H NMR (400 MHz, DMSO) δ 10.49 (s, 1H), 8.70 (d, <i>J</i> = 7.5 Hz, 1H), 8.04 -7.95 (m, 2H), 7.77 (q, <i>J</i> = 8.9 Hz, 4H), 7.37 - 7.26 (m, 3H), 4.69 - 4.58 (m, 1H), 4.41 (s, 1H), 3.51-3.38 (m, 2H), 1.93-1.70 (m, 2H), 1.67-1.51 (m, 3H), 1.05 (s, 6H), 1.00-0.89 (m, 6H).

I-21	494.2	^1H NMR (400 MHz, DMSO) δ 10.49 (s, 1H), 8.70 (d, J = 7.6 Hz, 1H), 8.04-7.93 (m, 2H), 7.76 (q, J = 9.0 Hz, 4H), 7.36-7.26 (m, 3H), 4.73-4.58 (m, 1H), 4.40 (t, J = 4.8 Hz, 1H), 3.52-3.36 (m, 2H), 1.87- 1.70 (m, 2H), 1.65-1.53 (m, 3H), 1.05 (s, 6H), 0.99- 0.87 (m, 6H).
------	-------	---

Example 7: Synthesis of (S)-N-(1-((1-(N-(tert-butyl)sulfamoyl)piperidin-4-yl)amino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide (I-58) and (S)-N-(tert-butyl)-4-(2-(4-fluorobenzamido)-3-phenylpropanamido)piperidine-1-carboxamide (I-57)



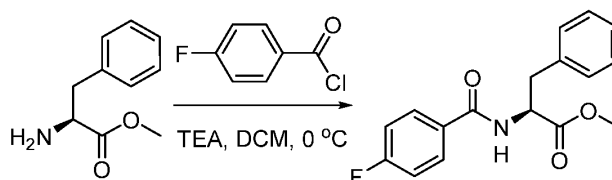
[00430] Step 1: methyl L-phenylalaninate, hydrochloride



[00431] Methyl (tert-butoxycarbonyl)-L-phenylalaninate (2.0 g, 7.17 mmol, 1.00 equiv) was dissolved in hydrochloric acid in dioxane (20 mL, 4.0 M HCl) and the mixture was stirred at room

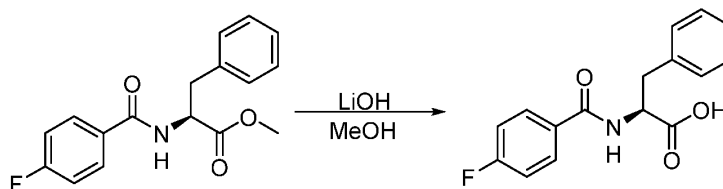
temperature for 1 hour. The mixture was concentrated to afford methyl L-phenylalaninate hydrochloride as a white solid (1.5 g, 97 % yield). MS (ESI⁺) *m/z* 180.1 [M+H]⁺.

[00432] Step 2: methyl (4-fluorobenzoyl)-L-phenylalaninate



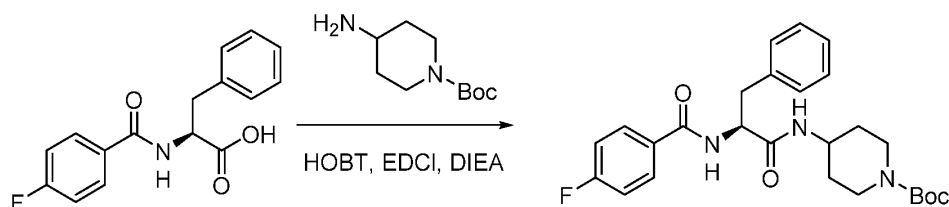
[00433] To a solution of 1.5 g methyl L-phenylalaninate hydrochloride (6.98 mmol, 1.00 equiv) and 1.91 g triethylamine (41.86 mmol, 6.00 equiv) in 20 mL dichloromethane was added dropwise 1.32 g 4-fluorobenzoyl chloride (8.37 mmol, 1.20 equiv) at 0 °C. The resulting mixture was stirred for 2 h at 0 °C. The resulting mixture was diluted with 20 mL water and extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (5:1)) afforded 2.0 g methyl (4-fluorobenzoyl)-L-phenylalaninate as a white solid (95 % yield). MS (ESI⁺) *m/z* 302.1 [M+H]⁺.

[00434] Step 3: (4-fluorobenzoyl)-L-phenylalanine



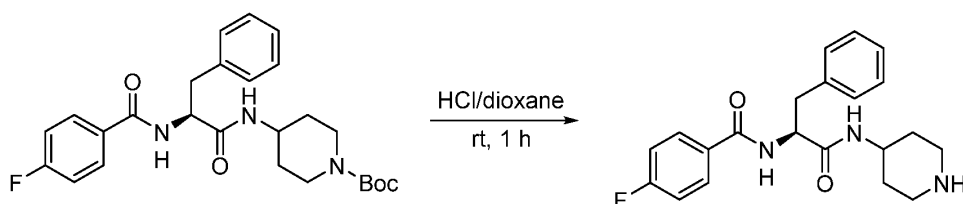
[00435] To a solution of (4-fluorobenzoyl)-L-phenylalaninate (2.0 g, 6.64 mmol, 1.0 equiv) in 30 mL methanol was added dropwise the solution of 1.59 g lithium hydroxide (66.45 mmol, 10.0 equiv) in 10 mL water at 0 °C, the mixture was stirred at room temperature overnight. The mixture was concentrated. The residue was diluted with 20 mL water, adjusted to PH=5-6 and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo to give (4-fluorobenzoyl)-L-phenylalanine (1.8 g, 94 % yield) as a white solid. MS (ESI⁺) *m/z* 288.1 [M+H]⁺.

[00436] Step 4: tert-butyl (S)-4-(2-(4-fluorobenzamido)-3-phenylpropanamido)piperidine-1-carboxylate



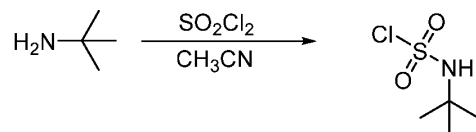
[00437] A mixture of 1.0 g (4-fluorobenzoyl)-L-phenylalanine (3.5 mmol, 1.00 equiv), 700 mg tert-butyl 4-aminopiperidine-1-carboxylate (3.5 mmol, 1.0 equiv), 1.0 g N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (5.25 mmol, 1.50 equiv), 567 mg 1-hydroxybenzotriazole (4.2 mmol, 1.2 equiv) and 903 mg N,N-diisopropylethylamine (7 mmol, 2.00 equiv) in 20 mL N,N-dimethylformamide was stirred at room temperature overnight. The reaction was diluted with 100 mL ethyl acetate and washed with water (3 x 100 mL). The organic phase was concentrated and the residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate (1:1, v:v)) to give 1.6 g tert-butyl (S)-4-(2-(4-fluorobenzamido)-3-phenylpropanamido)piperidine-1-carboxylate as a white solid (97 % yield). MS (ESI⁺) m/z 470.2 [M+H]⁺.

[00438] Step 5: (S)-4-fluoro-N-(1-oxo-3-phenyl-1-(piperidin-4-ylamino)propan-2-yl)benzamide



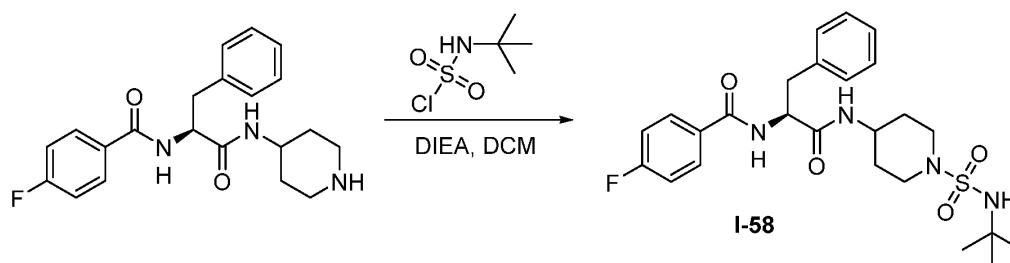
[00439] A solution of tert-butyl (S)-4-(2-(4-fluorobenzamido)-3-phenylpropanamido)piperidine-1-carboxylate (1.6 g, 3.41 mmol, 1.00 equiv) in hydrochloric acid in dioxane (20 mL, 4.0 M HCl) was stirred at room temperature for 1 hour. The mixture was concentrated to afford (S)-4-fluoro-N-(1-oxo-3-phenyl-1-(piperidin-4-ylamino)propan-2-yl)benzamide as a white solid (1.24 g, 99 % yield). MS (ESI⁺) m/z 370.2 [M+H]⁺.

[00440] Preparation of tert-butylsulfamoyl chloride

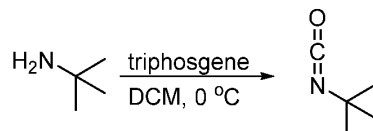


[00441] To a solution of 1.0 g 2-methylpropan-2-amine (13.67 mmol, 1.0 equiv) in 4 mL acetonitrile was added dropwise 4 mL sulfuryl dichloride (54.68 mmol, 4.0 equiv) at 0 °C. The resulting mixture was stirred for 16 h at 84 °C. The mixture was concentrated to give 0.9 g tert-butylsulfamoyl chloride as a colorless oil liquid (39 % yield).

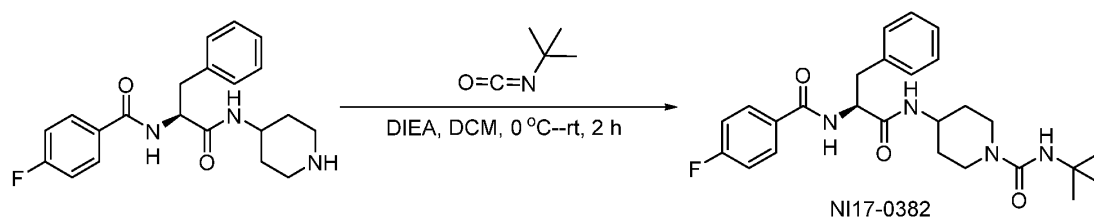
[00442] **Step 6: (S)-N-(1-((1-(N-(tert-butyl)sulfamoyl)piperidin-4-yl)amino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide (I-58)**



[00443] To a mixture of 232.6 mg tert-butylsulfamoyl chloride (1.36 mmol, 5.0 equiv) and 174.8 mg N,N-diisopropylethylamine (1.36 mmol, 5.00 equiv) in 10 mL dichloromethane was added 100 mg (S)-4-fluoro-N-(1-oxo-3-phenyl-1-(piperidin-4-ylamino)propan-2-yl)benzamide (0.27 mmol, 1.00 equiv). The mixture was stirred at room temperature for 1 hour and concentrated in vacuo. The residue was purified by Prep-HPLC with the following conditions: Column, Xbridge Prep C18 19*250mm 5um; Mobile Phase, A:0.1%NH₃H₂O/H₂O B:CAN; Gradient : 30% increase to 80%B within 15min.UV detection at 254/220 nm to give 25.0 mg (S)-N-(1-((1-(N-(tert-butyl)sulfamoyl)piperidin-4-yl)amino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide (**I-58**) as a white solid (18 % yield). MS (ESI⁺) m/z 505.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO) δ 8.58 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 7.90-7.85 (m, 2H), 7.33 (d, *J* = 7.2 Hz, 2H), 7.29-7.23 (m, 4H), 7.16 (t, *J* = 7.3 Hz, 1H), 6.87 (s, 1H), 4.68-4.62 (m, 1H), 3.66 (d, *J* = 7.5 Hz, 1H), 3.44 (t, *J* = 13.5 Hz, 2H), 3.05-2.94 (m, 2H), 2.75-2.68 (m, 2H), 1.80-1.71 (m, 2H), 1.49-1.33 (m, 2H), 1.22 (s, 9H).

[00444] Preparation of 2-isocyanato-2-methylpropane

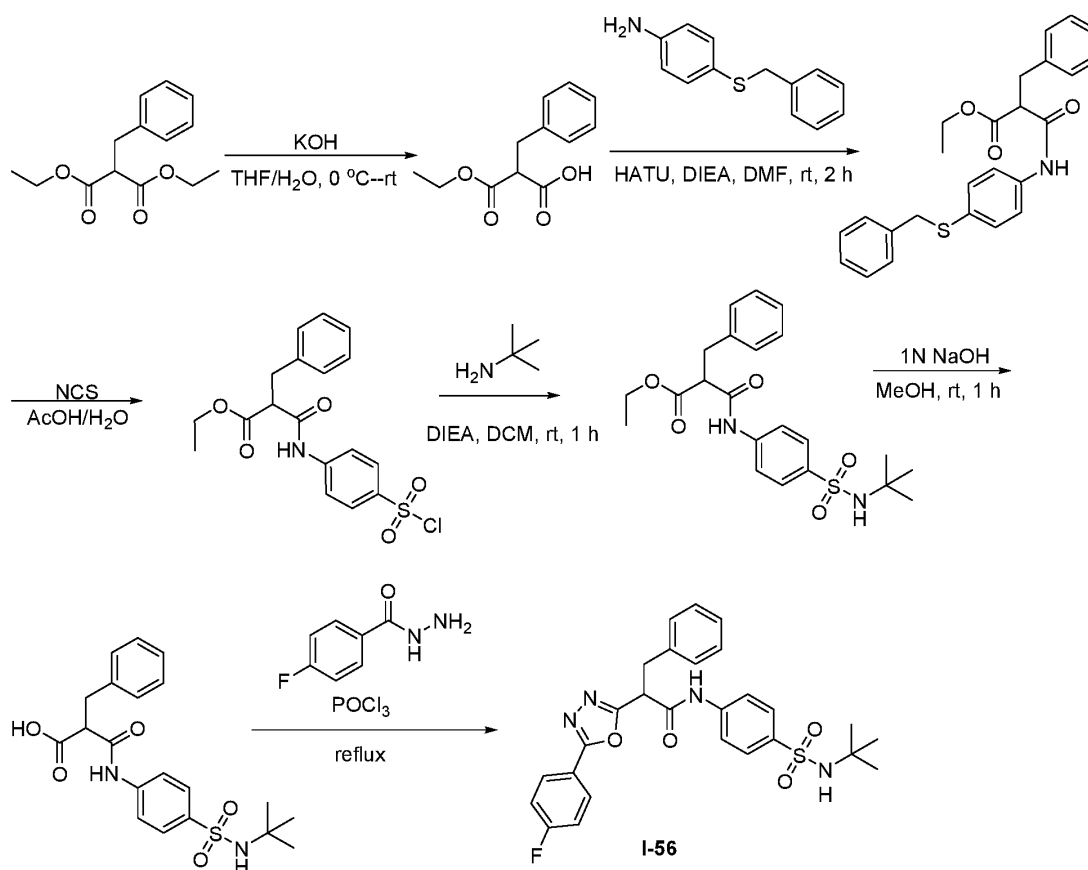
[00445] To a mixture of 500 mg 2-methylpropan-2-amine (6.84 mmol, 1.0 equiv) and 1.38 g TEA (13.7 mmol, 2.00 equiv) in 10 mL dichloromethane was added 2.0 g triphosgene (6.84 mmol, 1.00 equiv) at 0 °C. The mixture was stirred at room temperature for 2 hours. The resulting mixture was diluted with 20 mL water and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo to give 534 mg 2-isocyanato-2-methylpropane as a colorless oil liquid (79 % yield).

[00446] Step 7: (S)-N-(tert-butyl)-4-(2-(4-fluorobenzamido)-3-phenylpropanamido)piperidine-1-carboxamide (I-57)

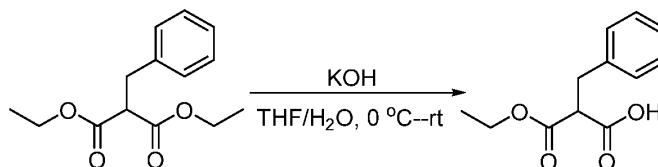
[00447] To a mixture of 135 mg 2-isocyanato-2-methylpropane (1.36 mmol, 5.0 equiv) and 174.8 mg N,N-diisopropylethylamine (1.36 mmol, 5.00 equiv) in 10 mL dichloromethane was added 100 mg (S)-4-fluoro-N-(1-oxo-3-phenyl-1-(piperidin-4-ylamino)propan-2-yl)benzamide (0.27 mmol, 1.00 equiv). The mixture was stirred at room temperature for 1 hour and concentrated in vacuo. The residue was purified by Prep-HPLC with the following conditions: Column, Xbridge Prep C18 19*250mm 5um; Mobile Phase, A:0.1%NH₃H₂O/H₂O B:CAN; Gradient : 20% increase to 50%B within 15min.UV detection at 254/220 nm to give 28.0 mg (S)-N-(tert-butyl)-4-(2-(4-fluorobenzamido)-3-phenylpropanamido)piperidine-1-carboxamide (**I-57**) as a white solid (22 % yield). MS (ESI⁺) m/z 469.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO) δ 8.57 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.90-7.84 (m, 2H), 7.32 (d, *J* = 7.3 Hz, 2H), 7.29-7.23 (m, 4H), 7.16 (t, *J* = 7.3 Hz, 1H), 5.75 (s, 1H), 4.68-4.62 (m, 1H), 3.81 (t, *J* = 14.6 Hz, 2H),

3.72-3.65 (m, 1H), 3.04-2.95 (m, 2H), 2.74-2.67 (m, 2H), 1.67-1.56 (m, 2H), 1.30 (d, $J = 11.5$ Hz, 1H), 1.24 (s, 9H), 1.20-1.16 (m, 1H).

Example 8: Synthesis of 1-N-(4-(N-(tert-butyl)sulfamoyl)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-3-phenylpropanamide (I-56)



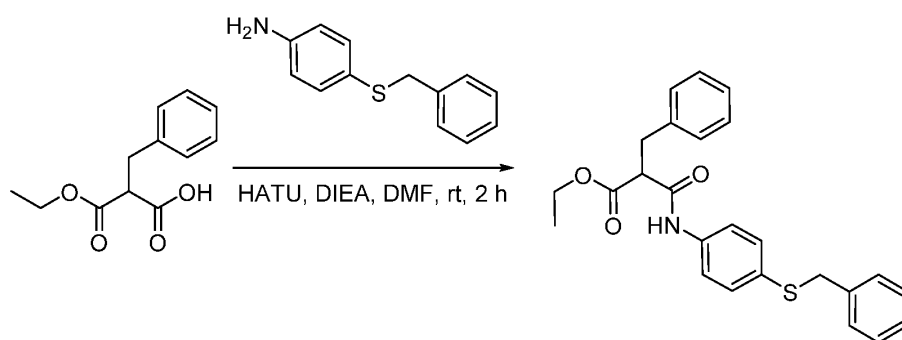
[00448] Step 1: 2-benzyl-3-methoxy-3-oxopropanoic acid



[00449] NaOH(1N, 15 mL, 15mmol, 1.5 equiv.) was added to a solution of 2.5 g diethyl 2-benzylmalonate (10 mmol, 1.00 equiv) in MeOH (50 mL). The resulting mixture was stirred for

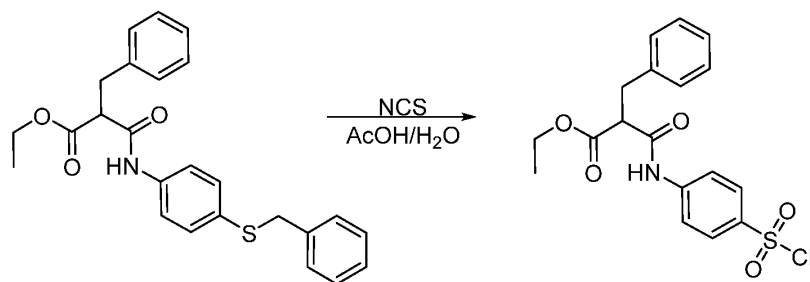
17 hours at room temperature. The mixture was concentrated. The residue was diluted with water (50 mL) and extracted with EA (2 x 50 mL). The water phase was adjusted to
[00450] PH=5, and then extracted with EA (3 x 50 mL). The organic phase was dried over Na_2SO_4 , filtered and the filtrate was concentrated to provide 1.95 g 2-benzyl-3-methoxy-3-oxopropanoic acid as colorless oil (80.0% yield). MS (ESI⁻) m/z 207.1 [M-H]⁻.

[00451] Step 2: methyl 2-benzyl-3-((4-(benzylthio)phenyl) amino)-3-oxopropanoate



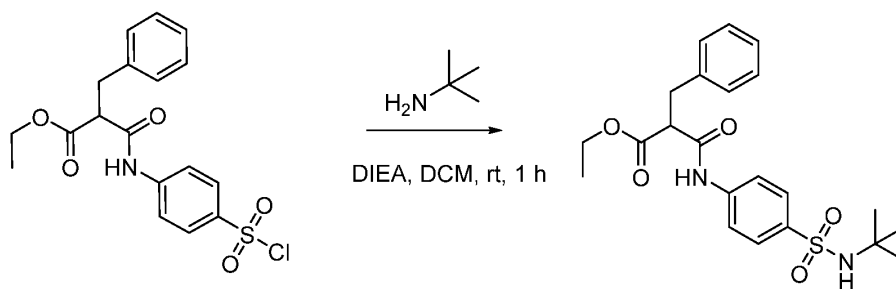
[00452] HATU (4 g, 10.5mmol, 1.2 equiv.) was added to a solution of 2-benzyl-3-methoxy-3-oxopropanoic acid (1.95 g, 8.78 mmol, 1.00 equiv), 4-(benzylthio)aniline (1.89 g, 8.78 mmol, 1.00 equiv) and DIEA (3.4 g, 26.3 mmol, 3.00 equiv) in DMF (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 hours. The resulting mixture was diluted with 100 mL water and extracted with EA (2 x 50 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (4:1)) afforded 3.5 g methyl 2-benzyl-3-((4-(benzylthio)phenyl)amino)-3-oxopropanoate as a yellow solid (95.1 % yield). MS (ESI⁺) m/z 406.1 [M+H]⁺.

[00453] Step 3: methyl 2-benzyl-3-((4-(chlorosulfonyl)phenyl) amino)-3-oxopropanoate



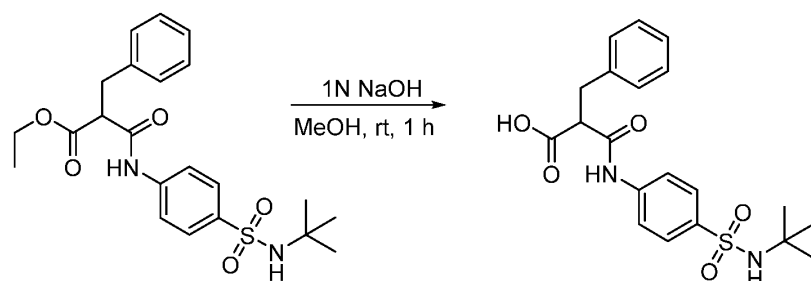
[00454] To a solution of 419 mg methyl 2-benzyl-3-((4-(benzylthio) phenyl)amino)-3-oxopropanoate (1 mmol, 1.00 equiv) in 6 mL acetic acid and 2 mL water was added 533.2 mg N-chlorosuccinimide (4 mmol, 4.00 equiv) at 0 °C. The resulting mixture was stirred at 0 °C for 1 hour. The mixture was diluted with 10 mL water and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (4:1)) afforded 200 mg methyl 2-benzyl-3-((4-(chlorosulfonyl)phenyl)amino)-3-oxopropanoate as a yellow solid (45.1 % yield). MS (ESI⁺) m/z 382.1 [M+H]⁺.

[00455] Step 4: methyl 2-benzyl-3-((4-(N-(tert-butyl)sulfamoyl) phenyl)amino)-3-oxopropanoate



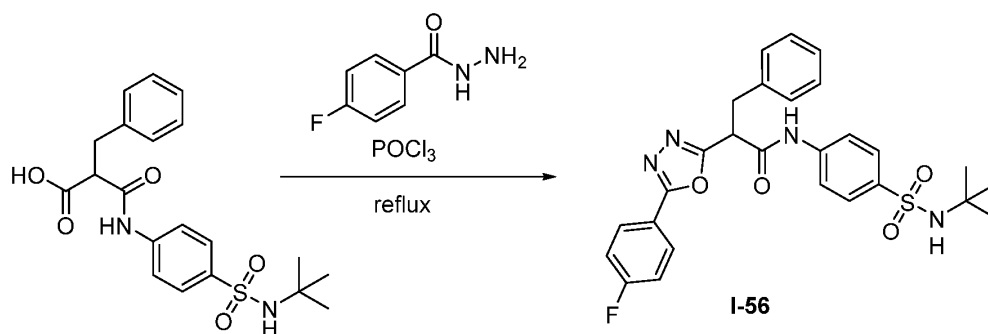
[00456] To a mixture of 184.8 mg 2-methylpropan-2-amine (2.53 mmol, 5.0 equiv) and 653 mg N,N-diisopropylethylamine (5.06 mmol, 10.00 equiv) in 10 mL dichloromethane was added 200 mg methyl 2-benzyl-3-((4-(chlorosulfonyl)phenyl) amino)-3-oxopropanoate (0.51 mmol, 1.00 equiv). The mixture was stirred at room temperature for 1 hour. The mixture was diluted with 10 mL water and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (1:1)) afforded 170 mg methyl 2-benzyl-3-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-3-oxopropanoate as a yellow solid (79.4 % yield). MS (ESI⁺) m/z 419.2 [M+H]⁺.

[00457] Step 5: 2-benzyl-3-((4-(N-(tert-butyl)sulfamoyl)phenyl) amino)-3-oxopropanoic acid



[00458] NaOH (1N, 0.59 mL, 0.59 mmol, 1.5 equiv.) was added to a solution of 170 mg methyl 2-benzyl-3-((4-(N-(tert-butyl)sulfamoyl)phenyl) amino)-3-oxopropanoate (0.39 mmol, 1.00 equiv) in MeOH (10 mL). The resulting mixture was stirred for 2 hours at room temperature. The mixture was concentrated and the residue was diluted with water (20 mL) and extracted with EA (2 x 10 mL). The water phase was adjusted to PH=5, and then extracted with EA (3 x 50 mL). The organic phase was dried over Na₂SO₄, filtered and the filtrate was concentrated to provide 120 mg 2-benzyl-3-((4-(N-(tert-butyl)sulfamoyl)phenyl) amino)-3-oxopropanoic acid as a yellow solid (70.6% yield). MS (ESI⁺) m/z 403.2 [M-H]⁺.

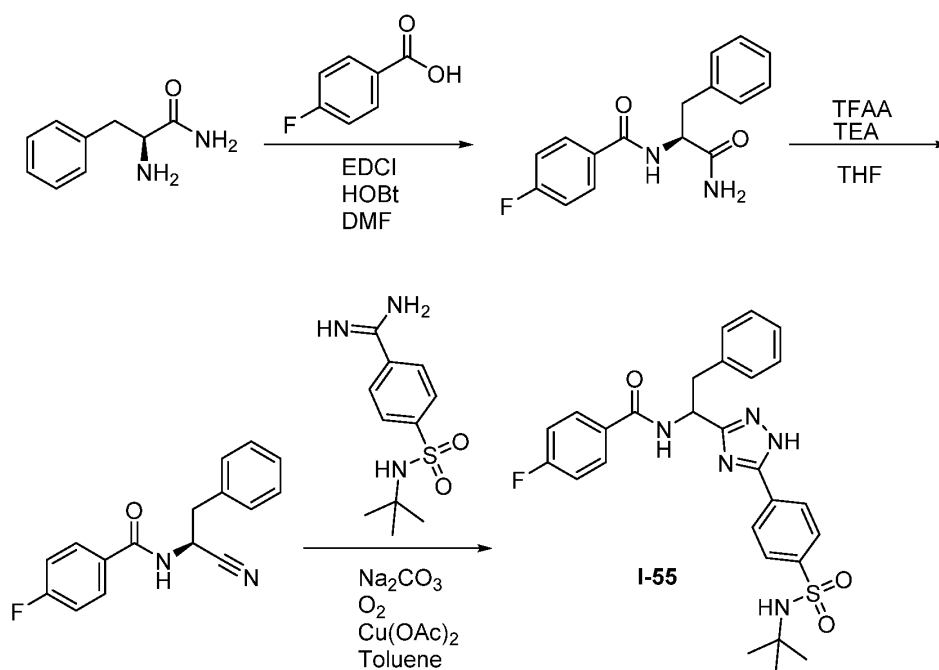
[00459] Step 6: N-(4-(N-(tert-butyl)sulfamoyl)phenyl)-2- (5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-3-phenylpropanamide (I-56)

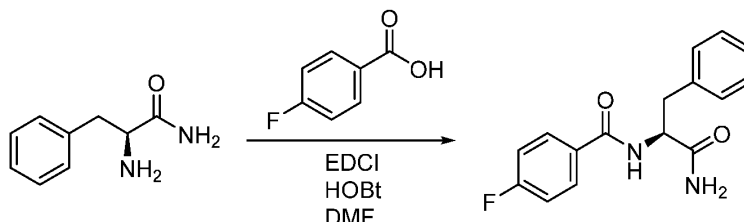


[00460] POCl₃ (76.8 mg, 0.5 mmol, 5.00 equiv) was added to a solution of 40.4 mg 2-benzyl-3-((4-(N-(tert-butyl)sulfamoyl)phenyl) amino)-3-oxopropanoic acid (0.1 mmol, 1.00 equiv.) and 23.1 mg 4-fluorobenzohydrazide (0.15 mmol, 1.50 equiv) in 3 mL dioxane. The resulting mixture was stirred for 2 hours at 50 °C. The resulting mixture was concentrated. The residue was diluted with 20 mL water and extracted with EA (2 x 20 mL). The combined organic layers

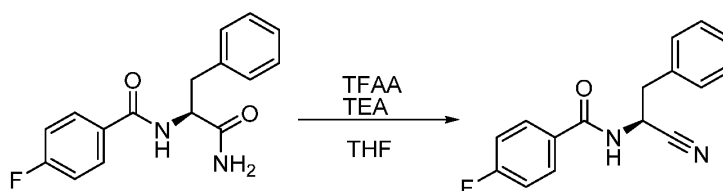
were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. The crude product was purified by Prep-HPLC with the following conditions: Column, Xbridge Prep C18 19*250mm 5um; Mobile Phase, A:0.1%NH₃H₂O/H₂O B:CAN; Gradient : 20% increase to 50%B within 15min, UV detection at 254/220 nm. to afford N-(4-(N-(tert-butyl)sulfamoyl)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-3-phenylpropanamide (**I-56**) as a white solid (31.5 % yield). MS (ESI⁺) m/z 523.2 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 8.11-8.02 (m, 2H), 7.84-7.74 (m, 2H), 7.70-7.63 (m, 2H), 7.34-7.26 (m, 6H), 7.22-7.16 (m, 1H), 4.54-4.50 (m, 1H), 3.64-3.43 (m, 2H), 1.16 (s, 9H).

Example 9: Synthesis of 1- N-(4-(N-(tert-butyl)sulfamoyl)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-3-phenylpropanamide (I-55)



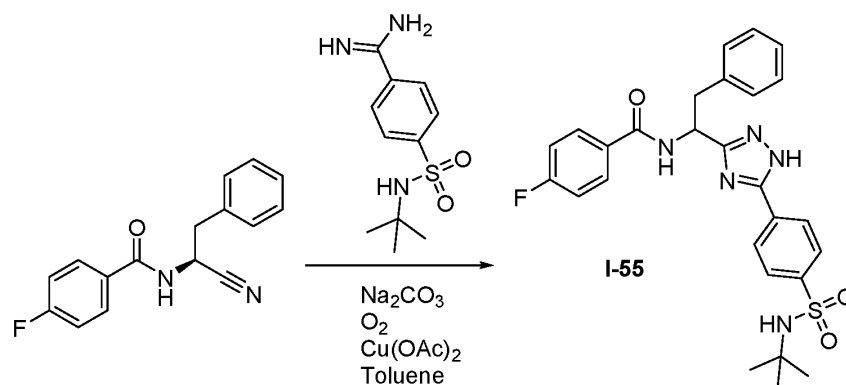
[00461] Step 1: (S)-N-(1-amino-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide

[00462] A mixture of (S)-2-amino-3-phenylpropanamide (1.0 g, 6.09 mmol, 1.0 equiv), 4-fluorobenzoic acid (853.27 mg, 6.09 mmol, 1.0 equiv), *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (1.75 g, 9.13 mmol, 1.5 equiv), 1-hydroxybenzotriazole (987.47 mg, 7.31 mmol, 1.2 equiv) and *N,N*-diisopropylethylamine (1.57 g, 12.18 mmol, 2.0 equiv) in *N,N*-dimethylformamide (20 mL) was stirred at room temperature for 3 hours. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (100 mL x 2). The organic phase was concentrated and the residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate (3/1, v/v)) to give (S)-N-(1-amino-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide (1.6 g, 91.77 % yield) as a yellow solid. MS (ESI⁺) *m/z* 287.2 [M+H]⁺.

[00463] Step 2: (S)-N-(1-cyano-2-phenylethyl)-4-fluorobenzamide

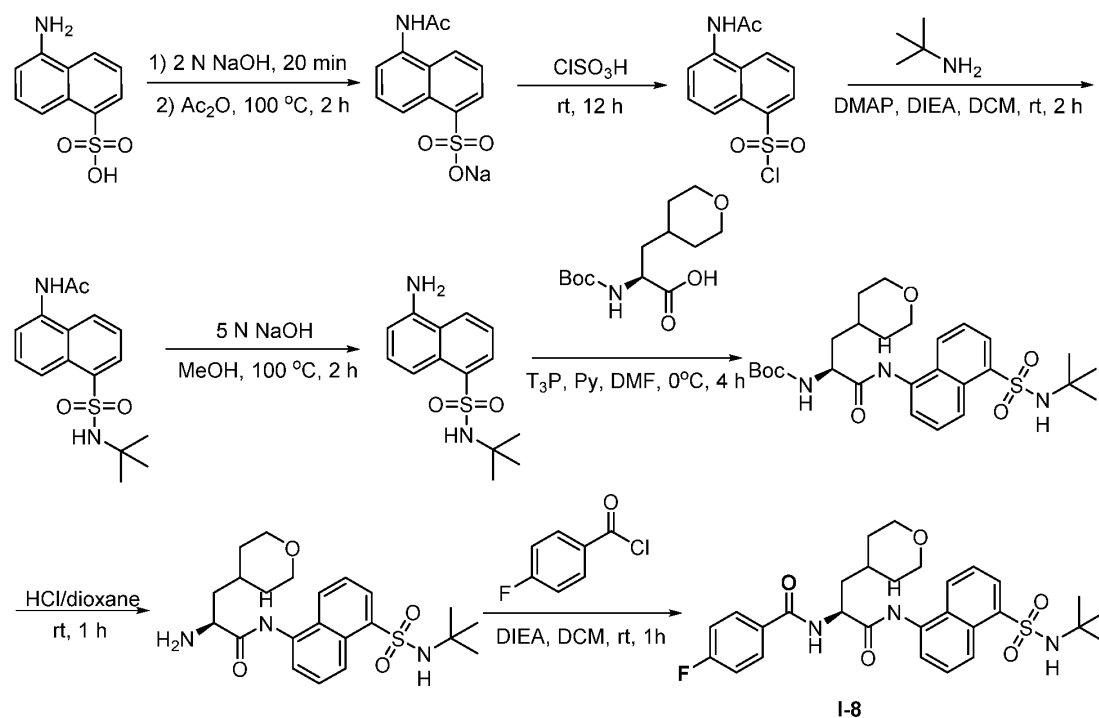
[00464] To a solution of (S)-N-(1-amino-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide (1.5 g, 5.24 mmol, 1.0 equiv), triethylamine (1.06 g, 10.48 mmol, 2.0 equiv) in THF (20 mL) was added trifluoroacetic anhydride (1.32 g, 6.29 mmol, 1.2 equiv) at 0 °C. The mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (100 mL x 2). The organic phase was concentrated and the residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate (5/1, v/v)) to give (S)-N-(1-cyano-2-phenylethyl)-4-fluorobenzamide (800 mg, 56.9 % yield) as a yellow solid. MS (ESI⁺) *m/z* 269.1 [M+H]⁺.

[00465] Step 3: N-(1-(5-(4-(N-(tert-butyl)sulfamoyl)phenyl)-1H-1,2,4-triazol-3-yl)-2-phenylethyl)-4-fluorobenzamide (I-55)

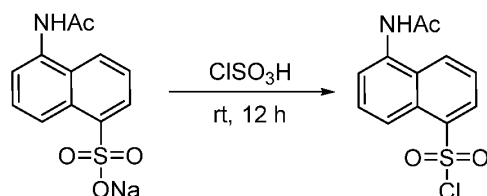


[00466] A solution of (S)-N-(1-cyano-2-phenylethyl)-4-fluorobenzamide (100 mg, 0.373 mmol, 1.0 equiv), 4-(N-(tert-butyl)sulfamoyl)benzimidamide (95.17 mg, 0.373 mmol, 1.0 equiv), Na₂CO₃ (118.51 mg, 1.12 mmol, 3.0 equiv) and CuBr (26.73 mg, 0.186 mmol, 0.5 equiv) in DMSO (3.0 mL) was stirred at 120 °C for 1 hour under microwave. The mixture was diluted with ethyl acetate (10 mL) and washed with water (10 mL x 3). The organic phase was concentrated and the residue was purified by Prep-HPLC with the following conditions: Column, Xbridge Prep C18 19*250mm 5um; Mobile Phase, A:0.1%NH₃H₂O/H₂O B:CAN; Gradient : 10% increase to 60%B within 15min.UV detection at 254/220 nm.. The product-containing fractions were combined and evaporated partially in vacuo and lyophilized overnight to give N-(1-(5-(4-(N-(tert-butyl)sulfamoyl)phenyl)-1H-1,2,4-triazol-3-yl)-2-phenylethyl)-4-fluorobenzamide (**I-55**) (4 mg, 2.06 % yield) as a white solid. MS (ESI⁺, m/z) 522.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO) δ 9.09 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 2H), 7.96-7.87 (m, 4H), 7.59 (s, 1H), 7.30-7.28 (m, 6H), 7.17 (t, *J* = 16.0 Hz, 1H), 5.48-5.46 (m, 1H), 3.29 (d, 1H), 3.26 (s, 1H), 1.10 (s, 9H).

Example 10: Synthesis of (S)-N-(1-((5-(N-(tert-butyl)sulfamoyl)naphthalen-1-yl)amino)-1-oxo-3-(tetrahydro-2H-pyran-4-yl)propan-2-yl)-4-fluorobenzamide (I-8)

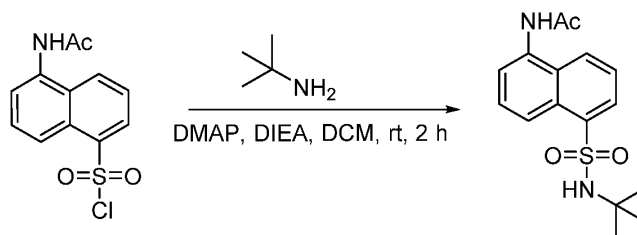


[00467] Step 1: 5-acetamidonaphthalene-1-sulfonyl chloride



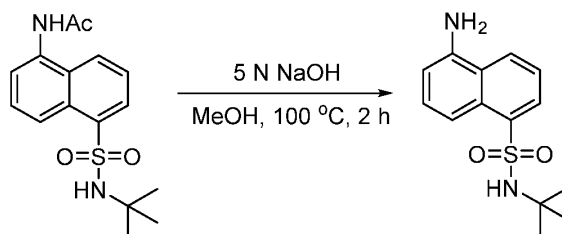
[00468] A solution of 4.23 g sodium 5-acetamidonaphthalene-1-sulfonate (14.74 mmol, 1.00 equiv) in 25 mL sulfurochloridic acid was stirred for 12 hours at room temperature. The mixture was poured onto ice water. The crude product was precipitated out. The solid was filtered, dried under vacuum to afford 2.96 g 5-acetamidonaphthalene-1-sulfonyl chloride as a white solid (71% yield). MS (ESI⁺) m/z 284 and 286 [M+H]⁺.

[00469] Step 2: N-(5-(N-(tert-butyl)sulfamoyl)naphthalen-1-yl)acetamide



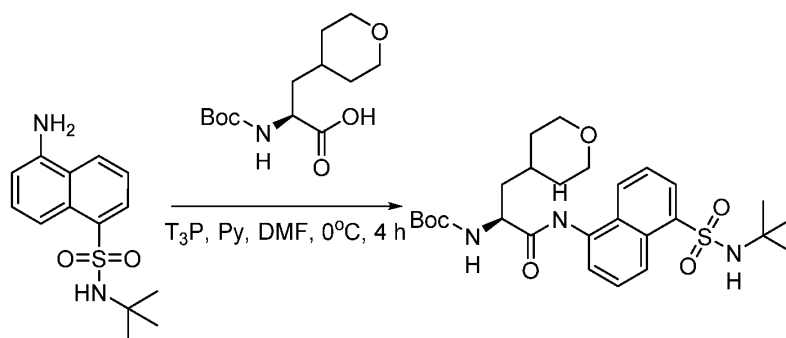
[00470] To a solution of 257 mg 2-methylpropan-2-amine (3.5 mmol, 1.00 equiv), 1.35 g DIEA (10.5 mmol, 3.00 equiv) and 42.7 mg DMAP (0.35 mmol, 0.10 equiv) in 30 mL dichloromethane was added 1 g 5-acetamidonaphthalene-1-sulfonyl chloride (3.5 mmol, 1.00 equiv) at 0 °C. The resulting mixture was stirred for 2 hours at room temperature. The mixture was diluted with 100 mL water and extracted with dichloromethane (3 x 200 mL). The combined organic layers were washed with brine (3x100 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (3:1)) provided 850 mg N-(5-(N-(tert-butyl)sulfamoyl)naphthalen-1-yl)acetamide as a yellow solid (75.9% yield). MS (ESI⁺) m/z 321.1 [M+H]⁺.

[00471] Step 3: 5-amino-N-(tert-butyl)naphthalene-1-sulfonamide



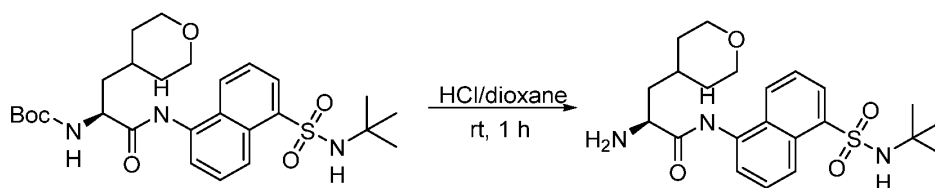
[00472] To a solution of 850 mg N-(5-(N-(tert-butyl)sulfamoyl)naphthalen-1-yl)acetamide (2.66 mmol, 1.00 equiv) in 15 mL methanol was added 4.27 mL of a 5 N sodium hydroxide solution. The mixture was stirred for 2 hours at 100 °C. The mixture was cooled to room temperature, concentrated in vacuo and diluted with 50 mL water. The pH value of the solution was adjusted to 8 with 2N hydrochloric acid. The crude product was precipitated out. The solid was filtered, dried under vacuum to afford 690 mg 5-amino-N-(tert-butyl)naphthalene-1-sulfonamide as a light yellow solid (93.2 % yield). MS (ESI⁺) m/z 279.1 [M+H]⁺.

[00473] Step 4: tert-butyl (S)-(1-((5-(N-(tert-butyl)sulfamoyl) naphthalen-1-yl)amino)-1-oxo-3-(tetrahydro-2H-pyran-4-yl)propan-2-yl)carbamate



[00474] To a solution of 690 mg 5-amino-N-(tert-butyl)naphthalene-1-sulfonamide (2.48 mmol, 1.00 equiv), 677 mg (S)-2-((tert-butoxycarbonyl)amino)-3-(tetrahydro-2H-pyran-4-yl)propanoic acid (2.48 mmol, 1.00 equiv) and 1.96 g pyridine (24.8 mmol, 10.00 equiv) in 10 mL N,N-dimethylformamide was added dropwise a solution 12.28 g propanephosphonic acid cyclic anhydride in ethyl acetate (50%, 12.4 mmol, 5.00 equiv) at 0 °C. The resulting mixture was stirred for 4 hours at 0 °C. The mixture was diluted with 50 mL water and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (3x50 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (1:1)) provided 1.0 g tert-butyl (S)-(1-((5-(N-(tert-butyl)sulfamoyl)naphthalen-1-yl)amino)-1-oxo-3-(tetrahydro-2H-pyran-4-yl)propan-2-yl)carbamate as a yellow solid (75.8% yield). MS (ESI⁺) m/z 478.2 [M-56+H]⁺.

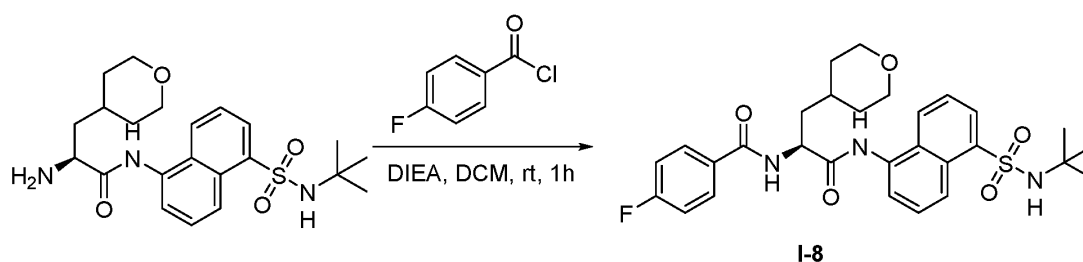
[00475] Step 5: (S)-2-amino-N-(5-(N-(tert-butyl)sulfamoyl) naphthalen-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide hydrochloride



[00476] A mixture of 1.0 g tert-butyl (S)-(1-((5-(N-(tert-butyl)sulfamoyl)naphthalen-1-yl)amino)-1-oxo-3-(tetrahydro-2H-pyran-4-yl)propan-2-yl)carbamate (1.88 mmol, 1.00 equiv) in

30 mL HCl /1,4-dioxane (4.0 M) was stirred at room temperature for 1 hour. The mixture was concentrated to afford 1.0 g crude (S)-2-amino-N-(5-(N-(tert-butyl)sulfamoyl)naphthalen-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide hydrochloride as a light yellow solid (100 % yield). MS (ESI⁺) m/z 434.2 [M+H]⁺.

[00477] Step 6: (S)-N-(1-((5-(N-(tert-butyl)sulfamoyl)naphthalen-1-yl)amino)-1-oxo-3-(tetrahydro-2H-pyran-4-yl)propan-2-yl)-4-fluorobenzamide (I-8)



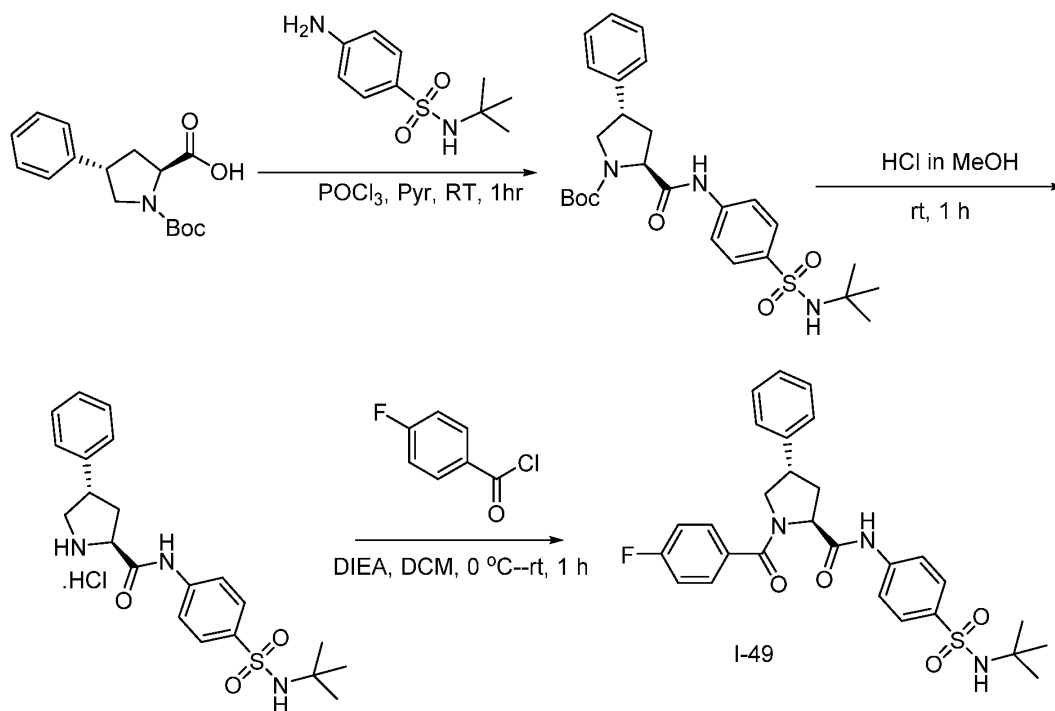
[00478] To a mixture of 100 mg (S)-2-amino-N-(5-(N-(tert-butyl)sulfamoyl)naphthalen-1-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide hydrochloride (0.23 mmol, 1.0 equiv) and 148.35 mg N,N-diisopropylethylamine (1.15 mmol, 5.00 equiv) in 10 mL dichloromethane was added 36.34 mg 4-fluorobenzoyl chloride (0.23 mmol, 1.00 equiv) at 0 °C. The mixture was stirred at room temperature for 1 hour. The mixture was diluted with 10 mL water and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions: Column, Xbridge Prep C18 19*250mm 5um; Mobile Phase, A:0.1%NH₃H₂O/H₂O B:CAN; Gradient : 10% increase to 70%B within 30min, UV detection at 254/220 nm. The product-containing fractions were combined and evaporated partially in vacuo and lyophilized overnight to afford 43.6 mg (S)-N-(1-((5-(N-(tert-butyl)sulfamoyl)naphthalen-1-yl)amino)-1-oxo-3-(tetrahydro-2H-pyran-4-yl)propan-2-yl)-4-fluorobenzamide (**I-8**) as a white solid.

[00479] The compounds in **Table 9** were made by a method analogous to the method used to make **I-8**, substituting the appropriate amine intermediate in Step.

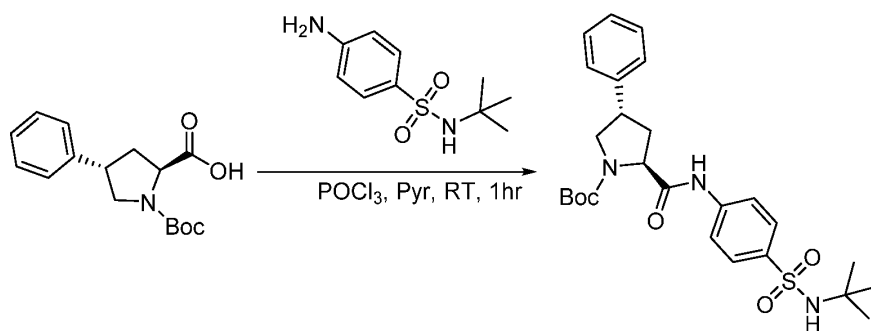
Table 9. Compounds made by a method analogous to I-8

Cmpd No.	MS [M+H] ⁺	¹ H NMR
I-8	556.2	¹ H NMR (400 MHz, DMSO) δ 10.27 (s, 1H), 8.77 (d, J = 7.3 Hz, 1H), 8.57 (d, J = 7.6 Hz, 1H), 8.31 (d, J = 8.5 Hz, 1H), 8.21 (d, J = 6.9 Hz, 1H), 8.07-8.02 (m, 2H), 7.80 (s, 1H), 7.70-7.65 (m, 3H), 7.33 (t, J = 8.8 Hz, 2H), 4.83 (s, 1H), 3.87 (d, J = 8.3 Hz, 2H), 3.28-3.22 (m, 2H), 1.96-1.82 (m, 2H), 1.70 (d, J = 13.1 Hz, 3H), 1.32-1.23 (m, 2H), 1.05 (s, 9H).
I-9	528.2	¹ H NMR (400 MHz, DMSO) δ 10.30 (s, 1H), 8.78 (d, J = 7.4 Hz, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.33 (d, J = 8.5 Hz, 1H), 8.16-8.13 (m, 1H), 8.07-8.02 (m, 2H), 7.94 (t, J = 5.6 Hz, 1H), 7.72-7.65 (m, 3H), 7.35-7.30 (m, 2H), 4.87-4.80 (m, 1H), 3.87 (d, J = 8.0 Hz, 2H), 3.26 (t, J = 9.1 Hz, 2H), 2.85-2.78 (m, 2H), 1.97-1.81 (m, 2H), 1.70 (d, J = 13.2 Hz, 3H), 1.35-1.24 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H).
I-10	556.2	¹ H NMR (400 MHz,) δ 10.31 (s, 1H), 8.92 (s, 1H), 8.77 (d, J = 7.5 Hz, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.35 (d, J = 8.6 Hz, 1H), 8.12 (d, J = 7.0 Hz, 1H), 8.07-8.02 (m, 2H), 7.77-7.72 (m, 1H), 7.72-7.67 (m, 2H), 7.33 (t, J = 8.8 Hz, 2H), 4.83 (s, 1H), 4.42-4.38 (m, 2H), 4.35 (s, 1H), 4.23-4.19 (m, 2H), 3.87 (d, J = 7.9 Hz, 2H), 3.24 (d, J = 11.6 Hz, 2H), 1.95-1.83 (m, 2H), 1.70 (d, J = 13.4 Hz, 3H), 1.34-1.25 (m, 2H).

Example 11: Synthesis of (2S,4S)-N-(4-(N-(tert-butyl)sulfamoyl)phenyl)-1-(4-fluorobenzoyl)-4-phenylpyrrolidine-2-carboxamide (I-49)



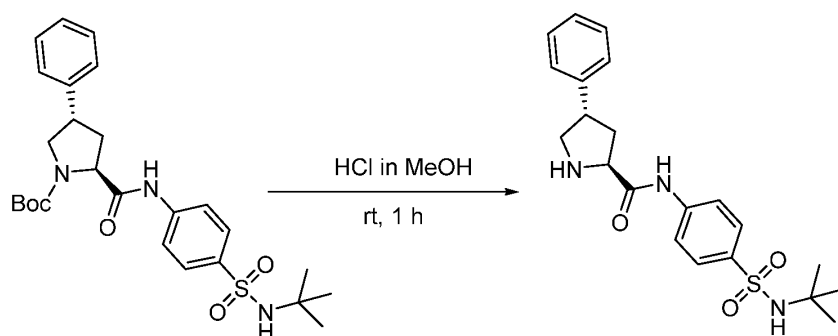
[00480] Step 1: tert-butyl (2S,4S)-2-((4-(N-(tert-butyl)sulfamoyl) phenyl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate



[00481] POCl₃ (488 mg, 3.195 mmol, 3.00 equiv) was added dropwise to a solution of 310 mg (2S,4S)-1-(tert-butoxycarbonyl)-4-phenylpyrrolidine-2-carboxylic acid (1.065 mmol, 1.00 equiv) and 243 mg 4-amino-N-(tert-butyl)benzenesulfonamide (1.065 mmol, 1.00 equiv) in pyridine (5 mL) in 10 mL at 0 °C. The resulting mixture was stirred for 2 hours at 0 °C. The solvent was

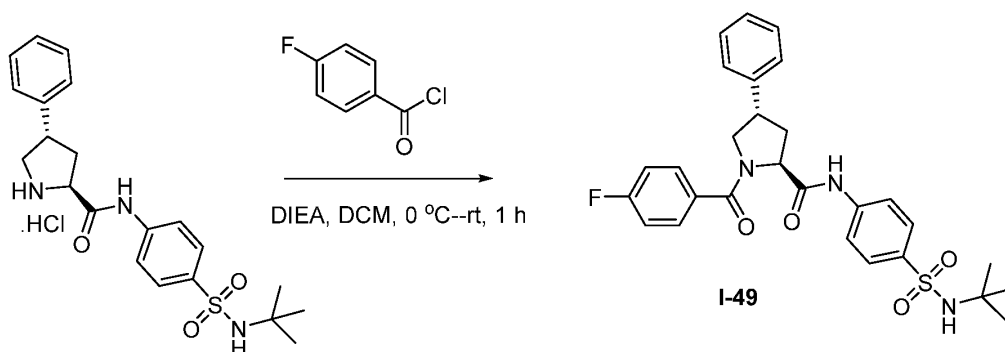
concentrated. The residue was diluted with 50 mL water and extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (4:1 to 1:1)) provided 230 mg tert-butyl (2S,4S)-2-((4-(N-(tert-butyl)sulfamoyl)phenyl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate as a white solid (55% yield). MS (ESI⁺) m/z 502.2[M+H]⁺.

[00482] Step 2: (2S,4S)-N-(4-(N-(tert-butyl)sulfamoyl)phenyl)-4-phenylpyrrolidine-2-carboxamide hydrochloride



[00483] A mixture of 230 mg tert-butyl (2S,4S)-2-((4-(N-(tert-butyl)sulfamoyl)phenyl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate (0.46 mmol, 1.00 equiv) in 10 mL HCl/1,4-dioxane (4.0 M) was stirred at room temperature for 1 hour. The mixture was concentrated to afford 200 mg crude (2S,4S)-N-(4-(N-(tert-butyl)sulfamoyl)phenyl)-4-phenylpyrrolidine-2-carboxamide hydrochloride as a light yellow solid (100 % yield). MS (ESI⁺) m/z 402.2 [M+H]⁺.

[00484] Step 3: (2S,4S)-N-(4-(N-(tert-butyl)sulfamoyl)phenyl)-1-(4-fluorobenzoyl)-4-phenylpyrrolidine-2-carboxamide (I-49)



[00485] To a solution of 230 mg (2S,4S)-N-(4-(N-(tert-butyl)sulfamoyl)phenyl)-4-phenylpyrrolidine-2-carboxamide hydrochloride (0.57 mmol, 1.00 equiv) and 220 mg DIEA (1.71 mmol, 3.00 equiv) in 10 mL dichloromethane was added dropwise 90.6 mg 4-fluorobenzoyl chloride (0.57 mmol, 1.00 equiv) at 0 °C. The resulting mixture was stirred for 2 hours at 0 °C. The resulting mixture was diluted with 20 mL water and extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine (1x30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. The crude product was purified by Prep-HPLC with the following conditions: Column, Xbridge Prep C18 19*250mm 5um; Mobile Phase, A:0.1%NH₃H₂O/H₂O B:CAN; Gradient : 20% increase to 50%B within 15min, UV detection at 254/220 nm. The product-containing fractions were combined and evaporated partially in vacuo and lyophilized overnight to afford 70 mg (2S,4S)-N-(4-(N-(tert-butyl)sulfamoyl) phenyl)-1-(4-fluorobenzoyl)-4-phenylpyrrolidine-2-carboxamide (**I-49**) as a white solid (23.5% yield).

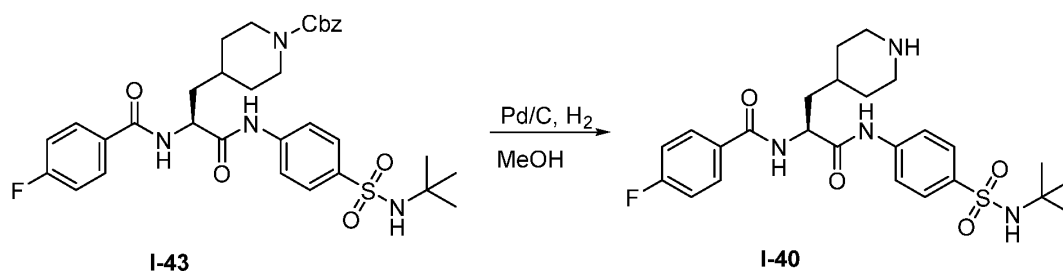
[00486] The compounds in **Table 10** were made by a method analogous to the method used to make **I-49**, substituting the appropriate amino acid starting material in Step 1.

Table 10. Compounds made by a method analogous to I-49

Cmpd #	MS	¹ H NMR
	[M+H] ⁺	
I-49	524.4	¹ H NMR (400 MHz, CDCl ₃) δ 9.92 (s, 1H), 7.81 (d, <i>J</i> = 8.8 Hz, 2H), 7.68 (d, <i>J</i> = 8.7 Hz, 2H), 7.56-7.53 (m, 2H), 7.32 (t, <i>J</i> = 7.3 Hz, 2H),

		7.27 (d, J = 1.3 Hz, 1H), 7.25 (d, J = 6.3 Hz, 1H), 7.19 (d, J = 7.1 Hz, 2H), 7.11 (t, J = 8.6 Hz, 2H), 5.17 (d, J = 6.3 Hz, 1H), 4.53 (s, 1H), 4.00-3.98 (m, 1H), 3.86-3.70 (m, 1H), 3.50 (t, J = 9.7 Hz, 1H), 2.96-2.94 (m, 1H), 2.31-2.14 (m, 1H), 1.22 (s, 9H).
I-25	478.2	^1H NMR (400 MHz, DMSO) δ 10.46 (s, 1H), 8.70 (d, J = 7.8 Hz, 1H), 8.08-7.87 (m, 2H), 7.87-7.67 (m, 4H), 7.39 (s, 1H), 7.31 (t, J = 8.9 Hz, 2H), 4.79-4.59 (m, 1H), 1.95-1.82 (m, 1H), 1.77-1.64 (m, 1H), 1.08 (s, 9H), 0.97 (s, 9H).
I-43	639.1	^1H NMR (400 MHz, DMSO) δ 10.47 (s, 1H), 8.73 (d, J = 7.5 Hz, 1H), 8.01-7.98 (m, 2H), 7.79-7.74 (m, 4H), 7.39-7.29 (m, 8H), 5.06 (s, 2H), 4.71-4.62 (m, 1H), 4.05-3.93 (m, 2H), 2.88-2.69 (m, 2H), 1.90-1.81 (m, 1H), 1.75-1.66 (m, 4H), 1.19-1.10 (m, 2H), 1.07 (s, 9H).

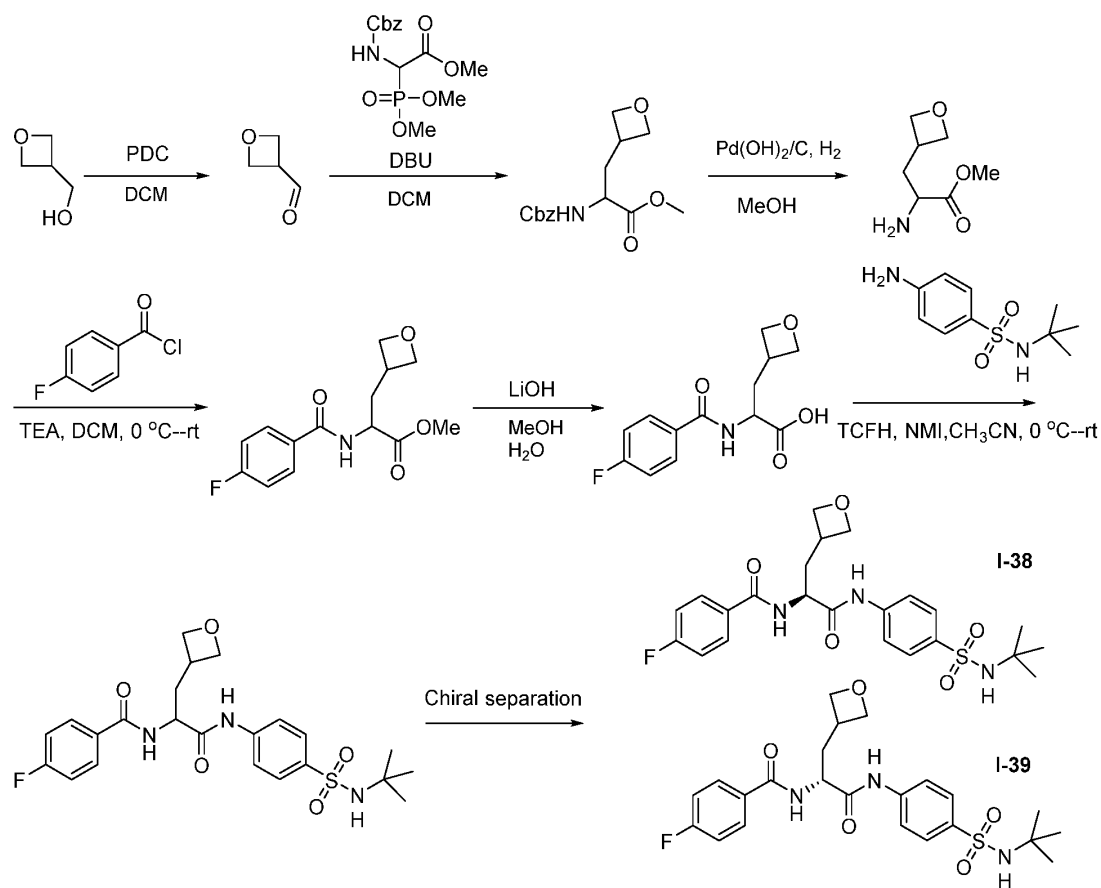
Synthesis of I-40 from I-43



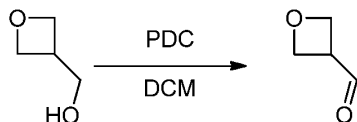
A mixture of 50 mg benzyl (S)-4-(3-((4-(N-(tert-butyl)sulfamoyl) phenyl)amino)-2-(4-fluorobenzamido)-3-oxopropyl)piperidine-1-carboxylate **I-43** (0.078 mmol, 1.00 equiv) and 10 mg Pd/C in 10 mL methanol was stirred at room temperature under H_2 (1atm) for 1 h. The mixture was filtered and the filtrate was concentrated in vacuo and the residue was purified via Prep-TLC(DCM:MeOH (10:1)) to afford 16 mg (S)-N-(1-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-1-oxo-3-(piperidin-4-yl)propan-2-yl)-4-fluorobenzamide (**I-40**) as a white solid (34 % yield, ee%: 57.34%). MS (ESI⁺) m/z 505.1 [$\text{M}+\text{H}$]⁺. ^1H NMR (400 MHz, DMSO) δ 10.47 (s, 1H), 8.71 (d, J = 7.5 Hz, 1H), 8.01-7.97 (m, 2H), 7.79-7.74 (m, 4H), 7.39 (s,

1H), 7.31 (t, $J = 8.9$ Hz, 2H), 4.69-4.66 (m, 1H), 2.94- 2.86 (m, 2H), 2.46-2.32 (m, 3H), 1.86-1.74 (m, 1H), 1.68-1.58 (m, 3H), 1.57-1.46 (m, 1H), 1.12-1.02 (m, 11H).

Example 12: Synthesis of (S)-N-(1-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-3-(oxetan-3-yl)-1-oxopropan-2-yl)-4-fluorobenzamide (I-38) & (R)-N-(1-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-3-(oxetan-3-yl)-1-oxopropan-2-yl)-4-fluorobenzamide (I-39)

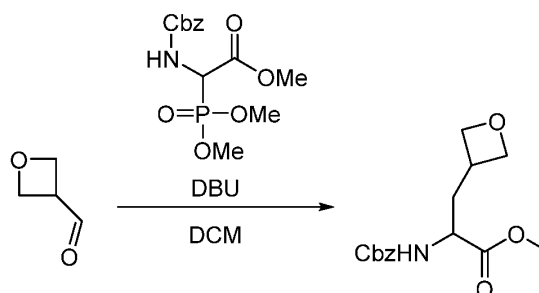


[00487] Step 1: oxetane-3-carbaldehyde



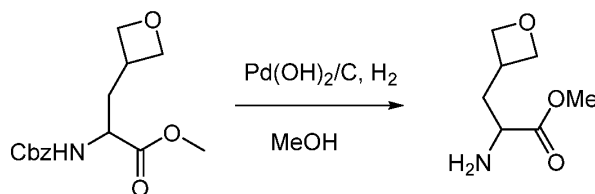
[00488] A mixture of oxetan-3-ylmethanol (7.0 g, 79.45 mmol, 1.0 equiv), Pyridinium Dichromate (19.4 g, 54.57 mmol, 0.65 equiv) in DCM (200 mL) was stirred at room temperature overnight. The mixture was filtered. The filtrate was used directly in the next step.

[00489] Step 2: methyl 2-(((benzyloxy)carbonyl)amino)-3-(oxetan-3-yl)acrylate

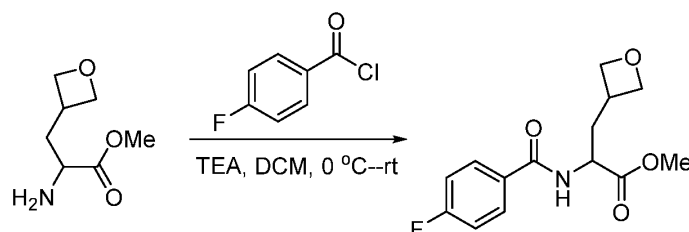


[00490] To the mixture which was obtained in the above step was added methyl 2-(((benzyloxy)carbonyl)amino)-2-(dimethoxyphosphoryl)acetate (26.0 g, 79.45 mmol, 1.0 equiv) and DBU (12 g, 79.45 mmol, 1.0 equiv) at 0 °C. The mixture was slowly warmed to room temperature and stirred overnight. The mixture was concentrated and purified with column chromatography on silica gel (petroleum ether:ethyl acetate (1/1, v/v)) to give methyl 2-(((benzyloxy)carbonyl)amino)-3-(oxetan-3-yl)acrylate as a light yellow solid (4.5 g, 19 % yield for two steps). MS (ESI⁺) *m/z* 292.2 [M+H]⁺.

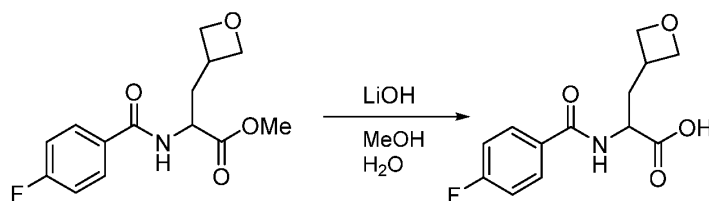
[00491] Step 3: methyl 2-amino-3-(oxetan-3-yl)propanoate



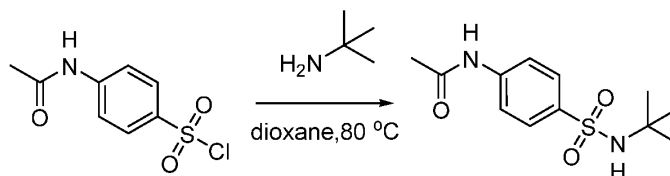
[00492] A mixture of methyl 2-(((benzyloxy)carbonyl)amino)-3-(oxetan-3-yl)acrylate (4.5 g, 15.44 mmol, 1.0 equiv), Pd(OH)₂/C (400 mg) in MeOH (40 mL) was stirred under hydrogen atmosphere (H₂ balloon pressure) at room temperature. The mixture was filtered. The filtrate was concentrated to give methyl 2-amino-3-(oxetan-3-yl)propanoate (2.3 g, 93 % yield) as a light yellow oil. MS (ESI⁺) *m/z* 160.0 [M+H]⁺.

[00493] Step 4: methyl 2-(4-fluorobenzamido)-3-(oxetan-3-yl)propanoate

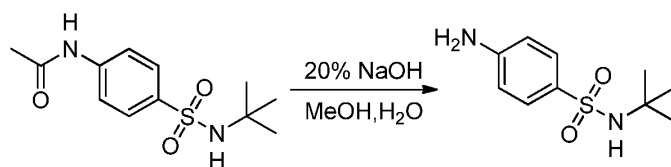
[00494] To a solution of 500 mg methyl 2-amino-3-(oxetan-3-yl)propanoate (3.12 mmol, 1.00 equiv.) and 0.9 mL TEA (6.25 mmol, 2.00 equiv) in 10 mL dichloromethane was added dropwise 497 mg 4-fluorobenzoyl chloride (3.12 mmol, 1.00 equiv) at 0 °C. The resulting mixture was stirred for 2 hours at 0 °C. The resulting mixture was diluted with 20 mL water and extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine (1x30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (1:1)) afforded 230 mg methyl 2-(4-fluorobenzamido)-3-(oxetan-3-yl)propanoate as a yellow solid (26.2 % yield). MS (ESI⁺) m/z 282.1 [M+H]⁺.

[00495] Step 5: 2-(4-fluorobenzamido)-3-(oxetan-3-yl)propanoic acid

[00496] LiOH (49 mg, 2.05mmol, 2.5 equiv.) was added to a solution of 230 mg methyl 2-(4-fluorobenzamido)-3-(oxetan-3-yl)propanoate (0.819 mmol, 1.00 equiv) in MeOH /THF/H₂O (3/3/3 mL) at 0 °C. The resulting mixture was stirred for 1 hour at room temperature. The mixture was concentrated. The residue was diluted with water (20 mL) and adjusted to PH=5, then extracted with EA (3 x 20 mL). The organic phase was dried over Na₂SO₄, filtered and the filtrate was concentrated to provide 200 mg 2-(4-fluorobenzamido)-3-(oxetan-3-yl)propanoic acid as a white solid (87% yield). MS (ESI⁻) m/z 266.1 [M-H]⁻.

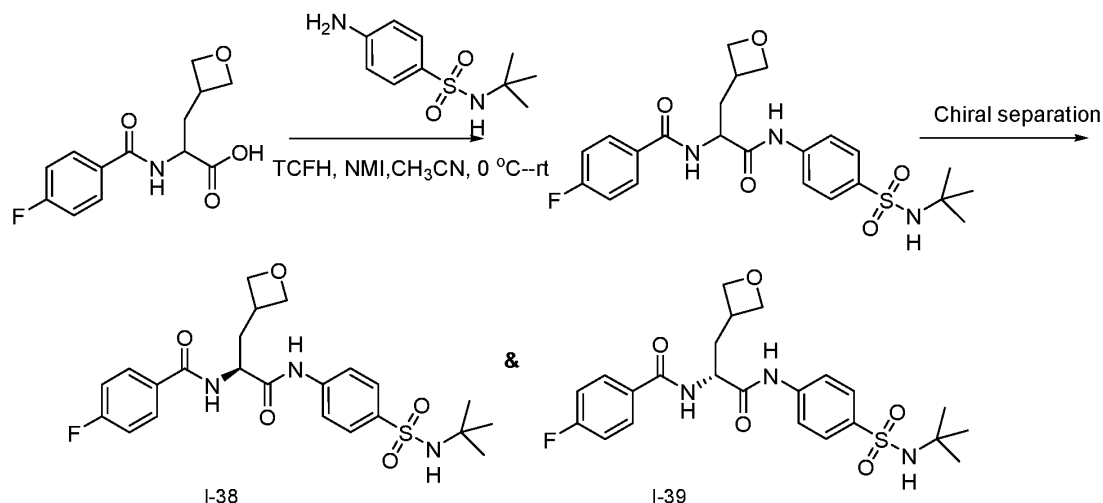
[00497] Step 6: N-(4-(N-(tert-butyl)sulfamoyl)phenyl)acetamide

[00498] A mixture of 3.13 g 2-methylpropan-2-amine (42.88 mmol, 2.0 equiv) and 5 g 4-acetamidobenzenesulfonyl chloride (21.5 mmol, 1.00 equiv) in dioxane (20 mL) was stirred at 80 °C for 1 hour. The resulting mixture was concentrated. 50 mL water was added to the residue and the solid was filtered to provide 5 g crude N-(4-(N-(tert-butyl)sulfamoyl)phenyl)acetamide as a yellow solid (86% yield). MS (ESI⁺) m/z 271.1 [M+H]⁺.

[00499] Step 7: 4-amino-N-(tert-butyl)benzenesulfonamide

[00500] To a solution of 5 g N-(4-(N-(tert-butyl)sulfamoyl)phenyl)acetamide (18.5 mmol, 1.00 equiv) in 100 mL methanol was added 20 mL of a 5 N sodium hydroxide solution. The mixture was stirred for 2 hours at 80 °C. The mixture was cooled to room temperature, concentrated in vacuo and diluted with 50 mL water. The pH value of the solution was adjusted to 8 with 2N hydrochloric acid. The crude product was precipitated out. The solid was filtered, dried under vacuum to afford 4 g 5-amino-N-(tert-butyl)naphthalene-1-sulfonamide as a white solid (89% yield). MS (ESI⁺) m/z 229.1 [M+H]⁺.

[00501] Step 8: (S)-N-(1-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-3-(oxetan-3-yl)-1-oxopropan-2-yl)-4-fluorobenzamide (I-38) & (R)-N-(1-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-3-(oxetan-3-yl)-1-oxopropan-2-yl)-4-fluorobenzamide (I-39)



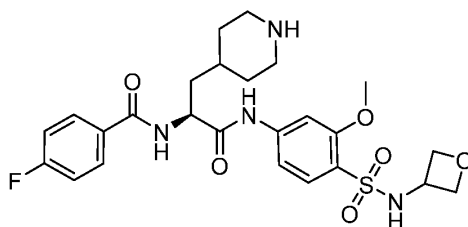
[00502] A mixture of 200 mg 2-(4-fluorobenzamido)-3-(oxetan-3-yl)propanoic acid (0.75 mmol, 1.00 equiv), 341 mg 4-amino-N-(tert-butyl)benzenesulfonamide (1.5 mmol, 2.00 equiv), 184 mg 1-Methylimidazole (2.25 mmol, 3.00 equiv) and 251 mg N,N,N',N'-Tetramethylchloroformamidinium hexafluorophosphate (0.90 mmol, 1.2 equiv) in 10 mL acetonitrile were stirred for 12 hours at room temperature. The resulting mixture was diluted with 20 mL water and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, petroleum ether:ethyl acetate (1:1)) afforded 190 mg N-(1-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-3-(oxetan-3-yl)-1-oxopropan-2-yl)-4-fluorobenzamide as a yellow solid (53.1 % yield). MS (ESI⁺) m/z 478.2 [M+H]⁺.

[00503] The racemates were separated via chiral Prep-HPLC with the following conditions: Column, OD-H, 0.46 cm I.D. *15 cm L; Mobile Phase, CO₂:EtOH (0.1%DEA)=70:30; Flow rate: 2.5 ml, Wave length UV 254 nm. to give 57.5 mg (R)-N-(1-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-3-(oxetan-3-yl)-1-oxopropan-2-yl)-4-fluorobenzamide (**I-39**). ¹H NMR (400 MHz, DMSO) δ 10.55 (s, 1H), 8.76 (s, 1H), 8.00-7.94(m, 2H), 7.76 (s, 4H), 7.41 (s,

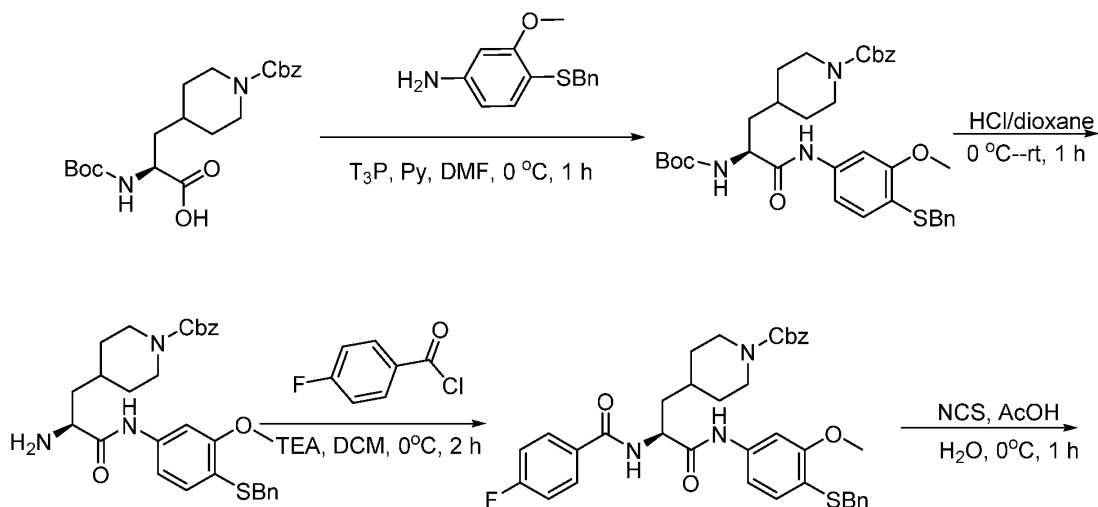
1H), 7.31 (t, $J = 8.9$ Hz, 2H), 4.67-4.56 (m, 2H), 4.52 (t, $J = 7.2$ Hz, 1H), 4.39-4.32 (m, 2H), 3.22-3.07 (m, 1H), 2.29-2.09 (m, 2H), 1.08 (s, 9H).

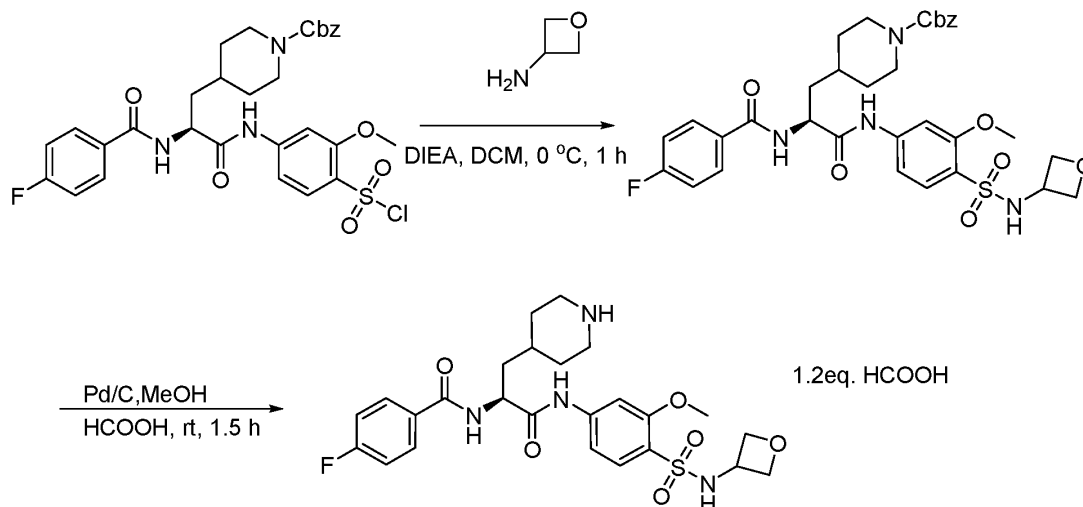
[00504] 54.5 mg (S)-N-(1-((4-(N-(tert-butyl)sulfamoyl) phenyl)amino)-3-(oxetan-3-yl)-1-oxopropan-2-yl)-4-fluorobenzamide (**I-38**). ^1H NMR (400 MHz, *d*-DMSO) δ 10.51 (s, 1H), 8.71 (d, $J = 7.6$ Hz, 1H), 8.02-7.91 (m, 2H), 7.77 (s, 4H), 7.40 (s, 1H), 7.32 (t, $J = 8.9$ Hz, 2H), 4.66-4.56 (m, 2H), 4.56-4.48 (m, 1H), 4.36 (t, $J = 6.1$ Hz, 2H), 3.20-3.07 (m, 1H), 2.28-2.06 (m, 2H), 1.08 (s, 9H).

Example 13: Synthesis of (S)-4-fluoro-N-(1-((3-methoxy-4-(N-(oxetan-3-yl)sulfamoyl)phenyl)amino)-1-oxo-3-(piperidin-4-yl)propan-2-yl)benzamide (I-109)

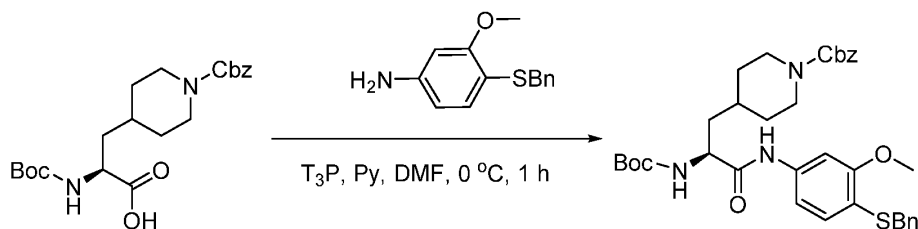


Synthesis Scheme





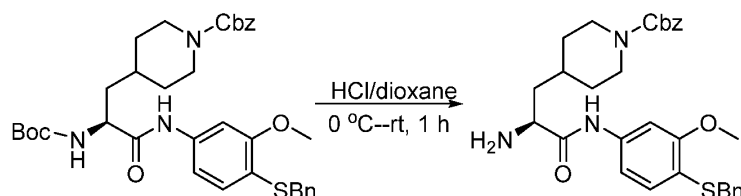
Part I - Preparation of benzyl (S)-4-(3-((4-(benzylthio)-3-methoxyphenyl)amino)-2-((tert-butoxycarbonyl)amino)-3-oxopropyl)piperidine-1-carboxylate



[00505] To a solution of 4-(benzylthio)-3-methoxyaniline (the preparation had been described in previous patent: WO2021/050992A1) (422 mg, 1.72 mmol, 1.00 equiv) and (S)-3-(1-((benzyloxy)carbonyl)piperidin-4-yl)-2-((tert-butoxycarbonyl)amino)propanoic acid (the preparation had been described in previous patent: WO2021/050992A1) (700 mg, 1.72 mmol, 1.00 equiv) in N,N-dimethylformamide (30 mL) at 0 °C was added a solution of 25.8 g propanephosphonic acid cyclic anhydride in DMF (50%, 2.18 g, 3.44 mmol, 2.00 equiv) dropwise, followed by pyridine (670 mg, 8.6 mmol, 5.00 equiv). The resulting mixture was stirred for 4 hours at 0 °C. The mixture was diluted with 100 mL water and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column (silica gel, PE: EA = 2:1) to provide benzyl (S)-4-(3-((4-(benzylthio)-3-

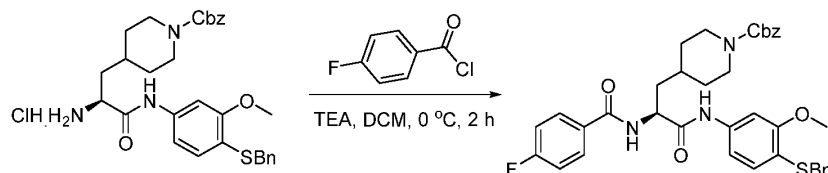
methoxyphenyl)amino)-2-((tert-butoxycarbonyl)amino)-3-oxopropyl)piperidine-1-carboxylate as a white solid (800 mg, 73.4% yield). MS (ESI⁺) m/z 579.2 [M-56+H]⁺.

Part II - Preparation of benzyl (S)-4-(2-amino-3-((4-(benzylthio)-3-methoxyphenyl)amino)-3-oxopropyl)piperidine-1-carboxylate hydrochloride



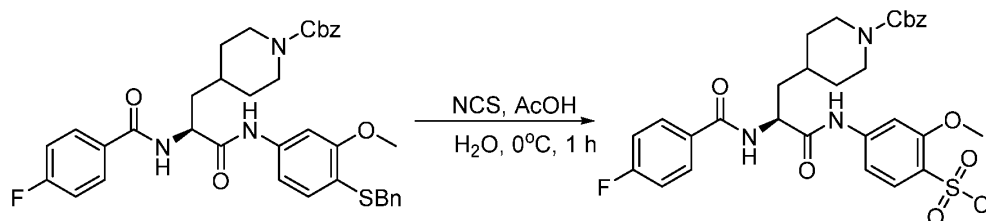
[00506] A mixture of benzyl (S)-4-(3-((4-(benzylthio)-3-methoxyphenyl)amino)-2-((tert-butoxycarbonyl)amino)-3-oxopropyl)piperidine-1-carboxylate (800 mg, 1.26 mmol, 1.00 equiv) and 30 mL hydrochloric acid in 1,4-dioxane (4.0 M) was stirred at room temperature for 3 hours. The mixture was concentrated to afford benzyl (S)-4-(2-amino-3-((4-(benzylthio)-3-methoxyphenyl)amino)-3-oxopropyl)piperidine-1-carboxylate hydrochloride as a light yellow solid (600 mg, 83.7 % yield). MS (ESI⁺) m/z 533.2 [M+H]⁺.

Part III - Preparation of benzyl (S)-4-(3-((4-(benzylthio)-3-methoxyphenyl)amino)-2-(4-fluorobenzamido)-3-oxopropyl)piperidine-1-carboxylate



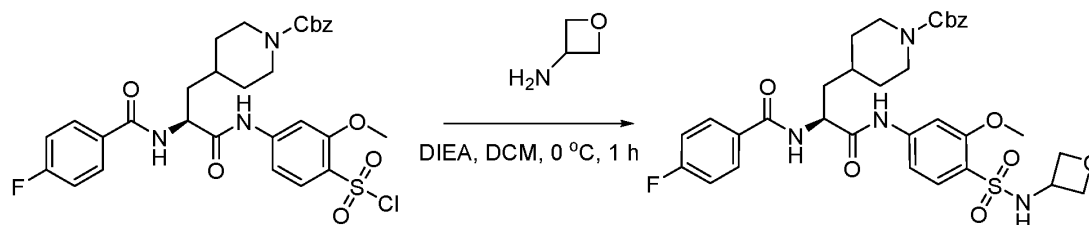
[00507] To a solution of (benzyl (S)-4-(2-amino-3-((4-(benzylthio)-3-methoxyphenyl)amino)-3-oxopropyl)piperidine-1-carboxylate hydrochloride (600 mg, 1.12 mmol, 1.00 equiv.) in DCM (40 mL) at 0 °C was added TEA (568.5 mg, 5.63 mmol, 5.00 equiv) dropwise, then added 4-fluorobenzoyl chloride (177 mg, 1.12 mmol, 1.00 equiv). The solution was stirred for 2 hours at 0 °C. The resulting mixture was diluted with water (50 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column (silica gel, PE: EA = 1:1) to provide benzyl (S)-4-(3-((4-(benzylthio)-3-methoxyphenyl)amino)-2-(4-fluorobenzamido)-3-oxopropyl)piperidine-1-carboxylate as a white solid (700 mg, 95.4 % yield). MS (ESI⁺) m/z 656.2 [M+H]⁺.

Part IV - Preparation of benzyl (S)-4-(3-((4-(chlorosulfonyl)-3-methoxyphenyl)amino)-2-(4-fluorobenzamido)-3-oxopropyl)piperidine-1-carboxylate



[00508] To a solution of benzyl (S)-4-(3-((4-(benzylthio)-3-methoxyphenyl)amino)-2-(4-fluorobenzamido)-3-oxopropyl)piperidine-1-carboxylate (200 mg, 0.30 mmol, 1.00 equiv) in 5 mL acetic acid and 0.5 mL water was added N-chlorosuccinimide (163 mg, 1.22 mmol, 4.00 equiv) at 0 °C. The resulting mixture was stirred at 0 °C for 1 hour. The mixture was diluted with 20 mL water and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated, to afford crude benzyl (S)-4-(3-((4-(chlorosulfonyl)-3-methoxyphenyl) amino)-2-(4-fluorobenzamido)-3-oxopropyl)piperidine-1-carboxylate as a yellow solid (200 mg, 100 % yield). MS (ESI⁺) m/z 632.2 [M+H]⁺.

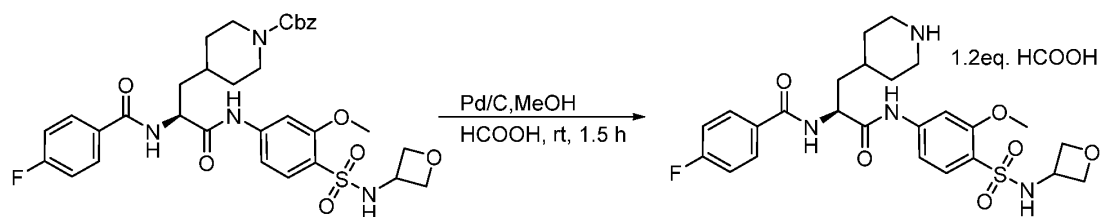
Part V - Preparation of benzyl (S)-4-(2-(4-fluorobenzamido)-3-((3-methoxy-4-(N-(oxetan-3-yl)sulfamoyl)phenyl)amino)-3-oxopropyl)piperidine-1-carboxylate



[00509] To a mixture of oxetan-3-amine (115.7 mg, 1.58 mmol, 5.0 equiv) and N,N-diisopropylethylamine (203.8 mg, 1.58 mmol, 5.00 equiv) in 15 mL DCM at 0 °C was added benzyl (S)-4-(3-((4-(chlorosulfonyl)-3-methoxyphenyl)amino)-2-(4-fluorobenzamido)-3-oxopropyl)piperidine-1-carboxylate (200 mg, 0.32 mmol, 1.00 equiv). The mixture was stirred at room temperature for 1 hour. The mixture was diluted with 10 mL water and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure.

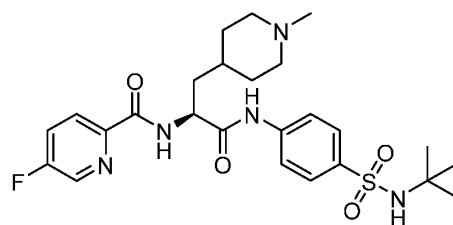
The residue was purified by flash column (silica gel, PE: EA = 1:1 to 0:1) to afford benzyl (S)-4-(2-(4-fluorobenzamido)-3-((3-methoxy-4-(N-(oxetan-3-yl)sulfamoyl)phenyl)amino)-3-oxopropyl)piperidine-1-carboxylate as a white solid (130 mg, 60.8 % yield). MS (ESI⁺) *m/z* 669.2 [M+H]⁺.

Part VI - Preparation of (S)-4-fluoro-N-(1-((3-methoxy-4-(N-(oxetan-3-yl)sulfamoyl)phenyl)amino)-1-oxo-3-(piperidin-4-yl)propan-2-yl)benzamide

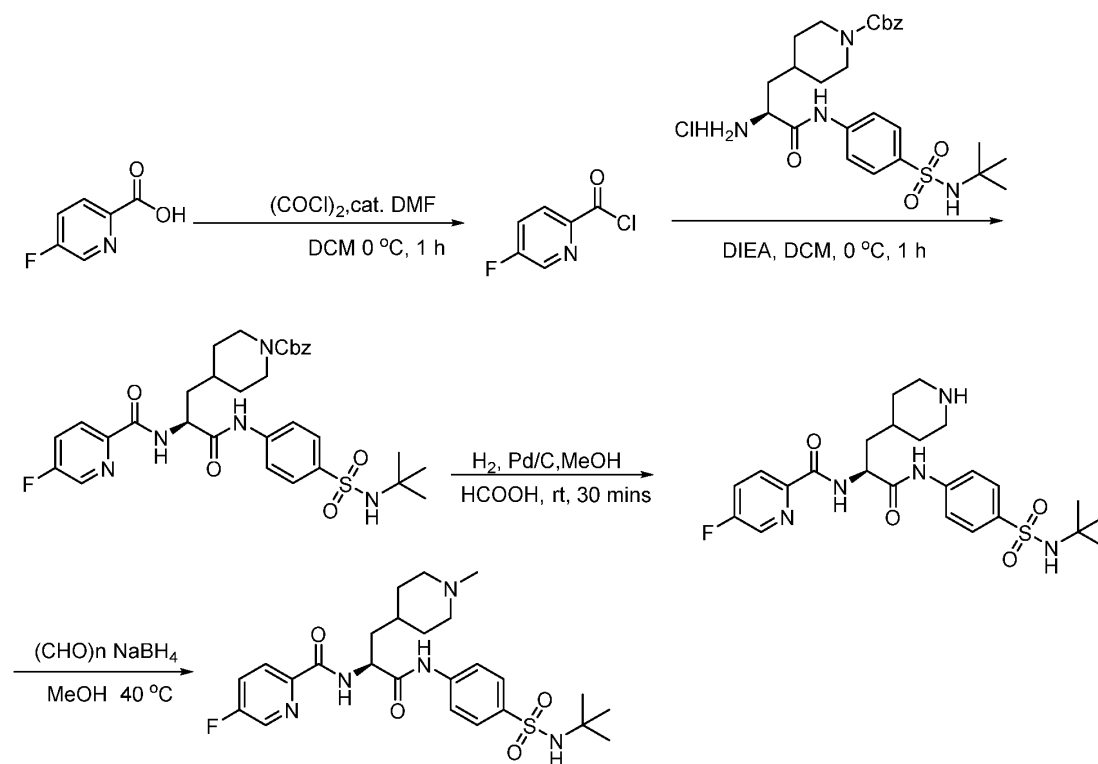


[00510] To a mixture of benzyl (S)-4-(2-(4-fluorobenzamido)-3-((3-methoxy-4-(N-(oxetan-3-yl)sulfamoyl)phenyl)amino)-3-oxopropyl)piperidine-1-carboxylate (130 mg, 0.19 mmol, 1.00 equiv) in MeOH (15 mL)/formic acid (1.5 mL) at rt was added Pd/C (13 mg, 10%w.t.). The mixture was stirred at room temperature for 1.5 hours. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was lyophilized to afford (S)-4-fluoro-N-(1-((3-methoxy-4-(N-(oxetan-3-yl)sulfamoyl)phenyl)amino)-1-oxo-3-(piperidin-4-yl)propan-2-yl)benzamide (1.2eq.FA, 70 mg, 69.3 % yield) (**I-109**). MS (ESI⁺, *m/z*): Calcd for C₂₅H₃₁FN₄O₆S: 534.19; found 535.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.66 (s, 1H), 8.90 (d, *J*=8Hz, 1H), 8.32 (s, 1H), 8.17 (s, 2H), 8.03–7.99 (m, 2H), 7.65 (d, *J*=8Hz, 1H), 7.58 (d, *J*=4Hz, 1H), 7.34–7.29 (m, 3H), 4.68–4.63 (m, 1H), 4.47–4.45 (m, 2H), 4.37–4.35 (m, 3H), 3.88 (s, 3H), 3.17–3.13 (m, 2H), 2.73–2.69 (m, 2H), 1.84–1.64 (m, 5H), 1.29–1.25 (m, 2H).

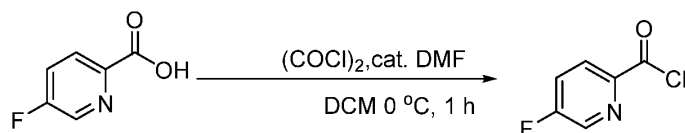
Example 14: Synthesis of (S)-N-(1-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-3-(1-methylpiperidin-4-yl)-1-oxopropan-2-yl)-5-fluoropicolinamide (I-185**)**



Synthesis Scheme:

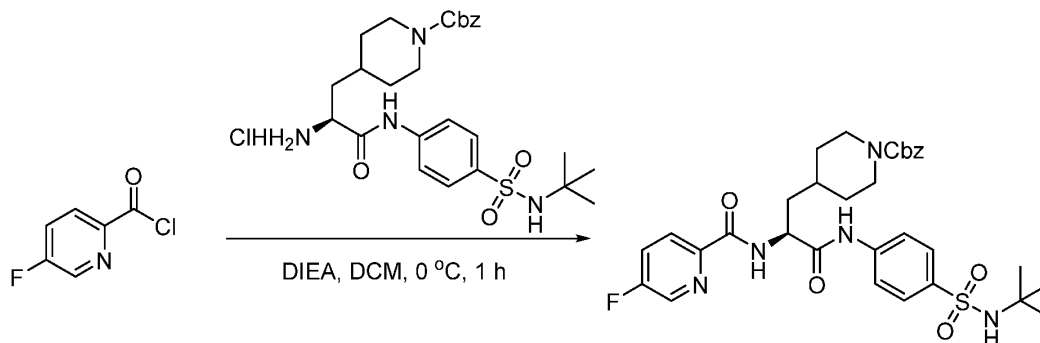


Part I - Preparation of 5-fluoropicolinoyl chloride



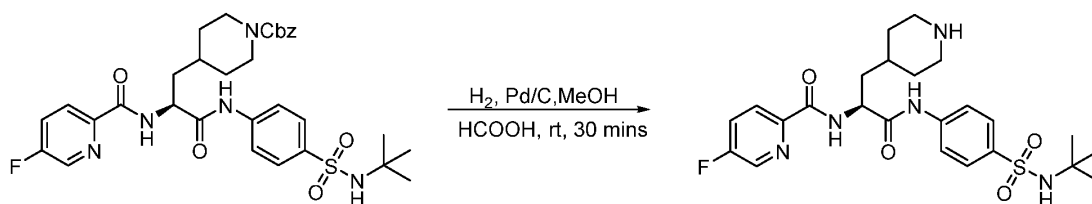
[00511] To a solution of 5-fluoropicolinic acid (208 mg, 1.47 mmol, 1.00 equiv.) in 10 mL DCM at 0 °C was added (COCl)₂ (937 mg, 7.38 mmol, 5.00 equiv) dropwise, then added cat.DMF (one drop). The solution was stirred for 2 hours at 0 °C. The reaction mixture was concentrated in vacuo to provide crude 5-fluoropicolinoyl chloride (200 mg, 87.7 % yield) which was used to the next step without further purification. MS (ESI⁺) m/z 156 [M+H]⁺(quenched with MeOH).

Part II - Preparation of benzyl (S)-4-(2-amino-3-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-3-oxopropyl)piperidine-1-carboxylate hydrochloride



[00512] To a solution of benzyl (S)-4-(2-amino-3-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-3-oxopropyl)piperidine-1-carboxylate hydrochloride (200 mg, 0.36 mmol, 1.00 equiv.) in DCM (10 mL) at 0 °C was added DIEA (232.2 mg, 1.8 mmol, 5.00 equiv) dropwise, then added 5-fluoropicolinoyl chloride (57.24 mg, 0.36 mmol, 1.00 equiv). The solution was stirred for 2 hours at 0 °C. The resulting mixture was diluted with water (50 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine (1x50 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column (silica gel, PE: EA = 1:1) to provide benzyl (S)-4-(3-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-2-(5-fluoropicolinamido)-3-oxopropyl)piperidine-1-carboxylate as a white solid (180 mg, 78.3 % yield). MS (ESI⁺) m/z 640.2 [M+H]⁺.

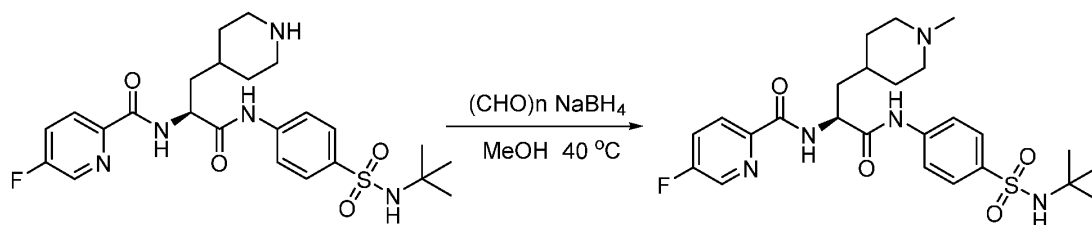
Part III - Preparation of (S)-N-(1-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-1-oxo-3-(piperidin-4-yl)propan-2-yl)-5-fluoropicolinamide (I-175)



[00513] To a mixture of benzyl (S)-4-(3-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-2-(5-fluoropicolinamido)-3-oxopropyl)piperidine-1-carboxylate (160 mg, 0.25 mmol, 1.00 equiv) in MeOH (10 mL)/formic acid (1 mL) at rt was added Pd/C (36 mg, 20%w.t.). The resulting mixture was diluted with water (50 mL) and extracted with EA (2 x 50 mL). The combined organic layers were washed with brine (1x50 mL), dried over anhydrous Na₂SO₄, filtered and the

filtrate was concentrated in vacuo. The residue was purified by flash column (silica gel, PE: EA = 1:1) to provide benzyl (S)-N-(1-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-1-oxo-3-(piperidin-4-yl)propan-2-yl)-5-fluoropicolinamide as a white solid (180 mg, 78.3 % yield) (**I-175**). MS (ESI⁺, m/z): Calcd for C₂₄H₃₂FN₅O₄S: 505.2; found 506.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*6) δ 10.65 (s, 1H), 8.76 (d, *J*=8.5 Hz, 1H), 8.71 (d, *J*=2.8 Hz, 1H), 8.43 (s, 1H), 8.15 – 8.10 (m, 1H), 7.96 – 7.90 (m, 1H), 7.76 (s, 4H), 7.41 (s, 1H), 4.81 – 4.72 (m, 1H), 3.16 – 3.06 (m, 2H), 2.70 – 2.58 (m, 2H), 1.91 – 1.82 (m, 2H), 1.77 – 1.67 (m, 2H), 1.62 – 1.53 (s, 1H), 1.35 – 1.24 (m, 2H), 1.07 (s, 9H).

Part IV - Preparation of (S)-N-(1-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-3-(1-methylpiperidin-4-yl)-1-oxopropan-2-yl)-5-fluoropicolinamide (I-185)

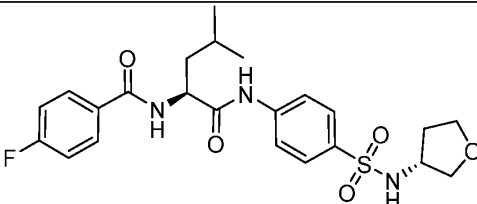
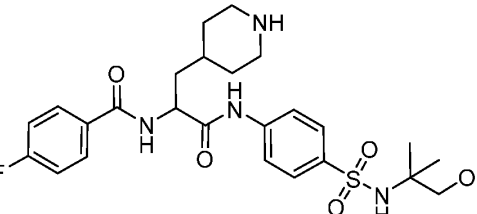
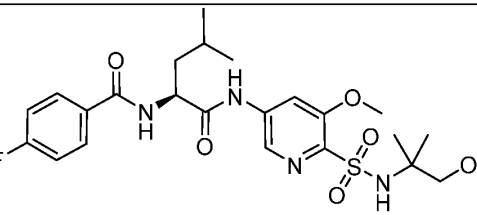
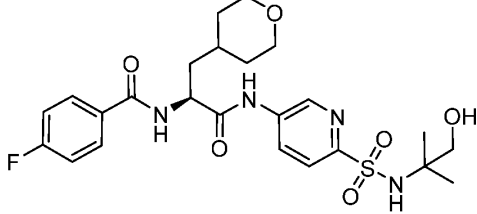
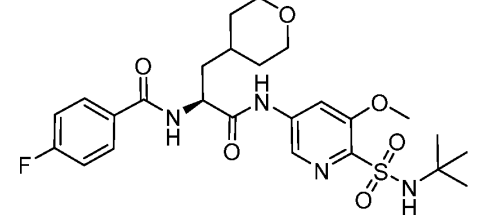


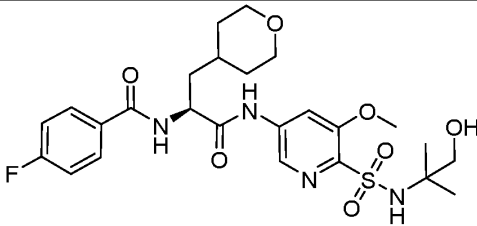
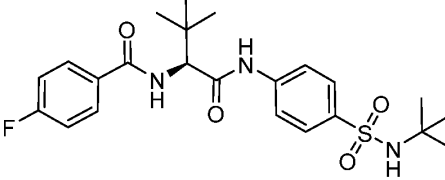
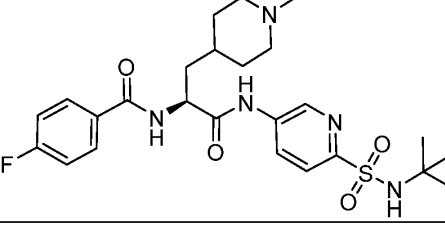
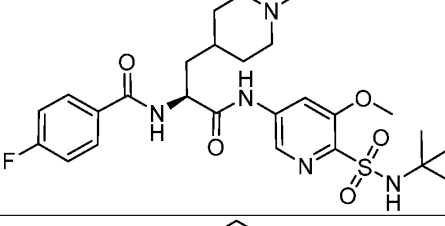
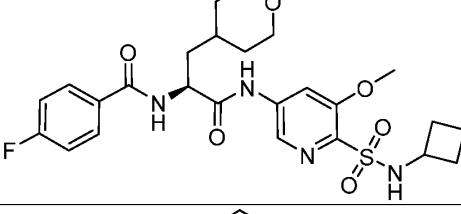
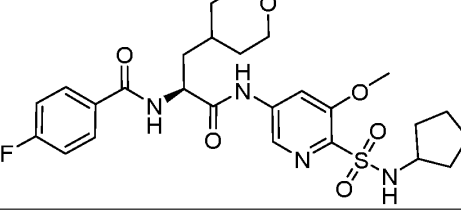
[00514] To a mixture of (S)-N-(1-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-1-oxo-3-(piperidin-4-yl)propan-2-yl)-5-fluoropicolinamide (30 mg, 0.06 mmol, 1.00 equiv) and paraformaldehyde (9 mg, 0.3 mmol, 5.00 equiv) in MeOH (5 mL) at rt was added NaBH₄ (11.4 mg, 0.3 mmol, 5.00 equiv). The mixture was stirred at 40 °C for 1.5 hours. The mixture diluted with water (10 mL) and extracted with DCM (2 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was lyophilized to afford (S)-N-(1-((4-(N-(tert-butyl)sulfamoyl)phenyl)amino)-3-(1-methylpiperidin-4-yl)-1-oxopropan-2-yl)-5-fluoropicolinamide (12 mg, 38.7 % yield) (**I-185**). MS (ESI⁺, m/z): Calcd for C₂₅H₃₄FN₅O₄S: 519.2; found 520.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*6) δ 10.54 (s, 1H), 8.73 – 8.67 (m, 2H), 8.14 – 8.10 (m, 1H), 7.96 – 7.90 (m, 1H), 7.76 (s, 4H), 7.40 (s, 1H), 4.78 – 4.70 (m, 1H), 2.75 – 2.66 (m, 2H), 2.09 (s, 3H), 1.87 – 1.62 (m, 6H), 1.32 – 1.26 (m, 1H), 1.22 – 1.12 (m, 2H), 1.07 (s, 9H).

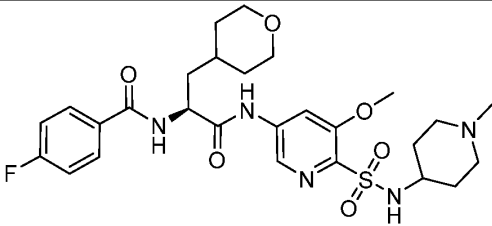
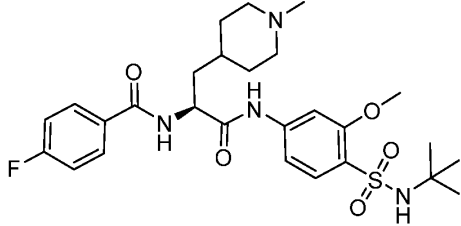
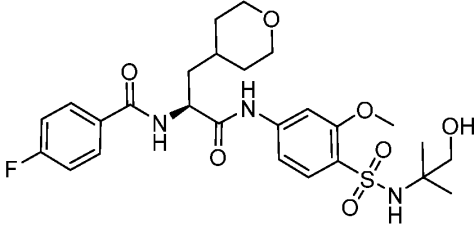
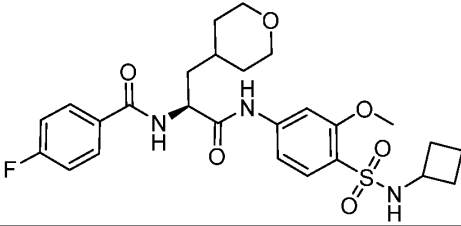
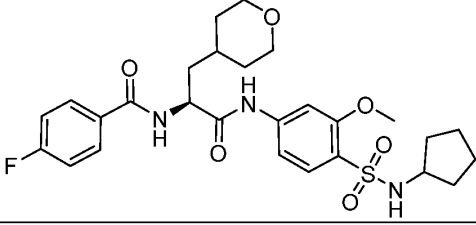
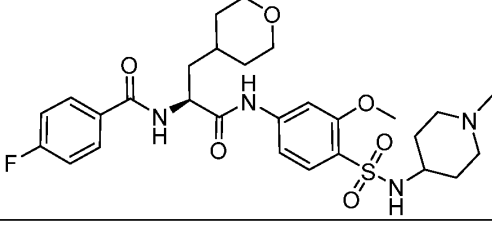
Example 15: Synthesis of Additional Compounds

[00515] The compounds in Table 11 below were prepared using procedures based on those described herein above.

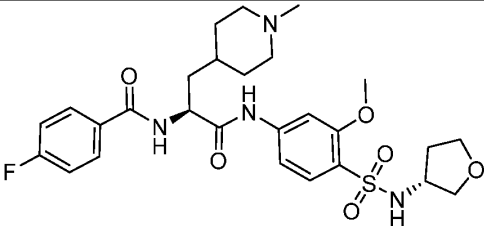
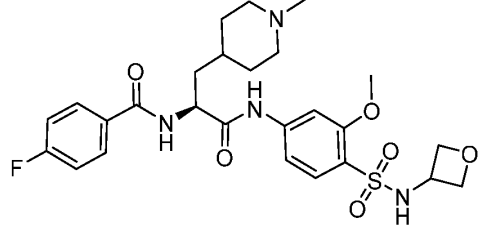
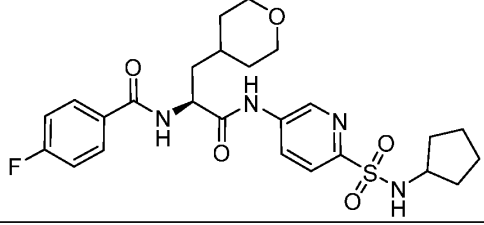
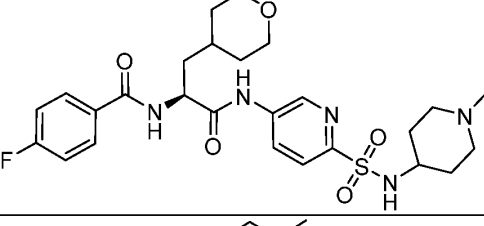
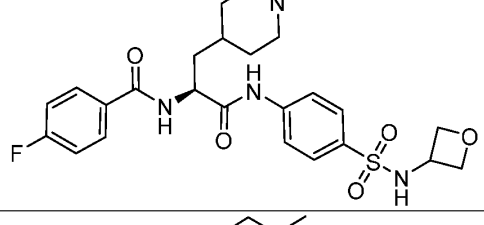
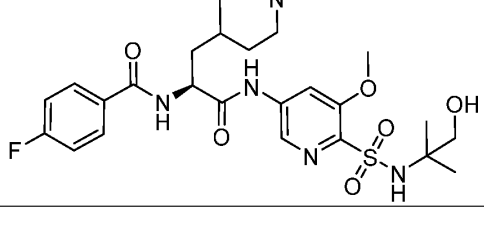
Table 11.

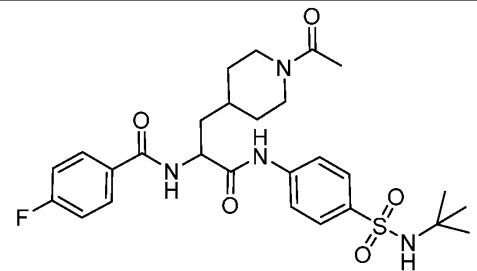
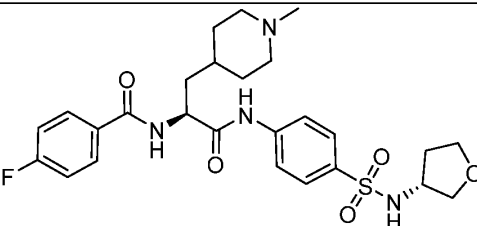
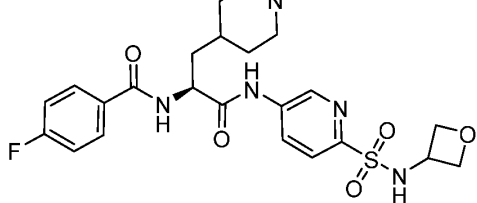
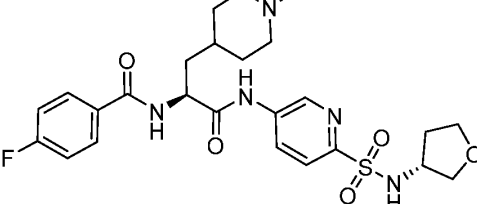
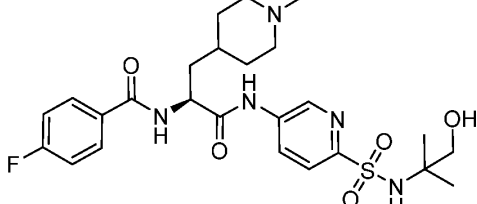
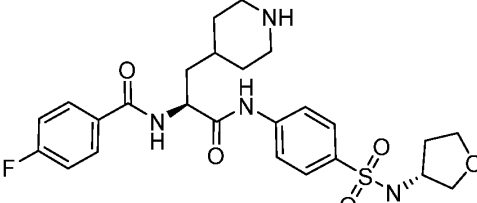
Compound No.	Structure
I-71	
I-72	
I-73	
I-74	
I-75	

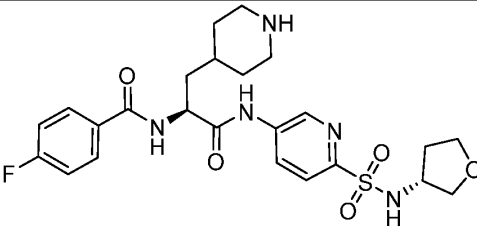
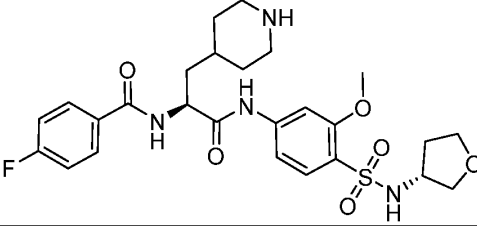
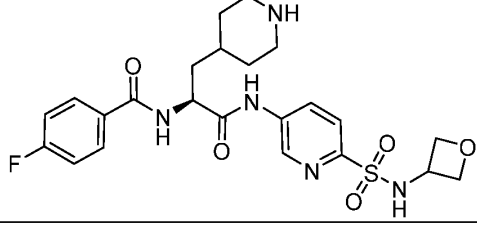
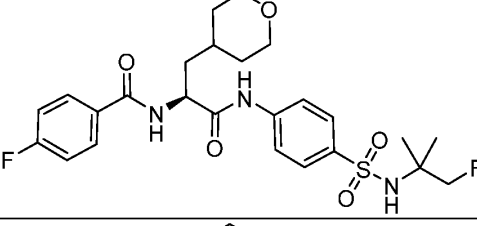
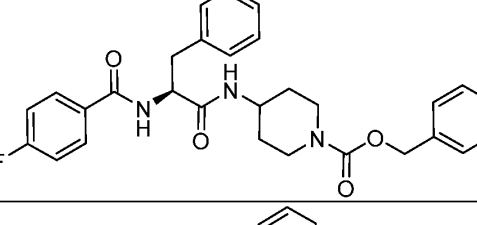
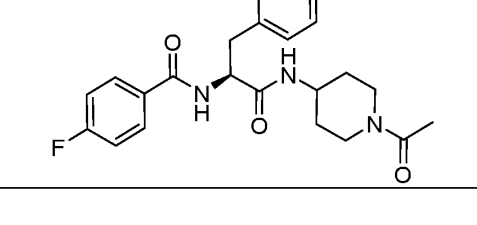
I-76	
I-77	
I-78	
I-80	
I-81	
I-82	

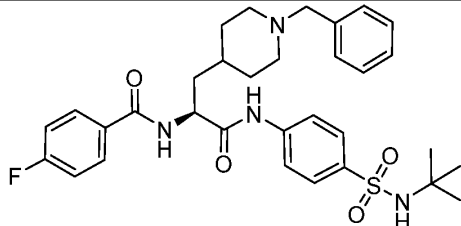
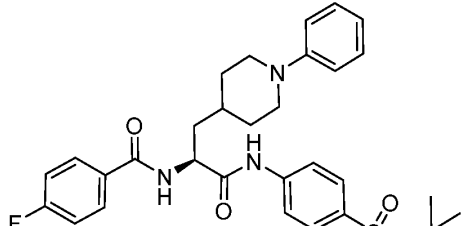
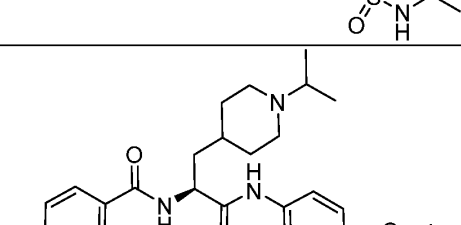
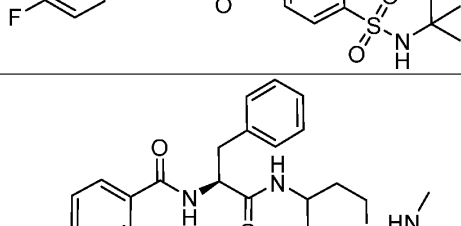
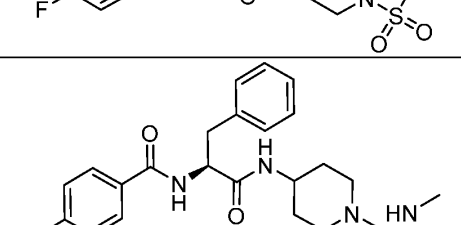
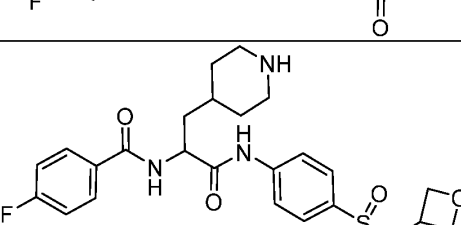
I-83	
I-84	
I-85	
I-86	
I-87	
I-88	

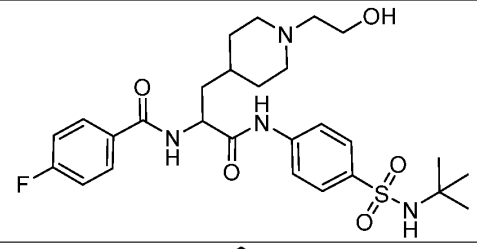
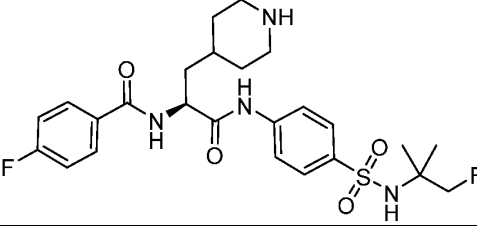
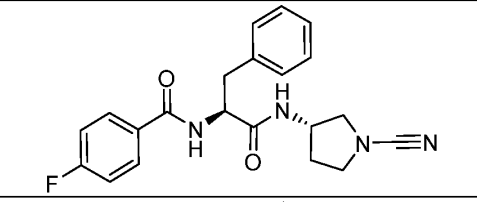
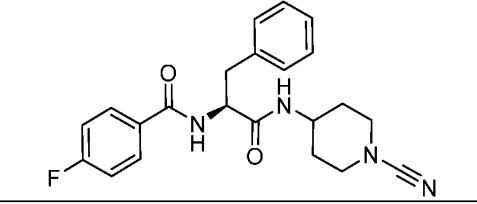
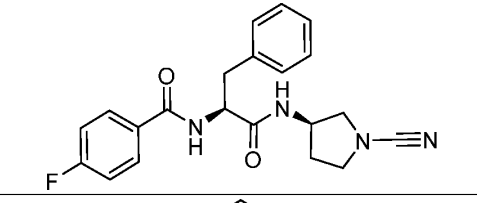
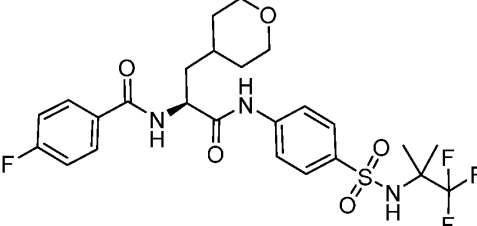
I-89	
I-90	
I-91	
I-92	
I-93	

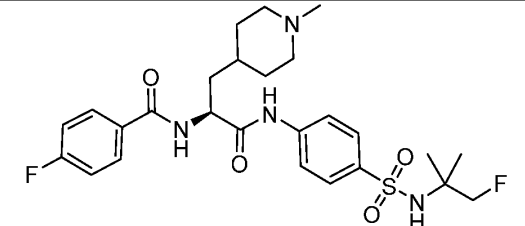
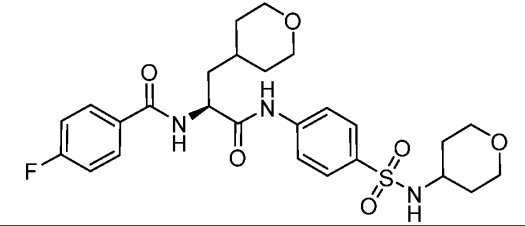
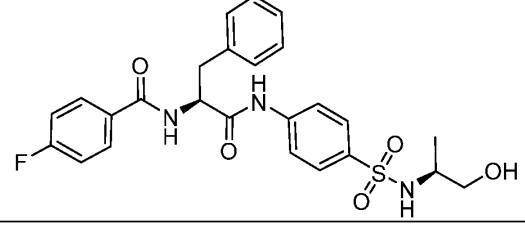
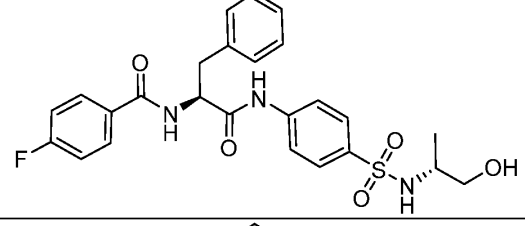
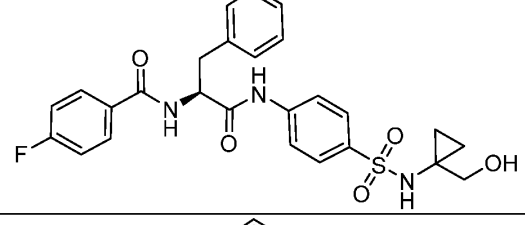
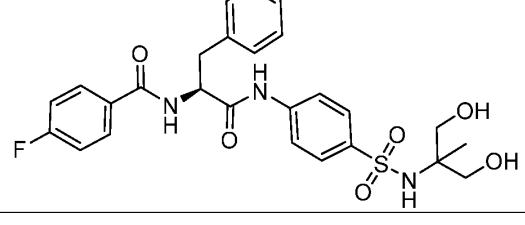
I-95	
I-96	
I-97	
I-98	
I-99	
I-100	

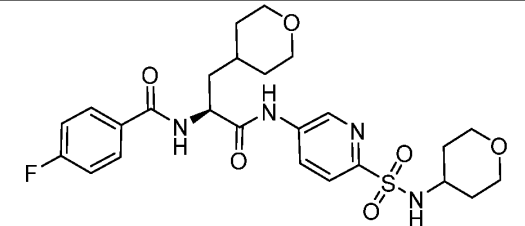
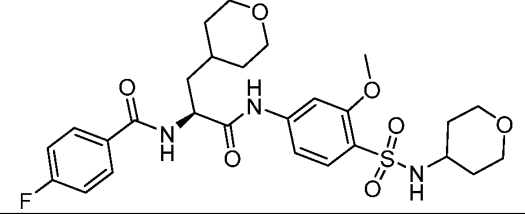
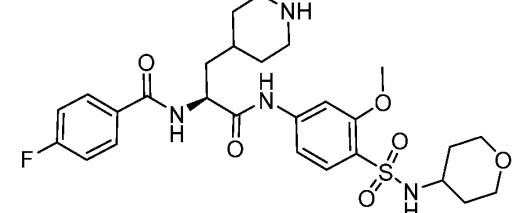
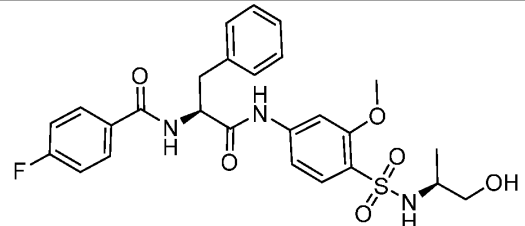
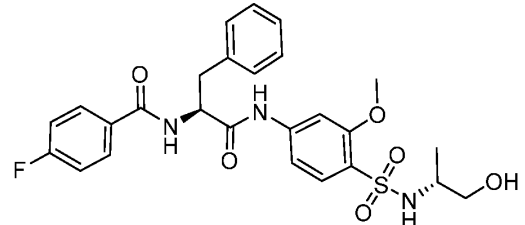
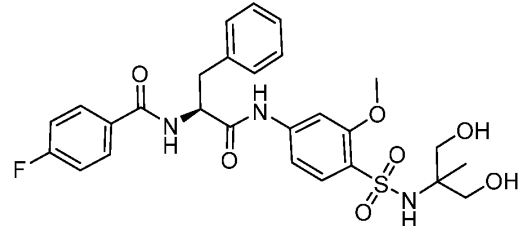
I-101	
I-103	
I-104	
I-105	
I-106	
I-107	

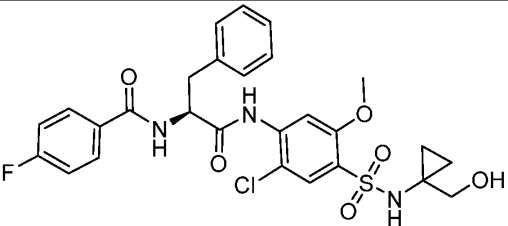
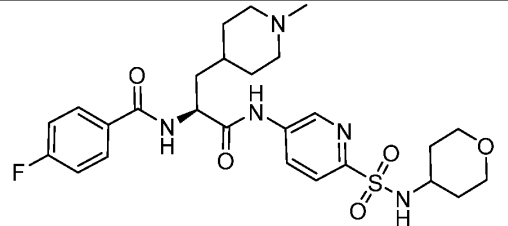
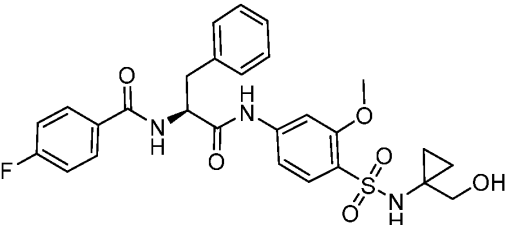
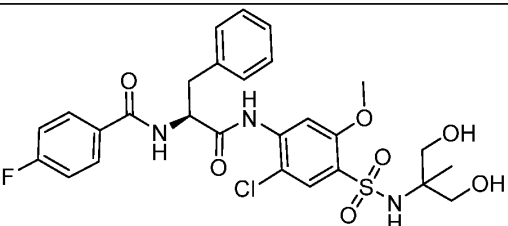
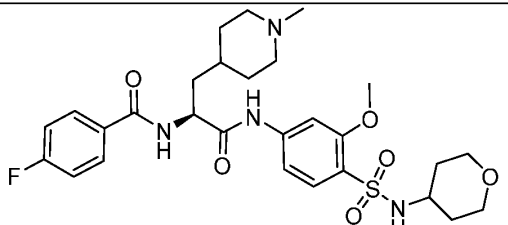
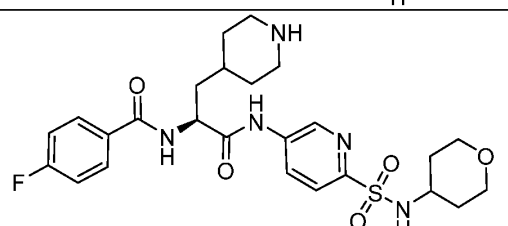
I-108	
I-110	
I-111	
I-112	
I-113	
I-114	

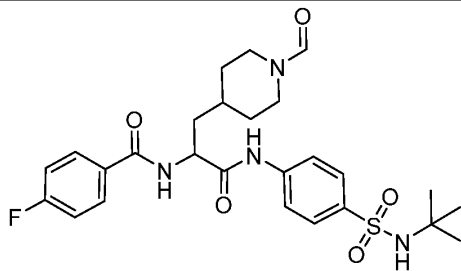
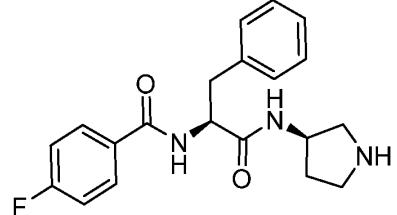
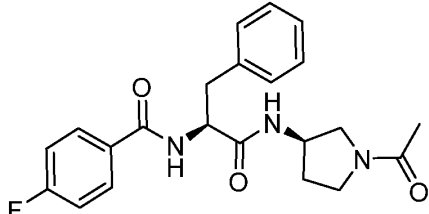
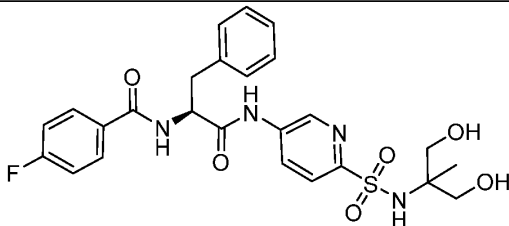
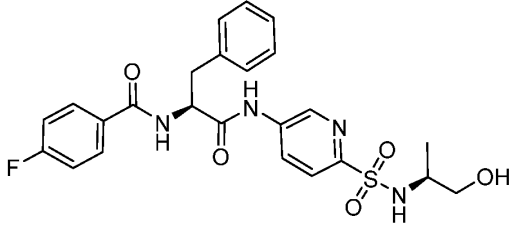
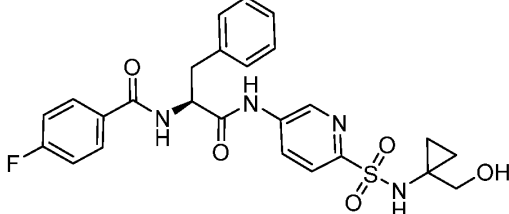
I-115	
I-116	
I-117	
I-118	
I-119	
I-120	

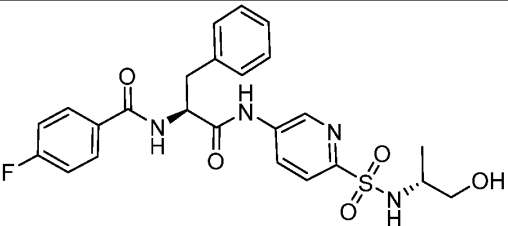
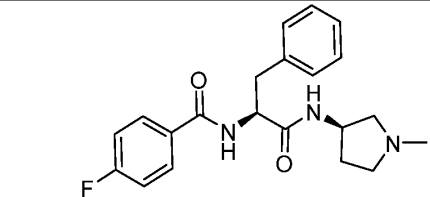
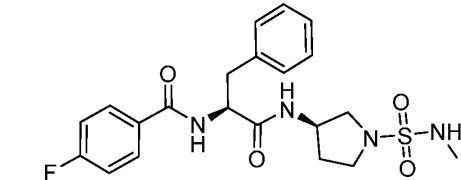
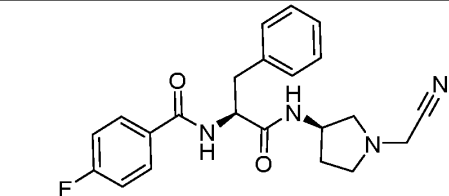
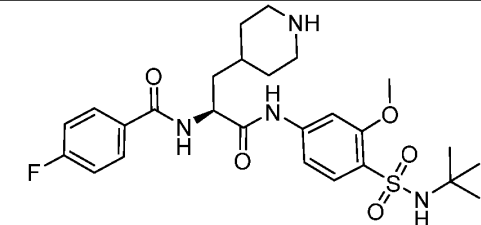
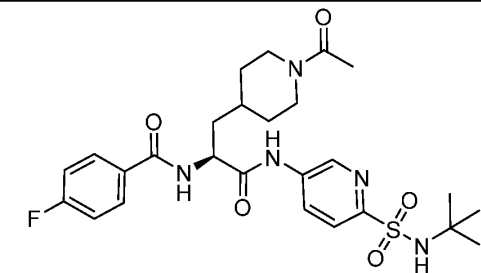
I-121	 <chem>CC(C)(N(S(=O)(=O)c1ccc(NC(=O)C[C@H](NC(=O)c2ccc(F)cc2)C3CCN(CCO)CC3)c1)c1ccc(NC(=O)C[C@H](NC(=O)c2ccc(F)cc2)C3CCN(CCO)CC3)c1</chem>
I-122	 <chem>CC(C)(N(S(=O)(=O)c1ccc(NC(=O)C[C@H](NC(=O)c2ccc(F)cc2)C3CCNCC3)c1)c1ccc(NC(=O)C[C@H](NC(=O)c2ccc(F)cc2)C3CCNCC3)c1</chem>
I-123	 <chem>N#NCCN(C(=O)C[C@H](NC(=O)c1ccc(F)cc1)C2CCNCC2)c1ccc(NC(=O)C[C@H](NC(=O)c2ccc(F)cc2)C3CCNCC3)c1</chem>
I-124	 <chem>N#NCCN(C(=O)C[C@H](NC(=O)c1ccc(F)cc1)C2CCNCC2)c1ccc(NC(=O)C[C@H](NC(=O)c2ccc(F)cc2)C3CCNCC3)c1</chem>
I-125	 <chem>N#NCCN(C(=O)C[C@H](NC(=O)c1ccc(F)cc1)C2CCNCC2)c1ccc(NC(=O)C[C@H](NC(=O)c2ccc(F)cc2)C3CCNCC3)c1</chem>
I-126	 <chem>CC(F)(F)F(C(F)(F)F)N(S(=O)(=O)c1ccc(NC(=O)C[C@H](NC(=O)c2ccc(F)cc2)C3CCNCC3)c1)c1ccc(NC(=O)C[C@H](NC(=O)c2ccc(F)cc2)C3CCNCC3)c1</chem>

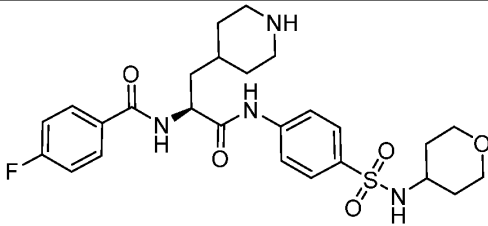
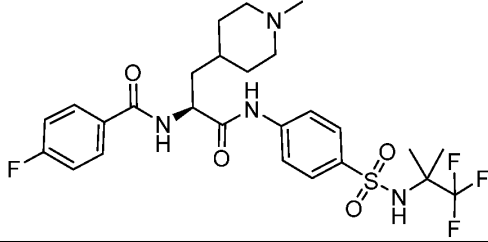
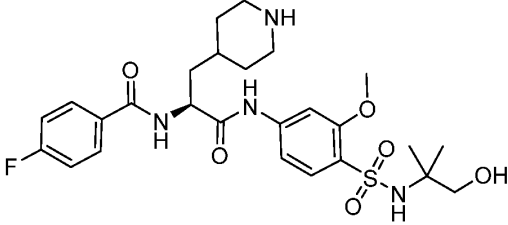
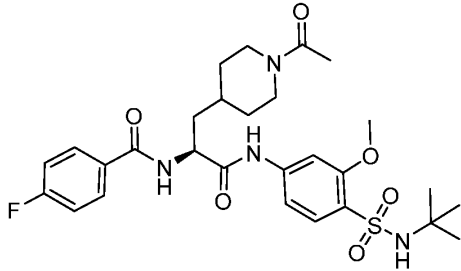
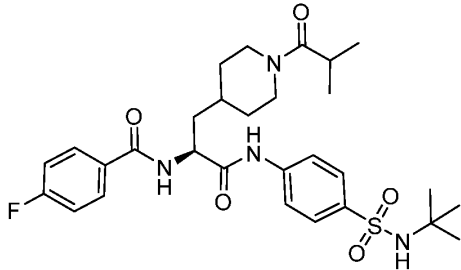
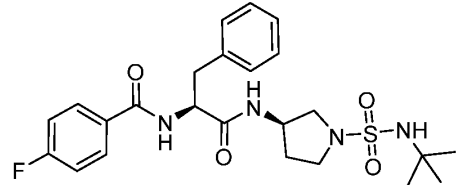
I-127	
I-128	
I-129	
I-130	
I-131	
I-132	

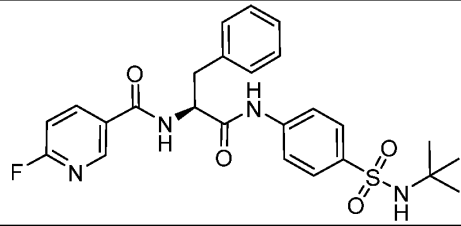
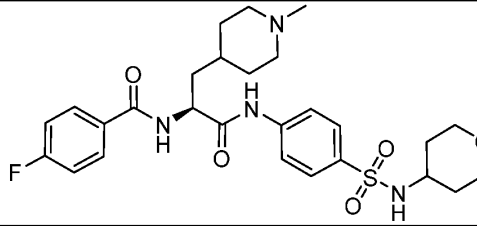
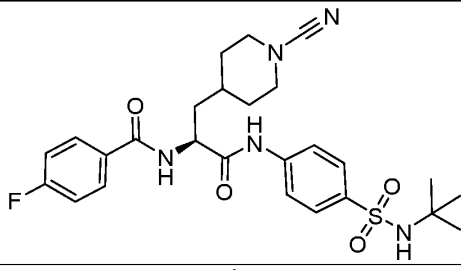
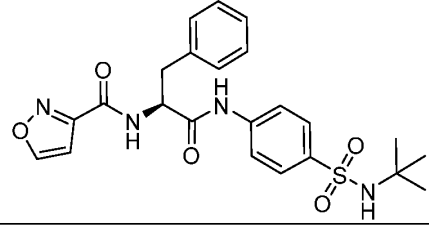
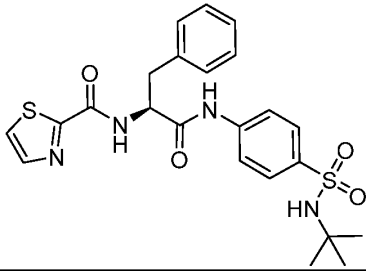
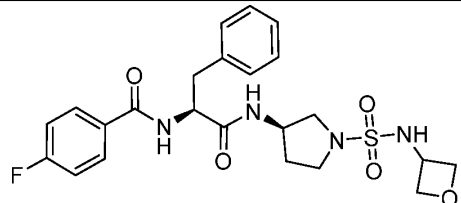
I-133	
I-134	
I-135	
I-136	
I-137	
I-138	

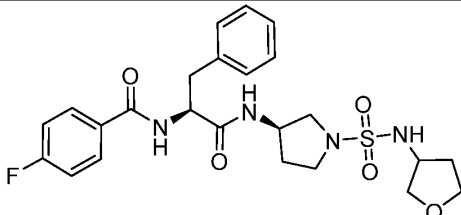
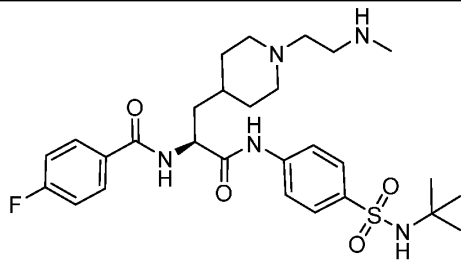
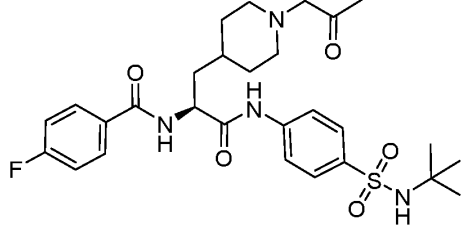
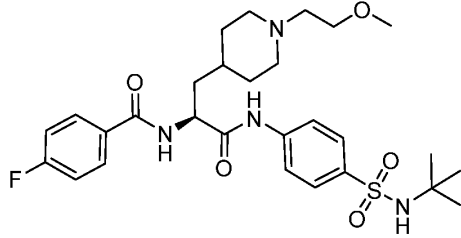
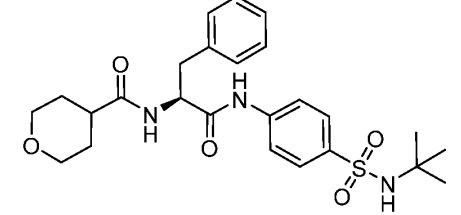
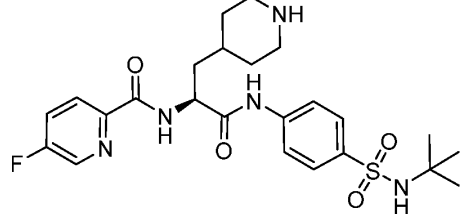
I-139	
I-140	
I-141	
I-142	
I-143	
I-144	

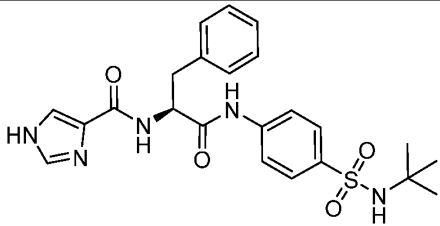
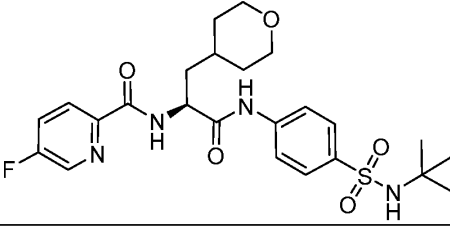
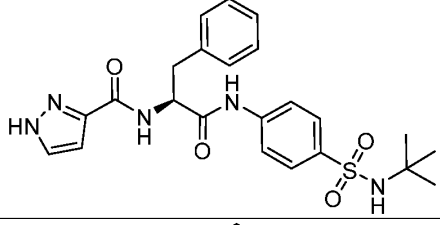
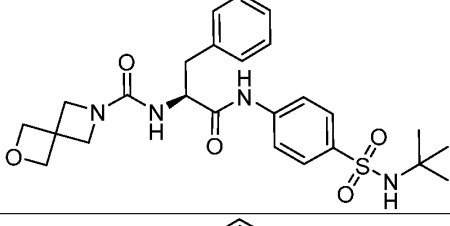
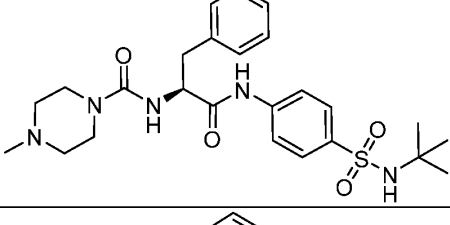
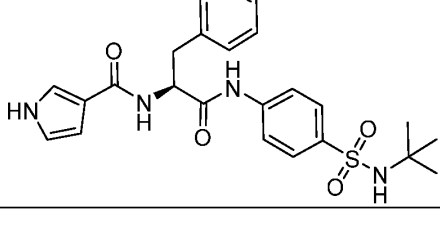
I-145	
I-146	
I-147	
I-148	
I-149	
I-150	

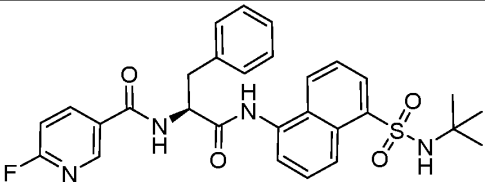
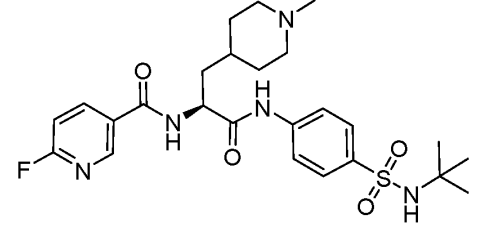
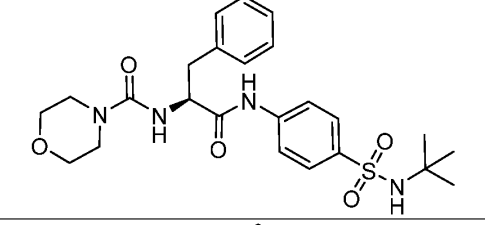
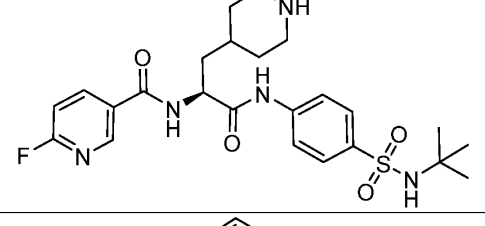
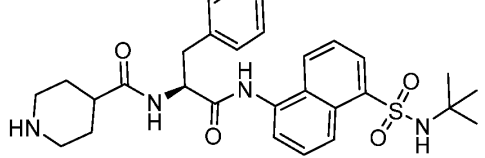
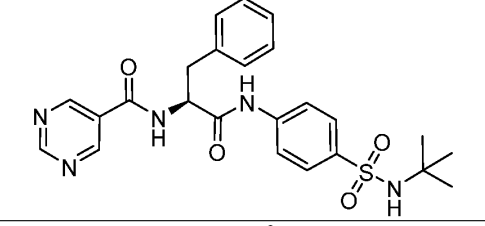
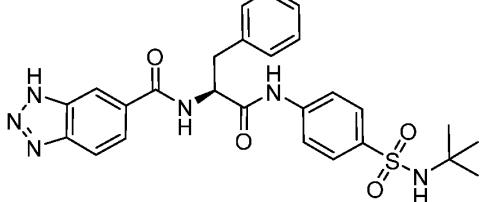
I-151	
I-152	
I-153	
I-154	
I-155	
I-156	

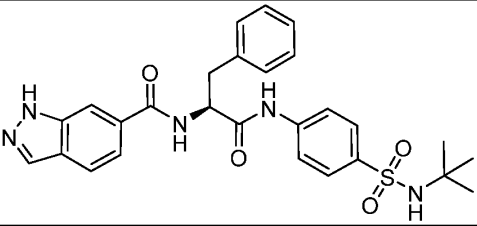
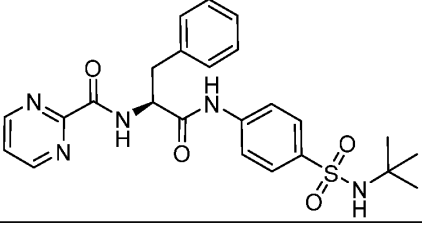
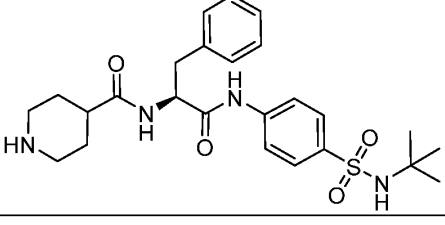
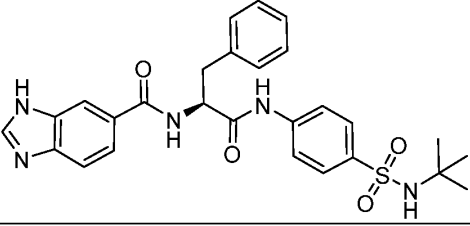
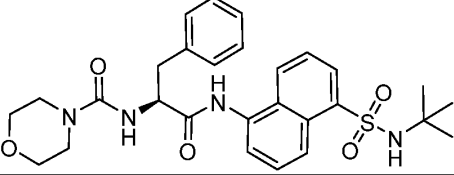
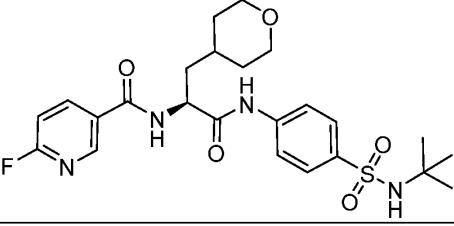
I-157	
I-158	
I-159	
I-160	
I-161	
I-162	

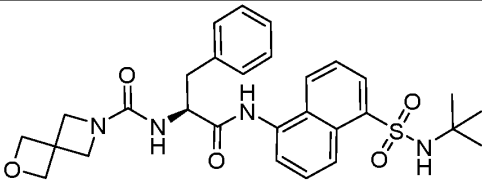
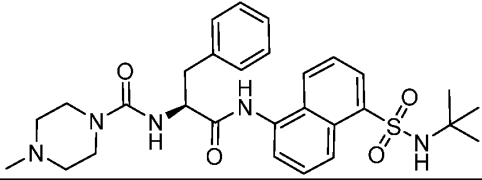
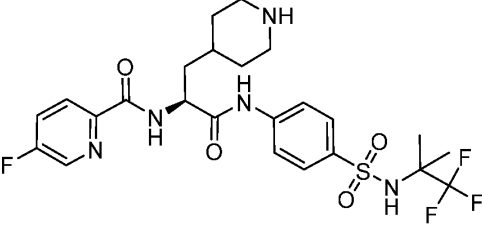
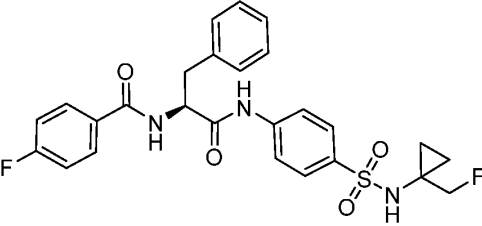
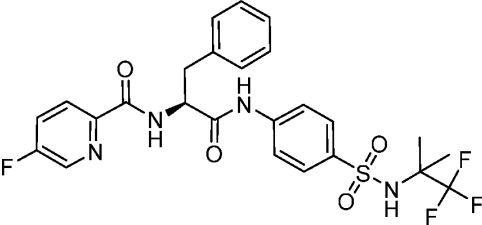
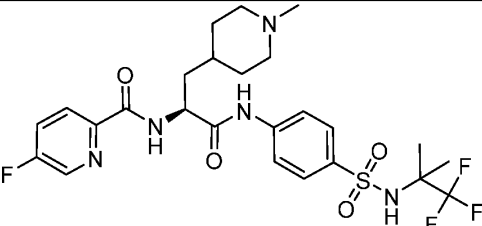
I-163	
I-164	
I-165	
I-167	
I-168	
I-169	

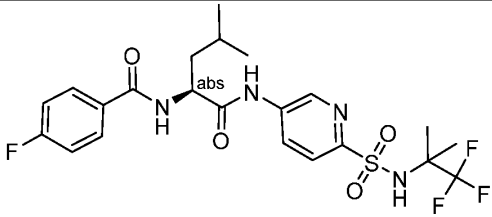
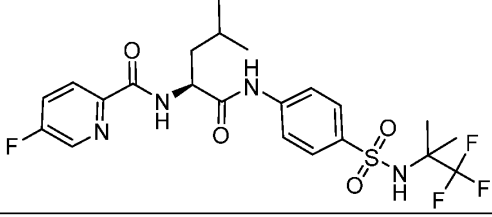
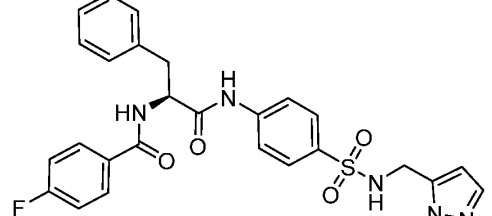
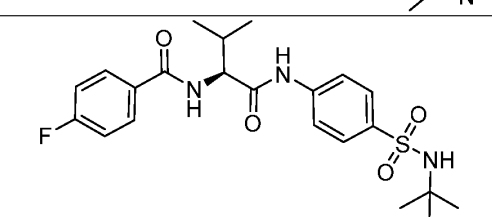
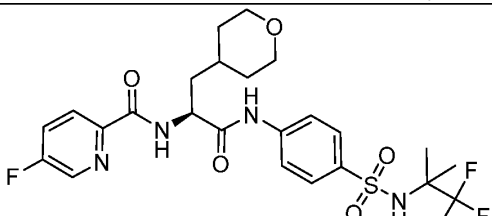
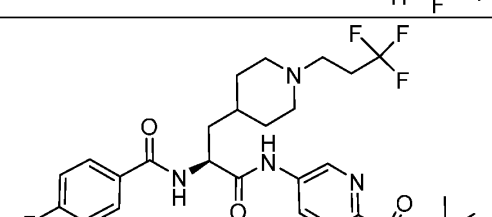
I-170	
I-171	
I-172	
I-173	
I-174	
I-175	

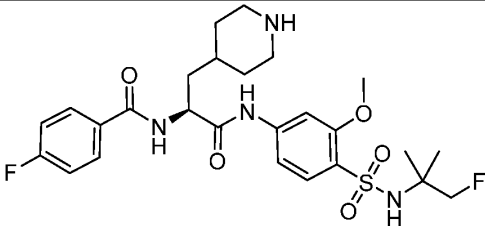
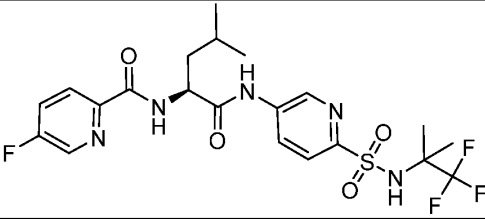
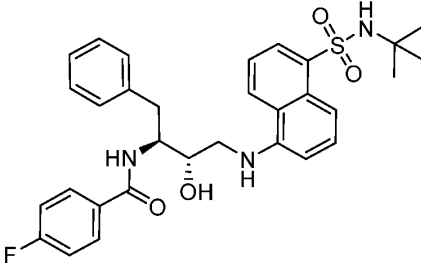
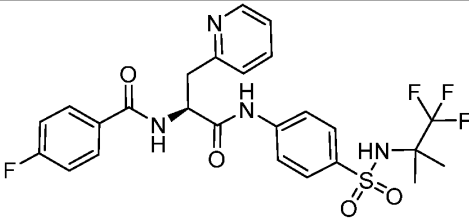
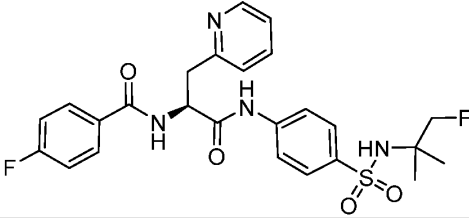
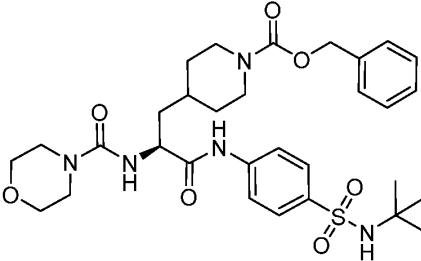
I-176	
I-177	
I-178	
I-179	
I-180	
I-181	

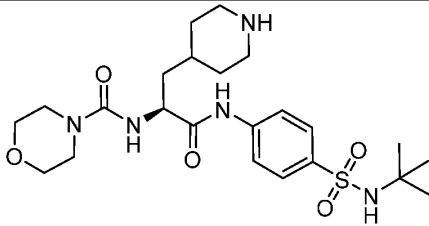
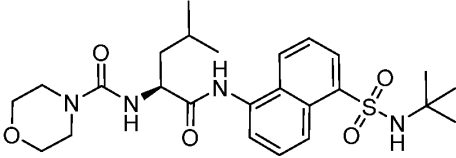
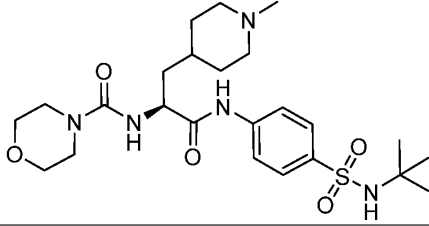
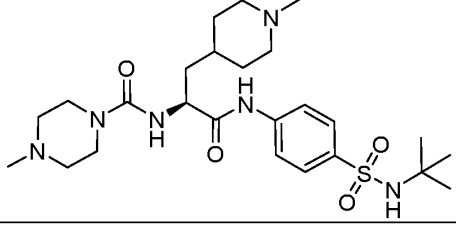
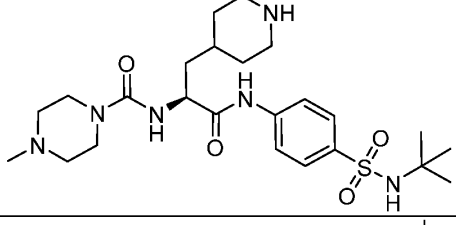
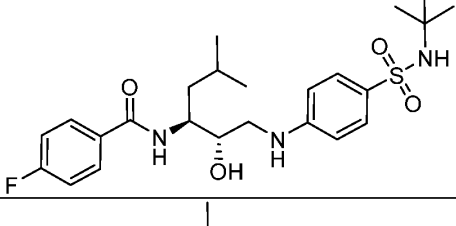
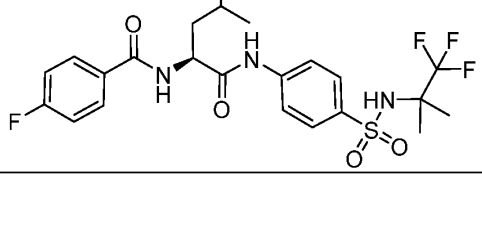
I-182	
I-183	
I-184	
I-186	
I-187	
I-188	
I-189	

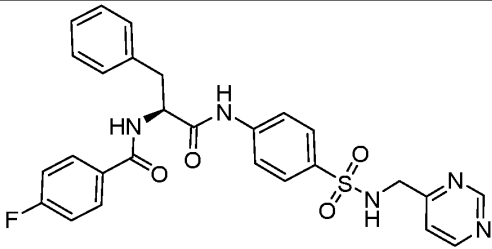
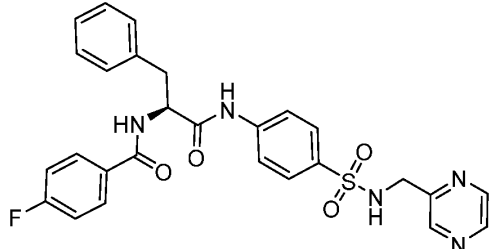
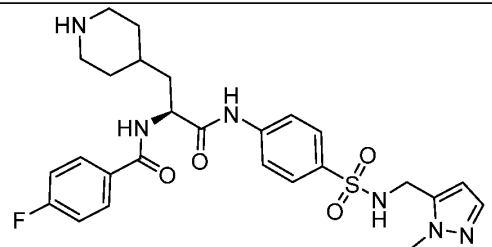
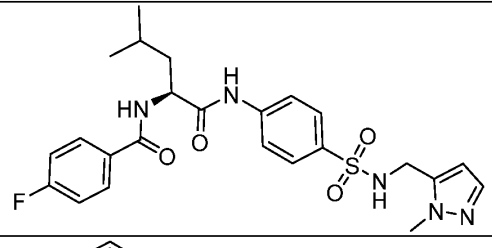
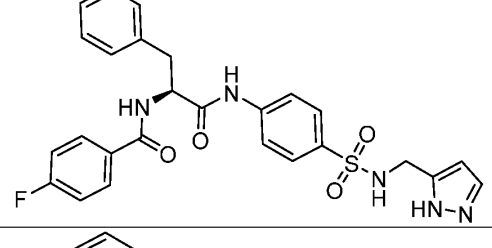
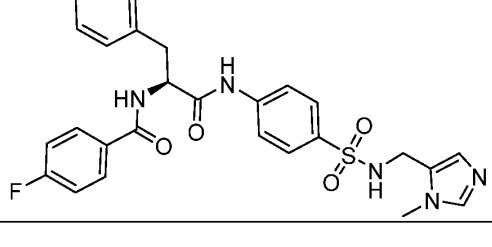
I-190	
I-191	
I-192	
I-194	
I-195	
I-196	

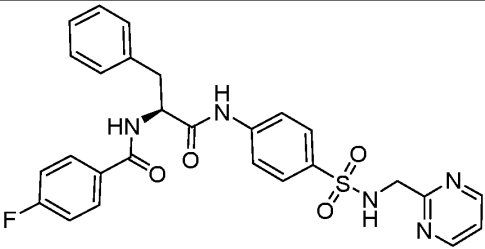
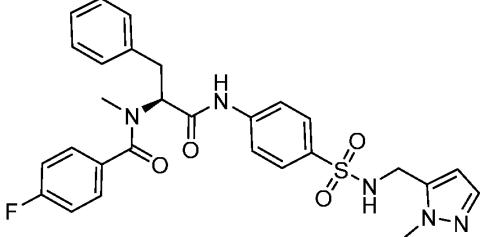
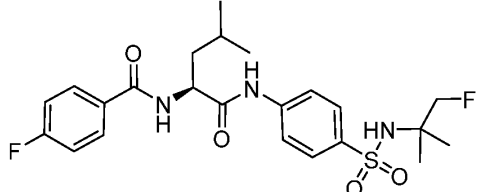
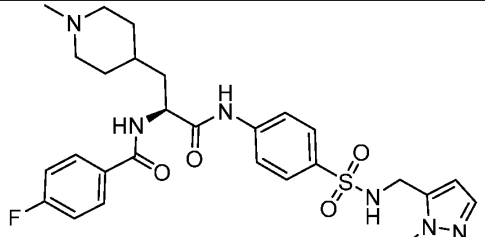
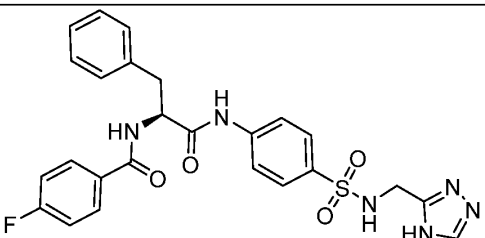
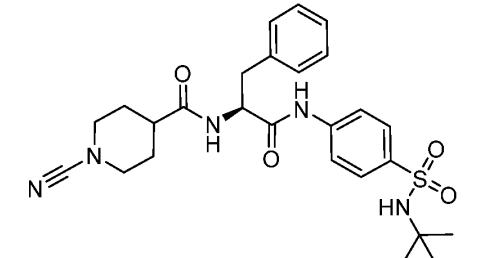
I-197	
I-198	
I-199	
I-200	
I-201	
I-202	

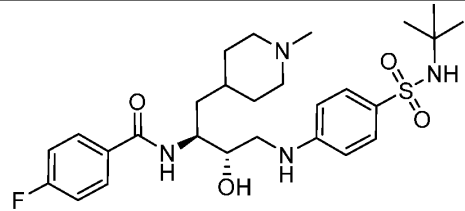
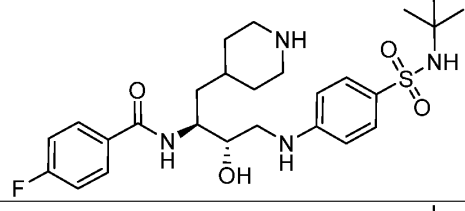
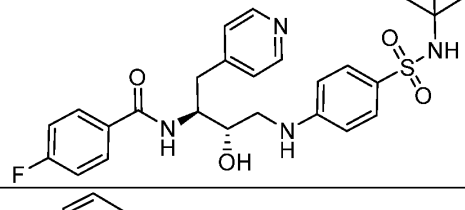
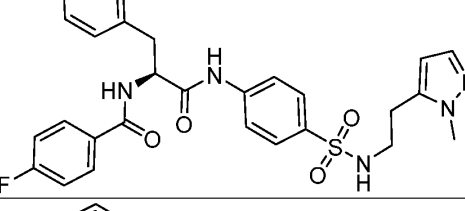
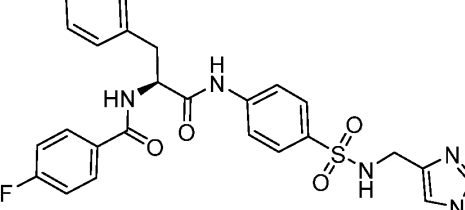
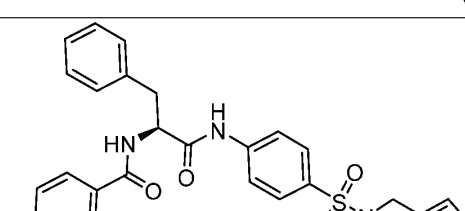
I-203	
I-204	
I-205	
I-206	
I-207	
I-208	

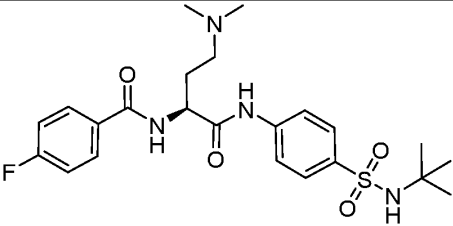
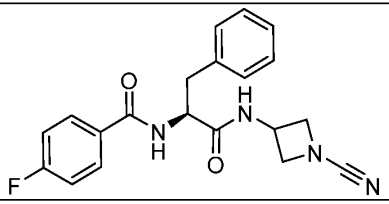
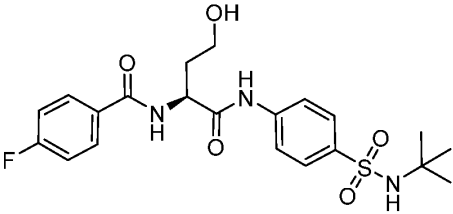
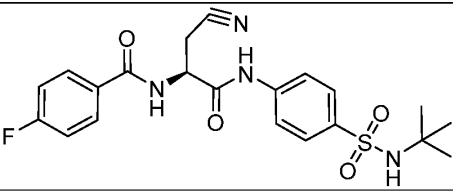
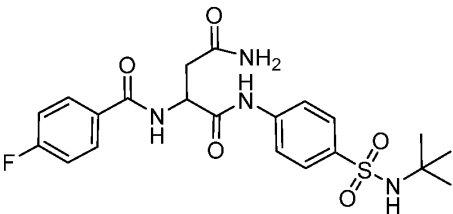
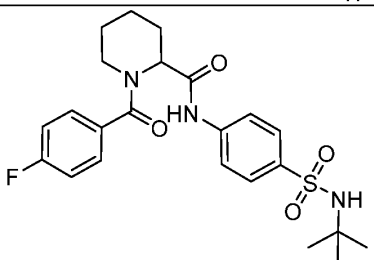
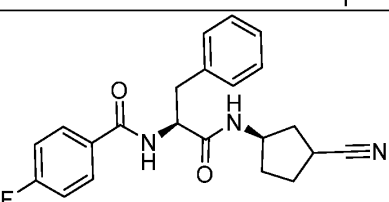
I-209	
I-210	
I-211	
I-212	
I-213	
I-214	

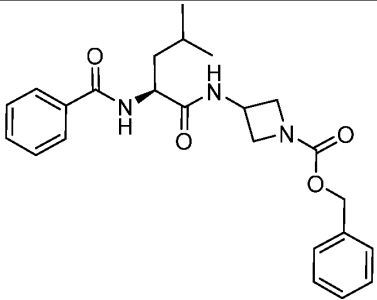
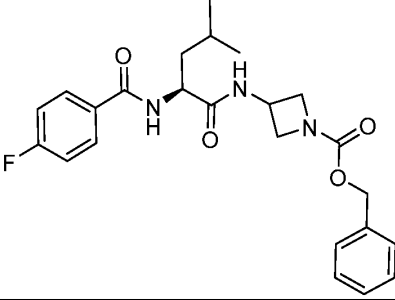
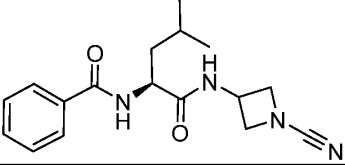
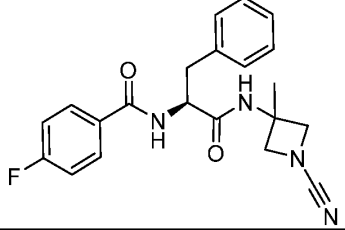
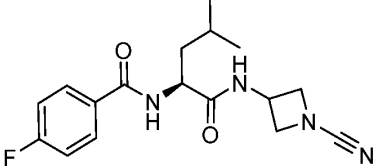
I-215	
I-216	
I-217	
I-218	
I-219	
I-220	
I-221	

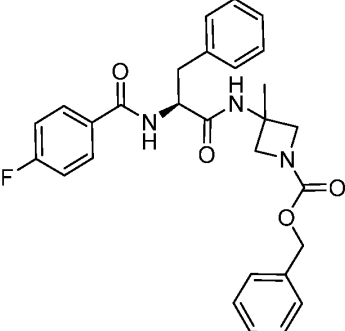
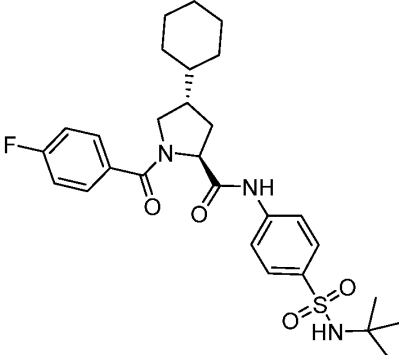
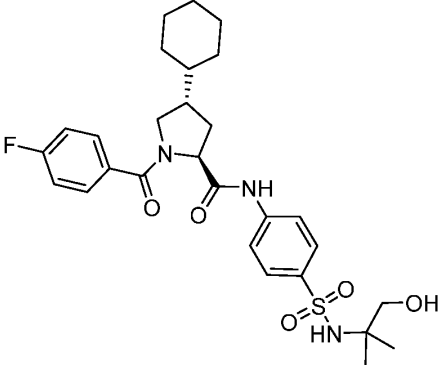
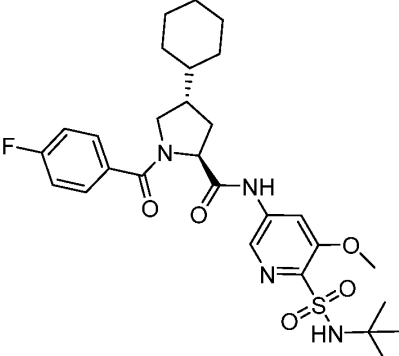
I-222	
I-223	
I-224	
I-225	
I-226	
I-227	

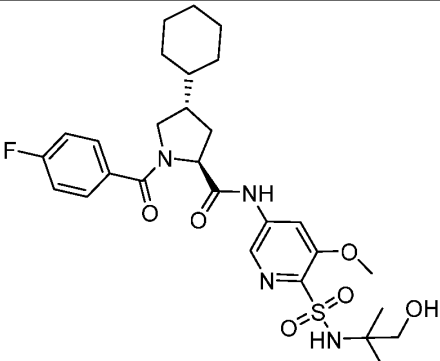
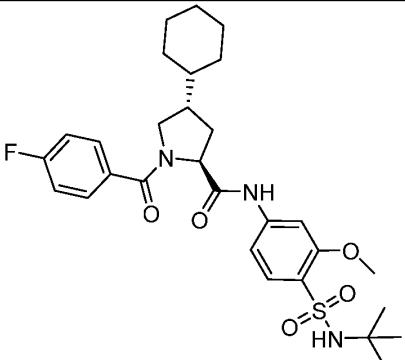
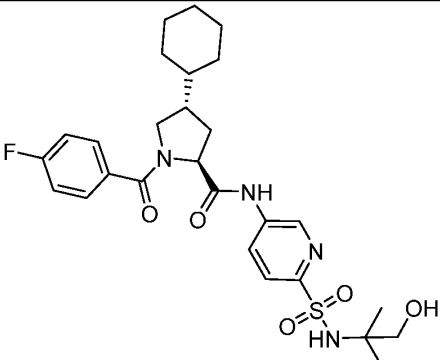
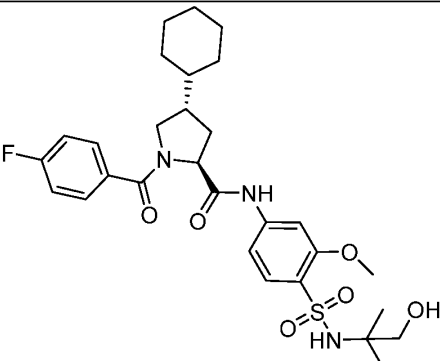
I-228	
I-229	
I-230	
I-231	
I-232	
I-233	

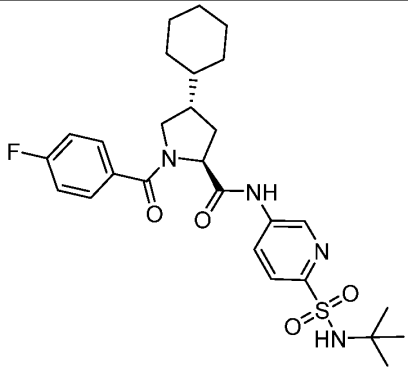
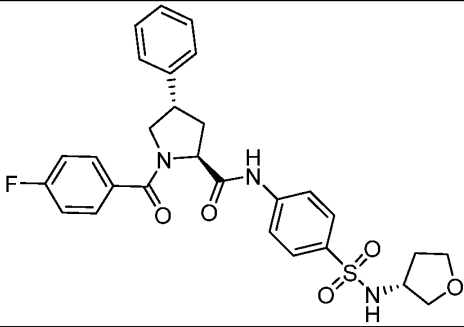
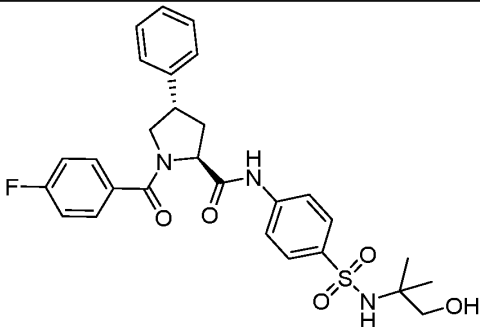
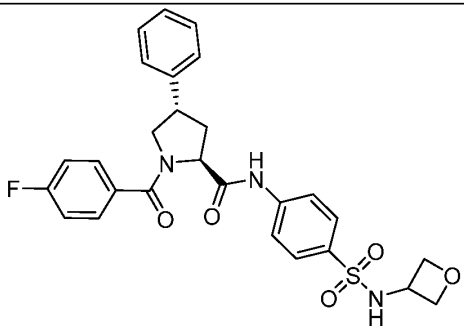
I-234	
I-235	
I-236	
I-237	
I-238	
I-239	

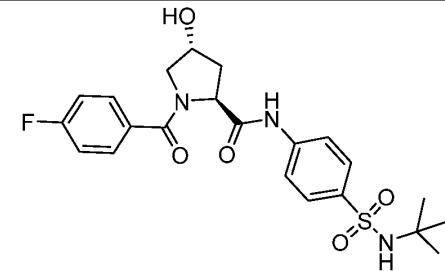
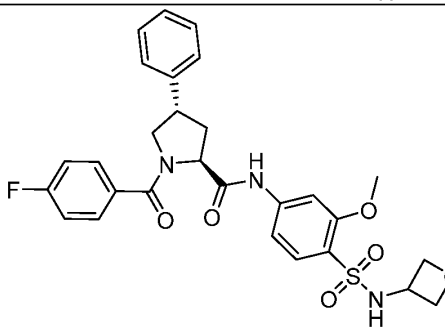
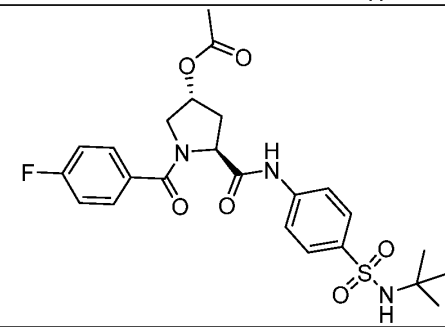
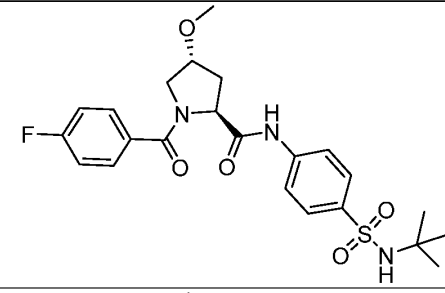
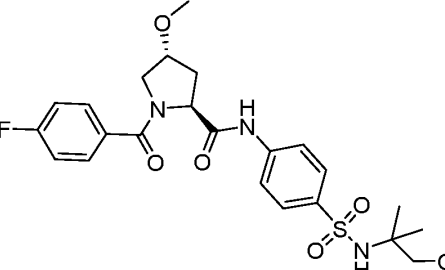
I-240	
I-241	
I-242	
I-243	
I-244	
I-245	
I-246	

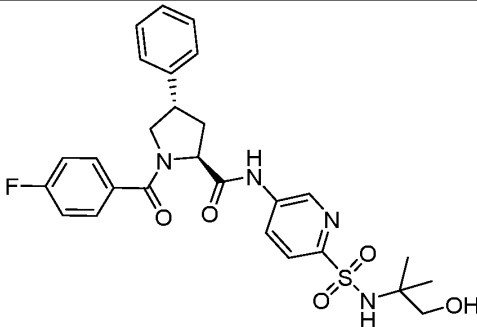
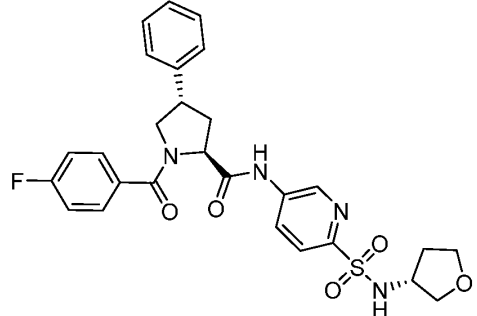
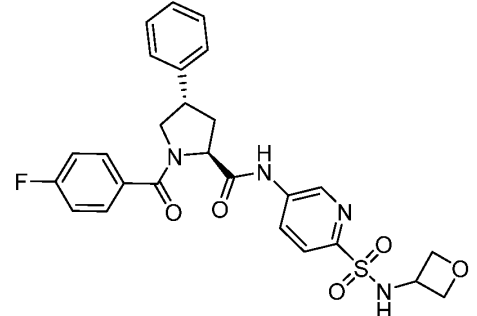
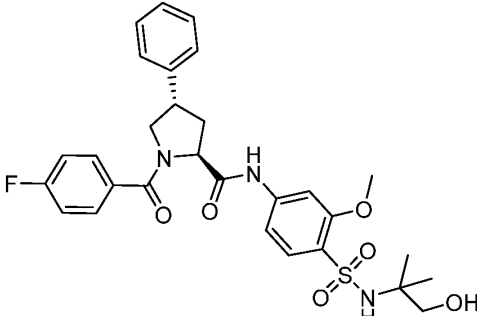
I-247	
I-248	
I-249	
I-250	
I-251	

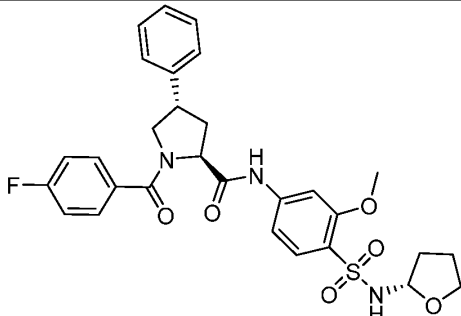
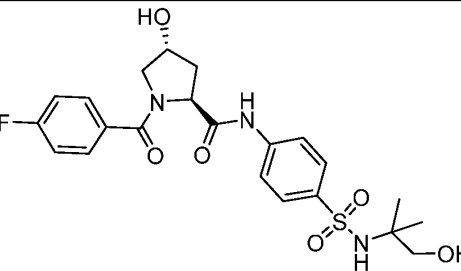
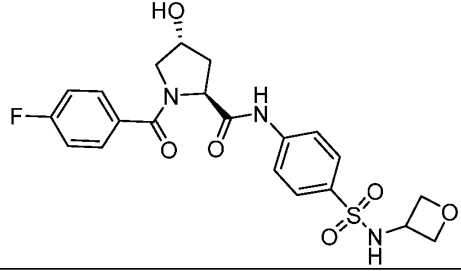
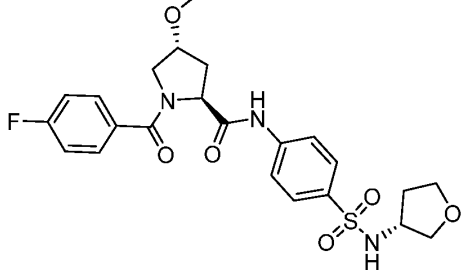
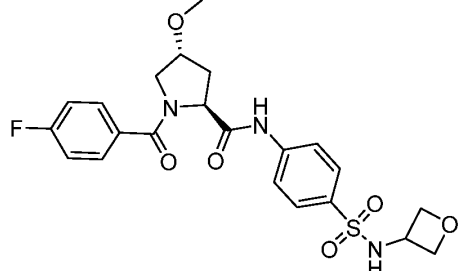
I-252	
I-253	
I-254	
I-255	

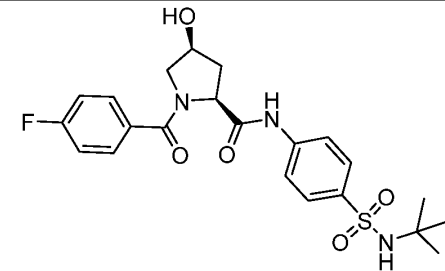
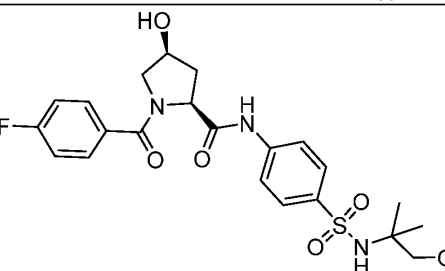
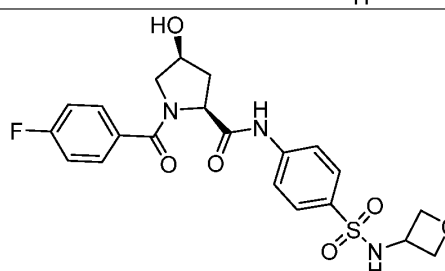
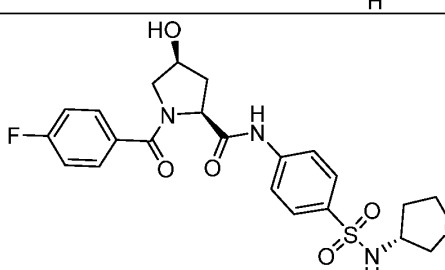
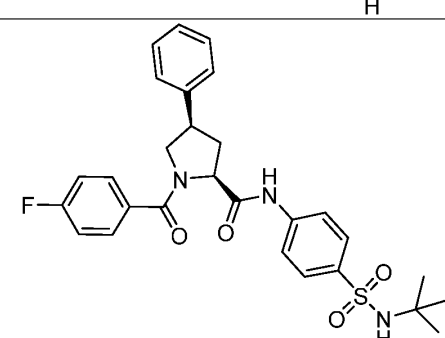
I-256	
I-257	
I-258	
I-259	

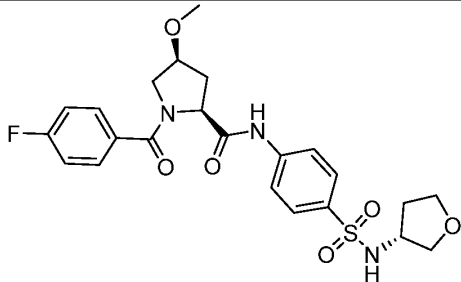
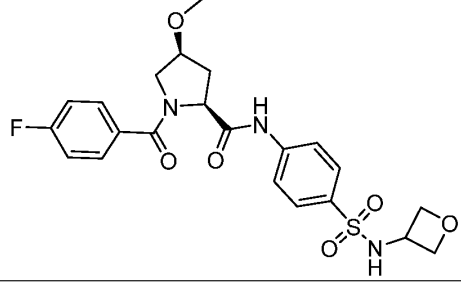
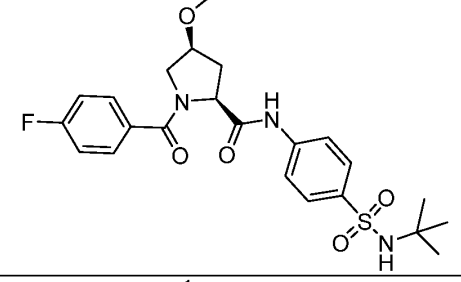
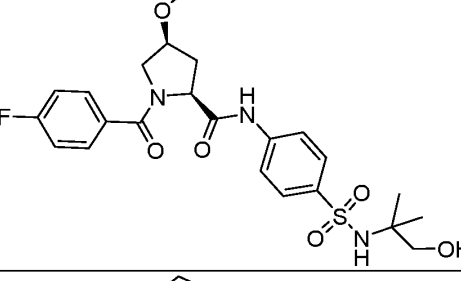
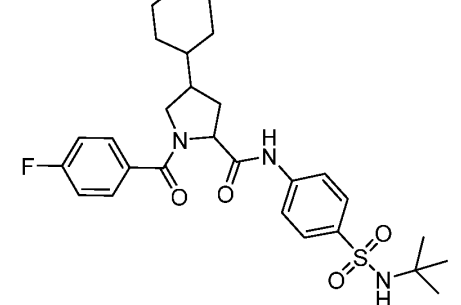
I-260	
I-261	
I-262	
I-263	

I-264	
I-265	
I-266	
I-267	
I-268	

I-269	
I-270	
I-271	
I-272	

I-273	
I-275	
I-276	
I-277	
I-278	

I-279	
I-280	
I-281	
I-282	
I-283	

I-288	
I-289	
I-290	
I-291	
I-292	

[00516] ^1H NMR and mass spectrometry data for select compounds is provided in the following table:

Cmpd No.	MS	^1H NMR
I-78	520.3[M+H] ⁺	^1H NMR (400 MHz, DMSO) δ 10.72 (s, 1H), 8.89 (d, J = 2.2 Hz, 1H), 8.75 (d, J = 7.4 Hz, 1H), 8.27 (dd, J = 8.7, 2.5 Hz, 1H), 8.03 – 7.96 (m, 2H), 7.93 (d, J = 8.6 Hz, 1H), 7.58 (s, 1H), 7.39 – 7.24 (m, 2H), 4.72 – 4.60 (m, 1H), 2.81 – 2.66 (m, 2H), 2.12 (s, 3H), 1.90 – 1.58 (m, 6H), 1.50 – 1.40 (m, 1H), 1.29 – 1.16 (m, 2H), 1.08 (s, 9H).
I-177	507.6[M+H] ⁺	^1H NMR (400 MHz, DMSO) δ 10.52 (s, 1H), 8.73 (d, J = 8.5 Hz, 1H), 8.71 (d, J = 2.8 Hz, 1H), 8.15 – 8.10 (m, 1H), 7.96 – 7.90 (m, 1H), 7.76 (s, 4H), 7.40 (s, 1H), 4.81 – 4.73 (m, 1H), 3.85 – 3.76 (m, 2H), 3.26 – 3.16 (m, 2H), 1.91 – 1.82 (m, 1H), 1.76 – 1.67 (m, 2H), 1.64 – 1.55 (m, 2H), 1.26 – 1.17 (m, 2H), 1.07 (s, 9H).
I-200	514.6[M+H] ⁺	^1H NMR (400 MHz, DMSO) δ 10.64 (s, 1H), 8.88 (d, J =7.9 Hz, 1H), 8.32 (s, 1H), 7.94 – 7.86 (m, 2H), 7.80 (d, J =8.9 Hz, 2H), 7.73 (d, J =8.9 Hz, 2H), 7.41 (d, J = 7.2 Hz, 2H), 7.33 – 7.24 (m, 4H), 7.18 (t, J =7.3 Hz, 1H), 4.88 – 4.80 (m, 1H), 4.24 (s, 1H), 4.12 (s, 1H), 3.21 – 2.98 (m, 2H), 0.76 – 0.52 (m, 4H).
I-201	553.0[M+H] ⁺	^1H NMR (400 MHz, DMSO) δ 10.64 (s, 1H), 8.75 (d, J = 8.2 Hz, 1H), 8.68 (d, J = 2.8 Hz, 1H), 8.33 (s, 1H), 8.08 – 8.04 (m, 1H), 7.92 – 7.89 (m, 1H), 7.79 (s, 4H), 7.37 – 7.13 (m, 5H), 5.02 – 4.85 (m, 1H), 3.24 – 3.13 (m, 2H), 1.26 (s, 6H).
I-86	534.5	^1H NMR (400 MHz, DMSO) δ 10.46 (s, 1H), 8.71 (d, J = 7.6 Hz, 1H), 8.06 – 7.95 (m, 2H), 7.64 (d, J = 8.6 Hz, 1H), 7.55 (d, J = 1.9 Hz, 1H), 7.46 (d, J = 9.3 Hz, 1H), 7.36 – 7.26 (m, 3H), 4.71 – 4.63 (m, 1H), 3.90 – 3.80 (m, 5H), 3.58 – 3.47 (m, 1H), 3.30 – 3.18 (m, 2H), 1.88 – 1.76 (m, 5H), 1.72 – 1.57 (m, 4H), 1.49 – 1.36 (m, 2H), 1.28 – 1.20 (m, 2H).
I-87	548.5	^1H NMR (400 MHz, DMSO) δ 10.47 (s, 1H), 8.71 (d, J = 7.5 Hz, 1H), 8.05 – 7.95 (m, 2H), 7.66 (d, J = 8.6 Hz, 1H), 7.56 (d, J = 1.9 Hz, 1H), 7.37 – 7.25 (m, 3H), 7.09 (d, J = 7.6 Hz, 1H), 4.71 – 4.63 (m, 1H), 3.88 – 3.80 (m, 5H), 3.29 – 3.19 (m, 2H), 1.89 – 1.80 (m, 1H), 1.74 – 1.58 (m, 4H), 1.56 – 1.46 (m, 4H), 1.38 – 1.18 (m, 7H).
I-97	519.2	^1H NMR (400 MHz, DMSO) δ 10.75 (s, 1H), 8.91 (d, J =2.1 Hz, 1H), 8.78 (d, J =7.5 Hz, 1H), 8.29 (dd, J =8.6, 2.5 Hz, 1H), 8.05 – 7.96 (m, 2H), 7.92 (d, J =8.6 Hz, 1H), 7.75 (d, J =7.4 Hz, 1H), 7.39 –

		7.26 (m, 2H), 4.76 – 4.62 (m, 1H), 3.90 – 3.76 (m, 2H), 3.51 (dd, $J=13.7, 6.8$ Hz, 1H), 3.30 – 3.15 (m, 2H), 1.92 – 1.79 (m, 1H), 1.61 (dddd, $J= 15.9, 9.7, 7.5, 3.1$ Hz, 8H), 1.41 – 1.15 (m, 6H).
I-112	524.2	^1H NMR (400 MHz, DMSO) δ 10.55 (s, 1H), 8.76 (d, $J=7.6$ Hz, 1H), 8.01 (dd, $J=8.7, 5.6$ Hz, 2H), 7.79 (q, $J=9.1$ Hz, 4H), 7.67 (s, 1H), 7.32 (t, $J= 8.8$ Hz, 2H), 4.69 (dd, $J= 12.5, 5.4$ Hz, 1H), 4.23 (s, 1H), 4.11 (s, 1H), 3.90 – 3.74 (m, 2H), 3.27 – 3.14 (m, 2H), 1.93 – 1.79 (m, 1H), 1.71 – 1.56 (m, 4H), 1.25 (d, $J= 5.8$ Hz, 2H), 1.06 (d, $J= 1.5$ Hz, 6H).
I-129	500.7	^1H NMR (400 MHz, DMSO) δ 10.63 (s, 1H), 8.90 (d, $J= 7.9$ Hz, 1H), 7.97 – 7.86 (m, 2H), 7.84 – 7.72 (m, 4H), 7.42 (d, $J= 7.5$ Hz, 3H), 7.35 – 7.25 (m, 4H), 7.19 (t, $J= 7.3$ Hz, 1H), 4.84 (ddd, $J= 10.1, 7.9, 4.9$ Hz, 1H), 4.68 (t, $J= 5.6$ Hz, 1H), 3.27 (t, $J= 5.5$ Hz, 1H), 3.21 – 3.00 (m, 4H), 0.88 (d, $J= 6.2$ Hz, 3H).
I-130	500.6	^1H NMR (400 MHz, DMSO) δ 10.64 (s, 1H), 8.90 (d, $J= 7.9$ Hz, 1H), 7.95 – 7.86 (m, 2H), 7.85 – 7.71 (m, 4H), 7.42 (d, $J= 7.1$ Hz, 3H), 7.35 – 7.24 (m, 4H), 7.19 (t, $J= 7.3$ Hz, 1H), 4.84 (ddd, $J= 10.1, 7.9, 4.9$ Hz, 1H), 4.69 (t, $J= 5.6$ Hz, 1H), 3.31 – 3.23 (m, 1H), 3.20 – 3.02 (m, 4H), 0.87 (d, $J= 6.2$ Hz, 3H).
I-131	512.2	^1H NMR (400 MHz, DMSO) δ 10.64 (s, 1H), 8.90 (d, $J= 7.9$ Hz, 1H), 8.03 (s, 1H), 7.97 – 7.84 (m, 2H), 7.76 (dd, $J= 25.9, 8.9$ Hz, 4H), 7.42 (d, $J= 7.2$ Hz, 2H), 7.34 – 7.24 (m, 4H), 7.20 (d, $J=7.4$ Hz, 1H), 4.91 – 4.77 (m, 1H), 4.60 (t, $J=5.8$ Hz, 1H), 3.26 (d, $J=5.8$ Hz, 2H), 3.13 (qd, $J=13.7, 7.6$ Hz, 2H), 0.54 (q, $J=7.4$ Hz, 2H), 0.51 – 0.43 (m, 2H).
I-141	542.2	^1H NMR (400 MHz, DMSO) δ 10.58 (s, 1H), 8.85 (d, $J= 7.9$ Hz, 1H), 7.98 – 7.84 (m, 2H), 7.66 (d, $J= 8.6$ Hz, 1H), 7.58 – 7.49 (m, 2H), 7.44 – 7.38 (m, 2H), 7.32 – 7.27 (m, 5H), 7.22 – 7.16 (m, 1H), 4.86 – 4.80 (m, 1H), 4.49 (t, $J= 5.7$ Hz, 1H), 3.85 (s, 3H), 3.23 (d, $J= 5.7$ Hz, 2H), 3.19 – 3.09 (m, 2H), 0.54 – 0.47 (m, 4H).
I-150	513.4	^1H NMR (400 MHz, DMSO) δ 10.81 (s, 1H), 8.92 (d, $J= 7.7$ Hz, 1H), 8.84 (d, $J= 2.4$ Hz, 1H), 8.30– 8.25 (m, 1H), 8.22 (s, 1H), 7.95 – 7.89 (m, 3H), 7.43 – 7.37 (m, 2H), 7.33–7.26 (m, 4H), 7.21 – 7.16 (m, 1H), 4.88 – 4.81 (m, 1H), 4.56 (t, $J= 5.9$ Hz, 1H), 3.30 (d, $J= 5.9$ Hz, 2H), 3.22 – 3.08 (m, 2H), 0.59 – 0.47 (m, 4H).
I-151	501.2	^1H NMR (400 MHz, DMSO) δ 10.82 (s, 1H), 8.93 (d, $J= 7.8$ Hz, 1H), 8.86 (d, $J= 2.3$ Hz, 1H), 8.28 (dd, $J= 8.6, 2.5$ Hz, 1H), 7.97 – 7.83 (m, 3H), 7.59 (d, $J= 7.4$ Hz, 1H), 7.40 (d, $J= 7.1$ Hz, 2H), 7.34 – 7.26 (m, 4H), 7.19 (t, $J= 7.3$ Hz, 1H), 4.85 (ddd, $J= 10.1, 7.8, 5.0$ Hz, 1H), 4.65 (t, $J= 5.6$ Hz, 1H), 3.31 – 3.06 (m, 5H), 0.92 (d, $J= 6.5$ Hz, 3H).

I-177	507.6	¹ H NMR (400 MHz, DMSO) δ 10.52 (s, 1H), 8.73 (d, J = 8.5 Hz, 1H), 8.71 (d, J = 2.8 Hz, 1H), 8.15–8.10 (m, 1H), 7.96–7.90 (m, 1H), 7.76 (s, 4H), 7.40 (s, 1H), 4.81–4.73 (m, 1H), 3.85–3.76 (m, 2H), 3.26–3.16 (m, 2H), 1.91–1.82 (m, 1H), 1.76–1.67 (m, 2H), 1.64–1.55 (m, 2H), 1.26–1.17 (m, 2H), 1.07 (s, 9H).
-------	-------	---

Example 16: Synthesis of Additional Compound

[00517] The compound in Table 12 below was prepared using procedures based on those described herein above.

Table 12.

Compound No.	Structure
I-293	

Example 17: Synthesis of Additional Compound

[00518] The compound in Table 13 below was prepared using procedures based on those described herein above.

Table 13.

Compound No.	Structure
I-294	

¹H NMR and mass spectrometry data for the above compound is provided in the following table:

MS	¹ H NMR
504.2[M+H] ⁺	¹ H NMR (400 MHz, DMSO) δ 10.47 (s, 1H), 8.70 (d, J = 4.0 Hz, 1H), 7.97–7.81 (m, 2H), 7.80–7.74 (m, 4H), 7.39 (s, 1H), 7.32 (t, J = 8.9 Hz, 2H), 4.68–4.63 (m, 1H), 1.79–1.60 (m, 8H), 1.16–1.12 (m, 3H), 1.10 (s, 9H), 1.08–0.82 (m, 2H).

Example A1. Dundee MALDI-TOF mass spectrometry assay (IC₅₀)

[00519] Compounds were tested in a MALDI-TOF assay based on the paper by Ritorto et al. (Ritorto et al. Screening of DUB activity and specificity by MALDI-TOF mass spectrometry. *Nat. Commun.* 5:4763).

[00520] USP30 (25ng/ μ l) tested against K48-linked diubiquitin (5.6 μ M). USP30 was diluted in a buffer containing 40mM Tris, 0.01% BSA, 1mM DTT and K48 in 40mM Tris, 0.01% BSA.

[00521] The compounds were pre-incubated with the USP30 for 5mins at room temp before the K48 dimer addition. The assay mixture was then incubated for 45mins at room temp. The assay was stopped by the addition of TFA to a final concentration of 2%(v/v).

[00522] Acidified samples of the DUB assays were mixed with 0.5 mM 15N-ubiquitin and then with one part of 2% (v/v) TFA and one part of 2,5 DHAP matrix solution (7.6 mg of 2,5 DHAP in 375 ml ethanol and 125 ml of an aqueous 12 mg/ml 1 diammonium hydrogen citrate). Then 250 nl of these solutions were spotted onto an MTP AnchorChip 1,536 TF and this is analysed on the Bruker rapifleX MALDI-TOF.

[00523] Compounds I-1, I-65, I-66, I-67, I-68, I-69 and I-70 were tested, and all these compounds demonstrated an IC₅₀ of less than 0.05 μ M. Additionally, the compounds in the following table were tested, where ** indicates an IC₅₀ of less than 0.05 μ M, and * indicates an IC₅₀ in the range of 0.05 μ M to 1 μ M.

Compound No.	USP30 IC ₅₀ μ M (avg)
I-71	**
I-72	*
I-78	**
I-82	**
I-84	**

Compound No.	USP30 IC ₅₀ μ M (avg)
I-85	*
I-86	**
I-87	**
I-91	**
I-93	*
I-97	**
I-99	*
I-101	**
I-103	*
I-105	*
I-106	*
I-107	*
I-109	**
I-110	*
I-112	**
I-115	**
I-117	**
I-121	**
I-122	**
I-125	*
I-128	**
I-129	**
I-130	**
I-131	**
I-132	**
I-133	**
I-136	**
I-137	**
I-138	**
I-141	**
I-143	*
I-145	**
I-148	*
I-149	**
I-150	**
I-151	**
I-155	**
I-156	**
I-157	*

Compound No.	USP30 IC ₅₀ μ M (avg)
I-158	**
I-159	*
I-160	**
I-161	**
I-163	**
I-164	**
I-165	**
I-167	*
I-168	**
I-171	**
I-172	**
I-173	**
I-174	*
I-175	**
I-177	**
I-182	**
I-185	**
I-186	*
I-196	**
I-199	*
I-200	**
I-201	**
I-202	**
I-205	*
I-208	*
I-209	*
I-227	*
I-266	*
I-269	*
I-272	*
I-273	*
I-293	**
I-293	**

Example A2. In vitro USP30 biochemical assay.

[00524] *In vitro* biochemical assay to establish the potency of compounds for USP30 inhibition: a 384-well plate assay using a fluorophore tagged substrate of USP30 was used for *in vitro* screening of compounds. Each compound was tested at

[00525] 10 different concentrations (0.5 to 10,000 nM) in duplicate wells. Compounds were pre-incubated at 25 °C for 30 min in an assay buffer consisting of 20 mM Tris/HCl, pH8.0, 1 mM GSH, 0.01% Triton X-100, 0.03% BGG and 1.5 nM recombinant USP30 (amino acids 57-517 of the human sequence with a C-terminal 6-His tag). Following the pre-incubation, Ubiquitin-Rhodamine substrate dissolved in the assay buffer was added at the final concentration of 25 nM to each well and plates were incubated at 25 °C for an additional 75 minutes. The reaction was stopped by adding 10 mM citric acid and fluorescence was read using excitation wavelength 485 nm, emission of 535 nm. Data were analyzed using Graph Pad Prism software with a four-parameter (floating slope) fit to log concentration data to determine IC₅₀s.

[00526] Tables A2 and A3 present IC₅₀ values for the USP30 biochemical assay.

[00527] Tables A2 and A3 show the activity of selected compounds of this invention in the USP30 biochemical assay. The compound numbers correspond to the compound numbers in Table 1. Compounds having an activity designated as "A" provided an IC₅₀ ≤ 0.05 μM; compounds having an activity designated as "B" provided an IC₅₀ of >0.05-1.0 μM; compounds having an activity designated as "C" provided an IC₅₀ of 1.0 to 10.0 μM; and compounds having an activity designated as "D" provided an IC₅₀ ≥ 10.0 μM.

Table A2. IC₅₀ results.

Cmpd No.	USP30 IC ₅₀ μM (avg)	Cmpd No.	USP30 IC ₅₀ μM (avg)
I-1	A	I-17	B
I-2	A	I-18	B
I-3	B	I-19	C
I-4	A	I-20	B
I-5	B	I-21	D
I-6	A	I-22	B
I-7	B	I-23	A
I-8	A	I-24	B
I-9	B	I-25	B
I-10	C	I-26	B
I-11	A	I-27	C
I-12	D	I-28	C
I-13	B	I-29	C
I-14	B	I-30	C
I-15	B	I-31	C
I-16	A	I-32	C

Cmpd No.	USP30 IC ₅₀ μ M (avg)
I-33	C
I-34	C
I-35	C
I-36	D
I-37	D
I-38	B
I-39	D
I-40	B
I-41	B
I-42	B
I-43	B
I-44	B
I-45	B
I-46	B
I-47	B
I-48	C
I-49	B
I-50	C
I-51	D

Cmpd No.	USP30 IC ₅₀ μ M (avg)
I-52	C
I-53	C
I-54	C
I-55	C
I-56	C
I-57	C
I-58	C
I-59	B
I-60	B
I-61	B
I-62	C
I-63	A
I-64	B
I-65	B
I-66	B
I-67	B
I-68	B
I-69	B
I-70	A

[00528] Table A3. IC₅₀ results.

Compound No.	USP30 IC ₅₀ μ M (avg)
I-71	B
I-72	B
I-73	C
I-74	B
I-75	B
I-76	B
I-77	C
I-78	B
I-80	B
I-81	B
I-82	B
I-83	C
I-84	B
I-85	B
I-86	A

Compound No.	USP30 IC ₅₀ μ M (avg)
I-87	A
I-88	B
I-89	D
I-90	D
I-91	B
I-92	C
I-93	B
I-95	B
I-96	B
I-97	A
I-98	C
I-99	B
I-100	C
I-101	A
I-103	B
I-104	C
I-105	B
I-106	B
I-107	B
I-108	B
I-109	B
I-110	B
I-111	C
I-112	A
I-113	D
I-114	D
I-115	A
I-116	A
I-117	A
I-118	D
I-119	D
I-120	B
I-121	A
I-122	B
I-123	C
I-124	D
I-125	B
I-126	A
I-127	B

Compound No.	USP30 IC ₅₀ μ M (avg)
I-128	B
I-129	B
I-130	A
I-131	A
I-132	B
I-133	B
I-134	B
I-135	B
I-136	B
I-137	B
I-138	B
I-139	C
I-140	B
I-141	B
I-142	C
I-143	B
I-144	B
I-145	A
I-146	D
I-147	D
I-148	B
I-149	B
I-150	B
I-151	B
I-152	D
I-153	D
I-154	D
I-155	B
I-156	A
I-157	B
I-158	B
I-159	B
I-160	A
I-161	A
I-162	D
I-163	A
I-164	B
I-165	A
I-167	B

Compound No.	USP30 IC ₅₀ μ M (avg)
I-168	B
I-169	D
I-170	D
I-171	A
I-172	B
I-173	A
I-174	B
I-175	A
I-176	D
I-177	A
I-178	C
I-179	C
I-180	C
I-181	D
I-182	A
I-183	B
I-184	C
I-185	A
I-186	B
I-187	D
I-188	B
I-189	B
I-190	C
I-191	D
I-192	C
I-194	C
I-195	B
I-196	A
I-197	B
I-198	D
I-199	B
I-200	B
I-201	B
I-202	A
I-203	B
I-204	B
I-205	B
I-206	B
I-207	B

Compound No.	USP30 IC ₅₀ μ M (avg)
I-208	B
I-209	B
I-210	B
I-211	D
I-212	B
I-213	B
I-214	B
I-215	C
I-216	C
I-217	C
I-218	D
I-219	D
I-220	D
I-221	B
I-222	B
I-223	B
I-224	B
I-225	B
I-226	B
I-227	B
I-228	B
I-229	C
I-230	B
I-231	B
I-232	C
I-233	B
I-234	C
I-235	C
I-236	B
I-237	B
I-238	A
I-239	B
I-240	B
I-241	B
I-242	B
I-243	B
I-244	D
I-245	D
I-246	D

Compound No.	USP30 IC ₅₀ μ M (avg)
I-247	C
I-248	D
I-249	A
I-250	A
I-251	A
I-252	D
I-253	B
I-254	C
I-255	C
I-256	D
I-257	B
I-258	C
I-259	B
I-260	B
I-261	C
I-262	C
I-263	C
I-264	D
I-265	B
I-266	B
I-267	C
I-268	D
I-269	B
I-270	C
I-271	C
I-272	B
I-273	B
I-275	D
I-276	D
I-277	B
I-278	D
I-279	C
I-280	D
I-281	D
I-282	D
I-283	B
I-284	D
I-285	C
I-286	C

Compound No.	USP30 IC ₅₀ μ M (avg)
I-287	A
I-288	D
I-289	D
I-290	C
I-291	D
I-292	B
I-293	A
I-294	A

Example A3. In-cell Tom20 loss assay.

[00529] To evaluate Tom20 loss following treatment with compounds and/or antimycin/oligomycin, a 96-well plate assay was performed on differentiated RenCell VM. These were seeded into laminin-coated 96-well plates at 5000 cells/well in normal growth medium (ReNcell NSC maintenance medium + 20 ng/ml FDF-2 and 20 ng/ml EGF). After 3 days, growth medium was replaced with differentiation medium (ReNCell NSC medium + 0.1 mM dibutyryl cAMP and 2ng/ml GDNF). On days 1 and 4 following addition of differentiation medium, the media was removed and replaced with fresh differentiation medium. On the 7th day compounds or DMSO were added, and 1 hour later, some wells also received additions of oligomycin (1 μ M and antimycin (1 μ M). 20 h after compound addition, cells were fixed by adding formaldehyde to a final concentration of 3.7%, incubated 20 minutes at room temperature, then washed with PBS. Blocking buffer (3% bovine serum albumin, 2% fetal bovine serum, 0.2% Triton X100 in PBS) was added to all wells for two hours, then removed and replaced with blocking buffer containing antibody against Tom20 overnight. After washing with PBS, secondary antibody (Donkey anti-mouse conjugated to Cy3) was added along with DAPI to mark nuclei, and incubated two hours. After again washing with PBS, cells were imaged using GE INCell 6000 at 40X and quantified using HCA-based quantification algorithm of fluorescence density x area normalized to the number of nuclei.

[00530] Compounds I-1 and I-11 were tested, and both compounds demonstrated an IC₅₀ of less than 0.5 μ M.

Example A4. Kinetic Solubility.

[00531] To 396 μ L of a 100 mM phosphate buffered saline (PBS) was added 4 μ L of a 10 mM stock solution of the compound. The mixture was shaken at 1000 rpm for 1 hour at room

temperature. The solution was filtered and the compound concentration in the resulting filtrate/supernatant was then determined by LC-MS/MS using an Agilent 1290 tandem with Sciex 5500 Qtrap with a ACQUITY-BEH-C18 (2.1*50 mm, 1.7 μ m). Compound concentration was calculated by comparison to a standard calibration curve. The assay was done in duplicate. The results are reported in μ Mol.

[00532] **Table A4** shows the solubility of selected compounds of this invention in the kinetic solubility assay. The compound numbers correspond to the compound numbers in **Table 1**. Compounds having an activity designated as “A” demonstrated a solubility of ≥ 75.0 μ Mol; compounds having an activity designated as “B” demonstrated a solubility of ≥ 50.0 μ Mol and < 75.0 μ Mol; compounds having an activity designated as “C” demonstrated a solubility ≥ 1.0 μ Mol and < 50.0 μ Mol; and compounds having an activity designated as "D" demonstrated a solubility of < 1.0 μ Mol.

Table A4. Kinetic Solubility Assay results.

Cmpd No.	Kinetic Solubility (μ Mol)
I-2	C
I-3	A
I-4	A
I-6	B
I-8	C
I-20	B
I-23	D
I-41	A
I-42	A
I-59	D
I-60	D
I-61	D
I-62	C
I-63	C
I-66	B

Cmpd No.	Kinetic Solubility (μMol)
I-67	B
I-70	D
I-294	C
I-78	A
I-86	B
I-87	C
I-97	B
I-109	A
I-112	B
I-129	C
I-130	C
I-131	D
I-141	C
I-150	D
I-151	C
I-175	A
I-177	A
I-185	D
I-200	C

Example A5. Metabolic Stability and Intrinsic Clearances in Liver Microsomes

[00533] Test compounds were incubated with microsomes supplemented with co-factors at 37°C. Typical conditions were: compound concentration of 1 μM and 5 sampling time-points (0, 15, 30, 45 and 60 minutes), in duplicates. At each time-point, the reactions were terminated by the addition of organic solvent. The samples were centrifuged and the parent compound concentration was evaluated by LC-MS/MS measurements.

[00534] **Table A5** shows the half-life of selected compounds of this invention as measured in the metabolic stability and intrinsic clearance in liver microsomes assay, reported for human, rat

and mouse microsomes. The compound numbers correspond to the compound numbers in **Table 1**. Compounds having an activity designated as “A” had a half-life ≥ 360 minutes; compounds having an activity designated as “B” had a half-life ≥ 120 minutes and < 360 minutes; compounds having an activity designated as “C” provided a half-life of ≥ 15 and < 120 minutes; and compounds having an activity designated as “D” provided half-life of < 15 minutes.

Table A5. Metabolic Stability and Intrinsic Clearances Assay results.

Cmpd No.	Half-life in human microsomes	Half-life in rat microsomes	Half-life in mouse microsomes
I-2	A	B	C
I-3	B	A	C
I-4	C	D	D
I-6	B	C	C
I-8	C	C	C
I-13	B	C	D
I-16	A	B	C
I-63	B	B	B
I-294	D	D	D
I-109	A	B	A
I-112	B	C	C
I-129	B	B	B
I-130	A	B	B
I-131	C	C	C
I-141	C	C	C
I-150	C	C	C
I-151	A	B	B
I-200	A	-	C

Example A6. Caco-2 Permeability Screening Assay

[00535] Caco-2 cells were used after a 21-day cell culture in 24-well Transwell plates. Test and reference compounds (Metoprolol, Enalapril and Erythromycin) were prepared in DMSO and added to either the apical or basolateral chambers of the transwell plate assembly at a concentration of 10 μ M. Lucifer Yellow was added to the donor buffer in all wells to assess integrity of the cell layers by monitoring Lucifer Yellow permeation. As Lucifer Yellow (LY) cannot freely permeate

lipophilic barriers, a high degree of LY transport indicates poor integrity of the cell layer. After 1.5 hrs incubation at 37°C, aliquots were taken from both apical (A) and basal (B) chambers and added to stop solution in a 96 well plate. Concentrations of compound in the samples were measured by LC-MS/MS. The Efflux ratios, as an indication of active efflux from the apical cell surface, were calculated using the ratio of Papp B>A/ Papp A>B.

[00536] **Table A6** shows the ratio of Papp B>A/ Papp A>B of selected compounds of this invention as measured in the Caco-2 permeability screening assay, reported in cm/s. The compound numbers correspond to the compound numbers in **Table 1**. Compounds having an efflux ratio >0 and ≤2 are designated as “A”; compounds having an efflux ratio >2 and ≤6 are designated as “B”; and compounds having an efflux ratio >6 are designated as “C”.

Table A6. Caco-2 Permeability Screening Assay results.

Cmpd No.	Papp(A-B) (10 ⁻⁶ , cm/sec)	Efflux Ratio
I-2	2.24	C
I-4	1.83	C
I-6	2.88	B
I-8	2.9	B
I-13	9.6	B
I-16	9.7	B
I-63	2.6	B
I-294	1.8	B
I-86	1.3	C
I-87	1.4	C
I-97	1.6	C
I-109	1.2	A
I-112	2.8	C
I-129	2.5	C
I-130	1.8	C
I-131	1.3	C
I-141	1.6	C

Cmpd No.	Papp(A-B) (10 ⁻⁶ , cm/sec)	Efflux Ratio
I-150	1.6	C
I-151	1.7	C
I-200	6.5	B
I-177	1.4	A
I-185	7.6	B
I-200	2.4	A

Example A7. Plasma Protein Binding Assay.

[00537] Plasma spiked with test compound was added to the donor chamber of a high throughput dialysis device (HTD). Blank, isotonic sodium phosphate buffer was added to the other chamber of the HTD device and the plate was incubated at 37° C. Aliquots of the buffer and the plasma were taken at pre-determined time points and the concentration of free and bound test compound was determined by LC/MS/MS analysis. Plasma stability was determined at the five hour timepoint and reported as the percentage of the parent compound remaining.

[00538] **Table A7** shows the percentage of compound bound to proteins in human plasma, for select compounds of the invention. Analogous measurements are also reported for rat and mouse plasma. The compound numbers correspond to the compound numbers in **Table 1**. Compounds having an activity designated as “A” demonstrated protein binding of <80%; compounds having an activity designated as “B” demonstrated protein binding of ≥80% and <95%; and compounds having an activity designated as “C” demonstrated protein binding of ≥95%.

Table A7. Plasma Protein Binding Assay results.

Cmpd No.	Human - % protein bound	Rat - % protein bound	Mouse- % protein bound
I-2	B	B	B
I-3	A	A	A
I-4	A	A	-
I-6	A	A	-
I-8	C	C	B
I-20	B	B	B
I-61	C	C	C
I-62	C	C	C

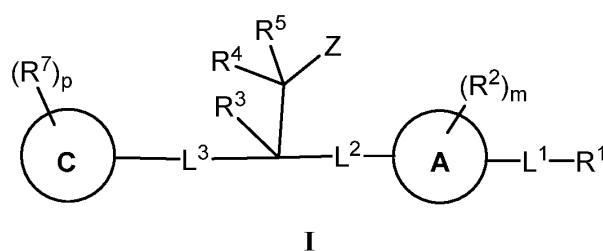
Cmpd No.	Human - % protein bound	Rat - % protein bound	Mouse- % protein bound
I-63	C	C	-
I-66	C	C	C
I-67	C	C	C
I-200	C	C	C
I-78	A	B	A
I-86	B	B	B
I-87	B	B	B
I-97	B	A	-
I-109	A	A	A
I-112	A	A	A
I-129	B	A	A
I-130	B	B	B
I-131	B	B	B
I-141	B	B	B
I-150	B	B	B
I-151	B	B	B
I-200	B	B	B
I-177	A	A	-
I-185	C	C	C
I-200	C	C	-

[00539] While a number of embodiments of this invention have been described herein, it is apparent that these basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

CLAIMS

We claim:

1. A compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

L^1 is a covalent bond or a C_{1-3} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-C(CF_3)H-$, $-N(R)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-C(O)N(R)-$, $-N(R)C(O)-$, $-S(O)-$, $-S(O)_2-$, $-S(O)N(R)-$, $-S(O)_2N(R)-$, or $-S(O)(R)=N-$;

each R is independently hydrogen or an optionally substituted C_{1-3} aliphatic group; or:

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur; or

an R group and R^1 on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;

R^1 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered

saturated or partially unsaturated bridged bicyclic carbocyclic ring, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^2 is independently halogen, $-CF_3$, $-CN$, $-C(O)NHR$, $-NO_2$, $-NHR$, $-NHC(O)R$, $-NHS(O)_2R$, $-N(R)_2$, or $-OR$, or an optionally substituted C_{1-6} aliphatic group; or

two R^2 on the same carbon are optionally taken together to form $=O$;

L^2 is selected from the group consisting of $-C(O)N(R')$ -, $-CH_2O$ -, $-CH_2N(R')$ -, $-C(OH)(H)CH_2N(R')$ -, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R' is hydrogen or a C_{1-3} aliphatic group;

L^3 is selected from the group consisting of $-C(O)N(R'')$ -, $-OC(O)N(R'')$ -, $-CH_2O$ -, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R'' is hydrogen or a C_{1-3} aliphatic group;

R^3 is hydrogen or C_{1-3} aliphatic; or:

R^3 and R^4 are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring; or

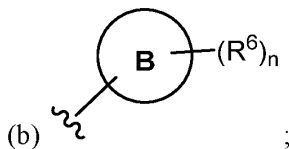
R^3 and R^5 are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring;

R^4 is hydrogen or C_{1-3} aliphatic;

R^5 is hydrogen or C_{1-3} aliphatic;

Z is:

(a) selected from an optionally substituted C_{1-6} aliphatic group, and $-OR$;



(c) taken together with R^4 and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 ;

(d) taken together with R⁵ and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R⁶; or

(e) taken together with R'' and their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the nitrogen of L³, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R⁶;

Ring B is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R⁶ is independently halogen, phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -CN, -NO₂, -NHR, -N(R)₂, -OR, -C(O)R, -C(O)OR, or an optionally substituted C₁₋₆ aliphatic group; or:

two R⁶ on the same carbon are optionally taken together to form =O;

an R⁶ group and R' group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur;

an R⁶ group and R³ group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated spiro-fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen or sulfur; or

an R⁶ group and R'' group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur;

Ring C is phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms

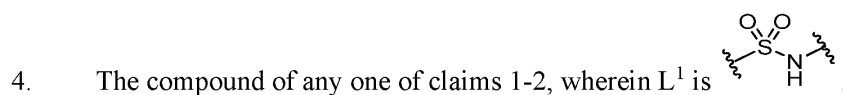
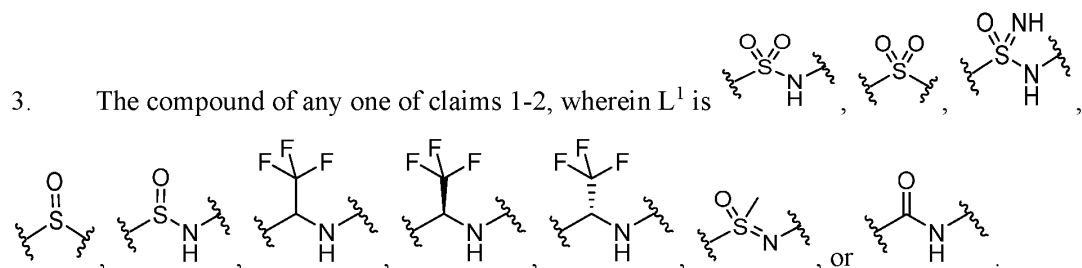
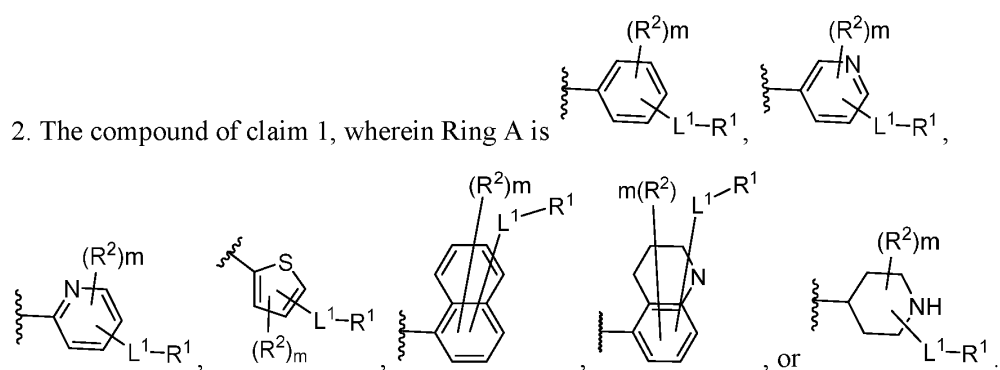
independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^7 is independently halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{NHR}$, $-\text{N(R)}_2$, $-\text{OR}$, or an optionally substituted C_{1-6} aliphatic group; or

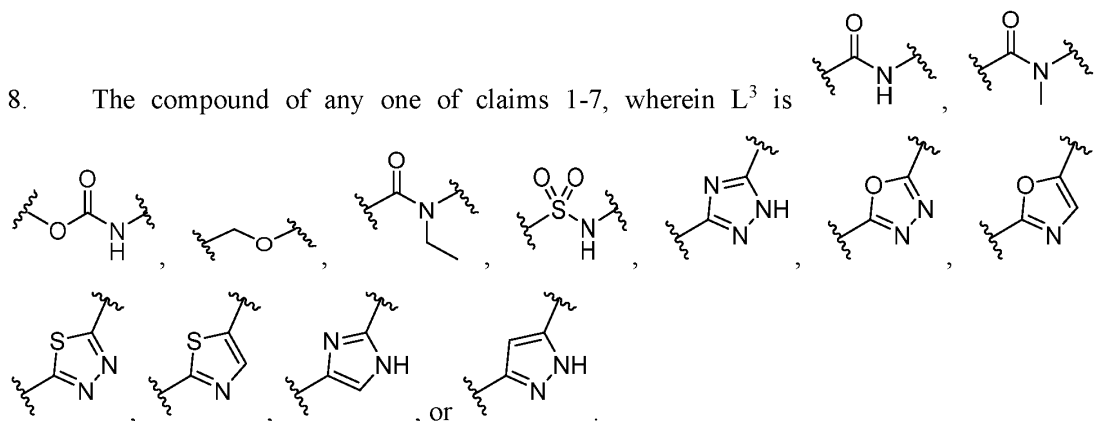
two R^7 on the same carbon are optionally taken together to form $=\text{O}$;

each of m , n , and p is independently 0, 1, 2, 3 or 4; and

the compound is other than one depicted in **Table 1-X**.



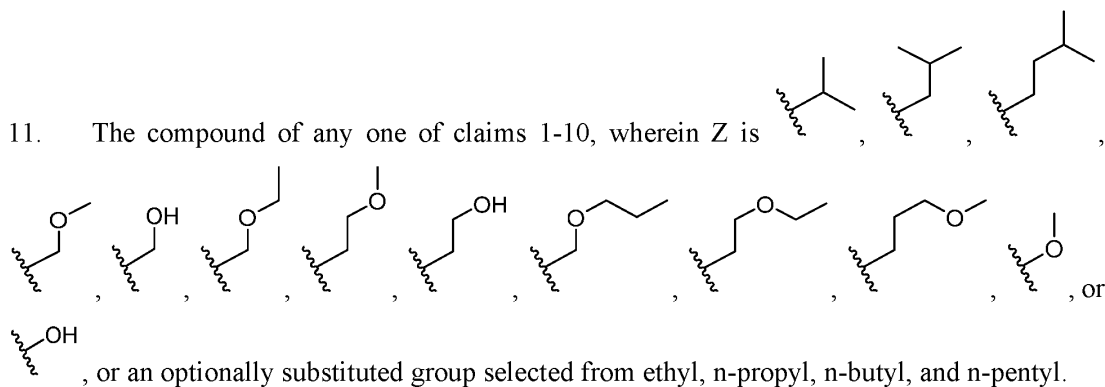
8. The compound of any one of claims 1-7, wherein L^3 is



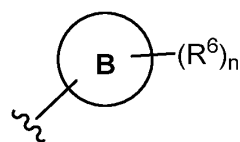
9. The compound of any one of claims 1-8, wherein at least one of L^2 and L^3 is a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

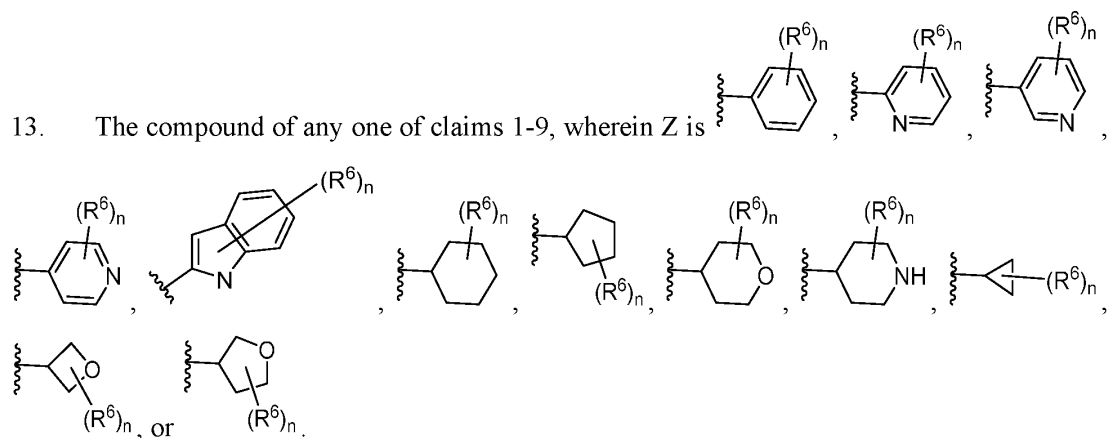
10. The compound of any one of claims 1-9, wherein Z is selected from an optionally substituted C_{1-6} aliphatic group, and $-OR$.

11. The compound of any one of claims 1-10, wherein Z is



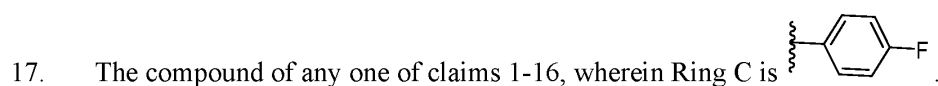
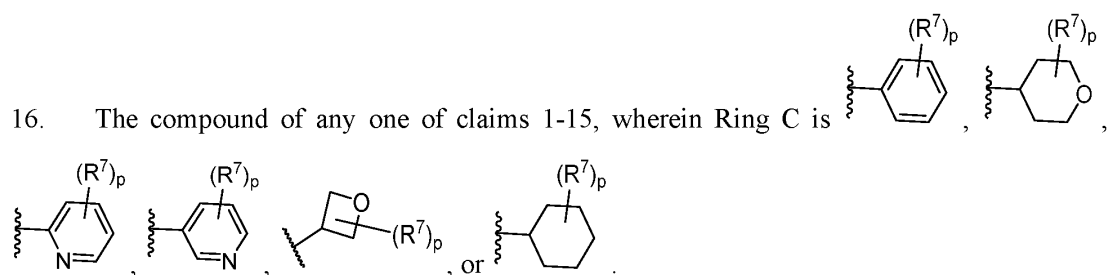
12. The compound of any one of claims 1-9, wherein Z is



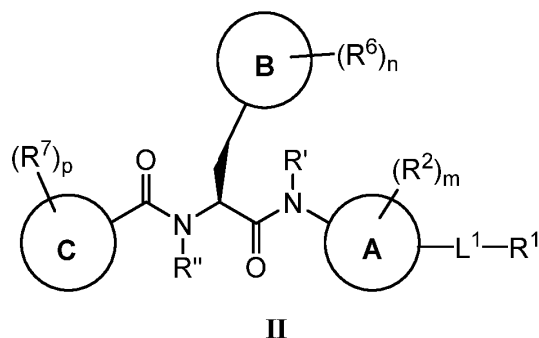


14. The compound of any one of claims 1-9, wherein Z is taken together with R^4 and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 ; or Z is taken together with R^5 and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 .

15. The compound of any one of claims 1-9, wherein Z is taken together with R'' and their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the nitrogen of L^3 , independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of R^6 .

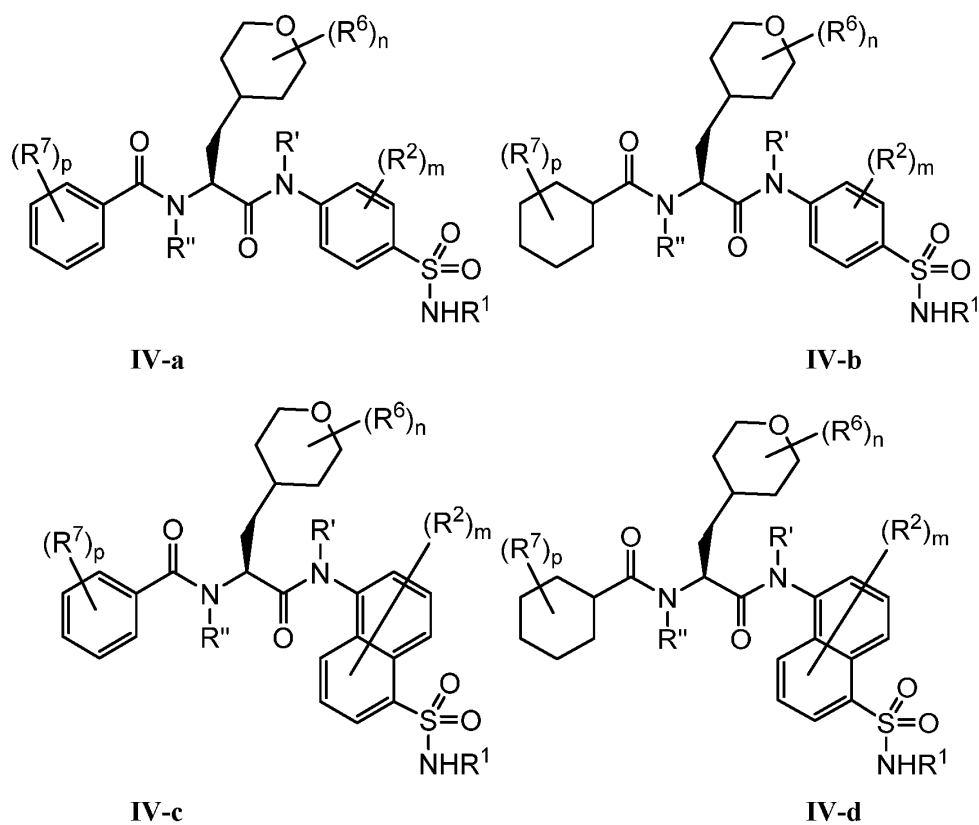


18. The compound of claim 1, of formula **II**:



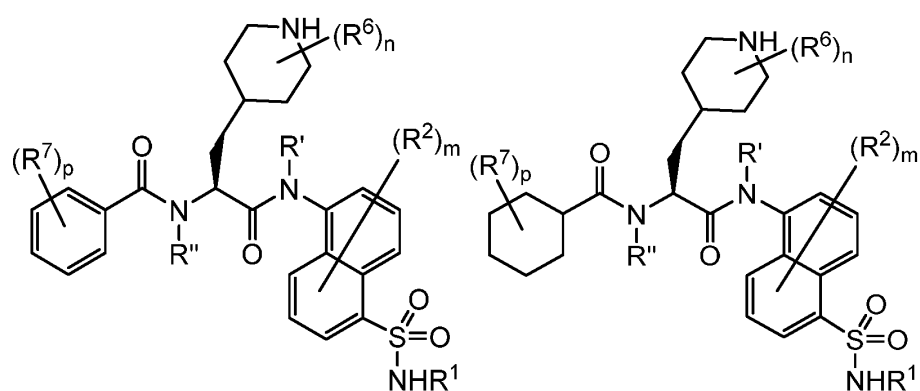
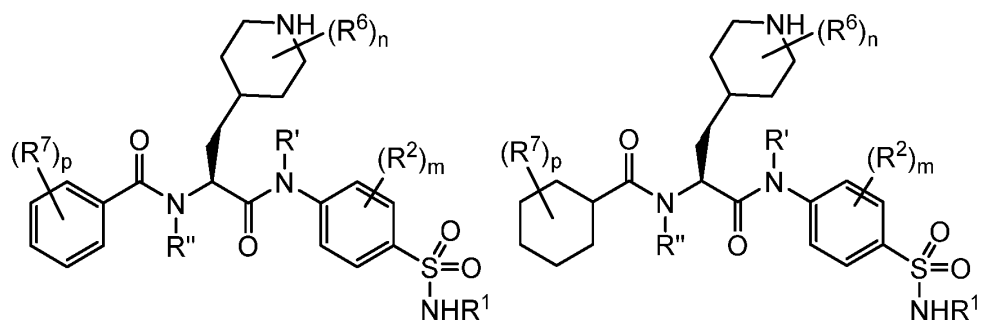
or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1, of formulae **IV-a**, **IV-b**, **IV-c**, or **IV-d**:



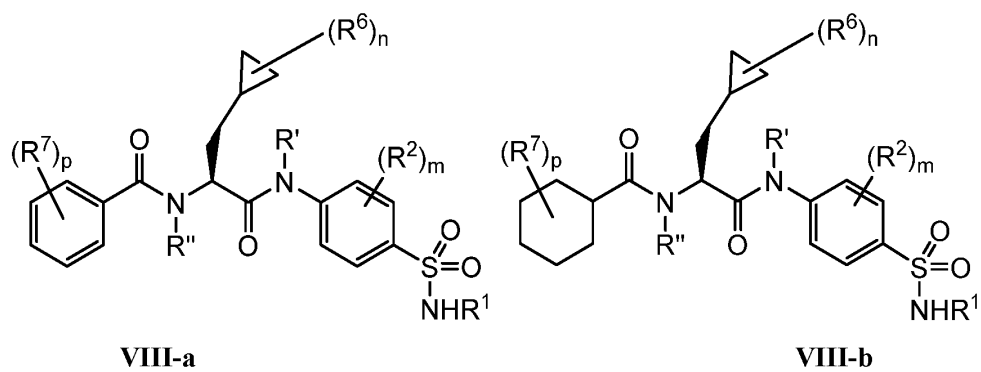
or a pharmaceutically acceptable salt thereof.

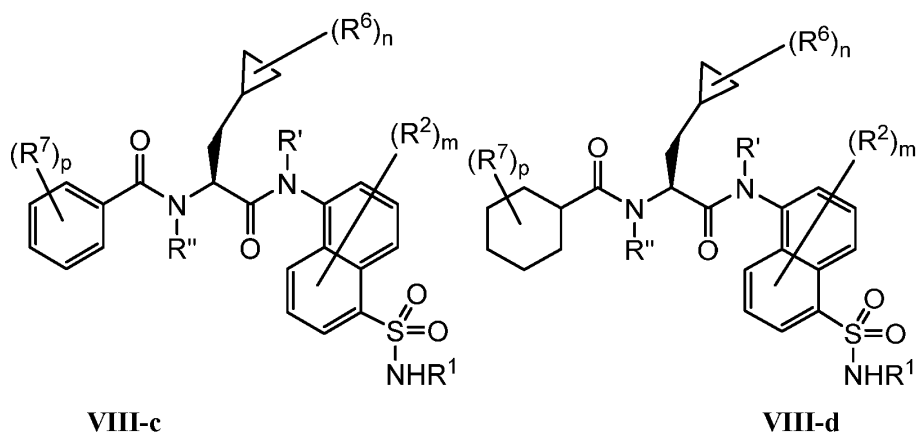
20. The compound of claim 1, of formulae **VI-a**, **VI-b**, **VI-c**, or **VI-d**:



or a pharmaceutically acceptable salt thereof.

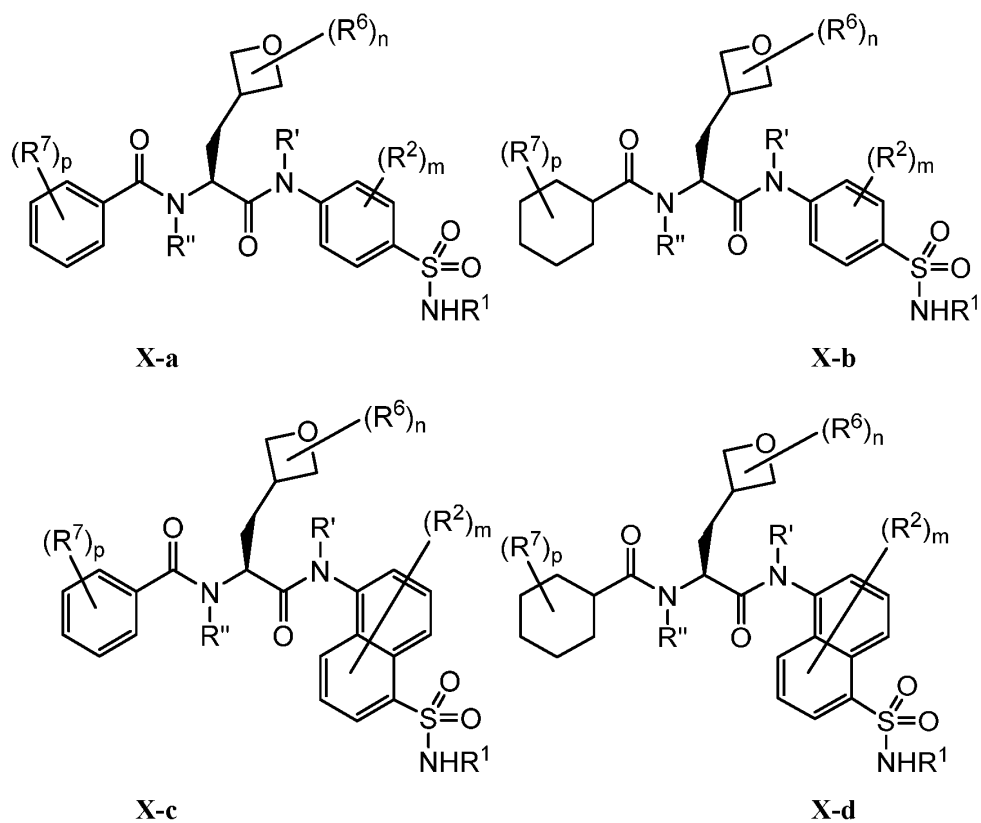
21. The compound of claim 1, of formulae **VIII-a**, **VIII-b**, **VIII-c**, or **VIII-d**:





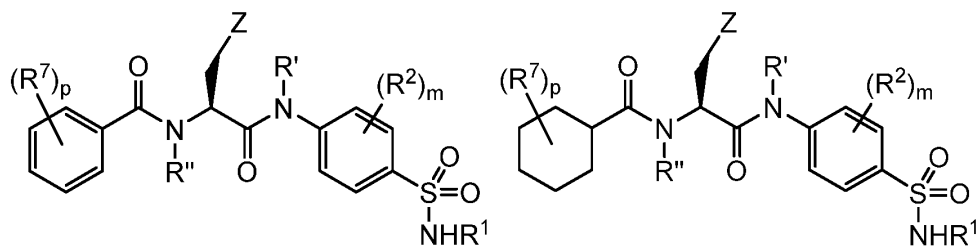
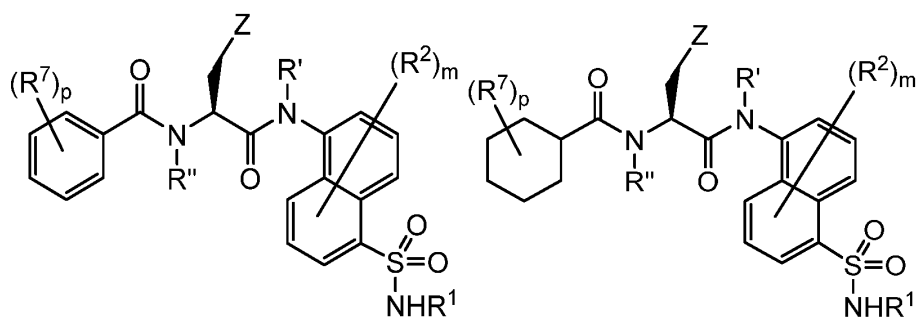
or a pharmaceutically acceptable salt thereof.

22. The compound of claim 1, of formulae **X-a**, **X-b**, **X-c**, or **X-d**:



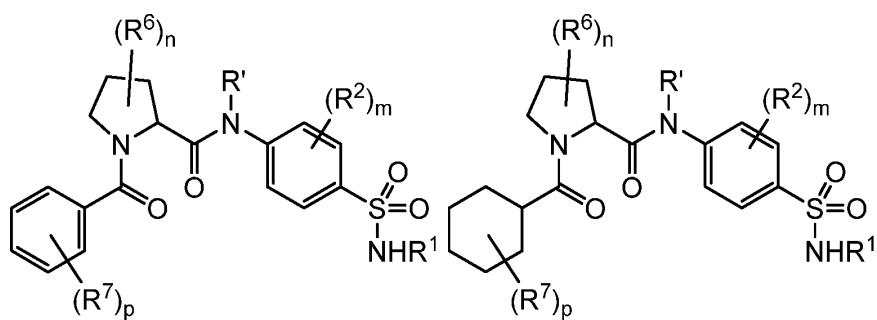
or a pharmaceutically acceptable salt thereof.

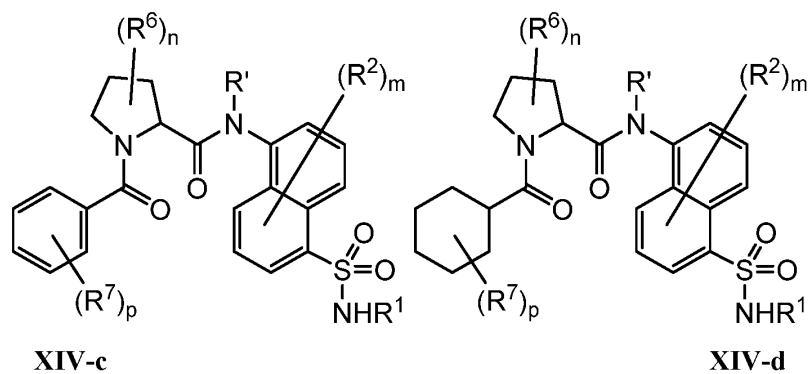
23. The compound of claim 1, of formulae **XII-a**, **XII-b**, **XII-c**, or **XII-d**:

**XII-a****XII-b****XII-c****XII-d**

or a pharmaceutically acceptable salt thereof.

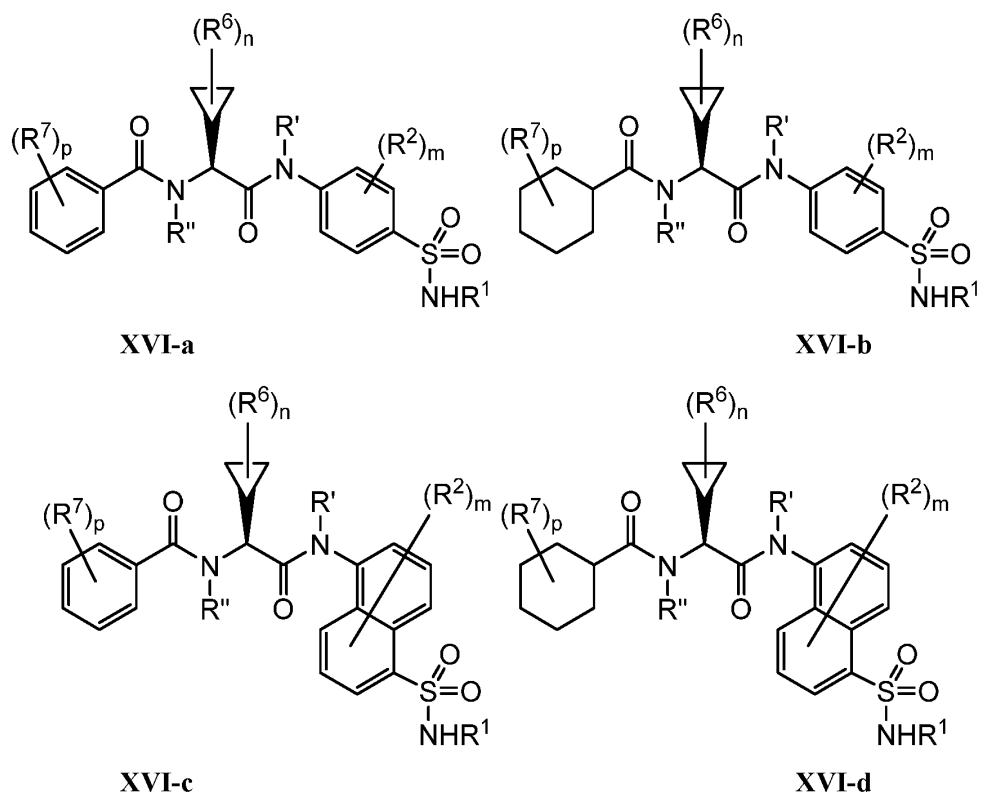
24. The compound of claim 1, of formulae **XIV-a**, **XIV-b**, **XIV-c**, or **XIV-d**:

**XIV-a****XIV-b**



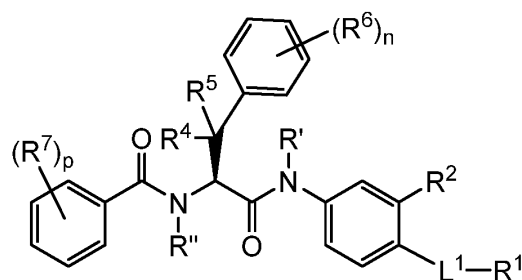
or a pharmaceutically acceptable salt thereof.

25. The compound of claim 1, of formulae **XVI-a**, **XVI-b**, **XVI-c**, and **XVI-d** respectively:



or a pharmaceutically acceptable salt thereof.

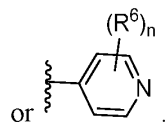
26. The compound of claim 1, of formula **XVII**:



XVII

or a pharmaceutically acceptable salt thereof.

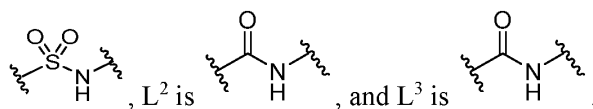
27. The compound of any one of claims 1-4, wherein Z is , , ,



28. The compound of any one of claims 1-4, wherein Z is or .

29. The compound of any one of claims 1-4, wherein Z is or .

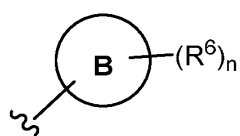
30. The compound of any one of claims 27-29, wherein Ring C is , L¹ is



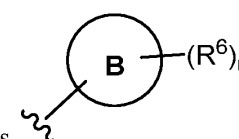
31. The compound of any one of claims 1-4 or 18-30, wherein R¹ is
- ,
32. The compound of any one of claims 1-4 or 18-30, wherein R¹ is
- ,
33. The compound of any one of claims 1-4 or 18-30, wherein R¹ is
- ,
34. The compound of claim 1, wherein Ring A is phenyl; L¹ is -S(O)₂N(H)-; R is a C₁ aliphatic group; R¹ is C₄ aliphatic or a 4-membered saturated heterocyclic ring having 1 oxygen atom; R² is -OR; L² is -C(O)N(H)-; L³ is -C(O)N(H)-; R³ is hydrogen; R⁴ is hydrogen; R⁵ is
-
- hydrogen; Z is ; Ring B is a 6-membered saturated heterocyclic ring having 1 oxygen atom; Ring C is phenyl; R⁷ is halogen; m is 1; p is 1; and n is 0.
35. The compound of claim 1, wherein Ring A is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; L¹ is -S(O)₂N(H)-; R¹ is C₄ aliphatic; L² is -C(O)N(H)-; L³ is -

C(O)N(H)-; R³ is hydrogen; R⁴ is hydrogen; R⁵ is hydrogen; Z is a C₃ aliphatic group; Ring C is phenyl; R⁷ is halogen; m is 0; and p is 1.

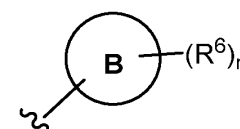
36. The compound of claim 1, wherein Ring A is phenyl; L¹ is -S(O)₂N(H)-; R is a C₁ aliphatic group; R¹ is an optionally substituted 3-membered saturated monocyclic carbocyclic ring; R² is -OR; L² is -C(O)N(H)-; L³ is -C(O)N(H)-; R³ is hydrogen; R⁴ is hydrogen; R⁵ is

hydrogen; Z is ; Ring B is phenyl; Ring C is phenyl; R⁷ is halogen; m is 0 or 1; p is 1; and n is 0.

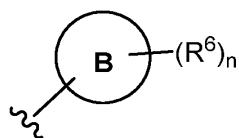
37. The compound of claim 1, wherein Ring A is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; L¹ is -S(O)₂N(H)-; R is a C₁ aliphatic group; R¹ is a C₄ aliphatic or 4-membered heterocyclic ring with 1 oxygen atom; R² is -OR; L² is -C(O)N(H)-; L³ is -C(O)N(H)-

; R³ is hydrogen; R⁴ is hydrogen; R⁵ is hydrogen; Z is ; Ring B is a 6-membered saturated heterocyclic ring having 1 nitrogen atom; R⁶ is a C₁ aliphatic group; Ring C is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; R⁷ is halogen; m is 0 or 1; p is 1; and n is 0 or 1.

38. The compound of claim 1, wherein Ring A is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; L¹ is -S(O)₂N(H)-; R is a C₁ aliphatic group; R¹ is an optionally substituted group selected from 3-membered saturated monocyclic carbocyclic ring or C₃₋₄ aliphatic; R² is -OR; L² is -C(O)N(H)-; L³ is -C(O)N(H)-; R³ is hydrogen; R⁴ is hydrogen; R⁵

is hydrogen; Z is ; Ring B is phenyl; Ring C is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; R⁷ is halogen; m is 0 or 1; p is 1; and n is 0.

39. The compound of claim 1, wherein Ring A is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; L^1 is $-S(O)_2N(H)-$; R is a C_1 aliphatic group; R^1 is an optionally substituted C_4 aliphatic or a 4-5 membered saturated monocyclic carbocyclic ring; R^2 is $-OR$; L^2 is $-C(O)N(H)-$; L^3 is $-C(O)N(H)-$; R^3 is hydrogen; R^4 is hydrogen; R^5 is hydrogen; Z is



; Ring B is a 6-membered saturated heterocyclic ring having 1 oxygen atom; Ring C is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; R^7 is halogen; m is 0 or 1; p is 1; and n is 0.

40. The compound of claim 1, wherein said compound is selected from those depicted in **Table 1** of the specification, or a pharmaceutically acceptable salt thereof.

41. The compound of claim 1, wherein said compound is selected from those depicted in **Table 11** of the specification, or a pharmaceutically acceptable salt thereof.

42. A compound depicted in **Table 12** of the specification, or a pharmaceutically acceptable salt thereof.

43. A pharmaceutical composition comprising a compound according to any one of claims 1-42, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

44. A method of inhibiting USP30 in a biological sample comprising contacting the sample with the compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof.

45. A method of treating an USP30-mediated disorder, disease, or condition in a patient comprising administering to said patient the pharmaceutical composition of claim 43.

46. The method of claim 45, wherein the disorder, disease, or condition is selected from the group consisting of a neurodegenerative disease; mitochondrial myopathy, encephalopathy,

lactic acidosis, and stroke-like episodes (MELAS) syndrome; Leber's hereditary optic neuropathy (LHON); neuropathy, ataxia, retinitis pigmentosa- maternally inherited Leigh syndrome (NARP-MILS); Danon disease; ischemic heart disease leading to myocardial infarction; multiple sulfatase deficiency (MSD); mucopolipidosis II (ML II); mucopolipidosis III (ML III); mucopolipidosis IV (ML IV); GM1 -gangliosidosis (GM1); neuronal ceroid- lipofuscinoses (NCL1); Alpers disease; Barth syndrome; Beta-oxidation defects; carnitine- acyl-carnitine deficiency; carnitine deficiency; creatine deficiency syndromes; coenzyme Q10 deficiency; complex I deficiency; complex II deficiency; complex III deficiency; complex IV deficiency; complex V deficiency; COX deficiency; chronic progressive external ophthalmoplegia syndrome (CPEO); CPT I deficiency; CPT II deficiency; glutaric aciduria type II; Kearns-Sayre syndrome; lactic acidosis; long-chain acyl-CoA dehydrogenase deficiency (LCHAD); Leigh disease or syndrome; lethal infantile cardiomyopathy (LIC); Luft disease; glutaric aciduria type II; medium-chain acyl-CoA dehydrogenase deficiency (MCAD); myoclonic epilepsy and ragged-red fiber (MERRF) syndrome; mitochondrial recessive ataxia syndrome; mitochondrial cytopathy; mitochondrial DNA depletion syndrome; myoneurogastrointestinal disorder and encephalopathy; Pearson syndrome; pyruvate carboxylase deficiency; pyruvate dehydrogenase deficiency; POLG mutations; medium/short-chain 3-hydroxyacyl-CoA dehydrogenase (M/SCHAD) deficiency; and very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency.

47. The method of claim 45, wherein the disorder, disease, or condition is a neurodegenerative disease selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, ischemia, stroke, dementia with Lewy bodies, and frontotemporal dementia.

48. The method of claim 47, wherein the neurodegenerative disease is Alzheimer's disease or Parkinson's disease.

49. The method of claim 45, wherein the disorder, disease, or condition is a neoplastic disease selected from the group consisting of metastatic carcinoma, multiple myeloma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, nasopharyngeal carcinoma, and leukemia.

50. The method of claim 45, wherein the disorder, disease, or condition is cardiovascular disease, kidney disease, pulmonary fibrosis, ophthalmic conditions, cancer, cognitive disease, peroxisome related disease, natural aging, or an age-related disease.

51. The method of claim 45, wherein the disorder, disease, or condition is a peroxisome related disease selected from the group consisting of Ataxia-telangiectasia mutated, Heimler syndrome, Infantile refsum disease, Neonatal adrenoleukodystrophy, Rhizomelic chondrodysplasia punctate, White matter dementia, Zellweger syndrome, and Zellweger spectrum disorder.