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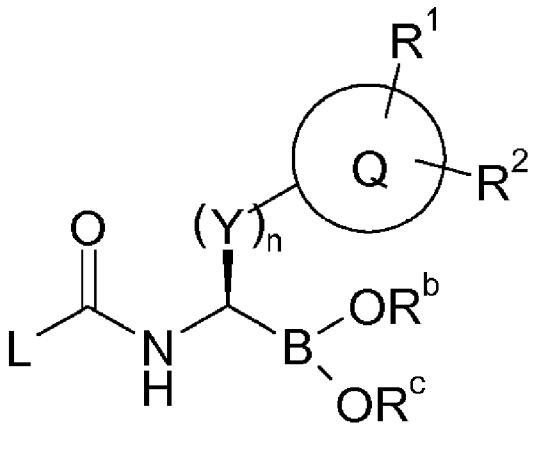
(54) Title: ALPHA-AMINO BORONIC ACID DERIVATIVES, SELECTIVE IMMUNOPROTEASOME INHIBITORS



(I)

(57) Abstract: The present invention provides compounds of Formula (I) as inhibitors of LMP7 for the treatment of autoimmune and inflammatory diseases. In formula (I), R^b and R^c are independently selected from one another from H or C_1-C_6-alkyl; whereby R^b and R^c may be linked to form a 5 or 6 membered-ring containing the oxygen atoms to which they are linked; Q denotes Ar, Het or cycloalkyl; R^1 R^2 independently from each other denotes H, OR^a, Hal, C_1-C_6-alkyl wherein 1 to 5 H atoms may be independently replaced by OH or Hal; Y denotes CR $^3R^4$, preferably CH_2 or $C(CH_3)_2$; R ^{3}, R^4 independently of one another denote H or C_1-C_6-alkyl; L denotes L_1 or L_2 or alkyl; n is an integer selected from 0 to 3; L $_1$ is Q_1-CO-M- wherein Q $_1$ is Ar or Het, preferably, phenyl, naphthyl or pyridine, optionally substituted with 1 to 5 groups independently selected from OR^a, Hal, phenyl, and C_1-C_6-alkyl wherein 1 to 5 H atoms may be independently replaced by OH or Hal; L_2 is Q_2-M- wherein Q $_2$ is a fused bicyclic system containing 1 nitrogen atom and 1 to 3 additional groups independently selected from O, S, N, or CO, and wherein at least one of the rings is aromatic whereby the fused bicyclic system is optionally substituted with 1 to 5 groups independently selected from OR^a, Hal, phenyl, and C_1-C_6-alkyl wherein 1 to 5 H atoms may be independently replaced by OH or Hal; or Q $_2$ is unsaturated or aromatic 5 membered-ring system containing 1 to 3 heteroatoms selected from N, O, S and CO, and optionally substituted

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with a phenyl ring or pyridine ring whereby phenyl ring and pyridine ring are optionally substituted with 1 to 4 groups independently selected from OR^a, Hal, phenyl, and C_1-C_6-alkyl wherein 1 to 5 H atoms may be independently replaced by OH or Hal; M is a linear or branched alkylene having 1 to 5 carbon atoms wherein 1 or 2 H atoms may be replaced by OR a or a phenyl ring optionally substituted with 1 to 5 groups independently selected from Hal, OR^a, and C1-C6-alkyl optionally substituted with 1 to 5 groups independently selected from OH, and Hal; or M denotes a cycloalkylene having 3 to 7 carbon atoms; or M denotes a thiazolidinyl group; R^a is H or C_1-C_6-alkyl wherein 1 to 5 H atom may be independently replaced by OH or Hal; Ar denotes a 6 membered-aromatic carbocyclic ring optionally fused with another carbocyclic saturated, unsaturated or aromatic ring having 5 to 8 carbon atoms; Het denotes a 5- or 6-membered saturated, unsaturated or aromatic heterocyclic ring having 1 to 3 heteroatoms independently selected from N, N+O-, O, S, SO, and SO_2, and optionally fused with another saturated, unsaturated or aromatic ring having 5 to 8 atoms and optionally containing 1 to 3 heteroatoms selected from N, O, and S; Hal denotes CI, Br, I of F; preferably CI or F.

ALPHA-AMINO BORONIC ACID DERIVATIVES, SELECTIVE IMMUNOPROTEASOME INHIBITORS

The present invention provides α-Amino boronic acid derivatives and their use in the treatment of inflammatory and autoimmune diseases, neurodegenerative diseases, and proliferative diseases. In particular, the compounds of the present invention are selective imunoproteasome inhibitors.

The proteasome (also known as macropain, the multicatalytic protease, and 20S protease) is a high molecular weight, multisubunit protease which has been identified in every examined species from an archaebacterium to human. The enzyme has a native molecular weight of approximately 650,000 and, as revealed by electron microscopy, a distinctive cylinder-shaped morphology (Rivett, (1989) Arch. Biochem. Biophys. 268:1-8; and Orlowski, (1990) Biochemistry 29:10289-10297). The proteasome subunits range in molecular weight from 20,000 to 35,000 (3-5), and are homologous to one another but not to any other known protease.

The 20S proteasome is a 700 kDa cylindrical-shaped multicatalytic protease complex comprised of 28 subunits, classified as a- and β-type, that are arranged in 4 stacked heptameric rings. In yeast and other eukaryotes, 7 different a subunits form the outer rings and 7 different β subunits comprise the inner rings. The a subunits serve as binding sites for the 19S (PA700) and 1 IS (PA28) regulatory complexes, as well as a physical barrier for the inner proteolytic chamber formed by the two β subunit rings. Thus, in vivo, the proteasome is believed to exist as a 26S particle ("the 26S proteasome"). In vivo experiments have shown that inhibition of the 20S form of the proteasome can be readily correlated to inhibition of 26S proteasome.

Cleavage of amino-terminal prosequences of β subunits during particle formation expose amino-terminal threonine residues, which serve as the catalytic nucleophiles. The subunits responsible for catalytic activity in proteasome thus possess an amino terminal nucleophilic residue, and these subunits belong to the family of N-terminal nucleophile (Ntn) ATTY REF: 26500-0023WO1 hydrolases (where the nucleophilic N-terminal residue is, for example, Cys, Ser, Thr, and other nucleophilic moieties). This family includes, for example, penicillin G acylase (PGA), penicillin V acylase (PVA), glutamine PRPP amidotransferase (GAT), and bacterial glycosylasparaginase. In addition to the ubiquitously expressed β subunits, higher vertebrates also possess three interferon- γ- inducible β subunits (LMP7, LMP2 and MECLI), which replace their normal counterparts, β5, β1 and β2, respectively. When all three IFN- γ- inducible subunits are

present, the proteasome is referred to as an "immunoproteasome". Thus, eukaryotic cells can possess two forms of proteasomes in varying ratios.

Through the use of different peptide substrates, three major proteolytic activities have been defined for the eukaryote 20S proteasomes: chymotrypsin-like activity (CT-L), which cleaves after large hydrophobic residues; trypsin-like activity (T-L), which cleaves after basic residues; and peptidylglutamyl peptide hydrolyzing activity (PGPH), which cleaves after acidic residues. Two additional less characterized activities have also been ascribed to the proteasome: BrAAP activity, which cleaves after branched-chain amino acids; and SNAAP activity, which cleaves after small neutral amino acids. Although both forms of the proteasome possess all five enzymatic activities, differences in the extent of the activities between the forms have been described based on specific substrates. For both forms of the proteasome, the major proteasome proteolytic activities appear to be contributed by different catalytic sites within the 20S core.

In eukaryotes, protein degradation is predominately mediated through the ubiquitin pathway in which proteins targeted for destruction are ligated to the 76 amino acid polypeptide ubiquitin. Once targeted, ubiquitinated proteins then serve as substrates for the 26S proteasome, which cleaves proteins into short peptides through the action of its three major proteolytic activities. While having a general function in intracellular protein turnover, proteasome-mediated degradation also plays a key role in many processes such as major histocompatibility complex (MHC) class I presentation, apoptosis and cell viability, antigen processing, NF-κB activation, and transduction of pro- inflammatory signals.

Proteasome activity is high in muscle wasting diseases that involve protein breakdown such as muscular dystrophy, cancer and AIDS. Evidence also suggests a possible role for the proteasome in the processing of antigens for the class I MHC molecules (Goldberg, et al. (1992) Nature 357:375-379).

Proteasomes are involved in neurodegenerative diseases and disorders such as Amyotrophic Lateral Sclerosis (ALS), (J Biol Chem 2003, Allen S et al., Exp Neurol 2005, Puttaparthi k et al.), Sjogren Syndrome (Arthritis & Rheumatism, 2006, Egerer T et al.) , systemic lupus erythematoses and lupus nephritis (SLE/LN), (Arthritis & rheuma 2011, Ichikawa et al., J Immunol, 2010, Lang VR et al., Nat Med, 2008, Neubert K et al), glomerulonephritis (J Am Soc nephrol 2011, Bontscho et al.), Rheumatoid Arthritis (Clin Exp Rheumatol, 2009, Van der Heiden JW et al.), Inflammatory bowel disease (IBD), ulcerative colitis, crohn's diseases, (Gut 2010, Schmidt N et al., J Immunol 2010, Basler

M et al., Clin Exp Immunol, 2009, Inoue S et al.), multiple sclerosis (Eur J Immunol 2008, Fissolo N et al., J Mol Med 2003, Elliott PJ et al., J Neuroimmunol 2001, Hosseini et al., J Autoimmun 2000, Vanderlugt CL et al.), Amyotrophic lateral sclerosis (ALS), (Exp Neurol 2005, Puttaparthi k et al., J Biol Chem 2003, Allen S et al.), osteoarthritis (Pain 2011, Ahmed s et al., Biomed Mater Eng 2008, Etienne S et al.), Atherosclerosis (J Cardiovasc Pharmacol 2010, Feng B et al., Psoriasis (Genes & Immunity, 2007, Kramer U et al.), Myasthenia Gravis (J Immunol, 2011, Gomez AM et al.), Dermal fibrosis (Thorax 2011, Mutlu GM et al., Inflammation 2011, Koca SS et al., Faseb J 2006, Fineschi S et al.), renal fibrosis (Nephrology 2011 Sakairi T et al.), cardiac fibrosis (Biochem Pharmacol 2011, Ma y et al.,) Liver fibrosis (Am J Physiol gastrointest Liver Physiol 2006, Anan A et al.), Lung fibrosis (Faseb J 2006, Fineschi S et al et al.), Imunoglobuline A nephropathy (IGa nephropathy), (Kidney Int, 2009, Coppo R et al.), Vasculitis (J Am Soc nephrol 2011, Bontscho et al.), Transplant rejection (Nephrol Dial transplant 2011, Waiser J et al.), Hematological malignancies (Br J Haematol 2011, singh AV et al., Curr Cancer Drug Target 2011, Chen D et al.) and asthma.

Yet, it should be noted that commercially available proteasome inhibitors inhibit both the constitutive and immuno-forms of the proteasome. Even bortezomib, the FDA-approved proteasome inhibitor for the treatment of relapsed multiple myeloma patients, does not distinguish between the two forms (Altun et al, Cancer Res 65:7896, 2005).

Furthermore, the use of Bortezomib is associated with a treatment-emergent, painful peripheral neuropathy (PN), this bortezomib-induced neurodegeneration *in vitro* occurs via a proteasome-independent mechanism and that bortezomib inhibits several nonproteasomal targets *in vitro* and *in vivo* (Clin. Cancer Res, 17(9), May 1, 2011).

In addition to conventional proteasome inhibitors, a novel approach may be to specifically target the hematological-specific immunoproteasome, thereby increasing overall effectiveness and reducing negative off-target effects. It has been shown that immunoproteasome-specific inhibitor, could display enhanced efficiency on cells from a hematologic origin (Curr Cancer Drug Targets, 11(3), Mar, 2011).

Thus there is a need to provide new proteasome inhibitors that are selective of one specific form of the proteasome.

In another aspect, the present invention relates to a pharmaceutical preparation containing at least one of the compounds according to Formula (I) and related Formulae.

Such pharmaceutical preparation may also contain additional active agents. The additional active agents may be selected from immunosuppressors, anti-inflammatory agent or interferon.

In another aspect, the present invention relates to a process for making the compounds according to Formula (I) and related Formulae.

The present invention further relates to a set or a kit consisting of separate packs of

(a) an effective amount of a compound according to Formula (I) or related Formulae and/or pharmaceutically usable derivatives, tautomers, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios,

and

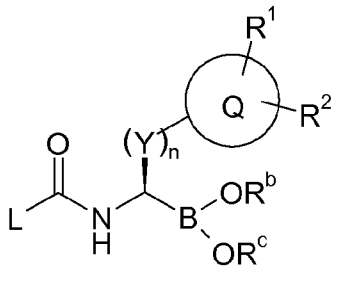
(b) an effective amount of a further medicament active ingredient.

The present invention encompasses compounds of Formula (I) and related Formulae either alone or in combination with one or several metabolites thereof.

Detailed description.

Compounds of the present invention are inhibitors of the immunoproteasome subunit LMP7. They preferably show selectivity on LMP7 over Beta5.

The present invention provides compounds of Formula (I):



(I)

Wherein

R^b and R^c are independently selected from one another from H or C_1-C_6-alkyl; whereby R^b and R^c may be linked to form a 5 or 6 membered-ring containing the oxygen atoms to which they are bond.

Q denotes Ar, Het or cycloalkyl;

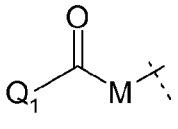
R^1, R^2 independently from each other denote H, OR^a, preferably methoxy, Hal, C_1-C_6-alkyl wherein 1 to 5 H atoms may be independently replaced by OH or Hal;

Y denotes CR^3R^4, preferably CH_2 or $C(CH_3)_2$;

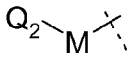
R^3, R^4 independently of one another denote H or C_1-C_6-alkyl, such as methyl;

L denotes L_1 or L_2, or alkyl, preferably methyl;

n is an integer selected from 0, 2 or 3 and is preferably 1;

L_1 is  wherein

Q_1 is Ar or Het, preferably phenyl, naphthyl or pyridine, optionally substituted with 1 to 5 groups independently selected from OR^a, Hal, phenyl, and C_1-C_6-alkyl wherein 1 to 5 H atoms may be independently replaced by OH or Hal;

L_2 is  wherein

Q_2 is a fused bicyclic system containing 1 nitrogen atom and 1 to 3 additional groups independently selected from O, S, N, or CO, and wherein at least one of the ring is aromatic whereby the fused bicyclic system is optionally substituted with 1 to 5 groups independently selected from OR^a, Hal, phenyl, and C_1-C_6-alkyl wherein 1 to 5 H atoms may be independently replaced by OH or Hal;

or

Q_2 is unsaturated or aromatic 5 membered-ring system containing 1 to 3 heteroatoms seleted from N, O, S and CO, and optionally substituted with a phenyl ring or pyridine ring whereby phenyl ring and pyridine ring are optionally substituted with 1 to 4 groups independently selected from OR^a, Hal, phenyl, and C_1-C_6-alkyl wherein 1 to 5 H atoms may be independently replaced by OH or Hal;

M is a linear or branched alkylen having 1 to 5 carbon atoms wherein 1 or 2 H atoms may be replaced by OR^a or a phenyl ring optionally substituted with 1 to 5 groups independently selected from Hal, OR^a, and C_1-C_6-alkyl optionally substituted with 1 to 5 groups independently selected from OH, and Hal; or
M denotes a cycloalkylen having 3 to 7 carbon atoms; or
M denotes a thiazolidinyl group.

R^a is H or C_1-C_6-alkyl wherein 1 to 5 H atom may be independently replaced by OH or Hal;

Ar denotes a 6 membered-aromatic carbocyclic ring optionally fused with another carbocyclic saturated, unsaturated or aromatic ring having 5 to 8 carbon atoms;

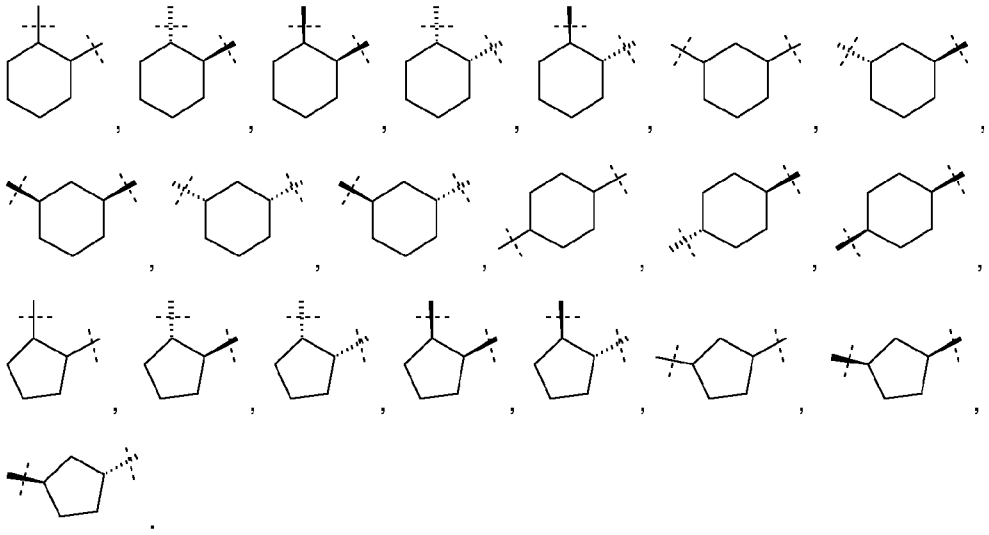
Het denotes a 5- or 6-membered saturated, unsaturated or aromatic heterocyclic ring having 1 to 3 heteroatoms independently selected from N, N^+O^-, O, S, SO, and SO_2, and optionally fused with another saturated, unsaturated or aromatic ring having 5 to 8 atoms and optionally containing 1 to 3 heteroatoms selected from N, O, and S;

Hal denotes Cl, Br, I of F; preferably Cl or F,

As well as enantiomers, diastereoisomers, and mixture thereof, and pharmaceutically acceptable salts thereof;

In case L contains 1 or several chiral centers, Formula (I) encompasses any isolated enantiomer and diastereoisomers as well as mixtures thereof in all ratios.

In a specific embodiment, the present invention provides compounds of Formula (I) and related Formulae, wherein L denotes L1, whereby M is a cycloalkylen having 3 to 7 carbon atoms. Preferably, M is selected from a 5- or 6-membered cycloalkylen. Examples of such cycloalkylen groups are the followings:

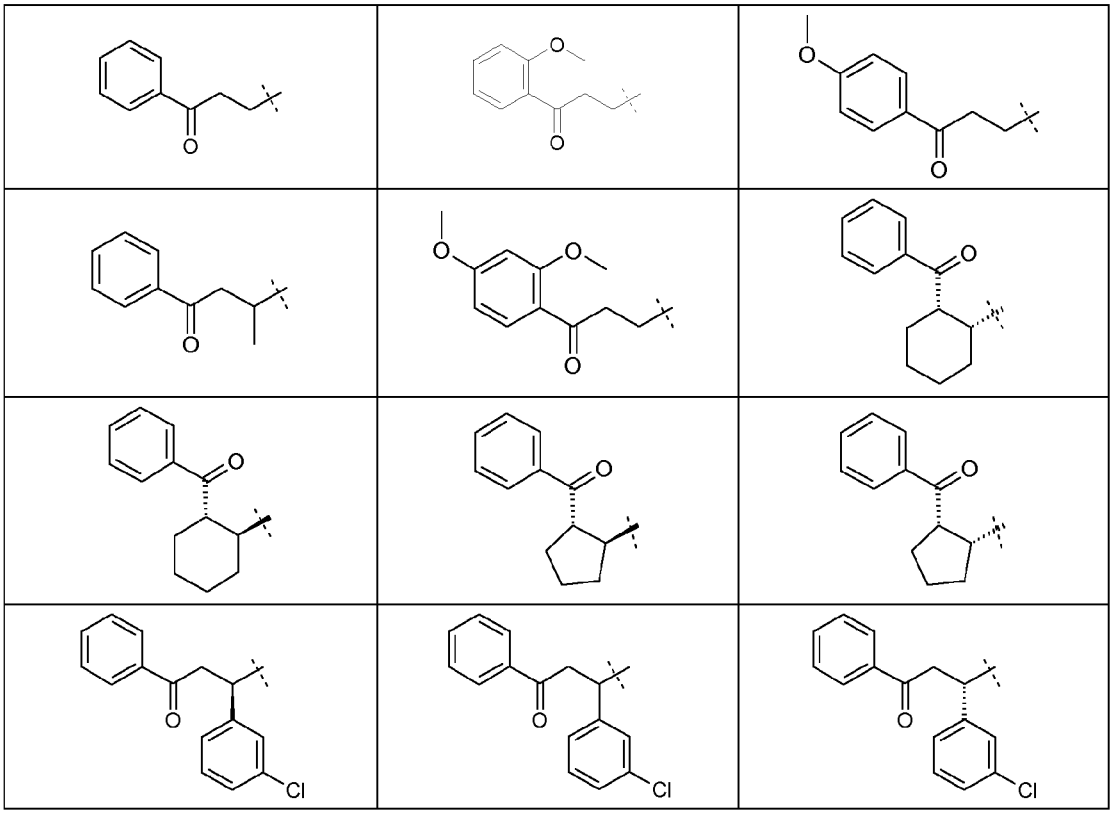


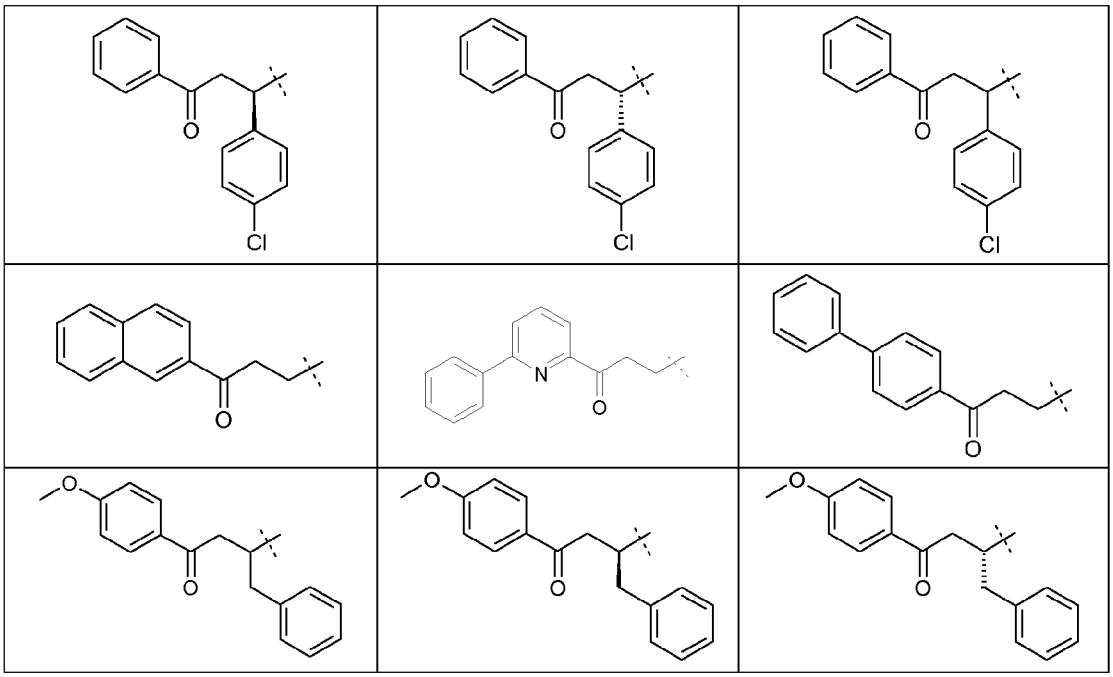
In another specific embodiment, the present invention provides compounds of Formula (I) and related Formulae, wherein L denotes L1 whereby M is a linear or branched

alkylen having 1 to 5 carbon atoms wherein 1 or 2 H atoms may be replaced by OR^a or a phenyl ring optionally substituted with 1 to 5 groups independently selected from Hal, OR^a, and C_1-C_6-alkyl optionally substituted with 1 to 5 groups independently selected from OH, and Hal.

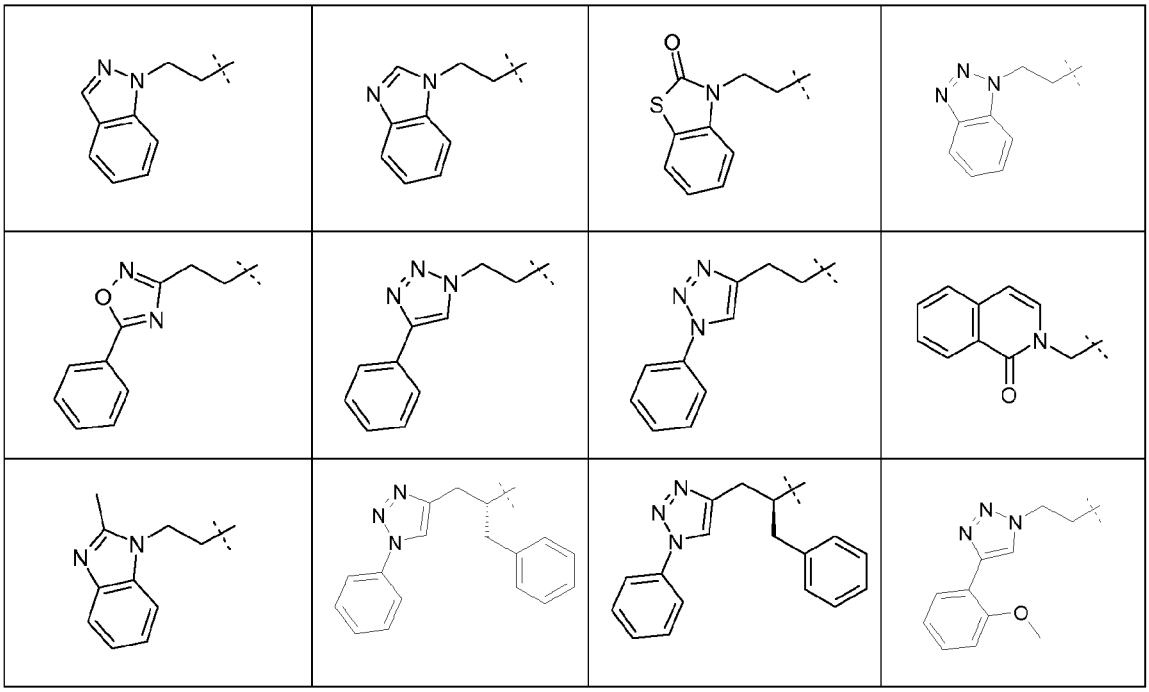
In another specific embodiment, the present invention provides compounds of Formula (I) and related Formulae, wherein L is L2 whereby M denotes a linear or branched alkylen having 1 to 5 carbon atoms wherein 1 or 2 H atoms may be replaced by OR^a or a phenyl ring optionally substituted with 1 to 5 groups independently selected from Hal, OR^a, and C_1-C_6-alkyl optionally substituted with 1 to 5 groups independently selected from OH, and Hal.
Preferably M in L2 is a non-substituted linear alkylen having 1 to 5 carbon atoms.

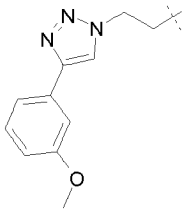
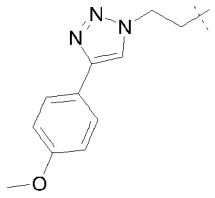
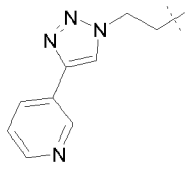
In another specific embodiment, the present invention provides compounds of Formula (I) and related Formulae, wherein L is L_1. L_1 is preferably selected from the following groups:

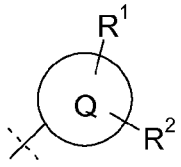


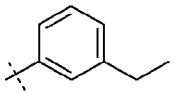
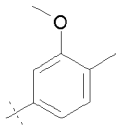
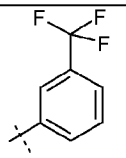
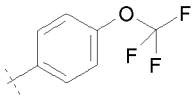
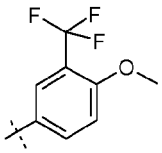
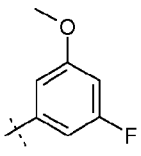
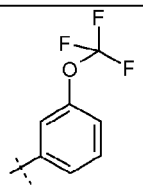
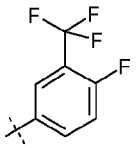
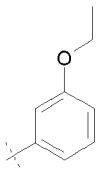
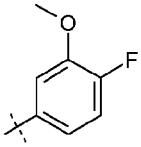


In another specific embodiment, the present invention provides compounds of Formula (I) and related Formulae, wherein L is L_2. L_2 is preferably selected from the following groups:



In another specific embodiment, the present invention provides compounds of Formula (I) and related Formulae wherein the group  is selected from the following groups:

Ar may be unsubstituted or monosubstituted, disubstituted or trisubstituted preferably by Hal, alkyl, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$, CF_3, OCF_3, $CON(R^3)_2$, $NR^3COalkyl$, $NR^3CON(R^3)_2$, NR^3SO_2alkyl, COR^3, $SO_2N(R^3)_2$, SOalkyl or SO_2alkyl, phenyl, pyridyl, pyrimidyl, O-phenyl, O-pyridy, O-pyrimidyl, $-[C(R^3)_2]_n-COOR^3$ and/or $-O[C(R^3)_2]_n-CON(R^3)_2$.

Ar denotes, for example, naphthyl, phenyl, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m- or p-(N-methylaminocarbonyl)phenyl, o-, m- or p-acetamidophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-ethoxycarbonylphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N,N-dimethyl-

aminocarbonyl)phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)-phenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-(methylsulfonamido)phenyl, o-, m- or p-(methylsulfonyl)phenyl, o, m or pamino-sulfanyl-phenyl, o-, m- or p-phenoxyphenyl, further preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2,4- or 2,5-dinitrophenyl, 2,5- or 3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 3-amino-4-chloro-, 2-amino-3-chloro-, 2-amino-4-chloro-, 2-amino-5-chloro- or 2-amino-6-chloro-phenyl, 2-nitro-4-N,N-dimethylamino- or 3-nitro-4-N,N-dimethylaminophenyl, 2,3-diaminophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl, 2,4,6-trimethoxy-phenyl, 2-hydroxy-3,5-dichlorophenyl, p-iodophenyl, 3,6-dichloro-4-aminophenyl, 4-fluoro-3-chlorophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 3-chloro-4-acetamidophenyl, 3-fluoro-4-methoxyphenyl, 3-amino-6-methylphenyl, 3-chloro-4-acetamidophenyl or 2,5-dimethyl-4-chlorophenyl.

Ar particularly preferably denotes, for example, phenyl which is unsubstituted or monosubstituted or disubstituted preferably monosubstituted, by F, OCH_3, CH_3, CF_3, phenyl and/or pyridyl, such as, for example, 2'-methoxy-phenyl-, 2'-trifluoromethyl-phenyl- (aryl bearing at least a 2' substituent), 2'-chloro-phenyl, 2',6'-dimethyl-phenyl- or 2'-alkyl-phenyl-, preferably 2'-methyl-phenyl.

Het is for example, 2- or 3-furyl, benzofuryl, 2- or 3-thienyl, benzothienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, indazolyl, 4- or 5-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benz-oxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxalinyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxazinyl, furthermore preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxane-6-yl, 2,1,3-benzothia-diazol-4- or -5-yl or 2,1,3-benzoxadiazol-5-yl.

The heterocyclic radicals in Het may also be partially or fully hydrogenated.

Het can thus also denote, for example, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxaneyl, 1,3-dioxane-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8-3,4-dihydro-2H-benzo-1,4-oxazinyl, furthermore preferably 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 2,3-ethylenedioxyphenyl, 3,4-ethylenedioxyphenyl, 3,4-(difluoro-methylenedioxy)phenyl, 2,3-dihydrobenzofuran-5- or -6-yl, 2,3-(2-oxomethylenedioxy)-phenyl or also 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl or 2,3-dihydro-2-oxofuranyl.

Het may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, alkyl, $-[C(R^3)_2]_n$-Ar, $-[C(R^3)_2]_n$-cycloalkyl, OR^3, CF_3, OCF_3, $N(R^3)_2$, $NR^3CON(R^3)_2$, NO_2, CN, $-[C(R^3)_2]_n$-$COOR^3$, $-[C(R^3)_2]_n$-$CON(R^3)_2$, $NR^3COalkyl$, NR^3SO_2alkyl, COR^3, $SO_2N(R^3)_2$, SOalkyl, O-phenyl, O-pyridy, O-pyrimidyl, phenyl, pyridyl and/or SO_2alkyl.

Alkyl is unbranched (linear) or branched, and has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. Alkyl preferably denotes methyl, furthermore ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, furthermore preferably, for example, trifluoromethyl.

Alkyl very particularly preferably denotes alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, trifluoromethyl, pentafluoroethyl, 1,1,1-trifluoroethyl. In a preferred embodiment alkyl is perfluorated.

Cycloalkyl preferably denotes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Cycloalkyl may be substituted preferably by alkyl, OH, O-alkyl, Hal.

In another specific embodiment, the compounds of the present invention are selected from the following group:

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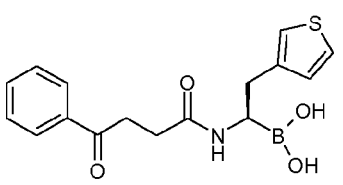
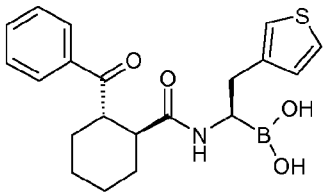
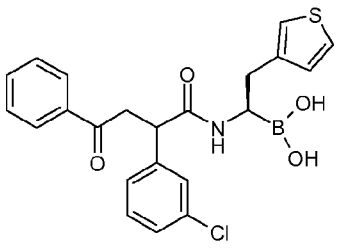
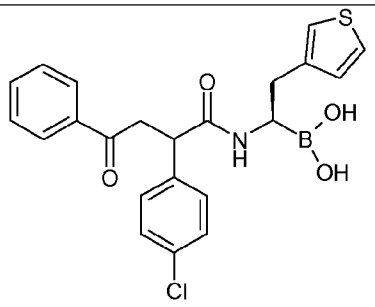
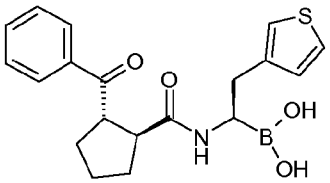
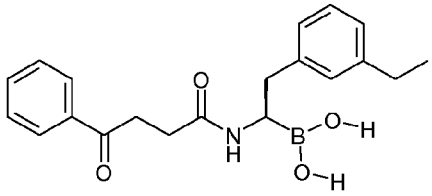
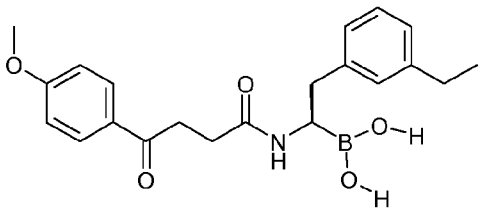
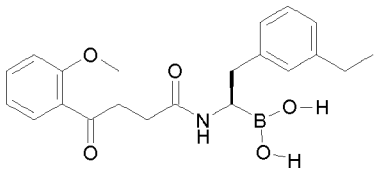
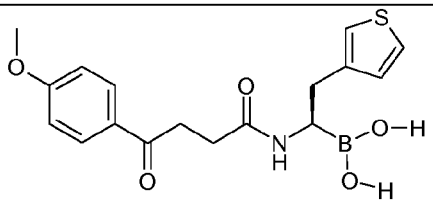
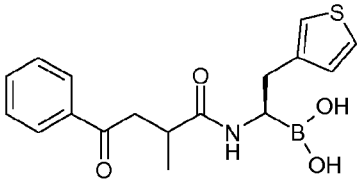
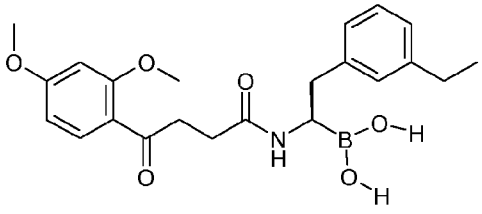
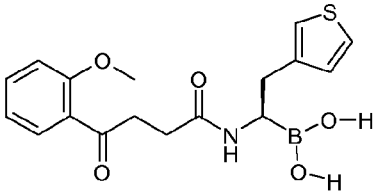
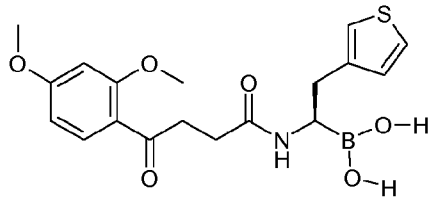
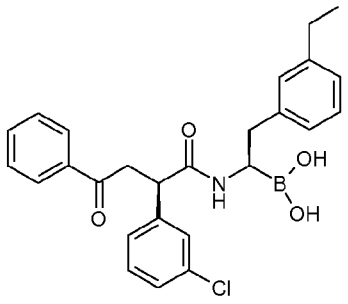
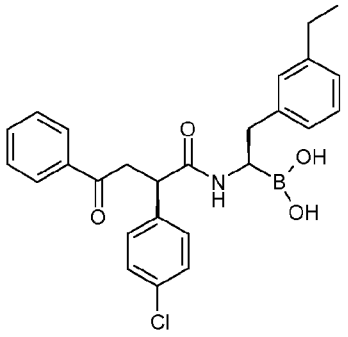
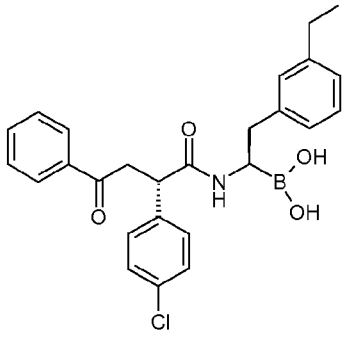
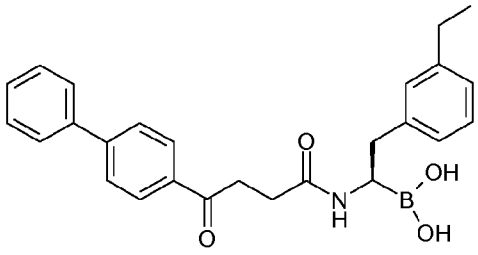
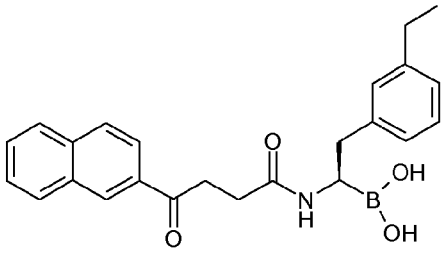
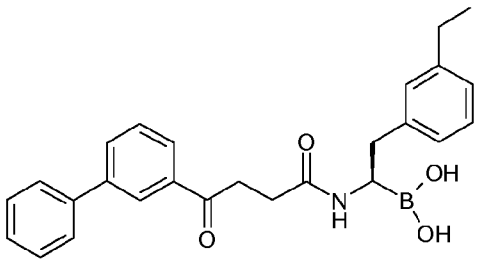
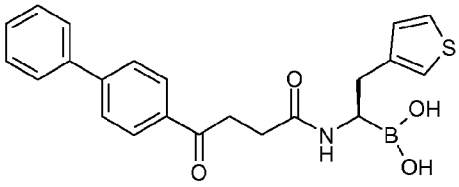
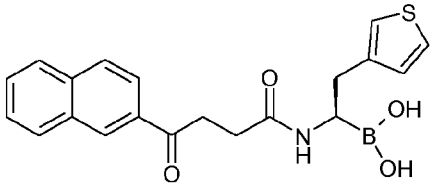
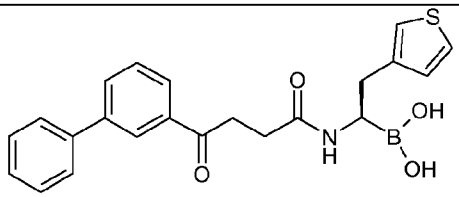
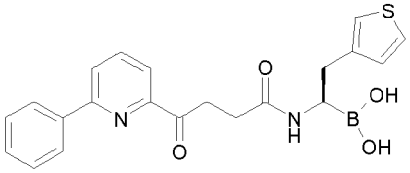
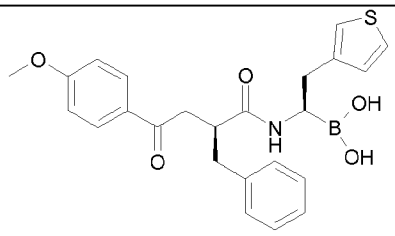
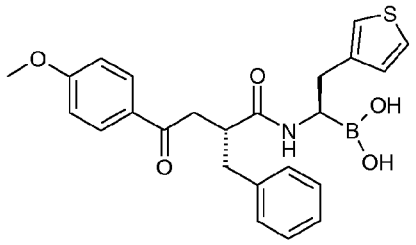
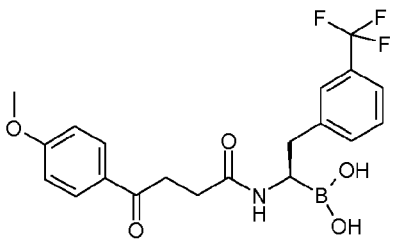
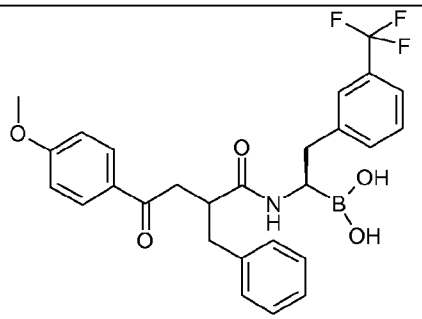
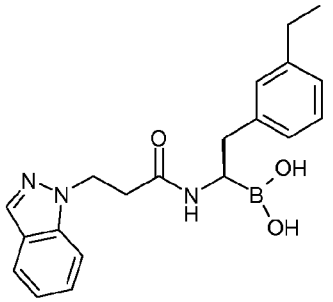
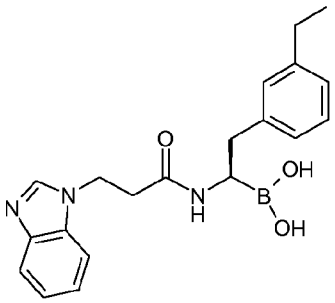
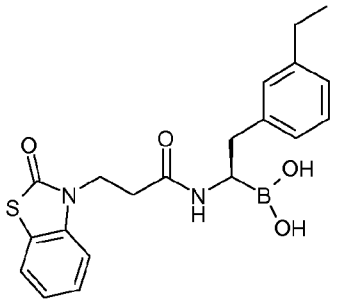
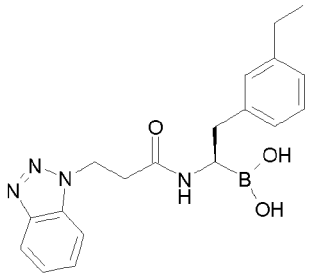
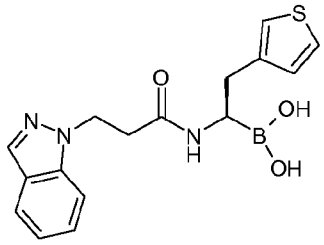
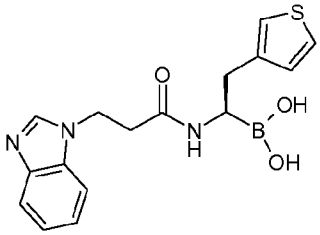
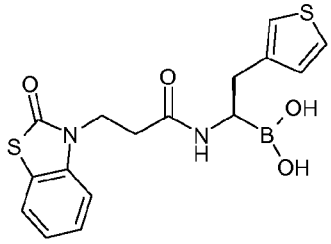
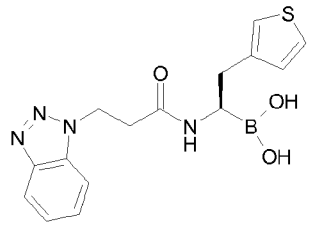
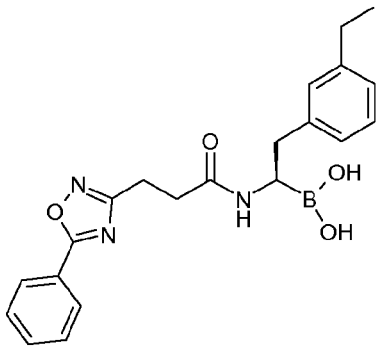
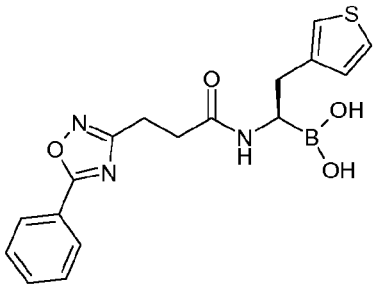
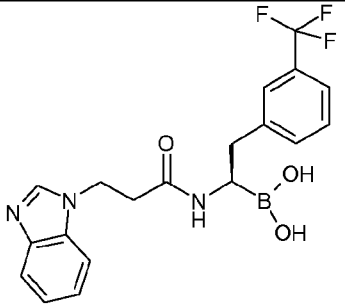
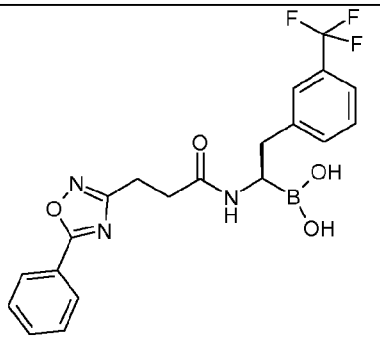
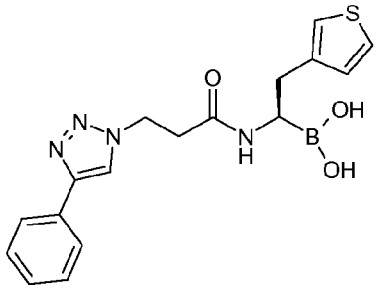
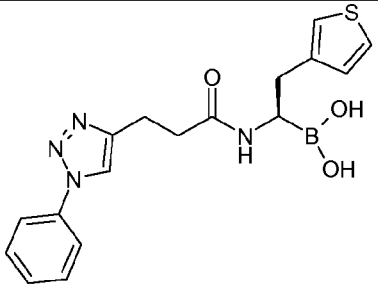
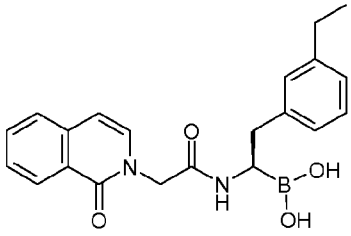
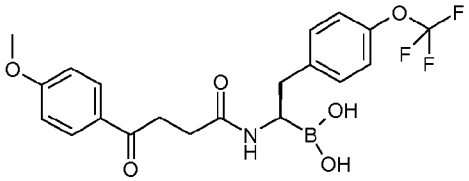
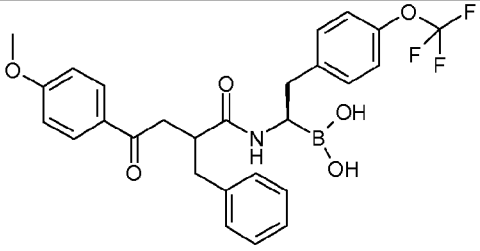
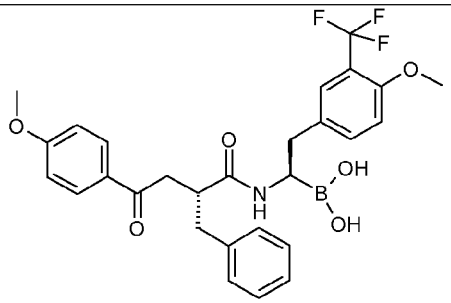
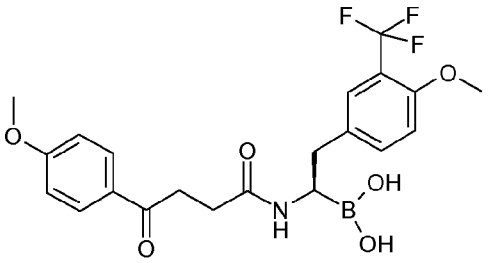
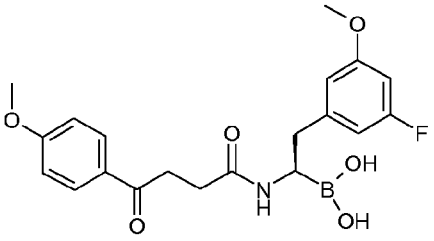
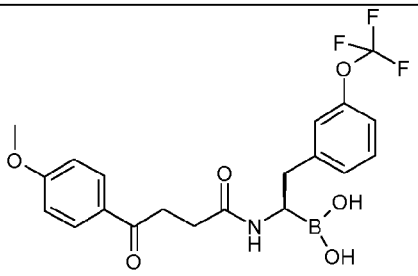
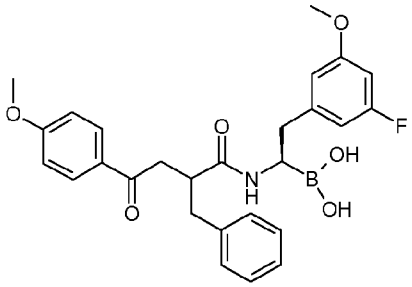
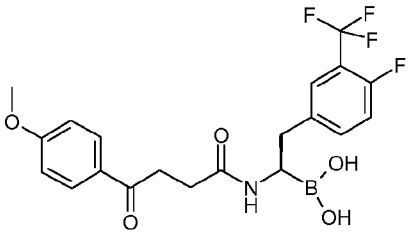
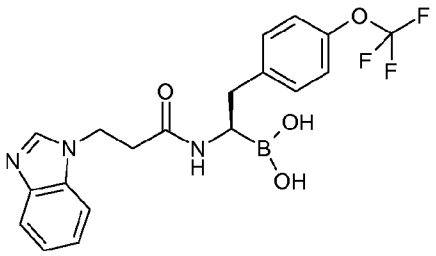
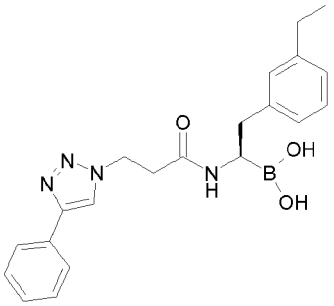
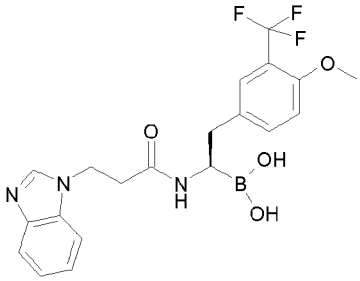
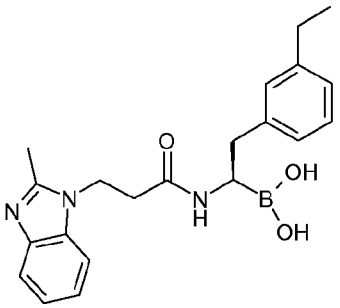
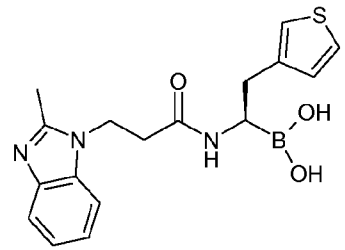
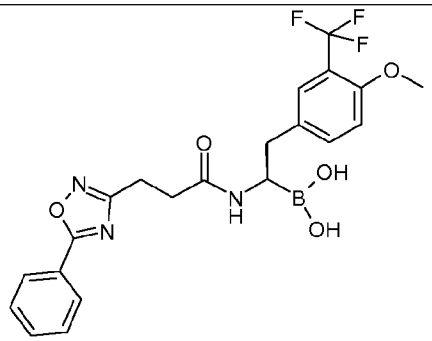
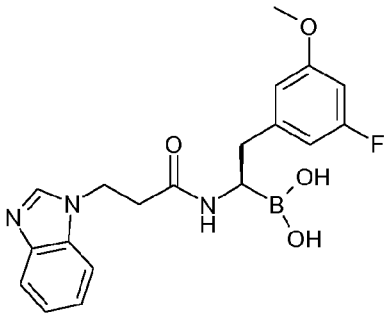
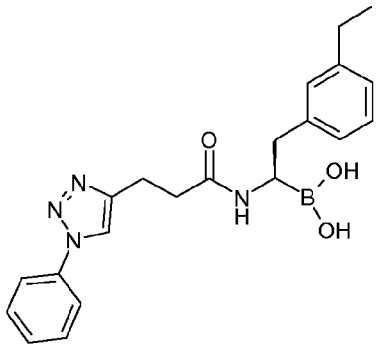
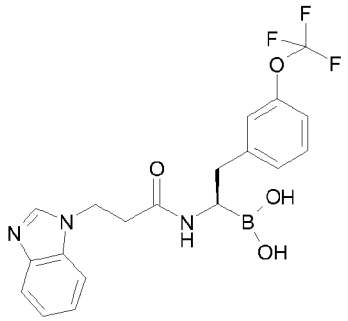
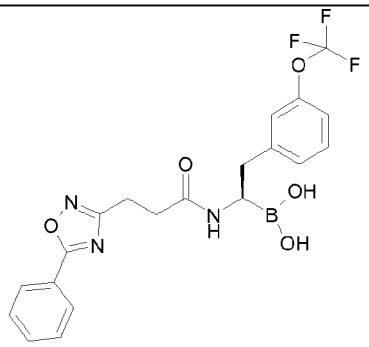
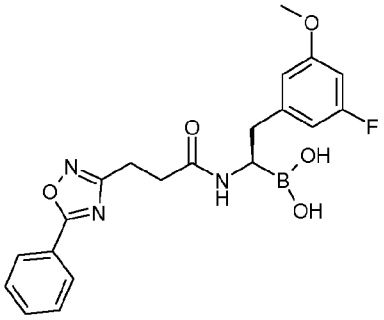
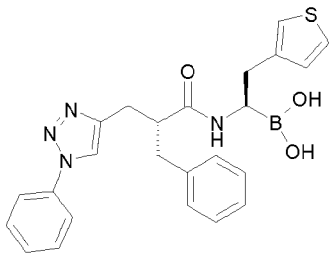
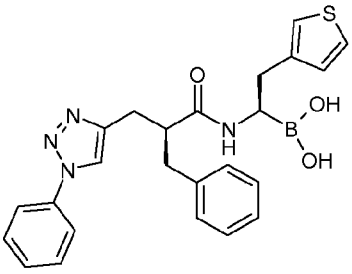
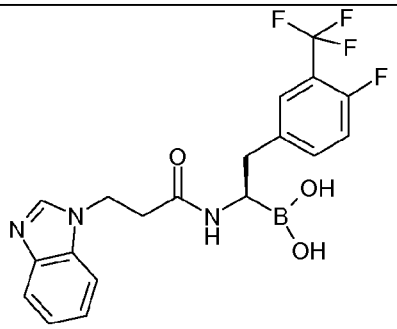
1		2	
3		4	
5		6	
7		8	
9		10	
11		12	

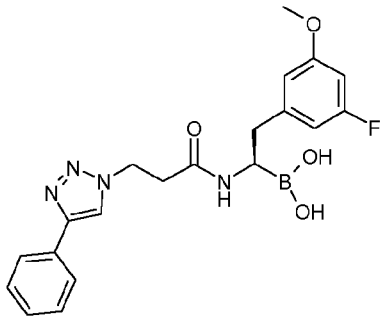
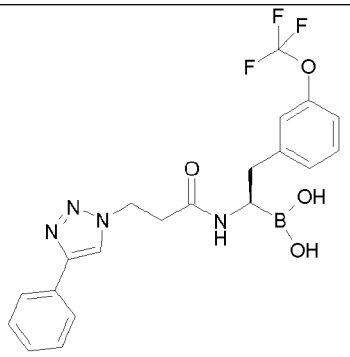
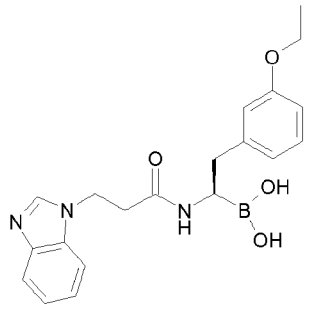
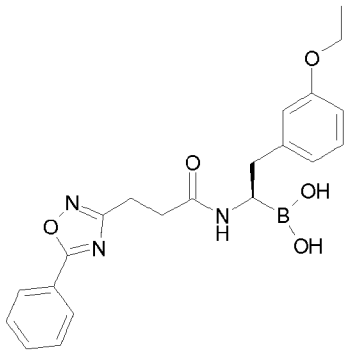
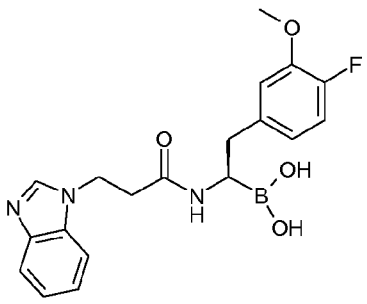
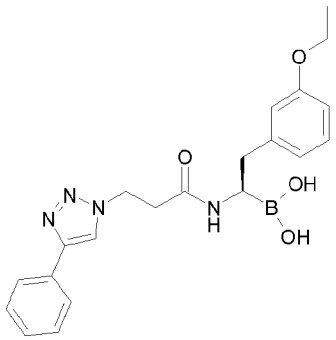
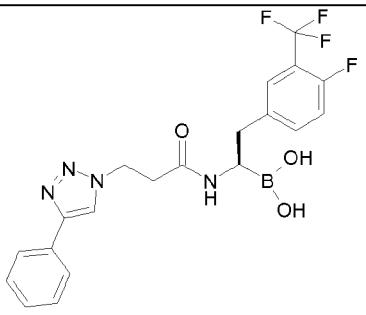
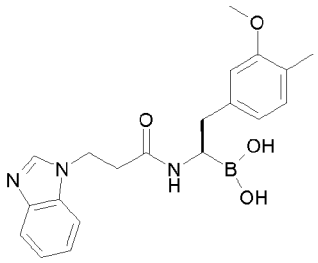
13		14	
15		16	
17		18	
19		20	
21		22	
23		24	

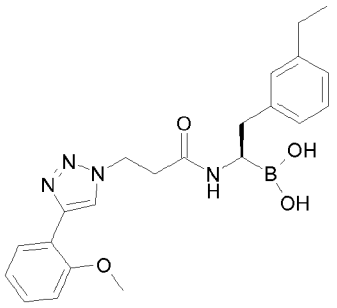
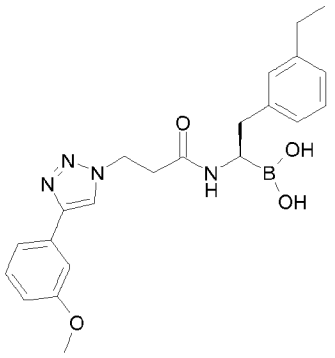
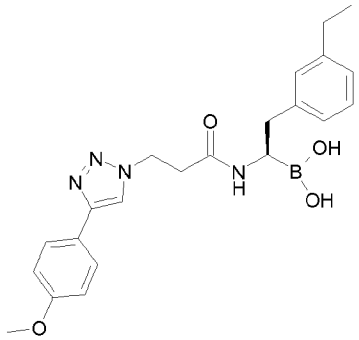
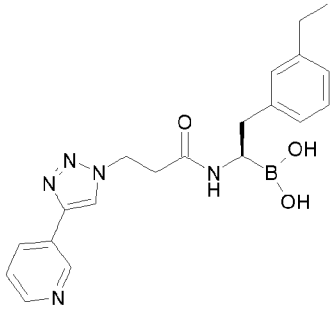
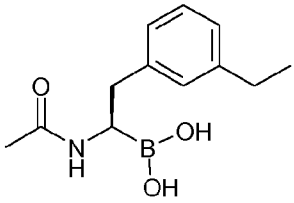
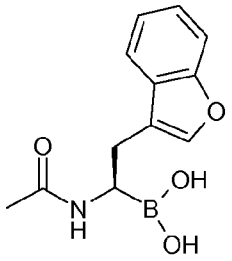
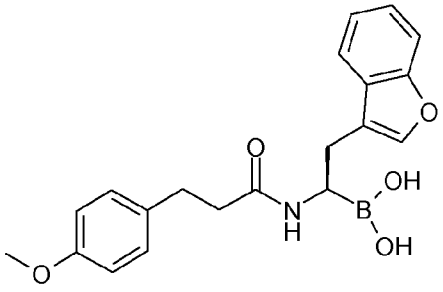
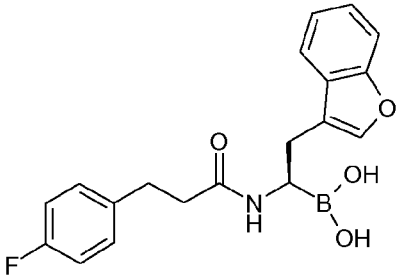
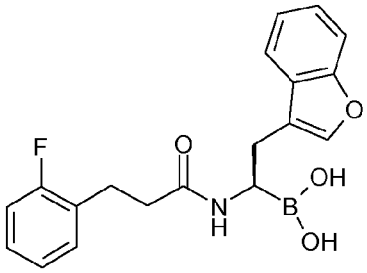
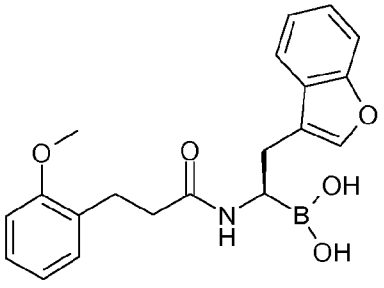
25		26	
27		28	
29		30	
31		32	
33		34	

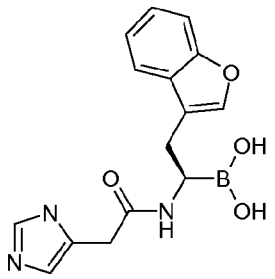
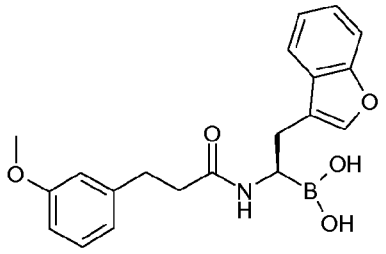
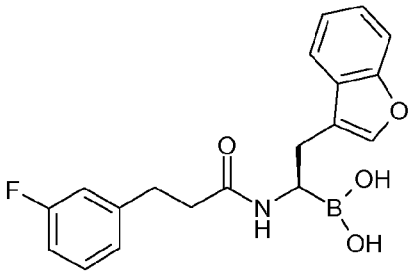
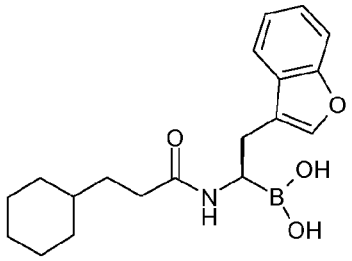
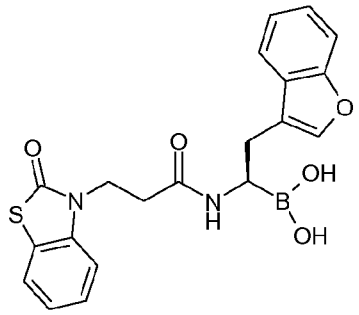
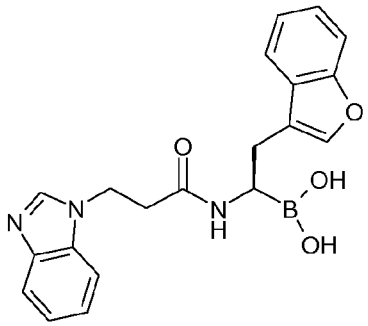
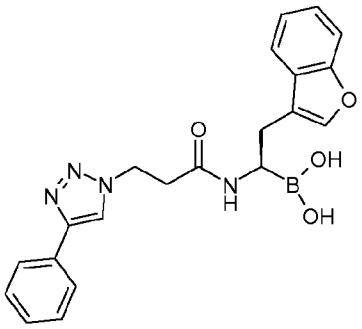
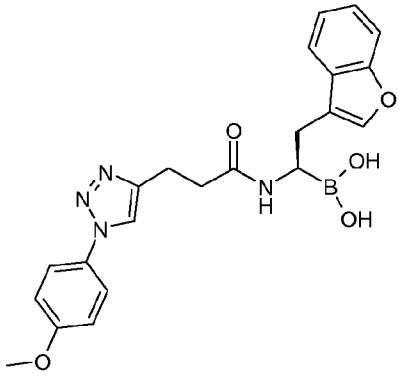
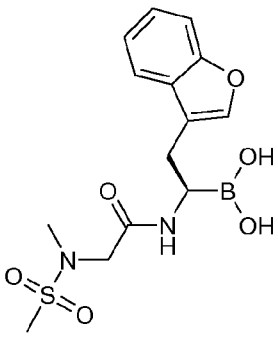
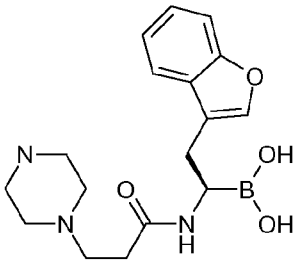
35		36	
37		38	
39		40	
41		42	
43		44	

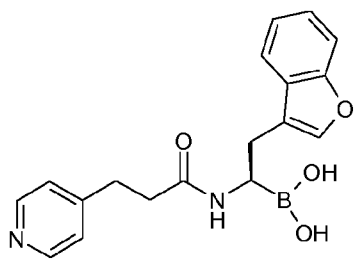
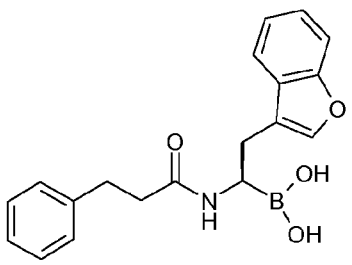
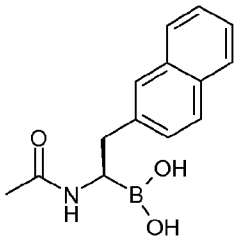
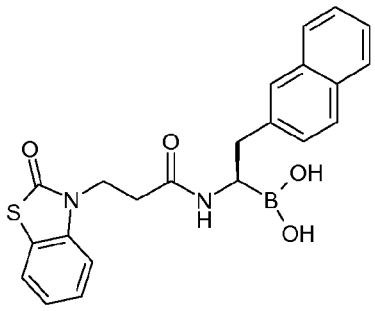
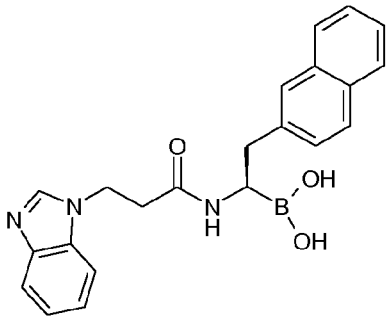
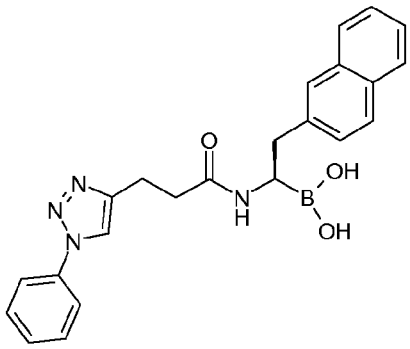
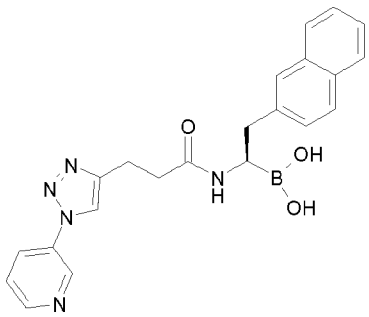
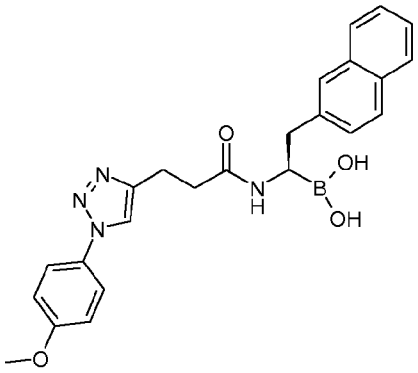
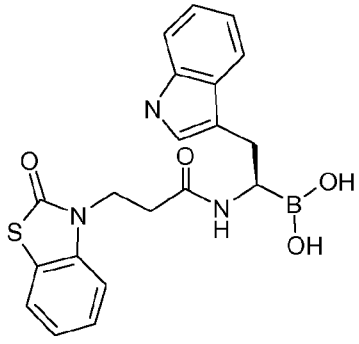
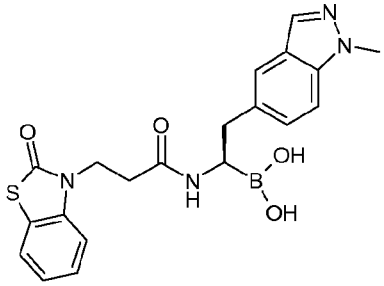
45		46	
47		48	
49		50	
51		52	
53		54	

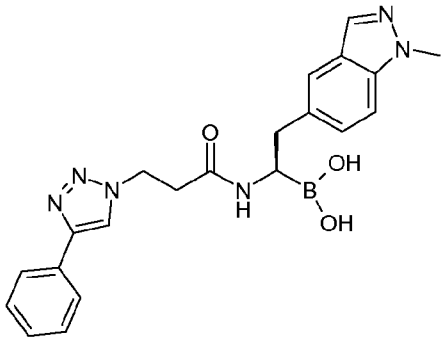
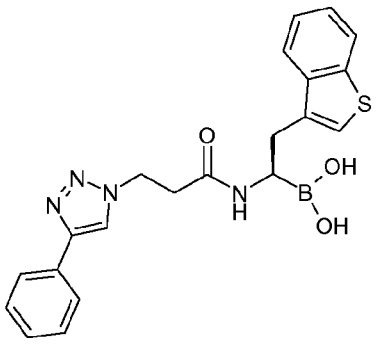
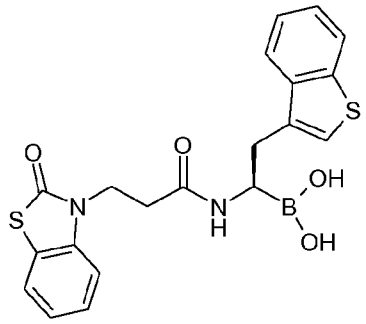
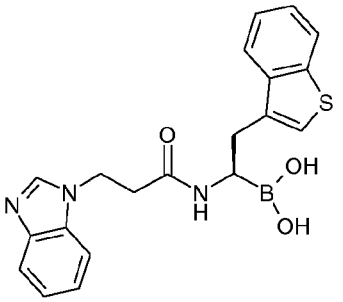
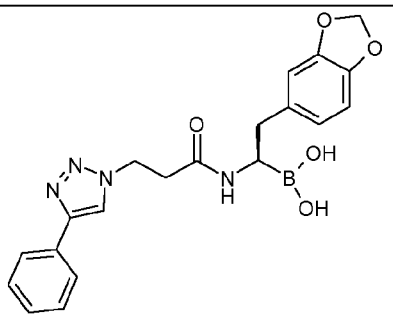
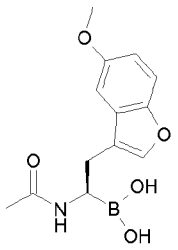
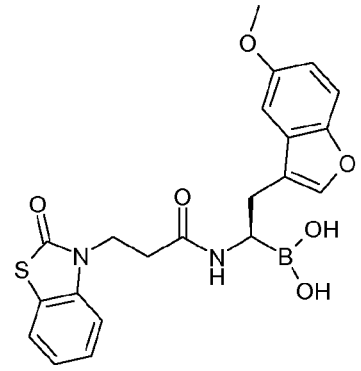
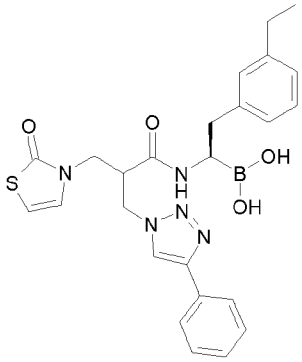
55		56	
57		58	
59		60	
61		62	
63		64	

65		66	
67		68	
69		70	
71		72	

73		74	
75		76	
77		78	
79		80	
81		82	

83		84	
85		86	
87		88	
89		90	
91		92	

93		94	
95		96	
97		98	
99		100	
101		102	

103		104	
105		106	
107		108	
109		110	

The following abbreviations refer to the abbreviations used below:

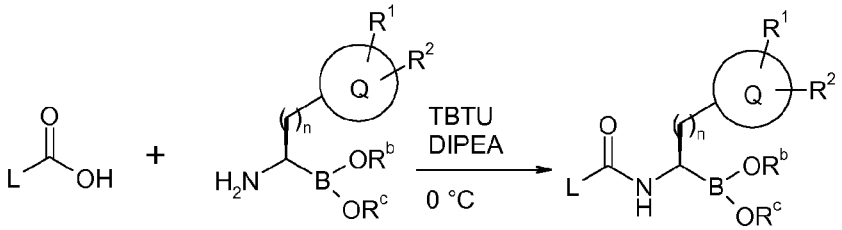
AcOH (acetic acid), BINAP (2,2'-bis(disphenylphosphino)-1,1'-binaphthalene), dba (dibenzylidene acetone), tBu (tert-Butyl), tBuOK (potassium tert-butoxide), CDI (1,1'-Carbonyldiimidazole), DBU (1,8-dizabicyclo[5.4.0]undec-7-ene), DCC

(dicyclohexylcarbodiimide), DCM (dichloromethane), DIAD (diisobutylazodicarboxylate), DIC (diisopropilcarbodiimide), DIEA (di-isopropyl ethylamine), DMA (dimethyl acetamide), DMAP (4-dimethylaminopyridine), DMSO (dimethyl sulfoxide), DMF (N,N-dimethylformamide), EDC.HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), EtOAc (ethyl acetate), EtOH (ethanol), g (gram), cHex (cyclohexane), HATU (dimethylamino-([1,2,3]triazolo[4,5-b]pyridin-3-yloxy)-methylene]-dimethyl-ammonium hexafluorophosphate), HOBt (*N*-hydroxybenzotriazole), HPLC (high performance liquid chromatography), hr (hour), MHz (Megahertz), MeOH (methanol), min (minute), mL (milliliter), mmol (millimole), mM (millimolar), mp (melting point), MS (mass spectrometry), MW (microwave), NMM (N-methyl morpholine), NMR (Nuclear Magnetic Resonance), NBS (N-bromo succinimide), PBS (phosphate buffered saline), PMB (para-methoxybenzyl), PyBOP (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate), RT (room temperature), TBAF (tetra-butylammonium fluoride), TBTU (N,N,N′,N′-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate), T3P (propane phosphonic acid anhydride), TEA (triethyl amine), TFA (trifluoroacetic acid), THF (tetrahydrofuran), PetEther (petroleum ether), TBME (tert-butyl methyl ether), TLC (thin layer chromatography), TMS (trimethylsilyl), TMSI (trimethylsilyl iodide), UV (ultraviolet).

Generally, compounds of Formula (I), wherein R^1, n, R^b, R^c, L and Q are defined as above, can be obtained from a compound of Formula (II) as outlined in Scheme 1.
The first step consists in the reaction of a compound of Formula (II), wherein L is defined as above, with a compound of Formula (III), wherein R^1, n, R^a, R^b, R^c and Q are defined as above. The reaction is performed using conditions and methods well known to those skilled in the art for the preparation of amides from a carboxylic acid with standard coupling agents, such as but not limited to HATU, TBTU, polymer-supported 1-alkyl-2-chloropyridinium salt (polymer-supported Mukaiyama's reagent), 1-methyl-2-chloropyridinium iodide (Mukaiyama's reagent), a carbodiimide (such as DCC, DIC, EDC) and HOBt, PyBOP® and other such reagents well known to those skilled in the art, preferably TBTU, in the presence or absence of bases such as TEA, DIEA, NMM, polymer-supported morpholine, preferably DIEA, in a suitable solvent such as DCM, THF or DMF, at a temperature between -10 °C to 50 °C, preferably at 0 °C, for a few hours, e.g. one hour to 24 h. Alternatively, the compounds of Formula (II) could be converted to carboxylic acid derivatives such as acyl halides or anhydrides, by methods well known to those skilled in the art, such as but not limited to treatment with $SOCl_2$, $POCl_3$, PCl_5, $(COCl)_2$, in the presence or absence of catalytic amounts of DMF, in the presence or absence of a suitable solvent such as toluene, DCM, THF, at a temperature rising from 20 °C to 100 °C,

preferably at 50 °C, for a few hours, e.g. one hour to 24 h. Conversion of the carboxylic acid derivatives to compounds of Formula (I), can be achieved using conditions and methods well known to those skilled in the art for the preparation of amides from a carboxylic acid derivative (e.g. acyl chloride) with alkyl amines, in the presence of bases such as TEA, DIEA, NMM in a suitable solvent such as DCM, THF or DMF, at a temperature rising from 20 °C to 100 °C, preferably at 50 °C, for a few hours, e.g. one hour to 24 h.

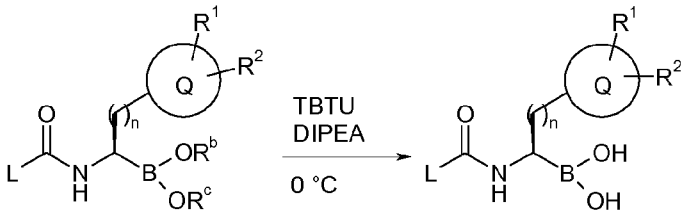
Scheme 1



(II) (III) (I)

Compounds of Formula (Ia), wherein R^1, n, L and Q are defined as above and wherein R^b and R^c are H, can be prepared starting from compounds of Formula (Ib), wherein R^1, n, L and Q are defined as above and wherein R^b and R^c are C_1-C_6-alkyl; whereby R^b and R^c may be linked to form a 5 or 6 membered-ring containing the oxygen atoms to which they are bond, using methods well known to those skilled in the art for the hydrolysis of boronic esters, such as but not limited to treatment with HCl, HBr, HI, TFA, in the presence or absence of an excess of a small molecular weight boronic acid, such as but not limited to i-$BuB(OH)_2$ (Scheme 2).

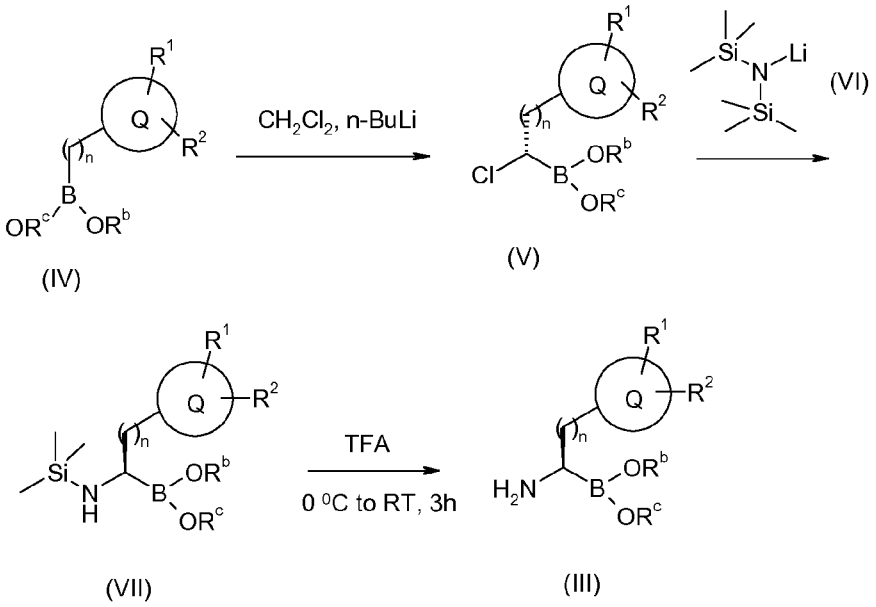
Scheme 2



(Ib) (Ia)

Compounds of Formula (III) can be prepared as outlined in Scheme 3.

Scheme 3



(IV) (V) (VII) (III)

Conversion of compounds of Formula (IV), wherein R^1, n, R^b, R^c and Q are defined as above, with the proviso that R^b, R^c do not represent H, to give compounds of Formula (V) , wherein R^1, n, R^b, R^c and Q are defined as above, with the proviso that R^b, R^c do not represent H, can be achieved by treatment with DCM, in the presence of strong bases such as nBuLi, tBuLi, MeLi, LDA, LiHMDS, preferably nBuLi, in a suitable solvent such as THF or dioxane, preferably THF, at a temperature rising from -100 °C to room temperature, for a few hours, e.g. one hour to 24 h. The reaction can give rise to enantiomerically enriched products when R^b and R^c are suitably selected. For example, when R^b and R^c together represent (1S, 2S, 3R, 5S)-(+)-pinanediol, the product with (S) configuration is preferentially formed. (Matteson, D. S.; Sadhu, K. M. J. Am. Chem. Soc. 1981, 103, 5241–5242)

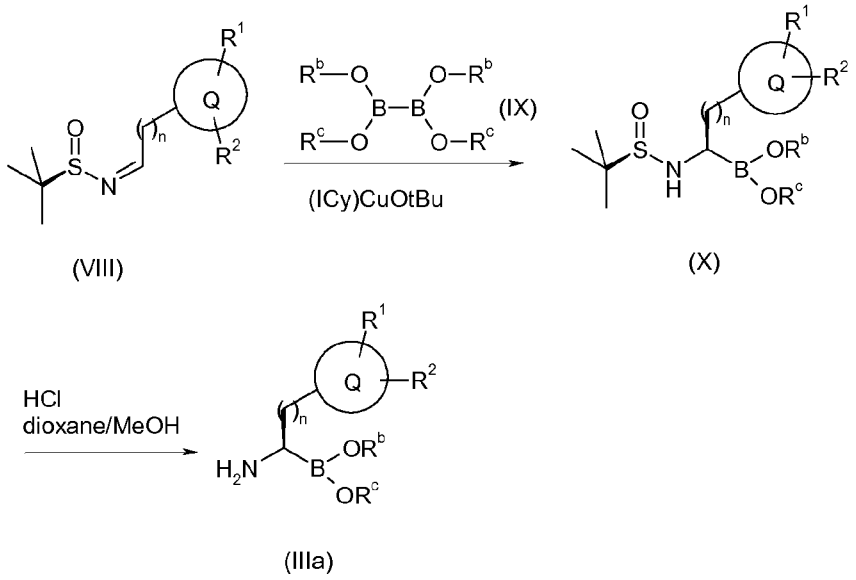
Conversion of compounds of Formula (V), wherein R^1, n, R^b, R^c, L and Q are defined as above, with the proviso that R^b, R^c do not represent H, to give compounds of Formula (VII), wherein R^1, n, R^b, R^c and Q are defined as above, with the proviso that R^b, R^c do not represent H, can be achieved by reaction with a compound of Formula (VI), in a suitable solvent such as THF or dioxane, preferably THF, at a temperature rising from -100 °C to room temperature, for a few hours, e.g. one hour to 24 h. The reaction generally proceeds with inversion of configuration, thereby if the compound of Formula (V) had an (S) configuration, a compound of Formula (VII) with (R) configuration would be obtained. (Matteson, D. S.; Sadhu, K. M. J. Am. Chem. Soc. 1981, 103, 5241–5242)

Finally, conversion of the compounds of Formula (VII) into compounds of Formula (II) can be achieved by treatment with a suitable acid, such as HCl or TFA, preferably TFA, in the

presence of a suitable solvent such as DCM, diethyl ether, diisopropyl ether, or THF, preferably diethylether, at a temperature between -30 °C to 30 °C, preferably at -10 °C, for a few hours, e.g. one hour to 48 h.

Alternatively, compounds of Formula (IIIa), wherein R^1, n, R^b, R^c and Q are defined as above and R^a represents H, can be prepared as outlined in Scheme 4.

Scheme 4



Compounds of Formula (VIII), wherein R^1 and Q are defined as above, can be converted into compounds of Formula (X), wherein R^1, n, R^b, R^c and Q are defined as above, by reaction with a compound of Formula (IX), wherein R^b and R^c are defined as above, in the presence of a suitable catalyst, such as but not limited to (1,3-dicyclohexylimidazol-2-ylidene)copper(I) tert-butoxide ((ICy)CuOtBu), in a suitable solvent such as benzene, toluene, dioxane, THF, at at a temperature between room temperature and 80 °C, for a few hours, e.g. one hour to 48 h.

Deprotection of the compounds of Formula (X) to give the compounds of Formula (IIIa) can be performed using an acid like HCl or TFA, preferably HCl, , in the presence of a suitable solvent such as DCM, diethyl ether, diisopropyl ether, THF, dioxane or methanol, preferably a mixture of dioxane and methanol, at a temperature between -10 °C to 40 °C, preferably at room temperature, for a few hours, e.g. one hour to 48 h.

If the above set of general synthetic methods is not applicable to obtain compounds according to Formula (I) and/or necessary intermediates for the synthesis of compounds of

Formula (I), suitable methods of preparation known by a person skilled in the art should be used.

In general, the synthesis pathways for any individual compounds of formula (I) will depend on the specific substitutents of each molecule and upon the ready availability of Intermediates necessary; again such factors being appreciated by those of ordinary skill in the art. For all the protection and de-protection methods, see Philip J. Kocienski, in "Protecting Groups", Georg Thieme Verlag Stuttgart, New York, 1994 and, Theodora W. Greene and Peter G. M. Wuts in "Protective Groups in Organic Synthesis", Wiley Interscience, 3rd Edition 1999.

Compounds of this invention can be isolated in association with solvent molecules by crystallization from evaporation of an appropriate solvent. The pharmaceutically acceptable acid addition salts of the compounds of formula (I), which contain a basic center, may be prepared in a conventional manner. For example, a solution of the free base may be treated with a suitable acid, either neat or in a suitable solution, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts may be obtained in an analogous manner by treating a solution of compounds of formula (I), which contain an acid center, with a suitable base. Both types of salts may be formed or interconverted using ion-exchange resin techniques.

Depending on the conditions used, the reaction times are generally between a few minutes and 14 days, and the reaction temperature is between about -30°C and 140°C, normally between -10°C and 90°C, in particular between about 0°C and about 70°C.

Compounds of the formula (I) can furthermore be obtained by liberating compounds of the formula (I) from one of their functional derivatives by treatment with a solvolysing or hydrogenolysing agent.

Preferred starting materials for the solvolysis or hydrogenolysis are those which conform to the formula (I), but contain corresponding protected amino and/or hydroxyl groups instead of one or more free amino and/or hydroxyl groups, preferably those which carry an amino-protecting group instead of an H atom bound to an N atom, in particular those which carry an R'-N group, in which R' denotes an amino-protecting group, instead of an HN group,

and/or those which carry a hydroxyl-protecting group instead of the H atom of a hydroxyl group, for example those which conform to the formula (I), but carry a -COOR" group, in which R" denotes a hydroxylprotecting group, instead of a -COOH group.

It is also possible for a plurality of – identical or different – protected amino and/or hydroxyl groups to be present in the molecule of the starting material. If the protecting groups present are different from one another, they can in many cases be cleaved off selectively.

The term "amino-protecting group" is known in general terms and relates to groups which are suitable for protecting (blocking) an amino group against chemical reactions, but which are easy to remove after the desired chemical reaction has been carried out elsewhere in the molecule. Typical of such groups are, in particular, unsubstituted or substituted acyl, aryl, aralkoxymethyl or aralkyl groups. Since the amino-protecting groups are removed after the desired reaction (or reaction sequence), their type and size are furthermore not crucial; however, preference is given to those having 1-20, in particular 1-8, carbon atoms. The term "acyl group" is to be understood in the broadest sense in connection with the present process. It includes acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids, and, in particular, alkoxy-carbonyl, aryloxycarbonyl and especially aralkoxycarbonyl groups. Examples of such acyl groups are alkanoyl, such as acetyl, propionyl and butyryl; aralkanoyl, such as phenylacetyl; aroyl, such as benzoyl and tolyl; aryloxyalkanoyl, such as POA; alkoxycarbonyl, such as methoxy-carbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC (tert-butoxy-carbonyl) and 2-iodoethoxycarbonyl; aralkoxycarbonyl, such as CBZ ("carbo-benz-oxy"), 4-methoxybenzyloxycarbonyl and FMOC; and aryl-sulfonyl, such as Mtr. Preferred amino-protecting groups are BOC and Mtr, furthermore CBZ, Fmoc, benzyl and acetyl.

The term "hydroxyl-protecting group" is likewise known in general terms and relates to groups which are suitable for protecting a hydroxyl group against chemical reactions, but are easy to remove after the desired chemical reaction has been carried out elsewhere in the molecule. Typical of such groups are the above-mentioned unsubstituted or substituted aryl, aralkyl or acyl groups, furthermore also alkyl groups. The nature and size of the hydroxyl-protecting groups are not crucial since they are removed again after the desired chemical reaction or reaction sequence; preference is given to groups having 1-20, in particular 1-10, carbon atoms. Examples of hydroxyl-protecting groups are, inter alia,

benzyl, 4-methoxybenzyl, p-nitro-benzoyl, p-toluenesulfonyl, tert-butyl and acetyl, where benzyl and tert-butyl are particu-larly preferred.

The term "solvates of the compounds" is taken to mean adductions of inert solvent molecules onto the compounds which form owing to their mutual attractive force. Solvates are, for example, mono- or dihydrates or alcoholates.

The compounds of the formula (I) are liberated from their functional derivatives – depending on the protecting group used – for example using strong acids, advantageously using TFA or perchloric acid, but also using other strong inorganic acids, such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids, such as trichloroacetic acid, or sulfonic acids, such as benzene- or p-toluenesulfonic acid. The presence of an additional inert solvent is possible, but is not always necessary. Suitable inert solvents are preferably organic, for example carboxylic acids, such as acetic acid, ethers, such as THF or dioxane, amides, such as DMF, halogenated hydrocarbons, such as DCM, furthermore also alcohols, such as methanol, ethanol or isopropanol, and water. Mixtures of the above-mentioned solvents are furthermore suitable. TFA is preferably used in excess without addition of a further solvent, and perchloric acid is preferably used in the form of a mixture of acetic acid and 70% perchloric acid in the ratio 9:1. The reaction temperatures for the cleavage are advantageously between about 0 and about 50°C, preferably between 15 and 30°C (RT).

The BOC, OBut and Mtr groups can, for example, preferably be cleaved off using TFA in DCM or using approximately 3 to 5N HCl in dioxane at 15-30°C, and the FMOC group can be cleaved off using an approximately 5 to 50% solution of dimethylamine, diethylamine or piperidine in DMF at 15-30°C.

Protecting groups which can be removed hydrogenolytically (for example CBZ, benzyl or the liberation of the amidino group from the oxadiazole derivative thereof) can be cleaved off, for example, by treatment with hydrogen in the presence of a catalyst (for example a noble-metal catalyst, such as palladium, advantageously on a support, such as carbon). Suitable solvents here are those indicated above, in particular, for example, alcohols, such as methanol or ethanol, or amides, such as DMF. The hydrogenolysis is generally carried out at temperatures between about 0 and 100°C and pressures between about 1 and 200 bar, preferably at 20-30°C and 1-10 bar. Hydrogenolysis of the CBZ group succeeds well,

for example, on 5 to 10% Pd/C in methanol or using ammonium formate (instead of hydrogen) on Pd/C in methanol/DMF at 20-30°C.

Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, tetrachloromethane, tri-fluoro-methylbenzene, chloroform or DCM; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofurane (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, N-methylpyrrolidone (NMP) or dimethyl-formamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); carbon disulfide; carboxylic acids, such as formic acid or acetic acid; nitro compounds, such as nitromethane or nitrobenzene; esters, such as EtOAc, or mixtures of the said solvents.

Esters can be saponified, for example, using LiOH, NaOH or KOH in water, water/THF, water/THF/ethanol or water/dioxane, at temperatures between 0 and 100°C. Furthermore, ester can be hydrolysed, for example, using acetic acid, TFA or HCL.

Free amino groups can furthermore be acylated in a conventional manner using an acyl chloride or anhydride or alkylated using an unsubstituted or substituted alkyl halide or reacted with CH3-C(=NH)-OEt, advantageously in an inert solvent, such as DCM or THF and/or in the presence of a base, such as triethylamine or pyridine, at temperatures between -60°C and +30°C.

Throughout the specification, the term leaving group preferably denotes Cl, Br, I or a reactively modified OH group, such as, for example, an activated ester, an imidazolide or alkylsulfonyloxy having 1 6 carbon atoms (preferably methylsulfonyloxy or trifluoromethylsulfonyloxy) or arylsulfonyloxy having 6 10 carbon atoms (preferably phenyl- or p tolylsulfonyloxy).
Radicals of this type for activation of the carboxyl group in typical acylation reactions are described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Meth¬ods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart).
Activated esters are advantageously formed in situ, for example through addition of HOBt or N hydroxysuccinimide.

The term "pharmaceutically usable derivatives" is taken to mean, for example, the salts of the compounds of the formula I and so-called prodrug compounds.

The term "prodrug derivatives" is taken to mean compounds of the formula I which have been modified with, for example, alkyl or acyl groups, sugars or oligopeptides and which are rapidly cleaved in the organism to form the active compounds.

These also include biodegradable polymer derivatives of the compounds according to the invention, as described, for example, in Int. J. Pharm. 115, 61-67 (1995).

Pharmaceutical salts and other forms

The said compounds of the formula (I) can be used in their final non-salt form. On the other hand, the present invention also relates to the use of these compounds in the form of their pharmaceutically acceptable salts, which can be derived from various organic and inorganic acids and bases by procedures known in the art. Pharmaceutically acceptable salt forms of the compounds of the formula I are for the most part prepared by conventional methods. If the compound of the formula I contains an acidic center, such as a carboxyl group, one of its suitable salts can be formed by reacting the compound with a suitable base to give the corresponding base-addition salt. Such bases are, for example, alkali metal hydroxides, including potassium hydroxide and sodium hydroxide; alkaline earth metal hydroxides, such as magnesium hydroxide and calcium hydroxide; and various organic bases, such as piperidine, diethanolamine and N-methyl-glucamine (meglumine), benzathine, choline, diethanolamine, ethylenediamine, benethamine, diethylamine, piperazine, lysine, L-arginine, ammonia, triethanolamine, betaine, ethanolamine, morpholine and tromethamine. In the case of certain compounds of the formula I, which contain a basic center, acid-addition salts can be formed by treating these compounds with pharmaceutically acceptable organic and inorganic acids, for example hydrogen halides, such as hydrogen chloride or hydrogen bromide, other mineral acids and corresponding salts thereof, such as sulfate, nitrate or phosphate and the like, and alkyl- and monoaryl-sulfonates, such as methanesulfonate, ethanesulfonate, toluenesulfonate and benzene-sulfonate, and other organic acids and corresponding salts thereof, such as carbonate, acetate, trifluoro-acetate, tartrate, maleate, succinate, citrate, benzoate, salicylate, ascorbate and the like. Accordingly, pharmaceutically acceptable acid-addition salts of the compounds of the formula I include the following: acetate, adipate, alginate, aspartate, benzoate, benzene-sulfonate (besylate), bisulfate, bisulfite, bromide, camphorate, camphor-sulfonate, caprate, caprylate, chloride, chlorobenzoate, citrate, cyclamate, cinnamate, digluconate, dihydrogen-phosphate, dinitrobenzoate,

dodecyl-sulfate, ethanesulfonate, formate, glycolate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptanoate, gluco-nate, glutamate, glycerophosphate, hemi-succinate, hemisulfate, heptanoate, hexanoate, hippurate, hydro-chloride, hydrobromide, hydroiodide, 2-hydroxy-ethane-sulfonate, iodide, isethionate, isobutyrate, lactate, lactobionate, malate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, mono-hydrogen-phosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, palmo-ate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate, phthalate, but this does not represent a restriction. Both types of salts may be formed or interconverted preferably using ion-exchange resin techniques.

Furthermore, the base salts of the compounds of the formula I include aluminium, ammonium, calcium, copper, iron (III), iron(II), lithium, magnesium, manganese(III), manganese(II), potassium, sodium and zink salts, but this is not intended to represent a restriction. Of the above-mentioned salts, preference is given to ammonium; the alkali metal salts sodium and potassium, and the alkaline earth metal salts calcium and magnesium. Salts of the compounds of the formula I which are derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines, also including naturally occurring substituted amines, cyclic amines, and basic ion exchanger resins, for example arginine, betaine, caffeine, chloroprocaine, choline, N,N'-dibenzyl-ethylen-ediamine (benzathine), dicyclohexylamine, diethanol-amine, diethyl-amine, 2-diethyl-amino-ethanol, 2-dimethyl-amino-ethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethyl-piperidine, glucamine, glucosamine, histidine, hydrabamine, isopropyl-amine, lido-caine, lysine, meglumine (N-methyl-D-glucamine), morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanol-amine, triethylamine, trimethylamine, tripropyl-amine and tris(hydroxy-methyl)-methylamine (tromethamine), but this is not intended to represent a restriction.

Compounds of the formula I of the present invention which contain basic N2-containing groups can be quaternised using agents such as (C1-C4)-alkyl halides, for example methyl, ethyl, isopropyl and tert-butyl chloride, bromide and iodide; di(C1-C4)alkyl sulfates, for example dimethyl, diethyl and diamyl sulfate; (C10-C18)alkyl halides, for example decyl, do-decyl, lauryl, myristyl and stearyl chloride, bromide and iodide; and aryl-(C1-C4)alkyl halides, for example benzyl chloride and phenethyl bromide. Both water- and oil-soluble compounds of the formula I can be prepared using such salts.

The above-mentioned pharmaceutical salts which are preferred include acetate, trifluoroacetate, besylate, citrate, fumarate, gluconate, hemisuccinate, hippurate, hydrochloride, hydrobromide, isethionate, mandelate, me-glumine, nitrate, oleate, phosphonate, pivalate, sodium phosphate, stearate, sulfate, sulfosalicylate, tartrate, thiomalate, tosylate and tro-meth-amine, but this is not intended to represent a restriction.

The acid-addition salts of basic compounds of the formula (I) are prepared by bringing the free base form into contact with a sufficient amount of the desired acid, causing the formation of the salt in a conventional manner. The free base can be regenerated by bringing the salt form into contact with a base and isolating the free base in a conventional manner. The free base forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts other-wise correspond to the respective free base forms thereof.

As mentioned, the pharmaceutically acceptable base-addition salts of the compounds of the formula I are formed with metals or amines, such as alkali metals and alkaline earth metals or organic amines. Preferred metals are sodium, potassium, magnesium and calcium. Preferred organic amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanol-amine, ethylenediamine, N-methyl-D-glucamine and procaine.

The base-addition salts of acidic compounds of the formula I are prepared by bringing the free acid form into contact with a sufficient amount of the desired base, causing the formation of the salt in a conventional manner. The free acid can be regenerated by bringing the salt form into contact with an acid and isolating the free acid in a conventional manner. The free acid forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts other-wise correspond to the respective free acid forms thereof.

If a compound of the formula (I) contains more than one group which is capable of forming pharmaceutically acceptable salts of this type, the formula I also encompasses multiple salts. Typical multiple salt forms include, for example, bitartrate, diacetate, difumarate,

dimeglumine, di-phosphate, disodium and trihydrochloride, but this is not intended to represent a restriction.

With regard to that stated above, it can be seen that the term "pharmaceutically acceptable salt" in the present connection is taken to mean an active ingredient which comprises a compound of the formula I in the form of one of its salts, in particular if this salt form imparts improved pharmacokinetic properties on the active ingredient compared with the free form of the active ingredient or any other salt form of the active ingredient used earlier. The pharmaceutically acceptable salt form of the active ingredient can also provide this active ingredient for the first time with a desired pharmacokinetic property which it did not have earlier and can even have a positive influence on the pharmacodynamics of this active ingredient with respect to its therapeutic efficacy in the body.

Owing to their molecular structure, the compounds of the formula (I) can be chiral and can accordingly occur in various enantiomeric forms. They can therefore exist in racemic or in optically active form.
Since the pharmaceutical activity of the racemates or stereoisomers of the compounds according to the invention may differ, it may be desirable to use the enantiomers. In these cases, the end product or even the Intermediates can be separated into enantiomeric compounds by chemical or physical measures known to the person skilled in the art or even employed as such in the synthesis.

In the case of racemic amines, diastereomers are formed from the mixture by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids, such as the (R) and (S) forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid, suitable N-protected amino acids (for example N-benzoylproline or N-benzenesulfonylproline), or the various optically active camphorsulfonic acids. Also advantageous is chromatographic enantiomer resolution with the aid of an optically active resolving agent (for example dinitrobenzoylphenylglycine, cellulose triacetate or other derivatives of carbohydrates or chirally derivatised methacrylate polymers immobilised on silica gel). Suitable eluents for this purpose are aqueous or alcoholic solvent mixtures, such as, for example, hexane/isopropanol/ acetonitrile, for example in the ratio 82:15:3.

The invention furthermore relates to the use of compounds of formula I, and related formulae in combination with at least one further medicament active ingredient, preferably medicaments used in the treatment of multiple sclerosis such as cladribine or another co-agent, such as interferon, e.g. pegylated or non-pegylated interferons, preferably interferon beta and/or with compounds improving vascular function or in combination with immunomodulating agents for example Fingolimod; cyclosporins, rapamycins or ascomycins, or their immunosuppressive analogs, e.g. cyclosporin A, cyclosporin G, FK-506, ABT-281, ASM981, rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin etc.; corticosteroids; cyclophosphamide; azathioprene; methotrexate; leflunomide; mizoribine; mycophenolic add; mycophenolate mofetil; 15-deoxyspergualine; diflucortolone valerate; difluprednate; Alclometasone dipropionate; amcinonide; amsacrine; asparaginase; azathioprine; basiliximab; beclometasone dipropionate; betamethasone; betamethasone acetate; betamethasone dipropionate; betamethasone phosphate sodique; betamethasone valerate; budesonide; captopril; chlormethine chlorhydrate; cladribine; clobetasol propionate; cortisone acetate; cortivazol; cyclophosphamide; cytarabine; daclizumab; dactinomycine; desonide; desoximetasone; dexamethasone; dexamethasone acetate; dexamethasone isonicotinate; dexamethasone metasulfobenzoate sodique; dexamethasone phosphate;dexamethasone tebutate;dichlorisone acetate; doxorubicine chlorhydrate; epirubicine chlorhydrate; fluclorolone acetonide; fludrocortisone acetate; fludroxycortide; flumetasone pivalate; flunisolide; fluocinolone acetonide; fluocinonide; fluocortolone; fluocortolone hexanoate; fluocortolone pivalate; fluorometholone; fluprednidene acetate; fluticasone propionate; gemcitabine chlorhydrate; halcinonide; hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone hemisuccinate; melphalan; meprednisone; mercaptopurine; methylprednisolone; methylprednisolone acetate; methylprednisolone hemisuccinate; misoprostol; muromonab-cd3; mycophenolate mofetil; paramethasone acetate; prednazoline, prednisolone; prednisolone acetate; prednisolone caproate; prednisolone metasulfobenzoate sodique; prednisolone phosphate sodique; prednisone; prednylidene; rifampicine; rifampicine sodique; tacrolimus; teriflunomide; thalidomide; thiotepa; tixocortol pivalate; triamcinolone; triamcinolone acetonide hemisuccinate; triamcinolone benetonide; triamcinolone diacetate; triamcinolone hexacetonide; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD40, CD45 or CD58 or their ligands; or other immunomodulatory compounds, e.g. CTLA41g, or other adhesion molecule inhibitors, e.g. mAbs or low molecular weight inhibitors including Selectin antagonists and VLA-4 antagonists. A preferred composition is with Cyclosporin A, FK506, rapamycin or 40-(2-hydroxy)ethyl-rapamycin and Fingolimod.. These further

medicaments, such as interferon beta, may be administered concomitantly or sequentially, e.g. by subcutaneous, intramuscular or oral routes.
These compositions can be used as medicaments in human and veterinary medicine.

Pharmaceutical formulations can be administered in the form of dosage units, which comprise a predetermined amount of active ingredient per dosage unit. Such a unit can comprise, for example, 0.5 mg to 1 g, preferably 1 mg to 700 mg, particularly preferably 5 mg to 100 mg, of a compound according to the invention, depending on the disease condition treated, the method of administration and the age, weight and condition of the patient, or pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Preferred dosage unit formulations are those which comprise a daily dose or part-dose, as indicated above, or a corresponding fraction thereof of an active ingredient. Furthermore, pharmaceutical formulations of this type can be prepared using a process, which is generally known in the pharmaceutical art.

Pharmaceutical formulations can be adapted for administration via any desired suitable method, for example by oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) methods. Such formulations can be prepared using all processes known in the pharmaceutical art by, for example, combining the active ingredient with the excipient(s) or adjuvant(s).

Pharmaceutical formulations adapted for oral administration can be administered as separate units, such as, for example, capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or foam foods; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Thus, for example, in the case of oral administration in the form of a tablet or capsule, the active-ingredient component can be combined with an oral, non-toxic and pharmaceutically acceptable inert excipient, such as, for example, ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing it with a pharmaceutical excipient comminuted in a similar manner, such as, for example, an edible carbohydrate, such as, for example, starch or mannitol. A flavour, preservative, dispersant and dye may likewise be present.

Capsules are produced by preparing a powder mixture as described above and filling shaped gelatine shells therewith. Glidants and lubricants, such as, for example, highly disperse silicic acid, talc, magnesium stearate, calcium stearate or polyethylene glycol in solid form, can be added to the powder mixture before the filling operation. A disintegrant or solubiliser, such as, for example, agar-agar, calcium carbonate or sodium carbonate, may likewise be added in order to improve the availability of the medica-ment after the capsule has been taken.

In addition, if desired or necessary, suitable binders, lubricants and disintegrants as well as dyes can likewise be incorporated into the mixture. Suitable binders include starch, gelatine, natural sugars, such as, for example, glucose or beta-lactose, sweeteners made from maize, natural and synthetic rubber, such as, for example, acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. The lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. The disintegrants include, without being restricted thereto, starch, methylcellulose, agar, bentonite, xanthan gum and the like. The tablets are formulated by, for example, preparing a powder mixture, granulating or dry-pressing the mixture, adding a lubricant and a disintegrant and pressing the entire mixture to give tablets. A powder mixture is prepared by mixing the compound comminuted in a suitable manner with a diluent or a base, as described above, and optionally with a binder, such as, for example, carboxymethylcellulose, an alginate, gelatine or polyvinyl-pyrrolidone, a dissolution retardant, such as, for example, paraffin, an absorption accelerator, such as, for example, a quaternary salt, and/or an absorbant, such as, for example, bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting it with a binder, such as, for example, syrup, starch paste, acadia mucilage or solutions of cellulose or polymer materials and pressing it through a sieve. As an alternative to granulation, the powder mixture can be run through a tableting machine, giving lumps of non-uniform shape which are broken up to form granules. The granules can be lubricated by addition of stearic acid, a stearate salt, talc or mineral oil in order to prevent sticking to the tablet casting moulds. The lubricated mixture is then pressed to give tablets. The active ingredients can also be combined with a free-flowing inert excipient and then pressed directly to give tablets without carrying out the granulation or dry-pressing steps. A transparent or opaque protective layer consisting of a shellac sealing layer, a layer of sugar or polymer material and a gloss layer of wax may be present. Dyes can be added to these coatings in order to be able to differentiate between different dosage units.

Oral liquids, such as, for example, solution, syrups and elixirs, can be prepared in the form of dosage units so that a given quantity comprises a pre-specified amount of the compounds. Syrups can be prepared by dissolving the compounds in an aqueous solution with a suitable flavour, while elixirs are prepared using a non-toxic alcoholic vehicle. Suspensions can be for-mulated by dispersion of the compounds in a non-toxic vehicle. Solubilisers and emulsifiers, such as, for example, ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavour additives, such as, for example, peppermint oil or natural sweeteners or saccharin, or other artificial sweeteners and the like, can likewise be added.

The dosage unit formulations for oral administration can, if desired, be encapsulated in microcapsules. The formulation can also be prepared in such a way that the release is extended or retarded, such as, for example, by coating or embedding of particulate material in polymers, wax and the like.

The compounds of the formula (I) and salts, solvates and physiologically functional derivatives thereof and the other active ingredients can also be administered in the form of liposome delivery systems, such as, for exam-ple, small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from various phospholipids, such as, for example, cholesterol, stearylamine or phosphatidylcholines.

The compounds of the formula (I) and the salts, solvates and physiologically functional derivatives thereof and the other active ingredients can also be delivered using monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds can also be coupled to soluble polymers as targeted medicament carriers. Such polymers may encompass polyvinylpyrrolidone, pyran copolymer, polyhydroxypropyl-methacrylamidophenol, polyhydroxyethylaspartamidophenol or polyethylene oxide polylysine, substituted by palmitoyl radicals. The compounds may furthermore be coupled to a class of biodegradable polymers which are suitable for achieving controlled release of a medicament, for example polylactic acid, poly-epsilon-caprolactone, polyhydroxybutyric acid, poly-orthoesters, polyacetals, polydihydroxypyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration can be administered as independent plasters for extended, close contact with the epidermis of the recipient.

Thus, for example, the active ingredient can be delivered from the plaster by iontophoresis, as described in general terms in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical compounds adapted for topical administration can be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For the treatment of the eye or other external tissue, for example mouth and skin, the formulations are preferably applied as topical ointment or cream. In the case of formulation to give an ointment, the active ingredient can be employed either with a paraffinic or a water-miscible cream base. Alternatively, the active ingredient can be formulated to give a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical application to the eye include eye drops, in which the active ingredient is dissolved or sus-pended in a suitable carrier, in particular an aqueous solvent.

Pharmaceutical formulations adapted for topical application in the mouth encompass lozenges, pastilles and mouthwashes.

Pharmaceutical formulations adapted for rectal administration can be administered in the form of suppositories or enemas.

Pharmaceutical formulations adapted for nasal administration in which the carrier substance is a solid comprise a coarse powder having a particle size, for example, in the range 20-500 microns, which is administered in the manner in which snuff is taken, i.e. by rapid inhalation via the nasal passages from a container containing the powder held close to the nose. Suitable formulations for administration as nasal spray or nose drops with a liquid as carrier substance encompass active-ingredient solutions in water or oil.

Pharmaceutical formulations adapted for administration by inhalation encompass finely particulate dusts or mists, which can be generated by various types of pressurised dispensers with aerosols, nebulisers or insuf-flators.

Pharmaceutical formulations adapted for vaginal administration can be administered as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions comprising antioxidants, buffers, bacteriostatics and solutes, by means of which the formulation is rendered isotonic with the blood of the recipient to be treated; and aqueous and non-aqueous sterile suspensions, which may comprise suspension media and thickeners. The formulations can be administered in single-dose or multidose containers, for example sealed ampoules and vials, and stored in freeze-dried (lyophilised) state, so that only the addition of the sterile carrier liquid, for example water for injection purposes, immediately before use is necessary.

Injection solutions and suspensions prepared in accordance with the recipe can be prepared from sterile powders, granules and tablets.

It goes without saying that, in addition to the above particularly mentioned constituents, the formulations may also comprise other agents usual in the art with respect to the particular type of formulation; thus, for example, formulations which are suitable for oral administration may comprise flavours.

A therapeutically effective amount of a compound of the formula I and of the other active ingredient depends on a number of factors, including, for example, the age and weight of the animal, the precise disease condition which requires treatment, and its severity, the nature of the formulation and the method of administration, and is ultimately determined by the treating doctor or vet. However, an effective amount of a compound is generally in the range from 0.1 to 100 mg/kg of body weight of the recipient (mammal) per day and particularly typically in the range from 1 to 10 mg/kg of body weight per day. Thus, the actual amount per day for an adult mammal weighing 70 kg is usually between 70 and 700 mg, where this amount can be administered as an individual dose per day or usually in a series of part-doses (such as, for example, two, three, four, five or six) per day, so that the total daily dose is the same. An effective amount of a salt or solvate or of a physiologically functional derivative thereof can be determined as the fraction of the effective amount of the compound per se.

The present invention furthermore relates to a method for treating a subject suffering from a sphingosine 1-phosphate associated disorder, comprising administering to said subject an effective amount of a compounds of formula (I). The present invention preferably relates to a method, wherein the sphingosine 1-phosphate-1 associated disorder is an autoimmune disorder or condition associated with an overactive immune response.

The present invention furthermore relates to a method of treating a subject suffering from an immunerogulatory abnomality, comprising administering to said subject a compounds of formula (I) in an amount that is effective for treating said immunoregulatory abnormality.The present invention preferably relates to a method wherein the immunoregulatory abnormality is an autoimmune or chronic inflammatory disease.

Experimental:

The HPLC data provided in the examples described below were obtained as followed.

Condition A: Column Waters Xbridge^{TM} C_8 50 mm x 4.6 mm at a flow of 2 mL/min; 8 min gradient from 0.1 % TFA in H_2O to 0.07 % TFA in CH_3CN.

Condition B: Column : XTERRA RP18 (250 x 4.6 mm, 5 □m). at a flow of 1 mL/min; 20 min gradient from 95% (10mM K_2HPO_4 in H_2O) / 5% CH_3CN to 100% CH_3CN. Column temperature 55 °C

Chiral HPLC: Column CHIRALPAK AD-H (250X4.6) mm, 5µm at a flow of 1 mL/min; mobile phase: 0.1%TFA in hexane: isopropyl alcohol (80:20).

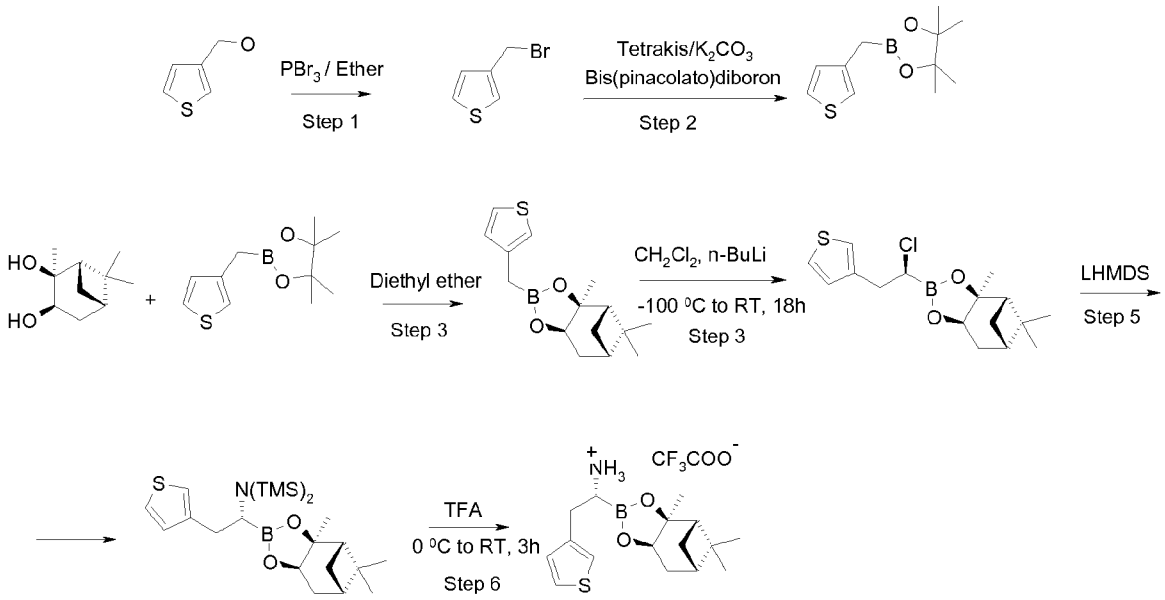
UV detection (maxplot) for all conditions.

The MS data provided in the examples described below were obtained as followed: Mass spectrum: LC/MS Waters ZMD (ESI) or a Waters Acquity SQD (ESI)

The NMR data provided in the examples described below were obtained as followed: ^{1}H-NMR: Bruker DPX 400 MHz. All NMR of final compounds were obtaind using d_6-DMSO, with the addition of a few drops of D_2O. Spectra were recorded 15-120 minutes after sample preparation.

The compounds of invention have been named according to the standards used in the program „ACD/Name Batch“ from Advanced Chemistry Development Inc., ACD/Labs (7.00 Release). Product version: 7.10, build: 15 Sep 2003

Intermediate 1: [(1*R*)-1-amino-2-(3-thienyl)ethyl]boronic acid (+)-pinanediol ester trifluroacetate



Step 1: 3-(bromomethyl)thiophene

A cooled (0 °C) solution of 3-thiophenemethanol (5.00 g, 43.7mmol) in diethyl ether (40 mL) was treated with phosphorus tribromide (1.35 mL, 14.4 mmol) and the reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was then poured into ice and extracted with diethyl ether. The organic layer was dried over sodium sulfate and concentrated to afford the title compound (5.23 g, 67%), which was used without further purification.
^{1}H NMR (400MHz, $CDCl_3$) δ 7.32-7.30 (m, 2H), 7.14 (d, *J*= 4.6 Hz, 2H), 4.54 (s, 1H).

Step 2: 4,4,5,5-tetramethyl-2-(3-thienylmethyl)-1,3,2-dioxaborolane

A solution of 3-(bromomethyl)thiophene (5.23 g, 29.7 mmol) in degassed 1,4-dioxane (90 ml) was treated with bis(pinacolato)diboron (9.0 g, 36 mmol), potassium carbonate (12.3 g, 89.1 mmol) and tetrakis(triphenyl phosphine) palladium (1.72 g, 1.48 mmol) and the reaction mixture was heated at 100 °C for 12 h. The mixture was cooled to room temperature and filtered through a Celite bed. The filtrate was concentrated and the crude was purified by column chromatography on silica, eluting with 5-10% of ethyl acetate in petroleum ether to afford the title compound (3.55 g, 55%) as a yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.20 (m, 1H), 6.96-6.93 (m, 2H), 2.28 (s, 2H), 1.24 (s, 12H).

Step 3: (3-thienylmethyl)boronic acid (+)-pinanediol ester

A solution of 4,4,5,5-tetramethyl-2-(3-thienylmethyl)-1,3,2-dioxaborolane (3.55 g, 15.8 mmol) in diethyl ether (40 ml) was treated with (1S, 2S, 3R, 5S)-(+)-pinanediol (3.1 g, 18 mmol). The reaction mixture was stirred at room temperature for 2 days. The reaction mass was washed with water (2 x 15 ml), brine and dried over anhydrous sodium sulphate and concentrated to get a crude product which was purified by column chromatography on silica gel, eluting with 5% of ethyl acetate in petroleum ether, to afford the title compound (4.0 g, 90%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, *J*= 7.8, 3.2 Hz, 1H), 6.97-6.95 (m, 2H), 4.31 (dd, *J*= 8.8, 2.0 Hz, 1H), 2.36-2.30 (m, 3H), 2.2-2.18 (m, 1H), 2.07 (t, *J*= 5.2Hz, 1H), 1.92-1.90 (m, 1H), 1.87-1.84 (m, 1H) 1.40 (s, 3H), 1.32 (s, 3H), 1.10 (d, *J*= 10.9 Hz, 1H), 0.84 (s, 3H).

Step 4: [(1*S*)-1-chloro-2-(3-thienyl)ethyl]boronic acid acid (+)-pinanediol ester

To a cooled (-100 °C) solution of dichloromethane (1.42 ml, 21.7mmol) and tetrahydrofuran (10 ml) was added n-butyl lithium (2.5 M in THF; 3.18 ml; 7.96mmol) over 10 min. After stirring for 20 min. a solution of (3-thienylmethyl)boronic acid (+)-pinanediol ester (2.00 g, 7.24 mmol) in THF (9 ml) was added over 10 min, keeping the temperature at -100 °C. Then a solution of zinc chloride (0.5M in THF; 13 mL, 6.5 mmol) was added at -100 °C over 30min. The mixture was allowed to reach room temperature and stirred for 18h and concentrated. To the resulting oil was added diethyl ether and saturated ammonium chloride (50 ml each) and stirred vigorously. The aqueous layer was extracted with diethyl ether three times and the combined organic layers were dried over anhydrous sodium sulphate and concentrated in vacuo to afford the title compound (2.1 g, 89%), which was used as such for the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J*= 8.3 Hz, 1H), 7.11 (m, 1H), 7.03 (dd, *J*= 6.1, 1.1 Hz, 1H), 4.36 (dd, *J*= 10.7, 2 Hz, 1H), 3.75 (m, 1H), 3.21 (m, 1H), 2.34 (m, 1H), 2.19 (m, 1H), 2.07 (t, *J*= 5.2, Hz, 2H), 1.91-1.84 (m, 2H), 1.35 (s, 3H), 1.28 (s, 3H), 1.05 (d, *J*= 11 Hz, 1H), 0.84 (s, 3H).

Step 5: [(1*R*)-1-[bis(trimethylsilyl)amino]-2-(3-thienyl)ethyl]boronic acid

To a cooled (-78 °C) solution of [(1*S*)-1-chloro-2-(3-thienyl)ethyl]boronic acid acid (+)-pinanediol ester (2.30 g, 7.09 mmol) in 10 ml of anhydrous THF was added Lithium bis(trimethylsilyl) amide (1 M in THF, 10.6 ml, 10.6 mmol). The mixture was allowed to room temperature, stirred for 18 h and concentrated to dryness. To the resulting residue was added hexane, and then the precipitated solid was filtered off. The filtrate was

concentrated to give the title compound (1.72 g, 53%), which was used as such for the next step without further purification.

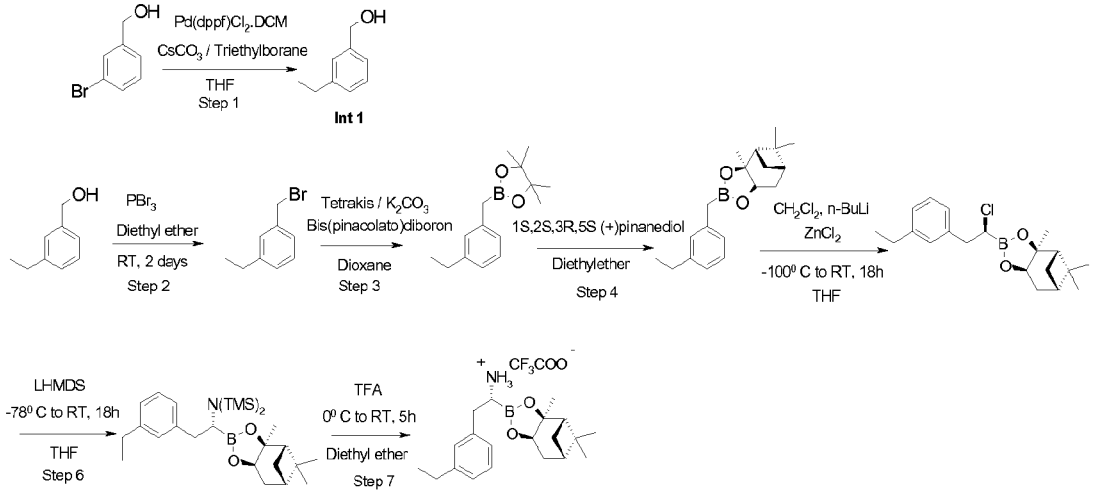
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.17 (m, 1H), 7.01-6.99 (m, 2H), 4.29-4.27 (m, 1H), 3.07-3.05 (m, 1H), 2.79 (m, 1H), 2.68 (m, 1H), 2.3 (m, 1H), 2.15 (m, 1H), 2.02 (t, *J*= 5.2 Hz, 1H), 1.87-1.86 (m, 1H), 1.79 (m, 1H), 1.36 (s, 3H), 1.25 (s, 3H), 0.94 (m, 1H), 0.85 (s, 3H), 0.08 (s, 18H).

Step 6: [(1*R*)-1-amino-2-(3-thienyl)ethyl]boronic acid acid (+)-pinanediol ester trifluroacetate

To a cooled (0 °C) solution [(1*R*)-1-[bis(trimethylsilyl)amino]-2-(3-thienyl)ethyl]boronic acid (1.72 g, 3.82 mmol) in diethyl ether (25 ml) was added trifluoroacetic acid (0.88 ml, 11.48 mmol) dropwise. Reaction was stirred for 3 h at room temperature. The reaction mixture was cooled with ice-methanol to -10 °C and the white solid formed was filtered, washed with ether and dried, to give the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.8 (bs, 3H), 7.33-7.27 (m, 1H), 7.23 (m, 1H), 7.01-6.99 (dd, *J*= 5.0 hz, 1.2 Hz, 1H), 4.35-4.32 (m, 1H), 3.18-3.10 (m, 3H), 2.28-2.15 (m, 3H), 1.99 (m, 1H), 1.90 (m, 1H), 1.85 (t, *J*= 5.2 Hz, 1H), 1.80 (m, 1H), 1.34 (s, 3H), 1.29 (s, 3H), 1.04-1.02 (m, 1H), 0.81 (s, 3H).

Intermediate 2: [(1*R*)-1-amino-2-(3-ethylphenyl)ethyl]boronic acid (+)-pinanediol ester trifluroacetate



Step 1: (3-ethylphenyl)methanol

A solution of 3-bromo benzyl alcohol (5.00 g, 26.7mmol) in degassed tetrahydrofuran (50 ml) was placed in a pressure bottle and treated with cesium carbonate (26.0 g, 80.2 mmol), 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(1:1) complex with DCM (40 mg,

0.54 mmol). Triethylborane (1.0 M in THF, 80 mL, 80 mmol) was added and the reaction mixture was heated at 70 °C for 5 h. The contents of the pressure bottle were cooled to 0 °C and quenched by an aqueous (10%) NaOH solution and an aqueous (30%) H_2O_2 solution. The reaction mixture was stirred for 30 min. at room temperature, acidified with dilute aqueous HCl and extracted with diethyl ether. The organic layer was dried (Na_2SO_4) and concentrated. The crude was purified by flash chromatography on silica gel, eluting with 5-10% of ethyl acetate in petroleum ether to get the required product (3.5 g, 90%) as pale yellow liquid.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.31-7.27 (m, 1H), 7.22-7.14 (m, 3H), 4.68 (s, 2H) 2.70-2.64 (m, 2H), 1.27-1.24 (t, *J*=7.6, 3H).

Step 2: 1-(bromomethyl)-3-ethylbenzene

A cold (0 °C) solution of (3-ethylphenyl)methanol (3.50 g, 25.7 mmol) in diethyl ether (40 mL) was treated with phosphorus tribromide (0.8 mL, 8.5 mmol) and the reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was then poured into ice and extracted with ether. The organic layer was dried over sodium sulfate and concentrated. The crude (3.1 g, 60%) was taken as such for next step without further purification.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.29-7.15 (m, 3H), 7.15-7.14 (m, 1H), 4.50 (s, 2H) 2.69-2.63 (m, 2H), 1.27-1.23 (t, *J*= 7.6, 3H).

Step 3: 2-(3-ethylbenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

A solution of 1-(bromomethyl)-3-ethylbenzene (1.7g, 8.59 mmol) in degassed 1, 4-dioxane (40 ml) was treated with bis(pinacolato)diboron (2.61g, 10.3mmol), potassium carbonate (3.56 g, 25.8mmol), tetrakis(triphenylphosphine) palladium(0) (0.497 g, 0.429 mmol) and the mixture heated at 100 °C for 12h The contents of the flask were cooled to room temperature and filtered through a celite bed. Filtrate was concentrated and the crude was purified by column chromatography on silica gel, eluting with 5-10% of ethylacetate in petroleum ether to get the title compound (1.4 g, 66%) as yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.18-7.14 (m, 3H), 7.03-6.96 (m, 3H), 2.64-2.58 (m, 2H), 2.28 (s, 2H), 1.24-1.21 (m, 15H).

Step 4: (3-ethylbenzyl)boronic acid (+)-pinanediol ester

A solution of 2-(3-ethylbenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.4 g, 5.68 mmol) in diethyl ether (30 ml) was treated with (1S, 2S, 3R, 5S)-(+)-pinanediol (1.45 g, 8.53 mmol). The reaction mixture was stirred at room temperature for 12 h then the mixture was

washed with water twice, then with brine and dried over anhydrous sodium sulphate, then concentrated. The crude product was purified by column chromatography on silica gel, eluting with 5% of ethyl acetate in petroleum ether, to afford the title compound (1.43 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.15 (m, 1H), 7.04-7.01 (m, 2H), 6.98-6.96 (m, 1H), 4.29-4.27 (m, 1H), 2.64-2.58 (m, 2H), 2.34-2.28 (m, 3H), 2.20-2.19 (m, 1H), 2.07-2.04 (m, 1H), 1.89-1.81 (m, 2H), 1.29 (s, 3H), 1.25-1.21 (m, 3H), 1.1-1.08 (m, 1H), 0.84 (s, 3H).
GCMS: m/z: 298

Step 5: [(1*S*)-1-chloro-2-(3-ethylphenyl)ethyl]boronic acid (+)-pinanediol ester

To a cooled (-100 °C) mixture of dichloromethane (0.89 ml, 13.7 mmol) and anhydrous tetrahydrofuran (6 ml) was added n-butyl lithium (2.5 M in hexanes, 2.0 ml, (3.7 mmol) over 10 min. After stirring for 20 min. at -100 °C, a solution of (3-ethylbenzyl)boronic acid (+)-pinanediol ester (1.36 g, 4.56 mmol) in anhydrous THF (4 ml) was added over 10 min. Then a solution of zinc chloride (0.5 M in THF, 8.2 mL, 4.1mmol) was added at -100 °C over 30min. The mixture was allowed to reach room temperature and stirred for 18 h and concentrated. To the resulting oil was added diethyl ether and saturated ammonium chloride (25 ml each) and stirred vigorously. The aqueous layer was extracted with diethyl ether three times and the combined organic layers were dried over anhydrous sodium sulphate and concentrated in vacuo. The residue (1.5 g, 94%) was taken as such for the next step.
GCMS: m/z: 346

Step 6: [(1*R*)-1-[bis(trimethylsilyl)amino]-2-(3-ethylphenyl)ethyl]boronic acid (+)-pinanediol ester

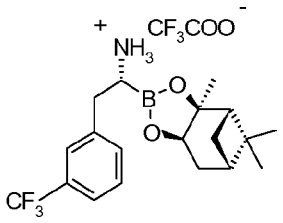
To a cooled (-78 °C) solution of [(1*S*)-1-chloro-2-(3-ethylphenyl)ethyl]boronic acid (+)-pinanediol ester (1.5 g, 4.32 mmol) in 15 ml of anhydrous tetrahydrofuran was added lithium bis(trimethylsilyl)amide (1M in THF, 6.5 ml, 6.5 mmol). The mixture was allowed to room temperature, stirred for 18 h and concentrated to dryness. To the resulting residue was added hexane, and then the precipitated solid was filtered off. The filtrate was concentrated to give the required crude product (1.2 g, 58%) which was taken as such for the next step without further purification.

Step 7: [(1*R*)-1-amino-2-(3-ethylphenyl)ethyl]boronic acid (+)-pinanediol ester trifluroacetate

A cooled (0 °C) solution of [(1R)-1-[bis(trimethylsilyl)amino]-2-(3-ethylphenyl)ethyl]boronic acid (+)-pinanediol ester (1.20 g, 2.54 mmol) in diethyl ether (20 ml) was treated with trifluoroacetic acid (0.87 ml, 7.6 mmol) dropwise. The reaction mixture was evaporated under reduced pressure at a temperature below 30 °C. The crude was taken up in toluene and evaporated, and this sequence was repeated four times. The white solid obtained (1.0 g, 89%) was used without further purification for the next step.

^{1}H NMR (400 MHz, DMSO-d6): δ 7.22-7.26 (m, 1H), 7.09-7.11 (m, 3H), 4.31-4.33 (m, 1H), 3.00-3.19 (m, 3H), 2.59-2.65 (m, 2H), 2.18-2.23 (m, 2H), 1.90-1.98 (m, 1H), 1.80-1.89 (m, 1H), 1.33 (s, 3H), 1.20-1.26 (m, 6H), 1.06 (m, 1H), 0.80 (s, 3H)

Intermediate 3: [(1*R*)-1-amino-2-(3-trifluoromethyphenyl)ethyl]boronic acid (+)-pinanediol ester trifluroacetate



Step 1: 2-(3-trifluoromethylbenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

A solution of 3-(trifluoromethyl) benzyl bromide (5.00 g, 20.9 mmol) in degassed 1,4-dioxane (100 ml) was treated with bis(pinacolato)diboron (6.4 g, 25 mmol), potassium carbonate (20.9 g, 62.7 mmol), tetrakis(triphenylphosphine) palladium(0) (1.2 g, 1.0 mmol) and the mixture heated at 100 °C for 12 h The contents of the flask were cooled to room temperature and filtered through a celite bed. Filtrate was concentrated and the crude was purified by column chromatography on silica gel, eluting with 2% of ethylacetate in petroleum ether to get the title compound (5.1 g, 85%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.33-7.40 (m, 3H), 2.36 (s, 2H), 1.25 (s, 12H).

GCMS: m/z=286

Step 2: (3-trifluoromethylbenzyl)boronic acid (+)-pinanediol ester

A solution of 2-(3-trifluoromethylbenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.10 g, 17.8 mmol) in diethyl ether (50 ml) was treated with (1S, 2S, 3R, 5S)-(+)-pinanediol (4.55 g, 26.7 mmol). The reaction mixture was stirred at room temperature for 12 h, then the mixture was washed with water twice, then with brine and dried over sodium sulphate, then concentrated. The crude product was purified by column chromatography on silica gel,

eluting with 2% of ethyl acetate in petroleum ether to afford the title compound (6.0 g, 99%) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (s, 1H), 7.35-7.38 (m, 3H), 4.29 (dd, *J*= 2.0, 8.8 Hz, 1H), 2.40 (s, 2H), 2.31-2.36 (m, 1H), 2.17-2.21 (m, 1H), 2.05 (t, *J*= 5.8 Hz, 1H), 1.90-1.92 (m, 1H), 1.80-1.85 (m, 1H), 1.39 (s, 3H), 1.29 (s, 3H), 1.02-1.05 (m, 1H), 0.84 (s, 3H). GCMS: m/z=338

Step 3: (1*S*)-1-chloro-2-(3-trifluoromethylbenzyl)-ethylboronic acid (+)-pinanediol ester

To a cooled (-100 °C) mixture of dichloromethane (1.70 mL, 26.6 mmol) and anhydrous tetrahydrofuran (17 ml) was added n-butyl lithium (1.6 M, 6.1 mL, 9.75 mmol) over 15 min. After stirring for 20 min. at -100 °C, a solution of (3-trifluoromethylbenzyl)boronic acid (+)-pinanediol ester (3.0 g, 8.87 mmol) in anhydrous THF (12 ml) was added over 15 min. Then a solution of zinc chloride (0.5 M in THF, 16.0 mL, 8.0 mmol) was added at -100 °C over 30 min. The mixture was allowed to reach room temperature and stirred for 18 h and concentrated. To the resulting oil was added diethyl ether and saturated ammonium chloride (25 ml each) and stirred vigorously. The aqueous layer was extracted with diethyl ether three times and the combined organic layers were dried over anhydrous sodium sulphate and concentrated in vacuo. The yellow liquid (3.4 g, 99%) was taken as such for the next step.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.54 (m, 4H), 4.36 (dd, *J*= 1.6, 8.9 Hz, 1H), 3.63-3.69 (m, 1H), 3.24-3.26 (m, 1H), 3.17-3.19 (m, 1H), 2.32-2.40 (m, 1H), 2.17-2.19 (m, 1H), 2.05-2.08 (m, 1H), 1.84-1.91 (m, 2H), 1.36 (s, 3H), 1.28 (s, 3H), 0.99-1.02 (m, 1H), 0.84 (s, 3H). GCMS: m/z=386

Step 4: [(1*R*)-1-[bis(trimethylsilyl)amino]-2-(3-trifluoromethylphenyl)ethyl]boronic acid (+)-pinanediol ester

To a cooled (-78 °C) solution of [(1*S*)-1-chloro-2-(3-trifluoromethylphenyl)ethyl]boronic acid (+)-pinanediol ester (3.4 g, 8.8 mmol) in 25 ml of anhydrous tetrahydrofuran was added lithium bis(trimethylsilyl)amide (1M in THF, 15 ml, 15 mmol). The mixture was allowed to room temperature, stirred for 18 h and concentrated to dryness. To the resulting residue was added hexane, and then the precipitated solid was filtered off. The filtrate was concentrated to give the title compound as a crude product which was taken as such for the next step without further purification.

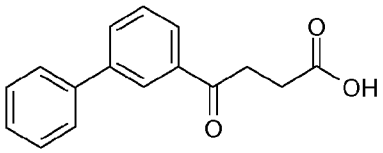
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.53 (m, 4H), 4.22-4.25 (m, 1H), 3.06-3.07 (m, 1H), 2.91-2.93 (m, 1H), 2.22-2.32 (m, 3H), 2.02-2.03 (m, 1H), 1.87-1.88 (m, 2H), 1.37 (s, 3H), 1.27 (s, 3H), 0.94-0.96 (m, 1H), 0.83 (s, 3H), 0.17 (s, 12H), 0.06 (s, 6H)

Step 5: [(1*R*)-1-amino-2-(3-trifluoromethyphenyl)ethyl]boronic acid (+)-pinanediol ester trifluroacetate

A cooled (0 °C) solution of [(1*R*)-1-[bis(trimethylsilyl)amino]-2-(3-trifluoromethylphenyl)ethyl]boronic acid (+)-pinanediol ester (1.5 g, 2.93 mmol) in diethyl ether (15 ml) and at 0 °C was treated with trifluoroacetic acid (0.67 ml, 8.8 mmol) dropwise. Reaction was stirred for 3 h at room temperature. The reaction mixture was evaporated under reduced pressure at a temperature below 30 °C. The crude was taken up in toluene and evaporated, and this sequence was repeated four times. The crude product obtained (1.7 g) was used without further purification for the next step.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.54 (m, 4H), 4.33-4.35 (m, 1H), 3.10-3.39 (m, 2H), 2.15-2.35 (m, 2H), 2.01-2.08 (m, 2H), 1.89-1.95 (m, 2H), 1.37 (s, 3H), 1.27 (s, 3H), 0.94-0.97 (m, 1H), 0.83 (s, 3H)

Intermediate 4: 4-Biphenyl-3-yl-4-oxo-butyric acid



Step 1: 4-biphenyl-3-yl-4-oxo-butyric acid ethyl ester

A mixture of 4-(3-bromo-phenyl)-4-oxo-butyric acid ethyl ester (500 mg, 1.75mmol), phenylboronic acid (340 mg, 2.62 mmol) and cesium fluoride (1.06g, 7 mmol) in dioxane: water (2:1, 20 mL) was degassed with nitrogen for 15 min, then treated with bis(triphenylphosphine)dichloropalladium (II) (11 mg, 0.175 mmol) and the reaction mixture was irradiated in a microwave reactor at 90 °C for 1 h. The reaction mixture was then diluted with ethyl acetate, filtered through celite, and the solvents evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel using ethyl acetate and petroleum ether as eluent, to give the Title compound (0.40 g, 83%).

MS(ESI+): 283.0, HPLC (Method A): Rt. 5.2 min, HPLC purity 95.3%

Step 2: 4-Biphenyl-3-yl-4-oxo-butyric acid

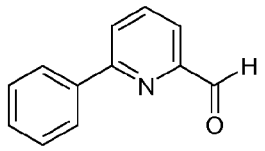
A solution of 4-biphenyl-3-yl-4-oxo-butyric acid ethyl ester (400 mg, 1.41 mmol) in tetrahydrofuran : water (4:1, 10 mL) was treated with $LiOH.H_2O$ (170 mg, 4.23 mmol) and

the reaction mixture was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure, the residue was diluted with water and extracted with ethyl acetate thrice. The aqueous layer was acidified with an aqueous solution of HCl (1.5N) and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated to afford the title compound (0.3 g, 83%).

^{1}H NMR (400 MHz, DMSO-d6): δ 8.20 (s, 1H), 7.92-7.98 (m, 2H), 7.72-7.74 (m, 2H), 7.60-7.64 (m, 1H), 7.50-7.51 (m, 2H), 7.40-7.41 (m, 1H), 3.32-3.35 (m, 2H), 2.59-2.61 (m, 2H).

MS(ESI+): 255.0, HPLC Rt. 4.0 min, HPLC purity 99.7 %.

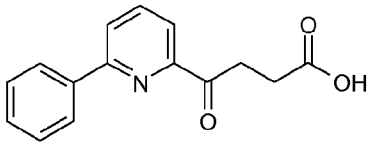
Intermediate 5: 6-Phenyl-pyridine-2-carbaldehyde



A mixture of 6-bromo pyridine-2-carboxaldehyde (500 mg, 2.68 mmol), phenylboronic acid (870 mg, 6.7mmol) and cesium fluoride (610 mg, 4.0 mmol) were taken in dioxane: water (2:1) 7.5 mL and degassed with nitrogen for 15 min. Then was added Bis(triphenylphosphine)dichloropalladium (II) (94 mg, 0.13 mmol) and the reaction mixture was irradiated in a microwave reactor at 90 °C for 2 h. The reaction mixture was then diluted with ethyl acetate, filtered through celite, and evaporated. The crude was purified by flash chromatography on silica gel using ethyl acetate and petroleum ether as eluent.

MS(ESI+): 184.0, HPLC (Method A) Rt. 3.3 min, HPLC purity 95.1 %

Intermediate 6: 4-Oxo-4-(6-phenyl-pyridin-2-yl)-butyric acid



Step 1: 4-Oxo-4-(6-phenyl-pyridin-2-yl)-butyric acid methyl ester

A solution of 6-phenyl-pyridine-2-carbaldehyde (Intermediate 5; 800 mg, 4.37 mmol) in methanol was treated with methyl acrylate (0.54 mL, 5.2mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazonium bromide (220 mg, 0.87 mmol) and triethylamine (1.8 mL, 13mmol). The reaction mixture was then refluxed at 70 °C for 1h. The reaction mixture was cooled to RT, quenched with a saturated NH_4Cl solution in water and extracted with ethyl acetate. The organic layer was separated, washed with $NaHCO_3$, brine, dried over Na_2SO_4 and

concentrated. The crude was purified by column chromatography on silica gel using ethyl acetate and petroleum ether as eluent (0.80 g; 68%).

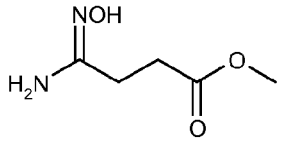
MS(ESI+): 270.0

Step 2: 4-Oxo-4-(6-phenyl-pyridin-2-yl)-butyric acid

A solution of 4-oxo-4-(6-phenyl-pyridin-2-yl)-butyric acid methyl ester (600 mg, 2.2 mmol) in tetrahydrofuran : water (4:1, 10mL) was treated with $LiOH.H_2O$ (280 mg, 6.68 mmol) and the reaction mixture was stirred at RT for overnight. The solvent was removed and the residue was diluted with water and washed with dichloromethane. The aqueous layer was then neutralized with an aqueous solution of HCl (1.5 N) and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated. The solid obtained was further purified by preparative HPLC.

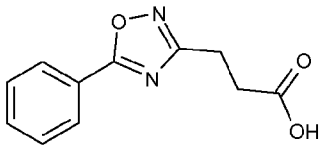
^{1}H NMR (400 MHz, DMSO-d6): δ 8.20-8.26 (m, 3H), 8.00-8.10 (m, 1H), 7.88-7.90 (m, 1H), 7.47-7.57 (m, 3H), 3.50-3.53 (m, 2H), 2.62-2.65 (m, 2H). HPLC (Method A) Rt. 3.9 min, HPLC purity 99.5 %

Intermediate7: 3-(N-Hydroxycarbamimidoyl)-propionic acid methyl ester



A mixture of 3-cyanopropionic acid methylester (2.00 g, 17.7 mmol), hydroxylamine hydrochloride (1.80 g, 26.5mmol) and triethylamine (5 mL, 35 mmol) in ethanol was refluxed at 85 °C for 2h. The reaction mixture was evaporated and azeotroped with toluene thrice and directly taken to next step without further purification (2.5 g, 96%).

Intermediate 8: 3-(5-Phenyl-[1,2,4]oxadiazol-3-yl)-propionic acid



Step 1: 3-(5-Phenyl-[1,2,4]oxadiazol-3-yl)-propionic acid methyl ester

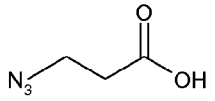
Benzoic acid (2.00 g, 16.4 mmol) and 1.1'-carbonyldiimidazole (3.8 g, 18 mmol) were stirred in dimethylformamide (25 mL) at RT for 2h. Then 3-(N-Hydroxycarbamimidoyl)-propionic acid methyl ester (Intermediate 7; 2.5 g, 18 mmol) was added and the reaction mixture was stirred at RT overnight. The reaction mixture was then heated at 100 °C for 2h.

The reaction mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude was purified by column chromatography on silica gel using dichloromethane and methanol as eluent.
^{1}H NMR (400 MHz, DMSO-d6): δ 8.06-8.09 (m, 2H), 7.67-7.72 (m, 1H), 7.60-7.64 (m, 2H), 3.61 (s, 3H), 3.03-3.06 (m, 2H), 2.80-2.84 (m, 2H). MS(ESI+): 233.0, HPLC (Method A) Rt 3.9 min, HPLC purity 95.5 %

Step 2: 3-(5-Phenyl-[1,2,4]oxadiazol-3-yl)-propionic acid

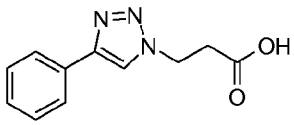
A solution of 3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-propionic acid methyl ester (800 mg, 3.44 mmol) in tetrahydrofuran : water (4:1) was treated with $LiOH.H_2O$ (400 mg, 10.3 mmol) and the reaction mixture was stirred at RT overnight. The solvent was removed under reduced pressure and the residue was diluted with water, washed with dichloromethane. The aqueous layer was then neutralized with an aqueous solution of HCl (1.5 N) and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated. The product was used without further purification in the next steps
^{1}H NMR (400 MHz, DMSO-d6): δ 8.07-8.10 (m, 2H), 7.60-7.72 (m, 3H), 2.98-3.01 (m, 2H), 2.71-2.74 (m, 2H). MS(ESI+): 219.0, HPLC (Method A) Rt 3.1 min, HPLC purity 99.6 %

Intermediate 9: 3-azido-propionic acid



A solution of beta-alanine (15.0 g, 168 mmol) in anhydrous methanol was treated with potassium carbonate (46.3 g, 336 mmol), $CuSO_4.5H_2O$ (0.83 g, 3.36 mmol) and imidazolium sulfonyl azide (35.0 g, 202 mmol) and the reaction mixture was stirred at RT for 16 hours. The reaction mixture was evaporated under reduced pressure at a temperature below 30 °C. The residue was diluted with water; the pH was adjusted to 6 and extracted with ethyl acetate. The pH of the aqueous phase was finally adjusted to 3 and the aqueous layer extracted with ethyl acetate; the organic layer was separated, dried over Na_2SO_4 and concentrated to give crude 3-azido-propionic acid.

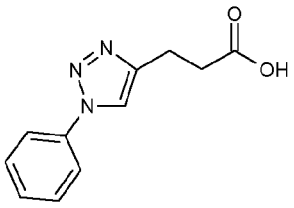
Intermediate 10: 3-(4-Phenyl-[1,2,3]triazol-1-yl)-propionic acid



A solution of phenyl acetylene (1.61 g, 15.8 mmol) and 3-azido-propionic acid (2.0 g, 17.4 mmol) in t-BuOH: H_2O (2:1, 45 mL) was treated with sodium ascorbate (469 mg, 2.37 mmol) and $CuSO_4.5H_2O$ (196 mg, 0.79 mmol) and the reaction mixture was stirred at RT for 12h. Ethyl acetate was added to the reaction mixture and extracted with water. Then the organic layer was washed with water followed by brine. The combined organic layers were concentrated, dried under vacuum to give the title compound as a white solid (1.6 g, 46%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.58 (s, 1H), 8.55 (s, 1H), 7.82 (d, *J*= 7.4 Hz, 2H), 7.44 (t, *J*= 7.4 Hz, 2H), 7.32 (t, *J*= 7.4 Hz, 1H), 4.60 (s, 2H), 3.01 (s, 2H). MS(ESI+): 218.0. HPLC (Method A) RT 2.7 min, HPLC purity 99.7 %.

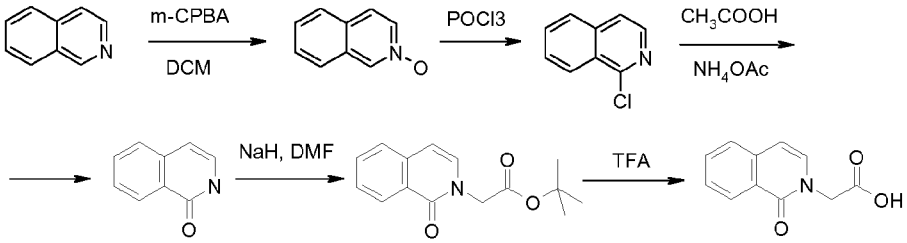
Intermediate 11: 3-(1-Phenyl-1H-[1,2,3]triazol-4-yl)-propionic acid



This intermediate was prepared according to the protocol described for Intermediate 10.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.25 (s, 1H), 8.57 (s, 1H), 7.87-7.85 (m, 2H), 7.60-7.56 (m, 2H), 7.46 (t, *J*= 7.4 Hz, 1H), 2.93 (t, *J*= 7.4 Hz, 2H), 2.66 (t, *J*= 7.4 Hz, 2H). MS(ESI+): 218.2. HPLC (Method A) RT 2.7 min, HPLC purity 99.8 %.

Intermediate 11: (1-oxoisoquinolin-2(1*H*)-yl)acetic acid



Step 1: isoquinolin-*N*-oxide

A solution of isoquinoline (20.0 g, 155 mmol) in dichloromethane (400 mL) was treated with *m*-chloroperbenzoic acid (40.0 g, 232 mmol) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered and the filtrate was evaporated and taken to next step without further purification (20.0 g, 89%).

MS (ESI+): M=146.3

Step 2: 1-chloroisoquinoline

Phosphorus oxychloride (200 mL) was added dropwise under ice-cold condition to isoquinolin-*N*-oxide (20.0 g). The reaction mixture was then heated to reflux at 105 °C overnight. Phosphorus oxychloride was evaporated under reduced pressure, then the residue was quenched with ice and extracted with dichloromethane. The organic layer was separated, dried over sodium sulfate and concentrated. The crude was purified by column chromatography on silica gel using ethylacetate and petroleum ether as eluent (21.0 g; 85%).

^{1}H NMR (400 MHz, DMSO-d6): δ 8.25-8.31 (m, 2H), 8.08 (d, *J*= 8.0 Hz, 1H), 7.88-7.91 (m, 2H), 7.80-7.84 (m, 1H). MS (ESI+): 164.0, HPLC (Method A) Rt 8.29min; HPLC purity 96.0 %

Step 3: isoquinolin-1(2*H*)-one

A solution of 1-chloroisoquinoline (8.1 g) in glacial acetic acid (170 mL) was treated with ammonium acetate (25 g). The reaction mixture was then heated at 100 °C for 3h. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was quenched with ice and the solid formed was filtered and dried on the filter (5.8 g, 80%).

^{1}H NMR (400 MHz, DMSO-d6): δ 11.24 (s, 1H), 8.18 (d, *J*= 8.4 Hz, 1H), 7.63-7.71 (m, 2H), 7.45-7.49 (m, 1H), 7.15-7.18 (m, 1H), 6.55 (d, *J*= 7.2 Hz, 1H). MS (ESI+): 146.0, HPLC (Method A) Rt 2.23min; HPLC purity 98.2 %

Step 4: tert-butyl (1-oxoisoquinolin-2(1*H*)-yl)acetate

A cold (0 °C) solutionof isoquinolin-1(2*H*)-one **3** (1.0 g, 6.9 mmol) and tertiary butyl acetate (2.0 mL, 13.8 mmol) in dimethyl formamide (15 mL) was treated with sodium hydride (60% in mineral oil, 660 mg, 17.2 mmol). After 10 minutes the reaction mixture was quenched with ice and the solid formed was filtered and dried (1.2 g; 60%).

^{1}H NMR 400 MHz, CDCl3: δ 8.42-8.44 (m, 1H), 7.63-7.67 (m, 1H), 7.47-7.53 (m, 2H), 7.01 (d, *J*= 8.0 Hz, 1H), 6.53 (d, *J*= 8.0 Hz, 1H), 4.64 (s, 2H), 1.49 (s, 9H). MS (ESI+): 204.3, HPLC (Method A) Rt 4.08min; HPLC purity 98.4 %

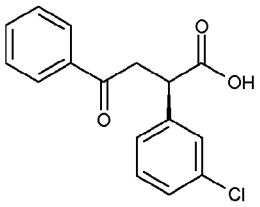
Step 5: (1-oxoisoquinolin-2(1*H*)-yl)acetic acid

A cold solution of tert-butyl (1-oxoisoquinolin-2(1*H*)-yl)acetate (1.2 g, 4.6mmol) in dichloromethane (20 mL) was treated with trifluoroacetic acid (10 mL) dropwise. The reaction mixture was then stirred at room temperature for 3h. The solvent was evaporated

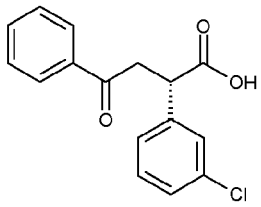
and the residue was azeotroped with toluene. The solid formed was triturated with ether to afford the title compound.

^{1}H NMR (400 MHz, DMSO-d6): δ 10.76 (s, 1H), 8.18-8.20 (m, 1H), 7.64-7.73 (m, 2H), 7.42-7.52 (m, 2H), 6.62 (d, *J*= 8.0 Hz, 1H), 4.67 (s, 2H). MS (ESI+): 204.3, HPLC (Method A) Rt 2.34 min; HPLC purity 99.3 %

Intermediates 12 and 13: (+)-2-(3-chlorophenyl)-4-oxo-4-phenylbutanoic acid and (-)-2-(3-chlorophenyl)-4-oxo-4-phenylbutanoic acid



and



Racemic 2-(3-chlorophenyl)-4-oxo-4-phenylbutanoic acid was separated by chiral preparative HPLC on a CHIRALPAK IA (250x20) mm, 5µm, Mobile Phase hexane : isopropyl alcohol (65:35), flow: 10 ml/min.

The two products elute at 13.7 min (Intermediate 12) and at 18.6 min (Intermediate 13).

The two products were analyzed using the following HPLC method:

Column: CHIRALPAK AD-H (250x4.6) mm, 5µm

Mobile Phase: 0.1%TFA in hexane : isopropyl alcohol (80:20)

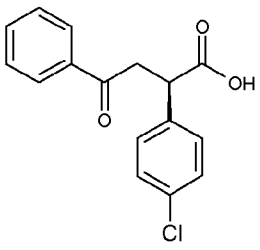
Flow: 1.0ml/min

Intermediate 12: Rt-10.8 min (Purity 100 %); αD +101.9°; ethanol, c= 1.0 g/100 mL

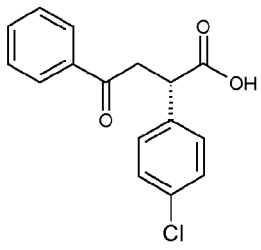
Intermediate 13: Rt-14.9 min (Purity 99.2 %)

Absolute assignment of the chiral centre as either (*R*) or (*S*) is arbitrary.

Intermediates 14 and 15: (+)-2-(4-chlorophenyl)-4-oxo-4-phenylbutanoic acid and (-)-2-(4-chlorophenyl)-4-oxo-4-phenylbutanoic acid



and



Racemic 2-(4-chlorophenyl)-4-oxo-4-phenylbutanoic acid was separated by chiral preparative HPLC on a CHIRALPAK IA (250x20) mm, 5µm, Mobile Phase hexane : isopropyl alcohol (60:40), flow: 10 ml/min.

The two products elute at 14.2 min (Intermediate 14) and at 21.4 min (Intermediate 15).

The two products were analyzed using the following HPLC method:

Column: CHIRALPAK AD-H (250x4.6) mm, 5µm

Mobile Phase: 0.1%TFA in hexane: isopropyl alcohol (80:20)

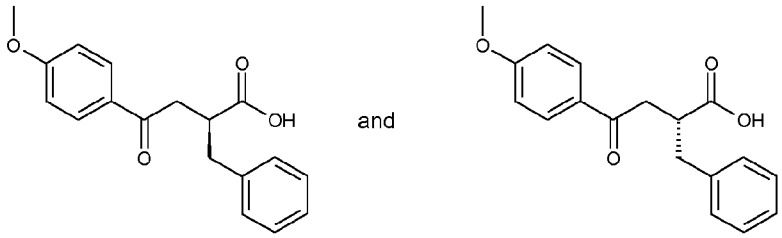
Flow: 1.0ml/min

Intermediate 14: Rt-15.4 min (Purity 99.3 %). αD +103.4°; ethanol, c= 0.57 g/100 mL

Intermediate 15: Rt-22.2 min (Purity 99.3 %). αD -111.5°; ethanol, c= 0.57 g/100 mL

Absolute assignment of the chiral centre as either (*R*) or (*S*) is arbitrary.

Intermediates 16 and 17: (+)-2-benzyl-4-(4-methoxyphenyl)-4-oxo-butyric acid and (-)-2-benzyl-4-(4-methoxyphenyl)-4-oxo-butyric acid



Racemic 2-benzyl-4-(4-methoxyphenyl)-4-oxo-butyric acid was separated by chiral preparative HPLC on a CHIRALCEL OJ-H (250x20) mm, 5µm, Mobile Phase hexane : isopropyl alcohol (75:25), flow: 10 ml/min.

The two products elute at 15.5 min (Intermediate 16) and at 20.2 min (Intermediate 17).

The two products were analyzed using the following HPLC method:

Column: CHIRALCEL OJ (250x4.6) mm, 5µm

Mobile Phase: 0.1%TFA in hexane : isopropyl alcohol (90:10)

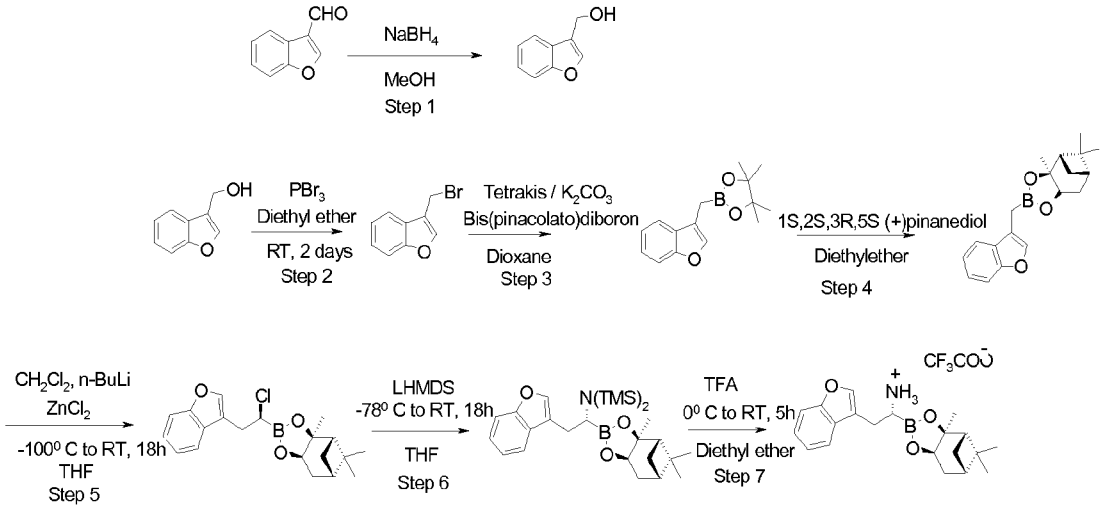
Flow: 1.0ml/min

Intermediate 16: Rt-22.3 min (Purity 98.7 %). αD +21.1°; ethanol, c= 1.0 g/100 mL

Intermediate 17: Rt-33.6 min (Purity 97.7 %). αD -21.0°; ethanol, c= 1.0 g/100 mL)

Absolute assignment of the chiral centre as either (*R*) or (*S*) is arbitrary.

Intermediate 18: (1R)-2-(benzofuran-3-yl)-1-(3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)ethanaminetrifluoroacetate



Step 1: benzofuran-3-ylmethanol

A solution of 1-Benzofuran-3-carbaldehyde (5g, 34.2 mmol) in methanol (50 mL) was cooled with ice and sodium borohydride (1.9g, 51.3 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated and the residue was partitioned between saturated ammonium chloride and dichloromethane. The organic layer was separated, dried over sodium sulfate and concentrated. The crude (5.0 g, 98%) was taken as such for next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.70 (m, 1H), 7.62 (s, 1H), 7.50-7.52 (m, 1H), 7.26-7.36 (m, 2H), 4.86 (s, 2H).

Step 2: 3-(bromomethyl)benzofuran

A cold (0 °C) solution of benzofuran-3-ylmethanol (5.0 g, 33.7 mmol) in diethyl ether (50 mL) was treated with phosphorus tribromide (1.1 mL, 11.2 mmol) and the reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was then poured into ice and extracted with ether. The organic layer was dried over sodium sulfate and concentrated. The crude (7.1 g, 100%) was taken as such for next step without further purification.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.71-7.74 (m, 2H), 7.53 (s, 1H), 7.31-7.39 (m, 2H), 4.65 (s, 2H).

Step 3: 2-(benzofuran-3-ylmethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

A solution of 3-(bromomethyl)benzofuran (7.1g, 33.8 mmol) in degassed 1, 4-dioxane (70 ml) was treated with bis(pinacolato)diboron (10.3g, 40.5mmol), potassium carbonate (13.9 g, 101.0mmol), tetrakis(triphenylphosphine) palladium(0) (1.9 g, 1.7 mmol) and the mixture

heated at 100 °C for 12h The contents of the flask were cooled to room temperature and filtered through a celite bed. Filtrate was concentrated and the crude was purified by column chromatography on silica gel, eluting with 2-5% of ethylacetate in petroleum ether to get the title compound (6.1 g, 69%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.57 (m, 2H), 7.44-7.46 (m, 1H), 7.21-7.30 (m, 2H), 2.23 (s, 2H), 1.29 (s, 12H).

Step 4: 2-(benzofuran-3-ylmethyl)boronic acid (+)-pinanediol ester

A solution of 2-(benzofuran-3-ylmethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.1 g, 23.6 mmol) in diethyl ether (60 ml) was treated with (1S, 2S, 3R, 5S)-(+)-pinanediol (6.0 g, 35.4 mmol). The reaction mixture was stirred at room temperature for 12 h then the mixture was washed with water twice, then with brine and dried over anhydrous sodium sulphate, then concentrated. The crude product was purified by column chromatography on silica gel, eluting with 5% of ethyl acetate in petroleum ether, to afford the title compound (6.3 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.58 (m, 1H), 7.53-7.55 (m, 1H), 7.44-7.46 (m, 1H), 7.23-7.28 (m, 2H), 4.33 (dd, *J* = 1.88, 8.76 Hz, 1H), 2.32-2.34 (m, 1H), 2.28 (s, 2H), 2.21-2.22 (m, 1H), 2.08 (t, *J* = 5.88 Hz, 1H), 1.42 (s, 3H), 1.29 (s, 3H), 1.13 (d, *J* = 10.92 Hz, 1H), 0.85 (s, 3H). GCMS: m/z: 310

Step 5: [(1*S*)-1-chloro-2-(benzofuran-3-ylmethyl)boronic acid (+)-pinanediol ester

To a cooled (-100 °C) mixture of dichloromethane (6.3 ml, 60.9 mmol) and anhydrous tetrahydrofuran (36 ml) was added n-butyl lithium (1.6 M in hexanes, 14.0 ml, (22.3 mmol) over 20 min. After stirring for 20 min. at -100 °C, a solution of 2-(benzofuran-3-ylmethyl)boronic acid (+)-pinanediol ester (6.3 g, 20.3 mmol) in anhydrous THF (22 ml) was added over 20 min. Then a solution of zinc chloride (0.5 M in THF, 36.5 mL, 18.2 mmol) was added at -100 °C over 30min. The mixture was allowed to reach room temperature and stirred for 18 h and concentrated. To the resulting oil was added diethyl ether and saturated ammonium chloride (100 ml each) and stirred vigorously. The aqueous layer was extracted with diethyl ether three times and the combined organic layers were dried over anhydrous sodium sulphate and concentrated in vacuo. The residue (7.3 g, 99%) was taken as such for the next step.

^{1}H NMR (400 MHz, DMSO-d6): δ 7.57-7.60 (m, 2H), 7.47-7.49 (m, 1H), 7.25-7.31 (m, 2H), 4.34-4.36 (m, 1H), 3.29-3.31 (m, 1H), 3.22-3.24 (m, 1H), 2.31-2.35 (m,

1H), 2.12-2.14 (m, 1H), 2.06 (t, *J* = 5.84 Hz, 1H), 1.86-1.90 (m, 2H), 1.42 (s, 3H), 1.04 (d, *J* = 11.04 Hz, 1H), 0.85 (s, 3H). GCMS: m/z: 358.2

Step 6: [(1*R*)-1-[bis(trimethylsilyl)amino]- 2-(benzofuran-3-ylmethyl)boronic acid (+)-pinanediol ester

To a cooled (-78 °C) solution of [(1*S*)-1-chloro-2-(benzofuran-3-ylmethyl)boronic acid (+)-pinanediol ester (7.3 g, 20.3 mmol) in 40 ml of anhydrous tetrahydrofuran was added lithium bis(trimethylsilyl)amide (1M in THF, 25.5 ml, 25.5 mmol). The mixture was allowed to room temperature, stirred for 18 h and concentrated to dryness. To the resulting residue was added hexane, and then the precipitated solid was filtered off. The filtrate was concentrated to give the required crude product (6.7 g, 68%) which was taken as such for the next step without further purification.

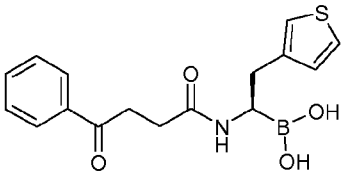
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.60 (m, 1H), 7.45-7.50 (m, 2H), 7.24-7.28 (m, 2H), 4.31 (dd, *J* = 1.56, 8.70 Hz, 1H), 3.14-3.18 (m, 1H), 2.90-2.92 (m, 1H), 2.72-2.75 (m, 1H), 2.30-2.34 (m, 1H), 2.14-2.15 (m, 1H), 2.03 (t, *J* = 5.68 Hz, 1H), 1.80-1.88 (m, 2H), 1.39 (s, 3H), 1.30 (s, 3H), 1.01 (d, *J* = 10.88 Hz, 1H), 0.84 (s, 3H), 0.09 (s, 18H).

Step 7: [(1*R*)-1-amino-2-(benzofuran-3-ylmethyl)boronic acid (+)-pinanediol ester trifluroacetate

A cooled (0 °C) solution of [(1*R*)-1-[bis(trimethylsilyl)amino]- 2-(benzofuran-3-ylmethyl)boronic acid (+)-pinanediol ester (6.7 g, 13.9 mmol) in diethyl ether (30 ml) was treated with trifluoroacetic acid (3.2 ml, 41.7 mmol) dropwise. The reaction mixture was evaporated under reduced pressure at a temperature below 30 °C. The crude was taken up in toluene and evaporated, and this sequence was repeated four times. The white solid obtained (2.3 g, 36%) was used without further purification for the next step.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.66 (s, 1H), 7.60-7.61 (m, 1H), 7.45-7.47 (m, 1H), 7.20-7.29 (m, 2H), 4.28-4.30 (m, 1H), 3.16-3.27 (m, 3H), 2.13-2.25 (m, 3H), 1.94 (t, *J* = 5.56 Hz, 1H), 1.81-1.86 (m, 2H), 1.25 (s, 6H), 1.01 (d, *J* = 8.00 Hz, 1H), 0.75 (s, 3H).

Example 1: [(1*R*)-1-[(4-oxo-4-phenylbutanoyl)amino]-2-(3-thienyl)ethyl]boronic acid



Step 1: [(1*R*)-1-[(4-oxo-4-phenylbutanoyl)amino]-2-(3-thienyl)ethyl]boronic acid (+)-pinanediol ester

A cooled (0 °C) solution of Intermediate 1 (100 mg, 0.24 mmol) anhydrous dichloromethane (15 ml) was treated with diisopropylethylamine (0.12 ml, 0.72 mmol) and 3-benzoyl propionic acid (42 mg, 0.24 mmol) and TBTU (91 mg, 0.29 mmol). The reaction mixture was stirred at 0 °C for 3h. The reaction mixture was concentrated under reduced pressure keeping an external bath temperature below 30 °C, and then 10 ml ethyl acetate were added. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The desired product was isolated by purification by chromatography on silica gel, eluting with pet ether/ethyl acetate 1:1.

MS (ESI+): 466.3, HPLC (Method A): Rt 5.44min 85.0 %

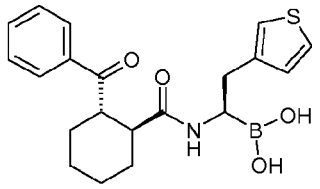
Step 2: [(1*R*)-1-[(4-oxo-4-phenylbutanoyl)amino]-2-(3-thienyl)ethyl]boronic acid

A cooled (0 °C) solution of [(1R)-1-[(4-oxo-4-phenylbutanoyl)amino]-2-(3-thienyl)ethyl]boronic acid (+)-pinanediol ester (74 mg, 0.16 mmol) in methanol / pentane (1:1, 15 mL) was treated with 2-methylpropyl boronic acid (64 mg, 0.636mmol) and an aqueous HCl solution (1.5 N, 0.4 mL) and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was then extracted with pentane thrice. The aqueous methanol layer was concentrated at temperature below 30 °C. The residue was treated with ice and basified with an aqueous (2N) solution of NaOH and extracted with dichloromethane thrice. The aqueous layer was then acidified with an aqueous (1.5 N) HCl solution and extracted with dichloromethane twice. The DCM layer was dried over sodium sulfate, filtered and concentrated to give a solid residue, which was purified by flash chromatography on high performance silica gel to obtain the title compound as a white solid.

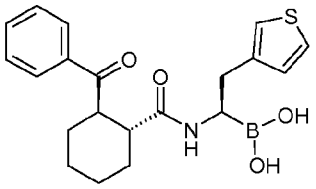
^{1}H NMR (400 MHz, DMSO-d6): δ 8.66 (s, 1H), 7.89-7.94 (m, 2H), 7.58-7.62 (m, 1H), 7.45-7.49 (m, 2H), 7.29-7.31 (m, 1H), 7.04 (s, 1H), 6.92-6.93 (m, 1H), 3.24-3.26 (m, 2H), 2.68-2.72 (m, 2H), 2.55-2.58 (m, 3H). MS (ESI+): 314.0 [M+H-H_2O], HPLC (Method A): Rt 2.89min; HPLC purity 95.8 %

The following compounds were synthesized using the same procedure followed for **Example 1:**

Example 2: [(1*R*)-1-({[(1*RS*,2*RS*)-2-benzoylcyclohexyl]carbonyl}amino)-2-(3-thienyl)ethyl]boronic acid

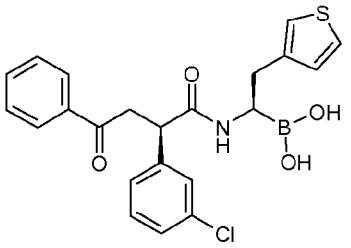


and

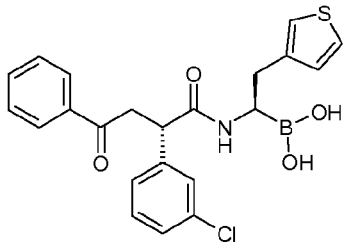


This Example is a mixture of diastereoisomers. The chiral centres on the cyclohexane ring have *trans* configuration. Prepared starting from *trans*-2-benzoylcyclohexane-1-carboxylic acid from Rielke Chemicals. Pale pink solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.14-8.84 (m, 1H), 7.82-7.91 (m, 2H), 7.25-7.58 (m, 4H), 6.77-6.88 (m, 2H), 3.60-3.63 (m, 1H), 2.63-2.69 (m, 1H), 2.43-2.49 (m, 1H), 2.13-2.28 (m, 1H), 1.86-1.89 (m, 1H), 1.66-1.76 (m, 3H), 1.30-1.40 (m, 2H), 1.18-1.23 (m, 3H), 1.06-1.08 (m, 2H). MS (ESI+): 368.0 [M+H-H_2O], HPLC (Method A): Rt 3.71min; HPLC purity 50.6%+45.6%

Example 3: [(1*R*)-1-{[2-(*RS*)-(3-chlorophenyl)-4-oxo-4-phenylbutanoyl]amino}-2-(3-thienyl)ethyl]boronic acid.

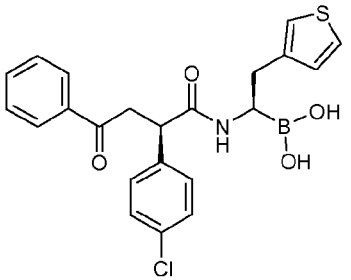


and

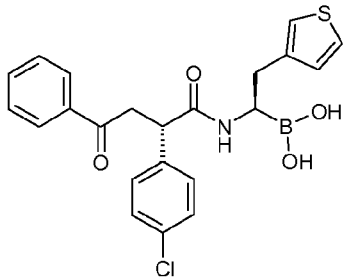


This Example is a mixture of diastereoisomers. Off-white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.95-7.96 (m, 2H), 7.58-7.60 (m, 1H), 7.48-7.50 (m, 2H), 7.42-7.44 (m, 1H), 7.22-7.34 (m, 4H), 6.88-6.95 (m, 1H), 6.60-6.62 (m, 1H), 4.13 (t, *J*= 5.1 Hz, 1H), 3.75-3.85 (m, 1H), 3.24-3.28 (m, 2H), 2.64-2.73 (m, 2H). MS (ESI+): 424.0 [M+H-H_2O], HPLC (Method A): Rt 8.57; 8.96min; HPLC purity 28.7%+67.9%

Example 4: [(1*R*)-1-{[2-(*RS*) -(4-chlorophenyl)-4-oxo-4-phenylbutanoyl]amino}-2-(3-thienyl)ethyl]boronic acid

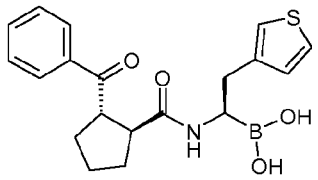


and

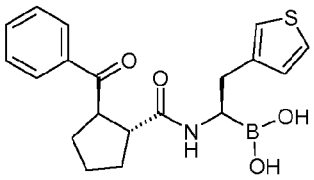


This Example is a mixture of diastereoisomers. White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.95-7.95 (m, 2H), 7.60-7.62 (m, 1H), 7.48-7.52 (m, 2H), 7.31-7.41 (m, 6H), 6.88-6.97 (m, 1H), 6.63-6.64 (m, 1H), 4.12-4.15 (m, 1H), 3.85-3.95 (m, 1H), 3.25-3.29 (m, 1H), 3.12-3.14 (m, 1H), 2.66-2.75 (m, 2H). MS (ESI+): 424.0 [M+H-H_2O], HPLC (Method A): Rt 8.56; 8.97min; HPLC purity 40.0%+53.4%

Example 5: [1-({[(1*RS*,2*SR*)-2-benzoylcyclopentyl]carbonyl}amino)-2-(3-thienyl)ethyl]boronic acid

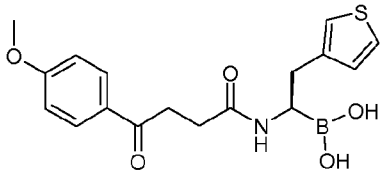


and



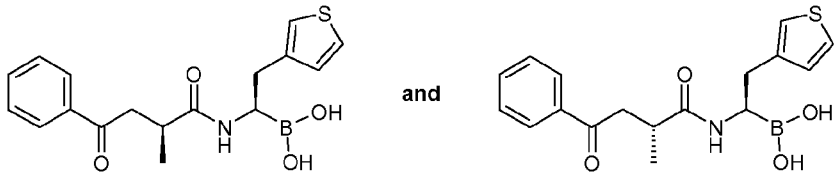
This Example is a mixture of diastereoisomers. The chiral centres on the cyclohexane ring have *trans* configuration. Prepared starting from *trans*-2-benzoylcyclopentane-1-carboxylic acid from Rielke Chemicals. Off-white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.91-7.93 (m, 1H), 7.82-7.84 (m, 1H), 7.59-7.61 (m, 1H), 7.55-7.57 (m, 1H), 7.33 (s, 1H), 7.25-7.26 (m, 1H), 6.87-6.92 (m, 1H), 6.78-6.86 (m, 1H), 4.01-4.02 (m, 1H), 3.00-3.15 (m, 2H), 2.66-2.68 (m, 2H), 2.00-2.03 (m, 1H), 1.85-1.92 (m, 1H), 1.56-1.68 (m, 4H). MS (ESI+): 354.3 [M+H-H_2O], HPLC (Method A): Rt 3.53min; HPLC purity 92.0 %

Example 9: [(1*R*)-1-{[4-(4-methoxyphenyl)-4-oxobutanoyl]amino}-2-(3-thienyl)ethyl]boronic acid



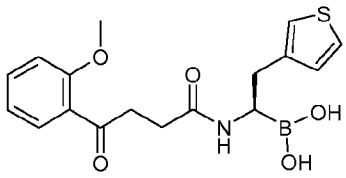
Off-white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.65 (s, 1H), 7.87-7.92 (m, 2H), 7.30-7.35 (m, 1H), 7.04 (s, 1H), 6.95-6.98 (m, 2H), 6.92-6.93 (m, 1H), 3.81 (s, 3H), 3.18-3.20 (m, 2H), 2.65-2.74 (m, 2H), 2.52-2.55 (m, 3H). MS (ESI+): 344.3 [M+H-H_2O], HPLC (Method A): Rt 3.00min; HPLC purity 96.2 %

Example 10: [(1*R*)-1-[(2-(*RS*) -methyl-4-oxo-4-phenylbutanoyl)amino]-2-(3-thienyl)ethyl]boronic acid



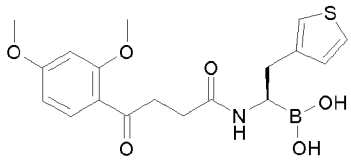
This Example is a mixture of diastereoisomers. The chiral centres on the cyclohexane ring have *trans* configuration. Prepared starting from 2-methyl-4-oxo-4-phenylbutyric acid fromABCR. Off-white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.56-8.61 (m, 1H), 7.87-7.91 (m, 2H), 7.57-7.59 (m, 1H), 7.46-7.51 (m, 2H), 7.26-7.28 (m, 1H), 7.09 (s, 1H), 6.93 (s, 1H), 3.20-3.30 (m, 1H), 3.04-3.09 (m, 1H), 2.93-2.96 (m, 1H), 2.65-2.74 (m, 2H), 2.48-2.50 (m, 1H), 1.02-1.05 (m, 3H). MS (ESI+): 328.3 [M+H-H_2O], HPLC (Method A): Rt 3.15min; HPLC purity 87.0%

Example 12:[(1*R*)-1-{[4-(2-methoxyphenyl)-4-oxobutanoyl]amino}-2-(3-thienyl)ethyl]boronic acid



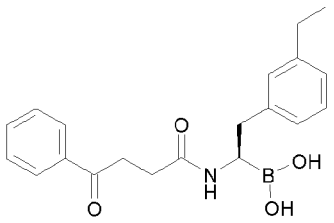
White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.51-7.53 (m, 2H), 7.49 (s, 1H), 7.14 (d, *J*= 8.1 Hz, 1H), 7.07 (s, 1H), 7.00-7.06 (m, 1H), 6.92-6.94 (m, 1H), 3.84 (s, 3H), 3.07-3.13 (m, 3H), 2.80-2.81 (m, 1H), 2.76-2.78 (m, 1H), 2.38 (t, *J*= 7.0 Hz, 2H).
MS (ESI+): 344.0 [M+H-H_2O], HPLC (Method A): Rt 3.03; HPLC purity 93.2%

Example 13: [(1*R*)-1-{[4-(2,4-dimethoxyphenyl)-4-oxobutanoyl]amino}-2-(3-thienyl)ethyl]boronic acid



White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.63 (d, *J*= 8.6 Hz, 1H), 7.34-7.36 (m, 1H), 7.06 (s, 1H), 6.94 (s, 1H), 6.57-6.60 (m, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.04-3.10 (m, 3H), 2.75-2.80 (m, 1H), 2.65-2.71 (m, 1H), 2.34-2.35 (m, 2H).
MS (ESI+): 374.0 [M+H-H_2O], HPLC (Method A): Rt 3.13; 3.41min; HPLC purity 99.0%

Example 6: {(1*R*)-2-(3-ethylphenyl)-1-[(4-oxo-4-phenylbutanoyl)amino]ethyl}boronic acid



Step 1: {(1*R*)-2-(3-ethylphenyl)-1-[(4-oxo-4-phenylbutanoyl)amino]ethyl}boronic acid (+)-pinanediol ester

A cold (-10 °C) solution of Intermediate 2 (150 mg, 0.34 mmol) in anhydrous dimethylformamide (10 ml) was treated with diisopropylethylamine (0.17 ml, 1.0 mmol). 3-benzoyl propionic acid (60 mg, 0.340mmol) and TBTU (130 mg, 0.41mmol). The reaction mixture was stirred at -10 °C for 3h then concentrated under reduced pressure keeping an external bath temperature below 30 °C, and then 10 ml ethyl acetate was added. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The desired product (120 mg,; 72%) was isolated by purification through Flash chromatography on silica gel, eluting with pet ether/ethyl acetate 1:1. MS (ESI+): 488.3, HPLC (Method A): Rt 6.08min; HPLC purity 91.0%

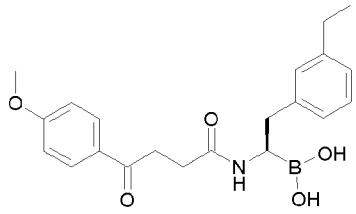
Step 2: {(1*R*)-2-(3-ethylphenyl)-1-[(4-oxo-4-phenylbutanoyl)amino]ethyl}boronic acid

A cold (0 °C) solution of {(1*R*)-2-(3-ethylphenyl)-1-[(4-oxo-4-phenylbutanoyl)amino]ethyl}boronic acid (+)-pinanediol ester (120 mg, 0.25 mmol) in methanol / pentane (1:1, 15mL) was treated with 2-methylpropyl boronic acid (99 mg, 0.99 mmol) and an aqueous solution of HCl (1.5 N, 0.5 mL) and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was then extracted with pentane thrice. The aqueous methanol layer was concentrated at temperature below 30 °C. The residue was purified by flash chromatography on high performance silica gel to obtain a solid, which was triturated with pentane to afford the Title compound as an off-white solid .

^{1}H NMR (400 MHz, DMSO-d6): δ 7.91-7.92 (m, 2H), 7.70-7.72 (m, 1H), 7.60-7.62 (m, 2H), 7.10-7.14 (m, 1H), 6.94-6.98 (m, 3H), 3.12-3.18 (m, 3H), 2.73-2.76 (m, 1H), 2.64-2.67 (m, 1H), 2.51-2.55 (m, 2H), 2.40-2.43 (m, 2H), 1.13 (t, *J*= 7.6 Hz, 3H). MS (ESI+): 336.0 [M+H-H_2O], HPLC (Method A): Rt 3.75min; HPLC purity 96.8%

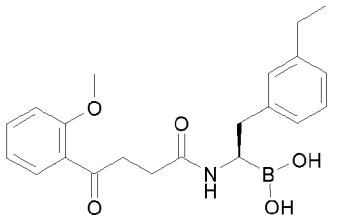
The following compounds were synthesized using the same procedure followed for **Example 6**:

Example 7: ((1*R*)-2-(3-ethylphenyl)-1-{[4-(4-methoxyphenyl)-4-oxobutanoyl]amino}ethyl)boronic acid



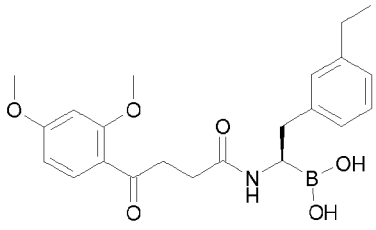
Off-white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.85-7.90 (m, 2H), 6.91-7.13 (m, 6H), 3.81 (s, 3H), 3.52-3.54 (m, 1H), 3.09-3.18 (m, 2H), 2.65-2.68 (m, 2H), 2.52-2.54 (m, 2H), 2.46-2.48 (m, 1H), 2.37-2.40 (m, 1H), 1.06-1.15 (m, 3H). MS (ESI+): 366.3 [M+H-H_2O], HPLC (Method A): Rt 3.77min; HPLC purity 96.4%

Example 8: ((1*R*)-2-(3-ethylphenyl)-1-{[4-(2-methoxyphenyl)-4-oxobutanoyl]amino}ethyl)boronic acid



Off-white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.49-7.53 (m, 2H), 7.10-7.15 (m, 2H), 6.93-7.02 (m, 4H), 3.84 (s, 3H), 3.05-3.14 (m, 3H), 2.76-2.78 (m, 1H), 2.73-2.74 (m, 1H), 2.48-2.49 (m, 2H), 2.33-2.37 (m, 2H), 1.08-1.14 (m, 3H). MS (ESI+): 366.3 [M+H-H_2O], HPLC (Method A): Rt 3.81min; HPLC purity 90.1%

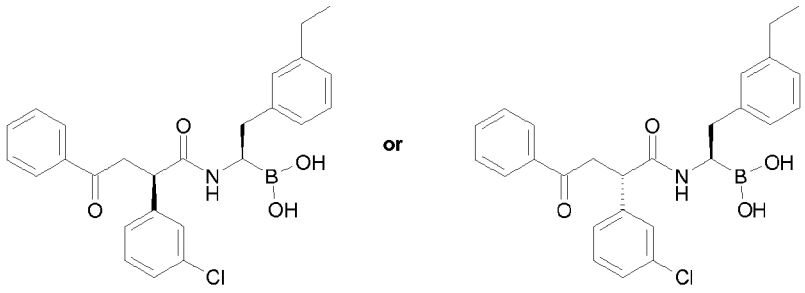
Example 11: [(1*R*)-1-{[4-(2,4-dimethoxyphenyl)-4-oxobutanoyl]amino}-2-(3-ethylphenyl)ethyl]boronic acid



Off-white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.49 (s, 1H), 7.64 (d, *J*= 8.7 Hz, 1H), 7.04-7.07 (m, 1H), 6.99 (s, 1H), 6.90-6.93 (m, 2H), 6.52-6.58 (m, 2H), 3.79 (s, 6H), 3.10-3.14 (m, 2H), 2.66-2.74 (m, 2H), 2.48-2.49 (m, 1H), 2.48 (m, 4H), 1.10 (t, *J*= 7.6 Hz, 3H).

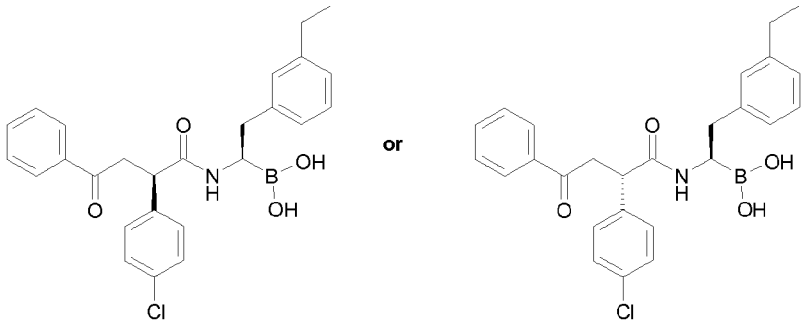
MS (ESI+): 396.2 [M+H-H_2O], HPLC (Method A): Rt 3.85min; HPLC purity 97.7 %

Example 14: [(1*R*)-1-{[(2*R*)-2-(3-chlorophenyl)-4-oxo-4-phenylbutanoyl]amino}-2-(3-ethylphenyl)ethyl]boronic acid



White solid. One diastereoisomer. The configuration at the chiral position most removed from the boronic acid group is arbitrarily assigned. This Example was prepared from Intermediate 12 (+)-2-(3-chlorophenyl)-4-oxo-4-phenylbutanoic acid (with αD +101.9°; ethanol, c= 1.0 g/100 mL). ^{1}H NMR (400 MHz, DMSO-d6): δ 7.95 (d, *J*= 8.0 Hz, 2H), 7.61-7.63 (m, 1H), 7.49-7.53 (m, 2H), 7.27-7.41 (m, 4H), 7.04-7.07 (m, 1H), 6.91-6.96 (m, 2H), 6.79-6.81 (m, 1H), 4.07-4.11 (m, 1H), 3.71-3.76 (m, 1H), 3.29-3.34 (m, 1H), 3.05-3.10 (m, 1H), 2.62-2.73 (m, 2H), 2.48-2.49 (m, 1H), 1.08 (t, *J*= 8.0 Hz, 3H). MS (ESI+): 446.0 [M+H-H_2O], HPLC (Method A): Rt 5.02min; HPLC purity 85.1%

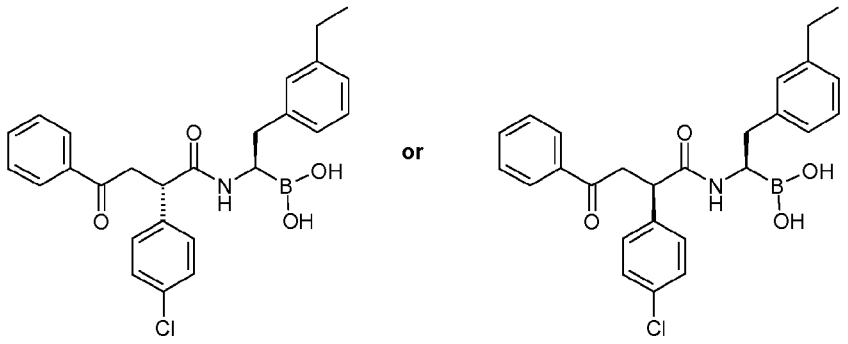
Example 15: [(1*R*)-1-{[(2*R*)-2-(4-chlorophenyl)-4-oxo-4-phenylbutanoyl]amino}-2-(3-ethylphenyl)ethyl]boronic acid



One diastereoisomer. The configuration at the chiral position most removed from the boronic acid group is arbitrarily assigned. This Example was prepared from Intermediate 14 (+)-2-(4-chlorophenyl)-4-oxo-4-phenylbutanoic acid (with αD +103.4°; ethanol, c= 0.57 g/100 mL). Off-white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.50 (s, 1H), 7.93-7.95 (m, 2H), 7.60-7.63 (m, 1H), 7.46-7.49 (m, 2H), 7.14-7.19 (m, 3H), 7.00-7.04 (m, 1H), 6.90-6.92

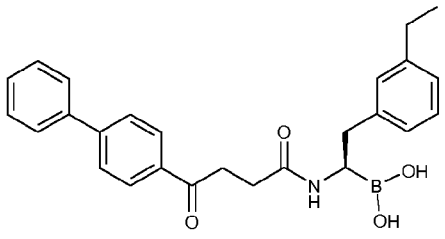
(m, 1H), 6.78-6.80 (m, 2H), 4.15-4.18 (m, 1H), 3.75-3.82 (m, 1H), 3.32-3.34 (m, 1H), 2.59-2.62 (m, 1H), 2.38-2.44 (m, 2H), 2.21-2.26 (m, 1H), 1.07 (t, *J*= 8.0 Hz, 3H).
MS (ESI+): 446.3 [M+H-H_2O], HPLC (Method A): Rt 13.54min; HPLC purity 97.1 %, CHIRAL HPLC Rt 5.48 min (98.3%)

Example 16: [(1*R*)-1-{[(2*R*)-2-(4-chlorophenyl)-4-oxo-4-phenylbutanoyl]amino}-2-(3-ethylphenyl)ethyl]boronic acid



One diastereoisomer. The configuration at the chiral position most removed from the boronic acid group is arbitrarily assigned. This Example was prepared starting from Intermediate 15 (-)-2-(4-chlorophenyl)-4-oxo-4-phenylbutanoic acid (with αD -111.5°; ethanol, c= 0.57 g/100 mL). Pale pink solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.75 (s, 1H), 7.85-7.87 (m, 2H), 7.55-7.59 (m, 1H), 7.41-7.43 (m, 2H), 7.30-7.39 (m, 2H), 7.21-7.23 (m, 2H), 7.00-7.04 (m, 1H), 6.89-6.91 (m, 1H), 6.83-6.85 (m, 1H), 4.17-4.21 (m, 1H), 3.67-3.74 (m, 1H), 3.39-3.40 (m, 2H), 2.63-2.67 (m, 1H), 2.57-2.59 (m, 1H), 2.45-2.48 (m, 2H), 1.10 (t, *J*= 7.6 Hz, 3H). MS (ESI+): 446.3 [M+H-H_2O], HPLC (Method A): Rt 13.58min; HPLC purity 97.1 %, CHIRAL HPLC Rt 8.15 min (98.3%)

Example 17: [(1*R*)-1-[(4-biphenyl-4-yl-4-oxobutanoyl)amino]-2-(3-ethylphenyl)ethyl]boronic acid



Step 1: [(1*R*)-1-[(4-biphenyl-4-yl-4-oxobutanoyl)amino]-2-(3-ethylphenyl)ethyl]boronic acid (+)-pinanediol ester

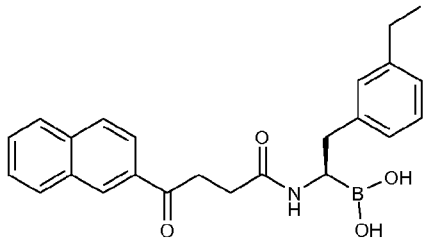
A cold (-10 °C) solution of Intermediate 2 (300 mg, 0.68 mmol) in anhydrous N, N-dimethylformamide (25 mL) was treated with *N,N*-diisopropylethylamine (0.35 mL, 2.0 mmol), 3-(4-phenylbenzoyl)propionic acid (173 mg, 0.68 mmol) and TBTU (262 mg, 0.815mmol). The reaction mixture was stirred at -10 °C for 3h, then diluted with ethyl acetate and washed with brine repeatedly. The organic layer was separated, dried over sodium sulfate and concentrated. The crude was purified by flash chromatography on silica gel eluting with ethylacetate and petroleum ether (pale yellow gummy liquid).
MS (ESI+): 564.3; HPLC (Method A): Rt. 6.6 min; HPLC purity 97.7 %; CHIRAL HPLC (Method A): Rt. 4.5 min; HPLC purity 98.5 %

Step 2: [(1*R*)-1-[(4-biphenyl-4-yl-4-oxobutanoyl)amino]-2-(3-ethylphenyl)ethyl]boronic acid

A cold (0 °C) solution of [(1*R*)-1-[(4-biphenyl-4-yl-4-oxobutanoyl)amino]-2-(3-ethylphenyl)ethyl]boronic acid (+)-pinanediol ester (167 mg, 0.296 mmol) in methanol / pentane (1:1, 30mL) was treated with 2-methylpropyl boronic acid (120 mg, 1.18 mmol) and an aqueous solution of HCl (1.5 N, 0.8 mL). The reaction mixture was stirred at RT for 15h, then evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel eluting with dichloromethane and methanol to obtain the Title compound as an off-white solid.
^{1}H NMR (400 MHz, DMSO-d6): δ 7.95-7.94 (m, 2H), 7.67-7.73 (m, 4H), 7.41-7.49 (m, 3H), 7.05-7.09 (m, 1H), 6.91-7.09 (m, 3H), 3.27-3.38 (m, 3H), 2.72-2.77 (m, 2H), 2.57-2.62 (m, 2H), 2.46-2.50 (m, 2H), 1.07-1.11 (m, 3H). MS (ESI+): 412.0 [M+H-H_2O]. HPLC (Method B): Rt 13.1 min; HPLC purity 91.9 %

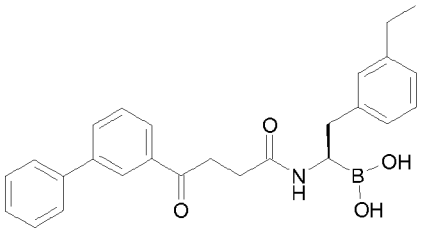
The following products were prepared according to the same two-steps protocol described for Example 17:

Example 18: ((1*R*)-2-(3-ethylphenyl)-1-{[4-(2-naphthyl)-4-oxobutanoyl]amino}ethyl)boronic acid



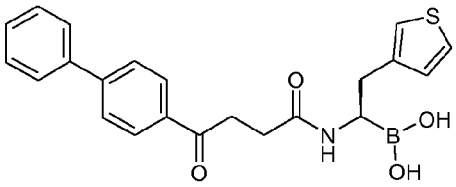
Off-white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.59 (s, 1H), 8.04 (d, *J*= 8.1 Hz, 1H), 7.89-7.95 (m, 3H), 7.55-7.66 (m, 2H), 6.94-7.05 (m, 3H), 6.87-6.89 (m, 1H), 3.40-3.42 (m, 2H), 2.73-2.76 (m, 2H), 2.64-2.66 (m, 2H), 2.40-2.50 (3H, m), 1.07 (t, *J*= 7.5 Hz, 3H). MS (ESI+): 386.3 [M+H-H_2O]; HPLC (Method B): Rt 12.7 min, HPLC purity 96.1%

Example 19: [(1*R*)-1-[(4-biphenyl-3-yl-4-oxobutanoyl)amino]-2-(3-ethylphenyl)ethyl]boronic acid



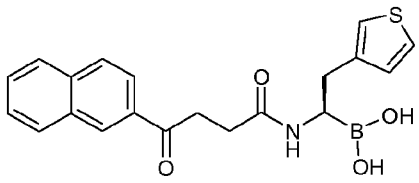
Off-white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.13 (s, 1H), 7.88 (d, *J*= 7.8 Hz, 2H), 7.78 (d, *J*= 8.6 Hz, 2H), 7.52-7.56 (m, 1H), 7.42-7.48 (m, 2H), 7.36-7.39 (m, 1H), 7.01-7.03 (m, 1H), 6.93-6.98 (m, 2H), 6.87 (d, *J*= 7.2 Hz, 1H), 3.31-0.00 (m, 2H), 2.70-2.80 (m, 2H), 2.48-2.62 (m, 5H), 1.05-1.09 (m, 3H). MS (ESI+): 412.0 [M+H-H_2O]; HPLC (Method A): Rt. 4.6 min, HPLC purity 96.4 %

Example 20: [(1*R*)-1-[(4-biphenyl-4-yl-4-oxobutanoyl)amino]-2-(3-thienyl)ethyl]boronic acid



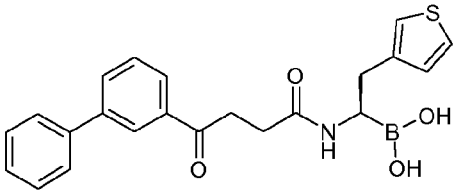
White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.98 (d, *J*= 8.0 Hz, 2H), 7.68-7.76 (m, 4H), 7.46-7.52 (m, 2H), 7.39-7.41 (m, 1H), 7.30 (m, 1H), 7.05 (s, 1H), 6.94 (d, *J*= 4.8 Hz, 1H), 3.29-3.31 (m, 2H), 2.70-2.72 (m, 2H), 2.54-2.59 (m, 3H). MS (ESI+): 390.0 [M+H-H_2O]. HPLC (Method A): Rt. 4.0 min, HPLC purity 97.8 %

Example 21: [(1*R*)-1-{[4-(2-naphthyl)-4-oxobutanoyl]amino}-2-(3-thienyl)ethyl]boronic acid



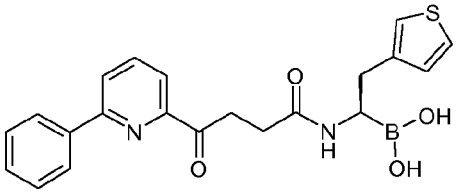
White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.65 (s, 1H), 8.13 (d, *J*= 8.0 Hz, 1H), 7.94-8.02 (m, 3H), 7.59-7.67 (m, 2H), 7.36-7.38 (m, 1H), 7.10 (s, 1H), 6.95-6.96 (m, 1H), 3.32-3.35 (m, 2H), 3.14-3.17 (m, 1H), 2.70-2.83 (m, 2H), 2.48-2.50 (m, 2H). MS (ESI+): 364.0 [M+H-H_2O]; HPLC (Method A): Rt. 3.6 min, HPLC purity 95.6 %

Example 22: [(1*R*)-1-[(4-biphenyl-3-yl-4-oxobutanoyl)amino]-2-(3-thienyl)ethyl]boronic acid



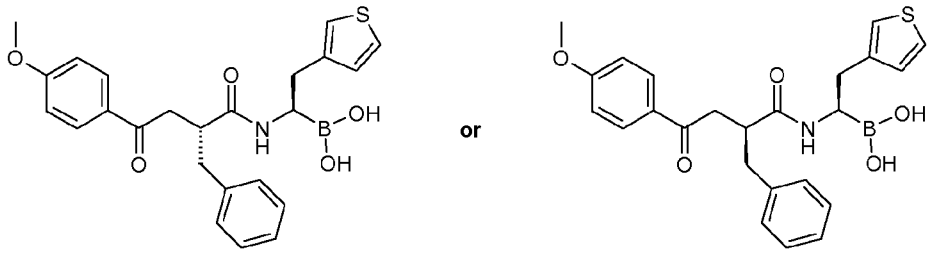
White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.12 (s, 1H), 7.89-7.93 (m, 2H), 7.69 (d, *J*= 7.6 Hz, 2H), 7.59-7.63 (m, 1H), 7.46-7.50 (m, 2H), 7.37-7.40 (m, 1H), 7.32-7.34 (m, 1H), 7.06 (s, 1H), 6.94 (d, *J*= 4.4 Hz, 1H), 3.24-3.27 (m, 2H), 3.08-3.11 (m, 1H), 2.66-2.81 (m, 2H), 2.45-2.49 (m, 2H). MS (ESI+): 390.0 [M+H-H_2O]. HPLC (Method A): Rt. 4.0 min, HPLC purity 96.5 %

Example 23: [(1*R*)-1-{[4-oxo-4-(6-phenylpyridin-2-yl)butanoyl]amino}-2-(3-thienyl)ethyl]boronic acid



Off-white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.17-8.23 (m, 3H), 8.07 (t, *J*= 7.6 Hz, 1H), 7.89 (d, *J*= 6.8 Hz, 1H), 7.46-7.56 (m, 3H), 7.35-7.37 (m, 1H), 7.09 (s, 1H), 6.95 (d, *J*= 5.2 Hz, 1H), 3.47-3.49 (m, 2H), 3.15 (t, *J*= 6.0 Hz, 1H), 2.63-2.83 (m, 3H). MS (ESI+): 413.3 [M+Na-H_2O]. HPLC (Method A): Rt. 3.8 min, HPLC purity 94.4 %

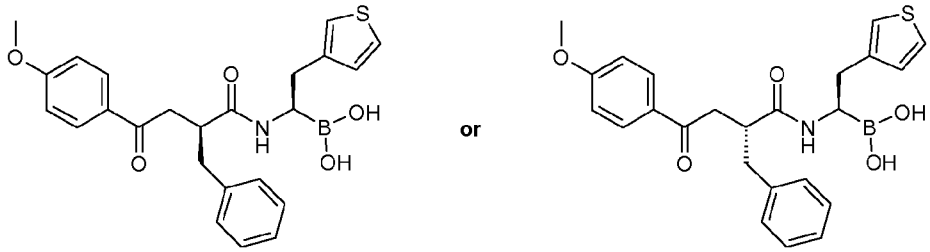
Example 24: [(1*R*)-1-{[(2*R*)-2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoyl]amino}-2-(3-thienyl)ethyl]boronic acid



One diastereoisomer. The configuration at the chiral position most removed from the boronic acid group is arbitrarily assigned. This Example was prepared starting from Intermediate 17 (-)-2-benzyl-4-(4-methoxyphenyl)-4-oxo-butyric acid (with αD -21.0°; ethanol, c= 1.0 g/100 mL). White solid.

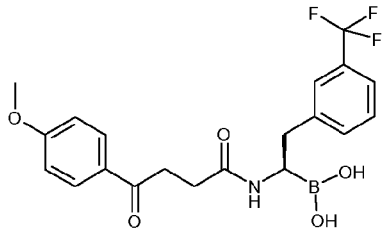
^{1}H NMR (400 MHz, DMSO-d6): δ 7.86 (d, *J*= 8.8 Hz, 2H), 7.32-7.34 (m, 1H), 7.20-7.26 (m, 4H), 7.14-7.18 (m, 1H), 7.00 (d, *J*= 8.8 Hz, 2H), 6.95 (s, 1H), 6.87-6.89 (m, 1H), 3.81 (s, 3H), 3.24-3.28 (m, 1H), 3.09-3.13 (m, 2H), 2.85-2.90 (m, 1H), 2.56-2.75 (m, 4H). MS (ESI+): 434.2 [M+H-H_2O]. HPLC (Method A): Rt. 4.1 min, HPLC purity 95.9 %

Example 25: [(1*R*)-1-{[(2*S*)-2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoyl]amino}-2-(3-thienyl)ethyl]boronic acid



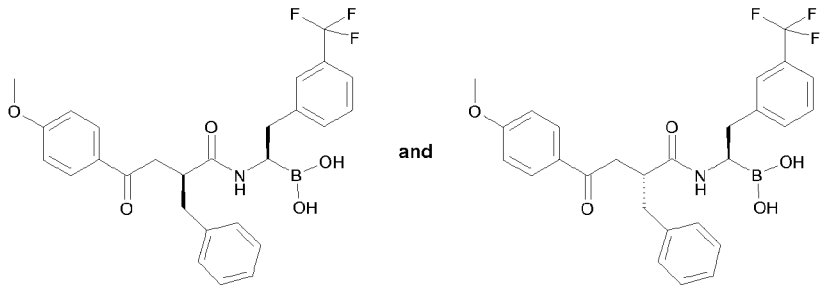
One diastereoisomer. The configuration at the chiral position most removed from the boronic acid group is arbitrarily assigned. This Example was prepared starting from Intermediate 16 (+)-2-benzyl-4-(4-methoxyphenyl)-4-oxo-butyric acid (with αD +21.1°; ethanol, c= 1.0 g/100 mL). Off-white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.86 (d, *J*= 8.8 Hz, 2H), 7.30-7.32 (m, 1H), 7.14-7.26 (m, 5H), 6.99 (d, *J*= 6.0 Hz, 2H), 6.79-6.83 (m, 2H), 3.80 (s, 3H), 3.16-3.27 (m, 2H), 3.04-3.00 (m, 1H), 2.75-2.83 (m, 2H), 2.48-2.69 (m, 3H). MS (ESI+): 434.2 [M+H-H_2O]. HPLC (Method A): Rt. 4.2 min, HPLC purity 92.7%

Example 26: {(1*R*)-1-{[4-(4-methoxyphenyl)-4-oxobutanoyl]amino}-2-[3-(trifluoromethyl)phenyl]ethyl}boronic acid



Pale brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 (d, *J*= 8.9 Hz, 2H), 7.45-7.49 (m, 4H), 7.02 (d, *J*= 8.9 Hz, 2H), 3.81 (s, 3H), 3.12-3.16 (m, 1H), 3.06-3.08 (m, 2H), 2.85-2.90 (m, 1H), 2.70-2.76 (m, 1H), 2.35-2.39 (m, 2H). MS (ESI+): 406.0 [M+H-H_2O]. HPLC (Method A): Rt. 3.9 min, HPLC purity 97.3%

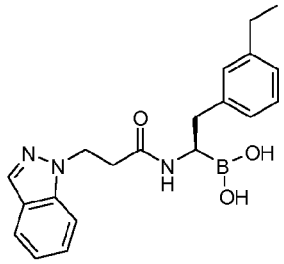
Example 27:{(1*R*)-1-{[2-(*RS*)-benzyl-4-(4-methoxyphenyl)-4-oxobutanoyl]amino}-2-[3-(trifluoromethyl)phenyl]ethyl}boronic acid



Mixture of diastereoisomers. Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 (d, *J*= 8.7 Hz, 1H), 7.37-7.46 (m, 3H), 7.30 (d, *J*= 7.6 Hz, 1H), 7.13-7.25 (m, 5H), 6.98 (d, *J*= 8.7 Hz, 2H), 3.81 (s, 3H), 3.37 (s, 1H), 3.21-3.23 (m, 1H), 3.17-3.19 (m, 1H), 3.06-3.10 (m, 1H), 2.97-3.00 (m, 1H), 2.74-2.83 (m, 3H), 2.56-2.67 (m, 2H). MS (ESI+): 496.2 [M+H-H_2O]. HPLC (Method A): Rt. 4.7 min, HPLC purity 73.9%+14.4%

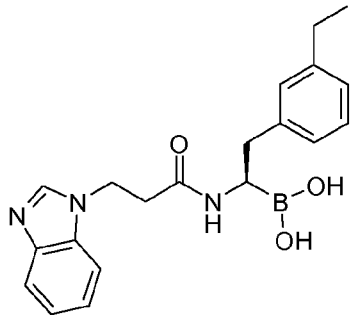
The following compounds were prepared according to the same two-steps protocol described for Example 1:

Example 28: ((1*R*)-2-(3-ethylphenyl)-1-{[3-(1*H*-indazol-1-yl)propanoyl]amino}ethyl)boronic acid



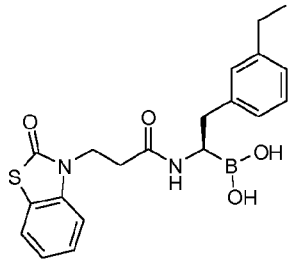
White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.04 (s, 1H), 7.70-7.75 (m, 1H), 7.56-7.61 (m, 1H), 7.23-7.27 (m, 1H), 7.02-7.10 (m, 2H), 6.90-6.95 (m, 1H), 6.81-6.85 (m, 1H), 6.73-6.75 (m, 1H), 4.61 (t, *J*= 6.80 Hz, 2H), 2.78-2.81 (m, 1H), 2.65-2.69 (m, 3H), 2.48-2.50 (m, 2H), 2.35-0.00 (m, 1H), 1.08-1.13 (m, 3H). MS (ESI+): 348.3 [M+H-H_2O]. HPLC (Method B): Rt 11.8 min, HPLC purity 87.9%

Example 29: [(1*R*)-1-{[3-(1*H*-benzimidazol-1-yl)propanoyl]amino}-2-(3-ethylphenyl)ethyl]boronic acid



White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.88 (s, 1H), 7.52-7.61 (m, 2H), 7.15-7.18 (m, 2H), 6.98-7.02 (m, 1H), 6.90 (m, 1H), 6.88 (s, 1H), 6.72-6.74 (m, 1H), 4.48-4.52 (m, 2H), 2.89-2.90 (m, 2H), 2.74 (m, 1H), 2.59-2.66 (m, 2H), 2.41-2.45 (m, 2H), 2.36-2.38 (m, 1H), 1.07 (m, 3H). MS (ESI+): 370.3 [M+Na-H_2O]. HPLC (Method A): Rt 2.8 min, HPLC purity 95.9%

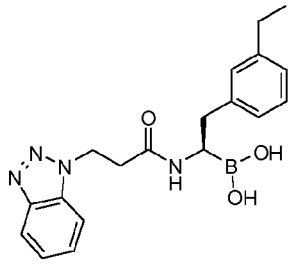
Example 30: ((1*R*)-2-(3-ethylphenyl)-1-{[3-(2-oxo-1,3-benzothiazol-3(2*H*)-yl)propanoyl]amino}ethyl)boronic acid



White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.51-7.65 (m, 1H), 7.24-7.34 (m, 2H), 7.14-7.18 (m, 1H), 7.05-7.09 (m, 1H), 6.89-6.93 (m, 1H), 6.82-6.91 (m, 2H), 4.12-4.15 (m, 2H), 2.61-2.71 (m, 5H), 2.50-2.52 (m, 1H), 2.30-2.40 (m, 1H), 1.09-1.11 (m, 3H)

MS (ESI+): 381.0 [M+H-H_2O]. HPLC (Method A): Rt 3.8 min, HPLC purity 95.7%

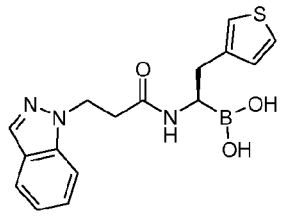
Example 31: [(1*R*)-1-{[3-(1*H*-1,2,3-benzotriazol-1-yl)propanoyl]amino}-2-(3-ethylphenyl)ethyl]boronic acid



White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.61-8.68 (m, 1H), 7.97-8.02 (m, 1H), 7.80-7.84 (m, 1H), 7.41-7.45 (m, 1H), 7.32-7.38 (m, 1H), 7.00-7.04 (m, 1H), 6.90-6.93 (m, 1H), 6.77 (s, 1H), 6.71 (d, *J*= 7.6 Hz, 1H), 4.90-4.93 (m, 2H), 2.92-2.95 (m, 2H), 2.65-2.67 (m, 2H), 2.50-2.45 (m, 2H), 2.30-2.31 (m, 1H), 1.06-1.10 (m, 3H)

MS (ESI+): 349.0 [M+H-H_2O]. HPLC (Method A): Rt 3.3 min, HPLC purity 96.4%

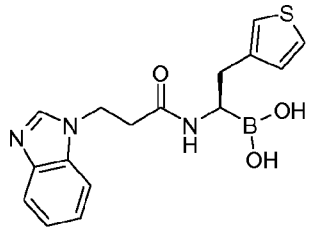
Example 32: [(1*R*)-1-{[3-(1*H*-indazol-1-yl)propanoyl]amino}-2-(3-thienyl)ethyl]boronic acid



Off-white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.02 (s, 1H), 7.73 (d, *J*= 8.4 Hz, 1H), 7.58 (d, *J*= 8.8 Hz, 1H), 7.34-7.38 (m, 1H), 7.23-7.25 (m, 1H), 7.09-7.12 (m, 1H), 6.67-6.70 (m, 2H), 4.50-4.56 (m, 2H), 3.03-3.06 (m, 1H), 2.48-2.65 (m, 4H)

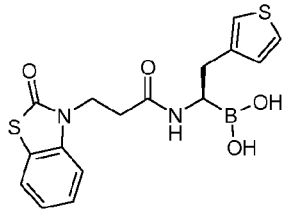
MS (ESI+): 326.0 [M+H-H_2O]; HPLC (Method A): Rt. 3.0 min, HPLC purity 95.4%

Example 33: [(1*R*)-1-{[3-(1*H*-benzimidazol-1-yl)propanoyl]amino}-2-(3-thienyl)ethyl]boronic acid



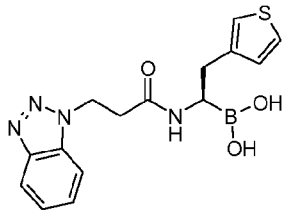
White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.09 (m, 1H), 7.56-7.63 (m, 2H), 7.18-7.26 (m, 3H), 6.72 (d, *J*= 4.4 Hz, 2H), 4.39-4.43 (m, 2H), 3.11-3.14 (m, 1H), 2.59-2.72 (m, 4H). MS (ESI+): 348.0 [M+Na-H_2O]. HPLC (Method A): Rt. 2.0 min, HPLC purity 96.6%

Example 34: [(1*R*)-1-{[3-(2-oxo-1,3-benzothiazol-3(2*H*)-yl)propanoyl]amino}-2-(3-thienyl)ethyl]boronic acid



White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.60-7.62 (m, 1H), 7.30-7.37 (m, 3H), 7.15-7.20 (m, 1H), 6.79-6.84 (m, 2H), 4.08 (t, *J*= 7.2 Hz, 2H), 3.11-3.15 (m, 1H), 2.61-2.73 (m, 2H), 2.42-2.48 (m, 2H). MS (ESI+): 359.0 [M+H-H_2O]. HPLC (Method A): Rt. 3.1 min, HPLC purity 98.9%

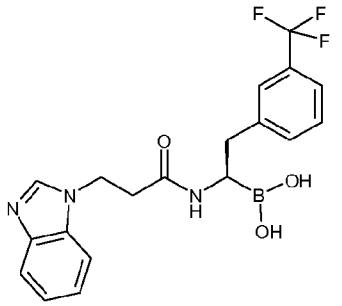
Example 35: [(1*R*)-1-{[3-(1*H*-1,2,3-benzotriazol-1-yl)propanoyl]amino}-2-(3-thienyl)ethyl]boronic acid



White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.01 (d, *J*= 8.0 Hz, 1H), 7.83 (d, *J*= 8.4 Hz, 1H), 7.51-7.54 (m, 1H), 7.36-7.40 (m, 1H), 7.26-7.28 (m, 1H), 6.72-6.74 (m, 2H), 4.80-4.90

(m, 2H), 3.11-3.15 (m, 1H), 2.76-2.80 (m, 2H), 2.57-2.71 (m, 2H). MS (ESI+): 327.0 [M+H-H_2O]. HPLC (Method A): Rt. 2.5 min, HPLC purity 86.4%

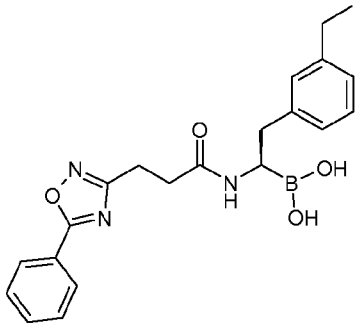
Example 38: {(1*R*)-1-{[3-(1*H*-benzimidazol-1-yl)propanoyl]amino}-2-[3-(trifluoromethyl)phenyl]ethyl}boronic acid



White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (s, 1H), 7.63 (d, *J*= 7.5 Hz, 1H), 7.55 (d, *J*= 7.5 Hz, 1H), 7.44 (d, *J*= 7.9 Hz, 1H), 7.40 (s, 1H), 7.17-7.29 (m, 3H), 7.08 (d, *J*= 7.8 Hz, 1H), 4.38 (t, *J*= 6.7 Hz, 2H), 3.15-3.19 (m, 1H), 2.77-2.82 (m, 1H), 2.63-2.68 (m, 1H), 2.58 (t, *J*= 6.8 Hz, 2H). MS (ESI+): 410.0 [M+Na-H_2O]. HPLC (Method A): Rt. 3.0 min, HPLC purity 95.3%

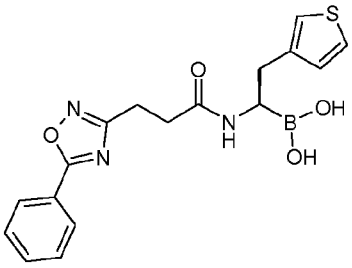
The following compounds were prepared according to the same two-steps protocol described for Example 6:

Example 36: ((1*R*)-2-(3-ethylphenyl)-1-{[3-(5-phenyl-1,2,4-oxadiazol-3-yl)propanoyl]amino}ethyl)boronic acid



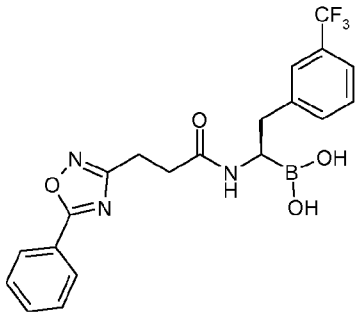
Pale brown solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.06-8.08 (m, 2H), 7.67-7.71 (m, 1H), 7.59-7.63 (m, 2H), 7.07-7.10 (m, 1H), 6.90-6.97 (m, 3H), 3.17-3.20 (m, 1H), 2.93 (t, *J*= 7.6 Hz, 2H), 2.65-2.79 (m, 2H), 2.48-2.54 (m, 4H), 1.13 (t, *J*= 7.9 Hz, 3H). MS (ESI+): 376.3 [M+H-H_2O]. HPLC (Method A): Rt. 4.0 min, HPLC purity 97.0%

Example 37: [(1*R*)-1-{[3-(5-phenyl-1,2,4-oxadiazol-3-yl)propanoyl]amino}-2-(3-thienyl)ethyl]boronic acid



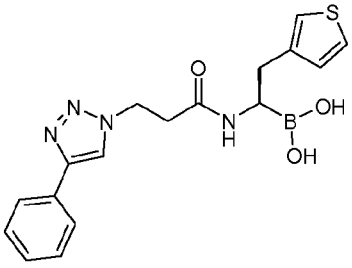
White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.06-8.09 (m, 2H), 7.67-7.71 (m, 1H), 7.59-7.63 (m, 2H), 7.31-7.33 (m, 1H), 7.03 (s, 1H), 6.89-6.91 (m, 1H), 3.15-3.19 (m, 1H), 2.93-2.97 (m, 2H), 2.68-2.83 (m, 2H), 2.55-2.57 (m, 2H). MS (ESI+): 354.0 [M+H-H_2O]. HPLC (Method A): Rt. 3.3 min, HPLC purity 97.8%

Example 39: {(1*R*)-1-{[3-(5-phenyl-1,2,4-oxadiazol-3-yl)propanoyl]amino}-2-[3-(trifluoromethyl)phenyl]ethyl}boronic acid



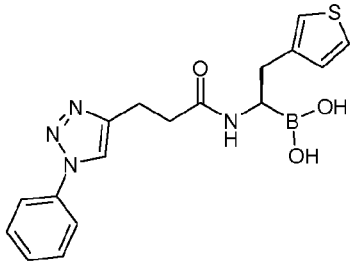
Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, *J*= 7.2 Hz, 2H), 7.66-7.69 (m, 1H), 7.58-7.62 (m, 2H), 7.40-7.45 (m, 4H), 3.17-3.20 (m, 1H), 2.85-2.91 (m, 3H), 2.70-2.76 (m, 1H), 2.49-2.51 (m, 2H). MS (ESI+): 416.2 [M+H-H_2O]. HPLC (Method B): Rt. 4.1 min, HPLC purity 96.9%

Example 40: [(1*R*)-1-{[3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl]amino}-2-(3-thienyl)ethyl]boronic acid



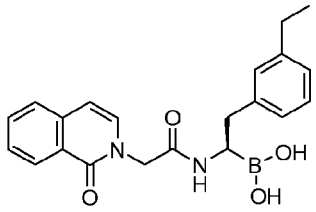
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.37 (s, 1H), 7.79 (d, *J*= 8.4 Hz, 2H), 7.42 (t, *J*= 8.4 Hz, 2H), 7.30-7.33 (m, 1H), 7.24-7.26 (m, 1H), 6.90 (s, 1H), 6.80 (d, *J*= 8.4 Hz, 2H), 4.53-4.62 (m, 2H), 3.12-3.16 (m, 1H), 2.63-2.77 (m, 4H). MS (ESI+): 353.0 [M+H-H_2O]. HPLC (Method A): Rt 3.0 min, HPLC purity 99.7%

Example 41: [(1*R*)-1-{[3-(1-phenyl-1*H*-1,2,3-triazol-4-yl)propanoyl]amino}-2-(3-thienyl)ethyl]boronic acid



Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (s, 1H), 7.78-7.80 (m, 2H), 7.54-7.58 (m, 2H), 7.44-7.47 (m, 1H), 7.27-7.29 (m, 1H), 6.91 (s, 1H), 6.85 (d, *J*= 4.8 Hz, 1H), 2.92-3.11 (m, 1H), 2.88-2.92 (m, 2H), 2.74-2.79 (m, 1H), 2.63-2.69 (m, 1H), 2.46-2.49 (m, 2H). MS (ESI+): 353.0 [M+H-H_2O]. HPLC (Method A): Rt 2.9 min, HPLC purity 95.1%

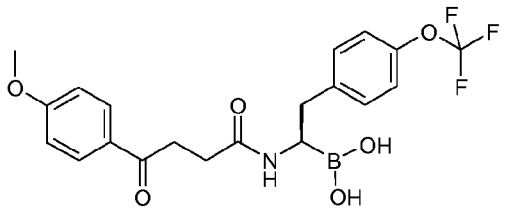
Example 42: ((1*R*)-2-(3-ethylphenyl)-1-{[(1-oxoisoquinolin-2(1*H*)-yl)acetyl]amino}ethyl)boronic acid



White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.82 (s, 1H), 8.19 (d, *J*= 8.0 Hz, 1H), 7.66-7.72 (m, 1H), 7.61-7.63 (m, 1H), 7.46-7.50 (m, 1H), 7.31 (d, *J*= 8.0 Hz, 1H), 6.98-7.02 (m, 1H), 6.87-6.92 (m, 2H), 6.57 (d, *J*= 8.0 Hz, 1H), 4.71-4.76 (m, 2H), 2.66-2.70 (m, 2H), 2.49-2.50 (m, 1H), 2.45-2.48 (m, 2H), 1.08 (t, *J*= 8.0 Hz, 3H). MS (ESI+): 361.3 [M+H-H_2O].

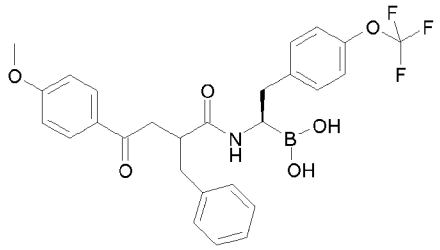
The following compounds were prepared according to the same two-step protocol described for Example 17:

Example 43: (R)-(1-(4-(4-methoxyphenyl)-4-oxobutanamido)-2-(4-(trifluoromethoxy)phenyl)ethyl)boronic acid



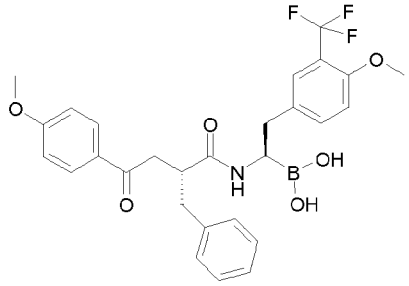
Pale brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (dd, *J* = 1.92, 6.96 Hz, 2H), 7.26 (d, *J* = 8.64 Hz, 2H), 7.18 (d, *J* = 8.12 Hz, 2H), 7.00-7.03 (m, 2H), 3.80 (s, 3H), 3.08-3.12 (m, 3H), 2.78-2.83 (m, 1H), 2.65-2.70 (m, 1H), 2.39 (t, *J* = 6.88 Hz, 2H). MS (ESI+): 422.2 [M+H-H_2O]. HPLC (Method A): Rt. 4.0 min, HPLC purity 97.3%

Example 44: ((1R)-1-(2-benzyl-4-(4-methoxyphenyl)-4-oxobutanamido)-2-(4-(trifluoromethoxy)phenyl)ethyl)boronic acid



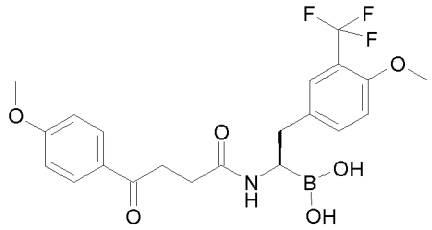
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 (d, *J* = 8.88 Hz, 2H), 7.22-7.26 (m, 2H), 7.14-7.18 (m, 3H), 7.05-7.07 (m, 4H), 6.98 (d, *J* = 8.92 Hz, 2H), 3.77 (s, 3H), 3.18-3.24 (m, 1H), 2.95-3.04 (m, 2H), 2.73-2.83 (m, 2H), 2.59-2.71 (m, 3H). MS (ESI+): 512.2 [M+H-H_2O]. HPLC (Method A): Rt. 4.9 min, HPLC purity 73.2%+19.5%

Example 45: ((R)-1-((R)-2-benzyl-4-(4-methoxyphenyl)-4-oxobutanamido)-2-(4-methoxy-3-(trifluoromethyl)phenyl)ethyl)boronic acid



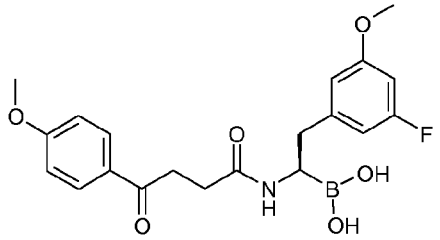
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 (d, *J* = 8.92 Hz, 2H), 7.32-7.32 (m, 1H), 7.21-7.26 (m, 3H), 7.13-7.18 (m, 3H), 6.97-6.99 (m, 3H), 3.81-3.83 (m, 3H), 3.74 (s, 3H), 3.14-3.16 (m, 1H), 2.98-3.07 (m, 2H), 2.68-2.84 (m, 3H), 2.53-2.60 (m, 2H). MS (ESI+): 526.2 [M+H-H_2O]. HPLC (Method A): Rt. 4.7 min, HPLC purity 95.8%

Example 46: (R)-(2-(4-methoxy-3-(trifluoromethyl)phenyl)-1-(4-(4-methoxyphenyl)-4-oxobutanamido)ethyl)boronic acid



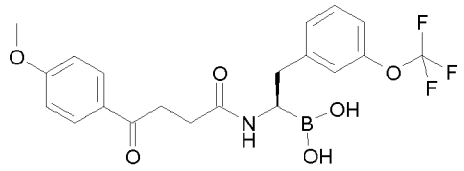
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88-7.92 (m, 2H), 7.38-7.39 (m, 2H), 7.10 (d, *J* = 8.84 Hz, 1H), 7.00-7.04 (m, 2H), 3.81 (s, 6H), 3.05-3.13 (m, 3H), 2.75-2.80 (m, 1H), 2.61-2.67 (m, 1H), 2.32-2.40 (m, 2H). MS (ESI+): 436.2 [M+H-H_2O]. HPLC (Method A): Rt. 3.9 min, HPLC purity 95.7%

Example 47: (R)-(2-(3-fluoro-5-methoxyphenyl)-1-(4-(4-methoxyphenyl)-4-oxobutanamido)ethyl)boronic acid



White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (d, *J* = 8.84 Hz, 2H), 7.02 (d, *J* = 8.88 Hz, 2H), 6.55-6.59 (m, 3H), 3.81 (s, 3H), 3.71 (s, 3H), 3.09-3.13 (m, 3H), 2.73-2.78 (m, 1H), 2.60-2.66 (m, 1H), 2.49-2.50 (m, 2H), 2.38-2.40 (m, 1H). MS (ESI+): 386.2 [M+H-H_2O]. HPLC (Method A): Rt. 3.4 min, HPLC purity 99.3%

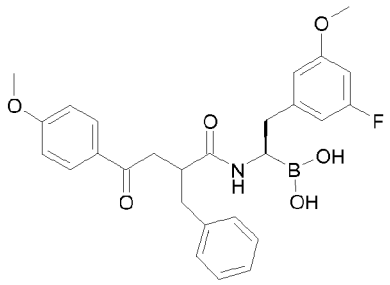
Example 48: (R)-(1-(4-(4-methoxyphenyl)-4-oxobutanamido)-2-(3-(trifluoromethoxy)phenyl)ethyl)boronic acid



Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89-7.92 (m, 2H), 7.34-7.38 (m, 1H), 7.18-7.20 (m, 1H), 7.13-7.14 (m, 2H), 7.00-7.04 (m, 2H), 3.82 (s, 3H), 3.08-3.17 (m, 3H),

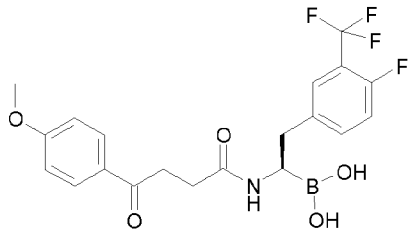
2.82-2.87 (m, 1H), 2.70-2.73 (m, 1H), 2.39-2.40 (m, 2H). MS (ESI+): 422.2 [M+H-H_2O]. HPLC (Method A): Rt. 4.0 min, HPLC purity 99.0%

Example 49: ((1R)-1-(2-benzyl-4-(4-methoxyphenyl)-4-oxobutanamido)-2-(3-fluoro-5-methoxyphenyl)ethyl)boronic acid



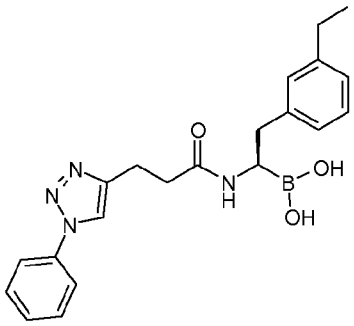
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79-7.80 (m, 2H), 7.11-7.25 (m, 5H), 6.95-6.97 (m, 2H), 6.43-6.49 (m, 2H), 6.35 (d, *J* = 9.36 Hz, 1H), 3.76 (s, 1H), 3.65 (s, 3H), 3.19-3.25 (m, 1H), 3.00-3.02 (m, 1H), 2.77-2.98 (m, 3H), 2.61-2.66 (m, 2H), 2.44-2.46 (m, 1H). MS (ESI+): 476.2 [M+H-H_2O]. HPLC (Method A): Rt. 4.4 min, HPLC purity 72.2%+23.0%

Example 50: (R)-(2-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(4-(4-methoxyphenyl)-4-oxobutanamido)ethyl)boronic acid



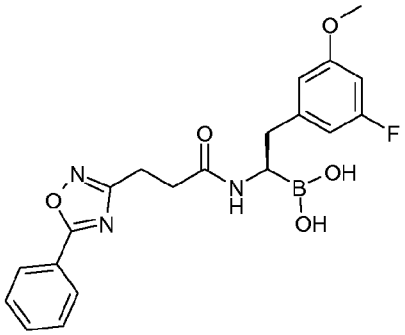
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 (d, *J* = 8.00 Hz, 2H), 7.48-7.52 (m, 2H), 7.29-7.34 (m, 1H), 7.01 (d, *J* = 8.00 Hz, 2H), 3.80 (s, 3H), 3.07-3.12 (m, 3H), 2.81-2.86 (m, 1H), 2.66-2.72 (m, 1H), 2.50-2.51 (m, 2H), 2.35-2.39 (m, 2H). MS (ESI+): 424.2 [M+H-H_2O]. HPLC (Method A): Rt. 4.0 min, HPLC purity 98.6%

Example 58: (R)-(2-(3-ethylphenyl)-1-(3-(1-phenyl-1H-1,2,3-triazol-4-yl)propanamido)ethyl)boronic acid



White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (s, 1H), 7.83-7.83 (m, 2H), 7.54-7.58 (m, 2H), 7.44-7.47 (m, 1H), 7.05-7.09 (m, 1H), 6.87-6.94 (m, 3H), 3.12-3.16 (m, 1H), 2.86-2.90 (m, 2H), 2.73-2.74 (m, 1H), 2.60-2.66 (m, 1H), 2.41-2.51 (m, 4H), 1.11 (t, *J* = 7.60 Hz, 3H). MS (ESI+): 375.2 [M+H-H_2O]. HPLC (Method A): Rt. 3.6 min, HPLC purity 96.8%

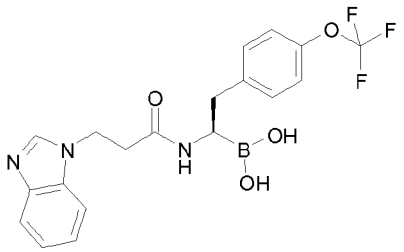
Example 61: (R)-(2-(3-fluoro-5-methoxyphenyl)-1-(3-(5-phenyl-1,2,4-oxadiazol-3-yl)propanamido)ethyl)boronic acid



White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03-8.03 (m, 2H), 7.57-7.68 (m, 3H), 6.47-6.52 (m, 3H), 3.65 (s, 3H), 3.11-3.14 (m, 1H), 2.90-2.94 (m, 2H), 2.71-2.76 (m, 1H), 2.58-2.63 (m, 1H), 2.51-2.53 (m, 2H). MS (ESI+): 396.2 [M+H-H_2O]. HPLC (Method A): Rt. 3.6 min, HPLC purity 97.1%

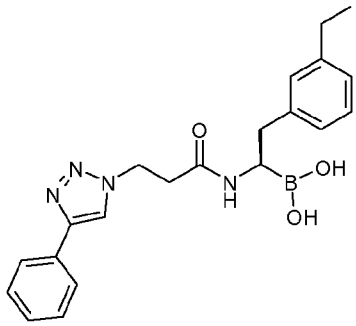
The following compounds were prepared according to the same two-step protocol described for Example 1:

Example 51: (R)-(1-(3-(1H-benzo[d]imidazol-1-yl)propanamido)-2-(4-(trifluoromethoxy)phenyl)ethyl)boronic acid



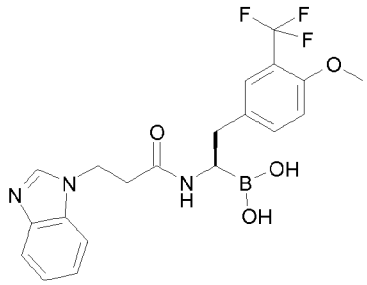
Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.09 (s, 1H), 7.64 (d, *J* = 7.56 Hz, 1H), 7.57 (d, *J* = 7.68 Hz, 1H), 7.19-7.28 (m, 2H), 6.96 (d, *J* = 8.08 Hz, 2H), 6.85 (d, *J* = 8.56 Hz, 2H), 4.40 (t, *J* = 6.32 Hz, 2H), 3.07-3.10 (m, 1H), 2.49-2.70 (m, 4H). MS (ESI+): 426.0 [M+Na-H_2O]. HPLC (Method A): Rt. 3.2 min, HPLC purity 96.5%

Example 52: (R)-(2-(3-ethylphenyl)-1-(3-(4-phenyl-1H-1,2,3-triazol-1-yl)propanamido)ethyl)boronic acid



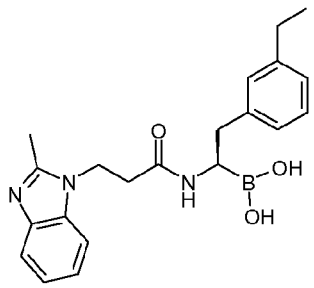
Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 7.77 (d, *J* = 7.20 Hz, 2H), 7.41 (t, *J* = 7.76 Hz, 3H), 7.29-7.33 (m, 1H), 7.00 (t, *J* = 7.52 Hz, 1H), 6.88 (d, *J* = 7.88 Hz, 1H), 6.81 (s, 1H), 6.75 (d, *J* = 7.40 Hz, 1H), 3.07-3.11 (m, 1H), 2.66-2.70 (m, 3H), 2.55-2.57 (m, 1H), 2.39-2.44 (m, 2H), 1.03 (t, *J* = 7.96 Hz, 3H). MS (ESI+): 397.2 [M+Na-H_2O]. HPLC (Method A): Rt. 3.7 min, HPLC purity 96.5%

Example 53: (R)-(1-(3-(1H-benzo[d]imidazol-1-yl)propanamido)-2-(4-methoxy-3-(trifluoromethyl)phenyl)ethyl)boronic acid



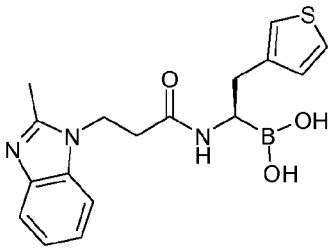
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.09 (s, 1H), 7.65 (d, *J* = 8.24 Hz, 1H), 7.56 (d, *J* = 7.40 Hz, 1H), 7.19-7.29 (m, 3H), 6.91 (dd, *J* = 1.92, 8.54 Hz, 1H), 6.81 (d, *J* = 8.56 Hz, 1H), 4.39 (t, *J* = 6.76 Hz, 2H), 3.76 (s, 3H), 3.09-3.13 (m, 1H), 2.67-2.70 (m, 1H), 2.54-2.61 (m, 3H). MS (ESI+): 440.0 [M+Na-H_2O]. HPLC (Method A): Rt. 3.0 min, HPLC purity 94.5%

Example 54: (R)-(2-(3-ethylphenyl)-1-(3-(2-methyl-1H-benzo[d]imidazol-1-yl)propanamido)ethyl)boronic acid



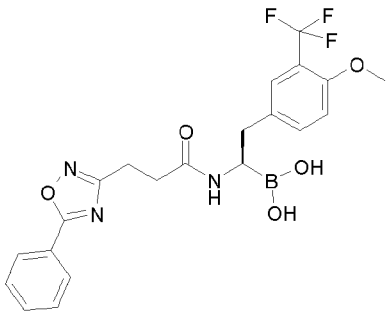
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43-7.50 (m, 2H), 7.13-7.17 (m, 2H), 6.89-6.99 (m, 2H), 6.77 (s, 1H), 6.59 (d, *J* = 7.40 Hz, 1H), 4.28-4.32 (m, 2H), 3.10-3.13 (m, 1H), 2.52-2.62 (m, 4H), 2.40-2.44 (m, 2H), 1.07 (t, *J* = 7.60 Hz, 3H).). MS (ESI+): 384.2 [M+Na-H_2O]. HPLC (Method A): Rt. 3.0 min, HPLC purity 98.7%

Example 55: (R)-(1-(3-(2-methyl-1H-benzo[d]imidazol-1-yl)propanamido)-2-(thiophen-3-yl)ethyl)boronic acid



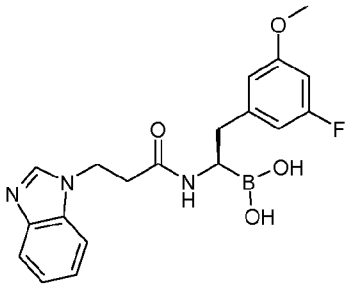
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44-7.50 (m, 2H), 7.11-7.25 (m, 3H), 6.65-6.68 (m, 2H), 4.28-4.37 (m, 2H), 3.09-3.12 (m, 1H), 2.51-2.68 (m, 7H). MS (ESI+): 362.2 [M+Na-H_2O]. HPLC (Method A): Rt. 2.0 min, HPLC purity 93.7%

Example 56: (R)-(2-(4-methoxy-3-(trifluoromethyl)phenyl)-1-(3-(5-phenyl-1,2,4-oxadiazol-3-yl)propanamido)ethyl)boronic acid



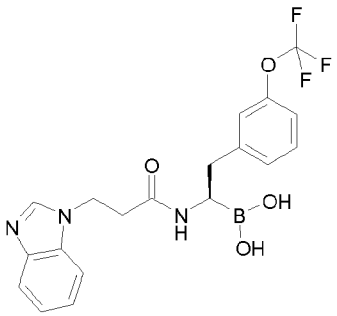
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (d, *J* = 7.20 Hz, 2H), 7.59-7.70 (m, 3H), 7.31-7.35 (m, 2H), 7.04 (d, *J* = 8.44 Hz, 1H), 3.76 (s, 3H), 3.14-3.17 (m, 1H), 2.90-2.94 (m, 2H), 2.76-2.81 (m, 1H), 2.63-2.68 (m, 1H), 2.48-249.00 (m, 2H). MS (ESI+): 446.2 [M+H-H_2O]. HPLC (Method A): Rt. 4.0 min, HPLC purity 97.7%

Example 57: (R)-(1-(3-(1H-benzo[d]imidazol-1-yl)propanamido)-2-(3-fluoro-5-methoxyphenyl)ethyl)boronic acid



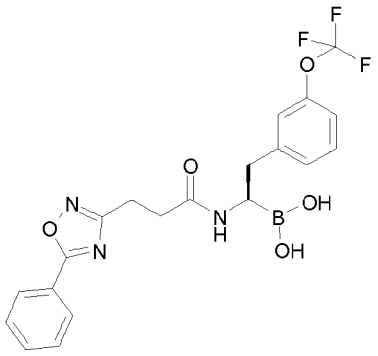
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (s, 1H), 7.54-7.62 (m, 2H), 7.17-7.26 (m, 2H), 6.51-6.54 (m, 1H), 6.50 (s, 1H), 6.37-6.45 (m, 1H), 4.36-4.40 (m, 2H), 3.64 (s, 3H), 3.11-3.14 (m, 1H), 2.53-2.69 (m, 4H). MS (ESI+): 390.2 [M+Na-H_2O]. HPLC (Method A): Rt. 2.5 min, HPLC purity 98.8%

Example 59: (R)-(1-(3-(1H-benzo[d]imidazol-1-yl)propanamido)-2-(3-(trifluoromethoxy)phenyl)ethyl)boronic acid



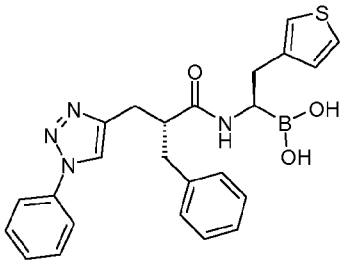
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (s, 1H), 7.55-7.57 (m, 1H), 7.61-7.63 (m, 1H), 7.15-7.26 (m, 3H), 7.05-7.07 (m, 1H), 7.00 (s, 1H), 6.81-6.83 (m, 1H), 4.39 (t, *J* = 6.72 Hz, 2H), 3.15 (t, *J* = 5.60 Hz, 1H), 2.73-2.78 (m, 1H), 2.57-2.65 (m, 3H). MS (ESI+): 426.2 [M+Na-H_2O]. HPLC (Method A): Rt. 3.1 min, HPLC purity 99.6%

Example 60: (R)-(1-(3-(5-phenyl-1,2,4-oxadiazol-3-yl)propanamido)-2-(3-(trifluoromethoxy)phenyl)ethyl)boronic acid



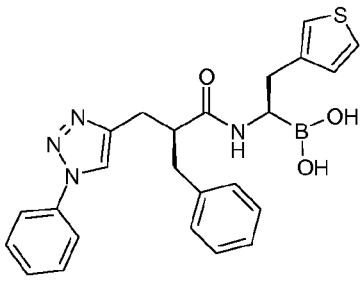
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04-8.05 (m, 2H), 7.58-7.70 (m, 3H), 7.29-7.33 (m, 1H), 7.08-7.29 (m, 3H), 3.17-3.21 (m, 1H), 2.82-2.93 (m, 3H), 2.67-2.73 (m, 1H), 2.49-2.51 (m, 2H). MS (ESI+): 432.0 [M+H-H_2O]. HPLC (Method A): Rt. 4.2 min, HPLC purity 98.3%

Example 62: ((R)-1-((R)-2-benzyl-3-(1-phenyl-1H-1,2,3-triazol-4-yl)propanamido)-2-(thiophen-3-yl)ethyl)boronic acid



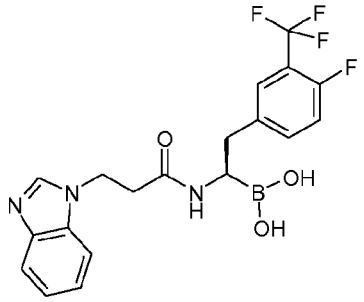
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (s, 1H), 7.76-7.78 (m, 2H), 7.53-7.57 (m, 2H), 7.44-7.46 (m, 1H), 7.23-7.27 (m, 3H), 7.16-7.18 (m, 3H), 6.62-6.67 (m, 2H), 3.07-3.10 (m, 1H), 2.81-2.94 (m, 3H), 2.71-2.75 (m, 1H), 2.56-2.66 (m, 3H). MS (ESI+): 443.2 [M+H-H_2O]. HPLC (Method A): Rt. 4.0 min, HPLC purity 97.7%

Example 63: ((R)-1-((S)-2-benzyl-3-(1-phenyl-1H-1,2,3-triazol-4-yl)propanamido)-2-(thiophen-3-yl)ethyl)boronic acid



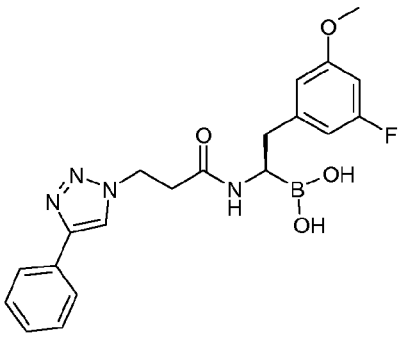
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (s, 1H), 7.75-7.77 (m, 2H), 7.52-7.56 (m, 2H), 7.44-7.45 (m, 1H), 7.23-7.27 (m, 2H), 7.15-7.19 (m, 4H), 6.61-6.64 (m, 2H), 2.84-2.95 (m, 4H), 2.63-2.70 (m, 3H), 2.52-2.54 (m, 1H). MS (ESI+): 443.2 [M+H-H_2O]. HPLC (Method A): Rt. 4.0 min, HPLC purity 99.6%

Example 64: (R)-(1-(3-(1H-benzo[d]imidazol-1-yl)propanamido)-2-(4-fluoro-3-(trifluoromethyl)phenyl)ethyl)boronic acid



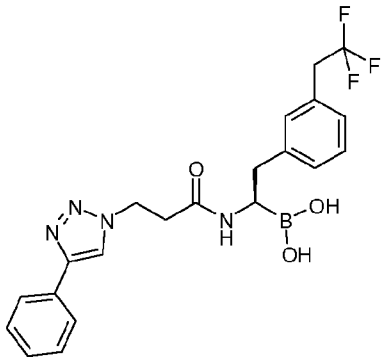
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (s, 1H), 7.63 (d, *J* = 8.00 Hz, 1H), 7.54 (d, *J* = 8.00 Hz, 1H), 7.39-7.41 (m, 1H), 7.18-7.27 (m, 2H), 7.04-7.10 (m, 2H), 4.38 (t, *J* = 6.60 Hz, 2H), 3.08-3.12 (m, 1H), 2.71-2.76 (m, 1H), 2.56-2.62 (m, 3H). MS (ESI+): 428.0 [M+Na-H_2O]. HPLC (Method A): Rt. 3.1 min, HPLC purity 98.8 %

Example 65: (R)-(2-(3-fluoro-5-methoxyphenyl)-1-(3-(4-phenyl-1H-1,2,3-triazol-1-yl)propanamido)ethyl)boronic acid



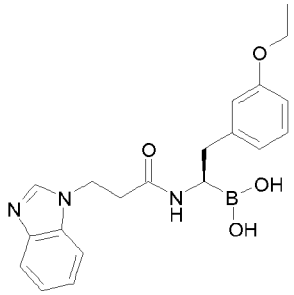
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.37 (s, 1H), 7.78 (d, *J* = 8.00 Hz, 2H), 7.39-7.43 (m, 2H), 7.29-7.32 (m, 1H), 6.46-6.53 (m, 3H), 4.55 (t, *J* = 6.80 Hz, 2H), 3.66 (s, 3H), 3.13-3.17 (m, 1H), 2.58-2.75 (m, 4H). MS (ESI+): 395.3 [M+H-H_2O]. HPLC (Method A): Rt. 3.4 min, HPLC purity 98.6%

Example 66: (R)-(1-(3-(4-phenyl-1H-1,2,3-triazol-1-yl)propanamido)-2-(3-(2,2,2-trifluoroethyl)phenyl)ethyl)boronic acid



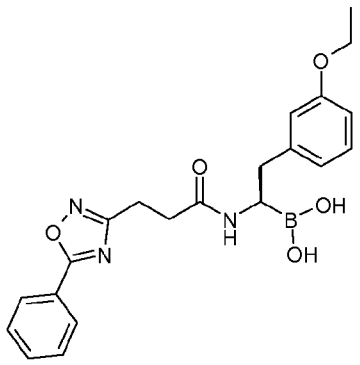
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (s, 1H), 7.77-7.80 (m, 2H), 7.40-7.43 (m, 2H), 7.23-7.33 (m, 2H), 7.01-7.05 (m, 3H), 4.54 (t, *J* = 6.80 Hz, 2H), 3.15-3.19 (m, 1H), 2.79-2.83 (m, 1H), 2.63-2.69 (m, 3H). MS (ESI+): 431.0 [M+H-H_2O]. HPLC (Method A): Rt. 4.0 min, HPLC purity 96.2%

Example 67: (R)-(1-(3-(1H-benzo[d]imidazol-1-yl)propanamido)-2-(3-ethoxyphenyl)ethyl)boronic acid



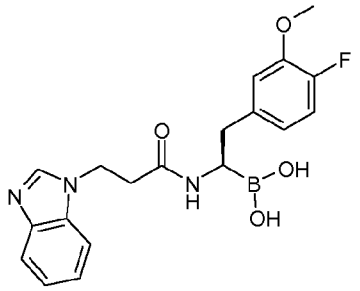
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (s, 1H), 7.62 (d, *J* = 7.60 Hz, 1H), 7.56 (d, *J* = 7.60 Hz, 1H), 7.17-7.26 (m, 2H), 6.95 (t, *J* = 8.00 Hz, 1H), 6.58-6.63 (m, 2H), 6.39 (d, *J* = 8.00 Hz, 1H), 4.39 (t, *J* = 6.40 Hz, 2H), 3.85-3.90 (m, 2H), 3.11-3.13 (m, 1H), 2.55-2.64 (m, 4H), 1.24 (t, *J* = 6.80 Hz, 3H). MS (ESI+): 386.2 [M+Na-H_2O]. HPLC (Method A): Rt. 2.5 min, HPLC purity 98.5 %

Example 68: (R)-(2-(3-ethoxyphenyl)-1-(3-(5-phenyl-1,2,4-oxadiazol-3-yl)propanamido)ethyl)boronic acid



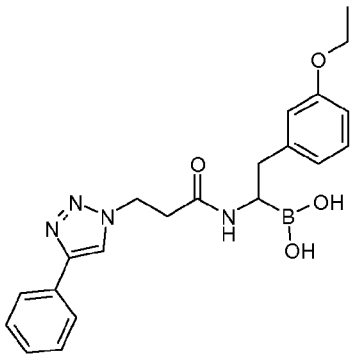
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (d, *J* = -8.00 Hz, 2H), 7.65-7.69 (m, 1H), 7.58-7.62 (m, 2H), 7.06 (t, *J* = 7.60 Hz, 1H), 6.63-6.67 (m, 3H), 3.89-3.94 (m, 2H), 3.14-3.17 (m, 1H), 2.92 (t, *J* = 7.60 Hz, 2H), 2.71-2.76 (m, 1H), 2.61-2.64 (m, 1H), 2.52-2.59 (m, 2H), 1.26-1.28 (m, 3H). MS (ESI+): 392.3 [M+H-H_2O]. HPLC (Method A): Rt. 3.7 min, HPLC purity 98.7%

Example 69: (R)-(1-(3-(1H-benzo[d]imidazol-1-yl)propanamido)-2-(4-fluoro-3-methoxyphenyl)ethyl)boronic acid



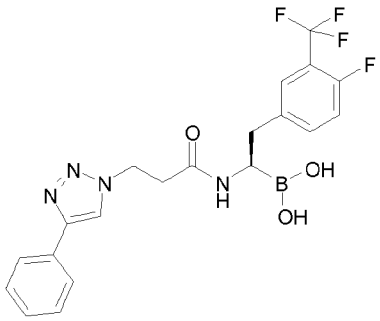
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (s, 1H), 7.62 (d, *J* = 8.00 Hz, 1H), 7.55 (d, *J* = 8.00 Hz, 1H), 7.19-7.27 (m, 2H), 6.74-6.81 (m, 2H), 6.27-6.30 (m, 1H), 4.40 (t, *J* = 6.40 Hz, 2H), 3.66 (s, 3H), 3.05-3.09 (m, 1H), 2.60-2.64 (m, 3H), 2.54-2.58 (m, 1H). MS (ESI+): 386.2 [M+H-H_2O]. HPLC (Method A): Rt. 2.4 min, HPLC purity 96.6%

Example 70: (2-(3-ethoxyphenyl)-1-(3-(4-phenyl-1H-1,2,3-triazol-1-yl)propanamido)ethyl)boronic acid



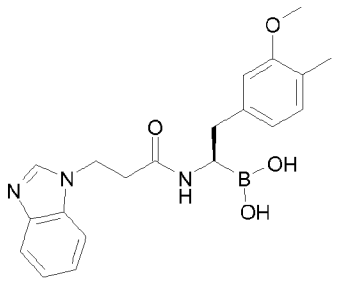
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (s, 1H), 7.78 (d, *J* = 8.00 Hz, 2H), 7.42 (t, *J* = 13.88 Hz, 2H), 7.29-7.33 (m, 1H), 6.99-7.03 (m, 1H), 6.59-6.62 (m, 2H), 6.55 (d, *J* = 8.00 Hz, 1H), 4.55 (t, *J* = 7.24 Hz, 2H), 3.85-3.91 (m, 2H), 3.12-3.15 (m, 1H), 2.66-2.71 (m, 3H), 2.58-2.61 (m, 1H), 1.24 (t, *J* = 7.00 Hz, 3H). MS (ESI+): 413.3 [M+Na-H_2O]. HPLC (Method A): Rt. 3.4 min, HPLC purity 98.5 %

Example 71: (R)-(2-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-(4-phenyl-1H-1,2,3-triazol-1-yl)propanamido)ethyl)boronic acid



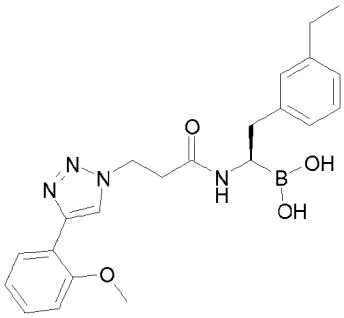
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (s, 1H), 7.76-7.78 (m, 2H), 7.39-7.45 (m, 3H), 7.29-7.32 (m, 2H), 7.15-7.20 (m, 1H), 4.53 (t, *J* = 8.00 Hz, 2H), 3.11-3.14 (m, 1H), 2.77-2.82 (m, 1H), 2.62-2.69 (m, 3H). MS (ESI+): 433.3 [M+H-H_2O]. HPLC (Method A): Rt. 3.9 min, HPLC purity 98.1%

Example 72: (R)-(1-(3-(1H-benzo[d]imidazol-1-yl)propanamido)-2-(3-methoxy-4-methylphenyl)ethyl)boronic acid



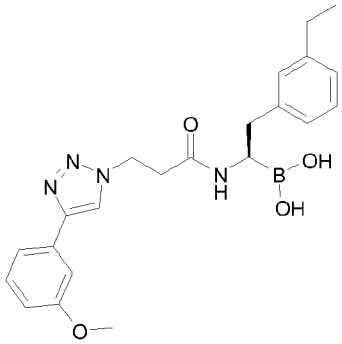
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (s, 1H), 7.62 (d, *J* = 8.00 Hz, 1H), 7.54 (d, *J* = 8.00 Hz, 1H), 7.19-7.27 (m, 2H), 6.77 (d, *J* = 8.00 Hz, 1H), 6.54 (s, 1H), 6.26 (d, *J* = 8.00 Hz, 1H), 4.40 (t, *J* = 6.40 Hz, 2H), 3.59 (s, 3H), 3.09 (t, *J* = 7.20 Hz, 1H), 2.58-2.63 (m, 4H), 1.98 (s, 3H). MS (ESI+): 386.2 [M+Na-H_2O]. HPLC (Method A): Rt. 2.7 min, HPLC purity 97.1%

Example 73: (R)-(2-(3-ethylphenyl)-1-(3-(4-(2-methoxyphenyl)-1H-1,2,3-triazol-1-yl)propanamido)ethyl)boronic acid



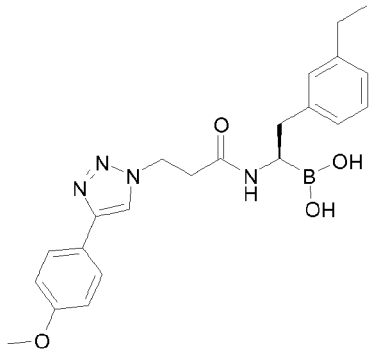
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (s, 1H), 8.07-8.09 (m, 1H), 7.28-7.32 (m, 1H), 6.97-7.09 (m, 3H), 6.87 (d, *J* = 8.00 Hz, 1H), 6.82 (s, 1H), 6.77 (d, *J* = 8.00 Hz, 1H), 4.56 (t, *J* = 8.00 Hz, 2H), 3.85 (s, 3H), 3.13-3.17 (m, 1H), 2.59-2.71 (m, 4H), 2.37-2.43 (m, 2H), 1.03 (t, *J* = 8.00 Hz, 3H). MS (ESI+): 427.2 [M+Na-H_2O]. HPLC (Method A): Rt. 3.8 min, HPLC purity 97.6%

Example 74: (R)-(2-(3-ethylphenyl)-1-(3-(4-(3-methoxyphenyl)-1H-1,2,3-triazol-1-yl)propanamido)ethyl)boronic acid



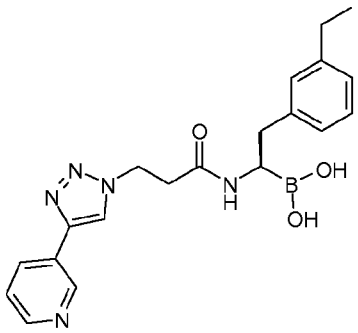
White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.37 (s, 1H), 7.33-7.35 (m, 3H), 6.99-7.03 (m, 1H), 6.84-6.90 (m, 3H), 6.78 (d, *J* = 8.00 Hz, 1H), 4.55 (t, *J* = 12.00 Hz, 2H), 3.79 (s, 3H), 3.10-3.14 (m, 1H), 2.65-2.69 (m, 3H), 2.58-2.60 (m, 1H), 2.41-2.46 (m, 2H), 1.06-1.08 (m, 3H). MS (ESI+): 427.2 [M+Na-H_2O]. HPLC (Method A): Rt. 3.7 min, HPLC purity 98.0%

Example 75: (R)-(2-(3-ethylphenyl)-1-(3-(4-(4-methoxyphenyl)-1H-1,2,3-triazol-1-yl)propanamido)ethyl)boronic acid



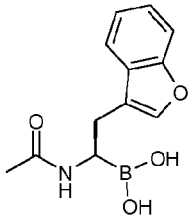
White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.23 (s, 1H), 7.71 (d, *J* = 8.00 Hz, 2H), 6.96-7.04 (m, 4H), 6.85-6.91 (m, 1H), 6.79 (d, *J* = 8.00 Hz, 1H), 4.53 (t, *J* = 8.00 Hz, 2H), 3.11-3.15 (m, 1H), 2.54-2.73 (m, 4H), 2.42-2.45 (m, 2H), 1.05-1.09 (m, 3H). MS (ESI+): 427.2 [M+Na-H_2O]. HPLC (Method A): Rt. 3.6 min, HPLC purity 98.1%

Example 76: (R)-(2-(3-ethylphenyl)-1-(3-(4-(pyridin-3-yl)-1H-1,2,3-triazol-1-yl)propanamido)ethyl)boronic acid



White solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.95 (s, 1H), 8.45-8.49 (m, 2H), 8.15-8.17 (m, 1H), 7.46-7.49 (m, 1H), 6.98-7.02 (m, 1H), 6.83-6.88 (m, 2H), 6.77 (d, *J* = 8.00 Hz, 1H), 4.55-4.59 (m, 2H), 3.11-3.13 (m, 1H), 2.67-2.70 (m, 3H), 2.57-2.59 (m, 1H), 2.39-2.45 (m, 2H), 1.04 (t, *J* = 8.00 Hz, 3H). MS (ESI+): 398.3 [M+Na-H_2O]. HPLC (Method A): Rt. 2.4 min, HPLC purity 97.9%

Example 78: **(R)-(1-acetamido-2-(benzofuran-3-yl)ethyl)boronic acid**



Step 1: (R)-(1-acetamido-2-(benzofuran-3-yl)ethyl)boronic acid(+)-pinanediol ester
A cooled (-10 °C) solution of Intermediate 18 (700 mg, 1.54 mmol) in anhydrous dichloromethane (20 ml) was treated with diisopropylethylamine (0.8 ml, 4.6 mmol) and acetyl chloride (0.09 ml, 1.54 mmol). The reaction mixture was stirred at -10 °C for 3h. The reaction mixture was concentrated under reduced pressure keeping an external bath temperature below 30 °C, and then 25 ml ethyl acetate were added. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The desired product (520 mg, 88 %) was isolated by purification by chromatography on silica gel, eluting with 2 % methanol in dichloromethane.
MS (ESI+): 382.3

Step 2: (R)-(1-acetamido-2-(benzofuran-3-yl)ethyl)boronic acid
A cooled (0 °C) solution of (R)-(1-acetamido-2-(benzofuran-3-yl)ethyl)boronic acid(+)-pinanediol ester (520 mg, 1.35 mmol) in methanol / pentane (1:1, 30 mL) was treated with 2-methylpropyl boronic acid (545 mg, 5.4 mmol) and an aqueous HCl solution (1.5 N, 1 mL) and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture

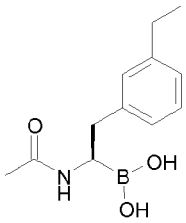
was then extracted with pentane thrice. The aqueous methanol layer was concentrated at temperature below 30 °C. The residue was treated with ice and basified with an aqueous (2N) solution of NaOH and extracted with dichloromethane thrice (discarded). The aqueous layer was then acidified with an aqueous (1.5 N) HCl solution and extracted with dichloromethane thrice. The DCM layer was dried over sodium sulfate, filtered and concentrated to give a solid residue, which was triturated with diethylether and lyophilized to obtain the title compound (42 mg, 26 %) as a white solid.

^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.64 (s, 1H), 7.58-7.60 (d, *J* =8.0 Hz, 1H), 7.48-7.50 (d, *J* = 8.0 Hz, 1H), 7.19-7.28 (m, 2H), 3.09-3.13 (m, 1H), 2.81-2.86 (m, 1H), 2.69-2.75 (m, 1H), 1.77 (s, 3H).

MS (ESI+): 230.0 [M+H-H_2O], HPLC (Method A): Rt 2.0min; HPLC purity 98.8%

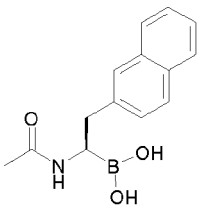
The following compounds were synthesized using the same procedure followed for Example 78

Example 77: (R)-(1-acetamido-2-(3-ethylphenyl)ethyl)boronic acid



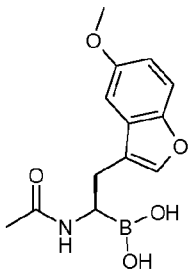
Pale pink solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.11-7.15 (m, 1H), 6.93-6.98 (m, 3H), 2.98-3.01 (m, 1H), 2.71-2.76 (m, 1H), 2.49-2.54 (m, 3H), 1.77 (s, 3H), 1.10-1.14 (m, 3H). MS (ESI+): 218.0 [M+H-H_2O]. HPLC (Method A): Rt. 2.4 min, HPLC purity 98.0%

Example 95: (R)-(1-acetamido-2-(naphthalen-2-yl)ethyl)boronic acid



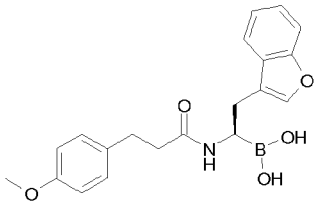
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.76-7.78 (m, 3H), 7.61 (s, 1H), 7.38-7.46 (m, 2H), 7.32-7.35 (m, 1H), 3.04-3.08 (m, 1H), 2.90-2.95 (m, 1H), 2.73-2.78 (m, 1H), 1.79 (s, 3H). MS (ESI+): 240.3 [M+H-H_2O]. HPLC (Method A): Rt. 2.6 min, HPLC purity 92.4%

Example 108: (R)-(1-acetamido-2-(5-methoxybenzofuran-3-yl)ethyl)boronic acid



White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.60 (s, 1H), 7.38 (d, *J* = 8.88 Hz, 1H), 7.09-7.10 (m, 1H), 6.84 (dd, *J* = 2.56, 8.92 Hz, 1H), 3.76 (s, 3H), 3.08-3.12 (m, 1H), 2.78-2.83 (m, 1H), 2.66-2.72 (m, 1H), 1.79 (s, 3H). MS (ESI+): 260.0 [M+H-H_2O]. HPLC (Method A): Rt. 2.2 min, HPLC purity 96.5%

Example 79: **(R)-(2-(benzofuran-3-yl)-1-(3-(4-methoxyphenyl)propanamido)ethyl) boronic acid**



Step 1: (R)-(2-(benzofuran-3-yl)-1-(3-(4-methoxyphenyl)propanamido)ethyl) boronic acid pinacol ester.

A cooled (-10 °C) solution of Intermediate 18 (170 mg, 0.37 mmol) in anhydrous N,N-dimethylformamide (20 ml) was treated with diisopropylethylamine (0.2 ml, 1.1 mmol) and 3-(4-methoxyphenyl)propionic acid (67 mg, 0.37 mmol) and TBTU (142 mg, 0.44 mmol). The reaction mixture was stirred at -10 °C for 3h. The reaction mixture was concentrated under reduced pressure keeping an external bath temperature below 30 °C, and then 25 ml ethyl acetate were added. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The desired product (160 mg, 86 %) was isolated by purification by chromatography on silica gel, eluting with 40 % ethylacetate in petroleum ether.
MS (ESI+): 502.2

Step 2: (R)-(2-(benzofuran-3-yl)-1-(3-(4-methoxyphenyl)propanamido)ethyl) boronic acid

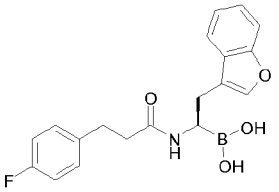
A cooled (0 °C) solution of (R)-(2-(benzofuran-3-yl)-1-(3-(4-methoxyphenyl)propan amido)ethyl)boronicacid pinacol ester (160 mg, 0.32 mmol) in methanol / pentane (1:1, 20 mL) was treated with 2-methylpropyl boronic acid (129 mg, 1.3 mmol) and an aqueous HCl solution (1.5 N, 0.5 mL) and the reaction mixture was stirred at room temperature for 15 h.

The reaction mixture was then extracted with pentane thrice. The aqueous methanol layer was concentrated at temperature below 30 °C. The residue was treated with ice and basified with an aqueous (2N) solution of NaOH and extracted with dichloromethane thrice (discarded). The aqueous layer was then acidified with an aqueous (1.5 N) HCl solution and extracted with dichloromethane thrice. The DCM layer was dried over sodium sulfate, filtered and concentrated to give a solid residue, which was triturated with diethylether and lyophilized to obtain the title compound (25 mg, 21 %) as a white solid.

^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.57 (d, *J* = 7.68 Hz, 1H), 7.49 (t, *J* = 3.92 Hz, 2H), 7.21-7.26 (m, 2H), 7.06 (d, *J* = 8.44 Hz, 2H), 6.77 (d, *J* = 8.48 Hz, 2H), 3.67 (s, 3H), 3.15-3.17 (m, 1H), 2.65-2.81 (m, 5H), 2.30 (t, *J* = 7.32 Hz, 2H). MS (ESI+): 350.3 [M+H-H_2O]. HPLC (Method A): Rt. 3.5 min, HPLC purity 93.8%

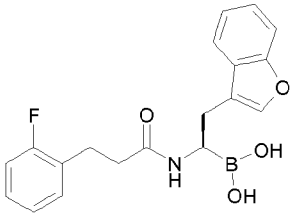
The following compounds were synthesized using the same procedure followed for Example 79

Example 80: (R)-(2-(benzofuran-3-yl)-1-(3-(4-fluorophenyl)propanamido)ethyl) boronic acid



Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 400 MHz, DMSO-d6: δ 7.57 (d, *J* = 7.16 Hz, 1H), 7.48 (d, *J* = 6.88 Hz, 1H), 7.15-7.28 (m, 4H), 6.99-7.04 (m, 2H), 3.18 (t, *J* = 5.72 Hz, 1H), 2.80-2.81 (m, 1H), 2.71-2.75 (m, 3H), 2.32 (t, *J* = 7.28 Hz, 2H). MS (ESI+): 338.3 [M+H-H_2O]. HPLC (Method A): Rt. 3.7 min, HPLC purity 99.0%

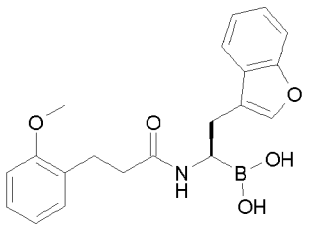
Example 81: (R)-(2-(benzofuran-3-yl)-1-(3-(2-fluorophenyl)propanamido)ethyl) boronic acid



Off-white solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.57 (d, *J* = 7.2 Hz, 1H), 7.50-7.52 (m, 2H), 7.18-7.28 (m, 4H), 7.02-7.12 (m, 2H), 3.18-3.21 (m, 1H), 2.73-2.82 (m, 4H), 2.34 (t, *J*

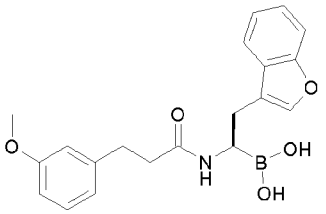
= 7.36 Hz, 2H). MS (ESI+): 338.3 [M+H-H_2O]. HPLC (Method A): Rt. 3.7 min, HPLC purity 97.9%

Example 82: (R)-(2-(benzofuran-3-yl)-1-(3-(2-methoxyphenyl)propanamido)ethyl) boronic acid



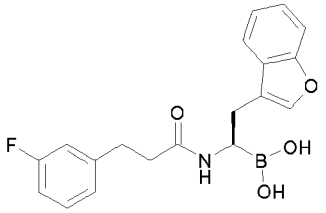
Pale pink solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.57 (d, *J* = 7.00 Hz, 1H), 7.48 (d, *J* = 7.36 Hz, 2H), 7.20-7.28 (m, 2H), 7.12-7.19 (m, 1H), 7.05-7.07 (m, 1H), 6.91 (d, *J* = 7.80 Hz, 1H), 6.77-6.81 (m, 1H), 3.73 (s, 1H), 3.12-3.15 (m, 1H), 2.79-2.81 (m, 1H), 2.68-2.74 (m, 3H), 2.29 (t, *J* = 7.20 Hz, 2H). MS (ESI+): 350.3 [M+H-H_2O]. HPLC (Method A): Rt. 3.7 min, HPLC purity 98.1%

Example 84: (R)-(2-(benzofuran-3-yl)-1-(3-(3-methoxyphenyl)propanamido)ethyl) boronic acid



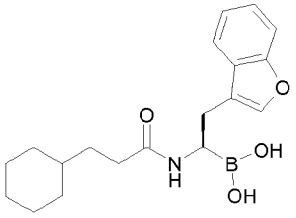
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.57 (d, *J* = 7.08 Hz, 1H), 7.47-7.49 (m, 2H), 7.19-7.28 (m, 2H), 7.14 (t, *J* = 7.96 Hz, 1H), 6.70-6.73 (m, 3H), 3.68 (s, 3H), 3.16-3.19 (m, 1H), 2.80-2.81 (m, 1H), 2.69-2.74 (m, 3H), 2.34 (t, *J* = 7.32 Hz, 2H). MS (ESI+): 350.3 [M+H-H_2O]. HPLC (Method A): Rt. 3.6 min, HPLC purity 99.7%

Example 85: (R)-(2-(benzofuran-3-yl)-1-(3-(3-fluorophenyl)propanamido)ethyl) boronic acid



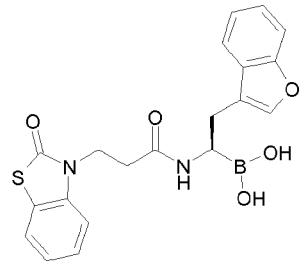
White solid. ^{1}H NMR :(400 MHz, DMSO-d_6): δ 7.56-7.58 (m, 1H), 7.47-7.49 (m, 2H), 7.19-7.28 (m, 3H), 6.93-7.00 (m, 3H), 3.17-3.20 (m, 1H), 2.68-2.85 (m, 4H), 2.36 (t, *J* = 7.36 Hz, 2H). MS (ESI+): 338.3 [M+H-H_2O]. HPLC (Method A): Rt. 3.7 min, HPLC purity 98.4%

Example 86: (R)-(2-(benzofuran-3-yl)-1-(3-cyclohexylpropanamido)ethyl)boronic acid



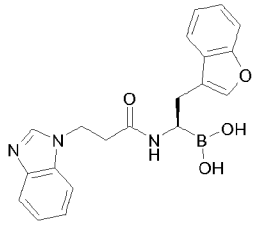
White solid. ^{1}H NMR:(400 MHz, DMSO-d_6): δ 7.58-7.62 (m, 2H), 7.48 (d, *J* = 7.92 Hz, 1H), 7.19-7.28 (m, 2H), 3.10-3.13 (m, 1H), 2.80-2.85 (m, 1H), 2.68-2.72 (m, 1H), 2.05 (t, *J* = 7.92 Hz, 2H), 1.56-1.59 (m, 5H), 1.27-1.32 (m, 2H), 1.04-1.08 (m, 4H), 0.74-0.80 (m, 2H). MS (ESI+): 326.3 [M+H-H_2O]. HPLC (Method A): Rt. 4.2 min, HPLC purity 99.2%

Example 87: (R)-(2-(benzofuran-3-yl)-1-(3-(2-oxobenzo[d]thiazol-3(2H)-yl)propanamido)ethyl)boronic acid



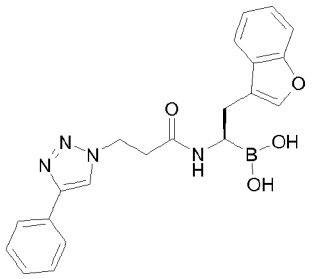
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.57 (d, *J* = 7.84 Hz, 1H), 7.52 (d, *J* = 7.56 Hz, 1H), 7.46 (d, *J* = 8.04 Hz, 1H), 7.41 (s, 1H), 7.13-7.34 (m, 5H), 4.05-4.09 (m, 2H), 3.14-3.84 (m, 1H), 2.75-2.80 (m, 1H), 2.64-2.70 (m, 1H), 2.43-2.49 (m, 2H). MS (ESI+): 393.0 [M+H-H_2O]. HPLC (Method A): Rt. 3.6 min, HPLC purity 98.8%

Example 88: (R)-(1-(3-(1H-benzo[d]imidazol-1-yl)propanamido)-2-(benzofuran-3-yl)ethyl)boronic acid



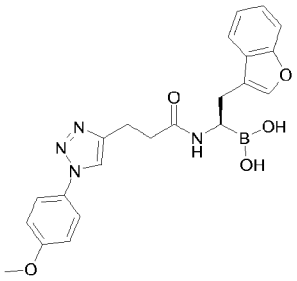
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.09 (s, 1H), 7.61-7.63 (m, 1H), 7.56 (d, *J* = 7.44 Hz, 1H), 7.43-7.46 (m, 2H), 7.18-7.27 (m, 4H), 7.09-7.13 (m, 1H), 4.39-4.43 (m, 2H), 3.13-3.17 (m, 1H), 2.72-2.86 (m, 1H), 2.50-2.66 (m, 3H). MS (ESI+): 382.3 [M+Na-H_2O]. HPLC (Method A): Rt. 2.6 min, HPLC purity 94.3%

Example 89: (R)-(2-(benzofuran-3-yl)-1-(3-(4-phenyl-1H-1,2,3-triazol-1-yl) propanamido)ethyl)boronic acid



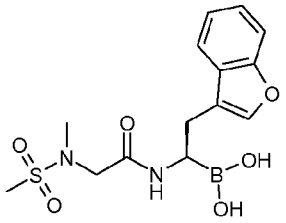
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.34 (s, 1H), 7.76 (d, *J* = 7.48 Hz, 2H), 7.48 (d, *J* = 7.28 Hz, 2H), 7.41 (t, *J* = 7.52 Hz, 3H), 7.31 (t, *J* = 7.40 Hz, 1H), 7.23 (t, *J* = 7.52 Hz, 1H), 7.16 (t, *J* = 7.16 Hz, 1H), 4.55-4.56 (m, 2H), 3.16-3.18 (m, 1H), 2.77-2.86 (m, 1H), 2.66-2.73 (m, 3H). MS (ESI+): 409.2 [M+Na-H_2O]. HPLC (Method A): Rt. 3.5 min, HPLC purity 94.8%

Example 90: (R)-(2-(benzofuran-3-yl)-1-(3-(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)propanamido)ethyl)boronic acid



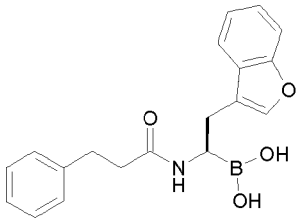
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 7.68 (d, *J* = 8.92 Hz, 2H), 7.55-7.57 (m, 2H), 7.45 (d, *J* = 7.96 Hz, 1H), 7.18-7.27 (m, 2H), 7.08 (d, *J* = 9.00 Hz, 2H), 3.79 (s, 3H), 3.17-3.21 (m, 1H), 2.82-2.90 (m, 3H), 2.67-2.76 (m, 1H), 2.43-2.50 (m, 2H). MS (ESI+): 439.3 [M+Na-H_2O]. HPLC (Method A): Rt. 3.4 min, HPLC purity 95.0%

Example 91: (R)-(2-(benzofuran-3-yl)-1-(2-(N-methylmethylsulfonamido) acetamido)ethyl)boronic acid



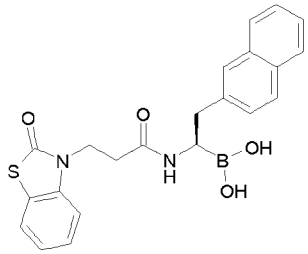
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.60-7.60 (m, 2H), 7.48 (d, *J* = 7.84 Hz, 1H), 7.19-7.28 (m, 2H), 3.68 (d, *J* = 8.12 Hz, 2H), 3.33-3.36 (m, 1H), 2.87-2.92 (m, 4H), 2.76-2.82 (m, 1H), 2.66 (s, 3H). MS (ESI+): 337.0 [M+H-H_2O]. HPLC (Method A): Rt. 2.8 min, HPLC purity 97.5%

Example 94: (R)-(2-(benzofuran-3-yl)-1-(3-phenylpropanamido)ethyl)boronic acid



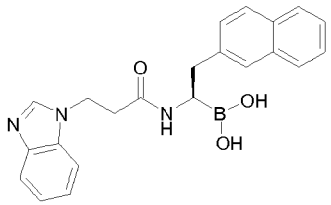
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.56 (d, *J* = 7.68 Hz, 1H), 7.46-7.49 (m, 2H), 7.18-7.28 (m, 4H), 7.11-7.15 (m, 3H), 3.13-3.15 (m, 1H), 2.79-2.80 (m, 1H), 2.71-2.75 (m, 3H), 2.34 (t, *J* = 7.32 Hz, 2H). MS (ESI+): 320.2 [M+H-H_2O]. HPLC (Method A): Rt. 3.6 min, HPLC purity 97.6%

Example 96: (R)-(2-(naphthalen-2-yl)-1-(3-(2-oxobenzo[d]thiazol-3(2H)-yl) propanamido)ethyl)boronic acid



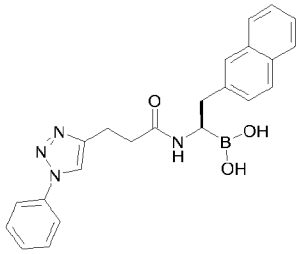
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): 400 MHz, DMSO-d6: δ 7.80 (d, *J* = 8.32 Hz, 1H), 7.71 (d, *J* = 8.48 Hz, 2H), 7.60 (d, *J* = 7.76 Hz, 1H), 7.37-7.43 (m, 3H), 7.30-7.34 (m, 1H), 7.25 (d, *J* = 8.00 Hz, 1H), 7.15-7.18 (m, 2H), 4.04 (t, *J* = 6.96 Hz, 2H), 3.19-3.23 (m, 1H), 2.82-2.87 (m, 1H), 2.71-2.77 (m, 1H), 2.41 (t, *J* = 7.00 Hz, 2H). MS (ESI+): 403.0 [M+H-H_2O]. HPLC (Method A): Rt. 3.9 min, HPLC purity 98.6%

Example 97: (R)-(1-(3-(1H-benzo[d]imidazol-1-yl)propanamido)-2-(naphthalen-2-yl)ethyl)boronic acid



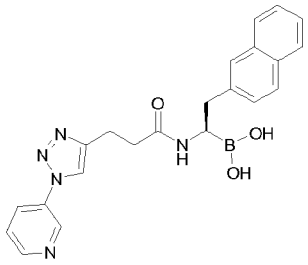
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.09 (s, 1H), 7.75-7.77 (m, 1H), 7.59-7.65 (m, 3H), 7.54 (dd, *J* = 2.04, 6.80 Hz, 1H), 7.36-7.41 (m, 2H), 7.29 (s, 1H), 7.20-7.27 (m, 2H), 7.06 (dd, *J* = 1.52, 8.40 Hz, 1H), 4.38-4.41 (m, 2H), 3.20 (d, *J* = 2.32 Hz, 1H), 2.74-2.81 (m, 1H), 2.59-2.61 (m, 1H), 2.49-2.57 (m, 2H). MS (ESI+): 392.3 [M+Na-H_2O]. HPLC (Method A): Rt. 2.9 min, HPLC purity 96.5%

Example 98: (R)-(2-(naphthalen-2-yl)-1-(3-(1-phenyl-1H-1,2,3-triazol-4-yl) propanamido)ethyl)boronic acid



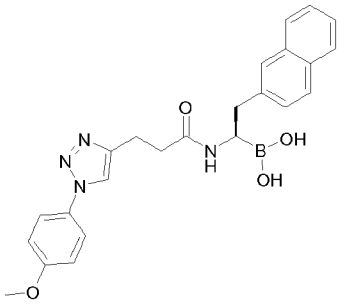
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.37 (s, 1H), 7.78-7.78 (m, 3H), 7.69-7.72 (m, 2H), 7.52-7.57 (m, 3H), 7.46 (d, *J* = 7.40 Hz, 1H), 7.36-7.41 (m, 2H), 7.25 (dd, *J* = 1.48, 8.44 Hz, 1H), 3.17-3.20 (m, 1H), 2.87-2.94 (m, 3H), 2.75-2.81 (m, 1H), 2.42-2.50 (m, 2H). MS (ESI+): 419.2 [M+Na-H_2O]. HPLC (Method A): Rt. 3.7 min, HPLC purity 96.7%

Example 99: (R)-(2-(naphthalen-2-yl)-1-(3-(1-(pyridin-3-yl)-1H-1,2,3-triazol-4-yl) propanamido)ethyl)boronic acid



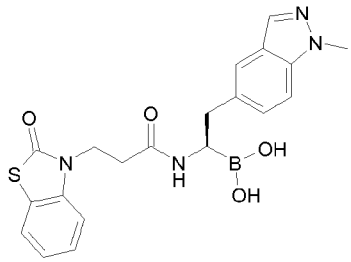
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.90 (s, 1H), 8.58-8.59 (m, 1H), 8.33 (s, 1H), 8.14 (d, *J* = 8.04 Hz, 1H), 7.57-7.71 (m, 4H), 7.44 (s, 1H), 7.33-7.35 (m, 2H), 7.20 (d, *J* = 8.24 Hz, 1H), 3.04-3.07 (m, 1H), 2.86-2.94 (m, 3H), 2.65-2.71 (m, 1H), 2.49-2.50 (m, 2H). MS (ESI+): 420.2 [M+Na-H_2O]. HPLC (Method A): Rt. 2.7 min, HPLC purity 95.9%

Example 100: (R)-(1-(3-(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)propanamido)-2-(naphthalen-2-yl)ethyl)boronic acid



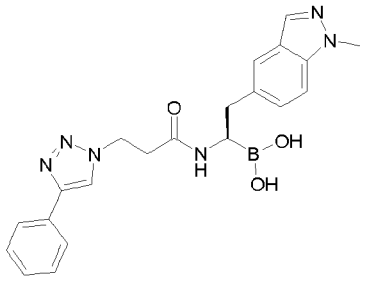
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.24 (s, 1H), 7.65-7.78 (m, 5H), 7.51 (s, 1H), 7.38-7.42 (m, 2H), 7.23-7.26 (m, 1H), 7.06-7.08 (m, 2H), 3.77 (s, 3H), 3.15-3.18 (m, 1H), 2.85-2.94 (m, 3H), 2.74-2.80 (m, 1H), 2.42-2.50 (m, 2H). MS (ESI+): 449.2 [M+Na-H_2O]. HPLC (Method A): Rt. 3.7 min, HPLC purity 90.2%

Example 102: (R)-(2-(1-methyl-1H-indazol-5-yl)-1-(3-(2-oxobenzo[d]thiazol-3(2H)-yl)propanamido)ethyl)boronic acid



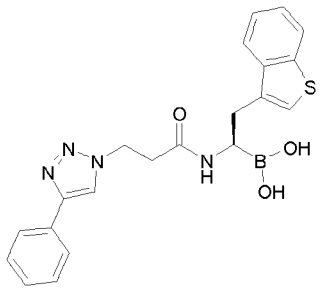
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.85 (s, 1H), 7.61 (d, *J* = 8.68 Hz, 1H), 7.39 (d, *J* = 8.64 Hz, 1H), 7.35-7.31 (m, 1H), 7.26 (d, *J* = 7.56 Hz, 1H), 7.19-7.15 (m, 2H), 7.04 (dd, *J* = 1.36, 8.66 Hz, 1H), 4.05 (t, *J* = 7.00 Hz, 2H), 3.92 (s, 3H), 3.15-3.14 (m, 1H), 2.74 (t, *J* = 5.36 Hz, 1H), 2.66 (t, *J* = 5.28 Hz, 1H), 2.41 (t, *J* = 6.92 Hz, 2H). MS (ESI+): 429.2 [M+Na-H_2O]. HPLC (Method A): Rt. 2.8 min, HPLC purity 98.0%

Example 103: (R)-(2-(1-methyl-1H-indazol-5-yl)-1-(3-(4-phenyl-1H-1,2,3-triazol-1-yl) propanamido)ethyl)boronic acid



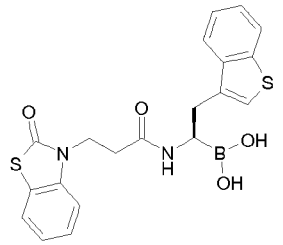
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.36 (s, 1H), 7.79 (d, *J* = 8.40 Hz, 3H), 7.44-7.43 (m, 2H), 7.34-7.33 (m, 2H), 7.27 (s, 1H), 7.05 (dd, *J* = 1.48, 8.66 Hz, 1H), 4.60-4.58 (m, 2H), 3.88 (s, 3H), 3.15 (t, *J* = 5.64 Hz, 1H), 2.80 (t, J = 5.36 Hz, 1H), 2.74-2.72 (m, 1H), 2.68 (t, *J* = 6.52 Hz, 2H). MS (ESI+): 423.3 [M+Na-H_2O]. HPLC (Method A): Rt. 2.7 min, HPLC purity 95.0%

Example 104: (R)-(2-(benzo[b]thiophen-3-yl)-1-(3-(4-phenyl-1H-1,2,3-triazol-1-yl) propanamido)ethyl)boronic acid



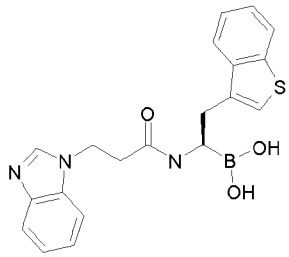
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.34 (s, 1H), 7.83-7.86 (m, 1H), 7.76-7.78 (m, 2H), 7.68-7.71 (m, 1H), 7.39-7.43 (m, 2H), 7.28-7.34 (m, 3H), 7.12 (s, 1H), 4.56 (t, *J* = 6.68 Hz, 2H), 3.22-3.25 (m, 1H), 2.96-3.01 (m, 1H), 2.81-2.87 (m, 1H), 2.69 (t, *J* = 6.56 Hz, 2H). MS (ESI+): 425.2 [M+Na-H_2O]. HPLC (Method A): Rt. 3.6 min, HPLC purity 94.8%

Example 105: (R)-(2-(benzo[b]thiophen-3-yl)-1-(3-(2-oxobenzo[d]thiazol-3(2H)-yl) propanamido)ethyl)boronic acid



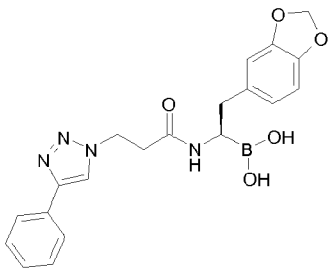
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.87-7.89 (m, 1H), 7.72-7.74 (m, 1H), 7.58 (d, *J* = 7.20 Hz, 1H), 7.26-7.37 (m, 4H), 7.14-7.18 (m, 1H), 7.03 (s, 1H), 4.05-4.08 (m, 2H), 3.20-3.24 (m, 1H), 2.93-2.98 (m, 1H), 2.83-2.86 (m, 1H), 2.41-2.49 (m, 2H).
MS (ESI+): 409.0 [M+H-H_2O]. HPLC (Method A): Rt. 3.8 min, HPLC purity 86.0%

Example 106: (R)-(1-(3-(1H-benzo[d]imidazol-1-yl)propanamido)-2-(benzo [b]thiophen-3-yl)ethyl)boronic acid



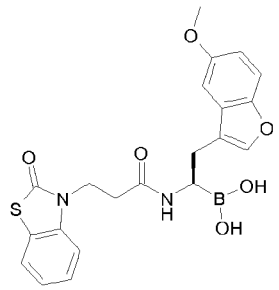
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.09 (s, 1H), 7.85-7.87 (m, 1H), 7.67-7.70 (m, 1H), 7.63 (d, *J* = 7.48 Hz, 1H), 7.55 (d, *J* = 7.56 Hz, 1H), 7.28-7.30 (m, 2H), 7.19-7.26 (m, 2H), 6.86 (s, 1H), 4.39-4.42 (m, 2H), 3.18-3.21 (m, 1H), 2.92-2.95 (m, 1H), 2.76-2.82 (m, 1H), 2.58-2.61 (m, 2H). MS (ESI+): 398.0 [M+Na-H_2O]. HPLC (Method A): Rt. 2.7 min, HPLC purity 96.0%

Example 107: (R)-(2-(benzo[d][1,3]dioxol-5-yl)-1-(3-(4-phenyl-1H-1,2,3-triazol-1-yl) propanamido)ethyl)boronic acid



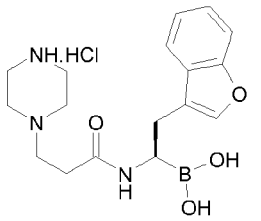
White solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.25 (s, 1H), 7.72-7.74 (m, 2H), 7.38-7.42 (m, 2H), 7.29-7.33 (m, 1H), 6.45-6.48 (m, 2H), 6.25 (d, *J* = 7.92 Hz, 1H), 5.73 (s, 2H), 4.59-4.61 (m, 2H), 2.74-2.84 (m, 3H), 2.49-2.56 (m, 1H), 2.26-2.32 (m, 1H). MS (ESI+): 413.0 [M+Na-H_2O]. HPLC (Method A): Rt. 3.1 min, HPLC purity 95.2%

Example 109: (R)-(2-(5-methoxybenzofuran-3-yl)-1-(3-(2-oxobenzo[d]thiazol-3(2H)-yl)propanamido)ethyl)boronic acid



Pale brown solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.58 (d, *J* = 7.16 Hz, 1H), 7.34-7.39 (m, 2H), 7.31 (d, *J* = 8.16 Hz, 1H), 7.27 (d, *J* = 7.36 Hz, 1H), 7.13-7.17 (m, 1H), 7.07-7.08 (m, 1H), 6.83 (dd, *J* = 2.56, 8.88 Hz, 1H), 4.06 (t, *J* = 7.68 Hz, 2H), 3.74 (s, 3H), 3.17-3.20 (m, 1H), 2.73-2.74 (m, 1H), 2.64-2.68 (m, 1H), 2.42-2.46 (m, 2H). MS (ESI+): 423.0 [M+H-H_2O]. HPLC (Method A): Rt. 3.6 min, HPLC purity 92.6%

Example 92: (R)-(2-(benzofuran-3-yl)-1-(3-(piperazin-1-yl) propanamido)ethyl) boronic acid hydrochloride



Step 1: (R)-(2-(benzofuran-3-yl)-1-(3-(4-(tert-butoxycarbonyl)piperazin-1-yl) propanamido)ethyl)boronic acid pinacol ester.

A cooled (-10 °C) solution of Intermediate 18 (300 mg, 0.66 mmol) in anhydrous N,N-dimethylformamide (10 ml) was treated with diisopropylethylamine (0.3 ml, 1.9 mmol) and 3-(4-(tert-butoxycarbonyl)piperazin-1-yl)propanoic acid (170 mg, 0.66 mmol) and TBTU (254 mg, 0.79 mmol). The reaction mixture was stirred at -10 °C for 3h. The reaction mixture was concentrated under reduced pressure keeping an external bath temperature below 30 °C, and then 25 ml ethyl acetate were added. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The desired product (350 mg, 87%) was isolated by purification by chromatography on silica gel, eluting with 4 % methanol in dichloromethane.

MS (ESI+): 580.4

Step 2: (R)-(2-(benzofuran-3-yl)-1-(3-(4-(tert-butoxycarbonyl)piperazin-1-yl) propanamido)ethyl)boronic acid.

A cooled (0 °C) solution of (R)-(2-(benzofuran-3-yl)-1-(3-(4-(tert-butoxycarbonyl) piperazin-1-yl) propanamido)ethyl)boronic acid pinacol ester (350 mg, 0.6 mmol) in methanol / pentane (1:1, 30 mL) was treated with 2-methylpropyl boronic acid (242 mg, 2.4 mmol) and an aqueous HCl solution (1.5 N, 0.7 mL) and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was then extracted with pentane thrice. The aqueous methanol layer was concentrated at temperature below 30 °C. The residue was treated with ice and basified with an aqueous (2N) solution of NaOH and extracted with dichloromethane thrice (discarded). The aqueous layer was then acidified with an aqueous (1.5 N) HCl solution and extracted with dichloromethane thrice. The DCM layer was dried over sodium sulfate, filtered and concentrated. The desired product (85 mg, 31%) was isolated by purification by chromatography on silica gel, eluting with 30 % methanol in dichloromethane.

MS (ESI+): 450.2 [M+Na-H_2O].

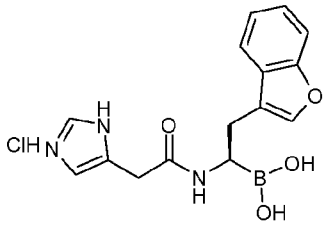
Step 3: (R)-(2-(benzofuran-3-yl)-1-(3-(piperazin-1-yl) propanamido)ethyl) boronic acid hydrochloride.

The compound (R)-(2-(benzofuran-3-yl)-1-(3-(4-(tert-butoxycarbonyl)piperazin-1-yl) propanamido)ethyl)boronic acid (0.085g, 0.19 mmol) was taken in 1,4-dioxane (5 mL) and cooled to 10 °C. To this was added 4 N HCl in dioxane (5 mL) and stirred at RT overnight. The reaction mixture was concentrated under reduced pressure and the residue was washed with diethyl ether to get solid. The solid was further lyophilized to obtain the title compound (47 mg, 64 %) as a pale brown solid.

^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.66 (s, 1H), 7.62 (d, *J* = 7.24 Hz, 1H), 7.49 (d, *J* = 8.12 Hz, 1H), 7.21-7.29 (m, 2H), 3.25-3.37 (m, 11H), 2.88-2.93 (m, 1H), 2.75-2.81 (m, 1H), 2.55-

2.56 (m, 2H). MS (ESI+): 350.3 [M+Na-H_2O]. HPLC (Method A): Rt. 2.0 min, HPLC purity 93.5%

Example 83: (R)-(1-(2-(1H-imidazol-5-yl)acetamido)-2-(benzofuran-3-yl)ethyl) boronic acid hydrochloride



Step 1: (R)-(1-(2-(1H-imidazol-5-yl)acetamido)-2-(benzofuran-3-yl)ethyl) boronic acid pinacol ester.

A cooled (-10 °C) solution of Intermediate 18 (170 mg, 0.37 mmol) in anhydrous N,N-dimethylformamide (20 ml) was treated with diisopropylethylamine (0.2 ml, 1.1 mmol) and 2-(1H)-imidazole-5-yl-acetic acid (47 mg, 0.37 mmol) and TBTU (142 mg, 0.44 mmol). The reaction mixture was stirred at -10 °C for 3h. The reaction mixture was concentrated under reduced pressure keeping an external bath temperature below 30 °C, and then 25 ml ethyl acetate were added. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The desired product (110 mg, 66 %) was isolated by purification by chromatography on silica gel, eluting with 7 % methanol in dichloromethane.
MS (ESI+): 448.2

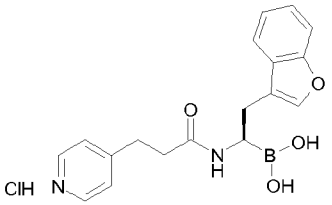
Step 2: (R)-(1-(2-(1H-imidazol-5-yl)acetamido)-2-(benzofuran-3-yl)ethyl) boronic acid hydrochloride

A cooled (0 °C) solution of (R)-(1-(2-(1H-imidazol-5-yl)acetamido)-2-(benzofuran-3-yl)ethyl) boronic acid pinacol ester (110 mg, 0.24 mmol) in methanol / pentane (1:1, 20 mL) was treated with 2-methylpropyl boronic acid (96 mg, 0.96 mmol) and an aqueous HCl solution (1.5 N, 0.5 mL) and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was then extracted with pentane thrice. The aqueous methanol layer was concentrated at temperature below 30 °C. To the residue was added water and extracted with dichloromethane thrice. The aqueous layer was lyophilized to obtain the title compound (25 mg, 32 %) as a pale brown semi solid.

^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.68 (s, 1H), 7.58 (t, *J* = 7.60 Hz, 2H), 7.47 (d, *J* = 8.08 Hz, 1H), 7.18-7.28 (m, 3H), 3.52 (s, 2H), 3.26-3.30 (m, 2H), 2.86-2.88 (m, 1H), 2.78-2.80 (m, 1H). MS (ESI+): 318.3 [M+Na-H_2O]. HPLC (Method A): Rt. 2.1 min, HPLC purity 95.2%

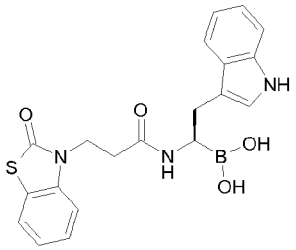
The following compound was synthesized using the same procedure followed for Example 83

Example 93: (R)-(2-(benzofuran-3-yl)-1-(3-(pyridin-4-yl)propanamido)ethyl)boronic acid hydrochloride



Pale brown semi solid. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.65 (d, J = 6.56 Hz, 2H), 7.83 (d, *J* = 6.48 Hz, 2H), 7.55-7.58 (m, 2H), 7.48 (d, *J* = 7.96 Hz, 1H), 7.19-7.28 (m, 2H), 3.20-3.23 (m, 1H), 3.03 (t, *J* = 7.16 Hz, 2H), 2.81-2.86 (m, 1H), 2.66-2.73 (m, 1H), 2.54-2.51 (m, 2H). MS (ESI+): 343.2 [M+Na-H_2O]. HPLC (Method A): Rt. 2.0 min, HPLC purity 96.1%

Example 101: (R)-(2-(1H-indol-3-yl)-1-(3-(2-oxobenzo[d]thiazol-3(2H)-yl) propanamido)ethyl)boronic acid



Step 1: tert-butyl 3-((2R)-2-(3-(2-oxobenzo[d]thiazol-3(2H)-yl)propanamido)-2-(3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)ethyl)-1H-indole-1-carboxylate.

A cooled (-10 °C) solution of [(1*R*)-1-amino-2-(1H-indol-3-yl)ethyl]boronic acid (+)-pinanediol ester trifluroacetate (500 mg, 0.90 mmol) in anhydrous N,N-dimethyl formamide (20 ml) was treated with diisopropylethylamine (0.5 ml, 2.7 mmol) and [3-(2-oxo-benzothiazol-3-yl) propionic acid] (190 mg, 0.9 mmol) and TBTU (346 mg, 1.1 mmol). The reaction mixture was stirred at -10 °C for 3h. The reaction mixture was concentrated under reduced pressure keeping an external bath temperature below 30 °C, and then 25 ml ethyl

acetate were added. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The desired product (280 mg, 48 %) was isolated by purification by chromatography on silica gel, eluting with 30 % ethylacetate in petroleum ether.
MS (ESI+): 644.2

Step 2: N-((1R)-2-(1H-indol-3-yl)-1-(3a,5,5-trimethylhexahydro-4,6-methanobenzo [d][1,3,2]dioxaborol-2-yl)ethyl)-3-(2-oxobenzo[d]thiazol-3(2H)-yl)propanamide hydrochloride.

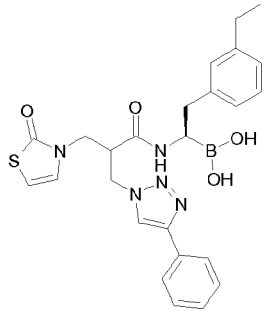
The compound tert-butyl 3-((2R)-2-(3-(2-oxobenzo[d]thiazol-3(2H)-yl)propanamido)-2-(3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)ethyl)-1H-indole-1-carboxylate (280 mg, 0.43 mmol) was taken in dichloromethane (10 mL) and cooled to 10 °C. To this was added 4 N HCl in dioxane (10 mL) and stirred at RT overnight. The reaction mixture was concentrated under reduced pressure and the residue was washed with diethyl ether to obtain the desired product (200 mg, 85 %).

Step 3: (R)-(2-(1H-indol-3-yl)-1-(3-(2-oxobenzo[d]thiazol-3(2H)-yl) propanamido) ethyl)boronic acid

A cooled (0 °C) solution of N-((1R)-2-(1H-indol-3-yl)-1-(3a,5,5-trimethylhexahydro-4,6-methanobenzo [d][1,3,2]dioxaborol-2-yl)ethyl)-3-(2-oxobenzo[d]thiazol-3(2H)-yl)propanamide hydrochloride (200 mg, 0.36 mmol) in methanol / pentane (1:1, 20 mL) was treated with 2-methylpropyl boronic acid (145 mg, 1.4 mmol) and an aqueous HCl solution (1.5 N, 0.5 mL) and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was then extracted with pentane thrice. The aqueous methanol layer was concentrated at temperature below 30 °C. The residue was treated with ice and basified with an aqueous (2N) solution of NaOH and extracted with dichloromethane thrice (discarded). The aqueous layer was then acidified with an aqueous (1.5 N) HCl solution and extracted with dichloromethane thrice. The DCM layer was dried over sodium sulfate, filtered and concentrated to give a solid residue, which was triturated with diethylether and lyophilized to obtain the title compound (13 mg, 15 %) as an off- white solid.

^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.59 (d, *J* = 7.80 Hz, 1H), 7.42 (d, *J* = 7.92 Hz, 1H), 7.26-7.34 (m, 3H), 7.17 (t, *J* = 7.36 Hz, 1H), 7.01 (t, *J* = 7.60 Hz, 1H), 6.88-6.93 (m, 2H), 4.05-4.09 (m, 2H), 3.17-3.21 (m, 1H), 2.80-2.85 (m, 1H), 2.70-2.75 (m, 1H), 2.41-2.44 (m, 2H).
MS (ESI+): 392.0 [M+H-H_2O]. HPLC (Method A): Rt. 3.2 min, HPLC purity 92.1%.

Example 110: ((1R)-2-(3-ethylphenyl)-1-(3-(2-oxothiazol-3(2H)-yl)-2-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)propanamido)ethyl)boronic acid



Step 1: Ethyl-2-(azidomethyl)acrylate

To a solution of ethyl-2-(bromomethyl)acrylate (5 g, 26.1 mmol) in DMSO (50 mL) was added sodium azide (2.5 g, 38.4 mmol) and the reaction mixture was stirred at RT for 2h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated. The crude (5.0 g) was taken to next step without further purification (Ethyl-2-(azidomethyl)acrylate was found to be unstable on standing for few hours).

Step 2: Ethyl-2-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)acrylate

To a solution of phenyl acetylene (3.0 g, 29.4 mmol) and Ethyl-2-(azidomethyl)acrylate (5.0 g, 32.3 mmol) in t-BuOH: H_2O (2:1) (50 mL) were added sodium ascorbate (0.87 g, 4.4 mmol) and CuSO4.5H_2O (0.36 g, 1.5 mmol). The reaction mixture was stirred at RT for 12h. The reaction mixture was diluted with ethyl acetate and washed with water, brine solution. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated. The solid obtained (3.0 g, 39%) was taken to next step without further purification.

^{1}H NMR: (400 MHz, DMSO-d6): δ 8.5 (s, 1H), 7.8 (d, *J* = 8.2 Hz, 2H), 7.4 (t, *J* = 7.7 Hz, 2H), 7.30-7.34 (m, 1H), 6.4 (s, 1H), 5.8 (s, 1H), 5.3 (s, 2H), 4.2 (q, *J* = 7.0 Hz, 2H), 1.2 (t, *J* = 7.0 Hz, 3H)

Step 3: Ethyl-3-(2-oxothiazol-3(2H)-yl)-2-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl) propanoate

To a solution of Ethyl-2-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)acrylate (3.0 g, 11.6 mmol) in acetonitrile (30 mL) was added thiazol-2(3H)-one (1.2 g, 11.6 mmol) and DBU (2.6 g, 17.4 mmol) at RT and the reaction mixture was stirred at RT for overnight. The reaction mixture was concentrated under reduced pressure and the residue was extracted with ethyl acetate and washed with water, brine solution. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated. The crude compound was purified by column chromatography using ethyl acetate and petroleum ether as eluent to afford the title compound (1.2 g, 28 %).

MS (ESI+): 359.2 [M+H]

Step 4: 3-(2-oxothiazol-3(2H)-yl)-2-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)propanoic acid

To a solution of Ethyl-3-(2-oxothiazol-3(2H)-yl)-2-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl) propanoate (1.2 g, 3.3mmol) in THF:H_2O (20 mL) was added Lithium hydroxide monohydrate (0.41 g, 9.9 mmol) and the reaction mixture was stirred at RT overnight. The reaction mixture was evaporated. To the residue was added water and extracted with dichloromethane thrice (discarded). The aqueous layer was then just acidified and extracted with dichloromethane. The organic layer was then dried over anhydrous sodium sulphate and concentrated to get the title compound (200 mg, 18 %).

MS (ESI+): 331.0 [M+H]

Step 5: ((1R)-2-(3-ethylphenyl)-1-(3-(2-oxothiazol-3(2H)-yl)-2-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)propanamido)ethyl)boronic acid pinacol ester.

A cooled (-10 °C) solution of [(1*R*)-1-amino-2-(3-ethylphenyl)ethyl]boronic acid (+)-pinanediol ester trifluroacetate (200 mg, 0.45 mmol) in anhydrous N,N-dimethyl formamide (10 ml) was treated with diisopropylethylamine (0.2 ml, 1.3 mmol) and 3-(2-oxothiazol-3(2H)-yl)-2-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)propanoicacid (148 mg, 0.45 mmol) and TBTU (173 mg, 0.54 mmol). The reaction mixture was stirred at -10 °C for 3h. The reaction mixture was concentrated under reduced pressure keeping an external bath temperature below 30 °C, and then 25 ml ethyl acetate were added. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The desired product (290 mg, 99 %) was isolated by purification by chromatography on silica gel, eluting with 25 % ethylacetate in petroleum ether.

MS (ESI+): 640.3

Step 6: ((1R)-2-(3-ethylphenyl)-1-(3-(2-oxothiazol-3(2H)-yl)-2-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)propanamido)ethyl)boronic acid

A cooled (0 °C) solution of ((1R)-2-(3-ethylphenyl)-1-(3-(2-oxothiazol-3(2H)-yl)-2-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)propanamido)ethyl)boronic acid pinacol ester (290 mg, 0.45 mmol) in methanol / pentane (1:1, 20 mL) was treated with 2-methylpropyl boronic acid (181 mg, 1.8 mmol) and an aqueous HCl solution (1.5 N, 0.5 mL) and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was then extracted with pentane thrice. The aqueous methanol layer was concentrated at temperature below 30 °C. The residue was treated with ice and basified with an aqueous (2N) solution of NaOH and extracted with dichloromethane thrice (discarded). The aqueous layer was then acidified with an aqueous (1.5 N) HCl solution and extracted with dichloromethane thrice. The DCM layer was dried over sodium sulfate, filtered and concentrated to give a solid residue, which was triturated with diethylether and lyophilized to obtain the title compound (61 mg, 26 %) as a pale pink solid.

^{1}H NMR:(400 MHz, DMSO-d6): δ 8.20 (d, *J* = 8.56 Hz, 1H), 7.79-7.82 (m, 2H), 7.43 (t, *J* = 7.76 Hz, 2H), 7.33-7.37 (m, 1H), 6.93-7.08 (m, 3H), 6.80-6.86 (m, 1H), 6.71-6.75 (m, 1H), 6.31-6.35 (m, 1H), 4.56-4.62 (m, 1H), 4.37-4.44 (m, 1H), 3.82-3.84 (m, 1H), 3.33-3.34 (m, 1H), 3.20-3.22 (m, 1H), 2.62-2.67 (m, 2H), 2.44-2.49 (m, 2H), 1.05-1.11 (m, 3H).
MS (ESI+): 488.3 [M+H-H_2O]. HPLC (Method A): Rt. 4.4 min, HPLC purity 91.0%

Example 111: Determination of LMP7 activity

Measurement of LMP7 inhibition is performed in 384 well format based on fluorescence intensity assay.

Purified human immuno proteasome (0.5 nM) and serial diluted compounds in DMSO (range of concentrations from 10 µM to 38 pM) or controls (0.5% DMSO) are incubated for 30 minutes at 37 °C in assay buffer containing 50 mM Tris pH 7.4 and 0.03% SDS. The reaction is initiated by the addition of the fluorogenic peptide substrate, Suc-LLVY-AMC (Bachem I-1395), at a concentration of 40µM. After 90 minutes of incubation at 37 °C, fluorescence intensity is measured at λ_{ex} =350 nm and λ_{em} = 450 nm with a fluorescence reader (BMG Pherastar reader or equivalent).

For examples 79, 80, 83, 84, 85, 87, 88, 89, 90, 91, 93, 94, 96, 97, 101 and 110 the measurement of LMP7 inhibition is performed in 384 well format based on fluorescence intensity assay.

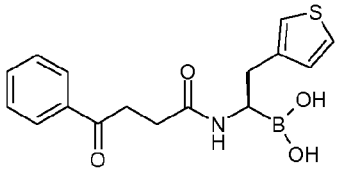
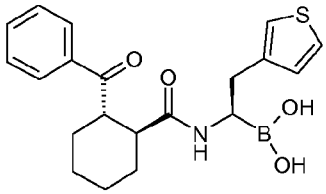
Purified human immuno proteasome (0.25 nM) and serial diluted compounds in DMSO (range of concentrations from 10 µM to 38 pM) or controls (0.5% DMSO) are incubated for 30 minutes at 37 °C in assay buffer containing 50 mM Tris pH 7.4 and 0.03% SDS. The reaction is initiated by the addition of the fluorogenic peptide substrate, Suc-LLVY-AMC (Bachem I-1395), at a concentration of 40µM. After 90 minutes of incubation at 37 °C, fluorescence intensity is measured at λ_{ex} =350 nm and λ_{em} = 450 nm with a fluorescence reader (BMG Pherastar reader or equivalent).

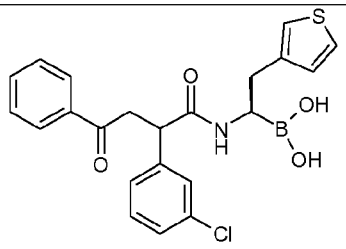
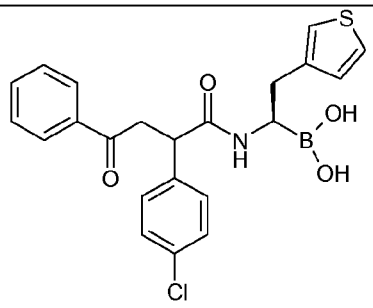
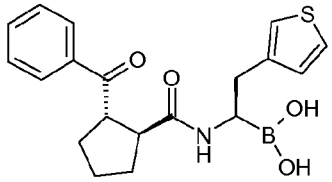
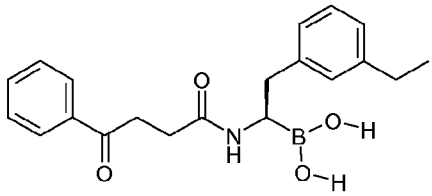
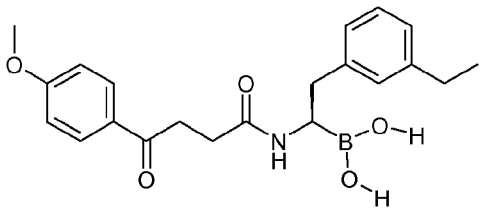
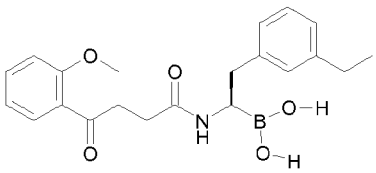
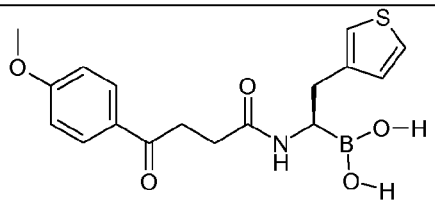
Example 112: Determination of Beta5 activity

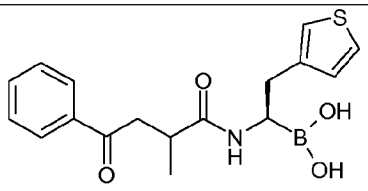
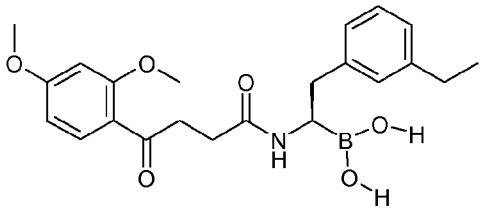
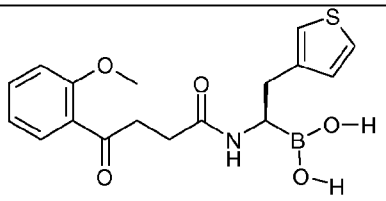
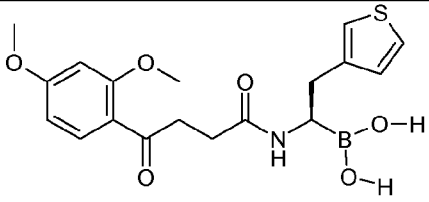
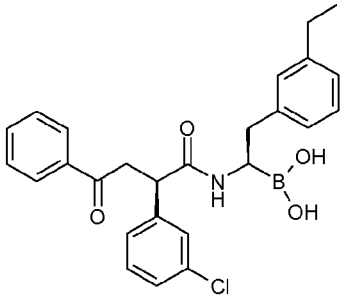
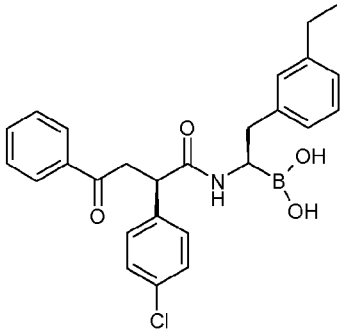
Measurement of Beta5 inhibition is performed in 384 well format based on fluorescence intensity assay.

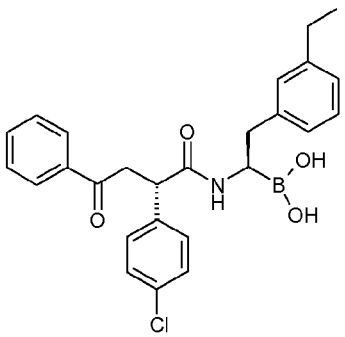
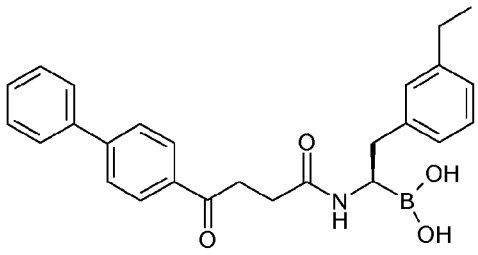
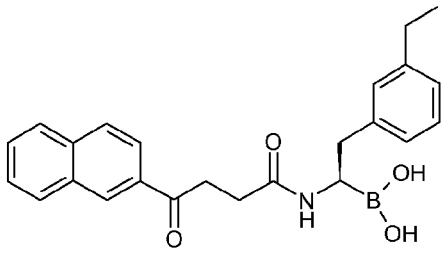
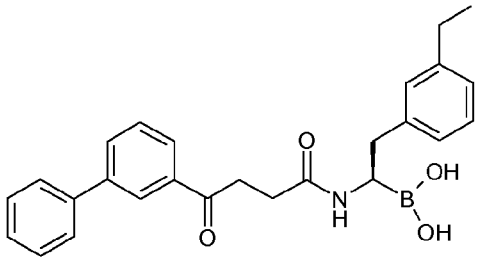
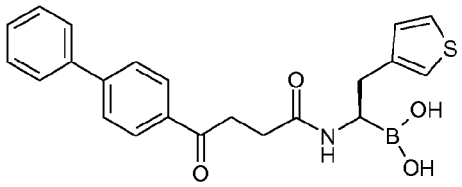
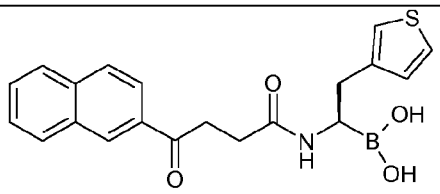
Purified human costitutive proteasome (1.0 nM) and serial diluted compounds in DMSO (range of concentrations from 10µM to 38pM) or controls (0.5% DMSO) are incubated for 30 minutes at 37 °C in assay buffer containing 50 mM Tris pH 7.4 and 0.03% SDS. The reaction is initiated by the addition of the fluorogenic peptide substrate, Suc-LLVY-AMC (Bachem I-1395), at a concentration of 40 µM. After 90 minutes of incubation at 37 °C, fluorescence intensity is measured at λ_{ex} =350 nm and λ_{em} = 450 nm with a fluorescence reader (BMG Pherastar reader or equivalent).

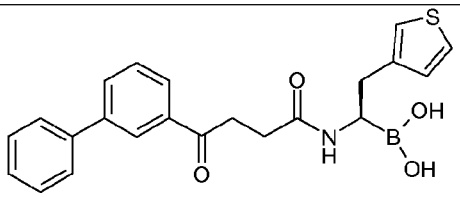
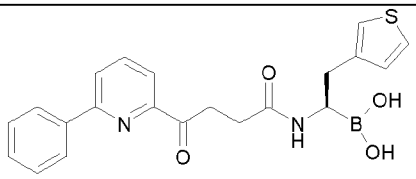
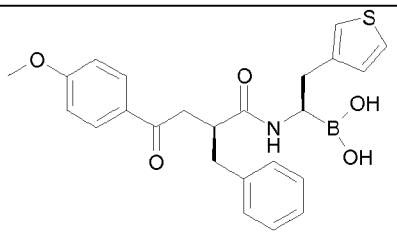
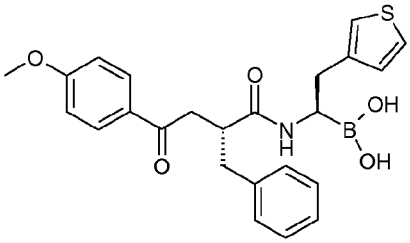
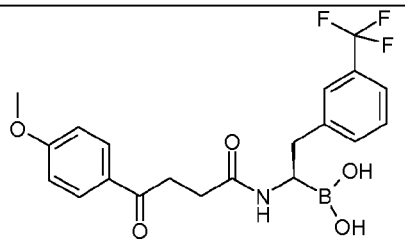
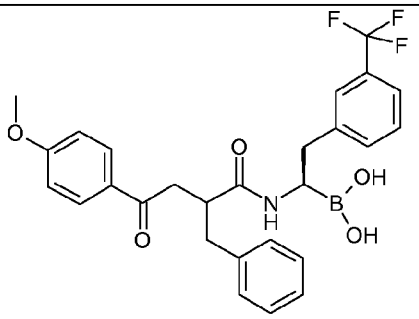
The biological activity of the compounds is summarized in the following table :

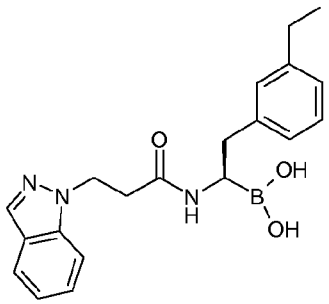
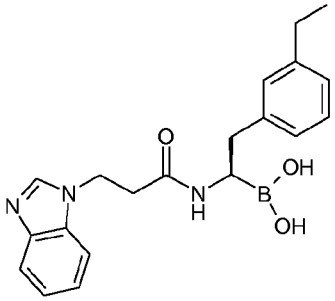
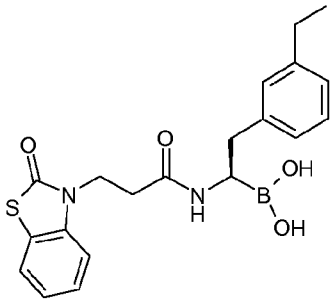
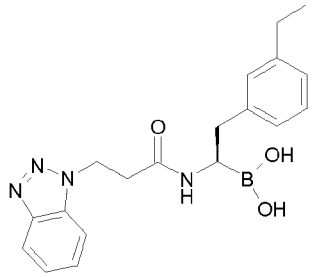
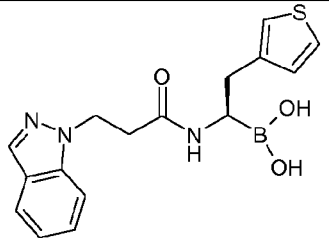
Ex	Formula	LMP7 IC50 (M)	Beta5 IC50 (M)	Selectivity LMP7 vs Beta5
1		***	**	++
2		**	*	nd

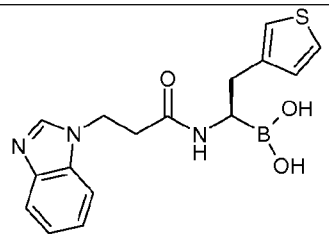
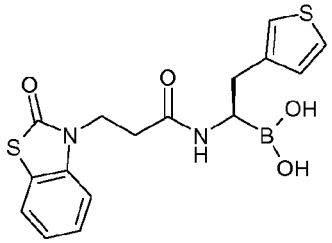
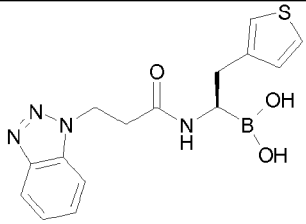
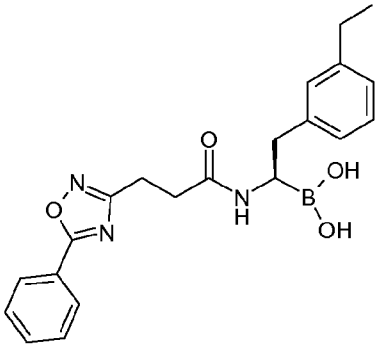
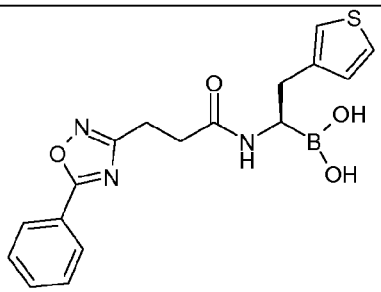
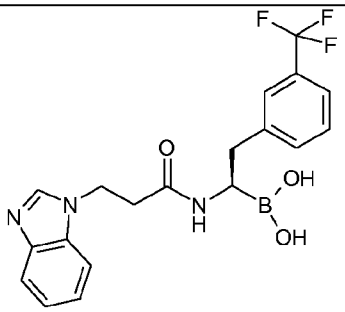
3		***	*	+++
4		***	**	+++
5		**	*	nd
6		***	*	+++
7		***	*	+++
8		***	*	nd
9		***	**	++

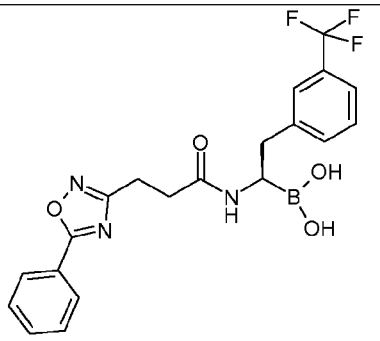
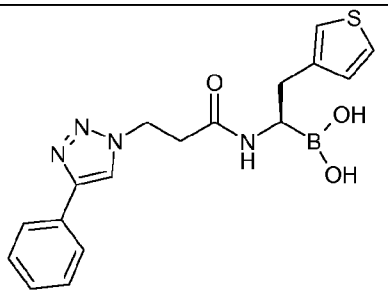
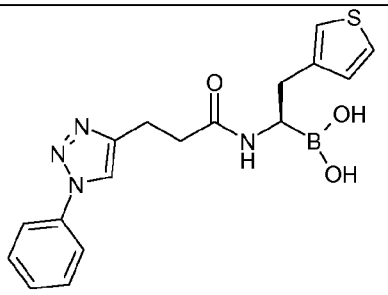
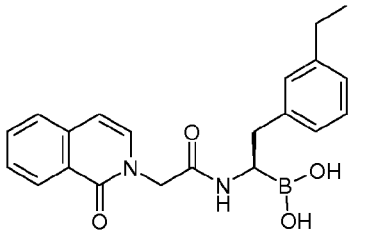
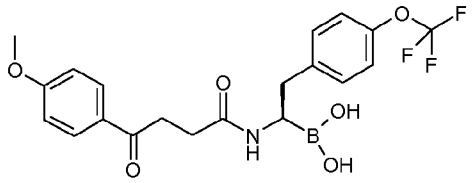
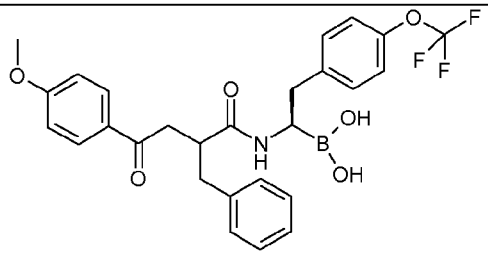
10		**	*	nd
11		***	*	+++
12		**	*	nd
13		***	*	++
14		***	**	+++
15		***	*	+++

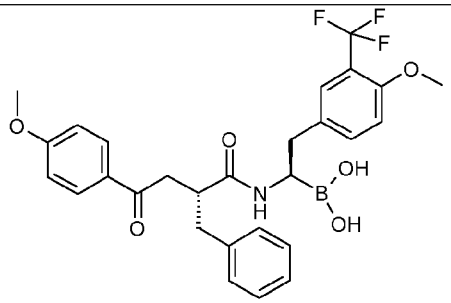
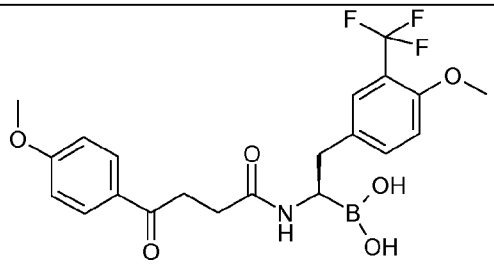
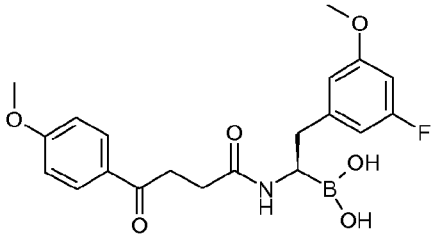
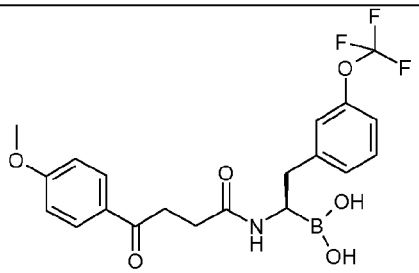
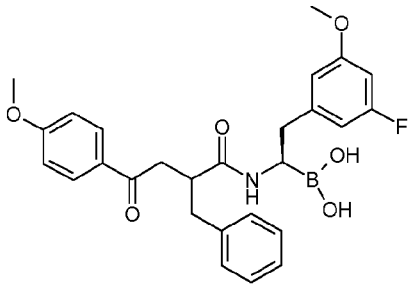
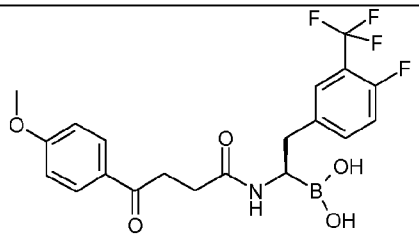
16		**	*	nd
17		***	**	++
18		***	**	+++
19		***	**	++
20		***	**	+
21		***	**	++

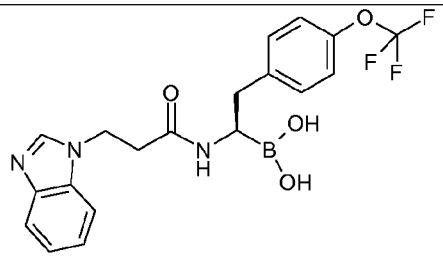
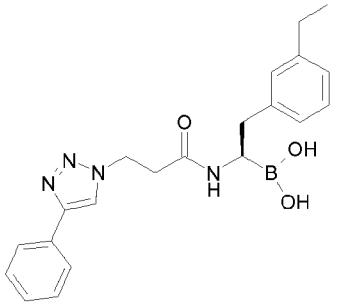
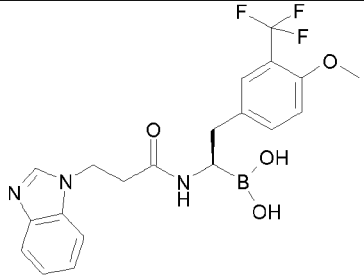
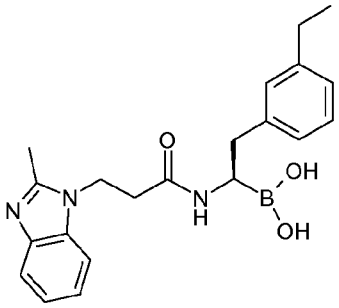
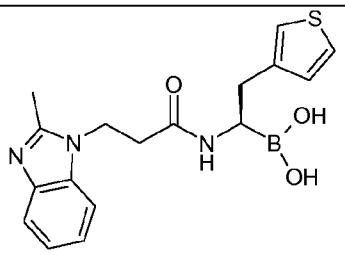
22		***	**	++
23		***	**	++
24		****	***	+++
25		***	*	+++
26		***	*	+++
27		****	**	+++

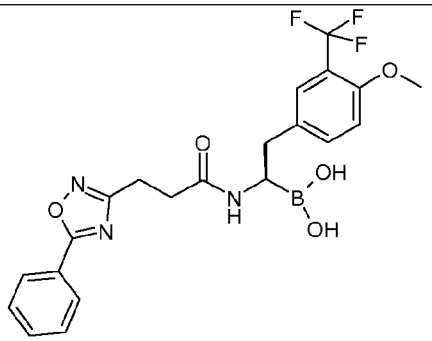
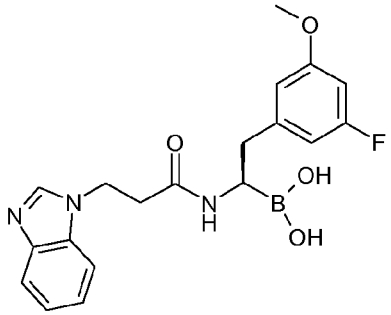
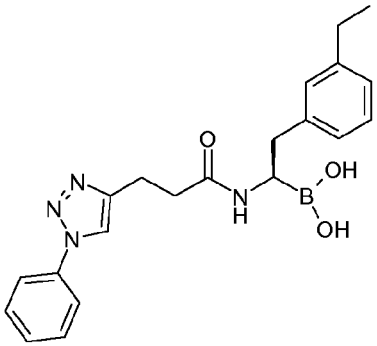
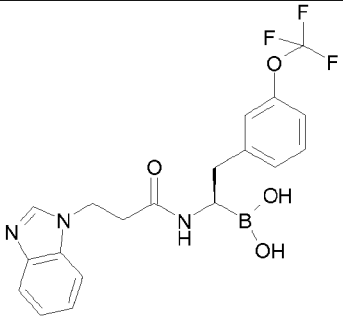
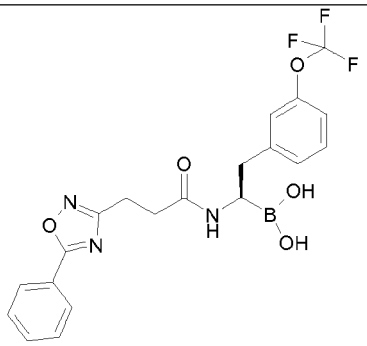
28		***	**	++
29		****	***	++
30		****	***	++
31		****	***	++
32		***	***	+

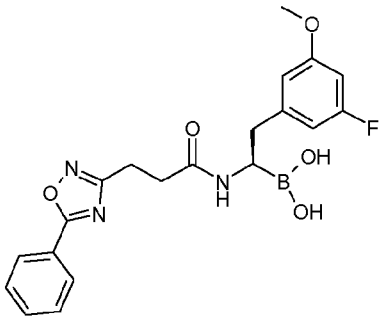
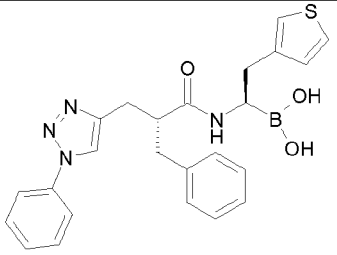
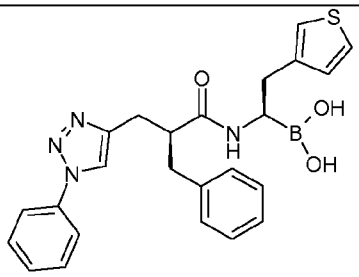
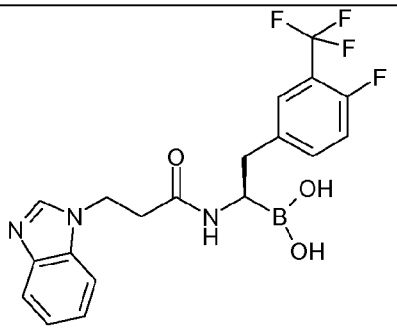
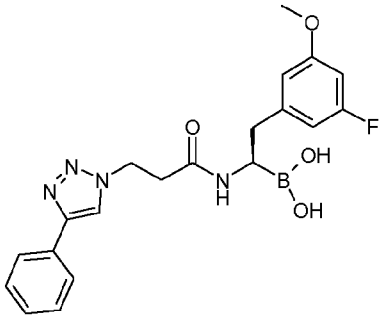
33		***	***	+
34		****	***	+
35		****	***	+
36		****	**	+++
37		***	**	++
38		****	***	++

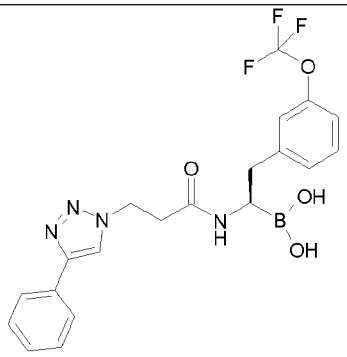
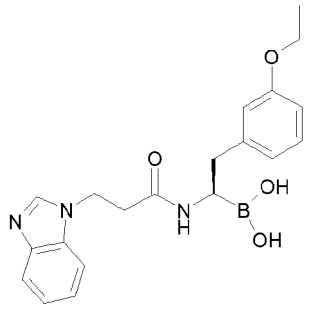
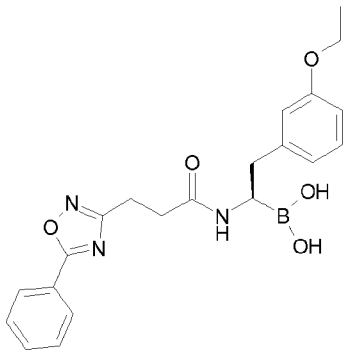
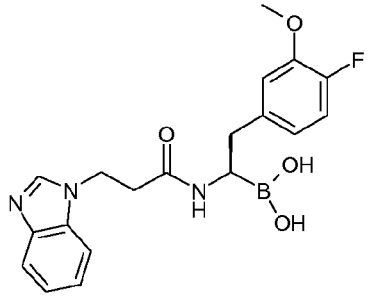
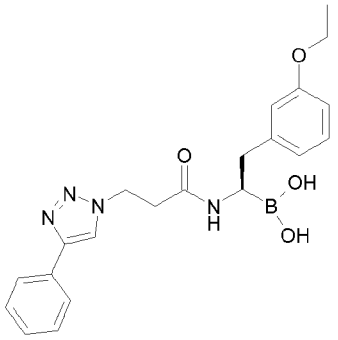
39		***	**	+++
40		****	***	++
41		****	**	+++
42		***	**	++
43		***	**	++
44		****	***	++

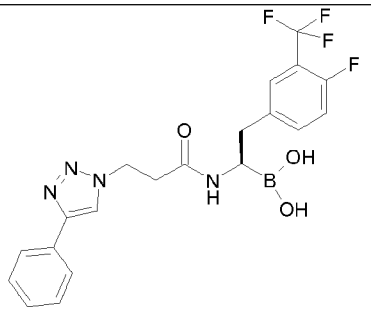
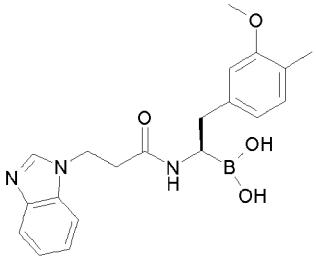
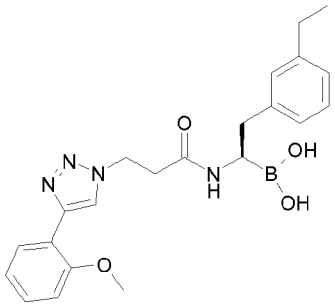
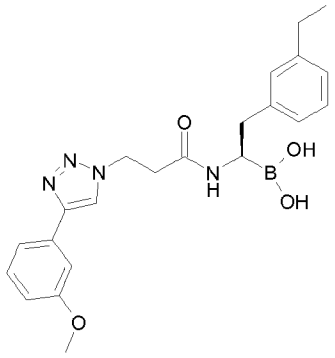
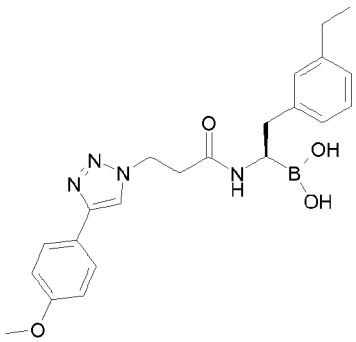
45		****	**	+++
46		***	*	nd
47		***	*	+++
48		***	**	++
49		****	***	++
50		***	*	++

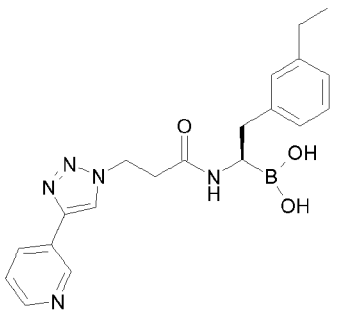
51		****	***	+
52		****	***	+++
53		****	***	+
54		****	***	++
55		****	***	+

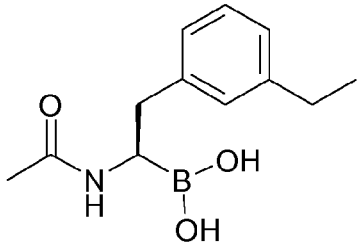
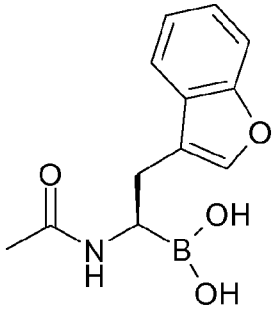
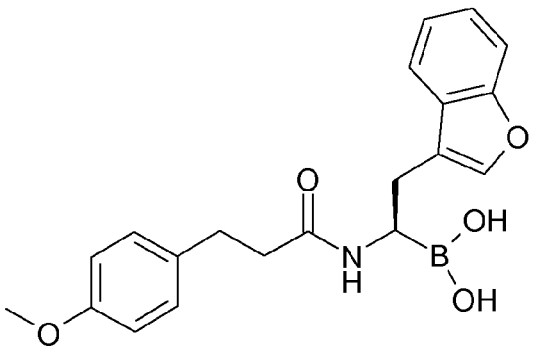
56		***	**	++
57		****	***	++
58		***	*	+++
59		****	***	+
60		***	**	++

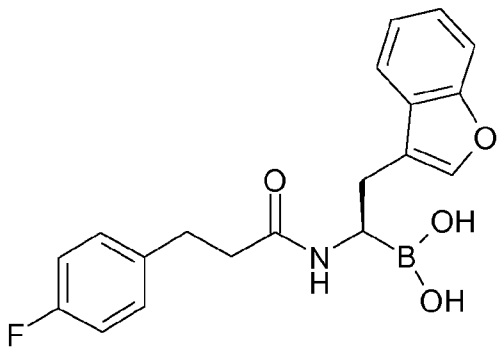
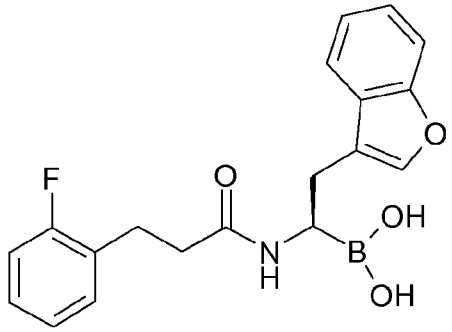
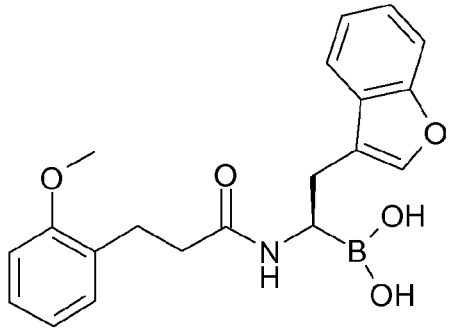
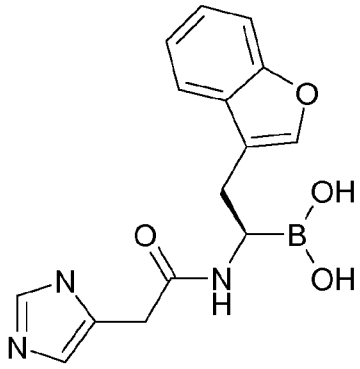
61		****	**	+++
62		****	***	++
63		****	****	++
64		****	***	++
65		****	***	++

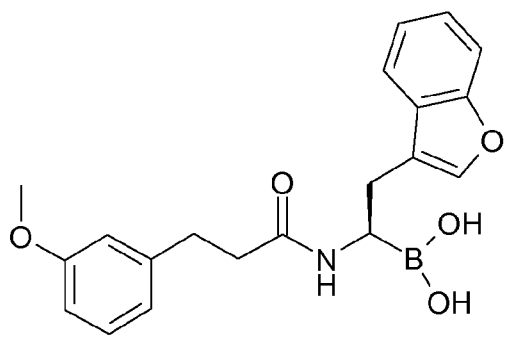
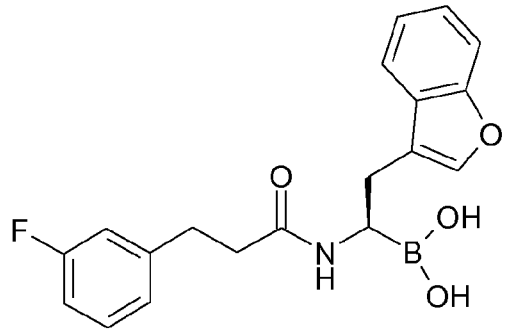
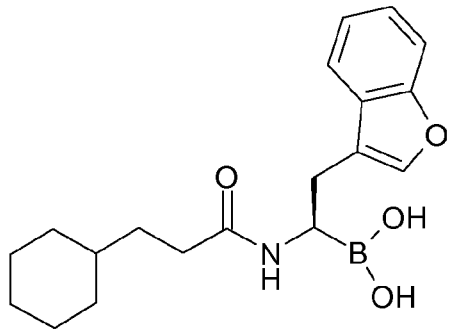
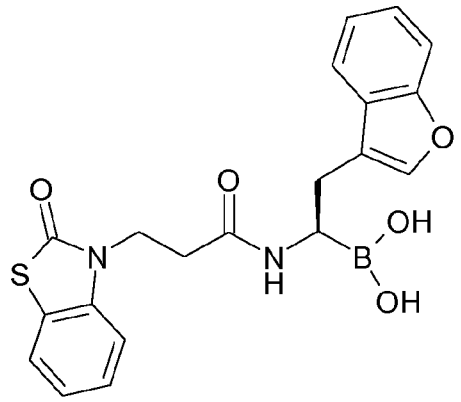
66		****	***	++
67		****	***	++
68		****	**	+++
69		***	**	+
70		****	***	++

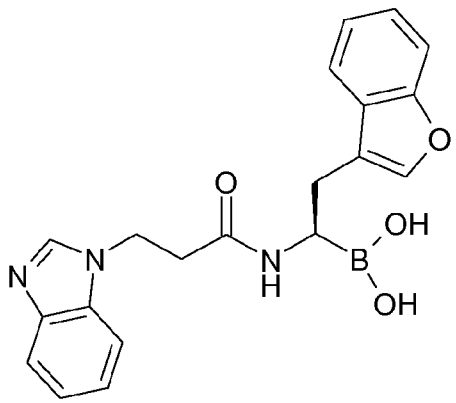
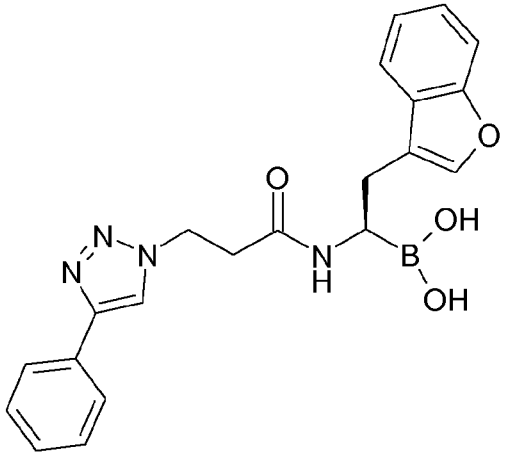
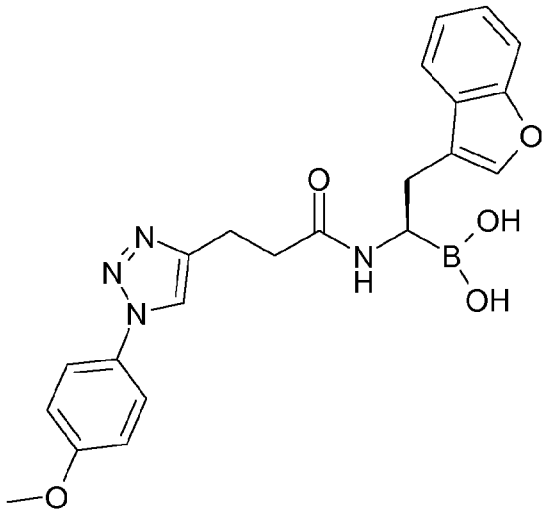
71		****	***	++
72		***	**	++
73		****	***	+++
74		****	***	+++
75		****	***	+++

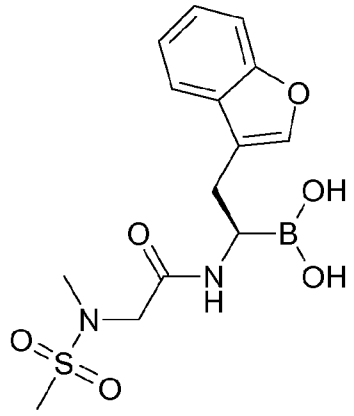
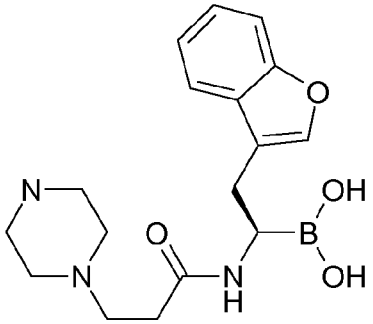
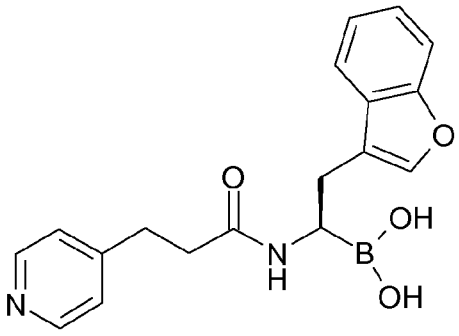
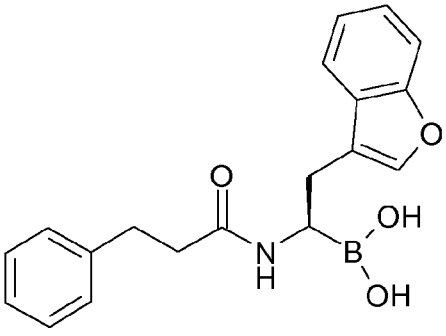
76		****	**	+++

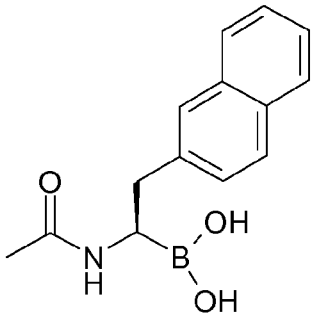
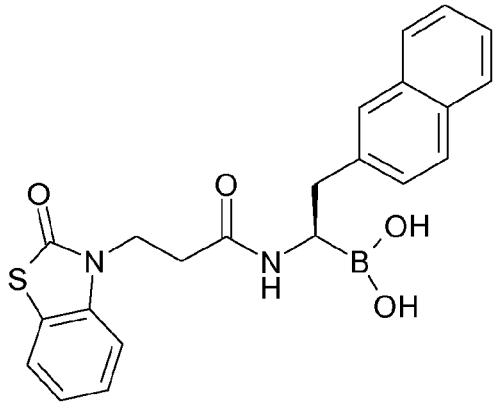
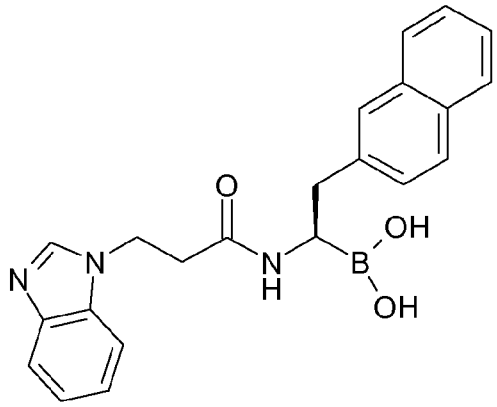
77		**		nd
78		****	**	+++
79		****	***	+++

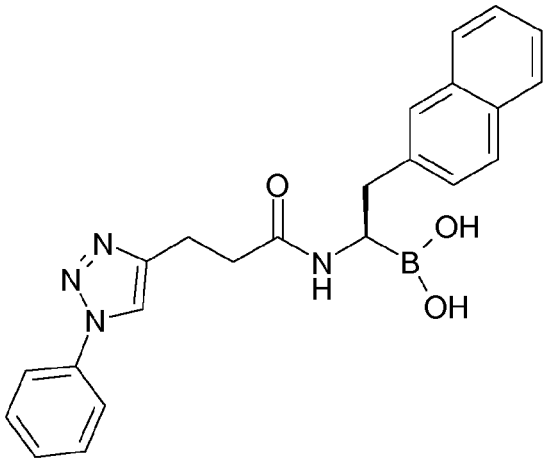
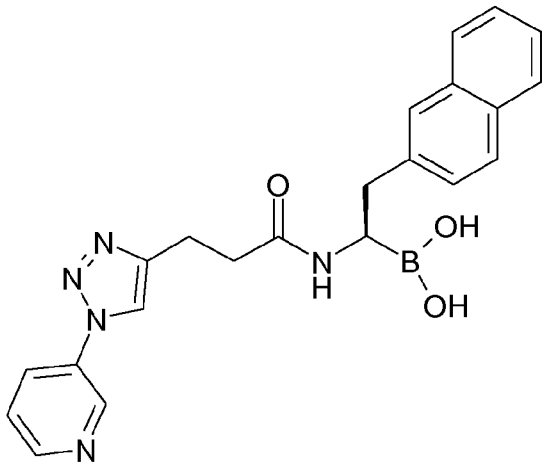
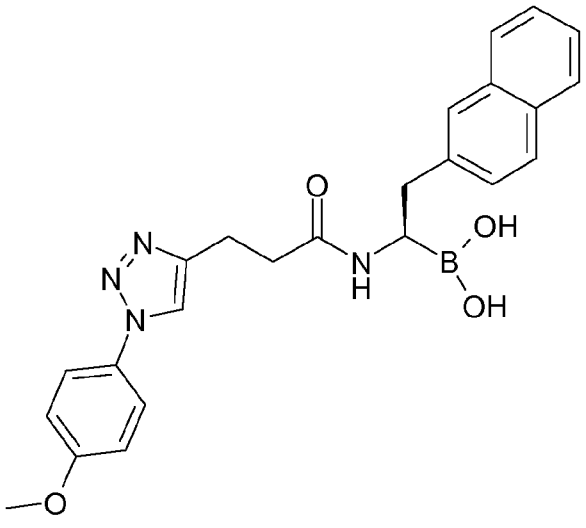
80		****	****	+++
81		****	****	++
82		****	****	++
83		****	***	++

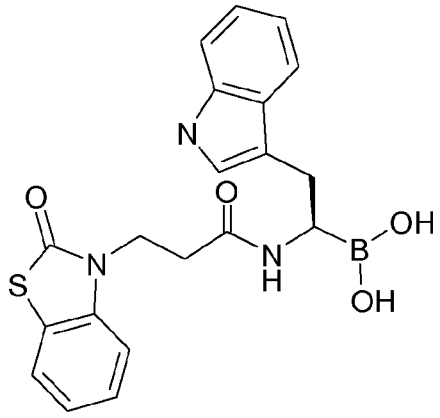
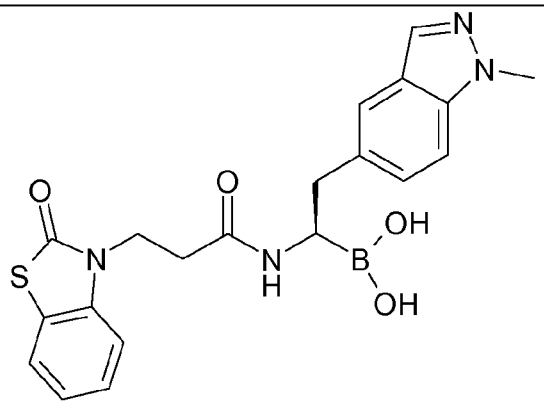
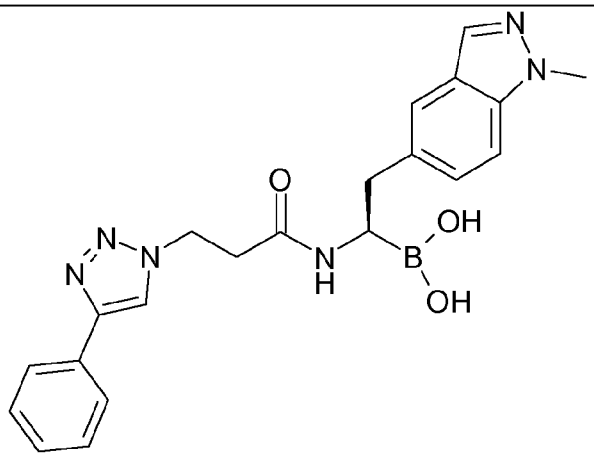
84		****	****	++
85		****	****	+++
86		****	***	+++
87		****	****	++

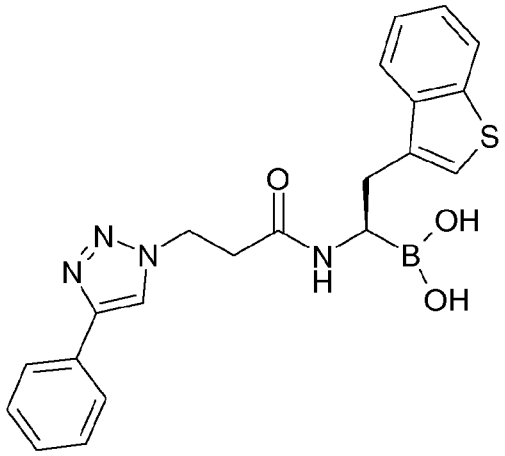
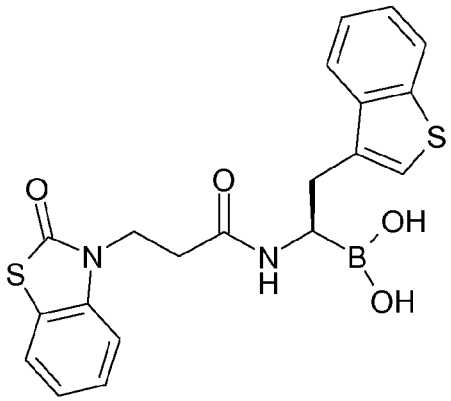
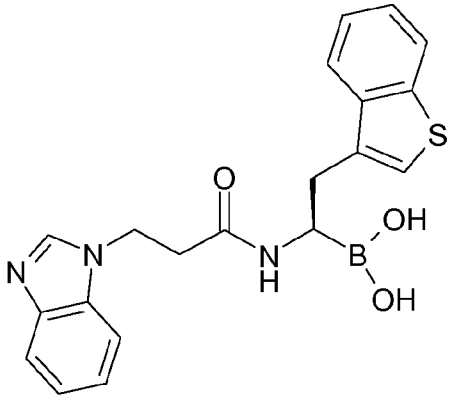
88		****	****	++
89		****	****	++
90		****	****	+++

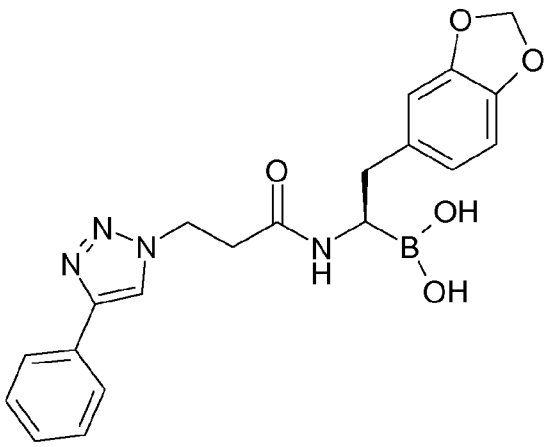
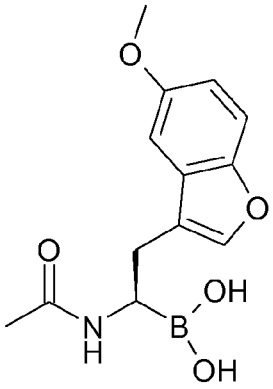
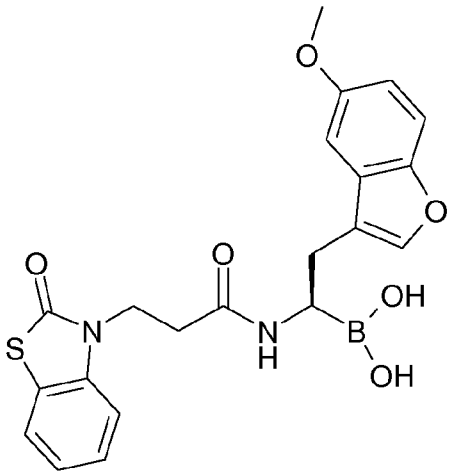
91		****	***	+++
92		****	***	+++
93		****	****	++
94		****	****	+++

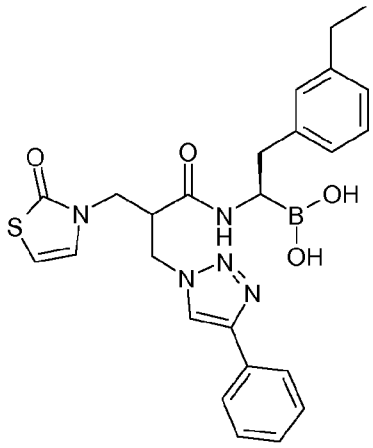
95		***	**	+++
96		****	****	+++
97		****	****	++

98		****	***	++
99		****	**	+++
100		****	***	++

101		****	****	+++
102		****	****	++
103		****	****	++

104		****	****	+
105		****	****	++
106		****	****	++

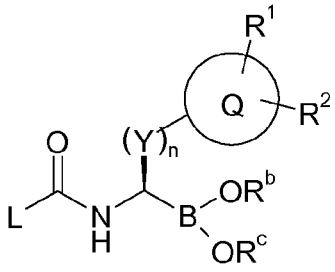
107		****	****	++
108		*	*	+
109		****	***	+

110		****	****	++

*: IC_{50} > 5 μM, **: 0.5 μM < IC_{50} < 5 μM, ***: 0.05 μM < IC_{50} < 0.5 μM, ****: IC_{50} < 0.05 μM, +: Selectivity < 10, ++: 10 < Selectivity < 30, +++: Selectivity > 30, n.d: not determined.

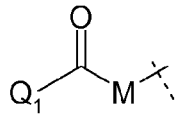
Claims :

1. A compound of Formula (I)

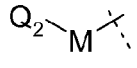


(I)

Wherein

- R^b and R^c are independently selected from one another from H or C_1-C_6-alkyl; whereby R^b and R^c may be linked to form a 5 or 6 membered-ring containing the oxygen atoms to which they are linked.
- Q denotes Ar, Het or cycloalkyl;
- R^1, R^2 independently from each other denotes H, OR^a, Hal, C_1-C_6-alkyl wherein 1 to 5 H atoms may be independently replaced by OH or Hal;
- Y denotes CR^3R^4, preferably CH_2 or $C(CH_3)_2$;
- R^3, R^4 independently of one another denote H or C_1-C_6-alkyl;
- L denotes L_1 or L_2 or alkyl;
- n is an integer selected from 0 to 3;
- L_1 is  wherein

  Q_1 is Ar or Het, preferably, phenyl, naphthyl or pyridine, optionally substituted with 1 to 5 groups independently selected from ORa, Hal, phenyl, and C1-C6-alkyl wherein 1 to 5 H atoms may be independently replaced by OH or Hal;

- L_2 is  wherein

  Q_2 is a fused bicyclic system containing 1 nitrogen atom and 1 to 3 additional groups independently selected from O, S, N, or CO, and wherein at least one of the ring is aromatic whereby the fused bicyclic system is optionally substituted with 1 to 5 groups independently selected from OR^a, Hal, phenyl, and C_1-C_6-alkyl wherein 1 to 5 H atoms may be independently replaced by OH or Hal;

  or

Q_2 is unsaturated or aromatic 5 membered-ring system containing 1 to 3 heteroatoms seleted from N, O, S and CO, and optionally substituted with a phenyl ring or pyridine ring whereby phenyl ring and pyridine ring are optionally substituted with 1 to 4 groups independently selected from OR^a, Hal, phenyl, and C_1-C_6-alkyl wherein 1 to 5 H atoms may be independently replaced by OH or Hal;

- M is a linear or branched alkylen having 1 to 5 carbon atoms wherein 1 or 2 H atoms may be replaced by OR^a or a phenyl ring optionally substituted with 1 to 5 groups independently selected from Hal, OR^a, and C_1-C_6-alkyl optionally substituted with 1 to 5 groups independently selected from OH, and Hal; or
  M denotes a cycloalkylen having 3 to 7 carbon atoms; or
  M denotes a thiazolidinyl group.

- R^a is H or C_1-C_6-alkyl wherein 1 to 5 H atom may be independently replaced by OH or Hal;

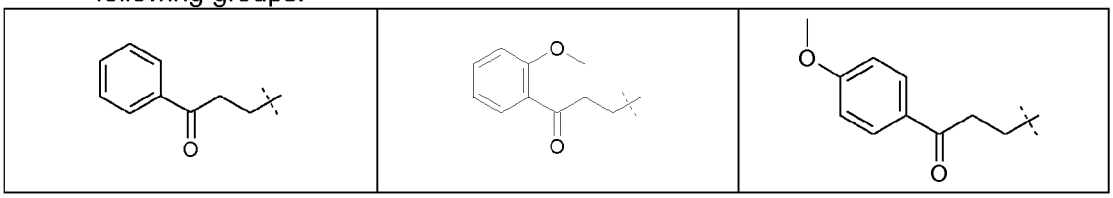
- Ar denotes a 6 membered-aromatic carbocyclic ring optionally fused with another carbocyclic saturated, unsaturated or aromatic ring having 5 to 8 carbon atoms;

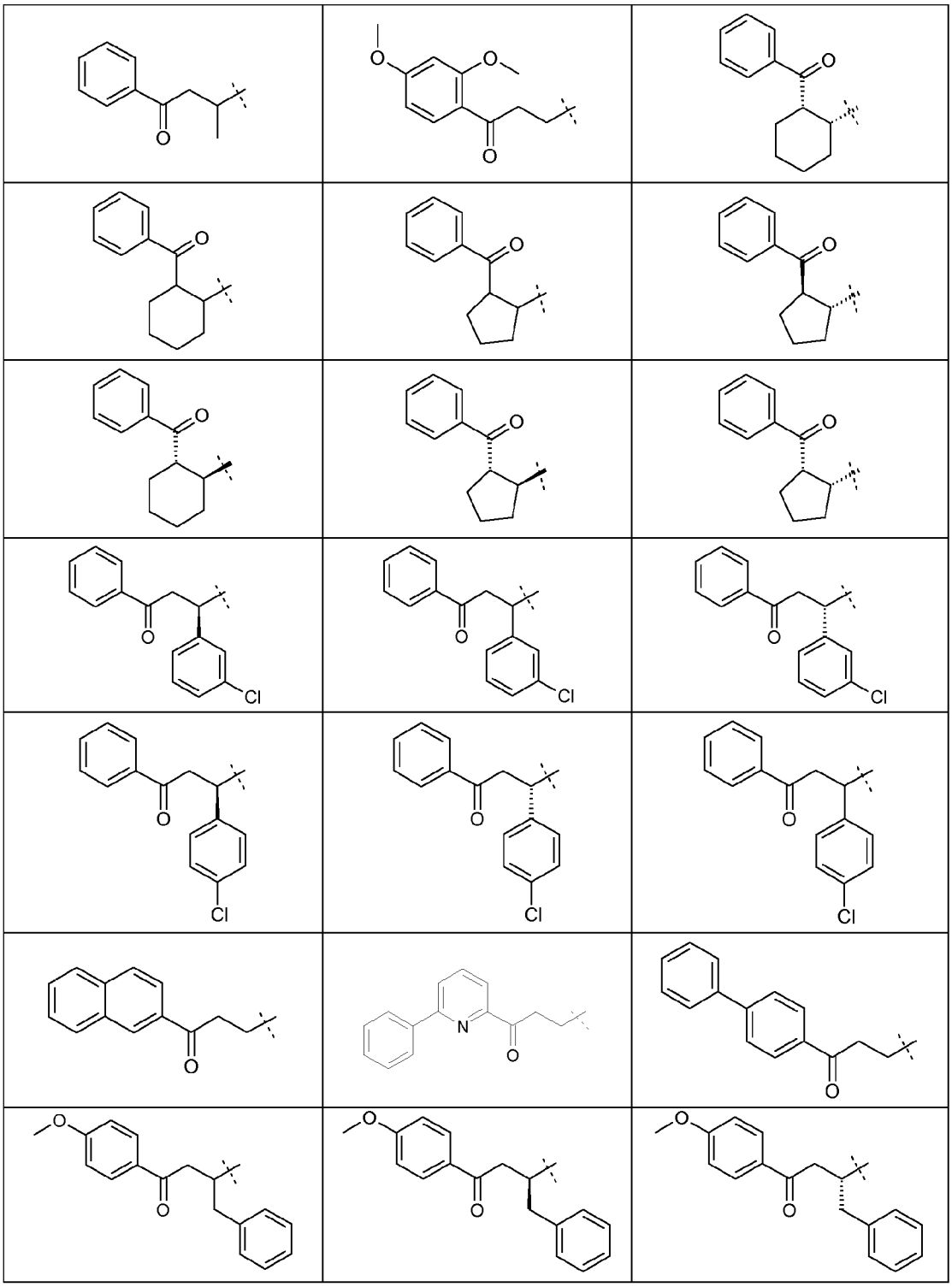
- Het denotes a 5- or 6-membered saturated, unsaturated or aromatic heterocyclic ring having 1 to 3 heteroatoms independently selected from N, N+O-, O, S, SO, and SO_2, and optionally fused with another saturated, unsaturated or aromatic ring having 5 to 8 atoms and optionally containing 1 to 3 heteroatoms selected from N, O, and S;

- Hal denotes Cl, Br, I of F; preferably Cl or F,

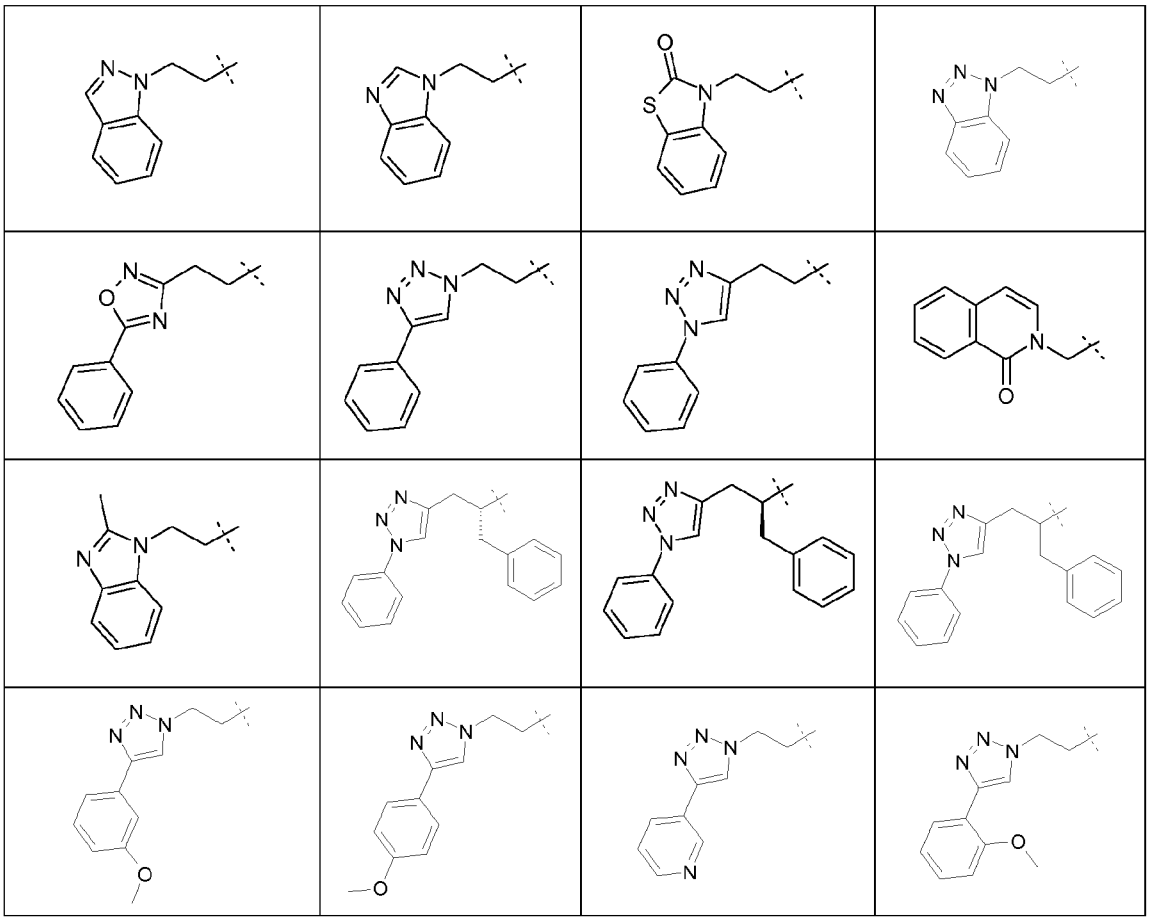
As well as enantiomers, diastereoisomers, and pharmaceutically acceptable salts thereof;

2. The compound of Formula (I) according to claim 1 wherein L is selected from the following groups:

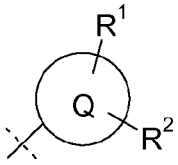




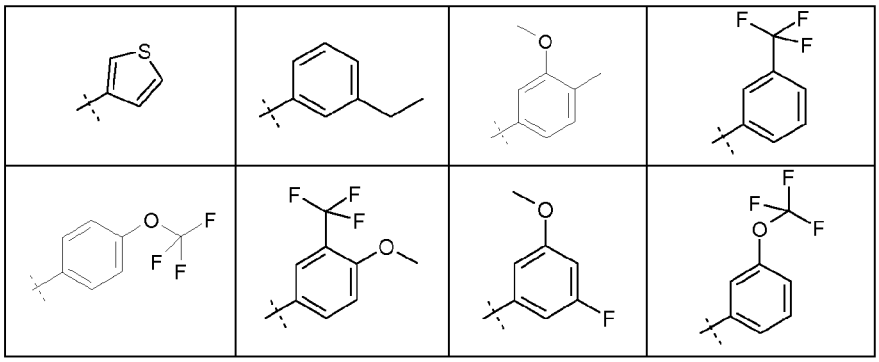
Or wherein L is selected from the following groups:

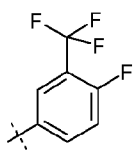
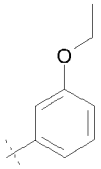
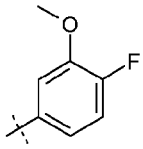


3. The compound of Formula (I) according to claims 1 or 2 wherein the group

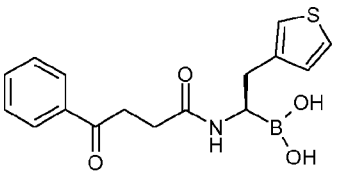
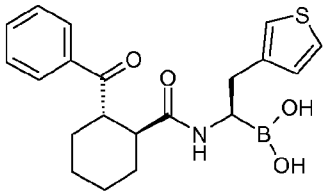
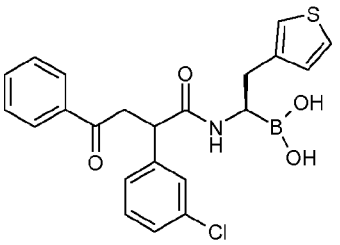
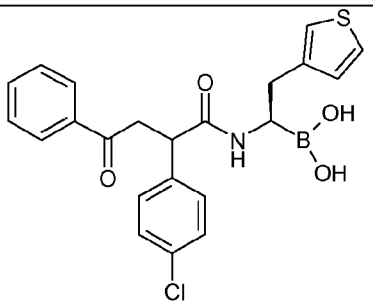
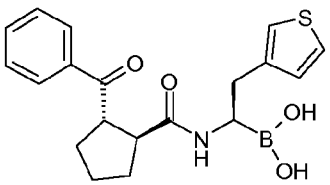
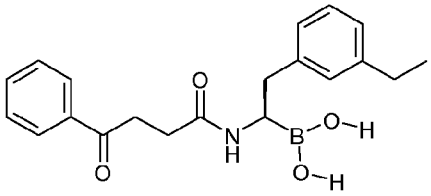
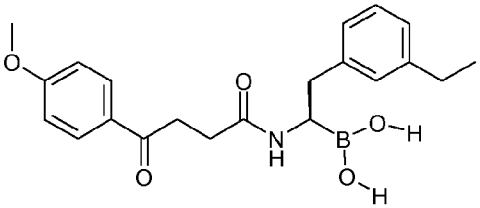
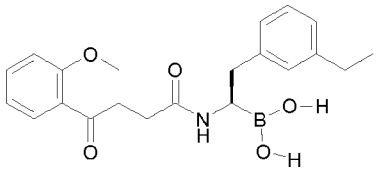
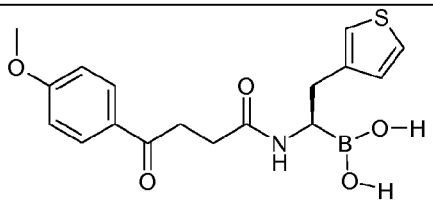
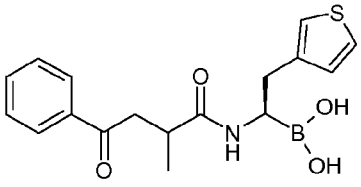


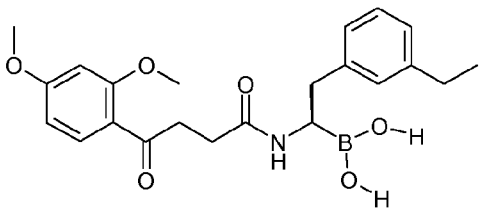
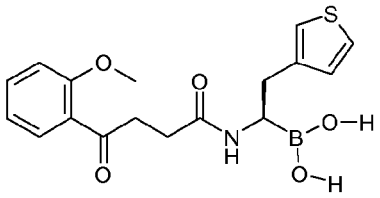
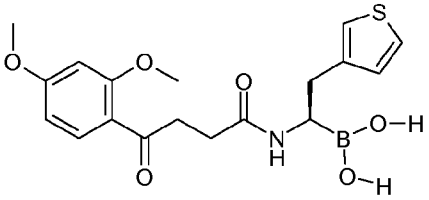
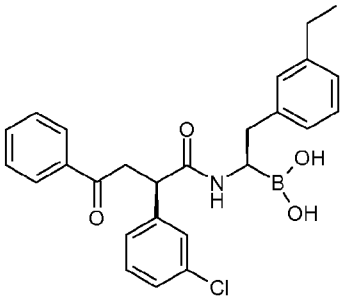
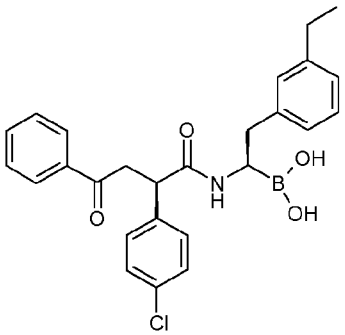
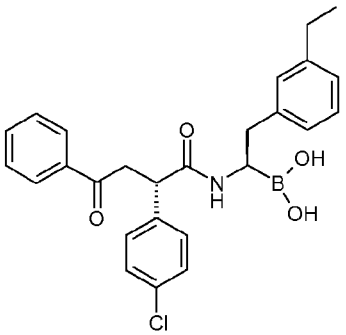
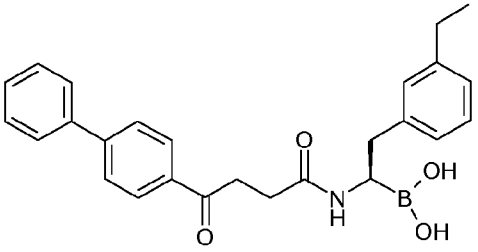
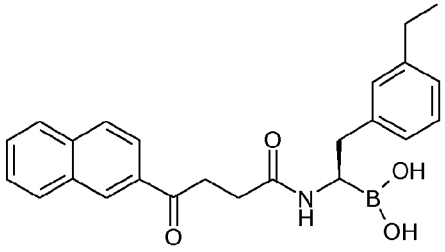
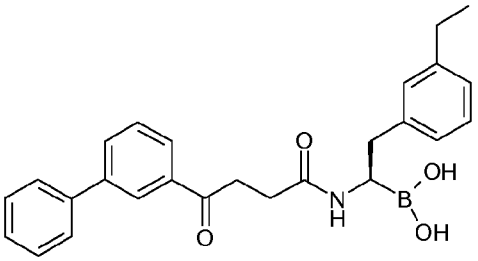
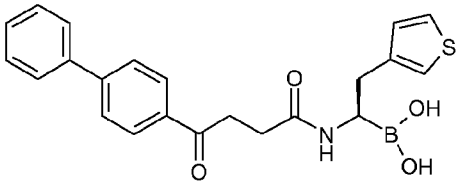
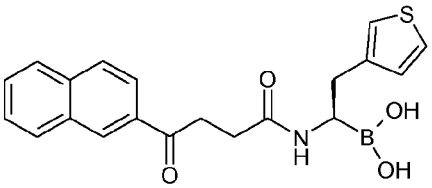
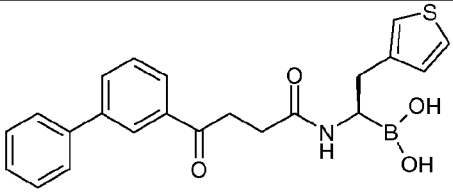
is selected from the following groups:

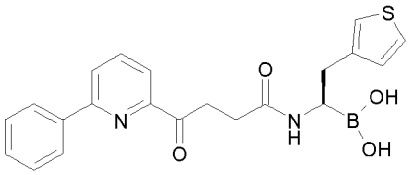
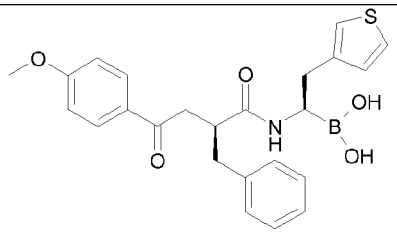
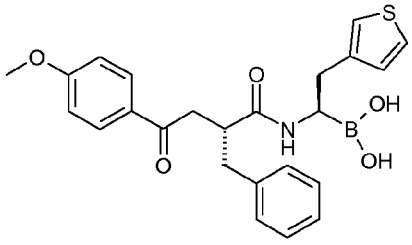
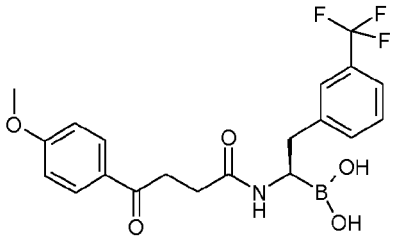
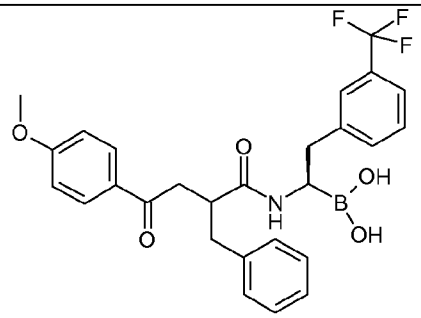
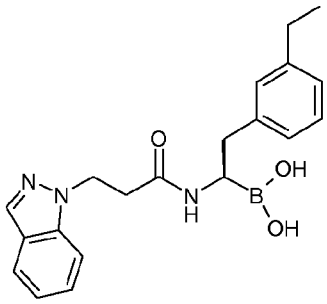
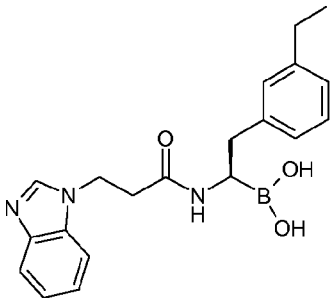
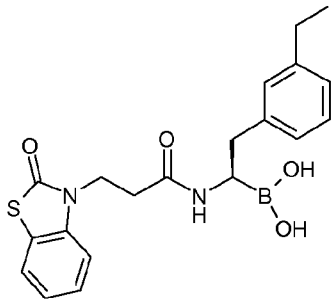
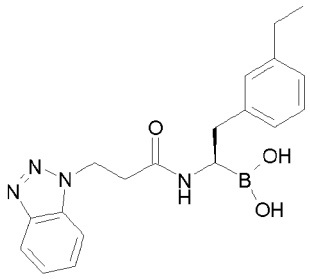
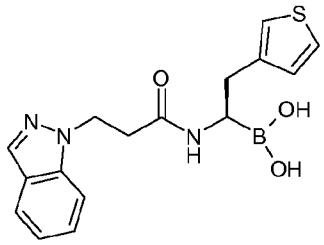
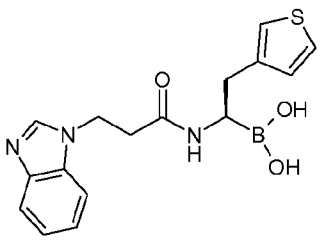
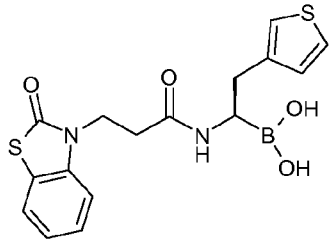


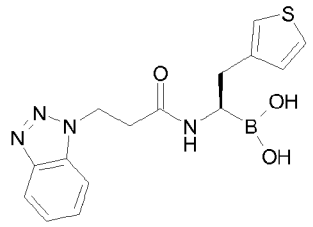
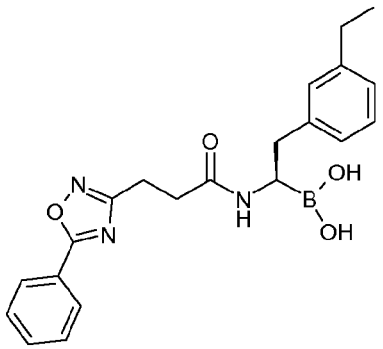
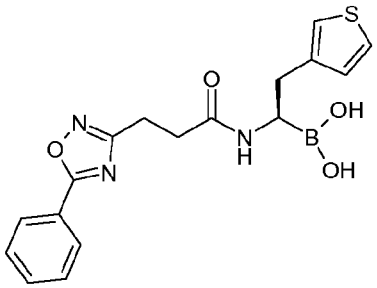
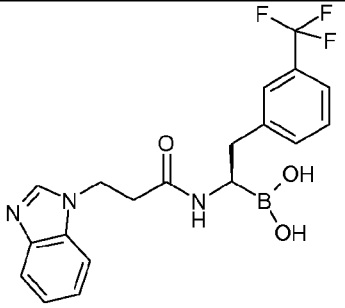
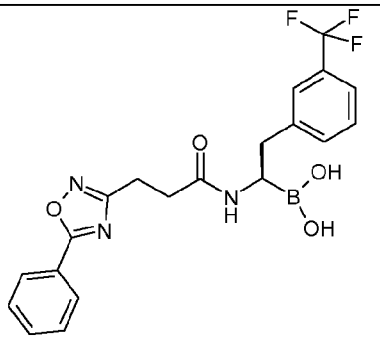
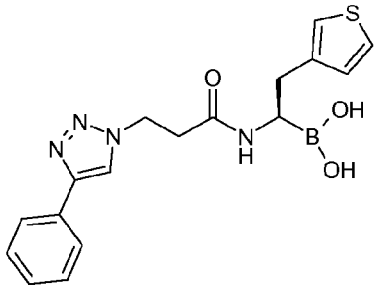
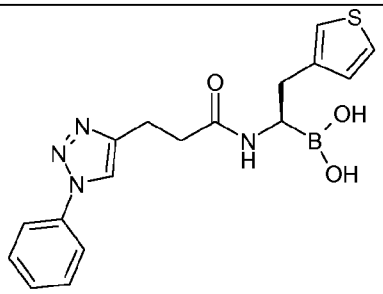
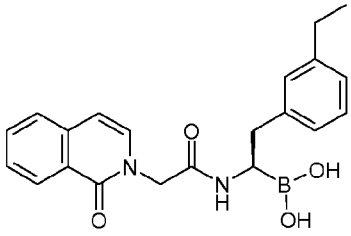
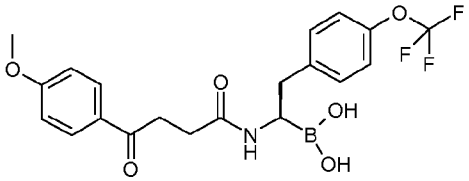
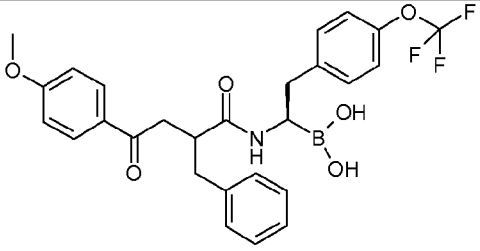
			

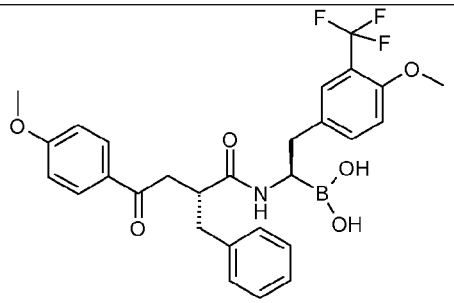
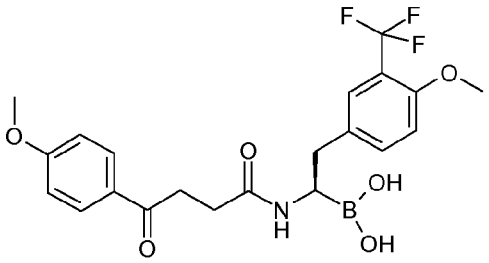
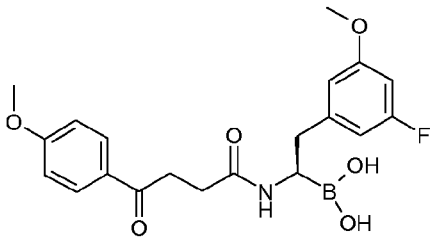
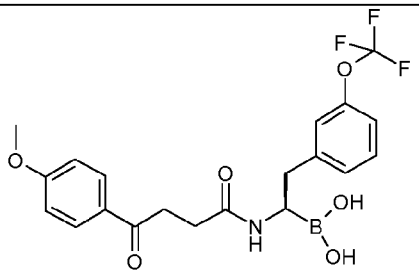
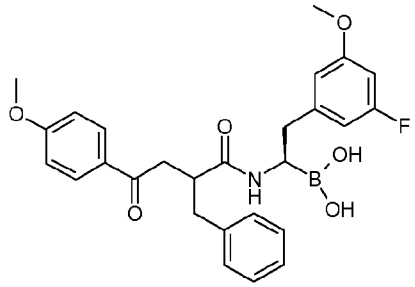
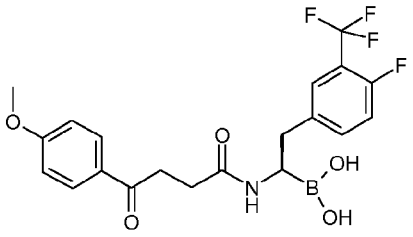
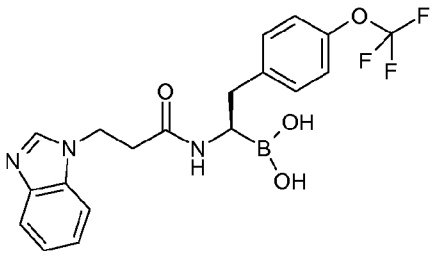
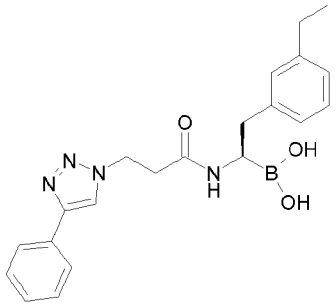
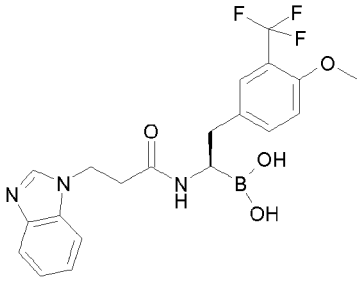
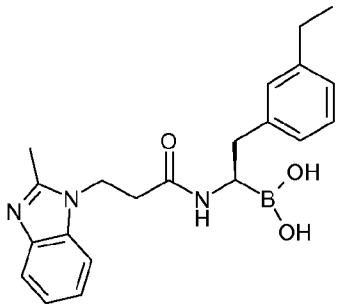
4. The compound of Formula (I) according to claim 1 wherein the compound is selected from the following group.

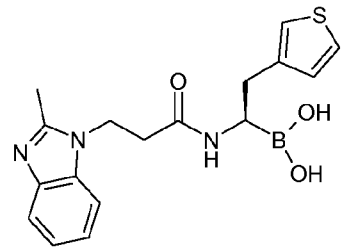
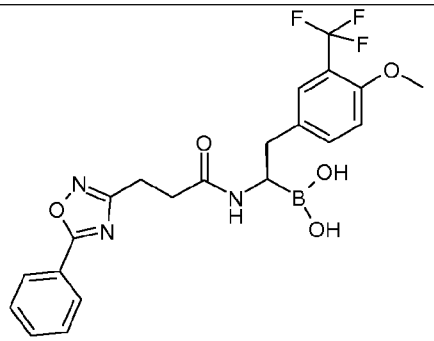
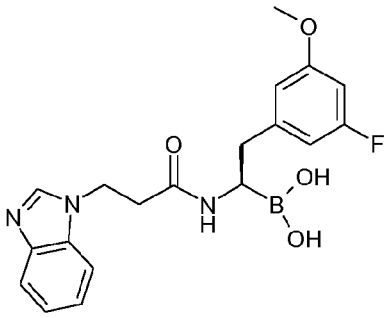
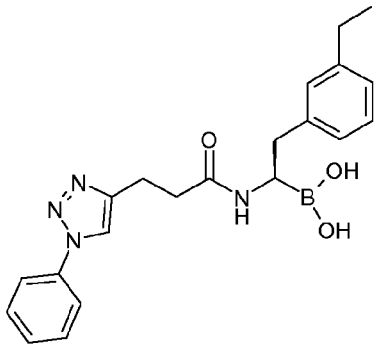
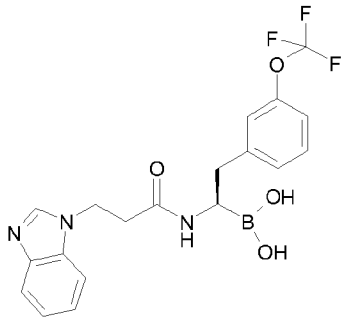
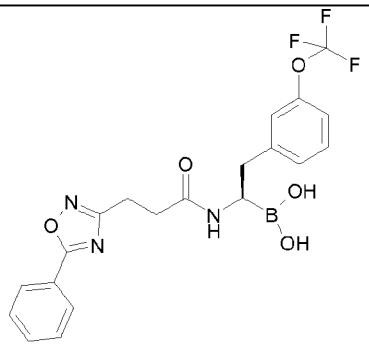
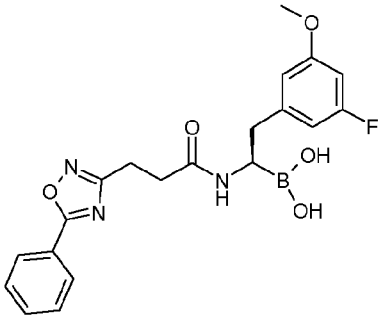
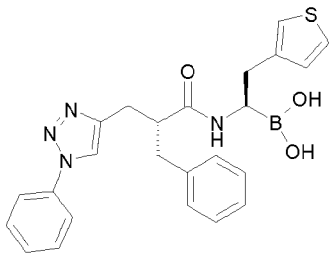
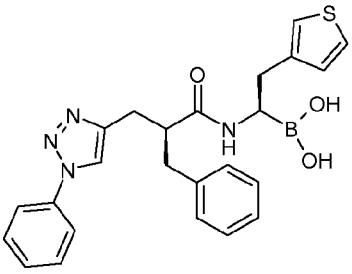
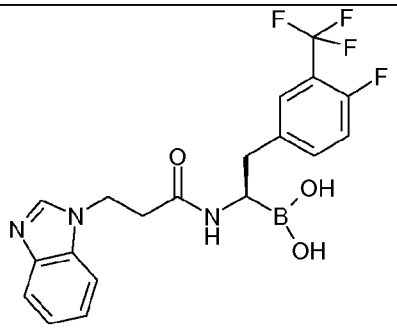
Ex	Formula	Ex	Formula
1		2	
3		4	
5		6	
7		8	
9		10	

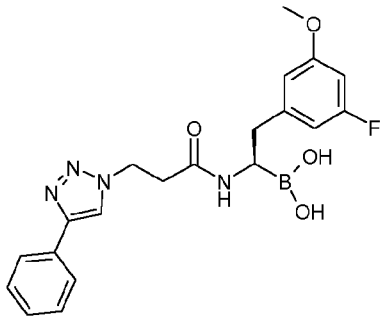
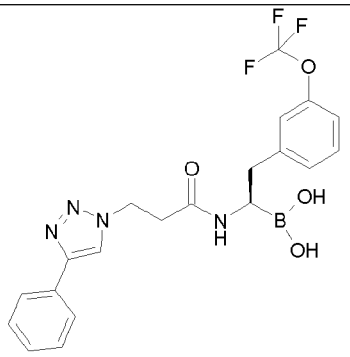
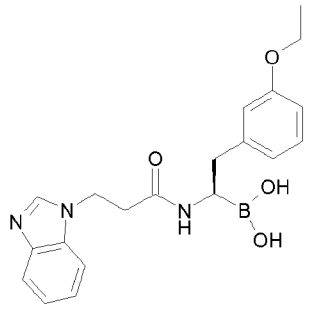
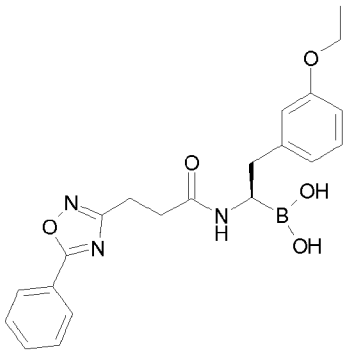
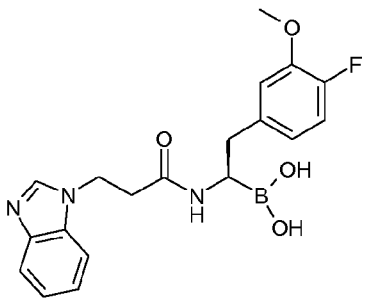
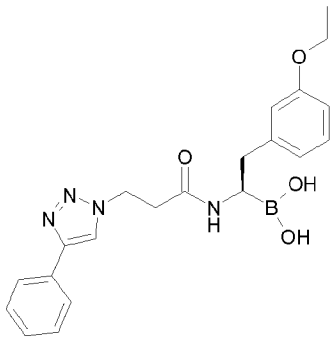
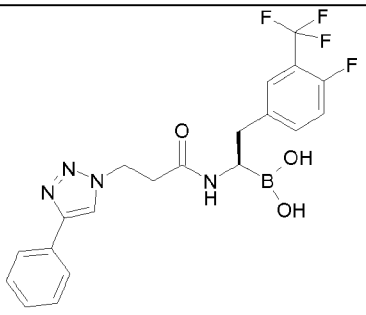
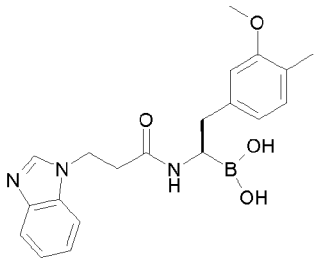
11		12	
13		14	
15		16	
17		18	
19		20	
21		22	

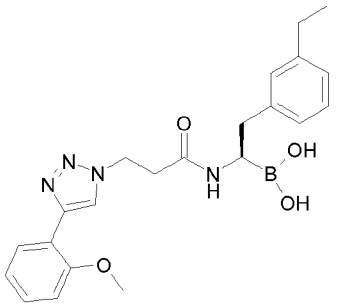
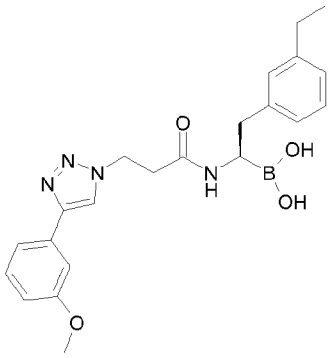
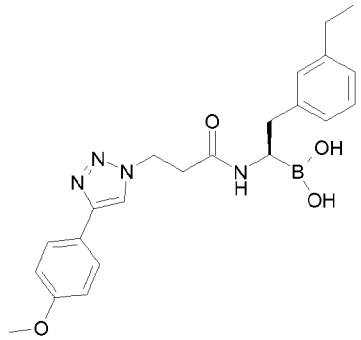
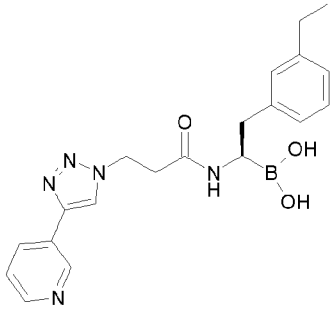
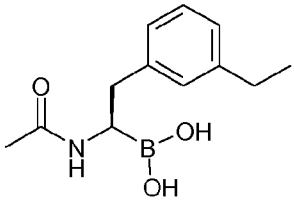
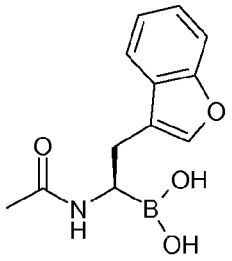
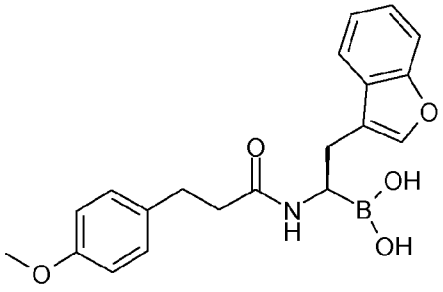
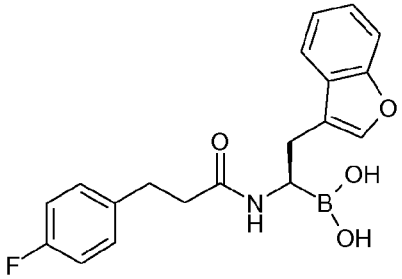
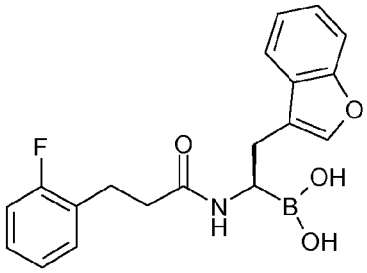
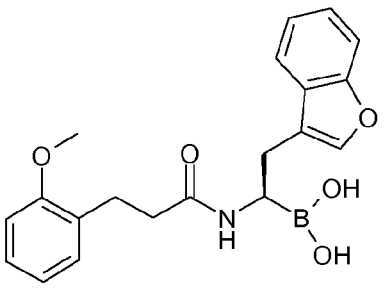
23		24	
25		26	
27		28	
29		30	
31		32	
33		34	

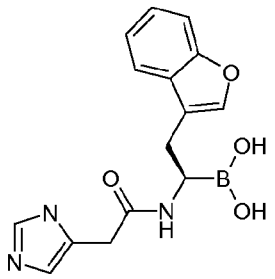
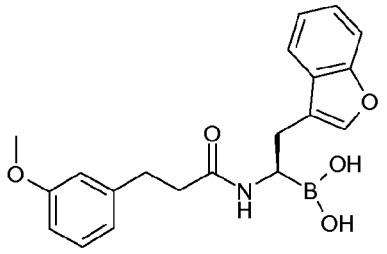
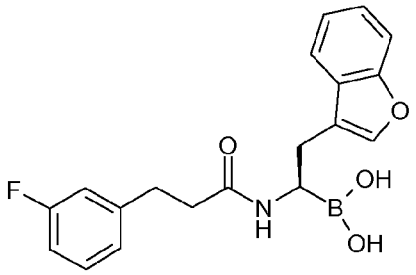
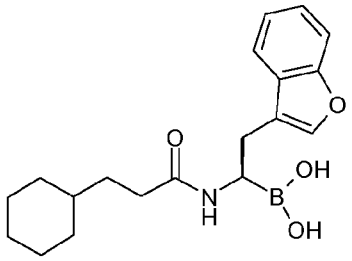
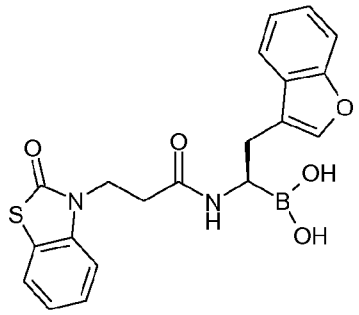
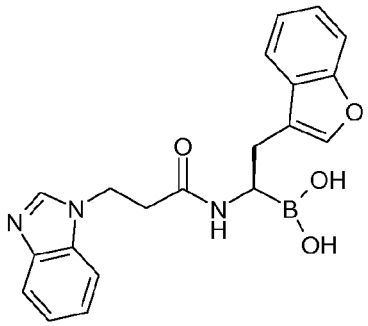
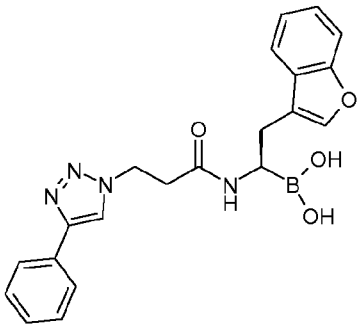
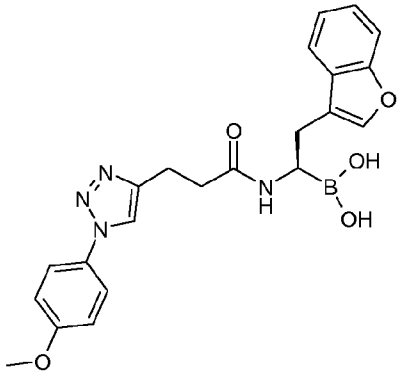
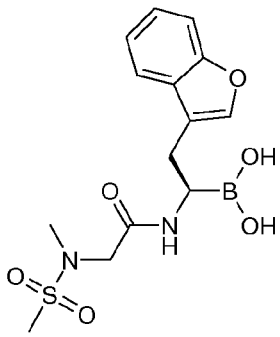
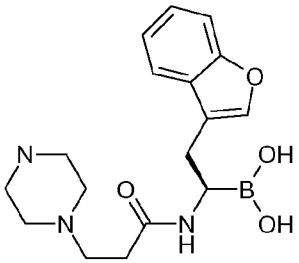
35		36	
37		38	
39		40	
41		42	
43		44	

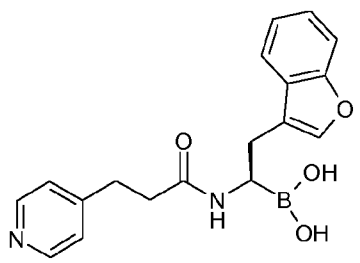
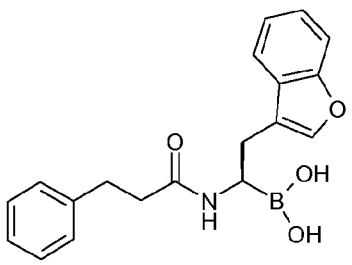
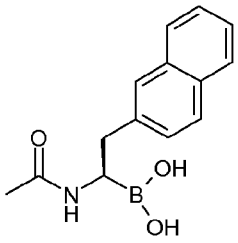
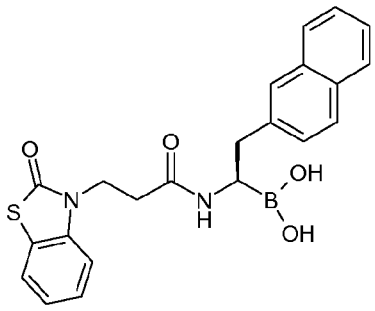
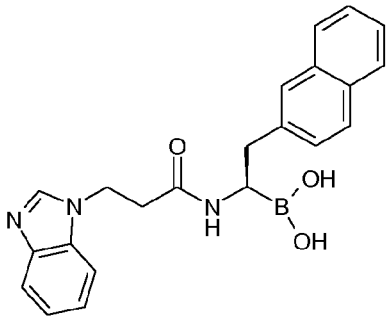
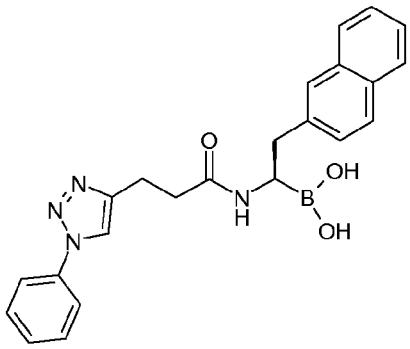
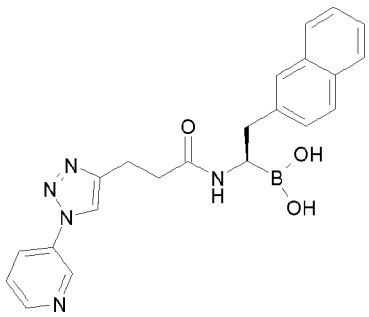
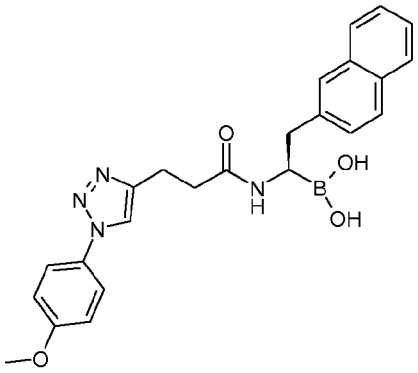
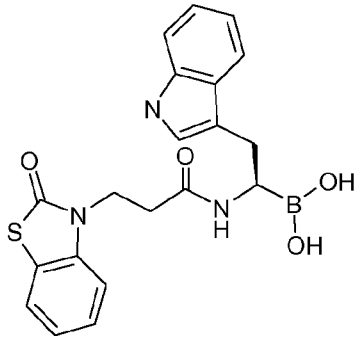
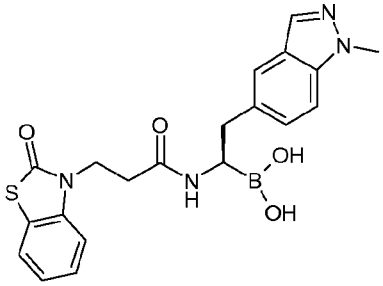
45		46	
47		48	
49		50	
51		52	
53		54	

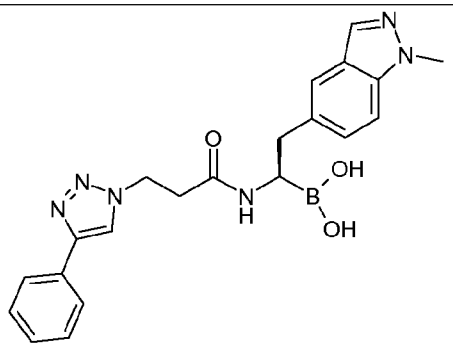
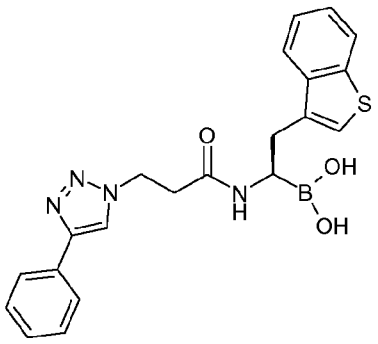
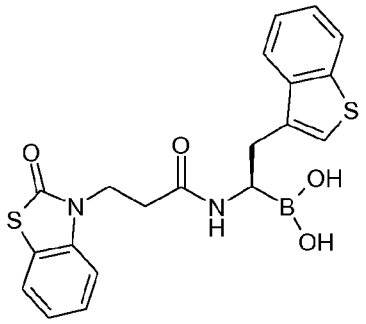
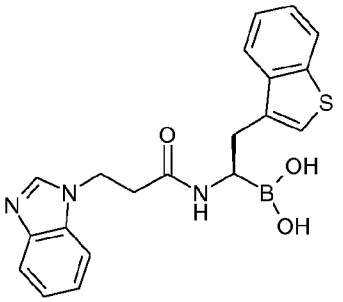
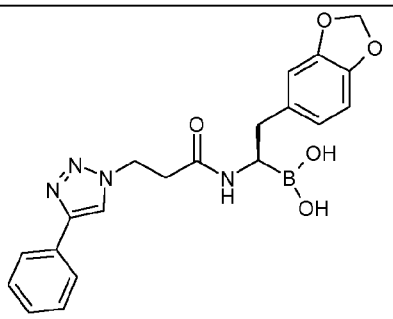
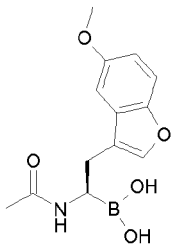
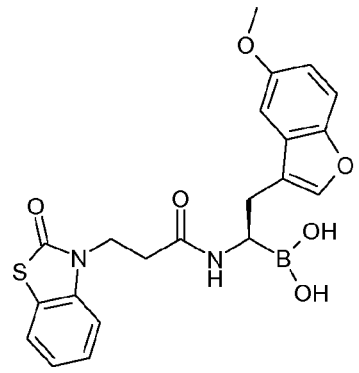
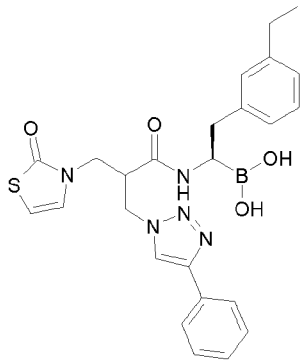
55		56	
57		58	
59		60	
61		62	
63		64	

65		66	
67		68	
69		70	
71		72	

73		74	
75		76	
77		78	
79		80	
81		82	

83		84	
85		86	
87		88	
89		90	
91		92	

93		94	
95		96	
97		98	
99		100	
101		102	

103		104	
105		106	
107		108	
109		110	

5. A pharmaceutical composition comprising at least one compound of Formula (I) according to one or more of claims 1 to 4 and/or pharmaceutically usable salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

6. A pharmaceutical composition comprising at least one compound of Formula (I) according to one or more of claims 1 to 4 and/or pharmaceutically usable salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further active ingredient.

7. Set (kit) consisting of separate packs of
   (a) an effective amount of a compound of Formula (I) according to one or more of claims 1 to 4 and/or pharmaceutically usable salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and
   (b) an effective amount of a further medicament active ingredient.

8. Compounds according to one or more of claims 1 to 4 and pharmaceutically usable salts, tautomers, solvates and stereoisomers thereof, including mixtures thereof in all ratios, for use in the preparation of a medicament for the treatment and/or prophylaxis of an autoimmune disorder or condition associated with an overactive immune response.

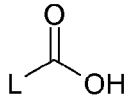
9. Compounds according to one or more of claims 1 to 4, and pharmaceutically usable salts, tautomers, solvates and stereoisomers thereof, including mixtures thereof in all ratios, for use in the preparation of a medicament for the treatment and/or prophylaxis of an immunoregulatory abnomality.

10. Compounds according to claims 8 or 9, wherein the immunoregulatory abnormality is an autoimmune or chronic inflammatory disease selected from the group consisting of: systemic lupus erythematosis, chronic rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), atherosclerosis, scleroderma, autoimmune hepatitis, Sjogren Syndrome, lupus nephritis, glomerulonephritis, Rheumatoid Arthritis, Psoriasis, Myasthenia Gravis, Imunoglobuline A nephropathy, Vasculitis, Transplant rejection, and asthma.

11. Compounds according to one or more of claims 1 to 4 and pharmaceutically usable salts, tautomers, solvates and stereoisomers thereof, including mixtures thereof in all ratios, for use in the preparation of a medicament for the treatment and/or prophylaxis of a LMP7 associated disorder.

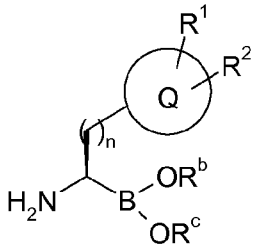
12. Compounds according to claim 11 wherein the LMP7 associated disorder is selected from Amyotrophic Lateral Sclerosis, Sjogren Syndrome, systemic lupus erythematoses, lupus nephritis, glomerulonephritis, Rheumatoid Arthritis, Inflammatory bowel disease, ulcerative colitis, crohn's diseases, multiple sclerosis, Amyotrophic lateral sclerosis, osteoarthritis, Atherosclerosis, Psoriasis, Myasthenia Gravis, Dermal fibrosis, renal fibrosis, cardiac fibrosis, Liver fibrosis, Lung fibrosis, Imunoglobuline A nephropathy, Vasculitis, Transplant rejection, Hematological malignancies and asthma.

13. A process for the synthesis of compound of Formula (I) as defined in claim 1 comprising the step of reacting a compound of Formula (II)



(II)

Wherein L is as defined in Claim 1,
With a compound of Formula (III)



(III)

Wherein R1, R2, Q, Ra, Rb and n are as defined in claim 1.

14. A process according to claim 13 wherein the reaction between the compound of Formula (II) and the compound of Formula (III) is performed in the presence of a coupling agent selected from HATU, TBTU, polymer-supported 1-alkyl-2-chloropyridinium salt (polymer-supported Mukaiyama's reagent), 1-methyl-2-chloropyridinium iodide (Mukaiyama's reagent), a carbodiimide.

15. A compound according to claims 1 to 4 for use as a medicament.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/076595

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/69 C07F5/02 A61P37/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07F A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JIN S ET AL: "Identification of the first fluorescent alpha-amidoboronic acids that change fluorescent properties upon sugar binding", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 19, no. 6, 15 March 2009 (2009-03-15) , pages 1596-1599, XP026005834, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2009.02.011 figure 1; compounds D-1, L-1 ----- -/--	1

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 2013	05/02/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Elliott, Adrian

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	MATTESON D S ET AL: "Cesium alkyltrifluoroborates from asymmetric boronic esters", SYNLETT, no. 20, 2006, pages 3501-3503, XP009140246, ISSN: 0936-5214, DOI: 10.1055/s-2006-956476 compound 1l	1
X	MATTESON D S ET AL: "Hydrolysis of Substituted 1,3,2-Dioxaborolanes and an Asymmetric Synthesis of a Differentially Protected syn , syn -3-Methyl-2,4-hexanediol", JOURNAL OF ORGANIC CHEMISTRY, vol. 61, no. 17, 23 August 1996 (1996-08-23), pages 6047-6051, XP055050726, ISSN: 0022-3263, DOI: 10.1021/jo960684m compound 21b	1
X	MATTESON D S ET AL: "Synthesis of 1-amino-2-phenylethane-1-boronic acid derivatives", ORGANOMETALLICS, vol. 3, no. 4, April 1984 (1984-04), pages 614-618, XP055050728, ISSN: 0276-7333, DOI: 10.1021/om00082a019 compounds 4a, 4b, 4c, 5a, 5b, 5c	1
A	ELLIOTT P J ET AL: "Proteasome inhibition: a new anti-inflammatory strategy", JOURNAL OF MOLECULAR MEDICINE, vol. 81, no. 4, April 2003 (2003-04), pages 235-245, XP055028458, DOI: 10.1007/s00109-003-0422-2 cited in the application * the whole document, in particular, compound PS-341 in Figure 4 on page 238 *	1-15
A	WO 2011/123502 A1 (MILLENNIUM PHARMACEUTICALS INCORPORATED) 6 October 2011 (2011-10-06) the whole document	1-15
A	WO 2010/036357 A1 (MILLENNIUM PHARMACEUTICALS INCORPORATED) 1 April 2010 (2010-04-01) the whole document	1-15

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 2009/064413 A1 (PROTEZ PHARMACEUTICALS INCORPORATED) 22 May 2009 (2009-05-22) * compounds of claim 7 *	1-15

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Information on patent family members

International application No
PCT/EP2012/076595

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Information on patent family members

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61/579076 2011.12.22 US

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2014.06.20

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PCT/EP2012/076595 2012.12.21

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WO2013/092979 EN 2013.06.27

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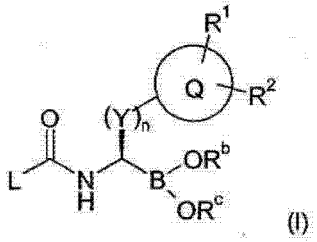
(54)发明名称

α-氨基硼酸衍生物,选择性免疫蛋白酶体抑制剂

(57)摘要

本发明提供作为LMP7抑制剂用于治疗自身免疫性疾病和炎性疾病的式(I)化合物。在式(I)中,R^b和R^c彼此独立地选自H和C_1-C_6烷基;其中R^b和R^c可连接形成含氧原子的5或6元环,所述氧原子与R^b和R^c连接;Q表示Ar、Het或环烷基;R^1和R^2彼此独立地选自H、OR^a、Hal、C_1-C_6烷基,其中1-5个H原子可以独立地被OH或Hal替代;Y表示CR^3R^4,优选为CH_2或$C(CH_3)_2$;R^3,R^4彼此独立地表示H或C_1-C_6烷基;L表示L_1或L_2或烷基;n为选自0-3的整数;L_1是Q_1-CO-M-,其中Q_1是Ar或Het,优选为苯基、萘基或吡啶,任选地被1-5个独立地选自OR^a、Hal、苯基、及其中1-5个H原子可以独立地被OH或Hal替代的C_1-C_6烷基的基团取代;L_2是Q_2-M-,其中Q_2是含有1个氮原子和1-3个独立地选自O、S、N或CO的另外的基团的稠合双环系统,和其中至少一个环是芳族的,由此稠合双环系统任选地被1-5个独立地选自OR^a、Hal、苯基、及其中1-5个H原子可以独立地被OH或Hal替代的C_1-C_6烷基的基团取代;Q_2是含有1-3个选自N、O、S和CO的杂原子的不饱和或芳族5元环系统,且任选地被苯环或吡啶环取代,其中苯环和吡啶环任选地被1-4个独立地选自OR^a、Hal、苯基、及其中1-5个H原子可以独立地被OH或Hal替代的C_1-C_6烷基的基团取代;M是具有1-5个碳原子的线性或分支亚烷基,其中1-2个H原子可被OR^a或苯基替代,所述苯基任选地被1-5个独立地选自Hal、OR^a、及任选地被1-5个独立地选自OH和Hal的基团取代的C_1-C_6烷基的基团取代;或M表示具有3-7个碳原子的亚环烷基;或者M表示噻唑烷基;R^a是H或C_1-C_6烷基,其中1-5个H原子可以独立地被OH或Hal替代;Ar表示6元芳族碳环,其任选地与另一个具有5-8个碳原子的饱和、不饱和或芳族碳环稠合;Het表示含有1-3个独立地选自N、N+O-、O、S、SO和SO_2的杂原子的5或6元饱和、不饱和或芳族杂环,且任选地与另一个具有5-8个原子和任选地含1-3个选自N、O和S的杂原子的饱和、不饱和或芳族环稠合;Hal表示Cl、Br、I或F;优选Cl或F。



(I)

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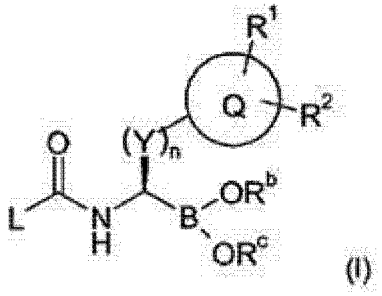
1. 一种式 (I) 化合物



(I)

其中

R^b 和 R^c 彼此独立地选自 H 或 C_1-C_6 烷基；其中 R^b 和 R^c 可连接形成含氧原子的 5 或 6 元环，所述氧原子与 R^b 和 R^c 连接；

Q 表示 Ar、Het 或环烷基；

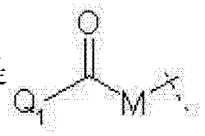
R^1 和 R^2 彼此独立地选自 H、OR^a、Hal、其中 1-5 个 H 原子可以独立地被 OH 或 Hal 替代的 C_1-C_6 烷基；

Y 表示 CR^3R^4，优选为 CH_2 或 $C(CH_3)_2$；

R^3，R^4 彼此独立地表示 H 或 C_1-C_6 烷基；

L 表示 L_1 或 L_2 或烷基；

n 为选自 0-3 的整数；

L_1 是  ，其中

Q_1 是 Ar 或 Het，优选为苯基、萘基或吡啶，任选地被 1-5 个独立地选自 OR^a、Hal、苯基、及其中 1-5 个 H 原子可以独立地被 OH 或 Hal 替代的 C_1-C_6 烷基的基团取代；

L_2 是  ，其中

Q_2 是含有 1 个氮原子和 1-3 个独立地选自 O、S、N 或 CO 的另外的基团的稠合双环系统，和其中至少一个环是芳族的，由此稠合的双环系统任选地被 1-5 个独立地选自 OR^a、Hal、苯基、及其中 1-5 个 H 原子可以独立地被 OH 或 Hal 替代的 C_1-C_6 烷基的基团取代；或

Q_2 是含有 1-3 个选自 N、O、S 或 CO 的杂原子的不饱和或芳族 5 元环系统，且任选地被苯环或吡啶环取代，其中苯环或吡啶环任选地被 1-4 个独立地选自 OR^a、Hal、苯基、及其中 1-5 个 H 原子可以独立地被 OH 或 Hal 替代的 C_1-C_6 烷基的基团取代；

M 是具有 1-5 个碳原子的线性或分支亚烷基，其中 1-2 个 H 原子可被 OR^a 或苯基替代，所述苯基任选地被 1-5 个独立地选自 Hal、OR^a、及任选地被 1-5 个独立地选自 OH 和 Hal 的基团取代的 C_1-C_6 烷基的基团取代；或

M 表示具有 3-7 个碳原子的亚环烷基；或

M 表示噻唑烷基；

R^a 是 H 或其中 1-5 个 H 原子可以独立地被 OH 或 Hal 替代的 C_1-C_6 烷基；

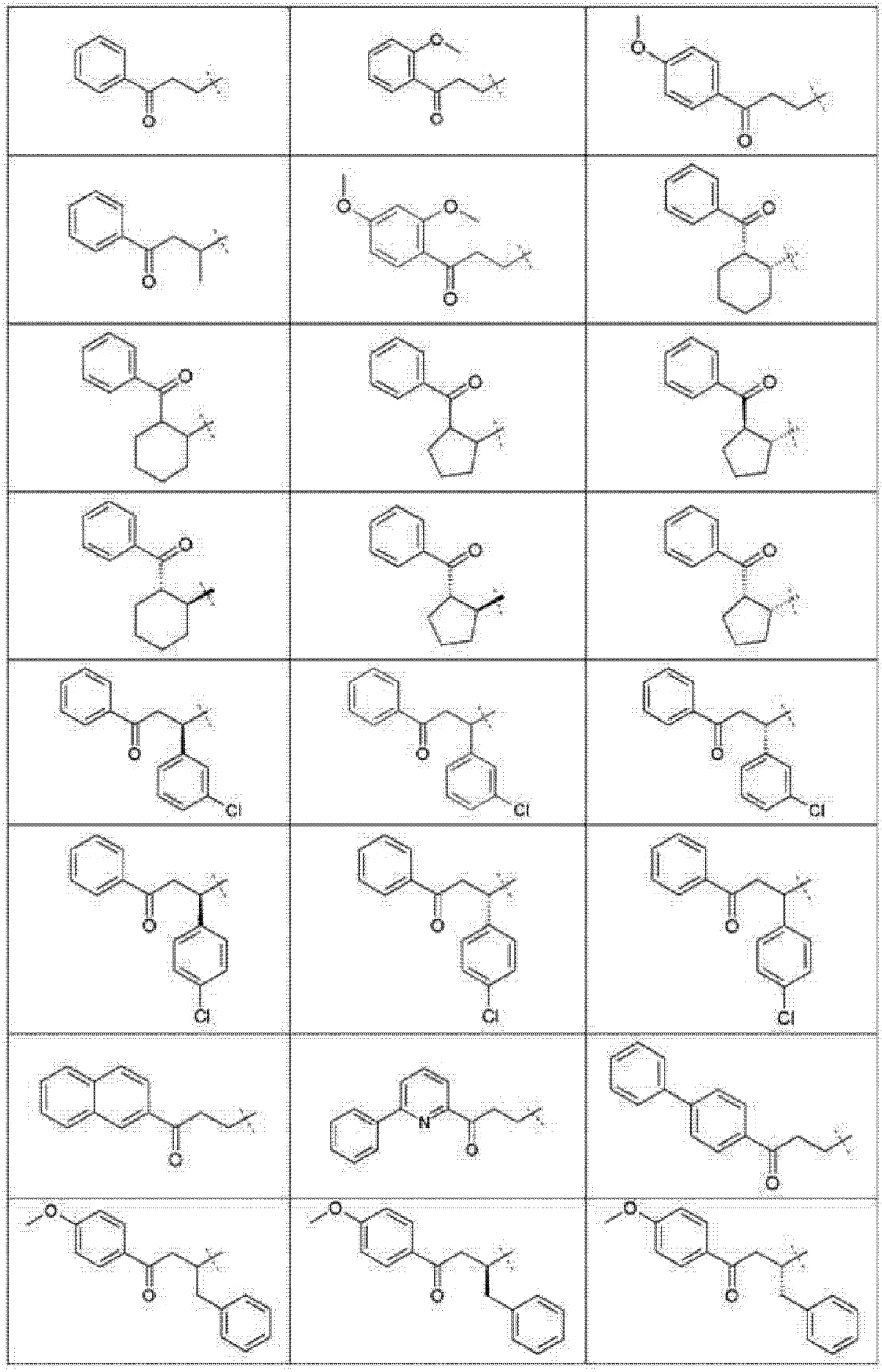
Ar 表示 6 元芳族碳环，其任选地与另一个具有 5-8 个碳原子的饱和、不饱和或芳族碳环稠合；

Het 表示含有 1-3 个独立地选自 N、N+O-、O、S、SO 和 SO_2 的杂原子的 5 或 6 元饱和、不饱和或芳族杂环，且任选地与另一个具有 5-8 个原子和任选地含 1-3 个选自 N、O 和 S 的杂原子的饱和、不饱和或芳族环稠合；

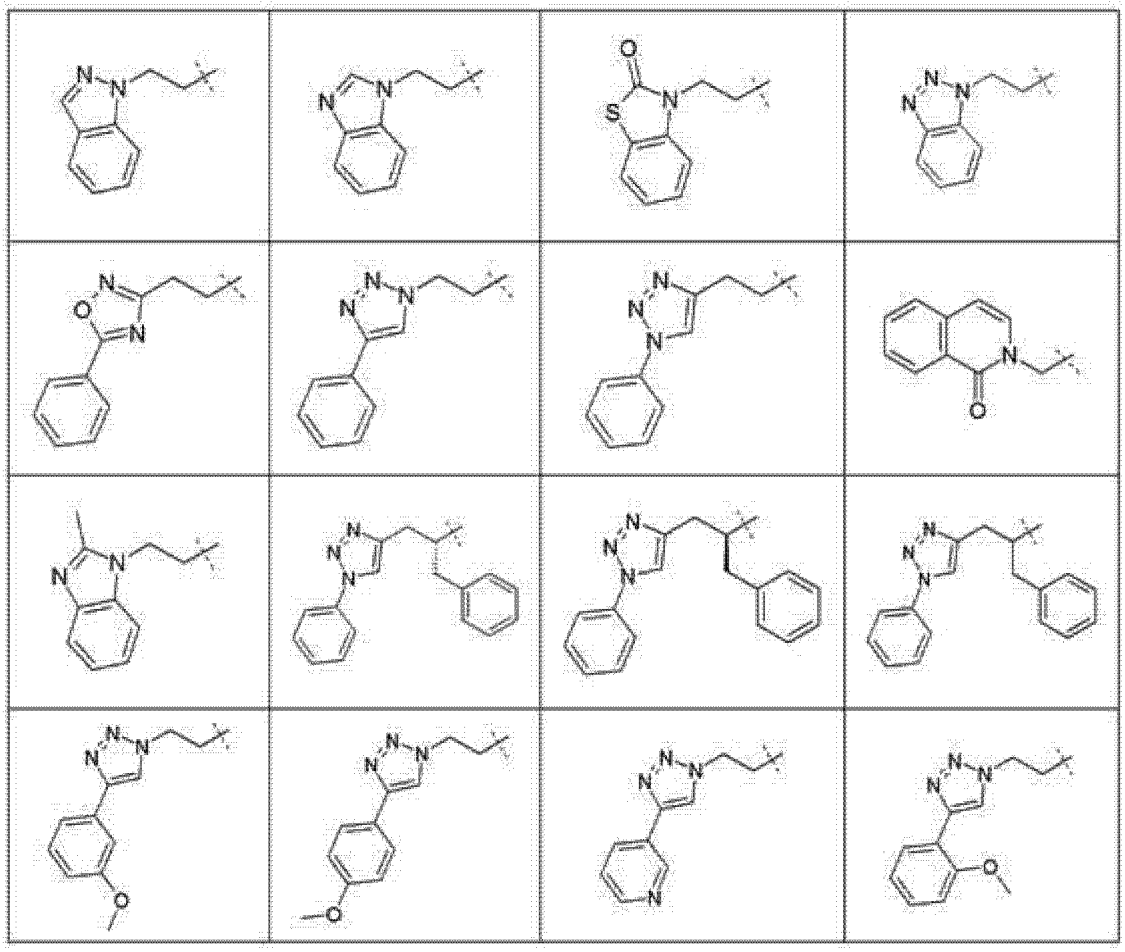
Hal 表示 Cl、Br、I 或 F；优选 Cl 或 F，

及其对映体、非对映体，及其药学上可接受的盐。

2. 权利要求 1 的式 (I) 化合物，其中 L 选自以下基团：



或者其中 L 选自以下的基团：



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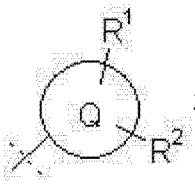
3. 权利要求 1 或 2 的式 (I) 化合物,其中基团



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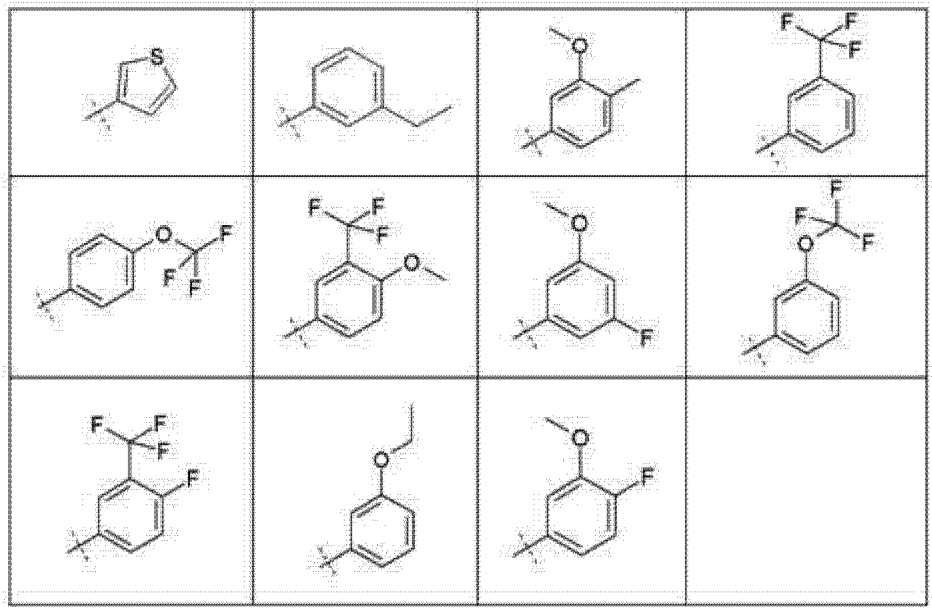

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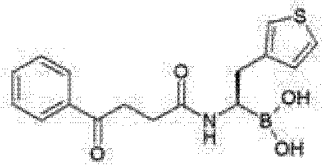
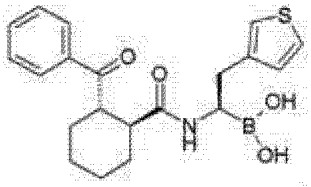
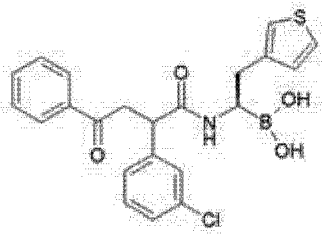
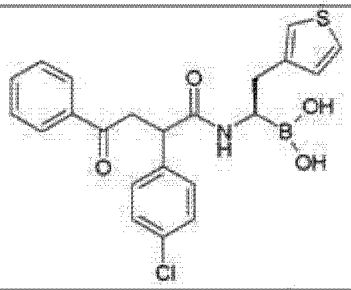
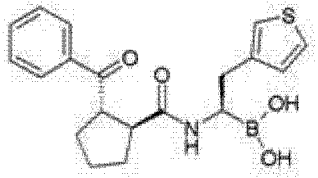
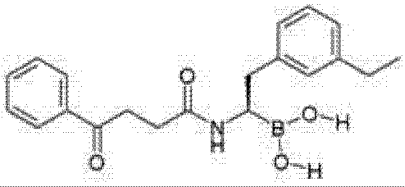
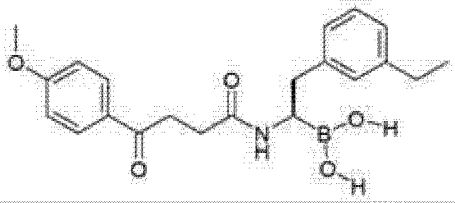
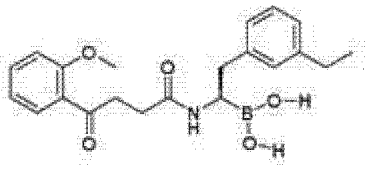
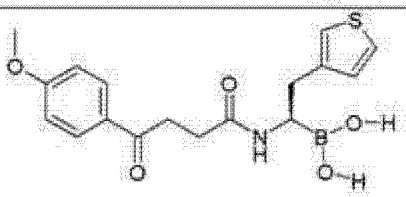
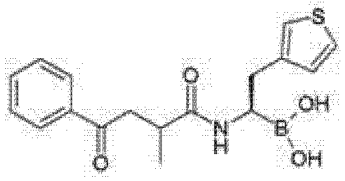
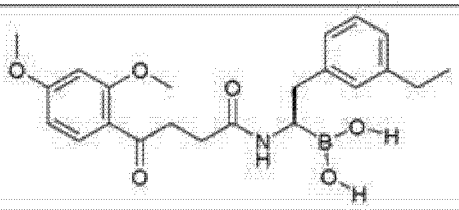
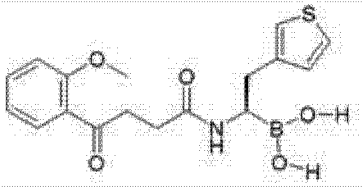
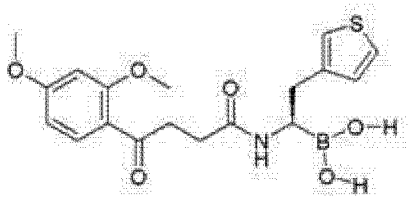
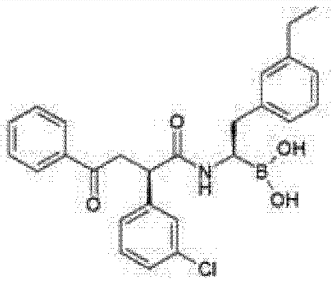
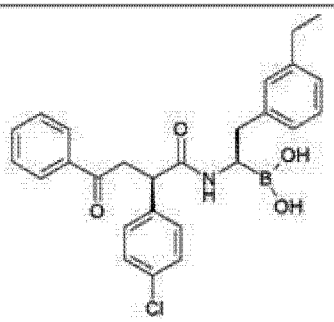
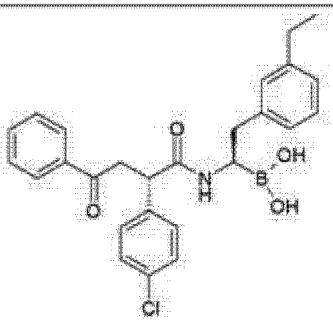
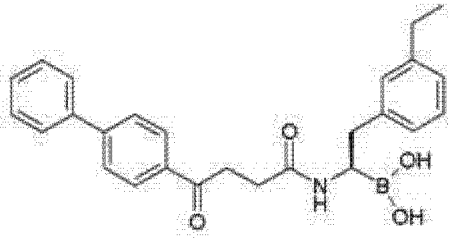
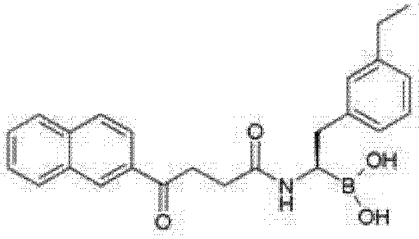
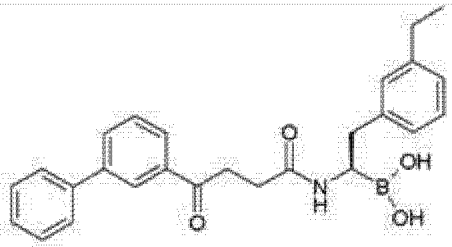
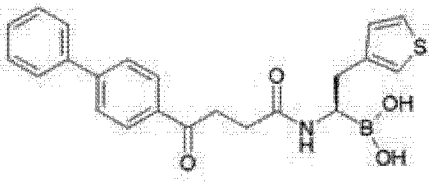
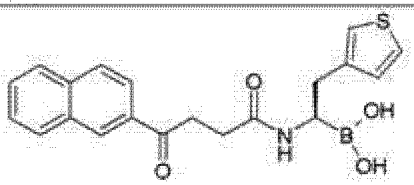
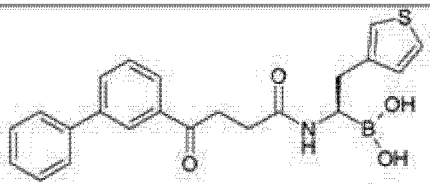
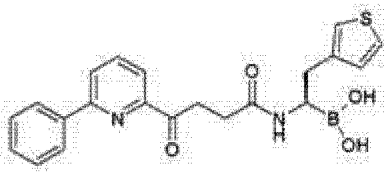
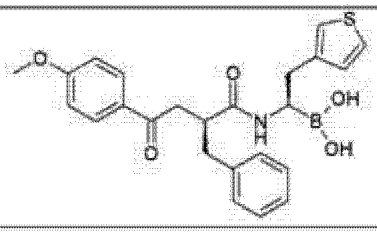
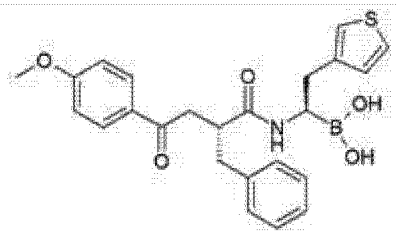
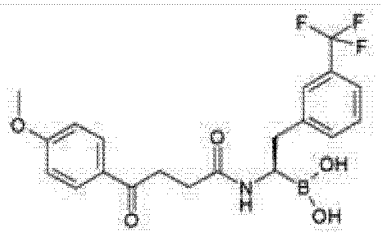
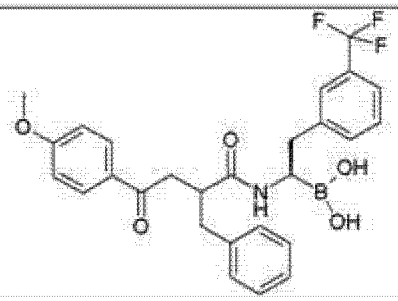
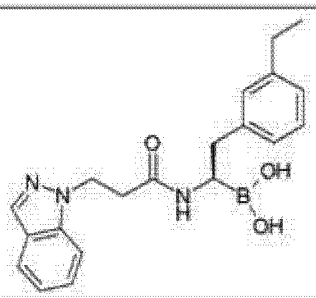
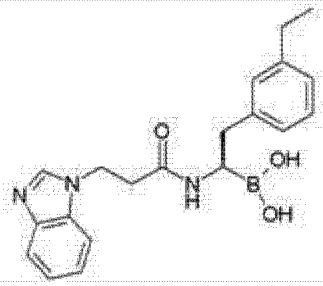
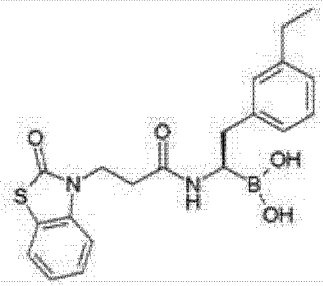
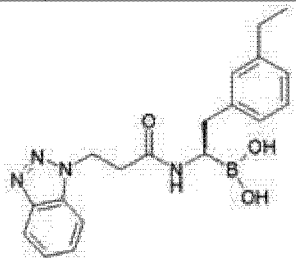
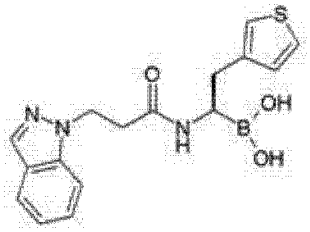
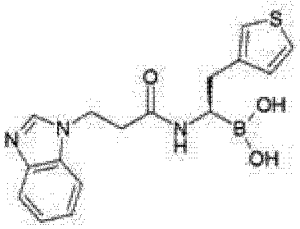
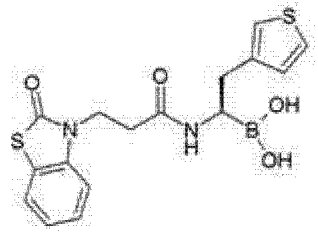
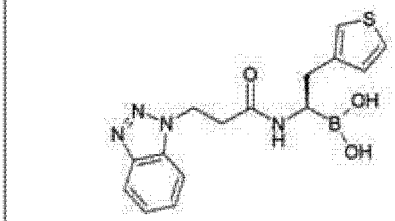
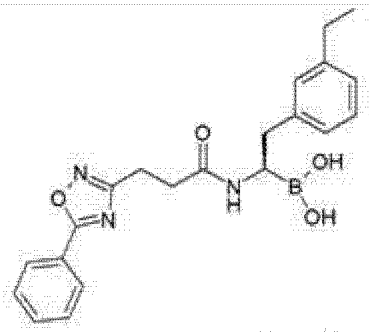
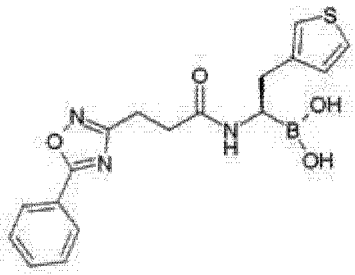
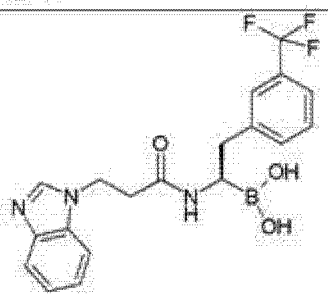
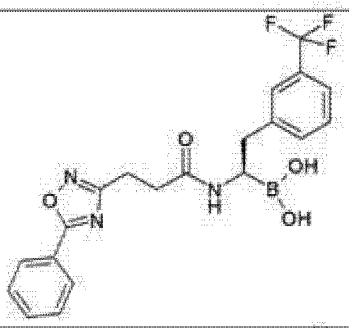
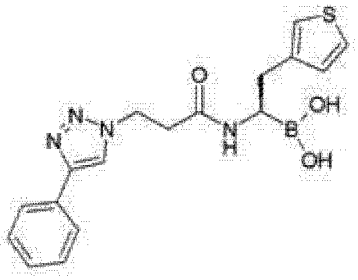
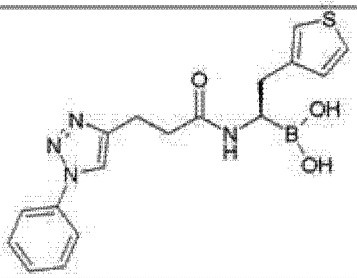
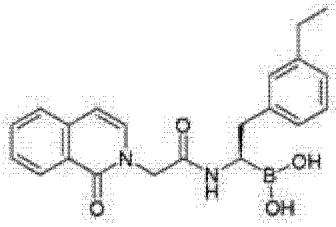
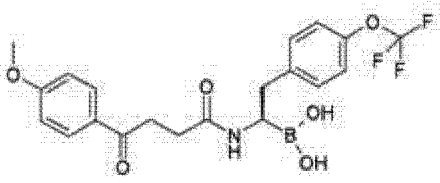
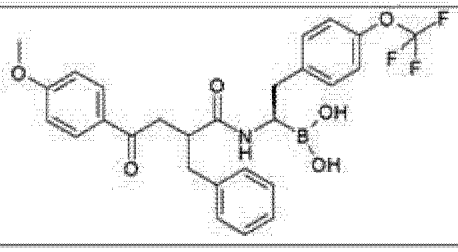
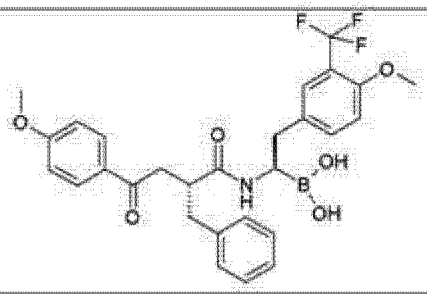
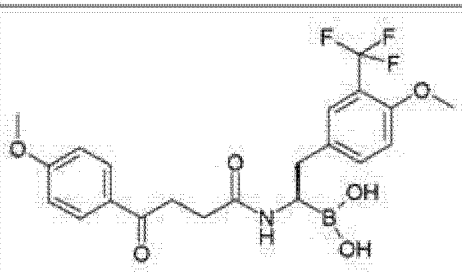
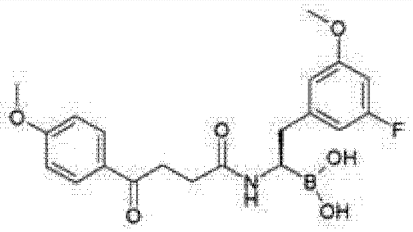
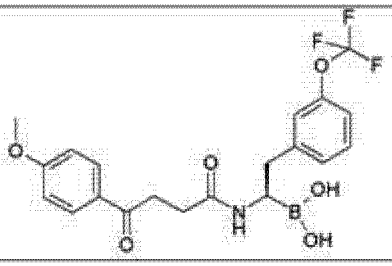
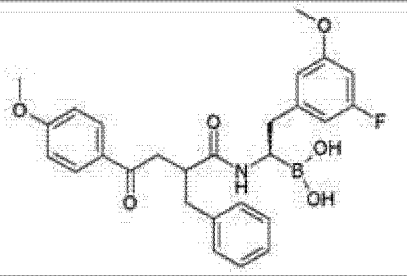
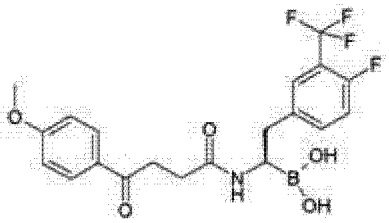
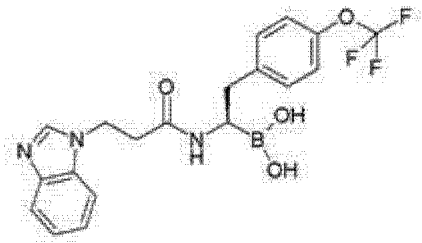
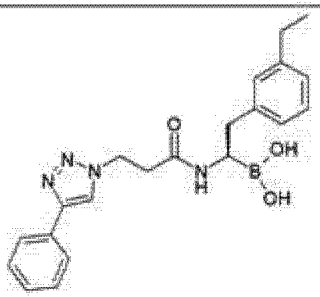
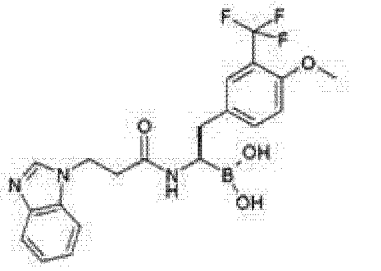
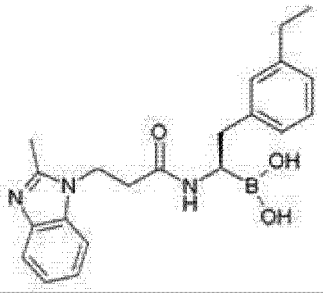
4. 权利要求 1 的式 (I) 化合物,其中所述化合物选自以下组 :

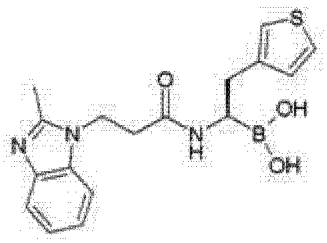
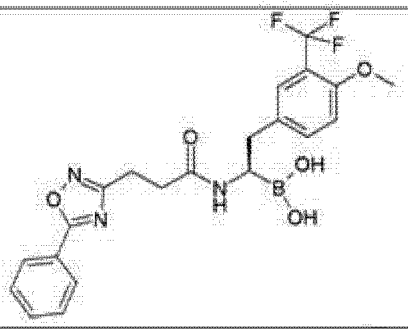
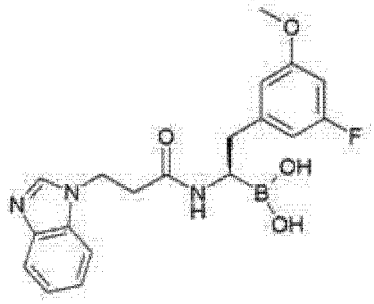
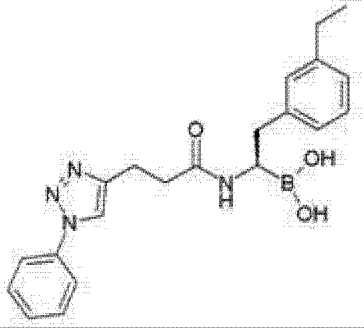
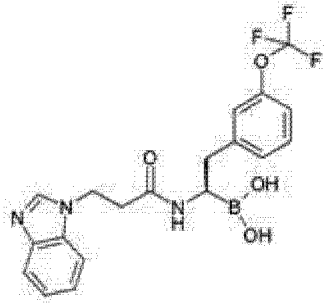
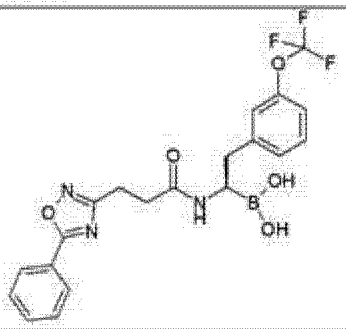
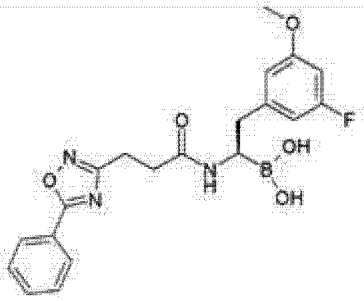
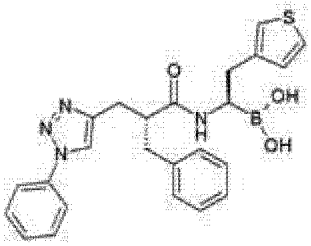
实施例	式	实施例	式
1		2	
3		4	
5		6	
7		8	
9		10	
11		12	

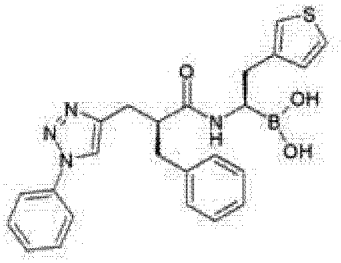
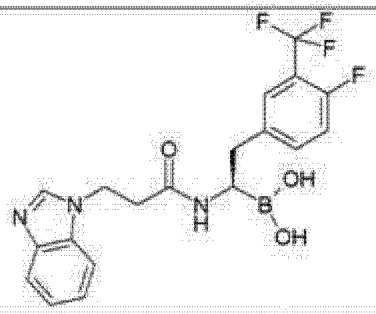
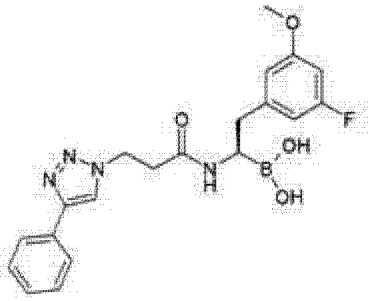
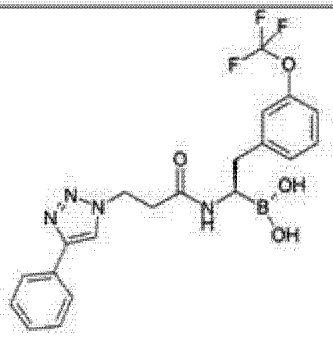
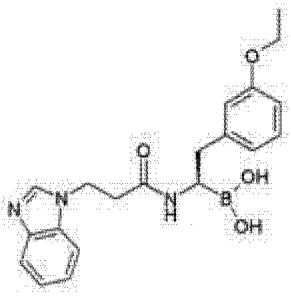
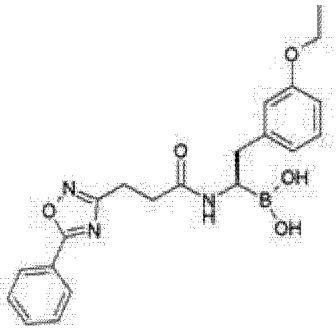
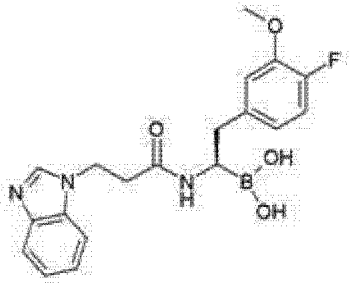
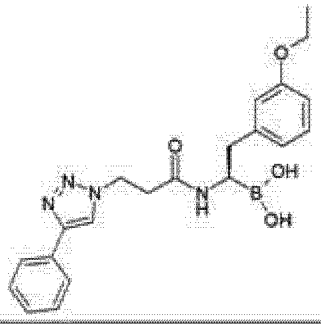
13		14	
15		16	
17		18	
19		20	
21		22	
23		24	

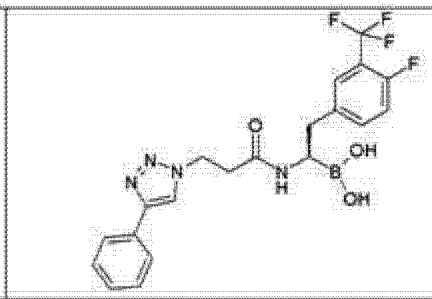
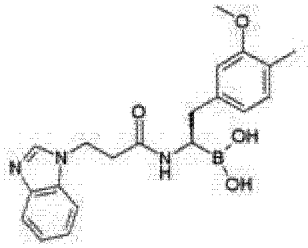
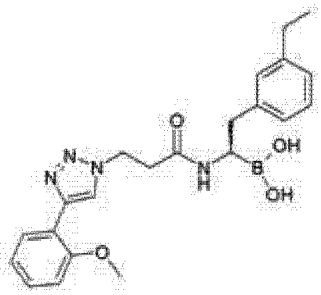
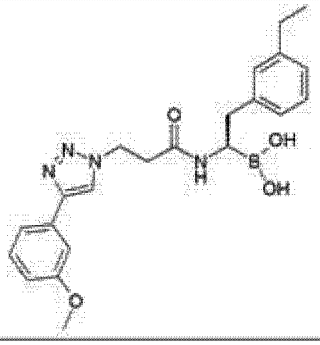
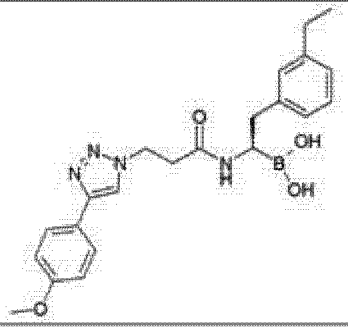
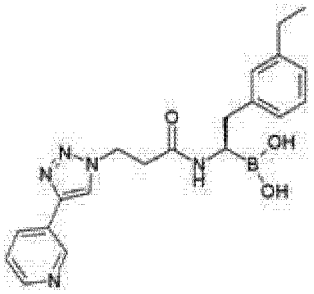
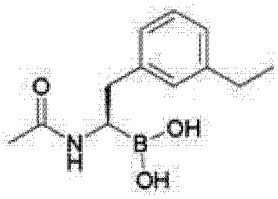
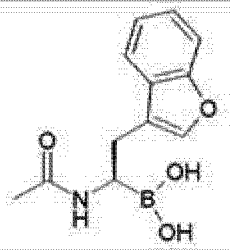
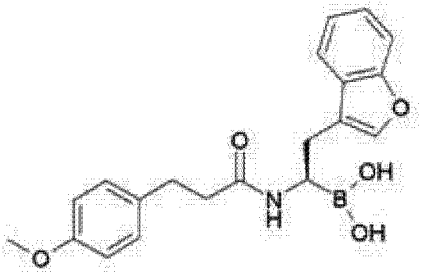
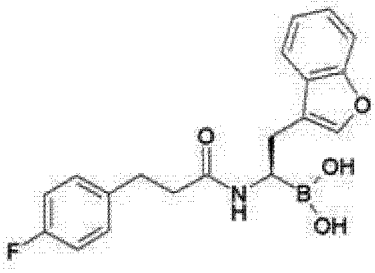
25		26	
27		28	
29		30	
31		32	
33		34	

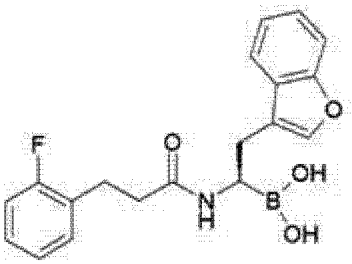
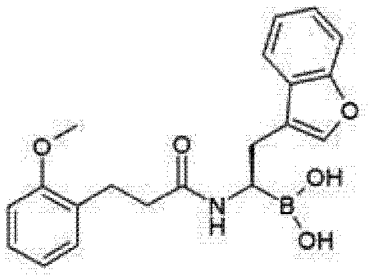
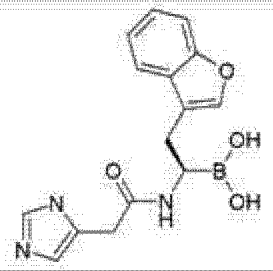
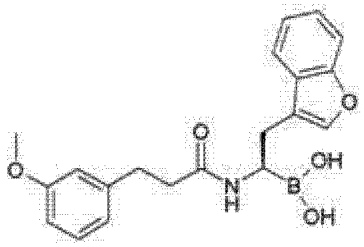
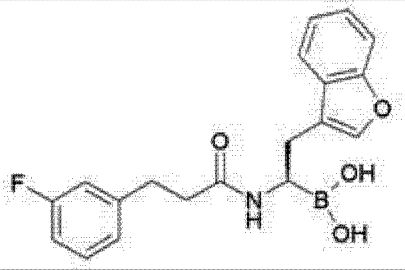
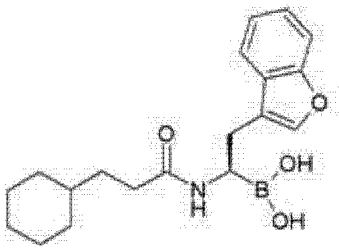
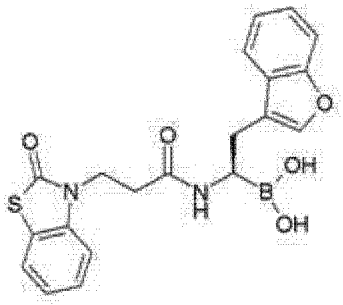
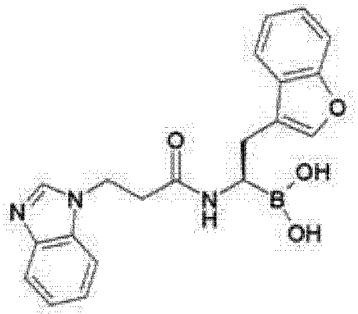
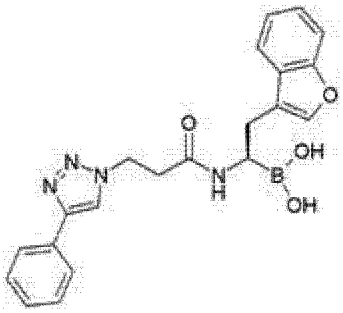
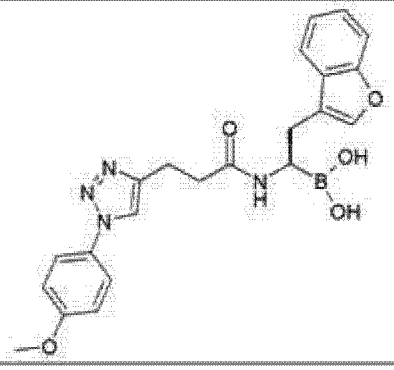
35		36	
37		38	
39		40	
41		42	
43		44	

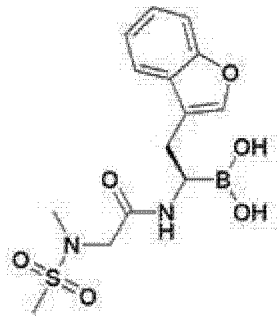
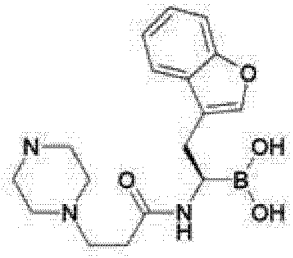
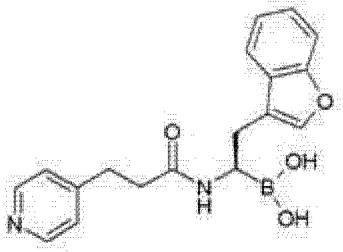
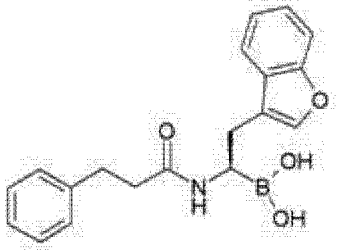
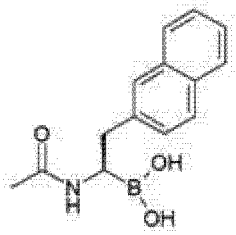
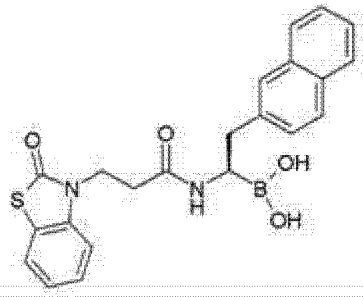
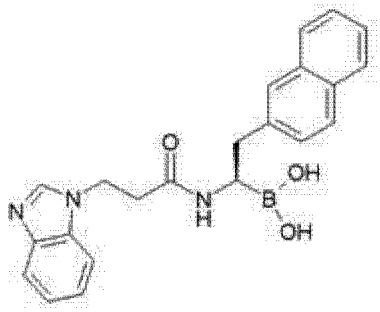
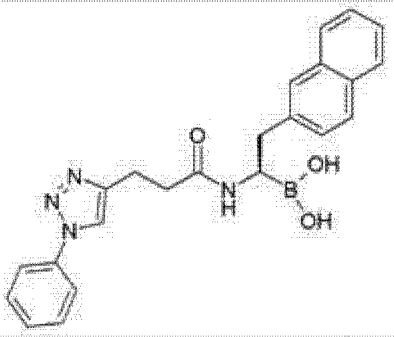
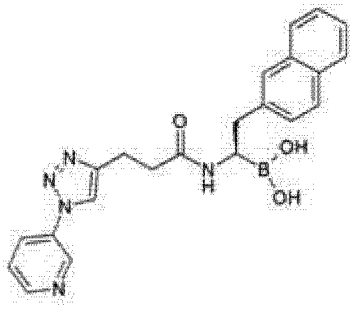
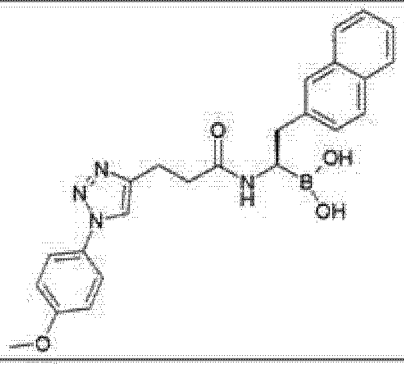
45		46	
47		48	
49		50	
51		52	
53		54	

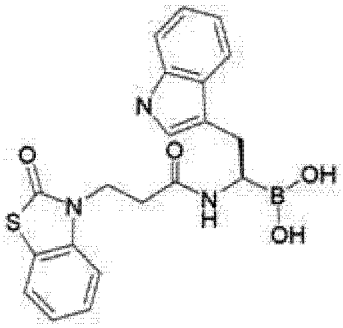
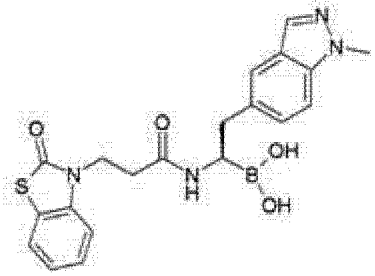
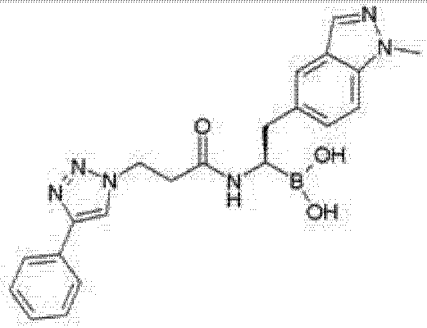
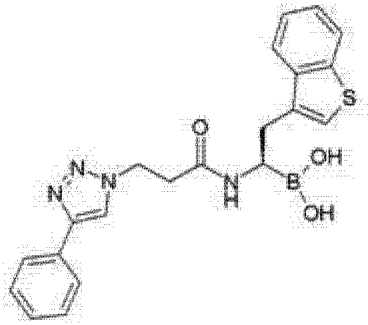
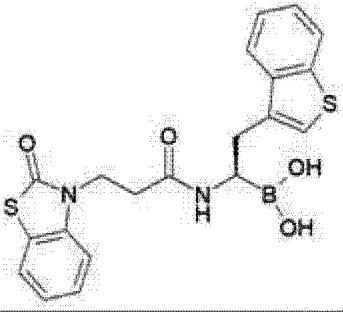
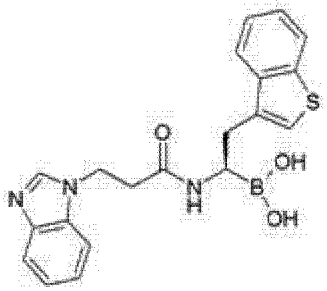
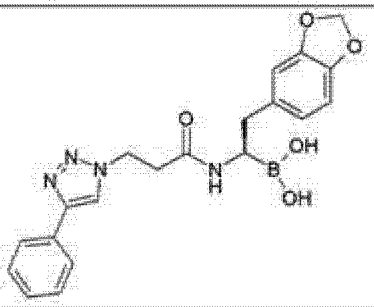
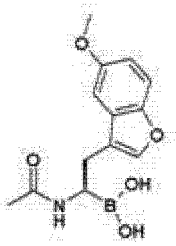
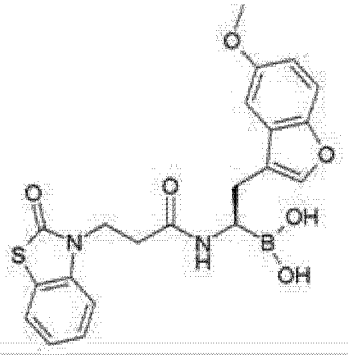
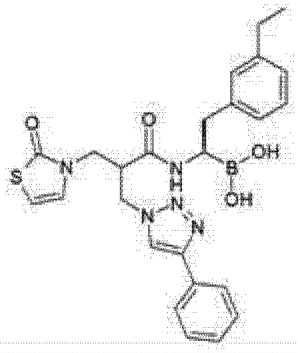
55		56	
57		58	
59		60	
61		62	

63		64	
65		66	
67		68	
69		70	

71		72	
73		74	
75		76	
77		78	
79		80	

81		82	
83		84	
85		86	
87		88	
89		90	

91		92	
93		94	
95		96	
97		98	
99		100	

101		102	
103		104	
105		106	
107		108	
109		110	

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5. 一种药用组合物，其包含权利要求 1-4 中一项或多项的至少一种式 (I) 化合物和 / 或其药学可用盐、溶剂合物和立体异构体，包括其所有比例的混合物，和任选的赋形剂和 / 或辅助剂。

6. 一种药用组合物，其包含权利要求 1-4 中一项或多项的至少一种式 (I) 化合物和 / 或其药学可用盐、溶剂合物和立体异构体，包括其所有比例的混合物，和至少一种另外的活性成分。

7. 由以下单独的包构成的药物套装（药剂盒）：

(a) 有效量的权利要求 1-4 中一项或多项的式 (I) 化合物和 / 或其药学可用盐、溶剂合物和立体异构体，包括其所有比例的混合物，

和

(b) 有效量的其它药物活性成分。

8. 权利要求 1-4 中一项或多项的化合物及其药学可用盐、互变异构体、溶剂合物和立体异构体，包括其所有比例的混合物，用于制备治疗和 / 或预防与过度活性免疫应答相关的自身免疫紊乱或病症的药物。

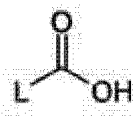
9. 权利要求 1-4 中一项或多项的化合物及其药学可用盐、互变异构体、溶剂合物和立体异构体，包括其所有比例的混合物，用于制备治疗和 / 或预防免疫调节异常的药物。

10. 权利要求 8 或 9 的化合物，其中所述免疫调节异为选自以下的自身免疫疾病或慢性炎性疾病：系统性红斑狼疮、慢性类风湿性关节炎、炎性肠道疾病、多发性硬化、肌萎缩性侧索硬化 (ALS)、动脉硬化症、硬皮病、自身免疫肝炎、干燥综合征、狼疮性肾炎、肾小球性肾炎、类风湿性关节炎、银屑病、重症肌无力、免疫球蛋白 A 肾病、血管炎、移植排斥和哮喘。

11. 权利要求 1-4 中一项或多项的化合物及其药学可用盐、互变异构体、溶剂合物和立体异构体，包括其所有比例的混合物，用于制备治疗和 / 或预防 LMP7 相关疾病的药物。

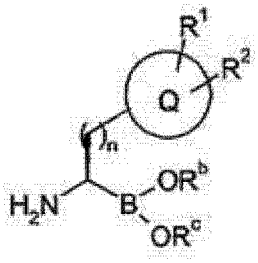
12. 权利要求 11 的化合物，其中所述 LMP7 相关疾病选自肌萎缩性侧索硬化、干燥综合征、系统性红斑狼疮、狼疮性肾炎、肾小球性肾炎、类风湿性关节炎、炎性肠道疾病、溃疡性结肠炎、克罗恩氏病、多发性硬化、肌萎缩性侧索硬化、骨关节炎、动脉硬化症、银屑病、重症肌无力、皮肤纤维化、肾纤维化、心纤维化、肝纤维化、肺纤维化、免疫球蛋白 A 肾病、血管炎、移植排斥、血液恶性肿瘤和哮喘。

13. 一种合成权利要求 1 的式 (I) 化合物的方法，其包括使式 (II) 化合物与式 (III) 化合物反应的步骤，



(II)

其中 L 如权利要求 1 所定义，



(III)

其中 R^1、R^2、Q、R^a、R^b 和 n 如权利要求 1 所定义。

14. 权利要求 13 的方法，其中式 (II) 化合物和式 (III) 化合物之间的反应在选自以下的偶联剂的存在下进行：HATU、TBTU、聚合物担载的 1- 烷基 -2- 氯代吡啶鎓盐（聚合物担载的 Mukaiyama 试剂）、碘化 1- 甲基 -2- 氯代吡啶鎓 (Mukaiyama 试剂)、碳二亚胺。

15. 权利要求 1-4 的化合物，其用作药物。

α－氨基硼酸衍生物，选择性免疫蛋白酶体抑制剂

[0001] 本发明提供 α－氨基硼酸衍生物，及其在治疗炎性疾病和自身免疫性疾病、神经退行性疾病、及增殖性疾病中的用途。具体地说，本发明的化合物是选择性免疫蛋白酶体抑制剂。

[0002] 所述蛋白酶体（也称为巨蛋白因子 (macropain)、多催化性蛋白酶和 20S 蛋白酶）是一种高分子量、多亚单位蛋白酶，其已经在从古细菌 (archaebacterium) 到人的每一种检测的物种中被鉴别出。该酶具有约 650,000 的天然分子量，并且如电子显微镜所显示的，具有独特的圆柱形形态 (Rivett, (1989) Arch. Biochem. Biophys. 268:1-8；和 Orlowski, (1990) Biochemistry 29:10289-10297)。该蛋白酶体亚单位的分子量在 20,000-35,000 (3-5) 的范围，并且彼此是同源的，但不与任何其它已知的蛋白酶同源。

[0003] 20S 蛋白酶体是包含 28 个分类为 α－和 β－型的亚单位的 700 kDa 圆柱形多催化性蛋白酶复合物，所述亚单位以 4 个堆积的七聚体环排列。在酵母和其它真核细胞中，7 个不同的 α 亚单位形成外环且 7 个不同的 β 亚单位构成内环。α 亚单位用作 19S (PA700) 和 1 IS (PA28) 调节复合物的结合位点，以及用作由两个 β 亚单位环形成的内部蛋白水解室的物理屏障。因此，在体内，认为该蛋白酶体作为 26S 颗粒（“26S 蛋白酶体”）存在。体内试验已表明，蛋白酶体的 20S 形式的抑制可能容易地与 26S 蛋白酶体的抑制相关。

[0004] 在颗粒形成期间，β 亚单位的氨基端前导序列 (prosequences) 的裂解暴露氨基端苏氨酸残基，所述苏氨酸残基起催化性亲核物质的作用。因此，负责蛋白酶体的催化活性的亚单位具有氨基端亲核残基，并且这些亚单位属于 N- 末端亲核物质 (Ntn) ATTY REF:26500-0023WO1 水解酶的种类（这里亲核的 N- 末端残基为例如 Cys、Ser、Thy，和其它亲核部分）。这个种类包括，例如，青霉素 G 酰基转移酶 (PGA)、青霉素 V 酰基转移酶 (PVA)、谷氨酸 PRPP 氨基转移酶 (GAT)，和细菌糖基天冬酰胺酶。除了遍在表达的 β 亚单位外，高级脊椎动物还具有三种干扰素－γ－可诱导的 β 亚单位 (LMP7、LMP2 和 MECLI)，其分别替代它们的正常负体，β5、β1 和 β2。当所有三种 IFN-γ－可诱导的 β 亚单位存在时，该蛋白酶体被称为“免疫蛋白酶体”。因此，真核细胞可具有不同比例的两种形式的蛋白酶体。

[0005] 尽管使用不同的肽底物，对真核细胞 20S 蛋白酶体已定义了三种主要的蛋白水解活性：胰凝乳蛋白酶样活性 (CT-L)，其在大的疏水残基后裂解；胰蛋白酶样活性 (T-L)，其在碱性残基后裂解；和肽基谷氨酰肽水解活性 (PGPH)，其在酸性残基后裂解。两种另外的较少特征性的活性也被认为属于蛋白酶体：BrAAP 活性，其在支链氨基酸后裂解；和 SNAAP 活性，其在小的中性氨基酸后裂解。尽管两种形式的蛋白酶体具有所有 5 种酶促活性，但基于特异性底物描述了这些形式之间的活性程度的差异。对于两种形式的蛋白酶体，主要的蛋白酶体蛋白水解活性似乎归因于 20S 核心内的不同催化位点。

[0006] 在真核细胞中，蛋白降解主要地通过泛素途径介导，其中靶向破坏的蛋白连接于 76 个氨基酸多肽泛素。一旦选定靶标，则遍在蛋白用作 26S 蛋白酶体的底物，该蛋白酶体通过其三种主要蛋白水解活性的作用将蛋白裂解为短肽。虽然具有细胞内蛋白更新的一般功能，但蛋白酶体介导的降解在许多过程中也起着重要的作用，如主要的组织相容性复合体 (MHC) I 型呈递、细胞凋亡和细胞生存力、抗原加工、NF-κ B 激活，和促炎信号的转导。

[0007] 蛋白酶体活性在涉及蛋白分解的肌肉萎缩症(muscle wasting diseases)中是高的,例如肌肉营养失调、癌症和AIDS。证据也表示蛋白酶体在I型MHC分子的抗原加工中的可能的作用(Goldberg, et al. (1992) Nature 357:375-379)。

[0008] 蛋白酶体涉及神经退行性疾病和紊乱例如肌萎缩性侧索硬化(ALS),(J Biol Chem 2003, Allen S et al., Exp Neurol 2005, Puttaparthi k et al.),干燥综合征(Sjogren syndrome) (Arthritis & Rheumatism, 2006, Egerer T et al.),系统性红斑狼疮和狼疮性肾炎(SLE/LN),(Arthritis & rheuma 2011, lchikawa et al., J Immunol, 2010, Lang VR et al., Nat Med, 2008, Neubert K et al),肾小球性肾炎(J Am Soc nephrol 2011, Bontscho et al.),类风湿性关节炎(Clin Exp Rheumatol, 2009, Van der Heiden JW et al.),炎性肠道疾病(IBD),溃疡性结肠炎,克罗恩氏病,(Gut 2010, Schmidt N et al., J Immunol 2010, Basler M et al., Clin Exp Immunol, 2009, Inoue S et al.)、多发性硬化(Eur J Immunol 2008, Fissolo N et al., J Mol Med 2003, Elliott PJ et al., J Neuroimmunol 2001, Hosseini et al., J Autoimmun 2000, Vanderlugt CL et al.),肌萎缩性侧索硬化(ALS),(Exp Neurol 2005, Puttaparthi k et al., J Biol Chem 2003, Allen S et al.),骨关节炎(Pain 2011, Ahmed s et al., Biomed Mater Eng 2008, Etienne S et al.),动脉硬化症(J Cardiovasc Pharmacol 2010, Feng B et al.,银屑病(Genes & Immunity, 2007, Kramer U et al.),重症肌无力(J Immunol, 2011, Gomez AM et al.),皮肤纤维化(Thorax 2011, Mutlu GM et al., Inflammation 2011, Koca SS et al., Faseb J 2006, Fineschi S et al.),肾纤维化(Nephrology 2011 Sakairi T et al.),心纤维化(Biochem Pharmacol 2011, Ma y et al.,) 肝纤维化(Am J Physiol gastrointest Liver肝Physiol 2006, Anan A et al.),肺纤维化(Faseb J 2006, Fineschi S et al et al.),免疫球蛋白A肾病(IGa肾病),(Kidney Int, 2009, Coppo R et al.),血管炎(J Am Soc nephrol 2011, Bontscho et al.),移植排斥(Nephrol Dial transplant 2011, Waiser J et al.),血液恶性肿瘤(Br J Haematol 2011, singh AV et al., Curr Cancer Drug Target 2011, Chen D et al.)和哮喘。

[0009] 然而,应该注意到,可市售获得的蛋白酶体抑制剂抑制蛋白酶体的组成性和免疫性两种形式。甚至硼替佐米(Bortezomib),其为FDA批准的用于治疗复发的多发性骨髓瘤患者的蛋白酶体抑制剂,也不区分这两种形式(Altun et al, Cancer Res 65:7896, 2005)。

[0010] 此外,硼替佐米的使用与治疗紧急出现的疼痛性外周神经病(PN)相关,这种硼替佐米诱导的神经退行性病变在体外经由不依赖蛋白酶体的机制发生并且硼替佐米在体外和体内抑制几种非蛋白酶体靶标(Clin. Cancer Res, 17(9), 5月1日 , 2011)。

[0011] 除了常规的蛋白酶体抑制剂,一种新的途径可以特异性地靶向血液学特异性免疫蛋白酶体,由此增加整体效果并减少负面的脱靶效应。已经表明免疫蛋白酶体-特异性抑制剂可对来自血液源的细胞显示增强的效果(Curr Cancer Drug Targets, 11 (3), 3月, 2011)。

[0012] 因此存在对提供新的蛋白酶体抑制剂的需求,所述抑制剂对一种特异性形式的蛋白酶体有选择性。

[0013] 在另一方面，本发明涉及包含至少一种依据式 (I) 和相关式的化合物的药物制剂。

[0014] 这样的药物制剂也可包含另外的活性剂。所述另外的活性剂可选自免疫抑制剂、抗炎药或干扰素。

[0015] 在另一方面，本发明涉及制备依据式 (I) 和相关式的化合物的方法。

[0016] 本发明还涉及由以下单独的包构成的药物套装或药剂盒：

(a) 有效量的依据式 (I) 或相关式的化合物和 / 或其药学可用衍生物、互变异构体、盐、溶剂合物和立体异构体，包括其所有比例的混合物，

和

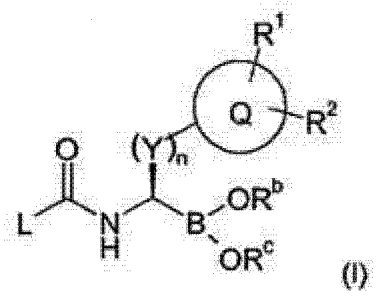
(b) 有效量的另一药物活性成分。

[0017] 本发明涵盖或者单独的式 (I) 和相关式的化合物或者与一种或多种其代谢物组合的式 (I) 和相关式的化合物。

[0018] 详述

本发明的化合物为免疫蛋白酶体亚单位 LMP7 的抑制剂。优选地，它们显示对 LMP7 超过 Beta5 的选择性。

[0019] 本发明提供式 (I) 化合物：



(I)

其中

R^b 和 R^c 彼此独立地选自 H 和 C_1-C_6 烷基；其中 R^b 和 R^c 可连接形成含氧原子的 5 或 6 元环，所述氧原子与 R^b 和 R^c 连接；

Q 表示 Ar、Het 或环烷基；

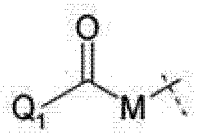
R^1、R^2 彼此独立地选自 H、OR^a（优选甲氧基）、Hal、其中 1-5 个 H 原子可以独立地被 OH 或 Hal 替代的 C_1-C_6 烷基；

Y 表示 CR^3R^4，优选为 CH_2 或 $C(CH_3)_2$；

R^3，R^4 彼此独立地表示 H 或 C_1-C_6 烷基，例如甲基；

L 表示 L_1 或 L_2 或烷基，优选甲基；

n 为选自 0、2 或 3 的整数并且优选地为 1；

L_1 是 

，其中

Q_1 是 Ar 或 Het，优选为苯基、萘基或吡啶，任选地被 1-5 个独立地选自 OR^a、Hal、苯基 \ 及其中 1-5 个 H 原子可以独立地被 OH 或 Hal 替代的 C_1-C_6 烷基的基团取代；

L_2 是 

，其中

Q_2 是含有 1 个氮原子和 1-3 个独立地选自 O、S、N 或 CO 的另外的基团的稠合双环系统，和其中至少一个环是芳族的，由此稠合双环系统任选地被 1-5 个独立地选自 OR^a、Hal、苯基、及其中 1-5 个 H 原子可以独立地被 OH 或 Hal 替代的 C_1-C_6 烷基的基团取代；

或

Q_2 是含有 1-3 个选自 N、O、S 或 CO 的杂原子的不饱和或芳族 5 元环系统，且任选地被苯环或吡啶环取代，其中苯环或吡啶环任选地被 1-4 个独立地选自 OR^a、Hal、苯基、及其中 1-5 个 H 原子可以独立地被 OH 或 Hal 替代的 C_1-C_6 烷基的基团取代；

M 是具有 1-5 个碳原子的线性或分支亚烷基，其中 1-2 个 H 原子可被 OR^a、或任选地被 1-5 个独立地选自 Hal、OR^a 及任选地被 1-5 个独立地选自 OH 和 Hal 的基团取代的 C_1-C_6 烷基的基团取代的苯基替代；或

M 表示具有 3-7 个碳原子的亚环烷基；或

M 表示噻唑烷基；

R^a 是 H 或其中 1-5 个 H 原子可以独立地被 OH 或 Hal 替代的 C_1-C_6 烷基；

Ar 表示 6 元芳族碳环，其任选地与另一个具有 5-8 个碳原子的饱和、不饱和或芳族碳环稠合；

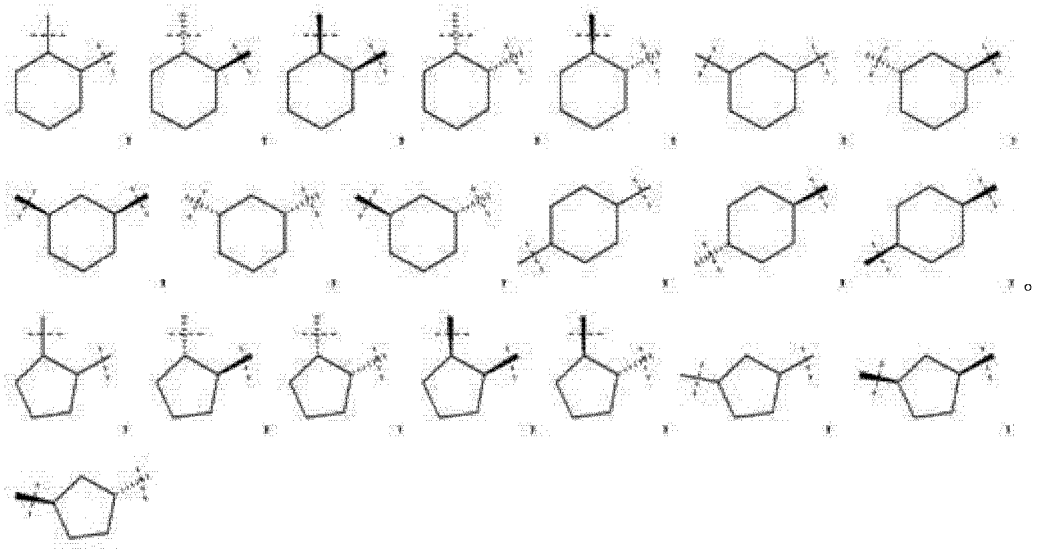
Het 表示含有 1-3 个独立地选自 N、N^+O^-、O、S、SO 和 SO_2 的杂原子的 5 或 6 元饱和、不饱和或芳族杂环，且任选地与另一个具有 5-8 个原子和任选地含 1-3 个独立地选自 N、O 和 S 的杂原子的饱和、不饱和或芳族环稠合；

Hal 表示 Cl、Br、I 或 F；优选 Cl 或 F，

及其对映体、非对映体和混合物，及其药学上可接受的盐；

在 L 含有 1 或数个手性中心的情况下，式 (I) 涵盖任何分离的对映体和非对映体，及其所有比例的混合物。

[0020] 在一个具体的实施方案中，本发明提供式 (I) 和相关式的化合物，其中 L 表示 L1，从而 M 为具有 3-7 个碳原子的亚环烷基。优选地，M 选自 5- 或 6- 元亚环烷基。这样的亚环烷基的实例如下：



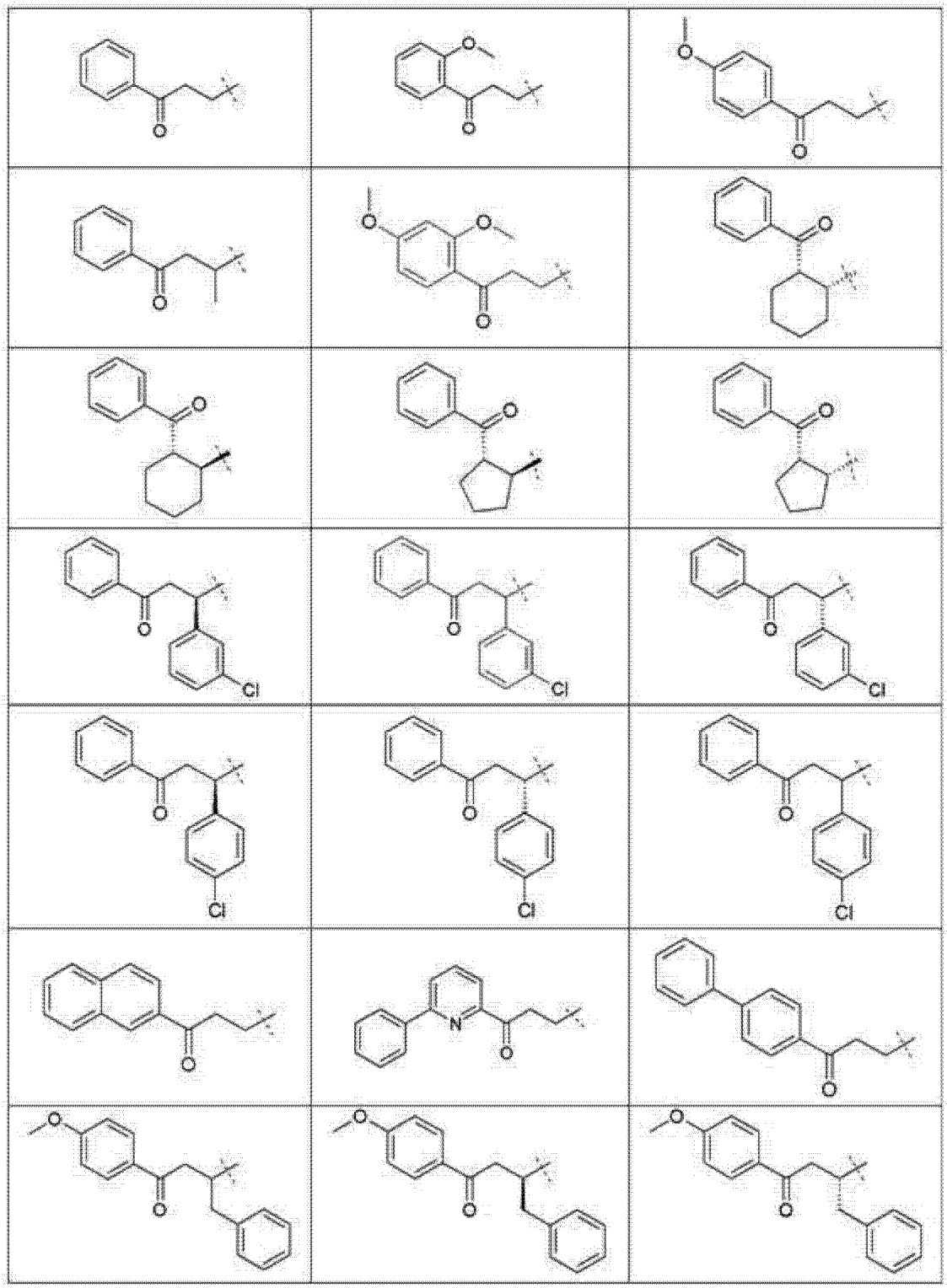
[0021] 在另一个具体的实施方案中，本发明提供式 (I) 和相关式的化合物，其中 L 表示 L1，从而 M 为具有 1-5 个碳原子的线性或分支亚烷基，其中 1 或 2 个 H 原子可被 OR^a 或苯基

替代，所述苯基任选地被 1-5 个独立地选自 Hal、OR^a 及 C_1-C_6 烷基的基团取代，所述 C_1-C_6 烷基任选地被 1-5 个独立地选自 OH 和 Hal 的基团取代。

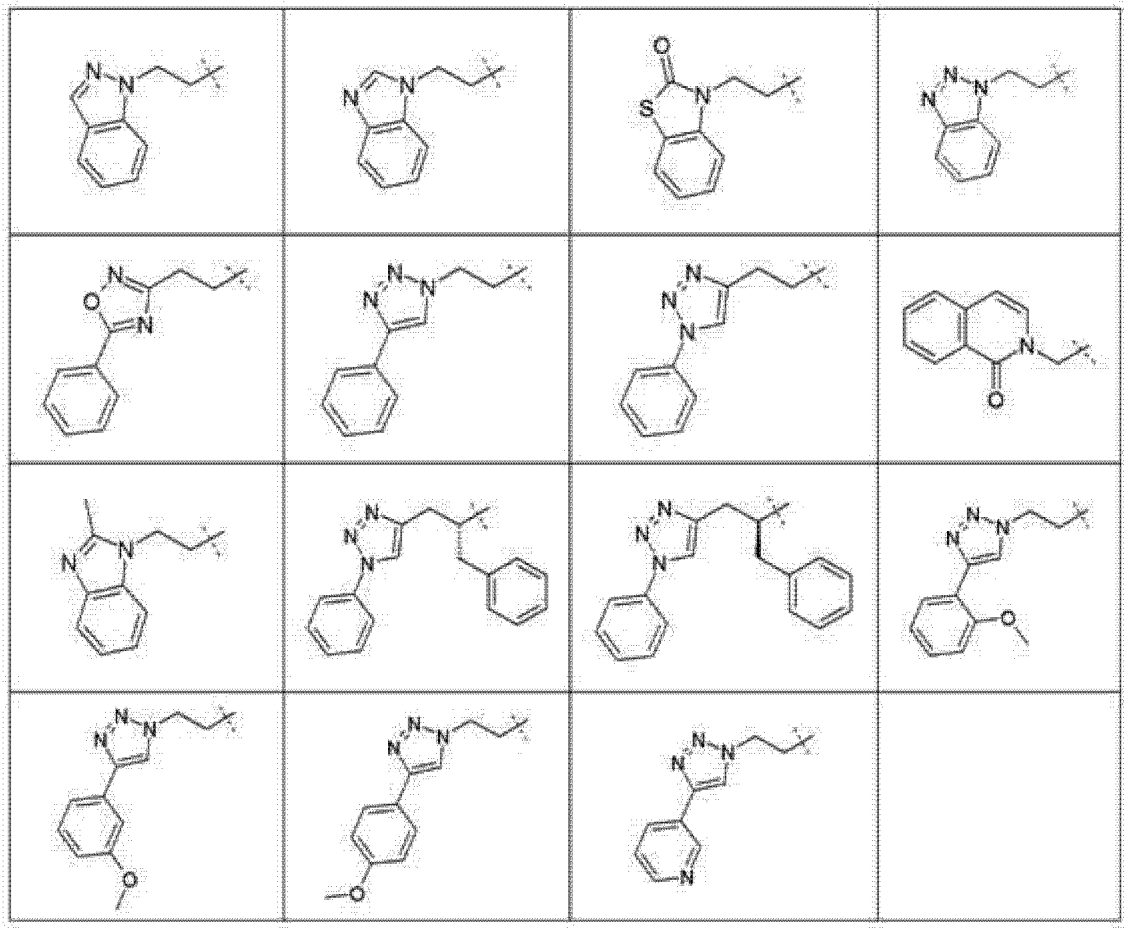
[0022] 在另一个具体的实施方案中，本发明提供式 (I) 和相关式的化合物，其中 L 是 L2，从而 M 表示具有 1-5 个碳原子的线性或分支亚烷基，其中 1 或 2 个 H 原子可被 OR^a 苯基替代，所述苯基任选地被 1-5 个独立地选自 Hal、OR^a 及 C_1-C_6 烷基的基团取代，所述 C_1-C_6 烷基任选地被 1-5 个独立地选自 OH 和 Hal 的基团取代。

[0023] 优选 L2 中的 M 为具有 1-5 个碳原子的未取代的线性亚烷基。

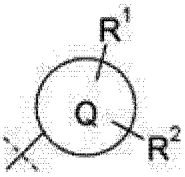
[0024] 在另一个具体的实施方案中，本发明提供式 (I) 和相关式的化合物，其中 L 是 L_1。L_1 优选选自以下基团：



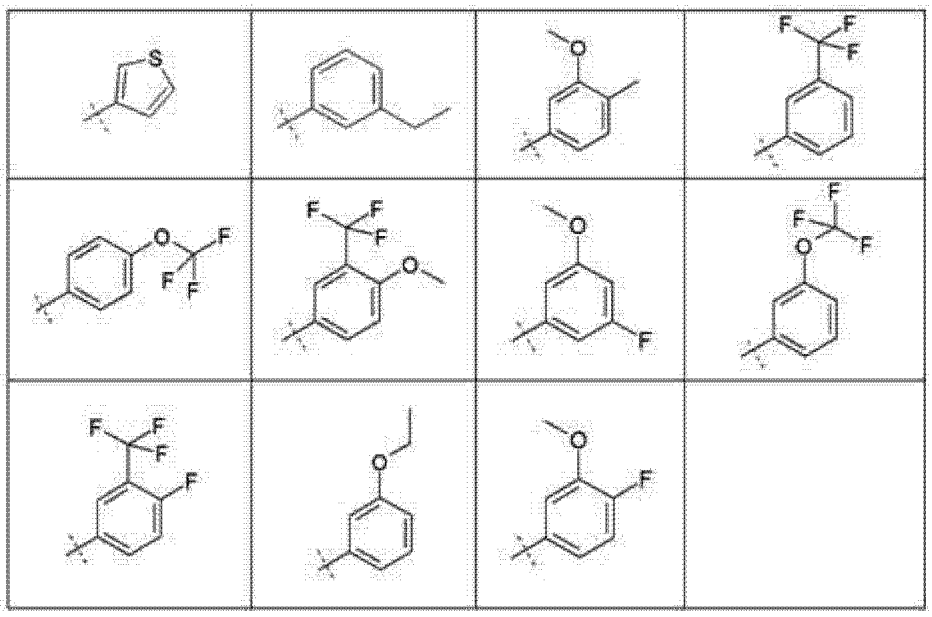
在另一个具体的实施方案中，本发明提供式 (I) 和相关式的化合物，其中 L 是 L_2。L_2 优选选自以下基团：



在另一个具体的实施方案中，本发明提供式 (I) 和相关式的化合物，其中所述基团



选自以下基团：



Ar 可以是未取代的或优选由以下基团一取代、二取代或三取代：Hal、烷基、OR^3、$N(R^3)_2$、

NO_2、CN、$COOR^3$、CF_3、OCF_3、$CON(R^3)_2$、NR^3CO 烷基、$NR^3CON(R^3)_2$、NR^3SO_2 烷基、COR^3、$SO_2N(R^3)_2$、SO 烷基或 SO_2 烷基、苯基、吡啶基、嘧啶基、O- 苯基、O- 吡啶基、O- 嘧啶基、$-[C(R^3)_2]_n-COOR^3$ 和 / 或 $-O[C(R^3)_2]_n-CON(R^3)_2$。

[0025] Ar 表示，例如，萘基、苯基、邻 -、间 - 或对 - 甲苯基、邻 -、间 - 或对 - 乙基苯基、邻 -、间 - 或对 - 丙基苯基、邻 -、间 - 或对 - 异丙基苯基、邻 -、间 - 或对 - 叔丁基苯基、邻 -、间 - 或对 - 羟基苯基、邻 -、间 - 或对 - 硝基苯基、邻 -、间 - 或对 - 氨基苯基、邻 -、间 - 或对 -(N- 甲基氨基）苯基、邻 -、间 - 或对 -(N- 甲基氨基羰基）苯基、邻 -、间 - 或对 - 乙酰氨基 - 苯基、邻 -、间 - 或对 - 甲氧基苯基、邻 -、间 - 或对 - 乙氧基苯基、邻 -、间 - 或对 - 乙氧基羰基 - 苯基、邻 -、间 - 或对 -(N,N- 二甲基氨基）苯基、邻 -、间 - 或对 -(N,N- 二甲基 - 氨基羰基）苯基、邻 -、间 - 或对 -(N- 乙基氨基）苯基、邻 -、间 - 或对 -(N,N- 二乙基氨基）- 苯基、邻 -、间 - 或对 - 氟代苯基、邻 -、间 - 或对 - 溴代苯基、邻 -、间 - 或对 - 氯代苯基、邻 -、间 - 或对 -（甲基磺酰氨基）苯基、邻 -、间 - 或对 -（甲基磺酰基）苯基、邻、间或对氨基 - 硫烷基 - 苯基、邻 -、间 - 或对 - 苯氧基苯基，更优选 2,3-，2,4-，2,5-，2,6-，3,4- 或 3,5- 二甲基苯基，2,3-，2,4-，2,5-，2,6-，3,4- 或 3,5- 二氟苯基，2,3-，2,4-，2,5-，2,6-，3,4- 或 3,5- 二氯苯基，2,3-，2,4-，2,5-，2,6-，3,4- 或 3,5- 二溴苯基，2,4- 或 2,5- 二硝基苯基，2,5- 或 3,4- 二甲氧基苯基，3- 硝基 -4- 氯代苯基，3- 氨基 -4- 氯代 -，2- 氨基 -3- 氯代 -，2- 氨基 -4- 氯代 -，2- 氨基 -5- 氯代 - 或 2- 氨基 -6- 氯代 - 苯基，2- 硝基 -4-N,N- 二甲基氨基 - 或 3- 硝基 -4-N,N- 二甲基氨基苯基，2,3- 二氨基苯基，2,3,4-，2,3,5-，2,3,6-，2,4,6- 或 3,4,5- 三氯苯基，2,4,6- 三甲氧基 - 苯基，2- 羟基 -3,5- 二氯苯基，对 - 碘代苯基，3,6- 二氯 -4- 氨基苯基，4- 氟 -3- 氯代苯基，2- 氟 -4- 溴代苯基，2,5- 二氟 -4- 溴代苯基，3- 溴代 -6- 甲氧基苯基，3- 氯代 -6- 甲氧基苯基，3- 氯代 -4- 乙酰氨基苯基，3- 氟 -4- 甲氧基苯基，3- 氨基 -6- 甲基苯基，3- 氯代 -4- 乙酰氨基苯基或 2,5- 二甲基 -4- 氯代苯基。

[0026] Ar 特别优选地表示，例如，未取代的或由以下基团一取代或二取代的苯基，优选为一取代的苯基 :F、OCH_3、CH_3、CF_3、苯基和 / 或吡啶基，例如，2’- 甲氧基 - 苯基 -、2’- 三氟甲基 - 苯基 -（携带至少一个 2’ 取代基的芳基）、2’- 氯代 - 苯基、2’,6’- 二甲基 - 苯基 - 或 2’- 烷基 - 苯基 -，优选 2’- 甲基 - 苯基。

[0027] Het 为例如，2- 或 3- 呋喃基、苯并呋喃基、2- 或 3- 噻吩基、苯并噻吩基、1-，2- 或 3- 吡咯基、1-，2-，4- 或 5- 咪唑基、1-，3-，4- 或 5- 吡唑基、2-，4- 或 5- 噁唑基、3-，4- 或 5- 异噁唑基、2-，4- 或 5- 噻唑基、3-，4- 或 5- 异噻唑基、2-，3- 或 4- 吡啶基、2-，4-，5- 或 6- 嘧啶基，此外优选 1,2,3- 三唑 -1-，-4- 或 -5- 基、1,2,4- 三唑 -1-，-3- 或 -5- 基、1- 或 5- 四唑基、1,2,3- 噁二唑 -4- 或 -5- 基、1,2,4- 噁二唑 -3- 或 -5- 基、1,3,4- 噻二唑 -2- 或 -5- 基、1,2,4- 噻二唑 -3- 或 -5- 基、1,2,3- 噻二唑 -4- 或 -5- 基、3- 或 4- 哒嗪基、吡嗪基、1-，2-，3-，4-，5-，6- 或 7- 吲哚基、吲唑基、4- 或 5- 异吲哚基、1-，2-，4- 或 5- 苯并咪唑基、1-，3-，4-，5-，6- 或 7- 苯并吡唑基、2-，4-，5-，6- 或 7- 苯并噁唑基、3-，4-，5-，6- 或 7- 苯并异噁唑基、2-，4-，5-，6- 或 7- 苯并噻唑基、2-，4-，5-，6- 或 7- 苯并异噻唑基、4-，5-，6- 或 7- 苯并 -2,1,3- 噁二唑基、2-，3-，4-，5-，6-，7- 或 8- 喹啉基、1-，3-，4-，5-，6-，7- 或 8- 异喹啉基、3-，4-，5-，6-，7- 或 8- 肉啉基、2-，4-，5-，6-，7- 或 8- 喹唑啉基、5- 或 6- 喹喔啉基、2-，3-，5-，6-，7- 或 8-2H- 苯并 -1,4- 噁嗪基，此外优选 1,3- 苯并间二氧杂环戊烯 -5- 基、1,4- 苯并二氧

杂环己烷 -6- 基、2,1,3- 苯并噻二唑 -4- 或 -5- 基或 2,1,3- 苯并噁二唑 -5- 基。

[0028] Het 中的杂环基也可以部分地或完全地被氢化。

[0029] 因此 Het 也可表示，例如，2,3- 二氢 -2-，-3-，-4- 或 -5- 呋喃基、2,5- 二氢 -2-，-3-，-4- 或 -5- 呋喃基、四氢 -2- 或 -3- 呋喃基、1,3- 二氧杂环戊烷 -4- 基、四氢 -2- 或 -3- 噻吩基、2,3- 二氢 -1-，-2-，-3-，-4- 或 -5- 吡咯基、2,5- 二氢 -1-，-2-，-3-，-4- 或 -5- 吡咯基、1-，2- 或 3- 吡咯烷基、四氢 -1-，-2- 或 -4- 咪唑基、2,3- 二氢 -1-，-2-，-3-，-4- 或 -5- 吡唑基、四氢 -1-，-3- 或 -4- 吡唑基、1,4- 二氢 -1-，-2-，-3- 或 -4- 吡啶基、1,2,3,4- 四氢 -1-，-2-，-3-，-4-，-5- 或 -6- 吡啶基、1-，2-，3- 或 4- 哌啶基、2-，3- 或 4- 吗啉基、四氢 -2-，-3- 或 -4- 吡喃基、1,4- 二氧杂环己烷基、1,3- 二氧杂环己烷 -2-，-4- 或 -5- 基、六氢 -1-，-3- 或 -4- 哒嗪基、六氢 -1-，-2-，-4- 或 -5- 嘧啶基、1-，2- 或 3- 哌嗪基、1,2,3,4- 四氢 -1-，-2-，-3-，-4-，-5-，-6-，-7- 或 -8- 喹啉基、1,2,3,4- 四氢 -1-，-2-，-3-，-4-，-5-，-6-，-7- 或 -8- 异喹啉基、2-，3-，5-，6-，7- 或 8-3,4- 二氢 -2H- 苯并 -1,4- 噁嗪基，此外优选 2,3- 亚甲基二氧基苯基、3,4- 亚甲基二氧基苯基、2,3- 亚乙基二氧基苯基、3,4- 亚乙基二氧基苯基、3,4-(二氟 - 亚甲基二氧基) 苯基、2,3- 二氢苯并呋喃 -5- 或 -6- 基、2,3-(2- 氧代亚甲基二氧基)- 苯基或还表示 3,4- 二氢 -2H-1,5- 苯并二氧杂环庚烯 -6- 或 -7- 基，此外优选 2,3- 二氢苯并呋喃基或 2,3- 二氢 -2- 氧代呋喃基。

[0030] Het 可以是未取代的或由以下基团一取代、二取代或三取代 :Hal、烷基、$-[C(R^3)_2]_n-Ar$、$-[C(R^3)_2]_n-$ 环烷基、OR^3、CF_3、OCF_3、$N(R^3)_2$、$NR^3CON(R^3)_2$、NO_2、CN、$-[C(R^3)_2]_n-COOR^3$、$-[C(R^3)_2]_n-CON(R^3)_2$、NR^3CO 烷基、NR^3SO_2 烷基、COR^3、$SO_2N(R^3)_2$、SO 烷基、O- 苯基、O- 吡啶基、O- 嘧啶基、苯基、吡啶基和 / 或 SO_2 烷基。

[0031] 烷基为未分支 (线性) 或分支的，并具有 1、2、3、4、5、6、7、8、9、10、11 或 12 个碳原子。烷基优选地表示甲基，此外表示乙基、丙基、异丙基、丁基、异丁基、仲丁基或叔丁基，此外还表示戊基、1-，2- 或 3- 甲基丁基、1,1-，1,2- 或 2,2- 二甲基丙基、1- 乙基丙基、己基、1-，2-，3- 或 4- 甲基戊基、1,1-，1,2-，1,3-，2,2-，2,3- 或 3,3- 二甲基丁基、1- 或 2- 乙基丁基、1- 乙基 -1- 甲基丙基、1- 乙基 -2- 甲基丙基、1,1,2- 或 1,2,2- 三甲基丙基，此外优选表示，例如，三氟甲基。

[0032] 烷基非常特别优选地表示具有 1，2，3，4，5 或 6 个碳原子的烷基，优选甲基、乙基、丙基、异丙基、丁基、异丁基、仲丁基、叔丁基、戊基、己基、三氟甲基、五氟乙基、1,1,1- 三氟乙基。在一个优选的实施方案中，烷基为全氟代的。

[0033] 环烷基优选地表示环丙基、环丁基、环戊基、环己基或环庚基。环烷基可优选地被烷基、OH、O- 烷基、Hal 取代。

[0034] 在另一个具体的实施方案中，本发明的化合物选自以下基团 :

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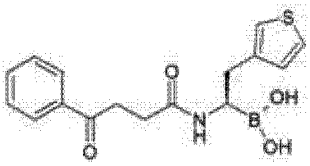
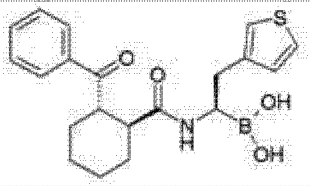
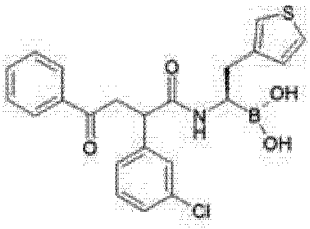
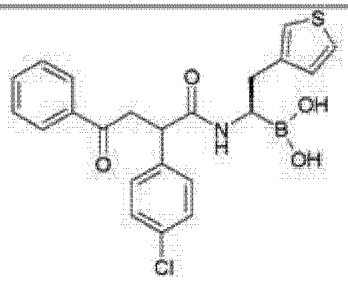
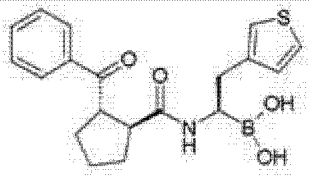
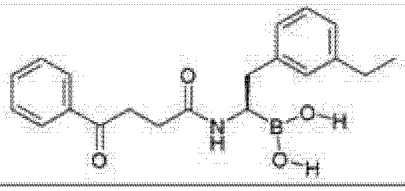
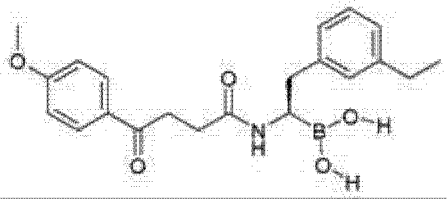
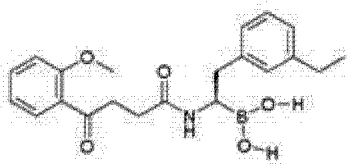
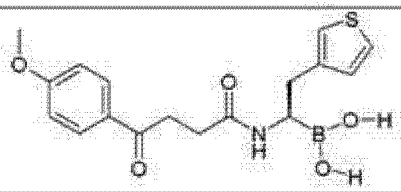
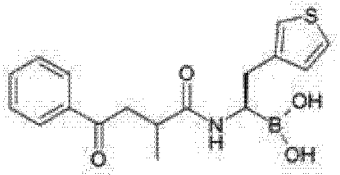
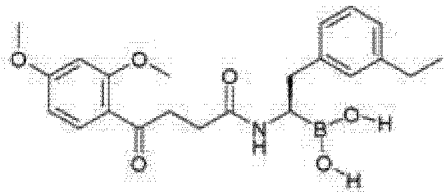
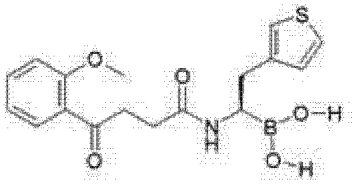
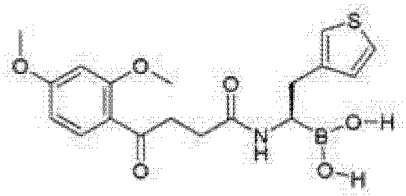
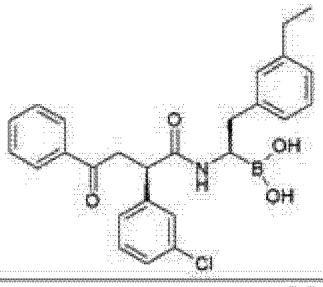
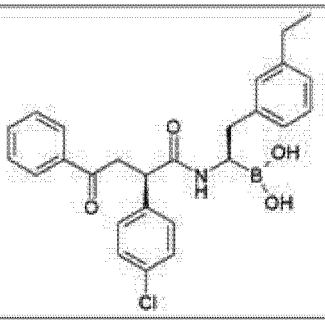
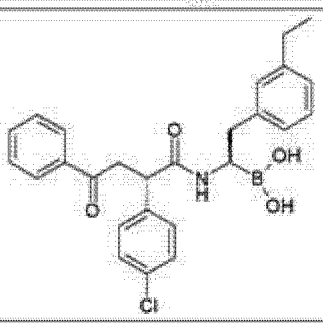
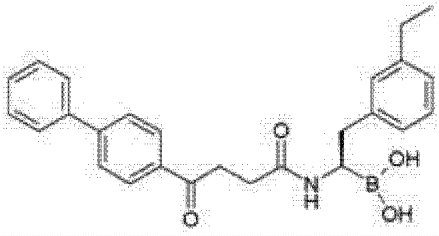
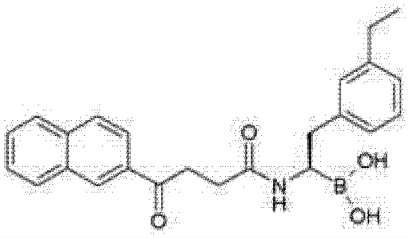
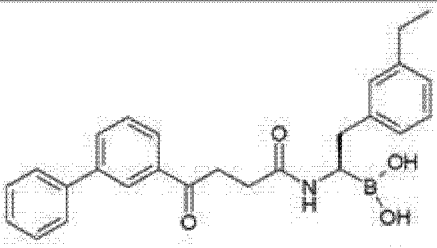
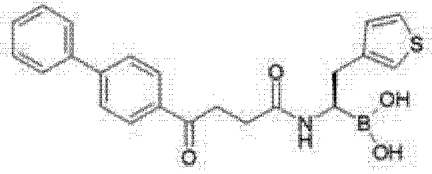
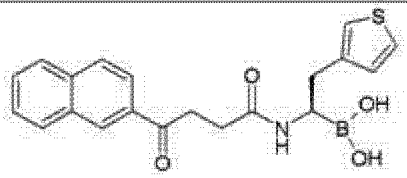
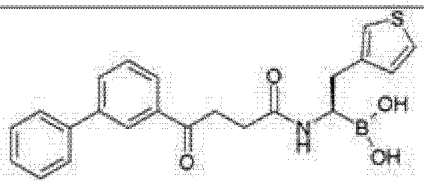
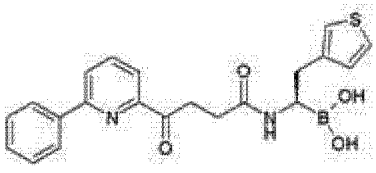
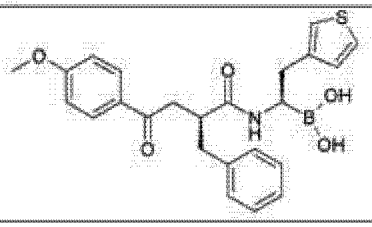
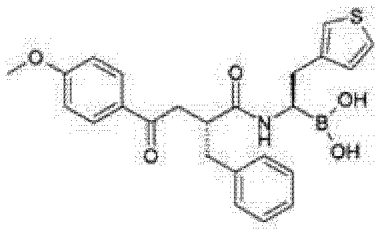
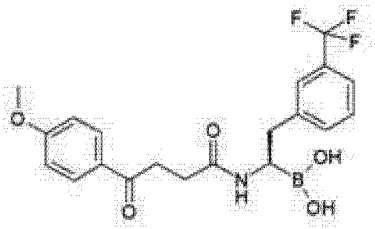
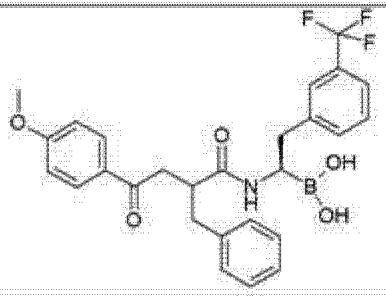
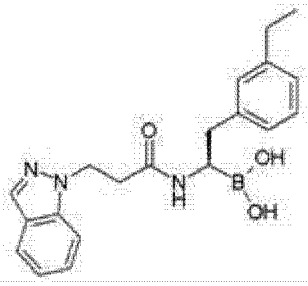
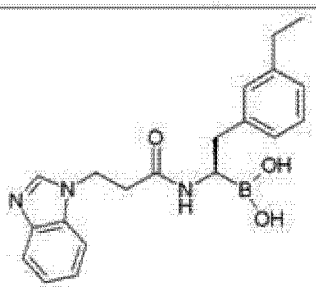
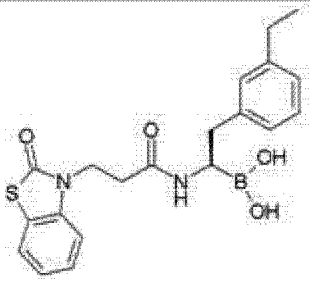
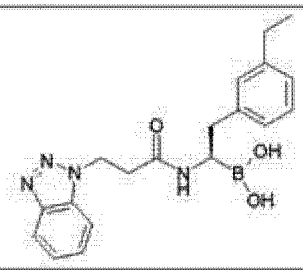
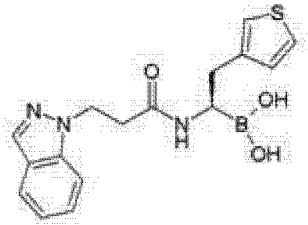
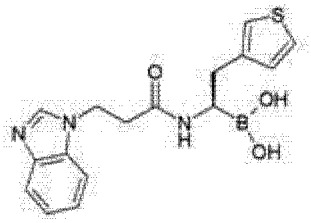
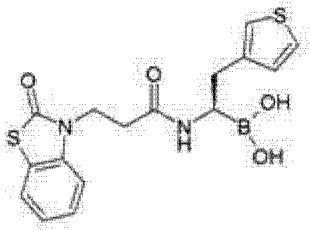
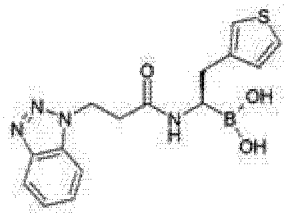
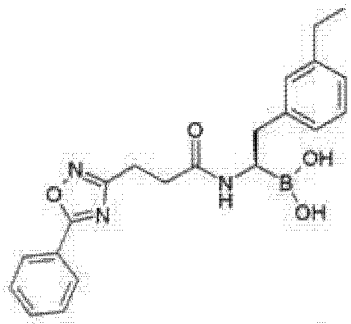
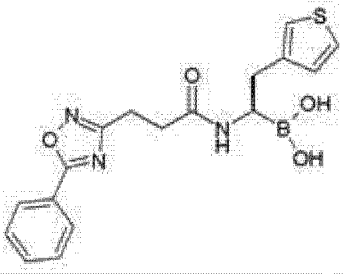
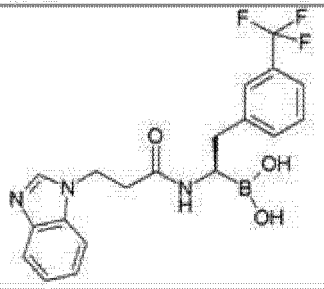
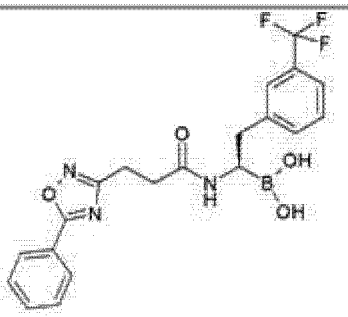
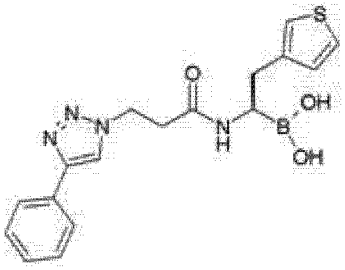
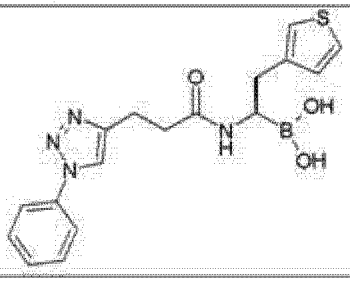
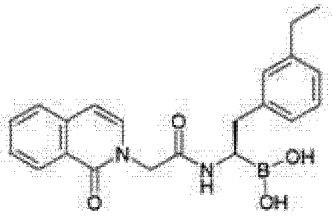
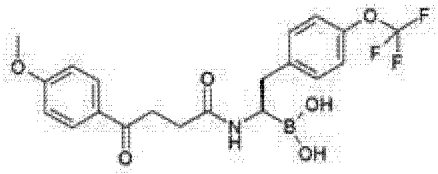
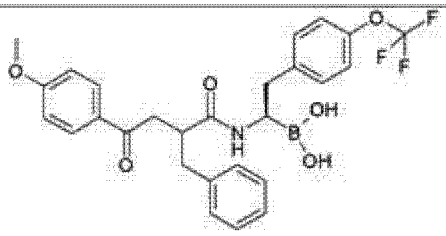
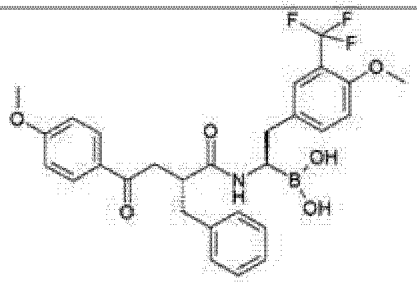
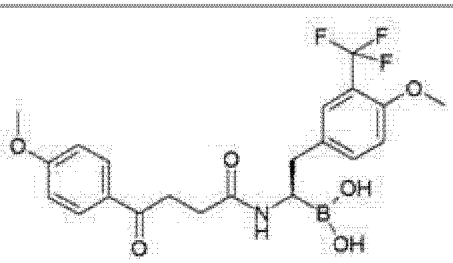
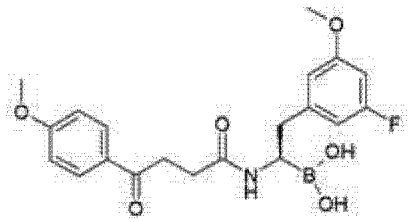
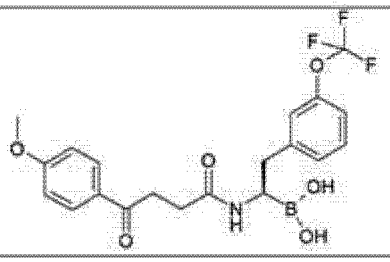
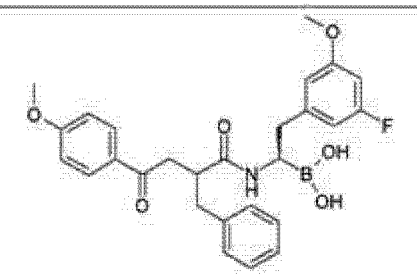
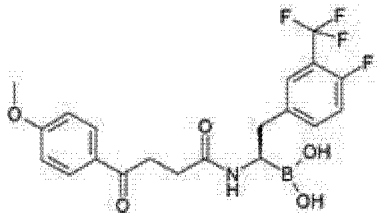
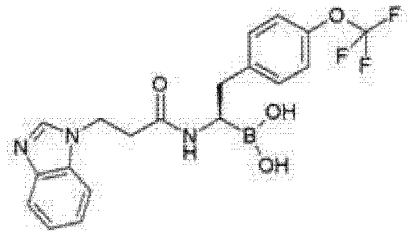
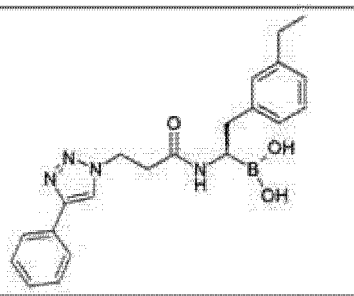
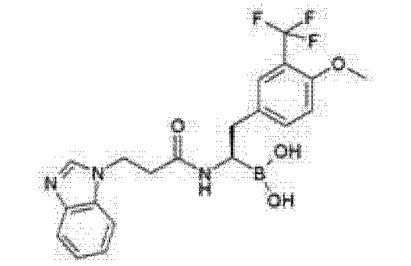
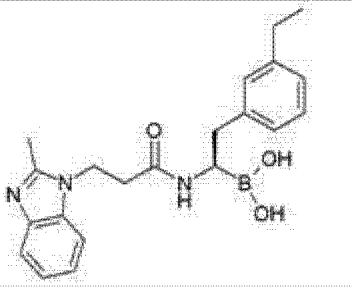
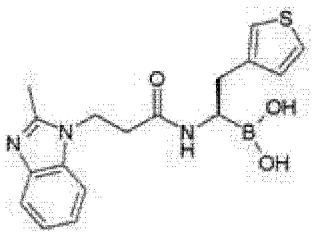
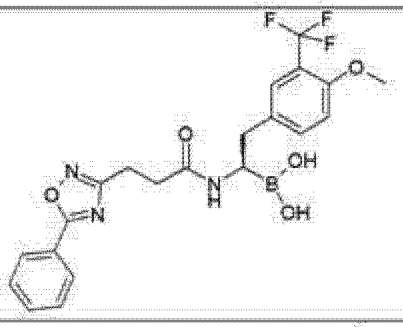
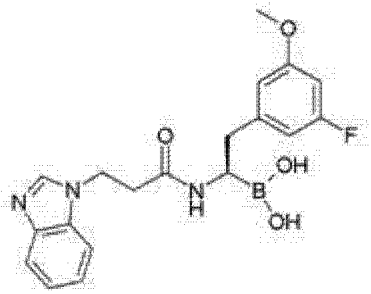
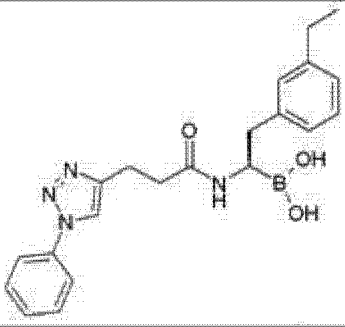
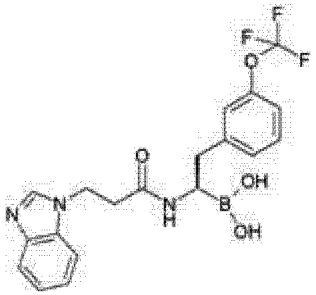
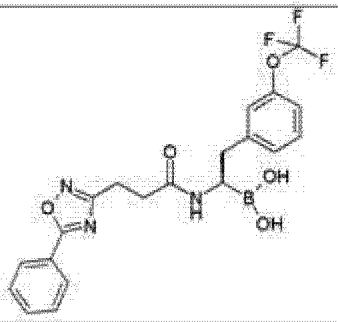
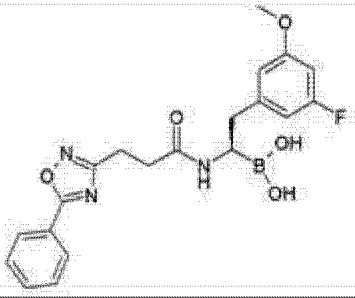
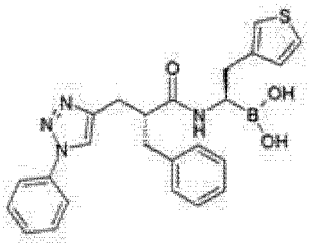
1		2	
3		4	
5		6	
7		8	
9		10	
11		12	

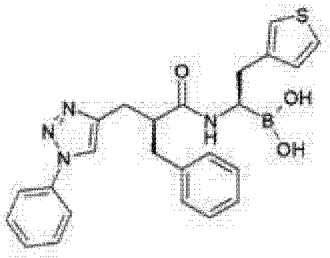
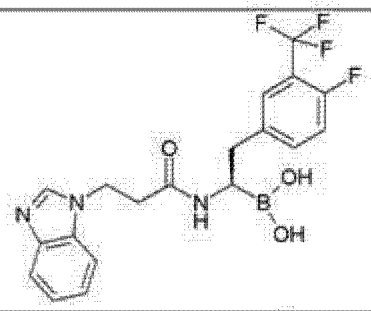
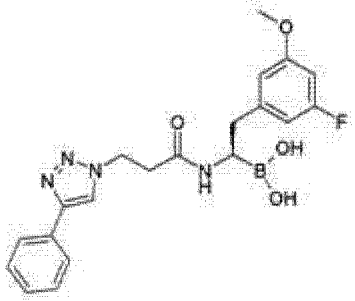
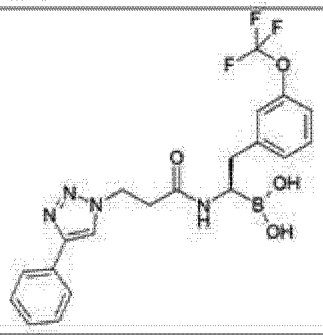
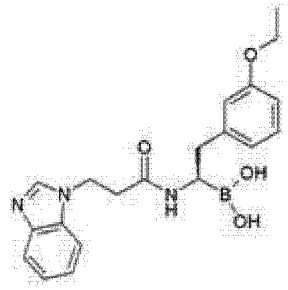
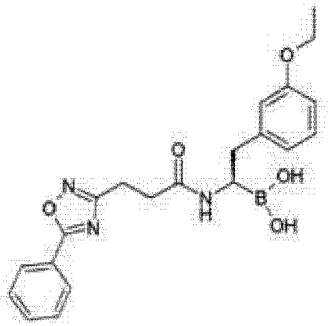
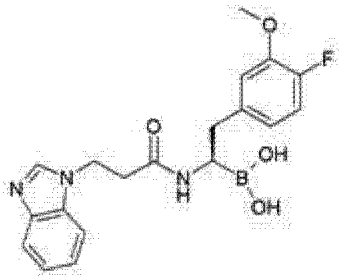
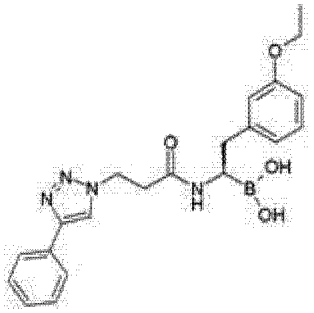
13		14	
15		16	
17		18	
19		20	
21		22	
23		24	

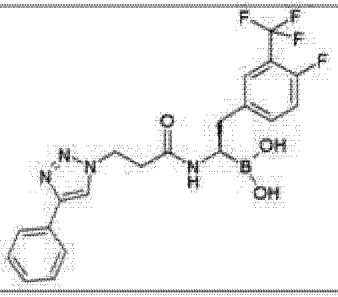
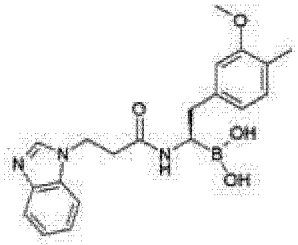
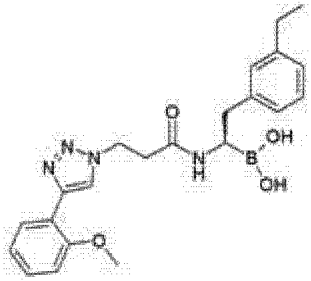
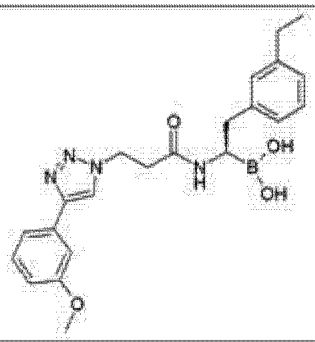
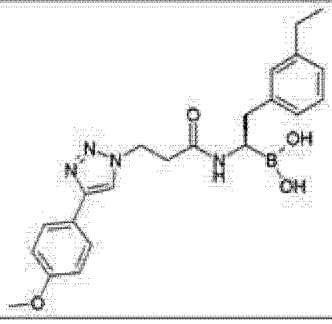
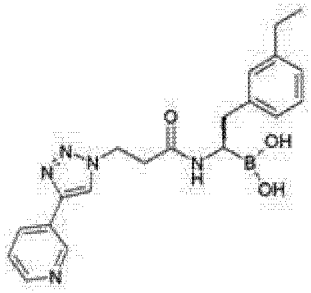
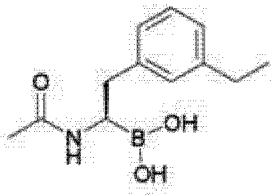
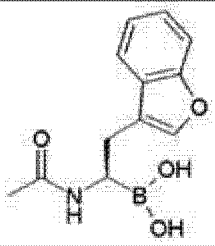
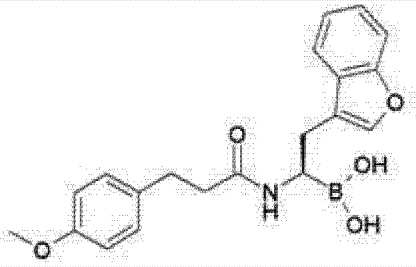
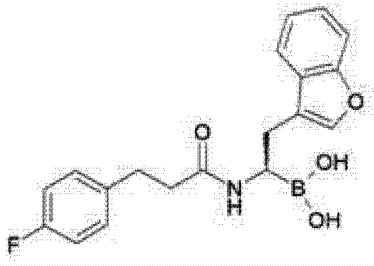
25		26	
27		28	
29		30	
31		32	
33		34	

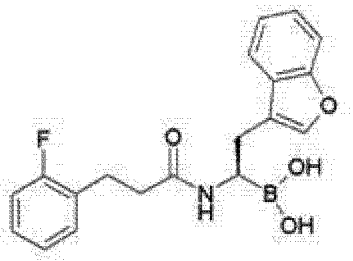
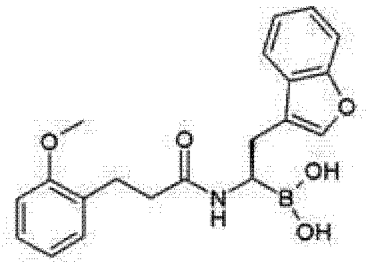
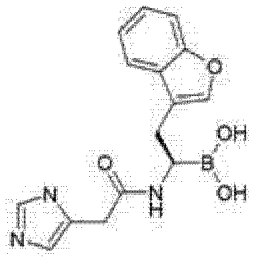
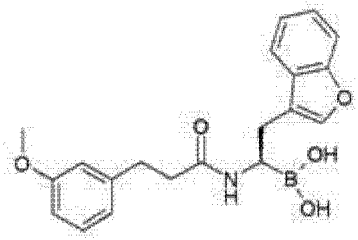
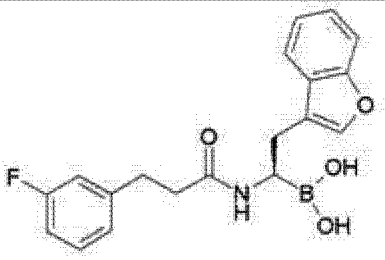
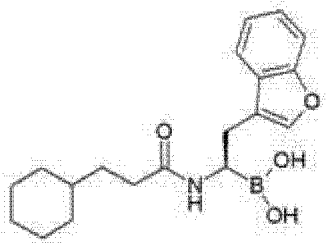
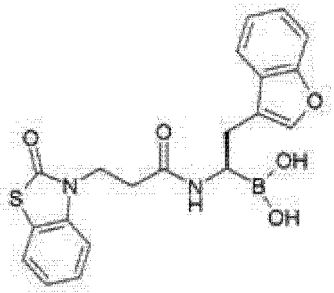
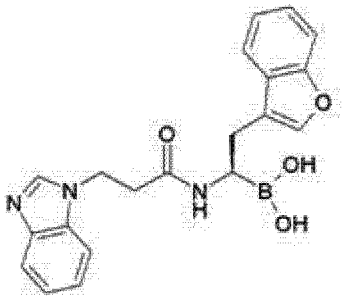
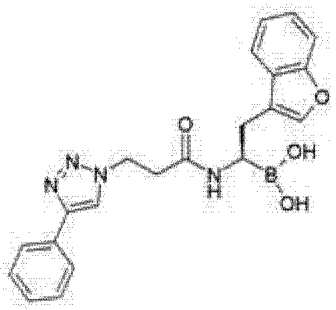
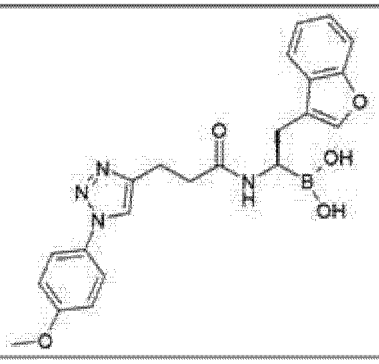
35		36	
37		38	
39		40	
41		42	
43		44	

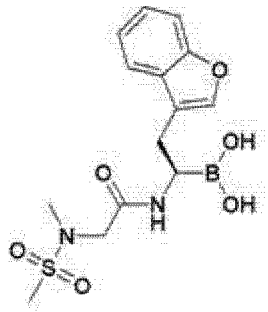
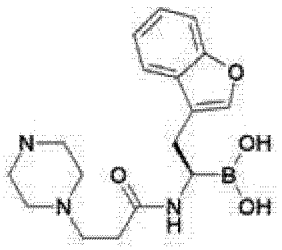
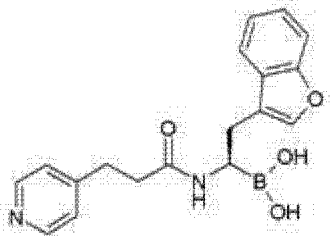
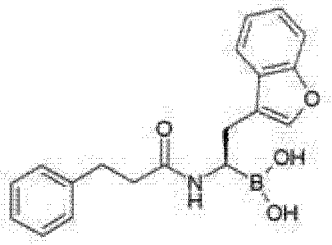
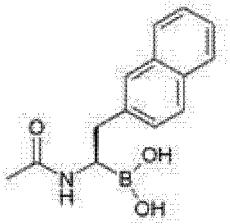
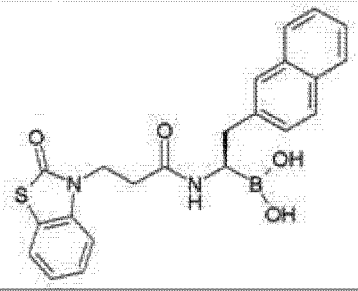
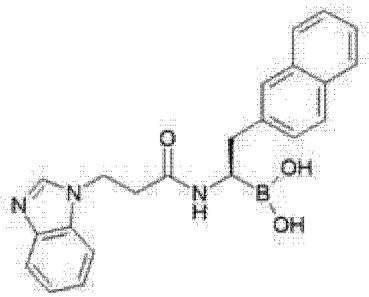
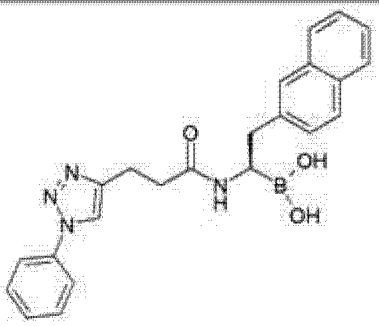
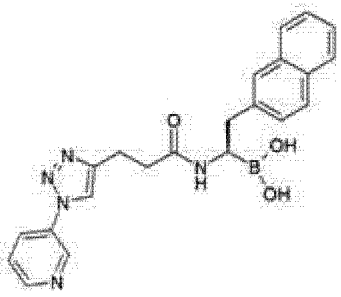
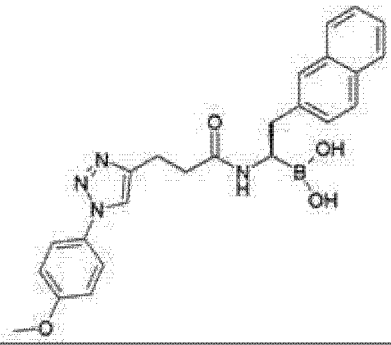
45		46	
47		48	
49		50	
51		52	
53		54	

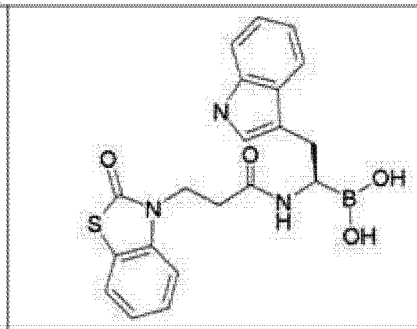
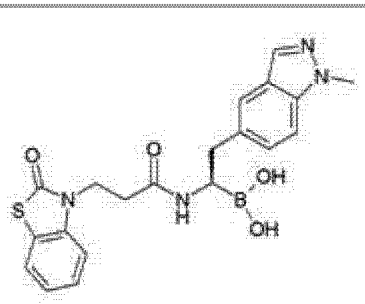
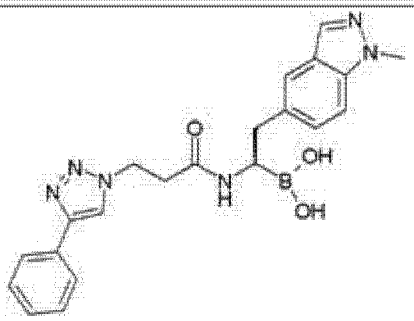
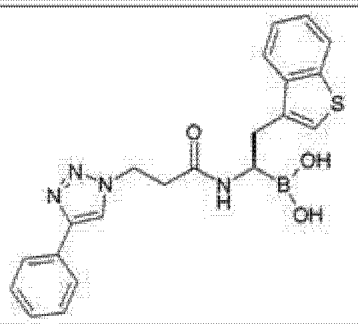
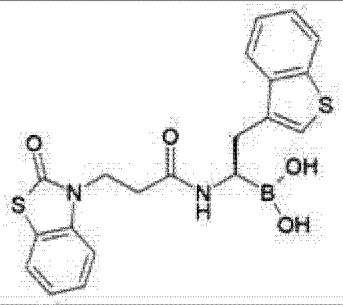
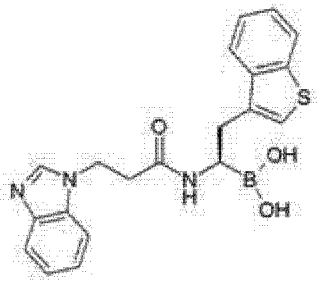
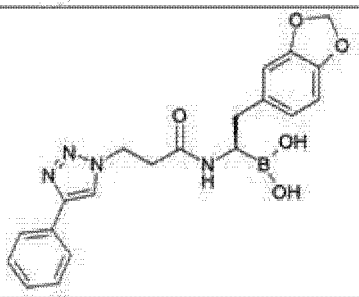
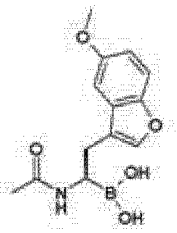
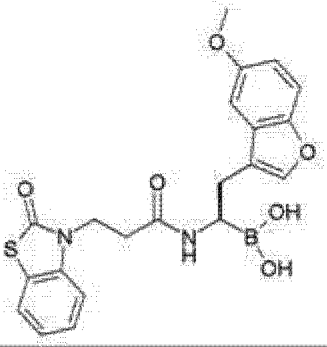
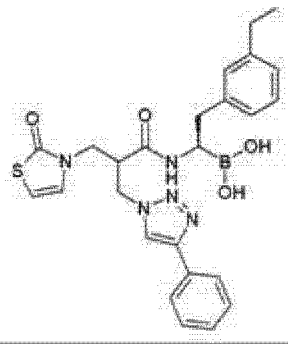
55		56	
57		58	
59		60	
61		62	

63		64	
65		66	
67		68	
69		70	

71		72	
73		74	
75		76	
77		78	
79		80	

81		82	
83		84	
85		86	
87		88	
89		90	

91		92	
93		94	
95		96	
97		98	
99		100	

101		102	
103		104	
105		106	
107		108	
109		110	

下文缩写指以下所用的缩写：

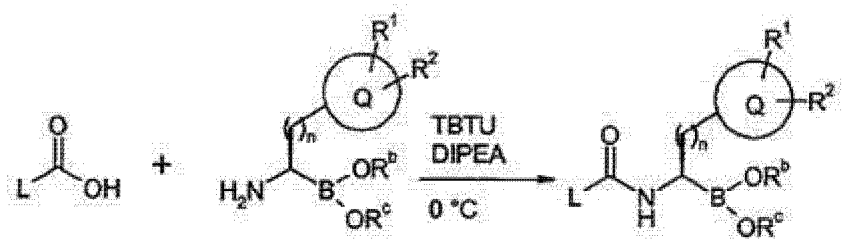
AcOH（乙酸）、BINAP（2,2'-双（二苯基膦基）-1,1-联二萘）、dba（二亚苄基丙酮）、tBu（叔丁基）、tBuOK（叔丁醇钾）、CDI（1,1'-羰基二咪唑）、DBU（1,8-氮杂双环[5.4.0]十一碳-7-烯）、DCC（二环已基碳二亚胺）、DCM（二氯甲烷）、DIAD（偶氮二羧酸二异丁酯）、DIC（二异丙基碳二亚胺(diisopropilcarbodiimide)）、DIEA（二异丙基乙胺）、

DMA（二甲基乙酰胺）、DMAP（4-二甲基氨基吡啶）、DMSO（二甲基亚砜）、DMF（N,N-二甲基甲酰胺）、EDC.HCl（1-乙基-3-(3-二甲基氨基丙基）碳二亚胺盐酸盐）、EtOAc（乙酸乙酯）、EtOH（乙醇）、g（克）、cHex（环己烷）、HATU（二甲基氨基-([1,2,3]三唑并[4,5-b]吡啶-3-基氧基)-亚甲基]-二甲基-铵六氟磷酸盐）、HOBt（N-羟基苯并三唑）、HPLC（高效液相层析）、hr（小时）、MHz（兆赫）、MeOH（甲醇）、min（分钟）、mL（毫升）、mmol（毫摩尔）、mM（毫摩尔浓度）、mp（熔点）、MS（质谱法）、MW（微波）、NMM(N-甲基吗啉）、NMR（核磁共振）、NBS（N-溴代琥珀酰亚胺）、PBS（磷酸盐缓冲盐水）、PMB（对-甲氧基苄基）、PyBOP（苯并三唑-1-基-氧基三吡咯烷基鏻六氟磷酸盐）、RT（室温）、TBAF（氟化四丁基铵）、TBTU（N,N,N',N'-四甲基-O-(苯并三唑-1-基）脲鎓四氟硼酸盐）、T3P（丙烷膦酸酐）、TEA（三乙胺）、TFA（三氟乙酸）、THF（四氢呋喃）、PetEther（石油醚）、TBME（叔丁基甲基醚）、TLC（薄层层析）、TMS（三甲基甲硅烷基）、TMSI（三甲基甲硅烷基碘化物）、UV（紫外线）。

[0035] 一般地，式(I)化合物，其中R^1、n、R^b、R^c、L和Q如上所定义，可从如在流程1中概述的式(II)化合物获得。

[0036] 第一步包括式(II)化合物（其中L如上所定义）与式(III)化合物（其中R^1、n、R^a、R^b、R^c和Q如上所定义）的反应。采用本领域技术人员熟知的用于由羧酸与标准偶联剂（例如但不限于HATU、TBTU、聚合物担载的1-烷基-2-氯代吡啶鎓盐（聚合物担载的Mukaiyama试剂）、1-甲基-2-氯代吡啶鎓碘化物(Mukaiyama试剂）、碳二亚胺（例如DCC、DIC、EDC)和HOBt，PyBOP®和本领域技术人员熟知的其它的此类试剂，优选TBTU)制备酰胺的条件和方法，在碱（例如TEA、DIEA、NMM、聚合物担载的吗啉（优选DIEA））存在或不存在下，在合适的溶剂例如DCM、THF或DMF中，在-10℃至50℃之间的温度下，优选在0℃，进行该反应数小时，例如1小时-24小时。作为选择，通过本领域技术人员熟知的方法，例如但不限于用$SOCl_2$、$POCl_3$、PCl_5、$(COCl)_2$在催化量的DMF存在或不存在下，在合适的溶剂例如甲苯、DCM、THF存在或不存在下，在从20℃上升至100℃的温度下，优选地在50℃，处理数小时，例如1小时-24小时，可将式(II)化合物转化为羧酸衍生物例如酰基卤化物或酐。采用本领域技术人员熟知的用于由羧酸衍生物（例如酰氯）与烷基胺制备酰胺的条件和方法，在碱例如TEA、DIEA、NMM的存在下，在合适的溶剂例如DCM、THF或DMF中，在从20℃上升至100℃的温度下，优选地在50℃，进行数小时，例如1小时-24小时，可实现羧酸衍生物向式(I)化合物的转化。

[0037] 流程1

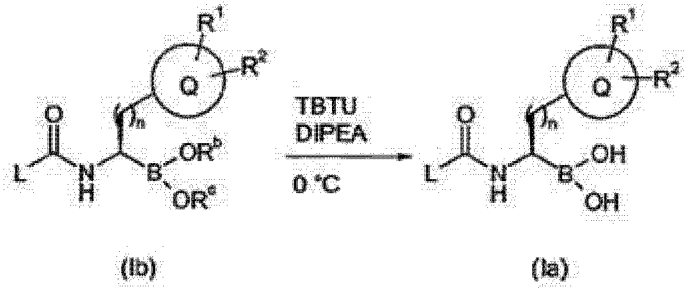


(II) (III) (I)

式(Ia)化合物，其中R^1、n、L和Q如上所定义，其中R^b和R^c是H，可由式(Ib)化合物起始制备，其中R^1、n、L和Q如上所定义，其中R^b和R^c是C_1-C_6烷基；从而采用本领域技术人

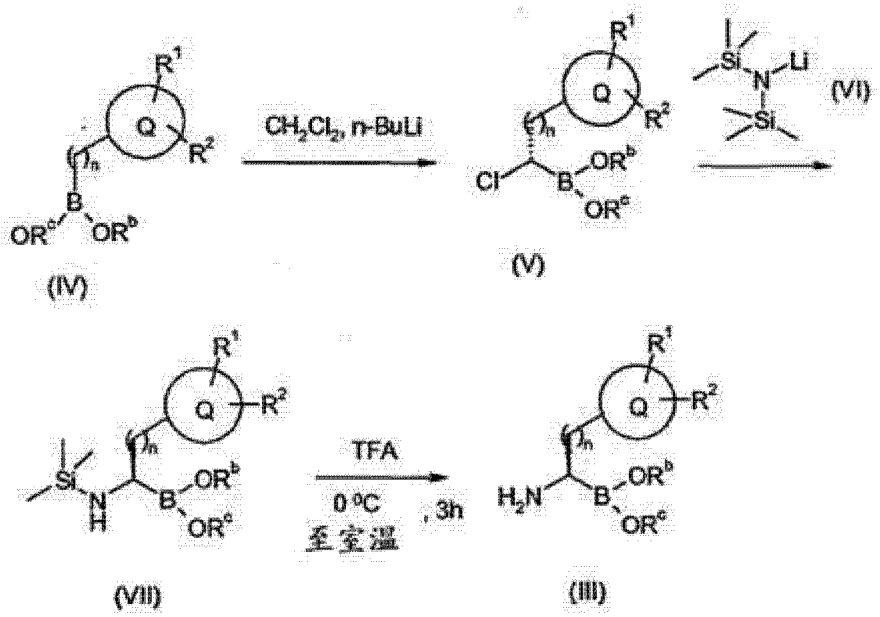
员熟知的用于水解硼酸酯的方法，例如但不限于用 HCl、HBr、HI、TFA 在过量的小分子量硼酸(例如但不限于 i-BuB(OH)$_2$)存在或不存在下处理，R^b 和 R^c 可连接形成含氧原子的 5 或 6 元环，所述氧原子与 R^b 和 R^c 键合（流程 2）。

[0038] 流程 2



式 (III) 化合物可如在流程 3 中概述的制备。

[0039] 流程 3



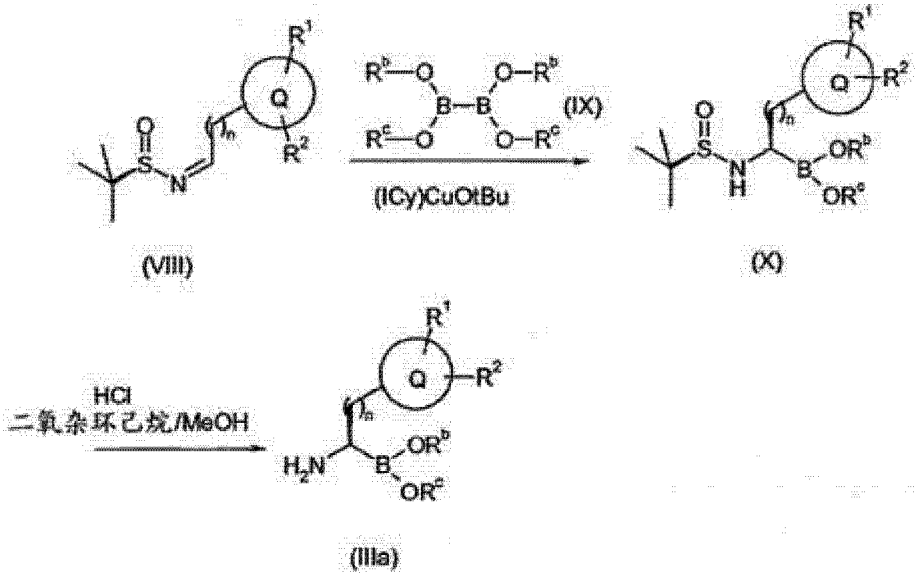
式 (IV) 化合物（其中 R^1、n、R^b、R^c 和 Q 如上所定义，附带条件是 R^b、R^c 不表示 H) 的转化得到式 (V) 化合物（其中 R^1、n、R^b、R^c 和 Q 如上所定义，附带条件是 R^b、R^c 不表示 H) 可通过用 DCM 在强碱例如 nBuLi、tBuLi、MeLi、LDA、LiHMDS（优选 nBuLi）的存在下，在合适的溶剂例如 THF 或二氧杂环己烷(优选 THF）中，在从 -100℃上至室温的温度下处理数小时，例如 1 小时 -24 小时来实现。当适当地选择 R^b 和 R^c 时，反应可产生对映体富集的产物。例如，当 R^b 和 R^c 一起表示 (1S, 2S, 3R, 5S)-(+)- 蒎烷二醇时，优先形成具有 (S) 构型的产物 (Matteson, D. S. ;Sadhu, K. M. J. Am. Chem. Soc. 1981, 103, 5241-5242)。

[0040] 式 (V) 化合物（其中 R^1、n、R^b、R^c、L 和 Q 如上所定义，附带条件是 R^b, R^c 不表示 H) 得到式 (VII) 化合物（其中 R^1、n、R^b、R^c 和 Q 如上所定义，附带条件是 R^b、R^c 不表示 H) 的转化可通过与式 (VI) 化合物在合适的溶剂例如 THF 或二氧杂环己烷，优选在 THF 中，在从 -100℃上升至室温的温度下反应数小时，例如 1 小时 -24 小时来实现。反应通常伴随构型反转而进行，从而如果式 (V) 化合物具有 (S) 构型，则将获得具有 (R) 构型的式 (VII) 化合物 (Matteson, D. S. ;Sadhu, K. M. J. Am. Chem. Soc. 1981, 103, 5241-5242)。

[0041] 最后，式 (VII) 化合物向式 (II) 化合物的转化可通过用合适的酸，例如 HCl 或 TFA，优选 TFA，在合适的溶剂例如 DCM、二二乙醚、二异丙基醚或 THF，优选二二乙醚中，在 -30℃至 30℃之间的温度下，优选地在 -10℃处理数小时，例如 1 小时 -48 小时来实现。

[0042] 作为选择，式 (IIIa) 化合物，其中 R^1、n、R^b、R^c 和 Q 如上所定义和 R^a 表示 H，可如在流程 4 中概述的制备。

[0043] 流程 4



式 (VIII) 化合物（其中 R^1 和 Q 如上所定义）可通过与式 (IX) 化合物（其中 R^b 和 R^c 如上所定义）在合适的催化剂（例如但不限于 (1,3- 二环己基咪唑 -2- 亚基）叔丁醇铜 (I) ((ICy)CuOtBu) 的存在下，在合适的溶剂例如苯、甲苯、二氧杂环己烷、THF 中，在室温和 80℃之间的温度下反应数小时，例如 1 小时 -48 小时，转化为式 (X) 化合物，其中 R^1、n、R^b、R^c 和 Q 如上所定义。

[0044] 可采用酸像 HCl 或 TFA，优选 HCl，在合适的溶剂例如 DCM、二二乙醚、二异丙基醚、THF、二氧杂环己烷或甲醇，优选二氧杂环己烷和甲醇的混合物中，在 -10℃至 40℃之间的温度下，优选在室温进行数小时，例如 1 小时 -48 小时，使式 (X) 化合物去保护，得到式 (IIIa) 化合物。

[0045] 如果上述组的通用合成方法不适用于获得依据式 (I) 的化合物和 / 或用于合成式 (I) 化合物的必需中间体，则应采用本领域技术人员已知的合适的制备方法。

[0046] 一般来说，任何单独的式 (I) 化合物的合成途径将取决于各个分子的特定取代基和取决于必需的中间体的现成的可获得性；以及本领域普通技术人员认识到的此类因素。对于所有的保护和去保护方法，参见 Philip J. Kocienski, 于 "Protecting Groups（保护基团）", Georg Thieme Verlag Stuttgart, New York, 1994 和，Theodora W. Greene 和 Peter G. M. Wuts 于 "Protective Groups in Organic Synthesis（有机合成中的保护基团）", Wiley Interscience, 第 3 版 1999。

[0047] 本发明的化合物可通过从适宜溶剂蒸发的结晶，与溶剂分子缔合地分离。式 (I) 化合物的药学上可接受的酸加成盐，其包括碱性中心，可以常规的方式制备。例如，游离碱的溶液可用合适的酸（纯的或者在合适的溶液中）处理，并且通过过滤或通过在真空下蒸发反应溶剂分离得到的盐。药学上可接受的碱加成盐可以类似的方式，通过用合适的碱处理

包含酸性中心的式 (I) 化合物的溶液而获得。两种类型的盐可采用离子交换树脂技术形成或互换。

[0048] 取决于所用的条件，反应时间通常在数分钟和 14 天之间，且反应温度在约 -30℃和 140℃之间，通常在 -10℃和 90℃之间，特别是在约 0℃和约 70℃之间。

[0049] 此外，式 (I) 化合物可通过用溶剂分解剂或氢解剂处理，由其功能性衍生物之一释出式 (I) 化合物而获得。

[0050] 用于溶剂分解或氢解的优选的起始原料为符合式 (I) 的那些原料，但包含相应的受保护的氨基和 / 或羟基而非一个或多个游离的氨基和 / 或羟基，优选携带氨基 - 保护基团而非结合于 N 原子的 H 原子的那些原料，特别是携带 R'-N 基团(其中 R' 表示氨基 - 保护基团) 而不是 HN 基团的那些原料，和 / 或携带羟基 - 保护基团而不是羟基的 H 原子的那些原料，例如符合式 (I) 的那些原料，但携带 -COOR" 基团，其中 R" 表示羟基保护基团，而不是 -COOH 基团。

[0051] 多个相同的或不同的受保护氨基和 / 或羟基存在于起始原料的分子中也是可能的。如果存在的保护基团彼此不同，则在许多情况下可选择性地使它们解离。

[0052] 术语 " 氨基 - 保护基团 " 在通用术语中为已知的并涉及适用于保护 (封闭) 氨基免受化学反应的基团，但在所需的化学反应已在分子别处进行后可容易地将其除去。典型的此类基团特别是，未取代或取代的酰基、芳基、芳烷氧基甲基或芳烷基。因为氨基 - 保护基团在所需反应 (或反应序列) 后除去，它们的类型和大小不是特别至关重要的 ；然而，优选具有 1-20，特别是 1-8 个碳原子的那些保护基团。术语 " 酰基 " 在广义上应与本方法联系起来理解。其包括衍生自脂族、芳脂族、芳族或杂环羧酸或磺酸的酰基，且特别是烷氧基 - 羰基、芳基氧基羰基和尤其是芳烷氧基羰基。此类酰基的实例是烷酰基，例如乙酰基、丙酰基和丁酰基 ；芳烷酰基，例如苯基乙酰基 ；芳酰基，例如苯甲酰基和甲苯基 ；芳基氧基烷酰基，例如 POA ；烷氧基羰基、例如甲氧基 - 羰基、乙氧基羰基、2,2,2- 三氯乙氧基羰基、BOC (叔丁氧基 - 羰基) 和 2- 碘代乙氧基羰基 ；芳烷氧基羰基，例如 CBZ (" 苄氧羰基 (carbo-benz-oxy)")、4- 甲氧基苄基氧基羰基和 FMOC ；和芳基 - 磺酰基、例如 Mtr。优选的氨基 - 保护基团是 BOC 和 Mtr，此外还有 CBZ、Fmoc、苄基和乙酰基。

[0053] 术语 " 羟基 - 保护基团 " 同样在通用术语中是已知的并涉及适用于保护羟基免受化学反应，但在所需的化学反应已在分子别处进行后可容易地除去的基团。典型的此类基团为上述未取代或取代的芳基、芳烷基或酰基，进一步为烷基。羟基 - 保护基团的性质和大小不是至关重要的，因为它们在所需化学反应或反应序列后同样被除去 ；优选具有 1-20，特别是 1-10 个碳原子的基团。羟基 - 保护基团的实例尤其是苄基、4- 甲氧基苄基、对 - 硝基 - 苯甲酰基、对 - 甲苯磺酰基、叔丁基和乙酰基，其中苄基和叔丁基是特别优选的。

[0054] 采用术语 " 化合物的溶剂合物 " 指惰性溶剂分子加合到由于它们的相互吸引力而形成的化合物中。溶剂合物是例如单水合物或二水合物或醇合物。

[0055] 式 (I) 化合物从它们的官能衍生物中释出 - 取决于所用的保护基团 - 例如采用强酸，有利地采用 TFA 或高氯酸，但也采用其它强无机酸，例如盐酸或硫酸，强有机羧酸，例如三氯乙酸，或磺酸，例如苯磺酸或对 - 甲苯磺酸。存在另外的惰性溶剂是可能的，但不总是必要的。合适的惰性溶剂优选地为有机的，例如羧酸，例如乙酸 ；醚，例如 THF 或二氧杂环己烷 ；酰胺，例如 DMF ；卤代烃，例如 DCM ；此外还有醇，例如甲醇、乙醇或异丙醇，和水。此外，

上述溶剂的混合物也是合适的。TFA 优选地以过量所用，而不加入更多的溶剂，且高氯酸优选地以乙酸和 70% 高氯酸的比例 9:1 的混合物的形式使用。用于分解的反应温度有利地在约 0 和约 50℃之间，优选地在 15 和 30℃之间 (RT)。

[0056] BOC、OBut 和 Mtr 基团可，例如，优选地采用在 DCM 中的 TFA 或采用在二氧杂环己烷中约 3-5N HCl 在 15-30℃下分解，且 FMOC 基团可采用二甲胺、二乙胺或哌啶在 DMF 中的约 5-50% 溶液在 15-30℃下解离。

[0057] 可氢解除去的保护基团（例如 CBZ、苄基或从其噁二唑衍生物中释出脒基）可例如通过在催化剂（例如贵金属催化剂，例如钯，有利地在载体例如碳上）的存在下，用氢处理而解离。本文的合适的溶剂为上文指出的那些溶剂，特别是，例如醇，例如甲醇或乙醇，或酰胺，例如 DMF。氢解通常在约 0 和 100℃之间的温度下和在约 1 和 200 巴之间的压力下进行，优选地在 20-30℃和 1-10 巴下进行。CBZ 基团的氢解，例如，在 5-10% Pd/C 上在甲醇中，或采用甲酸铵（代替氢）在 Pd/C 上在甲醇 /DMF 中，在 20-30℃下很好地进行。

[0058] 合适的惰性溶剂的实例为烃，例如己烷、石油醚、苯、甲苯或二甲苯；氯代烃，例如三氯乙烯、1,2- 二氯乙烷、四氯甲烷、三氟 - 甲基苯、氯仿或 DCM；醇，例如甲醇、乙醇、异丙醇、正丙醇、正丁醇或叔丁醇；醚，例如二乙醚、二异丙基醚、四氢呋喃 (THF) 或二氧杂环己烷；二醇醚，例如乙二醇单甲基或单乙基醚或乙二醇二甲基醚（二甘醇二甲醚）；酮，例如丙酮或丁酮；酰胺，例如乙酰胺、二甲基乙酰胺、N- 甲基吡咯烷酮 (NMP) 或二甲基 - 甲酰胺 (DMF)；腈，例如乙腈；亚砜，例如二甲基亚砜 (DMSO)；二硫化碳；羧酸，例如甲酸或乙酸；硝基化合物，例如硝基甲烷或硝基苯；酯，例如 EtOAc，或所述溶剂的混合物。

[0059] 酯可例如，采用 LiOH、NaOH 或 KOH 在水、水 /THF、水 /THF/ 乙醇或水 / 二氧杂环己烷中，在 0 和 100℃之间的温度下皂化。此外，可例如采用乙酸、TFA 或 HCL 水解酯。

[0060] 此外，游离的氨基可以常规的方式，采用酰氯或酐酰化，或采用未取代或取代的烷基卤烷基化，或与 CH3-C(=NH)-OEt，有利地在惰性溶剂例如 DCM 或 THF 中和 / 或在碱例如三乙胺或吡啶的存在下，在 -60℃和 +30℃之间的温度下反应。

[0061] 贯穿本说明书，术语离去基团优选地表示 Cl、Br、I 或反应性修饰的 OH 基团，例如，活性酯、咪唑鎓 (imidazolide) 或具有 1 至 6 个碳原子的烷基磺酰基氧基（优选甲基磺酰基氧基或三氟甲基磺酰基氧基）或具有 6 至 10 个碳原子的芳基磺酰基氧基（优选苯基 - 或对甲苯基磺酰基氧基）。

[0062] 用于在典型的酰化反应中激活羧基的这种类型的基团在文献（例如在标准著作，例如 Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry（有机化学的方法）], Georg-Thieme-Verlag, Stuttgart) 中描述。

[0063] 活性酯有利地原位形成，例如通过加入 HOBt 或 N 羟基琥珀酰亚胺来进行。

[0064] 采用术语 " 药学可用衍生物 " 指例如式 I 化合物的盐和所谓的前药化合物。

[0065] 采用术语 " 前药衍生物 " 指已用例如烷基或酰基、糖或寡肽修饰和在生物体中快速地裂解以形成活性化合物的式 I 化合物。

[0066] 这些也包括如例如在 Int. J. Pharm. 115, 61-67 (1995) 中描述的依据本发明化合物的可生物降解的聚合物衍生物。

[0067] 药学可用盐和其它形式

所述式 (I) 化合物可以其最终的非盐形式使用。另一方面，本发明也涉及这些化合物

以其药学上可接受的盐形式的使用，其可通过本领域已知的程序衍生自各种有机和无机酸和碱。式 I 化合物的药学上可接受的盐形式大部分通过常规的方法制备。如果式 I 化合物含有酸性中心，例如羧基，则其合适的盐之一可通过化合物与合适的碱反应来形成，得到相应的碱 - 加成盐。这样的碱为例如碱金属氢氧化物，包括氢氧化钾和氢氧化钠；碱土金属氢氧化物，例如氢氧化镁和氢氧化钙；和各种有机碱，例如哌啶、二乙醇胺和 N- 甲基 - 葡糖胺（甲葡胺）、苄星、胆碱、二乙醇胺、乙二胺、苯乙苄胺、二乙胺、哌嗪、赖氨酸、L- 精氨酸、氨、三乙胺、甜菜碱、乙醇胺、吗啉和氨丁三醇。在某些包含碱性中心的式 I 化合物的情况下，酸 - 加成盐可通过用药学上可接受的有机和无机酸处理这些化合物来形成，所述有机和无机酸例如卤化氢，例如氯化氢或溴化氢，其它矿物酸及其相应的盐，例如硫酸盐、硝酸盐或磷酸盐等，和烷基 - 和单芳基 - 磺酸盐，例如甲烷磺酸盐、乙烷磺酸盐、甲苯磺酸盐和苯 - 磺酸盐，和其它有机酸及其相应的盐，例如碳酸盐、乙酸盐、三氟 - 乙酸盐、酒石酸盐、马来酸盐、琥珀酸盐、柠檬酸盐、苯甲酸盐、水杨酸盐、抗坏血酸盐等。因此，式 I 化合物的药学上可接受的酸 - 加成盐包括以下：乙酸盐、己二酸盐、藻酸盐、天冬氨酸盐、苯甲酸盐、苯 - 磺酸盐 (besylate)、硫酸氢盐、亚硫酸氢盐、溴化物、樟脑酸盐 (camphorate)、樟脑 - 磺酸盐、癸酸盐、辛酸盐、氯化物、氯代苯甲酸盐、柠檬酸盐、环己基氨基磺酸盐、肉桂酸盐、二葡糖酸盐、二氢 - 磷酸盐、二硝基苯甲酸盐、十二烷基 - 硫酸盐、乙烷磺酸盐、甲酸盐、羟乙酸盐、富马酸盐、半乳糖二酸盐 (galacterate)（来自粘酸）、半乳糖醛酸盐、葡糖庚酸盐、葡糖酸盐、谷氨酸盐、甘油磷酸盐、半 - 琥珀酸盐、半硫酸盐、庚酸盐、己酸盐、马尿酸盐、盐酸盐、氢溴酸盐、氢碘酸盐、2- 羟基 - 乙烷 - 磺酸盐、碘化物、羟乙磺酸盐、异丁酸盐、乳酸盐、乳糖酸盐、苹果酸盐、马来酸盐、丙二酸盐、扁桃酸盐、偏磷酸盐、甲烷磺酸盐、甲基苯甲酸盐、单 - 氢 - 磷酸盐、2- 萘磺酸盐、烟酸盐、硝酸盐、草酸盐、油酸盐、棕榈酸盐、果胶酸盐、过硫酸盐、苯基乙酸盐、3- 苯基丙酸盐、磷酸盐、膦酸盐、邻苯二甲酸盐，但这并不表示限制。两种类型的盐可优选地采用离子 - 交换树脂技术形成或互换。

[0068] 此外，式 I 化合物的碱盐包括铝、铵、钙、铜、铁 (III)、铁 (II)、锂、镁、锰 (111)、锰 (II)、钾、钠和锌盐，但这不意味着表示限制。上述盐中优选铵；碱金属盐钠和钾，和碱土金属盐钙和镁。衍生自药学上可接受的有机非毒性碱的式 I 化合物的盐包括以下的盐：伯胺、仲胺和叔胺，取代的胺，也包括天然存在的取代的胺，环胺，和碱性离子交换树脂，例如精氨酸、甜菜碱、咖啡因、氯普鲁卡因、胆碱、N，N'- 二苄基 - 乙二胺（苄星）、二环己基胺、二乙醇 - 胺、二乙基 - 胺、2- 二乙基 - 氨基 - 乙醇、2- 二甲基 - 氨基 - 乙醇、乙醇胺、乙二胺、N- 乙基吗啉、N- 乙基 - 哌啶、葡糖胺、氨基葡糖、组氨酸、海巴明、异丙基 - 胺、利多卡因、赖氨酸、甲葡胺 (N- 甲基 -D- 葡糖胺)、吗啉、哌嗪、哌啶、聚胺树脂、普鲁卡因、嘌呤、可可碱、三乙醇 - 胺、三乙胺、三甲胺、三丙基 - 胺和三（羟基 - 甲基）- 甲基胺（氨丁三醇），但这不旨在表示限制。

[0069] 包含碱性含 N2 基团的本发明式 I 化合物可采用以下试剂季铵化，所述试剂为例如 (C1-C4)- 烷基卤化物，例如甲基、乙基、异丙基和叔丁基的氯化物、溴化物和碘化物；二 (C1-C4) 烷基硫酸盐，例如二甲基、二乙基和二戊基硫酸盐；(C10-C18) 烷基卤化物，例如癸基、十二烷基、月桂基、十四烷基和十八烷基的氯化物、溴化物和碘化物；和芳基 -(C1-C4) 烷基卤化物，例如苄基氯和苯乙基溴。水溶性和油溶性式 I 化合物两者都可采用这样的盐制备。

[0070] 优选的上述药学盐包括乙酸盐、三氟乙酸盐、苯磺酸盐、柠檬酸盐、富马酸盐、葡糖酸盐、半琥珀酸盐、马尿酸盐、盐酸盐、氢溴酸盐、羟乙磺酸盐、扁桃酸盐、甲葡胺、硝酸盐、油酸盐、膦酸盐、三甲基乙酸盐、磷酸钠、硬脂酸盐、硫酸盐、磺基水杨酸盐、酒石酸盐、硫代苹果酸盐、甲苯磺酸盐和氨丁三醇，但这不旨在表示限制。

[0071] 碱性式 (I) 化合物的酸 - 加成盐通过以常规的方式使游离碱形式与足量的所需酸接触，导致盐形成来制备。游离碱可通过使盐形式与碱接触并以常规的方式分离游离碱来再生。游离碱形式在某些方面（关于某些物理性质，例如在极性溶剂中的溶解性）与其相应的盐形式不同；然而，为了本发明的目的，盐在其他方面对应于其各自的游离碱形式。

[0072] 如所提及的，式 I 化合物的药学上可接受的碱 - 加成盐用金属或胺，例如碱金属和碱土金属或有机胺形成。优选的金属是钠、钾、镁和钙。优选的有机胺是 N，N'- 二苄基乙二胺、氯普鲁卡因、胆碱、二乙醇 - 胺、乙二胺、N- 甲基 -D- 葡糖胺和普鲁卡因。

[0073] 酸性式 I 化合物的碱 - 加成盐通过使游离酸形式与足量的所需碱接触，以常规的方式引起盐形成来制备。游离酸可通过使盐形式与酸接触并以常规的方式分离游离酸来再生。游离酸形式在某些方面（关于某些物理性质，例如在极性溶剂中的溶解性）与其相应的盐形式不同；然而，为了本发明的目的，盐在其他方面对应于其各自的游离酸形式。

[0074] 如果式 (I) 化合物含有超过一个的能够形成这种类药学上可接受的盐的基团，则式 I 也涵盖复盐。典型的复盐形式包括，例如，二酒石酸盐、二乙酸盐、二富马酸盐、二甲葡胺、二 - 磷酸盐、二钠和三盐酸盐，但这不旨在表示限制。

[0075] 根据以上所述，可以发现，采用本文中的术语〃药学上可接受的盐〃指包含形式为其盐的一种的式 I 化合物的活性成分，特别是如果与游离形式的活性成分或较早使用的活性成分的任何其它盐形式比较，这种盐形式赋予活性成分改进的药代动力学性质。活性成分的药学上可接受的盐形式也可第一次为这种活性成分提供其较早时不具有的所需药代动力学性质，并可甚至具有对这种活性成分在其体内治疗效果方面的药效学的正面影响。

[0076] 由于其分子结构，式 (I) 化合物可以是手性的并可相应地以各种对映异构形式存在。因此它们可以外消旋的或以光学活性形式存在。

[0077] 由于依据本发明的化合物的外消旋体或立体异构体的药学活性可以不同，因此使用对映体可能是合乎需要的。在这些情况下，通过本领域技术人员已知的化学或物理手段或甚至在合成使用的相同手段，可将终产物或甚至中间体分离为对映体化合物。

[0078] 在外消旋胺的情况下，通过与光学活性拆分剂反应从混合物形成非对映体。合适的拆分剂的实例为光学活性酸，例如以下的 (R) 和 (S) 形式：酒石酸、二乙酰基酒石酸、二苯甲酰基酒石酸、扁桃酸、苹果酸、乳酸、合适的 N- 受保护的氨基酸（例如 N- 苯甲酰基脯氨酸或 N- 苯磺酰基脯氨酸），或各种光学活性樟脑磺酸。借助于光学活性拆分剂（例如二硝基苯甲酰基苯基甘氨酸、纤维素三乙酸盐或其它碳水化合物的衍生物或固定在二氧化硅胶体上的手性衍生的甲基丙烯酸酯聚合物）的层析对映体拆分也是有利的。为了此目的，合适的洗脱剂为水性或醇性溶剂混合物，例如，己烷 / 异丙醇 / 乙腈，例如比例为 82:15:3。

[0079] 本发明还涉及式 I 及相关式的化合物的用途，其与至少一种其它药物活性成分组合，所述药物活性成分优选用于治疗多发性硬化的药物例如克拉屈滨，或另一种辅助剂，例如干扰素，例如聚乙二醇化或非聚乙二醇化干扰素，优选干扰素 β；和 / 或与改善血管功能的化合物组合或与免疫调节剂组合，所述免疫调节剂例如芬戈莫德；环孢菌素、雷帕霉

素或子囊霉素，或它们的免疫抑制类似物，例如环孢菌素 A、环孢菌素 G、FK-506、ABT-281、ASM981、雷帕霉素、40-O-(2- 羟基）乙基 - 雷帕霉素等；皮质类固醇；环磷酰胺；硫唑嘌呤；氨甲喋呤；来氟米特；咪唑立宾；麦考酚酸 (mycophenolic add)；麦考酚酸吗乙酯；15- 脱氧精胍菌素；戊酸二氟可龙；二氟泼尼酯；倍他米松二丙酸盐；安西奈德；安吖啶；天冬酰胺酶；硫唑嘌呤；巴利昔单抗；倍可松二丙酸盐；倍他米松；倍他米松乙酸盐；倍他米松二丙酸盐；倍他米松磷酸钠；倍他米松戊酸盐；布地奈德；卡托普利；氮芥盐酸盐；克拉屈滨；氯倍他索丙酸盐；可的松乙酸盐；可的伐唑；环磷酰胺；阿糖胞苷；达克珠单抗；放线菌素；地奈德；去羟米松；地塞米松；地塞米松乙酸盐；地塞米松异烟酸盐；地塞米松间磺基苯甲酸钠；地塞米松磷酸盐；地塞米松叔丁基乙酸盐；乙酸二氯松；多柔比星盐酸盐；表柔比星盐酸盐；氟氯奈德；氟氢可的松乙酸盐；氟氢缩松；氟米松三甲基乙酸盐；氟尼缩松；氟西奈德；醋酸氟轻松；氟可龙；氟可龙己酸盐；氟可龙三甲基乙酸盐；氟米松；氟泼尼定乙酸盐；氟替卡松丙酸盐；吉西他滨盐酸盐；哈西奈德；氢化可的松、氢化可的松乙酸盐、氢化可的松丁酸盐、氢化可的松半琥珀酸盐；美法仑；甲泼尼松；巯嘌呤；甲泼尼龙；甲泼尼龙乙酸盐；甲泼尼龙半琥珀酸盐；米索前列醇；莫罗单抗 -cd3；麦考酚酸吗乙酯；帕拉米松乙酸盐；泼那唑啉；泼尼松龙；泼尼松龙乙酸盐；泼尼松龙己酸盐；泼尼松龙间磺基苯甲酸钠；泼尼松龙磷酸钠；强的松；泼尼立定；利福平；利福平钠；他克莫司；特立氟胺；沙利度胺；塞替派；替可的松匹伐酯；曲安西龙；曲安奈德半琥珀酸盐；苯曲安奈德；双醋曲安西龙；己曲安奈德；免疫抑制单克隆抗体，例如，对白细胞受体的单克隆抗体，例如，MHC、CD2、CD3、CD4、CD7、CD25、CD28、B7、CD40、CD45 或 CD58 或它们的配体；或其它免疫调节化合物，例如 CTLA41g，或其它附着分子抑制剂，例如 mAbs 或低分子量抑制剂包括选择蛋白拮抗剂和 VLA-4 拮抗剂。优选的组合物带有环孢菌素 A、FK506、雷帕霉素或 40-(2- 羟基）乙基 - 雷帕霉素和芬戈莫德。这些另外的药物，例如干扰素 β，可例如通过皮下、肌肉内或口腔途径同时或顺序给药。

[0080] 这些组合物可用作人类和兽医的药物。

[0081] 药物制剂可按剂量单位形式给予，其在每剂量单位中包含预定量的活性成分。这样的单位可包含，例如，0.5 mg-1 g，优选地 1 mg-700 mg，特别优选地 5 mg-100 mg 的依据本发明的化合物，取决于治疗的病情、给药方法和患者的年龄、体重和状况，或药物制剂可按剂量单位形式给予，其在每剂量单位中包含预定量的活性成分。优选的剂量单位制剂为包含如上指定的日剂量或部分剂量、或其相应的分数的活性成分的那些制剂。此外，这种类型的药物制剂可采用制药领域通常已知的方法制备。

[0082] 药物制剂可适合于经由任何所需的合适方法给药，例如通过口服（包括含服或舌下）、直肠、鼻、局部（包括含服、舌下或经皮）、阴道或胃肠外（包括皮下、肌肉内、静脉内或皮内）方法。这样的制剂可采用制药领域已知的所有方法，通过例如使活性成分与赋形剂或辅助剂组合来制备。

[0083] 适合于口服给予的药物制剂可作为分开的单位给予，例如，胶囊或片剂；散剂或颗粒；在水性或非 - 水性液体中的溶液或混悬液；可食用泡沫或泡沫食物；或水包油液体乳剂或油包水液体乳剂。

[0084] 因此，例如，在以片剂或胶囊的形式口服给药的情况下，活性成分组分可与口服的、非毒性和药学上可接受的惰性赋形剂，例如，乙醇、甘油、水等组合。散剂通过将化合物

粉碎为合适的细微尺寸并使其与按类似的方式粉碎的药用赋形剂混合来制备，所述赋形剂为例如，可食用碳水化合物，例如，淀粉或甘露醇。同样可存在调味剂、防腐剂、分散剂和染料。

[0085] 胶囊通过制备如上所述的粉末混合物并填充到成形的明胶壳中生产。助流剂和润滑剂，例如高度分散的硅酸、滑石、硬脂酸镁、硬脂酸钙或固体形式的聚乙二醇，可在填充操作之前加入到粉末混合物中。崩解剂或增溶剂，例如，琼脂、碳酸钙或碳酸钠，同样可以加入以改善胶囊被摄取后药物的可用性。

[0086] 此外，如果需要或必需，合适的粘合剂、润滑剂和崩解剂以及染料同样可掺入到混合物中。合适的粘合剂包括淀粉、明胶、天然糖，例如，葡萄糖或 β-乳糖、由玉米制得的甜味剂，天然和合成橡胶，例如，阿拉伯胶 (aracia)、黄蓍胶或藻酸钠、羧甲基纤维素、聚乙二醇、蜡等。用于这些剂型的润滑剂包括油酸钠、硬脂酸钠、硬脂酸镁、苯甲酸钠、乙酸钠、氯化钠等。崩解剂包括淀粉、甲基纤维素、琼脂、膨润土、黄原胶等，不限于此。片剂通过例如制备粉末混合物，制粒或干燥-压制混合物，加入润滑剂和崩解剂并压制全部混合物以得到片剂来配制。粉末混合物通过使以下混合来制备：按适当的方式粉碎的化合物与稀释剂或如上所述的碱，并任选带有粘合剂例如羧甲基纤维素、藻酸盐、明胶或聚乙烯-吡咯烷酮，分解阻滞剂例如石蜡，吸收加速剂例如季胺盐，和/或吸收剂例如膨润土、高岭土或磷酸二钙。粉末混合物可通过用粘合剂(例如，糖浆、淀粉糊、acadia mucilage、胶或纤维素或聚合物材料的溶液)使其湿润并加压过筛来制粒。作为制粒的备选，可使粉末混合物通过压片机，得到非均匀形状的块，将块破碎以形成颗粒。颗粒可通过加入硬脂酸、硬脂酸盐、滑石或矿物油进行润滑，以防止粘附在片剂铸造模具上。然后压制经润滑的混合物得到片剂。活性成分也可与自由流动的惰性赋形剂组合然后直接压制得到片剂而无需进行制粒或干燥-压制步骤。可存在由虫胶密封层、糖或聚合物材料层和蜡的光泽层构成的透明的或不透明的保护层。可将染料加入到这些包衣中，以便能够在不同的剂量单位之间进行区分。

[0087] 口服液体，例如溶液、糖浆和酏剂，可按剂量单位形式制备，以使给出的量包含预先规定量的化合物。糖浆可通过使化合物溶于含有合适的调味剂的水溶液中制备，而酏剂采用非毒性的醇性媒介物制备。混悬液可通过将化合物分散于非毒性媒介物中来配制。同样可加入增溶剂和乳化剂，例如，乙氧基化的异硬脂醇和聚氧乙烯山梨醇醚、防腐剂、香料添加剂，例如，薄荷油或天然甜味剂或糖精，或其它人工甜味剂等。

[0088] 如果需要，口服给药的剂量单位制剂可包封在微囊中。制剂也可以这样一种方式制备，即例如，通过将微粒材料包衣或包埋在聚合物、蜡等中，使释放延长或延迟。

[0089] 式 (I) 化合物及其盐、溶剂合物和生理学上的功能衍生物和其它活性成分也可以脂质体传递系统，例如小单层囊泡、大单层囊泡和多层囊泡的形式给予。脂质体可由各种磷脂，例如，胆固醇、十八烷基胺或卵磷脂形成。

[0090] 式 (I) 化合物及其盐、溶剂合物和生理学上的功能衍生物和其它活性成分也可采用单克隆抗体传递，所述单克隆抗体作为化合物分子与其偶合的单独的载体。化合物也可偶合至作为靶向的药物载体的可溶性聚合物。这样的聚合物可包括聚乙烯吡咯烷酮、吡喃共聚物、聚羟丙基-甲基丙烯酰氨基苯酚、聚羟乙基天冬氨酸苯酚或聚氧乙烯聚赖氨酸，被棕榈酰基取代。此外，化合物可偶合至一类可生物降解的聚合物，所述聚合物适合于实现药物的控制释放，所述聚合物例如聚乳酸、聚-ε-己内酯、聚羟基丁酸、聚-原酸酯、聚缩醛、

聚二羟基吡喃、聚氰基丙烯酸酯和交联或两性的水凝胶嵌段共聚物。

[0091] 适合于透皮给药的药物制剂可作为长效的、与接受者的表皮密切接触的独立膏药来给予。因此，例如活性成分可从膏药经离子电渗疗法递送，如在药物研究(Pharmaceutical Research)，3(6)，318 (1986)中的通用术语所描述的。

[0092] 适合于局部给予的药用化合物可作为软膏剂、霜剂、混悬剂、洗剂、散剂、溶液剂、糊剂、凝胶剂、喷雾剂、气溶胶或涂油剂配制。

[0093] 为治疗眼睛或其它外部组织，例如嘴和皮肤，优选将制剂作为局部软膏剂或霜剂施用。在给出软膏剂的制剂的情况下，活性成分可与石蜡或者与水混溶的霜剂基质一起使用。作为选择，活性成分可用水包油霜剂基质或油包水基质配制以得到霜剂。

[0094] 适合于局部施用于眼睛的药物制剂包括滴眼剂，其中活性成分被溶解于或悬浮于合适的载体，特别是水性溶剂中。

[0095] 适合于在口中局部施用的药物制剂包括糖锭剂、锭剂和漱口水。

[0096] 适合于直肠给药的药物制剂可以栓剂或灌肠剂的形式给予。

[0097] 适合于鼻腔给药的药物制剂，其中载体物质为包含具有例如在20-500微米范围内粒径的粗制粉末的固体，其以采用吸入的方式给予，即经由鼻道从保持在贴近鼻的包含粉末的容器快速吸入。作为含有作为载体物质的液体的鼻腔喷雾剂或滴鼻剂给药的合适制剂包括在水或油中的活性成分溶液。

[0098] 适合于经吸入给药的药物制剂包含细颗粒尘或雾，其可通过各种类型的加压分药器，用气溶胶、气雾器或吹药器生成。

[0099] 适合于阴道给药的药物制剂可作为阴道栓、棉条、霜剂、凝胶剂、泡沫或喷雾制剂给予。

[0100] 适合于胃肠外给药的药物制剂包括水性和非水性无菌注射液，其含有抗氧化剂、缓冲剂、细菌抑制剂和溶质，藉此使制剂与待治疗的接受者的血液等渗；和水性和非水性无菌混悬液，其可包含悬浮介质和增稠剂。制剂可以单剂量或多剂量容器给予，例如密封的安瓿和小瓶，并以冷冻-干燥（冻干）的状态贮存，以便仅在必需使用之前即刻加入无菌载体液体，例如用于注射目的的水。

[0101] 按照处方制备的注射液和混悬液可由无菌粉剂、颗粒和片剂制备。

[0102] 不言而喻，除了上面具体提及的组成，制剂也可包含本领域关于特定类型的制剂常用的试剂；因此，例如适合于口服给药的制剂可包含调味剂。

[0103] 式I化合物和其它活性成分的治疗有效量取决于许多因素，包括，例如，动物的年龄和体重，需要治疗的准确病情，及其严重性，制剂的性质和给药方法，并且由治疗医生和兽医最终决定。然而，有效量的化合物通常在 每日从0.1至100 mg/kg接受者（哺乳动物）体重范围内和特别典型地每日在从1-10 mg/kg体重范围内。因此，对于体重70 kg的成年哺乳动物，每日实际量通常在70和700 mg之间，其中该量可作为每日单独的剂量给予或通常地以每日一系列部分剂量（例如，2、3、4、5或6次）给予，以使总日剂量为相同的。盐或溶剂合物或其生理学上的功能衍生物的有效量可按化合物本身的有效量的分数来确定。

[0104] 本发明还涉及治疗罹患鞘氨醇1-磷酸酯相关疾病的患者的方法，包括给予所述患者有效量的式(I)化合物。本发明优选地涉及一种方法，其中鞘氨醇1-磷酸酯-1相关疾病为与过度活性免疫应答相关的自身免疫性紊乱或病症。

[0105] 本发明还涉及治疗罹患免疫调节异常的患者的方法，包括以有效治疗所述免疫调节异常的量的式 (I) 化合物给予所述患者。本发明优选地涉及一种方法，其中免疫调节异常为自身免疫或慢性炎性疾病。

[0106] 实验：

在以下描述的实施例中提供的 HPLC 数据如下获得。

[0107] 条件 A：柱 Waters Xbridge™ C_8 50 mm x 4.6 mm，流速 2 mL/min；8 分钟梯度，从在 H_2O 中 0.1 % TFA 至在 CH_3CN 中 0.07 % TFA。

[0108] 条件 B：柱：XTERRA RP18 (250 x 4.6 mm, 5 □m)，流速 1 mL/min；20 分钟梯度，从 95% (10mM K_2HPO_4 在 H_2O 中) / 5% CH_3CN 至 100% CH_3CN。柱温 55℃

手性 HPLC：柱 CHIRALPAK AD-H (250X4.6) mm, 5μm，流速 1 mL/min；流动相：在己烷中的 0.1 %TFA: 异丙醇 (80:20)。

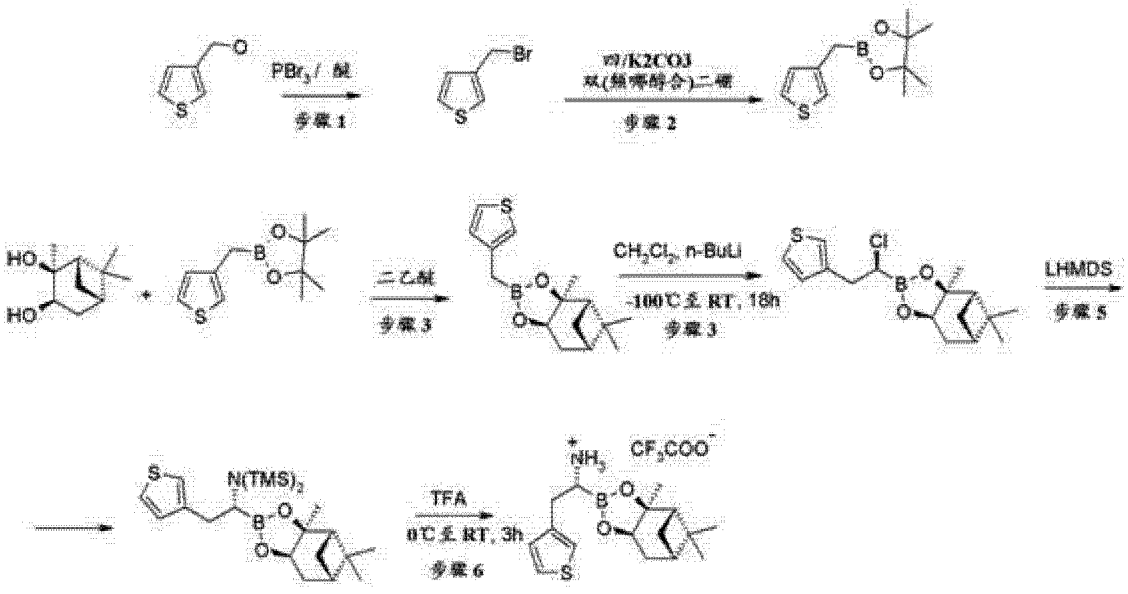
[0109] UV 检测 (maxplot) 用于所有条件。

[0110] 在以下描述的实施例中提供的 MS 数据如下获得：质谱：LC/MS Waters ZMD (ESI) 或 Waters Acquity SQD (ESI)

在以下描述的实施例中提供的 NMR 数据如下获得：^{1}H-NMR：Bruker DPX 400 MHz。采用 d_6-DMSO，加入数滴 D_2O，获得最终化合物的所有 NMR。光谱在样品制备 15-120 分钟后记录。

[0111] 本发明的化合物已根据来自 Advanced Chemistry Development Inc., ACD/Labs (7.00 Release). 产品版本：7.10, build：15 Sep 2003 的程序"ACD/Name Batch"中使用的的标准来命名。

[0112] 中间体 1：[(1R)-1- 氨基 -2-(3- 噻吩基) 乙基] 硼酸酸 (+)- 蒎烷二醇酯三氟乙酸盐



步骤 1：3-(溴代甲基) 噻吩

将 3- 噻吩甲醇 (5.00 g, 43.7mmol) 的二乙醚 (40 mL) 冷却 (0℃) 溶液用三溴化磷 (1.35 mL, 14.4 mmol) 处理并于 0℃搅拌反应混合物 30 min。然后将反应混合物倾入到冰中并用二乙醚提取。有机层经硫酸钠干燥并浓缩得到标题化合物 (5.23 g, 67%)，其无须进一步纯化而使用。

[0113] ^{1}H NMR (400MHz, $CDCl_3$) δ 7.32-7.30 (m, 2H), 7.14 (d, J= 4.6 Hz, 2H),

4.54 (s, 1H)。

[0114] 步骤 2 :4,4,5,5- 四甲基 -2-(3- 噻吩基甲基)-1,3,2- 二氧硼杂环戊烷

将 3-(溴代甲基) 噻吩 (5.23 g, 29.7 mmol) 在脱气的 1,4- 二氧杂环己烷 (90 ml) 中的溶液用双 (频哪醇合) 二硼 (9.0 g, 36 mmol)、碳酸钾 (12.3 g, 89.1 mmol) 和四 (三苯基膦) 钯 (1.72 g, 1.48 mmol) 处理并将反应混合物于 100℃加热 12 h。使该混合物冷却至室温并通过 C 盐床过滤。浓缩滤液,粗品经二氧化硅柱层析纯化,用在石油醚中的 5-10% 乙酸乙酯洗脱,得到标题化合物 (3.55 g, 55%),为黄色油状物。

[0115] ^{1}H NMR (400 MHz, $CDCI_3$) δ 7.22-7.20 (m, 1H), 6.96-6.93 (m, 2H), 2.28 (s, 2H), 1.24 (s, 12H).

步骤 3 :(3- 噻吩基甲基) 硼酸 (+)- 蒎烷二醇酯

将 4,4,5,5- 四甲基 -2-(3- 噻吩基甲基)-1,3,2- 二氧硼杂环戊烷 (3.55 g, 15.8 mmol) 的二乙醚 (40 ml) 溶液用 (1S, 2S, 3R, 5S)-(+)- 蒎烷二醇 (3.1 g, 18 mmol) 处理。将反应混合物于室温下搅拌 2 天。反应物质用水 (2 x 15 ml)、盐水洗涤,经无水硫酸钠干燥并浓缩得到粗产物,其经硅胶柱层析纯化,用在石油醚中的 5% 乙酸乙酯洗脱,得到标题化合物 (4.0 g, 90%)

^{1}H NMR (400 MHz, $CDCI_3$) δ 7.23 (dd, J= 7.8, 3.2 Hz, 1H), 6.97-6.95 (m, 2H), 4.31 (dd, J= 8.8, 2.0 Hz, 1H), 2.36-2.30 (m, 3H), 2.2-2.18 (m, 1H), 2.07 (t, J= 5.2Hz, 1H), 1.92-1.90 (m, 1H), 1.87-1.84 (m, 1H) 1.40 (s, 3H), 1.32 (s, 3H), 1.10 (d, J= 10.9 Hz, 1H), 0.84 (s, 3H).

步骤 4 :[(1S)-1- 氯代 -2-(3- 噻吩基) 乙基] 硼酸酸 (+)- 蒎烷二醇酯

经 10 分钟向二氯甲烷 (1.42 ml, 21.7 mmol) 和四氢呋喃 (10 ml) 的冷却 (-100℃) 溶液加入正丁基锂 (2.5 M 在 THF 中 ;3.18 ml ;7.96mmol)。搅拌 20 分钟后,经 10 分钟加入 (3- 噻吩基甲基) 硼酸 (+)- 蒎烷二醇酯 (2.00 g, 7.24 mmol) 的 THF (9 ml) 溶液,保持温度在 -100℃。然后于 -100℃经 30 分钟加入氯化锌 (0.5M 在 THF 中 ;13 mL, 6.5 mmol) 溶液。使该混合物达到室温并搅拌 18h 和浓缩。向生成的油状物中加入二乙醚和饱和的氯化铵 (各 50 ml) 并剧烈搅拌。水层用二乙醚提取 3 次,合并的有机层经无水硫酸钠干燥并真空浓缩,得到标题化合物 (2.1 g, 89%),其无须进一步纯化而原样用于随后的步骤。

[0116] ^{1}H NMR (400 MHz, $CDCI_3$) δ 7.26 (dd, J= 8.3 Hz, 1H), 7.11 (m, 1H), 7.03 (dd, J= 6.1, 1.1 Hz, 1H), 4.36 (dd, J= 10.7, 2 Hz, 1H), 3.75 (m, 1H), 3.21 (m, 1H), 2.34 (m, 1H), 2.19 (m, 1H), 2.07 (t, J= 5.2, Hz, 2H), 1.91-1.84 (m, 2H), 1.35 (s, 3H), 1.28 (s, 3H), 1.05 (d, J= 11 Hz, 1H), 0.84 (s, 3H).

步骤 5 :[(1R)-1-[双 (三甲基甲硅烷基) 氨基]-2-(3- 噻吩基) 乙基] 硼酸

向 [(1S)-1- 氯代 -2-(3- 噻吩基) 乙基] 硼酸酸 (+)- 蒎烷二醇酯 (2.30 g, 7.09 mmol) 的 10 ml 无水 THF 冷却 (-78℃) 溶液中加入双 (三甲基甲硅烷基) 氨化锂 (1 M 在 THF 中, 10.6 ml, 10.6 mmol)。使该混合物达到室温,搅拌 18 h 并浓缩至干。向生成的残留物中加入己烷,然后滤除沉淀的固体。浓缩滤液得到标题化合物 (1.72 g, 53%),其无须进一步纯化而原样用于随后的步骤。

[0117] ^{1}H NMR (400 MHz, $CDCI_3$) δ 7.19-7.17 (m, 1H), 7.01-6.99 (m, 2H), 4.29-4.27 (m, 1H), 3.07-3.05 (m, 1H), 2.79 (m, 1H), 2.68 (m, 1H), 2.3 (m, 1H),

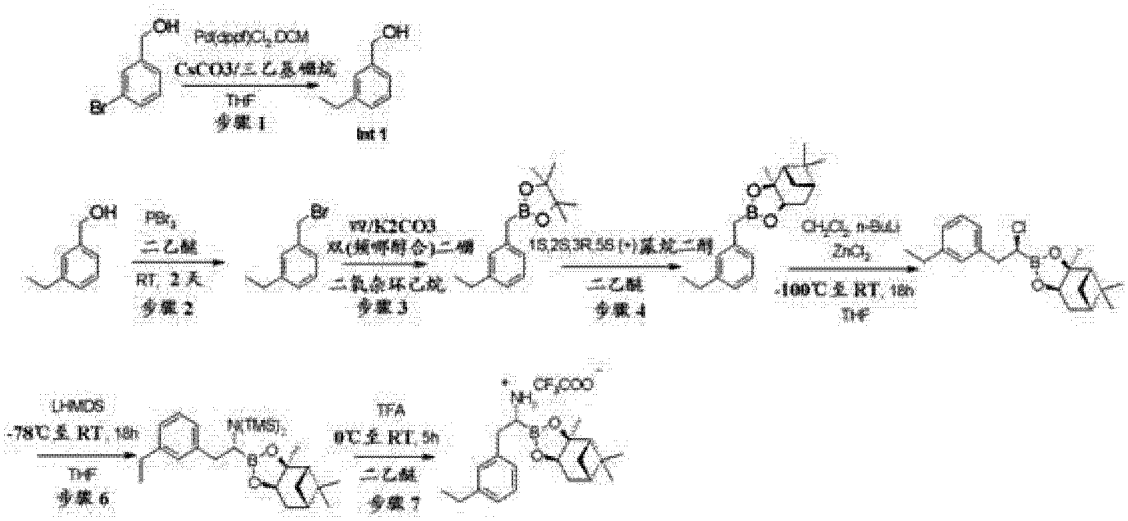
2.15 (m, 1H), 2.02 (t, J= 5.2 Hz, 1H), 1.87-1.86 (m, 1H), 1.79 (m, 1H), 1.36 (s, 3H), 1.25 (s, 3H), 0.94 (m, 1H), 0.85 (s, 3H), 0.08 (s, 18H).

步骤 6 :[(1R)-1- 氨基 -2-(3- 噻吩基) 乙基] 硼酸酸 (+)- 蒎烷二醇酯三氟乙酸盐

向 [(1R)-1-[双 (三甲基甲硅烷基) 氨基]-2-(3- 噻吩基) 乙基] 硼酸 (1.72 g, 3.82 mmol) 在二乙醚 (25 ml) 中的冷却 (0℃) 溶液中滴加入三氟乙酸 (0.88 ml, 11.48 mmol)。于室温下搅拌反应 3 h。用冰 - 甲醇将反应混合物冷却至 -10℃并过滤形成的白色固体,用乙醚洗涤并干燥, 得到标题化合物。

[0118] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.8 (bs, 3H), 7.33-7.27 (m, 1H), 7.23 (m, 1H), 7.01-6.99 (dd, J= 5.0 hz, 1.2 Hz, 1H), 4.35-4.32 (m, 1H), 3.18-3.10 (m, 3H), 2.28-2.15 (m, 3H), 1.99 (m, 1H), 1.90 (m, 1H), 1.85 (t, J= 5.2 Hz, 1 H), 1.80 (m, 1H), 1.34 (s, 3H), 1.29 (s, 3H), 1.04-1.02 (m, 1H), 0.81 (s, 3H).

中间体 2 :[(1R)-1- 氨基 -2-(3- 乙基苯基) 乙基] 硼酸 (+)- 蒎烷二醇酯三氟乙酸盐



步骤 1 :(3- 乙基苯基) 甲醇

将 3- 溴代苄基醇 (5.00 g, 26.7mmol) 在脱气的四氢呋喃 (50 ml) 中的溶液置于耐压瓶中并用碳酸铯 (26.0 g, 80.2 mmol)、与 DCM (40 mg, 0.54 mmol) 复合的 1,1 ’- 双 (二苯基膦基) 二茂铁二氯化钯 (1:1) 处理。加入三乙基硼烷 (1.0 M 在 THF 中, 80 ml, 80 mmol) 并将反应混合物于 70℃加热 5 h。将耐压瓶中的内容物冷却至 0℃并经 NaOH 水溶液 (10%) 和 H_2O_2 水溶液 (30%) 猝灭。将反应混合物于室温下搅拌 30 分钟,用稀释含水 HCl 酸化并用二乙醚提取。将有机层干燥 (Na_2SO_4) 并浓缩。经硅胶快速层析纯化粗品,用在石油醚中的 5-10% 乙酸乙酯洗脱,得到所需的产物 (3.5 g, 90%),为淡黄色液体。

[0119] ^{1}H NMR (400MHz, $CDCl_3$) δ 7.31-7.27 (m, 1H), 7.22-7.14 (m, 3H), 4.68 (s, 2H) 2.70-2.64 (m, 2H), 1.27-1.24 (t, J=7.6, 3H).

步骤 2 :1-(溴代甲基)-3- 乙基苯

将 (3- 乙基苯基) 甲醇 (3.50 g, 25.7 mmol) 在二乙醚 (40 ml) 中的冷 (0℃) 溶液用三溴化磷 (0.8 ml, 8.5 mmol) 处理并将反应混合物于 0℃搅拌 30 min。然后将反应混合物倾入到冰中并用乙醚提取。有机层经硫酸钠干燥并浓缩。粗品 (3.1 g, 60%) 无须进一步纯化而原样用于随后的步骤。

[0120] ^{1}H NMR (400MHz, $CDCl_3$) δ 7.29-7.15 (m, 3H), 7.15-7.14 (m, 1H), 4.50

(s, 2H) 2.69-2.63 (m, 2H), 1.27-1.23 (t, J= 7.6, 3H).

步骤 3 :2-(3- 乙基苄基)-4,4,5,5- 四甲基 -1,3,2- 二氧硼杂环戊烷

将 1-(溴代甲基)-3- 乙基苯 (1.7g, 8.59 mmol) 在脱气的 1, 4- 二氧杂环己烷 (40 ml) 中的溶液用双 (频哪醇合) 二硼 (2.61 g, 10.3mmol)、碳酸钾 (3.56 g, 25.8mmol)、四 (三苯基膦) 钯 (0) (0.497 g, 0.429 mmol) 处理并将混合物于 100℃加热 12h。使烧瓶中的内容物冷却至室温并通过 C 盐床过滤。浓缩滤液,粗品经硅胶柱层析纯化,用在石油醚中的 5-10% 乙酸乙酯洗脱,得到标题化合物 (1.4 g, 66%),为黄色油状物。

[0121] ^{1}H NMR (400MHz, $CDCI_3$) δ 7.18-7.14 (m, 3H), 7.03-6.96 (m, 3H), 2.64-2.58 (m, 2H), 2.28 (s, 2H), 1.24-1.21 (m, 15H).

步骤 4 :(3- 乙基苄基) 硼酸 (+)- 蒎烷二醇酯

将 2-(3- 乙基苄基)-4 ,4,5, 5- 四甲基 -1,3,2- 二氧硼杂环戊烷 (1.4 g, 5.68 mmol) 的二乙醚 (30 ml) 溶液用 (1S, 2S, 3R, 5S)-(+)- 蒎烷二醇 (1.45 g, 8.53 mmol) 处理。将反应混合物于室温下搅拌 12 h,然后混合物用水洗涤两次,然后用盐水洗涤,经无水硫酸钠干燥,然后浓缩。粗产物经硅胶柱层析纯化,用在石油醚中的 5% 乙酸乙酯洗脱 , 得到标题化合物 (1.43 g, 84%)。

[0122] ^{1}H NMR (400 MHz, $CDCI_3$) δ 7.19-7.15 (m, 1H), 7.04-7.01 (m, 2H), 6.98-6.96 (m, 1H), 4.29-4.27 (m, 1H), 2.64-2.58 (m, 2H), 2.34-2.28 (m, 3H), 2.20-2.19 (m, 1H), 2.07-2.04 (m, 1H), 1.89-1.81 (m, 2H), 1.29 (s, 3H), 1.25-1.21 (m, 3H), 1.1-1.08 (m, 1H), 0.84 (s, 3H). GCMS :m/z :298

步骤 5 :[(1S)-1- 氯代 -2-(3- 乙基苯基) 乙基] 硼酸 (+)- 蒎烷二醇酯

经 10 分钟向二氯甲烷 (0.89 ml, 13.7 mmol) 和无水四氢呋喃 (6 ml) 的冷却 (-100℃) 混合物中加入正丁基锂 (2.5 M 在己烷中 , 2.0 ml, (3.7 mmol)。于 -100℃搅拌 20 分钟后,经 10 分钟加入 (3- 乙基苄基) 硼酸 (+)- 蒎烷二醇酯 (1.36 g, 4.56 mmol) 的无水 THF (4 ml) 溶液。然后于 -100℃经 30 分钟加入氯化锌 (0.5 M 在 THF 中 , 8.2 ml, 4.1 mmol) 溶液。使该混合物达到室温并搅拌 18 h 和浓缩。向生成的油状物中加入二乙醚和饱和的氯化铵 (各 25 ml) 并剧烈搅拌。水层用二乙醚提取 3 次,合并的有机层经无水硫酸钠干燥并真空浓缩。残留物 (1.5 g, 94%) 原样用于下一步骤。

[0123] GCMS :m/z :346

步骤 6 :[(1R)-1-[双 (三甲基甲硅烷基) 氨基]-2-(3- 乙基苯基) 乙基] 硼酸 (+)- 蒎烷二醇酯

向 [(1S)-1- 氯代 -2-(3- 乙基苯基) 乙基] 硼酸 (+)- 蒎烷二醇酯 (1.5 g, 4.32 mmol) 在 15 ml 无水四氢呋喃中的冷却 (-78℃) 溶液中加入双 (三甲基甲硅烷基) 氨化锂 (1 M 在 THF 中 , 6.5 ml, 6.5 mmol)。使该混合物达到室温,搅拌 18 h 并浓缩至干。向生成的残留物中加入己烷,然后滤除沉淀的固体。浓缩滤液得到所需的粗产物 (1.2 g, 58%),其无须进一步纯化而原样用于随后的步骤。

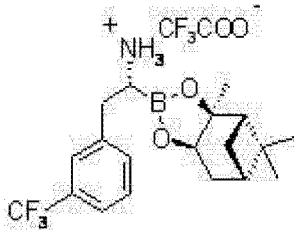
[0124] 步骤 7 :[(1R)-1- 氨基 -2-(3- 乙基苯基) 乙基] 硼酸 (+)- 蒎烷二醇酯三氟乙酸盐

将 [(1R)-1-[双 (三甲基甲硅烷基) 氨基]-2-(3- 乙基苯基) 乙基] 硼酸 (+)- 蒎烷二醇酯 (1.20 g, 2.54 mmol) 在二乙醚 (20 ml) 中的冷却 (0℃) 溶液用三氟乙酸 (0.87 ml,

7.6 mmol）逐滴处理。将反应混合物在低于30℃的温度下减压蒸发。使粗品溶于甲苯并蒸发，并将此顺序重复4次。获得的白色固体（1.0 g，89%）无须进一步纯化而用于随后的步骤。

[0125] ^{1}H NMR（400 MHz，DMSO-d6）：δ 7.22-7.26（m，1H），7.09-7.11（m，3H），4.31-4.33（m，1H），3.00-3.19（m，3H），2.59-2.65（m，2H），2.18-2.23（m，2H），1.90-1.98（m，1H），1.80-1.89（m，1H），1.33（s，3H），1.20-1.26（m，6H），1.06（m，1H），0.80（s，3H）

中间体3：[(1R)-1-氨基-2-(3-三氟甲基苯基）乙基]硼酸(+)-蒎烷二醇酯三氟乙酸盐



步骤1：2-(3-三氟甲基苄基)-4,4,5,5-四甲基-1,3,2-二氧硼杂环戊烷

将溴化3-（三氟甲基）苄基（5.00 g，20.9 mmol）在脱气的1,4-二氧杂环己烷（100 ml）中的溶液用双（频哪醇合）二硼（6.4 g，25 mmol）、碳酸钾（20.9 g，62.7 mmol）、四（三苯基膦）钯（0）（1.2 g，1.0 mmol）处理并将混合物于100℃加热12 h。使烧瓶中的内容物冷却至室温并通过C盐床过滤。浓缩滤液，粗品经硅胶柱层析纯化，用石油醚中的2%乙酸乙酯洗脱，得到标题化合物（5.1 g，85%），为无色液体。

[0126] ^{1}H NMR（400 MHz，$CDCl_3$）：δ 7.45（s，1H），7.33-7.40（m，3H），2.36（s，2H），1.25（s，12H）. GCMS：m/z=286

步骤2：(3-三氟甲基苄基）硼酸(+)-蒎烷二醇酯

将2-(3-三氟甲基苄基)-4,4，5，5-四甲基-1,3,2-二氧硼杂环戊烷(5.10 g，17.8 mmol）的二乙醚（50 ml）溶液用（1S，2S，3R，5S)-(+)-蒎烷二醇（4.55 g，26.7 mmol）处理。将反应混合物于室温下搅拌12 h，然后混合物用水洗涤两次，然后用盐水洗涤并经硫酸钠干燥，然后浓缩。粗产物经硅胶柱层析纯化，用石油醚中的2%乙酸乙酯洗脱，得到标题化合物（6.0 g，99%），为无色液体。

[0127] ^{1}H NMR（400 MHz，$CDCl_3$）：δ 7.40（s，1H），7.35-7.38（m，3H），4.29（dd，J= 2.0，8.8 Hz，1H），2.40（s，2H），2.31-2.36（m，1H），2.17-2.21（m，1H），2.05（t，J= 5.8 Hz，1H），1.90-1.92（m，1H），1.80-1.85（m，1H），1.39（s，3H），1.29（s，3H），1.02-1.05（m，1H），0.84（s，3H）. GCMS：m/z=338

步骤3：(1S)-1-氯代-2-(3-三氟甲基苄基)-乙基硼酸(+)-蒎烷二醇酯

经15分钟向二氯甲烷（1.70 mL，26.6 mmol）和无水四氢呋喃（17 ml）的冷却(-100℃）混合物中加入正丁基锂（1.6 M，6.1 mL，9.75 mmol）。于-100℃搅拌20分钟后，经15 分钟加入(3-三氟甲基苄基）硼酸(+)-蒎烷二醇酯(3.0 g，8.87 mmol）在无水THF（12 ml）中的溶液。然后于-100℃经30分钟加入氯化锌（0.5 M在THF中，16.0 mL，8.0 mmol）溶液。使该混合物达到室温并搅拌18 h和浓缩。向生成的油状物中加入二乙醚和饱和的氯化铵（各25 ml）并剧烈搅拌。水层用二乙醚提取3次，合并的有机层经无

水硫酸钠干燥并真空浓缩。将黄色液体 (3.4 g, 99%) 原样用于随后的步骤。

[0128] ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.27-7.54 (m, 4H), 4.36 (dd, J= 1.6, 8.9 Hz, 1H), 3.63-3.69 (m, 1H), 3.24-3.26 (m, 1H), 3.17-3.19 (m, 1H), 2.32-2.40 (m, 1H), 2.17-2.19 (m, 1H), 2.05-2.08 (m, 1H), 1.84-1.91 (m, 2H), 1.36 (s, 3H), 1.28 (s, 3H), 0.99-1.02 (m, 1H), 0.84 (s, 3H). GCMS :m/z=386

步骤 4 :[(1R)-1-[双 (三甲基甲硅烷基) 氨基]-2-(3- 三氟甲基苯基) 乙基] 硼酸 (+)- 蒎烷二醇酯

向 [(1S)-1- 氯代 -2-(3- 三氟甲基苯基) 乙基] 硼酸 (+)- 蒎烷二醇酯 (3.4 g, 8.8 mmol) 在 25 ml 无水四氢呋喃中的冷却 (-78℃) 溶液中加入双 (三甲基甲硅烷基) 氨化锂 (1 M 在 THF 中, 15 ml, 15 mmol)。使该混合物达到室温,搅拌 18 h 并浓缩至干。向生成的残留物中加入己烷,然后滤除沉淀的固体。浓缩滤液得到作为粗产物的标题化合物,其无须进一步纯化而原样用于随后的步骤。

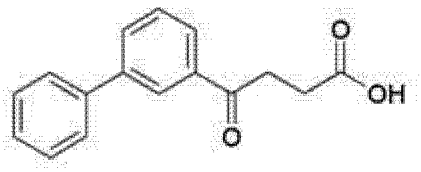
[0129] ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.27-7.53 (m, 4H), 4.22-4.25 (m, 1H), 3.06-3.07 (m, 1H), 2.91-2.93 (m, 1H), 2.22-2.32 (m, 3H), 2.02-2.03 (m, 1H), 1.87-1.88 (m, 2H), 1.37 (s, 3H), 1.27 (s, 3H), 0.94-0.96 (m, 1H), 0.83 (s, 3H), 0.17 (s, 12H), 0.06 (s, 6H)

步骤 5 :[(1R)-1- 氨基 -2-(3- 三氟甲基苯基) 乙基] 硼酸 (+)- 蒎烷二醇酯三氟乙酸盐

于 0℃,将 [(1R)-1-[双 (三甲基甲硅烷基) 氨基]-2-(3- 三氟甲基苯基) 乙基] 硼酸 (+)- 蒎烷二醇酯 (1.5 g, 2.93 mmol) 在二乙醚 (15 ml) 中的冷却 (0℃) 溶液用三氟乙酸 (0.67 ml, 8.8 mmol) 逐滴处理。于室温下搅拌反应 3 h。将反应混合物在低于 30℃的温度下减压蒸发。使粗品溶于甲苯并蒸发,并将此顺序重复 4 次。获得的粗产物 (1.7 g) 无须进一步纯化而用于随后的步骤。

[0130] ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.27-7.54 (m, 4H), 4.33-4.35 (m, 1H), 3.10-3.39 (m, 2H), 2.15-2.35 (m, 2H), 2.01-2.08 (m, 2H), 1.89-1.95 (m, 2H), 1.37 (s, 3H), 1.27 (s, 3H), 0.94-0.97 (m, 1H), 0.83 (s, 3H)

中间体 4 :4- 联苯 -3- 基 -4- 氧代 - 丁酸



步骤 1 :4- 联苯 -3- 基 -4- 氧代 - 丁酸乙基酯

将 4-(3- 溴代 - 苯基)-4- 氧代 - 丁酸乙基酯 (500 mg, 1.75mmol)、苯基硼酸 (340 mg, 2.62 mmol) 和氟化铯 (1.06g, 7 mmol) 在二氧杂环己烷 : 水 (2:1, 20 ml) 中的混合物用氮气脱气 15 min,然后用双 (三苯基膦) 二氯化钯 (II) (11 mg, 0.175 mmol) 处理并将反应混合物在微波反应器中于 90℃辐照 1 h。然后用乙酸乙酯稀释反应混合物,通过 C 盐过滤,并在减压下蒸发溶剂。经硅胶快速层析纯化粗品,采用乙酸乙酯和石油醚作为洗脱剂,得到标题化合物 (0.40 g, 83%)。

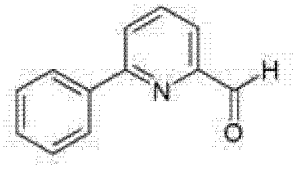
[0131] MS(ESI+) :283.0, HPLC (方法 A) :Rt. 5.2 min, HPLC 纯度 95.3%

步骤 2 :4- 联苯 -3- 基 -4- 氧代 - 丁酸

将 4- 联苯 -3- 基 -4- 氧代 - 丁酸乙基酯 (400 mg, 1.41 mmol) 在四氢呋喃 : 水 (4:1, 10 mL) 中的溶液用 LiOH.H_2O (170 mg, 4.23 mmol) 处理并将反应混合物于室温下搅拌过夜。在减压下浓缩反应混合物,残留物用水稀释并用乙酸乙酯提取三次。水层用 HCl (1.5N) 水溶液酸化并用二氯甲烷提取。有机层经硫酸钠干燥并浓缩,得到标题化合物 (0.3 g, 83%).

^{1}H NMR (400 MHz, DMSO-d6) : δ 8.20 (s, 1H), 7.92-7.98 (m, 2H), 7.72-7.74 (m, 2H), 7.60-7.64 (m, 1H), 7.50-7.51 (m, 2H), 7.40-7.41 (m, 1H), 3.32-3.35 (m, 2H), 2.59-2.61 (m, 2H). MS(ESI+) :255.0, HPLC Rt. 4.0 min, HPLC 纯度 99.7 %.

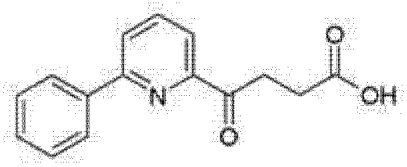
中间体 5 :6- 苯基 - 吡啶 -2- 甲醛



将 6- 溴代吡啶 -2- 甲醛 (500 mg, 2.68 mmol)、苯基硼酸 (870 mg, 6.7mmol) 和氟化铯 (610 mg, 4.0 mmol) 的混合物溶于二氧杂环己烷 : 水 (2:1) 7.5 mL 中并用氮气脱气 15 min。然后加入双 (三苯基膦) 二氯化钯 (II) (94 mg, 0.13 mmol) 并将反应混合物在微波反应器中于 90℃辐照 2 h。然后用乙酸乙酯稀释反应混合物,通过 C 盐过滤并蒸发。经硅胶快速层析纯化粗品,采用乙酸乙酯和石油醚作为洗脱剂。

[0132] MS(ESI+) :184.0, HPLC (方法 A) Rt. 3.3 min, HPLC 纯度 95.1 %

中间体 6 :4- 氧代 -4-(6- 苯基 - 吡啶 -2- 基)- 丁酸



步骤 1 :4- 氧代 -4-(6- 苯基 - 吡啶 -2- 基)- 丁酸甲基酯

将 6- 苯基 - 吡啶 -2- 甲醛 (中间体 5 ;800 mg, 4.37 mmol) 的甲醇溶液用丙烯酸甲酯 (0.54 mL, 5.2mmol)、3- 乙基 -5-(2- 羟基乙基)-4- 甲基 -1,3- 噻唑鎓溴化物 (220 mg, 0.87 mmol) 和三乙胺 (1.8 mL, 13mmol) 处理。然后将反应混合物于 70℃回流 1 h。使反应混合物冷却至 RT,用在水中的饱和 NH_4Cl 溶液猝灭并用乙酸乙酯提取。分离有机层,用 $NaHCO_3$、盐水洗涤,经 Na_2SO_4 干燥并浓缩。粗品经硅胶柱层析纯化,采用乙酸乙酯和石油醚作为洗脱剂 (0.80 g ;68%)。

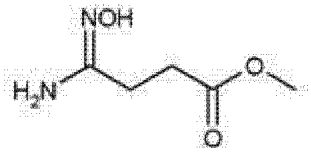
[0133] MS(ESI+) :270.0

步骤 2 :4- 氧代 -4-(6- 苯基 - 吡啶 -2- 基)- 丁酸

将 4- 氧代 -4-(6- 苯基 - 吡啶 -2- 基)- 丁酸甲基酯 (600 mg, 2.2 mmol) 在四氢呋喃 : 水 (4:1, 10ml) 中的溶液用 LiOH.H_2O (280 mg, 6.68 mmol) 处理并将反应混合物于室温下搅拌过夜。除去溶剂,残留物用水稀释并用二氯甲烷洗涤。然后用 HCl 水溶液 (1.5 N) 中和水层并用二氯甲烷提取。有机层经硫酸钠干燥并浓缩。通过制备型 HPLC 进一步纯化获得的固体。

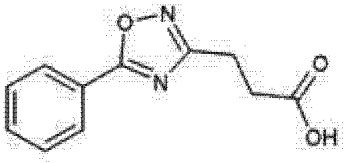
[0134] ^{1}H NMR (400 MHz, DMSO-d6) : δ 8.20-8.26 (m, 3H), 8.00-8.10 (m, 1H), 7.88-7.90 (m, 1H), 7.47-7.57 (m, 3H), 3.50-3.53 (m, 2H), 2.62-2.65 (m, 2H). HPLC (方法 A) Rt. 3.9 min, HPLC 纯度 99.5 %

中间体 7 :3-(N- 羟基甲脒基)- 丙酸甲基酯



将 3- 氰基丙酸甲基酯 (2.00 g, 17.7 mmol)、羟胺盐酸盐 (1.80 g, 26.5mmol) 和三乙胺 (5 mL, 35 mmol) 在乙醇中的混合物于 85℃回流 2h。蒸发反应混合物并与甲苯共沸三次并无须进一步纯化而直接用于随后的步骤 (2.5 g, 96%)。

[0135] 中间体 8 :3-(5- 苯基 -[1,2,4] 噁二唑 -3- 基)- 丙酸



步骤 1 :3-(5- 苯基 -[1,2,4] 噁二唑 -3- 基)- 丙酸甲基酯

于室温下,将苯甲酸 (2.00 g, 16.4 mmol) 和 1.1 ’- 羰基二咪唑 (3.8 g, 18 mmol) 在二甲基甲酰胺 (25 mL) 中搅拌 2h。然后加入 3-(N- 羟基甲脒基)- 丙酸甲基酯 (中间体 7 ;2.5 g, 18 mmol) 并将反应混合物于室温下搅拌过夜。然后将反应混合物于 100℃加热 2h。用乙酸乙酯稀释反应混合物并用盐水洗涤。有机层经硫酸钠干燥并浓缩。粗品经硅胶柱层析纯化,采用二氯甲烷和甲醇作为洗脱剂。

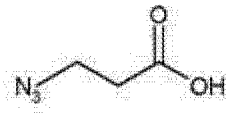
[0136] ^{1}H NMR (400 MHz, DMSO-d6) : δ 8.06-8.09 (m, 2H), 7.67-7.72 (m, 1H), 7.60-7.64 (m, 2H), 3.61 (s, 3H), 3.03-3.06 (m, 2H), 2.80-2.84 (m, 2H). MS(ESI+) :233.0, HPLC (方法 A) Rt 3.9 min, HPLC 纯度 95.5 %

步骤 2 :3-(5- 苯基 -[1,2,4] 噁二唑 -3- 基)- 丙酸

将 3-(5- 苯基 -[1,2,4] 噁二唑 -3- 基)- 丙酸甲基酯 (800 mg, 3.44 mmol) 在四氢呋喃 : 水 (4:1) 中的溶液用 LiOH.H_2O (400 mg, 10.3 mmol) 处理并将反应混合物于室温下搅拌过夜。在减压下除去溶剂,残留物用水稀释,用二氯甲烷洗涤。然后用 HCl 水溶液 (1.5 N) 中和水层并用二氯甲烷提取。有机层经硫酸钠干燥并浓缩。产物无须进一步纯化而用于随后的步骤。

[0137] ^{1}H NMR (400 MHz, DMSO-d6) : δ 8.07-8.10 (m, 2H), 7.60-7.72 (m, 3H), 2.98-3.01 (m, 2H), 2.71-2.74 (m, 2H). MS(ESI+) :219.0, HPLC (方法 A) Rt 3.1 min, HPLC 纯度 99.6 %

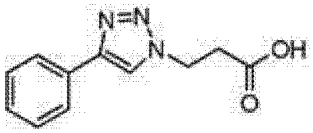
中间体 9 :3- 叠氮基 - 丙酸



将 β- 丙氨酸 (15.0 g, 168 mmol) 的无水甲醇溶液用碳酸钾 (46.3 g, 336 mmol)、

$CuSO_4.5H_2O$ (0.83 g, 3.36 mmol)和咪唑磺酰基叠氮化物(35.0 g, 202 mmol)处理并将反应混合物于室温下搅拌 16 小时。在低于 30℃的温度下,在减压下蒸发反应混合物。残留物用水稀释;将 pH 调节至 6 并用乙酸乙酯提取。将含水相的 pH 最终调节至 3 并用乙酸乙酯提取水层;分离有机层,经 Na_2SO_4 干燥并浓缩,得到粗品 3- 叠氮基 - 丙酸。

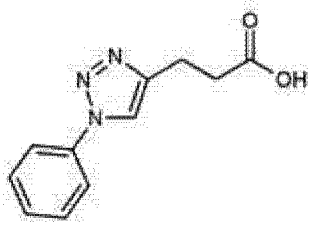
[0138] 中间体 10:3-(4- 苯基 -[1,2,3] 三唑 -1- 基)- 丙酸



将苯基乙炔(1.61 g, 15.8 mmol)和 3- 叠氮基 - 丙酸(2.0 g, 17.4 mmol)在 t-BuOH:H_2O (2:1, 45 ml)中的溶液用抗坏血酸钠(469 mg, 2.37 mmol)和 $CuSO_4.5H_2O$ (196 mg, 0.79 mmol)处理并将反应混合物于室温下搅拌 12h。将乙酸乙酯加入到反应混合物并用水提取。然后用水接着用盐水洗涤有机层。浓缩合并的有机层,在真空下干燥,得到为白色固体的标题化合物(1.6 g, 46%)。

[0139] ^1H NMR (400 MHz, DMSO-d_6):δ 12.58 (s, 1H), 8.55 (s, 1H), 7.82 (d, J= 7.4 Hz, 2H), 7.44 (t, J= 7.4 Hz, 2H), 7.32 (t, J= 7.4 Hz, 1H), 4.60 (s, 2H), 3.01 (s, 2H). MS(ESI+):218.0. HPLC (方法 A) RT 2.7 min, HPLC 纯度 99.7 %.

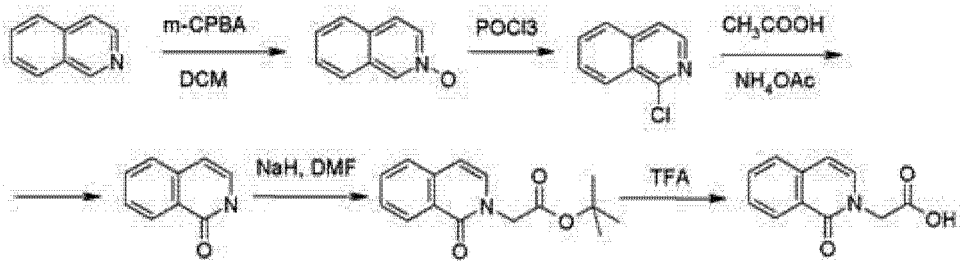
中间体 11:3-(1- 苯基 -1H-[1,2,3] 三唑 -4- 基)- 丙酸



根据对中间体 10 描述的方案制备该中间体。

[0140] ^1H NMR (400 MHz, DMSO-d_6):δ 12.25 (s, 1H), 8.57 (s, 1H), 7.87-7.85 (m, 2H), 7.60-7.56 (m, 2H), 7.46 (t, J= 7.4 Hz, 1H), 2.93 (t, J= 7.4 Hz, 2H), 2.66 (t, J= 7.4 Hz, 2H). MS(ESI+):218.2. HPLC (方法 A) RT 2.7 min, HPLC 纯度 99.8 %.

中间体 11:(1- 氧代异喹啉 -2(1H)- 基)乙酸



步骤 1:异喹啉 -N- 氧化物

将异喹啉(20.0 g, 155 mmol)的二氯甲烷(400 mL)溶液用间 - 氯过苯甲酸(40.0 g, 232 mmol)处理并将反应混合物于室温下搅拌过夜。过滤反应混合物,蒸发滤液并无须进一步纯化而用于后面的步骤(20.0 g, 89%)。

[0141] MS (ESI+):M=146.3

步骤 2 :1- 氯代异喹啉

将磷酰氯 (200 ml) 在冰冷条件下滴加到异喹啉 -N- 氧化物 (20.0 g) 中。然后将反应混合物加热至回流,于 105℃过夜。在减压下蒸发磷酰氯,然后残留物用冰骤冷并用二氯甲烷提取。分离有机层,经硫酸钠干燥并浓缩。粗品经硅胶柱层析纯化,采用乙酸乙酯和石油醚作为洗脱剂 (21.0 g ;85%)。

[0142] ^{1}H NMR (400 MHz, DMSO-d6) : δ 8.25-8.31 (m, 2H), 8.08 (d, J= 8.0 Hz, 1H), 7.88-7.91 (m, 2H), 7.80-7.84 (m, 1H). MS (ESI+) :164.0, HPLC (方法 A) Rt 8.29min ;HPLC 纯度 96.0 %

步骤 3 :异喹啉 -1(2H)- 酮

将 1- 氯代异喹啉 (8.1 g) 在冰醋酸 (170 mL) 中的溶液用乙酸铵 (25 g) 处理。然后将反应混合物于 100℃加热 3h。使反应混合物冷却至室温并在减压下蒸发溶剂。残留物用冰骤冷,过滤形成的固体并在过滤器上干燥 (5.8 g, 80%)。

[0143] ^{1}H NMR (400 MHz, DMSO-d6) : δ 11.24 (s, 1H), 8.18 (d, J= 8.4 Hz, 1H), 7.63-7.71 (m, 2H), 7.45-7.49 (m, 1H), 7.15-7.18 (m, 1H), 6.55 (d, J= 7.2 Hz, 1H). MS (ESI+) :146.0, HPLC (方法 A) Rt 2.23min ;HPLC 纯度 98.2 %

步骤 4 :(1- 氧代异喹啉 -2(1H)- 基) 乙酸叔丁酯

将异喹啉 -1(2H)- 酮 3 (1.0 g, 6.9 mmol) 和乙酸叔丁酯 (2.0 mL, 13.8 mmol) 在二甲基甲酰胺 (15 mL) 中的冷 (0℃) 溶液用氢化钠 (60% 在矿物油中 , 660 mg, 17.2 mmol) 处理。10 分钟后,将反应混合物用冰骤冷,过滤形成的固体并干燥 (1.2 g ;60%)。

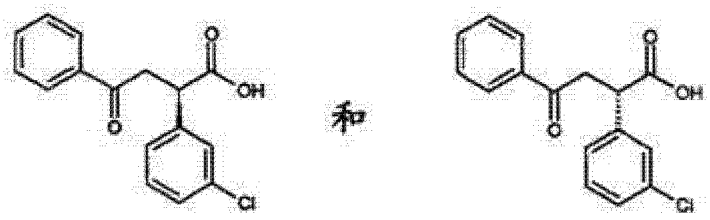
[0144] ^{1}H NMR 400 MHz, CDCI3 : δ 8.42-8.44 (m, 1H), 7.63-7.67 (m, 1H), 7.47-7.53 (m, 2H), 7.01 (d, J= 8.0 Hz, 1H), 6.53 (d, J= 8.0 Hz, 1H), 4.64 (s, 2H), 1.49 (s, 9H). MS (ESI+) :204.3, HPLC (方法 A) Rt 4.08min ;HPLC 纯度 98.4 %

步骤 5 :(1- 氧代异喹啉 -2(1H)- 基) 乙酸

将 (1- 氧代异喹啉 -2(1H)- 基) 乙酸叔丁酯 (1.2 g, 4.6mmol) 在二氯甲烷 (20 mL) 中的冷溶液用三氟乙酸 (10 mL) 逐滴处理。然后将反应混合物于室温下搅拌 3h。蒸发溶剂并使该残留物与甲苯共沸。用乙醚研磨形成的固体,得到标题化合物。

[0145] ^{1} H NMR (400 MHz, DMSO-d6) : δ 10.76 (s, 1H), 8.18-8.20 (m, 1H), 7.64-7.73 (m, 2H), 7.42-7.52 (m, 2H), 6.62 (d, J= 8.0 Hz, 1H), 4.67 (s, 2H). MS (ESI+) :204.3, HPLC (方法 A) Rt 2.34 min ;HPLC 纯度 99.3 %

中间体 12 和 13 :(+)-2-(3- 氯代苯基)-4- 氧代 -4- 苯基丁酸和 (-)-2-(3- 氯代苯基)-4- 氧代 -4- 苯基丁酸



外消旋的 2-(3- 氯代苯基)-4- 氧代 -4- 苯基丁酸通过手性制备型 HPLC 在 CHIRALPAK IA (250x20) mm, 5μm 上分离 , 流动相己烷 : 异丙基醇 (65:35), 流速 :10 ml/min。

[0146] 两种产物在 13.7 min (中间体 12) 和在 18.6 min (中间体 13) 洗脱。两种产物

采用以下 HPLC 方法分析：

柱 :CHIRALPAK AD-H (250x4.6) mm, 5μm

流动相 :0.1 %TFA 在己烷：异丙基醇 (80:20) 中

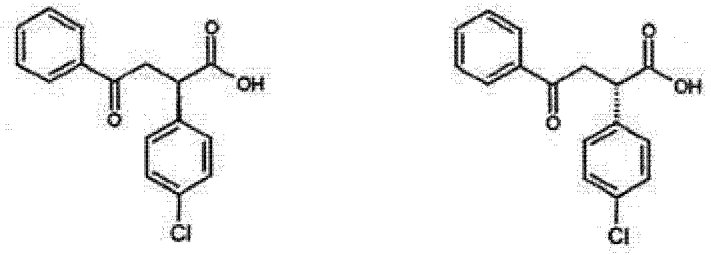
流速 :1.0ml/min

中间体 12 :Rt-10.8 min （纯度 100 %）;αD +101.9° ;乙醇， c= 1.0 g/100 mL

中间体 13 :Rt-14.9 min （纯度 99.2 %）

手性中心绝对指定作为 (R) 或者 (S) 是任意的。

[0147] 中间体 14 和 15 :(+)-2-(4- 氯代苯基)-4- 氧代 -4- 苯基丁酸和 (-)-2-(4- 氯代苯基)-4- 氧代 -4- 苯基丁酸



外消旋的 2-(4- 氯代苯基)-4- 氧代 -4- 苯基丁酸通过手性制备型 HPLC 在 CHIRALPAK IA (250x20) mm, 5μm 上分离， 流动相己烷：异丙基醇 (60:40)， 流速 :10 ml/min。

[0148] 两种产物在 14.2 min （中间体 14) 和在 21.4 min （中间体 15) 洗脱。两种产物采用以下 HPLC 方法分析：

柱 :CHIRALPAK AD-H (250x4.6) mm, 5μm

流动相 :0.1 %TFA 在己烷：异丙基醇 (80:20) 中

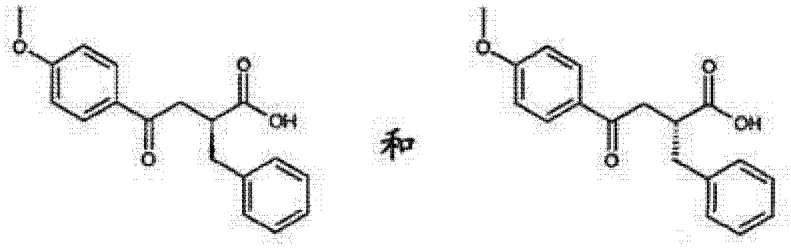
流速 :1.0ml/min

中间体 14 :Rt-15.4 min （纯度 99.3 %). αD +103.4° ;乙醇， c= 0.57 g/100 mL

中间体 15 :Rt-22.2 min （纯度 99.3 %). αD -111.5° ;乙醇， c= 0.57 g/100 mL

手性中心绝对指定作为 (R) 或者 (S) 是任意的。

[0149] 中间体 16 和 17 :(+)-2- 苄基 -4-(4- 甲氧基苯基)-4- 氧代 - 丁酸和 (-)-2- 苄基 -4-(4- 甲氧基苯基)-4- 氧代 - 丁酸



外消旋的 2- 苄基 -4-(4- 甲氧基苯基)-4- 氧代 - 丁酸通过手性制备型 HPLC 在 CHIRALCEL OJ-H (250x20) mm, 5μm 上分离， 流动相己烷：异丙基醇 (75:25)， 流速 :10 ml/min.

两种产物在 15.5 min （中间体 16) 和在 20.2 min （中间体 17) 洗脱。两种产物采用以下 HPLC 方法分析：

柱 :CHIRALCEL OJ (250x4.6) mm, 5μm

流动相 :0.1 %TFA 在己烷：异丙基醇 (90:10) 中

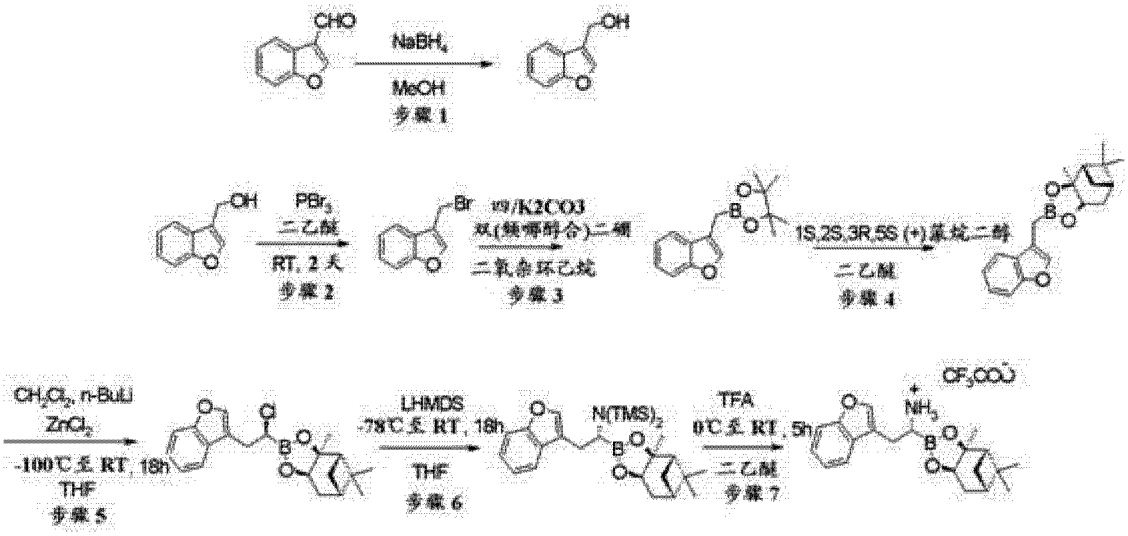
流速 :1.0ml/min

中间体 16 :Rt-22.3 min （纯度 98.7 %). αD +21.1 ° ;乙醇， c= 1.0 g/100 mL

中间体 17 :Rt-33.6 min （纯度 97.7 %). αD -21.0° ;乙醇， c= 1.0 g/100 mL)

手性中心绝对指定作为 (R) 或者 (S) 是任意的。

[0150] 中间体 18 :(1R)-2-（苯并呋喃 -3- 基）-1-(3a,5,5- 三甲基六氢 -4,6- 亚甲基苯并 [d][1,3,2] 二氧硼杂环戊烷 -2- 基）乙胺三氟乙酸盐



步骤 1 :苯并呋喃 -3- 基甲醇

将 1- 苯并呋喃 -3- 甲醛 (5g, 34.2 mmol) 的甲醇 (50 ml) 溶液用冰冷却并分部分加入硼氢化钠 (1.9g, 51.3 mmol)。将反应混合物于室温下搅拌 1 h。浓缩反应混合物，使残留物在饱和氯化铵和二氯甲烷之间分配。分离有机层，经硫酸钠干燥并浓缩。粗品 (5.0 g, 98%) 无须进一步纯化而原样用于随后的步骤。

[0151] ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.68-7.70 (m, 1H), 7.62 (s, 1H), 7.50-7.52 (m, 1H), 7.26-7.36 (m, 2H), 4.86 (s, 2H).

步骤 2 :3-（溴代甲基）苯并呋喃

将苯并呋喃 -3- 基甲醇 (5.0 g, 33.7 mmol) 在二乙醚 (50 ml) 的冷 (0℃）溶液用三溴化磷 (1.1 ml, 11.2 mmol) 处理并将反应混合物于 0℃搅拌 30 min。然后将反应混合物倾入到冰中并用乙醚提取。有机层经硫酸钠干燥并浓缩。粗品 (7.1 g, 100%) 无须进一步纯化而原样用于随后的步骤。

[0152] ^{1}H NMR (400MHz, $CDCl_3$) : δ 7.71-7.74 (m, 2H), 7.53 (s, 1H), 7.31-7.39 (m, 2H), 4.65 (s, 2H).

步骤 3 :2-（苯并呋喃 -3- 基甲基）-4,4,5,5- 四甲基 -1,3,2- 二氧硼杂环戊烷

将 3-（溴代甲基）苯并呋喃 (7.1 g, 33.8 mmol) 在脱气的 1, 4- 二氧杂环己烷 (70 ml) 中的溶液用双（频哪醇合）二硼 (10.3g, 40.5mmol)、碳酸钾 (13.9 g, 101.0mmol)、四（三苯基膦）钯 (0) (1.9 g, 1.7 mmol) 处理并将混合物于 100℃加热 12h。使烧瓶中的内容物冷却至室温并通过 C 盐床过滤。浓缩滤液，粗品经硅胶柱层析纯化，用在石油醚中的 2-5% 乙酸乙酯洗脱，得到标题化合物 (6.1 g, 69%)，为黄色油状物。

[0153] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.57 (m, 2H), 7.44-7.46 (m, 1H), 7.21-7.30 (m, 2H), 2.23 (s, 2H), 1.29 (s, 12H).

步骤 4 :2-(苯并呋喃 -3- 基甲基) 硼酸 (+)- 蒎烷二醇酯

将 2-(苯并呋喃 -3- 基甲基)-4,4,5,5- 四甲基 -1,3,2- 二氧硼杂环戊烷 (6.1 g, 23.6 mmol) 的二乙醚 (60 ml) 溶液用 (1S, 2S, 3R, 5S)-(+)- 蒎烷二醇 (6.0 g, 35.4 mmol) 处理。将反应混合物于室温下搅拌 12 h,然后混合物用水洗涤两次,然后用盐水洗涤,经无水硫酸钠干燥,然后浓缩。粗产物经硅胶柱层析纯化,用在石油醚中的 5% 乙酸乙酯洗脱 , 得到标题化合物 (6.3 g, 82%)。

[0154] ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.56-7.58 (m, 1H), 7.53-7.55 (m, 1H), 7.44-7.46 (m, 1H), 7.23-7.28 (m, 2H), 4.33 (dd, J = 1.88, 8.76 Hz, 1H), 2.32-2.34 (m, 1H), 2.28 (s, 2H), 2.21-2.22 (m, 1H), 2.08 (t, J = 5.88 Hz, 1H), 1.42 (s, 3H), 1.29 (s, 3H), 1.13 (d, J = 10.92 Hz, 1H), 0.85 (s, 3H). GCMS :m/z :310

步骤 5 :[(1S)-1- 氯代 -2-(苯并呋喃 -3- 基甲基) 硼酸 (+)- 蒎烷二醇酯

经 20 分钟向二氯甲烷 (6.3 ml, 60.9 mmol) 和无水四氢呋喃 (36 ml) 的冷却 (-100℃) 混合物中加入正丁基锂 (1.6 M 在己烷中 , 14.0 ml, (22.3 mmol)。搅拌 20 分钟后,经 20 分钟于 -100℃加入 2-(苯并呋喃 -3- 基甲基) 硼酸 (+)- 蒎烷二醇酯 (6.3 g, 20.3 mmol) 在无水 THF (22 ml) 中的溶液。然后于 -100℃经 30 分钟加入氯化锌 (0.5 M 在 THF 中 , 36.5 ml, 18.2 mmol) 溶液。使该混合物达到室温并搅拌 18 h 和浓缩。向生成的油状物中加入二乙醚和饱和的氯化铵 (各 100 ml) 并剧烈搅拌。水层用二乙醚提取 3 次,合并的有机层经无水硫酸钠干燥并真空浓缩。残留物 (7.3 g, 99%) 原样用于下一步骤。

[0155] ^{1}H NMR (400 MHz, DMSO-d6) : δ 7.57-7.60 (m, 2H), 7.47-7.49 (m, 1H), 7.25-7.31 (m, 2H), 4.34-4.36 (m, 1H), 3.29-3.31 (m, 1H), 3.22-3.24 (m, 1H), 2.31-2.35 (m, 1H), 2.12-2.14 (m, 1H), 2.06 (t, J = 5.84 Hz, 1H), 1.86-1.90 (m, 2H), 1.42 (s, 3H), 1.04 (d, J = 11.04 Hz, 1H), 0.85 (s, 3H). GCMS :m/z :358.2

步骤 6 :[(1R)-1-[双 (三甲基甲硅烷基) 氨基]- 2-(苯并呋喃 -3- 基甲基) 硼酸 (+)- 蒎烷二醇酯

向 [(1S)-1- 氯代 -2-(苯并呋喃 -3- 基甲基) 硼酸 (+)- 蒎烷二醇酯 (7.3 g, 20.3 mmol) 在 40 ml 无水四氢呋喃中的冷却 (-78℃) 溶液中加入双 (三甲基甲硅烷基) 氨化锂 (1 M 在 THF 中 , 25.5 ml, 25.5 mmol)。使该混合物达到室温,搅拌 18 h 并浓缩至干。向生成的残留物中加入己烷,然后滤除沉淀的固体。浓缩滤液得到所需的粗产物 (6.7 g, 68%),其无须进一步纯化而用于随后的步骤。

[0156] ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.59-7.60 (m, 1H), 7.45-7.50 (m, 2H), 7.24-7.28 (m, 2H), 4.31 (dd, J = 1.56, 8.70 Hz, 1H), 3.14-3.18 (m, 1H), 2.90-2.92 (m, 1H), 2.72-2.75 (m, 1H), 2.30-2.34 (m, 1H), 2.14-2.15 (m, 1H), 2.03 (t, J = 5.68 Hz, 1H), 1.80-1.88 (m, 2H), 1.39 (s, 3H), 1.30 (s, 3H), 1.01 (d, J = 10.88 Hz, 1H), 0.84 (s, 3H), 0.09 (s, 18H).

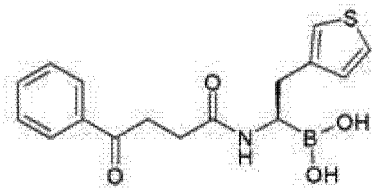
步骤 7 :[(1R)-1- 氨基 -2-(苯并呋喃 -3- 基甲基) 硼酸 (+)- 蒎烷二醇酯三氟乙酸盐

将 [(1R)-1-[双 (三甲基甲硅烷基) 氨基]- 2-(苯并呋喃 -3- 基甲基) 硼酸 (+)- 蒎烷二醇酯 (6.7 g, 13.9 mmol) 在二乙醚 (30 ml) 中的冷却 (0℃) 溶液用三氟乙酸 (3.2 ml, 41.7 mmol) 滴加处理。反应混合物在低于 30℃温度下在减压下蒸发。使粗品溶于甲

苯并蒸发，并将此顺序重复 4 次。获得的白色固体 (2.3 g, 36%)，其无须进一步纯化而用于随后的步骤。

[0157] ^{1}H NMR (400 MHz, DMSO-d_6) : δ 7.66 (s, 1H), 7.60-7.61 (m, 1H), 7.45-7.47 (m, 1H), 7.20-7.29 (m, 2H), 4.28-4.30 (m, 1H), 3.16-3.27 (m, 3H), 2.13-2.25 (m, 3H), 1.94 (t, J = 5.56 Hz, 1H), 1.81-1.86 (m, 2H), 1.25 (s, 6H), 1.01 (d, J = 8.00 Hz, 1H), 0.75 (s, 3H).

实施例 1 :[(1R)-1-[(4- 氧代 -4- 苯基丁酰基) 氨基]-2-(3- 噻吩基) 乙基] 硼酸



步骤 1 :[(1R)-1-[(4- 氧代 -4- 苯基丁酰基) 氨基]-2-(3- 噻吩基) 乙基] 硼酸 (+)- 蒎烷二醇酯

将中间体 1 (100 mg, 0.24 mmol) 在无水二氯甲烷 (15 ml) 中的冷却 (0℃) 溶液用二异丙基乙胺 (0.12 ml, 0.72 mmol) 和 3- 苯甲酰基丙酸 (42 mg, 0.24 mmol) 和 TBTU (91 mg, 0.29 mmol) 处理。将反应混合物于 0℃搅拌 3h。在减压下浓缩反应混合物，保持外浴温度低于 30℃，然后加入 10 ml 乙酸乙酯。有机层用盐水洗涤，经硫酸钠干燥并浓缩。所需产物经硅胶层析纯化来分离，用石油醚 / 乙酸乙酯 1:1 洗脱。

[0158] MS (ESI+) :466.3, HPLC (方法 A) :Rt 5.44min 85.0 %

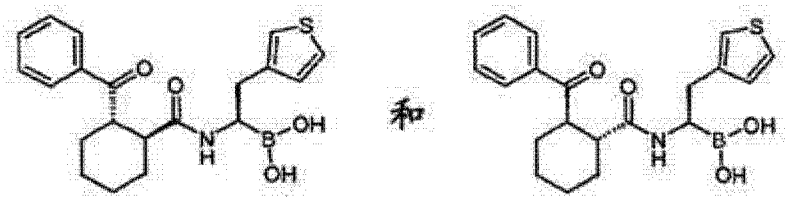
步骤 2 :[(1R)-1-[(4- 氧代 -4- 苯基丁酰基) 氨基]-2-(3- 噻吩基) 乙基] 硼酸

将 [(1R)-1-[(4- 氧代 -4- 苯基丁酰基) 氨基]-2-(3- 噻吩基) 乙基] 硼酸 (+)- 蒎烷二醇酯 (74 mg, 0.16 mmol) 在甲醇 / 戊烷 (1:1, 15 ml) 中的冷却 (0℃) 溶液用 2- 甲基丙基硼酸 (64 mg, 0.636mmol) 和 HCl 水溶液 (1.5 N, 0.4 mL) 处理并将反应混合物于室温下搅拌 15 h。然后用戊烷提取反应混合物三次。在低于 30℃的温度下浓缩含水的甲醇层。残留物用冰处理，用 NaOH 水溶液 (2N) 碱化并用二氯甲烷提取三次。然后用 HCl 水溶液 (1.5 N) 酸化水层并用二氯甲烷提取两次。DCM 层经硫酸钠干燥、过滤并浓缩，得到固体残留物，其经高效硅胶快速层析纯化，获得为白色固体的标题化合物。

[0159] ^{1}H NMR (400 MHz, DMSO-d6) : δ 8.66 (s, 1H), 7.89-7.94 (m, 2H), 7.58-7.62 (m, 1H), 7.45-7.49 (m, 2H), 7.29-7.31 (m, 1H), 7.04 (s, 1H), 6.92-6.93 (m, 1H), 3.24-3.26 (m, 2H), 2.68-2.72 (m, 2H), 2.55-2.58 (m, 3H). MS (ESI+) :314.0 [M+H-H_2O], HPLC (方法 A) :Rt 2.89min ;HPLC 纯度 95.8 %。

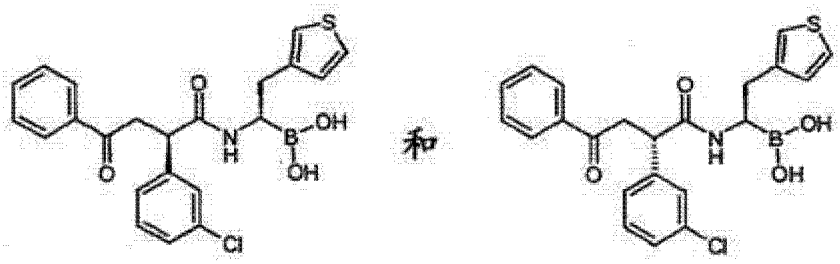
[0160] 以下化合物采用实施例 1 遵照的相同程序合成 :

实施例 2 :[(1R)-1-({[(1RS,2RS)-2- 苯甲酰基环己基] 羰基 } 氨基)-2-(3- 噻吩基) 乙基] 硼酸



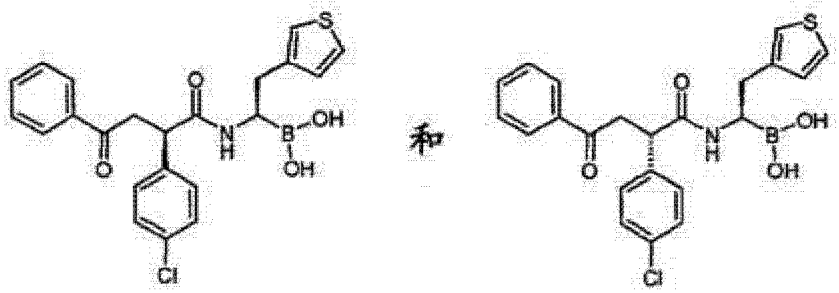
该实施例为非对映体的混合物。在环己烷环上的手性中心具有反式构型。从得自 Rielke Chemicals 的反式 -2- 苯甲酰基环己烷 -1- 羧酸起始制备。淡粉红色固体。^{1}H NMR (400 MHz, DMSO-d6) :δ 8.14-8.84 (m, 1H), 7.82-7.91 (m, 2H), 7.25-7.58 (m, 4H), 6.77-6.88 (m, 2H), 3.60-3.63 (m, 1H), 2.63-2.69 (m, 1H), 2.43-2.49 (m, 1H), 2.13-2.28 (m, 1H), 1.86-1.89 (m, 1H), 1.66-1.76 (m, 3H), 1.30-1.40 (m, 2H), 1.18-1.23 (m, 3H), 1.06-1.08 (m, 2H). MS (ESI+) :368.0 [M+H-H_2O], HPLC (方法A) : Rt 3.71 min ;HPLC 纯度 50.6%+45.6%。

[0161] 实施例 3 :[(1R)-1-{[2-(RS)-(3- 氯代苯基)-4- 氧代 -4- 苯基丁酰基] 氨基 }-2-(3- 噻吩基) 乙基] 硼酸



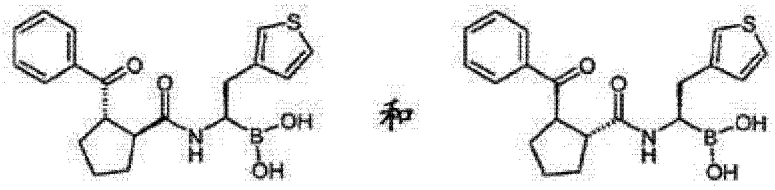
该实施例为非对映体的混合物。灰白色固体。^{1} H NMR (400 MHz, DMSO-d6) :δ 7.95-7.96 (m, 2H), 7.58-7.60 (m, 1H), 7.48-7.50 (m, 2H), 7.42-7.44 (m, 1H), 7.22-7.34 (m, 4H), 6.88-6.95 (m, 1H), 6.60-6.62 (m, 1H), 4.13 (t, J= 5.1 Hz, 1H), 3.75-3.85 (m, 1H), 3.24-3.28 (m, 2H), 2.64-2.73 (m, 2H). MS (ESI+) :424.0 [M+H-H_2O], HPLC (方法 A) :Rt 8.57 ;8.96min ;HPLC 纯度 28.7%+67.9%。

[0162] 实施例 4 :[(1R)-1-{[2-(RS) -(4- 氯代苯基)-4- 氧代 -4- 苯基丁酰基] 氨基 }-2-(3- 噻吩基) 乙基] 硼酸



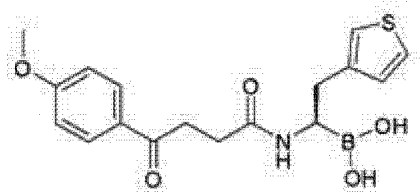
该实施例为非对映体的混合物。白色固体。^{1} H NMR (400 MHz, DMSO-d6) :δ 7.95-7.95 (m, 2H), 7.60-7.62 (m, 1H), 7.48-7.52 (m, 2H), 7.31-7.41 (m, 6H), 6.88-6.97 (m, 1H), 6.63-6.64 (m, 1H), 4.12-4.15 (m, 1H), 3.85-3.95 (m, 1H), 3.25-3.29 (m, 1H), 3.12-3.14 (m, 1H), 2.66-2.75 (m, 2H). MS (ESI+) :424.0 [M+H-H_2O], HPLC (方法 A) :Rt 8.56 ;8.97min ;HPLC 纯度 40.0%+53.4%。

[0163] 实施例 5 :[1-({[(1RS,2SR)-2- 苯甲酰基环戊基] 羰基 } 氨基)-2-(3- 噻吩基) 乙基] 硼酸



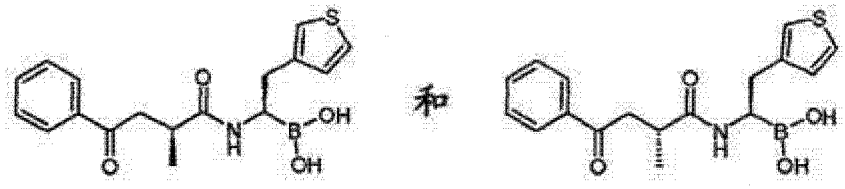
该实施例为非对映体的混合物。在环己烷环上的手性中心具有反式构型。从得自 Rielke Chemicals 的反式 -2- 苯甲酰基环戊烷 -1- 甲酸起始制备。灰白色固体。[1] H NMR (400 MHz, DMSO-d6) :δ 7.91-7.93 (m, 1H), 7.82-7.84 (m, 1H), 7.59-7.61 (m, 1H), 7.55-7.57 (m, 1H), 7.33 (s, 1H), 7.25-7.26 (m, 1H), 6.87-6.92 (m, 1H), 6.78-6.86 (m, 1H), 4.01-4.02 (m, 1H), 3.00-3.15 (m, 2H), 2.66-2.68 (m, 2H), 2.00-2.03 (m, 1H), 1.85-1.92 (m, 1H), 1.56-1.68 (m, 4H). MS (ESI+) :354.3 [M+H-H_2O], HPLC (方法 A) :Rt 3.53min ;HPLC 纯度 92.0 %。

[0164] 实施例 9 :[(1R)-1-{[4-(4- 甲氧基苯基)-4- 氧代丁酰基] 氨基 }-2-(3- 噻吩基) 乙基] 硼酸



灰白色固体。[1] H NMR (400 MHz, DMSO-d6) :δ 8.65 (s, 1H), 7.87-7.92 (m, 2H), 7.30-7.35 (m, 1H), 7.04 (s, 1H), 6.95-6.98 (m, 2H), 6.92-6.93 (m, 1H), 3.81 (s, 3H), 3.18-3.20 (m, 2H), 2.65-2.74 (m, 2H), 2.52-2.55 (m, 3H). MS (ESI+) : 344.3 [M+H-H_2O], HPLC (方法 A) :Rt 3.00min ;HPLC 纯度 96.2 %。

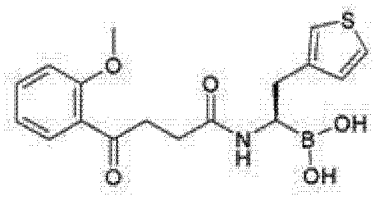
[0165] 实施例 10 :[(1R)-1-[(2-(RS) - 甲基 -4- 氧代 -4- 苯基丁酰基) 氨基]-2-(3- 噻吩基) 乙基] 硼酸



该实施例为非对映体的混合物。在环己烷环上的手性中心具有反式构型。由得自 ABCR 的 2- 甲基 -4- 氧代 -4- 苯基丁酸起始制备。灰白色固体。[1]H NMR (400 MHz, DMSO-d6) : δ 8.56-8.61 (m, 1H), 7.87-7.91 (m, 2H), 7.57-7.59 (m, 1H), 7.46-7.51 (m, 2H), 7.26-7.28 (m, 1H), 7.09 (s, 1H), 6.93 (s, 1H), 3.20-3.30 (m, 1H), 3.04-3.09 (m, 1H), 2.93-2.96 (m, 1H), 2.65-2.74 (m, 2H), 2.48-2.50 (m, 1H), 1.02-1.05 (m, 3H). MS (ESI+) :328.3 [M+H-H_2O], HPLC (方法 A) :Rt 3.15min ;

HPLC 纯度 87.0%。

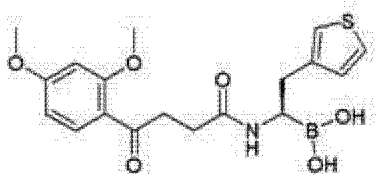
[0166] 实施例 12 :[(1R)-1-{[4-(2- 甲氧基苯基)-4- 氧代丁酰基] 氨基 }-2-(3- 噻吩基) 乙基] 硼酸



白色固体。^{1} H NMR (400 MHz, DMSO-d6) : δ 7.51-7.53 (m, 2H), 7.49 (s, 1H), 7.14 (d, J= 8.1 Hz, 1H), 7.07 (s, 1H), 7.00-7.06 (m, 1H), 6.92-6.94 (m, 1H), 3.84 (s, 3H), 3.07-3.13 (m, 3H), 2.80-2.81 (m, 1H), 2.76-2.78 (m, 1H), 2.38 (t, J= 7.0 Hz, 2H).

MS (ESI+) :344.0 [M+H-H_2O], HPLC (方法 A) :Rt 3.03 ;HPLC 纯度 93.2%。

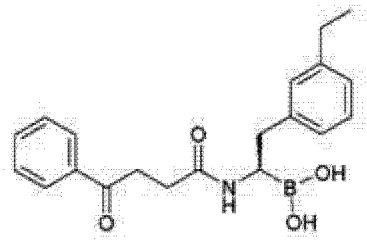
[0167] 实施例 13 :[(1R)-1-{[4-(2,4- 二甲氧基苯基)-4- 氧代丁酰基] 氨基 }-2-(3- 噻吩基) 乙基] 硼酸



白色固体。^{1} H NMR (400 MHz, DMSO-d6) : δ 7.63 (d, J= 8.6 Hz, 1H), 7.34-7.36 (m, 1H), 7.06 (s, 1H), 6.94 (s, 1H), 6.57-6.60 (m, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.04-3.10 (m, 3H), 2.75-2.80 (m, 1H), 2.65-2.71 (m, 1H), 2.34-2.35 (m, 2H).

MS (ESI+) :374.0 [M+H-H_2O], HPLC (方法 A) :Rt 3.13 ;3.41 min ;HPLC 纯度 99.0% 。

[0168] 实施例 6 :{(1R)-2-(3- 乙基苯基)-1-[(4- 氧代 -4- 苯基丁酰基) 氨基] 乙基 } 硼酸



步骤 1 :{(1R)-2-(3- 乙基苯基)-1-[(4- 氧代 -4- 苯基丁酰基) 氨基] 乙基 } 硼酸 (+)- 蒎烷二醇酯

将中间体 2 (150 mg, 0.34 mmol) 在无水二甲基甲酰胺 (10 ml) 中的冷 (-10℃) 溶液用二异丙基乙胺 (0.17 ml, 1.0 mmol)、3- 苯甲酰基丙酸 (60 mg, 0.340mmol) 和 TBTU (130 mg, 0.41 mmol) 处理。将反应混合物于 -10℃搅拌 3h,然后在减压下浓缩,保持外浴温度低于 30℃,然后加入 10 ml 乙酸乙酯。有机层用盐水洗涤,经硫酸钠干燥并浓缩。所需产物 (120 mg, 72%) 经硅胶快速层析纯化来分离,用石油醚 / 乙酸乙酯 1:1 洗脱。MS (ESI+) : 488.3, HPLC (方法 A) :Rt 6.08min ;HPLC 纯度 91.0%。

[0169] 步骤 2 :{(1R)-2-(3- 乙基苯基)-1-[(4- 氧代 -4- 苯基丁酰基) 氨基] 乙基 } 硼酸

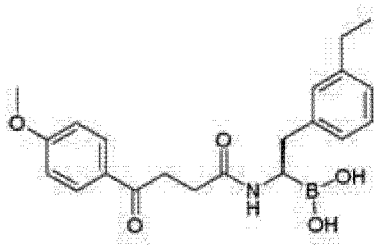
将 {(1R)-2-(3- 乙基苯基)-1-[(4- 氧代 -4- 苯基丁酰基) 氨基] 乙基 } 硼酸 (+)- 蒎

烷二醇酯 (120 mg, 0.25 mmol) 在甲醇 / 戊烷 (1:1, 15ml) 中的冷 (0℃) 溶液用 2- 甲基丙基硼酸 (99 mg, 0.99 mmol) 和 HCl 水溶液 (1.5 N, 0.5 mL) 处理并将反应混合物于室温下搅拌 15 h。然后用戊烷提取反应混合物三次。在低于 30℃的温度下浓缩含水甲醇层。残留物经高效硅胶快速层析纯化，获得固体，其用戊烷研磨，得到为灰白色固体的标题化合物。

[0170] ^{1}H NMR (400 MHz, DMSO-d6) : δ 7.91-7.92 (m, 2H), 7.70-7.72 (m, 1H), 7.60-7.62 (m, 2H), 7.10-7.14 (m, 1H), 6.94-6.98 (m, 3H), 3.12-3.18 (m, 3H), 2.73-2.76 (m, 1H), 2.64-2.67 (m, 1H), 2.51-2.55 (m, 2H), 2.40-2.43 (m, 2H), 1.13 (t, J= 7.6 Hz, 3H). MS (ESI+) :336.0 [M+H-H_2O], HPLC (方法 A) :Rt 3.75min ; HPLC 纯度 96.8%。

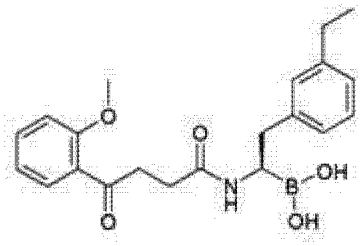
[0171] 以下化合物采用实施例 6 遵照的相同程序合成 :

实施例 7 :((1R)-2-(3- 乙基苯基)-1-{[4-(4- 甲氧基苯基)-4- 氧代丁酰基] 氨基 } 乙基) 硼酸



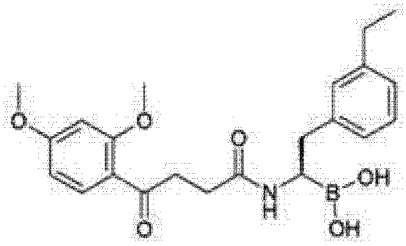
灰白色固体。^{1}H NMR (400 MHz, DMSO-d6) : δ 7.85-7.90 (m, 2H), 6.91-7.13 (m, 6H), 3.81 (s, 3H), 3.52-3.54 (m, 1H), 3.09-3.18 (m, 2H), 2.65-2.68 (m, 2H), 2.52-2.54 (m, 2H), 2.46-2.48 (m, 1H), 2.37-2.40 (m, 1H), 1.06-1.15 (m, 3H). MS (ESI+) :366.3 [M+H-H_2O], HPLC (方法 A) :Rt 3.77min ;HPLC 纯度 96.4%。

[0172] 实施例 8 :((1R)-2-(3- 乙基苯基)-1-{[4-(2- 甲氧基苯基)-4- 氧代丁酰基] 氨基 } 乙基) 硼酸



灰白色固体。^{1}H NMR (400 MHz, DMSO-d6) : δ 7.49-7.53 (m, 2H), 7.10-7.15 (m, 2H), 6.93-7.02 (m, 4H), 3.84 (s, 3H), 3.05-3.14 (m, 3H), 2.76-2.78 (m, 1H), 2.73-2.74 (m, 1H), 2.48-2.49 (m, 2H), 2.33-2.37 (m, 2H), 1.08-1.14 (m, 3H). MS (ESI+) :366.3 [M+H-H_2O], HPLC (方法 A) :Rt 3.81 min ;HPLC 纯度 90.1%。

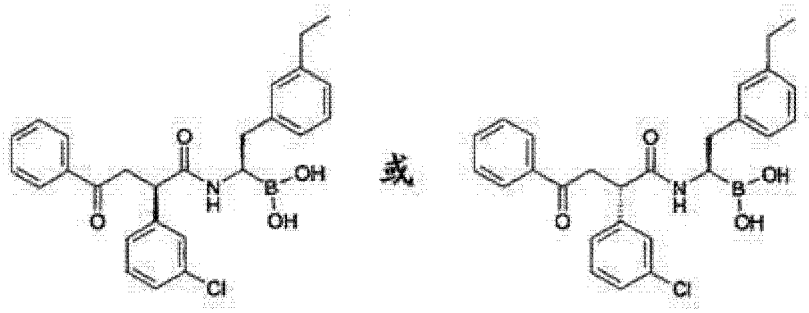
[0173] 实施例 11 :[(1R)-1-{[4-(2,4- 二甲氧基苯基)-4- 氧代丁酰基] 氨基 }-2-(3- 乙基苯基) 乙基] 硼酸



灰白色固体。^{1}H NMR (400 MHz, DMSO-d6) : δ 8.49 (s, 1H), 7.64 (d, J= 8.7 Hz, 1H), 7.04-7.07 (m, 1H), 6.99 (s, 1H), 6.90-6.93 (m, 2H), 6.52-6.58 (m, 2H), 3.79 (s, 6H), 3.10-3.14 (m, 2H), 2.66-2.74 (m, 2H), 2.48-2.49 (m, 1H), 2.48 (m, 4H), 1.10 (t, J= 7.6 Hz, 3H).

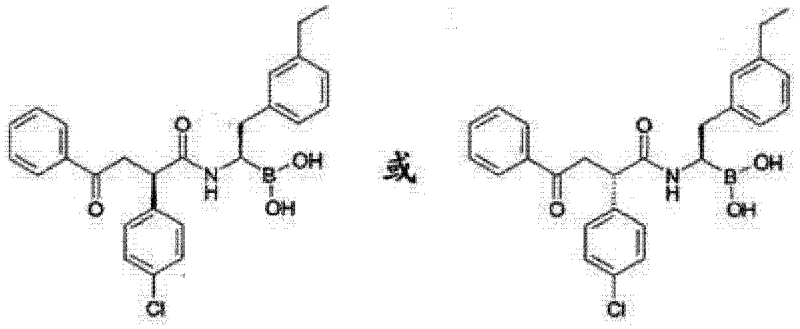
MS (ESI+) :396.2 [M+H-H_2O], HPLC (方法A) :Rt 3.85min ;HPLC 纯度 97.7 %。

[0174] 实施例 14 :[(1R)-1-{[(2R)-2-(3- 氯代苯基)-4- 氧代 -4- 苯基丁酰基]氨基}-2-(3- 乙基苯基) 乙基] 硼酸



白色固体。一种非对映体。大多数从硼酸基团移动的手性位置的构型被任意指定。该实施例由中间体 12 (+)-2-(3- 氯代苯基)-4- 氧代 -4- 苯基丁酸制备 (具有 αD +101.9° ; 乙醇, c= 1.0 g/100 ml). ^{1}H NMR (400 MHz, DMSO-d6) : δ 7.95 (d, J= 8.0 Hz, 2H), 7.61- 7.63 (m, 1H), 7.49-7.53 (m, 2H), 7.27-7.41 (m, 4H), 7.04-7.07 (m, 1H), 6.91-6.96 (m, 2H), 6.79-6.81 (m, 1H), 4.07-4.11 (m, 1H), 3.71-3.76 (m, 1H), 3.29-3.34 (m, 1H), 3.05-3.10 (m, 1H), 2.62-2.73 (m, 2H), 2.48-2.49 (m, 1H), 1.08 (t, J= 8.0 Hz, 3H). MS (ESI+) :446.0 [M+H- H_2O], HPLC (方法A) :Rt 5.02min ; HPLC 纯度 85.1 %。

[0175] 实施例 15 :[(1R)-1-{[(2R)-2-(4- 氯代苯基)-4- 氧代 -4- 苯基丁酰基]氨基}-2-(3- 乙基苯基) 乙基] 硼酸

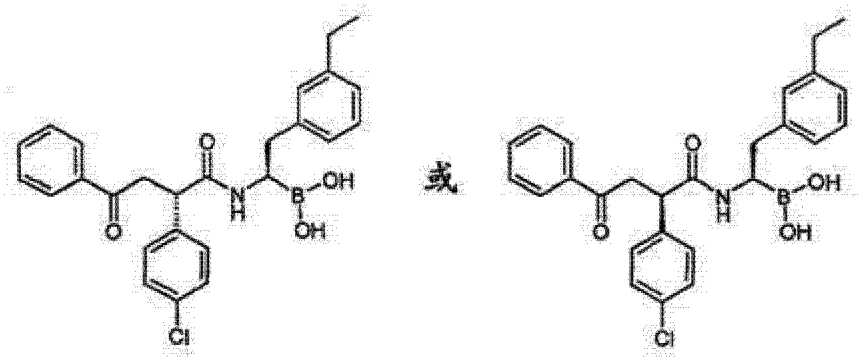


一种非对映体。大多数从硼酸基团移动的手性位置的构型被任意指定。该实施例由中间体 14 (+)-2-(4- 氯代苯基)-4- 氧代 -4- 苯基丁酸制备 (具有 αD +103.4° ;乙

醇，c= 0.57 g/100 mL). 灰白色固体. ^{1}H NMR (400 MHz, DMSO-d6)：δ 8.50 (s, 1H), 7.93-7.95 (m, 2H), 7.60-7.63 (m, 1H), 7.46-7.49 (m, 2H), 7.14-7.19 (m, 3H), 7.00-7.04 (m, 1H), 6.90-6.92 (m, 1H), 6.78-6.80 (m, 2H), 4.15-4.18 (m, 1H), 3.75-3.82 (m, 1H), 3.32-3.34 (m, 1H), 2.59-2.62 (m, 1H), 2.38-2.44 (m, 2H), 2.21-2.26 (m, 1H), 1.07 (t, J= 8.0 Hz, 3H).

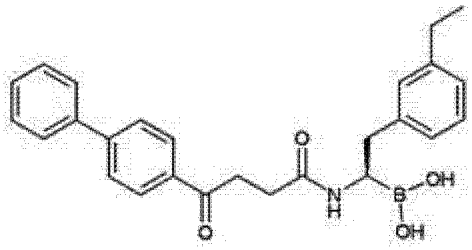
MS (ESI+)：446.3 [M+H-H_2O], HPLC（方法A)：Rt 13.54min；HPLC纯度97.1 %, CHIRAL HPLC Rt 5.48 min (98.3%)。

[0176] 实施例16：[(1R)-1-{[(2R)-2-(4-氯代苯基)-4-氧代-4-苯基丁酰基]氨基}-2-(3-乙基苯基）乙基]硼酸



一种非对映体。大多数从硼酸基团移动的手性位置的构型被任意指定。该实施例由中间体15 (-)-2-(4-氯代苯基)-4-氧代-4-苯基丁酸起始制备（具有 αD -11 1.5°；乙醇，c= 0.57 g/100 ml). 淡粉红色固体. ^{1}H NMR (400 MHz, DMSO-d6)：δ 8.75 (s, 1H), 7.85-7.87 (m, 2H), 7.55-7.59 (m, 1H), 7.41-7.43 (m, 2H), 7.30-7.39 (m, 2H), 7.21-7.23 (m, 2H), 7.00-7.04 (m, 1H), 6.89-6.91 (m, 1H), 6.83-6.85 (m, 1H), 4.17-4.21 (m, 1H), 3.67-3.74 (m, 1H), 3.39-3.40 (m, 2H), 2.63-2.67 (m, 1H), 2.57-2.59 (m, 1H), 2.45-2.48 (m, 2H), 1.10 (t, J= 7.6 Hz, 3H). MS (ESI+)：446.3 [M+H-H_2O], HPLC（方法A)：Rt 13.58min；HPLC纯度97.1 %, CHIRAL HPLC Rt 8.15 min (98.3%)。

[0177] 实施例17：[(1R)-1-[(4-联苯-4-基-4-氧代丁酰基）氨基]-2-(3-乙基苯基）乙基]硼酸



步骤1：[(1R)-1-[(4-联苯-4-基-4-氧代丁酰基）氨基]-2-(3-乙基苯基）乙基]硼酸 (+)-蒎烷二醇酯

将中间体2 (300 mg, 0.68 mmol) 在无水N,N-二甲基甲酰胺 (25 ml) 中的冷 (-10℃) 溶液用N,N-二异丙基乙胺 (0.35 ml, 2.0 mmol)、3-(4-苯基苯甲酰基）丙酸 (173 mg, 0.68 mmol) 和TBTU (262 mg, 0.815mmol) 处理。将反应混合物于-10℃搅拌3h，然后用乙酸乙酯稀释并用盐水反复洗涤。分离有机层，经硫酸钠干燥并浓缩。经硅胶快速层析纯化

粗品，用乙酸乙酯和石油醚洗脱（淡黄色胶状液体）。

[0178] MS (ESI+)：564.3；HPLC（方法A)：Rt. 6.6 min；HPLC纯度97.7 %；CHIRAL HPLC（方法A)：Rt. 4.5 min；HPLC纯度98.5 %

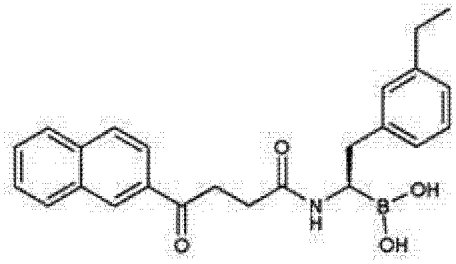
步骤2：[(1R)-1-[(4-联苯-4-基-4-氧代丁酰基）氨基]-2-(3-乙基苯基）乙基]硼酸

将[(1R)-1-[(4-联苯-4-基-4-氧代丁酰基）氨基]-2-(3-乙基苯基）乙基]硼酸(+)-蒎烷二醇酯(167 mg, 0.296 mmol)在甲醇/戊烷(1:1, 30mL)中的冷(0℃）溶液用2-甲基丙基硼酸(120 mg, 1.18 mmol)和HCl水溶液(1.5 N, 0.8 ml)处理。将反应混合物于室温下搅拌15h，然后在减压下蒸发。经硅胶快速层析纯化粗品，用二氯甲烷和甲醇洗脱，获得为灰白色固体的标题化合物。

[0179] ^{1}H NMR (400 MHz, DMSO-d6)：δ 7.95-7.94 (m, 2H), 7.67-7.73 (m, 4H), 7.41-7.49 (m, 3H), 7.05-7.09 (m, 1H), 6.91-7.09 (m, 3H), 3.27-3.38 (m, 3H), 2.72-2.77 (m, 2H), 2.57-2.62 (m, 2H), 2.46-2.50 (m, 2H), 1.07-1.11 (m, 3H). MS (ESI+)：412.0 [M+H-H_2O]. HPLC（方法B)：Rt 13.1 min；HPLC纯度91.9 %。

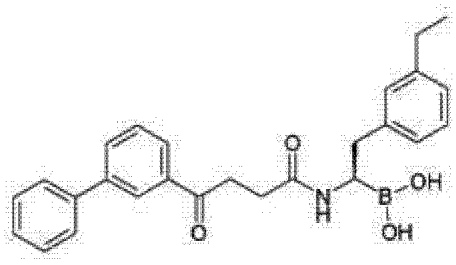
[0180] 以下产物根据对实施例17描述的相同两步方案制备：

实施例18：((1R)-2-(3-乙基苯基)-1-{[4-(2-萘基)-4-氧代丁酰基]氨基}乙基）硼酸



灰白色固体。^{1}H NMR (400 MHz, DMSO-d6)：δ 8.59 (s, 1H), 8.04 (d, J= 8.1 Hz, 1H), 7.89-7.95 (m, 3H), 7.55-7.66 (m, 2H), 6.94-7.05 (m, 3H), 6.87-6.89 (m, 1H), 3.40-3.42 (m, 2H), 2.73-2.76 (m, 2H), 2.64-2.66 (m, 2H), 2.40-2.50 (3H, m), 1.07 (t, J= 7.5 Hz, 3H). MS (ESI+)：386.3 [M+H-H_2O]；HPLC（方法B)：Rt 12.7 min, HPLC纯度96.1 %。

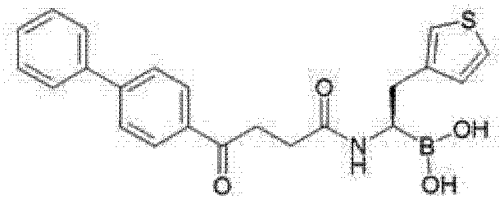
[0181] 实施例19：[(1R)-1-[(4-联苯-3-基-4-氧代丁酰基）氨基]-2-(3-乙基苯基）乙基]硼酸



灰白色固体。^{1}H NMR (400 MHz, DMSO-d6)：δ 8.13 (s, 1H), 7.88 (d, J= 7.8 Hz, 2H), 7.78 (d, J= 8.6 Hz, 2H), 7.52-7.56 (m, 1H), 7.42-7.48 (m, 2H), 7.36-7.39 (m, 1H), 7.01-7.03 (m, 1H), 6.93-6.98 (m, 2H), 6.87 (d, J= 7.2 Hz, 1H),

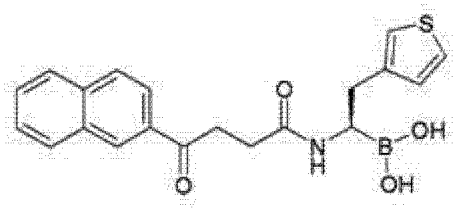
3.31-0.00 (m, 2H), 2.70-2.80 (m, 2H), 2.48-2.62 (m, 5H), 1.05-1.09 (m, 3H). MS (ESI+) :412.0 [M+H-H_2O] ;HPLC (方法 A) :Rt. 4.6 min, HPLC 纯度 96.4 %。

[0182] 实施例 20 :[(1R)-1-[(4- 联苯 -4- 基 -4- 氧代丁酰基) 氨基]-2-(3- 噻吩基) 乙基] 硼酸



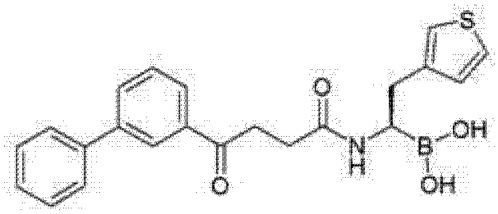
白色固体。^{1}H NMR (400 MHz, DMSO-d6) : δ 7.98 (d, J= 8.0 Hz, 2H), 7.68-7.76 (m, 4H), 7.46-7.52 (m, 2H), 7.39-7.41 (m, 1H), 7.30 (m, 1H), 7.05 (s, 1H), 6.94 (d, J= 4.8 Hz, 1H), 3.29-3.31 (m, 2H), 2.70-2.72 (m, 2H), 2.54-2.59 (m, 3H). MS (ESI+) :390.0 [M+H-H_2O]. HPLC (方法 A) :Rt. 4.0 min, HPLC 纯度 97.8 %。

[0183] 实施例 21 :[(1R)-1-{[4-(2- 萘基)-4- 氧代丁酰基] 氨基}-2-(3- 噻吩基) 乙基] 硼酸



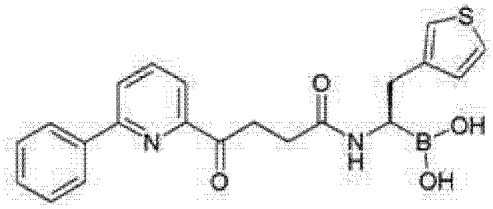
白色固体。^{1} H NMR (400 MHz, DMSO-d6) : δ 8.65 (s, 1H), 8.13 (d, J= 8.0 Hz, 1H), 7.94-8.02 (m, 3H), 7.59-7.67 (m, 2H), 7.36-7.38 (m, 1H), 7.10 (s, 1H), 6.95-6.96 (m, 1H), 3.32-3.35 (m, 2H), 3.14-3.17 (m, 1H), 2.70-2.83 (m, 2H), 2.48-2.50 (m, 2H). MS (ESI+) :364.0 [M+H-H_2O] ;HPLC (方法 A) :Rt. 3.6 min, HPLC 纯度 95.6 %。

[0184] 实施例 22 :[(1R)-1-[(4- 联苯 -3- 基 -4- 氧代丁酰基) 氨基]-2-(3- 噻吩基) 乙基] 硼酸



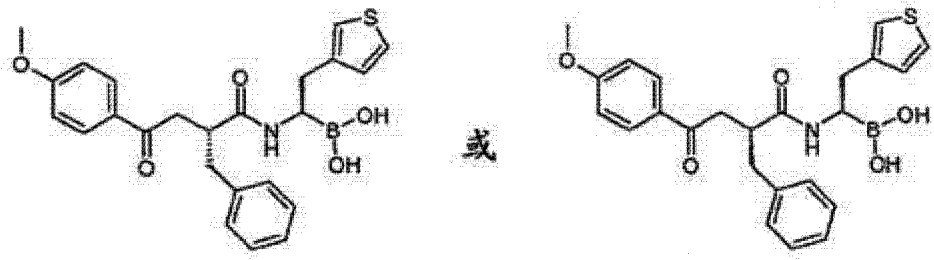
白色固体。^{1} H NMR (400 MHz, DMSO-d6) : δ 8.12 (s, 1H), 7.89-7.93 (m, 2H), 7.69 (d, J= 7.6 Hz, 2H), 7.59-7.63 (m, 1H), 7.46-7.50 (m, 2H), 7.37-7.40 (m, 1H), 7.32-7.34 (m, 1H), 7.06 (s, 1H), 6.94 (d, J= 4.4 Hz, 1H), 3.24-3.27 (m, 2H), 3.08-3.11 (m, 1H), 2.66-2.81 (m, 2H), 2.45-2.49 (m, 2H). MS (ESI+) :390.0 [M+H-H_2O]. HPLC (方法 A) :Rt. 4.0 min, HPLC 纯度 96.5 %。

[0185] 实施例 23 :[(1R)-1-{[4- 氧代 -4-(6- 苯基吡啶 -2- 基) 丁酰基] 氨基}-2-(3- 噻吩基) 乙基] 硼酸



灰白色固体。[1] H NMR (400 MHz, DMSO-d6) : δ 8.17-8.23 (m, 3H), 8.07 (t, J= 7.6 Hz, 1H), 7.89 (d, J= 6.8 Hz, 1H), 7.46-7.56 (m, 3H), 7.35-7.37 (m, 1H), 7.09 (s, 1H), 6.95 (d, J= 5.2 Hz, 1H), 3.47-3.49 (m, 2H), 3.15 (t, J= 6.0 Hz, 1H), 2.63-2.83 (m, 3H). MS (ESI+) :413.3 [M+Na-H_2O]. HPLC (方法A) :Rt. 3.8 min, HPLC 纯度 94.4 %。

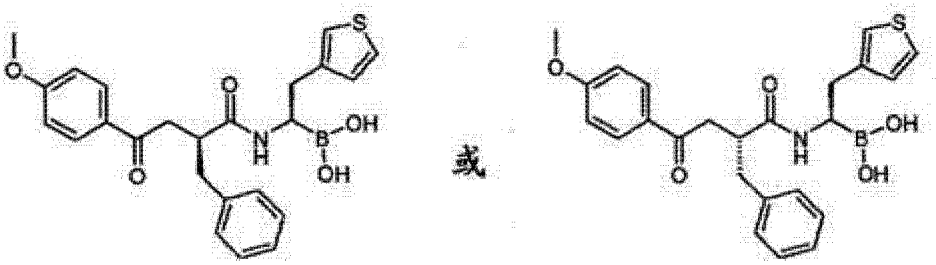
[0186] 实施例 24 :[(1R)-1-{[(2R)-2- 苄基 -4-(4- 甲氧基苯基)-4- 氧代丁酰基] 氨基 }-2-(3- 噻吩基) 乙基] 硼酸



一种非对映体 . 大多数从硼酸基团移动的手性位置的构型被任意指定。该实施例由中间体 17 (-)-2- 苄基 -4-(4- 甲氧基苯基)-4- 氧代 - 丁酸起始制备 (具有 αD -21.0° ; 乙醇 , c= 1.0 g/100 ml)。白色固体。

[0187] ^{1}H NMR (400 MHz, DMSO-d6) : δ 7.86 (d, J= 8.8 Hz, 2H), 7.32-7.34 (m, 1H), 7.20-7.26 (m, 4H), 7.14-7.18 (m, 1H), 7.00 (d, J= 8.8 Hz, 2H), 6.95 (s, 1H), 6.87-6.89 (m, 1H), 3.81 (s, 3H), 3.24-3.28 (m, 1H), 3.09-3.13 (m, 2H), 2.85-2.90 (m, 1H), 2.56-2.75 (m, 4H). MS (ESI+) :434.2 [M+H-H_2O]. HPLC (方法A) : Rt. 4.1 min, HPLC 纯度 95.9 %。

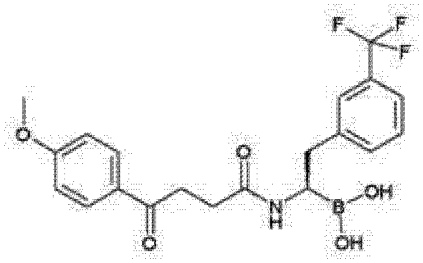
[0188] 实施例 25 :[(1R)-1-{[(2S)-2- 苄基 -4-(4- 甲氧基苯基)-4- 氧代丁酰基] 氨基 }-2-(3- 噻吩基) 乙基)] 硼酸



一种非对映体。大多数从硼酸基团移动的手性位置的构型被任意指定。该实施例由中间体 16 (+)-2- 苄基 -4-(4- 甲氧基苯基)-4- 氧代 - 丁酸起始制备 (具有 αD +21.1 ° ;乙醇 , c= 1.0 g/100 ml). 灰白色固体 . ^{1}H NMR (400 MHz, DMSO-d6) : δ 7.86 (d, J= 8.8 Hz, 2H), 7.30-7.32 (m, 1H), 7.14-7.26 (m, 5H), 6.99 (d, J= 6.0 Hz, 2H), 6.79-6.83 (m, 2H), 3.80 (s, 3H), 3.16-3.27 (m, 2H), 3.04-3.00 (m, 1H),

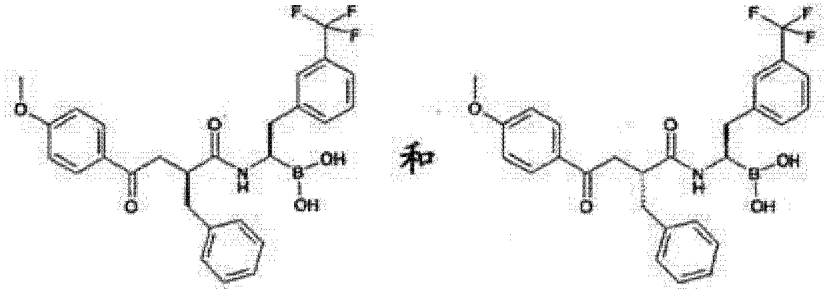
2.75-2.83 (m, 2H), 2.48-2.69 (m, 3H). MS (ESI+) :434.2 [M+H-H_2O]. HPLC (方法A) : Rt. 4.2 min, HPLC 纯度 92.7%。

[0189] 实施例 26 :{(1R)-1-{[4-(4- 甲氧基苯基)-4- 氧代丁酰基] 氨基 }-2-[3-(三氟甲基) 苯基] 乙基 } 硼酸



浅棕色固体。^{1}H NMR (400 MHz, DMSO-d_6) : δ 7.89 (d, J= 8.9 Hz, 2H), 7.45-7.49 (m, 4H), 7.02 (d, J= 8.9 Hz, 2H), 3.81 (s, 3H), 3.12-3.16 (m, 1H), 3.06-3.08 (m, 2H), 2.85-2.90 (m, 1H), 2.70-2.76 (m, 1H), 2.35-2.39 (m, 2H). MS (ESI+) : 406.0 [M+H-H_2O]. HPLC (方法 A) :Rt. 3.9 min, HPLC 纯度 97.3%。

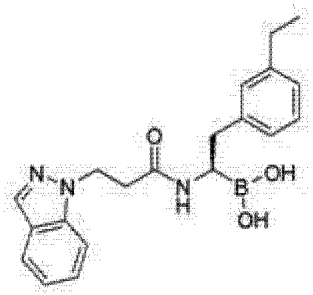
[0190] 实施例 27 :{(1R)-1-{[2-(RS)- 苄基 -4-(4- 甲氧基苯基)-4- 氧代丁酰基] 氨基 }-2-[3-(三氟甲基) 苯基] 乙基 } 硼酸



非对映体的混合物。黄色固体。^{1}H NMR (400 MHz, DMSO-d_6) : δ 7.82 (d, J= 8.7 Hz, 1H), 7.37-7.46 (m, 3H), 7.30 (d, J= 7.6 Hz, 1H), 7.13-7.25 (m, 5H), 6.98 (d, J= 8.7 Hz, 2H), 3.81 (s, 3H), 3.37 (s, 1H), 3.21-3.23 (m, 1H), 3.17-3.19 (m, 1H), 3.06-3.10 (m, 1H), 2.97-3.00 (m, 1H), 2.74-2.83 (m, 3H), 2.56-2.67 (m, 2H). MS (ESI+) :496.2 [M+H-H_2O]. HPLC (方法 A) :Rt. 4.7 min, HPLC 纯度 73.9%+14.4%。

[0191] 以下化合物根据对实施例 1 描述的相同两步方案制备 :

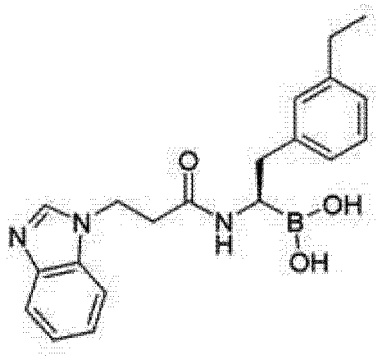
实施例 28 :((1R)-2-(3- 乙基苯基)-1-{[3-(1H- 吲唑 -1- 基) 丙酰基] 氨基 } 乙基) 硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d6) : δ 8.04 (s, 1H), 7.70-7.75 (m, 1H),

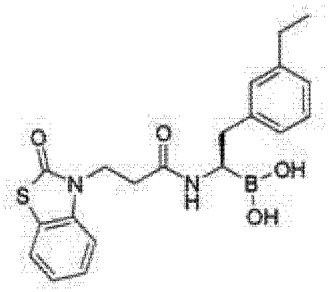
7.56-7.61 (m, 1H), 7.23-7.27 (m, 1H), 7.02-7.10 (m, 2H), 6.90-6.95 (m, 1H), 6.81-6.85 (m, 1H), 6.73-6.75 (m, 1H), 4.61 (t, J= 6.80 Hz, 2H), 2.78-2.81 (m, 1H), 2.65-2.69 (m, 3H), 2.48-2.50 (m, 2H), 2.35-0.00 (m, 1H), 1.08-1.13 (m, 3H). MS (ESI+):348.3 [M+H-H_2O]. HPLC (方法 B):Rt 11.8 min, HPLC 纯度 87.9%。

[0192] 实施例 29:[(1R)-1-{[3-(1H- 苯并咪唑 -1- 基) 丙酰基] 氨基}-2-(3- 乙基苯基) 乙基] 硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d6):δ 7.88 (s, 1H), 7.52-7.61 (m, 2H), 7.15-7.18 (m, 2H), 6.98-7.02 (m, 1H), 6.90 (m, 1H), 6.88 (s, 1H), 6.72-6.74 (m, 1H), 4.48-4.52 (m, 2H), 2.89-2.90 (m, 2H), 2.74 (m, 1H), 2.59-2.66 (m, 2H), 2.41-2.45 (m, 2H), 2.36-2.38 (m, 1H), 1.07 (m, 3H). MS (ESI+):370.3 [M+Na-H_2O]. HPLC (方法 A):Rt 2.8 min, HPLC 纯度 95.9%。

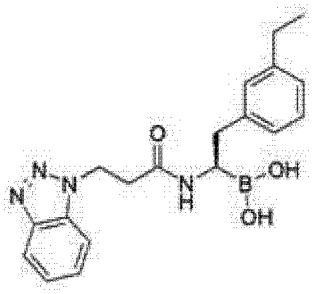
[0193] 实施例 30:((1R)-2-(3- 乙基苯基)-1-{[3-(2- 氧代 -1,3- 苯并噻唑 -3(2H)- 基) 丙酰基] 氨基} 乙基) 硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d6):δ 7.51-7.65 (m, 1H), 7.24-7.34 (m, 2H), 7.14-7.18 (m, 1H), 7.05-7.09 (m, 1H), 6.89-6.93 (m, 1H), 6.82-6.91 (m, 2H), 4.12-4.15 (m, 2H), 2.61-2.71 (m, 5H), 2.50-2.52 (m, 1H), 2.30-2.40 (m, 1H), 1.09-1.11 (m, 3H)

MS (ESI+):381.0 [M+H-H_2O]. HPLC (方法 A):Rt 3.8 min, HPLC 纯度 95.7%。

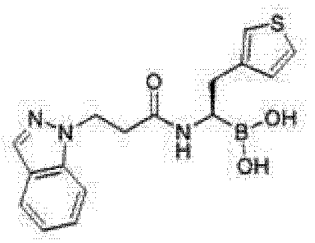
[0194] 实施例 31:[(1R)-1-{[3-(1H-1,2,3- 苯并三唑 -1- 基) 丙酰基] 氨基}-2-(3- 乙基苯基) 乙基] 硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d6) : δ 8.61-8.68 (m, 1H), 7.97-8.02 (m, 1H), 7.80-7.84 (m, 1H), 7.41-7.45 (m, 1H), 7.32-7.38 (m, 1H), 7.00-7.04 (m, 1H), 6.90-6.93 (m, 1H), 6.77 (s, 1H), 6.71 (d, J= 7.6 Hz, 1H), 4.90-4.93 (m, 2H), 2.92-2.95 (m, 2H), 2.65-2.67 (m, 2H), 2.50-2.45 (m, 2H), 2.30-2.31 (m, 1H), 1.06-1.10 (m, 3H)

MS (ESI+) :349.0 [M+H-H_2O]. HPLC (方法 A) :Rt 3.3 min, HPLC 纯度 96.4%。

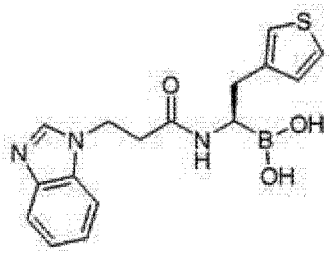
[0195] 实施例 32 :[(1R)-1-{[3-(1H- 吲唑 -1- 基) 丙酰基] 氨基}-2-(3- 噻吩基) 乙基] 硼酸



灰白色固体。^{1}H NMR (400 MHz, DMSO-d6) : δ 8.02 (s, 1H), 7.73 (d, J= 8.4 Hz, 1H), 7.58 (d, J= 8.8 Hz, 1H), 7.34-7.38 (m, 1H), 7.23-7.25 (m, 1H), 7.09-7.12 (m, 1H), 6.67-6.70 (m, 2H), 4.50-4.56 (m, 2H), 3.03-3.06 (m, 1H), 2.48-2.65 (m, 4H)

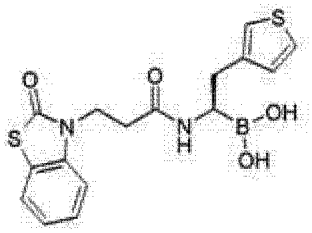
MS (ESI+) :326.0 [M+H-H_2O] ;HPLC (方法 A) :Rt. 3.0 min, HPLC 纯度 95.4%。

[0196] 实施例 33 :[(1R)-1-{[3-(1H- 苯并咪唑 -1- 基) 丙酰基] 氨基}-2-(3- 噻吩基) 乙基] 硼酸



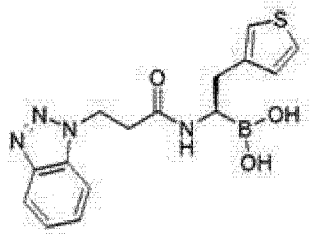
白色固体。^{1}H NMR (400 MHz, DMSO-d6) : δ 8.09 (m, 1H), 7.56-7.63 (m, 2H), 7.18-7.26 (m, 3H), 6.72 (d, J= 4.4 Hz, 2H), 4.39-4.43 (m, 2H), 3.11-3.14 (m, 1H), 2.59-2.72 (m, 4H). MS (ESI+) :348.0 [M+Na-H_2O]. HPLC (方法A) :Rt. 2.0 min, HPLC 纯度 96.6%。

[0197] 实施例 34 :[(1R)-1-{[3-(2- 氧代 -1,3- 苯并噻唑 -3(2H)- 基) 丙酰基] 氨基}-2-(3- 噻吩基) 乙基] 硼酸



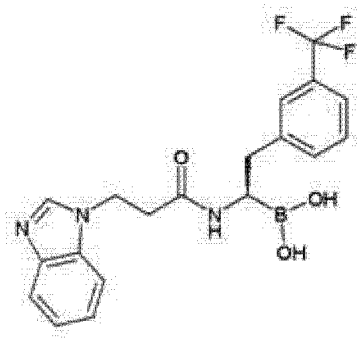
白色固体。^{1}H NMR (400 MHz, DMSO-d6) :δ 7.60-7.62 (m, 1H), 7.30-7.37 (m, 3H), 7.15-7.20 (m, 1H), 6.79-6.84 (m, 2H), 4.08 (t, J= 7.2 Hz, 2H), 3.11-3.15 (m, 1H), 2.61-2.73 (m, 2H), 2.42-2.48 (m, 2H). MS (ESI+) :359.0 [M+H-H_2O]. HPLC (方法 A) :Rt. 3.1 min, HPLC 纯度 98.9%。

[0198] 实施例 35 :[(1R)-1-{[3-(1H-1,2,3- 苯并三唑 -1- 基) 丙酰基] 氨基}-2-(3- 噻吩基) 乙基] 硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d6) :δ 8.01 (d, J= 8.0 Hz, 1H), 7.83 (d, J= 8.4 Hz, 1H), 7.51-7.54 (m, 1H), 7.36-7.40 (m, 1H), 7.26-7.28 (m, 1H), 6.72-6.74 (m, 2H), 4.80-4.90 (m, 2H), 3.11-3.15 (m, 1H), 2.76-2.80 (m, 2H), 2.57-2.71 (m, 2H). MS (ESI+) :327.0 [M+H-H_2O]. HPLC (方法 A) :Rt. 2.5 min, HPLC 纯度 86.4%。

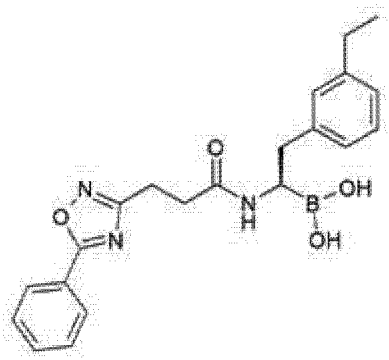
[0199] 实施例 38 :{(1R)-1-{[3-(1H- 苯并咪唑 -1- 基) 丙酰基] 氨基}-2-[3-(三氟甲基) 苯基] 乙基} 硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 8.07 (s, 1H), 7.63 (d, J= 7.5 Hz, 1H), 7.55 (d, J= 7.5 Hz, 1H), 7.44 (d, J= 7.9 Hz, 1H), 7.40 (s, 1H), 7.17-7.29 (m, 3H), 7.08 (d, J= 7.8 Hz, 1H), 4.38 (t, J= 6.7 Hz, 2H), 3.15-3.19 (m, 1H), 2.77-2.82 (m, 1H), 2.63-2.68 (m, 1H), 2.58 (t, J= 6.8 Hz, 2H). MS (ESI+) :410.0 [M+Na-H_2O]. HPLC (方法 A) :Rt. 3.0 min, HPLC 纯度 95.3%。

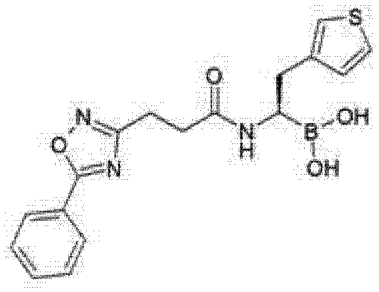
[0200] 以下化合物根据对实施例 6 描述的相同两步方案制备 :

实施例 36 :((1R)-2-(3- 乙基苯基)-1-{[3-(5- 苯基 -1,2,4- 噁二唑 -3- 基) 丙酰基] 氨基} 乙基) 硼酸



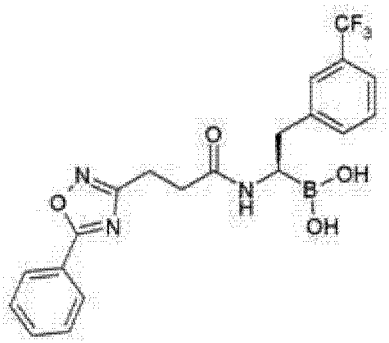
浅棕色固体。^{1}H NMR (400 MHz, DMSO-d6) : δ 8.06-8.08 (m, 2H), 7.67-7.71 (m, 1H), 7.59-7.63 (m, 2H), 7.07-7.10 (m, 1H), 6.90-6.97 (m, 3H), 3.17-3.20 (m, 1H), 2.93 (t, J= 7.6 Hz, 2H), 2.65-2.79 (m, 2H), 2.48-2.54 (m, 4H), 1.13 (t, J= 7.9 Hz, 3H). MS (ESI+) :376.3 [M+H-H_2O]. HPLC (方法 A) :Rt. 4.0 min, HPLC 纯度 97.0% 。

[0201] 实施例 37 :[(1R)-1-{[3-(5- 苯基 -1,2,4- 噁二唑 -3- 基) 丙酰基] 氨基}-2-(3- 噻吩基) 乙基] 硼酸



白色固体。^{1} H NMR (400 MHz, DMSO-d6) : δ 8.06-8.09 (m, 2H), 7.67-7.71 (m, 1H), 7.59-7.63 (m, 2H), 7.31-7.33 (m, 1H), 7.03 (s, 1H), 6.89-6.91 (m, 1H), 3.15-3.19 (m, 1H), 2.93-2.97 (m, 2H), 2.68-2.83 (m, 2H), 2.55-2.57 (m, 2H). MS (ESI+) :354.0 [M+H-H_2O]. HPLC (方法 A) :Rt. 3.3 min, HPLC 纯度 97.8%。

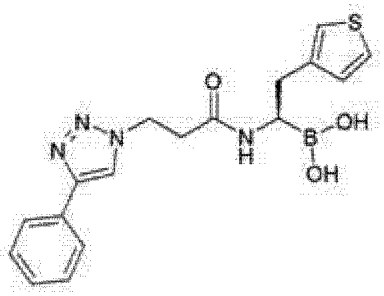
[0202] 实施例 39 :{(1R)-1-{[3-(5- 苯基 -1,2,4- 噁二唑 -3- 基) 丙酰基] 氨基}-2-[3-(三氟甲基) 苯基] 乙基} 硼酸



灰白色固体。^{1} H NMR (400 MHz, DMSO-d_6) : δ 8.04 (d, J= 7.2 Hz, 2H), 7.66-7.69 (m, 1H), 7.58-7.62 (m, 2H), 7.40-7.45 (m, 4H), 3.17-3.20 (m, 1H), 2.85-2.91 (m, 3H), 2.70-2.76 (m, 1H), 2.49-2.51 (m, 2H). MS (ESI+) :416.2 [M+H-H_2O]. HPLC (方法 B) :Rt. 4.1 min, HPLC 纯度 96.9%。

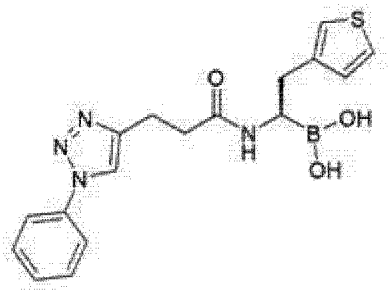
[0203] 实施例 40 :[(1R)-1-{[3-(4- 苯基 -1H-1,2,3- 三唑 -1- 基) 丙酰基] 氨

基}-2-(3-噻吩基)乙基]硼酸



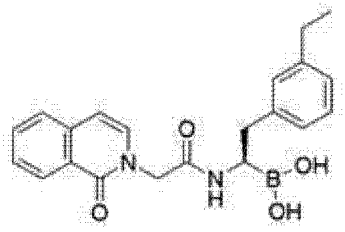
白色固体。^{1}H NMR (400 MHz, DMSO-d_6):δ 8.37 (s, 1H), 7.79 (d, J= 8.4 Hz, 2H), 7.42 (t, J= 8.4 Hz, 2H), 7.30-7.33 (m, 1H), 7.24-7.26 (m, 1H), 6.90 (s, 1H), 6.80 (d, J= 8.4 Hz, 2H), 4.53-4.62 (m, 2H), 3.12-3.16 (m, 1H), 2.63-2.77 (m, 4H). MS (ESI+):353.0 [M+H-H_2O]. HPLC (方法A):Rt 3.0 min, HPLC纯度99.7%。

[0204] 实施例41:[(1R)-1-{[3-(1-苯基-1H-1,2,3-三唑-4-基)丙酰基]氨基}-2-(3-噻吩基)乙基]硼酸



灰白色固体。^{1}H NMR (400 MHz, DMSO-d_6):δ 8.39 (s, 1H), 7.78-7.80 (m, 2H), 7.54-7.58 (m, 2H), 7.44-7.47 (m, 1H), 7.27-7.29 (m, 1H), 6.91 (s, 1H), 6.85 (d, J= 4.8 Hz, 1H), 2.92-3.11 (m, 1H), 2.88-2.92 (m, 2H), 2.74-2.79 (m, 1H), 2.63-2.69 (m, 1H), 2.46-2.49 (m, 2H). MS (ESI+):353.0 [M+H-H_2O]. HPLC (方法A):Rt 2.9 min, HPLC纯度95.1 %。

[0205] 实施例42:((1R)-2-(3-乙基苯基)-1-{[(1-氧代异喹啉-2(1H)-基)乙酰基]氨基}乙基)硼酸

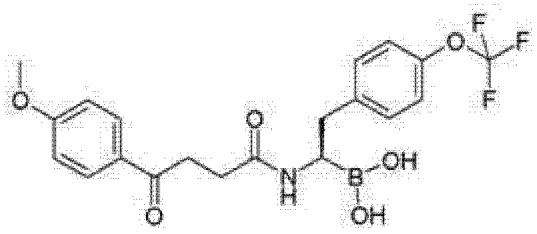


白色固体。^{1}H NMR (400 MHz, DMSO-d_6):δ 8.82 (s, 1H), 8.19 (d, J= 8.0 Hz, 1H), 7.66-7.72 (m, 1H), 7.61-7.63 (m, 1H), 7.46-7.50 (m, 1H), 7.31 (d, J= 8.0 Hz, 1H), 6.98-7.02 (m, 1H), 6.87-6.92 (m, 2H), 6.57 (d, J= 8.0 Hz, 1H), 4.71-4.76 (m, 2H), 2.66-2.70 (m, 2H), 2.49-2.50 (m, 1H), 2.45-2.48 (m, 2H), 1.08 (t, J= 8.0 Hz, 3H). MS (ESI+):361.3 [M+H-H_2O]。

[0206] 以下化合物根据对实施例17描述的相同两步方案制备:

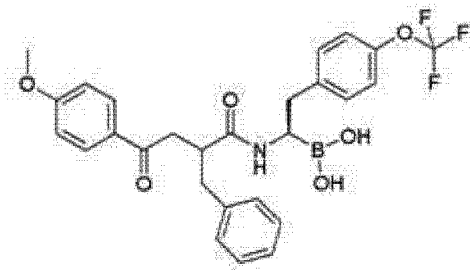
实施例43:(R)-(1-(4-(4-甲氧基苯基)-4-氧代丁酰氨基)-2-(4-(三氟甲氧基)苯

基）乙基）硼酸



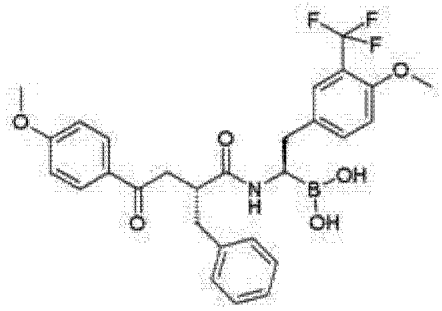
浅棕色固体。^{1}H NMR (400 MHz, DMSO-d_6)：δ 7.90 (dd, J = 1.92, 6.96 Hz, 2H), 7.26 (d, J = 8.64 Hz, 2H), 7.18 (d, J = 8.12 Hz, 2H), 7.00-7.03 (m, 2H), 3.80 (s, 3H), 3.08-3.12 (m, 3H), 2.78-2.83 (m, 1H), 2.65-2.70 (m, 1H), 2.39 (t, J = 6.88 Hz, 2H). MS (ESI+)：422.2 [M+H-H_2O]. HPLC（方法 A)：Rt. 4.0 min, HPLC 纯度 97.3%。

[0207] 实施例 44：((1R)-1-(2-苄基-4-(4-甲氧基苯基)-4-氧代丁酰氨基)-2-(4-(三氟甲氧基）苯基）乙基）硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d_6)：δ 7.82 (d, J = 8.88 Hz, 2H), 7.22-7.26 (m, 2H), 7.14-7.18 (m, 3H), 7.05-7.07 (m, 4H), 6.98 (d, J = 8.92 Hz, 2H), 3.77 (s, 3H), 3.18-3.24 (m, 1H), 2.95-3.04 (m, 2H), 2.73-2.83 (m, 2H), 2.59-2.71 (m, 3H). MS (ESI+)：512.2 [M+H-H_2O]. HPLC（方法 A)：Rt. 4.9 min, HPLC 纯度 73.2%+19.5%。

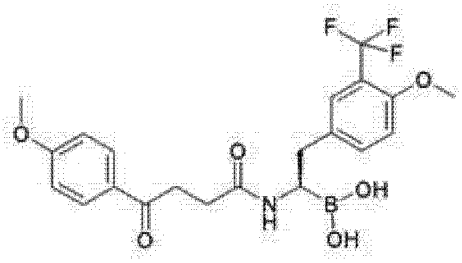
[0208] 实施例 45：((R)-1-((R)-2-苄基-4-(4-甲氧基苯基)-4-氧代丁酰氨基)-2-(4-甲氧基-3-(三氟甲基）苯基）乙基）硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d_6)：δ 7.82 (d, J = 8.92 Hz, 2H), 7.32-7.32 (m, 1H), 7.21-7.26 (m, 3H), 7.13-7.18 (m, 3H), 6.97-6.99 (m, 3H), 3.81-3.83 (m, 3H), 3.74 (s, 3H), 3.14-3.16 (m, 1H), 2.98-3.07 (m, 2H), 2.68-2.84 (m, 3H), 2.53-2.60 (m, 2H). MS (ESI+)：526.2 [M+H-H_2O]. HPLC（方法 A)：Rt. 4.7 min, HPLC 纯度 95.8%。

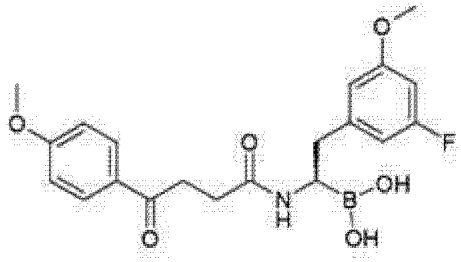
[0209] 实施例 46：(R)-(2-(4-甲氧基-3-(三氟甲基）苯基)-1-(4-(4-甲氧基苯

基）-4- 氧代丁酰氨基）乙基）硼酸



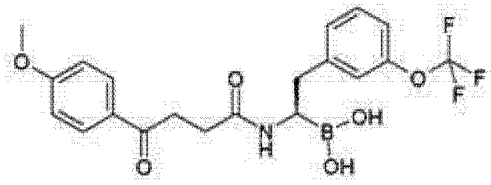
白色固体。^{1}H NMR (400 MHz, DMSO-d_6)：δ 7.88-7.92 (m, 2H), 7.38-7.39 (m, 2H), 7.10 (d, J = 8.84 Hz, 1H), 7.00-7.04 (m, 2H), 3.81 (s, 6H), 3.05-3.13 (m, 3H), 2.75-2.80 (m, 1H), 2.61-2.67 (m, 1H), 2.32-2.40 (m, 2H). MS (ESI+)：436.2 [M+H-H_2O]. HPLC（方法 A）：Rt. 3.9 min, HPLC 纯度 95.7%。

[0210] 实施例 47：(R)-(2-(3- 氟 -5- 甲氧基苯基）-1-(4-(4- 甲氧基苯基）-4- 氧代丁酰氨基）乙基）硼酸



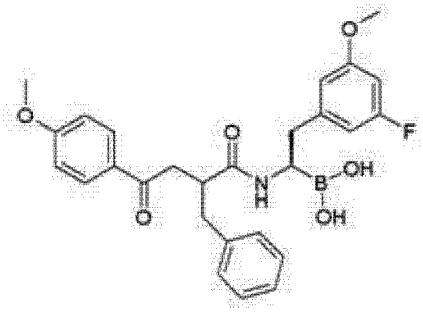
白色固体。^{1}H NMR (400 MHz, DMSO-d_6)：δ 7.91 (d, J = 8.84 Hz, 2H), 7.02 (d, J = 8.88 Hz, 2H), 6.55-6.59 (m, 3H), 3.81 (s, 3H), 3.71 (s, 3H), 3.09-3.13 (m, 3H), 2.73-2.78 (m, 1H), 2.60-2.66 (m, 1H), 2.49-2.50 (m, 2H), 2.38-2.40 (m, 1H). MS (ESI+)：386.2 [M+H-H_2O]. HPLC（方法 A）：Rt. 3.4 min, HPLC 纯度 99.3%。

[0211] 实施例 48：(R)-(1-(4-(4- 甲氧基苯基）-4- 氧代丁酰氨基）-2-(3-（三氟甲氧基）苯基）乙基）硼酸



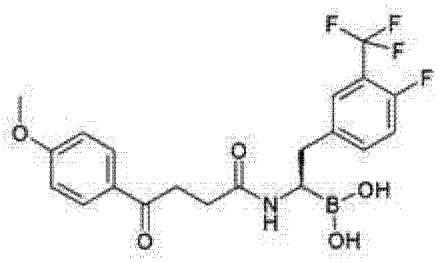
灰白色固体。^{1}H NMR (400 MHz, DMSO-d_6)：δ 7.89-7.92 (m, 2H), 7.34-7.38 (m, 1H), 7.18-7.20 (m, 1H), 7.13-7.14 (m, 2H), 7.00-7.04 (m, 2H), 3.82 (s, 3H), 3.08-3.17 (m, 3H), 2.82-2.87 (m, 1H), 2.70-2.73 (m, 1H), 2.39-2.40 (m, 2H). MS (ESI+)：422.2 [M+H-H_2O]. HPLC（方法 A）：Rt. 4.0 min, HPLC 纯度 99.0%。

[0212] 实施例 49：((1R)-1-(2- 苄基 -4-(4- 甲氧基苯基）-4- 氧代丁酰氨基）-2-(3- 氟 -5- 甲氧基苯基）乙基）硼酸



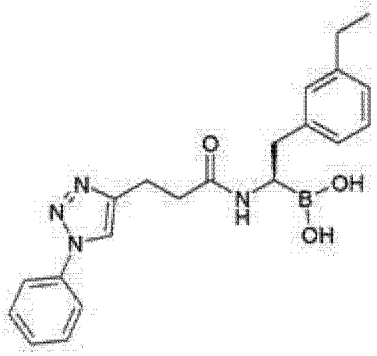
白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 7.79-7.80 (m, 2H), 7.11-7.25 (m, 5H), 6.95-6.97 (m, 2H), 6.43-6.49 (m, 2H), 6.35 (d, J = 9.36 Hz, 1H), 3.76 (s, 1H), 3.65 (s, 3H), 3.19-3.25 (m, 1H), 3.00-3.02 (m, 1H), 2.77-2.98 (m, 3H), 2.61-2.66 (m, 2H), 2.44-2.46 (m, 1H). MS (ESI+) :476.2 [M+H-H_2O]. HPLC (方法A) : Rt. 4.4 min, HPLC 纯度 72.2%+23.0%。

[0213] 实施例 50 :(R)-(2-(4- 氟 -3-(三氟甲基) 苯基)-1-(4-(4- 甲氧基苯基)-4- 氧代丁酰氨基) 乙基) 硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 7.89 (d, J = 8.00 Hz, 2H), 7.48-7.52 (m, 2H), 7.29-7.34 (m, 1H), 7.01 (d, J = 8.00 Hz, 2H), 3.80 (s, 3H), 3.07-3.12 (m, 3H), 2.81-2.86 (m, 1H), 2.66-2.72 (m, 1H), 2.50-2.51 (m, 2H), 2.35-2.39 (m, 2H). MS (ESI+) :424.2 [M+H-H_2O]. HPLC (方法 A) :Rt. 4.0 min, HPLC 纯度 98.6%。

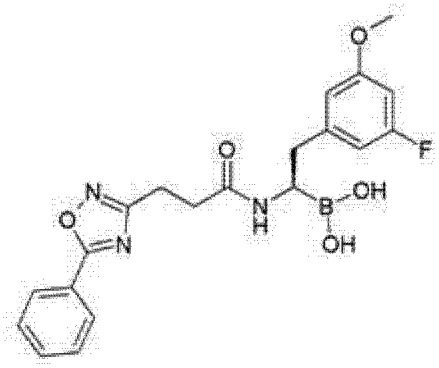
[0214] 实施例 58 :(R)-(2-(3- 乙基苯基)-1-(3-(1- 苯基 -1H-1,2,3- 三唑 -4- 基) 丙酰氨基) 乙基) 硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 8.40 (s, 1H), 7.83-7.83 (m, 2H), 7.54-7.58 (m, 2H), 7.44-7.47 (m, 1H), 7.05-7.09 (m, 1H), 6.87-6.94 (m, 3H), 3.12-3.16 (m, 1H), 2.86-2.90 (m, 2H), 2.73-2.74 (m, 1H), 2.60-2.66 (m, 1H), 2.41-2.51 (m, 4H), 1.11 (t, J = 7.60 Hz, 3H). MS (ESI+) :375.2 [M+H-H_2O]. HPLC (方法 A) :Rt. 3.6 min, HPLC 纯度 96.8%。

[0215] 实施例 61 :(R)-(2-(3- 氟 -5- 甲氧基苯基)-1-(3-(5- 苯基 -1,2,4- 噁二

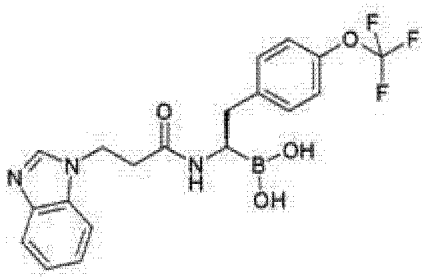
唑 -3- 基) 丙酰氨基) 乙基) 硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.03-8.03 (m, 2H), 7.57-7.68 (m, 3H), 6.47-6.52 (m, 3H), 3.65 (s, 3H), 3.11-3.14 (m, 1H), 2.90-2.94 (m, 2H), 2.71-2.76 (m, 1H), 2.58-2.63 (m, 1H), 2.51-2.53 (m, 2H). MS (ESI+) :396.2 [M+H-H_2O]. HPLC (方法 A) :Rt. 3.6 min, HPLC 纯度 97.1 %。

[0216] 以下化合物根据对实施例 1 描述的相同两步方案制备 :

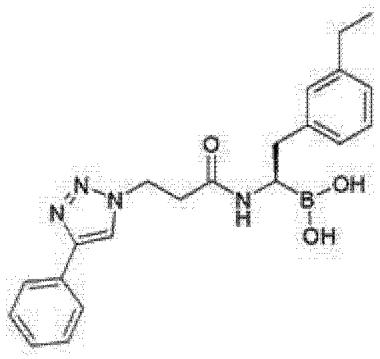
实施例 51 :(R)-(1-(3-(1H- 苯并 [d] 咪唑 -1- 基) 丙酰氨基)-2-(4-(三氟甲氧基) 苯基) 乙基) 硼酸



灰白色固体。^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.09 (s, 1H), 7.64 (d, J = 7.56 Hz, 1H), 7.57 (d, J = 7.68 Hz, 1H), 7.19-7.28 (m, 2H), 6.96 (d, J = 8.08 Hz, 2H), 6.85 (d, J = 8.56 Hz, 2H), 4.40 (t, J = 6.32 Hz, 2H), 3.07-3.10 (m, 1H), 2.49-2.70 (m, 4H). MS (ESI+) :426.0

[M+Na-H_2O]. HPLC (方法 A) :Rt. 3.2 min, HPLC 纯度 96.5%。

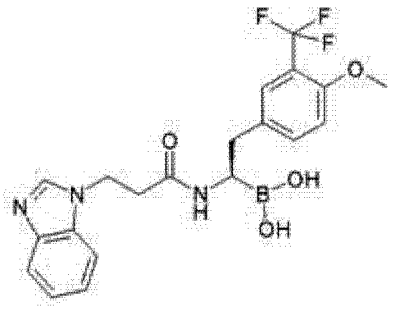
[0217] 实施例 52 :(R)-(2-(3- 乙基苯基)-1-(3-(4- 苯基 -1H-1,2,3- 三唑 -1- 基) 丙酰氨基) 乙基) 硼酸



灰白色固体。^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.30 (s, 1H), 7.77 (d, J = 7.20 Hz, 2H), 7.41 (t, J = 7.76 Hz, 3H), 7.29-7.33 (m, 1H), 7.00 (t, J = 7.52 Hz, 1H),

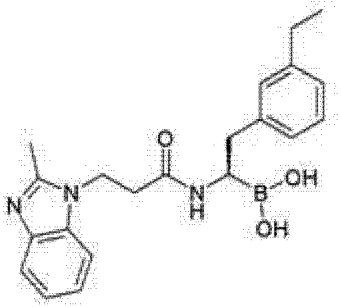
6.88 (d, J = 7.88 Hz, 1H), 6.81 (s, 1H), 6.75 (d, J = 7.40 Hz, 1H), 3.07-3.11 (m, 1H), 2.66-2.70 (m, 3H), 2.55-2.57 (m, 1H), 2.39-2.44 (m, 2H), 1.03 (t, J = 7.96 Hz, 3H). MS (ESI+) :397.2 [M+Na-H_2O]. HPLC (方法 A) :Rt. 3.7 min, HPLC 纯度 96.5%。

[0218] 实施例 53 :(R)-(1-(3-(1H- 苯并 [d] 咪唑 -1- 基) 丙酰氨基)-2-(4- 甲氧基 -3-(三氟甲基) 苯基) 乙基) 硼酸



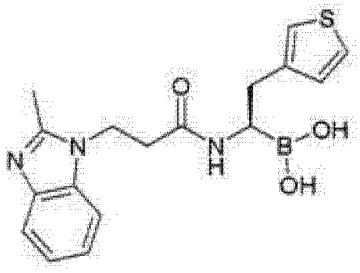
白色固体。^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.09 (s, 1H), 7.65 (d, J = 8.24 Hz, 1H), 7.56 (d, J = 7.40 Hz, 1H), 7.19-7.29 (m, 3H), 6.91 (dd, J = 1.92, 8.54 Hz, 1H), 6.81 (d, J = 8.56 Hz, 1H), 4.39 (t, J = 6.76 Hz, 2H), 3.76 (s, 3H), 3.09-3.13 (m, 1H), 2.67-2.70 (m, 1H), 2.54-2.61 (m, 3H). MS (ESI+) :440.0 [M+Na-H_2O]. HPLC (方法 A) :Rt. 3.0 min, HPLC 纯度 94.5%。

[0219] 实施例 54 :(R)-(2-(3- 乙基苯基)-1-(3-(2- 甲基 -1H- 苯并 [d] 咪唑 -1- 基) 丙酰氨基) 乙基) 硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d_6) : δ 7.43-7.50 (m, 2H), 7.13-7.17 (m, 2H), 6.89-6.99 (m, 2H), 6.77 (s, 1H), 6.59 (d, J = 7.40 Hz, 1H), 4.28-4.32 (m, 2H), 3.10-3.13 (m, 1H), 2.52-2.62 (m, 4H), 2.40-2.44 (m, 2H), 1.07 (t, J = 7.60 Hz, 3H).). MS (ESI+) :384.2 [M+Na-H_2O]. HPLC (方法 A) :Rt. 3.0 min, HPLC 纯度 98.7%。

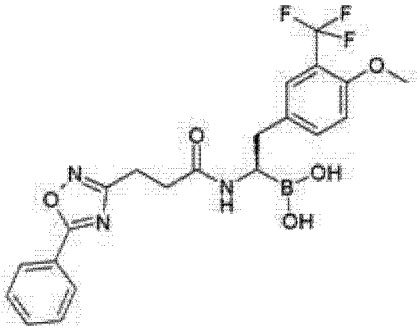
[0220] 实施例 55 :(R)-(1-(3-(2 - 甲基 -1H- 苯并 [d] 咪唑 -1- 基) 丙酰氨基)-2-(噻吩 -3- 基) 乙基) 硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d_6) : δ 7.44-7.50 (m, 2H), 7.11-7.25 (m, 3H),

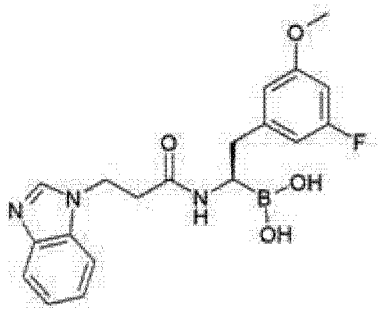
6.65-6.68 (m, 2H), 4.28-4.37 (m, 2H), 3.09-3.12 (m, 1H), 2.51-2.68 (m, 7H). MS (ESI+) :362.2 [M+Na-H_2O]. HPLC (方法 A) :Rt. 2.0 min, HPLC 纯度 93.7%。

[0221] 实施例 56 :(R)-(2-(4- 甲氧基 -3-(三氟甲基) 苯基)-1-(3-(5- 苯基 -1,2,4- 噁二唑 -3- 基) 丙酰氨基) 乙基) 硼酸



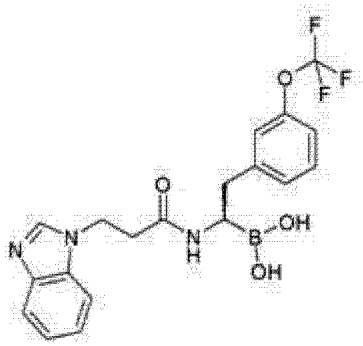
白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 8.06 (d, J = 7.20 Hz, 2H), 7.59-7.70 (m, 3H), 7.31-7.35 (m, 2H), 7.04 (d, J = 8.44 Hz, 1H), 3.76 (s, 3H), 3.14-3.17 (m, 1H), 2.90-2.94 (m, 2H), 2.76-2.81 (m, 1H), 2.63-2.68 (m, 1H), 2.48-249.00 (m, 2H). MS (ESI+) :446.2 [M+H-H_2O]. HPLC (方法 A) :Rt. 4.0 min, HPLC 纯度 97.7%。

[0222] 实施例 57 :(R)-(1-(3-(1H- 苯并 [d] 咪唑 -1- 基) 丙酰氨基)-2-(3- 氟 -5- 甲氧基苯基) 乙基) 硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 8.07 (s, 1H), 7.54-7.62 (m, 2H), 7.17-7.26 (m, 2H), 6.51-6.54 (m, 1H), 6.50 (s, 1H), 6.37-6.45 (m, 1H), 4.36-4.40 (m, 2H), 3.64 (s, 3H), 3.11-3.14 (m, 1H), 2.53-2.69 (m, 4H). MS (ESI+) :390.2 [M+Na-H_2O]. HPLC (方法 A) :Rt. 2.5 min, HPLC 纯度 98.8%。

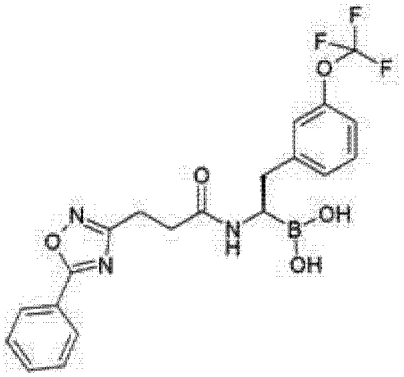
[0223] 实施例 59 :(R)-(1-(3-(1H- 苯并 [d] 咪唑 -1- 基) 丙酰氨基)-2-(3-(三氟甲氧基) 苯基) 乙基) 硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 8.08 (s, 1H), 7.55-7.57 (m, 1H),

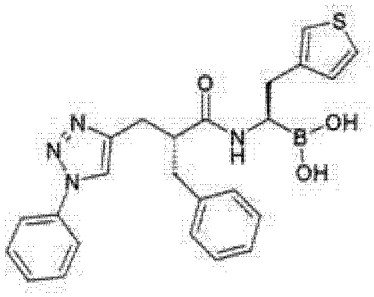
7.61-7.63 (m, 1H), 7.15-7.26 (m, 3H), 7.05-7.07 (m, 1H), 7.00 (s, 1H), 6.81-6.83 (m, 1H), 4.39 (t, J = 6.72 Hz, 2H), 3.15 (t, J = 5.60 Hz, 1H), 2.73-2.78 (m, 1H), 2.57-2.65 (m, 3H). MS (ESI+):426.2 [M+Na-H_2O]. HPLC (方法A):Rt. 3.1 min, HPLC 纯度 99.6%。

[0224] 实施例 60:(R)-(1-(3-(5-苯基-1,2,4-噁二唑-3-基)丙酰氨基)-2-(3-(三氟甲氧基)苯基)乙基)硼酸



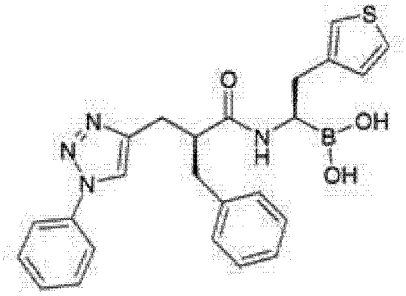
白色固体。^{1}H NMR (400 MHz, DMSO-d_6):δ 8.04-8.05 (m, 2H), 7.58-7.70 (m, 3H), 7.29-7.33 (m, 1H), 7.08-7.29 (m, 3H), 3.17-3.21 (m, 1H), 2.82-2.93 (m, 3H), 2.67-2.73 (m, 1H), 2.49-2.51 (m, 2H). MS (ESI+):432.0 [M+H-H_2O]. HPLC (方法A):Rt. 4.2 min, HPLC 纯度 98.3%。

[0225] 实施例 62:((R)-1-((R)-2-苄基-3-(1-苯基-1H-1,2,3-三唑-4-基)丙酰氨基)-2-(噻吩-3-基)乙基)硼酸



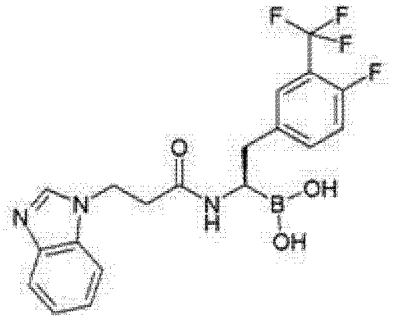
白色固体。^{1}H NMR (400 MHz, DMSO-d_6):δ 8.39 (s, 1H), 7.76-7.78 (m, 2H), 7.53-7.57 (m, 2H), 7.44-7.46 (m, 1H), 7.23-7.27 (m, 3H), 7.16-7.18 (m, 3H), 6.62-6.67 (m, 2H), 3.07-3.10 (m, 1H), 2.81-2.94 (m, 3H), 2.71-2.75 (m, 1H), 2.56-2.66 (m, 3H). MS (ESI+):443.2 [M+H-H_2O]. HPLC (方法A):Rt. 4.0 min, HPLC 纯度 97.7%。

[0226] 实施例 63:((R)-1-((S)-2-苄基-3-(1-苯基-1H-1,2,3-三唑-4-基)丙酰氨基)-2-(噻吩-3-基)乙基)硼酸



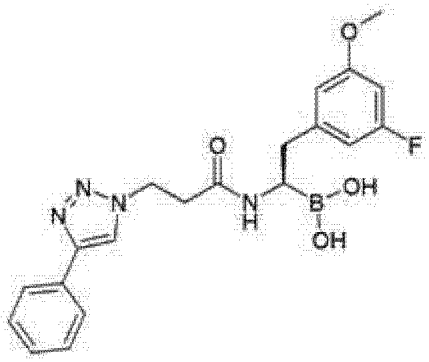
白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 8.39 (s, 1H), 7.75-7.77 (m, 2H), 7.52-7.56 (m, 2H), 7.44-7.45 (m, 1H), 7.23-7.27 (m, 2H), 7.15-7.19 (m, 4H), 6.61-6.64 (m, 2H), 2.84-2.95 (m, 4H), 2.63-2.70 (m, 3H), 2.52-2.54 (m, 1H). MS (ESI+) :443.2 [M+H-H_2O]. HPLC (方法 A) :Rt. 4.0 min, HPLC 纯度 99.6%。

[0227] 实施例 64 :(R)-(1-(3-(1H- 苯并 [d] 咪唑 -1- 基) 丙酰氨基)-2-(4- 氟 -3-(三氟甲基) 苯基) 乙基) 硼酸



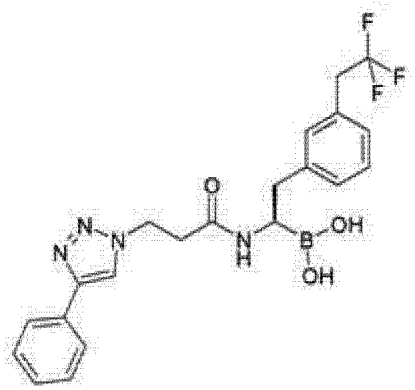
白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 8.07 (s, 1H), 7.63 (d, J = 8.00 Hz, 1H), 7.54 (d, J = 8.00 Hz, 1H), 7.39-7.41 (m, 1H), 7.18-7.27 (m, 2H), 7.04-7.10 (m, 2H), 4.38 (t, J = 6.60 Hz, 2H), 3.08-3.12 (m, 1H), 2.71-2.76 (m, 1H), 2.56-2.62 (m, 3H). MS (ESI+) :428.0 [M+Na-H_2O]. HPLC (方法A) :Rt. 3.1 min, HPLC 纯度 98.8 %。

[0228] 实施例 65 :(R)-(2-(3- 氟 -5- 甲氧基苯基)-1-(3-(4- 苯基 -1H-1,2,3- 三唑 -1- 基) 丙酰氨基) 乙基) 硼酸



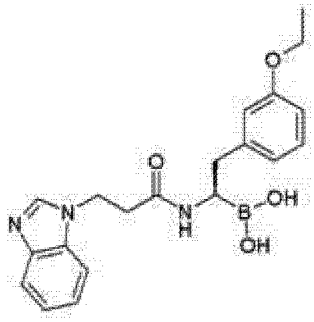
白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 8.37 (s, 1H), 7.78 (d, J = 8.00 Hz, 2H), 7.39-7.43 (m, 2H), 7.29-7.32 (m, 1H), 6.46-6.53 (m, 3H), 4.55 (t, J = 6.80 Hz, 2H), 3.66 (s, 3H), 3.13-3.17 (m, 1H), 2.58-2.75 (m, 4H). MS (ESI+) : 395.3 [M+H-H_2O]. HPLC (方法 A) :Rt. 3.4 min, HPLC 纯度 98.6%。

[0229] 实施例 66 :(R)-(1-(3-(4- 苯基 -1H-1,2,3- 三唑 -1- 基) 丙酰氨基)-2-(3-(2,2,2- 三氟乙基) 苯基) 乙基) 硼酸



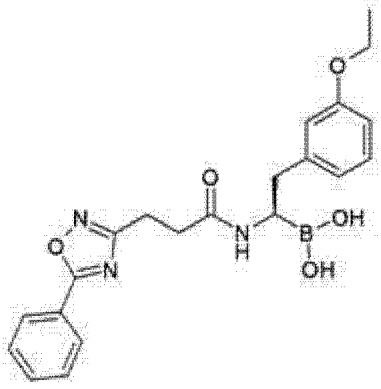
白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 8.40 (s, 1H), 7.77-7.80 (m, 2H), 7.40-7.43 (m, 2H), 7.23-7.33 (m, 2H), 7.01-7.05 (m, 3H), 4.54 (t, J = 6.80 Hz, 2H), 3.15-3.19 (m, 1H), 2.79-2.83 (m, 1H), 2.63-2.69 (m, 3H). MS (ESI+) :431.0 [M+H-H_2O]. HPLC (方法 A) :Rt. 4.0 min, HPLC 纯度 96.2%。

[0230] 实施例 67 :(R)-(1-(3-(1H- 苯并 [d] 咪唑 -1- 基) 丙酰氨基)-2-(3- 乙氧基苯基) 乙基) 硼酸



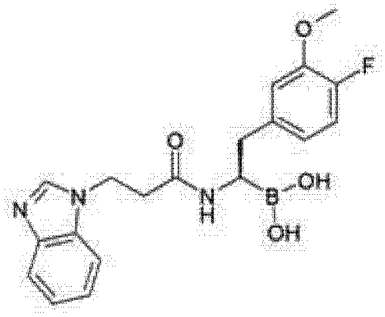
白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 8.07 (s, 1H), 7.62 (d, J = 7.60 Hz, 1H), 7.56 (d, J = 7.60 Hz, 1H), 7.17-7.26 (m, 2H), 6.95 (t, J = 8.00 Hz, 1H), 6.58-6.63 (m, 2H), 6.39 (d, J = 8.00 Hz, 1H), 4.39 (t, J = 6.40 Hz, 2H), 3.85-3.90 (m, 2H), 3.11-3.13 (m, 1H), 2.55-2.64 (m, 4H), 1.24 (t, J = 6.80 Hz, 3H). MS (ESI+) :386.2 [M+Na-H_2O]. HPLC (方法 A) :Rt. 2.5 min, HPLC 纯度 98.5 %。

[0231] 实施例 68 :(R)-(2-(3- 乙氧基苯基)-1-(3-(5- 苯基 -1,2,4- 噁二唑 -3- 基) 丙酰氨基) 乙基) 硼酸



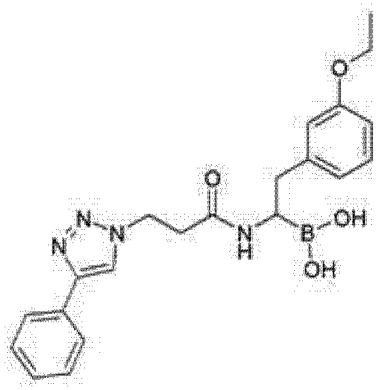
白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 8.05 (d, J = -8.00 Hz, 2H), 7.65-7.69 (m, 1H), 7.58-7.62 (m, 2H), 7.06 (t, J = 7.60 Hz, 1H), 6.63-6.67 (m, 3H), 3.89-3.94 (m, 2H), 3.14-3.17 (m, 1H), 2.92 (t, J = 7.60 Hz, 2H), 2.71-2.76 (m, 1H), 2.61-2.64 (m, 1H), 2.52-2.59 (m, 2H), 1.26-1.28 (m, 3H). MS (ESI+) :392.3 [M+H-H_2O]. HPLC (方法 A) :Rt. 3.7 min, HPLC 纯度 98.7%。

[0232] 实施例 69 :(R)-(1-(3-(1H- 苯并 [d] 咪唑 -1- 基) 丙酰氨基)-2-(4- 氟 -3- 甲氧基苯基) 乙基) 硼酸



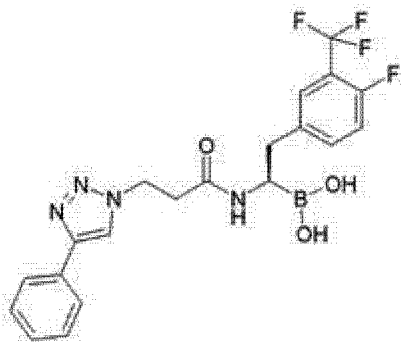
白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 8.07 (s, 1H), 7.62 (d, J = 8.00 Hz, 1H), 7.55 (d, J = 8.00 Hz, 1H), 7.19-7.27 (m, 2H), 6.74-6.81 (m, 2H), 6.27-6.30 (m, 1H), 4.40 (t, J = 6.40 Hz, 2H), 3.66 (s, 3H), 3.05-3.09 (m, 1H), 2.60-2.64 (m, 3H), 2.54-2.58 (m, 1H). MS (ESI+) :386.2 [M+H-H_2O]. HPLC (方法 A) : Rt. 2.4 min, HPLC 纯度 96.6%。

[0233] 实施例 70 :(2-(3- 乙氧基苯基)-1-(3-(4- 苯基 -1H-1,2,3- 三唑 -1- 基) 丙酰氨基) 乙基) 硼酸



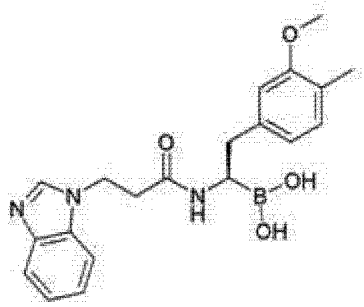
白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 8.34 (s, 1H), 7.78 (d, J = 8.00 Hz, 2H), 7.42 (t, J = 13.88 Hz, 2H), 7.29-7.33 (m, 1H), 6.99-7.03 (m, 1H), 6.59-6.62 (m, 2H), 6.55 (d, J = 8.00 Hz, 1H), 4.55 (t, J = 7.24 Hz, 2H), 3.85-3.91 (m, 2H), 3.12-3.15 (m, 1H), 2.66-2.71 (m, 3H), 2.58-2.61 (m, 1H), 1.24 (t, J = 7.00 Hz, 3H). MS (ESI+) :413.3 [M+Na-H_2O]. HPLC (方法 A) :Rt. 3.4 min, HPLC 纯度 98.5 %。

[0234] 实施例 71 :(R)-(2-(4- 氟 -3-(三氟甲基) 苯基)-1-(3-(4- 苯基 -1H-1,2,3- 三唑 -1- 基) 丙酰氨基) 乙基) 硼酸



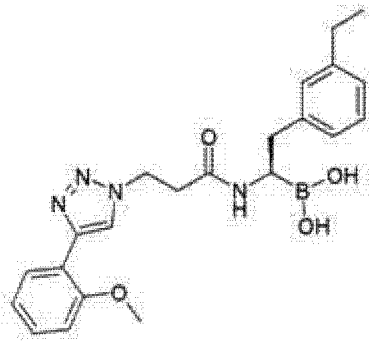
白色固体。^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.35 (s, 1H), 7.76-7.78 (m, 2H), 7.39-7.45 (m, 3H), 7.29-7.32 (m, 2H), 7.15-7.20 (m, 1H), 4.53 (t, J = 8.00 Hz, 2H), 3.11-3.14 (m, 1H), 2.77-2.82 (m, 1H), 2.62-2.69 (m, 3H). MS (ESI+) :433.3 [M+H-H_2O]. HPLC (方法 A) :Rt. 3.9 min, HPLC 纯度 98.1%。

[0235] 实施例 72 :(R)-(1-(3-(1H-苯并[d]咪唑-1-基)丙酰氨基)-2-(3-甲氧基-4-甲基苯基)乙基)硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.06 (s, 1H), 7.62 (d, J = 8.00 Hz, 1H), 7.54 (d, J = 8.00 Hz, 1H), 7.19-7.27 (m, 2H), 6.77 (d, J = 8.00 Hz, 1H), 6.54 (s, 1H), 6.26 (d, J = 8.00 Hz, 1H), 4.40 (t, J = 6.40 Hz, 2H), 3.59 (s, 3H), 3.09 (t, J = 7.20 Hz, 1H), 2.58-2.63 (m, 4H), 1.98 (s, 3H). MS (ESI+) : 386.2 [M+Na-H_2O]. HPLC (方法 A) :Rt. 2.7 min, HPLC 纯度 97.1 %。

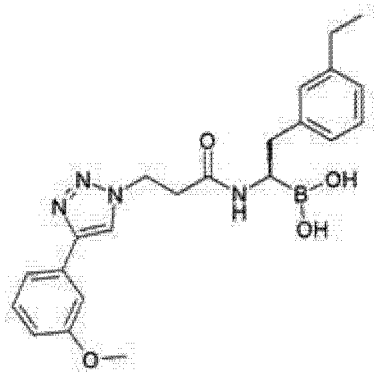
[0236] 实施例 73 :(R)-(2-(3-乙基苯基)-1-(3-(4-(2-甲氧基苯基)-1H-1,2,3-三唑-1-基)丙酰氨基)乙基)硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.25 (s, 1H), 8.07-8.09 (m, 1H), 7.28-7.32 (m, 1H), 6.97-7.09 (m, 3H), 6.87 (d, J = 8.00 Hz, 1H), 6.82 (s, 1H), 6.77 (d, J = 8.00 Hz, 1H), 4.56 (t, J = 8.00 Hz, 2H), 3.85 (s, 3H), 3.13-3.17 (m, 1H), 2.59-2.71 (m, 4H), 2.37-2.43 (m, 2H), 1.03 (t, J = 8.00 Hz, 3H). MS

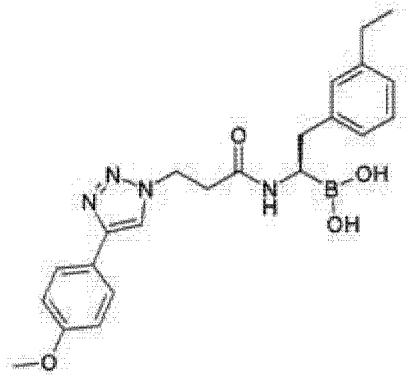
(ESI+) :427.2 [M+Na-H_2O]. HPLC (方法 A) :Rt. 3.8 min, HPLC 纯度 97.6%。

[0237] 实施例 74 :(R)-(2-(3- 乙基苯基)-1-(3-(4-(3- 甲氧基苯基)-1H-1,2,3- 三唑 -1- 基) 丙酰氨基) 乙基) 硼酸



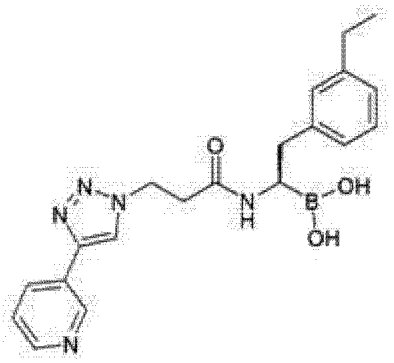
白色固体。^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.37 (s, 1H), 7.33-7.35 (m, 3H), 6.99-7.03 (m, 1H), 6.84-6.90 (m, 3H), 6.78 (d, J = 8.00 Hz, 1H), 4.55 (t, J = 12.00 Hz, 2H), 3.79 (s, 3H), 3.10-3.14 (m, 1H), 2.65-2.69 (m, 3H), 2.58-2.60 (m, 1H), 2.41-2.46 (m, 2H), 1.06-1.08 (m, 3H). MS (ESI+) :427.2 [M+Na-H_2O]. HPLC (方法 A) :Rt. 3.7 min, HPLC 纯度 98.0%。

[0238] 实施例 75 :(R)-(2-(3- 乙基苯基)-1-(3-(4-(4- 甲氧基苯基)-1H-1,2,3- 三唑 -1- 基) 丙酰氨基) 乙基) 硼酸



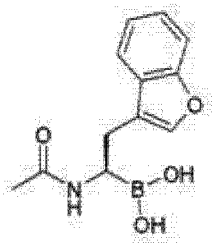
白色固体。^{1}H NMR (400 MHz, DMSO-d6) : δ 8.23 (s, 1H), 7.71 (d, J = 8.00 Hz, 2H), 6.96-7.04 (m, 4H), 6.85-6.91 (m, 1H), 6.79 (d, J = 8.00 Hz, 1H), 4.53 (t, J = 8.00 Hz, 2H), 3.11-3.15 (m, 1H), 2.54-2.73 (m, 4H), 2.42-2.45 (m, 2H), 1.05-1.09 (m, 3H). MS (ESI+) :427.2 [M+Na-H_2O]. HPLC (方法A) :Rt. 3.6 min, HPLC 纯度 98.1 %。

[0239] 实施例 76 :(R)-(2-(3- 乙基苯基)-1-(3-(4-(吡啶 -3- 基)-1H-1,2,3- 三唑 -1- 基) 丙酰氨基) 乙基) 硼酸



白色固体。^{1}H NMR (400 MHz, DMSO-d6) : δ 8.95 (s, 1H), 8.45-8.49 (m, 2H), 8.15-8.17 (m, 1H), 7.46-7.49 (m, 1H), 6.98-7.02 (m, 1H), 6.83-6.88 (m, 2H), 6.77 (d, J = 8.00 Hz, 1H), 4.55-4.59 (m, 2H), 3.11-3.13 (m, 1H), 2.67-2.70 (m, 3H), 2.57-2.59 (m, 1H), 2.39-2.45 (m, 2H), 1.04 (t, J = 8.00 Hz, 3H). MS (ESI+) :398.3 [M+Na-H_2O]. HPLC (方法 A) :Rt. 2.4 min, HPLC 纯度 97.9%。

[0240] 实施例 78 :(R)-(1- 乙酰氨基 -2-(苯并呋喃 -3- 基) 乙基) 硼酸



步骤 1 :(R)-(1- 乙酰氨基 -2-(苯并呋喃 -3- 基) 乙基) 硼酸 (+)- 蒎烷二醇酯

将中间体 18 (700 mg, 1.54 mmol) 在无水二氯甲烷 (20 ml) 中的冷却 (-10℃) 溶液用二异丙基乙胺 (0.8 ml, 4.6 mmol) 和乙酰氯 (0.09 ml, 1.54 mmol) 处理。将反应混合物于 -10℃搅拌 3h。在减压下浓缩反应混合物,保持外浴温度低于 30℃,然后加入 25 ml 乙酸乙酯。有机层用盐水洗涤,经硫酸钠干燥并浓缩。所需产物 (520 mg, 88 %) 经硅胶层析纯化来分离,用在二氯甲烷中的 2 % 甲醇洗脱。

[0241] MS (ESI+) :382.3

步骤 2 :(R)-(1- 乙酰氨基 -2-(苯并呋喃 -3- 基) 乙基) 硼酸

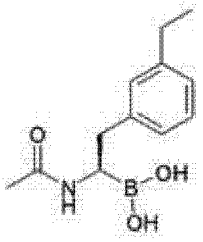
将 (R)-(1- 乙酰氨基 -2-(苯并呋喃 -3- 基) 乙基) 硼酸 (+)- 蒎烷二醇酯 (520 mg, 1.35 mmol) 在甲醇 / 戊烷 (1:1, 30 mL) 中的冷却 (0℃) 溶液用 2- 甲基丙基硼酸 (545 mg, 5.4 mmol) 和 HCl 水溶液 (1.5 N, 1 mL) 处理并将反应混合物于室温下搅拌 15 h。然后将反应混合物用戊烷提取三次。在低于 30℃的温度下浓缩含水甲醇层。残留物用冰处理,用 NaOH 的水溶液 (2N) 碱化并用二氯甲烷提取三次 (弃去)。然后水层用 HCl 的水溶液 (1.5 N) 酸化并用二氯甲烷提取三次。DCM 层经硫酸钠干燥,过滤并浓缩,得到固体残留物,其用二乙醚研磨并冻干,获得标题化合物 (42 mg, 26 %),为白色固体。

[0242] ^{1}H NMR :(400 MHz, DMSO-d_6) : δ 7.64 (s, 1H), 7.58-7.60 (d, J =8.0 Hz, 1H), 7.48-7.50 (d, J = 8.0 Hz, 1H), 7.19-7.28 (m, 2H), 3.09-3.13 (m, 1H), 2.81-2.86 (m, 1H), 2.69-2.75 (m, 1H), 1.77 (s, 3H).

MS (ESI+) :230.0 [M+H-H_2O], HPLC (方法 A) :Rt 2.0min ;HPLC 纯度 98.8%。

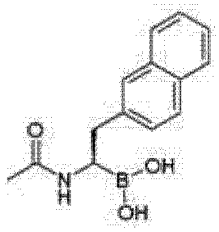
[0243] 以下化合物采用实施例 78 遵照的相同程序合成。

[0244] 实施例 77 :(R)-(1- 乙酰氨基 -2-(3- 乙基苯基) 乙基) 硼酸



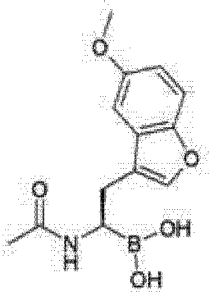
淡粉红色固体。^{1}H NMR (400 MHz, DMSO-d_6) :δ 7.11-7.15 (m, 1H), 6.93-6.98 (m, 3H), 2.98-3.01 (m, 1H), 2.71-2.76 (m, 1H), 2.49-2.54 (m, 3H), 1.77 (s, 3H), 1.10-1.14 (m, 3H). MS (ESI+) :218.0 [M+H-H_2O]. HPLC (方法 A) :Rt. 2.4 min, HPLC 纯度 98.0%。

[0245] 实施例 95 :(R)-(1- 乙酰氨基 -2-(萘 -2- 基) 乙基) 硼酸



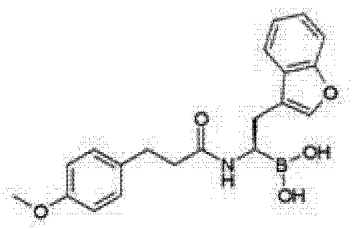
白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) :δ 7.76-7.78 (m, 3H), 7.61 (s, 1H), 7.38-7.46 (m, 2H), 7.32-7.35 (m, 1H), 3.04-3.08 (m, 1H), 2.90-2.95 (m, 1H), 2.73-2.78 (m, 1H), 1.79 (s, 3H). MS (ESI+) :240.3 [M+H-H_2O]. HPLC (方法 A) :Rt. 2.6 min, HPLC 纯度 92.4%。

[0246] 实施例 108 :(R)-(1- 乙酰氨基 -2-(5- 甲氧基苯并呋喃 -3- 基) 乙基) 硼酸



白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) :δ 7.60 (s, 1H), 7.38 (d, J = 8.88 Hz, 1H), 7.09- 7.10 (m, 1H), 6.84 (dd, J = 2.56, 8.92 Hz, 1H), 3.76 (s, 3H), 3.08-3.12 (m, 1H), 2.78-2.83 (m, 1H), 2.66-2.72 (m, 1H), 1.79 (s, 3H). MS (ESI+) :260.0 [M+H-H_2O]. HPLC (方法 A) :Rt. 2.2 min, HPLC 纯度 96.5%。

[0247] 实施例 79 :(R)-(2-(苯并呋喃 -3- 基)-1-(3-(4- 甲氧基苯基) 丙酰氨基) 乙基) 硼酸



步骤 1 :(R)-(2-(苯并呋喃 -3- 基)-1-(3-(4- 甲氧基苯基) 丙酰氨基) 乙基) 硼酸频哪醇酯 .

将中间体 18 (170 mg, 0.37 mmol) 在无水 N,N- 二甲基甲酰胺 (20 ml) 中的冷却 (-10℃) 溶液用二异丙基乙胺 (0.2 ml, 1.1 mmol) 和 3-(4- 甲氧基苯基) 丙酸 (67 mg, 0.37 mmol) 和 TBTU (142 mg, 0.44 mmol) 处理。将反应混合物于 -10℃搅拌 3h。在减压下浓缩反应混合物,保持外浴温度低于 30℃,然后加入 25 ml 乙酸乙酯。有机层用盐水洗涤,经硫酸钠干燥并浓缩。所需产物 (160 mg, 86 %) 经硅胶层析纯化来分离,用在石油醚中的 40 % 乙酸乙酯洗脱。

[0248] MS (ESI+) :502.2

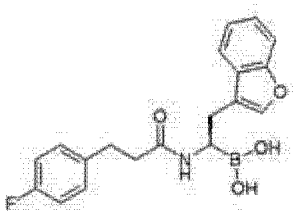
步骤 2 :(R)-(2-(苯并呋喃 -3- 基)-1-(3-(4- 甲氧基苯基) 丙酰氨基) 乙基) 硼酸

将 (R)-(2-(苯并呋喃 -3- 基)-1-(3-(4- 甲氧基苯基) 丙酰氨基) 乙基) 硼酸频哪醇酯 (160 mg, 0.32 mmol) 在甲醇 / 戊烷 (1:1, 20 mL) 中的冷却 (0℃) 溶液用 2- 甲基丙基硼酸 (129 mg, 1.3 mmol) 和 HCl 水溶液 (1.5 N, 0.5 mL) 处理并将反应混合物于室温下搅拌 15 h。然后用戊烷提取反应混合物三次。在低于 30℃的温度下浓缩含水甲醇层。残留物用冰处理,用 NaOH 的水溶液 (2N) 碱化并用二氯甲烷提取三次 (弃去)。然后水层用 HCl 的水溶液 (1.5 N) 酸化并用二氯甲烷提取三次。DCM 层经硫酸钠干燥,过滤并浓缩,得到固体残留物,其用二乙醚研磨并冻干获得标题化合物 (25 mg, 21 %),为白色固体。

[0249] ^{1}H NMR :(400 MHz, DMSO-d_6) : δ 7.57 (d, J = 7.68 Hz, 1H), 7.49 (t, J = 3.92 Hz, 2H), 7.21-7.26 (m, 2H), 7.06 (d, J = 8.44 Hz, 2H), 6.77 (d, J = 8.48 Hz, 2H), 3.67 (s, 3H), 3.15-3.17 (m, 1H), 2.65-2.81 (m, 5H), 2.30 (t, J = 7.32 Hz, 2H). MS (ESI+) :350.3 [M+H-H_2O]. HPLC (方法 A) :Rt. 3.5 min, HPLC 纯度 93.8%。

[0250] 以下化合物采用实施例 79 遵照的相同程序合成。

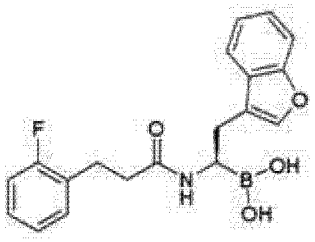
[0251] 实施例 80 :(R)-(2-(苯并呋喃 -3- 基)-1-(3-(4- 氟代苯基) 丙酰氨基) 乙基) 硼酸



灰白色固体。^{1}H NMR (400 MHz, DMSO-d_6) :400 MHz, DMSO-d6 : δ 7.57 (d, J = 7.16 Hz, 1H), 7.48 (d, J = 6.88 Hz, 1H), 7.15-7.28 (m, 4H), 6.99-7.04 (m, 2H), 3.18 (t, J = 5.72 Hz, 1H), 2.80-2.81 (m, 1H), 2.71-2.75 (m, 3H), 2.32 (t, J = 7.28 Hz, 2H). MS (ESI+) :338.3

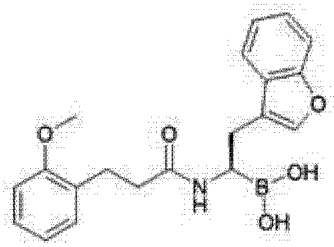
[M+H-H_2O]. HPLC (方法 A) :Rt. 3.7 min, HPLC 纯度 99.0%。

[0252] 实施例 81 :(R)-(2-(苯并呋喃 -3- 基)-1-(3-(2- 氟代苯基) 丙酰氨基) 乙基) 硼酸



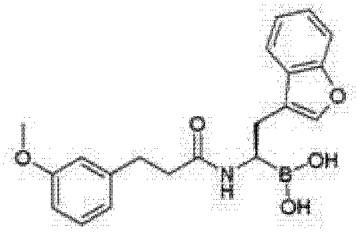
灰白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) : δ 7.57 (d, J = 7.2 Hz, 1H), 7.50-7.52 (m, 2H), 7.18-7.28 (m, 4H), 7.02-7.12 (m, 2H), 3.18-3.21 (m, 1H), 2.73-2.82 (m, 4H), 2.34 (t, J = 7.36 Hz, 2H). MS (ESI+) :338.3 [M+H-H_2O]. HPLC (方法 A) : Rt. 3.7 min, HPLC 纯度 97.9%。

[0253] 实施例 82 :(R)-(2-(苯并呋喃 -3- 基)-1-(3-(2- 甲氧基苯基) 丙酰氨基) 乙基) 硼酸



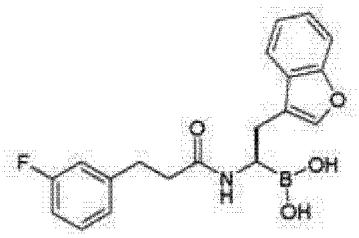
淡粉红色固体。^{1}H NMR :(400 MHz, DMSO-d_6) : δ 7.57 (d, J = 7.00 Hz, 1H), 7.48 (d, J = 7.36 Hz, 2H), 7.20-7.28 (m, 2H), 7.12-7.19 (m, 1H), 7.05-7.07 (m, 1H), 6.91 (d, J = 7.80 Hz, 1H), 6.77-6.81 (m, 1H), 3.73 (s, 1H), 3.12-3.15 (m, 1H), 2.79-2.81 (m, 1H), 2.68-2.74 (m, 3H), 2.29 (t, J = 7.20 Hz, 2H). MS (ESI+) : 350.3 [M+H-H_2O]. HPLC (方法 A) :Rt. 3.7 min, HPLC 纯度 98.1 %。

[0254] 实施例 84 :(R)-(2-(苯并呋喃 -3- 基)-1-(3-(3- 甲氧基苯基) 丙酰氨基) 乙基) 硼酸



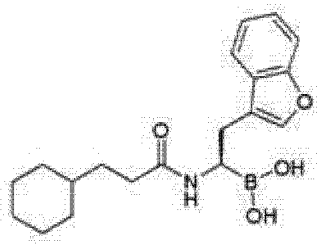
白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) : δ 7.57 (d, J = 7.08 Hz, 1H), 7.47-7.49 (m, 2H), 7.19-7.28 (m, 2H), 7.14 (t, J = 7.96 Hz, 1H), 6.70-6.73 (m, 3H), 3.68 (s, 3H), 3.16-3.19 (m, 1H), 2.80-2.81 (m, 1H), 2.69-2.74 (m, 3H), 2.34 (t, J = 7.32 Hz, 2H). MS (ESI+) :350.3 [M+H-HzO]. HPLC (方法 A) :Rt. 3.6 min, HPLC 纯度 99.7%。

[0255] 实施例 85 :(R)-(2-(苯并呋喃 -3- 基)-1-(3-(3- 氟代苯基) 丙酰氨基) 乙基) 硼酸



白色固体。^{1}H NMR：(400 MHz, DMSO-d_6)：δ 7.56-7.58 (m, 1H), 7.47-7.49 (m, 2H), 7.19-7.28 (m, 3H), 6.93-7.00 (m, 3H), 3.17-3.20 (m, 1H), 2.68-2.85 (m, 4H), 2.36 (t, J = 7.36 Hz, 2H). MS (ESI+)：338.3 [M+H-H_2O]. HPLC (方法 A)：Rt. 3.7 min, HPLC 纯度 98.4%。

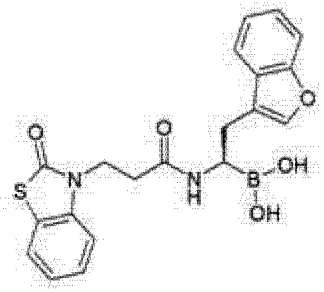
[0256] 实施例 86：(R)-(2-(苯并呋喃 -3- 基)-1-(3- 环己基丙酰氨基) 乙基) 硼酸



白色固体。^{1}H NMR:(400 MHz, DMSO-d_6)：δ 7.58-7.62 (m, 2H), 7.48 (d, J = 7.92 Hz, 1H), 7.19-7.28 (m, 2H), 3.10-3.13 (m, 1H), 2.80-2.85 (m, 1H), 2.68-2.72 (m, 1H), 2.05 (t, J = 7.92 Hz, 2H), 1.56-1.59 (m, 5H), 1.27-1.32 (m, 2H), 1.04-1.08 (m, 4H), 0.74-0.80 (m, 2H).

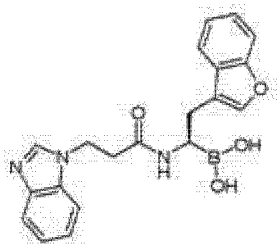
MS (ESI+)：326.3 [M+H-H_2O]. HPLC (方法 A)：Rt. 4.2 min, HPLC 纯度 99.2%。

[0257] 实施例 87：(R)-(2-(苯并呋喃 -3- 基)-1-(3-(2- 氧代苯并 [d] 噻唑 -3(2H)- 基) 丙酰氨基) 乙基) 硼酸



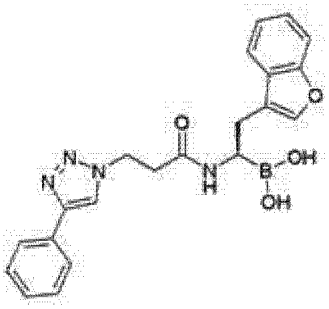
白色固体。^{1}H NMR：(400 MHz, DMSO-d_6)：δ 7.57 (d, J = 7.84 Hz, 1H), 7.52 (d, J = 7.56 Hz, 1H), 7.46 (d, J = 8.04 Hz, 1H), 7.41 (s, 1H), 7.13-7.34 (m, 5H), 4.05-4.09 (m, 2H), 3.14-3.84 (m, 1H), 2.75-2.80 (m, 1H), 2.64-2.70 (m, 1H), 2.43-2.49 (m, 2H). MS (ESI+)：393.0 [M+H-H_2O]. HPLC (方法 A)：Rt. 3.6 min, HPLC 纯度 98.8%。

[0258] 实施例 88：(R)-(1-(3-(1H- 苯并 [d] 咪唑 -1- 基) 丙酰氨基)-2-(苯并呋喃 -3- 基) 乙基) 硼酸



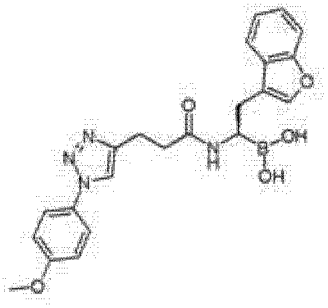
白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) : δ 8.09 (s, 1H), 7.61-7.63 (m, 1H), 7.56 (d, J = 7.44 Hz, 1H), 7.43-7.46 (m, 2H), 7.18-7.27 (m, 4H), 7.09-7.13 (m, 1H), 4.39-4.43 (m, 2H), 3.13-3.17 (m, 1H), 2.72-2.86 (m, 1H), 2.50-2.66 (m, 3H). MS (ESI+) :382.3 [M+Na-H_2O]. HPLC (方法 A) :Rt. 2.6 min, HPLC 纯度 94.3%。

[0259] 实施例 89 :(R)-(2-(苯并呋喃 -3- 基)-1-(3-(4- 苯基 -1H-1,2,3- 三唑 -1- 基) 丙酰氨基) 乙基) 硼酸



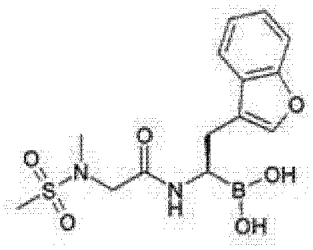
白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) : δ 8.34 (s, 1H), 7.76 (d, J = 7.48 Hz, 2H), 7.48 (d, J = 7.28 Hz, 2H), 7.41 (t, J = 7.52 Hz, 3H), 7.31 (t, J = 7.40 Hz, 1H), 7.23 (t, J = 7.52 Hz, 1H), 7.16 (t, J = 7.16 Hz, 1H), 4.55-4.56 (m, 2H), 3.16-3.18 (m, 1H), 2.77-2.86 (m, 1H), 2.66-2.73 (m, 3H). MS (ESI+) :409.2 [M+Na-H_2O]. HPLC (方法 A) :Rt. 3.5 min, HPLC 纯度 94.8%。

[0260] 实施例 90 :(R)-(2-(苯并呋喃 -3- 基)-1-(3-(1-(4- 甲氧基苯基)-1H-1,2,3- 三唑 -4- 基) 丙酰氨基) 乙基) 硼酸



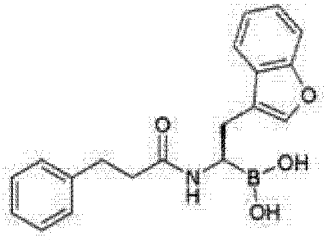
白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) : δ 8.31 (s, 1H), 7.68 (d, J = 8.92 Hz, 2H), 7.55-7.57 (m, 2H), 7.45 (d, J = 7.96 Hz, 1H), 7.18-7.27 (m, 2H), 7.08 (d, J = 9.00 Hz, 2H), 3.79 (s, 3H), 3.17-3.21 (m, 1H), 2.82-2.90 (m, 3H), 2.67-2.76 (m, 1H), 2.43-2.50 (m, 2H). MS (ESI+) :439.3 [M+Na-H_2O]. HPLC (方法 A) :Rt. 3.4 min, HPLC 纯度 95.0%。

[0261] 实施例 91 :(R)-(2-(苯并呋喃 -3- 基)-1-(2-(N- 甲基甲基磺酰氨基) 乙酰氨基) 乙基) 硼酸



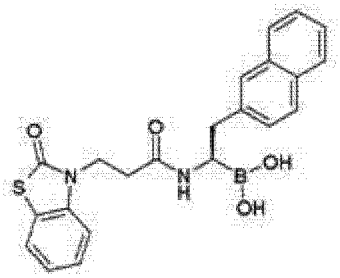
白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) :δ 7.60-7.60 (m, 2H), 7.48 (d, J = 7.84 Hz, 1H), 7.19-7.28 (m, 2H), 3.68 (d, J = 8.12 Hz, 2H), 3.33-3.36 (m, 1H), 2.87-2.92 (m, 4H), 2.76-2.82 (m, 1H), 2.66 (s, 3H). MS (ESI+) :337.0 [M+H-H_2O]. HPLC (方法 A) :Rt. 2.8 min, HPLC 纯度 97.5%。

[0262] 实施例 94 :(R)-(2-(苯并呋喃 -3- 基)-1-(3- 苯基丙酰氨基) 乙基) 硼酸



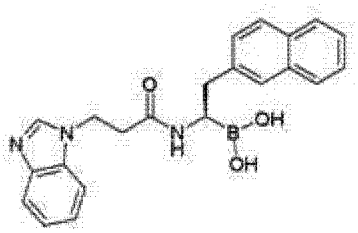
白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) :δ 7.56 (d, J = 7.68 Hz, 1H), 7.46-7.49 (m, 2H), 7.18-7.28 (m, 4H), 7.11-7.15 (m, 3H), 3.13-3.15 (m, 1H), 2.79-2.80 (m, 1H), 2.71-2.75 (m, 3H), 2.34 (t, J = 7.32 Hz, 2H). MS (ESI+) :320.2 [M+H-H_2O]. HPLC (方法 A) :Rt. 3.6 min, HPLC 纯度 97.6%。

[0263] 实施例 96 :(R)-(2-(萘 -2- 基)-1-(3-(2- 氧代苯并 [d] 噻唑 -3(2H)- 基) 丙酰氨基) 乙基) 硼酸



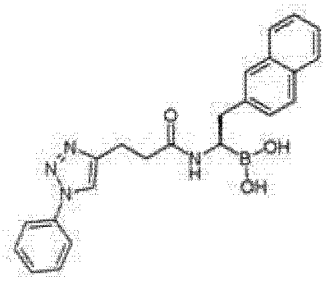
白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) :400 MHz, DMSO-d6 :δ 7.80 (d, J = 8.32 Hz, 1H), 7.71 (d, J = 8.48 Hz, 2H), 7.60 (d, J = 7.76 Hz, 1H), 7.37-7.43 (m, 3H), 7.30-7.34 (m, 1H), 7.25 (d, J = 8.00 Hz, 1H), 7.15-7.18 (m, 2H), 4.04 (t, J = 6.96 Hz, 2H), 3.19-3.23 (m, 1H), 2.82-2.87 (m, 1H), 2.71-2.77 (m, 1H), 2.41 (t, J = 7.00 Hz, 2H). MS (ESI+) :403.0 [M+H-H_2O]. HPLC (方法 A) :Rt. 3.9 min, HPLC 纯度 98.6% 。

[0264] 实施例 97 :(R)-(1-(3-(1H- 苯并 [d] 咪唑 -1- 基) 丙酰氨基)-2-(萘 -2- 基) 乙基) 硼酸



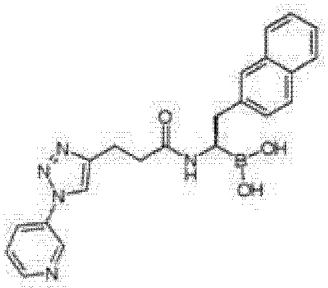
白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) :δ 8.09 (s, 1H), 7.75-7.77 (m, 1H), 7.59-7.65 (m, 3H), 7.54 (dd, J = 2.04, 6.80 Hz, 1H), 7.36-7.41 (m, 2H), 7.29 (s, 1H), 7.20-7.27 (m, 2H), 7.06 (dd, J = 1.52, 8.40 Hz, 1H), 4.38-4.41 (m, 2H), 3.20 (d, J = 2.32 Hz, 1H), 2.74-2.81 (m, 1H), 2.59-2.61 (m, 1H), 2.49-2.57 (m, 2H). MS (ESI+) :392.3 [M+Na-H_2O]. HPLC (方法A) :Rt. 2.9 min, HPLC 纯度 96.5%。

[0265] 实施例 98 :(R)-(2-(萘-2-基)-1-(3-(1-苯基-1H-1,2,3-三唑-4-基)丙酰氨基)乙基)硼酸



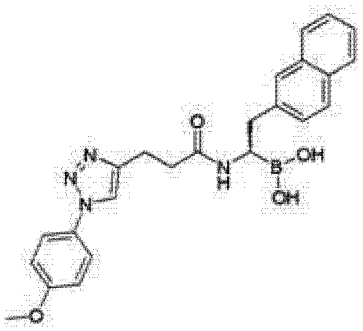
白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) :δ 8.37 (s, 1H), 7.78-7.78 (m, 3H), 7.69-7.72 (m, 2H), 7.52-7.57 (m, 3H), 7.46 (d, J = 7.40 Hz, 1H), 7.36-7.41 (m, 2H), 7.25 {dd, J = 1.48, 8.44 Hz, 1H), 3.17-3.20 (m, 1H), 2.87-2.94 (m, 3H), 2.75-2.81 (m, 1H), 2.42-2.50 (m, 2H). MS (ESI+) :419.2 [M+Na-H_2O]. HPLC (方法A) :Rt. 3.7 min, HPLC 纯度 96.7%。

[0266] 实施例 99 :(R)-(2-(萘-2-基)-1-(3-(1-(吡啶-3-基)-1H-1,2,3-三唑-4-基)丙酰氨基)乙基)硼酸



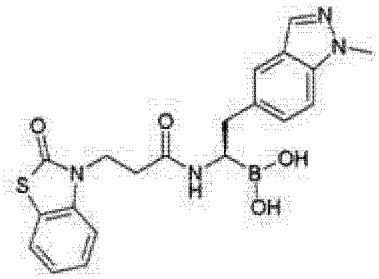
白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) :δ 8.90 (s, 1H), 8.58-8.59 (m, 1H), 8.33 (s, 1H), 8.14 (d, J = 8.04 Hz, 1H), 7.57-7.71 (m, 4H), 7.44 (s, 1H), 7.33-7.35 (m, 2H), 7.20 (d, J = 8.24 Hz, 1H), 3.04-3.07 (m, 1H), 2.86-2.94 (m, 3H), 2.65-2.71 (m, 1H), 2.49-2.50 (m, 2H). MS (ESI+) :420.2 [M+Na-H_2O]. HPLC (方法A) :Rt. 2.7 min, HPLC 纯度 95.9%。

[0267] 实施例 100 :(R)-(1-(3-(1-(4-甲氧基苯基)-1H-1,2,3-三唑-4-基)丙酰氨基)-2-(萘-2-基)乙基)硼酸



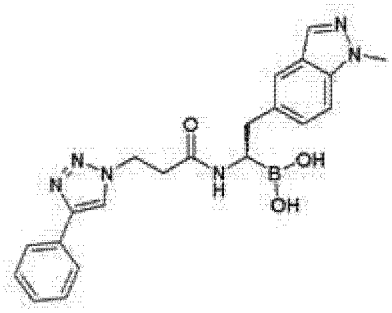
白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) : δ 8.24 (s, 1H), 7.65-7.78 (m, 5H), 7.51 (s, 1H) 7.38-7.42 (m, 2H), 7.23-7.26 (m, 1H), 7.06-7.08 (m, 2H), 3.77 (s, 3H), 3.15-3.18 (m, 1H), 2.85-2.94 (m, 3H), 2.74-2.80 (m, 1H), 2.42-2.50 (m, 2H). MS (ESI+) :449.2 [M+Na-H_2O]. HPLC (方法 A) :Rt. 3.7 min, HPLC 纯度 90.2%。

[0268] 实施例 102 :(R)-(2-(1- 甲基 -1H- 吲唑 -5- 基)-1-(3-(2- 氧代苯并 [d] 噻唑 -3(2H)- 基) 丙酰氨基) 乙基) 硼酸



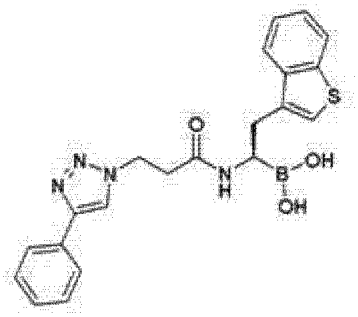
白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) : δ 7.85 (s, 1 H), 7.61 (d, J = 8.68 Hz, 1H), 7.39 (d, J = 8.64 Hz, 1H), 7.35-7.31 (m, 1H), 7.26 (d, J = 7.56 Hz, 1H), 7.19-7.15 (m, 2H), 7.04 (dd, J = 1.36, 8.66 Hz, 1H), 4.05 (t, J = 7.00 Hz, 2H), 3.92 (s, 3H), 3.15-3.14 (m, 1H), 2.74 (t, J = 5.36 Hz, 1H), 2.66 (t, J = 5.28 Hz, 1H), 2.41 (t, J = 6.92 Hz, 2H). MS (ESI+) :429.2 [M+Na-H_2O]. HPLC (方法 A) : Rt. 2.8 min, HPLC 纯度 98.0%。

[0269] 实施例 103 :(R)-(2-(1- 甲基 -1H- 吲唑 -5- 基)-1-(3-(4- 苯基 -1H-1,2,3- 三唑 -1- 基) 丙酰氨基) 乙基) 硼酸



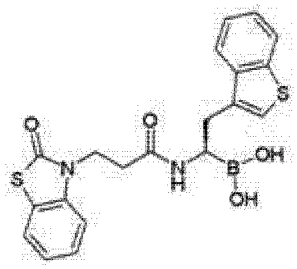
白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) : δ 8.36 (s, 1H), 7.79 (d, J = 8.40 Hz, 3H), 7.44-7.43 (m, 2H), 7.34-7.33 (m, 2H), 7.27 (s, 1H), 7.05 (dd, J = 1.48, 8.66 Hz, 1H), 4.60-4.58 (m, 2H), 3.88 (s, 3H), 3.15 (t, J = 5.64 Hz, 1H), 2.80 (t, J = 5.36 Hz, 1H), 2.74-2.72 (m, 1H), 2.68 (t, J = 6.52 Hz, 2H). MS (ESI+) : 423.3 [M+Na-H_2O]. HPLC (方法 A) :Rt. 2.7 min, HPLC 纯度 95.0%。

[0270] 实施例104:(R)-(2-(苯并[b]噻吩-3-基)-1-(3-(4-苯基-1H-1,2,3-三唑-1-基)丙酰氨基)乙基)硼酸



白色固体。^{1}H NMR:(400 MHz, DMSO-d_6):δ 8.34 (s, 1H), 7.83-7.86 (m, 1H), 7.76-7.78 (m, 2H), 7.68-7.71 (m, 1H), 7.39-7.43 (m, 2H), 7.28-7.34 (m, 3H), 7.12 (s, 1H), 4.56 (t, J = 6.68 Hz, 2H), 3.22-3.25 (m, 1H), 2.96-3.01 (m, 1H), 2.81-2.87 (m, 1H), 2.69 (t, J = 6.56 Hz, 2H). MS (ESI+):425.2 [M+Na-H_2O]. HPLC(方法A):Rt. 3.6 min, HPLC纯度94.8%。

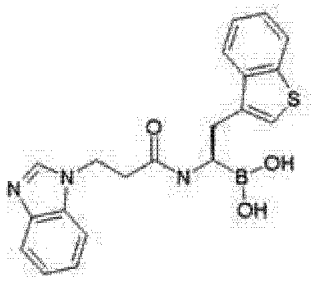
[0271] 实施例105:(R)-(2-(苯并[b]噻吩-3-基)-1-(3-(2-氧代苯并[d]噻唑-3(2H)-基)丙酰氨基)乙基)硼酸



白色固体。^{1}H NMR:(400 MHz, DMSO-d_6):δ 7.87-7.89 (m, 1H), 7.72-7.74 (m, 1H), 7.58 (d, J = 7.20 Hz, 1H), 7.26-7.37 (m, 4H), 7.14-7.18 (m, 1H), 7.03 (s, 1H), 4.05-4.08 (m, 2H), 3.20-3.24 (m, 1H), 2.93-2.98 (m, 1H), 2.83-2.86 (m, 1H), 2.41-2.49 (m, 2H).

MS (ESI+):409.0 [M+H-H_2O]. HPLC(方法A):Rt. 3.8 min, HPLC纯度86.0%。

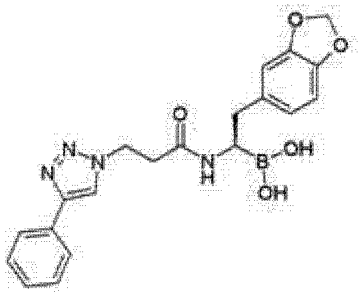
[0272] 实施例106:(R)-(1-(3-(1H-苯并[d]咪唑-1-基)丙酰氨基)-2-(苯并[b]噻吩-3-基)乙基)硼酸



白色固体。^{1}H NMR:(400 MHz, DMSO-d_6):δ 8.09 (s, 1H), 7.85-7.87 (m, 1H), 7.67-7.70 (m, 1H), 7.63 (d, J = 7.48 Hz, 1H), 7.55 (d, J = 7.56 Hz, 1H), 7.28-7.30 (m, 2H), 7.19-7.26 (m, 2H), 6.86 (s, 1H), 4.39-4.42 (m, 2H), 3.18-3.21 (m, 1H), 2.92-2.95 (m, 1H), 2.76-2.82 (m, 1H), 2.58-2.61 (m, 2H). MS

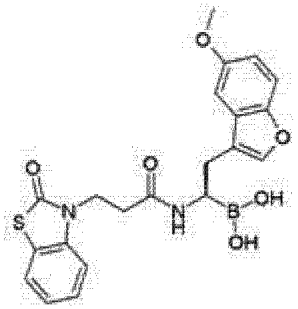
(ESI+) :398.0 [M+Na-H_2O]. HPLC (方法 A) :Rt. 2.7 min, HPLC 纯度 96.0%。

[0273] 实施例 107 :(R)-(2-(苯并[d][1,3]间二氧杂环戊烯-5-基)-1-(3-(4-苯基-1H-1,2,3-三唑-1-基)丙酰氨基)乙基)硼酸



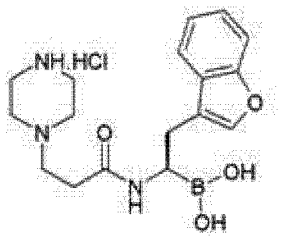
白色固体。^{1}H NMR :(400 MHz, DMSO-d_6) :δ 8.25 (s, 1H), 7.72-7.74 (m, 2H), 7.38-7.42 (m, 2H), 7.29-7.33 (m, 1H), 6.45-6.48 (m, 2H), 6.25 (d, J = 7.92 Hz, 1H), 5.73 (s, 2H), 4.59-4.61 (m, 2H), 2.74-2.84 (m, 3H), 2.49-2.56 (m, 1H), 2.26-2.32 (m, 1H). MS (ESI+) :413.0 [M+Na-H_2O]. HPLC (方法A) :Rt. 3.1 min, HPLC 纯度 95.2%。

[0274] 实施例 109 :(R)-(2-(5-甲氧基苯并呋喃-3-基)-1-(3-(2-氧代苯并[d]噻唑-3(2H)-基)丙酰氨基)乙基)硼酸



浅棕色固体。^{1}H NMR :(400 MHz, DMSO-d_6) :δ 7.58 (d, J = 7.16 Hz, 1H), 7.34-7.39 (m, 2H), 7.31 (d, J = 8.16 Hz, 1H), 7.27 (d, J = 7.36 Hz, 1H), 7.13-7.17 (m, 1H), 7.07-7.08 (m, 1H), 6.83 (dd, J = 2.56, 8.88 Hz, 1H), 4.06 (t, J = 7.68 Hz, 2H), 3.74 (s, 3H), 3.17-3.20 (m, 1H), 2.73-2.74 (m, 1H), 2.64-2.68 (m, 1H), 2.42-2.46 (m, 2H). MS (ESI+) :423.0 [M+H-H_2O]. HPLC (方法A) :Rt. 3.6 min, HPLC 纯度 92.6%。

[0275] 实施例 92 :(R)-(2-(苯并呋喃-3-基)-1-(3-(哌嗪-1-基)丙酰氨基)乙基)硼酸盐酸盐



步骤 1 :(R)-(2-(苯并呋喃-3-基)-1-(3-(4-(叔丁氧基羰基)哌嗪-1-基)丙酰氨基)乙基)硼酸频哪醇酯.

将中间体 18 (300 mg, 0.66 mmol) 在无水 N,N-二甲基甲酰胺 (10 ml) 中的冷却

(-10℃)溶液用二异丙基乙胺(0.3 ml, 1.9 mmol)和3-(4-(叔丁氧基羰基)哌嗪-1-基)丙酸(170 mg, 0.66 mmol)和TBTU (254 mg, 0.79 mmol)处理。将反应混合物于-10℃搅拌3h。在减压下浓缩反应混合物,保持外浴温度低于30℃,然后加入25 ml乙酸乙酯。有机层用盐水洗涤,经硫酸钠干燥并浓缩。所需产物(350 mg, 87%)经硅胶层析纯化来分离,用在二氯甲烷中的4 %甲醇洗脱。

[0276] MS (ESI+):580.4

步骤2:(R)-(2-(苯并呋喃-3-基)-1-(3-(4-(叔丁氧基羰基)哌嗪-1-基)丙酰氨基)乙基)硼酸.

将(R)-(2-(苯并呋喃-3-基)-1-(3-(4-(叔丁氧基羰基)哌嗪-1-基)丙酰氨基)乙基)硼酸频哪醇酯(350 mg, 0.6 mmol)在甲醇/戊烷(1:1, 30 mL)中的冷却(0℃)溶液用2-甲基丙基硼酸(242 mg, 2.4 mmol)和HCl水溶液(1.5 N, 0.7 mL)处理并将反应混合物于室温下搅拌15 h。然后用戊烷提取反应混合物三次。在低于30℃的温度下浓缩含水甲醇层。残留物用冰处理,用NaOH的水溶液(2N)碱化并用二氯甲烷提取三次(弃去)。然后水层用HCl的水溶液(1.5 N)酸化并用二氯甲烷提取三次。DCM层经硫酸钠干燥,过滤并浓缩。所需产物(85 mg, 31 %)经硅胶层析纯化来分离,用在二氯甲烷中的30 %甲醇洗脱。

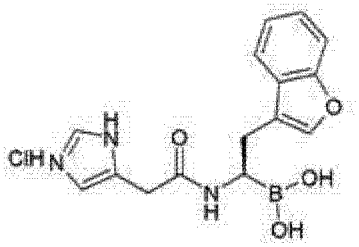
[0277] MS (ESI+):450.2 [M+Na-H_2O].

步骤3:(R)-(2-(苯并呋喃-3-基)-1-(3-(哌嗪-1-基)丙酰氨基)乙基)硼酸盐酸盐.

将化合物(R)-(2-(苯并呋喃-3-基)-1-(3-(4-(叔丁氧基羰基)哌嗪-1-基)丙酰氨基)乙基)硼酸(0.085g, 0.19 mmol)溶于1,4-二氧杂环己烷(5 mL)并冷却至10℃。向其中加入在二氧杂环己烷(5 mL)中的4 N HCl并于室温下搅拌过夜。将反应混合物在减压下浓缩并用二乙醚洗涤残留物,得到固体。将该固体进一步冻干,获得标题化合物(47 mg, 64 %),为浅棕色固体。

[0278] ^{1}H NMR:(400 MHz, DMSO-d_6):δ 7.66 (s, 1H), 7.62 (d, J = 7.24 Hz, 1H), 7.49 (d, J = 8.12 Hz, 1H), 7.21-7.29 (m, 2H), 3.25-3.37 (m, 11 H), 2.88-2.93 (m, 1H), 2.75-2.81 (m, 1H), 2.55-2.56 (m, 2H). MS (ESI+):350.3 [M+Na-H_2O]. HPLC(方法A):Rt. 2.0 min, HPLC纯度93.5%。

[0279] 实施例83:(R)-(1-(2-(1H-咪唑-5-基)乙酰氨基)-2-(苯并呋喃-3-基)乙基)硼酸盐酸盐



步骤1:(R)-(1-(2-(1H-咪唑-5-基)乙酰氨基)-2-(苯并呋喃-3-基)乙基)硼酸频哪醇酯.

将中间体18 (170 mg, 0.37 mmol)在无水N,N-二甲基甲酰胺(20 ml)中的冷却(-10℃)溶液用二异丙基乙胺(0.2 ml, 1.1 mmol)和2-(1H)-咪唑-5-基-乙酸(47 mg,

0.37 mmol）和 TBTU（142 mg，0.44 mmol）处理。将反应混合物于 -10℃搅拌 3h。在减压下浓缩反应混合物，保持外浴温度低于 30℃，然后加入 25 ml 乙酸乙酯。有机层用盐水洗涤，经硫酸钠干燥并浓缩。所需产物（110 mg，66 %）经硅胶层析纯化来分离，用在二氯甲烷中的 7 % 甲醇洗脱。

[0280] MS（ESI+）：448.2

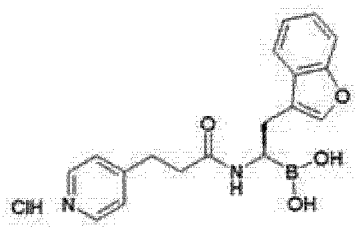
步骤 2：(R)-(1-(2-(1H- 咪唑 -5- 基）乙酰氨基）-2-（苯并呋喃 -3- 基）乙基）硼酸盐酸盐

将 (R)-(1-(2-(1H- 咪唑 -5- 基）乙酰氨基）-2-（苯并呋喃 -3- 基）乙基）硼酸频哪醇酯（110 mg，0.24 mmol）在甲醇 / 戊烷（1:1，20 mL）中的冷却（0℃）溶液用 2- 甲基丙基硼酸（96 mg，0.96 mmol）和 HCl 水溶液（1.5 N，0.5 mL）处理并将反应混合物于室温下搅拌 15 h。然后用戊烷提取反应混合物三次。在低于 30℃的温度下浓缩含水甲醇层。向该残留物中加入水并用二氯甲烷提取三次。冻干水层获得标题化合物（25 mg，32 %），为浅棕色半固体。

[0281] ^{1}H NMR：(400 MHz，DMSO-d_6)：δ 8.68（s，1H），7.58（t，J = 7.60 Hz，2H），7.47（d，J = 8.08 Hz，1H），7.18-7.28（m，3H），3.52（s，2H），3.26-3.30（m，2H），2.86-2.88（m，1H），2.78-2.80（m，1H）. MS（ESI+）：318.3 [M+Na-H_2O]. HPLC（方法 A）：Rt. 2.1 min，HPLC 纯度 95.2%。

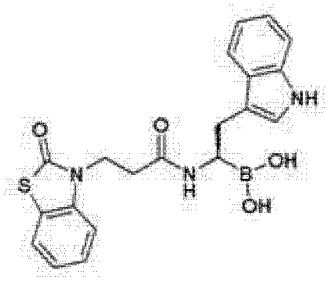
[0282] 以下化合物采用实施例 83 遵照的相同程序合成。

[0283] 实施例 93：(R)-(2-（苯并呋喃 -3- 基）-1-(3-（吡啶 -4- 基）丙酰氨基）乙基）硼酸盐酸盐



浅棕色半固体。^{1}H NMR：(400 MHz，DMSO-d_6)：δ 8.65（d，J = 6.56 Hz，2H），7.83（d，J = 6.48 Hz，2H），7.55-7.58（m，2H），7.48（d，J = 7.96 Hz，1H），7.19-7.28（m，2H），3.20-3.23（m，1H），3.03（t，J = 7.16 Hz，2H），2.81-2.86（m，1H），2.66-2.73（m，1H），2.54-2.51（m，2H）. MS（ESI+）：343.2 [M+Na-H_2O]. HPLC（方法 A）：Rt. 2.0 min，HPLC 纯度 96.1 %。

[0284] 实施例 101：(R)-(2-(1H- 吲哚 -3- 基）-1-(3-(2- 氧代苯并 [d] 噻唑 -3(2H)- 基）丙酰氨基）乙基）硼酸



步骤 1：叔丁基 3-((2R)-2-(3-(2- 氧代苯并 [d] 噻唑 -3(2H)- 基）丙酰氨

基)-2-(3a,5,5-三甲基六氢-4,6-亚甲基苯并[d][1,3,2]二氧硼杂环戊烷-2-基)乙基)-1H-吲哚-1-甲酸酯.

将[(1R)-1-氨基-2-(1H-吲哚-3-基)乙基]硼酸(+)-蒎烷二醇酯三氟乙酸盐(500 mg, 0.90 mmol)在无水N,N-二甲基甲酰胺(20 ml)中的冷却(-10℃)溶液用二异丙基乙胺(0.5 ml, 2.7 mmol)和[3-(2-氧代-苯并噻唑-3-基)丙酸](190 mg, 0.9 mmol)和TBTU(346 mg, 1.1 mmol)处理。将反应混合物于-10℃搅拌3h。在减压下浓缩反应混合物,保持外浴温度低于30℃,然后加入25 ml乙酸乙酯。有机层用盐水洗涤,经硫酸钠干燥并浓缩。所需产物(280 mg, 48 %)经硅胶层析纯化来分离,用在石油醚中的30 %乙酸乙酯洗脱。

[0285] MS(ESI+):644.2

步骤2:N-((1R)-2-(1H-吲哚-3-基)-1-(3a,5,5-三甲基六氢-4,6-亚甲基苯并[d][1,3,2]二氧硼杂环戊烷-2-基)乙基)-3-(2-氧代苯并[d]噻唑-3(2H)-基)丙酰胺盐酸盐.

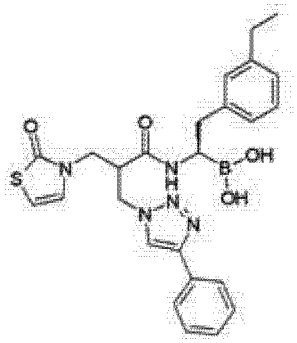
将化合物叔丁基3-((2R)-2-(3-(2-氧代苯并[d]噻唑-3(2H)-基)丙酰氨基)-2-(3a,5,5-三甲基六氢-4,6-亚甲基苯并[d][1,3,2]二氧硼杂环戊烷-2-基)乙基)-1H-吲哚-1-甲酸酯(280 mg, 0.43 mmol)溶于二氯甲烷(10 mL)和冷却至10℃。向其中加入在二氧杂环己烷(10 mL)中的4 N HCl并于室温下搅拌过夜。反应混合物在减压下浓缩并用二乙醚洗涤残留物,获得所需产物(200 mg, 85 %)。

[0286] 步骤3:(R)-(2-(1H-吲哚-3-基)-1-(3-(2-氧代苯并[d]噻唑-3(2H)-基)丙酰氨基)乙基)硼酸

将N-((1R)-2-(1H-吲哚-3-基)-1-(3a,5,5-三甲基六氢-4,6-亚甲基苯并[d][1,3,2]二氧硼杂环戊烷-2-基)乙基)-3-(2-氧代苯并[d]噻唑-3(2H)-基)丙酰胺盐酸盐(200 mg, 0.36 mmol)在甲醇/戊烷(1:1, 20 mL)中的冷却(0℃)溶液用2-甲基丙基硼酸(145 mg, 1.4 mmol)和HCl水溶液(1.5 N, 0.5 mL)处理并将反应混合物于室温下搅拌15 h。然后用戊烷提取反应混合物三次。在低于30℃的温度下浓缩含水甲醇层。残留物用冰处理,用NaOH的水溶液(2N)碱化并用二氯甲烷提取三次(弃去)。然后水层用HCl的水溶液(1.5 N)酸化并用二氯甲烷提取三次。DCM层经硫酸钠干燥,过滤并浓缩,得到固体残留物,其用二乙醚研磨并冻干获得标题化合物(13 mg, 15 %),为灰白色固体。

[0287] ^{1}H NMR:(400 MHz, DMSO-d_6):δ 7.59(d, J = 7.80 Hz, 1H), 7.42(d, J = 7.92 Hz, 1H), 7.26-7.34(m, 3H), 7.17(t, J = 7.36 Hz, 1H), 7.01(t, J = 7.60 Hz, 1H), 6.88-6.93(m, 2H), 4.05-4.09(m, 2H), 3.17-3.21(m, 1H), 2.80-2.85(m, 1H), 2.70-2.75(m, 1H), 2.41-2.44(m, 2H). MS(ESI+):392.0 [M+H-H_2O]. HPLC(方法A):Rt. 3.2 min, HPLC纯度92.1 %。

[0288] 实施例110:((1R)-2-(3-乙基苯基)-1-(3-(2-氧代噻唑-3(2H)-基)-2-((4-苯基-1H-1,2,3-三唑-1-基)甲基)丙酰氨基)乙基)硼酸



步骤 1 :乙基 -2-(叠氮基甲基) 丙烯酸酯

向乙基 -2-(溴代甲基) 丙烯酸酯 (5 g, 26.1 mmol) 在 DMSO (50 ml) 中的溶液中加入叠氮化钠 (2.5 g, 38.4 mmol) 并将反应混合物于室温下搅拌 2h。用水猝灭反应并用乙酸乙酯提取。分离有机层,经无水硫酸钠干燥并浓缩。粗品 (5.0 g) 无须进一步纯化而用于后面的步骤 (发现乙基 -2-(叠氮基甲基) 丙烯酸酯放置数小时后不稳定)。

[0289] 步骤 2 :乙基 -2-((4- 苯基 -1H-1,2,3- 三唑 -1- 基) 甲基) 丙烯酸酯

向苯基乙炔 (3.0 g, 29.4 mmol) 和乙基 -2-(叠氮基甲基) 丙烯酸酯 (5.0 g, 32.3 mmol) 在 t-BuOH:H_2O (2:1) (50 ml.) 中的溶液中加入抗坏血酸钠 (0.87 g, 4.4 mmol) 和 CuSO4.$5H_2O$ (0.36 g, 1.5 mmol)。将反应混合物于室温下搅拌 12h。用乙酸乙酯稀释反应混合物并用水、盐水溶液洗涤。分离有机层,经无水硫酸钠干燥并浓缩。获得的固体 (3.0 g, 39%) 无须进一步纯化而用于后面的步骤。

[0290] ^{1}H NMR :(400 MHz, DMSO-d6) : δ 8.5 (s, 1H), 7.8 (d, J = 8.2 Hz, 2H), 7.4 (t, J = 7.7 Hz, 2H), 7.30-7.34 (m, 1H), 6.4 (s, 1H), 5.8 (s, 1H), 5.3 (s, 2H), 4.2 (q, J = 7.0 Hz, 2H), 1.2 (t, J = 7.0 Hz, 3H)。

[0291] 步骤 3 :乙基 -3-(2- 氧代噻唑 -3(2H)- 基)-2-((4- 苯基 -1H-1,2,3- 三唑 -1- 基) 甲基) 丙酸酯

于室温下,向乙基 -2-((4- 苯基 -1H-1,2,3- 三唑 -1- 基) 甲基) 丙烯酸酯 (3.0 g, 11.6 mmol) 在乙腈 (30 ml.) 中的溶液中加入噻唑 -2(3H)- 酮 (1.2 g, 11.6 mmol) 和 DBU (2.6 g, 17.4 mmol) 并将反应混合物于室温下搅拌过夜。将反应混合物在减压下浓缩并将残留物用乙酸乙酯提取并用水、盐水溶液洗涤。分离有机层,经无水硫酸钠干燥并浓缩。粗制化合物经柱层析纯化,采用乙酸乙酯和石油醚作为洗脱剂,得到标题化合物 (1.2 g, 28 %)。

[0292] MS (ESI+) :359.2 [M+H]

步骤 4 :3-(2- 氧代噻唑 -3(2H)- 基)-2-((4- 苯基 -1H-1,2,3- 三唑 -1- 基) 甲基) 丙酸

向乙基 -3-(2- 氧代噻唑 -3(2H)- 基)-2-((4- 苯基 -1H-1,2,3- 三唑 -1- 基) 甲基) 丙酸酯 (1.2 g, 3.3mmol) 在 THF:H_2O (20 m L) 中的溶液中加入氢化锂单水合物 (0.41 g, 9.9 mmol) 并将反应混合物于室温下搅拌过夜。蒸发反应混合物。向残留物加入水并用二氯甲烷提取三次 (弃去)。然后即刻酸化含水层并用二氯甲烷提取。然后经无水硫酸钠干燥有机层并浓缩,得到标题化合物 (200 mg, 18 %)。

[0293] MS (ESI+) :331.0 [M+H]

步骤 5 :((1R)-2-(3- 乙基苯基)-1-(3-(2- 氧代噻唑 -3(2H)- 基)-2-((4- 苯

基 -1H-1,2,3- 三唑 -1- 基) 甲基) 丙酰氨基) 乙基) 硼酸频哪醇酯 .

将 [(1R)-1- 氨基 -2-(3- 乙基苯基) 乙基] 硼酸 (+)- 蒎烷二醇酯三氟乙酸盐 (200 mg, 0.45 mmol) 在无水 N,N- 二甲基甲酰胺 (10 ml) 中的冷却 (-10℃) 溶液用二异丙基乙胺 (0.2 ml, 1.3 mmol) 和 3-(2- 氧代噻唑 -3(2H)- 基)-2-((4- 苯基 -1H-1,2,3- 三唑 -1- 基) 甲基) 丙酸 (148 mg, 0.45 mmol) 和 TBTU (173 mg, 0.54 mmol) 处理。将反应混合物于 -10℃搅拌 3h。在减压下浓缩反应混合物,保持外浴温度低于 30℃,然后加入 25 ml 乙酸乙酯。有机层用盐水洗涤,经硫酸钠干燥并浓缩。所需产物 (290 mg, 99 %) 经硅胶层析纯化来分离,用在石油醚中的 25 % 乙酸乙酯洗脱。

[0294] MS (ESI+) :640.3

步骤 6 :((1R)-2-(3- 乙基苯基)-1-(3-(2- 氧代噻唑 -3(2H)- 基)-2-((4- 苯基 -1H-1,2,3- 三唑 -1- 基) 甲基) 丙酰氨基) 乙基) 硼酸

将 ((1R)-2-(3- 乙基苯基)-1-(3-(2- 氧代噻唑 -3(2H)- 基)-2-((4- 苯基 -1H-1,2,3- 三唑 -1- 基) 甲基) 丙酰氨基) 乙基) 硼酸频哪醇酯 (290 mg, 0.45 mmol) 在甲醇 / 戊烷 (1:1, 20 mL) 中的冷却 (0℃) 溶液用 2- 甲基丙基硼酸 (181 mg, 1.8 mmol) 和 HCl 水溶液 (1.5 N, 0.5 mL) 处理并将反应混合物于室温下搅拌 15 h。然后用戊烷提取反应混合物三次。在低于 30℃的温度下浓缩含水甲醇层。残留物用冰处理,用 NaOH 的水溶液 (2N) 碱化并用二氯甲烷提取三次 (弃去)。然后水层用 HCl 的水溶液 (1.5 N) 酸化并用二氯甲烷提取三次。DCM 层经硫酸钠干燥,过滤并浓缩,得到固体残留物,其用二乙醚研磨并冻干获得标题化合物 (61 mg, 26 %),为淡粉红色固体。

[0295] ^{1}H NMR:(400 MHz, DMSO-d6) :δ 8.20 (d, J = 8.56 Hz, 1H), 7.79-7.82 (m, 2H), 7.43 (t, J = 7.76 Hz, 2H), 7.33-7.37 (m, 1H), 6.93-7.08 (m, 3H), 6.80-6.86 (m, 1H), 6.71-6.75 (m, 1H), 6.31-6.35 (m, 1H), 4.56-4.62 (m, 1H), 4.37-4.44 (m, 1H), 3.82-3.84 (m, 1H), 3.33-3.34 (m, 1H), 3.20-3.22 (m, 1H), 2.62-2.67 (m, 2H), 2.44-2.49 (m, 2H), 1.05-1.11 (m, 3H).

MS (ESI+) :488.3 [M+H-H_2O]. HPLC (方法 A) :Rt. 4.4 min, HPLC 纯度 91.0%。

[0296] 实施例 111 :LMP7 活性的测定

LMP7 抑制作用的测量在基于荧光强度分析的 384 孔格式板上进行。

[0297] 将纯化的人免疫蛋白酶体 (0.5 nM) 和在 DMSO 中的系列稀释化合物 (浓度范围从 10 μ M 至 38 pM) 或对照品 (0.5% DMSO) 于 37℃在包含 50 mM Tris pH 7.4 和 0.03% SDS 的分析缓冲液中培育 30 分钟。通过加入浓度 40 μ M 的荧光肽底物 Suc-LLVY-AMC (Bachem I-1395) 来引发反应。于 37℃培育 90 分钟后,用荧光读出仪 (BMG Pherastar 读出仪或等同物) 于 λ_{ex} =350 nm 和 λ_{em} = 450 nm 测量荧光强度。

[0298] 对于实施例 79、80、83、84、85、87、88、89、90、91、93、94、96、97、101 和 110,LMP7 抑制作用的测量在基于荧光强度分析的 384 孔格式板上进行。

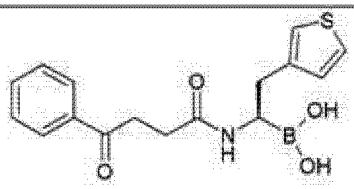
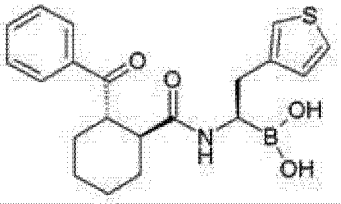
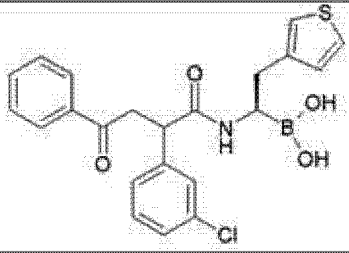
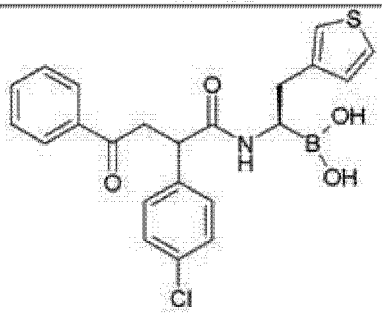
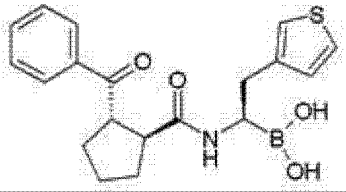
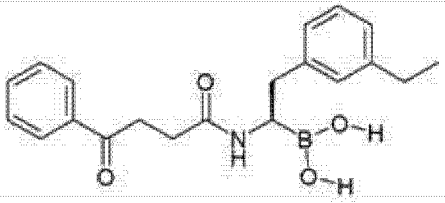
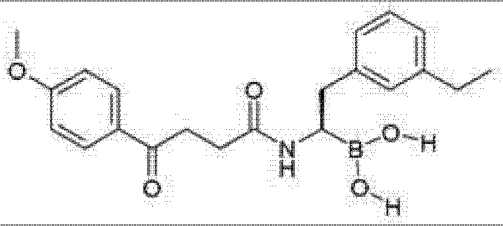
[0299] 将纯化的人免疫蛋白酶体 (0.25 nM) 和在 DMSO 中的系列稀释化合物 (浓度范围从 10 μ M 至 38 pM) 或对照品 (0.5% DMSO) 于 37℃在包含 50 mM Tris pH 7.4 和 0.03% SDS 的分析缓冲液中培育 30 分钟。通过加入浓度 40 μ M 的荧光肽底物 Suc-LLVY-AMC (Bachem I-1395) 来引发反应。于 37℃培育 90 分钟后,用荧光读出仪 (BMG Pherastar 读出仪或等同物) 于 λ_{ex} =350 nm 和 λ_{em} = 450 nm 测量荧光强度。

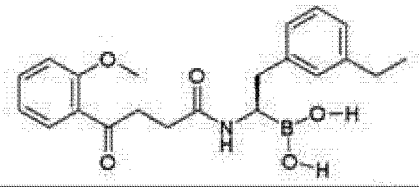
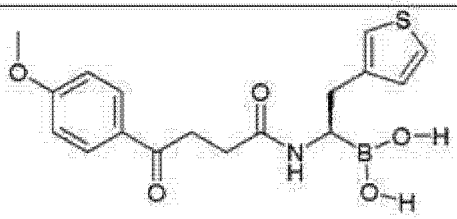
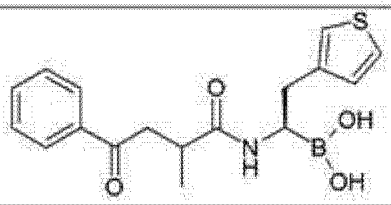
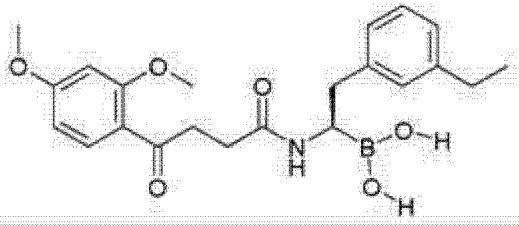
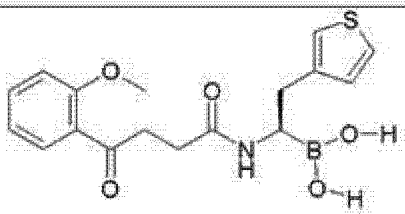
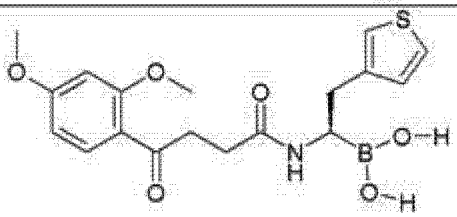
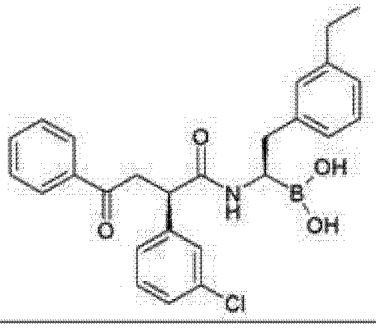
[0300] 实施例 112 ：β5 活性的测定

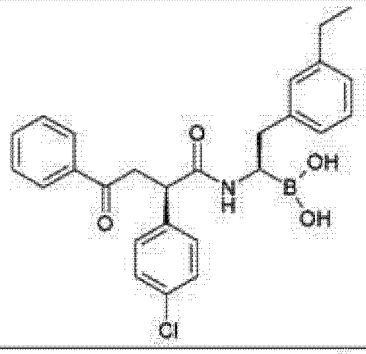
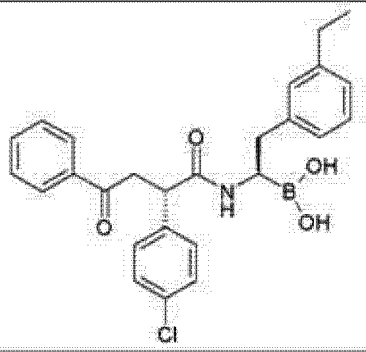
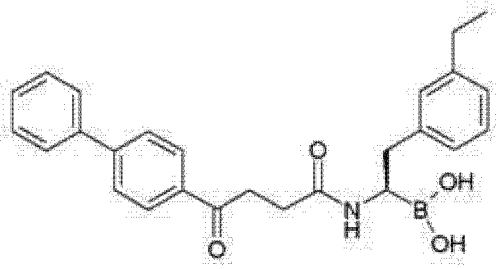
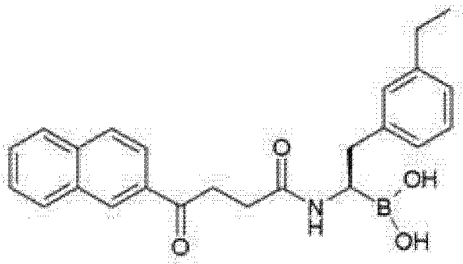
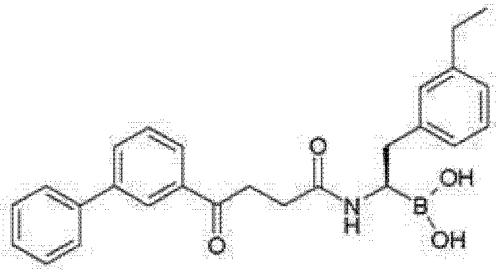
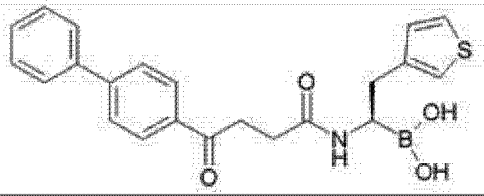
β5 抑制作用的测量在基于荧光强度分析的 384 孔格式板上进行。

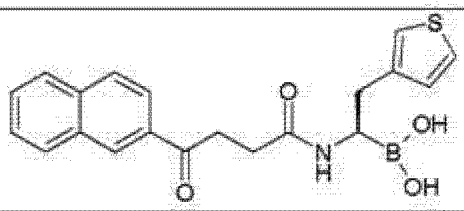
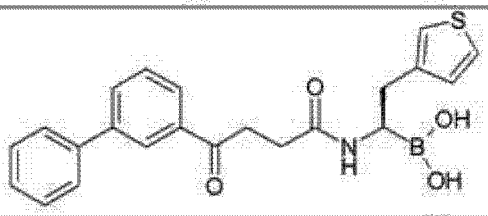
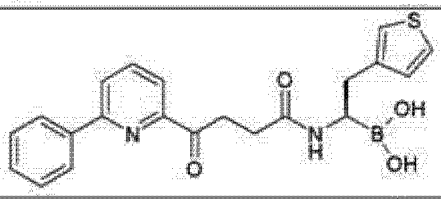
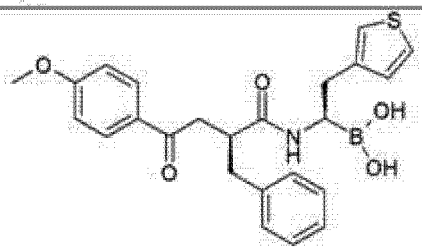
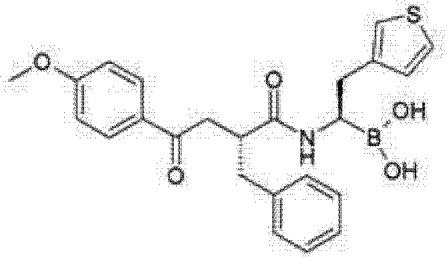
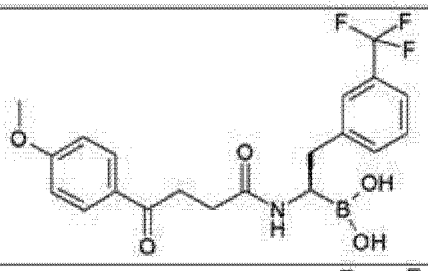
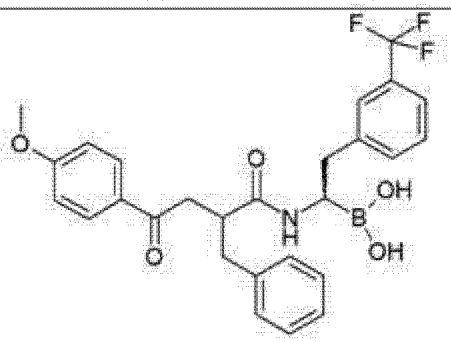
[0301] 将纯化的人组成型蛋白酶体 (1.0 nM) 和在 DMSO 中的系列稀释化合物 (浓度范围从 10 μM 至 38 pM) 或对照品 (0.5% DMSO) 于 37℃在包含 50 mM Tris pH 7.4 和 0.03% SDS 的分析缓冲液中培育 30 分钟。通过加入浓度 40μM 的荧光肽底物 Suc-LLVY-AMC (Bachem I-1395) 来引发反应。于 37℃培育 90 分钟后，用荧光读出仪 (BMG Pherastar 读出仪或等同物) 于 λ_{ex} =350 nm 和 λ_{em} = 450 nm 测量荧光强度。

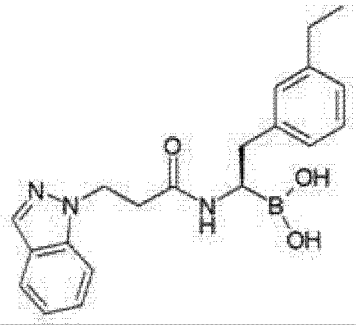
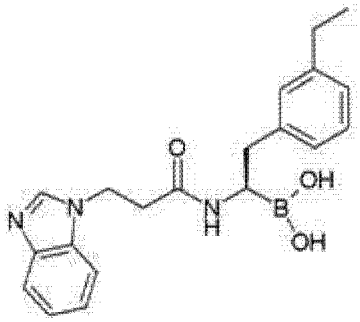
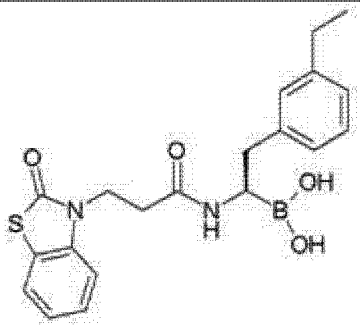
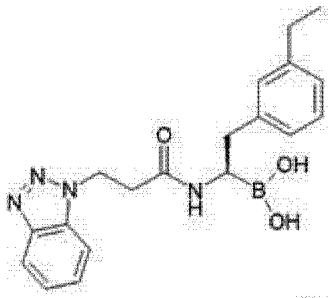
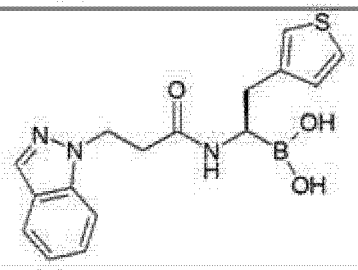
[0302] 所述化合物的生物学活性概述于下表中 ：

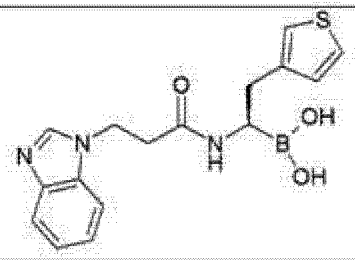
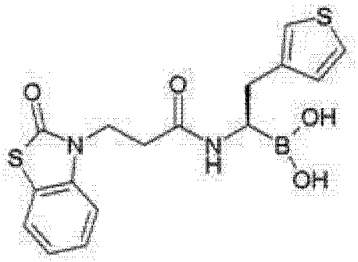
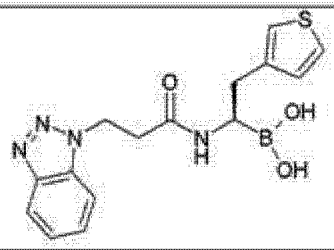
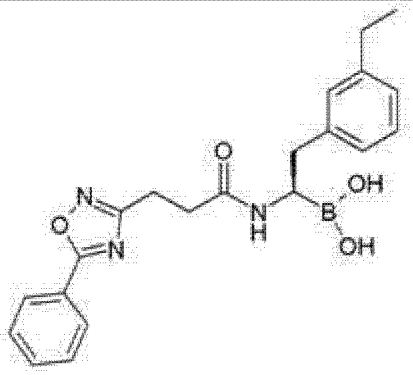
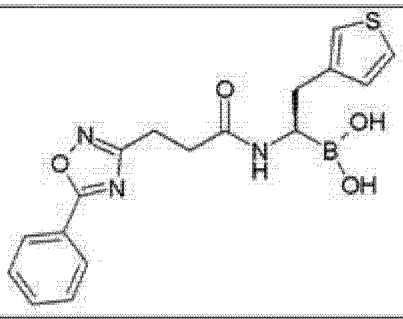
实施例	式	LMP7 IC50 (M)	β5 IC50 (M)	选择性 LMP7 对比 β5
1		***	**	++
2		**	*	nd
3		***	*	+++
4		***	**	+++
5		**	*	nd
6		***	*	+++
7		***	*	+++

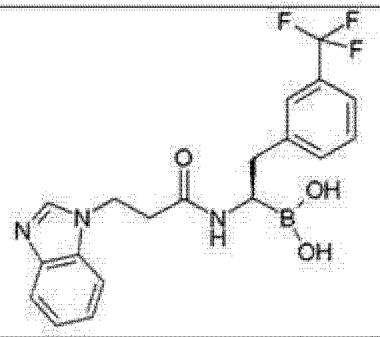
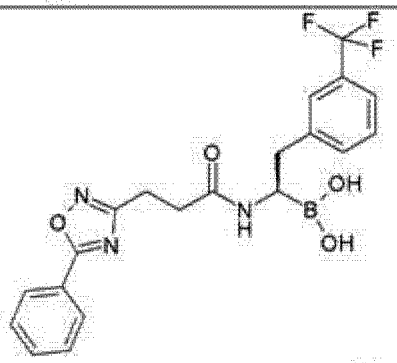
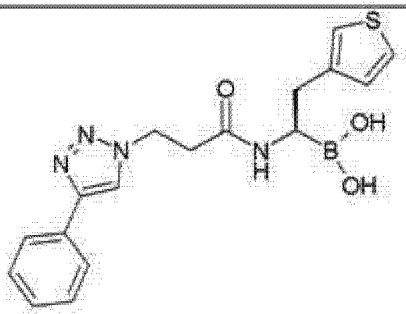
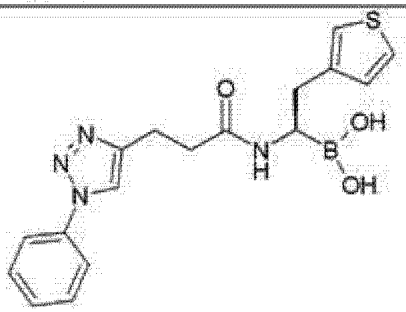
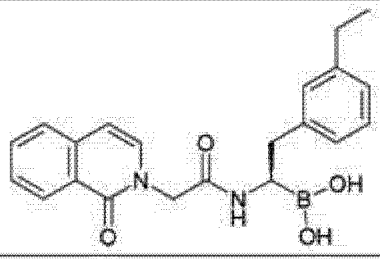
8		***	*	nd
9		***	**	++
10		**	*	nd
11		***	*	+++
12		**	*	nd
13		***	*	++
14		***	**	+++

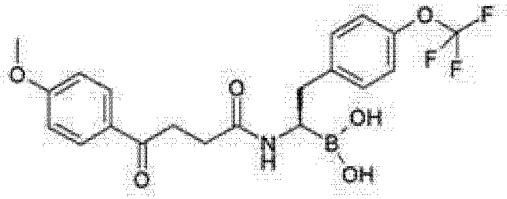
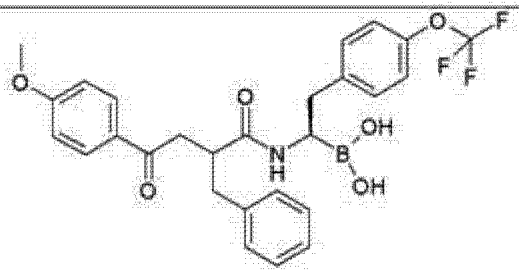
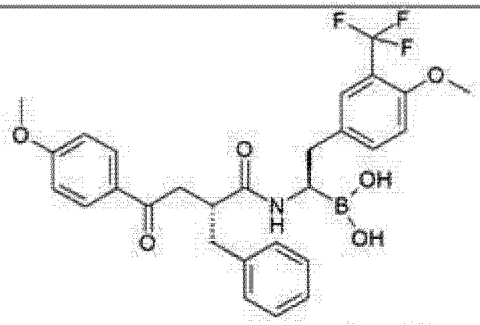
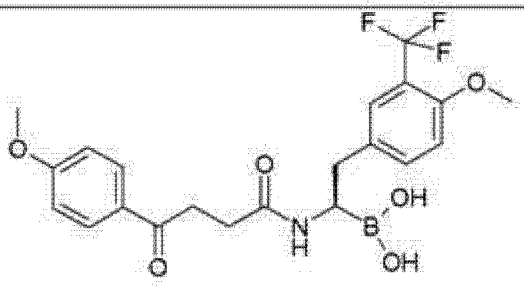
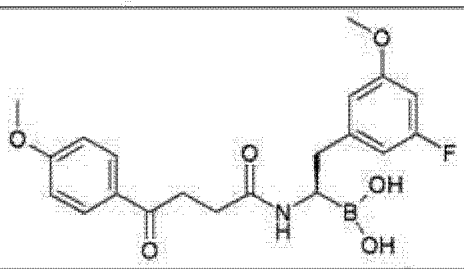
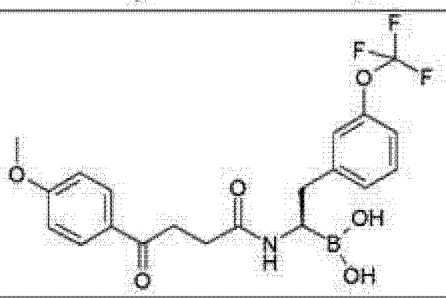
15		***	*	+++
16		**	*	nd
17		***	**	++
18		***	**	+++
19		***	**	++
20		***	**	+

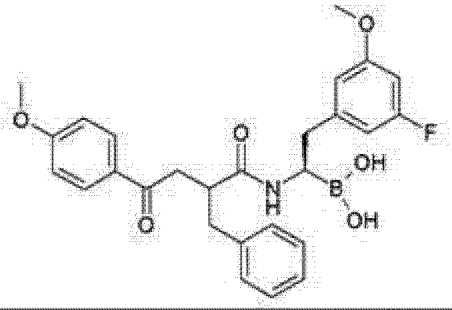
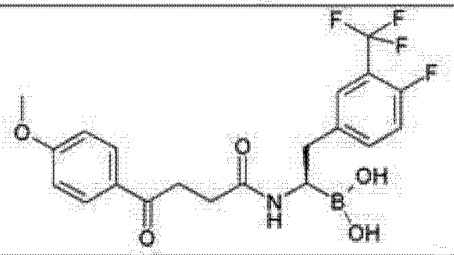
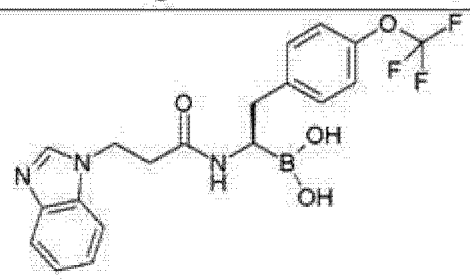
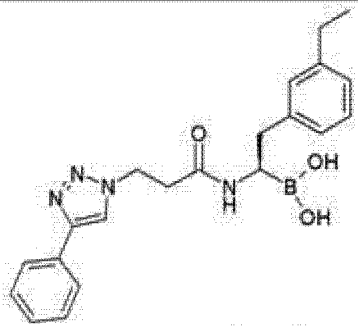
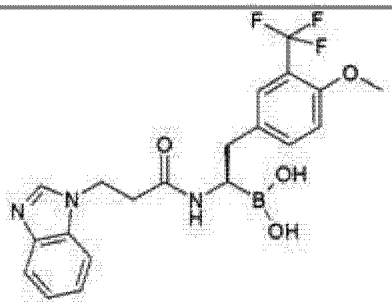
21		***	**	++
22		***	**	++
23		***	**	++
24		****	***	+++
25		***	*	+++
26		***	*	+++
27		****	**	+++

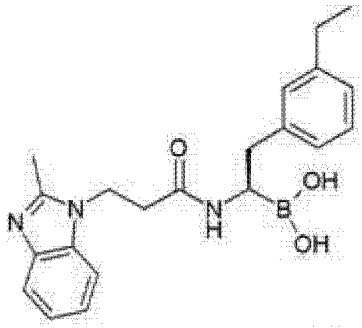
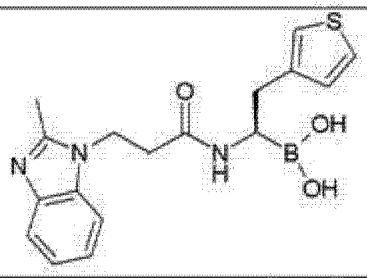
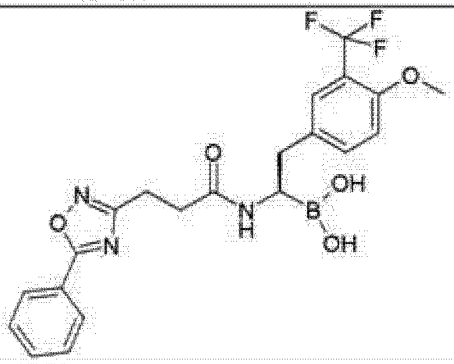
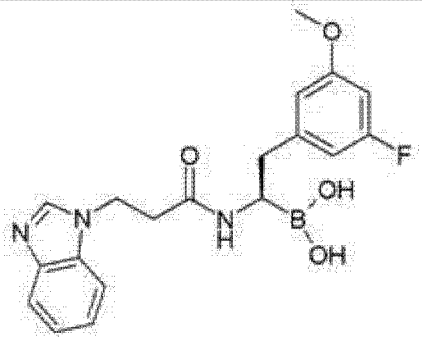
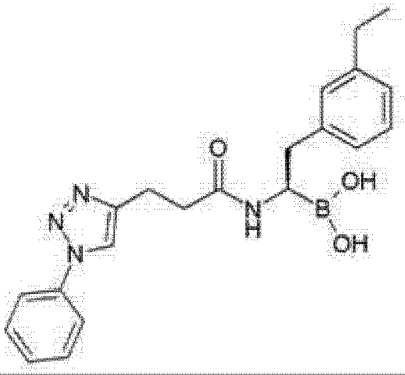
28		***	**	++
29		****	***	++
30		****	***	++
31		****	***	++
32		***	***	+

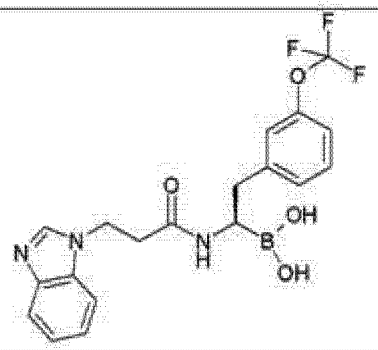
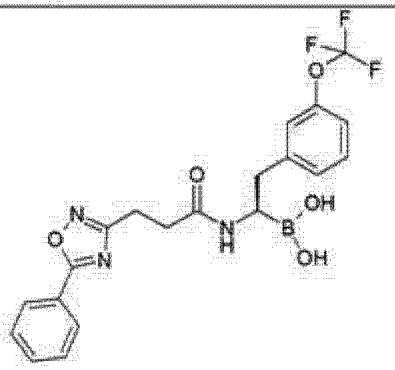
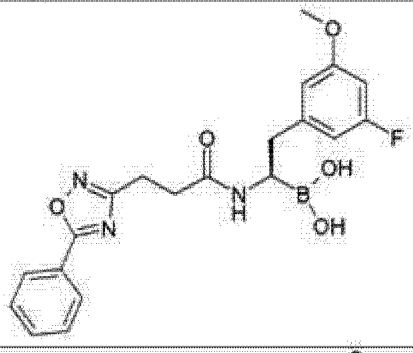
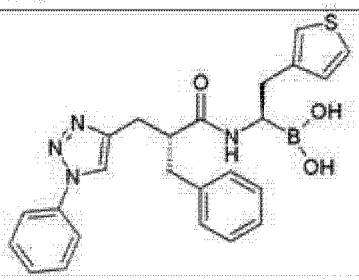
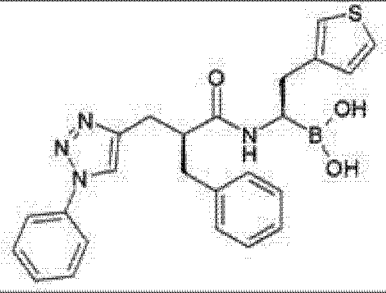
33		***	***	+
34		****	***	+
35		****	***	+
36		****	**	+++
37		***	**	++

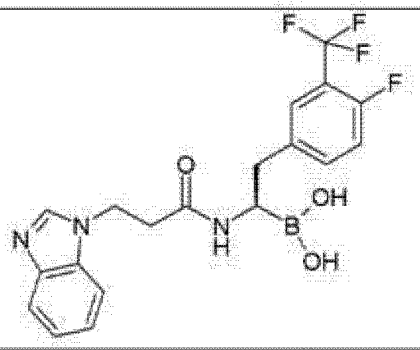
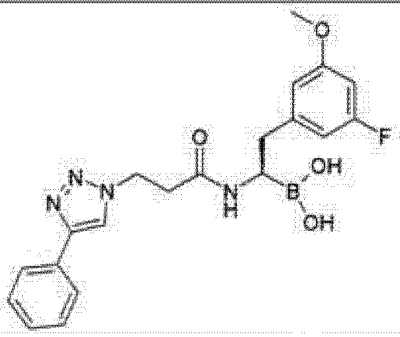
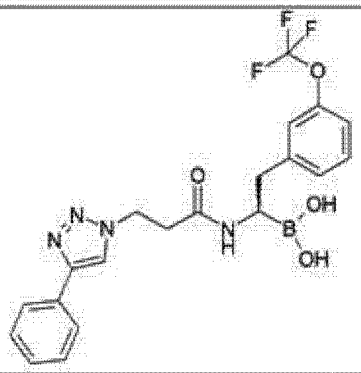
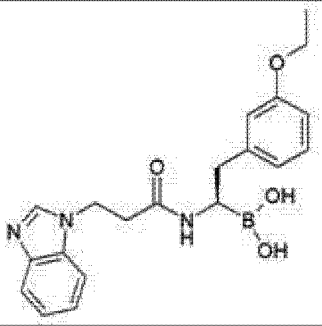
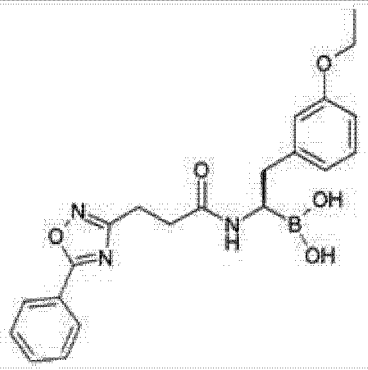
38		****	***	++
39		***	**	+++
40		****	***	++
41		****	**	+++
42		***	**	++

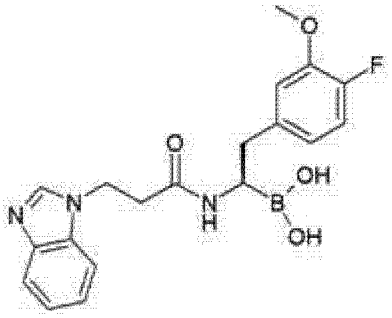
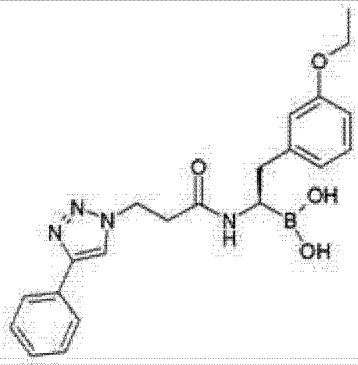
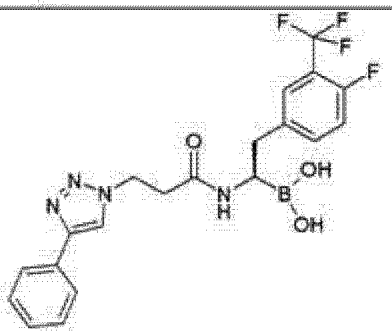
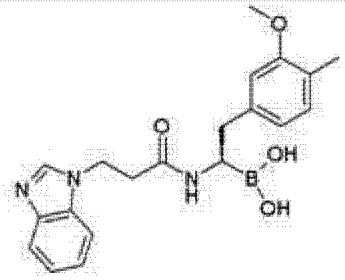
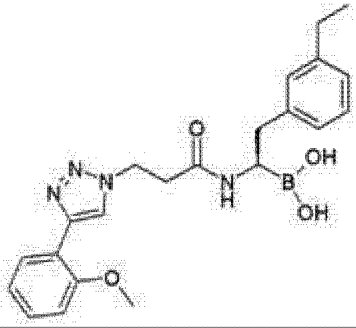
43		***	**	++
44		****	***	++
45		****	**	+++
46		***	*	nd
47		***	*	+++
48		***	**	++

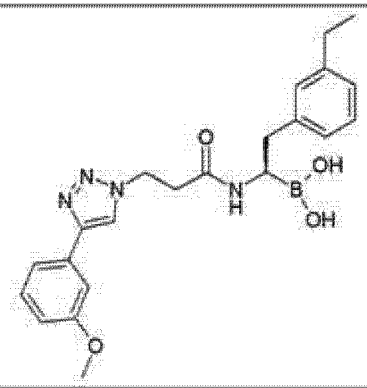
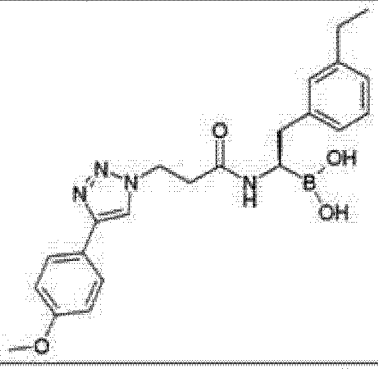
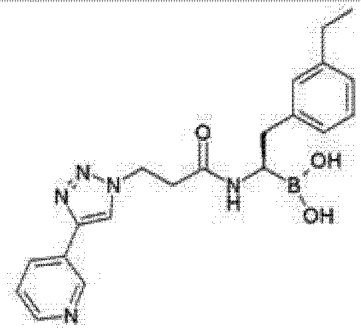
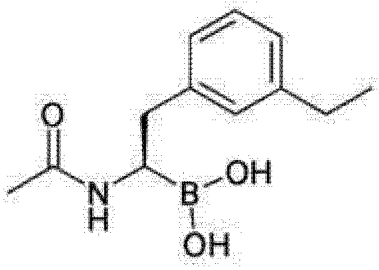
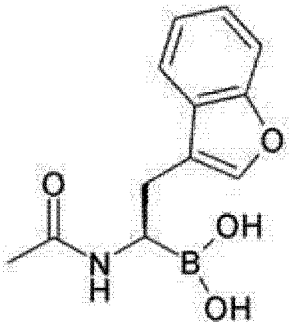
49		****	***	++
50		***	*	++
51		****	***	+
52		****	***	+++
53		****	***	+

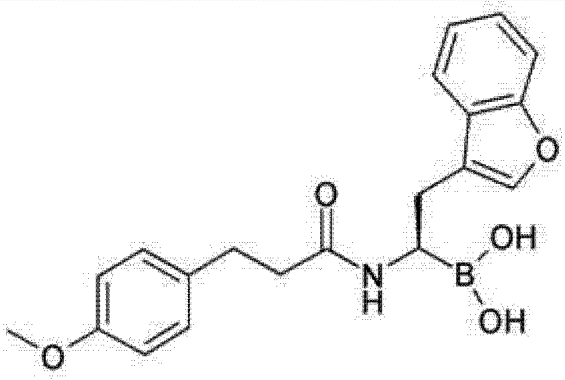
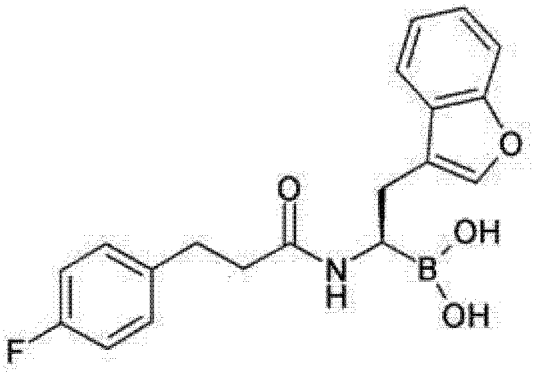
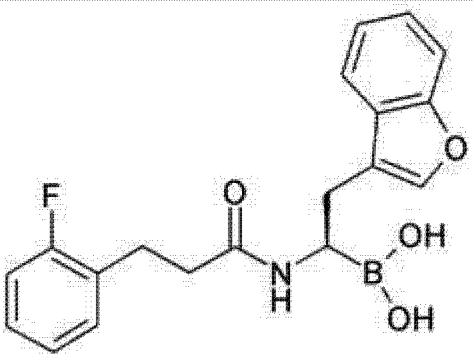
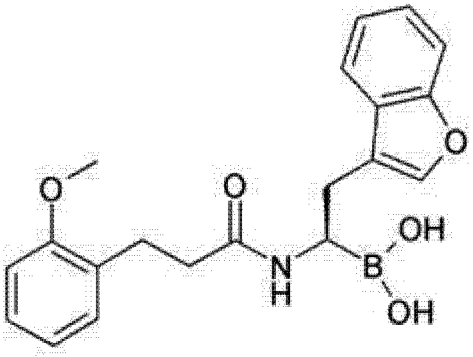
54		****	***	++
55		****	***	+
56		***	**	++
57		****	***	++
58		***	*	+++

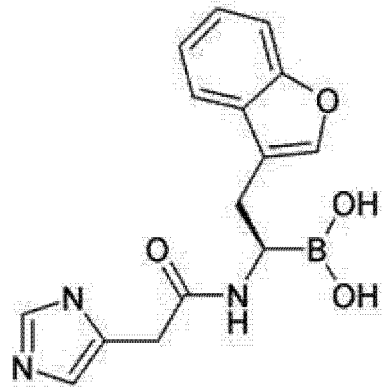
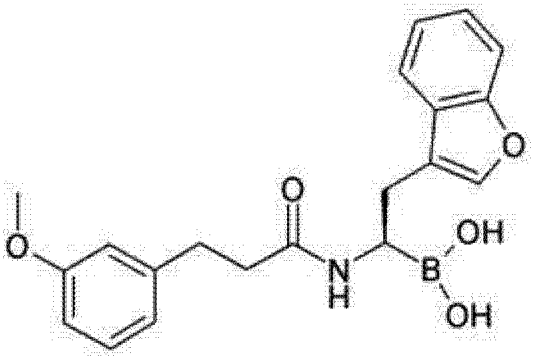
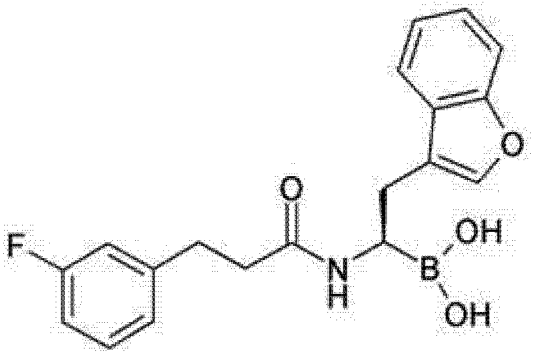
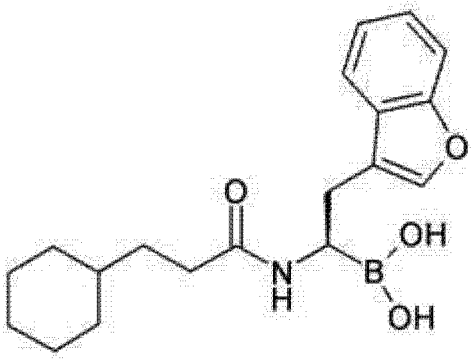
59		****	***	+
60		***	**	++
61		****	**	+++
62		****	***	++
63		****	****	++

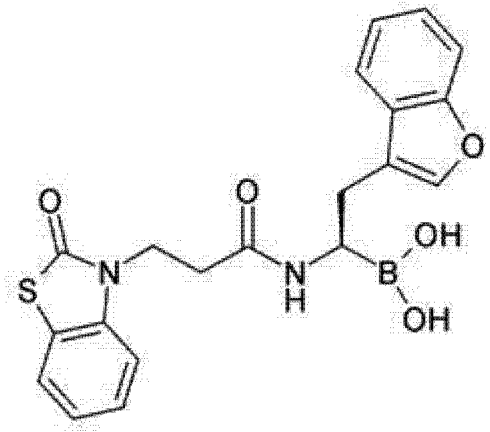
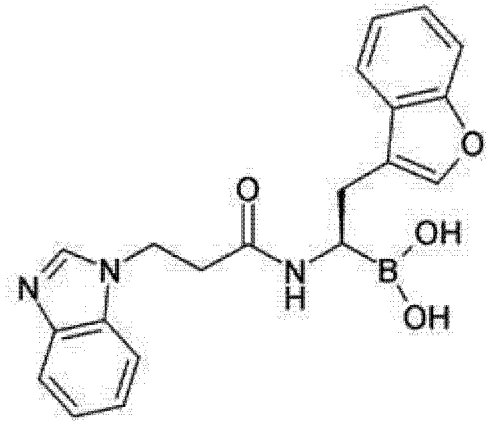
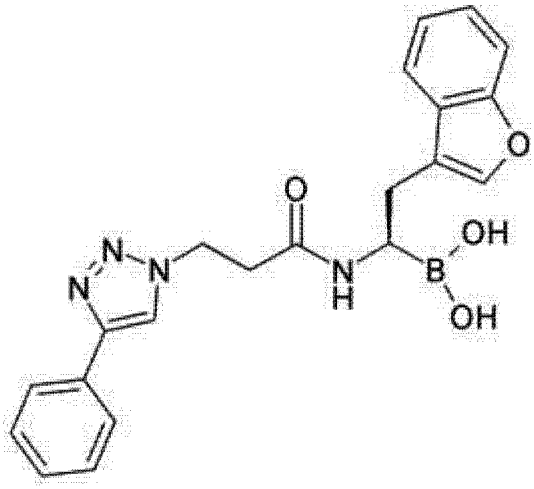
64		****	***	++
65		****	***	++
66		****	***	++
67		****	***	++
68		****	**	+++

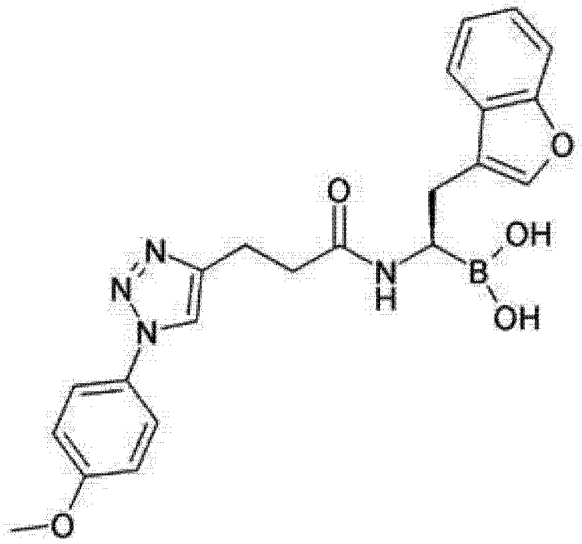
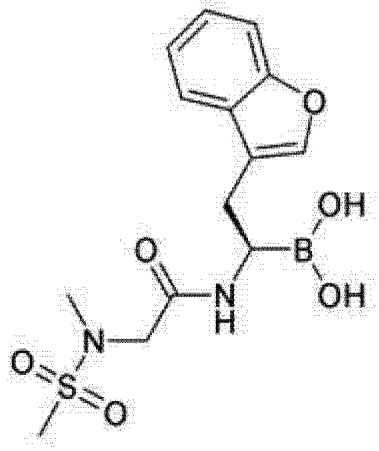
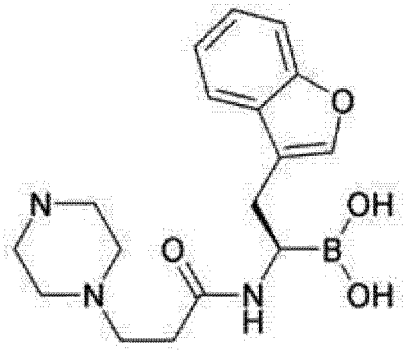
69		***	**	+
70		****	***	++
71		****	***	++
72		***	**	++
73		****	***	+++

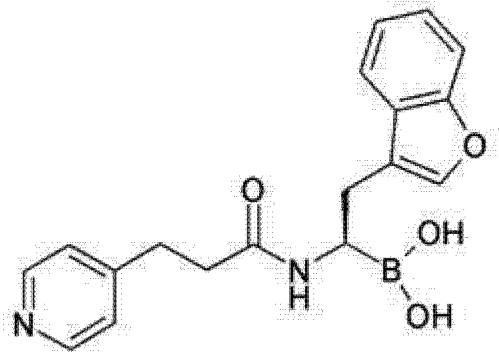
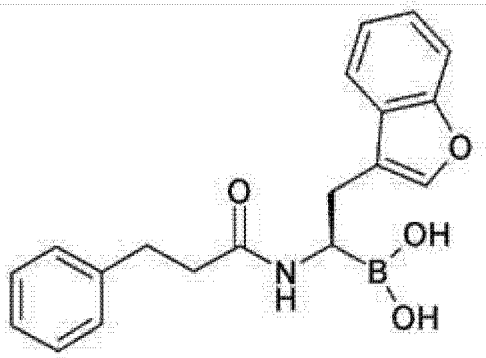
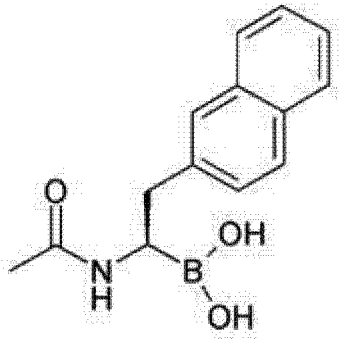
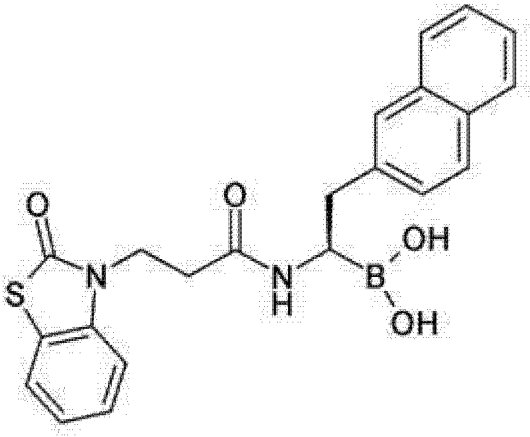
74		****	***	+++
75		****	***	+++
76		****	**	+++
77		**		nd
78		****	**	+++

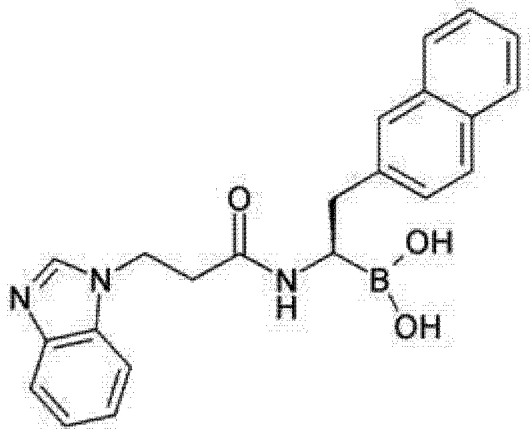
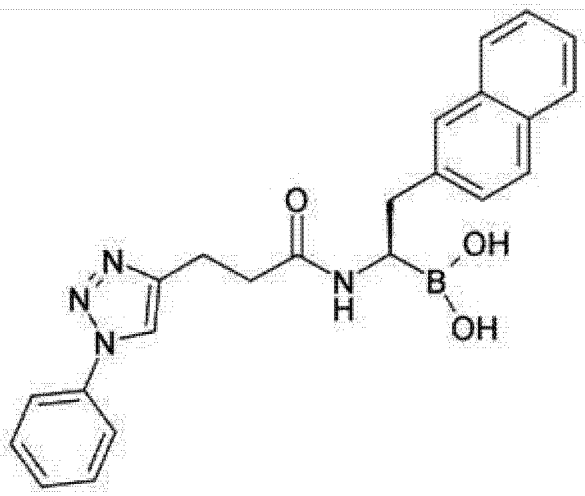
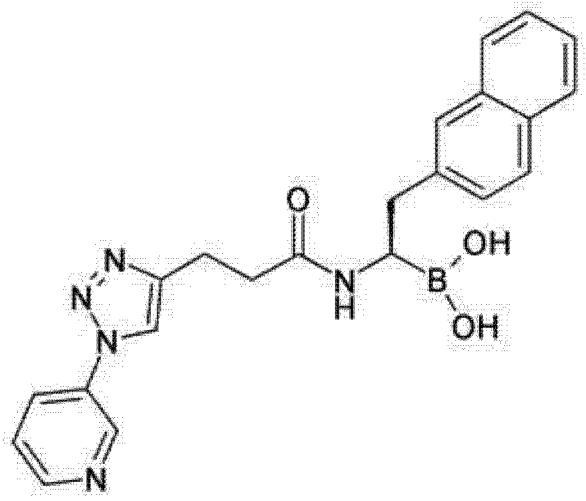
79		****	***	+++
80		****	****	+++
81		****	****	++
82		****	****	++

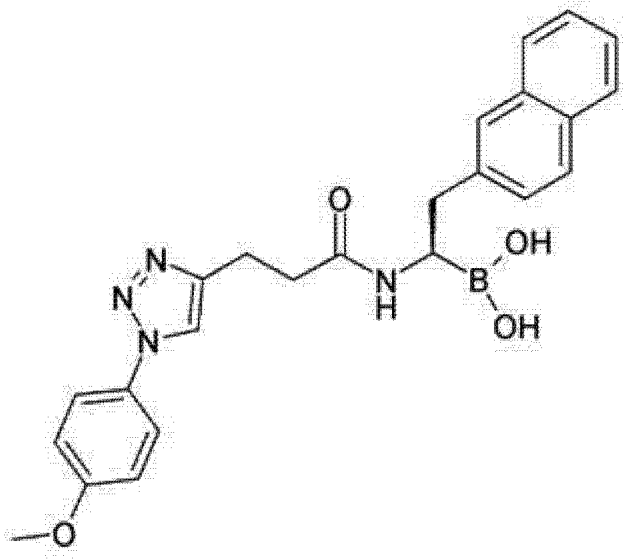
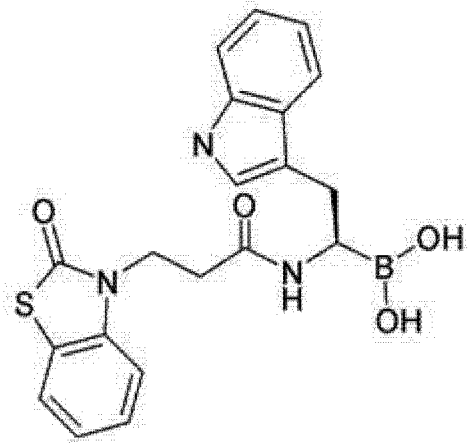
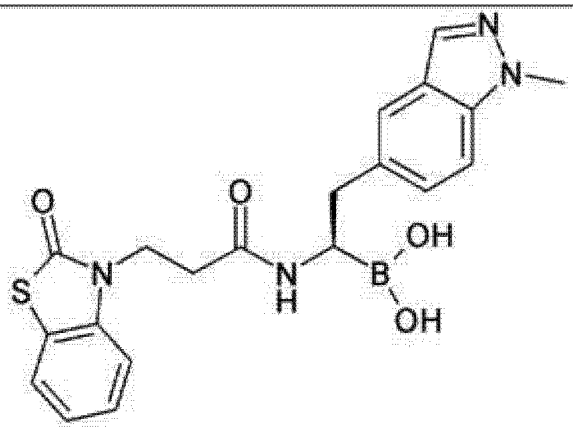
83		****	***	++
84		****	****	++
85		****	****	+++
86		****	***	+++

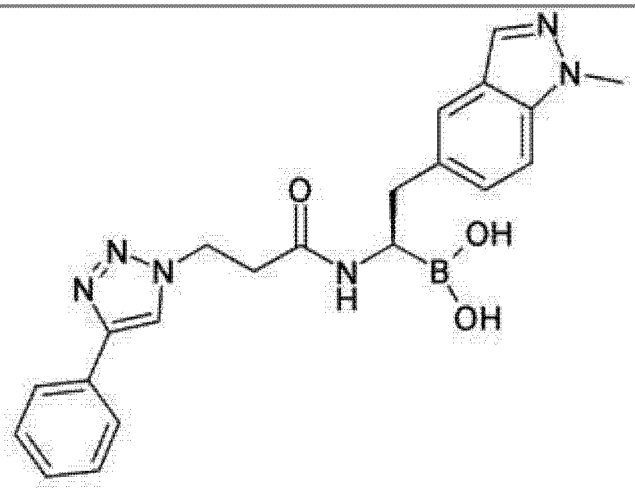
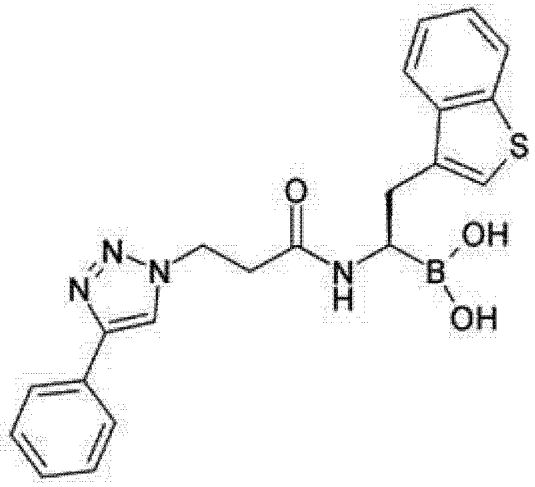
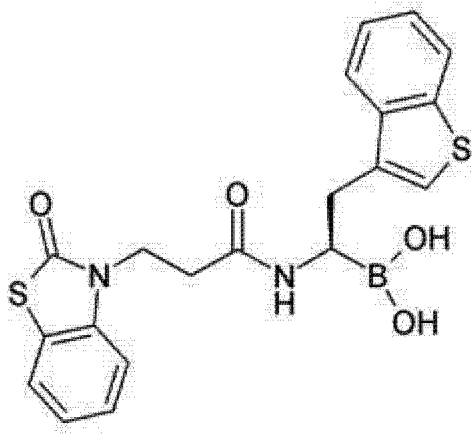
87		****	****	++
88		****	****	++
89		****	****	++

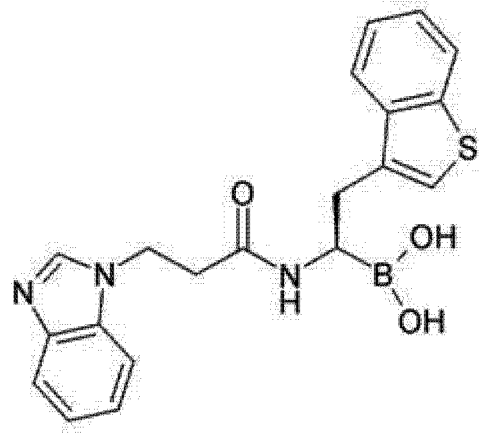
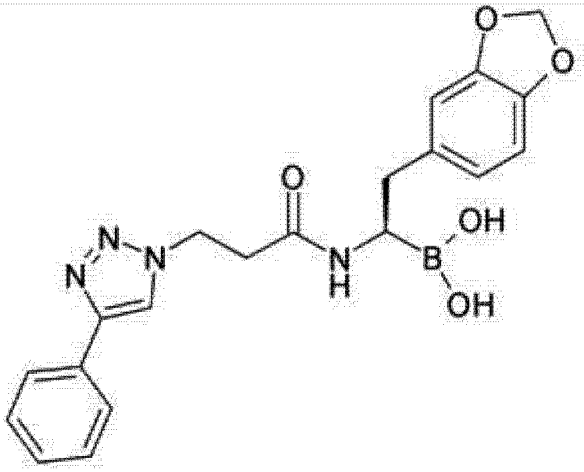
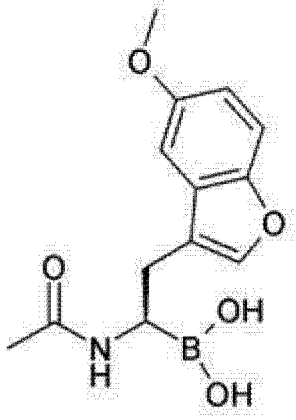
90		****	****	+++
91		****	***	+++
92		****	***	+++

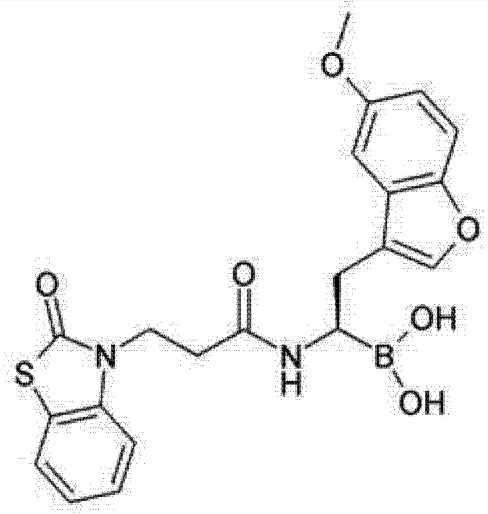
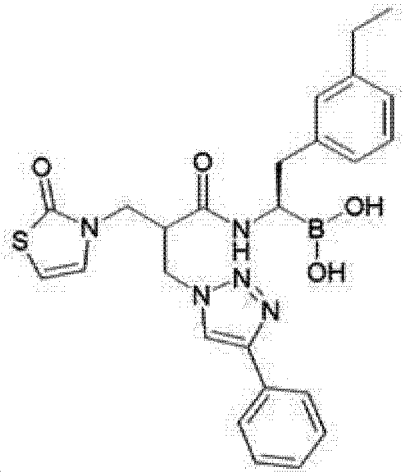
93		****	****	++
94		****	****	+++
95		***	**	+++
96		****	****	+++

97		****	****	++
98		****	***	++
99		****	**	+++

100		****	***	++
101		****	****	+++
102		****	****	++

103		****	****	++
104		****	****	+
105		****	****	++

106		****	****	++
107		****	****	++
108		*	*	+

109		****	***	+
110		****	****	++

*: IC_{50} > 5 μM, **: 0.5 μM < IC_{50} < 5 μM, ***: 0.05 μM < IC_{50} < 0.5 μM, ****: IC_{50} < 0.05 μM, +: 选择性< 10, ++: 10 <选择性< 30, +++: 选择性> 30, n.d: 未测定。