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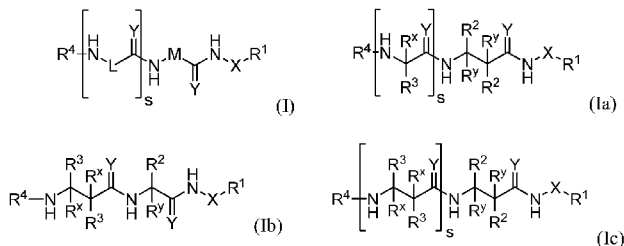
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- (54) **Title:** DIPEPTIDOMIMETICS AS INHIBITORS OF HUMAN IMMUNOPROTEASOMES



- (57) **Abstract:** The compounds of the present invention are represented by the following compounds having Formula (I), where the substituents R<sup>1</sup>, R<sup>4</sup>, L, M, X, Y, and s are as defined herein. The compounds of the present invention are also represented by the following compounds having Formula (Ia), Formula (Ib), or Formula (Ic), where the substituents R<sup>1</sup>-R<sup>4</sup>, R<sup>x</sup>, R<sup>y</sup>, X, Y, and s are as defined herein. These compounds are used in the treatment of cancer, immunologic disorders, autoimmune disorders, neurodegenerative disorders, or inflammatory disorders or for providing immunosuppression for transplanted organs or tissues.

**DIPEPTIDOMIMETICS AS INHIBITORS OF HUMAN IMMUNOPROTEASOMES**

[0001] This application claims the benefit of U.S. Provisional Patent Application Serial No. 62/038,636, filed August 18, 2014, which is hereby incorporated by reference in its entirety.

5 [0002] This invention was made with government support under grant number 5R21AI101393 awarded by the National Institutes of Health. The government has certain rights in this invention.

**FIELD OF THE INVENTION**

10 [0003] The present invention relates to inhibitors of human immunoproteasomes.

**BACKGROUND OF THE INVENTION**

[0004] The proteasome is a large, ATP-dependent, multi-subunit, barrel-shaped N-terminal nucleophile hydrolase present in the cytosol and nucleus of eukaryotic cells, and is responsible for the degradation of the majority of cellular proteins (Baumeister et al., "The Proteasome: Paradigm of a Self-Compartmentalizing Protease," *Cell* 92:367-380 (1998); Goldberg, A.L., "Functions of the Proteasome: From Protein Degradation and Immune Surveillance to Cancer Therapy," *Biochemical Society Transactions* 35:12-17 (2007)). The proteasome not only controls many critical cellular checkpoints through degradation, but also generates peptides for antigen presentation (Goldberg, A.L., "Functions of the Proteasome: From Protein Degradation and Immune Surveillance to Cancer Therapy," *Biochemical Society Transactions* 35:12-17 (2007); Rock et al., "Inhibitors of the Proteasome Block the Degradation of Most Cell Proteins and the Generation of Peptides Presented on MHC Class I Molecules," *Cell* 78:761-771 (1994)). Highly specific proteasome inhibitors can markedly limit the overall supply of peptides for MHC class I molecules and thus block antigen presentation (Rock et al., "Protein Degradation and the Generation of MHC Class I-Presented Peptides," *Advances in Immunology* 80:1-70 (2002)). The constitutive proteasome core particle is called 20S (c-20S) because of its sedimentation properties. Inside the c-20S core reside two copies of each of three proteases with distinct specificities,  $\beta$ 1 (caspase-like),  $\beta$ 2 (tryptic-like) and  $\beta$ 5 (chymotryptic-like) (Bedford et al., "Ubiquitin-Like Protein Conjugation and the Ubiquitin-Proteasome System as Drug Targets," *Nature Reviews. Drug Discovery* 10:29-46 (2011)). However, lymphocytes and cells that have responded to interferon- $\gamma$  express a different proteasome, called the immunoproteasome (i-20S), in which the corresponding proteases are the products of different genes:  $\beta$ 1i,  $\beta$ 2i and  $\beta$ 5i. Intermediate proteasomes that contain mixed  $\beta$  subunits are found in

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many cells, for example in the mucosa of the colon and small bowel (Guillaume et al., “Two Abundant Proteasome Subtypes that Uniquely Process Some Antigens Presented by HLA Class I Molecules,” *Proc. Nat’l Acad. Sci. USA* 107:18599-18604 (2010)). The effects of replacement of constitutive subunits by immuno- $\beta$  subunits include increased proteolytic activity and altered peptide preferences of the active sites (Rock et al., “Proteases in MHC Class I Presentation and Cross-Presentation,” *Journal of Immunology* 184:9-15d (2010)). For example, the caspase-like  $\beta$ 1 replacement,  $\beta$ 1i, preferentially cleaves after small hydrophobic residues rather than after aspartate (Huber et al., “Immuno- and Constitutive Proteasome Crystal Structures Reveal Differences in Substrate and Inhibitor Specificity,” *Cell* 148:727-738 (2012)). This results in altered peptide products, such that mice with combined deficiency of  $\beta$ 1i,  $\beta$ 2i, and  $\beta$ 5i are viable, fertile and healthy but express a different antigenic peptide repertoire than wild type mice, as evidenced by their rejection of syngeneic wild type splenocytes (Kincaid et al., “Mice Completely Lacking Immunoproteasomes Show Major Changes in Antigen Presentation,” *Nature Immunology* 13:129-135 (2012)). Hu c-20S and i-20S appear to regulate cytokine production through different pathways (Muchamuel et al., “A Selective Inhibitor of the Immunoproteasome Subunit LMP7 Blocks Cytokine Production and Attenuates Progression of Experimental Arthritis,” *Nature Medicine* 15:781-787 (2009)). Hu c-20S controls the activation of NF- $\kappa$ B via the degradation of I $\kappa$ B, the binding partner of NF- $\kappa$ B in the cytosol (Perkins, N.D., “Integrating Cell-Signalling Pathways with NF-[Kappa]B and IKK Function,” *Nat. Rev. Mol. Cell Biol.* 8:49-62 (2007)), and inhibition of c-20S blocks the activation of NF- $\kappa$ B (Meng et al., “Epoxomicin, a Potent and Selective Proteasome Inhibitor, Exhibits In Vivo Antiinflammatory Activity,” *Proc. Nat’l Acad. Sci. USA* 96:10403-10408 (1999)). For its part, among other potential pathways, i-20S appears to control the co-translocation of TLR9 and Unc93B1, an endoplasmic reticulum (ER)-resident protein, to endosomes (Hirai et al., “Bortezomib Suppresses Function and Survival of Plasmacytoid Dendritic Cells by Targeting Intracellular Trafficking of Toll-Like Receptors and Endoplasmic Reticulum Homeostasis,” *Blood* 117:500-509 (2011)). Proteasomes control diverse cellular functions, among them signal transduction for inflammatory cytokine release, antigen presentation, and the ability of plasma cells to secrete antibodies without dying from accumulation of misfolded immunoglobulins (Goldberg, A.L., “Functions of the Proteasome: From Protein Degradation and Immune Surveillance to Cancer Therapy,” *Biochemical Society Transactions* 35:12-17 (2007); Bedford et al., “Ubiquitin-Like Protein Conjugation and the Ubiquitin-Proteasome System as Drug Targets,” *Nature Reviews. Drug Discovery* 10:29-46 (2011); Neubert et al., “The Proteasome Inhibitor Bortezomib Depletes Plasma Cells and Protects Mice with Lupus-Like Disease from Nephritis,” *Nature*

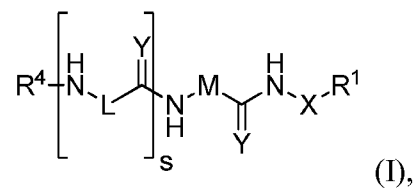
*Medicine* 14:748-755 (2008)). Thus the proteasome could be a target for treating autoimmune and inflammatory diseases. For example, inhibition of the proteasome in plasmacytoid dendritic cells (pDCs) prevents the trafficking of TLRs, resulting in a block of nuclear translocation of IRF-7, consequently suppressing the production of IFN $\alpha$  (Hirai et al., "Bortezomib Suppresses Function and Survival of Plasmacytoid Dendritic Cells by Targeting Intracellular Trafficking of Toll-Like Receptors and Endoplasmic Reticulum Homeostasis," *Blood* 117:500-509 (2011)), a cytokine implicated in systemic lupus erythematosus (SLE). However, by the same token, widespread inhibition of proteasomes can be expected to be toxic and has proven toxic in the clinic.

10 **[0005]** Two proteasome inhibitors approved by the FDA for treatment of malignancy, Bortezomib and Carfilzomib, inhibit both the c-20S  $\beta$ 5c and the i-20S  $\beta$ 5i (Huber et al., "Inhibitors for the Immuno- and Constitutive Proteasome: Current and Future Trends in Drug Development," *Angewandte Chemie* 51:8708-8720 (2012)). Bortezomib, a dipeptidyl boronate, is a slow-binding, covalent but reversible inhibitor, whereas Carfilzomib is a peptide with an epoxyketone warhead that inhibits proteasomes irreversibly. In addition to treatment of malignancy, Bortezomib has been reported to be effective in inflammatory bowel disease (IBD), SLE, graft-versus-host disease, antibody-mediated graft rejection, rheumatoid arthritis (RA), and other immunologic, autoimmune and/or inflammatory conditions. However, such a broad-spectrum inhibitor is too toxic for chronic treatment of non-malignant diseases. ONX 0914, another peptide epoxyketone, has modest selectivity for i-20S  $\beta$ 5i (Muchamuel et al., "A Selective Inhibitor of the Immunoproteasome Subunit LMP7 Blocks Cytokine Production and Attenuates Progression of Experimental Arthritis," *Nature Medicine* 15:781-787 (2009)) and is reported to have efficacy in rheumatoid arthritis (Muchamuel et al., "A Selective Inhibitor of the Immunoproteasome Subunit LMP7 Blocks Cytokine Production and Attenuates Progression of Experimental Arthritis," *Nature Medicine* 15:781-787 (2009)), SLE (Ichikawa et al., "Beneficial Effect of Novel Proteasome Inhibitors in Murine Lupus Via Dual Inhibition of Type I Interferon and Autoantibody-Secreting Cells," *Arthritis and Rheumatism* 64:493-503 (2012)), experimental colitis (Basler et al., "Prevention of Experimental Colitis by a Selective Inhibitor of the Immunoproteasome," *Journal of Immunology* 185:634-641 (2010)), and multiple sclerosis (Basler et al., "Inhibition of the immunoproteasome ameliorates experimental autoimmune encephalomyelitis," *EMBO Mol. Med.* 6:226-238 (2014)). Nonetheless, it, too, acts irreversibly and has considerable toxicity.

30 **[0006]** The present invention is directed to overcoming these and other deficiencies in the art.

## SUMMARY OF THE INVENTION

[0007] One aspect of the present invention relates to a compound of Formula (I):



wherein

5 L is  $\text{---}(\text{CR}^3\text{R}^x)_p\text{---}$ ;

M is  $\text{---}(\text{CR}^2\text{R}^y)_r\text{---}$ ;

R<sup>1</sup> is selected from the group consisting of monocyclic and bicyclic aryl,  
 10 biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and  
 monocyclic and bicyclic non-aromatic heterocycle, wherein monocyclic and bicyclic aryl,  
 biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and  
 monocyclic and bicyclic non-aromatic heterocycle can be optionally substituted from 1 to 3  
 15 times with a substituent selected independently at each occurrence thereof from the group  
 consisting of halogen, cyano,  $\text{---CF}_3$ , C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

R<sup>2</sup> is independently selected at each occurrence thereof from the group consisting  
 of H, D, C<sub>1-6</sub> alkyl,  $\text{---CH}_2\text{OC}_{1-6}$  alkyl,  $\text{---CH}_2\text{Ar}$ , and  $\text{---CH}_2\text{heteroaryl}$ , wherein aryl (Ar) can be  
 optionally substituted from 1 to 3 times with a substituent selected independently at each  
 20 occurrence thereof from the group consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

R<sup>3</sup> is independently selected at each occurrence thereof from the group consisting  
 of H, D,  $\text{---CH}_2\text{OC}_{1-6}$  alkyl,  $\text{---}(\text{CH}_2)_m\text{C}(\text{O})\text{NHR}^5$ ,  $\text{---}(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^6\text{R}^7$ ,  $\text{---}(\text{CH}_2)_m\text{C}(\text{O})\text{OH}$ , and  
 $\text{---}(\text{CH}_2)_m\text{C}(\text{O})\text{OBn}$ ;

25 R<sup>4</sup> is selected from the group consisting of H,  $\text{---C}(\text{O})(\text{CH}_2)_n\text{Ph}$ ,  $\text{---}$   
 $\text{C}(\text{O})\text{CH}_2\text{NR}^6\text{R}^7$ ,  $\text{---SO}_2\text{Ar}$ ,  $\text{---SO}_2\text{C}_{1-6}$  alkyl,  $\text{---SO}_2\text{C}_{3-6}$  cycloalkyl,  $\text{---C}(\text{O})(\text{CH}_2)_n\text{Het}$ ,  $\text{---}$   
 $\text{C}(\text{O})\text{C}(\text{O})\text{Het}$ ,  $\text{---C}(\text{O})\text{C}_{1-6}$  alkyl,  $\text{---C}(\text{O})\text{OC}_{1-6}$  alkyl,  $\text{---C}(\text{O})\text{CF}_3$ , heteroaryl, and  $\text{---}$   
 $(\text{CH}_2)_n\text{NR}^6\text{R}^7$ , wherein aryl (Ar) and heteroaryl (Het) can be optionally substituted from 1 to 3  
 30 times with a substituent selected independently at each occurrence thereof from the group  
 consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

$R^5$  is selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, non-aromatic heterocycle,  $-NR^6R^7$ , and  $-CR^8R^9$ ;

5  $R^6$ ,  $R^7$ ,  $R^8$ , and  $R^9$  are each independently selected from the group consisting of H, D,  $C_{1-6}$  alkyl, and  $-(CH_2)_kOH$ ;

or  $R^6$  and  $R^7$  are taken together with the nitrogen to which they are attached to form a morpholine ring;

10 or  $R^8$  and  $R^9$  are taken together with the carbon to which they are attached to form an oxetane ring;

$R^x$  is independently selected at each occurrence thereof from the group consisting  
15 of H, D,  $-CH_2OC_{1-6}$  alkyl,  $-(CH_2)_mC(O)NHR^5$ ,  $-(CH_2)_mC(O)NR^6R^7$ , and  $-CH_2C(O)R^5$ ;

$R^y$  is independently selected at each occurrence thereof from the group consisting  
of H, D,  $C_{1-6}$  alkyl,  $-CH_2OC_{1-6}$  alkyl,  $-CH_2Ar$ , and  $-CH_2$ heteroaryl, wherein aryl (Ar) can be  
optionally substituted from 1 to 3 times with a substituent selected independently at each  
20 occurrence thereof from the group consisting of halogen, cyano,  $C_{1-6}$  alkyl, and  $C_{1-6}$  alkoxy;

X is  $-(CH_2)_q-$ ,  $-O-$ , or  $-(CD_2)_q-$ ;

Y is O or S;

25

k is 1, 2, or 3;

m is 0, 1, 2, 3, 4, or 5;

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n is 0, 1, 2, or 3;

p is 1 or 2;

q is 0, 1, or 2;

r is 1 or 2; and

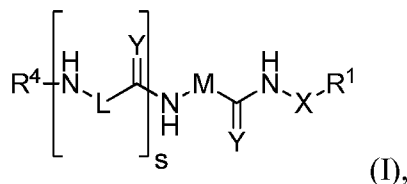
s is 0 or 1;

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with a proviso that when s is 0, then r is 2; and when s is 1, then  $r + p \geq 3$ ,

or an oxide thereof, a pharmaceutically acceptable salt thereof, a solvate thereof, or a prodrug thereof.

10 **[0008]** Another aspect of the present invention relates to a method of treating cancer, immunologic disorders, autoimmune disorders, neurodegenerative disorders, or inflammatory disorders in a subject or for providing immunosuppression for transplanted organs or tissues in a subject. This method includes administering to the subject in need thereof a compound of the Formula (I):



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wherein

L is  $-(\text{CR}^3\text{R}^x)_p-$ ;

M is  $-(\text{CR}^2\text{R}^y)_r-$ ;

20

$R^1$  is selected from the group consisting of monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and monocyclic and bicyclic non-aromatic heterocycle, wherein monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and monocyclic and bicyclic non-aromatic heterocycle can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $-\text{CF}_3$ ,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

25

$R^2$  is independently selected at each occurrence thereof from the group consisting of H, D,  $\text{C}_{1-6}$  alkyl,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-\text{CH}_2\text{Ar}$ , and  $-\text{CH}_2$ heteroaryl, wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

30

$R^3$  is independently selected at each occurrence thereof from the group consisting of H, D,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NHR}^5$ ,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^6\text{R}^7$ ,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{OH}$ , and  $-(\text{CH}_2)_m\text{C}(\text{O})\text{OBn}$ ;

5

$R^4$  is selected from the group consisting of H,  $-\text{C}(\text{O})(\text{CH}_2)_n\text{Ph}$ ,  $-\text{C}(\text{O})\text{CH}_2\text{NR}^6\text{R}^7$ ,  $-\text{SO}_2\text{Ar}$ ,  $-\text{SO}_2\text{C}_{1-6}$  alkyl,  $-\text{SO}_2\text{C}_{3-6}$  cycloalkyl,  $-\text{C}(\text{O})(\text{CH}_2)_n\text{Het}$ ,  $-\text{C}(\text{O})\text{C}(\text{O})\text{Het}$ ,  $-\text{C}(\text{O})\text{C}_{1-6}$  alkyl,  $-\text{C}(\text{O})\text{OC}_{1-6}$  alkyl,  $-\text{C}(\text{O})\text{CF}_3$ , heteroaryl, and  $-(\text{CH}_2)_n\text{NR}^6\text{R}^7$ , wherein aryl (Ar) and heteroaryl (Het) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

10

$R^5$  is selected from the group consisting of  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy, non-aromatic heterocycle,  $-\text{NR}^6\text{R}^7$ , and  $-\text{CR}^8\text{R}^9$ ;

15

$R^6$ ,  $R^7$ ,  $R^8$ , and  $R^9$  are each independently selected from the group consisting of H, D,  $\text{C}_{1-6}$  alkyl, and  $-(\text{CH}_2)_k\text{OH}$ ;

20

or  $R^6$  and  $R^7$  are taken together with the nitrogen to which they are attached to form a morpholine ring;

or  $R^8$  and  $R^9$  are taken together with the carbon to which they are attached to form an oxetane ring;

25

$R^x$  is independently selected at each occurrence thereof from the group consisting of H, D,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NHR}^5$ ,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^6\text{R}^7$ , and  $-\text{CH}_2\text{C}(\text{O})\text{R}^5$ ;

30

$R^y$  is independently selected at each occurrence thereof from the group consisting of H, D,  $\text{C}_{1-6}$  alkyl,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-\text{CH}_2\text{Ar}$ , and  $-\text{CH}_2\text{heteroaryl}$ , wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

X is  $-(\text{CH}_2)_q-$ ,  $-\text{O}-$ , or  $-(\text{CD}_2)_q-$ ;

Y is O or S;

k is 1, 2, or 3;

5 m is 0, 1, 2, 3, 4, or 5;

n is 0, 1, 2, or 3;

p is 1 or 2;

10

q is 0, 1, or 2;

r is 1 or 2; and

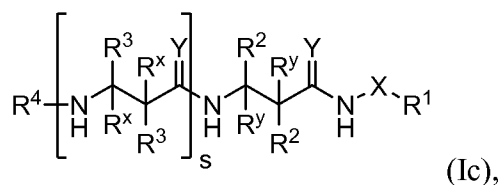
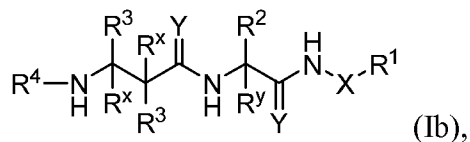
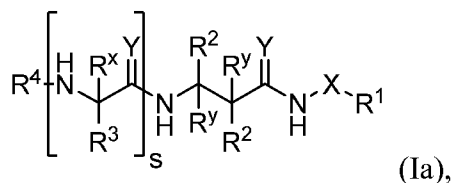
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s is 0 or 1;

with a proviso that when s is 0, then r is 2; and when s is 1, then  $r + p \geq 3$ .

[0009] Another aspect of the present invention relates to a compound of Formula (Ia),  
Formula (Ib), or Formula (Ic):

20



wherein

25  $\text{R}^1$  is selected from the group consisting of monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and monocyclic and bicyclic non-aromatic heterocycle, wherein monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and

monocyclic and bicyclic non-aromatic heterocycle can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $-\text{CF}_3$ ,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

5  $\text{R}^2$  is independently selected at each occurrence thereof from the group consisting of H, D,  $\text{C}_{1-6}$  alkyl,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-\text{CH}_2\text{Ar}$ , and  $-\text{CH}_2\text{heteroaryl}$ , wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

10  $\text{R}^3$  is independently selected at each occurrence thereof from the group consisting of H, D,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NHR}^5$ , and  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^6\text{R}^7$ ;

$\text{R}^4$  is selected from the group consisting of  $-\text{C}(\text{O})(\text{CH}_2)_n\text{Ph}$ ,  $-\text{C}(\text{O})\text{CH}_2\text{NR}^6\text{R}^7$ ,  $-\text{SO}_2\text{Ar}$ ,  $-\text{SO}_2\text{C}_{1-6}$  alkyl,  $-\text{SO}_2\text{C}_{3-6}$  cycloalkyl,  $-\text{C}(\text{O})(\text{CH}_2)_n\text{Het}$ ,  $-\text{C}(\text{O})\text{C}(\text{O})\text{Het}$ ,  $-\text{C}(\text{O})\text{C}_{1-6}$  alkyl,  $-\text{C}(\text{O})\text{OC}_{1-6}$  alkyl,  $-\text{C}(\text{O})\text{CF}_3$ , heteroaryl, and  $-(\text{CH}_2)_n\text{NR}^6\text{R}^7$ , wherein aryl (Ar) and heteroaryl (Het) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

20  $\text{R}^5$  is selected from the group consisting of  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy, non-aromatic heterocycle,  $-\text{NR}^6\text{R}^7$ , and  $-\text{CR}^8\text{R}^9$ ;

$\text{R}^6$ ,  $\text{R}^7$ ,  $\text{R}^8$ , and  $\text{R}^9$  are each independently selected from the group consisting of H, D,  $\text{C}_{1-6}$  alkyl, and  $-(\text{CH}_2)_k\text{OH}$ ;

25 or  $\text{R}^6$  and  $\text{R}^7$  are taken together with the nitrogen to which they are attached to form a morpholine ring;

30 or  $\text{R}^8$  and  $\text{R}^9$  are taken together with the carbon to which they are attached to form an oxetane ring;

$\text{R}^x$  is independently selected at each occurrence thereof from the group consisting of H, D,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NHR}^5$ ,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^6\text{R}^7$ , and  $-\text{CH}_2\text{C}(\text{O})\text{R}^5$ ;

$R^y$  is independently selected at each occurrence thereof from the group consisting of H, D,  $C_{1-6}$  alkyl,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-\text{CH}_2\text{Ar}$ , and  $-\text{CH}_2\text{heteroaryl}$ , wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $C_{1-6}$  alkyl, and  $C_{1-6}$  alkoxy;

5

X is  $-(\text{CH}_2)_q-$ ,  $-\text{O}-$ , or  $-(\text{CD}_2)_q-$ ;

Y is O or S;

10

k is 1, 2, or 3;

m is 0, 1, 2, 3, 4, or 5;

n is 0, 1, 2, or 3;

15

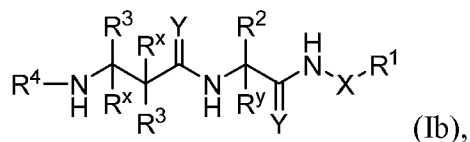
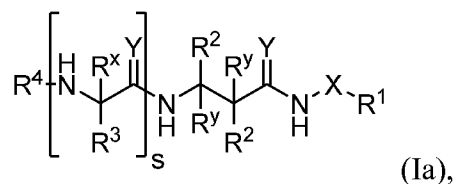
q is 0, 1, or 2; and

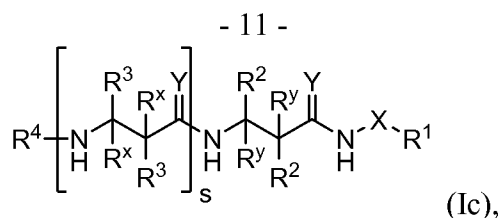
s is 0 or 1;

20 or an oxide thereof, a pharmaceutically acceptable salt thereof, a solvate thereof, or a prodrug thereof.

**[0010]** Yet another aspect of the present invention relates to a method of treating cancer, immunologic disorders, autoimmune disorders, neurodegenerative disorders, or inflammatory disorders in a subject or for providing immunosuppression for transplanted organs or tissues in a subject. This method includes administering to the subject in need thereof a compound of the Formula (Ia), Formula (Ib), or Formula (Ic):

25





wherein

R<sup>1</sup> is selected from the group consisting of monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and  
 5 monocyclic and bicyclic non-aromatic heterocycle, wherein monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and monocyclic and bicyclic non-aromatic heterocycle can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, —CF<sub>3</sub>, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

10

R<sup>2</sup> is independently selected at each occurrence thereof from the group consisting of H, D, C<sub>1-6</sub> alkyl, —CH<sub>2</sub>OC<sub>1-6</sub> alkyl, —CH<sub>2</sub>Ar, and —CH<sub>2</sub>heteroaryl, wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

15

R<sup>3</sup> is independently selected at each occurrence thereof from the group consisting of H, D, —CH<sub>2</sub>OC<sub>1-6</sub> alkyl, —(CH<sub>2</sub>)<sub>m</sub>C(O)NHR<sup>5</sup>, and —(CH<sub>2</sub>)<sub>m</sub>C(O)NR<sup>6</sup>R<sup>7</sup>;

R<sup>4</sup> is selected from the group consisting of —C(O)(CH<sub>2</sub>)<sub>n</sub>Ph, —C(O)CH<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>,  
 20 —SO<sub>2</sub>Ar, —SO<sub>2</sub>C<sub>1-6</sub> alkyl, —SO<sub>2</sub>C<sub>3-6</sub> cycloalkyl, —C(O)(CH<sub>2</sub>)<sub>n</sub>Het, —C(O)C(O)Het, —C(O)C<sub>1-6</sub> alkyl, —C(O)OC<sub>1-6</sub> alkyl, —C(O)CF<sub>3</sub>, heteroaryl, and —(CH<sub>2</sub>)<sub>n</sub>NR<sup>6</sup>R<sup>7</sup>, wherein aryl (Ar) and heteroaryl (Het) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

25

R<sup>5</sup> is selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, non-aromatic heterocycle, —NR<sup>6</sup>R<sup>7</sup>, and —CR<sup>8</sup>R<sup>9</sup>;

R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, and R<sup>9</sup> are each independently selected from the group consisting of H,  
 30 D, C<sub>1-6</sub> alkyl, and —(CH<sub>2</sub>)<sub>k</sub>OH;

or R<sup>6</sup> and R<sup>7</sup> are taken together with the nitrogen to which they are attached to form a morpholine ring;

5 or R<sup>8</sup> and R<sup>9</sup> are taken together with the carbon to which they are attached to form an oxetane ring;

R<sup>x</sup> is independently selected at each occurrence thereof from the group consisting of H, D, —CH<sub>2</sub>OC<sub>1-6</sub> alkyl, —(CH<sub>2</sub>)<sub>m</sub>C(O)NHR<sup>5</sup>, —(CH<sub>2</sub>)<sub>m</sub>C(O)NR<sup>6</sup>R<sup>7</sup>, and —CH<sub>2</sub>C(O)R<sup>5</sup>;

10 R<sup>y</sup> is independently selected at each occurrence thereof from the group consisting of H, D, C<sub>1-6</sub> alkyl, —CH<sub>2</sub>OC<sub>1-6</sub> alkyl, —CH<sub>2</sub>Ar, and —CH<sub>2</sub>heteroaryl, wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

15 X is —(CH<sub>2</sub>)<sub>q</sub>—, —O—, or —(CD<sub>2</sub>)<sub>q</sub>—;

Y is O or S;

k is 1, 2, or 3;

20 m is 0, 1, 2, 3, 4, or 5;

n is 0, 1, 2, or 3;

25 q is 0, 1, or 2; and

s is 0 or 1.

**[0011]** Selective inhibition of the i-20S is believed to impact the immune system but would otherwise be far less toxic than combined inhibition of both constitutive and immuno-  
 30 proteasomes. Here are presented inhibitors that act both with high selectivity and full reversibility on hu i-20S β5i over hu c-20S. Inhibitors that are selective for the i-20S β5i are expected to be equally if not more efficacious in treating autoimmune disease, with less toxicity. These inhibitors could open a new path to the treatment of immunologic, autoimmune, inflammatory, neurodegenerative, and certain neoplastic disorders such as: systemic lupus

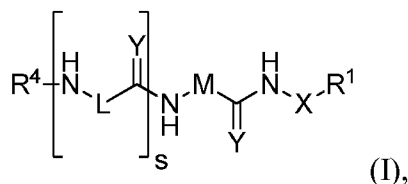
erythematosus, chronic rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), atherosclerosis, scleroderma, systemic sclerosis, autoimmune hepatitis, Sjogren Syndrome, lupus nephritis, glomerulonephritis, rheumatoid arthritis, psoriasis, Myasthenia Gravis, Immunoglobuline A nephropathy, atherosclerosis, vasculitis, renal fibrosis, lung fibrosis, liver fibrosis, transplant rejection, idiopathic pulmonary fibrosis, asthma, and inflammation driven cancers such as: triple negative breast cancers.

### BRIEF DESCRIPTION OF THE DRAWINGS

10 [0012] Figure 1 is a graph showing inhibition of human i-20S  $\beta 5i$  and c-20S  $\beta 5c$  by selected dipeptidomimetics.

### DETAILED DESCRIPTION OF THE INVENTION

[0013] One aspect of the present invention relates to a compound of Formula (I):



15

wherein

L is  $-(\text{CR}^3\text{R}^x)_p-$ ;

M is  $-(\text{CR}^2\text{R}^y)_r-$ ;

20

$R^1$  is selected from the group consisting of monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and monocyclic and bicyclic non-aromatic heterocycle, wherein monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and monocyclic and bicyclic non-aromatic heterocycle can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $-\text{CF}_3$ ,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

$R^2$  is independently selected at each occurrence thereof from the group consisting of H, D,  $\text{C}_{1-6}$  alkyl,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-\text{CH}_2\text{Ar}$ , and  $-\text{CH}_2$ heteroaryl, wherein aryl (Ar) can be

30

optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

5 R<sup>3</sup> is independently selected at each occurrence thereof from the group consisting of H, D, —CH<sub>2</sub>OC<sub>1-6</sub> alkyl, —(CH<sub>2</sub>)<sub>m</sub>C(O)NHR<sup>5</sup>, —(CH<sub>2</sub>)<sub>m</sub>C(O)NR<sup>6</sup>R<sup>7</sup>, —(CH<sub>2</sub>)<sub>m</sub>C(O)OH, and —(CH<sub>2</sub>)<sub>m</sub>C(O)OBn;

10 R<sup>4</sup> is selected from the group consisting of H, —C(O)(CH<sub>2</sub>)<sub>n</sub>Ph, —C(O)CH<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, —SO<sub>2</sub>Ar, —SO<sub>2</sub>C<sub>1-6</sub> alkyl, —SO<sub>2</sub>C<sub>3-6</sub> cycloalkyl, —C(O)(CH<sub>2</sub>)<sub>n</sub>Het, —C(O)C(O)Het, —C(O)C<sub>1-6</sub> alkyl, —C(O)OC<sub>1-6</sub> alkyl, —C(O)CF<sub>3</sub>, heteroaryl, and —(CH<sub>2</sub>)<sub>n</sub>NR<sup>6</sup>R<sup>7</sup>, wherein aryl (Ar) and heteroaryl (Het) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

15 R<sup>5</sup> is selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, non-aromatic heterocycle, —NR<sup>6</sup>R<sup>7</sup>, and —CR<sup>8</sup>R<sup>9</sup>;

20 R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, and R<sup>9</sup> are each independently selected from the group consisting of H, D, C<sub>1-6</sub> alkyl, and —(CH<sub>2</sub>)<sub>k</sub>OH;

or R<sup>6</sup> and R<sup>7</sup> are taken together with the nitrogen to which they are attached to form a morpholine ring;

25 or R<sup>8</sup> and R<sup>9</sup> are taken together with the carbon to which they are attached to form an oxetane ring;

R<sup>x</sup> is independently selected at each occurrence thereof from the group consisting of H, D, —CH<sub>2</sub>OC<sub>1-6</sub> alkyl, —(CH<sub>2</sub>)<sub>m</sub>C(O)NHR<sup>5</sup>, —(CH<sub>2</sub>)<sub>m</sub>C(O)NR<sup>6</sup>R<sup>7</sup>, and —CH<sub>2</sub>C(O)R<sup>5</sup>;

30 R<sup>y</sup> is independently selected at each occurrence thereof from the group consisting of H, D, C<sub>1-6</sub> alkyl, —CH<sub>2</sub>OC<sub>1-6</sub> alkyl, —CH<sub>2</sub>Ar, and —CH<sub>2</sub>heteroaryl, wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

X is  $-(\text{CH}_2)_q-$ ,  $-\text{O}-$ , or  $-(\text{CD}_2)_q-$  ;

Y is O or S;

5 k is 1, 2, or 3;

m is 0, 1, 2, 3, 4, or 5;

n is 0, 1, 2, or 3;

10

p is 1 or 2;

q is 0, 1, or 2;

15

r is 1 or 2; and

s is 0 or 1;

with a proviso that when s is 0, then r is 2; and when s is 1, then  $r + p \geq 3$ ,

20

or an oxide thereof, a pharmaceutically acceptable salt thereof, a solvate thereof, or a prodrug thereof.

**[0014]** As used above, and throughout the description herein, the following terms, unless otherwise indicated, shall be understood to have the following meanings. If not defined otherwise herein, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this technology belongs. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

**[0015]** The term "alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. Exemplary alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, and 3-pentyl.

**[0016]** The term "cycloalkyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 7 carbon atoms, preferably of about 5 to about 7 carbon atoms. Exemplary monocyclic cycloalkyls include cyclopentyl, cyclohexyl, cycloheptyl, and the like.

**[0017]** The term "aryl" means an aromatic monocyclic or multicyclic ring system of 6 to about 14 carbon atoms, preferably of 6 to about 10 carbon atoms. Representative aryl groups include phenyl and naphthyl.

**[0018]** The term "heteroaryl" means an aromatic monocyclic or multicyclic ring system of about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is/are element(s) other than carbon, for example, nitrogen, oxygen, or sulfur. In the case of multicyclic ring system, only one of the rings needs to be aromatic for the ring system to be defined as "Heteroaryl". Preferred heteroaryls contain about 5 to 6 ring atoms. The prefix aza, oxa, thia, or thio before heteroaryl means that at least a nitrogen, oxygen, or sulfur atom, respectively, is present as a ring atom. A nitrogen atom of a heteroaryl is optionally oxidized to the corresponding N-oxide. Representative heteroaryls include pyridyl, 2-oxo-pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, 2-oxoindolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl, benzo[1,3]dioxolyl, quinolinyl, isoquinolinyl, quinazolyl, cinnolinyl, pthalazinyl, quinoxalyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indoliziny, quinoliziny, 6*aH*-thieno[2,3-*d*]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, and the like.

**[0019]** As used herein, "heterocyclyl" or "heterocycle" refers to a stable 3- to 18-membered ring (radical) which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. For purposes of this

application, the heterocycle may be a monocyclic, or a polycyclic ring system, which may include fused, bridged, or spiro ring systems; and the nitrogen, carbon, or sulfur atoms in the heterocycle may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the ring may be partially or fully saturated. Examples of such heterocycles include, without  
5 limitation, azepinyl, azocanyl, pyranyl dioxanyl, dithianyl, 1,3-dioxolanyl, tetrahydrofuryl, dihydropyrrolidinyl, decahydroisoquinolyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, oxazolidinyl, oxiranyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydropyranyl, thiamorpholinyl, thiamorpholinyl  
10 sulfoxide, and thiamorpholinyl sulfone. Further heterocycles and heteroaryls are described in Katritzky et al., eds., *Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Use of Heterocyclic Compounds*, Vol. 1-8, Pergamon Press, N.Y. (1984), which is hereby incorporated by reference in its entirety.

**[0020]** The term “non-aromatic heterocycle” means a non-aromatic monocyclic system  
15 containing 3 to 10 atoms, preferably 4 to about 7 carbon atoms, in which one or more of the atoms in the ring system is/are element(s) other than carbon, for example, nitrogen, oxygen, or sulfur. Representative non-aromatic heterocycle groups include pyrrolidinyl, 2-oxopyrrolidinyl, piperidinyl, 2-oxopiperidinyl, azepanyl, 2-oxoazepanyl, 2-oxooxazolidinyl, morpholino, 3-oxomorpholino, thiomorpholino, 1,1-dioxothiomorpholino, piperazinyl, tetrahydro-2H-oxazinyl,  
20 and the like.

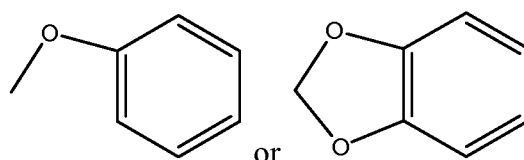
**[0021]** The term “monocyclic” used herein indicates a molecular structure having one ring.

**[0022]** The term “polycyclic” or “multi-cyclic” used herein indicates a molecular structure having two or more rings, including, but not limited to, fused, bridged, or spiro rings.

**[0023]** Terminology related to “protecting”, “deprotecting,” and “protected”  
25 functionalities occurs throughout this application. Such terminology is well understood by persons of skill in the art and is used in the context of processes which involve sequential treatment with a series of reagents. In that context, a protecting group refers to a group which is used to mask a functionality during a process step in which it would otherwise react, but in  
30 which reaction is undesirable. The protecting group prevents reaction at that step, but may be subsequently removed to expose the original functionality. The removal or “deprotection” occurs after the completion of the reaction or reactions in which the functionality would interfere. Thus, when a sequence of reagents is specified, as it is in the processes described herein, the person of ordinary skill can readily envision those groups that would be suitable as

“protecting groups.” Suitable groups for that purpose are discussed in standard textbooks in the field of chemistry, such as Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York (1991), which is hereby incorporated by reference in its entirety.

[0024] The term “alkoxy” means groups of from 1 to 8 carbon atoms of a straight, branched, or cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like. Lower-alkoxy refers to groups containing one to four carbons. For the purposes of the present patent application, alkoxy also includes methylenedioxy and ethylenedioxy in which each oxygen atom is bonded to the atom, chain, or ring from which the methylenedioxy or ethylenedioxy group is pendant so as to form a ring. Thus, for example,



phenyl substituted by alkoxy may be, for example,

[0025] A compound with a hydroxy group drawn next to a nitrogen on a heterocycle can exist as the “keto” form. For example, 3-(2-hydroxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)propanoic acid can exist as 3-(2-oxo-2,3-dihydro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)propanoic acid.

[0026] The term "halo" or "halogen" means fluoro, chloro, bromo, or iodo.

[0027] The term "substituted" or "substitution" of an atom means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded.

[0028] "Unsubstituted" atoms bear all of the hydrogen atoms dictated by their valency. When a substituent is keto (i.e., =O), then two hydrogens on the atom are replaced. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds; by "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0029] The term “optionally substituted” is used to indicate that a group may have a substituent at each substitutable atom of the group (including more than one substituent on a single atom), provided that the designated atom's normal valency is not exceeded and the identity of each substituent is independent of the others. Up to three H atoms in each residue are replaced with alkyl, halogen, haloalkyl, hydroxy, loweralkoxy, carboxy, carboalkoxy (also referred to as alkoxycarbonyl), carboxamido (also referred to as alkylaminocarbonyl), cyano, carbonyl, nitro, amino, alkylamino, dialkylamino, mercapto, alkylthio, sulfoxide, sulfone,

acylamino, amidino, phenyl, benzyl, heteroaryl, phenoxy, benzyloxy, or heteroaryloxy.

“Unsubstituted” atoms bear all of the hydrogen atoms dictated by their valency. When a substituent is keto (i.e., =O), then two hydrogens on the atom are replaced. Combinations of substituents and/or variables are permissible only if such combinations result in stable

5 compounds; by “stable compound” or “stable structure” is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

**[0030]** The term “method of treating” means amelioration or relief from the symptoms and/or effects associated with the disorders described herein. As used herein, reference to  
10 “treatment” of a patient is intended to include prophylaxis.

**[0031]** The term "compounds of the invention", and equivalent expressions, are meant to embrace compounds of general formula (I), formula (Ia), formula (Ib), and formula (Ic) as hereinbefore described, which expression includes the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g. hydrates, where the context so permits. Similarly, reference to  
15 intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the text, but these instances are purely illustrative and it is not intended to exclude other instances when the context so permits.

**[0032]** The term "pharmaceutically acceptable salts" means the relatively non-toxic,  
20 inorganic, and organic acid addition salts, and base addition salts, of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds. In particular, acid addition salts can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Exemplary acid addition salts include the hydrobromide, hydrochloride, sulfate,  
25 bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, sulphamates, malonates, salicylates, propionates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methane-sulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates,  
30 cyclohexylsulphamates and quaternaryammonium salts, and the like (see, for example, Berge et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 66:1-9 (1977) and Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, which are hereby incorporated by reference in their entirety). Base addition salts can also be prepared by separately reacting the purified compound in its acid form with a suitable organic or inorganic

base and isolating the salt thus formed. Base addition salts include pharmaceutically acceptable metal and amine salts. Suitable metal salts include the sodium, potassium, calcium, barium, zinc, magnesium, and aluminum salts. The sodium and potassium salts are preferred. Suitable inorganic base addition salts are prepared from metal bases which include, for example, sodium  
5 hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminium hydroxide, lithium hydroxide, magnesium hydroxide, and zinc hydroxide. Suitable amine base addition salts are prepared from amines which have sufficient basicity to form a stable salt, and preferably include those amines which are frequently used in medicinal chemistry because of their low toxicity and acceptability for medical use, such as ammonia, ethylenediamine, N-methyl-  
10 glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, triethylamine, dibenzylamine, ephedrine, dehydroabietylamine, N-ethylpiperidine, benzylamine, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine,  
15 ethylamine, basic amino acids, e.g., lysine and arginine, dicyclohexylamine, and the like.

**[0033]** The term "pharmaceutically acceptable prodrugs" as used herein means those prodrugs of the compounds useful according to the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a  
20 reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" means compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. Functional groups which may be rapidly transformed, by metabolic cleavage, *in vivo* form a class of groups reactive with the carboxyl  
25 group of the compounds of this invention. They include, but are not limited to, such groups as alkanoyl (such as acetyl, propionyl, butyryl, and the like), unsubstituted and substituted aroyl (such as benzoyl and substituted benzoyl), alkoxy carbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethylsilyl), monoesters formed with dicarboxylic acids (such as succinyl), and the like. Because of the ease with which the metabolically cleavable groups of the  
30 compounds useful according to this invention are cleaved *in vivo*, the compounds bearing such groups act as pro-drugs. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. A thorough discussion of prodrugs is provided in the following:

*Design of Prodrugs*, H. Bundgaard, ed., Elsevier (1985); *Methods in Enzymology*, K. Widder et al, Ed., Academic Press, 42, p.309-396 (1985); *A Textbook of Drug Design and Development*, Krogsgaard-Larsen and H. Bundgaard, ed., Chapter 5; "Design and Applications of Prodrugs" p.113-191 (1991); *Advanced Drug Delivery Reviews*, H. Bundgaard, 8, p.1-38 (1992); *J. Pharm. Sci.*, 77:285 (1988); Nakeya et al, *Chem. Pharm. Bull.*, 32:692 (1984); Higuchi et al., "Pro-drugs as Novel Delivery Systems," Vol. 14 of the *A.C.S. Symposium Series, and Bioreversible Carriers in Drug Design*, Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press (1987), which are incorporated herein by reference in their entirety. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the invention.

**[0034]** The term "solvate" refers to a compound of Formula (I), Formula (Ia), Formula (Ib), and Formula (Ic) in the solid state, wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent for therapeutic administration is physiologically tolerable at the dosage administered. Examples of suitable solvents for therapeutic administration are ethanol and water. When water is the solvent, the solvate is referred to as a hydrate. In general, solvates are formed by dissolving the compound in the appropriate solvent and isolating the solvate by cooling or using an antisolvent. The solvate is typically dried or azeotroped under ambient conditions.

**[0035]** The term "therapeutically effective amounts" is meant to describe an amount of compound of the present invention effective to produce the desired therapeutic effect. Such amounts generally vary according to a number of factors well within the purview of ordinarily skilled artisans given the description provided herein to determine and account for. These include, without limitation: the particular subject, as well as its age, weight, height, general physical condition, and medical history; the particular compound used, as well as the carrier in which it is formulated and the route of administration selected for it; and, the nature and severity of the condition being treated.

**[0036]** The term "pharmaceutical composition" means a composition comprising a compound of Formula (I) Formula (Ia), Formula (Ib), and Formula (Ic) and at least one component comprising pharmaceutically acceptable carriers, diluents, adjuvants, excipients, or vehicles, such as preserving agents, fillers, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms. Examples of suspending agents include ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline

cellulose, aluminum metahydroxide, bentonite, agar—agar and tragacanth, or mixtures of these substances. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin. Examples of suitable carriers, diluents, solvents, or vehicles include water, ethanol, polyols, suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Examples of excipients include lactose, milk sugar, sodium citrate, calcium carbonate, and dicalcium phosphate. Examples of disintegrating agents include starch, alginic acids, and certain complex silicates. Examples of lubricants include magnesium stearate, sodium lauryl sulphate, talc, as well as high molecular weight polyethylene glycols.

**[0037]** The term "pharmaceutically acceptable" means it is, within the scope of sound medical judgement, suitable for use in contact with the cells of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio.

**[0038]** The term "pharmaceutically acceptable dosage forms" means dosage forms of the compound of the invention, and includes, for example, tablets, dragees, powders, elixirs, syrups, liquid preparations, including suspensions, sprays, inhalants tablets, lozenges, emulsions, solutions, granules, capsules, and suppositories, as well as liquid preparations for injections, including liposome preparations. Techniques and formulations generally may be found in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., latest edition.

**[0039]** Compounds described herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. Each chiral center may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. This technology is meant to include all such possible isomers, as well as mixtures thereof, including racemic and optically pure forms. Optically active (R)- and (S)-, (-)- and (+)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

**[0040]** This technology also envisions the "quaternization" of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized

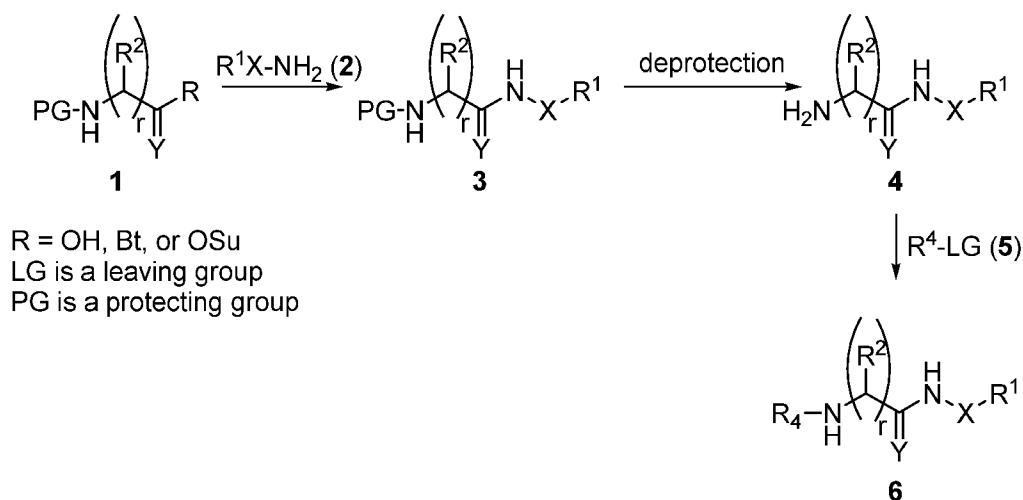
with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization.

**[0041]** In the characterization of some of the substituents, it is recited that certain substituents may combine to form rings. Unless stated otherwise, it is intended that such rings may exhibit various degrees of unsaturation (from fully saturated to fully unsaturated), may include heteroatoms and may be substituted with lower alkyl or alkoxy.

**[0042]** Compounds of the present invention can be produced according to known methods. For example, compounds of the present invention wherein *s* is 0 can be prepared according to Scheme 1 and Scheme 2 outlined below.

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Scheme 1

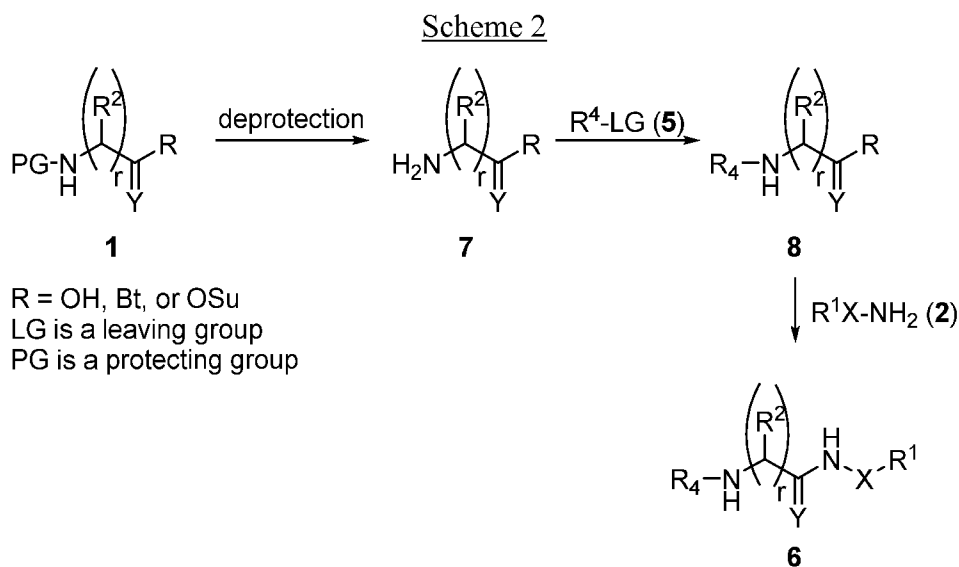


**[0043]** Reaction of the carboxylic acid derivative (1) with amine  $\text{R}^1\text{X-NH}_2$  (2) leads to formation of the compound (3). The reaction can be carried out in a variety of solvents, for example in methylene chloride ( $\text{CH}_2\text{Cl}_2$ ), tetrahydrofuran (THF), dimethylformamide (DMF), or other such solvents or in the mixture of such solvents. During the reaction process, the non-participating carboxylic acids or amines on the reacting set of amino acids or peptide fragments can be protected by a suitable protecting group which can be selectively removed at a later time if desired. A detailed description of these groups and their selection and chemistry is contained in "The Peptides, Vol. 3", Gross and Meinenhofer, Eds., Academic Press, New York, 1981, which is hereby incorporated by reference in its entirety. Thus, useful protective groups for the amino group are benzyloxycarbonyl (Cbz), t-butyloxycarbonyl (t-BOC), 2,2,2-

25

trichloroethoxycarbonyl (Troc), t-amylloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-(trichlorosilyl)ethoxycarbonyl, 9-fluorenylmethoxycarbonyl (Fmoc), phthaloyl, acetyl (Ac), formyl, trifluoroacetyl, and the like. Following the deprotection, amine (4) is reacted with R<sup>4</sup>-LG (5) (wherein LG is a suitable leaving group) to form final product (6).

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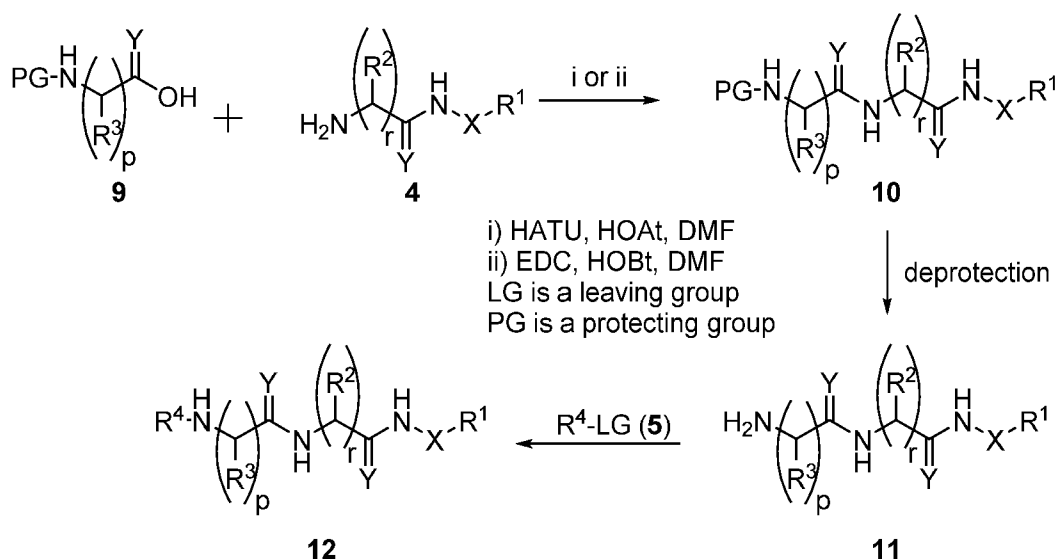


[0044] Alternatively, carboxylic acid derivative bearing protecting group (PG) (1) can be first deprotected and then reacted with the R<sup>4</sup>-LG (5) (wherein LG is a suitable leaving group) to form compound (8). Compound (8) can be then reacted with amine (2), R<sup>1</sup>X-NH<sub>2</sub>, to form final product (6).

[0045] Compounds of the present invention wherein s is 1 can be prepared according to the general schemes outlined below (Schemes 3-7).

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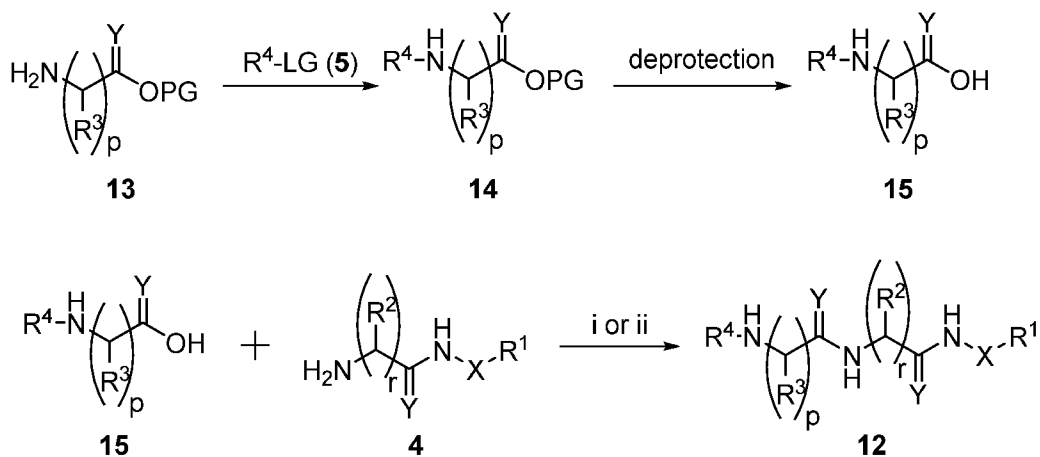
- 25 -  
Scheme 3



**[0046]** The compounds of the present invention may be prepared by stepwise coupling of  
 5 the amino acids. The coupling reactions are conducted in solvents such as methylene chloride ( $\text{CH}_2\text{Cl}_2$ ), tetrahydrofuran (THF), dimethylformamide (DMF), or other such solvents. During the coupling process, the non-participating carboxylic acids or amines on the reacting set of amino acids or peptide fragments can be protected by a suitable protecting group which can be selectively removed at a later time if desired. A detailed description of these groups and their  
 10 selection and chemistry is contained in "The Peptides, Vol. 3", Gross and Meinenhofer, Eds., Academic Press, New York, 1981, which is hereby incorporated by reference in its entirety. Thus, useful protective groups for the amino group are benzyloxycarbonyl (Cbz), t-butylloxycarbonyl (t-BOC), 2,2,2-trichloroethoxycarbonyl (Troc), t-amylloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-(trichlorosilyl)ethoxycarbonyl, 9-fluorenylmethoxycarbonyl  
 15 (Fmoc), phthaloyl, acetyl (Ac), formyl, trifluoroacetyl, and the like. Carboxylic acid bearing protecting group (PG) (9) is coupled with the amine (4) to form compound (10). Following the deprotection reaction, compound (11) is reacted with  $R^4\text{-LG (5)}$  to form final product (12).

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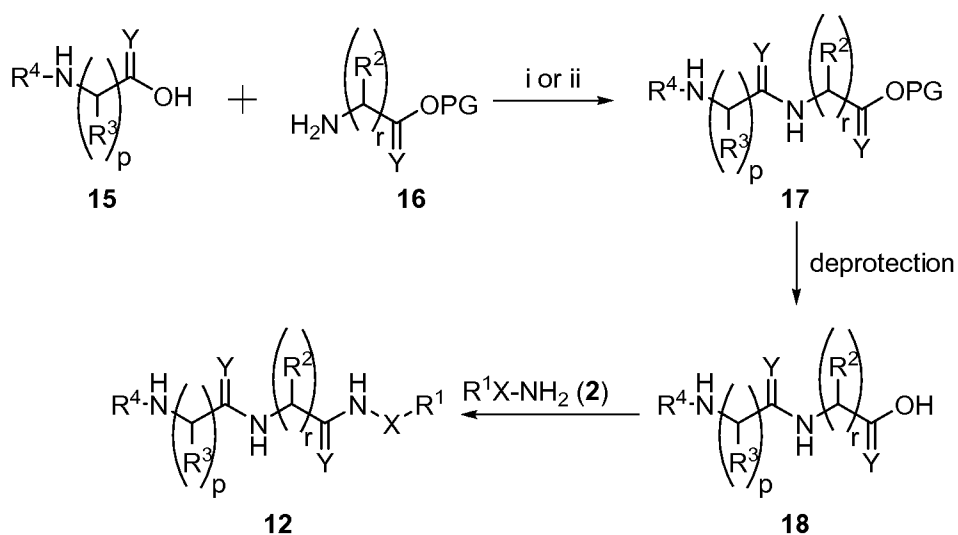
## Scheme 4



i) HATU, HOAt, DMF  
 ii) EDC, HOBT, DMF  
 LG is a leaving group  
 PG is a protecting group

[0047] Alternatively, carboxylic acid bearing protecting group (PG) (13) can be first  
 5 reacted with  $\text{R}^4\text{-LG}$  (wherein LG is a suitable leaving group) (5) to form compound (14). Then,  
 following the deprotection reaction, acid (15) can be coupled with amine (4) to form final  
 product (12).

## Scheme 5

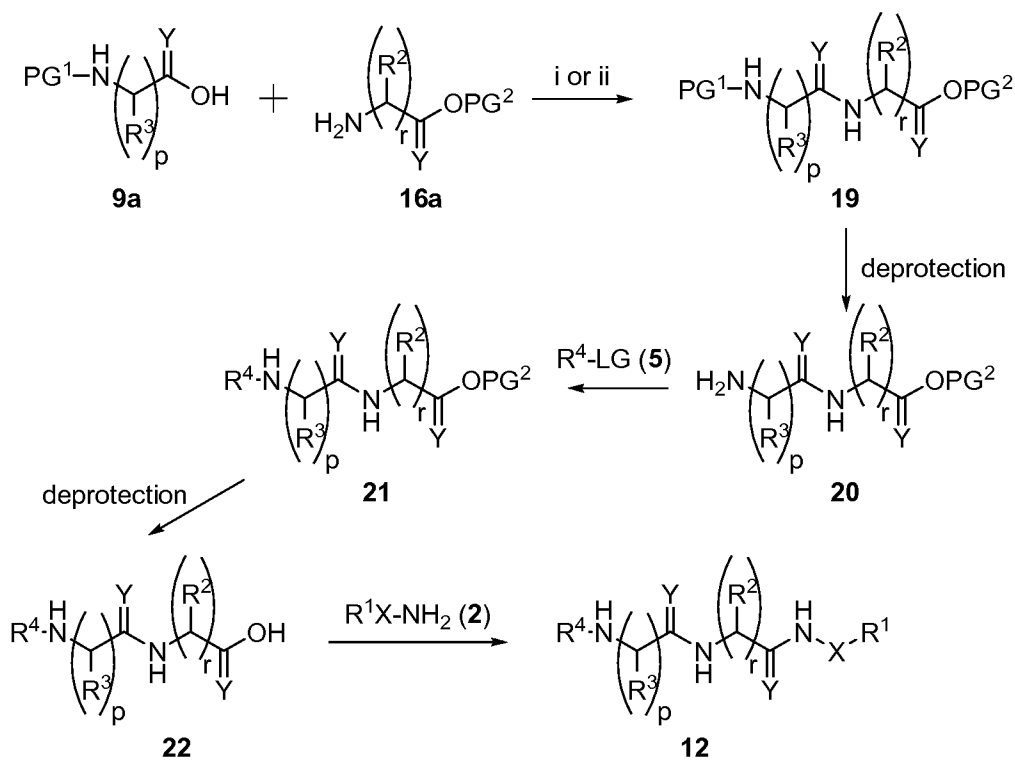


i) HATU, HOAt, DMF  
 ii) EDC, HOBT, DMF  
 LG is a leaving group  
 PG is a protecting group

[0048] Alternatively, acid (15) can be first coupled with amino acid (16) to form compound (17). Following the deprotection reaction, acid (18) can be reacted with amine (2),  $R^1X-NH_2$ , to form final product (12).

5

Scheme 6



i) HATU, HOAt, DMF

ii) EDC, HOBT, DMF

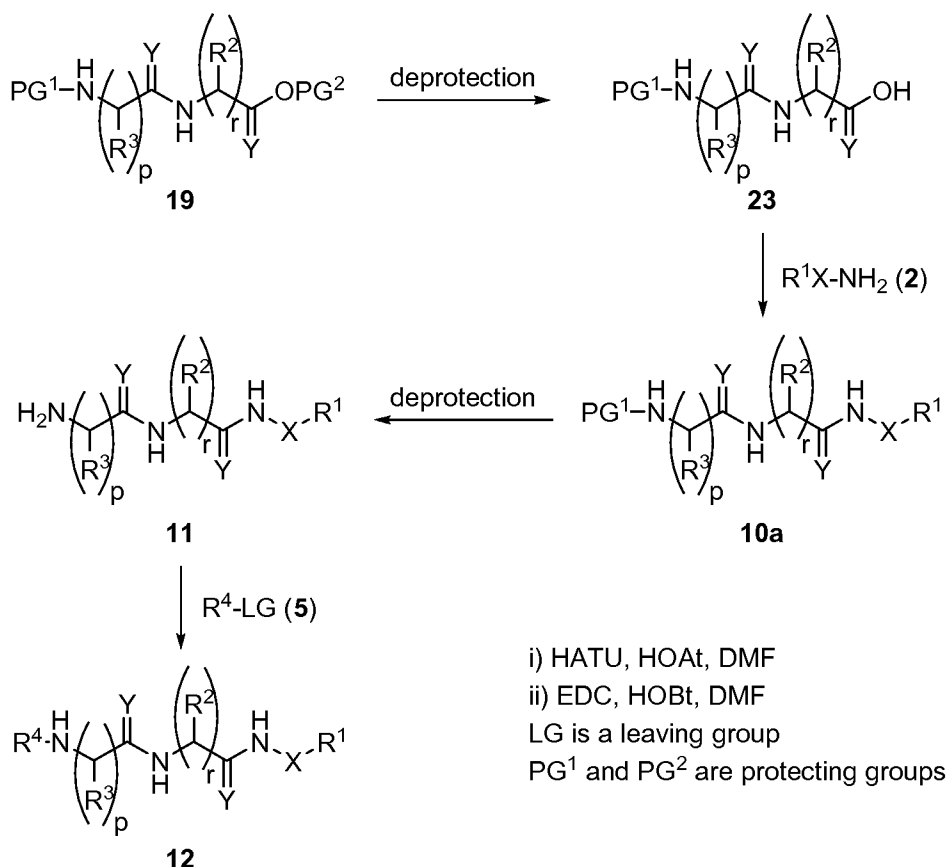
LG is a leaving group

$PG^1$  and  $PG^2$  are protecting groups

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[0049] Alternatively, amino acid (9a) can be coupled with amino acid (16a) to form compound (19). Following the deprotection reaction, acid (20) can be reacted with  $R^4-LG$  (wherein LG is a suitable leaving group) (5) to form compound (21). Following the deprotection reaction, acid (22) can be coupled with amine (2),  $R^1X-NH_2$ , to form final product (12).

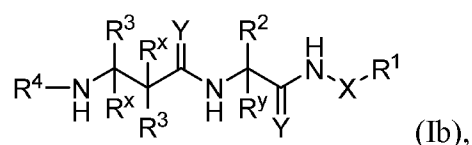
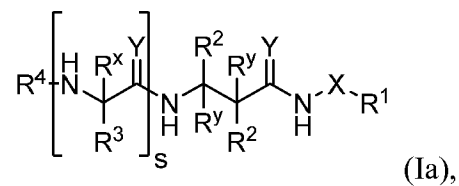
- 28 -  
Scheme 7

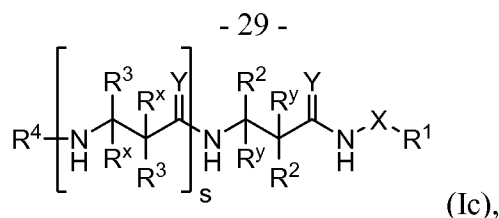


**[0050]** Alternatively, following the deprotection reaction, acid (23) can be coupled with amine (2), R<sup>1</sup>X-NH<sub>2</sub>, to form compound (10a). Following the deprotection reaction, amine (11) can then be reacted with R<sup>4</sup>-LG (wherein LG is a suitable leaving group) (5) to form final product (12).

**[0051]** Compounds of the present invention wherein Y is O can be easily converted to their analogs wherein Y is S, according to known methods. For example by using Lawesson's reagent.

10 **[0052]** Another aspect of the present invention relates to a compound of Formula (Ia), Formula (Ib), or Formula (Ic):





wherein

R<sup>1</sup> is selected from the group consisting of monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and monocyclic and bicyclic non-aromatic heterocycle, wherein monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and monocyclic and bicyclic non-aromatic heterocycle can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, —CF<sub>3</sub>, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

R<sup>2</sup> is independently selected at each occurrence thereof from the group consisting of H, D, C<sub>1-6</sub> alkyl, —CH<sub>2</sub>OC<sub>1-6</sub> alkyl, —CH<sub>2</sub>Ar, and —CH<sub>2</sub>heteroaryl, wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

R<sup>3</sup> is independently selected at each occurrence thereof from the group consisting of H, D, —CH<sub>2</sub>OC<sub>1-6</sub> alkyl, —(CH<sub>2</sub>)<sub>m</sub>C(O)NHR<sup>5</sup>, and —(CH<sub>2</sub>)<sub>m</sub>C(O)NR<sup>6</sup>R<sup>7</sup>;

R<sup>4</sup> is selected from the group consisting of —C(O)(CH<sub>2</sub>)<sub>n</sub>Ph, —C(O)CH<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, —SO<sub>2</sub>Ar, —SO<sub>2</sub>C<sub>1-6</sub> alkyl, —SO<sub>2</sub>C<sub>3-6</sub> cycloalkyl, —C(O)(CH<sub>2</sub>)<sub>n</sub>Het, —C(O)C(O)Het, —C(O)C<sub>1-6</sub> alkyl, —C(O)OC<sub>1-6</sub> alkyl, —C(O)CF<sub>3</sub>, heteroaryl, and —(CH<sub>2</sub>)<sub>n</sub>NR<sup>6</sup>R<sup>7</sup>, wherein aryl (Ar) and heteroaryl (Het) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

R<sup>5</sup> is selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, non-aromatic heterocycle, —NR<sup>6</sup>R<sup>7</sup>, and —CR<sup>8</sup>R<sup>9</sup>;

R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, and R<sup>9</sup> are each independently selected from the group consisting of H, D, C<sub>1-6</sub> alkyl, and —(CH<sub>2</sub>)<sub>k</sub>OH;

or R<sup>6</sup> and R<sup>7</sup> are taken together with the nitrogen to which they are attached to form a morpholine ring;

5 or R<sup>8</sup> and R<sup>9</sup> are taken together with the carbon to which they are attached to form an oxetane ring;

R<sup>x</sup> is independently selected at each occurrence thereof from the group consisting of H, D, —CH<sub>2</sub>OC<sub>1-6</sub> alkyl, —(CH<sub>2</sub>)<sub>m</sub>C(O)NHR<sup>5</sup>, —(CH<sub>2</sub>)<sub>m</sub>C(O)NR<sup>6</sup>R<sup>7</sup>, and —CH<sub>2</sub>C(O)R<sup>5</sup>;

10 R<sup>y</sup> is independently selected at each occurrence thereof from the group consisting of H, D, C<sub>1-6</sub> alkyl, —CH<sub>2</sub>OC<sub>1-6</sub> alkyl, —CH<sub>2</sub>Ar, and —CH<sub>2</sub>heteroaryl, wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

15 X is —(CH<sub>2</sub>)<sub>q</sub>—, —O—, or —(CD<sub>2</sub>)<sub>q</sub>— ;

Y is O or S;

k is 1, 2, or 3;

20 m is 0, 1, 2, 3, 4, or 5;

n is 0, 1, 2, or 3;

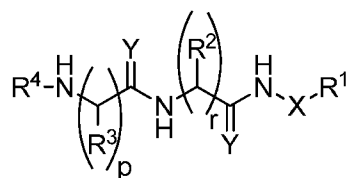
25 q is 0, 1, or 2; and

s is 0 or 1;

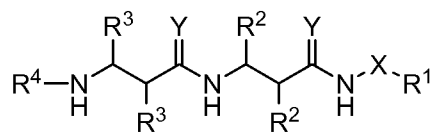
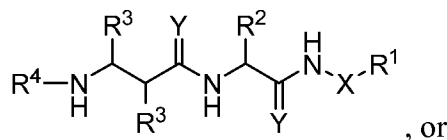
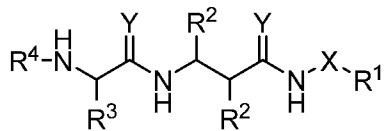
30 or an oxide thereof, a pharmaceutically acceptable salt thereof, a solvate thereof, or a prodrug thereof.

**[0053]** Compounds according to the present invention include compounds of Formula (I), Formula (Ia), Formula (Ib), and Formula (Ic). In one embodiment compound according to the present invention is a compound of Formula (I). In another embodiment the compound according to the present invention is a compound of Formula (Ia), Formula (Ib), or Formula (Ic).

[0054] In one embodiment, compound has the formula :

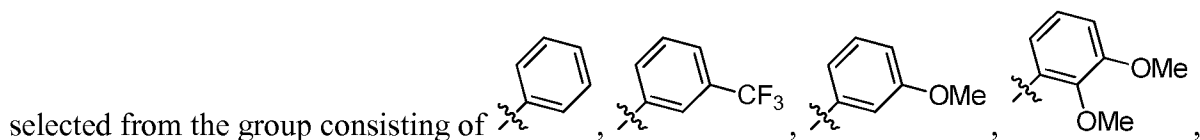


[0055] In another embodiment, compound has the formula

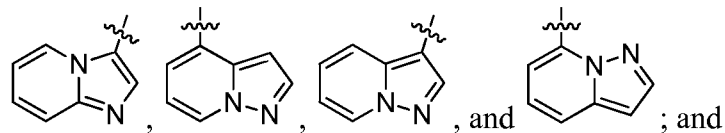
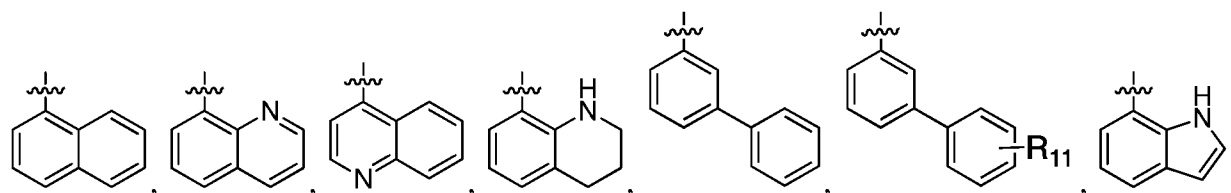


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[0056] One embodiment relates to the compounds of the present invention where R<sup>1</sup> is



selected from the group consisting of

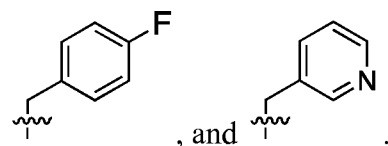


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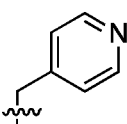
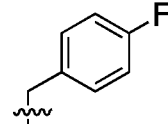
R<sup>11</sup> is selected from the group consisting of halogen, cyano, —CF<sub>3</sub>, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy.

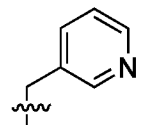
[0057] Another embodiment relates to the compounds of the present invention where R<sup>2</sup>

15 is selected from the group consisting of H, Me, —CH<sub>2</sub>(Me)<sub>2</sub>, —CH<sub>2</sub>OMe, ,



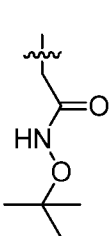
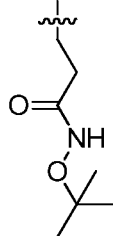
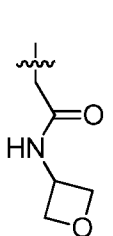
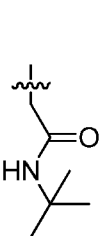
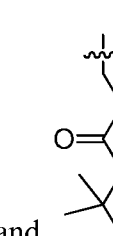
[0058] Another embodiment relates to the compounds of the present invention where R<sup>2</sup>

is selected from the group consisting of Me, —CH<sub>2</sub>(Me)<sub>2</sub>, —CH<sub>2</sub>OMe, , ,

and .

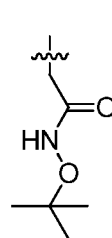
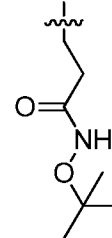
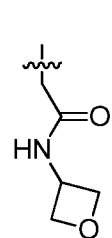
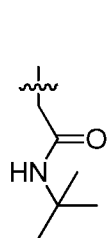
[0059] One embodiment relates to the compounds of the present invention where R<sup>3</sup> is

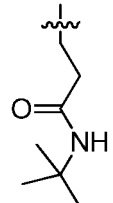
5 selected from the group consisting of —CH<sub>2</sub>OMe, —CH<sub>2</sub>C(O)OH, —CH<sub>2</sub>C(O)OBn,

, , , , and .

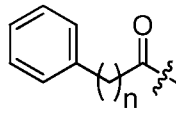
—(CH<sub>2</sub>)<sub>2</sub>C(O)OBn, —(CH<sub>2</sub>)<sub>2</sub>C(O)OH,

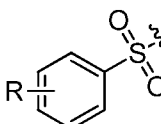
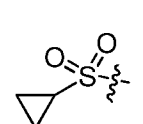
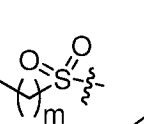
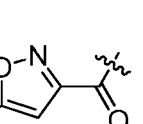
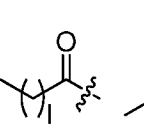
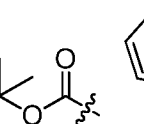
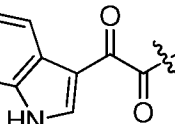
[0060] Another embodiment relates to the compounds of the present invention where

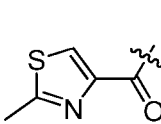
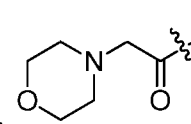
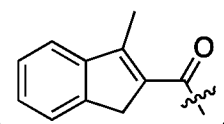
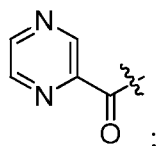
R<sup>3</sup> is selected from the group consisting of —CH<sub>2</sub>OMe, , , , ,

and .

10 [0061] Another embodiment relates to the compounds of the present invention where R<sup>4</sup>

is selected from the group consisting of H, trifluoroacetyl, ,

, , , , , , ,

, , , and ;

l is 0, 1, 2, 3, or 4;

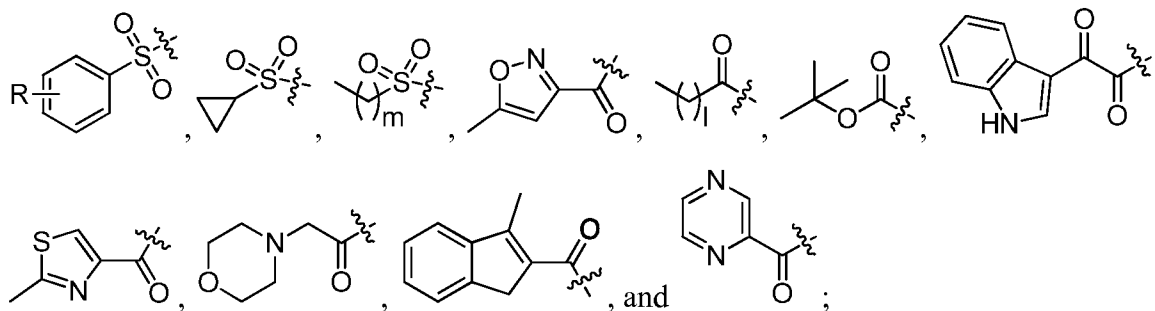
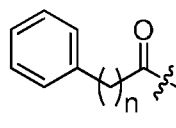
m is 0, 1, 2, 3, 4, or 5;

5 n is 0, 1, 2, or 3; and

R is selected from the group consisting of H, halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy.

[0062] Yet another embodiment relates to the compounds of the present invention where

10 R<sup>4</sup> is selected from the group consisting of trifluoroacetyl,



l is 0, 1, 2, 3, or 4;

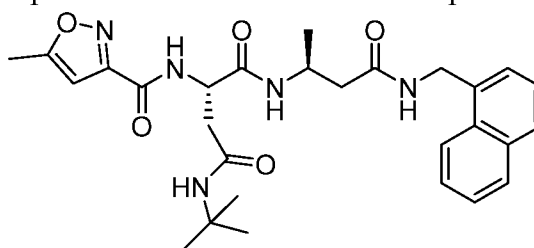
15

m is 0, 1, 2, 3, 4, or 5;

n is 0, 1, 2, or 3; and

20 R is selected from the group consisting of H, halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy.

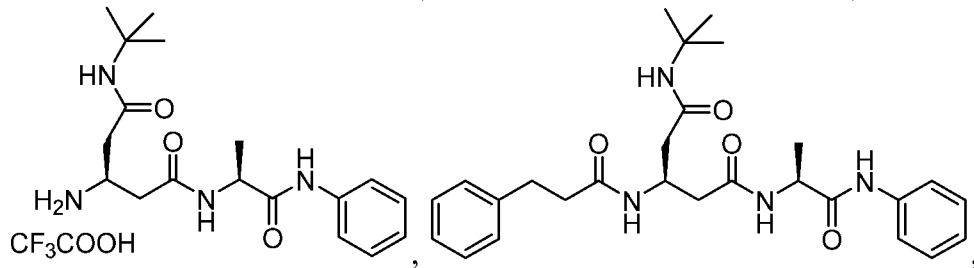
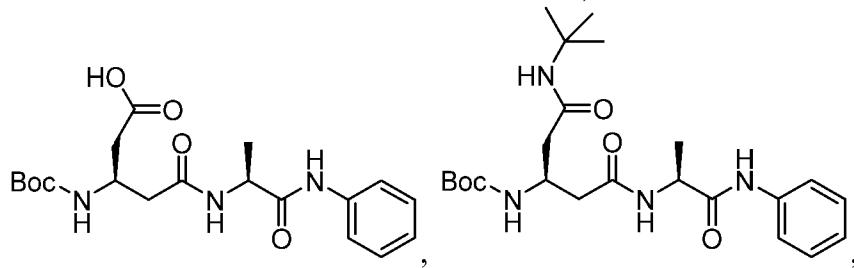
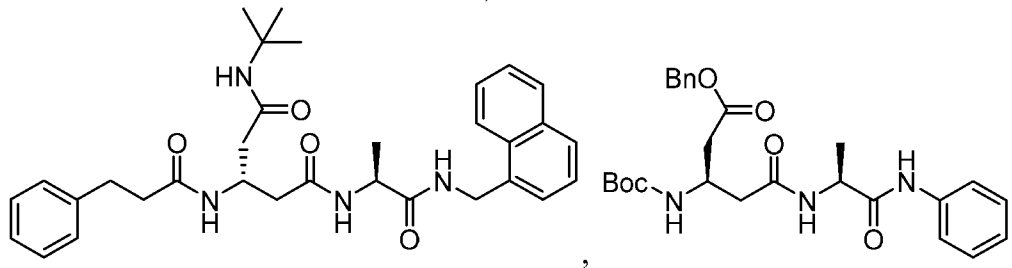
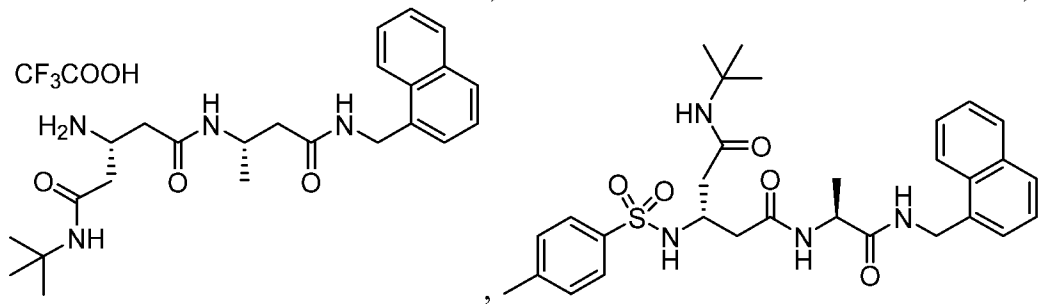
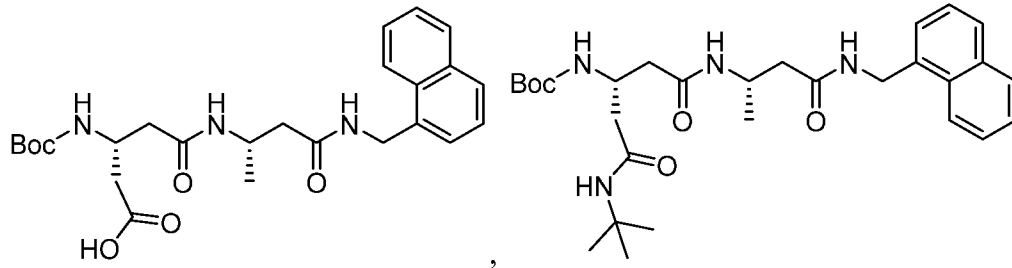
One embodiment relates to the compounds of the present invention where the compound has a



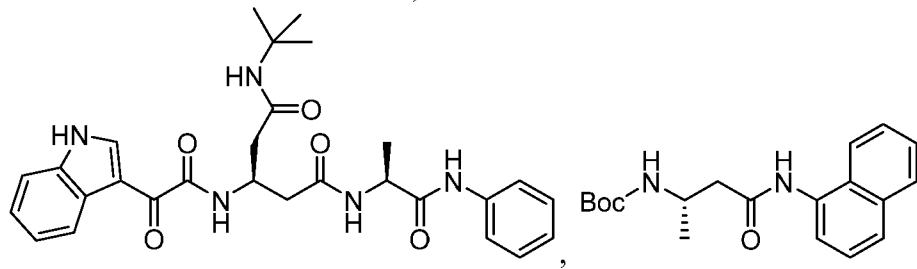
structure selected from the group consisting of:



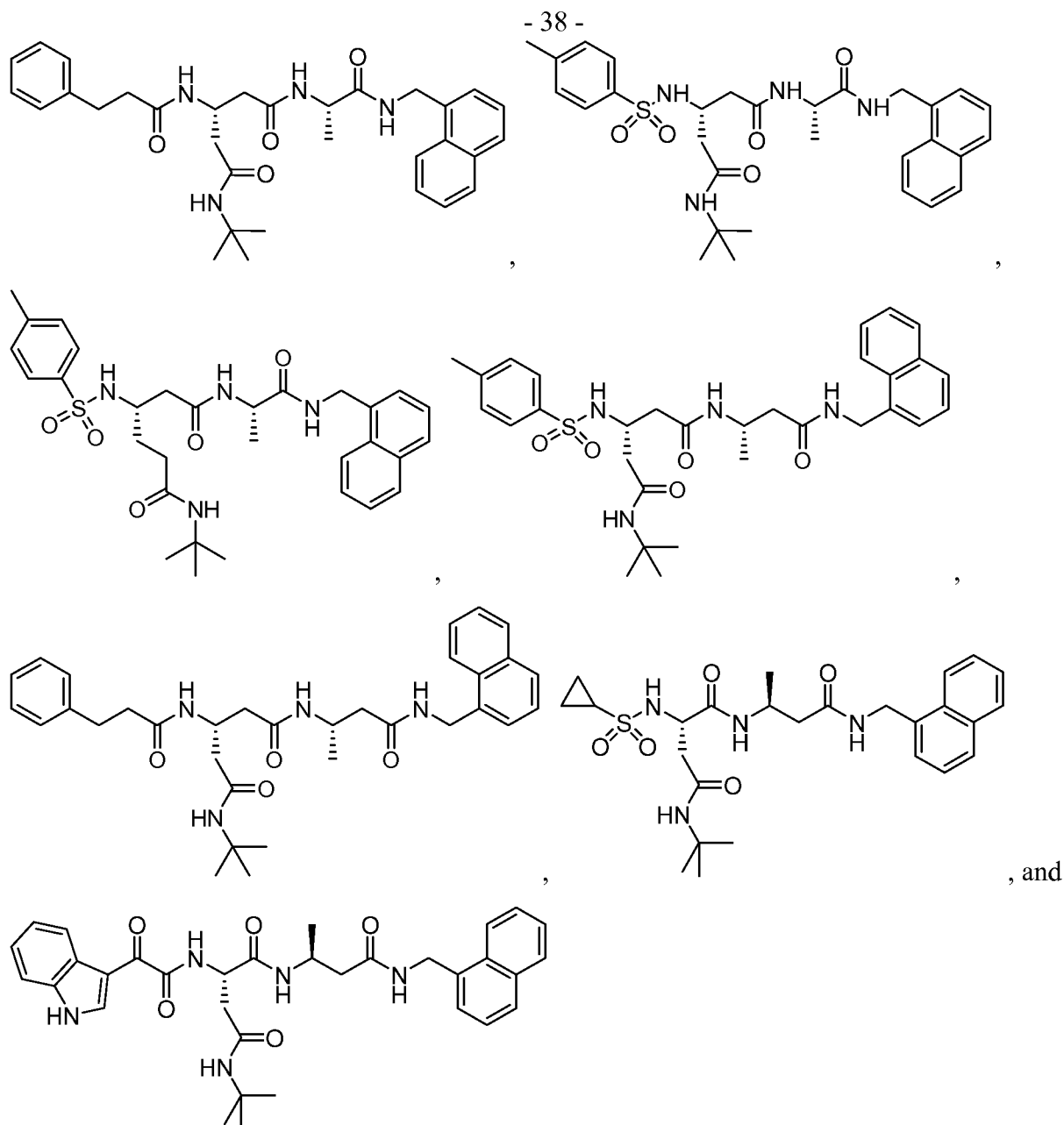




5







5 [0064] While it may be possible for compounds of the present invention to be administered as raw chemicals, it will often be preferable to present them as a part of a pharmaceutical composition. Accordingly, another aspect of the present invention is a pharmaceutical composition containing a therapeutically effective amount of the compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, and a

10 pharmaceutically acceptable carrier. The carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0065] Compounds according to the present invention include compounds of Formula (I), Formula (Ia), Formula (Ib), and Formula (Ic). In one embodiment compound according to the

present invention is a compound of Formula (I). In another embodiment the compound according to the present invention is a compound of Formula (Ia), Formula (Ib), or Formula (Ic).

**[0066]** In practicing the method of the present invention, agents suitable for treating a subject can be administered using any method standard in the art. The agents, in their appropriate delivery form, can be administered orally, intradermally, intramuscularly, intraperitoneally, intravenously, subcutaneously, or intranasally. The compositions of the present invention may be administered alone or with suitable pharmaceutical carriers, and can be in solid or liquid form, such as tablets, capsules, powders, solutions, suspensions, or emulsions.

**[0067]** The agents of the present invention may be orally administered, for example, with an inert diluent, or with an assimilable edible carrier, or it may be enclosed in hard or soft shell capsules, or it may be compressed into tablets, or they may be incorporated directly with the food of the diet. Agents of the present invention may also be administered in a time release manner incorporated within such devices as time-release capsules or nanotubes. Such devices afford flexibility relative to time and dosage. For oral therapeutic administration, the agents of the present invention may be incorporated with excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, and the like. Such compositions and preparations should contain at least 0.1% of the agent, although lower concentrations may be effective and indeed optimal. The percentage of the agent in these compositions may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of the unit. The amount of an agent of the present invention in such therapeutically useful compositions is such that a suitable dosage will be obtained.

**[0068]** Also specifically contemplated are oral dosage forms of the agents of the present invention. The agents may be chemically modified so that oral delivery of the derivative is efficacious. Generally, the chemical modification contemplated is the attachment of at least one moiety to the component molecule itself, where said moiety permits (a) inhibition of proteolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the component or components and increase in circulation time in the body. Examples of such moieties include: polyethylene glycol, copolymers of ethylene glycol and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone and polyproline. (Abuchowski and Davis, "Soluble Polymer-Enzyme Adducts," In: *Enzymes as Drugs*, Hocenberg and Roberts, eds., Wiley-Interscience, New York, N.Y., pp. 367-383 (1981), which are hereby incorporated by reference in their entirety). Other polymers that could be used are poly-1,3-dioxolane and poly-1,3,6-tioxocane. Preferred for pharmaceutical usage, as indicated above, are polyethylene glycol moieties.

[0069] The tablets, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch, or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose, sucralose, or saccharin.

5 When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

[0070] Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar, or both. A syrup may contain, in addition to active ingredient, sucrose as a sweetening agent, methyl and

10 propylparabens as preservatives, a dye, and flavoring such as cherry or orange flavor.

[0071] The agents of the present invention may also be administered parenterally. Solutions or suspensions of the agent can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid

15 polyethylene glycols, and mixtures thereof in oils. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. In general, water, saline, aqueous dextrose and related sugar solution, and glycols, such as propylene glycol or polyethylene glycol, are preferred liquid carriers, particularly for injectable solutions. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0072] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as

25 bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

[0073] When it is desirable to deliver the agents of the present invention systemically, they may be formulated for parenteral administration by injection, e.g., by bolus injection or

30 continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

**[0074]** Intraperitoneal or intrathecal administration of the agents of the present invention can also be achieved using infusion pump devices such as those described by Medtronic, Northridge, CA. Such devices allow continuous infusion of desired compounds avoiding multiple injections and multiple manipulations.

5 **[0075]** In addition to the formulations described previously, the agents may also be formulated as a depot preparation. Such long acting formulations may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

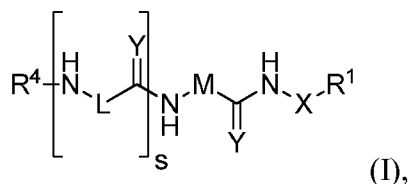
10 **[0076]** The agents of the present invention may also be administered directly to the airways in the form of an aerosol. For use as aerosols, the agent of the present invention in solution or suspension may be packaged in a pressurized aerosol container together with suitable propellants, for example, hydrocarbon propellants like propane, butane, or isobutane with conventional adjuvants. The agent of the present invention also may be administered in a non-pressurized form such as in a nebulizer or atomizer.

15 **[0077]** Effective doses of the compositions of the present invention, for the treatment of cancer or pathogen infection vary depending upon many different factors, including type and stage of cancer or the type of pathogen infection, means of administration, target site, physiological state of the patient, other medications or therapies administered, and physical state of the patient relative to other medical complications. Treatment dosages need to be titrated to  
20 optimize safety and efficacy.

**[0078]** The percentage of active ingredient in the compositions of the present invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the  
25 desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.01 to about 100 mg/kg body weight, preferably about 0.01 to about 10 mg/kg body weight per day by inhalation, from about 0.01 to about 100 mg/kg body weight, preferably 0.1 to 70 mg/kg body weight, more especially 0.1 to 10 mg/kg body weight per day by oral administration, and from about 0.01 to  
30 about 50 mg/kg body weight, preferably 0.01 to 10 mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health, and other characteristics which can influence the efficacy of the medicinal product.

[0079] The products according to the present invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. It goes without saying that, for other patients, it will be necessary to prescribe not more than one or two doses per day.

[0080] Another aspect of the present invention relates to a method of treating cancer, immunologic disorders, autoimmune disorders, neurodegenerative disorders, or inflammatory disorders in a subject or for providing immunosuppression for transplanted organs or tissues in a subject. This method includes administering to the subject in need thereof a compound of the Formula (I):



15 wherein

L is  $\text{---}(\text{CR}^3\text{R}^x)_p\text{---}$ ;

M is  $\text{---}(\text{CR}^2\text{R}^y)_r\text{---}$ ;

20  $\text{R}^1$  is selected from the group consisting of monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and monocyclic and bicyclic non-aromatic heterocycle, wherein monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and monocyclic and bicyclic non-aromatic heterocycle can be optionally substituted from 1 to 3  
 25 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $\text{---CF}_3$ ,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

$\text{R}^2$  is independently selected at each occurrence thereof from the group consisting of H, D,  $\text{C}_{1-6}$  alkyl,  $\text{---CH}_2\text{OC}_{1-6}$  alkyl,  $\text{---CH}_2\text{Ar}$ , and  $\text{---CH}_2$ heteroaryl, wherein aryl (Ar) can be  
 30 optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

$R^3$  is independently selected at each occurrence thereof from the group consisting of H, D,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NHR}^5$ ,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^6\text{R}^7$ ,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{OH}$ , and  $-(\text{CH}_2)_m\text{C}(\text{O})\text{OBn}$ ;

5  $R^4$  is selected from the group consisting of H,  $-\text{C}(\text{O})(\text{CH}_2)_n\text{Ph}$ ,  $-\text{C}(\text{O})\text{CH}_2\text{NR}^6\text{R}^7$ ,  $-\text{SO}_2\text{Ar}$ ,  $-\text{SO}_2\text{C}_{1-6}$  alkyl,  $-\text{SO}_2\text{C}_{3-6}$  cycloalkyl,  $-\text{C}(\text{O})(\text{CH}_2)_n\text{Het}$ ,  $-\text{C}(\text{O})\text{C}(\text{O})\text{Het}$ ,  $-\text{C}(\text{O})\text{C}_{1-6}$  alkyl,  $-\text{C}(\text{O})\text{OC}_{1-6}$  alkyl,  $-\text{C}(\text{O})\text{CF}_3$ , heteroaryl, and  $-(\text{CH}_2)_n\text{NR}^6\text{R}^7$ , wherein aryl (Ar) and heteroaryl (Het) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group  
10 consisting of halogen, cyano,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

$R^5$  is selected from the group consisting of  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy, non-aromatic heterocycle,  $-\text{NR}^6\text{R}^7$ , and  $-\text{CR}^8\text{R}^9$ ;

15  $R^6$ ,  $R^7$ ,  $R^8$ , and  $R^9$  are each independently selected from the group consisting of H, D,  $\text{C}_{1-6}$  alkyl, and  $-(\text{CH}_2)_k\text{OH}$ ;

or  $R^6$  and  $R^7$  are taken together with the nitrogen to which they are attached to form a morpholine ring;

20 or  $R^8$  and  $R^9$  are taken together with the carbon to which they are attached to form an oxetane ring;

25  $R^x$  is independently selected at each occurrence thereof from the group consisting of H, D,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NHR}^5$ ,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^6\text{R}^7$ , and  $-\text{CH}_2\text{C}(\text{O})\text{R}^5$ ;

30  $R^y$  is independently selected at each occurrence thereof from the group consisting of H, D,  $\text{C}_{1-6}$  alkyl,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-\text{CH}_2\text{Ar}$ , and  $-\text{CH}_2\text{heteroaryl}$ , wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

X is  $-(\text{CH}_2)_q-$ ,  $-\text{O}-$ , or  $-(\text{CD}_2)_q-$ ;

Y is O or S;

k is 1, 2, or 3;

m is 0, 1, 2, 3, 4, or 5;

5

n is 0, 1, 2, or 3;

p is 1 or 2;

10

q is 0, 1, or 2;

r is 1 or 2; and

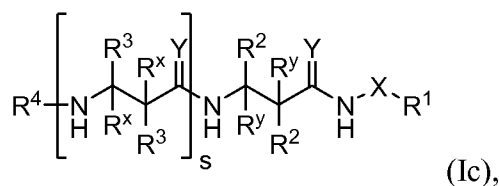
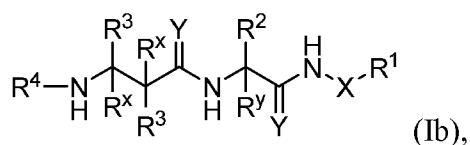
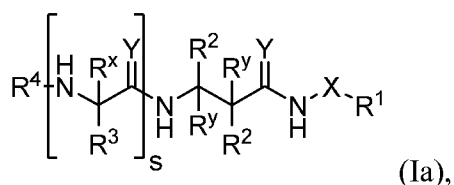
s is 0 or 1;

15

with a proviso that when s is 0, then r is 2; and when s is 1, then  $r + p \geq 3$ .

**[0081]** Yet another aspect of the present invention relates to a method of treating cancer, immunologic disorders, autoimmune disorders, neurodegenerative disorders, or inflammatory disorders in a subject or for providing immunosuppression for transplanted organs or tissues in a subject. This method includes administering to the subject in need thereof a compound of the Formula (Ia), Formula (Ib), or Formula (Ic):

20



25 wherein

$R^1$  is selected from the group consisting of monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and

monocyclic and bicyclic non-aromatic heterocycle, wherein monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and monocyclic and bicyclic non-aromatic heterocycle can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $-\text{CF}_3$ ,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

$\text{R}^2$  is independently selected at each occurrence thereof from the group consisting of H, D,  $\text{C}_{1-6}$  alkyl,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-\text{CH}_2\text{Ar}$ , and  $-\text{CH}_2\text{heteroaryl}$ , wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

$\text{R}^3$  is independently selected at each occurrence thereof from the group consisting of H, D,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NHR}^5$ , and  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^6\text{R}^7$ ;

$\text{R}^4$  is selected from the group consisting of  $-\text{C}(\text{O})(\text{CH}_2)_n\text{Ph}$ ,  $-\text{C}(\text{O})\text{CH}_2\text{NR}^6\text{R}^7$ ,  $-\text{SO}_2\text{Ar}$ ,  $-\text{SO}_2\text{C}_{1-6}$  alkyl,  $-\text{SO}_2\text{C}_{3-6}$  cycloalkyl,  $-\text{C}(\text{O})(\text{CH}_2)_n\text{Het}$ ,  $-\text{C}(\text{O})\text{C}(\text{O})\text{Het}$ ,  $-\text{C}(\text{O})\text{C}_{1-6}$  alkyl,  $-\text{C}(\text{O})\text{OC}_{1-6}$  alkyl,  $-\text{C}(\text{O})\text{CF}_3$ , heteroaryl, and  $-(\text{CH}_2)_n\text{NR}^6\text{R}^7$ , wherein aryl (Ar) and heteroaryl (Het) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

$\text{R}^5$  is selected from the group consisting of  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy, non-aromatic heterocycle,  $-\text{NR}^6\text{R}^7$ , and  $-\text{CR}^8\text{R}^9$ ;

$\text{R}^6$ ,  $\text{R}^7$ ,  $\text{R}^8$ , and  $\text{R}^9$  are each independently selected from the group consisting of H, D,  $\text{C}_{1-6}$  alkyl, and  $-(\text{CH}_2)_k\text{OH}$ ;

or  $\text{R}^6$  and  $\text{R}^7$  are taken together with the nitrogen to which they are attached to form a morpholine ring;

or  $\text{R}^8$  and  $\text{R}^9$  are taken together with the carbon to which they are attached to form an oxetane ring;

- 46 -

$R^x$  is independently selected at each occurrence thereof from the group consisting of H, D,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NHR}^5$ ,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^6\text{R}^7$ , and  $-\text{CH}_2\text{C}(\text{O})\text{R}^5$ ;

$R^y$  is independently selected at each occurrence thereof from the group consisting of H, D,  $\text{C}_{1-6}$  alkyl,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-\text{CH}_2\text{Ar}$ , and  $-\text{CH}_2\text{heteroaryl}$ , wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

X is  $-(\text{CH}_2)_q-$ ,  $-\text{O}-$ , or  $-(\text{CD}_2)_q-$ ;

Y is O or S;

k is 1, 2, or 3;

m is 0, 1, 2, 3, 4, or 5;

n is 0, 1, 2, or 3;

q is 0, 1, or 2; and

s is 0 or 1.

**[0082]** In one embodiment, an autoimmune disorder is treated. The autoimmune disorder is selected from the group consisting of arthritis, colitis, multiple sclerosis, lupus, systemic sclerosis, and sjögren syndrome. Alternatively, the autoimmune disorder is selected from the group consisting of arthritis, colitis, multiple sclerosis, and lupus.

**[0083]** In another embodiment, immunosuppression is provided for transplanted organs or tissues. The immunosuppression is used to prevent transplant rejection and graft-versus-host disease.

**[0084]** In another embodiment, an inflammatory disorder is treated. The inflammatory disorder is Crohn's disease, and ulcerative colitis. Alternatively, the inflammatory disorder is Crohn's disease.

**[0085]** In yet another embodiment, cancer is treated. The cancer is selected from the group consisting of neoplastic disorders, hematologic malignancies, and lymphocytic malignancies.

## EXAMPLES

[0086] The following examples are provided to illustrate embodiments of the present invention but are by no means intended to limit its scope.

5

### Example 1 – General Procedure for HATU Coupling

[0087] Carboxylic acid (1.0 eq.), *O*-(7-Azabenzotriazol-1-yl)-*N,N,N,N'*-tetramethyluronium hexafluorophosphate (HATU) (1.2 eq.), and 1-Hydroxy-7-Azabenzotriazole (HOAt) 0.6M in DMF (1.0 eq.) were dissolved in DMF under argon atmosphere. The solution was cooled to 0 °C and amine was added. After stirring for 5 minutes at 0 °C, Hünig's base (3 - 4 eq.) was added. The reaction mixture was stirred at 0 °C for 1 hour. After completion of reaction (1 hour, monitored by LCMS), water (10 mL) was added to reaction mixture and stirred 30 minutes. Product was isolated either by ethyl acetate extraction or filtering the precipitate.

15

### Example 2 – General Procedure for EDC Coupling

[0088] Carboxylic acid (1.0 eq.), *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC) (1.2 eq.), and 1-Hydroxybenzotriazole (HOBt) (1.3 eq.) were dissolved in DMF under argon atmosphere. The solution was cooled to 0 °C and *tert*-butylamine was added. After stirring for 5 minutes at 0 °C, Hünig's base (2 – 3 eq.) was added. The reaction mixture was allowed to warm to room temperature slowly and stirred at room temperature overnight.

25

### Example 3 – General Procedure for Boc-Deprotection

[0089] The substrate was dissolved in dichloromethane and the solution was cooled to 0 °C. Trifluoroacetic acid (20% v/v with respect to dichloromethane) was added to the solution drop wise at 0 °C with constant stirring. The mixture was allowed to warm to room temperature slowly (over a period of 1 hour), and stirred until the completion of reaction (monitored by LCMS). Excess trifluoroacetic acid and dichloromethane were evaporated and crude was dried under vacuum.

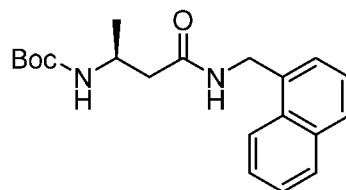
30

**Example 4 – General Procedure for *O*-Debenzylation**

[0090] The substrate was dissolved in methanol. Palladium on carbon (10%) was added  
5 carefully. Residual air from the flask was removed and the mixture was stirred at room  
temperature for 3 – 4 hours under hydrogen atmosphere using a hydrogen balloon. After  
completion of reaction, the mixture was filtered through celite. Filtrate was evaporated and dried  
under vacuum to give product.

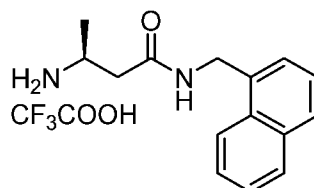
**10 Example 5 – General Procedure for *N*-Sulfonamide Preparation of Amines**

[0091] The primary amine (generally TFA salt) was dissolved in dichloromethane. The  
solution was cooled to 0 °C and triethylamine (2.0 – 3.0 eq.) was added. Sulfonyl chloride (1.5  
eq.) was added to the solution in one portion and reaction mixture was warmed to room  
15 temperature (over 15 minutes). After completion of reaction (2 - 3 hours), dichloromethane was  
evaporated and crude was purified by HPLC to give pure product.

**Example 6 – Preparation of *tert*-butyl (*S*)-(4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)carbamate (PKS2241, PKS2261)**

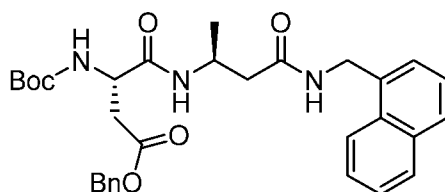
20 [0092] The title compound was synthesized by following the general protocol for HATU  
mediated coupling of Boc-L-β-homoalanine and 1-naphthylmethylamine on a 1.5 mmol scale.  
After completion of reaction, water was added to reaction mixture to give white precipitate.  
Precipitate was filtered, washed with water and dried in air to give product (490 mg, 95%) as a  
25 white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.38 (t, *J* = 5.7 Hz, 1H), 8.06 – 8.04 (m, 1H),  
7.95 – 7.93 (m, 1H), 7.86 – 7.84 (m, 1H), 7.56 – 7.52 (m, 2H), 7.48 – 7.42 (m, 2H), 6.72 (d, *J* =  
8.3 Hz, 1H), 4.76 – 4.68 (m, 2H), 3.89 – 3.80 (m, 1H), 2.35 (dd, *J* = 13.9, 5.7 Hz, 1H), 2.18 (dd,  
*J* = 13.9, 8.2 Hz, 1H), 1.37 (s, 9H), 1.01 (d, *J* = 6.5 Hz, 3H).

**Example 7 – Preparation of (S)-3-amino-N-(naphthalen-1-ylmethyl)butanamide 2,2,2-trifluoroacetate (PKS2245, PKS2262)**



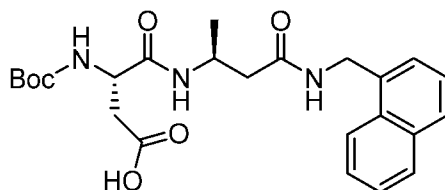
5 [0093] The title compound was prepared by following the general protocol for Boc-deprotection of PKS2261 (480 mg, 1.40 mmol). The crude yellow paste was triturated with diethyl ether and kept standing overnight. The white solid was filtered and dried to give product (480 mg, 96%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.69 (t, *J* = 5.7 Hz, 1H), 8.06 – 8.05 (m, 1H), 7.97 – 7.95 (m, 1H), 7.88 (dd, *J* = 7.4, 2.0 Hz, 1H), 7.80 (bs, 3H), 7.58 – 7.53 (m, 2H), 7.50 –  
10 7.45 (m, 2H), 4.79 (dd, *J* = 15.0, 5.7 Hz, 1H), 4.73 (dd, *J* = 15.0, 5.5 Hz, 1H), 3.57 – 3.50 (m, 1H), 2.51 – 2.43 (m, 2H), 1.17 (d, *J* = 6.5 Hz, 3H).

**Example 8 – Preparation of benzyl (S)-3-((tert-butoxycarbonyl)amino)-4-(((S)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)amino)-4-oxobutanoate (PKS2265)**



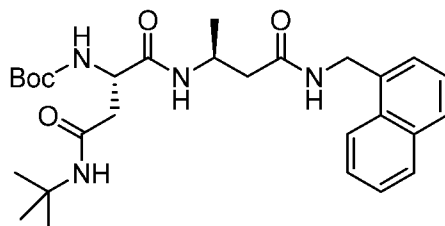
15 [0094] The title compound was synthesized by following the general protocol for HATU mediated coupling of Boc-Asp(OBn)-OH (142.3 mg, 0.44 mg) and PKS2262 (143 mg, 0.40 mmol). After completion of reaction, water was added to reaction mixture to give white  
20 precipitate. Precipitate was filtered, washed with water and dried in air to give product (202 mg, 92%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.41 (t, *J* = 5.8 Hz, 1H), 8.06 – 8.04 (m, 1H), 7.95 – 7.93 (m, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.47 – 7.42 (m, 2H), 7.36 – 7.29 (m, 5H), 7.11 (d, *J* = 8.3 Hz, 1H), 5.10 – 5.05 (m, 2H), 4.76 – 4.68 (m, 2H), 4.30 – 4.25 (m, 1H), 4.14 – 4.08 (m, 1H), 2.73 – 2.69 (m, 1H), 2.57 (dd, *J* =  
25 16.1, 8.8 Hz, 1H), 2.34 (dd, *J* = 14.1, 5.6 Hz, 1H), 2.23 (dd, *J* = 14.1, 7.5 Hz, 1H), 1.37 (s, 9H), 1.03 (d, *J* = 6.6 Hz, 3H).

**Example 9 – Preparation of (S)-3-((tert-butoxycarbonyl)amino)-4-(((S)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)amino)-4-oxobutanoic acid (PKS2267)**



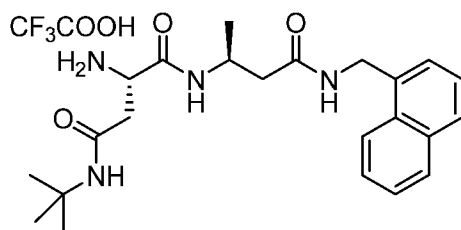
5 [0095] The title compound was synthesized by following the *O*-debenzylation protocol of PKS2265 (202 mg, 0.37 mmol). Product (168 mg, quant.) was isolated as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.44 – 8.41 (m, 1H), 8.06 – 8.04 (m, 1H), 7.95 – 7.94 (m, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.48 – 7.43 (m, 2H), 7.02 (d, *J* = 8.2 Hz, 1H), 4.75 (dd, *J* = 15.1, 5.7 Hz, 1H), 4.70 (dd, *J* = 15.1, 5.7 Hz, 1H), 4.21 – 4.16  
10 (m, 1H), 4.13 – 4.08 (m, 1H), 2.58 (dd, *J* = 16.4, 5.1 Hz, 1H), 2.43 (dd, *J* = 16.4, 8.5 Hz, 1H), 2.35 (dd, *J* = 14.1, 5.4 Hz, 1H), 2.23 (dd, *J* = 14.1, 7.7 Hz, 1H), 1.38 (s, 9H), 1.03 (d, *J* = 6.6 Hz, 3H).

15 **Example 10 – Preparation tert-butyl ((S)-4-(tert-butylamino)-1-(((S)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)amino)-1,4-dioxobutan-2-yl)carbamate (PKS2247, PKS2272)**



[0096] The title compound was synthesized following the general protocol of EDC mediated coupling of PKS2267 (168 mg, 0.367 mmol) and *tert*-butyl amine (58 μL, 0.551  
20 mmol). A white precipitate appeared which was filtered, washed with water and dried in air to give product (170 mg, 90%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.43 (t, *J* = 5.6 Hz, 1H), 8.06 – 8.04 (m, 1H), 7.95 – 7.94 (m, 1H), 7.86 – 7.81 (m, 2H), 7.57 – 7.52 (m, 2H), 7.48 – 7.43 (m, 2H), 7.34 (s, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 4.75 (dd, *J* = 15.1, 5.7 Hz, 1H), 4.70 (dd, *J* = 15.1, 5.5 Hz, 1H), 4.19 – 4.07 (m, 2H), 2.36 – 2.21 (m, 4H), 1.37 (s, 9H), 1.22 (s, 9H),  
25 1.03 (d, *J* = 6.6 Hz, 3H).

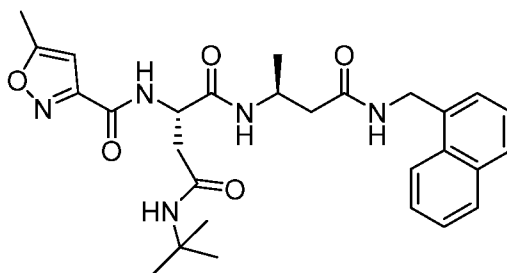
**Example 11 – Preparation of (S)-2-amino-N<sup>t</sup>-(tert-butyl)-N<sup>l</sup>-((S)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)succinamide 2,2,2-trifluoroacetate (PKS2248)**



5

[0097] The title compound was prepared by following the general protocol for Boc-Deprotection of PKS2272 (62 mg, 0.12 mmol). The crude was treated with diethyl ether and kept standing 3 hours. The white solid was filtered and dried to give product (60 mg, 95%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.47 (t, *J* = 5.6 Hz, 1H), 8.32 (d, *J* = 7.9 Hz, 1H), 8.06 – 8.03 (m, 4H), 7.96 – 7.95 (m, 1H), 7.87 – 7.85 (m, 1H), 7.80 (s, 1H), 7.57 – 7.53 (m, 2H), 7.49 – 7.43 (m, 2H), 4.78 (dd, *J* = 15.1, 5.8 Hz, 1H), 4.69 (dd, *J* = 15.1, 5.4 Hz, 1H), 4.21 – 4.13 (m, 1H), 3.95 (m, 1H), 2.60 (dd, *J* = 16.7, 4.6 Hz, 1H), 2.55 – 2.49 (m, 1H), 2.34 (dd, *J* = 14.1, 5.7 Hz, 1H), 2.26 (dd, *J* = 14.1, 8.0 Hz, 1H), 1.26 (s, 9H), 1.07 (d, *J* = 6.6 Hz, 3H).

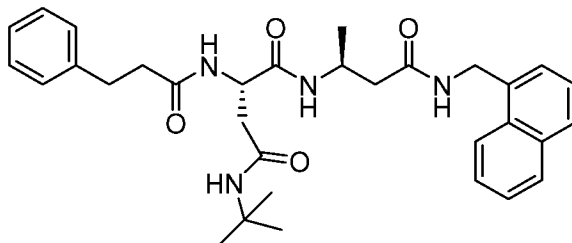
**Example 12 – Preparation of (S)-N<sup>t</sup>-(tert-butyl)-2-(5-methylisoxazole-3-carboxamido)-N<sup>l</sup>-((S)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)succinamide (PKS2249)**



[0098] The title compound was prepared by following the general protocol for HATU mediated coupling of 5-methylisoxazole-3-carboxylic acid (5.6 mg, 0.044 mmol) and PKS2248 (21.1 mg, 0.04 mmol). After completion of reaction, the mixture was purified by HPLC to give pure product (14.4 mg, 69%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.50 (d, *J* = 8.1 Hz, 1H), 8.41 (t, *J* = 5.7 Hz, 1H), 8.05 – 8.03 (m, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.95 – 7.93 (m, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.48 – 7.42 (m, 3H), 6.53 (s, 1H), 4.74 (dd, *J* = 15.1, 5.7 Hz, 1H), 4.68 (dd, *J* = 15.1, 5.5 Hz, 1H), 4.63 (td, *J* = 8.4, 4.8 Hz, 1H), 4.16 – 4.08 (m, 1H), 2.54 (dd, *J* = 14.3, 8.7 Hz, 1H), 2.45 (s, 3H), 2.41 (dd, *J* = 14.3, 4.8 Hz, 1H), 2.35 (dd, *J* = 14.0, 5.7 Hz, 1H), 2.25 (dd, *J* = 14.0, 7.7 Hz, 1H), 1.18 (s, 9H), 1.04 (d, *J* = 6.6 Hz, 3H). <sup>13</sup>C NMR (126 MHz, DMSO) δ 171.34, 169.90, 169.22, 168.86, 158.58, 158.24, 134.57, 133.32,

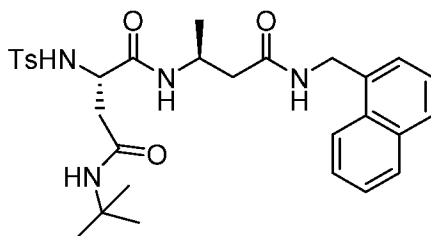
130.89, 128.53, 127.62, 126.25, 125.85, 125.62, 125.43, 123.52, 101.35, 50.51, 50.14, 42.57, 41.61, 40.19, 38.33, 28.38, 19.98, 11.86.

**Example 13 – Preparation of (S)-N<sup>t</sup>-(tert-butyl)-N<sup>1</sup>-((S)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)-2-(3-phenylpropanamido)succinamide (PKS2251)**



**[0099]** The title compound was prepared by following the general protocol for HATU mediated coupling of 3-phenylpropanoic acid (5.0 mg, 0.033 mmol) and PKS2248 (15.8 mg, 0.03 mmol). After completion of reaction, the mixture was purified by HPLC to give pure product (14.3 mg, 88%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.44 (t, *J* = 5.7 Hz, 1H), 8.06 – 8.04 (m, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.95 – 7.93 (m, 1H), 7.86 – 7.83 (m, 2H), 7.57 – 7.53 (m, 2H), 7.49 – 7.43 (m, 2H), 7.33 (s, 1H), 7.26 – 7.23 (m, 2H), 7.20 – 7.14 (m, 3H), 4.75 (dd, *J* = 15.1, 5.7 Hz, 1H), 4.71 (dd, *J* = 15.1, 5.6 Hz, 1H), 4.48 (td, *J* = 8.2, 5.6 Hz, 1H), 4.14 – 4.06 (m, 1H), 2.82 – 2.78 (m, 2H), 2.44 – 2.33 (m, 4H), 2.29 (dd, *J* = 14.6, 8.3 Hz, 1H), 2.23 (dd, *J* = 14.1, 7.8 Hz, 1H), 1.21 (s, 9H), 1.03 (d, *J* = 6.6 Hz, 3H). <sup>13</sup>C NMR (126 MHz, DMSO) δ 171.10, 169.97, 169.92, 168.75, 141.31, 134.56, 133.28, 130.86, 128.49, 128.25, 128.11, 127.57, 126.19, 125.82, 125.79, 125.56, 125.38, 123.48, 50.10, 50.02, 42.32, 41.50, 40.15, 38.73, 36.89, 31.00, 28.44, 19.87.

**Example 14 – Preparation of (S)-N<sup>t</sup>-(tert-butyl)-2-((4-methylphenyl)sulfonamido)-N<sup>1</sup>-((S)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)succinamide (PKS2252)**

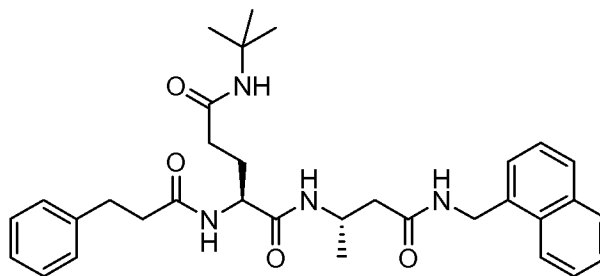


**[0100]** The title compound was prepared by following the general procedure for *N*-sulfonamide formation of PKS2248 (21.1 mg, 0.04 mmol) with tosyl chloride (11.5 mg, 0.06 mmol). The product was isolated as white solid (12.7 mg, 56%) after HPLC purification. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.38 (t, *J* = 5.7 Hz, 1H), 8.05 – 8.03 (m, 1H), 7.95 – 7.93 (m, 1H), 7.84 (d, *J* = 8.1 Hz, 1H),

- 53 -

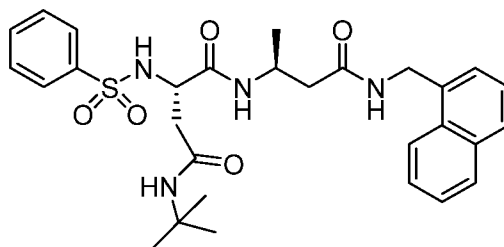
7.78 (d,  $J = 8.1$  Hz, 1H), 7.71 (bs, 1H), 7.65 (d,  $J = 8.2$  Hz, 2H), 7.56 – 7.52 (m, 2H), 7.48 – 7.41 (m, 2H), 7.32 – 7.29 (m, 3H), 4.73 (dd,  $J = 15.1, 5.7$  Hz, 1H), 4.68 (dd,  $J = 15.1, 5.6$  Hz, 1H), 4.01 (m, 1H), 3.94 – 3.85 (m, 1H), 2.33 (s, 3H), 2.29 – 2.15 (m, 3H), 2.11 (dd,  $J = 14.1, 8.2$  Hz, 1H), 1.18 (s, 9H), 0.83 (d,  $J = 6.6$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz, DMSO)  $\delta$  169.67, 168.87, 168.02, 142.36, 138.33, 134.59, 133.28, 130.86, 129.24, 128.48, 127.57, 126.63, 126.17, 125.79, 125.60, 125.37, 123.50, 53.60, 50.07, 42.18, 41.52, 40.13, 39.39, 28.40, 20.91, 19.43.

**Example 15 – Preparation of (S)-N<sup>5</sup>-(tert-butyl)-N<sup>1</sup>-((S)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)-2-(3-phenylpropanamido)pentanediamide (PKS2253)**



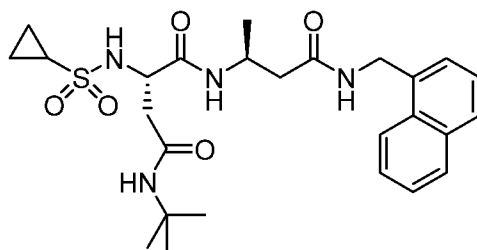
**[0101]** The title compound was synthesized by following the general protocol for HATU mediated coupling of PhCH<sub>2</sub>CH<sub>2</sub>C(O)-Glu(NHtBu)-OH (18.4 mg, 0.055 mmol) and H- $\beta$ -homo-Ala-CH<sub>2</sub>-naphth TFA salt (17.8 mg, 0.05 mmol). Purification by HPLC provided the product (23.5 mg, 84%) as a white solid.  $^1\text{H}$  NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.45 (t,  $J = 5.7$  Hz, 1H), 8.07 – 8.05 (m, 1H), 8.00 – 7.93 (m, 2H), 7.89 (d,  $J = 8.1$  Hz, 1H), 7.85 – 7.83 (m, 1H), 7.57 – 7.51 (m, 2H), 7.48 – 7.43 (m, 2H), 7.34 (s, 1H), 7.27 – 7.23 (m, 2H), 7.21 – 7.14 (m, 3H), 4.77 (dd,  $J = 15.1, 5.7$  Hz, 1H), 4.70 (dd,  $J = 15.1, 5.6$  Hz, 1H), 4.18 – 4.13 (m, 2H), 2.81 (t,  $J = 7.9$  Hz, 2H), 2.46 – 2.42 (m, 2H), 2.38 (dd,  $J = 14.0, 5.6$  Hz, 1H), 2.24 (dd,  $J = 14.0, 7.8$  Hz, 1H), 1.99 (t,  $J = 8.1$  Hz, 2H), 1.82 – 1.75 (m, 1H), 1.70 – 1.62 (m, 1H), 1.21 (s, 9H), 1.05 (d,  $J = 6.6$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz, DMSO)  $\delta$  171.24, 171.08, 170.30, 169.92, 141.35, 134.54, 133.28, 130.85, 128.48, 128.22, 128.16, 127.56, 126.19, 125.80, 125.52, 125.39, 123.49, 52.30, 49.80, 42.27, 41.82, 40.14, 36.78, 32.57, 31.06, 28.54, 28.51, 20.12.

**Example 16 – Preparation of (S)-N<sup>4</sup>-(tert-butyl)-N<sup>1</sup>-((S)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)-2-(phenylsulfonamido)succinamide (PKS2260)**



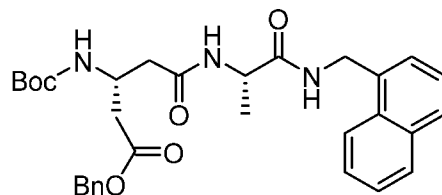
[0102] The title compound was prepared by following the general procedure for *N*-sulfonamide formation of PKS2248 (12.1 mg, 0.023 mmol) with phenylsulfonyl chloride (4  $\mu$ L, 0.028 mmol). The product was isolated as a white solid (10.0 mg, 79%) after HPLC purification.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-}d_6$ )  $\delta$  8.37 (t,  $J = 5.7$  Hz, 1H), 8.04 – 8.02 (m, 1H), 7.95 – 7.93 (m, 1H), 7.85 – 7.81 (m, 3H), 7.77 (d,  $J = 7.6$  Hz, 2H), 7.60 – 7.41 (m, 7H), 7.32 (s, 1H), 4.73 (dd,  $J = 15.1, 5.8$  Hz, 1H), 4.68 (dd,  $J = 15.1, 5.5$  Hz, 1H), 4.07 – 4.03 (m, 1H), 3.92 – 3.86 (m, 1H), 2.28 – 2.17 (m, 3H), 2.12 (dd,  $J = 14.1, 8.3$  Hz, 1H), 1.18 (s, 9H), 0.83 (d,  $J = 6.6$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{DMSO-}d_6$ )  $\delta$  169.67, 168.85, 167.98, 141.25, 134.59, 133.28, 132.17, 130.86, 128.80, 128.48, 127.57, 126.54, 126.19, 125.80, 125.60, 125.38, 123.50, 53.62, 50.07, 42.16, 41.55, 40.13, 39.69, 28.42, 19.49.

**Example 17 – Preparation of (*S*)-*N*<sup>t</sup>-(*tert*-butyl)-2-(cyclopropanesulfonamido)-*N*<sup>t</sup>-((*S*)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)succinamide (PKS2295)**



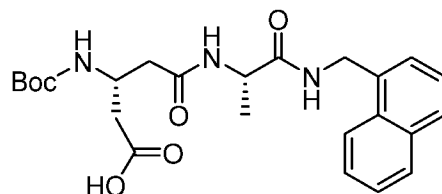
[0103] The title compound was prepared by following the general procedure for *N*-sulfonamide formation of PKS2248 (21.1 mg, 0.04 mmol) with cyclopropylsulfonyl chloride (6  $\mu$ L, 0.06 mmol). The product was isolated as a white solid (16.3 mg, 79%) after HPLC purification.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-}d_6$ )  $\delta$  8.42 (t,  $J = 5.6$  Hz, 1H), 8.06 – 8.04 (m, 1H), 7.97 – 7.94 (m, 2H), 7.85 (d,  $J = 7.9$  Hz, 1H), 7.57 – 7.52 (m, 2H), 7.48 – 7.43 (m, 2H), 7.40 (s, 1H), 7.26 (d,  $J = 9.1$  Hz, 1H), 4.75 (dd,  $J = 15.1, 5.7$  Hz, 1H), 4.70 (dd,  $J = 15.1, 5.5$  Hz, 1H), 4.17 – 4.06 (m, 2H), 2.50 – 2.46 (m, 1H), 2.41 – 2.32 (m, 3H), 2.25 (dd,  $J = 14.1, 8.0$  Hz, 1H), 1.23 (s, 9H), 1.04 (d,  $J = 6.6$  Hz, 3H), 0.90 – 0.82 (m, 4H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{DMSO-}d_6$ )  $\delta$  169.93, 169.75, 168.37, 134.57, 133.28, 130.87, 128.48, 127.58, 126.19, 125.80, 125.62, 125.38, 123.51, 53.71, 50.12, 42.41, 41.59, 40.15, 39.82, 30.28, 28.45, 19.80, 5.13, 4.84.

**Example 18 – Preparation of benzyl (*R*)-3-((*tert*-butoxycarbonyl)amino)-5-(((*S*)-1-((naphthalen-1-ylmethyl)amino)-1-oxopropan-2-yl)amino)-5-oxopentanoate (PKS2266)**



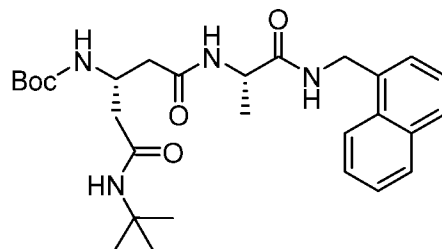
**[0104]** The title compound was synthesized by following the general protocol for HATU mediated coupling of *N*-Boc-*L*-β-glutamic acid 5-benzyl ester (84 mg, 0.25 mmol) and H-Ala-CH<sub>2</sub>-naphth TFA salt (94 mg, 0.275 mmol). After completion of reaction, water was added to reaction mixture to give white precipitate. Precipitate was filtered, washed with water and dried in air to give product (115 mg, 84%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.40 (t, *J* = 5.6 Hz, 1H), 8.11 (d, *J* = 7.4 Hz, 1H), 8.04 – 8.02 (m, 1H), 7.95 – 7.93 (m, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.47 – 7.41 (m, 2H), 7.37 – 7.30 (m, 5H), 6.82 (d, *J* = 8.3 Hz, 1H), 5.05 (s, 2H), 4.77 – 4.69 (m, 2H), 4.33 – 4.28 (m, 1H), 4.22 – 4.13 (m, 1H), 2.55 (dd, *J* = 15.0, 5.0 Hz, 1H), 2.49 – 2.44 (m, 1H), 2.38 (dd, *J* = 14.6, 6.3 Hz, 1H), 2.32 (dd, *J* = 14.6, 7.5 Hz, 1H), 1.34 (s, 9H), 1.21 (d, *J* = 7.1 Hz, 3H).

**15 Example 19 – Preparation of (*R*)-3-((*tert*-butoxycarbonyl)amino)-5-(((*S*)-1-((naphthalen-1-ylmethyl)amino)-1-oxopropan-2-yl)amino)-5-oxopentanoic acid (PKS2268)**



**[0105]** The title compound was synthesized by following the *O*-debenzylation protocol of PKS2266 (110 mg, 0.2 mmol). Product (92 mg, quant.) was isolated as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.49 (t, *J* = 5.8 Hz, 1H), 8.16 (d, *J* = 7.4 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 7.3 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.48 – 7.42 (m, 2H), 6.74 (d, *J* = 8.2 Hz, 1H), 4.74 – 4.71 (m, 2H), 4.33 – 4.28 (m, 1H), 4.11 – 4.04 (m, 1H), 2.41 – 2.29 (m, 4H), 1.35 (s, 9H), 1.23 (d, *J* = 7.1 Hz, 3H).

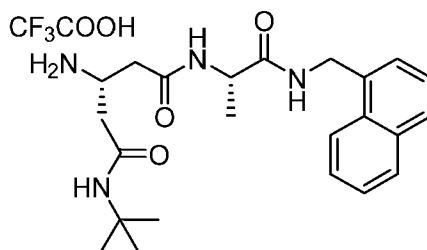
**Example 20 – Preparation of *tert*-butyl ((*R*)-1-(*tert*-butylamino)-5-(((*S*)-1-((naphthalen-1-ylmethyl)amino)-1-oxopropan-2-yl)amino)-1,5-dioxopentan-3-yl)carbamate (PKS2271)**



**[0106]** The title compound was prepared by following the general protocol for EDC mediated coupling of PKS2268 (92 mg, 0.2 mmol) and *tert*-butylamine (31.5  $\mu$ L, 0.3 mmol). After completion of reaction, water was added to reaction mixture to give white precipitate. Precipitate was filtered, washed with water and dried in air to give product (85 mg, 83%) as a white solid.  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  8.44 (t,  $J = 5.9$  Hz, 1H), 8.05 – 8.03 (m, 2H), 7.95 – 7.93 (m, 1H), 7.84 (d,  $J = 7.7$  Hz, 1H), 7.56 – 7.53 (m, 2H), 7.48 – 7.43 (m, 2H), 7.34 (s, 1H), 6.56 (d,  $J = 8.4$  Hz, 1H), 4.78 – 4.69 (m, 2H), 4.34 – 4.28 (m, 1H), 4.10 – 4.00 (m, 1H), 2.36 – 2.12 (m, 4H), 1.35 (s, 9H), 1.23 – 1.22 (m, 12H).

**Example 21 – Preparation of (*R*)-3-amino-*N*<sup>1</sup>-(*tert*-butyl)-*N*<sup>5</sup>-(((*S*)-1-((naphthalen-1-ylmethyl)amino)-1-oxopropan-2-yl)pentanediamide 2,2,2-trifluoroacetate (PKS2273)**

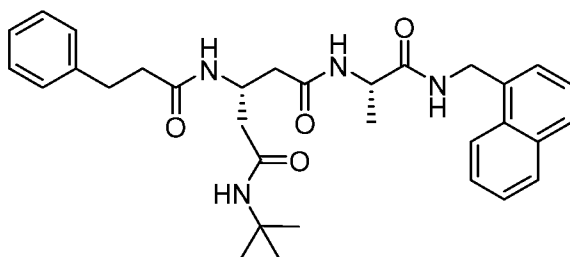
15



**[0107]** The title compound was synthesized by following the general protocol for Boc-deprotection of PKS2271 (80 mg, 0.156 mmol).  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  8.54 (t,  $J = 5.7$  Hz, 1H), 8.46 (d,  $J = 7.3$  Hz, 1H), 8.05 – 8.03 (m, 1H), 7.96 – 7.94 (m, 1H), 7.89 – 7.82 (m, 5H), 7.56 – 7.54 (m, 2H), 7.49 – 7.43 (m, 2H), 4.78 (dd,  $J = 15.4, 5.9$  Hz, 1H), 4.70 (dd,  $J = 15.4, 5.5$  Hz, 1H), 4.39 – 4.33 (m, 1H), 3.67 – 3.61 (m, 1H), 2.53 – 2.49 (m, 2H), 2.42 (dd,  $J = 15.9, 5.8$  Hz, 1H), 2.36 (dd,  $J = 15.9, 7.2$  Hz, 1H), 1.26 – 1.24 (m, 12H).

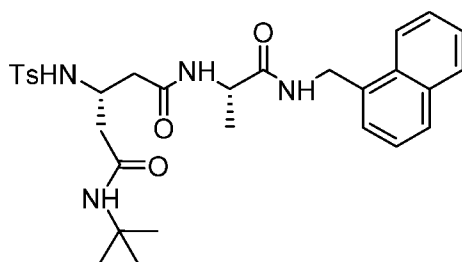
20

**Example 22 – Preparation of (*R*)-*N*<sup>1</sup>-(*tert*-butyl)-*N*<sup>5</sup>-((*S*)-1-((naphthalen-1-ylmethyl)amino)-1-oxopropan-2-yl)-3-(3-phenylpropanamido)pentanediamide (PKS2278)**



[0108] The title compound was synthesized by following the general protocol for HATU mediated coupling of 3-phenylpropanoic acid (6.6 mg, 0.044 mmol) and PKS2273 (21.1 mg, 0.04 mmol). After completion of reaction, mixture was purified by HPLC to give pure product (20.7 mg, 95%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.44 – 8.42 (m, 1H), 8.07 (d, *J* = 7.3 Hz, 1H), 8.02 – 8.00 (m, 1H), 7.95 – 7.93 (m, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.54 – 7.52 (m, 2H), 7.45 – 7.39 (m, 2H), 7.37 (s, 1H), 7.24 – 7.21 (m, 2H), 7.16 – 7.13 (m, 3H), 4.71 (d, *J* = 5.7 Hz, 2H), 4.33 – 4.29 (m, 2H), 2.76 – 2.73 (m, 2H), 2.37 – 2.16 (m, 6H), 1.24 – 1.22 (m, 12H). <sup>13</sup>C NMR (126 MHz, DMSO) δ 172.36, 170.51, 169.71, 169.42, 141.31, 134.41, 133.21, 130.74, 128.46, 128.23, 128.07, 127.39, 126.12, 125.79, 125.73, 125.37, 124.90, 123.32, 49.96, 48.42, 44.21, 40.73, 40.11, 39.75, 37.21, 31.14, 28.45, 18.27.

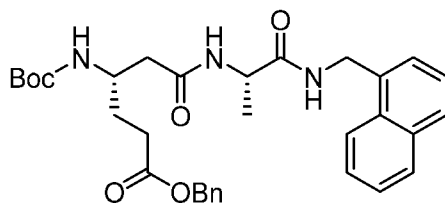
**Example 23 – Preparation of (*R*)-*N*<sup>1</sup>-(*tert*-butyl)-3-(4-methylphenylsulfonamido)-*N*<sup>5</sup>-((*S*)-1-((naphthalen-1-ylmethyl)amino)-1-oxopropan-2-yl)pentanediamide (PKS2279)**



[0109] The title compound was prepared by following the general procedure for *N*-sulfonamide formation of PKS2273 (21.1 mg, 0.04 mmol) with tosyl chloride (11.4 mg, 0.06 mmol). The product was isolated as a white solid (17.8 mg, 78%) after HPLC purification. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.42 (t, *J* = 5.8 Hz, 1H), 8.08 – 8.03 (m, 2H), 7.95 – 7.94 (m, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.55 – 7.53 (m, 2H), 7.48 – 7.42 (m, 3H), 7.39 (s, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 4.78 – 4.70 (m, 2H), 4.28 – 4.23 (m, 1H), 3.81 – 3.74 (m, 1H), 2.35 (s, 3H), 2.29 – 2.20 (m, 2H), 2.13 (d, *J* = 6.6 Hz, 2H), 1.20 – 1.18 (m, 12H). <sup>13</sup>C NMR (126 MHz, DMSO) δ 172.19, 169.22, 168.94, 142.43, 138.54, 134.41, 133.24, 130.77, 129.45,

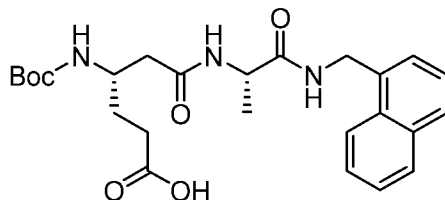
128.48, 127.46, 126.50, 126.14, 125.77, 125.38, 125.07, 123.37, 50.05, 48.51, 48.30, 40.71, 40.13, 39.95, 28.39, 20.94, 18.26.

**Example 24 – Preparation of (S)-benzyl 4-((tert-butoxycarbonyl)amino)-6-(((S)-1-((naphthalen-1-ylmethyl)amino)-1-oxopropan-2-yl)amino)-6-oxohexanoate (PKS2274)**



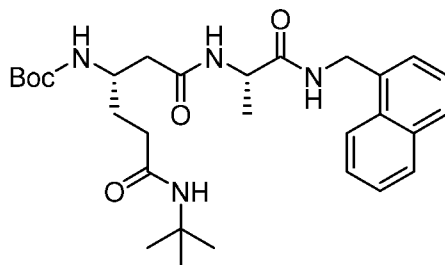
**[0110]** The title compound was synthesized by following the general protocol for HATU mediated coupling of (S)-3-(Boc-amino)adipic acid 6-benzyl ester (23.7 mg, 0.0675 mmol) and H-Ala-CH<sub>2</sub>-naphth TFA salt (23.1 mg, 0.0675 mmol). After completion of reaction, mixture was purified by HPLC to give product (23.0 mg, 61%) as a white solid. <sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 8.3 Hz, 1H), 7.86 – 7.84 (m, 1H), 7.78 (dd, *J* = 7.3, 2.1 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.42 – 7.38 (m, 2H), 7.36 – 7.28 (m, 5H), 6.66 – 6.64 (m, 1H), 6.24 (d, *J* = 7.2 Hz, 1H), 5.13 (d, *J* = 8.9 Hz, 1H), 5.05 – 5.00 (m, 2H), 4.91 (dd, *J* = 14.6, 5.6 Hz, 1H), 4.84 (dd, *J* = 14.6, 5.3 Hz, 1H), 4.45 – 4.39 (m, 1H), 3.75 – 3.70 (m, 1H), 2.37 – 2.23 (m, 4H), 1.73 – 1.61 (m, 2H), 1.39 (s, 9H), 1.37 (d, *J* = 7.0 Hz, 3H).

**Example 25 – Preparation of (S)-4-((tert-butoxycarbonyl)amino)-6-(((S)-1-((naphthalen-1-ylmethyl)amino)-1-oxopropan-2-yl)amino)-6-oxohexanoic acid (PKS2277)**



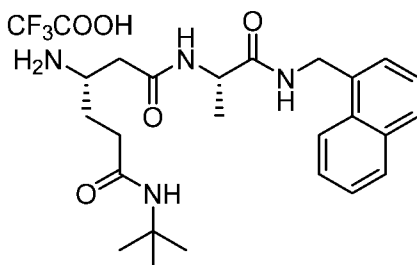
**[0111]** The title compound was synthesized by following the *O*-debenzylation protocol of PKS2274 (23 mg, 0.04 mmol). The crude was purified by HPLC to give product (17.5 mg, 91%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.44 (t, *J* = 5.8 Hz, 1H), 8.13 – 8.11 (m, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.95 – 7.93 (m, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.48 – 7.42 (m, 2H), 6.71 (d, *J* = 8.8 Hz, 1H), 4.72 – 4.71 (m, 2H), 4.33 – 4.31 (m, 1H), 3.75 (m, 1H), 2.32 – 2.14 (m, 4H), 1.70 – 1.65 (m, 1H), 1.57 – 1.51 (m, 1H), 1.36 (s, 9H), 1.22 (d, *J* = 7.2 Hz, 3H).

**Example 26 – Preparation of *tert*-butyl ((*S*)-6-(*tert*-butylamino)-1-(((*S*)-1-(naphthalen-1-ylmethyl)amino)-1-oxopropan-2-yl)amino)-1,6-dioxohexan-3-yl)carbamate (PKS2282)**



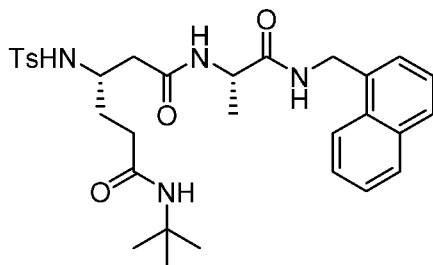
**[0112]** Title compound was prepared by following the general protocol for EDC mediated coupling of PKS2277 (17.5 mg, 0.037 mmol) and *tert*-butylamine (6.0  $\mu$ L, 0.056 mmol). After completion of reaction, mixture was purified by HPLC to give product (6.8 mg, 35%) as a white solid.  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  8.42 (t,  $J = 5.8$  Hz, 1H), 8.07 – 8.03 (m, 2H), 7.95 – 7.93 (m, 1H), 7.84 (d,  $J = 7.9$  Hz, 1H), 7.56 – 7.53 (m, 2H), 7.48 – 7.42 (m, 2H), 7.33 (s, 1H), 6.61 (d,  $J = 8.7$  Hz, 1H), 4.78 – 4.69 (m, 2H), 4.35 – 4.29 (m, 1H), 3.75 – 3.68 (m, 1H), 2.31 – 2.22 (m, 2H), 2.02 – 1.97 (m, 2H), 1.62 – 1.57 (m, 1H), 1.53 – 1.48 (m, 1H), 1.36 (s, 9H), 1.23 – 1.21 (m, 12H).

**Example 27 – Preparation of (*S*)-3-amino-*N*<sup>6</sup>-(*tert*-butyl)-*N*<sup>1</sup>-((*S*)-1-(naphthalen-1-ylmethyl)amino)-1-oxopropan-2-yl)hexanediamide 2,2,2-trifluoroacetate (PKS2289)**



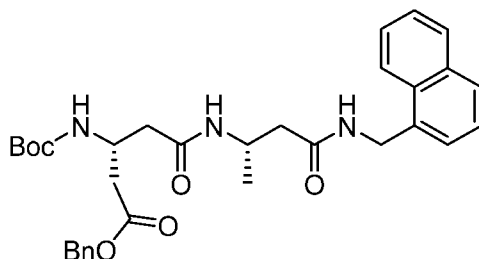
**[0113]** The title compound was synthesized by following the general protocol for Boc-deprotection of PKS2282 (6.8 mg, 0.013 mmol). The product was used in next step without further purification.  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  8.24 (s, 3H), 8.10 (m, 1H), 7.88 – 7.80 (m, 3H), 7.55 – 7.49 (m, 2H), 7.42 – 7.40 (m, 2H), 6.82 (m, 1H), 5.98 (s, 1H), 5.00 – 4.95 (m, 1H), 4.76 – 4.72 (m, 1H), 4.37 (m, 1H), 3.55 (m, 1H), 2.75 – 2.72 (m, 1H), 2.61 – 2.57 (m, 1H), 2.40 (t,  $J = 5.4$  Hz, 2H), 1.93 (m, 1H), 1.80 (m, 1H), 1.39 – 1.38 (m, 3H), 1.32 (s, 9H).

**Example 28 – Preparation of (S)-N<sup>6</sup>-(tert-butyl)-3-(4-methylphenylsulfonamido)-N<sup>1</sup>-((S)-1-((naphthalen-1-ylmethyl)amino)-1-oxopropan-2-yl)hexanediamide (PKS2290)**



**[0114]** The title compound was prepared by following the general procedure for N-sulfonamide formation of PKS2289 (crude from previous step, 0.013 mmol) with tosyl chloride (5.0 mg, 0.026 mmol). The product was isolated as a white solid (6.0 mg, 79% for 2 steps) after HPLC purification. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.41 (t, *J* = 5.8 Hz, 1H), 8.10 (d, *J* = 7.5 Hz, 1H), 8.03 – 8.01 (m, 1H), 7.96 -7.94 (m, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.55 – 7.52 (m, 2H), 7.47 – 7.40 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.31 (s, 1H), 4.74 (dd, *J* = 15.4, 5.8 Hz, 1H), 4.70 (dd, *J* = 15.4, 5.7 Hz, 1H), 4.28 – 4.22 (m, 1H), 3.45 – 3.39 (m, 1H), 2.36 (s, 3H), 2.20 – 2.00 (m, 3H), 1.94 – 1.88 (m, 1H), 1.57 – 1.50 (m, 1H), 1.47 – 1.39 (m, 1H), 1.20 (s, 9H), 1.18 (d, *J* = 7.4 Hz, 4H). <sup>13</sup>C NMR (126 MHz, DMSO) δ 172.13, 171.40, 169.29, 142.40, 138.78, 134.41, 133.23, 130.76, 129.54, 128.47, 127.44, 126.37, 126.12, 125.76, 125.37, 124.98, 123.35, 50.76, 49.80, 48.19, 40.72, 40.13, 32.47, 30.27, 28.47, 20.96, 18.27.

**Example 29 – Preparation of (R)-benzyl 3-((tert-butoxycarbonyl)amino)-5-(((S)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)amino)-5-oxopentanoate (PKS2281)**

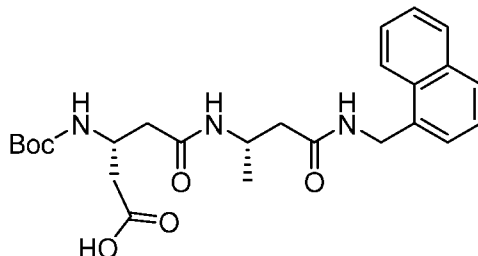


**[0115]** The title compound was synthesized by following the general protocol for HATU mediated coupling of N-Boc-L-beta-glutamic acid 5-benzyl ester (47 mg, 0.14 mmol) and H-homo-β-Ala-CH<sub>2</sub>-naphth TFA salt (50 mg, 0.14 mmol). The reaction mixture was purified by HPLC to give product (73 mg, 93%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.39 (t, *J* = 5.5 Hz, 1H), 8.06 – 8.04 (m, 1H), 7.95 – 7.93 (m, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.48 – 7.42 (m, 2H), 7.37 – 7.30 (m, 5H), 6.79 (d, *J* = 8.5 Hz,

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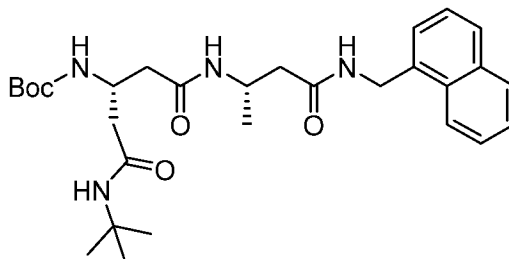
1H), 5.05 (s, 2H), 4.76 – 4.68 (m, 2H), 4.16 – 4.09 (m, 2H), 2.55 – 2.43 (m, 2H), 2.36 (dd,  $J = 14.0, 5.7$  Hz, 1H), 2.26 – 2.17 (m, 3H), 1.35 (s, 9H), 1.02 (d,  $J = 6.0$  Hz, 3H).

**Example 30 – Preparation of (*R*)-3-((*tert*-butoxycarbonyl)amino)-5-(((*S*)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)amino)-5-oxopentanoic acid (PKS2285)**



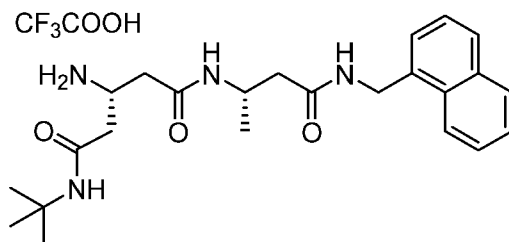
**[0116]** The title compound was synthesized by following the *O*-debenzylation protocol of PKS2281 (73 mg, 0.13 mmol). Yield 61.0 mg (quant.).  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  12.12 (s, 1H), 8.39 (t,  $J = 5.6$  Hz, 1H), 8.06 – 8.04 (m, 1H), 7.95 – 7.93 (m, 1H), 7.85 (d,  $J = 8.0$  Hz, 1H), 7.79 (d,  $J = 8.0$  Hz, 1H), 7.56 – 7.52 (m, 2H), 7.48 – 7.42 (m, 2H), 6.69 (d,  $J = 8.4$  Hz, 1H), 4.77 – 4.68 (m, 2H), 4.15 – 4.01 (m, 2H), 2.38 – 2.34 (m, 3H), 2.26 – 2.16 (m, 3H), 1.36 (s, 9H), 1.02 (d,  $J = 6.6$  Hz, 3H).

**Example 31 – Preparation of *tert*-butyl ((*R*)-1-(*tert*-butylamino)-5-(((*S*)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)amino)-1,5-dioxopentan-3-yl)carbamate (PKS2286)**



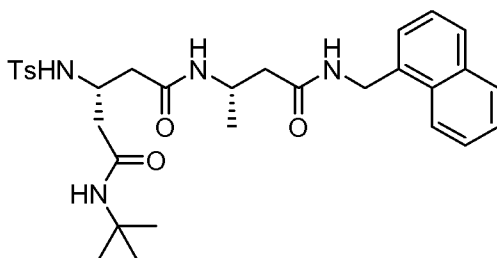
**[0117]** The title compound was prepared by following the general protocol for EDC mediated coupling of PKS2285 (61.0 mg, 0.13 mmol) and *tert*-butylamine (20.0  $\mu\text{L}$ , 0.195 mmol). After completion of reaction, mixture was purified by HPLC to give product (13.0 mg, 19%) as a white solid.  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  8.41 (t,  $J = 5.6$  Hz, 1H), 8.06 – 8.04 (m, 1H), 7.95 – 7.93 (m, 1H), 7.84 (d,  $J = 7.7$  Hz, 1H), 7.72 (d,  $J = 8.1$  Hz, 1H), 7.56- 7.51 (m, 2H), 7.48 – 7.43 (m, 2H), 7.31 (s, 1H), 6.50 (d,  $J = 8.7$  Hz, 1H), 4.77 – 4.68 (m, 2H), 4.18 – 4.10 (m, 1H), 4.06 – 3.98 (m, 1H), 2.36 (dd,  $J = 13.9, 5.6$  Hz, 1H), 2.22 – 2.14 (m, 5H), 1.36 (s, 9H), 1.22 (s, 9H), 1.02 (d,  $J = 6.5$  Hz, 3H).

**Example 32 – Preparation of (*R*)-3-amino-*N*<sup>1</sup>-(*tert*-butyl)-*N*<sup>5</sup>-((*S*)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)pentanediamide 2,2,2-trifluoroacetate (PKS2288)**



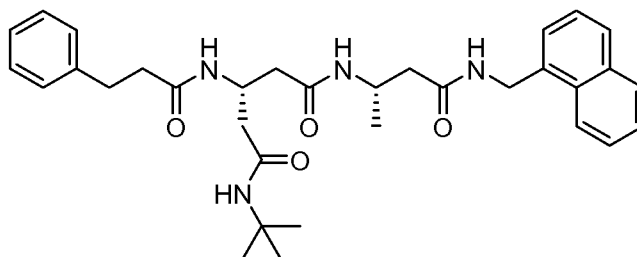
**[0118]** The title compound was synthesized by following the general protocol for Boc-deprotection of PKS2286 (13.0 mg, 0.025 mmol). Yield 13.5 mg (quant.). <sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 8.65 (bs, 3H), 8.47 (d, *J* = 7.9 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.82 – 7.78 (m, 1H), 7.57 – 7.49 (m, 2H), 7.43 – 7.40 (m, 2H), 6.52 (t, *J* = 5.3 Hz, 1H), 5.98 (s, 1H), 4.81 – 4.74 (m, 2H), 4.35 – 4.30 (m, 1H), 3.86 (m, 1H), 2.73 – 2.68 (m, 1H), 2.64 – 2.58 (m, 1H), 2.46 – 2.36 (m, 3H), 2.30 (dd, *J* = 14.2, 8.9 Hz, 1H), 1.32 (s, 9H), 1.18 (d, *J* = 6.6 Hz, 3H).

**Example 33 – Preparation of (*R*)-*N*<sup>1</sup>-(*tert*-butyl)-3-(4-methylphenylsulfonamido)-*N*<sup>5</sup>-((*S*)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)pentanediamide (PKS2291)**



**[0119]** The title compound was prepared by following the general procedure for N-sulfonamide formation of PKS2288 (6.5 mg, 0.012 mmol) with tosyl chloride (4.6 mg, 0.024 mmol). The product was isolated as a white solid (5.2 mg, 74%) after HPLC purification. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.40 (t, *J* = 5.6 Hz, 1H), 8.06 – 8.04 (m, 1H), 7.96 – 7.94 (m, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.67 – 7.66 (m, 2H), 7.55 – 7.52 (m, 2H), 7.47- 7.42 (m, 3H), 7.37 – 7.33 (m, 3H), 4.74 (dd, *J* = 15.2, 5.6 Hz, 1H), 4.70 (dd, *J* = 15.2, 5.6 Hz, 1H), 4.11 – 4.05 (m, 1H), 3.80 – 3.73 (m, 1H), 2.34 (s, 3H), 2.31 (dd, *J* = 13.9, 5.5 Hz, 1H), 2.18 – 2.08 (m, 5H), 1.18 (s, 9H), 0.98 (d, *J* = 6.6 Hz, 3H). <sup>13</sup>C NMR (126 MHz, DMSO) δ <sup>13</sup>C NMR (126 MHz, DMSO) δ 169.78, 168.94, 168.36, 142.43, 138.65, 134.60, 133.28, 130.86, 129.47, 128.48, 127.56, 126.49, 126.17, 125.80, 125.56, 125.36, 123.52, 50.02, 48.52, 42.19, 41.93, 40.54, 40.13, 40.09, 28.42, 20.93, 19.98.

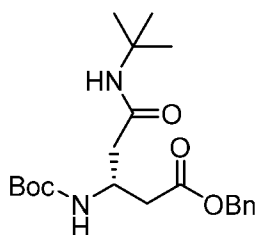
**Example 34 – Preparation of (*R*)-*N*<sup>1</sup>-(*tert*-butyl)-*N*<sup>5</sup>-((*S*)-4-((naphthalen-1-ylmethyl)amino)-4-oxobutan-2-yl)-3-(3-phenylpropanamido)pentanediamide (PKS2292)**



[0120] The title compound was synthesized by following the general protocol for HATU mediated coupling of 3-phenylpropanoic acid (2.0 mg, 0.012) and PKS2288 (6.5 mg, 0.012 mmol). The reaction mixture was purified by HPLC to give product (6.0 mg, 90%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.40 (t, *J* = 5.6 Hz, 1H), 8.06 – 8.04 (m, 1H), 7.95 – 7.93 (m, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.48 – 7.42 (m, 2H), 7.33 (s, 1H), 7.26 – 7.23 (m, 2H), 7.18 – 7.14 (m, 3H), 4.76 – 4.68 (m, 2H), 4.31 – 4.24 (m, 1H), 4.19 – 4.10 (m, 1H), 2.78 (t, *J* = 7.9 Hz, 2H), 2.38 – 2.30 (m, 3H), 2.23 – 2.17 (m, 5H), 1.22 (s, 9H), 1.02 (d, *J* = 6.6 Hz, 3H). <sup>13</sup>C NMR (126 MHz, DMSO) δ 170.46, 169.84, 169.42, 168.78, 141.31, 134.61, 133.27, 130.87, 128.47, 128.25, 128.09, 127.56, 126.18, 125.82, 125.79, 125.57, 125.37, 123.51, 49.94, 44.22, 42.16, 42.04, 40.59, 40.13, 40.06, 37.22, 31.19, 28.48, 20.06.

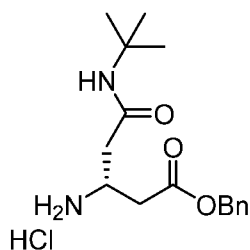
15

**Example 35 – Preparation of PKS3024**

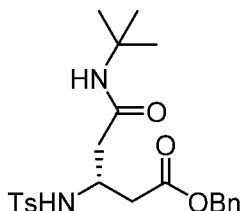


[0121] The title compound was prepared following the general procedure for EDC mediated coupling of *N*-Boc-L-β-glutamic acid 5-benzyl ester (168 mg, 0.5 mmol) and *tert*-butylamine (80 μL, 0.75 mmol). After completion of reaction, water was added to the mixture and extracted twice with ethyl acetate. The organic layer was washed with 1N HCl, water, aq. NaHCO<sub>3</sub>, water, and brine. The organic layer was dried over anhydrous sodium sulfate and evaporated and dried to give product (196 mg, quat.). Product was used in next step without any further purification. <sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 7.38 – 7.30 (m, 5H), 5.72 (bs, 1H), 5.59 (bs, 1H), 5.12 (s, 2H), 4.24 – 4.15 (m, 1H), 2.79 (dd, *J* = 16.3, 5.2 Hz, 1H), 2.58 (dd, *J* = 15.7, 7.5 Hz, 1H), 2.44 – 2.34 (m, 2H), 1.41 (s, 9H), 1.30 (s, 9H).

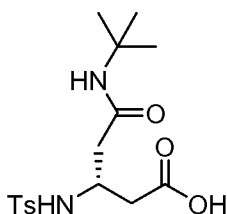
25

**Example 36 – Preparation of PKS3028**

[0122] PKS3024 (196 mg, 0.5 mmol) was dissolved in 5 mL 4N HCl (in dioxane) and mixture was stirred at room temperature for 1 hour. After completion of reaction, dioxane was evaporated and the mixture was diluted with water. The solution was washed with diethyl ether. Aqueous layer was frozen and lyophilized to give product (143 mg, 87%). Complex NMR due to 73:27 rotamers. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.35 – 8.26 (m, 2.1H), 8.17 (s, 0.9H), 7.87 (s, 1H), 7.48 – 7.26 (m, 4H), 5.12 (s, 2H), 3.75 – 3.66 (m, 0.73H), 3.66 – 3.56 (m, 0.27H), 2.83 (dd, *J* = 16.7, 6.6 Hz, 0.73H), 2.75 – 2.65 (m, 1.27H), 2.60 – 2.52 (m, 2H), 1.24 (d, *J* = 4.5 Hz, 9H).

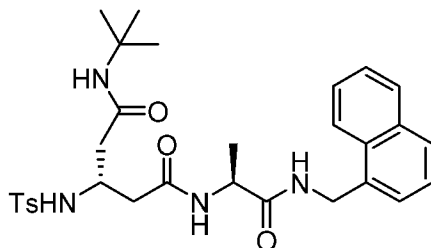
**Example 37 – Preparation of PKS3034**

[0123] The title compound was prepared by following the general procedure for *N*-sulfonamide formation of PKS3028 (72.3 mg, 0.22 mmol) with tosyl chloride (63 mg, 0.33 mmol). The product was isolated by dichloromethane extraction and purified by column chromatography to give product as a white solid (50.1 mg, 51%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 7.73 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 2H), 7.44 (s, 1H), 7.41 – 7.29 (m, 7H), 4.98 (d, *J* = 12.6 Hz, 1H), 4.90 (d, *J* = 12.6 Hz, 1H), 3.88 (dtd, *J* = 13.5, 8.0, 5.3 Hz, 1H), 2.46 (dd, *J* = 15.4, 5.4 Hz, 1H), 2.40 – 2.32 (m, 4H), 2.18 (dd, *J* = 14.6, 8.2 Hz, 1H), 2.12 (dd, *J* = 14.6, 5.4 Hz, 1H), 1.17 (s, 9H).

**Example 38 – Preparation of PKS3041**

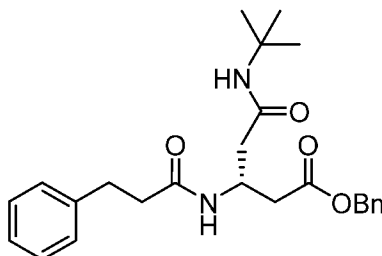
[0124] The title compound was synthesized by following the general protocol for *O*-debenzylation of PKS3034 (14.3 mg, 0.032 mmol). Filtrate was evaporated and dried under vacuum to give product (11.4 mg, quant.). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 7.66 (d, *J* = 7.9 Hz, 2H), 7.42 (s, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 3.75 – 3.66 (m, 1H), 2.37 (s, 3H), 2.20 – 2.11 (m, 4H), 1.18 (s, 9H).

### Example 39 – Preparation of PKS3044



[0125] The title compound was prepared following the general procedure for HATU mediated coupling of PKS3041 (11.4 mg, 0.032 mmol) and H-Ala-CH<sub>2</sub>-naphth TFA salt (13.1 mg, 0.038 mmol). Purification by HPLC gave product (8.0 mg, 44%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.45 (t, *J* = 5.8 Hz, 1H), 8.05 – 8.00 (m, 2H), 7.96 – 7.92 (m, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.55 – 7.50 (m, 2H), 7.47 – 7.40 (m, 3H), 7.39 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.74 (dd, *J* = 15.5, 5.7 Hz, 1H), 4.70 (dd, *J* = 15.5, 5.6 Hz, 1H), 4.28 – 4.18 (m, 1H), 3.86 – 3.76 (m, 1H), 2.37 (s, 3H), 2.22 (d, *J* = 6.8 Hz, 2H), 2.15 – 2.05 (m, 2H), 1.22 – 1.15 (m, 12H). <sup>13</sup>C NMR (126 MHz, DMSO) δ 172.35, 169.18, 168.95, 142.42, 138.82, 134.39, 133.23, 130.76, 129.48, 128.47, 127.44, 126.44, 126.13, 125.76, 125.38, 125.01, 123.36, 50.08, 48.60, 48.35, 40.75, 40.15, 40.10, 28.40, 20.96, 18.09.

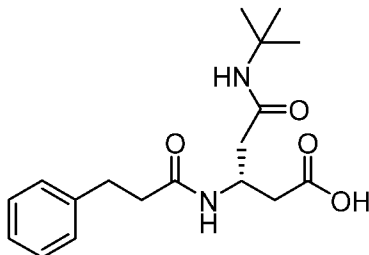
### 20 Example 40 – Preparation of PKS3035



[0126] Title compound was synthesized by following the general protocol for HATU mediated coupling of 3-phenylpropanoic acid (40 mg, 0.264 mmol) with PKS3028 (72.3 mg, 0.22 mmol). After completion of reaction, water was added to reaction mixture to give white precipitate. Precipitate was filtered, washed with water, and dried in air to give product (50 mg, 45%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 7.82 (d, *J* = 8.1 Hz, 1H), 7.40 (s, 1H),

7.38 – 7.28 (m, 5H), 7.28 – 7.22 (m, 2H), 7.20 – 7.13 (m, 3H), 5.05 (s, 2H), 4.43 – 4.30 (m, 1H), 2.82 – 2.68 (m, 2H), 2.55 (dd,  $J = 15.3, 5.6$  Hz, 1H), 2.41 – 2.08 (m, 5H), 1.22 (s, 9H).

#### Example 41 – Preparation of PKS3038



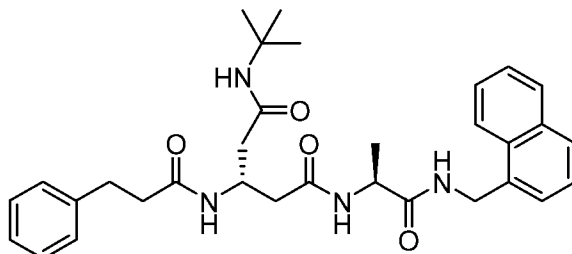
5

[0127] Title compound was prepared following the general protocol for O-debenzylation of PKS3035 (45 mg, 0.106 mmol). The product was isolated as a white solid (35 mg, quant.).

$^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  7.87 (d,  $J = 8.0$  Hz, 1H), 7.44 (s, 1H), 7.29 – 7.22 (m, 2H), 7.21 – 7.12 (m, 3H), 4.30 – 4.20 (m, 1H), 2.77 (t,  $J = 7.9$  Hz, 2H), 2.37 – 2.13 (m, 6H), 1.22 (s, 9H).

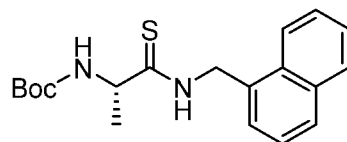
10

#### Example 42 – Preparation of PKS3039

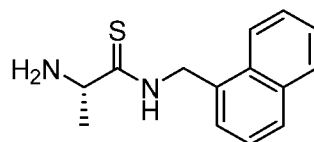


[0128] The title compound was prepared following the general procedure for HATU mediated coupling of PKS3038 (35.0 mg, 0.032 mmol) and H-Ala-CH<sub>2</sub>-naphth TFA salt (40.0 mg, 0.116 mmol). Purification by HPLC gave product (17.6 mg, 31%) as a white solid.  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  8.45 (t,  $J = 5.8$  Hz, 1H), 8.08 – 8.01 (m, 2H), 7.97 – 7.90 (m, 1H), 7.83 (dd,  $J = 7.2, 2.4$  Hz, 1H), 7.69 (d,  $J = 8.4$  Hz, 1H), 7.57 – 7.49 (m, 2H), 7.49 – 7.41 (m, 2H), 7.35 (s, 1H), 7.27 – 7.20 (m, 2H), 7.19 – 7.11 (m, 3H), 4.79 – 4.69 (m, 2H), 4.38 – 4.27 (m, 2H), 2.75 (t,  $J = 8.0$  Hz, 2H), 2.35 – 2.27 (m, 4H), 2.20 (d,  $J = 6.8$  Hz, 2H), 1.24 – 1.19 (m, 12H).  $^{13}\text{C}$  NMR (126 MHz, DMSO)  $\delta$  172.44, 170.56, 169.71, 169.40, 141.29, 134.44, 133.23, 130.77, 128.47, 128.26, 128.08, 127.43, 126.14, 125.83, 125.76, 125.38, 124.99, 123.36, 49.99, 48.36, 44.32, 40.82, 40.19, 40.01, 37.29, 31.15, 28.46, 18.22.

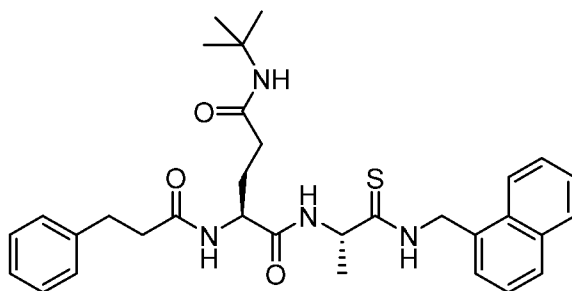
20

**Example 43 – Preparation of PKS3006**

[0129] Lawesson reagent (61 mg, 0.15 mmol) was suspended in 1 mL THF and a solution of Boc-Ala-CH<sub>2</sub>-naphth (98.5 mg, 0.3 mmol) in 2 mL THF was added at room temperature. The reaction mixture was stirred overnight. Reaction was not complete. Additional 30 mg of Lawesson reagent was added and the mixture was stirred additional 18 hours. THF was evaporated and crude was purified by column chromatography to give product (100 mg, 97%). Complex NMR due to rotamers. <sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 8.31 (s, 1H), 7.96 – 7.78 (m, 3H), 7.58 – 7.39 (m, 4H), 5.37 – 5.26 (m, 1H), 5.26 – 5.10 (m, 2H), 4.56 – 4.36 (m, 1H), 1.48 – 1.41 (m, 3H), 1.33 – 1.21 (m, 9H).

**Example 44 – Preparation of PKS3019**

[0130] To a stirred solution of PKS3006 (40 mg, 0.116 mmol) in 2 mL ethyl acetate, SnCl<sub>4</sub> (1M in heptane, 0.23 mL, 0.230 mmol) was added at room temperature. Reaction mixture was stirred at room temperature overnight. Solvent was evaporated and crude was triturated with diethyl ether. The solid was filtered and dried to give product as a white solid. The solid was dissolved in DMF and used in next step. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.01 – 7.91 (m, 3H), 7.63 – 7.46 (m, 5H), 5.25 (d, *J* = 15.2 Hz, 1H), 5.16 (d, *J* = 15.2 Hz, 1H), 4.28 – 4.17 (m, 1H), 1.40 (d, *J* = 6.6 Hz, 3H).

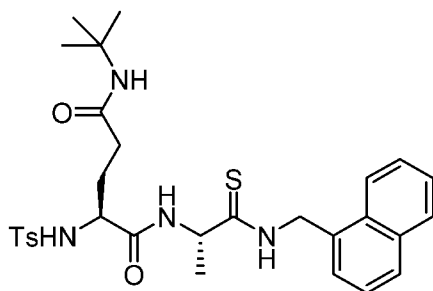
**Example 45 – Preparation of PKS3020**

[0131] The title compound was synthesized by following the general protocol for HATU mediated coupling of PhCH<sub>2</sub>CH<sub>2</sub>C(O)-Glu(CONHtBu)-OH (18.4 mg, 0.055) and PKS3019 (6.5 mg, 0.05 mmol). The reaction mixture was purified by HPLC to give product (17.3 mg, 62%) as

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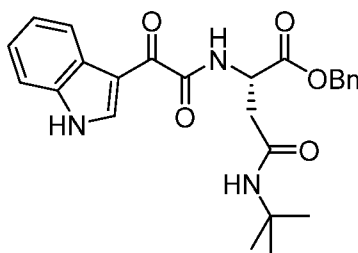
a white solid.  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  10.50 (t,  $J = 5.2$  Hz, 1H), 8.12 (d,  $J = 7.5$  Hz, 1H), 8.09 (d,  $J = 7.7$  Hz, 1H), 8.00 – 7.93 (m, 2H), 7.89 (dd,  $J = 6.5, 3.0$  Hz, 1H), 7.61 – 7.51 (m, 2H), 7.51 – 7.44 (m, 2H), 7.31 – 7.21 (m, 3H), 7.21 – 7.13 (m, 3H), 5.23 – 5.18 (m, 2H), 4.78 – 4.68 (m, 1H), 4.25 – 4.17 (m, 1H), 2.80 (t,  $J = 8.0$  Hz, 2H), 2.49 – 2.38 (m, 2H), 2.05 (t,  $J = 8.0$  Hz, 2H), 1.96 – 1.85 (m, 1H), 1.73 – 1.62 (m, 1H), 1.32 (d,  $J = 6.8$  Hz, 3H), 1.23 (s, 9H).  $^{13}\text{C}$  NMR (126 MHz, DMSO)  $\delta$  204.98, 171.62, 171.16, 170.69, 141.29, 133.29, 132.10, 131.01, 128.55, 128.26, 128.13, 127.98, 126.42, 125.99, 125.93, 125.83, 125.40, 123.39, 53.87, 52.35, 49.85, 46.77, 36.81, 32.68, 31.06, 28.53, 27.77, 21.40.

#### 10 Example 46 – Preparation of PKS3021



[0132] The title compound was synthesized by following the general protocol for HATU mediated coupling of Ts-Glu(CONHtBu)-OH (19.6 mg, 0.055) and PKS3019 (6.5 mg, 0.05 mmol). The reaction mixture was purified by HPLC to give product (15.4 mg, 53%) as a white solid.  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  10.44 (t,  $J = 5.2$  Hz, 1H), 8.18 (d,  $J = 7.4$  Hz, 1H), 7.99 – 7.94 (m, 1H), 7.94 – 7.90 (m, 1H), 7.90 – 7.83 (m, 2H), 7.63 (d,  $J = 8.3$  Hz, 2H), 7.58 – 7.50 (m, 2H), 7.50 – 7.40 (m, 2H), 7.34 – 7.29 (m, 3H), 5.20 – 5.14 (m, 2H), 4.51 – 4.42 (m, 1H), 3.76 – 3.67 (m, 1H), 2.35 (s, 3H), 2.10 – 1.95 (m, 2H), 1.80 – 1.70 (m, 1H), 1.64 – 1.53 (m, 1H), 1.21 (s, 9H), 1.17 (d,  $J = 6.7$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz, DMSO)  $\delta$  204.82, 171.07, 169.63, 142.42, 137.96, 133.27, 132.07, 130.98, 129.24, 128.53, 127.95, 126.67, 126.40, 125.91, 125.37, 123.37, 55.72, 53.85, 49.86, 46.67, 32.33, 28.77, 28.48, 20.99, 20.96.

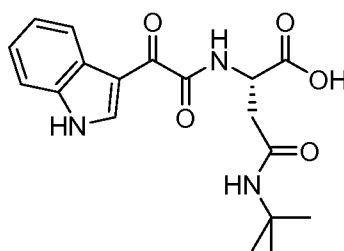
#### Example 47 – Preparation of PKS3049



[0133] The title compound was synthesized following the general protocol for HATU mediated coupling of 3-indoleglyoxylic acid (189 mg, 1.0 mmol) and H-Asp(CONHtBu)-OH

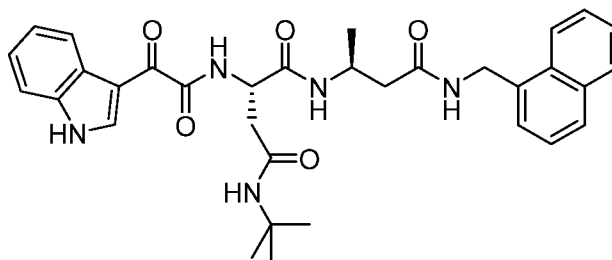
TFA salt (432 mg, 1.1 mmol). The compound was isolated by ethyl acetate extraction and purified by column chromatography to give product (270 mg, 60%) as an off-white solid. <sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 10.14 (s, 1H), 9.13 (d, *J* = 3.3 Hz, 1H), 8.42 – 8.34 (m, 2H), 7.47 (dd, *J* = 6.6, 2.3 Hz, 1H), 7.34 – 7.23 (m, 7H), 5.54 (s, 1H), 5.23 (d, *J* = 12.4 Hz, 1H), 5.19 – 5.12 (m, 1H), 5.11 – 5.03 (m, 1H), 2.80 (dd, *J* = 15.2, 5.8 Hz, 1H), 2.74 (dd, *J* = 15.2, 5.3 Hz, 1H), 1.29 (s, 9H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 179.61, 170.76, 168.78, 162.60, 139.33, 136.24, 135.30, 128.72, 128.56, 128.41, 126.86, 124.09, 123.31, 122.44, 113.14, 112.12, 67.73, 51.99, 49.58, 39.23, 28.78.

#### 10 Example 48 – Preparation of PKS3052



[0134] The title compound was synthesized following the general protocol for *O*-debenzylation of PKS3049 (265 mg, 0.59 mmol). Isolated crude was purified by HPLC to give product (112 mg, 53%) as an off-white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 12.81 (s, 1H), 12.27 (d, *J* = 3.3 Hz, 1H), 8.82 – 8.75 (m, 2H), 8.26 – 8.20 (m, 1H), 7.57 (s, 1H), 7.56 – 7.52 (m, 1H), 7.32 – 7.23 (m, 2H), 4.69 – 4.60 (m, 1H), 2.67 (dd, *J* = 15.1, 7.2 Hz, 1H), 2.59 (dd, *J* = 15.1, 5.0 Hz, 1H), 1.22 (s, 9H). <sup>13</sup>C NMR (126 MHz, DMSO) δ 181.25, 172.26, 168.78, 162.78, 138.64, 136.25, 126.14, 123.53, 122.66, 121.28, 112.60, 112.11, 50.16, 48.97, 37.16, 28.44.

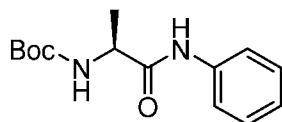
#### 20 Example 49 – Preparation of PKS3054



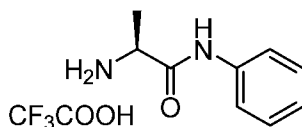
[0135] The title compound was synthesized by following the general protocol for HATU mediated coupling of 3-Ind-Glyoxylyl-Asp-(CONHtBu)-OH (7.2 mg, 0.02) and H-β-homo-Ala-CH<sub>2</sub>-naphth TFA salt (7.8 mg, 0.022 mmol). The reaction mixture was purified by HPLC to give product (4.0 mg, 34%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 12.24 (d, *J* = 3.6 Hz, 1H), 8.81 (d, *J* = 3.1 Hz, 1H), 8.70 (d, *J* = 8.4 Hz, 1H), 8.41 (t, *J* = 5.7 Hz, 1H), 8.28 – 8.21

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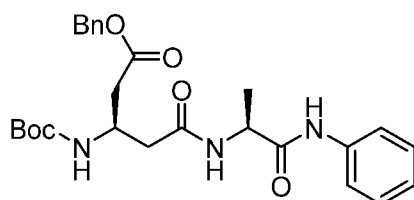
(m, 1H), 8.02 (dd,  $J = 6.3, 3.4$  Hz, 1H), 7.98 (d,  $J = 8.0$  Hz, 1H), 7.93 (dd,  $J = 6.2, 3.4$  Hz, 1H), 7.83 (d,  $J = 8.0$  Hz, 1H), 7.58 – 7.48 (m, 4H), 7.48 – 7.37 (m, 2H), 7.31 – 7.23 (m, 2H), 4.74 (dd,  $J = 15.2, 5.7$  Hz, 1H), 4.67 (dd,  $J = 15.2, 5.5$  Hz, 1H), 4.62 – 4.54 (m, 1H), 4.20 – 4.09 (m, 1H), 2.59 (dd,  $J = 14.5, 8.4$  Hz, 1H), 2.43 (dd,  $J = 14.5, 4.7$  Hz, 1H), 2.36 (dd,  $J = 14.0, 5.8$  Hz, 1H), 2.26 (dd,  $J = 14.0, 7.7$  Hz, 1H), 1.20 (s, 9H), 1.06 (d,  $J = 6.6$  Hz, 3H).

**Example 50 – Preparation of PKS3056**

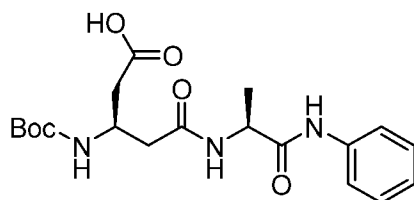
**[0136]** Boc-Ala-OSu (600 mg, 2.10 mmol) was dissolved in 10 mL dichloromethane and the solution was cooled to 0 °C. Aniline and triethylamine were added to the solution at 0 °C. Reaction mixture was allowed to warm to room temperature slowly (over 1 hour) and stirred overnight. Water was added to the reaction mixture and extracted twice with ethyl acetate. Combined organic layer was washed with 1N HCl and brine, dried over anhydrous sodium sulfate and evaporated to give product 468 mg (84%). Product was used in next step without further purification. <sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 8.42 (s, 1H), 7.55 – 7.48 (m, 2H), 7.31 (td,  $J = 7.5, 4.9$  Hz, 2H), 7.09 (t,  $J = 7.4$  Hz, 1H), 5.14 – 4.99 (m, 1H), 4.39 – 4.24 (m, 1H), 1.46 (s, 9H), 1.43 (d,  $J = 7.0$  Hz, 3H).

**Example 51 – Preparation of PKS3057**

**[0137]** The title compound was synthesized by following the general protocol for Boc-deprotection of Boc-Ala-NHPh (468 mg, 1.77 mmol). The crude obtained was suspended in diethyl ether. An off-white solid appeared. Diethyl ether was decanted and solid was dried to give product (411 mg, 84%). Product was used in next step without further purification. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 10.49 (s, 1H), 8.25 (s, 3H), 7.63 – 7.57 (m, 2H), 7.39 – 7.32 (m, 2H), 7.15 – 7.08 (m, 1H), 4.02 (d,  $J = 7.2$  Hz, 1H), 1.46 (d,  $J = 7.0$  Hz, 3H).

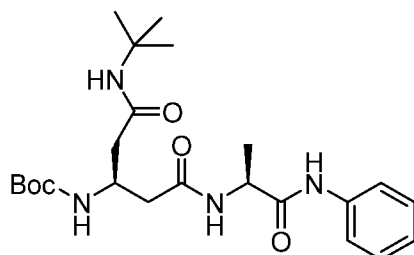
**Example 52 – Preparation of PKS3061**

[0138] The title compound was synthesized by following the general protocol for HATU mediated coupling of *N*-Boc-*L*-β-glutamic acid 5-benzyl ester (84 mg, 0.25 mmol) and PKS3057 (83 mg, 0.3 mmol). After completion of reaction, water was added to reaction mixture to give white precipitate. Precipitate was filtered, washed with water, and dried in air to give product (115 mg, 95%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 9.94 (s, 1H), 8.19 (t, *J* = 6.2 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.44 – 7.21 (m, 7H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.89 – 6.75 (m, 1H), 5.05 (s, 2H), 4.46 – 4.32 (m, 1H), 4.23 – 4.06 (m, 1H), 2.62 – 2.44 (m, 2H), 2.43 – 2.27 (m, 2H), 1.35 (s, 9H), 1.27 (d, *J* = 7.1 Hz, 3H).

**Example 53 – Preparation of PKS3063**

[0139] The title compound was synthesized by following the *O*-debenzylation protocol of PKS3061 (115 mg, 0.24 mmol) to give product (94.4 mg, quant.) as a white solid. Complex NMR due to 0.28:0.72 ratio of rotamers. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 12.15 (s, 1H), 10.01 (s, 0.28H), 9.95 (s, 0.82H), 8.18 (d, *J* = 7.1 Hz, 1H), 7.62 - 7.58 (m, 2H), 7.31 - 7.26 (m, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 0.28H), 6.71 (d, *J* = 8.4 Hz, 0.82H), 4.49 – 4.31 (m, 1H), 4.16 – 3.97 (m, 1H), 2.42 – 2.26 (m, 4H), 1.39 – 1.32 (m, 9H), 1.28 (d, *J* = 7.1 Hz, 3H).

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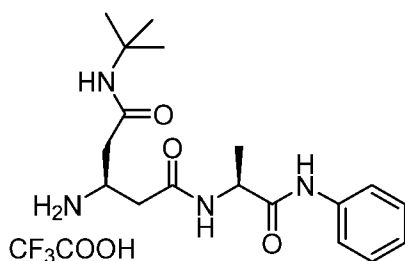
**Example 54 – Preparation of PKS3065**

[0140] The title compound was synthesized following the general protocol for EDC mediated coupling of PKS3063 (94.4 mg, 0.24 mmol) and *tert*-butylamine (38 mL, 0.36 mmol).

After completion of reaction water was added to give a white precipitate. Precipitate was filtered, washed with water, and dried in air to give product (85 mg, 79%) as an off-white solid.

$^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  9.96 (s, 0.28H), 9.93 (s, 0.82H), 8.11 (d,  $J = 7.3$  Hz, 1H), 7.60 (d,  $J = 8.0$  Hz, 2H), 7.35 – 7.26 (m, 3H), 7.04 (t,  $J = 7.4$  Hz, 1H), 6.59 – 6.51 (m, 1H), 4.46 – 4.36 (m, 1H), 4.09 – 4.00 (m, 1H), 2.37 – 2.24 (m, 2H), 2.24 – 2.13 (m, 2H), 1.35 and 1.34 (s, 9H), 1.31 – 1.25 (m, 3H), 1.23 (s, 9H).

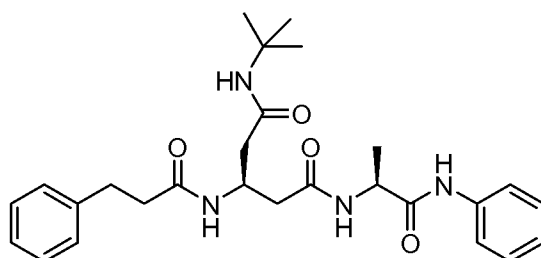
### Example 55 – Preparation of PKS3069



10 [0141] The title compound was synthesized following the general protocol for Boc-deprotection to give 87 mg product (quant.).  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  10.05 (s, 1H), 8.57 – 8.51 (m, 1H), 7.85 (d,  $J = 6.3$  Hz, 3H), 7.80 (s, 0.76H), 7.79 (s, 0.24H), 7.59 (d,  $J = 8.0$  Hz, 2H), 7.34 – 7.27 (m, 2H), 7.05 (t,  $J = 7.4$  Hz, 1H), 4.49 – 4.40 (m, 1H), 3.68 – 3.60 (m, 1H), 2.54 – 2.46 (m, 2H), 2.45 – 2.32 (m, 2H), 1.34 – 1.29 (m, 3H), 1.26 (s, 9H).

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### Example 56 – Preparation of PKS3076



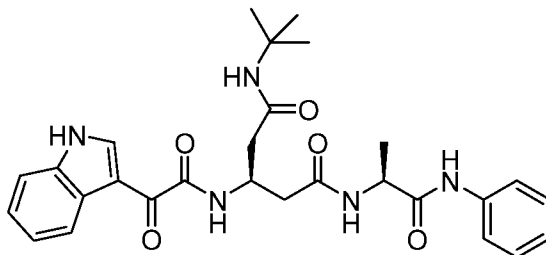
[0142] The title compound was synthesized following the general protocol for HATU mediated coupling of 3-phenylpropanoic acid (8.3 mg, 0.055 mmol) and PKS3076 (23.1 mg, 0.05 mmol). Purification by HPLC gave the product (20.0 mg, 83%) as a white solid. Complex NMR due to 0.28:0.72 ratio of rotamers.  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  9.97 (s, 0.28H), 9.94 (s, 0.72H), 8.15 – 8.09 (m, 1H), 7.66 (t,  $J = 7.8$  Hz, 1H), 7.62 – 7.57 (m, 2H), 7.36 – 7.29 (m, 1H), 7.29 – 7.21 (m, 4H), 7.21 – 7.12 (m, 3H), 7.07 – 7.00 (m, 1H), 4.46 – 4.38 (m, 1H), 4.34 – 4.26 (m, 1H), 2.82 – 2.72 (m, 2H), 2.40 – 2.26 (m, 4H), 2.24 – 2.18 (m, 2H), 1.30 – 1.25 (m, 3H), 1.22 (s, 9H).  $^{13}\text{C}$  NMR (126 MHz, DMSO)  $\delta$  171.33, 170.49, 169.79, 169.39, 141.32,

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138.94, 128.63, 128.23, 128.08, 125.78, 123.26, 119.24, 49.97, 48.97, 44.19, 40.78, 39.70, 37.21, 31.14, 28.47, 18.17.

### Example 57 – Preparation of PKS3077



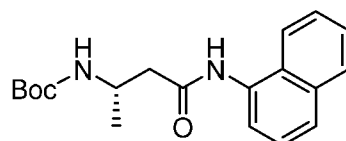
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[0143] The title compound was synthesized following the general protocol for HATU mediated coupling of 3-indoleglyoxylic acid (10.4 mg, 0.055 mmol) and PKS3076 (23.1 mg, 0.05 mmol). Purification by HPLC gave the product (15.0 mg, 58%) as an off-white solid.

Complex NMR due to 0.27:0.73 ratio of rotamers. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 12.21 (s, 1H), 9.98 (s, 0.27H), 9.93 (s, 0.73H), 8.81 – 8.77 (m, 1H), 8.64 (d, *J* = 8.9 Hz, 1H), 8.28 – 8.19 (m, 2H), 7.63 – 7.45 (m, 4H), 7.32 – 7.19 (m, 4H), 7.07 – 6.97 (m, 1H), 4.55 – 4.46 (m, 1H), 4.45 – 4.37 (m, 1H), 2.54 – 2.49 (m, 1H), 2.47 – 2.34 (m, 2H), 2.32 – 2.25 (m, 1H), 1.29 (d, *J* = 7.1 Hz, 2.3H), 1.24 - 1.22 (m, 9.7H). <sup>13</sup>C NMR (126 MHz, DMSO) δ 181.66, 171.23, 169.77, 169.36, 162.07, 138.85, 138.56, 136.18, 128.58, 126.25, 123.38, 123.23, 122.52, 121.26, 119.28, 112.51, 112.10, 50.05, 49.02, 44.19, 40.17, 39.19, 28.43, 18.10.

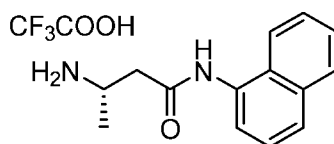
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### Example 58 – Preparation of PKS3071

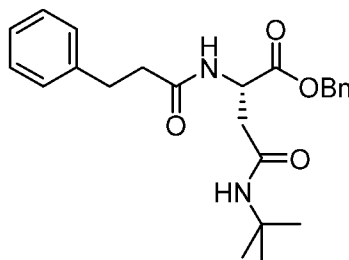


[0144] The title compound was synthesized by following the general protocol for HATU mediated coupling of Boc-L-β-homoalanine (50.8 mg, 0.25 mmol) and 1-naphthylamine hydrochloride (50 mg, 0.275 mmol). After completion of reaction water was added to give a white precipitate. Precipitate was filtered, washed with water, and dried in air to give product (62 mg, 76%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 9.87 (s, 1H), 8.09 – 8.02 (m, 1H), 7.93 (dd, *J* = 6.2, 3.3 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 7.3 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.51 – 7.44 (m, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 4.06 – 3.91 (m, 1H), 2.63 (dd, *J* = 13.9, 6.7 Hz, 1H), 2.57 – 2.51 (m, 1H), 1.38 (s, 9H), 1.16 (d, *J* = 6.5 Hz, 3H).

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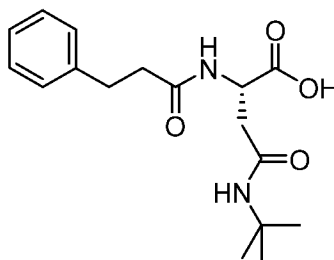
**Example 59 – Preparation of PKS3073**

[0145] The title compound was prepared by following the general protocol for Boc-deprotection of PKS3071 (57 mg, 0.174 mmol). The crude was triturated with diethyl ether and filtered. The solid was dried to give product (59 mg, quant.) as a brown solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 10.22 (s, 1H), 8.10 – 8.05 (m, 1H), 8.03 – 7.92 (m, 4H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 7.4 Hz, 1H), 7.60 – 7.47 (m, 3H), 3.74 – 3.58 (m, 1H), 2.85 (d, *J* = 6.6 Hz, 2H), 1.31 (d, *J* = 6.6 Hz, 3H).

10 **Example 60 – Preparation of PKS21012**

[0146] The title compound was synthesized by following the general procedure for the HATU mediated coupling of 3-phenylpropanoic acid (1.68 g, 11.17 mmol) with **PKS3047** (3.98 g, 10.15 mmol). After completion of reaction, water was added. A white precipitate was formed. The precipitate was filtered and washed with water. Precipitate was dried in air to give product (3.92 g, 94%) as a white solid. <sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.29 (m, 5H), 7.29 – 7.23 (m, 2H), 7.21 – 7.14 (m, 3H), 6.88 (d, *J* = 8.0 Hz, 1H), 5.32 (s, 1H), 5.20 (d, *J* = 12.3 Hz, 1H), 5.14 (d, *J* = 12.3 Hz, 1H), 4.84 – 4.77 (m, 1H), 2.95 (t, *J* = 7.9 Hz, 2H), 2.81 (dd, *J* = 15.7, 4.4 Hz, 1H), 2.61 – 2.47 (m, 3H), 1.28 (s, 9H).

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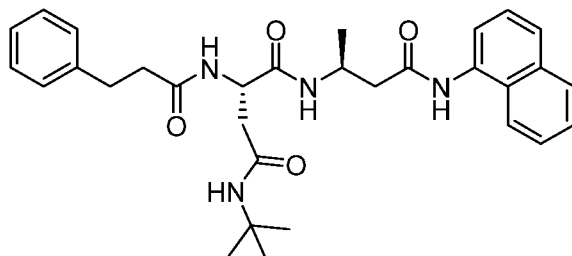
**Example 61 – Preparation of PKS21013**

[0147] The title compound was synthesized by following the procedure for *O*-debenzylation of PKS21012 (1.44 g, 3.50 mmol). Product (1.11 g, 99%) was isolated as a white

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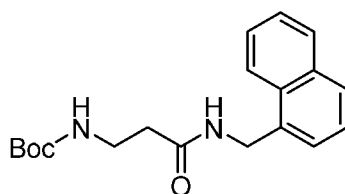
solid.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-}d_6$ )  $\delta$  12.54 (s, 1H), 8.04 (d,  $J = 8.0$  Hz, 1H), 7.45 (s, 1H), 7.29 – 7.23 (m, 2H), 7.23 – 7.13 (m, 3H), 4.52 – 4.44 (m, 1H), 2.83 – 2.76 (m, 2H), 2.49 – 2.44 (m, 1H), 2.44 – 2.34 (m, 3H), 1.22 (s, 9H).

### 5 Example 62 – Preparation of PKS3081



[0148] The title compound was synthesized following the general procedure for HATU mediated coupling of **PKS21013** (16.0 mg, 0.05 mmol) and **PKS3073** (18.8 mg, 0.055 mmol). Purification by HPLC gave the product (21.0 mg, 79%) as a white solid.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-}d_6$ )  $\delta$  9.95 (s, 1H), 8.05 (d,  $J = 8.0$  Hz, 1H), 8.00 (d,  $J = 8.2$  Hz, 1H), 7.96 – 7.89 (m, 2H), 7.76 (d,  $J = 8.2$  Hz, 1H), 7.64 (d,  $J = 7.4$  Hz, 1H), 7.58 – 7.50 (m, 2H), 7.48 (t,  $J = 7.8$  Hz, 1H), 7.32 (s, 1H), 7.28 – 7.21 (m, 2H), 7.20 – 7.12 (m, 3H), 4.60 – 4.47 (m, 1H), 4.32 – 4.14 (m, 1H), 2.82 – 2.75 (m, 2H), 2.65 (dd,  $J = 14.2, 5.9$  Hz, 1H), 2.58 (dd,  $J = 14.2, 7.2$  Hz, 1H), 2.45 – 2.35 (m, 3H), 2.31 (dd,  $J = 14.7, 8.6$  Hz, 1H), 1.21 (s, 9H), 1.17 (d,  $J = 6.5$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{DMSO}$ )  $\delta$  171.15, 170.16, 169.82, 168.77, 141.30, 133.68, 133.44, 128.27, 128.12, 128.07, 127.92, 125.97, 125.83, 125.82, 125.50, 125.32, 122.79, 122.06, 50.11, 50.05, 42.54, 42.29, 38.80, 36.90, 31.00, 28.45, 20.19.

### Example 63 – Preparation of PKS21204

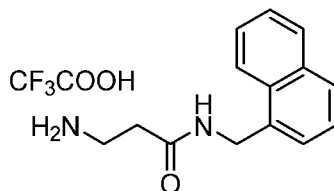


[0149] Boc- $\beta$ -Ala-OSu (286.28 mg, 1.00 mmol) was dissolved in dichloromethane (5.00 mL) and 1-naphthylmethanamine (157.21 mg, 1.00 mmol) was added. The solution was cooled to 0 °C and triethylamine (101.19 mg, 1.00 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 2 hours. After completion of reaction, dichloromethane was evaporated and water was added. A white precipitate appeared. Precipitate was filtered, washed with water and dried in air to give product (320 mg, 97%) as a white solid. Product was used in next step without further purification.  $^1\text{H}$  NMR (500 MHz,

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Chloroform-*d*)  $\delta$  7.99 (d,  $J$ = 8.3 Hz, 1H), 7.88 (d,  $J$ = 8.0 Hz, 1H), 7.85 – 7.78 (m, 1H), 7.59 – 7.48 (m, 2H), 7.45 – 7.40 (m, 2H), 5.90 (bs, 1H), 5.14 (bs, 1H), 4.93 – 4.85 (m, 2H), 3.48 – 3.37 (m, 2H), 2.45 – 2.36 (m, 2H), 1.39 (s, 9H).

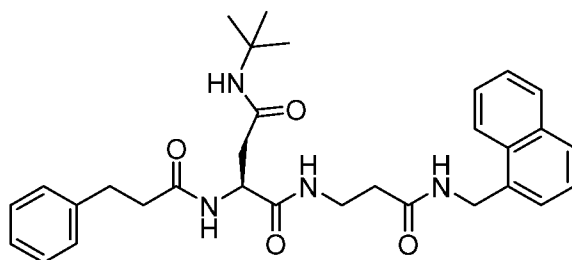
### 5 Example 64 – Preparation of PKS21211



[0150] The title compound was synthesized by following the general procedure for Boc-deprotection of **PKS21204** (320 mg, 0.974 mmol). After completion of reaction, excess trifluoroacetic acid and dichloromethane were evaporated. Crude was dried under vacuum and trituated with diethyl ether to give a white solid. Solid was filtered and dried in air to give product (320 mg, 96%). Product was used in next step without further purification.  $^1\text{H}$  NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.63 (t,  $J$ = 5.6 Hz, 1H), 8.10 – 8.02 (m, 1H), 7.96 (dd,  $J$ = 6.9, 2.2 Hz, 1H), 7.87 (dd,  $J$ = 7.0, 2.4 Hz, 1H), 7.71 (bs, 3H), 7.59 – 7.52 (m, 2H), 7.51 – 7.44 (m, 2H), 4.76 (d,  $J$ = 5.6 Hz, 2H), 3.10 – 2.96 (m, 2H), 2.53 (t,  $J$ = 6.8 Hz, 2H).

15

### Example 65 – Preparation of PKS21220



[0151] The title compound was synthesized by following the general procedure for HATU mediated coupling of **PKS21013** (16.0 mg, 50  $\mu\text{mol}$ ) and **PKS21211** (19.6 mg, 74%). After completion of reaction (1 h, temperature rose to 10  $^\circ\text{C}$ ), mixture was purified by preparative LCMS to give product (19.6 mg, 74%) as a white solid.  $^1\text{H}$  NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.43 (t,  $J$ = 5.7 Hz, 1H), 8.04 (d,  $J$ = 8.1 Hz, 1H), 7.99 (d,  $J$ = 8.1 Hz, 1H), 7.94 (d,  $J$ = 7.8 Hz, 1H), 7.84 (d,  $J$ = 8.0 Hz, 1H), 7.79 (t,  $J$ = 5.8 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.50 – 7.40 (m, 2H), 7.34 (s, 1H), 7.28 – 7.22 (m, 2H), 7.21 – 7.13 (m, 3H), 4.73 (d,  $J$ = 5.6 Hz, 2H), 4.55 – 4.45 (m, 1H), 3.31 – 3.21 (m, 2H), 2.80 (t,  $J$ = 8.0 Hz, 2H), 2.45 – 2.37 (m, 3H), 2.32 (t,  $J$ = 7.5 Hz, 2H), 2.30 – 2.24 (m, 1H), 1.21 (s, 9H).  $^{13}\text{C}$  NMR (126 MHz, DMSO)  $\delta$  171.17, 170.88,

25

170.25, 168.76, 141.29, 134.52, 133.27, 130.85, 128.49, 128.27, 128.11, 127.52, 126.22, 125.84, 125.77, 125.45, 125.41, 123.43, 50.09, 50.02, 40.15, 38.69, 36.92, 35.52, 35.09, 31.00, 28.45.

### Example 66 – Measurement of IC<sub>50</sub>s of Dipeptidomimetics Against Chymotryptic

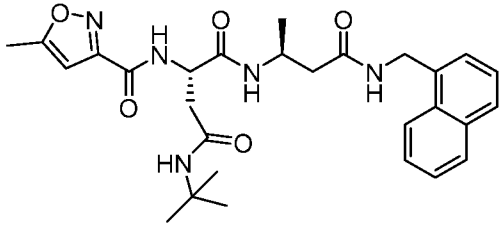
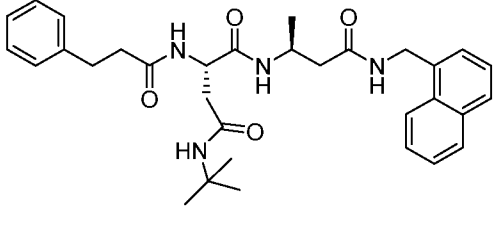
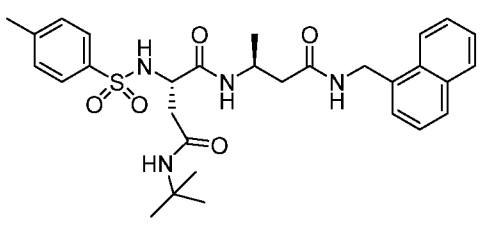
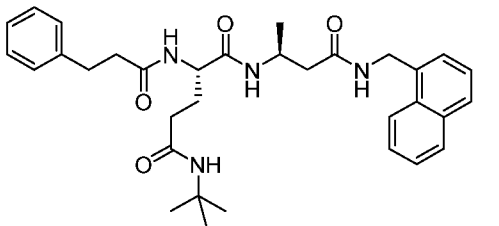
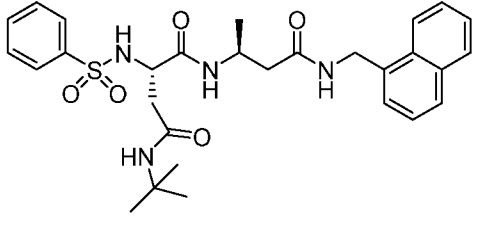
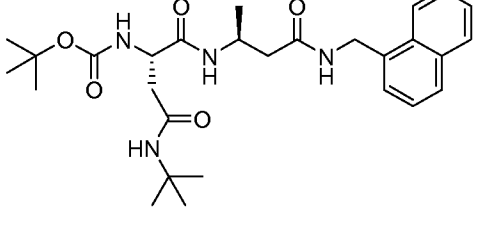
#### 5 Activities of the Human Constitutive Proteasome and Immunoproteasome

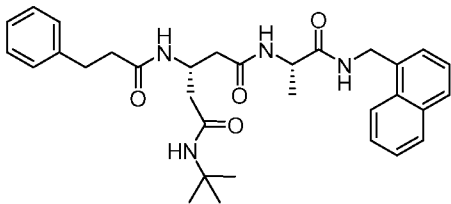
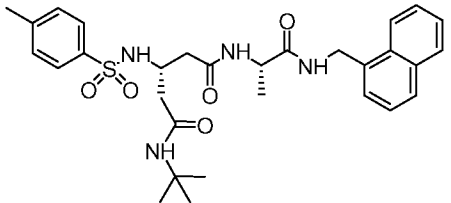
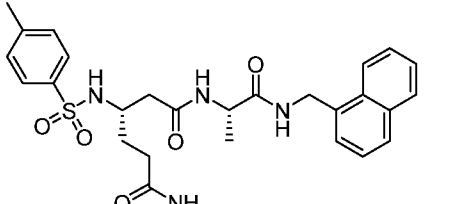
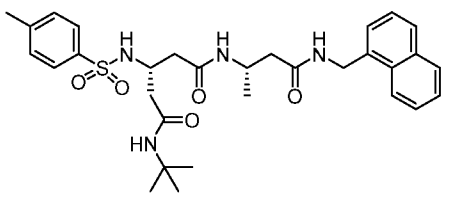
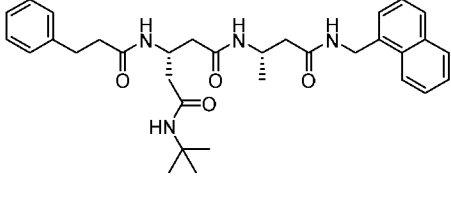
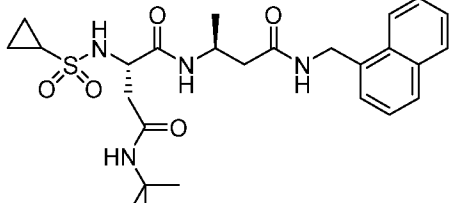
[0152] Assays were conducted on a SpectraMax Gemini plate-reader from Molecular Devices (Sunnyvale, CA). In a black 96-well plate, 100  $\mu$ L of pre-warmed assay mixture containing 0.4 nM Hu i-20S or 0.2 nM Hu c-20S, 15  $\mu$ M *N*-acetyl-Alanine-Asparagine-  
10 Tryptophan-7-amino-4-methylcoumarin (Ac-ANW-AMC) (substrate for i-20S) or 25  $\mu$ M *N*-succinyl-Leucine-Leucine-Valine-Tyrosine-7-amino-4-methylcoumarin (suc-LLVY-AMC) (substrate for c-20S), 0.02% SDS in buffer (50 mM HEPES, 0.5 mM EDTA, pH7.4) was added to the wells that contained 1  $\mu$ L inhibitor at 100x indicated concentrations in DMSO. The reaction progress of each well was recorded by monitoring fluorescence at 460 nm ( $\lambda_{\text{ex}} = 360$   
15 nm) for 120 minutes at 37°C. Velocities were derived from the initial linear range of the curves and the IC<sub>50</sub>s were obtained by plotting the percentage of inhibitor versus inhibitor concentrations (Figure 1).

### 20 Example 67 – Proteasome Inhibitory Studies of various N,C capped Dipeptidomimetics

[0153] A variety of dipeptidomimetics were synthesized and tested for their ability to inhibit the proteasomes, as described in Example 1. These compounds inhibited the proteasomes reversibly. The IC<sub>50</sub>s of these compounds against human immunoproteasome  $\beta$ 5i and constitutive proteasome  $\beta$ 5c are listed in Table 1. IC<sub>50</sub> curves are shown in Figure 1. These  
25 data show that compounds with substituents at amide side chain of the Asparagine (2nd amino acid from C-terminus) and C-terminal caps allowed the resulting dipeptides to selectively inhibit the human immunoproteasome  $\beta$ 5i active site over the human constitutive proteasome  $\beta$ 5c active site.

Table 1. Kinetic parameters and calculated logP of N,C-capped dipeptidomimetics

ID	Structures	IC50 ( $\mu\text{M}$ )		logP
		Hu i-20S	Hu c-20S	
PKS2249		0.18	16.1	0.55
PKS2251		0.045	32.2	2.75
PKS2252		0.0064	8.81	2.72
PKS2253		0.31	17.8	3.03
PKS2260		0.0112	16.55	2.23
PKS2272		0.152	>100	1.95

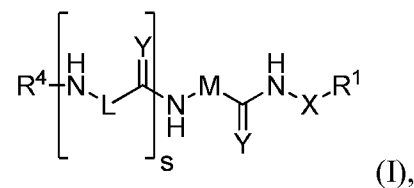
ID	Structures	IC50 ( $\mu\text{M}$ )		logP
		Hu i-20S	Hu c-20S	
PKS2278		2.26	>100	2.75
PKS2279		0.0145	34.7	3.73
PKS2290		1.60	13.9	4.19
PKS2291		8.68	>100	4.19
PKS2292		>100	>100	2.87
PKS2295		0.141	ND	0.69

ID	Structures	IC50 ( $\mu\text{M}$ )		logP
		Hu i-20S	Hu c-20S	
PKS3020		0.799	7.0	3.9
PKS3021		0.671	13.4	3.86
PKS3054		0.0048	0.234	1.47
PKS3065		>100	> 100	0.89
PKS3081		13.7	> 100	2.68
PKS21220		0.655	51.4	2.59

[0154] Although the invention has been described in detail, for the purpose of illustration, it is understood that such detail is for that purpose and variations can be made therein by those skilled in the art without departing from the spirit and scope of the invention which is defined by the following claims.

**WHAT IS CLAIMED:**

1. A compound of Formula (I):



wherein

5 L is  $-(\text{CR}^3\text{R}^x)_p-$ ;

M is  $-(\text{CR}^2\text{R}^y)_r-$ ;

R<sup>1</sup> is selected from the group consisting of monocyclic and bicyclic aryl,  
 10 biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and  
 monocyclic and bicyclic non-aromatic heterocycle, wherein monocyclic and bicyclic aryl,  
 biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and  
 monocyclic and bicyclic non-aromatic heterocycle can be optionally substituted from 1 to 3  
 15 times with a substituent selected independently at each occurrence thereof from the group  
 consisting of halogen, cyano,  $-\text{CF}_3$ , C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

R<sup>2</sup> is independently selected at each occurrence thereof from the group consisting  
 of H, D, C<sub>1-6</sub> alkyl,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-\text{CH}_2\text{Ar}$ , and  $-\text{CH}_2\text{heteroaryl}$ , wherein aryl (Ar) can be  
 optionally substituted from 1 to 3 times with a substituent selected independently at each  
 20 occurrence thereof from the group consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

R<sup>3</sup> is independently selected at each occurrence thereof from the group consisting  
 of H, D,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NHR}^5$ ,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^6\text{R}^7$ ,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{OH}$ , and  
 $-(\text{CH}_2)_m\text{C}(\text{O})\text{OBn}$ ;

25 R<sup>4</sup> is selected from the group consisting of H,  $-\text{C}(\text{O})(\text{CH}_2)_n\text{Ph}$ ,  $-\text{C}(\text{O})\text{CH}_2\text{NR}^6\text{R}^7$ ,  $-\text{SO}_2\text{Ar}$ ,  $-\text{SO}_2\text{C}_{1-6}$  alkyl,  $-\text{SO}_2\text{C}_{3-6}$  cycloalkyl,  $-\text{C}(\text{O})(\text{CH}_2)_n\text{Het}$ ,  $-\text{C}(\text{O})\text{C}(\text{O})\text{Het}$ ,  $-\text{C}(\text{O})\text{C}_{1-6}$  alkyl,  $-\text{C}(\text{O})\text{OC}_{1-6}$  alkyl,  $-\text{C}(\text{O})\text{CF}_3$ , heteroaryl, and  $-(\text{CH}_2)_n\text{NR}^6\text{R}^7$ , wherein aryl (Ar) and heteroaryl (Het) can be optionally substituted from 1 to 3  
 30 times with a substituent selected independently at each occurrence thereof from the group  
 consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

$R^5$  is selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, non-aromatic heterocycle,  $-NR^6R^7$ , and  $-CR^8R^9$ ;

5  $R^6$ ,  $R^7$ ,  $R^8$ , and  $R^9$  are each independently selected from the group consisting of H, D,  $C_{1-6}$  alkyl, and  $-(CH_2)_kOH$ ;

or  $R^6$  and  $R^7$  are taken together with the nitrogen to which they are attached to form a morpholine ring;

10 or  $R^8$  and  $R^9$  are taken together with the carbon to which they are attached to form an oxetane ring;

$R^x$  is independently selected at each occurrence thereof from the group consisting  
15 of H, D,  $-CH_2OC_{1-6}$  alkyl,  $-(CH_2)_mC(O)NHR^5$ ,  $-(CH_2)_mC(O)NR^6R^7$ , and  $-CH_2C(O)R^5$ ;

$R^y$  is independently selected at each occurrence thereof from the group consisting  
of H, D,  $C_{1-6}$  alkyl,  $-CH_2OC_{1-6}$  alkyl,  $-CH_2Ar$ , and  $-CH_2$ heteroaryl, wherein aryl (Ar) can be  
optionally substituted from 1 to 3 times with a substituent selected independently at each  
20 occurrence thereof from the group consisting of halogen, cyano,  $C_{1-6}$  alkyl, and  $C_{1-6}$  alkoxy;

X is  $-(CH_2)_q-$ ,  $-O-$ , or  $-(CD_2)_q-$ ;

Y is O or S;

25

k is 1, 2, or 3;

m is 0, 1, 2, 3, 4, or 5;

30

n is 0, 1, 2, or 3;

p is 1 or 2;

q is 0, 1, or 2;

r is 1 or 2; and

s is 0 or 1;

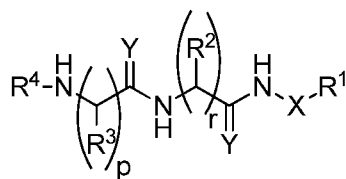
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with a proviso that when s is 0, then r is 2; and when s is 1, then  $r + p \geq 3$ ,

or an oxide thereof, a pharmaceutically acceptable salt thereof, a solvate thereof, or a prodrug thereof.

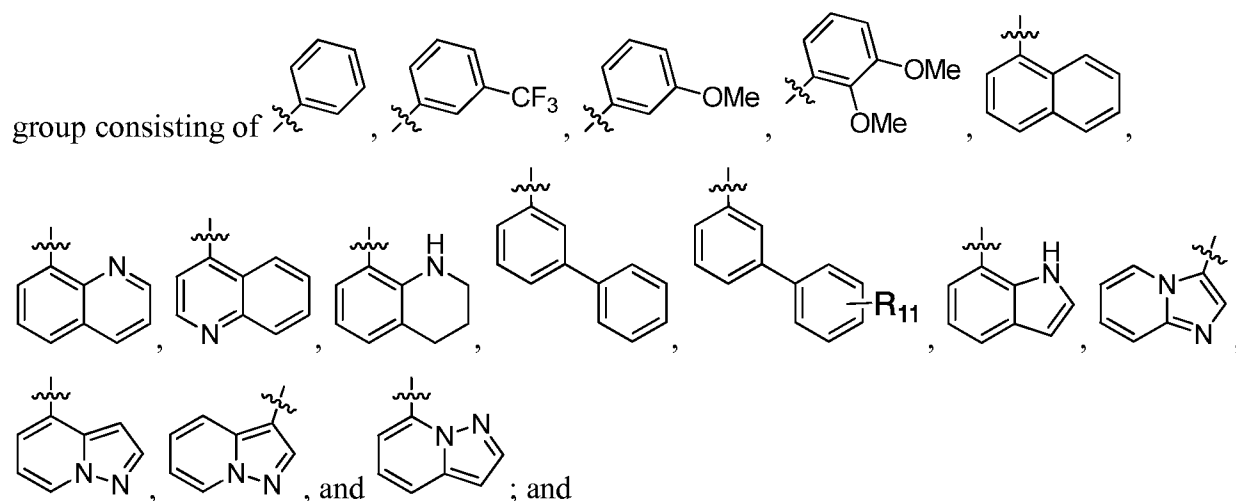
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2. The compound according to claim 1 which has the formula:



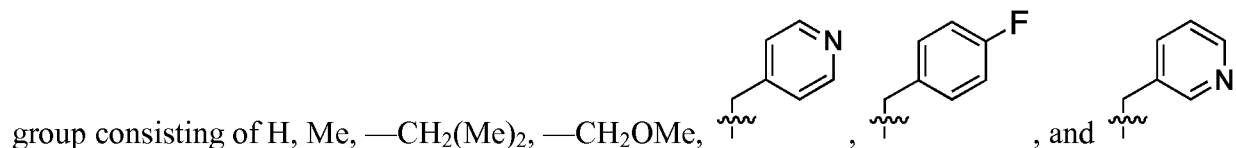
3. The compound according to claim 1, wherein  $R^1$  is selected from the

15

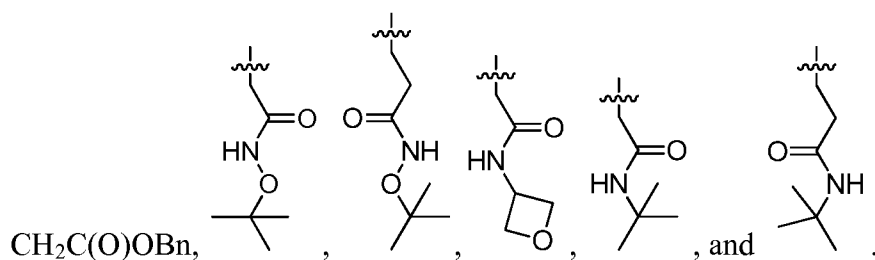


$R^{11}$  is selected from the group consisting of halogen, cyano,  $-\text{CF}_3$ ,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy.

4. The compound according to claim 1, wherein  $R^2$  is selected from the

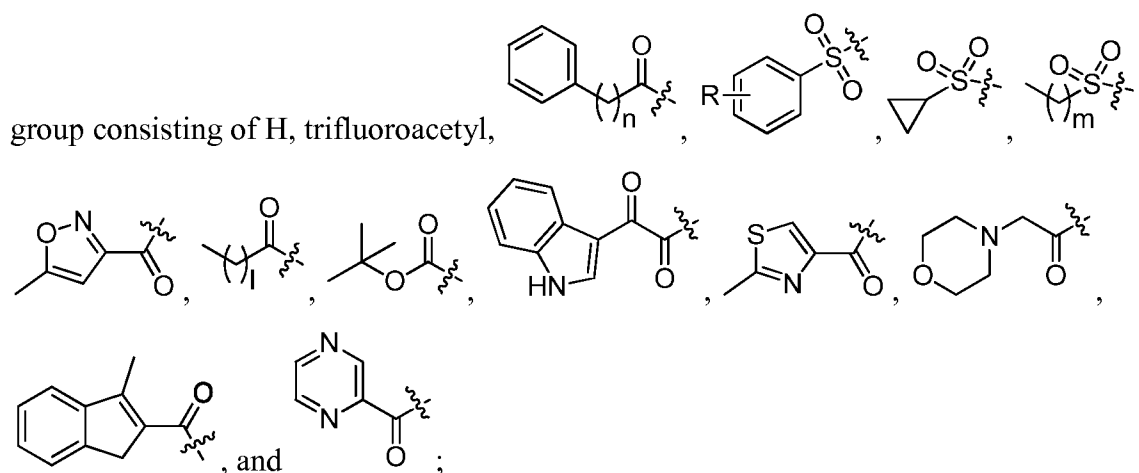


5. The compound according to claim 1, wherein R<sup>3</sup> is selected from the group consisting of —CH<sub>2</sub>OMe, —CH<sub>2</sub>C(O)OH, —(CH<sub>2</sub>)<sub>2</sub>C(O)OBn, —(CH<sub>2</sub>)<sub>2</sub>C(O)OH, —



5

6. The compound according to claim 1, wherein R<sup>4</sup> is selected from the



10

l is 0, 1, 2, 3, or 4;

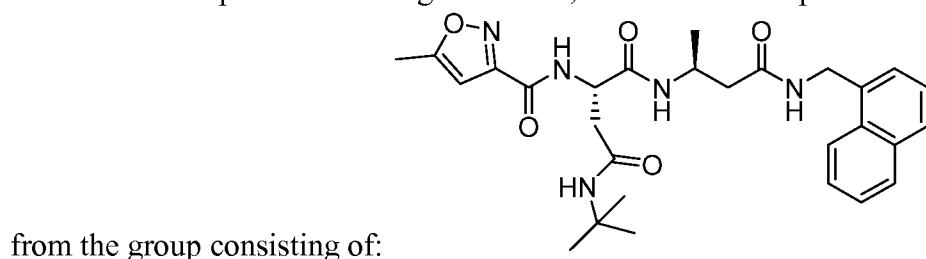
m is 0, 1, 2, 3, 4, or 5;

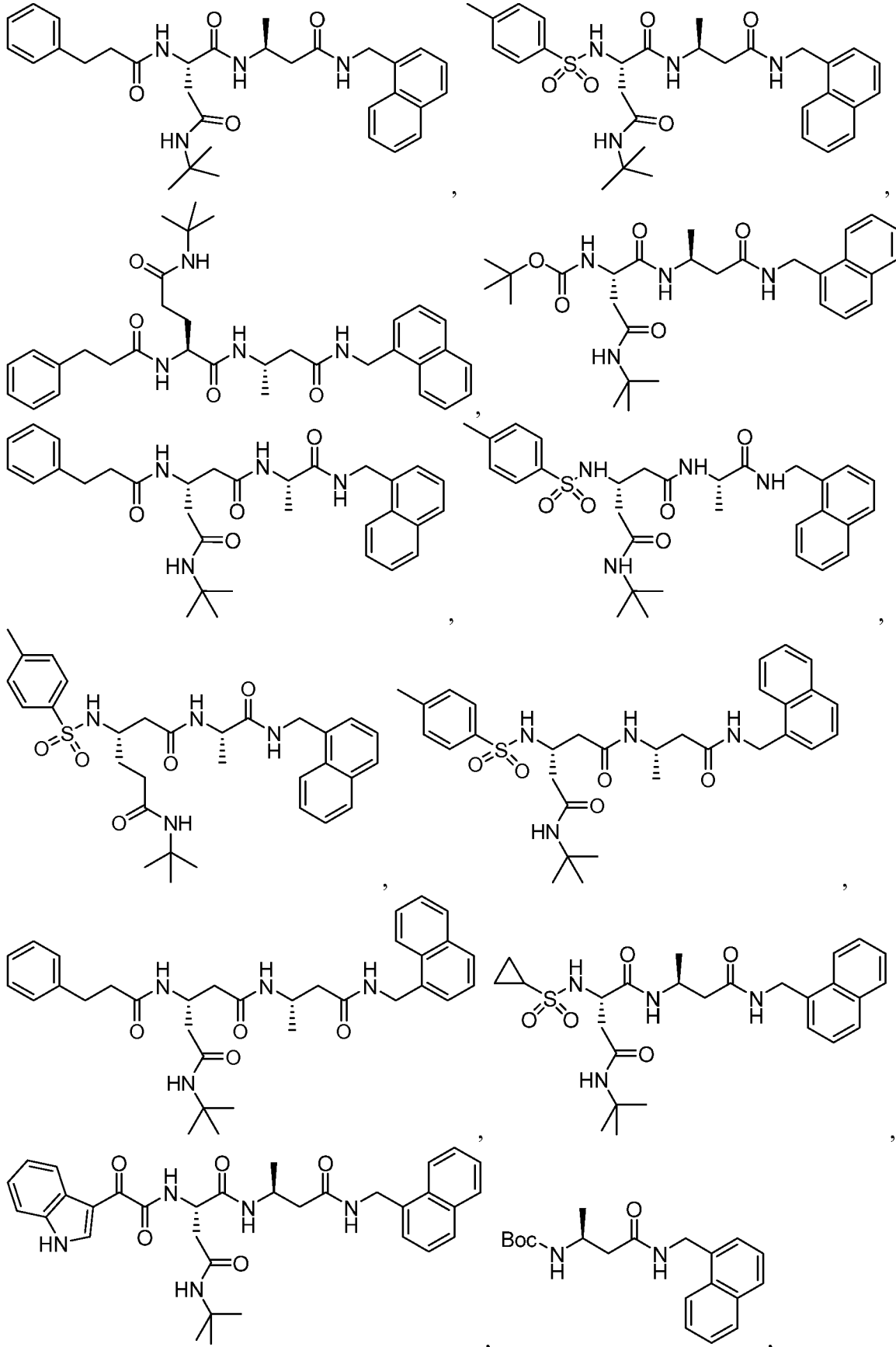
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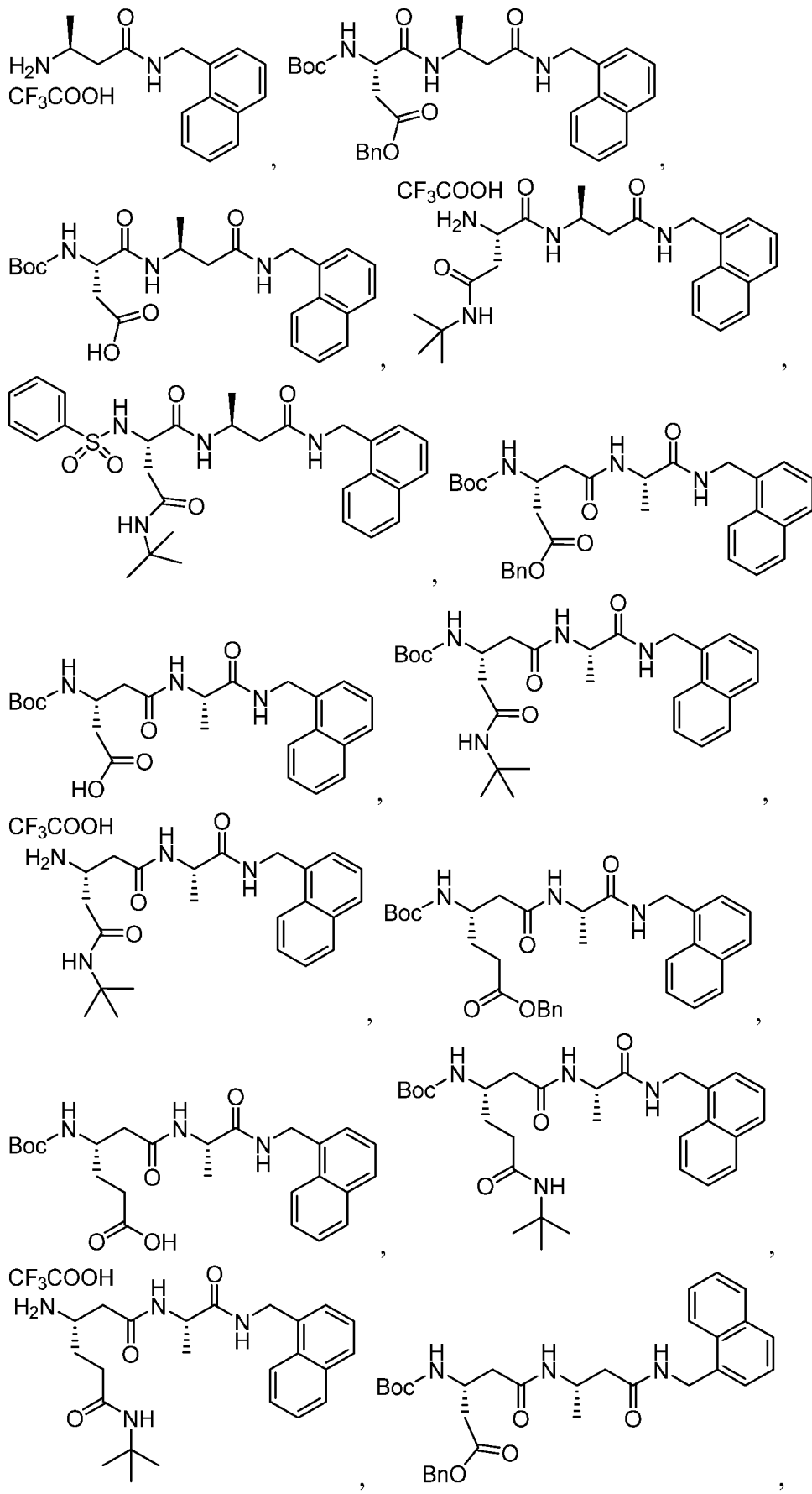
n is 0, 1, 2, or 3; and

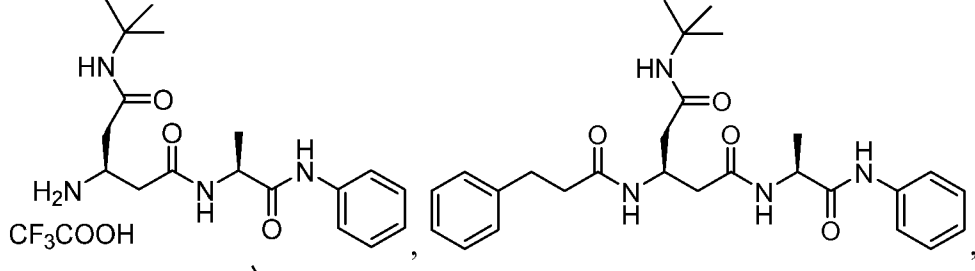
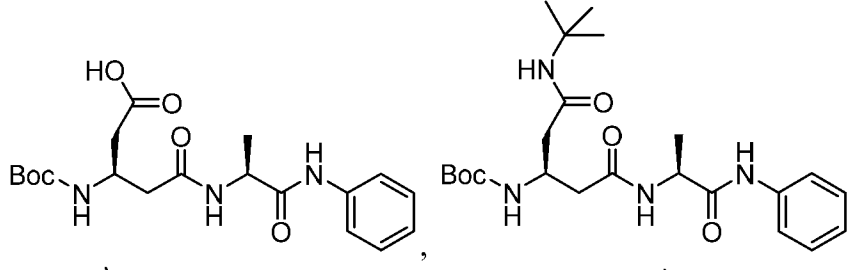
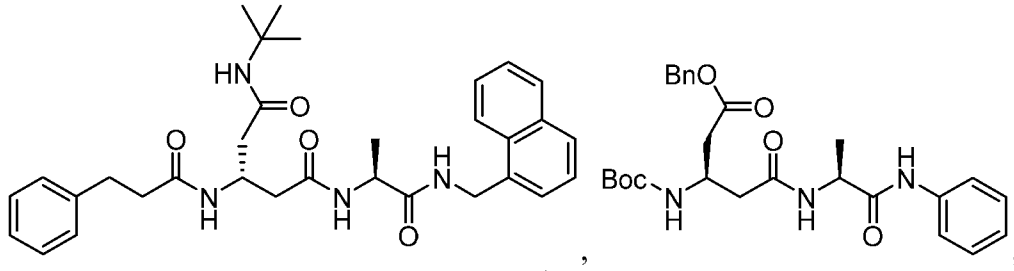
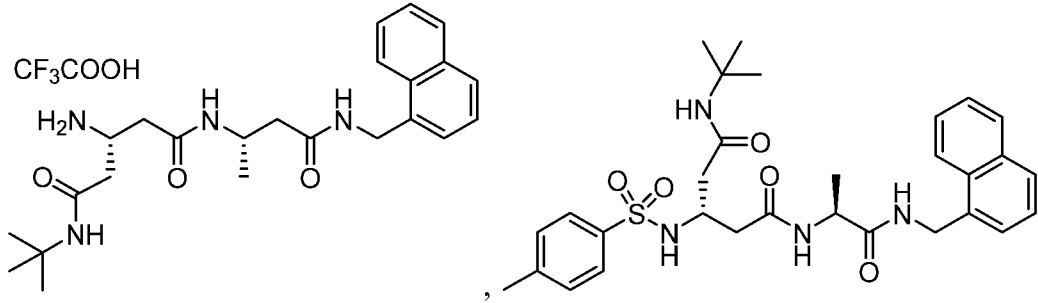
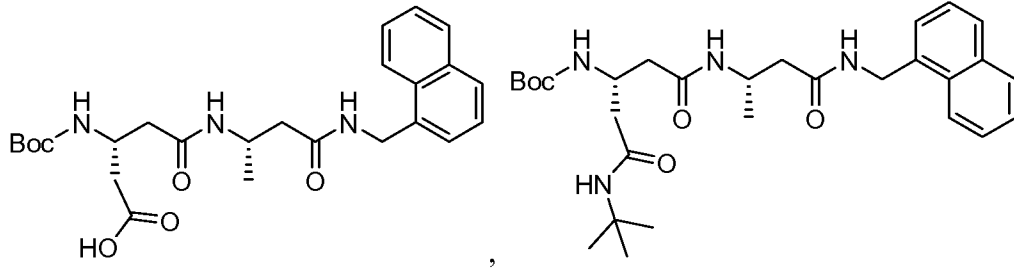
R is selected from the group consisting of H, halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy.

20 7. The compound according to claim 1, wherein the compound of Formula (I) is selected

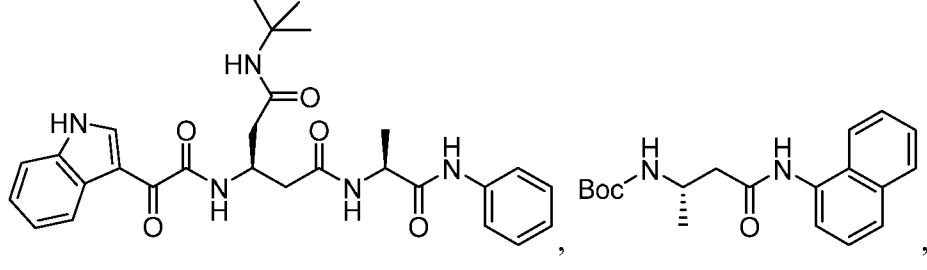








5





$R^2$  is independently selected at each occurrence thereof from the group consisting of H, D,  $C_{1-6}$  alkyl,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-\text{CH}_2\text{Ar}$ , and  $-\text{CH}_2\text{heteroaryl}$ , wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each  
5 occurrence thereof from the group consisting of halogen, cyano,  $C_{1-6}$  alkyl, and  $C_{1-6}$  alkoxy;

$R^3$  is independently selected at each occurrence thereof from the group consisting of H, D,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NHR}^5$ ,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^6\text{R}^7$ ,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{OH}$ , and  $-(\text{CH}_2)_m\text{C}(\text{O})\text{OBn}$ ;

10  $R^4$  is selected from the group consisting of H,  $-\text{C}(\text{O})(\text{CH}_2)_n\text{Ph}$ ,  $-\text{C}(\text{O})\text{CH}_2\text{NR}^6\text{R}^7$ ,  $-\text{SO}_2\text{Ar}$ ,  $-\text{SO}_2\text{C}_{1-6}$  alkyl,  $-\text{SO}_2\text{C}_{3-6}$  cycloalkyl,  $-\text{C}(\text{O})(\text{CH}_2)_n\text{Het}$ ,  $-\text{C}(\text{O})\text{C}(\text{O})\text{Het}$ ,  $-\text{C}(\text{O})\text{C}_{1-6}$  alkyl,  $-\text{C}(\text{O})\text{OC}_{1-6}$  alkyl,  $-\text{C}(\text{O})\text{CF}_3$ , heteroaryl, and  $-(\text{CH}_2)_n\text{NR}^6\text{R}^7$ , wherein aryl (Ar) and heteroaryl (Het) can be optionally substituted from 1 to 3  
15 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $C_{1-6}$  alkyl, and  $C_{1-6}$  alkoxy;

$R^5$  is selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, non-aromatic heterocycle,  $-\text{NR}^6\text{R}^7$ , and  $-\text{CR}^8\text{R}^9$ ;

20  $R^6$ ,  $R^7$ ,  $R^8$ , and  $R^9$  are each independently selected from the group consisting of H, D,  $C_{1-6}$  alkyl, and  $-(\text{CH}_2)_k\text{OH}$ ;

or  $R^6$  and  $R^7$  are taken together with the nitrogen to which they are attached to  
25 form a morpholine ring;

or  $R^8$  and  $R^9$  are taken together with the carbon to which they are attached to form an oxetane ring;

30  $R^x$  is independently selected at each occurrence thereof from the group consisting of H, D,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NHR}^5$ ,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^6\text{R}^7$ , and  $-\text{CH}_2\text{C}(\text{O})\text{R}^5$ ;

$R^y$  is independently selected at each occurrence thereof from the group consisting of H, D,  $C_{1-6}$  alkyl,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-\text{CH}_2\text{Ar}$ , and  $-\text{CH}_2\text{heteroaryl}$ , wherein aryl (Ar) can be

optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

X is  $-(CH_2)_q-$ ,  $-O-$ , or  $-(CD_2)_q-$ ;

5

Y is O or S;

k is 1, 2, or 3;

10

m is 0, 1, 2, 3, 4, or 5;

n is 0, 1, 2, or 3;

p is 1 or 2;

15

q is 0, 1, or 2;

r is 1 or 2; and

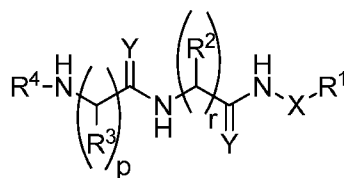
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s is 0 or 1;

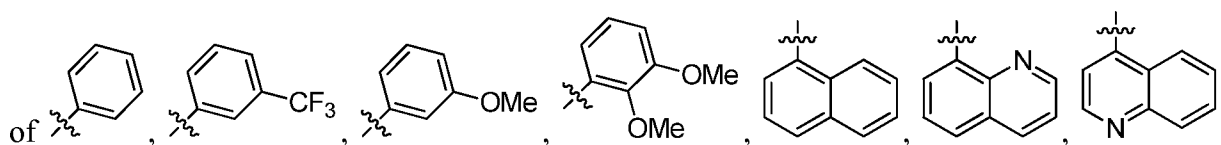
with a proviso that when s is 0, then r is 2; and when s is 1, then  $r + p \geq 3$ .

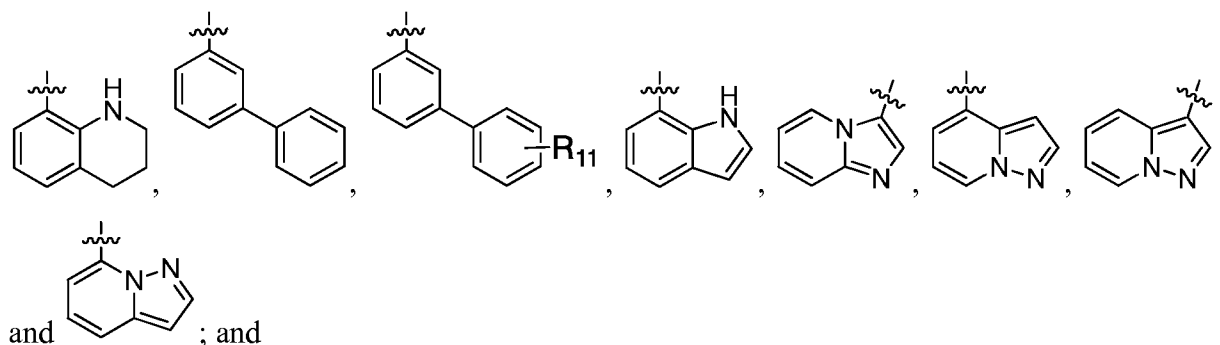
9. The method of claim 8, wherein the compound of Formula (I) has the

25 formula:



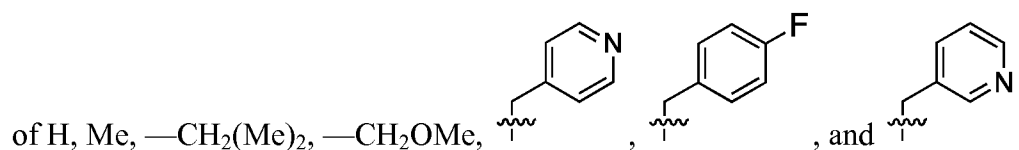
10. The method of claim 8, wherein R<sup>1</sup> is selected from the group consisting



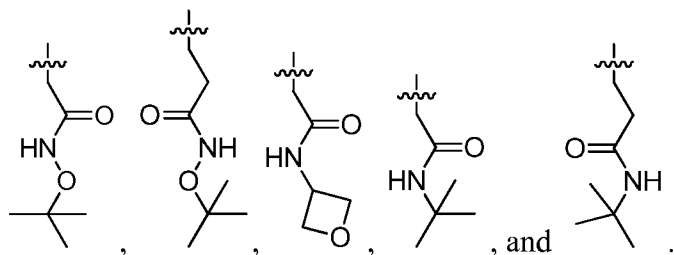


$R^{11}$  is selected from the group consisting of halogen, cyano,  $-\text{CF}_3$ ,  $\text{C}_{1-6}$  alkyl,  
5 and  $\text{C}_{1-6}$  alkoxy.

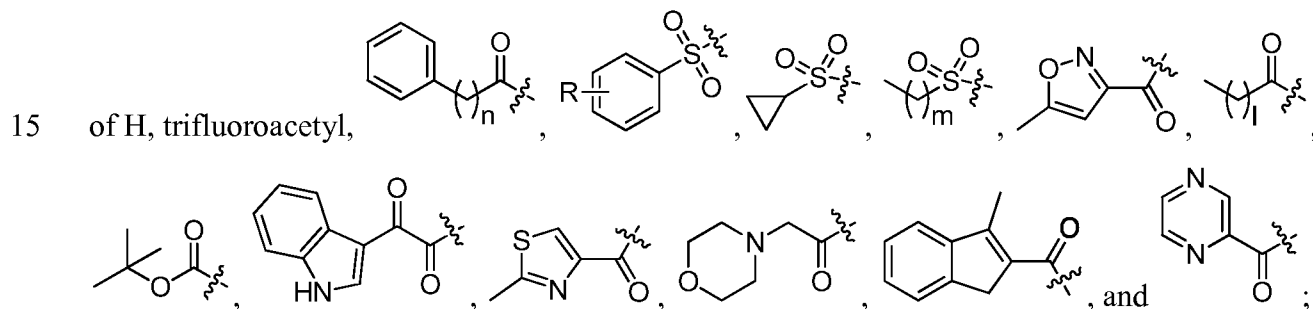
11. The method of claim 8, wherein  $R^2$  is selected from the group consisting



10 12. The method of claim 8, wherein  $R^3$  is selected from the group consisting  
of  $-\text{CH}_2\text{OMe}$ ,  $-\text{CH}_2\text{C}(\text{O})\text{OH}$ ,  $-\text{CH}_2\text{C}(\text{O})\text{OBn}$ ,  $-(\text{CH}_2)_2\text{C}(\text{O})\text{OBn}$ ,  $-(\text{CH}_2)_2\text{C}(\text{O})\text{OH}$ ,



13. The method of claim 8, wherein  $R^4$  is selected from the group consisting



l is 0, 1, 2, 3, or 4;

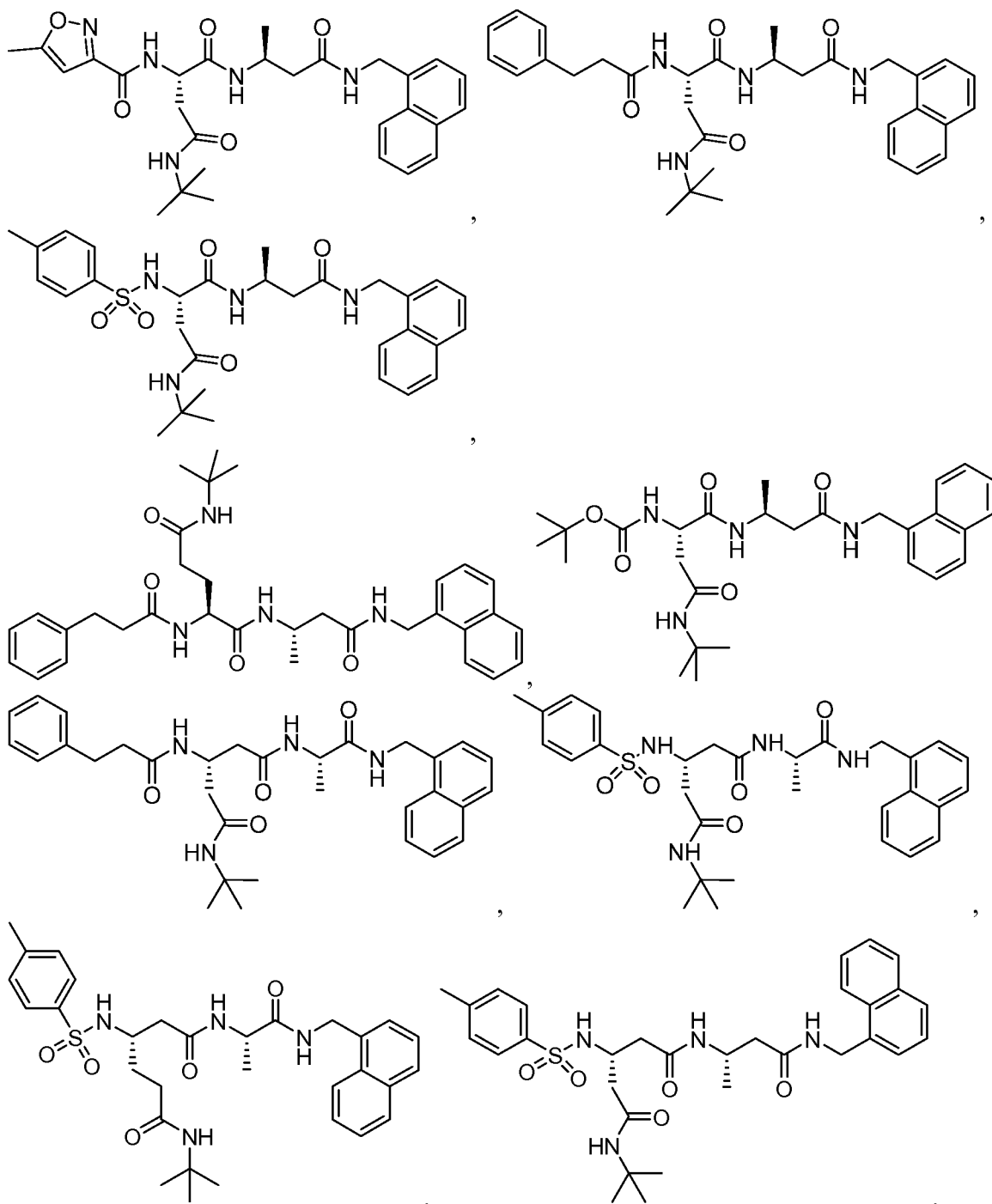
20 m is 0, 1, 2, 3, 4, or 5;

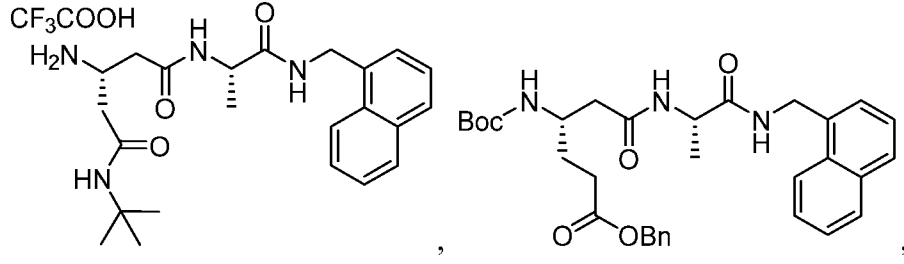
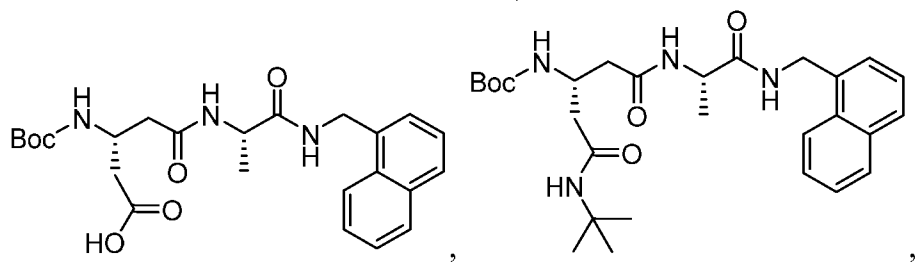
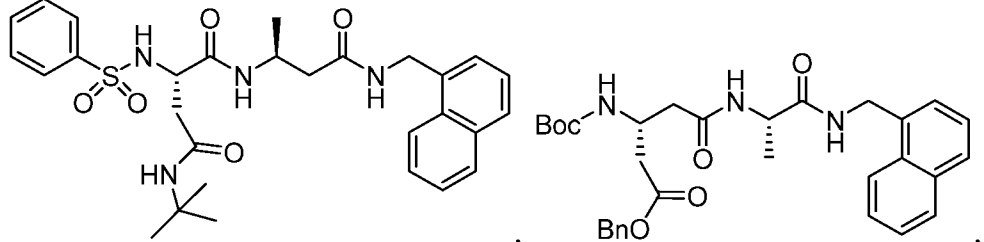
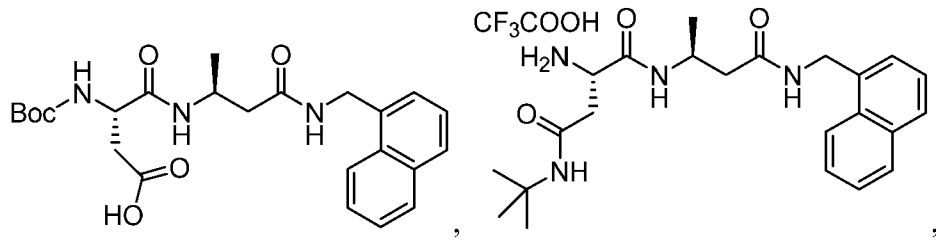
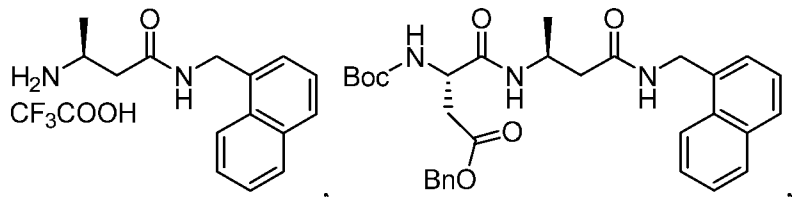
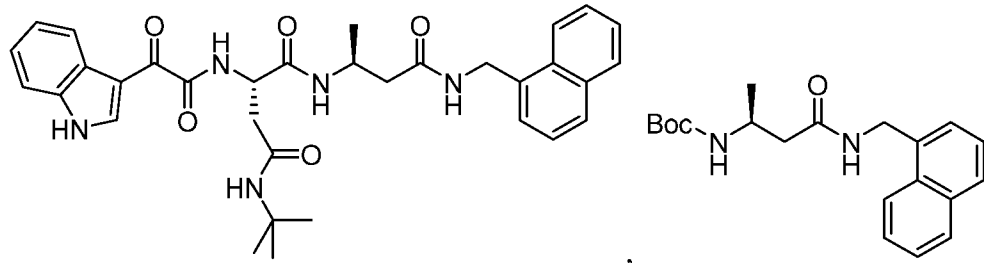
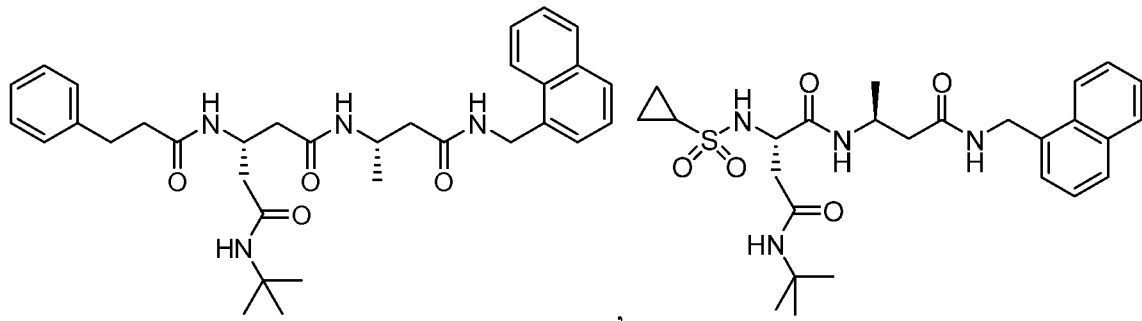
n is 0, 1, 2, or 3; and

R is selected from the group consisting of H, halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub>

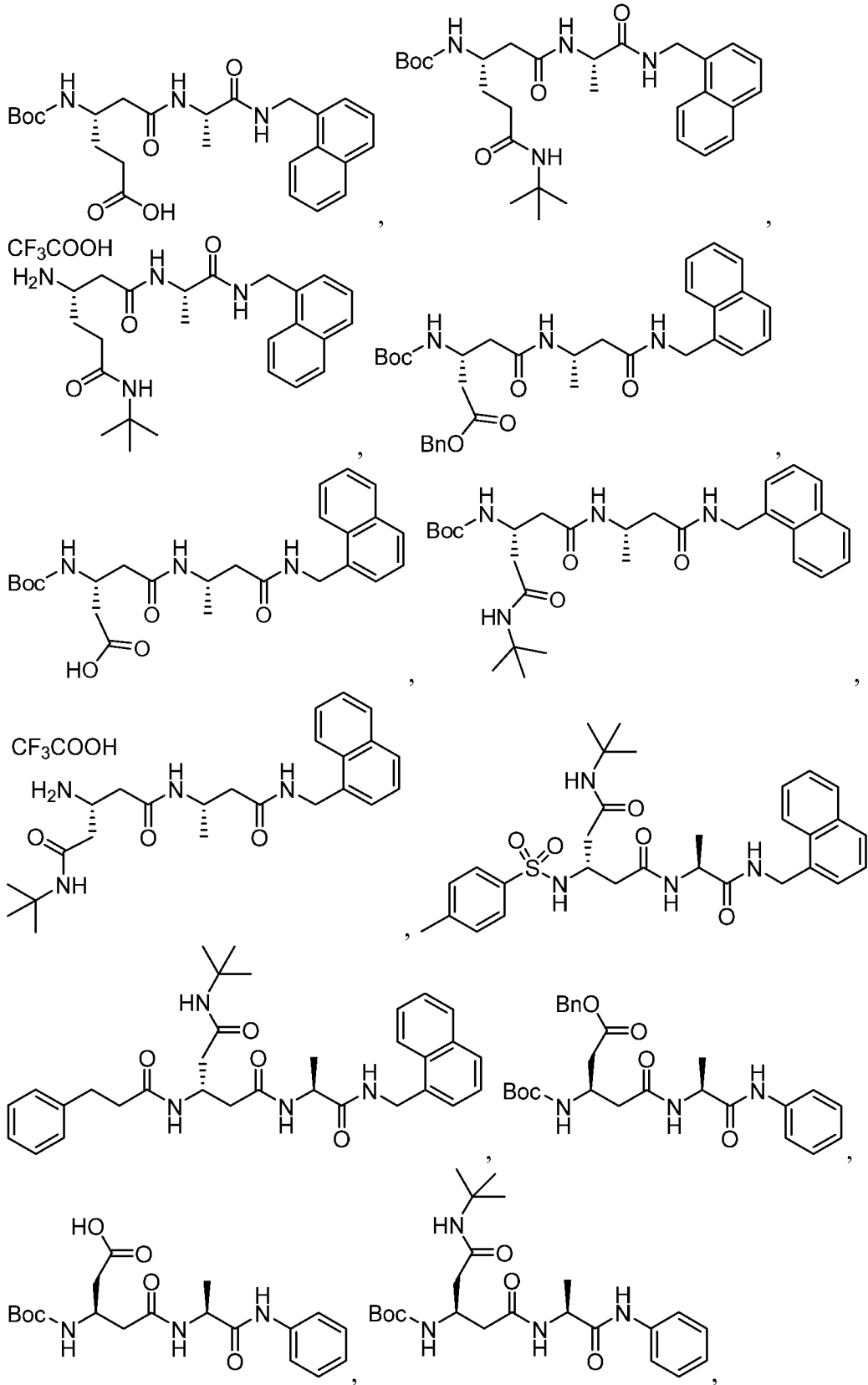
5 alkoxy.

14. The method of claim 8, wherein the compound of Formula (I) is selected from the group consisting of:

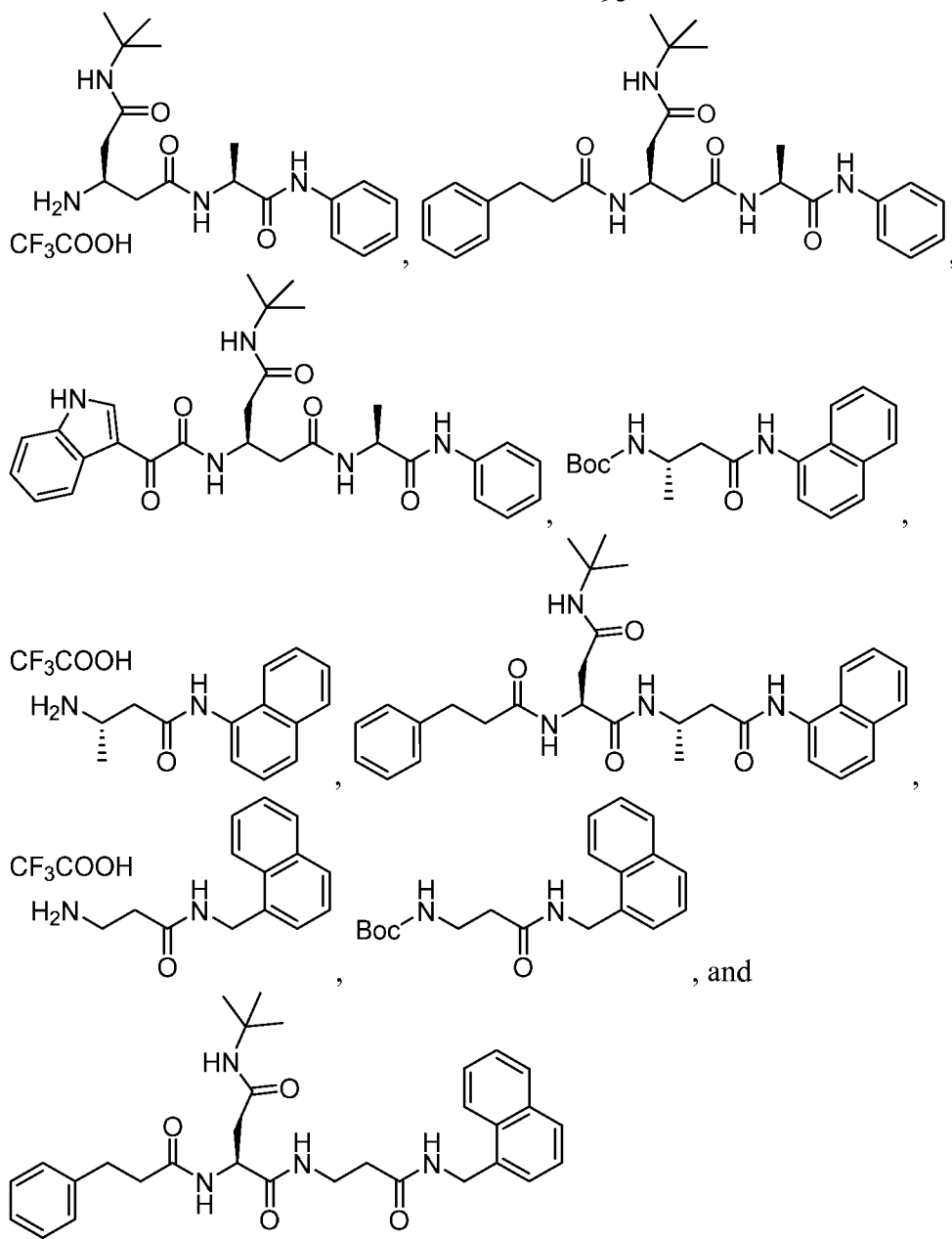




5



5



5

15. The method of claim 8, wherein an autoimmune disorder is treated, said autoimmune disorder being selected from the group consisting of arthritis, colitis, multiple sclerosis, lupus, systemic sclerosis, and sjögren syndrome.

10

16. The method of claim 8, wherein immunosuppression is provided for transplanted organs or tissues, said immunosuppression being used to prevent transplant rejection and graft-verse-host disease.

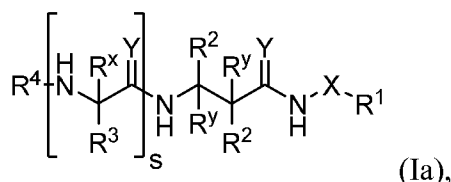
15

17. The method of claim 8, wherein an inflammatory disorder is treated, said inflammatory disorder being Crohn's disease and ulcerative colitis.

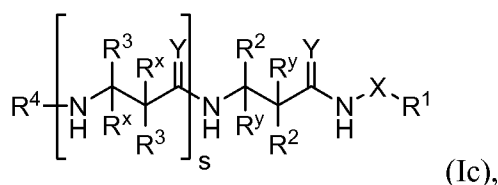
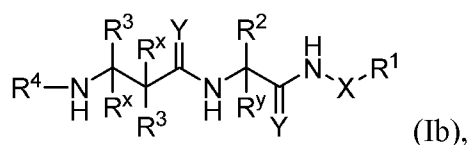
18. The method of claim 8, wherein cancer is treated, said cancer being selected from the group consisting of neoplastic disorders, hematologic malignancies, and lymphocytic malignancies.

5 19. A pharmaceutical composition comprising a therapeutically effective amount of the compound according to claim 1 and a pharmaceutically acceptable carrier.

20. A compound of Formula (Ia), Formula (Ib), or Formula (Ic):



10



wherein

15  $\text{R}^1$  is selected from the group consisting of monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and monocyclic and bicyclic non-aromatic heterocycle, wherein monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and monocyclic and bicyclic non-aromatic heterocycle can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $-\text{CF}_3$ ,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

20

$\text{R}^2$  is independently selected at each occurrence thereof from the group consisting of H, D,  $\text{C}_{1-6}$  alkyl,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-\text{CH}_2\text{Ar}$ , and  $-\text{CH}_2$ heteroaryl, wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

25

$\text{R}^3$  is independently selected at each occurrence thereof from the group consisting of H, D,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NHR}^5$ , and  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^6\text{R}^7$ ;

R<sup>4</sup> is selected from the group consisting of —C(O)(CH<sub>2</sub>)<sub>n</sub>Ph, —C(O)CH<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, —SO<sub>2</sub>Ar, —SO<sub>2</sub>C<sub>1-6</sub> alkyl, —SO<sub>2</sub>C<sub>3-6</sub> cycloalkyl, —C(O)(CH<sub>2</sub>)<sub>n</sub>Het, —C(O)C(O)Het, —C(O)C<sub>1-6</sub> alkyl, —C(O)OC<sub>1-6</sub> alkyl, —C(O)CF<sub>3</sub>, heteroaryl, and —(CH<sub>2</sub>)<sub>n</sub>NR<sup>6</sup>R<sup>7</sup>, wherein aryl (Ar) and heteroaryl (Het) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

R<sup>5</sup> is selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, non-aromatic heterocycle, —NR<sup>6</sup>R<sup>7</sup>, and —CR<sup>8</sup>R<sup>9</sup>;

R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, and R<sup>9</sup> are each independently selected from the group consisting of H, D, C<sub>1-6</sub> alkyl, and —(CH<sub>2</sub>)<sub>k</sub>OH;

or R<sup>6</sup> and R<sup>7</sup> are taken together with the nitrogen to which they are attached to form a morpholine ring;

or R<sup>8</sup> and R<sup>9</sup> are taken together with the carbon to which they are attached to form an oxetane ring;

R<sup>x</sup> is independently selected at each occurrence thereof from the group consisting of H, D, —CH<sub>2</sub>OC<sub>1-6</sub> alkyl, —(CH<sub>2</sub>)<sub>m</sub>C(O)NHR<sup>5</sup>, —(CH<sub>2</sub>)<sub>m</sub>C(O)NR<sup>6</sup>R<sup>7</sup>, and —CH<sub>2</sub>C(O)R<sup>5</sup>;

R<sup>y</sup> is independently selected at each occurrence thereof from the group consisting of H, D, C<sub>1-6</sub> alkyl, —CH<sub>2</sub>OC<sub>1-6</sub> alkyl, —CH<sub>2</sub>Ar, and —CH<sub>2</sub>heteroaryl, wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy;

X is —(CH<sub>2</sub>)<sub>q</sub>—, —O—, or —(CD<sub>2</sub>)<sub>q</sub>—;

Y is O or S;

k is 1, 2, or 3;

m is 0, 1, 2, 3, 4, or 5;

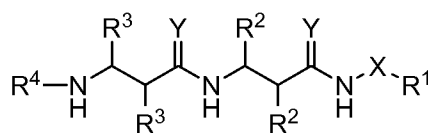
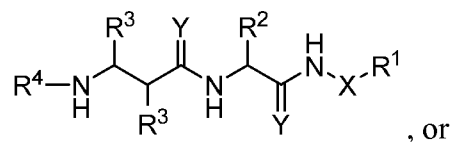
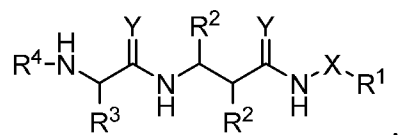
n is 0, 1, 2, or 3;

5 q is 0, 1, or 2; and

s is 0 or 1;

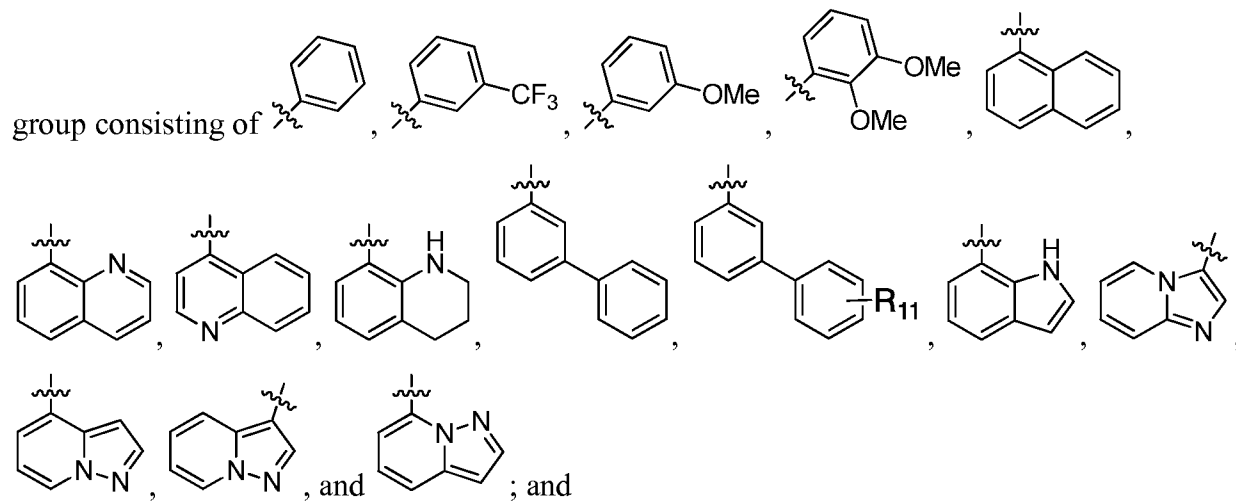
10 or an oxide thereof, a pharmaceutically acceptable salt thereof, a solvate thereof, or a prodrug thereof.

21. The compound according to claim 20 which has the formula:



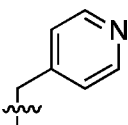
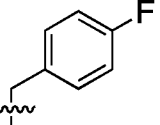
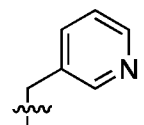
15

22. The compound according to claim 20, wherein  $R^1$  is selected from the

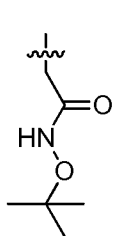
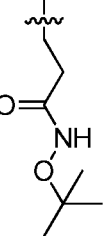
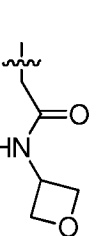
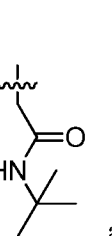
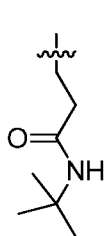


$R^{11}$  is selected from the group consisting of halogen, cyano,  $-\text{CF}_3$ ,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy.

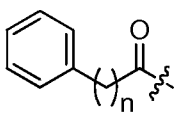
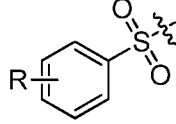
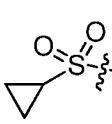
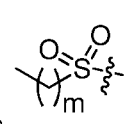
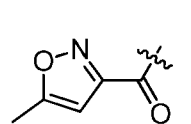
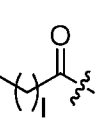
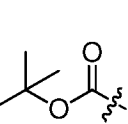
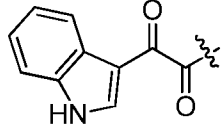
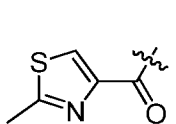
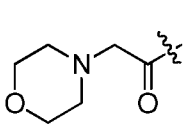
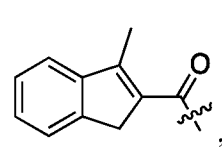
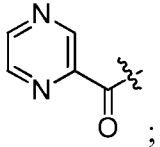
23. The compound according to claim 20, wherein  $R^2$  is selected from the

5 group consisting of Me,  $-\text{CH}_2(\text{Me})_2$ ,  $-\text{CH}_2\text{OMe}$ , , , and .

24. The compound according to claim 20, wherein  $R^3$  is selected from the

10 group consisting of  $-\text{CH}_2\text{OMe}$ , , , , , and .

10 25. The compound according to claim 20, wherein  $R^4$  is selected from the

group consisting of trifluoroacetyl, , , , , , , , , , , , and  ;

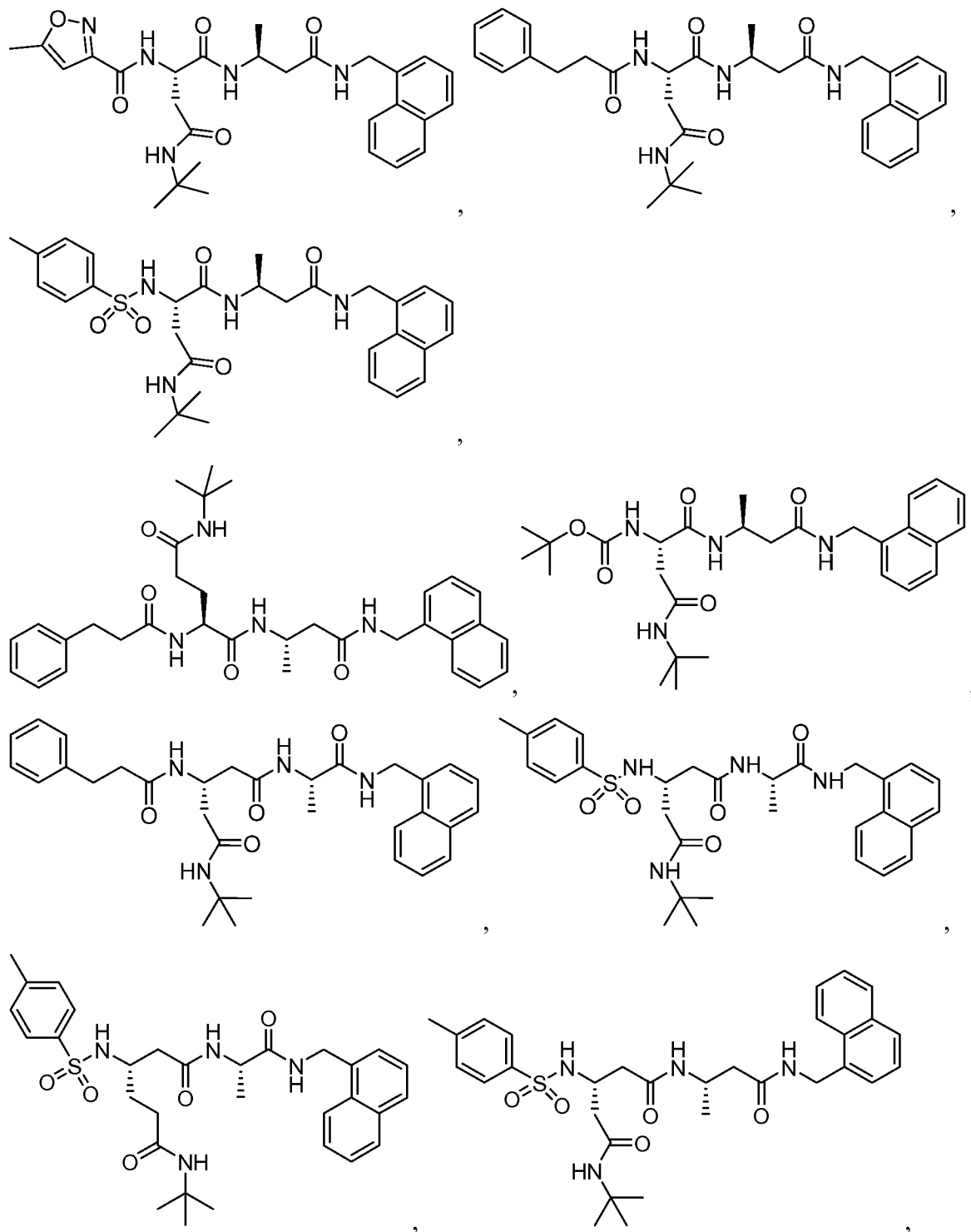
15 l is 0, 1, 2, 3, or 4;

m is 0, 1, 2, 3, 4, or 5;

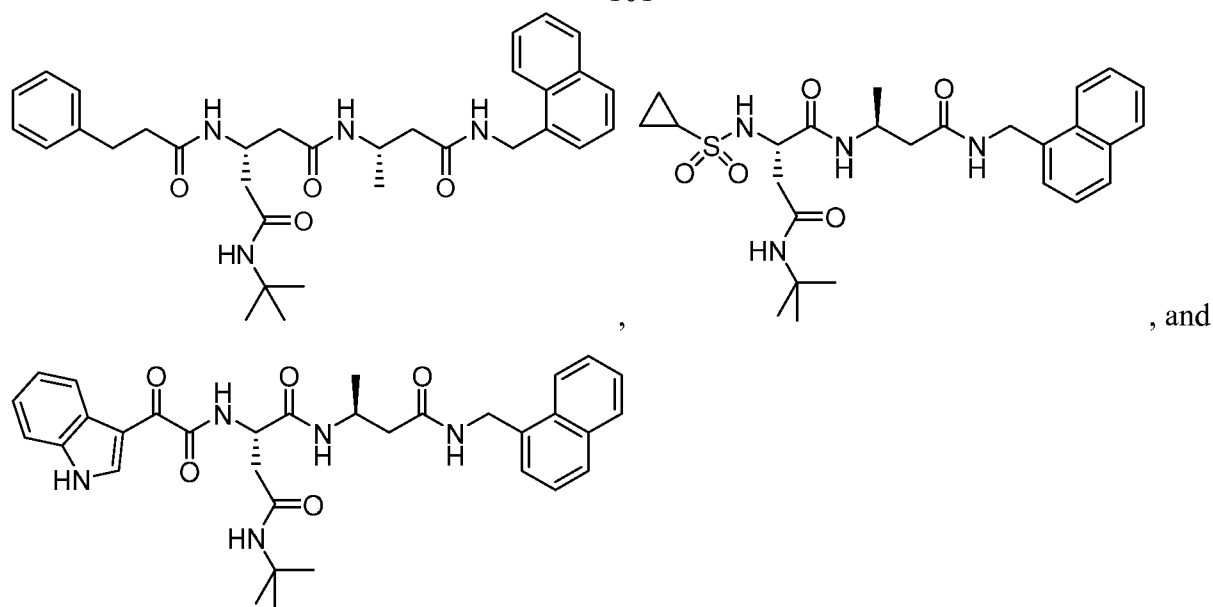
n is 0, 1, 2, or 3; and

20 R is selected from the group consisting of H, halogen, cyano,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy.

26. The compound according to claim 20, wherein the compound of Formula (Ia), Formula (Ib), or Formula (Ic) is selected from the group consisting of:

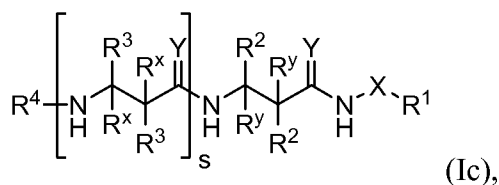
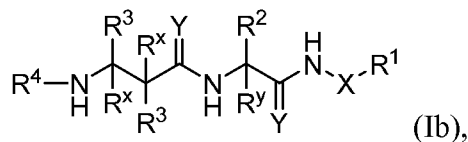
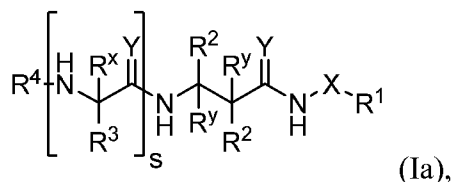


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27. A method of treating cancer, immunologic disorders, autoimmune disorders, neurodegenerative disorders, or inflammatory disorders in a subject or for providing immunosuppression for transplanted organs or tissues in a subject, said method comprising:

administering to the subject in need thereof a compound of the Formula (Ia), Formula (Ib), or Formula (Ic):



wherein

$R^1$  is selected from the group consisting of monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and monocyclic and bicyclic non-aromatic heterocycle, wherein monocyclic and bicyclic aryl, biphenyl, monocyclic and bicyclic heteroaryl, monocyclic and bicyclic heterocyclyl, and monocyclic and bicyclic non-aromatic heterocycle can be optionally substituted from 1 to 3

times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $-\text{CF}_3$ ,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

5  $\text{R}^2$  is independently selected at each occurrence thereof from the group consisting of H, D,  $\text{C}_{1-6}$  alkyl,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-\text{CH}_2\text{Ar}$ , and  $-\text{CH}_2\text{heteroaryl}$ , wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

10  $\text{R}^3$  is independently selected at each occurrence thereof from the group consisting of H, D,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NHR}^5$ , and  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^6\text{R}^7$ ;

15  $\text{R}^4$  is selected from the group consisting of  $-\text{C}(\text{O})(\text{CH}_2)_n\text{Ph}$ ,  $-\text{C}(\text{O})\text{CH}_2\text{NR}^6\text{R}^7$ ,  $-\text{SO}_2\text{Ar}$ ,  $-\text{SO}_2\text{C}_{1-6}$  alkyl,  $-\text{SO}_2\text{C}_{3-6}$  cycloalkyl,  $-\text{C}(\text{O})(\text{CH}_2)_n\text{Het}$ ,  $-\text{C}(\text{O})\text{C}(\text{O})\text{Het}$ ,  $-\text{C}(\text{O})\text{C}_{1-6}$  alkyl,  $-\text{C}(\text{O})\text{OC}_{1-6}$  alkyl,  $-\text{C}(\text{O})\text{CF}_3$ , heteroaryl, and  $-(\text{CH}_2)_n\text{NR}^6\text{R}^7$ , wherein aryl (Ar) and heteroaryl (Het) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy;

20  $\text{R}^5$  is selected from the group consisting of  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy, non-aromatic heterocycle,  $-\text{NR}^6\text{R}^7$ , and  $-\text{CR}^8\text{R}^9$ ;

$\text{R}^6$ ,  $\text{R}^7$ ,  $\text{R}^8$ , and  $\text{R}^9$  are each independently selected from the group consisting of H, D,  $\text{C}_{1-6}$  alkyl, and  $-(\text{CH}_2)_k\text{OH}$ ;

25 or  $\text{R}^6$  and  $\text{R}^7$  are taken together with the nitrogen to which they are attached to form a morpholine ring;

or  $\text{R}^8$  and  $\text{R}^9$  are taken together with the carbon to which they are attached to form an oxetane ring;

30  $\text{R}^x$  is independently selected at each occurrence thereof from the group consisting of H, D,  $-\text{CH}_2\text{OC}_{1-6}$  alkyl,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NHR}^5$ ,  $-(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^6\text{R}^7$ , and  $-\text{CH}_2\text{C}(\text{O})\text{R}^5$ ;

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$R^y$  is independently selected at each occurrence thereof from the group consisting of H, D,  $C_{1-6}$  alkyl,  $-CH_2OC_{1-6}$  alkyl,  $-CH_2Ar$ , and  $-CH_2$ heteroaryl, wherein aryl (Ar) can be optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano,  $C_{1-6}$  alkyl, and  $C_{1-6}$  alkoxy;

5

X is  $-(CH_2)_q-$ ,  $-O-$ , or  $-(CD_2)_q-$ ;

Y is O or S;

10

k is 1, 2, or 3;

m is 0, 1, 2, 3, 4, or 5;

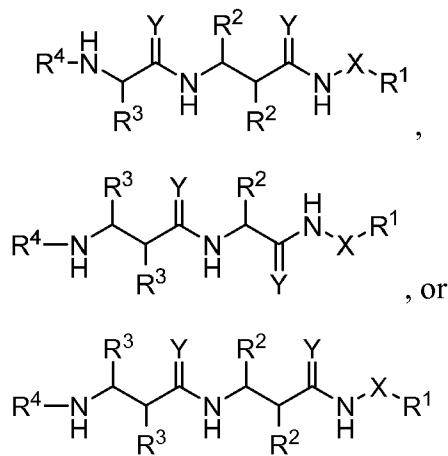
n is 0, 1, 2, or 3;

15

q is 0, 1, or 2; and

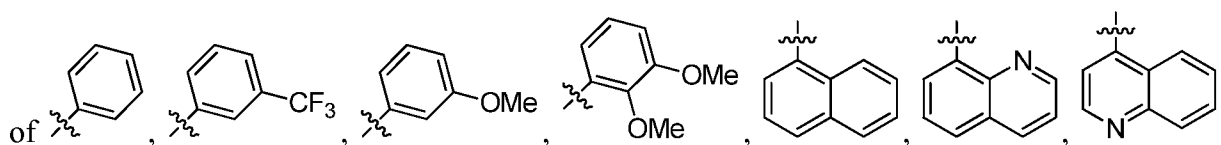
s is 0 or 1.

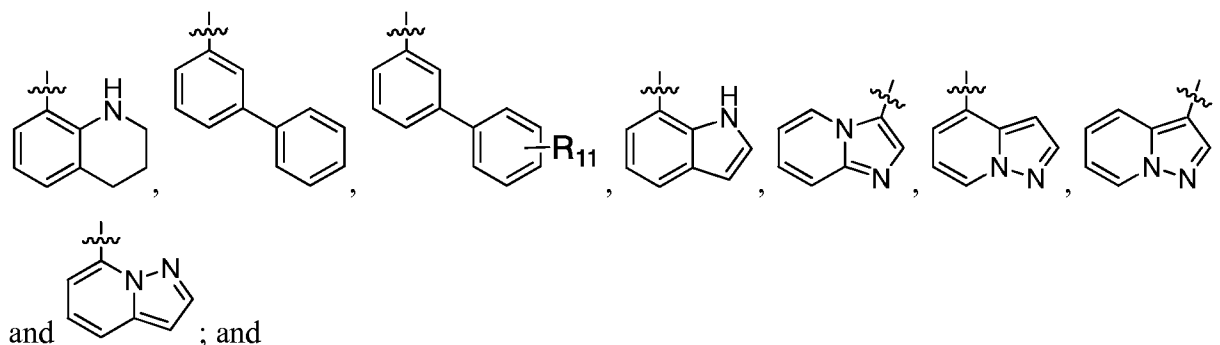
20 28. The method of claim 27, wherein the compound of Formula (Ia), Formula (Ib), or Formula (Ic) has the formula:



25

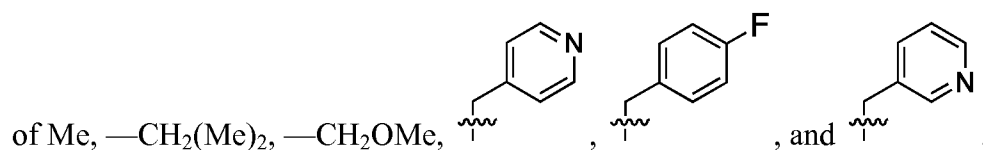
29. The method of claim 27, wherein  $R^1$  is selected from the group consisting



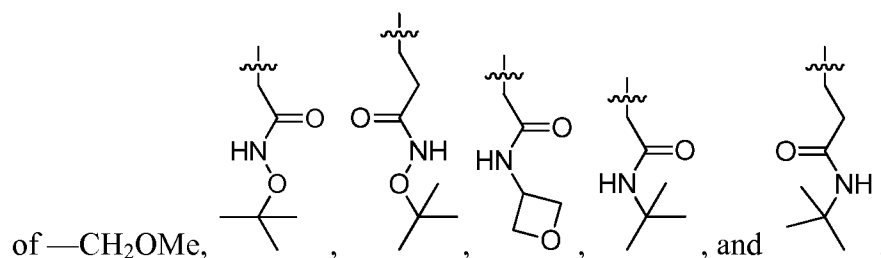


5  $R^{11}$  is selected from the group consisting of halogen, cyano,  $-\text{CF}_3$ ,  $\text{C}_{1-6}$  alkyl, and  $\text{C}_{1-6}$  alkoxy.

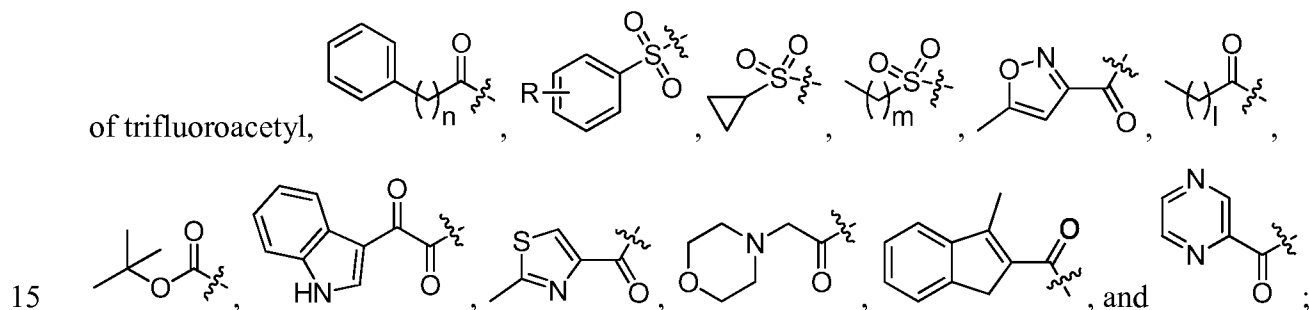
30. The method of claim 27, wherein  $R^2$  is selected from the group consisting



10 31. The method of claim 27, wherein  $R^3$  is selected from the group consisting



32. The method of claim 27, wherein  $R^4$  is selected from the group consisting



l is 0, 1, 2, 3, or 4;

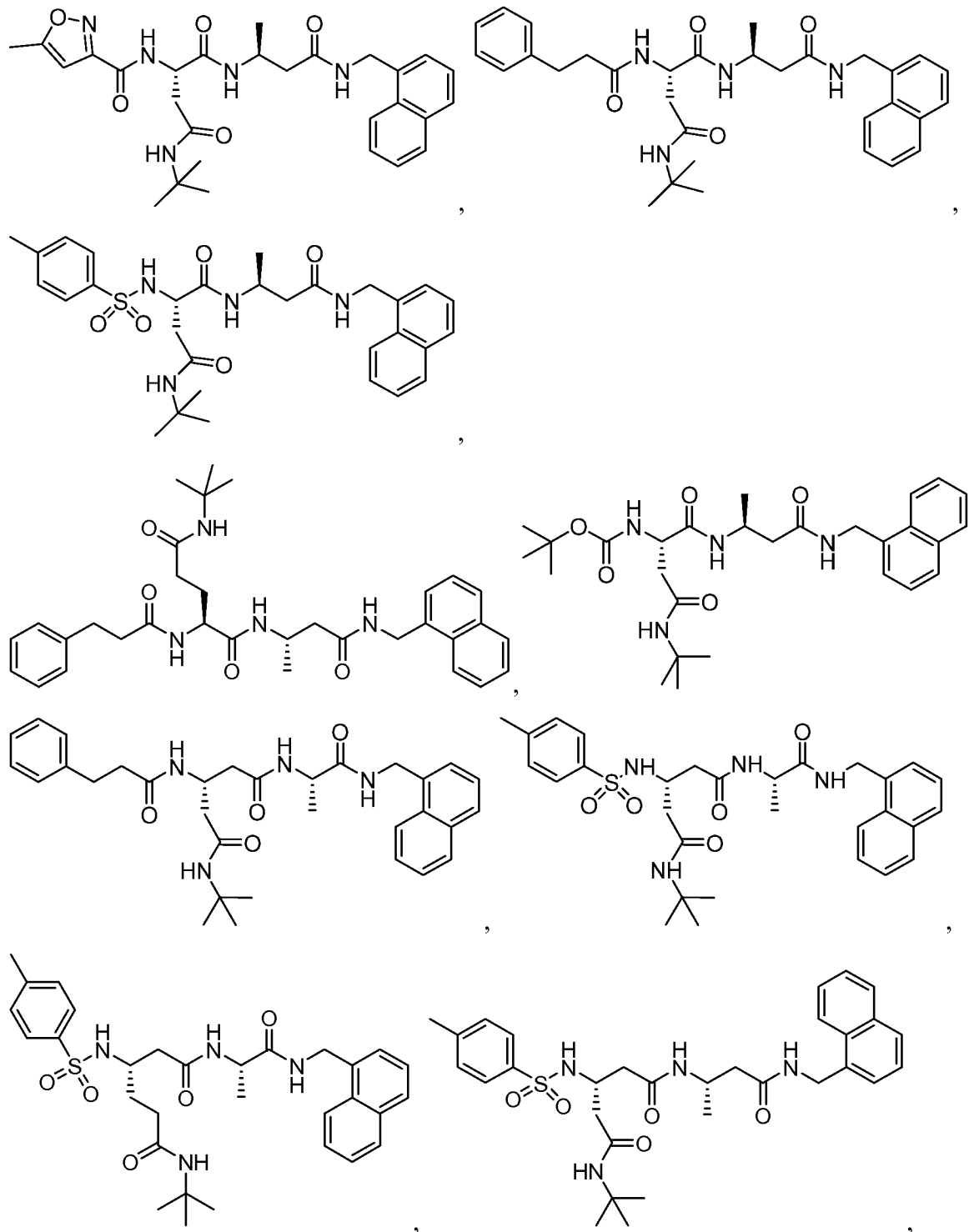
m is 0, 1, 2, 3, 4, or 5;

n is 0, 1, 2, or 3; and

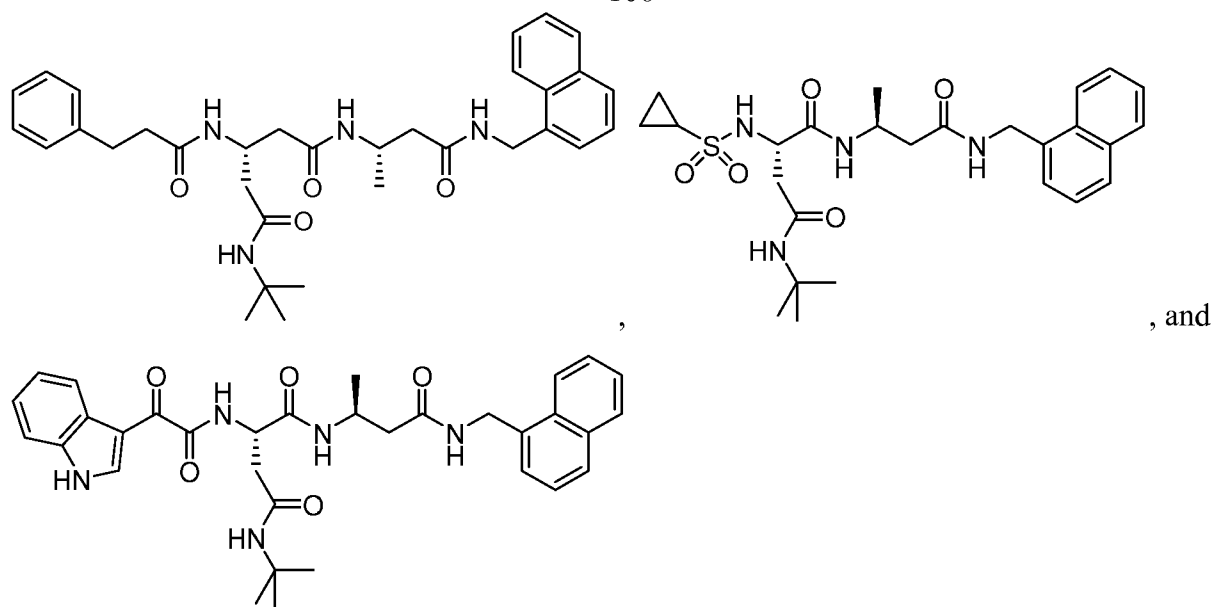
R is selected from the group consisting of H, halogen, cyano, C<sub>1-6</sub> alkyl, and C<sub>1-6</sub> alkoxy.

5

33. The method of claim 27, wherein the compound of Formula (Ia), Formula (Ib), or Formula (Ic) is selected from the group consisting of:



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34. The method of claim 27, wherein an autoimmune disorder is treated, said  
 5 autoimmune disorder being selected from the group consisting of arthritis, colitis, multiple sclerosis, and lupus.

35. The method of claim 27, wherein immunosuppression is provided for  
 transplanted organs or tissues, said immunosuppression being used to prevent transplant  
 10 rejection and graft-versus-host disease.

36. The method of claim 27, wherein an inflammatory disorder is treated, said  
 inflammatory disorder being Crohn's disease.

37. The method of claim 27, wherein cancer is treated, said cancer being  
 selected from the group consisting of neoplastic disorders, hematologic malignancies, and  
 15 lymphocytic malignancies.

38. A pharmaceutical composition comprising a therapeutically effective  
 20 amount of the compound according to claim 20 and a pharmaceutically acceptable carrier.

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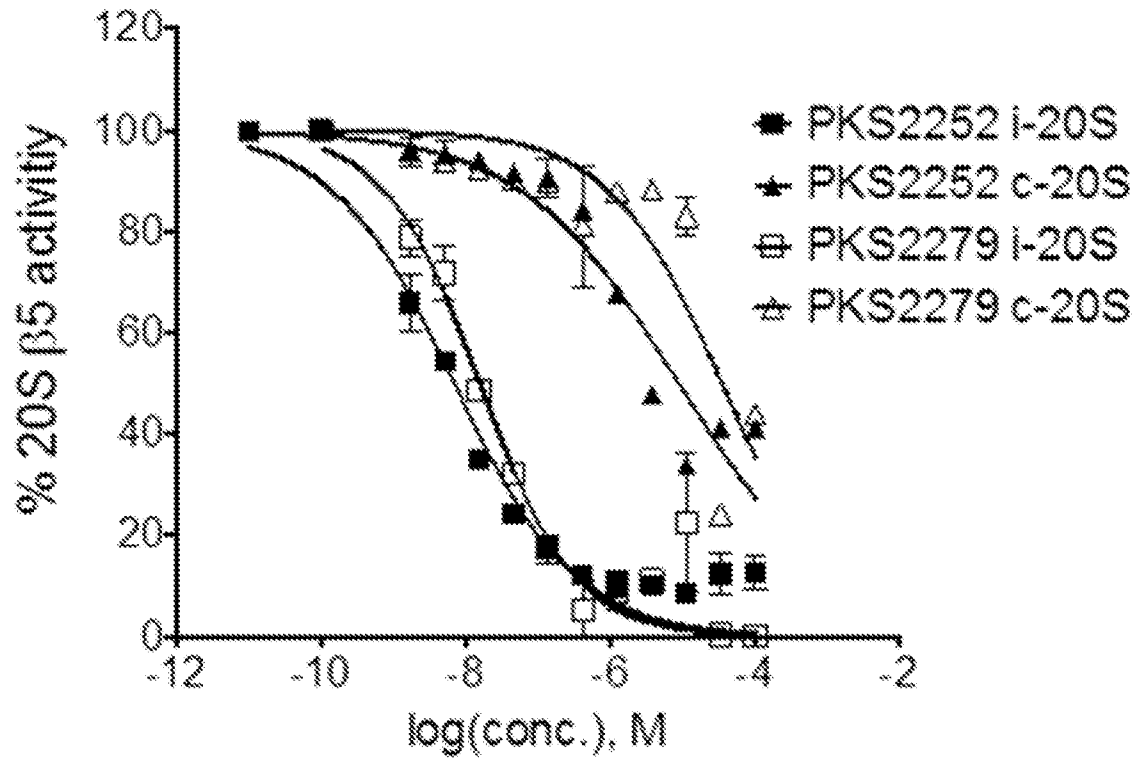


FIGURE 1