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(54) Title: AMIDE COMPOUNDS AS TRYPTOPHAN HYDROXYLASE INHIBITORS

(57) Abstract: The present invention is directed to amide compounds which are inhibitors of tryptophan hydroxylase (TPH), particularly isoform 1 (TPH1), that are useful in the treatment or prevention of diseases or disorders associated with peripheral serotonin including, for example, gastrointestinal, cardiovascular, pulmonary, inflammatory, metabolic, fibrotic, and low bone mass diseases, as well as cancer.

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AMIDE COMPOUNDS AS TRYPTOPHAN HYDROXYLASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to U.S. Provisional Application Serial Nos. 62/097,701, filed on December 30, 2014 and 62/190,481, filed on July 9, 2015, the contents of which are hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention is directed to amide compounds which are inhibitors of tryptophan hydroxylase (TPH), particularly isoform 1 (TPH1), that are useful in the treatment or prevention of diseases or disorders associated with peripheral serotonin including, for example, gastrointestinal, cardiovascular, pulmonary, inflammatory, metabolic, fibrotic, and low bone mass diseases, as well as cancer.

BACKGROUND OF THE INVENTION

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that modulates central and peripheral functions by acting on neurons, smooth muscle, and other cell types. 5-HT is involved in the control and modulation of multiple physiological and psychological processes. In the central nervous system (CNS), 5-HT regulates mood, appetite, and other behavioral functions. In the GI system, 5-HT plays a general prokinetic role and is an important mediator of sensation (e.g., nausea and satiety) between the GI tract and the brain.

Dysregulation of the peripheral 5-HT signaling system has been reported to be involved in the etiology of several conditions (see for example: Mawe, G. M. & Hoffman, J. M. Serotonin Signalling In The Gut-functions, Dysfunctions And Therapeutic Targets. *Nature Reviews. Gastroenterology & Hepatology* **10**, 473–486 (2013); Gershon, M. D. 5-hydroxytryptamine (serotonin) In The Gastrointestinal Tract. *Current Opinion in Endocrinology, Diabetes, and Obesity* **20**, 14–21 (2013); Lesurtel, M., Soll, C., Graf, R. & Clavien, P.-A. Role of Serotonin In The Hepato-gastrointestinal Tract: An Old Molecule For New Perspectives. *Cellular And Molecular Life Sciences : CMLS* **65**, 940–52 (2008)). These include osteoporosis (e.g. Kode, A. *et al.* FOXO1 Orchestrates The Bone-suppressing Function Of Gut-derived Serotonin. *The*

Journal of Clinical Investigation **122**, 3490–503 (2012); Yadav, V. K. *et al.* Pharmacological Inhibition Of Gut-derived Serotonin Synthesis Is A Potential Bone Anabolic Treatment For Osteoporosis. *Nature Medicine* **16**, 308–12 (2010); Yadav, V. K. *et al.* Lrp5 Controls Bone Formation By Inhibiting Serotonin Synthesis In The Duodenum. *Cell* **135**, 825–37 (2008)), cancer (e.g. Liang, C. *et al.* Serotonin Promotes The Proliferation Of Serum-deprived Hepatocellular Carcinoma Cells Via Upregulation Of FOXO3a. *Molecular Cancer* **12**, 14 (2013); Soll, C. *et al.* Serotonin Promotes Tumor Growth In Human Hepatocellular Cancer. *Hepatology* **51,** 1244–1254 (2010); Pai, V. P *et al.* Altered Serotonin Physiology In Human Breast Cancers Favors Paradoxical Growth And Cell Survival. *Breast Cancer Research : BCR* **11**, R81 (2009); Engelman, K., Lovenberg, W. & Sjoerdsma, A. Inhibition Of Serotonin Synthesis By Para-chlorophenylalanine In Patients With The Carcinoid Syndrome. *The New England Journal of Medicine* **277**, 1103–8 (1967)), cardiovascular (e.g. Robiolio, P. A. *et al.* Carcinoid Heart Disease : Correlation of High Serotonin Levels With Valvular Abnormalities Detected by Cardiac Catheterization and Echocardiography. *Circulation* **92**, 790–795 (1995).), diabetes (e.g. Sumara, G., Sumara, O., Kim, J. K. & Karsenty, G. Gut-derived Serotonin Is A Multifunctional Determinant To Fasting Adaptation. *Cell Metabolism* **16**, 588–600 (2012)), atherosclerosis (e.g. Ban, Y. *et al.* Impact Of Increased Plasma Serotonin Levels And Carotid Atherosclerosis On Vascular Dementia. *Atherosclerosis* **195**, 153–9 (2007)), as well as gastrointestinal (e.g. Manocha, M. & Khan, W. I. Serotonin and GI Disorders: An Update on Clinical and Experimental Studies. *Clinical and Translational Gastroenterology* **3**, e13 (2012); Ghia, J.-E. *et al.* Serotonin Has A Key Role In Pathogenesis Of Experimental Colitis. *Gastroenterology* **137**, 1649–60 (2009); Sikander, A., Rana, S. V. & Prasad, K. K. Role Of Serotonin In Gastrointestinal Motility And Irritable Bowel Syndrome. *Clinica Chimica Acta; International Journal of Clinical Chemistry* **403**, 47–55 (2009); Spiller, R. Recent Advances In Understanding The Role Of Serotonin In Gastrointestinal Motility In Functional Bowel Disorders: Alterations In 5-HT Signalling And Metabolism In Human Disease. *Neurogastroenterology and Motility: The Official Journal of The European Gastrointestinal Motility Society* **19 Suppl 2**, 25–31 (2007); Costedio, M. M., Hyman, N. & Mawe, G. M. Serotonin And Its Role In Colonic Function And In Gastrointestinal Disorders. *Diseases of the Colon and Rectum* **50**, 376–88 (2007); Gershon, M. D. & Tack, J. The Serotonin Signaling System: From Basic Understanding To Drug Development For Functional GI Disorders.

Gastroenterology **132**, 397–414 (2007); Mawe, G. M., Coates, M. D. & Moses, P. L. Review Article: Intestinal Serotonin Signalling In Irritable Bowel Syndrome. *Alimentary Pharmacology & Therapeutics* **23**, 1067–76 (2006); Crowell, M. D. Role Of Serotonin In The Pathophysiology Of The Irritable Bowel Syndrome. *British Journal of Pharmacology* **141**, 1285–93 (2004)), pulmonary (e.g. Lau, W. K. W. *et al.* The Role Of Circulating Serotonin In The Development Of Chronic Obstructive Pulmonary Disease. *PloS One* 7, e31617 (2012); Egermayer, P., Town, G. I. & Peacock, A. J. Role Of Serotonin In The Pathogenesis Of Acute And Chronic Pulmonary Hypertension. *Thorax* **54**, 161–168 (1999)), inflammatory (e.g. Margolis, K. G. *et al.* Pharmacological Reduction of Mucosal but Not Neuronal Serotonin Opposes Inflammation In Mouse Intestine. *Gut* doi:10.1136/gutjnl-2013-304901 (2013); Duerschmied, D. *et al.* Platelet Serotonin Promotes The Recruitment Of Neutrophils To Sites Of Acute Inflammation In Mice. *Blood* **121**, 1008–15 (2013); Li, N. *et al.* Serotonin Activates Dendritic Cell Function In The Context Of Gut Inflammation. *The American Journal of Pathology* **178**, 662–71 (2011)), liver diseases or disorders (e.g. Ebrahimkhani, M. R. *et al.* Stimulating Healthy Tissue Regeneration By Targeting The 5-HT2B Receptor In Chronic Liver Disease. *Nature Medicine* **17**, 1668–73 (2011)), idiopathic pulmonary fibrosis (IPF) (e.g. Eickelberg, O. *et al. Increased expression of 5-hydroxytryptamine$_{2A/B}$ receptors in idiopathic pulmonary fibrosis: a rationale for therapeutic intervention* **65**, 949-955 (2010); Dygai, A.M. *Effects of antiserotonin drug on the development of lung fibrosis and blood system reactions after intratracheal administration of bleomycin* **4**, 519-523 (2012); Distler, J. H. W. *Platelet-derived serotonin links vascular disease and tissue fibrosis* **208**, 961-972 (2011)), or Raynaud's syndrome (e.g. Black, C.M. *Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine* **40,** 1038-1043 (2001), Herrick, A. L. *The pathogenesis, diagnosis and treatment of Raynaud phenomenon* **8**, 469-479)). The large number of pharmaceutical agents that block or stimulate the various 5-HT receptors is also indicative of the wide range of medical disorders that have been associated with 5-HT dysregulation (see for example: Wacker, D. *et al.* Structural Features For Functional Selectivity At Serotonin Receptors. *Science (New York, N.Y.)* **340**, 615–9 (2013)).

The rate-limiting step in 5-HT biosynthesis is the hydroxylation of tryptophan by dioxygen, which is catalyzed by tryptophan hydroxylase (TPH; EC 1.14.16.4) in the presence of the cofactor (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4). The resulting oxidized product, 5-hydroxytryptophan (5-HTT) is subsequently decarboxylated by an aromatic amino acid

decarboxylase (AAAD; EC 4.1.1.28) to produce 5-HT. Together with phenylalanine hydroxylase (PheOH) and tyrosine hydroxylase (TH), TPH belongs to the pterin-dependent aromatic amino acid hydroxylase family.

Two vertebrate isoforms of TPH, namely TPH1 and TPH2, have been identified. TPH1 is primarily expressed in the pineal gland and non-neuronal tissues, such as enterochromaffin (EC) cells located in the gastrointestinal (GI) tract. TPH2 (the dominant form in the brain) is expressed exclusively in neuronal cells, such as dorsal raphe or myenteric plexus cells. The peripheral and central systems involved in 5-HT biosynthesis are isolated, with 5-HT being unable to cross the blood-brain barrier. Therefore, the pharmacological effects of 5-HT can be modulated by agents affecting TPH in the periphery, mainly TPH1 in the gut.

A small number of phenylalanine-derived TPH1 inhibitors are known. One example, p-chlorophenylalanine (pCPA), a very weak and unselective irreversible inhibitor of TPH, has proven effective in treating chemotherapy-induced emesis, as well as diarrhea, in carcinoid tumor patients. However, pCPA is distibuted centrally and, as a result, its administration has been linked to the onset of depression and other alterations of CNS functions in patients and animals. p-Ethynyl phenylalanine is a more selective and more potent TPH inhibitor than pCPA (Stokes, A. H. *et al.* p-Ethynylphenylalanine: A Potent Inhibitor Of Tryptophan Hydroxylase. *Journal of Neurochemistry* **74**, 2067–73 (2000), but also affects central 5-HT production and, like pCPA, is believed to irreversibly interfere with the synthesis of TPH (and possibly other proteins). For additional information related to pCPA, see Weber, L.J. "p-Chlorophenylalanine depletion of gastrointestinal 5-hydroxytryptamine," *Biochem Pharmaco.l* 19, 2169-2172 (1970) and (Alpini, G. et al. "Serotonin metabolism is dysregulated in cholangiocarcinoma, which has implications for tumor growth," *Cancer Res.* 68, 9184-9193 (2008).

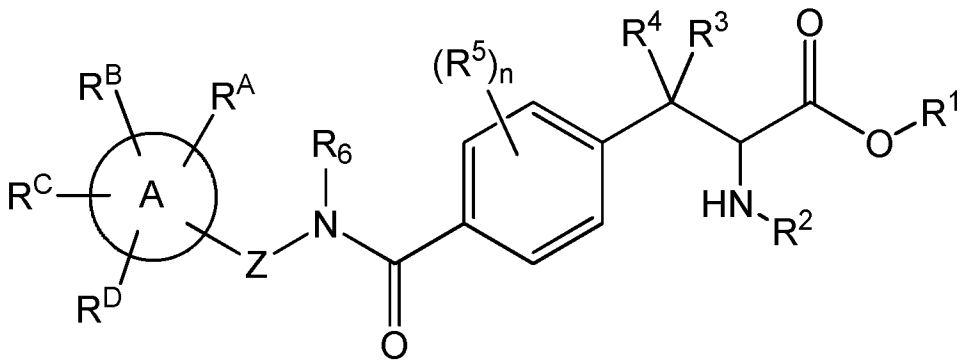
More recently, bulkier phenylalanine-derived TPH inhibitors have been reported to reduce intestinal 5-HT concentration without affecting brain 5-HT levels (Zhong, H. *et al.* Molecular dynamics simulation of tryptophan hydroxylase-1: binding modes and free energy analysis to phenylalanine derivative inhibitors. *International Journal of Molecular Sciences* **14**, 9947–62 (2013); Ouyang, L. *et al.* Combined Structure-Based Pharmacophore and 3D-QSAR Studies on Phenylalanine Series Compounds as TPH1 Inhibitors. *International Journal of Molecular Sciences* **13**, 5348–63 (2012); Camilleri, M. LX-1031, A Tryptophan 5-hydroxylase Inhibitor, And Its Potential In Chronic Diarrhea Associated With Increased Serotonin.

Neurogastroenterology and Motility: The Official Journal of The European Gastrointestinal Motility Society **23**, 193–200 (2011); Cianchetta, G. *et al.* Mechanism of Inhibition of Novel Tryptophan Hydroxylase Inhibitors Revealed by Co-crystal Structures and Kinetic Analysis. *Current chemical genomics* **4**, 19–26 (2010); Jin, H. *et al.* Substituted 3-(4-(1,3,5-triazin-2-yl)-phenyl)-2-aminopropanoic Acids As Novel Tryptophan Hydroxylase Inhibitors. *Bioorganic & Medicinal Chemistry Letters* **19**, 5229–32 (2009); Shi, Z.-C. *et al.* Modulation Of Peripheral Serotonin Levels By Novel Tryptophan Hydroxylase Inhibitors For The Potential Treatment Of Functional Gastrointestinal Disorders. *Journal of medicinal chemistry* **51**, 3684–7 (2008); Liu, Q. *et al.* Discovery And Characterization of Novel Tryptophan Hydroxylase Inhibitors That Selectively Inhibit Serotonin Synthesis In The Gastrointestinal Tract. *The Journal of Pharmacology and Experimental Therapeutics* **325**, 47–55 (2008)).

There is a current need to selectively reduce intestinal 5-HT levels as a means for treating and preventing 5-HT-associated diseases. The TPH1 inhibitors described herein are intended to address this need.

SUMMARY OF THE INVENTION

The present invention relates to a TPH-inhibiting compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein constituent variables are defined herein.

The present invention further relates to a pharmaceutical composition comprising a TPH-inhibiting compound of the invention, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

The present invention further relates to a method of inhibiting TPH, such as TPH1, by contacting the TPH enzyme with a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention further relates to a method of lowering peripheral serotonin in a patient comprising administering to the patient an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention further relates to a method of treating or preventing a disease in a patient comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

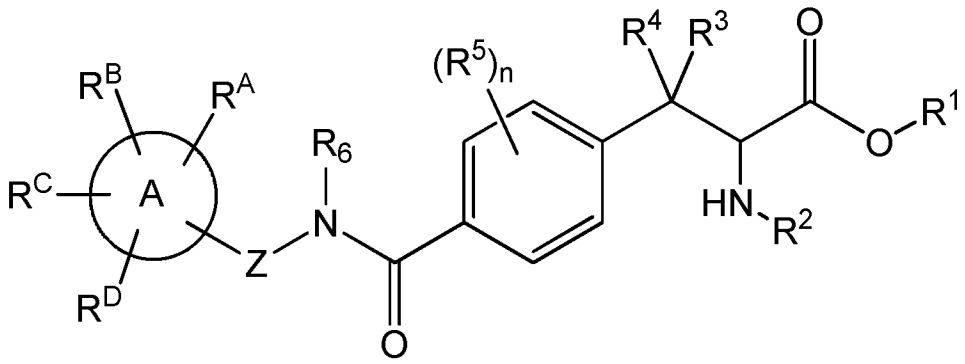
The present invention further relates to a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of disease in a patient.

The present invention further relates to use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment or prevention of disease in a patient.

DETAILED DESCRIPTION

Compounds

The present invention relates to a TPH-inhibiting compound of Formula I:



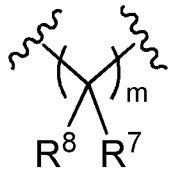
I

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is C_{3-14} cycloalkyl, C_{6-10} aryl, 4 to 14-membered heterocycloalkyl, or 5 to 10-membered heteroaryl;

Z is a bridging C_{3-14} cycloalkyl group, a bridging C_{6-10} aryl group, a bridging 4 to 14-membered heterocycloalkyl group, or a bridging 5 to 10-membered heteroaryl group, each optionally substituted by 1, 2, or 3 substituents independently selected from R^Z;

or Z is:



;

R^1 is H, C_{1-10} alkyl, C_{3-10} cycloalkyl, phenyl, $-(CR^9R^{10})_pOC(O)R^{11}$, $-(C R^9R^{10})_p NR^{11}R^{12}$, or $-(C R^9R^{10})_pC(O)NR^{11}R^{12}$, wherein said C_{1-10} alkyl, C_{3-10} cycloalkyl, and phenyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from F, Cl, Br, CN, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^2 is H, C_{1-4} alkyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, or $C(O)OR^{a1}$;

R^3 and R^4 are each independently selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, OH, and C_{1-4} alkoxy;

each R^5 is independently selected from halo, C_{1-4} alkyl, and C_{1-4} alkoxy;

R^6 is H or C_{1-4} alkyl;

or R^6 and Z, together with the N atom to which they are both attached, form a 4-7 membered heterocycloalkyl group optionally substituted by 1, 2, or 3 substituents independently selected from R^Z;

each R^7 is independently selected from H, halo, and C_{1-4} alkyl;

each R^8 is independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{8a}, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

or R^7 and R^8, when taken together with the single carbon atom to which they are both attached, form a C_{3-7} cycloalkyl group optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

each R^{8a} is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, 5-10 membered heteroaryl-C_{1-6} alkyl, and 4-10 membered heterocycloalkyl-C_{1-6} alkyl, each of which is optionally substituted by 1 or 2 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

R^9 are each independently selected from H and C_{1-4} alkyl;

R^{10} is C_{1-6} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from C_{1-6} haloalkyl, C_{3-10} cycloalkyl, OR^{a3}, and $NR^{c3}R^{d3}$;

R^{11} and R^{12} are each independently selected from H and C_{1-6} alkyl;

R^A is H, Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, or $S(O)_2NR^{c4}R^{d4}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$;

R^B is H, Cy^2, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}S(O)R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, or $S(O)_2NR^{c5}R^{d5}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl

are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from Cy^2, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}S(O)R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^C and R^D are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a6}, SR^{a6}, $C(O)R^{b6}$, $C(O)NR^{c6}R^{d6}$, $C(O)OR^{a6}$, $OC(O)R^{b6}$, $OC(O)NR^{c6}R^{d6}$, $NR^{c6}R^{d6}$, $NR^{c6}C(O)R^{b6}$, $NR^{c6}C(O)OR^{a6}$, $NR^{c6}C(O)NR^{c6}R^{d6}$, $NR^{c6}S(O)R^{b6}$, $NR^{c6}S(O)_2R^{b6}$, $NR^{c6}S(O)_2NR^{c6}R^{d6}$, $S(O)R^{b6}$, $S(O)NR^{c6}R^{d6}$, $S(O)_2R^{b6}$, and $S(O)_2NR^{c6}R^{d6}$;

wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a6}, SR^{a6}, $C(O)R^{b6}$, $C(O)NR^{c6}R^{d6}$, $C(O)OR^{a6}$, $OC(O)R^{b6}$, $OC(O)NR^{c6}R^{d6}$, $NR^{c6}R^{d6}$, $NR^{c6}C(O)R^{b6}$, $NR^{c6}C(O)OR^{a6}$, $NR^{c6}C(O)NR^{c6}R^{d6}$, $NR^{c6}S(O)R^{b6}$, $NR^{c6}S(O)_2R^{b6}$, $NR^{c6}S(O)_2NR^{c6}R^{d6}$, $S(O)R^{b6}$, $S(O)NR^{c6}R^{d6}$, $S(O)_2R^{b6}$, and $S(O)_2NR^{c6}R^{d6}$;

each R^Z is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with a substituent selected from halo, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

Cy^1 and Cy^2 are each independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy};

each R^{Cy} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl, CN, NO_2, OR^{a7}, SR^{a7}, $C(O)R^{b7}$, $C(O)NR^{c7}R^{d7}$, $C(O)OR^{a7}$, $OC(O)R^{b7}$, $OC(O)NR^{c7}R^{d7}$, $NR^{c7}R^{d7}$, $NR^{c7}C(O)R^{b7}$, $NR^{c7}C(O)OR^{a7}$, $NR^{c7}C(O)NR^{c7}R^{d7}$,

$NR^{c7}S(O)R^{b7}$, $NR^{c7}S(O)_2R^{b7}$, $NR^{c7}S(O)_2NR^{c7}R^{d7}$, $S(O)R^{b7}$, $S(O)NR^{c7}R^{d7}$, $S(O)_2R^{b7}$, and $S(O)_2NR^{c7}R^{d7}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, CN, NO_2, OR^{a7}, SR^{a7}, $C(O)R^{b7}$, $C(O)NR^{c7}R^{d7}$, $C(O)OR^{a7}$, $OC(O)R^{b7}$, $OC(O)NR^{c7}R^{d7}$, $NR^{c7}R^{d7}$, $NR^{c7}C(O)R^{b7}$, $NR^{c7}C(O)OR^{a7}$, $NR^{c7}C(O)NR^{c7}R^{d7}$, $NR^{c7}S(O)R^{b7}$, $NR^{c7}S(O)_2R^{b7}$, $NR^{c7}S(O)_2NR^{c7}R^{d7}$, $S(O)R^{b7}$, $S(O)NR^{c7}R^{d7}$, $S(O)_2R^{b7}$, and $S(O)_2NR^{c7}R^{d7}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl;

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6}, R^{a7}, R^{b2}, R^{b4}, R^{b5}, R^{b6}, R^{b7}, R^{c2}, R^{c3}, R^{c4}, R^{c5}, R^{c6}, R^{c7}, R^{d2}, R^{d3}, R^{d4}, R^{d5}, R^{d6}, and R^{d7} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-4} alkyl, halo, CN, OR^{a8}, $C(O)R^{b8}$, $C(O)NR^{c8}R^{d8}$, $C(O)OR^{a8}$, $OC(O)R^{b8}$, $OC(O)NR^{c8}R^{d8}$, $NR^{c8}R^{d8}$, $NR^{c8}C(O)R^{b8}$, $NR^{c8}C(O)NR^{c8}R^{d8}$, $NR^{c8}C(O)OR^{a8}$, $S(O)R^{b8}$, $S(O)NR^{c8}R^{d8}$, $S(O)_2R^{b8}$, $NR^{c8}S(O)_2R^{b8}$, $NR^{c8}S(O)_2NR^{c8}R^{d8}$, and $S(O)_2NR^{c8}R^{d8}$;

each R^{a8}, R^{b8}, R^{c8}, and R^{d8} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{3-7} cycloalkyl, phenyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl, wherein said C_{1-4} alkyl, C_{2-4} alkenyl, C_{3-7} cycloalkyl, phenyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl are each optionally substituted by 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, and di(C_{1-4} alkyl)amino;

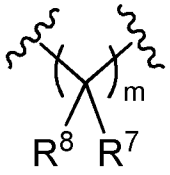
n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4; and

p is 1, 2, 3, or 4;

wherein:

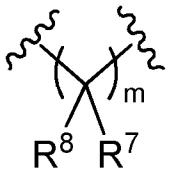
(1) when Z is:



,

R^2 is $C(O)OR^{a1}$, R^{a1} is C_{1-6} alkyl, m is 2, n is 0, R^3 is H, R^4 is H, R^6 is H, R^7 is H, R^8 is H, R^A is H, R^B is H, R^C is H, and R^D is H; then ring A is other than indolyl and naphthyl;

(2) when Z is:



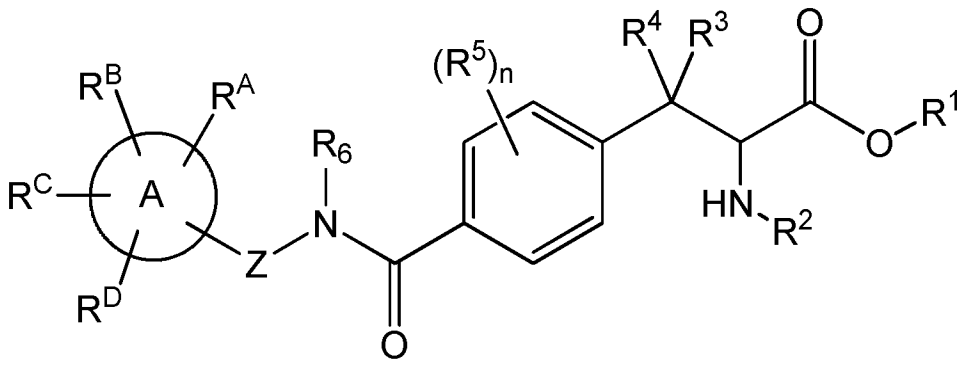
,

R^2 is $C(O)OR^{a1}$, R^{a1} is C_{1-6} alkyl, m is 2, n is 0, R^3 is H, R^4 is H, R^6 is H, R^7 is H, R^8 is H, R^A is cyclohexyl or phenyl, R^B is H, R^C is H, and R^D is H; then ring A is other than phenyl;

(3) when Z is unsubstituted bridging furanyl, R^2 is H, n is 0, R^3 is H, R^4 is H, R^6 is H, and one of R^A, R^B, R^C, and R^D is methoxy; then ring A is other than phenyl; and

(4) when Z is bridging phenyl substituted by amino, R^2 is H, n is 0, R^3 is H, R^4 is H, and R^6 is H; then ring A is other than thienyl.

In some embodiments, the present invention relates to a TPH-inhibiting compound of Formula I:



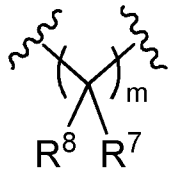
I

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is C_{3-14} cycloalkyl, C_{6-10} aryl, 4 to 14-membered heterocycloalkyl, or 5 to 10-membered heteroaryl;

Z is a bridging C_{3-14} cycloalkyl group, a bridging C_{6-10} aryl group, a bridging 4 to 14-membered heterocycloalkyl group, or a bridging 5 to 10-membered heteroaryl group, each optionally substituted by 1, 2, or 3 substituents independently selected from R^Z;

or Z is:



;

R^1 is H, C_{1-10} alkyl, C_{3-10} cycloalkyl, phenyl, $-(CR^9R^{10})_pOC(O)R^{11}$, $-(C\ R^9R^{10})_pNR^{11}R^{12}$, or $-(C\ R^9R^{10})_pC(O)NR^{11}R^{12}$, wherein said C_{1-10} alkyl, C_{3-10} cycloalkyl, and phenyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from F, Cl, Br, CN, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^2 is H, C_{1-4} alkyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, or $C(O)OR^{a1}$;

R^3 and R^4 are each independently selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, OH, and C_{1-4} alkoxy;

each R^5 is independently selected from halo, C_{1-4} alkyl, and C_{1-4} alkoxy;

R^6 is H or C_{1-4} alkyl;

or R^6 and Z, together with the N atom to which they are both attached, form a 4-7 membered heterocycloalkyl group optionally substituted by 1, 2, or 3 substituents independently selected from R^Z;

each R^7 is independently selected from H, halo, and C_{1-4} alkyl;

each R^8 is independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

or R^7 and R^8, when taken together with the single carbon atom to which they are both attached, form a C_{3-7} cycloalkyl group optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

R^9 are each independently selected from H and C_{1-4} alkyl;

R^{10} is C_{1-6} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from C_{1-6} haloalkyl, C_{3-10} cycloalkyl, OR^{a3}, and $NR^{c3}R^{d3}$;

R^{11} and R^{12} are each independently selected from H and C_{1-6} alkyl;

R^A is H, Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, or $S(O)_2NR^{c4}R^{d4}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$;

R^B is H, Cy^2, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}S(O)R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, or $S(O)_2NR^{c5}R^{d5}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from Cy^2, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}S(O)R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^C and R^D are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a6}, SR^{a6}, $C(O)R^{b6}$, $C(O)NR^{c6}R^{d6}$, $C(O)OR^{a6}$, $OC(O)R^{b6}$, $OC(O)NR^{c6}R^{d6}$, $NR^{c6}R^{d6}$, $NR^{c6}C(O)R^{b6}$, $NR^{c6}C(O)OR^{a6}$, $NR^{c6}C(O)NR^{c6}R^{d6}$, $NR^{c6}S(O)R^{b6}$, $NR^{c6}S(O)_2R^{b6}$, $NR^{c6}S(O)_2NR^{c6}R^{d6}$, $S(O)R^{b6}$, $S(O)NR^{c6}R^{d6}$, $S(O)_2R^{b6}$, and $S(O)_2NR^{c6}R^{d6}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a6}, SR^{a6}, $C(O)R^{b6}$, $C(O)NR^{c6}R^{d6}$, $C(O)OR^{a6}$, $OC(O)R^{b6}$, $OC(O)NR^{c6}R^{d6}$, $NR^{c6}R^{d6}$, $NR^{c6}C(O)R^{b6}$, $NR^{c6}C(O)OR^{a6}$, $NR^{c6}C(O)NR^{c6}R^{d6}$, $NR^{c6}S(O)R^{b6}$, $NR^{c6}S(O)_2R^{b6}$, $NR^{c6}S(O)_2NR^{c6}R^{d6}$, $S(O)R^{b6}$, $S(O)NR^{c6}R^{d6}$, $S(O)_2R^{b6}$, and $S(O)_2NR^{c6}R^{d6}$;

each R^Z is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with a substituent selected from halo, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

Cy^1 and Cy^2 are each independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy};

each R^{Cy} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl, CN, NO_2, OR^{a7}, SR^{a7}, $C(O)R^{b7}$, $C(O)NR^{c7}R^{d7}$, $C(O)OR^{a7}$, $OC(O)R^{b7}$, $OC(O)NR^{c7}R^{d7}$, $NR^{c7}R^{d7}$, $NR^{c7}C(O)R^{b7}$, $NR^{c7}C(O)OR^{a7}$, $NR^{c7}C(O)NR^{c7}R^{d7}$, $NR^{c7}S(O)R^{b7}$, $NR^{c7}S(O)_2R^{b7}$, $NR^{c7}S(O)_2NR^{c7}R^{d7}$, $S(O)R^{b7}$, $S(O)NR^{c7}R^{d7}$, $S(O)_2R^{b7}$, and $S(O)_2NR^{c7}R^{d7}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, CN, NO_2, OR^{a7}, SR^{a7}, $C(O)R^{b7}$, $C(O)NR^{c7}R^{d7}$, $C(O)OR^{a7}$, $OC(O)R^{b7}$, $OC(O)NR^{c7}R^{d7}$, $NR^{c7}R^{d7}$, $NR^{c7}C(O)R^{b7}$, $NR^{c7}C(O)OR^{a7}$, $NR^{c7}C(O)NR^{c7}R^{d7}$, $NR^{c7}S(O)R^{b7}$, $NR^{c7}S(O)_2R^{b7}$, $NR^{c7}S(O)_2NR^{c7}R^{d7}$, $S(O)R^{b7}$, $S(O)NR^{c7}R^{d7}$, $S(O)_2R^{b7}$, and $S(O)_2NR^{c7}R^{d7}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl;

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6}, R^{a7}, R^{b2}, R^{b4}, R^{b5}, R^{b6}, R^{b7}, R^{c2}, R^{c3}, R^{c4}, R^{c5}, R^{c6}, R^{c7}, R^{d2}, R^{d3}, R^{d4}, R^{d5}, R^{d6}, and R^{d7} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-4} alkyl, halo, CN, OR^{a8}, $C(O)R^{b8}$, $C(O)NR^{c8}R^{d8}$, $C(O)OR^{a8}$, $OC(O)R^{b8}$, $OC(O)NR^{c8}R^{d8}$, $NR^{c8}R^{d8}$, $NR^{c8}C(O)R^{b8}$, $NR^{c8}C(O)NR^{c8}R^{d8}$, $NR^{c8}C(O)OR^{a8}$, $S(O)R^{b8}$, $S(O)NR^{c8}R^{d8}$, $S(O)_2R^{b8}$, $NR^{c8}S(O)_2R^{b8}$, $NR^{c8}S(O)_2NR^{c8}R^{d8}$, and $S(O)_2NR^{c8}R^{d8}$;

each R^{a8}, R^{b8}, R^{c8}, and R^{d8} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{3-7} cycloalkyl, phenyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl, wherein said C_{1-4} alkyl, C_{2-4} alkenyl, C_{3-7} cycloalkyl, phenyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl are each optionally substituted by 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, and di(C_{1-4} alkyl)amino;

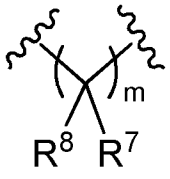
n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4; and

p is 1, 2, 3, or 4;

wherein:

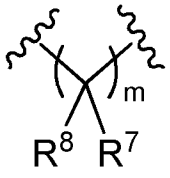
(1) when Z is:



,

R^2 is $C(O)OR^{a1}$, R^{a1} is C_{1-6} alkyl, m is 2, n is 0, R^3 is H, R^4 is H, R^6 is H, R^7 is H, R^8 is H, R^A is H, R^B is H, R^C is H, and R^D is H; then ring A is other than indolyl and naphthyl;

(2) when Z is:



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R^2 is $C(O)OR^{a1}$, R^{a1} is C_{1-6} alkyl, m is 2, n is 0, R^3 is H, R^4 is H, R^6 is H, R^7 is H, R^8 is H, R^A is cyclohexyl or phenyl, R^B is H, R^C is H, and R^D is H; then ring A is other than phenyl;

(3) when Z is unsubstituted bridging furanyl, R^2 is H, n is 0, R^3 is H, R^4 is H, R^6 is H, and one of R^A, R^B, R^C, and R^D is methoxy; then ring A is other than phenyl; and

(4) when Z is bridging phenyl substituted by amino, R^2 is H, n is 0, R^3 is H, R^4 is H, and R^6 is H; then ring A is other than thienyl.

In some embodiments, Ring A is C_{6-10} aryl or 5 to 10-membered heteroaryl.

In some embodiments, Ring A is phenyl, naphthyl, pyridyl, indazolyl, or imidazolyl.

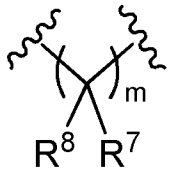
In some embodiments, Ring A is phenyl.

In some embodiments, Z is a bridging C_{3-14} cycloalkyl group, a bridging C_{6-10} aryl group, a bridging 4 to 14-membered heterocycloalkyl group, or a bridging 5 to 10-membered heteroaryl group, each optionally substituted by 1, 2, or 3 substituents independently selected from R^Z.

In some embodiments, Z is a bridging C_{3-7} cycloalkyl group.

In some embodiments, Z is a bridging cyclobutyl group or bridging cyclohexyl group.

In some embodiments, Z is:



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In some embodiments, R^6 and Z, together with the N atom to which they are both attached, form a 4-7 membered heterocycloalkyl group optionally substituted by 1, 2, or 3 substituents independently selected from R^Z.

In some embodiments, R^1 is H, C_{1-10} alkyl, or C_{3-10} cycloalkyl.

In some embodiments, R^1 is H or C_{1-10} alkyl.

In some embodiments, R^1 is H or C_{1-4} alkyl.

In some embodiments, R^1 is H or ethyl.

In some embodiments, R^1 is H.

In some embodiments, R^1 is ethyl.

In some embodiments, R^1 is C_{1-10} alkyl or C_{3-10} cycloalkyl.

In some embodiments, R^1 is ethyl, propyl, butyl, pentyl, or cyclopentyl.

In some embodiments, R^2 is H, C_{1-4} alkyl, $C(O)R^{b1}$, or $C(O)NR^{c1}R^{d1}$.

In some embodiments, R^2 is H.

In some embodiments, R^3 and R^4 are each independently selected from H and C_{1-4} alkyl.

In some embodiments, R^3 and R^4 are both H.

In some embodiments, R^6 is H or methyl.

In some embodiments, R^6 is H.

In some embodiments, each R^7 is independently selected from H and C_{1-4} alkyl.

In some embodiments, each R^7 is independently selected from H and methyl.

In some embodiments, R^7 is H.

In some embodiments, each R^8 is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, and OR^{a2}; wherein said C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{8a}, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

In some embodiments, each R^8 is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{8a}, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

In some embodiments, each R^8 is independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

In some embodiments, each R^8 is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, and OR^{a2}, wherein said C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$,

$OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

In some embodiments, each R^8 is independently selected from H, C_{1-6} alkyl, or C_{3-10} cycloalkyl, wherein said C_{1-6} alkyl and C_{3-10} cycloalkyl, are each optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

In some embodiments, each R^8 is independently selected from H, C_{1-6} alkyl, or C_{3-7} cycloalkyl, wherein said C_{1-6} alkyl is optionally substituted by hydroxyl and said C_{3-7} cycloalkyl is optionally substituted by 1 or 2 methyl groups.

In some embodiments, each R^8 is independently selected from H and 4-7 membered heterocycloalkyl optionally substituted with 1 or 2 substituents independently selected C_{1-6} alkyl and benzyl.

In some embodiments, each R^8 is independently selected from H, piperidinyl, and piperazinyl, each optionally substituted with 1 or 2 substituents independently selected C_{1-6} alkyl and benzyl.

In some embodiments, each R^8 is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^8 is independently selected from H and C_{3-7} cycloalkyl.

In some embodiments, each R^8 is independently selected from H and 2-propyl.

In some embodiments, R^7 and R^8, when taken together with the single carbon atom to which they are both attached, form a C_{3-7} cycloalkyl group optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

In some embodiments, R^7 and R^8, when taken together with the single carbon atom to which they are both attached, form a C_{3-7} cycloalkyl group.

In some embodiments, R^7 and R^8, when taken together with the single carbon atom to which they are both attached, form a cyclopropyl group or a cyclobutyl group.

In some embodiments, n is 0 or 1.

In some embodiments, n is 0.

In some embodiments, m is 1.

In some embodiments, m is 2.

In some embodiments, m is 3.

In some embodiments, m is 4.

In some embodiments, R^A is H, Cy^1, halo, C_{2-6} alkynyl, or OR^{a4}, wherein said C_{2-6} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$.

In some embodiments, R^A is Cy^1, halo, C_{2-6} alkynyl, or OR^{a4}, wherein said C_{2-6} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$.

In some embodiments, R^A is Cy^1.

In some embodiments, Cy^1 is selected from phenyl, pyrazolyl, pyrimidinyl, pyridyl, cyclohexyl, cyclohexenyl, indazolyl, quinolyl, isoquinolyl, piperidinyl, thiazolyl, imidazolyl, benzimidazolyl, and benzo[d][1,3]dioxolyl, each of which is optionally substituted by 1, 2, or 3 substituents independently selected from R^{Cy}.

In some embodiments, Cy^1 is phenyl optionally substituted by 1, 2, or 3 substituents independently selected from R^{Cy}.

In some embodiments, R^{Cy} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, OR^{a7}, $C(O)NR^{c7}R^{d7}$, $C(O)OR^{a7}$, and $NR^{c7}R^{d7}$, wherein said C_{1-6} alkyl is optionally substituted with 1 or 2 substituents independently selected from OR^{a7} and $NR^{c7}R^{d7}$.

In some embodiments, R^{Cy} is independently selected from F, Cl, methyl, ethyl, propyl, butyl, trifluoromethyl, phenyl, cyclopropyl, cyclobutyl, imidazolyl, oxazolyl, pyrazolyl, CN,

hydroxy, methoxy, ethoxy, amino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methoxymethyl, hydroxymethyl, hydroxyethyl, isopropyloxymethyl, aminomethyl, carboxyl, carboxy ethyl ester, oxetanyl, dimethylaminoethyloxy, t-butoxy, cyclopropyloxy,

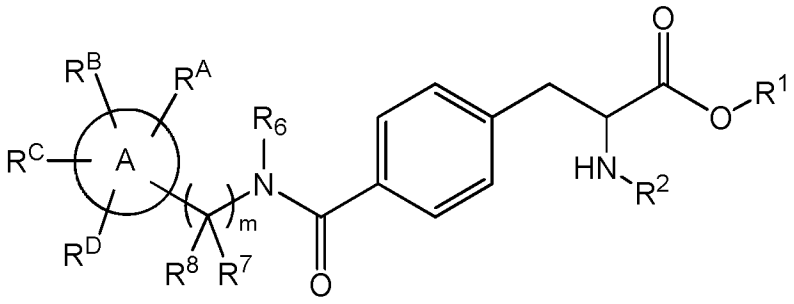
In some embodiments, R^B is H, halo, or OR^{a5}.

In some embodiments, R^B is H.

In some embodiments, R^C is H.

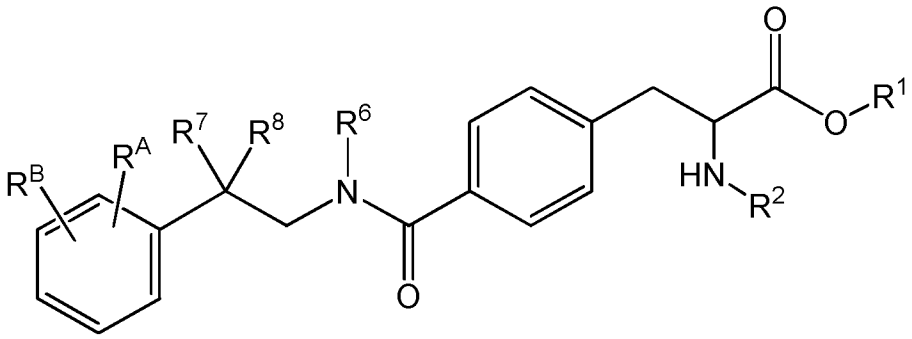
In some embodiments, R^D is H.

In some embodiments, the compound has Formula II:



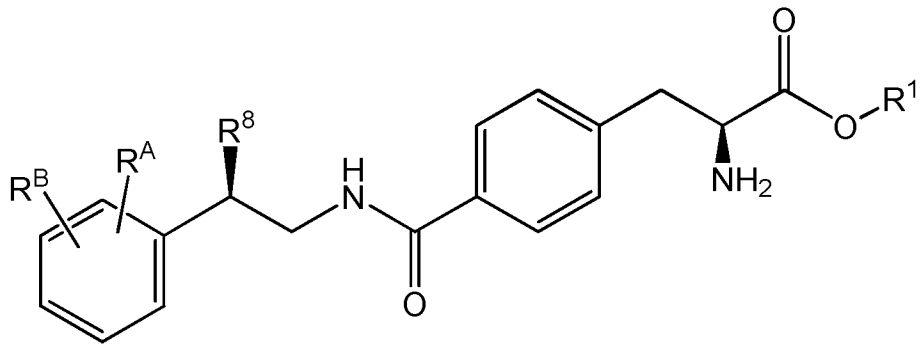
II.

In some embodiments, the compound has Formula III:



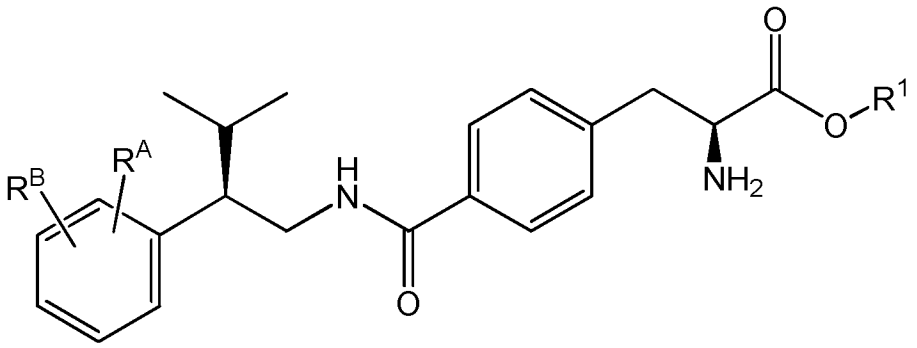
III.

In some embodiments, the compound has Formula IV:



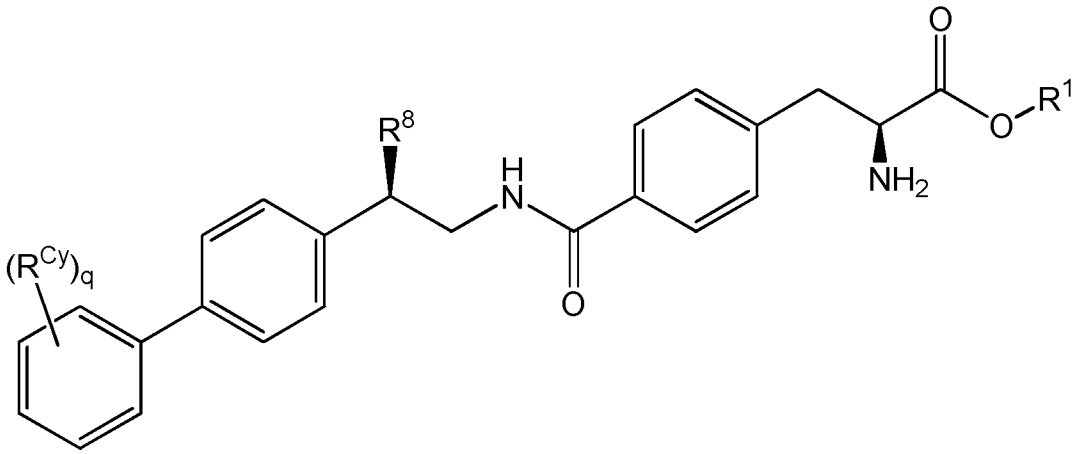
IV.

In some embodiments, the compound has Formula V:



V.

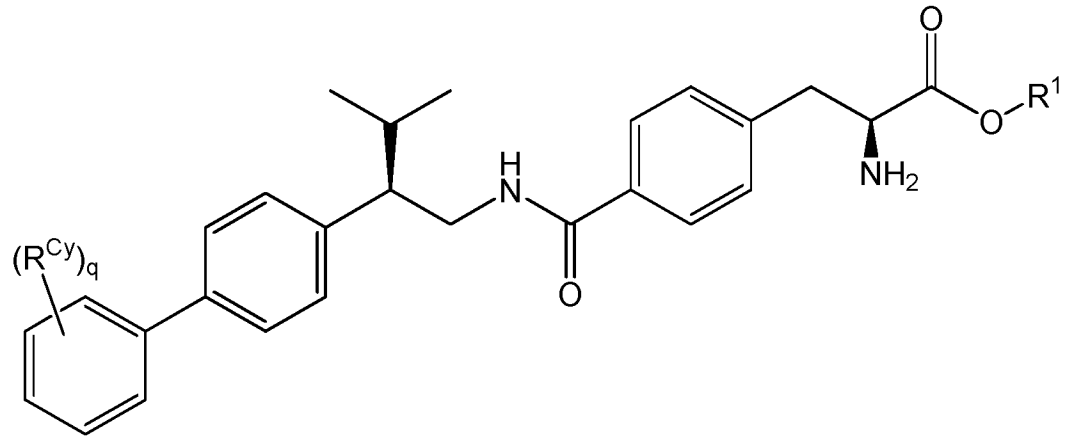
In some embodiments, the compound has Formula VI:



VI

wherein q is 0, 1, 2, or 3.

In some embodiments, the compound has Formula VII:



VII

wherein q is 0, 1, 2, or 3.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

The term "substituted" means that an atom or group of atoms formally replaces hydrogen as a "substituent" attached to another group. The hydrogen atom is formally removed and replaced by a substituent. A single divalent substituent, *e.g.*, oxo, can replace two hydrogen atoms. The term "optionally substituted" means unsubstituted or substituted. The substituents are independently selected, and substitution may be at any chemically accessible position. It is to be understood that substitution at a given atom is limited by valency. Throughout the definitions, the term "C_{i-j}" indicates a range which includes the endpoints, wherein i and j are integers and indicate the number of carbons. Examples include C_{1-4}, C_{1-6}, and the like.

The term "n-membered" where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring, and 1, 2, 3, 4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

At various places in the present specification various aryl, heteroaryl, cycloalkyl, and heterocycloalkyl rings are described. Unless otherwise specified, these rings can be attached to

the rest of the molecule at any ring member as permitted by valency. For example, the term “a pyridine ring” or “pyridinyl” may refer to a pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl ring.

For compounds of the invention in which a variable appears more than once, each variable can be a different moiety independently selected from the group defining the variable. For example, where a structure is described having two R groups that are simultaneously present on the same compound, the two R groups can represent different moieties independently selected from the group defined for R.

As used herein, the term "C_{i-j} alkyl," employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chain or branched, having i to j carbon atoms. In some embodiments, the alkyl group contains from 1 to 10, 1 to 6, 1 to 4, or from 1 to 3 carbon atoms. Examples of alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, *n*-propyl, isopropyl, n-butyl, s-butyl, and t-butyl.

As used herein, the term "C_{i-j} alkoxy," employed alone or in combination with other terms, refers to a group of formula -O-alkyl, wherein the alkyl group has i to j carbon atoms. Example alkoxy groups include methoxy, ethoxy, and propoxy (*e.g.*, n-propoxy and isopropoxy). In some embodiments, the alkyl group has 1 to 3 carbon atoms or 1 to 4 carbon atoms.

As used herein, "C_{i-j} alkenyl" refers to an alkyl group having one or more double carbon-carbon bonds and having i to j carbon atoms. In some embodiments, the alkenyl moiety contains 2 to 6 or to 2 to 4 carbon atoms. Example alkenyl groups include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl, and the like.

As used herein, “C_{i-j} alkynyl”, employed alone or in combination with other terms, refers to an alkyl group having one or more carbon-carbon triple bonds. In some embodiments, the alkynyl moiety contains 2 to 6 or 2 to 4 carbon atoms. Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl, and the like.

As used herein, the term "C_{i-j} alkylamino" refers to a group of formula -NH(alkyl), wherein the alkyl group has i to j carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "di-C_{i-j}-alkylamino" refers to a group of formula -N(alkyl)$_2$, wherein the two alkyl groups each has, independently, i to j carbon atoms. In some embodiments, each alkyl group independently has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "thio" refers to a group of formula -SH.

As used herein, the term "C_{i-j} alkylthio" refers to a group of formula -S-alkyl, wherein the alkyl group has i to j carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "amino" refers to a group of formula $–NH_2$.

As used herein, the term " C_{i-j} aryl," employed alone or in combination with other terms, refers to a monocyclic or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) aromatic hydrocarbon having i to j ring-forming carbon atoms, such as, but not limited to, phenyl, 1-naphthyl, 2-naphthyl, anthracenyl, phenanthrenyl, and the like. In some embodiments, aryl is C_{6-10} aryl. In some embodiments, the aryl group is a naphthalene ring or phenyl ring. In some embodiments, the aryl group is phenyl.

As used herein, the term "arylalkyl" refers to a group of formula $–C_{i-j}$ alkyl–(C_{i-j} aryl). In some embodiments, arylalkyl is C_{6-10} aryl-C_{1-3} alkyl. In some embodiments, arylalkyl is C_{6-10} aryl-C_{1-4} alkyl. In some embodiments, arylalkyl is benzyl.

As used herein, the term "carbonyl," employed alone or in combination with other terms, refers to a -C(=O)- group.

As used herein, the term "carboxy" refers to a group of formula -C(=O)OH.

As used herein, the term "C_{i-j} cycloalkyl," employed alone or in combination with other terms, refers to a non-aromatic cyclic hydrocarbon moiety having i to j ring-forming carbon atoms, which may optionally contain one or more alkenylene groups as part of the ring structure. Cycloalkyl groups can include mono- or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) ring systems. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings (aryl or heteroaryl) fused to the cycloalkyl ring, for example, benzo or pyrido derivatives of cyclopentane, cyclopentene, cyclohexane, and the like. Where the cycloalkyl group includes a fused aromatic ring, the cycloalkyl group can be attached at either an atom in the aromatic or non-aromatic portion. One or more ring-forming carbon atoms of a cycloalkyl group can be oxidized to form carbonyl linkages. In some embodiments, cycloalkyl is C_{3-10} or C_{3-7} cycloalkyl, which can be monocyclic or polycyclic. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, adamantanyl and the like. In some embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein, the term "cycloalkylalkyl" refers to a group of formula –C_{i-j} alkyl–(C_{i-j} cycloalkyl). In some embodiments, cycloalkylalkyl is C_{3-7} cycloalkyl-C_{1-3} alkyl, wherein the cycloalkyl portion is monocyclic. In some embodiments, cycloalkylalkyl is C_{3-7} cycloalkyl-C_{1-4} alkyl.

As used herein, the term "halo" refers to a halogen atom selected from F, Cl, I or Br. In some embodiments, "halo" refers to a halogen atom selected from F, Cl, or Br. In some embodiments, the halo group is F.

As used herein, the term "C_{i-j} haloalkyl," employed alone or in combination with other terms, refers to an alkyl group having from one halogen atom to 2s+1 halogen atoms which may be the same or different, where "s" is the number of carbon atoms in the alkyl group, wherein the alkyl group has i to j carbon atoms. In some embodiments, the haloalkyl group is fluoromethyl, difluoromethyl, or trifluoromethyl. In some embodiments, the haloalkyl group is trifluoromethyl. In some embodiments, the haloalkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "heteroaryl," employed alone or in combination with other terms, refers to a monocyclic or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) aromatic moiety, having one or more heteroatom ring members selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl group is a 5- to 10-membered heteroaryl ring, which is monocyclic or bicyclic and which has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl group is a 5- to 6-membered heteroaryl ring, which is monocyclic and which has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. When the heteroaryl group contains more than one heteroatom ring member, the heteroatoms may be the same or different. The nitrogen atoms in the ring(s) of the heteroaryl group can be oxidized to form N-oxides. Example heteroaryl groups include, but are not limited to, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, pyrazole, azolyl, oxazole, thiazole, imidazole, furan, thiophene, quinoline, isoquinoline, indole, benzothiophene, benzofuran, benzisoxazole, imidazo[1,2-*b*]thiazole, purine, and the like.

A 5-membered heteroaryl is a heteroaryl group having five ring-forming atoms comprising carbon and one or more (*e.g.*, 1, 2, or 3) ring atoms independently selected from N, O, and S. Example five-membered heteroaryls include thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-

thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl.

A six-membered heteroaryl is a heteroaryl group having six ring-forming atoms wherein one or more (*e.g.*, 1, 2, or 3) ring atoms are independently selected from N, O, and S. Example six-membered heteroaryls include pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

As used herein, the term "heteroarylalkyl" refers to a group of formula $-C_{i-j}$ alkyl-(heteroaryl). In some embodiments, heteroarylalkyl 5-10 membered heteteroaryl-C_{1-4} alkyl, wherein the heteroaryl portion is monocyclic or bicyclic and has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroarylalkyl is 5-6 membered heteteroaryl-C_{1-3} alkyl or 5-6 membered heteteroaryl-C_{1-4} alkyl, wherein the heteroaryl portion is monocyclic and has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen.

As used herein, the term "heterocycloalkyl," employed alone or in combination with other terms, refers to a non-aromatic ring or ring system, which optionally contains one or more alkenylene groups as part of the ring structure, and which has at least one heteroatom ring member independently selected from nitrogen, sulfur and oxygen. When the heterocycloalkyl groups contains more than one heteroatom, the heteroatoms may be the same or different. Heterocycloalkyl groups can include mono- or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) ring systems, including spiro systems. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings (aryl or heteroaryl) fused to the non-aromatic ring, for example, 1,2,3,4-tetrahydro-quinoline, dihydrobenzofuran and the like. Where the heterocycloalkyl group includes a fused aromatic ring, the heterocycloalkyl group can be attached at either an atom in the aromatic or non-aromatic portion. The carbon atoms or heteroatoms in the ring(s) of the heterocycloalkyl group can be oxidized (e.g. have one or two oxo substituents) to form a carbonyl, or sulfonyl group (or other oxidized linkage) or a nitrogen atom can be quaternized. In some embodiments, the heterocycloalkyl group is 5- to 10-membered, which can be monocyclic or bicyclic and which has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heterocycloalkyl group is 5- to 6-membered or 5- to 7-membered. Examples of heterocycloalkyl groups include 1, 2, 3, 4-tetrahydroquinoline, dihydrobenzofuran, azetidine, azepane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, and pyran. Further examples of

heterocycloalkyl groups include 2-oxotetrahydrofuranyl, 2-oxopyrrolidinyl, 2-oxoimidazolidinyl, 1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl, and 2-oxo-1,3-dioxolan-4-yl.

As used herein, the term "heterocycloalkylalkyl" refers to a group of formula $-C_{i-j}$ alkyl-(heterocycloalkyl). In some embodiments, heterocycloalkylalkyl is 5-10 membered heterocycloalkyl-C_{1-3} alkyl or 5-10 membered heterocycloalkyl-C_{1-4} alkyl, wherein the heterocycloalkyl portion is monocyclic or bicyclic and has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, heterocycloalkylalkyl is 5-6 membered heterocycloalkyl-C_{1-4} alkyl wherein the heterocycloalkyl portion is monocyclic and has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen.

As used herein, the term “bridging,” when used to describe a cyclic group (as in a ring), is meant to refer to a ring that connects at least two portions of a molecule. For example, when Z is a bridging aryl group, the aryl group is linked to both Ring A (lefthand side of molecule) and the nitrogen atom of the NR^6 moeity (righthand side of molecule) in compounds of Formula I. The two portions of the molecule which are linked via the bridging ring can be connected to the bridging ring at, for example, a single ring-forming atom of the bridging ring, adjacent ring-forming atoms of the bridging ring, or non-adjacent ring-forming atoms of the bridging ring.

The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereoisomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. *Cis* and *trans* geometric isomers of the compounds of the present invention may be isolated as a mixture of isomers or as separated isomeric forms.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallization using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and

L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β-camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α-methylbenzylamine (*e.g., S* and *R* forms, or diastereoisomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (*e.g.,* dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

Compounds of the invention can also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, amide - imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, *1H*- and *3H*-imidazole, *1H*-, *2H*- and 4H-1, 2, 4-triazole, *1H*- and *2H*- isoindole, and *1H*- and *2H*-pyrazole.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

The term "compound," as used herein, is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified. Compounds herein identified by name or structure without specifying the particular configuration of a stereocenter are meant to encompass all the possible configurations at the stereocenter. For example, if a particular stereocenter in a compound of the invention could be R or S, but the name or structure of the compound does not designate which it is, than the stereocenter can be either R or S.

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (*e.g.*, hydrates and solvates) or can be isolated.

In some embodiments, the compounds of the invention, or salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compounds of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the invention, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The expressions, "ambient temperature" and "room temperature," as used herein, are understood in the art, and refer generally to a temperature, *e.g.*, a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, EtOAc, alcohols (*e.g.*, methanol, ethanol, iso-propanol, or butanol) or acetonitrile (CH_3CN) are preferred. Lists of suitable salts are found in *Remington's*

Pharmaceutical Sciences, 17th Ed., (Mack Publishing Company, Easton, 1985), p. 1418, Berge *et al.*, *J. Pharm. Sci.*, **1977**, *66*(1), 1-19, and in Stahl *et al.*, *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (Wiley, 2002).

The below Table is a key to abbreviations that may be used throughout.

5

Abbreviations

AIBN	azobisisobutyronitrile
atm	atmosphere
Boc	tert-butyl-oxy-carbonyl
CAS#	Chemical Abstract Service registry number
CBS	Corey-Bakshi-Shibata (catalyst)
CH_3CN	acetonitrile
CBZ	carbobenzyloxy
CsOAc	cesium acetate
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethylether
DMF	dimethylformamide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	enantiomeric excess
EtOAc	ethyl acetate
h	hour(s)
min	minute(s)
Hex	hexanes
HOAT	1-hydroxy-7-azabenzotriazole
HOAc	acetic acid
HPLC	high-performance liquid chromatography
IPA	isopropyl acetate
iPr	isopropyl
KOAc	potassium acetate

LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
mCPBA	3-meta-chloroperoxybenzoic acid
MeOH	methanol
MS	mass spectrometry
MTBE	methyl t-butyl ether
NH_4OH	ammonium hydroxide
NBS	N-bromosuccinimide
NMP	1-methyl-2-pyrrolidone
PAH	pulmonary arterial hypertension
PCC	pyridinium chlorochromate
PE	petroleum ether
PheOH	phenylalanine hydroxylase
Pr	propyl
Prep-TLC	preparative thin-layer chromatography
p-TSA	para-toluene sulfonic acid
RT	room temperature
SNAr	nucleophilic aromatic substitution
TBAF	tetrabutylammonium fluoride
TBME	tert-butylmethyl ether
tBuOH	tert-butanol
TBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
TEA	triethylamine
TFA	trifluoroacetic acid
TH	tyrosine hydroxylase
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMSCN	trimethylsilyl cyanide
TMS	trimethylsilyl
TMSI	trimethylsilyl iodide
TPH	tryptophan hydroxylase

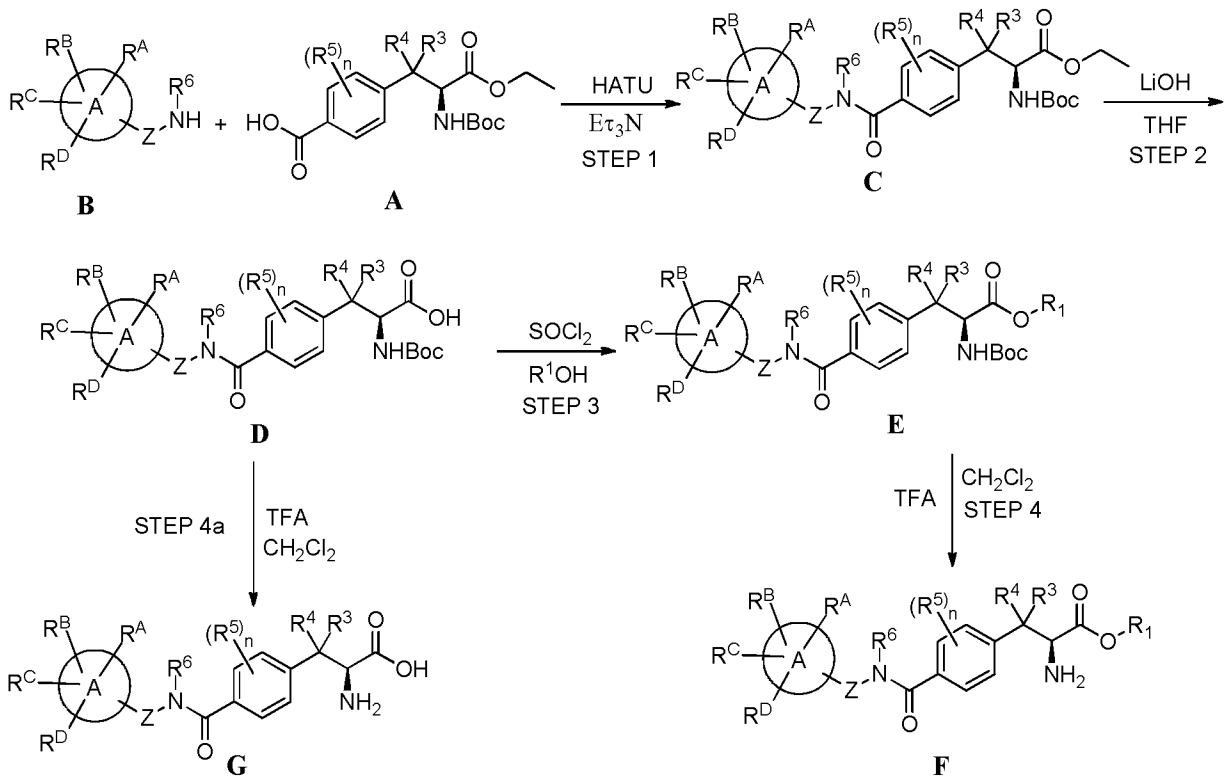
Synthesis

Procedures for making compounds described herein are provided below with reference to Schemes 1-5. Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures and other reaction conditions are readily selected by one of ordinary skill in the art. Specific procedures are provided in the Examples section. Compounds are named using the "structure to name" function included in ChemDraw® v.12 (Perkin-Elmer).

Typically, reaction progress may be monitored by thin layer chromatography (TLC) or HPLC-MS if desired. Intermediates and products may be purified by chromatography on silica gel, recrystallization, HPLC and/or reverse phase HPLC. In the reactions described below, it may be necessary to protect reactive functional groups (such as hydroxy, amino, thio, or carboxy groups) to avoid their unwanted participation in the reactions. The incorporation of such groups, and the methods required to introduce and remove them are known to those skilled in the art (for example, see Greene, Wuts, *Protective Groups in Organic Synthesis. 2nd Ed.* (1999)). One or more deprotection steps in the synthetic schemes may be required to ultimately afford compounds of Formula I. The protecting groups depicted in the schemes are used as examples, and may be replaced by other compatible alternative groups. Starting materials used in the following schemes can be purchased or prepared by methods described in the chemical literature, or by adaptations thereof, using methods known by those skilled in the art. The order in which the steps are performed can vary depending on the protecting or functional groups introduced and the reagents and reaction conditions used, but would be apparent to those skilled in the art.

Compounds of the invention can be prepared as shown in Scheme 1. Briefly, in Step 1, an amine (see, e.g., Intermediate **B**) is treated in DMF with Intermediate **A** in the presence of a coupling agent (e.g., HATU, Et_3N) to provide amide **C**. In Step 2, ethyl ester hydrolysis (e.g. with LiOH in aqueous THF) provides acid **D**. Various esters can be made by converting **D** to an acid chloride (e.g with $SOCl_2$) followed by the addition of another alcohol to provide **E**. Removal of the the N-Boc protecting group can be accomplished with a strong acid (e.g. TFA) to provide **F.** Alternatively, the amino acid **G**, can be prepared directly from **D** in Step 4a via removal of the the N-Boc protecting group directly with strong acid (e.g. TFA).

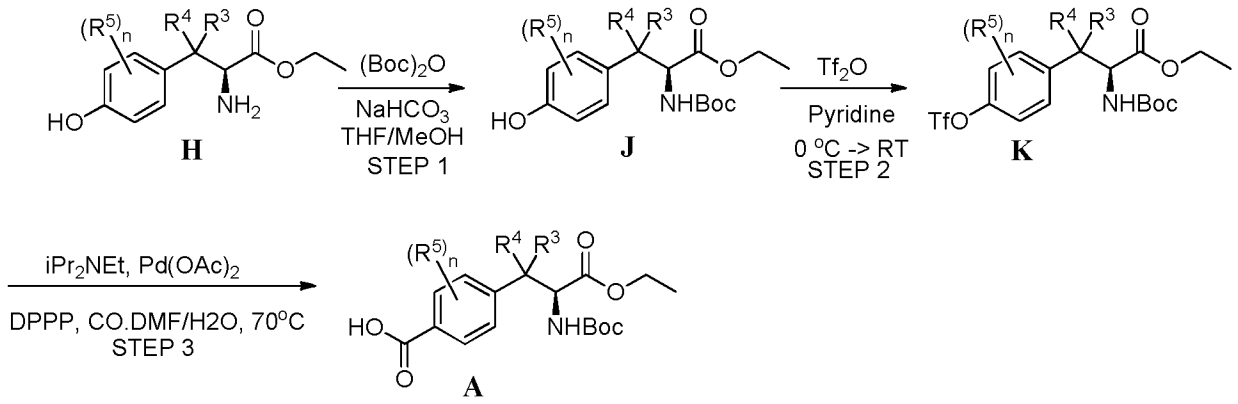
Scheme 1



The acid intermediate **A** used in Scheme 1 can be prepared according to Scheme 2. Briefly, in Step 1, (S)-ethyl 2-amino-3-(4-hydroxyphenyl)propanoate (**H**) is reacted with

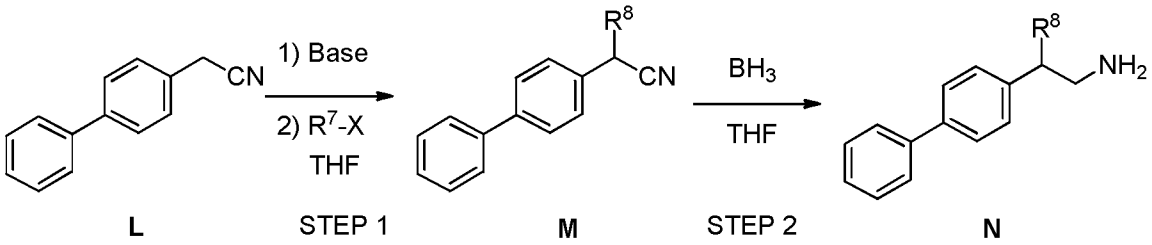
$(Boc)_2O$ in the presence of a base (e.g., $NaHCO_3$) in a solvent (e.g., THF/MeOH) to provide **J**. In Step 2, the hydroxyl group is converted to a triflate (e.g., with Tf_2O) in the presence of a base (e.g., pyridine) at low to ambient temperature to provide **K**. In Step 3, palladium-catalyzed hydroxycarbonylation is accomplished with a catalytic amount of palladium catalyst (e.g., $Pd(OAc)_2$) in the presence of CO (e.g., 1 atm) and a base (e.g., iPr_2NEt), and then mixture is heated for a period of time (e.g. 12-24 h) to provide **A**.

Scheme 2



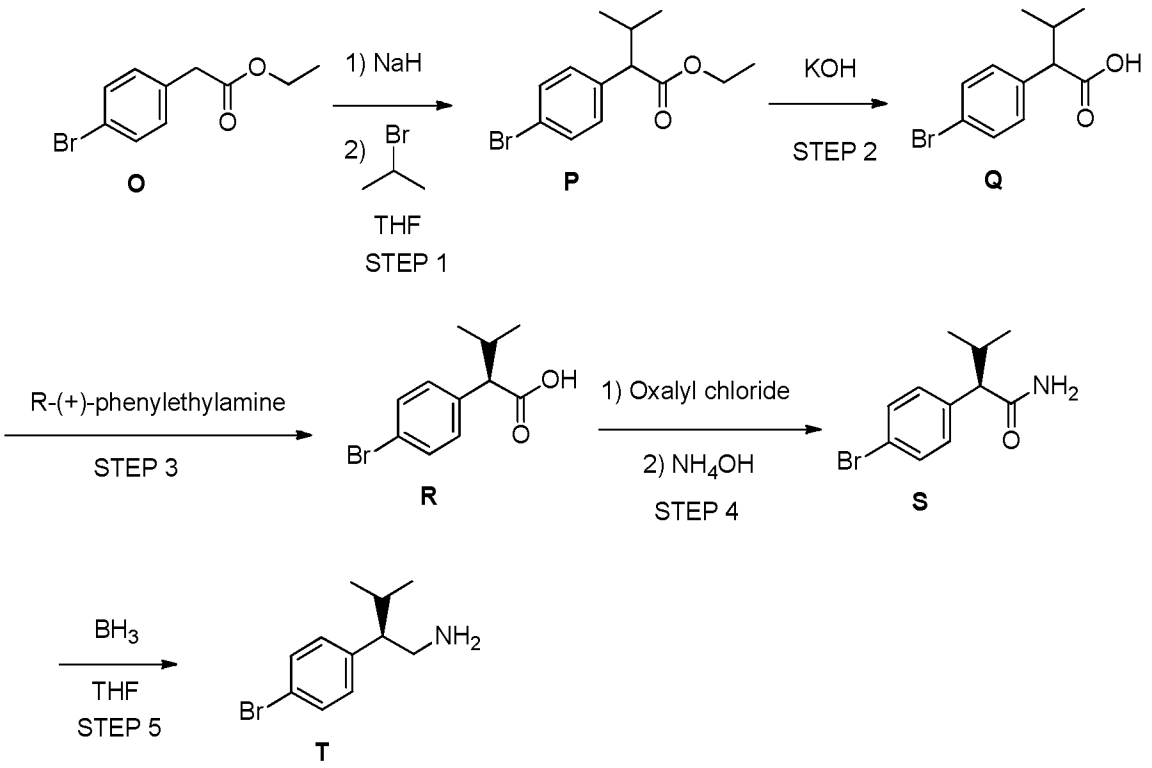
Amine **N** can be prepared as described in Scheme 3. Briefly, in Step 1, nitrile **L** is reacted with a base (e.g. LDA) at low temperature (e.g. -78 °C) in THF followed by the addition of an electrophilic reagent (e.g. R^8-X) to provide **M**. Step 2, nitrile **M** is then reduced (e.g. with BH_3-THF) in THF at low temperature (e.g. 0 °C) to provide **N**.

Scheme 3



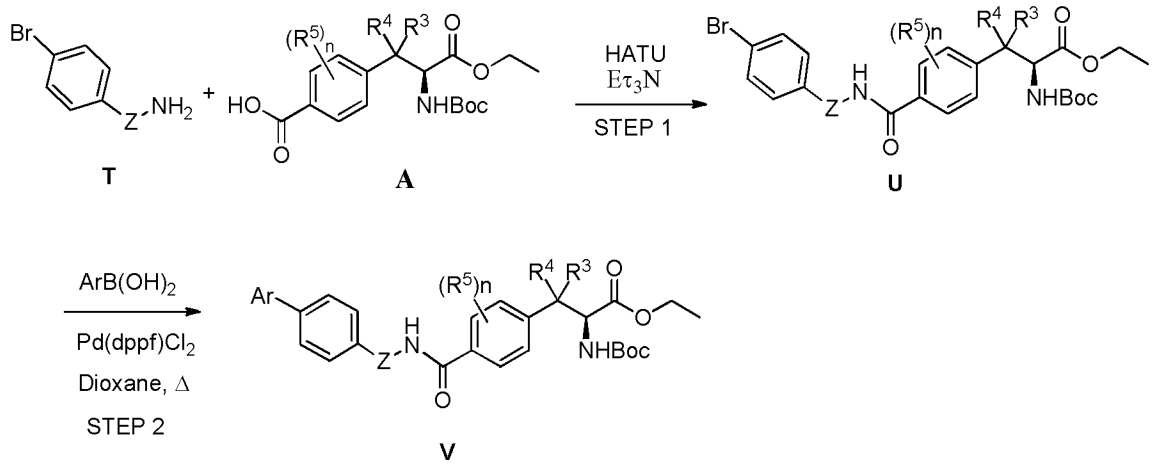
Amine **T** can be prepared as described in Scheme 4. Briefly, in Step 1, ethyl 2-(4-bromophenyl)acetate (**O**) is reacted with a base (e.g. NaH) at low temperature (e.g. -10 °C) in THF followed by addition of an electrophilic reagent (e.g. 2-bromopropane) to provide **P**. Step 2, the ethyl ester is hydrolyzed to the acid **Q** with base (e.g. KOH). In Step 3, diastereomeric salt formation and recrystallization (e.g. with R-(+)-phenylethylamine) provides **R**. Step 4, amide formation occurs via treating the acid with a coupling reagent (e.g. oxalyl chloride) and then treatment with NH_4OH to provide **S**. Step 5, amide **S** is reduced (e.g. with BH_3-THF) in THF at low temperature (e.g. 0 °C) to provide **T**.

Scheme 4



Biaryl compounds (**V**) can be prepared as described in Scheme 5 (Ar is an aromatic moiety like, for example, substituted or unsubstituted phenyl). Briefly, in Step 1, amine **T** is treated with Intermediate **A** in the presence of a coupling agent (e.g., HATU, Et_3N) to provide amide **S**. Aryl coupling (e.g. Suzuki) can be accomplished by treating **U** with a boronic acid (e.g. $ArB(OH)_2$) in the presence of a transition metal coupling agent (e.g. $Pd(dppf)Cl_2$) and heated in dioxane for 12-24 h to provide **T**. Compounds of this type can then be converted to either the amino ester or amino acid as described in Scheme 1 (steps 2-4 or steps 2 & 4a).

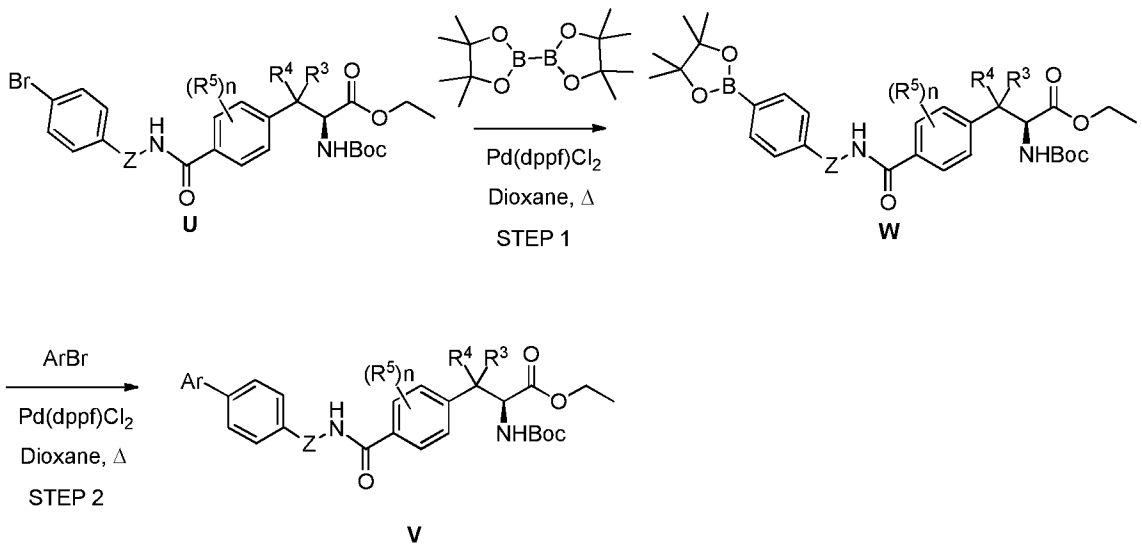
Scheme 5



Alternatively, biaryl compounds (**V**) can be prepared as described in Scheme 6. Briefly, in Step 1, bromide **U** is treated with bis(pinacolato)diboron in the presence of a transition metal coupling agent (e.g., $Pd(dppf)_2$) to provide amide **W**. Step 2, aryl coupling (e.g. Suzuki) can be accomplished by treating **W** and an aryl bromide (e.g. ArBr) in the presence of a transition metal

coupling agent (e.g. $Pd(dppf)Cl_2$) and heated in dioxane for 12-24 h to provide **V**. Compounds of this type can then be converted to either the amino ester or amino acid as described in Scheme 1.

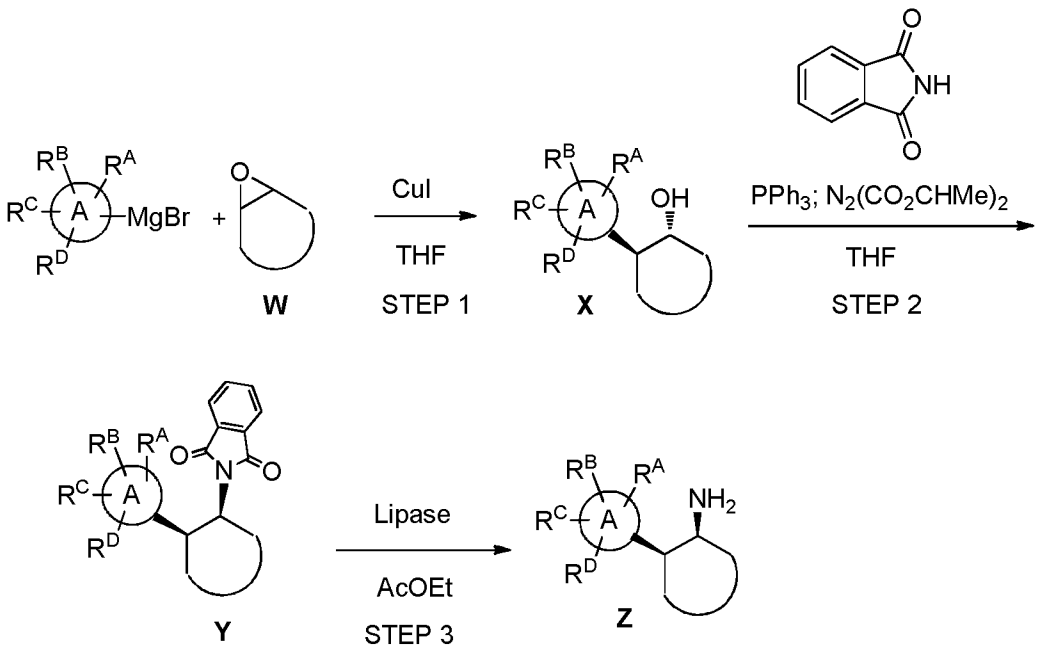
Scheme 6



Certain compounds where Z is a bridging ring can be prepared as described in Scheme 7. Briefly, in Step 1, epoxide **W** is treated with a Grignard reagent in the presence of a transition metal (e.g., CuI) to provide amine **X**. Step 2, under Mitsunobu conditions with **X** in the presence of phthalimide, triphenyl phosphine and diisopropyl azodicarboxylate provides **Y**. In Step 3,

aminolysis catalyzed by a lipase (e.g. lipase B from *Candida antarctica*) provides amino compound **Z** which can be used to prepare compounds of the invention by the methods described, for example, in Scheme 1.

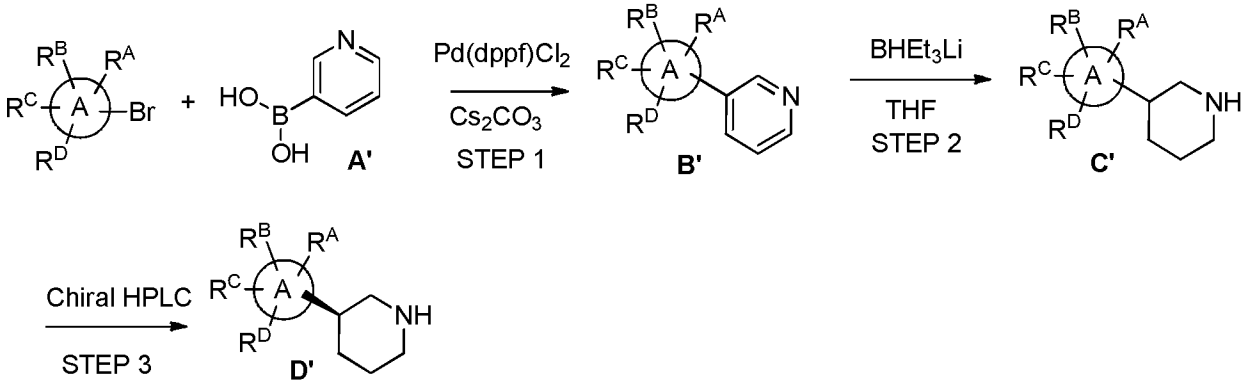
Scheme 7



Compounds where Z is taken together with R6 to form a ring can be prepared as described in Scheme 8. Briefly, in Step 1, Suzuki coupling with pyridine boronic acid A' provide B'. In Step 2, reduction of the pyridine B' with lithium triethylborohydride in a solvent (e.g. THF) provides piperidine C'. In Step 3, chiral HPLC allows for the seperation of both

enatiomers, as exmplified by D' which can be used to prepare compounds of the invention by the methods described, for example, in Scheme 1.

Scheme 8



Methods of Use

The compounds of the invention can be used to inhibit the activity of the TPH1 enzyme in a cell by contacting the cell with an inhibiting amount of a compound of the invention. The cell can be part of the tissue of a living organism, or can be in culture, or isolated from a living organism. Additionally, the compounds of the invention can be used to inhibit the activity of the TPH1 enzyme in an animal, individual, or patient, by administering an inhibiting amount of a compound of the invention to the cell, animal, individual, or patient.

Compounds of the invention can also lower peripheral serotonin levels in an animal, individual, or patient, by administering an effective amount of a compound of the invention to the animal, individual, or patient. In some embodiments, the compounds of the invention can lower levels of peripheral serotonin (e.g., 5-HT in the GI tract) selectively over non-peripheral serotonin (e.g., 5-HT in the CNS).

As TPH1 inhibitors that can lower peripheral serotonin levels, the compounds of the invention are useful in the treatment and prevention of various diseases associated with abnormal expression or activity of the TPH1 enzyme, or diseases associated with elevated or abnormal peripheral serotonin levels. In some embodiments, the treatment or prevention includes administering to a patient in need thereof a therapeutically effective amount of a TPH1 inhibitor of the invention. In some embodiments, the disease or disorder treatable by administration of

one or more of the compounds provided herein is characterized by an altered rate of the tryptophan-serotonin metabolism wherein the rate limiting step of tryptophan-serotonin metabolism is the hydroxylation of L-Tryp catalyzed by TPH (e.g., TPH1).

Biological assays, some of which are described herein, can be used to determine the inhibitory effect of compounds against TPH (such as TPH1) *in vitro* and/or *in vivo*. *In vitro* biochemical assays for human, mouse, and rat TPH1 and human TPH2, PheOH, and TH may be used to measure inhibition of enzyme activity and the selectivity among TPH1, TPH2, PheOH, and TH. In addition, the efficacy of these compounds can be determined, for example, by measuring their effect on intestinal 5-HT levels in rodents after oral administration.

Diseases treatable or preventable by administering a TPH1 inhibitor of the invention include bone disease such as, for example, osteoporosis, osteoporosis pseudoglioma syndrome (OPPG), osteopenia, osteomalacia, renal osteodystrophy, Paget's disease, fractures, and bone metastasis. In some embodiments, the disease is osteoporosis, such as primary type 1 (e.g., postmenopausal osteoporosis), primary type 2 (e.g., senile osteoporosis), and secondary (e.g., steroid- or glucocorticoid-induced osteoporosis).

The present invention further includes methods of treating or preventing bone fracture such as, for example, osteoporotic or traumatic fracture, or surgical fractures associated with an orthopedic procedure (e.g., limb lengthening, bunion removal, an increase in bone formation associated with a prosthesis, bone metastasis, or spinal fusion).

Further diseases treatable or preventable by the methods of the invention include cardiovascular diseases such as aortic and coronary artery diseases, atherosclerosis, hypertentsion (acute or chronic), and pulmonary hypertension (PH), including idiopathic or familial PH, and also including PH associated with or brought on by other diseases or conditions. In some embodiments, the PH disease is pulmonary arterial hypertension (PAH). See, e.g., Ciuclan, L. et al. "Imatinib attenuates hypoxia-induced pulmonary arterial hypertension pathology via reduction in 5-hydroxytryptamine through inhibition of tryptophan hydroxylase 1 expression." *Am J Respir Crit Care Med.* 187(1): 78-89 (2013).

The types of PAH treatable or preventable according to the methods of the invention include (1) idiopathic (IPAH), (2) familial (FPAH), and (3) associated (APAH) which is the most common type of PAH. The latter is PAH which is associated with other medical conditions including, for example, (1) collagen vascular disease (or connective tissue disease) which include

autoimmune diseases such as scleroderma or lupus; (2) congenital heart and lung disease; (3) portal hypertension (e.g., resulting from liver disease); (4) HIV infection; (5) drugs (e.g., appetite suppressants, cocaine, and amphetamines; (6) other conditions including thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders,and splenectomy. APAH can also be PAH associated with abnormal narrowing in the pulmonary veins and/or capillaries such as in pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis. Another type of PAH is associatead with persistent pulmonary hypertension of the newborn (PPHN). APAH can aslo be PAH associated with radiation pneumonitis.

Diseases treatable or preventable by administering a TPH1 inhibitor of the invention include fibrotic diseases, such as: pulmonary fibrosis (e.g., idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), interstitial lung disease, etc.), skin fibrosis (e.g., scleroderma), fibrosis of various other organ tissues such as heart fibrosis (e.g. fibrosis of the heart valves), kidney fibrosis, liver fibrosis, etc. any of which may be caused by chronic diseases such as fatty liver disease (e.g., in the case of liver fibrosis) and diabetic nephropathy (e.g., in the case of kidney fibrosis). See, e.g., "Lung fibrosis by serotonin receptor antagonists in mice." *Eur Respir J.* 2008, 32(2):426–36; Konigshoff, M. et al. "5-Hydroxytryptamine 2A/B receptors in idiopathic pulmonary fibrosis." *Thorax.* 2010, 65(11):949–55; "Scleroderma lung and skin fibrosis." *Best Pract Res Clin Rheumatol.* 2011, 25(6):843–58; "Platelet-derived serotonin links vascular disease and tissue fibrosis." *J Exp Med.* 2011, 208(5):961–72; "Molecular targets for therapy in systemic sclerosis." *Fibrogenesis Tissue Repair.* 2012;5:S19; "New cellular and molecular mechanisms of lung injury and fibrosis in idiopathic pulmonary fibrosis." *Lancet.* 2012; 380 (9842):680–8; "Treating skin and lung fibrosis in systemic sclerosis: a future filled with promise?" *Curr Opin Pharmacol.* 2013;13(3):455–62; Mann, D.A. et al. "Serotonin paracrine signaling in tissue fibrosis." *Biochim Biophys Acta.* 2013, 1832(7):905–10.

The compounds of the invention can be used in the treatment or prevention of liver disease including, for example, hepatitis. In some embodiments, the hepatitis is associated with or induced by an autoimmune process (e.g., autoimmune hepatitis or primary biliary cirrhosis). In some embodiments, the hepatitis is associated with or induced by alcoholic or toxic liver destruction. In some embodiments, the hepatitis is associated with or induced by a viral infection, such as an infection by HAV, HBV, HCV, HDV, HEV, or HGV.

Further diseases treatable or preventable by the methods of the invention include metabolic diseases such as diabetes and hyperlipidemia; pulmonary diseases such as pulmonary embolism, adult respiratory distress syndrome (ARDS); gastrointestinal diseases such as inflammatory bowel diseases (IBD), irritable bowel syndrome (e.g., post-infectious), colitis (e.g., ulcerative colitis), chemotherapy-induced emesis, diarrhea, carcinoid syndrome, celiac disease, Crohn's disease, celiac disease, abdominal pain, dyspepsia, constipation (e.g., idiopathic constipation), lactose intolerance, necrotizing entercolitis, Ogilvie's syndrome, pancreatic cholera syndrome, pancreatic insufficiency, Zollinger-Ellison Syndrome, or other gastrointestinal inflammatory conditions; cancers such as liver cancer, breast cancer, cholangiocarcinoma, colon cancer, colorectal cancer, neuroendocrine tumors, pancreatic cancer, prostate cancer, and bone cancer (e.g., osteosarcoma, chrondrosarcoma, Ewings sarcoma, osteoblastoma, osteoid osteoma, osteochondroma, carcinoid tumors, enchondroma, chondromyxoid fibroma, aneurysmal bone cyst, unicameral bone cyst, giant cell tumor, and bone tumors); blood diseases (e.g., myeoloproliferative syndrome, myelodysplastic syndrome, Hodgkin's lymphoma, non-Hodgkin's lymphoma, myeloma, and anemia such as aplastic anemia and anemia assocated with kidney disease; and blood cancers (e.g., leukemias such as acute lymphocytic leukemia (ALL), chronic lymphocytic leukemica (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML)). See, e.g., Ghia, J. E. et al. "Serotonin has a key role in pathogenesis of experimental colitis." *Gastroenterology* 137(5): 1649-1660 (2009); Brown, P. M. et al. "The tryptophan hydroxylase inhibitor LX1031 shows clinical benefit in patients with nonconstipating irritable bowel syndrome," *Gastroenterology* 141, 507-516 (2011); Engelman, K., et al. "Inhibition of serotonin synthesis by para-chlorophenylalanine in patients with the carcinoid syndrome." *N Engl J Med* 277(21): 1103-1108 (1967); Pai VP et al. "Altered serotonin physiology in human breast cancers favors paradoxical growth and cell survival." *Breast Cancer Res.* 11(6) (2009); Shinka T et al. "Serotonin synthesis and metabolism-related molecules in a human prostate cancer cell line." *Oncol Lett.* Mar;2(2):211-215 (2011); and Hicks, R.J. "Use of molecular targeted agents for the diagnosis, staging and therapy of neuroendocrine malignancy." *Cancer Imaging*. Oct 4;10 Spec. no. AS83-91 (2010).

The compounds of the invention are also useful in the treatment or prevention of myxomatous mitral valve disease. Lacerda, C. M. et al. "Local serotonin mediates cyclic strain-

induced phenotype transformation, matrix degradation, and glycosaminoglycan synthesis in cultured sheep mitral valves." *Am J Physiol Heart Circ Physiol.* 302(10): H1983-1990 (2012).

In some embodiments, the present invention includes methods of lowering plasma cholesterol, lowering plasma triglycerides, lowering plasma glycerol, lowering plasma free fatty acids in a patient by administering to said patient a therapeutically effective amount of a compound of the invention.

In some embodiments, the present invention includes methods of treating or preventing thrombosis, sleep disorders, pain, diabetes (type 1 or type 2), complications associated with liver transplantation or regeneration, serotonin syndrome, Raynaud's syndrome, subarachnoid hemorrhage, abdominal migraine, CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia), Gilbert's syndrome, nausea, multiple endocrine neoplasia (MEN) types I and II, pheochromacytoma, somatization disorder, functional anorectal disorders, functional bloating, immune tolerance and inflammatory diseases including, e.g. multiple sclerosis and systemic sclerosis. See, Nowak E.C. et al. "Tryptophan hydroxylase-1 regulates immune tolerance and inflammation." *J Exp Med.* Oct 22, 09(11):2127-35 (2012); Dees C. et al. "Platelet-derived serotonin links vascular disease and tissue fibrosis." *J Exp Med.* May 9, 208(5):961-72 (2011).

The compounds of the invention are also useful in the treatment or prevention of inflammatory disease, such as allergic airway inflammation (e.g., asthma). See, e.g., Durk, T. et al. "Production of serotonin by tryptophan hydroxylase 1 and release via platelets contribute to allergic airway inflammation." *Am J Respir Crit Care Med.* 187(5): 476-485 (2013).

As used herein, the term "cell" is meant to refer to a cell that is *in vitro*, *ex vivo* or *in vivo*. In some embodiments, an *ex vivo* cell can be part of a tissue sample excised from an organism such as a mammal. In some embodiments, an *in vitro* cell can be a cell in a cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" the enzyme with a compound of the invention includes the administration of a compound of the present invention to an individual or patient, such as a human, having the TPH1 enzyme, as well as, for example, introducing a compound of the invention into a sample containing a cellular or purified preparation containing the TPH1enzyme.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

As used herein the term "treating" or "treatment" refers to 1) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, arresting further development of the pathology and/or symptomatology), or 2) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, reversing the pathology and/or symptomatology).

As used herein the term "preventing" or "prevention" refers to inhibiting onset or worsening of the disease; for example, in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease.

Combination Therapy

One or more additional pharmaceutical agents or treatment methods can be used in combination with the compounds of the present invention for treatment or prevention of various diseases, disorders or conditions disclosed herein. The agents can be combined with the present compounds in a single dosage form, or the agents can be administered simultaneously or sequentially in separate dosage forms.

Example pharmaceutical agents that may be useful in a combination therapy for blood disorders like blood cancers include parathyroid hormone, anti-sclerostin antibodies, kathepsin K inhibitors, and anti-Dickopff 1.

Example pharmaceutical agents that may be useful in a combination therapy for cancer include leuprolide, goserelin, buserelin, flutamide, nilutamide, ketoconazole, aminoglutethimide, mitoxantrone, estramustine, doxorubicin, etoposide, vinblastine, paclitaxel, carboplatin, and

vinorelbine. Therapies that can be combined with TPH inhibition include radiation therapy, high-intensity focused ultrasound, or surgery (e.g., removal of diseased tissues). Other drugs for use in treating cancer include testolactone, anastrozole, letrozole, exemestane, vorozole, formestane, fadrozole, GnRH-analogues, temozolomide, bavituximab, cyclophosphamide, fluorouracil, fulvestrant, gefitinib, trastuzumab, IGF-1 antibodies, lapatinib, methotrexate, olaparib, BSI-201, pazopanib, rapamycin, ribavirin, sorafenib, sunitinib, tamoxifen, docetaxel, vatalinib, bevacizumab, and octreotide.

Example pharmaceutical agents that may be useful in combination therapy for cardiovascular or pulmonary diseases include endothelin receptor antagonists such as ambrisentan, BMS-193884, bosentan, darusentan, SB-234551, sitaxsentan, tezosentan and macitentan. Anticoagulants such as warfarin, acenocoumarol, phenprocoumon, phenindione, heparin, fondaparinux, argatroban, bivalirudin, lepirudin, and ximelagatran may also be useful in combination therapy. Pharmaceutical agents for combination therapy further include calcium channel blockers like amlodipine, felodipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, lacidipine, lercanidipine, phenylalkylamines, verapamil, gallopamil, diltiazem, and menthol. Prostacyclins like epoprostenol, iloprost and treprostinil may also be combined with the TPH inhibitors of the invention. Further pharmaceutical agents for combination therapy in cardiovascular or pulmonary diseases include PDE5 inhibitors like sildenafil, tadalafil, and vardenafil; diuretics like furosemide, ethacrynic acid, torasemide, bumetanide, hydrochlorothiazide, spironolactone, mannitol, nitric oxide or nitric oxide releasers, and soluble guanylate cyclase stimulators, such as riociguat. Yet further pharmaceutical agents for combination therapy include APJ receptor agonists (WO 2013/111110); IP receptor agonists (WO 2013/105057; WO 2013/105066; WO 2013/105061; WO 2013/105063; WO 2013/105065; WO 2013/105058); and PDGF receptor inhibitors (WO 2013/030802).

Example pharmaceutical agents that may be useful in combination therapy for metabolic disorders include HSL inhibitors such as those disclosed in International Patent Publications WO2006/074957; WO2005/073199; WO2004/11 1031; WO2004/111004; WO2004/035550; WO2003/051841; WO2003/051842; and WO2001/066531.

Example pharmaceutical agents that may be useful in combination therapy for bone disorders and diseases include bisphosphantes such as etidronate, clodronate, tiludronate, pamidronate, neridronate, olpadronate, alendronate, ibandronate, risedronate, cimadronate,

zoledronate, and the like. Serotonin receptor modulators, such as 5-HT_{1B} , 5-HT_{2A}, and 5-HT_{2B} agonists or antagonists, may also be useful in combination therapy for bone disease. Other useful agents for combination therapy include selective serotonin reuptake inhibitors (SSRI), anti-serotonin antibodies, and beta blockers such as IPS339, ICIl 18,551, butaxamine, metipranolol, nadol, oxprenolol, penbutolol, pindolol, propranolol, timolol, and sotalol. Further useful agents for combination therapy for the treatment of bone disorders, such as osteoporosis, include teriparatide, strontium ranelate, raloxifene, and denosumab.

Administration, Pharmaceutical Formulations, Dosage Forms

The compounds of the invention can be administered to patients (animals and humans) in need of such treatment in appropriate dosages that will provide prophylactic and/or therapeutic efficacy. The dose required for use in the treatment or prevention of any particular disease or disorder will typically vary from patient to patient depending on, for example, particular compound or composition selected, the route of administration, the nature of the condition being treated, the age and condition of the patient, concurrent medication or special diets then being followed by the patient, and other factors. The appropriate dosage can be determined by the treating physician.

A compound of this invention can be administered orally, subcutaneously, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. Parenteral administration can involve subcutaneous injections, intravenous or intramuscular injections or infusion techniques.

Treatment duration can be as long as deemed necessary by a treating physician. The compositions can be administered one to four or more times per day. A treatment period can terminate when a desired result, for example a particular therapeutic effect, is achieved. Or a treatment period can be continued indefinitely.

In some embodiments, the pharmaceutical compositions can be prepared as solid dosage forms for oral administration (e.g., capsules, tablets, pills, dragees, powders, granules and the like). A tablet can be prepared by compression or molding. Compressed tablets can include one or more binders, lubricants, glidants, inert diluents, preservatives, disintegrants, or dispersing

agents. Tablets and other solid dosage forms, such as capsules, pills and granules, can include coatings, such as enteric coatings.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration can include, for example, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. Suspensions can include one or more suspending agents

Dosage forms for transdermal administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants.

Compositions and compounds of the present invention can be administered by aerosol which can be administered, for example, by a sonic nebulizer.

Pharmaceutical compositions of this invention suitable for parenteral administration include a compound of the invention together with one or more pharmaceutically acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions. Alternatively, the composition can be in the form of a sterile powder which can be reconstituted into a sterile injectable solutions or dispersion just prior to use.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results. The compounds of the Examples were found to be inhibitors of TPH1 as described below.

EXAMPLES

The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. In the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be chosen to be the conditions standard for that reaction, unless otherwise indicated. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be

apparent to one skilled in the art, and alternate methods are therefore indicated. The starting materials for the examples are either commercially available or are readily prepared by standard methods from known materials.

^{1}H NMR Spectra were acquired on one or more of three instruments: (1) Agilent UnityInova 400 MHz spectrometer equipped with a 5 mm Automation Triple Broadband (ATB) probe (the ATB probe was simultaneously tuned to ^{1}H, ^{19}F and ^{13}C); (2) Agilent UnityInova 500 MHz spectrometer; or (3) Varian Mercury Plus 400 MHz spectrometer. Several NMR probes were used with the 500 MHz NMR spectrometer, including both 3 mm and 5 mm ^{1}H, ^{19}F and ^{13}C probes and a 3 mm X^{1}H^{19}F NMR probe (usually X is tuned to ^{13}C). For typical ^{1}H NMR spectra, the pulse angle was 45 degrees, 8 scans were summed and the spectral width was 16 ppm (-2 ppm to 14 ppm). Typically, a total of about 32768 complex points were collected during the 5.1 second acquisition time, and the recycle delay was set to 1 second. Spectra were collected at 25 °C. ^{1}H NMR Spectra were typically processed with 0.3 Hz line broadening and zero-filling to about 131072 points prior to Fourier transformation. Chemical shifts were expressed in ppm relative to tetramethylsilane. The following abbreviations are used herein: br = broad signal, s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, dt = double triplet, t = triplet, td = triple doublet, tt = triple triplet q = quartet, m = multiplet.

Liquid chromatography - mass spectrometry (LCMS) experiments to determine retention times and associated mass ions were performed using one or more of the following Methods A, B, and C:

Method A: Waters BEH C18, 3.0 x 30 mm, 1.7 μm, was used at a temperature of 50 °C and at a flow rate of 1.5 mL/min, 2 μL injection, mobile phase: (A) water with 0.1% formic acid and 1% acetonitrile, mobile phase (B) MeOH with 0.1% formic acid; retention time given in minutes. Method A details: (I) ran on a Binary Pump G1312B with UV/Vis diode array detector G1315C and Agilent 6130 mass spectrometer in positive and negative ion electrospray mode with UV PDA detection with a gradient of 15-95% (B) in a 2.2 min linear gradient (II) hold for 0.8 min at 95% (B) (III) decrease from 95-15% (B) in a 0.1 min linear gradient (IV) hold for 0.29 min at 15% (B);

Method B: An Agilent Zorbax Bonus RP, 2.1 x 50 mm, 3.5 μm, was used at a temperature of 50 °C and at a flow rate of 0.8 mL/min, 2 μL injection, mobile phase: (A) water with 0.1% formic acid and 1% acetonitrile, mobile phase (B) MeOH with 0.1% formic acid;

retention time given in minutes. Method details: (I) ran on a Binary Pump G1312Bwith UV/Vis diode array detector G1315C and Agilent 6130 mass spectrometer in positive and negative ion electrospray mode with UV-detection at 220 and 254 nm with a gradient of 5-95% (B) in a 2.5 min linear gradient (II) hold for 0.5 min at 95% (B) (III) decrease from 95-5% (B) in a 0.1 min linear gradient (IV) hold for 0.29 min at 5% (B).

Method C: An API 150EX mass spectrometer linked to a Shimadzu LC-10AT LC system with a diode array detector was used. The spectrometer had an electrospray source operating in positive and negative ion mode. LC was carried out using an Agilent ZORBAX XDB 50 x 2.1 mm C18 column and a 0.5 mL/minute flow rate. Solvent A: 95% water, 5% acetonitrile containing 0.01% formic acid; Solvent B: acetonitrile. The gradient was shown as below. 0-0.5 min: 2% solvent (B); 0.5-2.5 min: 2% solvent B to 95% solvent (B); 2.5-4.0 min: 95% solvent (B); 4.0-4.2 min: 95% solvent (B) to 2% solvent B; 4.2-6.0 min: 2% solvent (B).

Microwave experiments were carried out using a Biotage Initiator™, which uses a single-mode resonator and dynamic field tuning. Temperatures from 40-250 °C were achieved, and pressures of up to 20 bars were reached.

Preparative HPLC purification was carried out using either a C18-reverse-phase column from Genesis (C18) or a C6-phenyl column from Phenomenex (C6 Ph) (100 × 22.5 mm i.d. with 7 micron particle size, UV detection at 230 or 254 nm, flow 5-15mL/min), eluting with gradients from 100-0 to 0-100 % water/acetonitrile or water/MeOH containing 0.1% formic acid. Fractions containing the required product (identified by LCMS analysis) were pooled, the organic fraction removed by evaporation, and the remaining aqueous fraction lyophilised, to give the product.

Chiral HPLC was carried out with one of the following two conditions:

A) Instrument: Agilent 1100 HPLC

Column: CHIRALCEL OD-H, 4.6*250 mm, 5μm;

Mobil phase: Hex/Ethanol/TFA=99:0.5:0.1

Flow rate: 0.8 mL/min

Temperature: Room temperature

Wavelength: 220 nm

B) Instrument: Agilent 1100 HPLC

Column: CHIRALCEL OD-H, 4.6*250 mm, 5μm;

Mobil phase: Hex/IPA/TFA=91:9:0.1 or Hex/IPA/TFA=97:3:0.1

Flow rate: 0.8 mL/min

Temperature: Room temperature

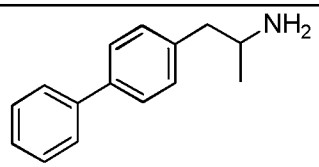
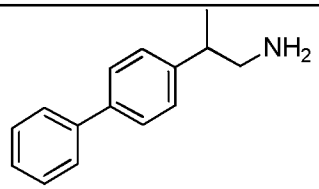
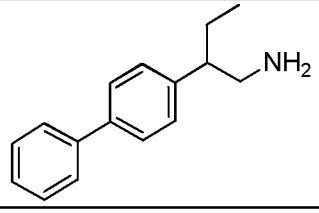
Wavelength: 220 nm

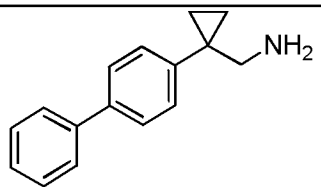
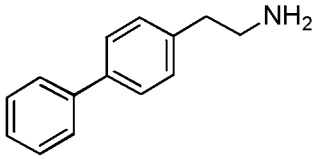
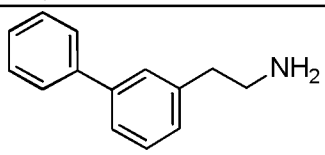
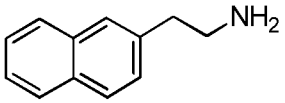
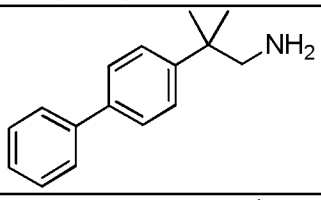
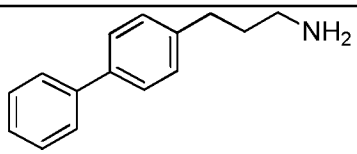
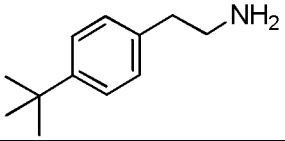
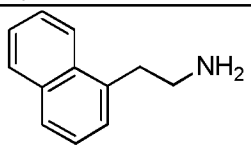
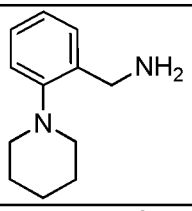
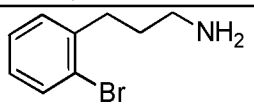
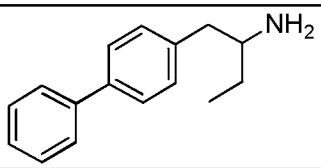
Compounds which required column chromatography were purified manually or fully automatically using either a Biotage SP1™ Flash Purification system with Touch Logic Control™ or a Combiflash Companion® with pre-packed silica gel Isolute® SPE cartridge, Biotage SNAP cartridge or Redisep® Rf cartridge respectively.

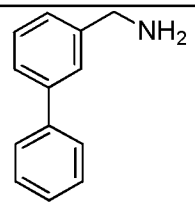
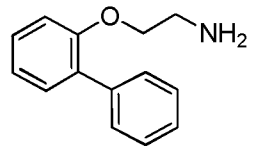
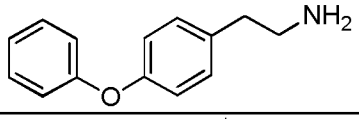
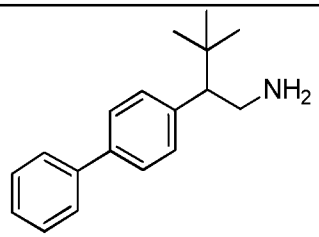
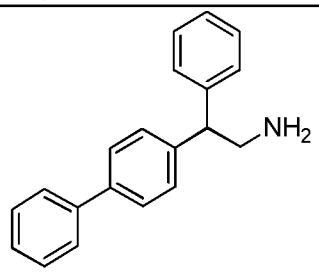
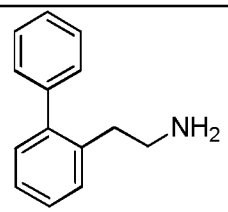
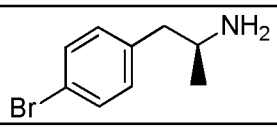
Preparation of Amine Intermediates

The following amines shown in Table 1 were used in preparing the compounds of the invention. They are either commercially available or can be prepared by known synthetic procedures. CAS registry numbers are provided for each.

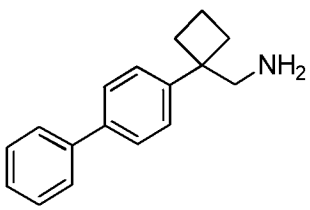
Table 1. Amine Intermediates

Int. No.	Structure	Name	CAS#
1		1-(4-phenylphenyl)propan-2-amine	92645-97-1
2		2-(4-phenylphenyl)propan-1-amine	20375-54-6
3		2-([1,1'-biphenyl]-4-yl)butan-1-amine	1369053-33-7

4		(1-([1,1'-biphenyl]-4-yl)cyclopropyl)methanamine	1368705-62-7
5		2-([1,1'-biphenyl]-4-yl)ethanamine	17027-51-9
6		2-([1,1'-biphenyl]-3-yl)ethanamine	802593-25-5
7		2-(naphthalen-2-yl)ethanamine	2017-68-7
8		2-([1,1'-biphenyl]-4-yl)-2-methylpropan-1-amine	1225534-81-5
9		[1,1'-biphenyl]-4-propanamine	872215-02-6
10		2-(4-(tert-butyl)phenyl)ethanamine	91552-82-8
11		2-(naphthalen-1-yl)ethanamine	4735-50-6
12		(2-(piperidin-1-yl)phenyl)methanamine	72752-54-6
13		3-(2-bromophenyl)propan-1-amine	65185-60-6
14		2-([1,1'-biphenyl]-3-yl)ethanamine	802593-25-5

15		[1,1'-biphenyl]-3-methyl amine	177976-49-7
16		2-([1,1'-biphenyl]-2-yloxy) ethylamine	23314-13-8
17		2-(4-phenoxyphenyl)ethanamine	118468-18-1
18		2-([1,1'-biphenyl]-4-yl)-3,3-dimethylbutan-1-amine	1528144-26-4
19		2-([1,1'-biphenyl]-4-yl)-2-phenylethanamine	496860-99-2
19b		[1,1'-biphenyl]-2-ethanamine	252984-00-2
19c		(S)-1-([1,1'-biphenyl]-4-yl)propan-2-amine	869567-02-2

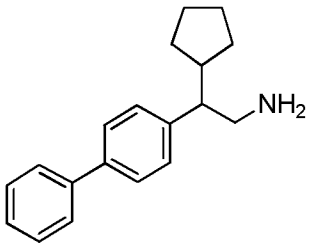
Intermediate 20: (1-([1,1'-biphenyl]-4-yl)cyclobutyl)methanamine



Step 1: To a solution of 2-([1,1'-biphenyl]-4-yl)acetonitrile (CAS# 31603-77-7, 500 mg, 2.6 mmol) in toluene (5 mL) was added sodium amide (222 mg, 10 mmol) at RT. The mixture was heated to 35 °C for 15 min. Then 1,3-diiodopropane (490 mg, 2.6 mmol) was added dropwwise and the reaction was stirred at 35 °C for 16 h. After this time, an additional equivalent of sodium amide was added and the reaction was heated to 50 °C for 4.5 h. The reaction was then cooled to RT, quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (heptanes:ethyl acetate /4:1) provided 1-([1,1'-biphenyl]-4-yl)cyclobutanecarbonitrile as a colorless oil.

Step 2: A solution of 1-([1,1'-biphenyl]-4-yl)cyclobutanecarbonitrile (119 mg, 0.5 mmol) in ether (5 mL) was cooled to 0 °C followed by the dropwise addition of LAH (1 mL of a 1M ether solution). The reaction was warmed to RT and stirred for 2 h. After this time, the reaction was cooled to 0 °C and quenched sequentially with water, 15% NaOH, and water, and then extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (CH_2Cl_2:MeOH:NH_2OH/90:10:1) provided the title compound as a colorless oil. LCMS (MH^+): 238.

Intermediate 21: 2-([1,1'-biphenyl]-4-yl)-2-cyclopentylethanamine



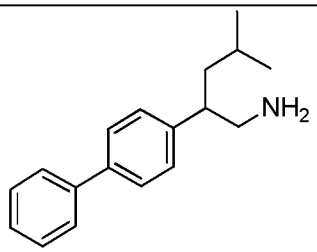
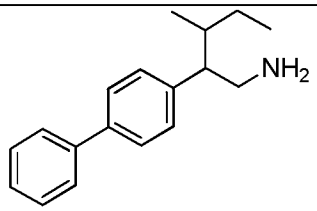
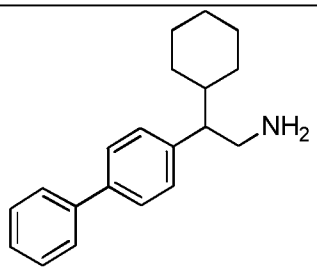
Step 1: A solution of diisopropyl amine (576 mg, 5.7 mmol) in THF (2.5 mL) was cooled to -78 °C and n-butyl lithium (2.5 M in hexanes, 1 mL) was added. The reaction was stirred for 30 min at -78 °C. After this time, 2-([1,1'-biphenyl]-4-yl)acetonitrile (CAS# 31603-77-7, 500 mg, 2.6 mmol) was added and the reaction was stirred for 5 min, then cyclopentyl bromide (CAS# 137-43-9, 467 mg, 3.1 mmol) was added. The reaction mixture was warmed to RT and stirred for 16 h. After this time, the reaction was quenched with HCl (1N) and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and

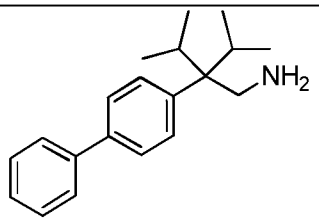
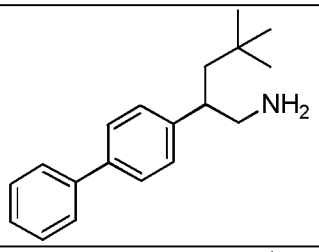
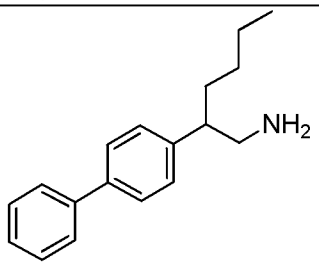
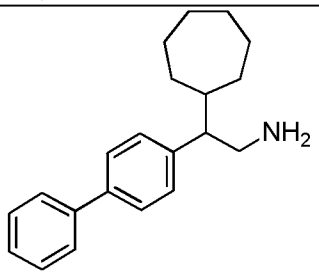
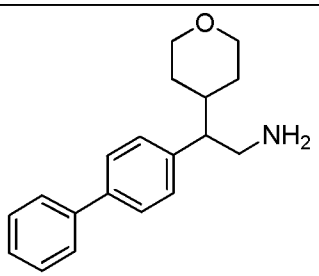
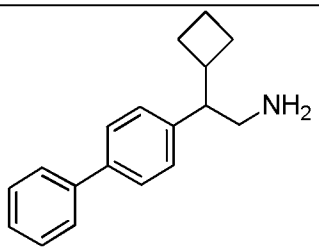
concentrated *in vacuo*. Purification via normal phase column chromatography (hexanes:ethyl acetate/4:1) provided 2-([1,1'-biphenyl]-4-yl)-2-cyclopentylacetonitrile as a colorless oil.

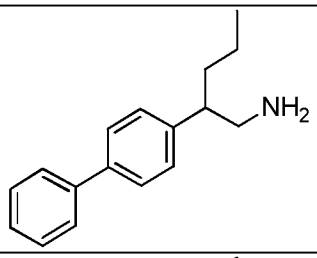
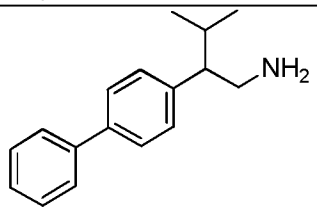
Step 2: To a solution of 2-([1,1'-biphenyl]-4-yl)-2-cyclopentylacetonitrile (173 mg, 0.7 mmol) in THF (5 mL) was added borane in THF (1 M, 9.9 mL). The reaction mixture was heated to 65 °C for 2 h. After this time, the reaction was cooled to RT and quenched with HCl (1 N, 5 mL), and then the pH was adjusted to ~8.5 with NaOH (1N) and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (CH_2Cl_2:MeOH:NH_4OH/ 90:10:1) provided the title compound as a colorless oil. LCMS (MH^+): 266.

The following amine intermediates of Table 2 were prepared as described above for 2-([1,1'-biphenyl]-4-yl)-2-cyclopentylethanamine (Intermediate 21).

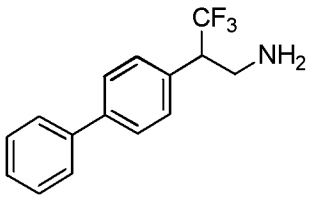
Table 2. Amine Intermediates

Int. No.	Name	Structure	LCMS (MH+)
22	2-([1,1'-biphenyl]-4-yl)-4-methylpentan-1-amine		254
23	2-([1,1'-biphenyl]-4-yl)-3-methylpentan-1-amine		254
24	2-([1,1'-biphenyl]-4-yl)-2-cyclohexylethanamine		280

25	2-([1,1'-biphenyl]-4-yl)-2-isopropyl-3-methylbutan-1-amine		282
26	2-([1,1'-biphenyl]-4-yl)-4,4-dimethylpentan-1-amine		268
27	2-([1,1'-biphenyl]-4-yl)hexan-1-amine		254
28	2-([1,1'-biphenyl]-4-yl)-2-cycloheptylethanamine		294
29	2-([1,1'-biphenyl]-4-yl)-2-(tetrahydro-2H-pyran-4-yl)ethanamine		282
30	2-([1,1'-biphenyl]-4-yl)-2-cyclobutylethanamine		252

54	2-([1,1'-biphenyl]-4-yl)pentan-1-amine		240
55	2-([1,1'-biphenyl]-4-yl)-3-methylbutan-1-amine		240

Intermediate 31: 2-([1,1'-biphenyl]-4-yl)-3,3,3-trifluoropropan-1-amine

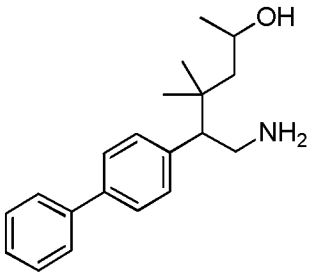


Step 1: To a solution of 2-([1,1'-biphenyl]-4-yl)acetonitrile (CAS# 31603-77-7, 250 mg, 1.3 mmol) in toluene (5 mL) was added sodium amide (0.1 mL, 1.3 mmol). After 20 min, 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (CAS#: 887144-94-7, 440 mg, 1.4 mmol) was added dropwise and the reaction was stirred at RT for 16 h. After this time, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide 2-([1,1'-biphenyl]-4-yl)-3,3,3-trifluoropropanenitrile that was used without further purification.

Step 2: The tile compound was prepared as described for 2-([1,1'-biphenyl]-4-yl)-2-cyclopentylethanamine (step 2) as a colorless oil. LCMS (MH^+): 266.

Intermediate 32: 5-([1,1'-biphenyl]-4-yl)-6-amino-4,4-dimethylhexan-2-ol

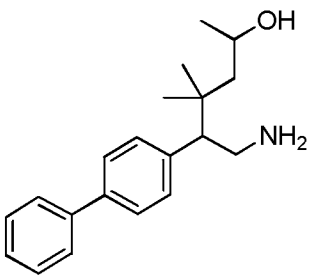
Diastereomer 1



Step 1: A solution of diisopropyl amine (576 mg, 5.7 mmol) in THF (2.5 mL) was cooled to -78 °C and n-butyl lithium (2.3 M in hexanes, 1 mL) was added. The reaction was stirred for 30 min at -78 °C. After this time, 2-([1,1'-biphenyl]-4-yl)acetonitrile (1.0 g, 5.6 mmol) was added and the reaction was stirred for 15 min at -78 C. Then acetone (1.9 mL, 26 mmol) was added and the reaction was warmed to RT for 16 h. The reaction was then quenched with HCl (1N) and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (heptanes:ethyl acetate/4:1) provided 2-([1,1'-biphenyl]-4-yl)-3,3-dimethyl-5-oxohexanenitrile as a colorless oil.

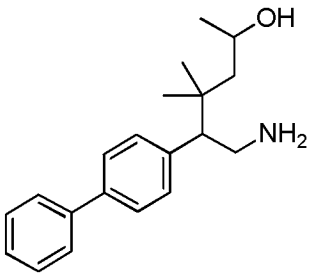
Step 2: To a solution of 2-([1,1'-biphenyl]-4-yl)-3,3-dimethyl-5-oxohexanenitrile (700 mg, 2.4 mmol) in THF (5 mL) was added borane in THF (1 M, 24 mL) and the reaction mixture was heated to 65 °C for 2 h. After this time, the reaction was cooled to RT and quenched with HCl (1 N, 5 mL), and then the pH was adjusted to ~8.5 with NaOH (1N) and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (CH_2Cl_2:MeOH:NH_2OH/ 90:10:1) provided the first fraction (R_f = 0.14 in CH_2Cl_2:MeOH: NH_2OH/90:10:1) as the title compound as a colorless oil. LCMS (MH^+): 298.

Intermediate 33: 5-([1,1'-biphenyl]-4-yl)-6-amino-4,4-dimethylhexan-2-ol Diastereomer 2



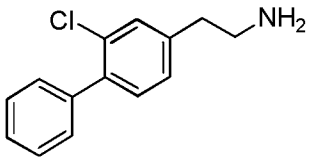
The title compound was isolated as a colorless oil as the 2nd fraction from the reduction of 2-([1,1'-biphenyl]-4-yl)-3,3-dimethyl-5-oxohexanenitrile (Step 2, Intermediate 32), (R_f = 0.10 in CH_2Cl_2:MeOH:NH_2OH/90:10:1). LCMS (MH^+): 298.

Intermediate 34: 5-([1,1'-biphenyl]-4-yl)-6-amino-4,4-dimethylhexan-2-ol Diastereomer 3 (stereochemistry not defined)



The title compound was isolated as a colorless oil as the 3rd fraction from the reduction of 2-([1,1'-biphenyl]-4-yl)-3,3-dimethyl-5-oxohexanenitrile (Step 2, Intermediate 32), (R_f = 0.05 in CH_2Cl_2:MeOH:NH_2OH/90:10:1). LCMS (MH^+): 298.

Intermediate 35: 2-(2-chloro-[1,1'-biphenyl]-4-yl)ethanamine



Step 1: A solution of 1-bromo-2-chloro-4-methylbenzene (1.0 g, 4.90 mmol), NBS (0.87 g, 4.90 mmol) and AIBN (1%) in CCl_4 (10 mL) was heated to reflux for 12 h. After cooling to RT, the reaction mixture was filtered and the filtrate was evaporated to provide 1-bromo-4-(bromomethyl)-2-chlorobenzene as a yellow oil.

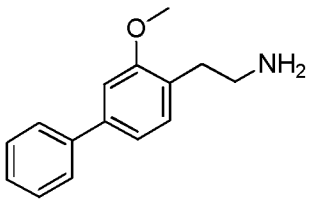
Step 2: A solution of 1-bromo-4-(bromomethyl)-2-chlorobenzene (1.38 g, 4.90 mmol), TMSCN (0.58 g, 5.9 mmol) and K_2CO_3 (0.81 g, 5.9 mmol) in CH_3CN (10 mL) was heated to 50 °C for 6 h. After this time, the reaction mixture was cooled to RT and concentrated *in vacuo*. The residue was extracted with ethyl acetate and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide 2-(4-bromo-3-chlorophenyl) acetonitrile as a colorless oil.

Step 3: To a solution of 2-(4-bromo-3-chlorophenyl) acetonitrile (800 mg, 3.47 mmol) and phenylboronic acid (508 mg, 4.16 mmol) in 1,4-dioxane (10 mL) was added aqueous

Na_2CO_3 (2M, 4mL) and $PdCl_2(PPh_3)_2$ (3%), and the reaction was heated to 95 °for 12 h. After this time, the reaction mixture was cooled to RT and quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide. Purification via normal phase column chromatography (hexane/ethyl acetate: 40/1) provided 2-(2-chlorobiphenyl-4-yl)acetonitrile as a yellow oil.

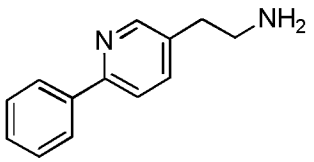
Step 4: A solution of 2-(2-chlorobiphenyl-4-yl)acetonitrile (376 mg, 1.65 mmol) and Raney-Ni (190 mg) in a solution of NH_3 in CH_3OH (6 mL) was stirred at RT for 12 h under 1 atm of H_2. After this time, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to provide the title compound as a yellow liquid. LCMS (MH^+): 232.08.

Intermediate 36: 2-(3-methoxy-[1,1'-biphenyl]-4-yl)ethanamine



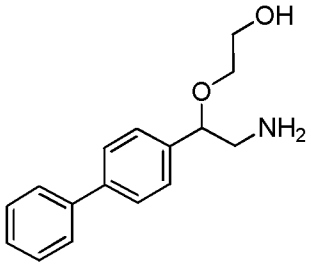
The title compound can be prepared as described for Intermediate 35: 2-(2-chloro-[1,1'-biphenyl]-4-yl)ethanamine starting with 1-bromo-3-methoxy-4-methylbenzene. LCMS (MH^+): 228.13.

Intermediate 37: 2-(6-phenylpyridin-3-yl)ethanamine



The title compound can be prepared as described for Intermediate 35: 2-(2-chloro-[1,1'-biphenyl]-4-yl)ethanamine starting with 2-bromo-5-methylpyridine. LCMS (MH^+): 199.12.

Intermediate 38: 2-(1-([1,1'-biphenyl]-4-yl)-2-aminoethoxy)ethanol



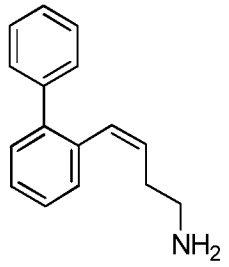
Step 1: To a solution of 4-bromobenzaldehyde (2.0 g, 10.8 mmol) and phenylboronic acid (1.58 g, 13.0 mmol) in 1,4-dioxane (10 mL) was added aqueous Na_2CO_3 (2M, 4mL) and $PdCl_2(PPh_3)_2$ (3%) and the reaction was heated to 95 °for 12 h. After this time, the reaction was cooled to RT and quenched with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexane/ethyl acetate= 100/1) provided biphenyl-4-carbaldehyde as white solid.

Step 2: A solution of biphenyl-4-carbaldehyde (500 mg, 2.74 mmol), ethane-1,2-diol (2 mL) and 4-methylbenzenesulfonic acid (47 mg, 0.274 mmol) in toluene (6 mL) was heated at 140 °C for 4 d. After this time, the reaction was cooled to RT and the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexane/ethyl acetate: 10/1) provided 2-(Biphenyl-4-yl)-1,3-dioxolane as a white solid.

Step 3: A solution of 2-(biphenyl-4-yl)-1,3-dioxolane (460 mg, 2.03 mmol), TMSCN (242 mg, 2.44 mmol) and ZnI_2 (1.3 g, 4.06 mmol) in CH_2Cl_2 (10 mL) was stirred at RT for 3.5 h. After this time, the reaction mixture was quenched with saturated Na_2CO_3 and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexane/ethyl acetate: 3/1) provided 2-(biphenyl-4-yl)-2-(2-hydroxyethoxy)acetonitrile as colorless gel.

Step 4: A solution of 2-(biphenyl-4-yl)-2-(2-hydroxyethoxy)acetonitrile (76 mg, 0.30 mmol) and Raney-Ni (50 mg) in a solution of NH_3 (7 N in CH_3OH) (6 mL) was stirred at RT for 12 h under 1 atm of H_2. After this time, the reaction was filtered and the filtrate was concentrated *in vacuo* to afford the title compound as a white solid that was used without further purification. LCMS[M+1] : 258.3.

Intermediate 39: (Z)-4-([1,1'-biphenyl]-2-yl)but-3-en-1-amine

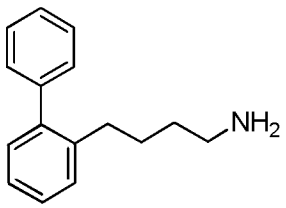


Step1: A solution of N-(3-bromopropyl)phthalimide (CAS#: 5460-29-7 , 13.4 g, 5 mmol) and triphenyl phosphine (13.2 g, 5 mmol) in m-xylene (75 mL) was heated to 145 °C for 40 h. After this time, the reaction was cooled to RT, filtered, washed with ether and dried *in vacuo* to provide (3-(1,3-dioxoisoindolin-2-yl)propyl)triphenylphosphonium bromide as a white solid.

Step 2: A solution of (3-(1,3-dioxoisoindolin-2-yl)propyl)triphenylphosphonium bromide (2.7 g, 5 mmol) in THF (30 mL) was cooled to 0 °C and potassium t-butoxide (0.56 g, 5 mmol) was added solution was stirred at 0 °C for 15 min and then [1,1'-biphenyl]-2-carbaldehyde (CAS#: 1203-68-5, 0.91 g, 5 mmol) was added. The reaction was warmed to RT and stirred for 12 h. After this time, the reaction was filtered, washed with ether and concentrated *in vacuo* to provide (Z)-2-(4-([1,1'-biphenyl]-2-yl)but-3-en-1-yl)isoindoline-1,3-dione as a white solid.

Step 3: A solution of (Z)-2-(4-([1,1'-biphenyl]-2-yl)but-3-en-1-yl)isoindoline-1,3-dione (550 mg, 1.56 mmol) in hydrazine (5 mL) and ethanol (10 mL) was heated to 75 °C for 2 h. After this time, the reaction was cooled to RT, concentrated *in vacuo* and purified directly via normal phase column chromatography ($MeOH:CH_2Cl_2:NH_4OH$/98:1:1) to provide the title compound as a clear oil. LCMS (MH^+): 224.4.

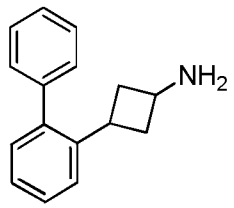
Intermediate 40: 4-([1,1'-biphenyl]-2-yl)butan-1-amine



A solution of (Z)-4-([1,1'-biphenyl]-2-yl)prop-2-en-1-amine (Intermediate 39, 100 mg, 0.45 mmol) and 10% Pd/C (50 mg) in 2.5 mL of ethanol was stirred at RT for 12 h under 1 atm of H_2. After this time, the reaction mixture was filtered through celite and concentrated *in vacuo*

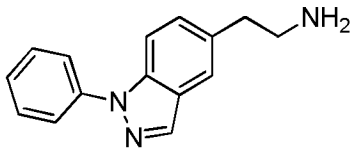
to provide the title compound as a clear oil that was used without further purification. LCMS (MH^+): 226.1.

Intermediate 41: 3-([1,1'-biphenyl]-2-yl)cyclobutanamine



A solution of 3-(2-bromophenyl)-cyclobutanamine (CAS#: 1156289-16-5, 26 mg, 0.10 mmol), phenyl boronic acid (18 mg, 0.15 mmol), $Pd(PPh_3)_2Cl_2$ (3 mg, 0.005 mmol), and Na_2CO_3 (21 mg, 0.2 mmol) in CH_3CN/H_2O (5 mL, 4:1) was heated to 90 °C for 2 h. After this time, the reaction was cooled to RT, filtered through celite and concentrated *in vacuo* to provide the title compound as a colorless oil that was used without further purification. LCMS (MH^+): 224.1.

Intermediate 42: 2-(1-phenyl-1H-indazol-5-yl)ethanamine



Step 1: To a solution of 4-fluoro-3-formyl-benzonitrile (CAS#: 146137-79-3, 6 g, 40.2 mmol) in DMF (30 mL) was added phenylhydrazine hydrochloride (6.12 g, 42.3 mmol). The reaction mixture was stirred for 2 h at 80 °C. Then K_2CO_3 (11.11 g, 80.5 mmol) was added and the reaction mixture was heated to 140 °C for an additional 12 h. After this time, the reaction was cooled to RT, and then poured into ice-water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexane/ethyl acetate: 2/1) to provide 1-phenyl-1H-indazole-5-carbonitrile as light yellow solid.

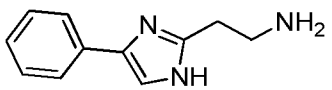
Step 2: A solution of 1-phenyl-1H-indazole-5-carbonitrile (2.1 g, 9.5 mmol) in EtOH (20 mL) and NaOH (40% in water, 20 mL) was heated to reflux for 12 h. After this time, the reaction was cooled to RT, and the reaction mixture was concentrated *in vacuo*. The pH of the residue was adjusted to ~3 by the addition of HCl (6.0 N) to provide an off-white solid that filtered to provide 1-phenyl-1H-indazole-5-carboxylic acid.

Step 3: To a solution of 1-phenyl-1H-indazole-5-carboxylic acid (2.0 g, 8.4 mmol) was added BH_3-THF (1.0 M, 20 mL) and the reaction mixture was heated to reflux for 12 h. After this time, the reaction was cooled to RT and the reaction mixture was quenched with concentrated HCl (10 mL) and then heated to reflux for an additional 3 h. The reaction mixture was then cooled to room temperature and $NaHCO_3$ (aq) was added dropwise to adjust the pH~7 and then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexane:ethyl acetate/2:1) provided a ~1:1 mixture of 5-(chloromethyl)-1-phenyl-1H-indazole and (1-phenyl-1H-indazol-5-yl)methanol that was used in the next step directly.

Step 4: To the 1:1 mixture of 5-(chloromethyl)-1-phenyl-1H-indazole and (1-phenyl-1H-indazol-5-yl) (1.0 g, 4.4 mmol) in DMF (10 mL) was added NaCN (428 mg, 8.7 mmol) and the reaction was heated to 50 °C for 48 h. After this time, the reaction mixture was cooled to RT and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexane/ethyl acetate: 2/1) provided 2-(1-phenyl-1H-indazol-5-yl)acetonitrile as an off-white solid.

Step 5: To a solution of 2-(1-phenyl-1H-indazol-5-yl)acetonitrile(730 mg, 3.13 mmol) in THF (10 mL) was added BH_3-THF (1.0 M, 15 mL) and the reaction was heated to reflux for 12 h. After this time, the reaction was cooled to RT and HCl (3.0 N, 10 mL) was added and the reaction mixture was then heated to reflux for 3 h. The reaction mixture was then cooled to RT and $NaHCO_3$ (aq) was added to adjust the pH~7. The reaction mixture was then extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexane:ethyl acetate/4:1) provided the title compound as a yellow oil. LCMS (MH^+): 238.1.

Intermediate 43: 2-(4-phenyl-1H-imidazol-2-yl)ethanamine



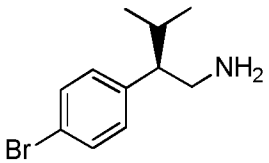
Step 1: To a solution of 3-((tert-butoxycarbonyl)amino)propanoic acid (CAS#: 26250-90-8, 2 g, 10.58 mmol) in DMF (20 mL) was added Cs_2CO_3 (1.72 g, 5.28 mmol) and the reaction mixture was stirred at RT for 1 h. After this time, 2-bromo-1-phenylethanone (CAS#: 70-11-1,

2.1 g, 0.256 mmol) was added and the reaction mixture was stirred for an additional 12 h at RT. The solvent was then removed *in vacuo* and ethyl acetate was added (50 mL) and the resultant white solid was filtered away from the reaction mixture. The filtrate was concentrated *in vacuo* to provide 2-oxo-2-phenylethyl 3-((tert-butoxycarbonyl)amino)propanoate as a light yellow solid that was used without further purification.

Step 2: To a solution of 2-oxo-2-phenylethyl 3-((tert-butoxycarbonyl)amino)propanoate (3 g, 9.8 mmol) in xylene (25 mL) was added ammonium acetate (7.84 g, 102 mmol). The reaction mixture was heated to 140 °C for 2 h. After this time, the reaction mixture was cooled to RT and then poured into saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexane:ethyl acetate/4:1) provided tert-butyl (2-(4-phenyl-1H-imidazol-2-yl)ethyl)carbamate as a light yellow oil.

Step 3: To a solution of tert-butyl (2-(4-phenyl-1H-imidazol-2-yl)ethyl)carbamate (200 mg, 0.7 mmol) in MeOH (2 mL) was added HCl (3.6 M in MeOH, 10 mL) and stirred at RT for 3 h. After this time, the reaction mixture was concentrated *in vacuo* to provide the title compound as a yellow oil that was used without further purification. LCMS (MH^+): 224.1.

Intermediate 44: (R)-2-(4-bromophenyl)-3-methylbutan-1-amine



Step 1: A solution of ethyl 2-(4-bromophenyl)acetate (CAS#: 14062-25-0, 40 g, 164.5 mmol) in DMF (200 mL) was cooled to -10 °C followed by the slow addition of NaH (60% in oil, 4.34g, 181 mmol) in several portions. The reaction mixture was stirred for 15 min and 2-bromopropane (22.2 g, 181 mmol) was added dropwise over 10 min. The reaction mixture was allowed to warm to RT and stirred for 12 h. After this time, the reaction mixture was concentrated *in vacuo* and then extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexanes:ethyl acetate/ 4:1) provided ethyl 2-(4-bromophenyl)-3-methylbutanoate as yellow oil.

Step 2: To a solution of ethyl 2-(4-bromophenyl)-3-methylbutanoate (26 g, 91.2 mmol) in EtOH (50 mL) was added aq. KOH (5 N,50 mL) and the reaction was heated to reflux for 12 h. The reaction mixture was then cooled to RT, and concentrated *in vacuo*. To the oily reside was adjusted the pH to ~3 with HCl (6.0 N) and the resulting solid was filtered and dried to provide 2-(4-bromophenyl)-3-methylbutanoic acid as an off-white solid that was used without further purification.

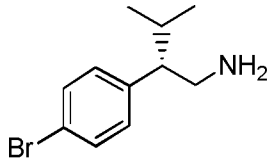
Step 3: To a solution of 2-(4-bromophenyl)-3-methylbutanoic acid (12.7 g, 49.4 mmol) in CH_3CN (75 mL) was added R-(+)-1-phenylethylamine (3.0 g, 24.7 mmol) in CH_3CN (50 mL). After 1 h, the crystalline precipitate was filtered off, washed with cold CH_3CN and dried *in vacuo*. To obtain high enantioselectivity, the crystalline diastereomeric salt was recrystallized an additional 3 times from MeOH and DMF (1:1) (filtering drying and then subjecting to the process each time). The corresponding diastereomeric salt was suspended in ether and treated with 3 N HCl to adjust the pH to ~1. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide (R)-2-(4-bromophenyl)-3-methylbutanoic acid as an off-white solid in >99%ee. Chiral HPLC analysis: Chiralcel OD-H (4.6 x 250 mm, 5 uM); hexanes:ethanol:TFA/99:5:1, retention time of 35.16 min. Optical rotation $[\alpha]_{20}^{D}$ = -41.4 (c = 0.408, $CHCl_3$).

Step 4: To a 0 °C solution of (R)-2-(4-bromophenyl)-3-methylbutanoic acid (6 g, 23.6 mmol) in CH_2Cl_2 (20 ml) was added oxalyl chloride (6 g, 47.2 mmol) dropwise over a 10 min period. After the complete addition of oxalyl chloride, DMF (2 drops) was added to and the reaction was warmed to RT for 2 h. After this time, the reaction mixture was then concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (15 mL), cooled to 0 °C and poured directly into ammonium hydroxide (28% NH_3 in water, 50 mL), warmed to RT and stirred for 2 h then concentrated *in vacuo*. To the residue was added HCl (3N) to adjust the pH to ~7 and the resulting solid was filtered, washed with water, and dried *in vacuo* to provide (R)-2-(4-bromophenyl)-3-methylbutanamide as a white solid that was used without further purification.

Step 5: To a solution of (R)-2-(4-bromophenyl)-3-methylbutanamide (5.5 g, 21.7 mmol) was added BH_3-THF (50 mL) and then heated to reflux for 12 h. After this time, the reaction mixture was cooled to RT and a second addition of BH_3-THF (50 mL) was added and the reaction mixture was heated to reflux for an additional 12 h. After this time, the reaction mixture was cooled to RT, and quenched with 3 N HCl, and then heated to reflux for 3 h. The reaction

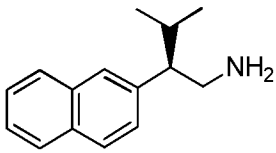
was then cooled to RT and 1 N NaOH was added dropwise to adjust the pH to ~7 and then the entire mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (CH_2Cl_2:MeOH/9:1) provided the title compound as a light yellow oil. LCMS (MH+): 242.05.

Intermediate 45: (S)-2-(4-bromophenyl)-3-methylbutan-1-amine



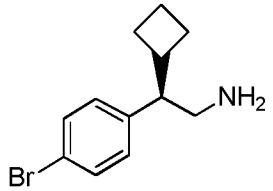
The title compound was made as described in Intermediate 44: (R)-2-(4-bromophenyl)-3-methylbutan-1-amine using S-(+)-1-phenylethylamine. Chiral HPLC analysis of (S)-2-(4-bromophenyl)-3-methylbutanoic: Chiralcel OD-H (4.6 x 250 mm, 5 uM); hexanes:ethanol:TFA/99:5:, retention time of 30.94 min. Optical rotation $[\alpha]_{20}^{D}$ = 40.0 (c = 1, MeOH). LCMS (MH+): 242.05.

Intermediate 46: (R)-3-methyl-2-(naphthalen-2-yl)butan-1-amine



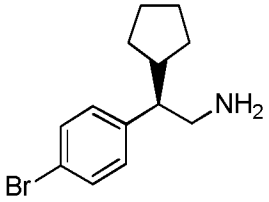
The title compound was made as described for Intermediate 44: starting with α-isopropyl-2-naphthaleneacetic acid (CAS#: 64497-79-6) in place of 2-(4-bromophenyl)-3-methylbutanoic acid. LCMS (MH+): 214.15.

Intermediate 47: (R)-2-(4-bromophenyl)-2-cyclobutylethanamine



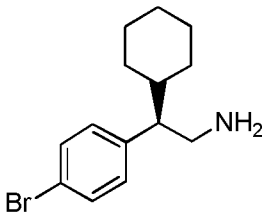
The title compound was made as described for Intermediate 44: (R)-2-(4 bromophenyl)-3-methylbutan-1-amine using bromocyclobutane (CAS#: 4399-47-7) in place of 2-bromopropane. LCMS (MH+): 254.05.

Intermediate 48: (R)-2-(4-bromophenyl)-2-cyclopentylethanamine



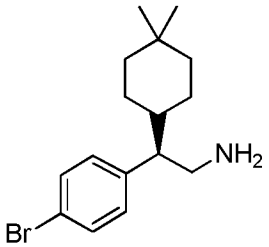
The title compound was made as described for Intermediate 44: (R)-2-(4 bromophenyl)-3-methylbutan-1-amine using bromocyclopentane (CAS#: 137-43-9) in place of 2-bromopropane. LCMS (MH+): 268.06.

Intermediate 49: (R)-2-(4-bromophenyl)-2-cyclohexylethanamine



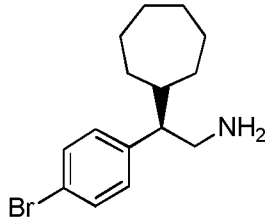
The title compound was made as described for Intermediate 44: (R)-2-(4 bromophenyl)-3-methylbutan-1-amine using bromocyclohexane (CAS#: 108-85-0) in place of 2-bromopropane. LCMS (MH+): 282.1.

Intermediate 50: (R)-2-(4-bromophenyl)-2-(4,4-dimethylcyclohexyl)ethanamine



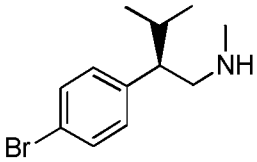
The title compound was made as described for Intermediate 44: (R)-2-(4 bromophenyl)-3-methylbutan-1-amine using 4-bromo-1,1-dimethyl- cyclohexane (CAS#: 25090-97-5) in place of 2-bromopropane. LCMS (MH+): 310.1.

Intermediate 51: (R)-2-(4-bromophenyl)-2-cycloheptylethanamine



The title compound was made in the identical manner as described for Intermediate 44: (R)-2-(4 bromophenyl)-3-methylbutan-1-amine using bromocycloheptane (CAS#: 137-43-9) in place of 2-bromopropane. LCMS (MH+): 295.10.

Intermediate 52: (R)-2-(4-bromophenyl)-N,3-dimethylbutan-1-amine



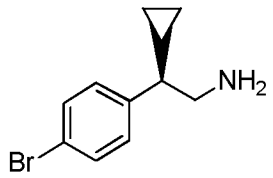
Step 1: To a solution of (R)-2-(4-bromophenyl)-3-methylbutan-1-amine (Intermediate 44,, 1 g, 4.1 mmol) in CH_2Cl_2 (10 mL) was added $(Boc)_2O$ (1 g, 4.5 mmol) and TEA (1.2 mL, 8.2 mmol) The reaction mixture was stirred at RT for 3 h and then diluted with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (CH_2Cl_2:MeOH/9:1) provided (R)-tert-butyl (2-(4-bromophenyl)-3-methylbutyl)carbamate as a yellow oil.

Step 2: To a 0 °C solution of (R)-tert-butyl (2-(4-bromophenyl)-3-methylbutyl)carbamate (300 mg, 0.87 mmol) in DMF (5 mL) was added NaH (39 mg, 0.964 mmol) and the reaction was stirred for 15 min. After this time, methyl iodide (254.33 mg, 1.75 mmol) was added, and the reaction was warmed to RT and stirred for 2 h. Then, the reaction was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography

(CH_2Cl_2:MeOH/10:1) provided (R)-tert-butyl (2-(4-bromophenyl)-3-methylbutyl) (methyl)carbamate as a yellow oil.

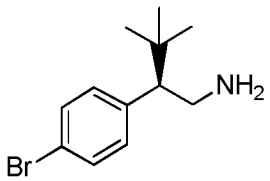
Step 3: To a 0 °C solution of (R)-tert-butyl (2-(4-bromophenyl)-3-methylbutyl) (methyl) carbamate in CH_2Cl_2 (6 mL) was added TFA (1.5 mL) and the reaction mixture was stirred for 1 h at 0 °C. After this time, the reaction mixture was concentrated, and saturated aqueous $NaHCO_3$ was added to adjust the pH 6-7 and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the title compound as a yellow solid that was used without further purification. LCMS (MH+): 256.10.

Intermediate 53: (R)-2-(4-bromophenyl)-2-cyclopropylethanamine



The title compound was made as described for Intermediate 44: (R)-2-(4 bromophenyl)-3-methylbutan-1-amine using bromocyclopropane (CAS#: 4333-56-6) in place of 2-bromopropane. LCMS (MH+): 240.03.

Intermediate 54: (R)-2-(4-bromophenyl)-3,3-dimethylbutan-1-amine



Step 1: t-Butyl magnesium chloride in ether (2M, 61 ml) was added to a solution of 4-bromo benzaldehyde (15g) in THF (200 ml) at 0 °C. The mixture was allowed to warm RT and stirred for 5 h. Saturated NH_4Cl solution was added and extracted with ethyl acetate. The organic layer was dried and concentrated. The crude was purified by flash chromatography (3% to 10% ethyl acetate in hexane) to provide (4-bromophenyl)(t-butyl)methanonol as a colorless oil. (7.9 g).

Step 2: To a solution of 1-(4-bromophenyl)-2,2-dimethylpropan-1-ol (3.8 g, 15.7 mmol) in CH_2Cl_2 (20 ml) was added a homogeneous mixture of PCC (12 g) and silica gel (12 g). The

mixture was stirred at room temperature for 4 h. Filtration of the reaction mixture through a short silica pad with excess CH_2Cl_2 provided (4-bromophenyl)(t-butyl)methanone (3.4 g).

Step 3: To a solution of methyl triphenylphosphonium bromide (8.8 g) in THF (100 mL) at -78 °C was added n-BuLi (2.5 M in hexane, 10.4 mL) slowly. The mixture was stirred at 0 °C for 30 min. To the reaction mixture was added a solution of (4-bromophenyl)(t-butyl)methanone (21) (5.3 g) in THF (10 mL). The mixture was allowed to warm to room temperature, stirred 24 h, and partitioned between TBME and saturated NH_4Cl solution. The combined organics were dried, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography with 50:1 hexane/EA to provide 3,3-dimethyl-2-(4-bromophenyl)-1-butene (3.7 g).

Step 4: To a solution of 3,3-dimethyl2-(4-bromophenyl)-1-butene(22) (2.5g) in THF at 0 °C, was added BH_3 (1 M in THF, 18 mL) dropwise. The mixture was allowed to warm to room temperature, and stirred for 1 h. 1 M Aqueous NaOH solution (21 mL) and H_2O_2 (30% in water, 2.6g) was slowly added. The mixture was stirred at room temperature for 1 hr, and then partitioned between TBME (50 mL) and water (50 mL). The aqueous layer was extracted with TBME (50 mL x 2). The combined organic layers were washed with brine, dried, and concentrated and then was purified by flash chromatography with 4:1 hexane/EA to provide 3,3-dimethyl-2-(4-bromophenyl)butanol (1.8 g) as a white solid.

Step 5: To a mixture 3,3-dimethyl-2-(4-bromophenyl)butanol (1.81g) in DMF (20 mL) at room temperature was added PDC (8.2 g) in portions. The mixture was stirred at room temperature overnight, and then diluted with EA (100 mL), filtered through a celite pad. The filtrate was washed with water, brine and dried, filtered and concentrated to give the crude product which was purified by flash chromatography with 4:1 hexane/EA to provide 3,3-dimethyl-2-(4-bromophenyl)butanoic acid as a white solid (0.7 g).

Step 6: A solution of 3,3-dimthyl-2-(4-bromophenyl)butanoic acid (0.7 g) in 4 mL of thionyl chloride was stirred at RT for 12 h. Thionyl chloride was removed under vacuum and chased twice with CH_2Cl_2. After drying under vacuum, 2-(4-bromophenyl)-3,3-dimethylbutanoyl chloride was obtained as an oil (0.6 g).

Step 7: To a solution of (R)-4-benzyl-2-oxazolidinone (0.5 g) in THF (20 mL) was cooled to -78 °C and n-BuLi (2.5 M in hexane, 1.5 mL) was added drop-wise. The mixture was stirred 30 min then a solution of 2-(4-bromophenyl)-3,3-dimethylbutanoyl chloride (0.6 g) in THF (3 mL) was added at -78°C. The mixture was stirred for 1 h and the saturated NH_4Cl

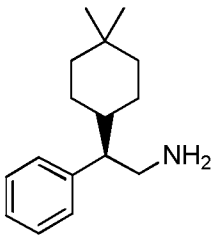
solution (20 mL) was added. The organic layer was separated and the aqueous layer was extracted twice with TBME (10 mL). The combine organic extracts were dried, filtered and concentrated *in vacuo*. The resulting diasteromers were separated with flash chromatography by gradient of hexane, 50:1 hexane/EA, then 10:1 hexane/EA to give (4R)-4-benzyl-3-[(2R)-2-tert-butyl-2-(4-bromophenyl)acetyl]-1.3-oxazolidin-2-one as an oil (0.32 g) (up spot) and (4R)-4-benzyl-3-[(2S)-2-tert-butyl-2-(4-bromophenyl)acetyl]-1.3-oxazolidin-2-one as a white solid (0.31 g) (low spot).

Step 8: To a solution of (4R)-4-benzyl-3-[(2R)-2-tert-butyl-2-(4-bromophenyl)acetyl]-1.3-oxazolidin-2-one (2 g, 4.65 mmol) in THF/water (60/20 mL) was added 30% H_2O_2 (3.8 mL) at 0 °C and stirred for 10 min. Then $LiOH.H_2O$ (400 mg, 9.3 mmol) was added. The reaction mixture was stirred at RT overnight. After cooling to 0 °C, Na_2SO_3 (4.8 g, 37.2 mmol) was added and the mixture was stirred for 30 min, and then extracted with EA. The aqueous layer was collected and acidified to pH=2 with 5% $KHSO_4$, extracted with ethyl acetate, dried, filtered, and concentrated to afford (R)-2-(4-bromophenyl)-3,3-dimethylbutanoic acid (900 mg) as an oil.

Step 9: To a solution of (R)-2-(4-bromophenyl)-3,3-dimethylbutanoic acid (900 mg, 3.32 mmol) in CH_2Cl_2 (10 mL) was added $(COCl)_2$ (1 mL) at 0 °C, then DMF (1 drop) was added and stirred for 2 h. After this time, the reaction mixture was concentrated, and the resulting residue was poured into $NH_3.H_2O$ and filtered. The solid was collected to afford (R)-2-(4-bromophenyl)-3,3-dimethylbutanamide (600 mg) that was used in the next step without further purification.

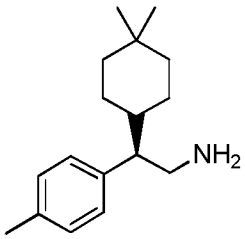
Step 10: A solution of (R)-2-(4-bromophenyl)-3,3-dimethylbutanamide (600 mg, 2.22 mmol) in THF was cooled to 0 °C to which BH_3.THF (50 mL) was added slowly, then the mixture was refluxed for 12 h. After this time, the reaction was cooled to RT and 3 N HCl (10 mL) was added. The mixture was refluxed for 2 h, then cooled to RT. The pH was adjusted to ~8 with aqueous $NaHCO_3$ and then extracted with ethyl acetate, dried, filtered, concentrated, and purified by flash column (CH_2Cl_2 /MeOH= 15/1 v/v) to afford the title compound (450 mg) as an oil. LCMS (MH+): 256.1.

Intermediate 55: (R)-2-(4,4-dimethylcyclohexyl)-2-phenylethanamine



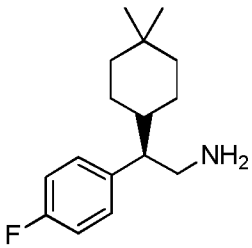
The title compound was made as described for Intermediate 44 ((R)-2-(4 bromophenyl)-3-methylbutan-1-amine) using 4-bromo-1,1-dimethyl cyclohexane (CAS#: 25090-97-5) in place of 2-bromopropane and ethyl phenylacetate (CAS# 101-97-3) in place of ethyl 2-(4-bromophenyl)acetate. LCMS (MH+): 232.2.

Intermediate 56: (R)-2-(4,4-dimethylcyclohexyl)-2-(p-tolyl)ethanamine



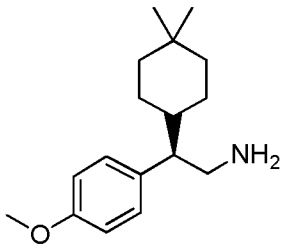
The title compound was made as described for Intermediate 44 ((R)-2-(4 bromophenyl)-3-methylbutan-1-amine) using 4-bromo-1,1-dimethyl cyclohexane (CAS#: 25090-97-5) in place of 2-bromopropane and ethyl 4-methylphenylacetate (CAS# 94-08-6) in place of ethyl 2-(4-bromophenyl)acetate. LCMS (MH+): 246.4.

Intermediate 57: (R)-2-(4,4-dimethylcyclohexyl)-2-(4-fluorophenyl)ethanamine



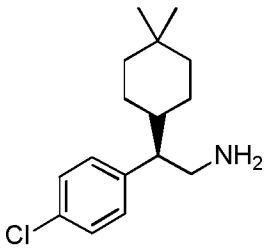
The title compound was made as described for Intermediate 44 ((R)-2-(4 bromophenyl)-3-methylbutan-1-amine) using 4-bromo-1,1-dimethyl cyclohexane (CAS#: 25090-97-5) in place of 2-bromopropane and ethyl 4-fluorophenylacetate (CAS# 587-88-2) in place of ethyl 2-(4-bromophenyl)acetate. LCMS (MH+): 250.4.

Intermediate 58: (R)-2-(4,4-dimethylcyclohexyl)-2-(4-methoxyphenyl)ethanamine



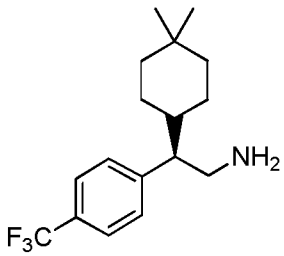
The title compound was made as described for Intermediate 44 ((R)-2-(4 bromophenyl)-3-methylbutan-1-amine) using 4-bromo-1,1-dimethyl cyclohexane (CAS#: 25090-97-5) in place of 2-bromopropane and ethyl 4-methoxyphenylacetate (CAS# 14062-18-1) in place of ethyl 2-(4-bromophenyl)acetate. LCMS (MH+): 262.4.

Intermediate 59: (R)-2-(4,4-dimethylcyclohexyl)-2-(4-chlorophenyl)ethanamine



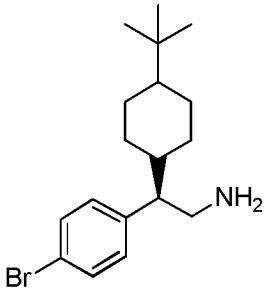
The title compound was made as described for Intermediate 44 ((R)-2-(4 bromophenyl)-3-methylbutan-1-amine) using 4-bromo-1,1-dimethyl cyclohexane (CAS#: 25090-97-5) in place of 2-bromopropane and ethyl 4-chlorophenylacetate (CAS# 14062-24-9) in place of ethyl 2-(4-bromophenyl)acetate. LCMS (MH+): 266.8.

Intermediate 60: (R)-2-(4,4-dimethylcyclohexyl)-2-(4-(trifluoromethyl)phenyl)-ethanamine



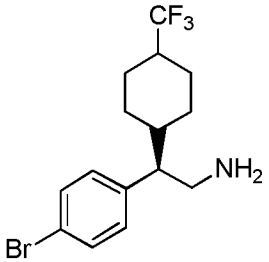
The title compound was made as described for Intermediate 44 ((R)-2-(4 bromophenyl)-3-methylbutan-1-amine) using 4-bromo-1,1-dimethyl cyclohexane (CAS#: 25090-97-5) in place of 2-bromopropane and ethyl 4-(trifluoromethyl)phenylacetate (CAS# 721-63-1) in place of ethyl 2-(4-bromophenyl)acetate. LCMS (MH+): 300.4.

Intermediate 61: (2R)-2-(4-bromophenyl)-2-(4-(tert-butyl)cyclohexyl)-ethanamine



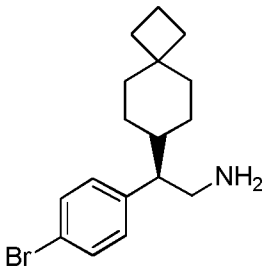
The title compound was made as described for Intermediate 44 ((R)-2-(4 bromophenyl)-3-methylbutan-1-amine) using 1-bromo-4-(tert-butyl)cyclohexane (CAS#: 7080-86-6) in place of 2-bromopropane. LCMS (MH+): 339.14.

Intermediate 62: (2R)-2-(4-bromophenyl)-2-(4-(trifluoromethyl) cyclohexyl) ethanamine



The title compound was made as described for Intermediate 44 ((R)-2-(4 bromophenyl)-3-methylbutan-1-amine) using 1-bromo-4-(trifluoromethyl)cyclohexane (CAS#: 30129-20-5) in place of 2-bromopropane. LCMS (MH+): 351.22.

Intermediate 63: (R)-2-(4-bromophenyl)-2-(spiro[3.5]nonan-7-yl)ethanamine

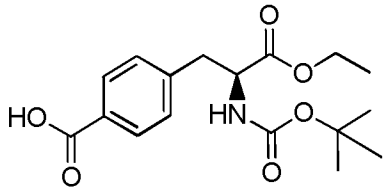


Step 1: To a 0 °C solution of spiro[3.5]nonan-7-ol (CAS#: 1393450-96-8, 1 g, 140 mmol) in CH_2Cl_2 was added triphenylphosphine (0.08 g, 0.28 mmol), imidazole (0.03 g, 0.43 mmol), and iodine (0.05 g, 0.03 mmol). The mixture was heated at 100 °C for 1 h then cooled to RT.

The mixture was poured into a saturated solution of $NaHCO_3$. Excess triphenylphosphine was destroyed by the addition of iodine until the iodine coloration persisted in the organic layer. The organic layer was washed twice with 5% (wt.) $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified on silica gel (hexanes/ethyl acetate, 8/1) to provide 7-iodospiro[3.5]nonane as as a light yellow oil.

Step 2: The title compound was made as described for Intermediate 44 ((R)-2-(4 bromophenyl)-3-methylbutan-1-amine) using 7-iodospiro[3.5]nonane in place of 2-bromopropane. LCMS (MH+): 322.11.

Intermediate A: (S)-4-(2-((tert-butoxycarbonyl)amino)-3-ethoxy-3-oxopropyl)benzoic acid

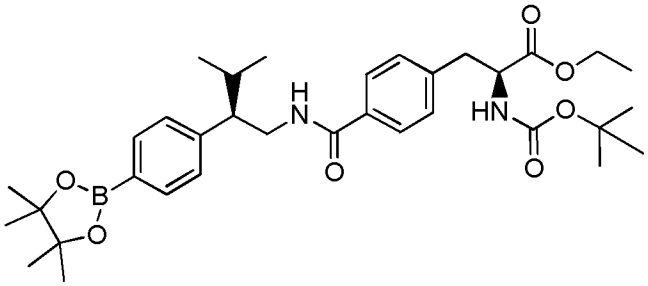


Step 1: To a 0 °C solution of (S)-ethyl 2-((tert-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanoate (CAS#: 72594-77-5, 7 g, 22.7 mmol) in CH_2Cl_2 (70 mL), was added pyridine (8.95 g, 113.2 mmol) followed by the dropwise addition of trifluoromethanesulfonic anhydride (6.7 g, 23.7 mmol) over a 30 min period. After this time, the reaction was stirred at 0 °C for 5 h, then extracted with CH_2Cl_2. The organic layer was washed sequentially with a 0.5 N NaOH solution , water, 1 N HCl, and brine, then dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide (S)-ethyl 2-((tert-butoxycarbonyl)amino)-3-(4-(((trifluoromethyl)sulfonyl) oxy)phenyl)propanoate as an off-white solid that was used without further purification.

Step 2: To a solution of (S)-ethyl 2-((tert-butoxycarbonyl)amino)-3-(4-(((trifluoromethyl) sulfonyl)oxy)phenyl)propanoate (10 g, 22.6 mmol) in DMF/H_2O (45 mL/15 mL) was added iPr_2NEt(5.8 g, 45.2 mmol), 1,3-bis(diphenylphosphino)propane (560 mg,1.4 mmol), and $Pd(OAc)_2$ (152 mg, 0.68 mmol). The reaction was stirred at 70 °C under 1 atm of CO for 12 h. After this time, the reaction was cooled to RT and extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$, 3N HCl, brine and then dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the title compound as a white solid that was used without further purification. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 8.09 – 8.03 (m, 2H), 7.46 (dt, J = 7.3, 1.1 Hz, 2H), 5.29 (t, J = 7.1 Hz, 1H), 4.19 (dq, J = 12.3, 8.0 Hz, 1H), 4.09 (dq, J = 12.5, 8.0 Hz,

1H), 3.37 (ddt, J = 12.4, 7.1, 1.0 Hz, 1H), 3.15 (ddt, J = 12.5, 7.2, 1.1 Hz, 1H), 1.44 (s, 9H), 1.18 (t, J = 8.0 Hz, 3H). LCMS (MH^+): 338.

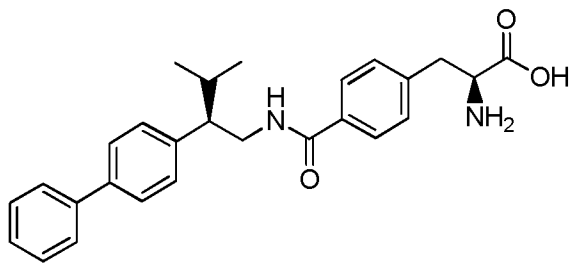
Intermediate B: (S)-ethyl 2-((tert-butoxycarbonyl)amino)-3-(4-(((R)-3-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butyl)carbamoyl)phenyl)propanoate



To a solution of (S)-ethyl 3-(4-(((R)-2-(4-bromophenyl)-3-methylbutyl) carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (from Step 1 of Example 1a, 2 g, 3.6 mmol) in dioxane (30 mL) was added $Pd(dppf)Cl_2$ (260 mg, 0.36 mmol), bis(pinacolato)diboron (1.8 g, 7.1 mmol), and KOAc (1.05 g, 10.68 mmol). The reaction mixture was heated to 90 °C for 12 h. After this time, the reaction was cooled to RT and extracted with ethyl acetate. The the organic layer was washed with $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification via normal phase column chromatography (hexanes:ethyl acetate/2:1 v/v) provided the title compound as an off-white solid (2.5 g). LCMS (MH^+): 553.4.

Representative experimental procedure

Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid



Step 1: To a solution of (S)-4-(2-((tert-butoxycarbonyl)amino)-3-ethoxy-3-oxopropyl)benzoic acid (Intermediate A, 200 mg, 0.82 mmol) in DMF (10 mL) was added (R)-2-

(4-bromophenyl)-3-methylbutan-1-amine (Intermediate 44, 278 mg, 1.24 mmol), HATU (623 mg, 1.64 mmol), and TEA (166 mg, 1.64 mmol), and the reaction was stirred for 48 h at RT. After this time, the reaction was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexanes:ethyl acetate/4:1 v/v) provided (S)-ethyl 3-(4-(((R)-2-(4-bromophenyl)-3-methylbutyl)carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate as a white solid.

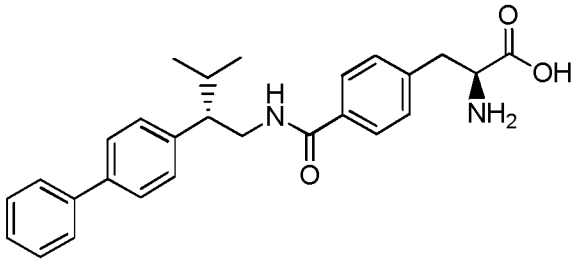
Step 2: To a solution of (S)-ethyl 3-(4-(((R)-2-(4-bromophenyl)-3-methylbutyl) carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (200 mg, 0.36 mmol) in dioxane (5.0 mL)/Na_2CO_3 (2.5 mL, 2.0 M, aq.) was added phenyl boronic acid (66 mg, 0.54 mmol) followed by Pd(dppf)Cl_2 (26 mg, 0.036 mmol). The reaction was purged with N_2 and then heated to 90 °C for 3 h. After this time, the reaction was cooled to RT and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexanes:ethyl acetate/4:1) provided (S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate as an off-white solid.

Step 3: To a 0 °C solution of (S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (150 mg, 0.27 mmol) in CH_2Cl_2 (6 mL), was added dropwise TFA (1.5 mL). The reaction was warmed to RT for 3 h, then concentrate *in vacuo*. To the resulting residue was added saturated aqueous solution of $NaHCO_3$ to adjust the pH to ~7.5 and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide (S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoate as an off-white solid.

Step 4: To a 0 °C solution of (S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoate (75 mg, 0.16 mmol) in MeOH (6 mL), was added dropwise 5 N NaOH (2 mL) and then the reaction mixture was warmed to RT for 3 h. After this time, the reaction mixture was acidified with 3N HCl to adjust the pH to 6-7, the MeOH was removed *in vacuo* and the resultant solid was filtered, washed with H_2O, and dried *in vacuo* to provide the title compound as a white solid.

1H NMR (400 MHz, MeOH-d4): δ ppm 7.61-7.50 (m, 7H), 7.40 (t, J = 7.5 Hz, 3H), 7.29 (dd, J = 11.4, 7.3 Hz, 6H), 3.88 (dd, J = 13.5, 5.1 Hz, 2H), 3.75 (s, 1H), 3.62 (t, J = 11.7 Hz, 2H), 3.34 (s, 1H), 3.02 (s, 1H), 2.84 (s, 1H), 2.03-1.96 (m, 1H), 1.09 (d, J = 6.5 Hz, 4H), 0.82 (d, J = 6.5 Hz, 4H). LCMS (MH^+): 430.54.

Example 1b: (S)-3-(4-(((S)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid

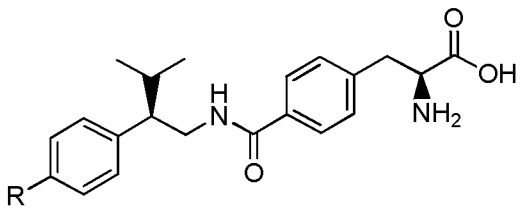


The title compound was prepared as described in Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid, starting with (S)-2-(4-bromophenyl)-3-methylbutan-1-amine (Intermediate 45).

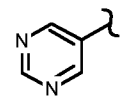
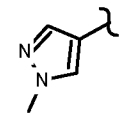
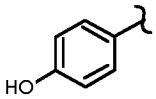
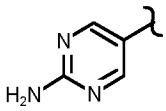
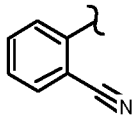
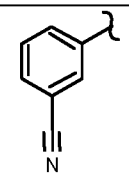
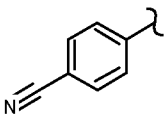
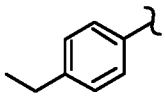
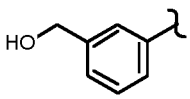
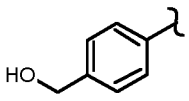
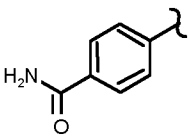
^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.56 (ddd, J = 12.9, 7.5, 3.2 Hz, 5H), 7.40 (t, J = 7.7 Hz, 2H), 7.29 (dd, J = 11.1, 8.0 Hz, 4H), 3.88 (dd, J = 13.3, 5.4 Hz, 1H), 3.74 (dd, J = 8.5, 4.5 Hz, 1H), 3.62 (dd, J = 13.3, 10.3 Hz, 1H), 3.01 (dd, J = 14.5, 8.6 Hz, 1H), 2.84 (td, J = 10.0, 9.2, 5.5 Hz, 1H), 2.00 (dq, J = 14.0, 7.0 Hz, 1H), 1.09 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H). LCMS (MH+): 430.54.

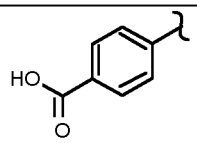
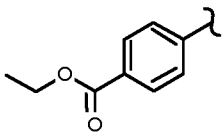
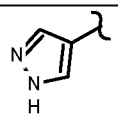
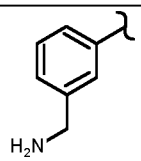
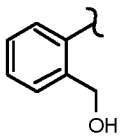
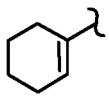
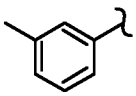
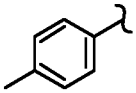
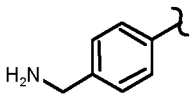
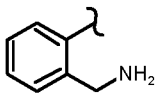
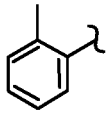
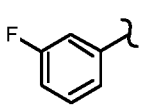
The following compounds in Table 3a were prepared as described above for (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid (Example 1a). NMR data is provided in Table 3b.

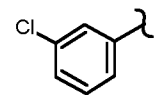
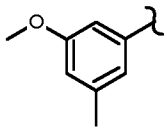
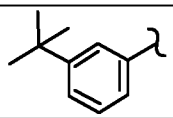
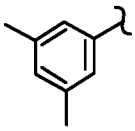
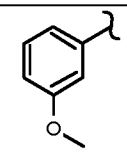
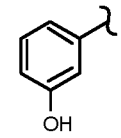
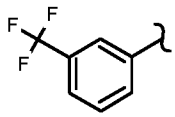
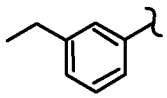
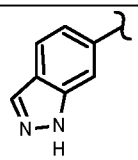
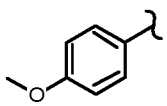
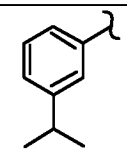
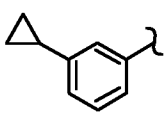
Table 3a

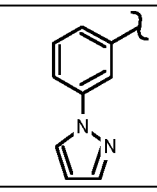
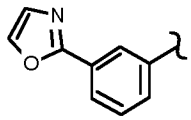
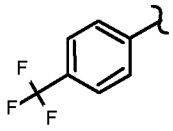
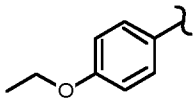
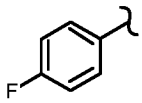
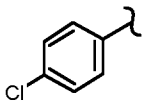
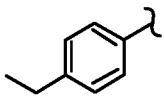
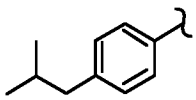
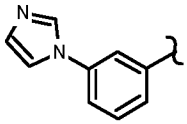
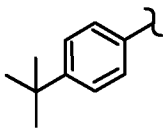
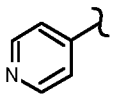


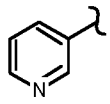
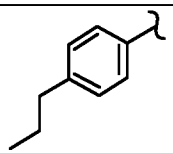
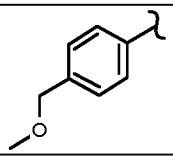
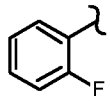
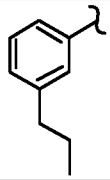
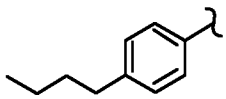
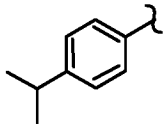
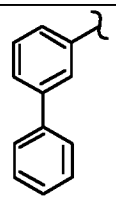
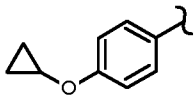
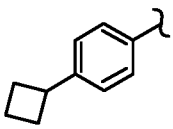
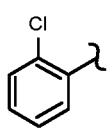
Ex. No.	R	Name	LCMS (MH+)

2		(S)-2-amino-3-(4-(((R)-3-methyl-2-(4-(pyrimidin-5-yl) phenyl)butyl)carbamoyl)phenyl)propanoic acid	433.51
3		(S)-2-amino-3-(4-(((R)-3-methyl-2-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)butyl)carbamoyl)phenyl)propanoic acid	435.51
4		(S)-2-amino-3-(4-(((R)-2-(4'-hydroxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	447.54
5		(S)-2-amino-3-(4-(((R)-2-(4-(2-aminopyrimidin-5-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	448.54
6		(S)-2-amino-3-(4-(((R)-2-(2'-cyano-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	456.51
7		(S)-2-amino-3-(4-(((R)-2-(3'-cyano-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	456.51
8		(S)-2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	456.55
9		(S)-2-amino-3-(4-(((R)-2-(4'-ethyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	459.59
10		(S)-2-amino-3-(4-(((R)-2-(3'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid	461.57
11		(S)-2-amino-3-(4-(((R)-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid	461.61
12		(S)-2-amino-3-(4-(((R)-2-(4'-carbamoyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	474.57

13		4'-((R)-1-(4-((S)-2-amino-2-carboxyethyl)benzamido)-3-methylbutan-2-yl)-[1,1'-biphenyl]-4-carboxylic acid	475.54
14		(S)-2-amino-3-(4-(((R)-2-(4'-(ethoxycarbonyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid	503.60
15		(S)-3-(4-(((R)-2-(4-(1H-pyrazol-4-yl)phenyl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid	421.50
16		(S)-2-amino-3-(4-(((R)-2-(3'-(aminomethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoic acid	460.60
17		(S)-2-amino-3-(4-(((R)-2-(2'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoic acid	461.56
18		(S)-2-amino-3-(4-(((R)-3-methyl-2-(2',3',4',5'-tetrahydro-[1,1'-biphenyl]-4-yl)butyl)carbamoyl) phenyl) propanoic acid	435.57
20		(S)-2-amino-3-(4-(((R)-3-methyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl) propanoic acid	445.56
21		(S)-2-amino-3-(4-(((R)-3-methyl-2-(4'-methyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl) propanoic acid	445.56
22		(S)-2-amino-3-(4-(((R)-2-(4'-(aminomethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl) phenyl)propanoic acid	460.58
23		(S)-2-amino-3-(4-(((R)-2-(2'-(aminomethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid	460.58
24		(S)-2-amino-3-(4-(((R)-3-methyl-2-(2'-methyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl) propanoic acid	445.56
25		(S)-2-amino-3-(4-(((R)-2-(3'-fluoro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	449.53

26		(S)-2-amino-3-(4-(((R)-2-(3'-chloro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	465.98
27		(S)-2-amino-3-(4-(((R)-2-(3'-methoxy-5'-methyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoic acid	475.59
28		(S)-2-amino-3-(4-(((R)-2-(3'-(tert-butyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoic acid	487.65
29		(S)-2-amino-3-(4-(((R)-2-(3',5'-dimethyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	459.59
30		(S)-2-amino-3-(4-(((R)-2-(3'-methoxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	461.57
31		(S)-2-amino-3-(4-(((R)-2-(3'-hydroxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	447.54
32		(S)-2-amino-3-(4-(((R)-3-methyl-2-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)butyl)carbamoyl) phenyl)propanoic acid	499.54
33		(S)-2-amino-3-(4-(((R)-2-(3'-ethyl-[1,1'-biphenyl]-4-yl)-3-methyl butyl)carbamoyl)phenyl)propanoic acid	459.59
34		(S)-3-(4-(((R)-2-(4-(1H-indazol-6-yl)phenyl)-3-methyl butyl)carbamoyl)phenyl)-2-aminopropanoic acid	471.56
35		(S)-2-amino-3-(4-(((R)-2-(4'-methoxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	461.57
36		(S)-2-amino-3-(4-(((R)-2-(3'-isopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl) propanoic acid	472.62
37		(S)-2-amino-3-(4-(((R)-2-(3'-cyclopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl) propanoic acid	471.60

38		(S)-3-(4-(((R)-2-(3'-(1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid	497.60
39		(S)-2-amino-3-(4-(((R)-3-methyl-2-(3'-(oxazol-2-yl)-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl) propanoic acid	498.59
40		(S)-2-amino-3-(4-(((R)-3-methyl-2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl) propanoic acid	499.54
41		(S)-2-amino-3-(4-(((R)-2-(4'-ethoxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl) propanoic acid	475.59
42		(S)-2-amino-3-(4-(((R)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl) propanoic acid	449.53
43		(S)-2-amino-3-(4-(((R)-2-(4'-chloro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl) propanoic acid	465.98
44		(S)-2-amino-3-(4-(((R)-2-(4'-ethyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	459.59
45		(S)-2-amino-3-(4-(((R)-2-(4'-isobutyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	515.70
46		(S)-3-(4-(((R)-2-(3'-(1H-imidazol-1-yl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid	497.60
47		(S)-2-amino-3-(4-(((R)-2-(4'-(tert-butyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	487.65
48		(S)-2-amino-3-(4-(((R)-3-methyl-2-(4-(pyridin-4-yl)phenyl)butyl)carbamoyl)phenyl)propanoic acid	432.53

49		(S)-2-amino-3-(4-(((R)-3-methyl-2-(4-(pyridin-3-yl)phenyl)butyl)carbamoyl)phenyl)propanoic acid	432.53
50		(S)-2-amino-3-(4-(((R)-3-methyl-2-(4'-propyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoic acid	473.62
51		(S)-2-amino-3-(4-(((R)-2-(4'-(methoxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoic acid	475.59
52		(S)-2-amino-3-(4-(((R)-2-(2'-fluoro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	449.53
53		(S)-2-amino-3-(4-(((R)-3-methyl-2-(3'-propyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl) propanoic acid	473.62
54		(S)-2-amino-3-(4-(((R)-2-(4'-butyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid	487.65
55		(S)-2-amino-3-(4-(((R)-2-(4'-isopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid	473.62
56		(S)-3-(4-(((R)-2-([1,1':3',1''-terphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid	507.64
57		(S)-2-amino-3-(4-(((R)-2-(4'-cyclopropoxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid	487.60
58		(S)-2-amino-3-(4-(((R)-2-(4'-cyclobutyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	484.63
59		(S)-2-amino-3-(4-(((R)-2-(2'-chloro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	429.53

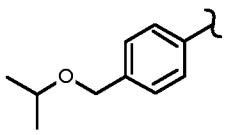
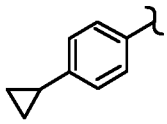
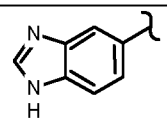
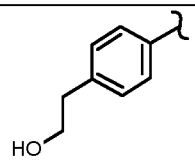
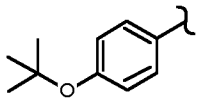
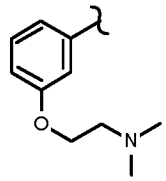
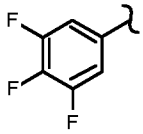
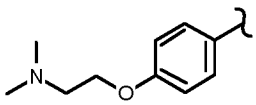
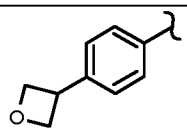
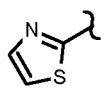
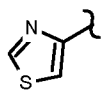
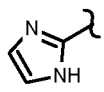
60		(S)-2-amino-3-(4-(((R)-2-(4'-(isopropoxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid	503.64
61		(S)-2-amino-3-(4-(((R)-2-(4'-cyclopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	471.60
62		(S)-3-(4-(((R)-2-(4-(1H-benzo[d]imidazol-5-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid	471.56
63		(S)-2-amino-3-(4-(((R)-2-(4'-(2-hydroxyethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid	475.59
64		(S)-2-amino-3-(4-(((R)-2-(4'-(tert-butoxy)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	503.64
65		(S)-2-amino-3-(4-(((R)-2-(3'-(2-(dimethylamino)ethoxy)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	518.66
66		(S)-2-amino-3-(4-(((R)-3-methyl-2-(3',4',5'-trifluoro-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoic acid	485.51
67		(S)-2-amino-3-(4-(((R)-2-(4'-(2-(dimethylamino)ethoxy)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid	518.66
68		(S)-2-amino-3-(4-(((R)-3-methyl-2-(4'-(oxetan-3-yl)-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoic acid	486.60
69		(S)-2-amino-3-(4-(((R)-3-methyl-2-(4-(thiazol-2-yl)phenyl) butyl)carbamoyl)phenyl)propanoic acid	438.55
70		(S)-2-amino-3-(4-(((R)-3-methyl-2-(4-(thiazol-4-yl)phenyl)butyl) carbamoyl)phenyl)propanoic acid	438.55
71		(S)-3-(4-(((R)-2-(4-(1H-imidazol-2-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid	421.50

Table 3b

Ex. No.	^{1}H NMR
2	1H NMR (400 MHz, MeOH-d4): δ ppm 9.10 (s, 1H), 9.04 (s, 2H), 7.66 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 7.8 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 3.87 (dd, J = 13.4, 5.4 Hz, 2H), 3.78 - 3.62 (m, 3H), 3.26 (d, J = 4.5 Hz, 3H), 3.02 (dd, J = 14.5, 8.6 Hz, 2H), 2.89 (s, 1H), 2.02 (q, J = 6.9 Hz, 2H), 1.09 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H)
3	1H NMR (400 MHz, DMSO-d6): δ ppm 8.16 (s, 1H), 7.77 (s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 7.8 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 3.82 (s, 3H), 3.66 (dd, J = 12.7, 6.4 Hz, 2H), 3.36 (d, J = 8.0 Hz, 32H), 3.10 (s, 2H), 2.91 - 2.73 (m, 4H), 0.92 (d, J = 6.7 Hz, 3H), 0.71 (d, J = 6.7 Hz, 3H)
4	1H NMR (400 MHz, MeOH-d4): δ ppm 8.11 (s, 1H), 7.55 (d, J = 7.9 Hz, 2H), 7.50 - 7.38 (m, 4H), 7.30 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 3.92 - 3.81 (m, 3H), 3.60 (s, 1H), 2.81 (s, 1H), 1.98 (dd, J = 14.0, 7.3 Hz, 2H), 1.29 (s, 2H), 1.08 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H)
5	1H NMR (400 MHz, MeOH-d4): δ ppm 8.50 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.30 (dd, J = 8.1, 5.3 Hz, 2H), 3.86 (dd, J = 13.3, 5.4 Hz, 1H), 3.73 (dd, J = 8.7, 4.3 Hz, 1H), 3.68 - 3.58 (m, 1H), 3.34 (s, 1H), 3.01 (dd, J = 14.5, 8.5 Hz, 1H), 2.84 (s, 1H), 2.04-1.94 (m, 1H), 1.28 (s, 1H), 1.08 (d, J = 6.6 Hz, 2H), 0.80 (d, J = 6.7 Hz, 2H)
6	1H NMR (400 MHz, MeOH-d4): δ ppm 7.81 (d, J = 7.9 Hz, 1H), 7.71 (t, J = 7.6 Hz, 2H), 7.60 – 7.47 (m, 8H), 7.33 (dd, J = 16.8, 7.8 Hz, 5H), 3.91 (dd, J = 13.3, 5.4 Hz, 2H), 3.71 (dd, J = 8.7, 4.4 Hz, 2H), 3.61 (dd, J = 13.3, 10.4 Hz, 2H), 3.03 – 2.90 (m, 3H), 2.89 (s, 1H), 2.03 (q, J = 7.0 Hz, 2H), 1.11 (d, J = 6.6 Hz, 4H), 0.83 (d, J = 6.7 Hz, 4H)
7	1H NMR (400 MHz, MeOH-d4): δ ppm 7.98 – 7.87 (m, 2H), 7.67 (dt, J = 7.7, 1.5 Hz, 1H), 7.58 (ddd, J = 14.7, 8.1, 4.1 Hz, 4H), 7.32 (dd, J = 10.7, 8.1 Hz, 3H), 3.87 (dd, J = 13.4, 5.4 Hz, 1H), 3.75 (dd, J = 8.4, 4.6 Hz, 1H), 3.65 (dd, J = 13.3, 10.2 Hz, 1H), 3.26 (d, J = 4.6 Hz, 1H), 3.02 (dd, J = 14.5, 8.5 Hz, 1H), 2.87 (s, 1H), 2.00 (dt, J = 13.7, 6.9 Hz, 1H), 1.09 (d, J = 6.6 Hz, 2H), 0.82 (d, J = 6.7 Hz, 2H).
8	1H NMR (400 MHz, MeOH-d4): δ ppm 7.83 - 7.73 (m, 4H), 7.58 (dd, J = 26.1, 7.8 Hz, 5H), 7.32 (dd, J = 14.7, 7.9 Hz, 5H), 3.94 - 3.82 (m, 2H), 3.65 (t, J = 11.8 Hz, 2H), 3.02 (dd, J = 14.5, 8.5 Hz, 2H), 2.87 (s, 1H), 2.01 (s, 1H), 1.09 (d, J = 6.6 Hz, 4H), 0.81 (d, J = 6.6 Hz, 4H)
9	11H NMR (400 MHz, MeOH-d4): δ ppm 7.58-7.46 (m, 4H), 7.34-7.21 (m, 4H), 3.88 (dd, J = 13.3, 5.4 Hz, 1H), 3.73 (dd, J = 8.7, 4.4 Hz, 1H), 3.61 (dd, J = 13.3, 10.3 Hz, 1H), 3.01 (dd, J = 14.5, 8.6 Hz, 1H), 2.83 (s, 1H), 2.66 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.6 Hz, 2H), 1.09 (d, J = 6.6 Hz, 2H), 0.82 (d, J = 6.7 Hz, 2H)
10	1H NMR (400 MHz, DMSO-d6): δ ppm 7.61-7.45 (m, 4H), 7.38 (t, J = 7.7 Hz, 1H), 7.33 - 7.24 (m, 3H), 4.65 (s, 1H), 3.88 (dd, J = 13.3, 5.4 Hz, 1H), 3.74 (dd, J = 8.6,

	4.5 Hz, 1H), 3.62 (dd, J = 13.3, 10.3 Hz, 1H), 3.30 (s, 2H), 3.01 (dd, J = 14.5, 8.6 Hz, 1H), 2.84 (p, J = 6.4, 5.8 Hz, 1H), 1.99 (dt, J = 13.4, 6.8 Hz, 1H), 1.09 (d, J = 6.6 Hz, 2H), 0.82 (d, J = 6.6 Hz, 2H)
11	1H NMR (400 MHz, DMSO-d6): δ ppm 7.57 (q, J = 10.1, 9.7 Hz, 6H), 7.35 (d, J = 7.7 Hz, 2H), 7.24 (t, J = 10.3 Hz, 4H), 4.48 (s, 2H), 3.68 (s, 2H), 3.12 (d, J = 14.3 Hz, 2H), 2.85 (d, J = 9.5 Hz, 2H), 1.91 (s, 1H), 1.20 (s, 1H), 0.93 (d, J = 6.5 Hz, 3H), 0.72 (d, J = 6.7 Hz, 3H)
12	1H NMR (400 MHz, DMSO-d6): δ ppm 8.16 (s, 1H), 7.90 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 8.2 Hz, 4H), 7.26 (dd, J = 8.2, 3.2 Hz, 4H), 3.74 - 3.66 (m, 2H), 3.54 (s, 2H), 3.19-3.09 (m, 2H), 2.86 (s, 2H), 1.93 (d, J = 7.3 Hz, 2H), 0.94 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.7 Hz, 3H)
13	1H NMR (400 MHz, DMSO-d6): δ ppm 7.96 (d, J = 7.9 Hz, 2H), 7.73 (d, J = 7.7 Hz, 2H), 7.61 (d, J = 6.8 Hz, 2H), 7.53 (d, J = 7.5 Hz, 2H), 7.29 – 7.19 (m, 3H), 3.79 (s, 2H), 3.63 (s, 2H), 3.09 (d, J = 14.8 Hz, 2H), 2.92 (s, 1H), 2.83 (s, 1H), 1.88 (s, 1H), 0.90 (d, J = 6.1 Hz, 2H), 0.69 (d, J = 6.5 Hz, 2H)
14	1H NMR (400 MHz, DMSO-d6): δ ppm 8.23 (s, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.61 (dd, J = 18.4, 7.7 Hz, 4H), 7.26 (t, J = 8.9 Hz, 4H), 4.29 (d, J = 7.3 Hz, 2H), 3.12 (d, J = 14.5 Hz, 2H), 2.85 (s, 2H), 1.92 (s, 1H), 1.30 (t, J = 6.9 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H).
15	1H NMR (400 MHz, DMSO-d6): δ ppm 8.19 (s, 1H), 7.98 (s, 1H), 7.60 (d, J = 7.8 Hz, 3H), 7.46 (d, J = 7.6 Hz, 3H), 7.25 (d, J = 7.8 Hz, 3H), 7.11 (d, J = 7.7 Hz, 3H), 3.12 (d, J = 14.2 Hz, 2H), 2.90 - 2.73 (m, 4H), 1.92 - 1.83 (m, 2H), 0.91 (d, J = 6.5 Hz, 4H), 0.70 (d, J = 6.6 Hz, 4H)
16	1H NMR (400 MHz, MeOH-d4): δ ppm 7.60 – 7.33 (m, 10H), 7.27 (t, J = 6.6 Hz, 6H), 4.33 (s, 1H), 3.85 (d, J = 17.3 Hz, 3H), 3.61 (t, J = 11.6 Hz, 2H), 3.43 (s, 1H), 3.09 (d, J = 13.3 Hz, 2H), 2.87 – 2.73 (m, 3H), 1.99 (dd, J = 14.0, 7.2 Hz, 2H), 1.30 (d, J = 14.3 Hz, 3H), 1.07 (d, J = 6.5 Hz, 4H), 0.81 (d, J = 6.6 Hz, 4H)
17	1H NMR (400 MHz, MeOH-d4): δ ppm 7.54 (dd, J = 16.2, 7.6 Hz, 2H), 7.39 – 7.17 (m, 6H), 4.45 (s, 1H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.73 (dd, J = 8.4, 4.5 Hz, 1H), 3.67 – 3.56 (m, 1H), 3.01 (dd, J = 14.3, 8.4 Hz, 1H), 2.85 (s, 1H), 2.02 (q, J = 6.9 Hz, 1H), 1.11 (d, J = 6.6 Hz, 2H), 0.84 (d, J = 6.7 Hz, 2H)
18	1H NMR (400 MHz, MeOH-d4): δ ppm 7.57 – 7.47 (m, 2H), 7.34 – 7.26 (m, 4H), 7.15 – 7.07 (m, 2H), 6.07 (dt, J = 4.2, 2.2 Hz, 1H), 4.57 (s, 1H), 3.85 (dd, J = 13.3, 5.5 Hz, 2H), 3.74 (dd, J = 8.4, 4.5 Hz, 2H), 3.55 (dd, J = 13.3, 10.2 Hz, 2H), 3.27 (d, J = 4.9 Hz, 6H), 3.02 (dd, J = 14.4, 8.6 Hz, 2H), 2.76 (s, 1H), 2.19 (dd, J = 6.7, 3.3 Hz, 2H), 1.94 (q, J = 7.2 Hz, 2H), 1.81 – 1.72 (m, 3H), 1.71 – 1.60 (m, 3H), 1.04 (dd, J = 6.8, 4.2 Hz, 3H), 0.77 (dd, J = 6.9, 3.9 Hz, 4H)
20	1H NMR (400 MHz, MeOH-d4): δ ppm 7.54 (dd, J = 11.3, 7.9 Hz, 3H), 7.42- 7.23 (m, 5H), 7.12 (d, J = 7.2 Hz, 1H), 3.88 (dd, J = 13.2, 5.4 Hz, 1H), 3.77- 3.69 (m, 1H), 3.67-3.56 (m, 1H), 3.30 (s, 5H), 3.01 (dd, J = 14.4, 8.6 Hz, 1H), 2.82 (d, J = 13.3 Hz, 1H), 2.38 (s, 2H), 2.05-1.94 (m, 1H), 1.09 (d, J = 6.6 Hz, 2H), 0.82 (d, J = 6.7 Hz, 3H)
21	1H NMR (400 MHz, MeOH-d4): δ ppm 7.58-7.43 (m, 8H), 7.33-7.18 (m, 8H), 4.59 (s, 1H), 3.88 (d, J = 11.0 Hz, 2H), 3.70 (s, 2H), 3.61 (t, J = 11.7 Hz, 3H), 3.30 (s, 17H), 3.00 (d, J = 11.1 Hz, 2H), 2.82 (s, 2H), 2.35 (s, 4H), 2.00 (s, 2H), 1.29 (s, 4H), 1.08 (d, J = 6.8 Hz, 4H), 0.89 (s, 2H), 0.81 (d, J = 6.6 Hz, 4H)

22	1H NMR (400 MHz, MeOH-d4): δ ppm 1H NMR 7.65 (d, J = 8.0 Hz, 1H), 7.59-7.44 (m, 3H), 7.29 (d, J = 7.9 Hz, 2H), 4.07 (s, 1H), 3.87 (dd, J = 13.4, 5.5 Hz, 1H), 3.76-3.58 (m, 2H), 3.24 (dd, J = 14.2, 4.9 Hz, 2H), 3.02 (dd, J = 14.4, 8.1 Hz, 1H), 2.85 (s, 1H), 2.00 (q, J = 7.0 Hz, 1H), 1.09 (d, J = 6.6 Hz, 2H), 0.82 (d, J = 6.6 Hz, 2H)
23	1H NMR (400 MHz, MeOH-d4): δ ppm 7.48 (dd, *J* = 16.8, 7.7 Hz, 3H), 7.36 – 7.23 (m, 7H), 7.18 (d, *J* = 7.5 Hz, 1H), 3.87 (d, *J* = 10.3 Hz, 1H), 3.71 (s, 2H), 3.62 (t, *J* = 11.8 Hz, 2H), 3.48 (s, 1H), 3.30 (s, 6H), 3.10 (d, *J* = 14.1 Hz, 1H), 2.86 (d, *J* = 9.3 Hz, 2H), 2.02 (s, 1H), 1.10 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H)
24	1H NMR (400 MHz, MeOH-d4): δ ppm 7.54 (d, *J* = 7.9 Hz, 1H), 7.35 – 7.08 (m, 6H), 3.89 (dd, *J* = 13.3, 5.5 Hz, 1H), 3.75 (dd, *J* = 8.6, 4.5 Hz, 1H), 3.62 (dd, *J* = 13.4, 10.2 Hz, 1H), 3.03 (dd, *J* = 14.5, 8.6 Hz, 1H), 2.85 (ddd, *J* = 10.2, 7.9, 5.6 Hz, 1H), 2.20 (s, 2H), 2.00 (dp, *J* = 14.4, 7.0 Hz, 1H), 1.10 (d, *J* = 6.6 Hz, 2H), 0.84 (d, *J* = 6.7 Hz, 2H)
25	1H NMR (400 MHz, DMSO-d6): δ ppm 7.60 (dd, J = 12.4, 8.0 Hz, 5H), 7.51 – 7.39 (m, 4H), 7.24 (dd, J = 8.2, 2.6 Hz, 5H), 7.11 (s, 1H), 4.14 (t, J = 6.6 Hz, 2H), 3.67 (dd, J = 13.4, 5.7 Hz, 2H), 3.55 (dd, J = 13.3, 9.1 Hz, 2H), 3.08 (d, J = 6.5 Hz, 3H), 2.84 (d, J = 7.6 Hz, 2H), 1.91 (q, J = 6.7 Hz, 2H), 1.19 (s, 1H), 0.93 (d, J = 6.6 Hz, 4H), 0.71 (d, J = 6.6 Hz, 4H)
26	1H NMR (400 MHz, DMSO-d6): δ ppm 8.42 – 8.25 (m, 1H), 7.70 – 7.57 (m, 6H), 7.45 (t, J = 7.8 Hz, 1H), 7.37 (dd, J = 7.9, 2.0 Hz, 1H), 7.27 (dd, J = 8.1, 4.3 Hz, 4H), 4.19 (d, J = 6.8 Hz, 1H), 3.70 (dt, J = 13.3, 5.3 Hz, 1H), 3.55 (ddd, J = 13.4, 9.0, 4.7 Hz, 1H), 3.10 (dd, J = 6.5, 2.4 Hz, 2H), 2.86 (dt, J = 8.7, 6.3 Hz, 1H), 1.94 (h, J = 6.7 Hz, 1H), 1.21 (s, 1H), 0.95 (d, J = 6.6 Hz, 3H), 0.73 (d, J = 6.7 Hz, 3H)
27	1H NMR (400 MHz, DMSO-d6): δ ppm 7.64 – 7.57 (m, 2H), 7.51 (d, J = 7.9 Hz, 2H), 7.22 (dd, J = 10.3, 8.0 Hz, 4H), 6.98 (s, 1H), 6.89 (t, J = 2.0 Hz, 1H), 6.69 (s, 1H), 4.13 (t, J = 6.5 Hz, 1H), 3.73 (s, 3H), 3.66 (dd, J = 13.3, 5.9 Hz, 2H), 3.54 (dd, J = 13.4, 9.2 Hz, 2H), 3.08 (d, J = 6.6 Hz, 2H), 2.82 (q, J = 6.9 Hz, 2H), 2.28 (s, 3H), 1.89 (h, J = 6.7 Hz, 2H), 0.91 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.7 Hz, 3H)
28	1H NMR (400 MHz, DMSO-d6): δ ppm 8.31 – 8.19 (m, 4H), 7.68 (d, J = 8.0 Hz, 2H), 7.67 – 7.52 (m, 3H), 7.45 – 7.32 (m, 3H), 7.26 (t, J = 8.6 Hz, 4H), 4.19 (s, 1H), 3.54 (dt, J = 14.0, 7.0 Hz, 1H), 3.09 (t, J = 6.0 Hz, 2H), 2.85 (q, J = 7.1 Hz, 1H), 1.95 (q, J = 6.7 Hz, 1H), 1.31 (s, 9H), 0.95 (d, J = 6.7 Hz, 3H), 0.75 (d, J = 6.7 Hz, 3H)
29	1H NMR (400 MHz, DMSO-d6): δ ppm 7.65 (d, J = 7.9 Hz, 2H), 7.51 (d, J = 7.9 Hz, 2H), 7.29 – 7.18 (m, 6H), 6.94 (s, 1H), 4.18 (t, J = 6.6 Hz, 1H), 3.54 (dd, J = 13.2, 9.0 Hz, 1H), 3.08 (dd, J = 6.3, 3.6 Hz, 2H), 2.99 (s, 1H), 2.83 (q, J = 7.2 Hz, 1H), 2.29 (s, 6H), 1.92 (q, J = 6.7 Hz, 1H), 0.94 (d, J = 6.7 Hz, 3H), 0.73 (d, J = 6.7 Hz, 3H)
30	1H NMR (400 MHz, DMSO-d6): δ 7.66 (d, J = 8.1 Hz, 4H), 7.56 (d, J = 8.0 Hz, 4H), 7.33 (t, J = 7.9 Hz, 2H), 7.29 – 7.07 (m, 13H), 6.89 (dd, J = 8.2, 2.4 Hz, 2H), 4.19 (t, J = 6.5 Hz, 2H), 3.78 (s, 5H), 3.69 (dd, J = 13.3, 6.0 Hz, 2H), 3.55 (d, J = 9.2 Hz, 1H), 3.16 – 3.01 (m, 4H), 2.84 (q, J = 7.3 Hz, 2H), 1.94 (tp, J = 14.8, 7.6 Hz, 3H), 1.21 (d, J = 3.3 Hz, 6H), 0.94 (d, J = 6.7 Hz, 6H), 0.77 – 0.64 (m, 6H)
31	1H NMR (400 MHz, DMSO-d6): δ ppm 7.49 (dd, J = 23.5, 7.9 Hz, 5H), 7.22 (dd, J = 15.2, 7.9 Hz, 5H), 7.05 – 6.94 (m, 2H), 6.70 (dd, J = 8.0, 2.3 Hz, 1H), 3.54 – 3.43

	(m, 1H), 3.39 (s, 1H), 3.08 (d, J = 13.2 Hz, 1H), 2.85 (d, J = 10.6 Hz, 2H), 1.92 (p, J = 6.9 Hz, 1H), 1.35 (d, J = 16.4 Hz, 1H), 0.93 (d, J = 6.6 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H)
32	1H NMR (400 MHz, DMSO-d6): δ ppm 7.97 – 7.87 (m, 2H), 7.69 – 7.60 (m, 6H), 7.27 (dd, J = 10.3, 8.0 Hz, 4H), 4.16 (t, J = 6.5 Hz, 1H), 3.69 (dd, J = 13.3, 6.1 Hz, 1H), 3.56 (dd, J = 13.3, 9.1 Hz, 1H), 3.09 (d, J = 6.5 Hz, 2H), 2.86 (q, J = 7.3 Hz, 1H), 1.92 (dt, J = 13.8, 6.9 Hz, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.73 (d, J = 6.6 Hz, 3H)
33	1H NMR (400 MHz, DMSO-d6): δ ppm 7.61 (d, J = 7.9 Hz, 2H), 7.53 (d, J = 7.8 Hz, 2H), 7.44 – 7.36 (m, 2H), 7.28 (dd, J = 32.0, 6.9 Hz, 3H), 7.22 (d, J = 6.0 Hz, 2H), 7.14 (d, J = 7.5 Hz, 1H), 4.13 (t, J = 6.5 Hz, 1H), 3.67 (dd, J = 13.3, 5.9 Hz, 1H), 3.55 (dd, J = 13.3, 9.3 Hz, 1H), 3.08 (d, J = 6.6 Hz, 2H), 2.83 (q, J = 7.3 Hz, 1H), 2.61 (q, J = 7.6 Hz, 2H), 1.16 (t, J = 7.5 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.6 Hz, 3H)
34	1H NMR (400 MHz, DMSO-d6): δ ppm 8.25 (d, J = 5.7 Hz, 1H), 8.05 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 7.59 (t, J = 8.6 Hz, 4H), 7.38 (d, J = 8.5 Hz, 1H), 7.25 (d, J = 7.7 Hz, 4H), 3.64 – 3.58 (m, 1H), 3.54 (s, 1H), 3.11 (dd, J = 14.4, 4.9 Hz, 1H), 2.93 (dd, J = 14.3, 7.7 Hz, 1H), 2.85 (q, J = 7.3 Hz, 1H), 1.92 (q, J = 6.7 Hz, 1H), 1.20 (d, J = 8.9 Hz, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.6 Hz, 3H)
35	1H NMR (400 MHz, DMSO-d6): δ ppm 7.64 (d, J = 7.9 Hz, 2H), 7.52 (dd, J = 21.9, 8.2 Hz, 4H), 7.22 (dd, J = 20.4, 7.9 Hz, 4H), 6.97 (d, J = 8.8 Hz, 2H), 4.16 (t, J = 6.5 Hz, 1H), 3.68 (dd, J = 13.3, 6.0 Hz, 1H), 3.54 (td, J = 13.3, 12.8, 8.0 Hz, 2H), 3.12 – 3.05 (m, 2H), 2.82 (q, J = 7.3 Hz, 1H), 1.91 (q, J = 6.8 Hz, 1H), 0.93 (d, J = 6.7 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H)
36	1H NMR (400 MHz, DMSO-d6): δ ppm 7.67 (d, J = 7.9 Hz, 2H), 7.55 (d, J = 7.9 Hz, 2H), 7.48 – 7.38 (m, 2H), 7.38 – 7.25 (m, 2H), 7.28 – 7.11 (m, 4H), 4.19 (t, J = 6.5 Hz, 1H), 3.70 (dd, J = 13.3, 6.0 Hz, 1H), 3.54 (dd, J = 13.4, 9.0 Hz, 1H), 3.16 – 3.05 (m, 2H), 2.99 – 2.79 (m, 2H), 1.95 (td, J = 13.8, 13.2, 6.9 Hz, 2H), 1.22 (d, J = 6.8 Hz, 8H), 0.95 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.6 Hz, 3H)
37	1H NMR (400 MHz, DMSO-d6): δ ppm 7.60 (d, J = 7.8 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.24 (p, J = 7.7 Hz, 6H), 6.97 (d, J = 7.5 Hz, 1H), 4.12 (s, 1H), 3.69 – 3.61 (m, 1H), 3.55 (s, 1H), 3.08 (d, J = 6.5 Hz, 2H), 2.88 – 2.77 (m, 1H), 1.94 – 1.85 (m, 2H), 0.95 – 0.88 (m, 5H), 0.68 (dd, J = 18.5, 5.8 Hz, 5H)
38	1H NMR (400 MHz, DMSO-d6): δ ppm 8.54 (d, J = 2.5 Hz, 1H), 8.01 (t, J = 1.8 Hz, 1H), 7.79 – 7.71 (m, 2H), 7.65 (d, J = 7.9 Hz, 2H), 7.61 – 7.49 (m, 4H), 7.26 (dd, J = 13.4, 7.9 Hz, 4H), 6.53 (t, J = 2.1 Hz, 1H), 3.54 (dd, J = 13.4, 9.1 Hz, 1H), 3.32 (s, 1H), 3.07 (dd, J = 14.1, 4.3 Hz, 1H), 2.86 (q, J = 7.3 Hz, 1H), 2.75 (dd, J = 14.0, 8.4 Hz, 1H), 1.93 (dt, J = 13.4, 6.6 Hz, 1H), 0.93 (d, J = 6.6 Hz, 3H), 0.73 (d, J = 6.7 Hz, 3H)
39	1H NMR (400 MHz, DMSO-d6): δ ppm 8.26 (d, J = 17.9 Hz, 2H), 8.18 (s, 1H), 7.94 (d, J = 7.7 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.64 (ddd, J = 20.8, 14.3, 7.8 Hz, 5H), 7.40 (s, 1H), 7.28 (t, J = 9.1 Hz, 4H), 4.21 (d, J = 7.2 Hz, 1H), 3.72 (dd, J = 13.2, 5.9 Hz, 1H), 3.09 (t, J = 6.1 Hz, 2H), 2.87 (q, J = 7.0 Hz, 1H), 1.97 (dt, J = 13.6, 6.7 Hz, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H)
40	1H NMR (400 MHz, DMSO-d6): δ ppm 7.84 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H), 7.62 (dd, J = 8.0, 3.3 Hz, 4H), 7.26 (dd, J = 16.5, 7.9 Hz, 4H), 4.14 (t, J =

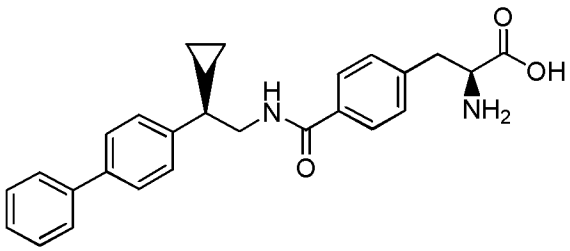
	6.5 Hz, 1H), 3.68 (dd, J = 13.5, 6.0 Hz, 1H), 3.56 (dd, J = 13.4, 9.2 Hz, 1H), 3.08 (d, J = 6.5 Hz, 2H), 2.85 (q, J = 7.3 Hz, 1H), 1.91 (dt, J = 13.5, 6.9 Hz, 1H), 0.93 (d, J = 6.6 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H)
41	1H NMR (400 MHz, DMSO-d6): δ ppm 7.63 (d, J = 8.2 Hz, 2H), 7.58 – 7.45 (m, 4H), 7.28 – 7.16 (m, 4H), 6.99 – 6.91 (m, 2H), 4.16 (t, J = 6.5 Hz, 1H), 4.01 (q, J = 7.0 Hz, 2H), 3.67 (dd, J = 13.3, 5.9 Hz, 1H), 3.11 – 3.04 (m, 2H), 2.81 (q, J = 7.1 Hz, 1H), 1.90 (h, J = 6.5 Hz, 1H), 1.30 (t, J = 6.9 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.72 (d, J = 6.7 Hz, 3H)
42	1H NMR (400 MHz, DMSO-d6): δ ppm 7.65 (t, J = 7.5 Hz, 4H), 7.53 (d, J = 7.8 Hz, 2H), 7.23 (q, J = 7.5 Hz, 6H), 4.16 (t, J = 6.6 Hz, 1H), 3.68 (dd, J = 13.3, 5.8 Hz, 1H), 3.54 (s, 1H), 3.08 (d, J = 6.5 Hz, 2H), 2.83 (d, J = 8.1 Hz, 1H), 1.91 (dd, J = 13.4, 7.0 Hz, 1H), 0.93 (d, J = 6.6 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H)
43	1H NMR (400 MHz, DMSO-d6): δ ppm 7.66 (dd, J = 8.5, 2.0 Hz, 4H), 7.57 (d, J = 8.0 Hz, 2H), 7.51 – 7.44 (m, 2H), 7.26 (dd, J = 8.1, 4.7 Hz, 4H), 4.20 (t, J = 6.6 Hz, 1H), 3.70 (dd, J = 13.3, 6.1 Hz, 1H), 3.53 (dd, J = 13.3, 8.9 Hz, 1H), 3.16 – 3.02 (m, 2H), 2.85 (q, J = 7.2 Hz, 1H), 1.94 (h, J = 6.8 Hz, 1H), 0.95 (d, J = 6.7 Hz, 3H), 0.73 (d, J = 6.7 Hz, 3H)
44	1H NMR (400 MHz, DMSO-d6): δ ppm 7.55 (d, J = 7.9 Hz, 2H), 7.47 (dd, J = 8.0, 3.2 Hz, 4H), 7.25 – 7.16 (m, 6H), 4.09 (t, J = 6.6 Hz, 1H), 3.69 – 3.49 (m, 2H), 3.08 (d, J = 6.5 Hz, 2H), 2.80 (q, J = 7.3 Hz, 1H), 1.86 (q, J = 7.1 Hz, 1H), 1.12 (t, J = 7.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.68 (d, J = 6.6 Hz, 3H)
45	1H NMR (400 MHz, DMSO-d6): δ ppm 7.59 – 7.44 (m, 6H), 7.25 – 7.11 (m, 6H), 4.09 (t, J = 6.4 Hz, 1H), 3.69 – 3.50 (m, 2H), 3.07 (d, J = 6.5 Hz, 2H), 2.80 (d, J = 8.0 Hz, 1H), 2.39 (d, J = 7.1 Hz, 2H), 1.86 (d, J = 7.0 Hz, 1H), 1.80 – 1.72 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.79 (d, J = 6.5 Hz, 6H), 0.68 (d, J = 6.6 Hz, 3H)
46	1H NMR (400 MHz, DMSO-d6): δ ppm 9.68 (s, 1H), 8.27 (s, 1H), 8.02 (s, 1H), 7.83 (s, 2H), 7.73 – 7.60 (m, 6H), 7.27 (dd, J = 19.2, 7.8 Hz, 4H), 4.13 (t, J = 6.6 Hz, 1H), 3.72 – 3.54 (m, 2H), 3.09 (d, J = 6.5 Hz, 2H), 2.87 (q, J = 7.3 Hz, 1H), 1.92 (dt, J = 12.3, 6.2 Hz, 1H), 0.92 (d, J = 6.6 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H)
47	1H NMR (400 MHz, DMSO-d6): δ ppm 7.62 – 7.47 (m, 6H), 7.41 (d, J = 8.0 Hz, 2H), 7.22 (t, J = 7.8 Hz, 4H), 3.66 (dd, J = 13.4, 5.9 Hz, 1H), 3.54 (t, J = 11.4 Hz, 1H), 3.08 (d, J = 6.5 Hz, 2H), 2.82 (d, J = 8.5 Hz, 1H), 1.88 (q, J = 6.7 Hz, 1H), 1.24 (s, 9H), 0.91 (d, J = 6.6 Hz, 3H), 0.70 (d, J = 6.6 Hz, 3H)
48	1H NMR (400 MHz, DMSO-d6): δ ppm 8.89 (d, J = 6.5 Hz, 2H), 8.41 – 8.34 (m, 2H), 7.96 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 4.16 (t, J = 6.5 Hz, 1H), 3.74 – 3.55 (m, 2H), 3.10 (d, J = 6.6 Hz, 2H), 2.93 (q, J = 6.8 Hz, 1H), 1.97 (h, J = 6.8 Hz, 1H), 0.95 (d, J = 6.6 Hz, 3H), 0.73 (d, J = 6.7 Hz, 3H)
49	1H NMR (400 MHz, DMSO-d6): δ ppm 9.20 (d, J = 2.1 Hz, 1H), 8.89 – 8.79 (m, 2H), 8.08 (dd, J = 8.2, 5.7 Hz, 1H), 7.78 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 4.15 (d, J = 5.9 Hz, 1H), 3.73 – 3.55 (m, 2H), 3.09 (d, J = 6.6 Hz, 2H), 2.90 (dt, J = 8.8, 6.5 Hz, 1H), 1.95 (h, J = 6.7 Hz, 1H), 0.94 (d, J = 6.7 Hz, 3H), 0.73 (d, J = 6.7 Hz, 3H)
50	1H NMR (400 MHz, DMSO-d6): δ ppm 8.25 (dd, J = 12.2, 5.8 Hz, 2H), 7.67 (d, J = 7.9 Hz, 2H), 7.54 (dd, J = 8.0, 2.8 Hz, 2H), 7.30 – 7.19 (m, 6H), 4.19 (s, 1H), 3.52 (dd, J = 14.4, 7.5 Hz, 1H), 3.09 (t, J = 6.2 Hz, 2H), 2.56 (t, J = 7.6 Hz, 2H), 1.94 (h,

	J = 6.6 Hz, 1H), 1.59 (h, J = 7.4 Hz, 2H), 0.98 – 0.85 (m, 6H), 0.74 (d, J = 6.6 Hz, 3H)
51	1H NMR (400 MHz, DMSO-d6): δ ppm 8.23 (s, 3H), 7.71 – 7.54 (m, 6H), 7.36 (d, J = 7.8 Hz, 2H), 7.26 (t, J = 8.3 Hz, 4H), 4.42 (s, 2H), 4.19 (s, 1H), 3.70 (q, J = 6.2, 5.4 Hz, 1H), 3.54 (p, J = 7.1, 6.6 Hz, 1H), 3.29 (s, 3H), 3.09 (t, J = 6.2 Hz, 2H), 2.85 (q, J = 7.3 Hz, 1H), 1.95 (q, J = 6.8 Hz, 1H), 0.95 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.7 Hz, 3H)
52	1H NMR (400 MHz, DMSO-d6): δ ppm 7.62 (d, J = 8.0 Hz, 2H), 7.45 (ddd, J = 16.3, 8.2, 1.9 Hz, 3H), 7.41 – 7.30 (m, 1H), 7.24 (dd, J = 7.2, 4.9 Hz, 6H), 4.15 (t, J = 6.5 Hz, 1H), 3.68 (dd, J = 13.4, 6.0 Hz, 1H), 3.54 (dd, J = 13.3, 9.2 Hz, 1H), 3.09 (d, J = 6.6 Hz, 2H), 2.90 – 2.80 (m, 1H), 1.91 (h, J = 6.7 Hz, 1H), 0.92 (d, J = 6.7 Hz, 3H), 0.72 (d, J = 6.7 Hz, 3H)
53	1H NMR (400 MHz, DMSO-d6): δ ppm 7.66 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.41 (d, J = 5.2 Hz, 2H), 7.31 (t, J = 7.8 Hz, 1H), 7.24 (dd, J = 11.0, 8.0 Hz, 4H), 7.13 (d, J = 7.6 Hz, 1H), 4.43 (s, 1H), 4.18 (t, J = 6.4 Hz, 1H), 3.69 (dd, J = 13.3, 6.1 Hz, 1H), 3.54 (dd, J = 13.3, 9.0 Hz, 1H), 3.16 – 3.01 (m, 2H), 2.94 (s, 1H), 2.84 (q, J = 7.3 Hz, 1H), 2.58 (t, J = 7.6 Hz, 2H), 1.92 (dt, J = 13.8, 6.9 Hz, 1H), 1.60 (h, J = 7.3 Hz, 2H), 0.97 – 0.83 (m, 6H), 0.73 (d, J = 6.7 Hz, 3H)
54	1H NMR (400 MHz, DMSO-d6): δ ppm 7.65 (d, J = 8.0 Hz, 2H), 7.53 (dd, J = 8.1, 3.6 Hz, 4H), 7.29 – 7.19 (m, 6H), 4.18 (t, J = 6.4 Hz, 1H), 3.53 (dd, J = 13.2, 9.2 Hz, 1H), 3.12 – 3.05 (m, 2H), 2.83 (d, J = 7.8 Hz, 1H), 2.58 (t, J = 7.7 Hz, 2H), 1.98 – 1.87 (m, 1H), 1.55 (t, J = 7.6 Hz, 2H), 1.29 (q, J = 7.4 Hz, 2H), 0.95 (s, 2H), 0.96 – 0.80 (m, 5H), 0.73 (d, J = 6.7 Hz, 3H)
55	1H NMR (400 MHz, DMSO-d6): δ ppm 7.65 (d, J = 8.3 Hz, 2H), 7.53 (dd, J = 8.3, 1.9 Hz, 4H), 7.32 – 7.19 (m, 6H), 4.19 (t, J = 6.5 Hz, 1H), 3.69 (dd, J = 13.3, 6.0 Hz, 1H), 3.52 (dd, J = 13.3, 9.1 Hz, 1H), 3.08 (dd, J = 6.5, 4.1 Hz, 2H), 2.95 – 2.78 (m, 2H), 1.92 (dt, J = 13.6, 6.7 Hz, 1H), 1.20 (d, J = 6.9 Hz, 6H), 0.94 (d, J = 6.7 Hz, 3H), 0.73 (d, J = 6.7 Hz, 3H)
56	1H NMR (400 MHz, DMSO-d6): 7.83 (s, 2H), 7.68-7.53 (m, 5H), 7.49-7.36 (m, 3H), 7.26 (dd, J = 8.0, 5.5 Hz, 1H), 3.69 (dd, J = 13.6, 6.1 Hz, 1H), 3.56 (dd, J = 13.2, 9.0 Hz, 1H), 3.08 (d, J = 6.4 Hz, 2H), 2.86 (d, J = 8.0 Hz, 1H), 1.93 (m, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.6 Hz, 3H)
57	1H NMR (400 MHz, DMSO-d6): δ ppm 7.63 (d, J = 7.8 Hz, 2H), 7.51 (dd, J = 21.3, 8.0 Hz, 4H), 7.22 (dd, J = 20.3, 7.8 Hz, 4H), 7.08 (d, J = 8.3 Hz, 2H), 4.16 (d, J = 7.8 Hz, 1H), 3.81 (s, 1H), 3.71 – 3.62 (m, 1H), 3.09 (d, J = 6.4 Hz, 2H), 2.82 (d, J = 8.1 Hz, 1H), 1.91 (s, 1H), 0.92 (d, J = 6.6 Hz, 3H), 0.74 (dd, J = 17.9, 6.5 Hz, 6H), 0.62 (s, 2H)
58	1H NMR (400 MHz, DMSO-d6): δ ppm 7.58 (d, J = 7.7 Hz, 2H), 7.51 (s, 3H), 7.23 (q, J = 8.6, 8.0 Hz, 6H), 3.65 (s, 1H), 3.55 (s, 1H), 3.08 (s, 2H), 2.81 (d, J = 7.9 Hz, 1H), 2.24 (s, 2H), 2.03 (s, 2H), 1.90 (s, 2H), 0.91 (d, J = 6.7 Hz, 3H), 0.70 (d, J = 6.6 Hz, 3H)
59	1H NMR (400 MHz, DMSO-d6): δ ppm 7.53 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 7.4 Hz, 1H), 7.31 (dt, J = 12.5, 7.7 Hz, 5H), 7.22 (dd, J = 8.0, 4.3 Hz, 4H), 4.48 (s, 2H), 4.10 (t, J = 6.5 Hz, 1H), 3.67 (dd, J = 13.5, 6.1 Hz, 1H), 3.53 (dd, J = 13.3, 9.3 Hz, 1H), 3.09 (d, J = 6.5 Hz, 2H), 2.84 (q, J = 7.4 Hz, 1H), 1.89 (q, J = 6.8 Hz, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.6 Hz, 3H)

60	1H NMR (400 MHz, DMSO-d6): 7.57 – 7.47 (m, 6H), 7.31 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 4H), 4.50 – 4.34 (m, 6H), 4.08 (t, J = 6.5 Hz, 1H), 3.69 – 3.50 (m, 3H), 3.07 (d, J = 6.6 Hz, 2H), 2.80 (q, J = 7.5 Hz, 1H), 1.85 (dt, J = 13.7, 6.9 Hz, 1H), 1.07 (d, J = 6.1 Hz, 6H), 0.89 (d, J = 6.6 Hz, 3H), 0.68 (d, J = 6.6 Hz, 3H)
61	1H NMR (400 MHz, DMSO-d6): 7.64 (d, J = 8.0 Hz, 2H), 7.49 (t, J = 8.6 Hz, 4H), 7.23 (dd, J = 16.5, 8.0 Hz, 4H), 7.10 (d, J = 8.1 Hz, 2H), 4.16 (t, J = 6.5 Hz, 1H), 3.68 (dd, J = 13.3, 6.1 Hz, 1H), 3.52 (dd, J = 13.3, 9.1 Hz, 1H), 3.08 (dd, J = 6.5, 2.8 Hz, 2H), 2.82 (dt, J = 9.0, 6.4 Hz, 1H), 1.90 (ddd, J = 13.4, 8.6, 5.4 Hz, 2H), 0.98 – 0.88 (m, 5H), 0.72 (d, J = 6.7 Hz, 3H), 0.69 – 0.60 (m, 2H)
62	1H NMR (400 MHz, DMSO-d6): δ ppm 8.19 (s, 1H), 7.78 (s, 1H), 7.63 (s, 1H), 7.56 (d, J = 13.5 Hz, 2H), 7.56 (s, 3H), 7.48 (d, J = 8.3 Hz, 1H), 7.24 (dd, J = 8.1, 4.5 Hz, 4H), 3.84 (s, 2H), 3.67 (dd, J = 13.3, 6.0 Hz, 1H), 3.53 (t, J = 11.3 Hz, 1H), 3.43 (dd, J = 8.1, 4.4 Hz, 1H), 3.10 (dd, J = 14.3, 4.3 Hz, 1H), 2.84 (s, 2H), 1.90 (q, J = 6.7 Hz, 1H), 0.93 (d, J = 6.6 Hz, 3H), 0.73 (d, J = 6.7 Hz, 3H)
63	1H NMR (400 MHz, DMSO-d6): δ ppm 8.27 (t, J = 5.6 Hz, 1H), 8.23 (s, 3H), 7.67 (d, J = 8.0 Hz, 2H), 7.53 (dd, J = 8.2, 3.3 Hz, 4H), 7.25 (dd, J = 14.8, 8.0 Hz, 6H), 4.19 (d, J = 5.0 Hz, 1H), 3.71 (dd, J = 13.2, 6.2 Hz, 1H), 3.62 (d, J = 7.0 Hz, 1H), 3.55 (d, J = 28.4 Hz, 2H), 3.08 (t, J = 6.1 Hz, 2H), 2.83 (q, J = 7.2 Hz, 1H), 2.73 (t, J = 7.0 Hz, 2H), 0.95 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.7 Hz, 3H)
64	1H NMR (400 MHz, DMSO-d6): δ ppm 7.50 – 7.30 (m, 6H), 7.23 – 7.12 (m, 4H), 6.97 (d, J = 8.5 Hz, 1H), 6.78 (d, J = 8.5 Hz, 1H), 4.49 (s, 7H), 4.50 – 4.36 (m, 1H), 4.08 (t, J = 6.6 Hz, 1H), 3.63 – 3.52 (m, 2H), 3.07 (d, J = 6.6 Hz, 2H), 2.75 (s, 1H), 1.83 (s, 1H), 1.41 (s, 9H), 1.21 (d, J = 1.1 Hz, 4H), 1.07 (s, 1H), 0.87 (dd, J = 6.8, 2.6 Hz, 3H), 0.65 (d, J = 6.6 Hz, 3H
65	1H NMR (400 MHz, DMSO-d6): δ ppm 7.56 (dd, J = 20.8, 8.0 Hz, 4H), 7.35 (t, J = 7.9 Hz, 1H), 7.26 – 7.16 (m, 6H), 6.93 (dd, J = 8.5, 2.4 Hz, 1H), 4.30 (t, J = 4.9 Hz, 2H), 4.10 (t, J = 6.6 Hz, 1H), 3.70 – 3.51 (m, 2H), 3.47 (s, 1H), 3.08 (d, J = 6.5 Hz, 2H), 2.82 (d, J = 2.0 Hz, 7H), 1.88 (q, J = 6.9 Hz, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.69 (d, J = 6.6 Hz, 3H)
66	1H NMR (400 MHz, DMSO-d6): δ ppm 7.47 (dd, *J* = 8.1, 5.5 Hz, 4H), 7.38 (dd, *J* = 9.2, 6.6 Hz, 4H), 7.20 (dd, *J* = 13.6, 8.0 Hz, 4H), 4.56 (s, 3H), 4.60 – 4.49 (m, 1H), 4.08 (t, *J* = 6.5 Hz, 2H), 3.67 – 3.50 (m, 4H), 3.07 (d, *J* = 6.6 Hz, 4H), 2.79 (t, *J* = 7.8 Hz, 2H), 1.83 (q, *J* = 6.8 Hz, 1H), 0.87 (d, *J* = 6.6 Hz, 6H), 0.65 (d, *J* = 6.7 Hz, 6H)
67	1H NMR (400 MHz, DMSO-d6): δ ppm 7.60 (dd, J = 24.8, 8.1 Hz, 4H), 7.49 (d, J = 7.9 Hz, 2H), 7.22 (dd, J = 17.2, 7.9 Hz, 4H), 7.04 (d, J = 8.3 Hz, 2H), 4.92 (s, 1H), 4.29 (t, J = 4.9 Hz, 2H), 4.14 (t, J = 6.5 Hz, 1H), 3.66 (dd, J = 13.4, 6.2 Hz, 1H), 3.59 – 3.46 (m, 3H), 3.08 (d, J = 6.5 Hz, 2H), 2.84 (s, 6H), 2.80 (d, J = 8.4 Hz, 1H), 1.89 (dq, J = 13.4, 6.6 Hz, 1H), 1.14 (d, J = 24.9 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.70 (d, J = 6.7 Hz, 3H)
68	1H NMR (400 MHz, DMSO-d6): δ ppm 7.61 – 7.48 (m, 6H), 7.41 (d, J = 7.9 Hz, 2H), 7.24 – 7.17 (m, 4H), 4.94 (dd, J = 8.4, 6.0 Hz, 2H), 4.58 (t, J = 6.4 Hz, 2H), 4.21 (q, J = 7.2 Hz, 1H), 4.09 (t, J = 6.6 Hz, 1H), 3.59 (dt, J = 23.0, 13.2 Hz, 2H), 3.07 (d, J = 6.5 Hz, 2H), 2.80 (d, J = 7.9 Hz, 1H), 1.86 (dd, J = 13.9, 7.1 Hz, 1H), 0.89 (d, J = 6.6 Hz, 3H), 0.68 (d, J = 6.6 Hz, 3H)
69	1H NMR (400 MHz, DMSO-d6): δ ppm 7.84 (dd, J = 16.3, 5.5 Hz, 3H), 7.68 (d, J =

	3.3 Hz, 1H), 7.61 (d, J = 7.8 Hz, 2H), 7.26 (dd, J = 15.7, 7.9 Hz, 4H), 4.86 (s, 2H), 4.16 (t, J = 6.4 Hz, 1H), 3.72 – 3.51 (m, 2H), 3.11 – 3.04 (m, 2H), 2.85 (q, J = 7.5 Hz, 1H), 1.92 (dt, J = 14.0, 7.0 Hz, 1H), 1.19 (s, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.70 (d, J = 6.6 Hz, 3H)
70	1H NMR (400 MHz, DMSO-d6): δ ppm 9.12 (d, J = 1.9 Hz, 1H), 8.02 (d, J = 1.9 Hz, 1H), 7.84 (d, J = 7.9 Hz, 2H), 7.61 (d, J = 7.9 Hz, 2H), 7.23 (dd, J = 8.1, 5.6 Hz, 4H), 5.04 (s, 1H), 4.94 (s, 2H), 4.15 (t, J = 6.4 Hz, 1H), 3.65 (dd, J = 13.3, 5.9 Hz, 1H), 3.56 (dd, J = 13.3, 9.5 Hz, 1H), 3.07 (dd, J = 6.5, 2.8 Hz, 2H), 2.82 (q, J = 7.3 Hz, 1H), 1.90 (q, J = 6.8 Hz, 1H), 0.93 (d, J = 6.6 Hz, 3H), 0.70 (d, J = 6.7 Hz, 3H)
71	1H NMR (400 MHz, DMSO-d6): δ ppm 7.78 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.31 (dd, J = 8.1, 5.7 Hz, 4H), 7.16 (s, 2H), 4.88 (d, J = 8.3 Hz, 4H), 3.86 (dd, J = 13.4, 5.4 Hz, 1H), 3.30 – 3.23 (m, 3H), 3.03 (m, 3H), 2.05 – 1.95 (m, 1H), 1.09 (d, J = 6.6 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H)

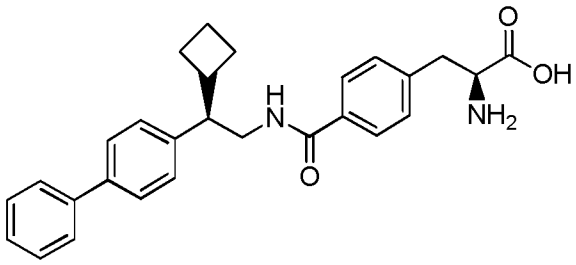
Example 72: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cyclopropylethyl) carbamoyl)phenyl)-2-aminopropanoic acid



The title compound was prepared as described for Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid starting with (R)-2-(4-bromophenyl)-2-cyclopropylethanamine (Intermediate 53).

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.73 (d, J = 7.8 Hz, 2H), 7.60 (dd, J = 19.6, 7.6 Hz, 4H), 7.43 (t, J = 7.6 Hz, 2H), 7.32 (dd, J = 18.8, 7.6 Hz, 5H), 4.22 (s, 1H), 3.62 (qd, J = 13.4, 7.4 Hz, 2H), 3.11 (t, J = 5.4 Hz, 2H), 2.26 (q, J = 8.3 Hz, 1H), 1.22 (s, 1H), 1.06 (s, 1H), 0.57 (d, J = 7.4 Hz, 1H), 0.30 (dt, J = 13.6, 7.4 Hz, 2H). LCMS (MH^+): 429.52.

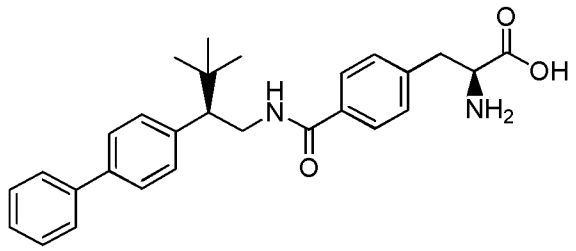
Example 73: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cyclobutylethyl) carbamoyl)phenyl)-2-aminopropanoic acid



The title compound was prepared as described for Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid starting with (R)-2-(4-bromophenyl)-2-cyclobutylethanamine (Intermediate 47).

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.68 (d, J = 8.0 Hz, 2H), 7.57 (dd, J = 22.4, 7.8 Hz, 3H), 7.42 (t, J = 7.6 Hz, 2H), 7.28 (dt, J = 16.1, 7.6 Hz, 4H), 4.18 (t, J = 6.5 Hz, 1H), 3.48 (dd, J = 13.3, 6.1 Hz, 2H), 3.36 (dd, J = 13.1, 8.4 Hz, 2H), 3.09 (dd, J = 6.6, 3.2 Hz, 2H), 2.97 (q, J = 8.4, 7.9 Hz, 2H), 2.63 – 2.53 (m, 2H), 2.12 (s, 1H), 1.80 (dt, J = 17.7, 8.9 Hz, 3H), 1.66 (s, 1H), 1.52 (q, J = 9.5 Hz, 2H). LCMS (MH^+): 443.55.

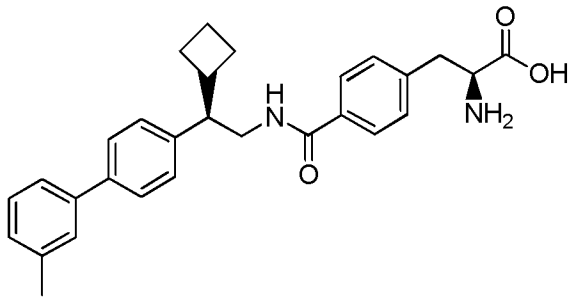
Example 74: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3,3-dimethylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid



The title compound was prepared as described for Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid starting with (R)-2-(4-bromophenyl)-3,3-dimethylbutan-1-amine (Intermediate 54).

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.50 (m, 2H), 8.20 (d, J = 5.4 Hz, 2H), 8.12 (s, 1H), 7.66 – 7.52 (m, 3H), 7.42 (t, J = 7.6 Hz, 1H), 7.35 – 7.19 (m, 3H), 4.16 (d, J = 6.1 Hz, 1H), 3.72 (d, J = 6.4 Hz, 1H), 3.13 – 2.98 (m, 1H), 0.92 (s, 5H). LCMS (MH^+): 445.57.

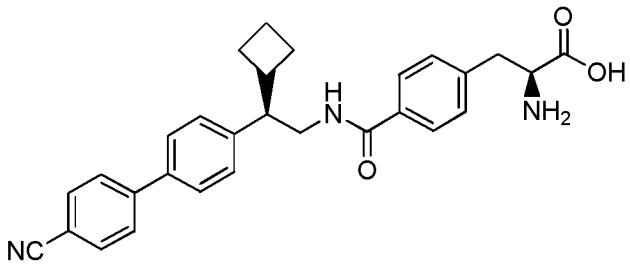
Example 75: (S)-2-amino-3-(4-(((R)-2-cyclobutyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid



The title compound was made as described for (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid (Example 1a) starting with (R)-2-(4-bromophenyl)-2-cyclobutylethanamine (Intermediate 47) and 3-methylphenyl bornic acid (CAS# 17933-03-8) in place of phenyl boronic acid.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 7.68 – 7.58 (m, 1H), 7.55 – 7.47 (m, 1H), 7.41 – 7.21 (m, 4H), 7.12 (d, J = 7.6 Hz, 1H), 3.76 (dd, J = 8.5, 4.5 Hz, 1H), 3.68 (dd, J = 13.3, 5.8 Hz, 1H), 3.44 (dd, J = 13.4, 9.1 Hz, 1H), 3.03 (dd, J = 14.6, 8.2 Hz, 2H), 2.69 (q, J = 9.2, 8.7 Hz, 1H), 2.38 (s, 2H), 2.03 – 1.75 (m, 4H), 1.64 (q, J = 9.2 Hz, 1H). LCMS (MH^+): 457.58.

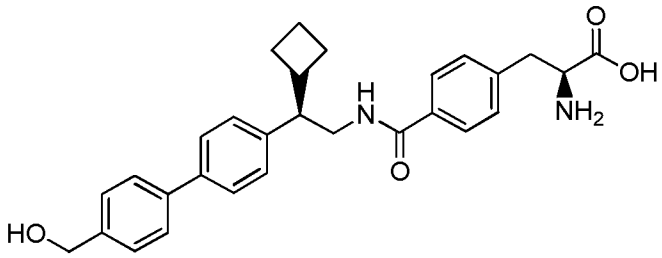
Example 76: (S)-2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-2-cyclobutylethyl)carbamoyl)phenyl)propanoic acid



The title compound was made as described for (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid (Example 1a) starting with (R)-2-(4-bromophenyl)-2-cyclobutylethanamine (Intermediate 47) and 4-cyanophenyl bornic acid (CAS# 126747-14-6) in place of phenyl boronic acid.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.32 (t, J = 5.6 Hz, 1H), 8.23 (d, J = 5.3 Hz, 1H), 7.86 (q, J = 8.4 Hz, 2H), 7.68 (dd, J = 19.3, 8.0 Hz, 2H), 7.30 (dd, J = 11.4, 8.0 Hz, 2H), 4.20 (d, J = 6.0 Hz, 1H), 3.50 (dt, J = 11.6, 5.5 Hz, 1H), 3.37 (dt, J = 13.5, 6.9 Hz, 1H), 3.17 – 2.95 (m, 2H), 2.61 (p, J = 8.8 Hz, 1H), 2.19 – 2.10 (m, 1H), 1.92 – 1.63 (m, 3H), 1.53 (q, J = 9.4 Hz, 1H), 1.34 (s, 1H). LCMS (MH^+): 468.56.

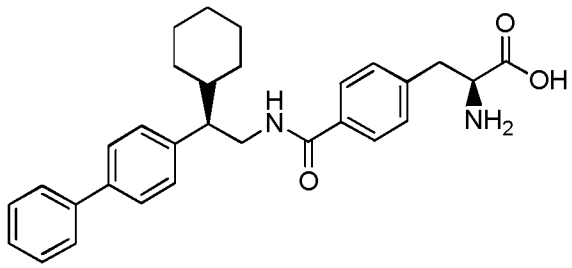
Example 77: (S)-2-amino-3-(4-(((R)-2-cyclobutyl-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid



The title compound was made as described for (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid (Example 1a) starting with (R)-2-(4-bromophenyl)-2-cyclobutylethanamine (Intermediate 47) and 4-hydroxymethylphenyl boronic acid (CAS# 59016-93-2) in place of phenyl boronic acid.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.44 – 8.38 (m, 1H), 7.69 (d, J = 7.9 Hz, 4H), 7.54 (dd, J = 10.6, 7.9 Hz, 8H), 7.35 (d, J = 7.9 Hz, 4H), 7.26 (dd, J = 16.7, 7.9 Hz, 8H), 4.49 (s, 4H), 4.17 (t, J = 6.5 Hz, 3H), 3.48 (dd, J = 13.2, 6.1 Hz, 3H), 3.35 (dd, J = 13.3, 8.3 Hz, 3H), 3.11 (d, J = 6.5 Hz, 4H), 3.00 – 2.91 (m, 3H), 2.58 (q, J = 8.6 Hz, 3H), 2.14 (d, J = 7.3 Hz, 2H), 2.11 (s, 1H), 1.84 (d, J = 8.9 Hz, 2H), 1.80 (s, 2H), 1.78 – 1.61 (m, 7H), 1.52 (q, J = 9.4 Hz, 4H), 1.19 (s, 3H), 0.83 (d, J = 5.3 Hz, 2H).LCMS (MH^+): 473.52.

Example 78: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cyclohexylethyl)-carbamoyl)phenyl)-2-aminopropanoic acid

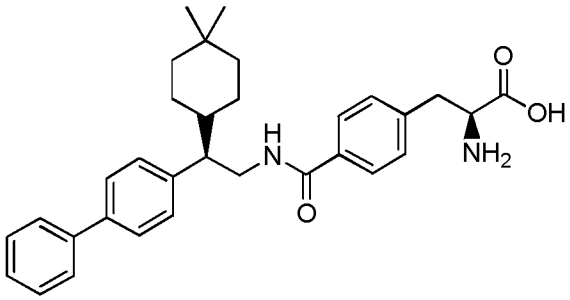


The title compound was made as described for (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid (Example 1a) starting with (R)-2-(4-bromophenyl)-2-cyclohexylethanamine (Intermediate 49).

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 7.66 – 7.51 (m, 15H), 7.41 (t, J = 7.6 Hz, 5H), 7.35 – 7.19 (m, 13H), 4.15 (t, J = 6.5 Hz, 3H), 3.70 (dd, J = 13.4, 5.9 Hz, 4H), 3.53 (dd, J = 13.3, 9.2

Hz, 4H), 3.08 (d, J = 6.5 Hz, 5H), 2.87 (q, J = 7.1 Hz, 4H), 1.83 (d, J = 12.5 Hz, 3H), 1.67 (d, J = 12.8 Hz, 4H), 1.58 – 1.46 (m, 9H), 1.20 (s, 3H), 1.02 (dp, J = 38.2, 13.1, 12.0 Hz, 12H), 0.76 (q, J = 11.8, 11.1 Hz, 5H). LCMS (MH^+): 471.60.

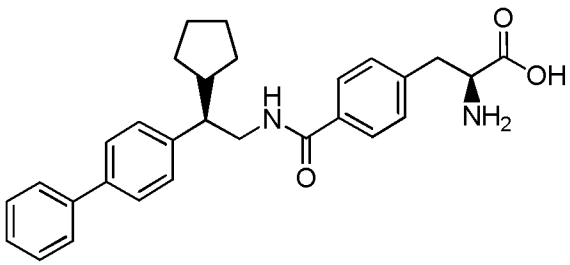
Example 79: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(4,4-dimethylcyclohexyl) ethyl)carbamoyl)phenyl)-2-aminopropanoic acid



The title compound was made as described for (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid (Example 1a, starting with (R)-2-(4-bromophenyl)-2-(4,4-dimethylcyclohexyl)ethanamine (Intermediate 50).

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 7.65 – 7.51 (m, 6H), 7.41 (t, J = 7.6 Hz, 2H), 7.28 (dd, J = 24.5, 6.9 Hz, 3H), 7.23 (d, J = 6.1 Hz, 2H), 4.15 (t, J = 6.5 Hz, 1H), 3.71 (dd, J = 13.0, 5.8 Hz, 1H), 3.58 – 3.47 (m, 1H), 3.08 (d, J = 6.5 Hz, 2H), 2.89 (q, J = 7.6 Hz, 1H), 1.38 – 1.10 (m, 5H), 1.00 (p, J = 12.7 Hz, 2H), 0.81 (s, 3H), 0.72 (s, 3H) LCMS (MH^+): 499.66.

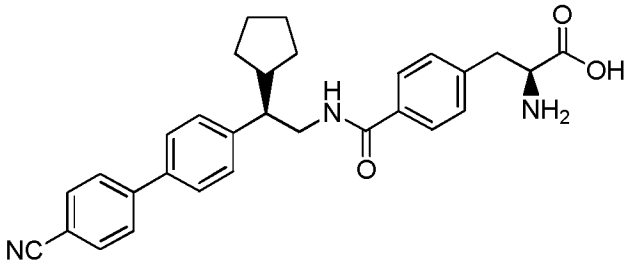
Example 80: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cyclopentylethyl) carbamoyl)phenyl)-2-aminopropanoic acid



The title compound was prepared as described in Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid, starting with (R)-2-(4-bromophenyl)-2-cyclopentylethanamine (Intermediate 48).

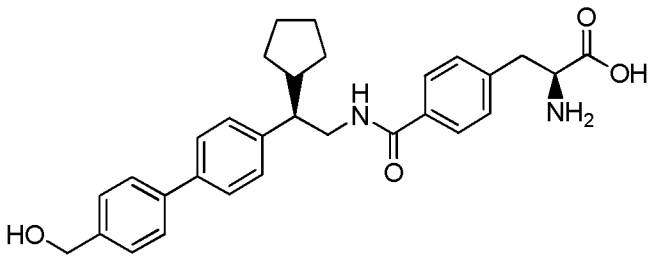
^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.63 – 7.49 (m, 10H), 7.40 (t, *J* = 7.6 Hz, 4H), 7.27 (dt, *J* = 18.9, 7.6 Hz, 9H), 4.12 (d, *J* = 6.6 Hz, 3H), 3.66 – 3.43 (m, 6H), 3.07 (d, *J* = 6.5 Hz, 4H), 2.80 (td, *J* = 9.6, 5.1 Hz, 3H), 2.05 (q, *J* = 9.0, 8.4 Hz, 3H), 1.92 (s, 2H), 1.39 – 1.21 (m, 8H), 1.16 (d, *J* = 19.3 Hz, 4H), 0.95 (dd, *J* = 12.7, 6.8 Hz, 3H), 0.74 (s, 1H). LCMS (MH$^+$): 457.57.

Example 81: (S)-2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-2-cyclopentylethyl)carbamoyl)phenyl)propanoic acid



The title compound was prepared as described for Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid starting with (R)-2-(4-bromophenyl)-2-cyclopentylethanamine (Intermediate 48) and 4-cyanophenyl boronic acid. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.75 (s, 3H), 7.55 (dd, *J* = 14.7, 7.9 Hz, 3H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 4.08 (t, *J* = 6.5 Hz, 1H), 3.60 (dd, *J* = 13.5, 5.0 Hz, 1H), 3.51 (t, *J* = 11.6 Hz, 1H), 3.07 (d, *J* = 6.5 Hz, 2H), 2.85 – 2.76 (m, 1H), 2.02 (d, *J* = 9.7 Hz, 1H), 1.89 (d, *J* = 9.6 Hz, 1H), 1.53 (s, 1H), 1.43 (s, 1H), 1.27 (s, 2H), 1.23 (d, *J* = 7.7 Hz, 1H), 0.90 (t, *J* = 10.3 Hz, 1H). LCMS (MH$^+$): 482.59.

Example 82: (S)-2-amino-3-(4-(((R)-2-cyclopentyl-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid

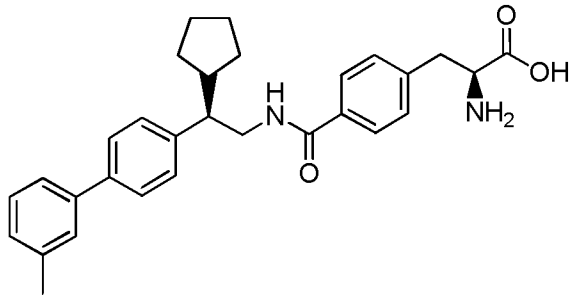


The title compound was prepared as described for Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid, starting with (R)-2-

(4-bromophenyl)-2-cyclopentylethanamine (Intermediate 48) and 4-hydroxymethylphenyl boronic acid.

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.59 – 7.49 (m, 3H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.24 (dd, *J* = 8.2, 3.8 Hz, 2H), 4.48 (s, 1H), 3.65 – 3.56 (m, 2H), 3.52 – 3.41 (m, 2H), 3.36 (s, 1H), 3.06 (s, 1H), 2.77 (dd, *J* = 14.5, 8.0 Hz, 2H), 2.09 – 2.00 (m, 2H), 1.91 (s, 1H), 1.56 (s, 1H), 1.44 (s, 1H), 1.33 (s, 1H), 1.30 (s, 1H), 1.19 (s, 1H), 0.94 (s, 1H). LCMS (MH^+): 487.60.

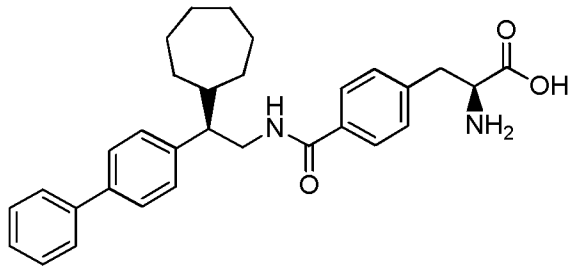
Example 83: (S)-2-amino-3-(4-(((R)-2-cyclopentyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid



The title compound was prepared as described for Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid, starting with (R)-2-(4-bromophenyl)-2-cyclopentylethanamine (Intermediate 48) and 3-methylphenyl boronic acid.

^{1}H NMR (400 MHz, DMSO-d6): 8.22 (s, 4H), 7.66 (d, J = 7.9 Hz, 3H), 7.53 (d, J = 7.9 Hz, 3H), 7.45 – 7.36 (m, 3H), 7.35 – 7.22 (m, 8H), 7.13 (d, J = 7.5 Hz, 2H), 4.19 (d, J = 6.2 Hz, 2H), 3.71 – 3.60 (m, 3H), 3.48 (td, J = 13.7, 11.1, 6.5 Hz, 3H), 3.16 – 3.00 (m, 5H), 2.97 (s, 1H), 2.82 (td, J = 9.6, 5.0 Hz, 3H), 2.34 (s, 4H), 2.10 (q, J = 8.3 Hz, 3H), 1.97 (q, J = 5.2, 4.5 Hz, 3H), 1.60 (s, 2H), 1.50 (s, 2H), 1.42 – 1.24 (m, 7H), 0.96 (dt, J = 11.3, 8.2 Hz, 3H). LCMS (MH^+): 471.60.

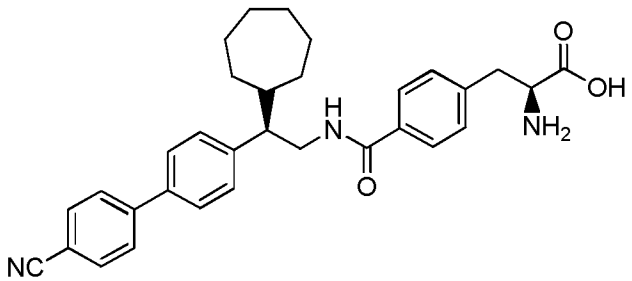
Example 84: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cycloheptylethyl) carbamoyl)phenyl)-2-aminopropanoic acid



The title compound was prepared as described for Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid, starting with (R)-2-(4-bromophenyl)-2-cycloheptylethanamine (Intermediate 51).

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.62 (t, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.35 – 7.21 (m, 3H), 4.15 (t, *J* = 6.6 Hz, 1H), 3.67 (dd, *J* = 13.5, 5.9 Hz, 1H), 3.55 (t, *J* = 11.4 Hz, 1H), 3.11 – 3.05 (m, 1H), 2.98 (d, *J* = 7.9 Hz, 1H), 1.78 (s, 1H), 1.60 (s, 1H), 1.49 (s, 1H), 1.36 (d, *J* = 9.0 Hz, 2H), 1.20 (s, 1H), 1.12 – 1.02 (m, 1H). LCMS (MH^+): 485.63.

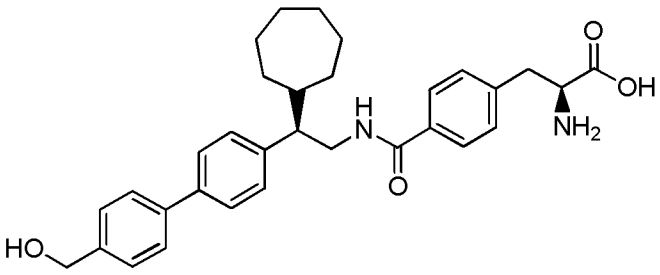
Example 85: (S)-2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-2-cycloheptylethyl)carbamoyl)phenyl)propanoic acid



The title compound was prepared as described for Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid, starting with (R)-2-(4-bromophenyl)-2-cycloheptylethanamine (Intermediate 51) and 4-cyanophenyl boronic acid.

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.79 (s, 3H), 7.57 (dd, *J* = 20.7, 7.8 Hz, 4H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 4.09 – 4.01 (m, 34H), 3.60 (qd, *J* = 13.5, 7.8 Hz, 3H), 3.07 (d, *J* = 6.6 Hz, 2H), 1.73 (d, *J* = 11.1 Hz, 2H), 1.57 (d, *J* = 18.6 Hz, 2H), 1.48 – 1.39 (m, 3H), 1.35 – 1.26 (m, 4H), 1.20 (s, 1H). LCMS (MH^+): 510.64.

Example 86: (S)-2-amino-3-(4-(((R)-2-cycloheptyl-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid

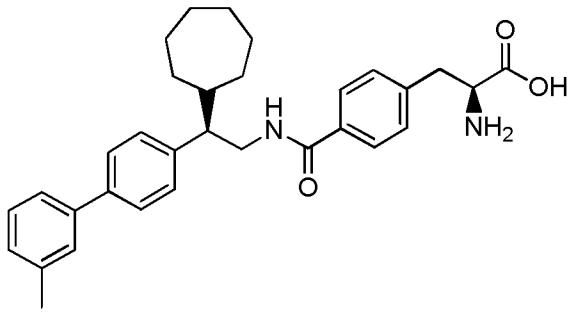


The title compound was prepared as described for Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid, starting with (R)-2-(4-bromophenyl)-2-cycloheptylethanamine (Intermediate 51) and 4-hydroxymethyl phenyl boronic acid.

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.67 – 7.50 (m, 5H), 7.35 (d, J = 7.7 Hz, 2H), 7.25 (t, J = 6.3 Hz, 3H), 4.49 (s, 2H), 4.14 (d, J = 6.4 Hz, 1H), 3.67 (dd, J = 13.7, 5.5 Hz, 1H), 3.55 (s, 1H), 3.10 (d, J = 6.4 Hz, 2H), 2.98 (d, J = 8.0 Hz, 1H), 1.78 (s, 1H), 1.60 (s, 1H), 1.47 (d, J = 13.9 Hz, 2H), 1.36 (d, J = 8.9 Hz, 3H), 1.25 (s, 1H), 1.19 (s, 1H), 1.06 (d, J = 11.4 Hz, 1H).

LCMS (MH^+): 515.66.

Example 87: (S)-2-amino-3-(4-(((R)-2-cycloheptyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid

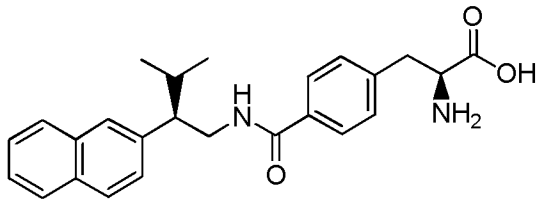


The title compound was prepared as described for Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid starting with (R)-2-(4-bromophenyl)-2-cycloheptylethanamine (Intermediate 51) and 4-hydroxymethyl phenyl boronic acid.

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.55 (dd, J = 37.6, 8.0 Hz, 7H), 7.38 (d, J = 11.6 Hz, 4H), 7.11 (d, J = 7.5 Hz, 2H), 4.24 – 4.06 (m, 3H), 3.99 – 3.82 (m, 1H), 3.70 – 3.50 (m, 3H), 3.08 (d, J = 6.5 Hz, 4H), 2.97 (s, 2H), 2.31 (s, 5H), 1.76 (s, 3H), 1.58 (s, 1H), 1.47 (s, 5H), 1.34

(d, J = 8.8 Hz, 5H), 1.23 (d, J = 9.2 Hz, 1H), 1.04 (q, J = 10.2, 9.8 Hz, 2H). LCMS (MH^+): 499.66.

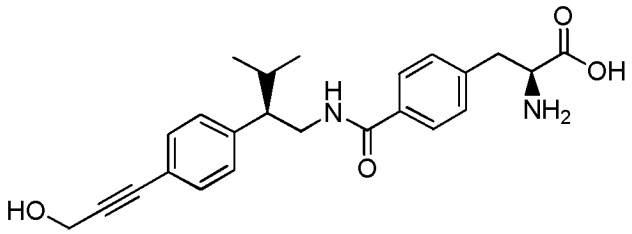
Example 88: (S)-2-amino-3-(4-(((R)-3-methyl-2-(naphthalen-2-yl) butyl) carbamoyl) phenyl)propanoic acid



The title compound was prepared as described for Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid, starting with (R)-3-methyl-2-(naphthalen-2-yl)butan-1-amine (Intermediate 46).

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.34 – 8.23 (m, 2H), 7.81 (dd, *J* = 10.8, 7.6 Hz, 2H), 7.67 – 7.58 (m, 2H), 7.48 – 7.42 (m, 1H), 7.38 (dd, *J* = 15.3, 7.3 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 4.14 (q, *J* = 6.0 Hz, 1H), 3.77 (dt, *J* = 13.3, 5.4 Hz, 1H), 3.62 (ddd, *J* = 13.8, 9.2, 6.3 Hz, 1H), 3.08 (d, *J* = 6.4 Hz, 1H), 2.96 (q, *J* = 7.4 Hz, 1H), 2.01 (h, *J* = 6.8 Hz, 1H), 0.98 (d, *J* = 6.6 Hz, 2H), 0.73 (d, *J* = 6.7 Hz, 2H). LCMS (MH^+): 405.50

Example 89: (S)-2-amino-3-(4-(((R)-2-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid



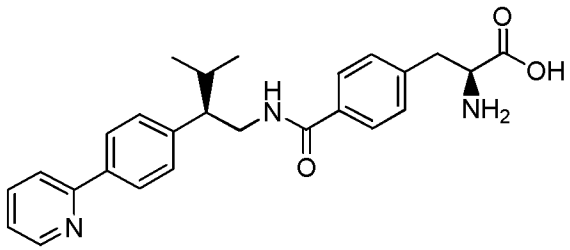
Step 1: To a solution of (S)-ethyl 3-(4-(((R)-2-(4-bromophenyl)-3-methylbutyl) carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (Example 1a, Step 2, (200 mg, 0.36 mmol) in DMF (10 mL) was add $Pd(PPh_3)_2Cl_2$ (38 mg, 0.054 mmol), CuI (14 mg, 0.072 mmol) and PPh_3 (19 mg, 0.072 mmol). After stirring for 5 min, prop-2-yn-1-ol (CAS#: 107-19-7, 61 mg, 1.08 mmol) and diethyl amine (53 mg, 0.72 mmol) were added and the reaction was heated to 80 °C for 12 h. After this time, the reaction was cooled to RT and extracted with ethyl

acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexanes:ethyl acetate/4:1) provided (S)-ethyl 2-((tert-butoxycarbonyl)amino)-3-(4-(((R)-2-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)propanoate as a yellow oil. LCMS (MH^+): 537.3.

The title compound was produced by following Steps 3-4 as described for Example 1a to provide a white solid.

^{1}H NMR (400 MHz, MeOH-d4): δ ppm 7.49 (d, J = 7.8 Hz, 3H), 7.30 (dd, J = 24.4, 7.8 Hz, 6H), 7.17 (d, J = 7.8 Hz, 3H), 4.37 (s, 3H), 3.82 (dd, J = 13.3, 5.3 Hz, 2H), 3.57 (t, J = 11.8 Hz, 2H), 3.45 (s, 1H), 3.30 (s, 5H), 3.10 (d, J = 13.6 Hz, 2H), 2.79 (t, J = 9.8 Hz, 3H), 2.01 (s, 1H), 1.98 – 1.86 (m, 3H), 1.30 (d, J = 15.1 Hz, 6H), 1.05 (d, J = 6.6 Hz, 5H), 0.89 (s, 1H), 0.76 (d, J = 6.6 Hz, 5H). LCMS (MH^+): 409.5.

Example 90: (S)-2-amino-3-(4-(((R)-3-methyl-2-(4-(pyridin-2-yl)phenyl)butyl) carbamoyl)phenyl)propanoic acid

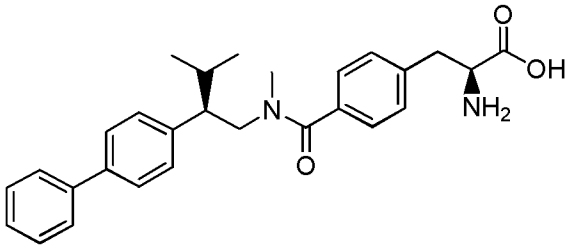


Step 1: A solution of Intermediate B: (S)-ethyl 2-((tert-butoxycarbonyl)amino)-3-(4-(((R)-3-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butyl)carbamoyl)phenyl) propanoate (200 mg, 0.33 mmol), 2-bromopyridine (80 mg, 0.493 mmol), Pd(dppf)Cl2 (24 mg, 0.0329 mmol) and 2M Na_2CO_3 (1 mL) in dioxane (3 mL) was purged with N_2 and then heated at 80 °C for 3 h. After this time, the reaction mixture was cooled to RT and the mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column to provide (S)-ethyl 2-((tert-butoxycarbonyl)amino)-3-(4-(((R)-3-methyl-2-(4-(pyridin-2-yl)phenyl)butyl)carbamoyl)phenyl)propanoate (105 mg) as a yellow solid.

Steps 2 & 3: The title compound was produced by following Steps 3-4 as described for Example 1a to provide a white solid.

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.60 (dt, J = 4.6, 1.5 Hz, 1H), 7.99 – 7.78 (m, 4H), 7.53 (d, J = 8.0 Hz, 2H), 7.33 – 7.23 (m, 3H), 7.20 (d, J = 7.9 Hz, 2H), 3.74 – 3.59 (m, 1H), 3.57 – 3.43 (m, 2H), 3.03 – 2.95 (m, 1H), 2.84 (q, J = 7.1 Hz, 1H), 2.54 (s, 1H), 1.94 (dt, J = 13.4, 6.7 Hz, 1H), 0.94 (d, J = 6.7 Hz, 3H), 0.72 (d, J = 6.7 Hz, 3H). LCMS (MH^+): 432.53.

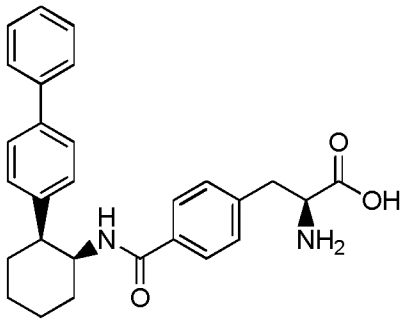
Example 91: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) (methyl) carbamoyl)phenyl)-2-aminopropanoic acid



The title compound was prepared as described for Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid starting with (R)-2-(4-bromophenyl)-N,3-dimethylbutan-1-amine (Intermediate 52).

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.73 (d, J = 7.8 Hz, 2H), 7.60 (dd, J = 19.6, 7.6 Hz, 4H), 7.43 (t, J = 7.6 Hz, 2H), 7.32 (dd, J = 18.8, 7.6 Hz, 5H), 4.22 (s, 1H), 3.62 (qd, J = 13.4, 7.4 Hz, 2H), 3.11 (t, J = 5.4 Hz, 2H), 2.26 (q, J = 8.3 Hz, 1H), 1.22 (s, 1H), 1.06 (s, 1H), 0.57 (d, J = 7.4 Hz, 1H), 0.30 (dt, J = 13.6, 7.4 Hz, 2H)LCMS (MH^+): 429.5.

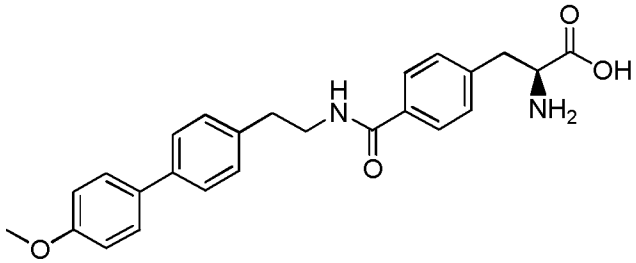
Example 92: (S)-3-(4-(((1S,2S)-2-([1,1'-biphenyl]-4-yl)cyclohexyl)carbamoyl) phenyl)-2-aminopropanoic acid



The title compound was prepared as described for Example 1a: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid starting with (1S, 2S)-2-(4-iodophenyl)cyclohexylamine (CAS# 1389386-47-3).

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.56 – 7.43 (m, 6H), 7.40 – 7.14 (m, 8H), 4.08 (q, J = 6.6, 5.5 Hz, 2H), 3.05 (d, J = 6.5 Hz, 2H), 2.76 (td, J = 11.7, 3.3 Hz, 1H), 1.87 (s, 1H), 1.78 (d, J = 14.9 Hz, 2H), 1.71 (d, J = 13.7 Hz, 2H), 1.57 – 1.41 (m, 1H), 1.41 (s, 2H), 1.30 (d, J = 11.7 Hz, 1H).. LCMS (MH^+): 443.5.

Example 93: (S)-2-amino-3-(4-((2-(4'-methoxy-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid



Step 1: To a solution of (S)-4-(2-((tert-butoxycarbonyl)amino)-3-ethoxy-3-oxopropyl)benzoic acid (Intermediate A, 200 mg, 0.82 mmol) in DMF (10 mL) was added 2-(4-bromophenyl)ethanamine (200 mg, 1.0 mmol), HATU (623 mg, 1.64 mmol), and TEA (166 mg, 1.64 mmol), and the reaction was stirred for 48 h at RT. After this time, the reaction was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexanes:ethyl acetate/4:1) provided (S)-ethyl 3-(4-((4-bromophenethyl) carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate as a white solid.

Step 2: To a solution of (S)-ethyl 3-(4-((4-bromophenethyl)carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (200 mg, 0.38 mmol) in dioxane (5.0 mL)/Na_2CO_3 (2.5 mL, 2.0 M, aq.) was added 4-methoxy phenyl boronic acid (70 mg, 0.55 mmol) followed by $Pd(dppf)Cl_2$ (30 mg, 0.038 mmol). The reaction was purged with N_2 and then heated to 90 °C for 3 h. After this time, the reaction was cooled to RT and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexanes:ethyl acetate/4:1) provided (S)-ethyl 2-((tert-butoxycarbonyl)amino)-3-(4-((2-(4'-methoxy-[1,1'-biphenyl]-4-yl)ethyl) carbamoyl)phenyl)propanoateas an off-white solid.

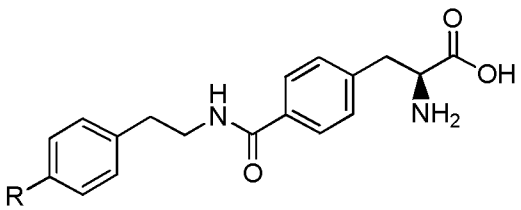
Step 3: To a 0 °C solution of (S)-ethyl 2-((tert-butoxycarbonyl)amino)-3-(4-((2-(4'-methoxy-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoate (125 mg, 0.23 mmol) in CH_2Cl_2 (6 mL), was added dropwise TFA (1.5 mL). The reaction was warmed to RT for 3 h, then concentrate *in vacuo*. To the resulting residue was added saturated aqueous solution of $NaHCO_3$ to adjust the pH to ~7.5 and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide (S)-ethyl 2-amino-3-(4-((2-(4'-methoxy-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoate as an off-white solid that was used without further purification.

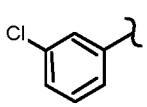
Step 4: To a 0 °C solution of (S)-ethyl 2-amino-3-(4-((2-(4'-methoxy-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoate (75 mg, 0.16 mmol) in MeOH (6 mL), was added dropwise 5 N NaOH (2 mL) and then the reaction mixture was warmed to RT for 3 h. After this time, the reaction mixture was acidified with 3N HCl to adjust the pH to 6-7, the MeOH was removed *in vacuo* and the resultant solid was filtered, washed with H_2O, and dried *in vacuo* to provide the title compound as a white solid.

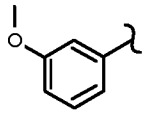
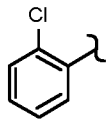
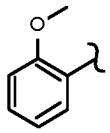
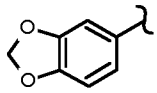
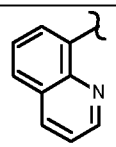
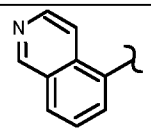
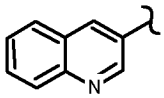
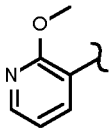
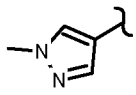
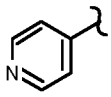
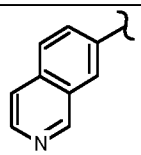
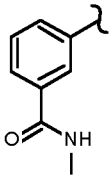
^{1}H NMR (400 MHz, MeOH-d4): δ ppm 2.87 (t, J=7.3 Hz, 2 H) 3.15 (dd, J=6.2, 4.5 Hz, 2 H) 3.49 - 3.55 (m, 2 H) 3.78 (s, 3 H) 4.20 - 4.27 (m, 1 H) 7.00 (q, J=5.2 Hz, 2 H) 7.29 (d, J=8.3 Hz, 2 H), 7.35 (d, J=8.3 Hz, 2 H) 7.52 - 7.55 (m, 2 H) 7.57 (q, J=5.2 Hz, 2 H) 7.81 (d, J=8.4 Hz, 2 H) 8.31 (d, J=4.5 Hz, 3 H) 8.58 (t, J=5.6 Hz, 1 H). LCMS (MH^+): 419.5.

The following compounds in Table 4a were prepared as described above for Example 93 using the appropriate boronic acid. NMR data is provided in Table 4b.

Table 4a



Ex. No.	R	Name	LCMS (MH+)
94		(S)-2-amino-3-(4-((2-(3'-chloro-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl) propanoic acid	422.9

95		(S)-2-amino-3-(4-((2-(3'-methoxy-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl) propanoic acid	418.49
96		(S)-2-amino-3-(4-((2-(2'-chloro-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl) propanoic acid	422.9
97		(S)-2-amino-3-(4-((2-(2'-methoxy-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl) propanoic acid	418.49
98		(S)-2-amino-3-(4-((4-(benzo[d][1,3]dioxol-5-yl)phenethyl)carbamoyl)phenyl) propanoic acid	432.47
99		(S)-2-amino-3-(4-((4-(quinolin-8-yl)phenethyl)carbamoyl)phenyl) propanoic acid	439.51
100		(S)-2-amino-3-(4-((4-(isoquinolin-5-yl)phenethyl)carbamoyl)phenyl) propanoic acid	440.51
101		(S)-2-amino-3-(4-((4-(quinolin-3-yl)phenethyl)-carbamoyl)-phenyl) propanoic acid	440.51
102		(S)-2-amino-3-(4-((4-(2-methoxypyridin-3-yl)phenethyl)carbamoyl)phenyl) propanoic acid	420.47
103		(S)-2-amino-3-(4-((4-(1-methyl-1H-pyrazol-4-yl)phenethyl)carbamoyl) phenyl)propanoic acid	393.45
104		(S)-2-amino-3-(4-((4-(pyridin-4-yl)phenethyl)carbamoyl)phenyl) propanoic acid	390.45
105		(S)-2-amino-3-(4-((4-(isoquinolin-7-yl)phenethyl)carbamoyl)phenyl) propanoic acid	440.51
106		S)-2-amino-3-(4-((2-(3'-(methylcarbamoyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)propanoic acid	446.51

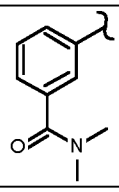
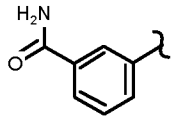
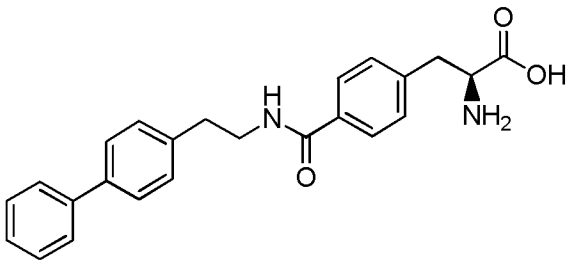
107		(S)-2-amino-3-(4-((2-(3'-(dimethylcarbamoyl)-[1,1'-biphenyl]-4-yl)ethyl) carbamoyl)phenyl)propanoic acid	460.54
108		(S)-2-amino-3-(4-((2-(3'-carbamoyl-[1,1'-biphenyl]-4-yl)ethyl) carbamoyl)phenyl)propanoic acid	432.48

Table 4b

Ex. No.	^{1}H NMR
94	$^{1H\ NMR}$ (400 MHz, DMSO-d6): δ ppm 2.90 (t, J=7.2 Hz, 2 H) 3.15 (dd, J=6.3, 2.1 Hz, 2 H) 3.53 (q, J=6.6 Hz, 2 H) 4.19 - 4.28 (m, 1 H) 7.35 (d, J=8.1 Hz, 4 H) 7.39 (dd, J=2.0, 1.1 Hz, 1 H) 7.47 (t, J=7.9 Hz, 1 H) 7.63 (d, J=8.2 Hz, 3 H) 7.69 (t, J=1.9 Hz, 1 H) 7.81 (d, J=8.3 Hz, 2 H) 8.32 (d, J=4.1 Hz, 3 H) 8.59 (t, J=5.6 Hz, 1 H)
95	$^{1H\ NMR}$ (400 MHz, DMSO-d6): δ ppm 2.89 (t, J=7.3 Hz, 2 H) 3.09 - 3.20 (m, 2 H) 3.49 - 3.56 (m, 2 H) 3.81 (s, 3 H) 4.19 - 4.28 (m, 1 H) 6.91 (ddd, J=8.2, 2.5, 0.8 Hz, 1 H) 7.15 (d, J=2.3 Hz, 1 H) 7.20 (ddd, J=7.7, 1.6, 0.9 Hz, 1 H) 7.33 (dd, J=11.6, 7.6 Hz, 5 H) 7.59 (d, J=8.3 Hz, 2 H), 7.81 (d, J=8.3 Hz, 2 H) 8.30 (d, J=4.8 Hz, 3 H) 8.58 (t, J=5.6 Hz, 1 H)
96	$^{1H\ NMR}$ (400 MHz, DMSO-d6): δ ppm 2.91 (t, J=7.4 Hz, 2 H) 3.00 - 3.08 (m, 1 H) 3.18 (dd, J=14.4, 5.6 Hz, 1 H) 3.49 - 3.58 (m, 2 H) 3.86 (t, J=6.3 Hz, 1 H) 7.39 (dq, J=6.7, 3.5 Hz, 10 H), 7.53 - 7.58 (m, 1 H) 7.80 (d, J=8.2 Hz, 2 H) 8.61 (t, J=5.6 Hz, 1 H)
97	$^{1H\ NMR}$ (400 MHz, DMSO-d6): δ ppm 2.88 (t, J=7.4 Hz, 2 H) 3.02 - 3.10 (m, 1 H) 3.14 - 3.22 (m, 1 H) 3.48 - 3.57 (m, 2 H) 3.75 (s, 3 H) 3.92 (t, J=6.3 Hz, 1 H) 7.01 (td, J=7.4, 0.9 Hz, 1 H), 7.09 (d, J=7.8 Hz, 1 H) 7.26 (dd, J=7.5, 1.8 Hz, 3 H) 7.31 (dd, J=7.0, 1.3 Hz, 1 H) 7.35 (d, J=8.2 Hz, 2 H) 7.40 (d, J=8.2 Hz, 2 H) 7.81 (d, J=8.3 Hz, 2 H) 8.60 (t, J=5.6 Hz, 1 H)
98	ND (not determined)
99	$^{1H\ NMR}$ (400 MHz, DMSO-d6): δ ppm 2.96 (t, J=7.3 Hz, 2 H) 3.20 (d, J=6.2 Hz, 2 H) 3.59 (q, J=6.8 Hz, 2 H) 4.14 - 4.25 (m, 1 H) 7.38 (d, J=8.3 Hz, 4 H) 7.59 (d, J=8.2 Hz, 2 H) 7.86 (d, J=7.3 Hz, 5 H) 8.12 (t, J=8.6 Hz, 1 H) 8.49 (t, J=6.4 Hz, 3 H) 8.71 (d, J=5.4 Hz, 2 H) 8.97 (d, J=4.5 Hz, 1 H)
100	ND (not determined)
101	ND (not determined)
102	ND (not determined)
103	ND (not determined)
104	$^{1H\ NMR}$ (400 MHz, DMSO-d6): δ ppm 2.97 (t, J=7.1 Hz, 2 H) 3.19 (d, J=5.8 Hz,

	2 H) 3.56 (q, J=6.6 Hz, 2 H) 4.13 - 4.23 (m, 1 H) 7.36 (d, J=8.1 Hz, 2 H) 7.50 (d, J=7.9 Hz, 2 H) 7.81 (d, J=8.1 Hz, 2 H) 7.98 (d, J=7.3 Hz, 2 H) 8.28 - 8.36 (m, 2 H) 8.50 (br. s., 3 H) 8.67 (d, J=4.1 Hz, 1 H), 8.90 (d, J=4.0 Hz, 2 H)
105	ND (not determined)
106	$^{1H\ NMR}$ (400 MHz, DMSO-d6): δ ppm 8.03 (s, 1H), 7.75 (d, J = 7.0 Hz, 3H), 7.62 (d, J = 7.7 Hz, 2H), 7.52 (d, J = 8.8 Hz, 1H), 7.32 (t, J = 10.5 Hz, 4H), 4.17 (s, 1H), 3.51 (s, 2H), 3.12 (d, J = 6.5 Hz, 2H), 2.87 (s, 2H), 2.78 (s, 3H
107	$^{1H\ NMR}$ (400 MHz, DMSO-d6): δ ppm 7.79 (d, J = 7.9 Hz, 2H), 7.69 (d, J = 7.8 Hz, 1H), 7.64-7.57 (m, 2H), 7.49 (t, J = 7.7 Hz, 1H), 7.33 (d, J = 7.9 Hz, 3H), 4.21 (d, J = 6.4 Hz, 1H), 3.51 (t, J = 7.3 Hz, 2H), 3.13 (d, J = 6.5 Hz, 2H), 2.98 (s, 2H), 2.94-2.83 (m, 4H)
108	$^{1H\ NMR}$ (400 MHz, DMSO-d6): δ ppm 8.10 (s, 1H), 7.79 (dd, J = 11.9, 7.7 Hz, 3H), 7.64 (d, J = 7.9 Hz, 2H), 7.51 (t, J = 7.7 Hz, 1H), 7.33 (t, J = 8.1 Hz, 3H), 4.20 (t, J = 6.5 Hz, 1H), 3.90 (s, 1H), 3.51 (t, J = 7.3 Hz, 2H), 3.13 (d, J = 6.5 Hz, 2H), 2.88 (t, J = 7.3 Hz, 2H)

Example 109: (S)-3-(4-((2-([1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid



Step 1: To a solution of (S)-4-(2-((tert-butoxycarbonyl)amino)-3-ethoxy-3-oxopropyl)benzoic acid (Intermediate A, 200 mg, 0.82 mmol) in DMF (10 mL) was added (2-([1,1'-biphenyl]-4-yl)ethanamine (Intermediate 5, 236 mg, 1.2 mmol), HATU (623 mg, 1.64 mmol) and TEA (166 mg, 1.64 mmol) and the mixture was stirred for 48 h at RT. After this time, the reaction was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexanes:ethyl acetate/4:1 v/v) provided (S)-ethyl 3-(4-((2-([1,1'-biphenyl]-4-yl)ethyl) carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate as a white solid.

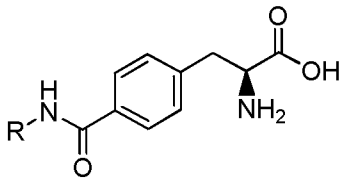
Step 2: To a 0 °C solution of (S)-ethyl 3-(4-((2-([1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (150 mg, 0.29 mmol) in CH_2Cl_2 (6 mL), was added dropwise TFA (1.5 mL). The reaction was warmed to RT for 3 h, then concentrated *in vacuo*. To the resulting residue was added saturated aqueous solution of $NaHCO_3$ to adjust the

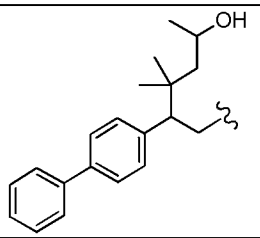
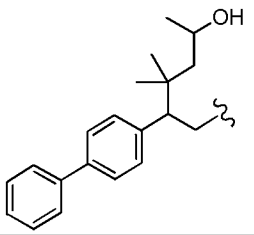
pH to ~7.5 and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide (S)-ethyl 3-(4-((2-([1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoate as an off-white solid that was used without further purification.

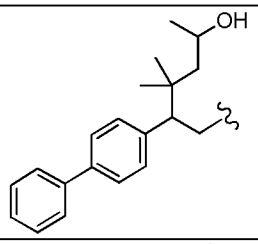
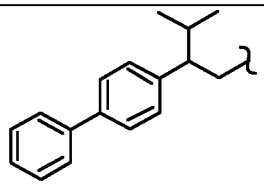
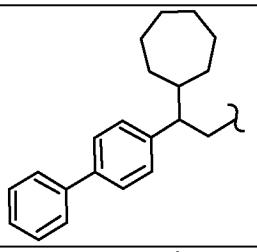
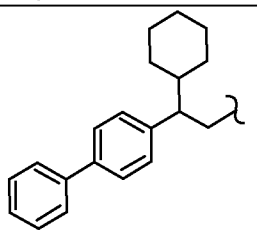
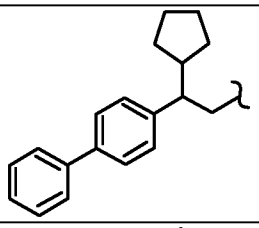
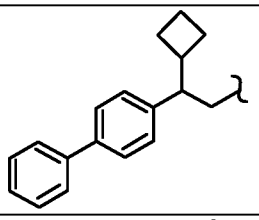
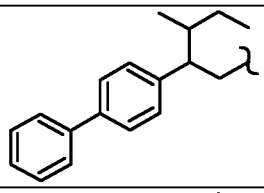
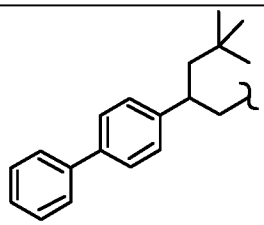
Step 3: To a 0 °C solution of (S)-ethyl 3-(4-((2-([1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)-2-aminopropanoate 75 mg, 0.18 mmol) in MeOH (6 mL), was added dropwise NaOH (5N, 2 mL) and the reaction mixture was warmed to RT for 3 h. After this time, the reaction mixture was acidified with HCl (3N) to adjust the pH to 6-7, then the MeOH was removed *in vacuo* and the resultant solid was filtered, washed with H_2O, and dried *in vacuo* to provide the title compound as a white solid. LCMS (MH+): 388.46. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.70 (s, 2 H),7.57-7.48 (m,6H),7.36-7.33 (t, J = 8.0 Hz, 2 H),7.29-7.25 (m,3H),4.64(s,1 H), 3.95 (s, 2H), 3.64-3.61 (m, 1H), 3.43-3.39 (m, 1H), 3.06 (s, 2 H).

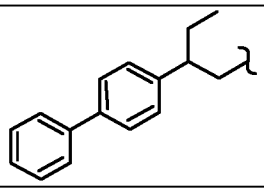
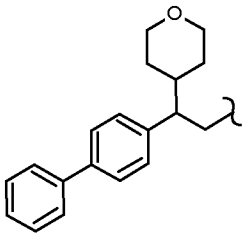
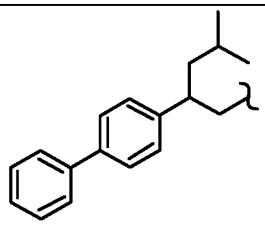
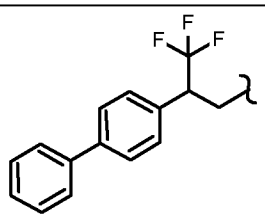
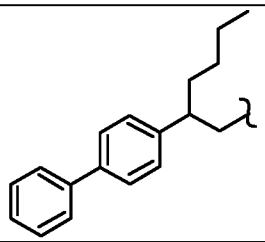
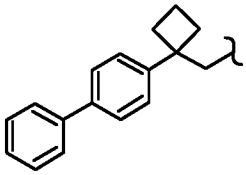
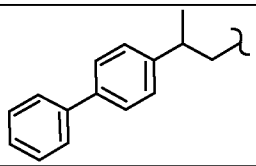
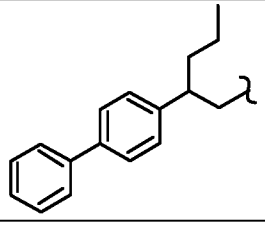
The compounds in Table 5a were made following the procedure for Example 109 starting with the appropriate amine intermediate indicated in the table. NMR data is provided in Table 5b.

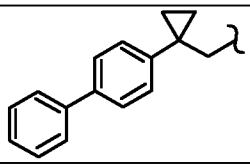
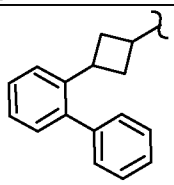
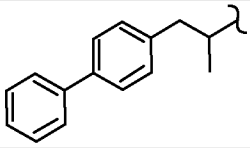
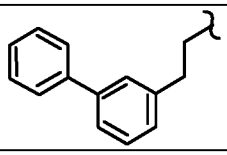
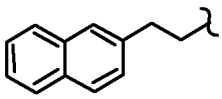
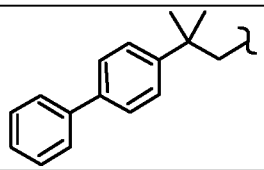
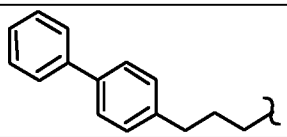
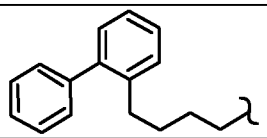
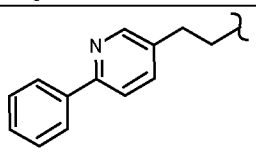
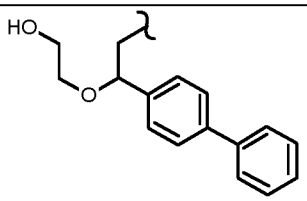
Table 5a

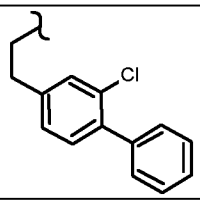
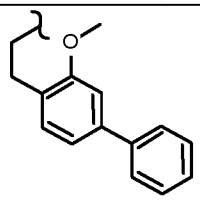
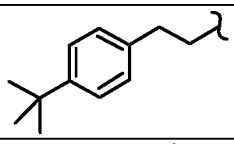
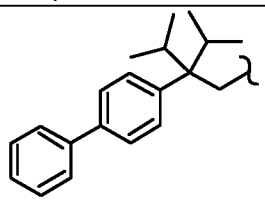
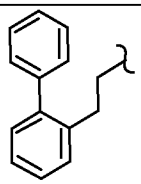
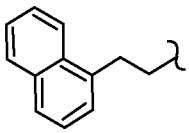
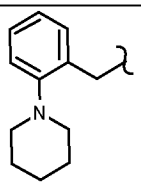
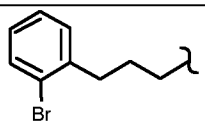
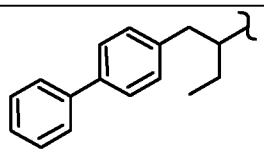
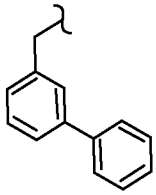


Ex. No.	Int. No.	R	Name	LCMS (MH+)
110	33		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-5-hydroxy-3,3-dimethylhexyl)carbamoyl) phenyl)-2-aminopropanoic acid (Stereoisomer 1)	488.62
111	32		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-5-hydroxy-3,3-dimethylhexyl)carbamoyl) phenyl)-2-aminopropanoic acid (Stereoisomer 2)	488.62

112	34		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-5-hydroxy-3,3-dimethylhexyl)carbamoyl) phenyl)-2-aminopropanoic acid (Stereoisomer 3)	488.62
113	55		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid	430.54
114	28		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-cycloheptylethyl) carbamoyl)phenyl)-2-aminopropanoic acid	484.63
115	24		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-cyclohexylethyl) carbamoyl)phenyl)-2-aminopropanoic acid	470.6
116	21		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-cyclopentylethyl) carbamoyl)phenyl)-2-aminopropanoic acid	456.58
117	30		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-cyclobutylethyl) carbamoyl)phenyl)-2-aminopropanoic acid	442.55
118	23		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-3-methylpentyl) carbamoyl)phenyl)-2-aminopropanoic acid	444.57
119	26		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-4,4-dimethylpentyl) carbamoyl) phenyl)-2-aminopropanoic acid	458.59

120	3		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)-2-aminopropanoic acid	416.51
121	29		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-(tetrahydro-2H-pyran-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid	472.58
122	22		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-4-methylpentyl) carbamoyl)phenyl)-2-aminopropanoic acid	444.57
123	31		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-3,3,3-trifluoropropyl) carbamoyl)phenyl)-2-aminopropanoic acid	456.46
124	27		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)hexyl)carbamoyl)phenyl)-2-aminopropanoic acid	444.57
125	20		(S)-3-(4-(((1-([1,1'-biphenyl]-4-yl)cyclobutyl)methyl)carbamoyl)phenyl)-2-aminopropanoic acid	428.52
126	2		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)propyl)carbamoyl)phenyl)-2-aminopropanoic acid	402.49
127	54		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)pentyl)carbamoyl)phenyl)-2-aminopropanoic acid	430.54

128	4		(S)-3-(4-(((1-([1,1'-biphenyl]-4-yl)cyclopropyl)methyl)carbamoyl)phenyl)-2-aminopropanoic acid	414.5
129	41		(S)-3-(4-((3-([1,1'-biphenyl]-2-yl)cyclobutyl)carbamoyl)phenyl)-2-aminopropanoic acid	414.5
130	1		(2S)-3-(4-((1-([1,1'-biphenyl]-4-yl)propan-2-yl)carbamoyl) phenyl)-2-aminopropanoic acid	402.49
131	6		(S)-3-(4-((2-([1,1'-biphenyl]-3-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid	388.46
132	7		(S)-2-amino-3-(4-((2-(naphthalen-2-yl)ethyl) carbamoyl)phenyl)propanoic acid	362.42
133	8		(S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-methylpropyl) carbamoyl)phenyl)-2-aminopropanoic acid	416.51
134	9		(S)-3-(4-((3-([1,1'-biphenyl]-4-yl)propyl)carbamoyl)phenyl)-2-aminopropanoic acid	402.49
135	40		(S)-3-(4-((4-([1,1'-biphenyl]-2-yl)butyl)carbamoyl)phenyl)-2-aminopropanoic acid	416.51
136	37		(S)-2-amino-3-(4-((2-(6-phenylpyridin-3-yl) ethyl)carbamoyl)phenyl) propanoic acid	389.45
137	38		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-(2-hydroxyethoxy) ethyl)carbamoyl)phenyl)-2-aminopropanoic acid	448.51

138	35		(S)-2-amino-3-(4-((2-(2-chloro-[1,1'-biphenyl]-4-yl) ethyl)carbamoyl)phenyl) propanoic acid	422.9
139	36		(S)-2-amino-3-(4-((2-(3-methoxy-[1,1'-biphenyl]-4-yl) ethyl)carbamoyl)phenyl) propanoic acid	418.49
140	10		(S)-2-amino-3-(4-((4-(tert-butyl)phenethyl)carbamoyl)phen yl)propanoic acid	368.47
141	25		(S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-isopropyl-3-methyl butyl)carbamoyl)phenyl)-2-aminopropanoic acid	473.62
142	19b		(S)-3-(4-((2-([1,1'-biphenyl]-2-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid	389.46
143	11		(S)-2-amino-3-(4-((2-(naphthalen-1-yl)ethyl)carbamoyl)phenyl) propanoic acid	363.42
144	12		(S)-2-amino-3-(4-((2-(piperidin-1-yl)benzyl)carbamoyl)phenyl) propanoic acid	382.47
145	13		(S)-2-amino-3-(4-((3-(2-bromophenyl)propyl)carbamoyl) phenyl)propanoic acid	406.29
146	14		(2S)-3-(4-((1-([1,1'-biphenyl]-4-yl)butan-2-yl) carbamoyl)phenyl)-2-aminopropanoic acid	417.51
147	15		(S)-3-(4-(([1,1'-biphenyl]-3-ylmethyl)carbamoyl)phenyl)-2-aminopropanoic acid	375.43

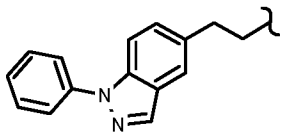
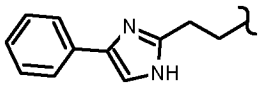
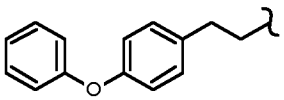
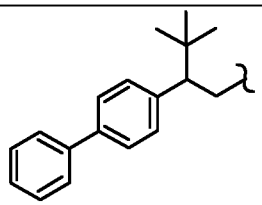
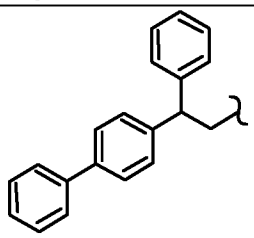
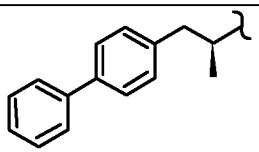
148	42		(S)-2-amino-3-(4-((2-(1-phenyl-1H-indazol-5-yl)ethyl)carbamoyl) phenyl)propanoic acid	429.50
149	43		(S)-2-amino-3-(4-((2-(4-phenyl-1H-imidazol-2-yl) ethyl)carbamoyl) phenyl)propanoic acid	379.42
150	17		(S)-2-amino-3-(4-((4-phenoxyphenethyl)carbamoyl) phenyl)propanoic acid	405.46
151	18		(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-3,3-dimethylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid	445.56
152	19		(S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-phenylethyl)carbamoyl) phenyl)-2-aminopropanoic acid	465.56
152a	19c		(S)-3-(4-(((S)-1-([1,1'-biphenyl]-4-yl)propan-2-yl) carbamoyl)phenyl)-2-aminopropanoic acid	402.49

Table 5b

Ex. No.	^{1}H NMR
110	1H NMR (400 MHz, MeOH-d4): δ ppm 0.88 (s, 3 H) 0.98 (s, 3 H) 1.09 (d, J=6.10 Hz, 3 H) 1.32 - 1.52 (m, 2 H) 2.96 - 3.16 (m, 3 H) 3.60 - 3.71 (m, 1 H) 3.72 - 3.84 (m, 1 H) 3.87 - 3.99 (m, 1 H) 4.18 (d, J=5.03 Hz, 1 H) 7.23 (d, J=8.20 Hz, 2 H) 7.26 - 7.37 (m, 3 H) 7.43 (t, J=7.64 Hz, 2 H) 7.57 (t, J=7.88 Hz, 4 H) 7.62 - 7.69 (m, 2 H) 8.08 (t, J=4.98 Hz, 1 H) 8.21 (d, J=3.12 Hz, 3 H)
111	1H NMR (400 MHz, DMSO-d6): δ ppm 0.88 (s, 3 H) 0.98 (s, 3 H) 1.09 (d, J=6.10 Hz, 3 H) 1.32 - 1.52 (m, 2 H) 2.96 - 3.16 (m, 3 H) 3.60 - 3.71 (m, 1 H) 3.72 - 3.84 (m, 1 H) 3.87 - 3.99 (m, 1 H) 4.18 (d, J=5.03 Hz, 1 H) 7.23 (d, J=8.20 Hz, 2 H) 7.26 - 7.37 (m, 3 H) 7.43 (t, J=7.64 Hz, 2 H) 7.57 (t, J=7.88 Hz, 4 H) 7.62 - 7.69 (m, 2 H) 8.08 (t, J=4.98 Hz, 1 H) 8.21 (d, J=3.12 Hz, 3 H)

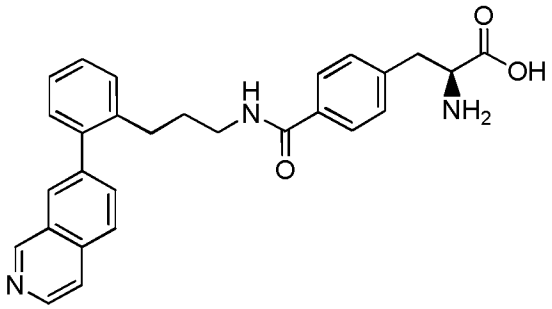
112	1H NMR (400 MHz, DMSO-d6): δ ppm 0.92 (s, 3 H) 0.97 (s, 3 H) 1.06 (d, J=6.15 Hz, 3 H) 1.28 (dd, J=14.23, 2.46 Hz, 1 H) 1.45 (dd, J=14.35, 7.96 Hz, 1 H) 2.98 - 3.15 (m, 3 H) 3.68 - 3.84 (m, 2 H) 3.85 - 3.95 (m, 1 H) 4.18 (m, J=5.70 Hz, 1 H) 7.25 (dd, J=13.32, 8.05 Hz, 4 H) 7.30 - 7.37 (m, 1 H) 7.43 (t, J=7.64 Hz, 2 H) 7.58 (dd, J=11.13, 8.25 Hz, 4 H) 7.63 - 7.69 (m, 2 H) 8.12 (br. s., 1 H) 8.21 (br. s., 3 H)
113	1H NMR (400 MHz, DMSO-d6): δ ppm 0.72 (d, J=6.74 Hz, 3 H) 0.93 (d, J=6.64 Hz, 3 H) 1.83 - 2.01 (m, 1 H) 2.75 - 2.89 (m, 1 H) 3.09 (d, J=6.54 Hz, 2 H) 3.50 (td, J=13.58, 5.93 Hz, 1 H) 3.69 (dd, J=12.84, 5.52 Hz, 1 H) 4.14 (br. s., 1 H) 7.18 - 7.34 (m, 5 H) 7.40 (t, J=7.64 Hz, 2 H) 7.54 (d, J=8.15 Hz, 2 H) 7.60 (d, J=7.37 Hz, 2 H) 7.66 (s, 2 H) 8.20 - 8.42 (m, 4 H)
114	1H NMR (400 MHz, DMSO-d6): δ ppm 1.00 - 1.17 (m, 1 H) 1.20 - 1.45 (m, 5 H) 1.45 - 1.73 (m, 5 H) 1.82 (br. s., 2 H) 2.92 - 3.03 (m, 1 H) 3.04 - 3.18 (m, 2 H) 3.46 - 3.63 (m, 1 H) 3.64 - 3.79 (m, 1 H) 4.21 (d, J=5.42 Hz, 1 H) 7.23 - 7.37 (m, 5 H) 7.43 (t, J=7.64 Hz, 2 H) 7.57 (d, J=8.20 Hz, 2 H) 7.64 (d, J=7.32 Hz, 2 H) 7.69 (d, J=8.20 Hz, 2 H) 8.16 - 8.33 (m, 4 H)
115	1H NMR (400 MHz, DMSO-d6): δ ppm 0.64 - 0.84 (m, 1 H) 0.86 - 1.28 (m, 4 H) 1.43 - 1.62 (m, 4 H) 1.66 (d, J=12.98 Hz, 1 H) 1.83 (d, J=11.81 Hz, 1 H) 2.79 - 2.92 (m, 1 H) 3.09 (d, J=6.35 Hz, 2 H) 3.45 - 3.53 (m, 2 H) 3.64 - 3.78 (m, 1 H) 4.13 (d, J=5.03 Hz, 1 H) 7.13 - 7.34 (m, 5 H) 7.36 - 7.45 (m, 2 H) 7.53 (d, J=8.20 Hz, 2 H) 7.57 - 7.68 (m, 4 H) 8.24 (t, J=5.52 Hz, 1 H) 8.33 (br. s., 3 H)
116	1H NMR (400 MHz, DMSO-d6): δ ppm 0.85 - 1.10 (m, 1 H) 1.24 - 1.73 (m, 6 H) 1.90 - 2.04 (m, 1 H) 2.05 - 2.21 (m, 1 H) 2.83 (td, J=9.53, 5.49 Hz, 1 H) 2.97 - 3.19 (m, 2 H) 3.39 - 3.58 (m, 1 H) 3.59 - 3.75 (m, 1 H) 4.21 (d, J=5.42 Hz, 1 H) 7.28 (dd, J=8.27, 2.56 Hz, 4 H) 7.30 - 7.38 (m, 1 H) 7.44 (t, J=7.64 Hz, 2 H) 7.57 (d, J=8.25 Hz, 2 H) 7.61 - 7.65 (m, 2 H) 7.69 (s, 2 H) 8.16 - 8.34 (m, 4 H)
117	1H NMR (400 MHz, DMSO-d6): δ ppm.45 - 1.61 (m, 1 H) 1.63 - 1.95 (m, 4 H) 2.09 - 2.21 (m, 1 H) 2.55 - 2.71 (m, 1 H) 2.94 - 3.04 (m, 1 H) 3.05 - 3.19 (m, 2 H) 3.28 - 3.44 (m, 1 H) 3.46 - 3.59 (m, 1 H), 4.15 - 4.30 (m, 1 H) 7.20 - 7.38 (m, 5 H) 7.39 - 7.48 (m, 2 H) 7.57 (d, J=8.25 Hz, 2 H) 7.64 (d, J=1.32 Hz, 2 H) 7.73 (d, J=8.25 Hz, 2 H) 8.26 (d, J=3.66 Hz, 3 H) 8.34 (t, J=5.59 Hz, 1 H)
118	1H NMR (400 MHz, DMSO-d6): δ ppm 0.75 (d, J=6.64 Hz, 1 H) 0.78 - 0.86 (m, 2 H) 0.87 - 1.01 (m, 4 H) 1.32 - 1.54 (m, 1 H) 1.64 - 1.83 (m, 1 H) 3.02 (dd, J=17.84, 7.44 Hz, 1 H) 3.13 (d, J=5.52 Hz, 2 H) 3.56 (d, J=6.20 Hz, 1 H) 3.70 (dd, J=12.74, 5.91 Hz, 1 H) 4.16 (br. s., 1 H) 7.20 - 7.38 (m, 5 H) 7.44 (t, J=7.15 Hz, 2 H) 7.57 (d, J=7.86 Hz, 2 H) 7.61 - 7.77 (m, 4 H) 8.15 - 8.59 (m, 4 H)
119	1H NMR (400 MHz, DMSO-d6): δ ppm 0.78 (s, 9 H) 1.54 - 1.82 (m, 2 H) 3.12 (br. s., 3 H) 3.36 (br. s., 2 H) 4.23 (br. s., 1 H) 7.33 (dd, J=12.18, 7.98 Hz, 6 H) 7.44 (t, J=7.57 Hz, 2 H) 7.62 (dd, J=19.96, 7.71 Hz, 4 H) 7.73 (d, J=8.00 Hz, 2 H) 8.27 (br. s., 3 H) 8.46 (br. s., 1 H)
120	1H NMR (400 MHz, DMSO-d6): δ ppm 0.76 (t, J=7.35 Hz, 3 H) 1.49 - 1.68 (m, 1 H) 1.69 - 1.87 (m, 1 H) 2.83 - 2.97 (m, 1 H) 3.16 (d, J=6.20 Hz, 2 H) 3.48 - 3.58 (m, 2 H) 4.18 (br. s., 1 H) 7.26 - 7.38 (m, 5 H) 7.45 (t, J=7.64 Hz, 2 H) 7.53 - 7.70 (m, 4 H) 7.76 (d, J=8.25 Hz, 2 H) 8.41 (br. s., 3 H) 8.48 (t, J=5.56 Hz, 1 H)
121	1H NMR (400 MHz, DMSO-d6): δ ppm 0.94 - 1.13 (m, 1 H) 1.15 - 1.34 (m, 2 H) 1.66 - 1.93 (m, 2 H) 2.76 - 2.91 (m, 1 H) 2.96 - 3.33 (m, 4 H) 3.41 - 3.58 (m, 1 H) 3.72 (d, J=7.52 Hz, 2 H) 3.82 (d, J=9.27 Hz, 1 H) 4.17 (d, J=5.32 Hz, 1 H) 7.17 -

	7.34 (m, 5 H) 7.40 (t, J=7.47 Hz, 2 H) 7.48 - 7.75 (m, 6 H) 8.07 - 8.34 (m, 4 H)
122	1H NMR (400 MHz, DMSO-d6): δ ppm 0.83 (dd, J=6.52, 2.22 Hz, 6 H) 1.28 - 1.41 (m, 1 H) 1.42 - 1.54 (m, 1 H) 1.55 - 1.68 (m, 1 H) 2.98 - 3.12 (m, 2 H) 3.12 - 3.20 (m, 2 H) 3.34 - 3.48 (m, 2 H) 3.90 (t, J=5.95 Hz, 1 H) 7.25 - 7.38 (m, 5 H) 7.40 - 7.49 (m, 2 H) 7.60 (d, J=8.25 Hz, 2 H) 7.65 (d, J=1.32 Hz, 2 H) 7.73 (d, J=8.30 Hz, 2 H) 8.43 (t, J=5.52 Hz, 1 H)
123	1H NMR (400 MHz, MeOH-d4): δ ppm 2.00 (br. s., 3 H) 3.10 (d, J=4.98 Hz, 2 H) 3.63 - 4.17 (m, 4 H) 7.04 - 7.93 (m, 13 H)
124	1H NMR (400 MHz, DMSO-d6): δ ppm 0.76 (t, J=7.22 Hz, 3 H) 1.00 - 1.14 (m, 2 H) 1.15 - 1.32 (m, 2 H) 1.45 - 1.62 (m, 1 H) 1.62 - 1.78 (m, 1 H) 2.86 - 2.99 (m, 1 H) 3.00 - 3.16 (m, 2 H) 3.30 - 3.55 (m, 2 H) 4.18 (q, J=5.40 Hz, 1 H) 7.20 - 7.34 (m, 5 H) 7.40 (t, J=7.64 Hz, 2 H) 7.56 (d, J=8.25 Hz, 2 H) 7.58 - 7.65 (m, 2 H) 7.71 (d, J=8.25 Hz, 2 H) 8.21 (br. d, J=4.00 Hz, 3 H) 8.40 (t, J=5.52 Hz, 1 H)
125	1H NMR (400 MHz, DMSO-d6): δ ppm 1.69 - 1.85 (m, 1 H) 1.92 - 2.11 (m, 1 H) 2.19 - 2.33 (m, 2 H) 2.36 - 2.47 (m, 2 H) 3.03 (dd, J=14.30, 7.08 Hz, 1 H) 3.17 (dd, J=14.06, 5.42 Hz, 1 H) 3.60 (d, J=6.10 Hz, 2 H) 3.82 (t, J=6.17 Hz, 1 H) 7.26 (d, J=8.30 Hz, 2 H) 7.29 - 7.39 (m, 3 H) 7.45 (t, J=7.66 Hz, 2 H) 7.55 - 7.68 (m, 4 H) 7.75 (d, J=8.20 Hz, 2 H) 8.35 (t, J=6.25 Hz, 1 H)
126	1H NMR (400 MHz, DMSO-d6): δ ppm 1.25 (d, J=7.0 Hz, 3 H) 2.97 - 3.06 (m, 1 H) 3.14 (ddd, J=13.7, 6.8, 6.6 Hz, 2 H) 3.45 (dd, J=12.6, 6.4 Hz, 2 H) 3.83 (t, J=6.2 Hz, 1 H) 7.34 (t, J=8.9 Hz, 5 H) 7.45 (t, J=7.7 Hz, 2 H) 7.62 (dd, J=15.0, 7.7 Hz, 4 H) 7.76 (d, J=8.3 Hz, 2 H) 8.50 (t, J=5.7 Hz, 1 H)
127	1H NMR (400 MHz, DMSO-d6): δ ppm 0.83 (t, J=7.30 Hz, 3 H) 1.05 - 1.25 (m, 2 H) 1.50 - 1.64 (m, 1 H) 1.64 - 1.76 (m, 1 H) 2.93 - 3.05 (m, 1 H) 3.05 - 3.20 (m, 2 H) 3.35 - 3.58 (m, 2 H) 4.15 - 4.30 (m, 1 H) 7.24 - 7.37 (m, 5 H) 7.44 (t, J=7.61 Hz, 2 H) 7.59 (d, J=8.20 Hz, 2 H) 7.64 (s, 2 H) 7.75 (d, J=8.25 Hz, 2 H) 8.25 (d, J=3.61 Hz, 3 H) 8.44 (t, J=5.44 Hz, 1 H)
128	1H NMR (400 MHz, DMSO-d6): δ ppm 0.74 - 0.85 (m, 2 H) 0.95 - 1.06 (m, 2 H) 3.07 (m, J=1.00, 1.00 Hz, 1 H) 3.17 (m, J=1.00, 1.00 Hz, 1 H) 3.60 (d, J=5.95 Hz, 2 H) 3.95 (t, J=6.39 Hz, 1 H) 7.29 - 7.36 (m, 3 H) 7.37 - 7.49 (m, 4 H) 7.57 (d, J=8.35 Hz, 2 H) 7.59 - 7.66 (m, 2 H) 7.78 (d, J=8.25 Hz, 2 H) 8.42 (t, J=5.76 Hz, 1 H)
129	1H NMR (400 MHz, MeOH-d4): δ ppm 7.82-7.84(d, J = 8.5 Hz, 2H),7.64-7.65(d, J = 7.5 Hz, 1H),7.38-7.42(m, 5H),7.33-7.35(d, J = 8.0 Hz, 1H),7.24-7.27 (m, 3H),7.18-7.19(m, 1H), 4.61 (m, 1H),4.30-4.31(m, 1H),3.81(m, 1H),3.36-3.37 (m, 1H) ,2.22-2.24 (m, 1H), 2.52-2.54(t, J = 6.5 Hz, 2H), 2.35-2.37-7.35(t, J = 3.5 Hz, 2H)
130	1H NMR (400 MHz, DMSO-d6): δ ppm 1.18 (d, J=6.6 Hz, 3 H) 2.79 (dd, J=13.6, 6.4 Hz, 1 H), 2.94 (dd, J=13.5, 7.8 Hz, 1 H) 3.16 (d, J=6.3 Hz, 2 H) 4.20 (ddd, J=8.4, 4.1, 4.0 Hz, 1 H) 4.23 -4.34 (m, 1 H), 7.34 (dd, J=7.9, 1.8 Hz, 5 H) 7.43 (t, J=7.6 Hz, 2 H) 7.57 (d, J=8.2 Hz, 2 H) 7.62 (d, J=7.2 Hz, 2 H) 7.80 (dd, J=8.2, 1.7 Hz, 2 H) 8.34 (d, J=8.2 Hz, 4 H)
131	1H NMR (400 MHz, TFA-d1): δ ppm 7.63-7.62 (d, J = 8.5 Hz, 2H),7.48-7.15 (m, 11H), 4.60(d, J = 2.5 Hz, 1H), 3.94-3.92 (d, J = 7.0 Hz, 2H), 3.56-3.55 (m, 1H), 3.39-3.37 (m, 1H),3.08-3.05 (t, J = 6.5 Hz, 2H)
132	1H NMR (400 MHz, DMSO-d6): δ ppm 3.02 (q, J=7.3 Hz, 3 H) 3.16 (dd, J=14.0, 5.9 Hz, 1 H), 3.59 (q, J=6.8 Hz, 2 H) 3.95 (br. s., 1 H) 7.33 (d, J=8.2 Hz, 2 H) 7.39 -

	7.51 (m, 3 H) 7.78 (d, J=8.2 Hz, 3 H), 7.82 - 7.90 (m, 3 H) 8.57 (t, J=5.6 Hz, 1 H)
133	1H NMR (400 MHz, DMSO-d6): δ ppm 1.33 (s, 6 H) 3.01 (dd, J=14.25, 7.37 Hz, 1 H) 3.12 - 3.20 (m, 1 H) 3.50 (d, J=6.25 Hz, 2 H) 3.77 (t, J=5.56 Hz, 1 H) 7.29 - 7.39 (m, 3 H) 7.45 (t, J=7.64 Hz, 2 H) 7.51 (d, J=8.49 Hz, 2 H) 7.58 - 7.69 (m, 4 H) 7.76 (d, J=8.20 Hz, 2 H) 8.23 (t, J=6.22 Hz, 1 H)
134	ND (not determined)
135	1H NMR (400 MHz, MeOH-d4): δ ppm 1.17 - 1.64 (m, 4 H) 2.48 - 2.71 (m, 2 H) 3.10 - 3.25 (m, 3 H) 3.31 - 3.41 (m, 1 H) 4.28 (dd, J=7.61, 5.81 Hz, 1 H) 6.98 - 7.47 (m, 11 H) 7.68 - 7.82 (m, 2 H)
136	1H NMR (400 MHz, DMSO-d6): δ ppm 2.96 (t, J=6.81 Hz, 2 H) 3.05 - 3.22 (m, 2 H) 3.52 - 3.63 (m, 2 H) 4.24 (d, J=4.49 Hz, 1 H) 7.34 (d, J=8.30 Hz, 2 H) 7.41 - 7.56 (m, 3 H) 7.79 (d, J=8.30 Hz, 2 H) 7.90 (dd, J=8.20, 2.05 Hz, 1 H) 7.95 - 8.01 (m, 1 H) 8.01 - 8.08 (m, 2 H) 8.29 (br. s., 3 H) 8.53 - 8.64 (m, 2 H)
137	1H NMR (400 MHz, DMSO-d6): δ ppm 2.87-2.93 (m, 1H), 3.17 (dd, J=4.0 Hz, 14.4Hz, 2H), 3.38-3.51 (m, 8H), 3.45-3.48 (m, 1H), 4.58-4.61 (m, 2H), 7.32-7.38 (m, 3H), 7.43-7.48 (m, 4H), 7.67 (d, J=8.0 Hz, 4H), 7.77 (d, J=8.0 Hz, 2H), 8.51 (t, J=5.6 Hz, 1H)
138	1H NMR (400 MHz, DMSO-d6): δ ppm 2.90 (t, J=6.4 Hz, 3H), 3.17 (dd, J=4.0 Hz, 14Hz, 2H), 3.53 (t, J=6 Hz, 3H), 7.28 (d, J=8.0 Hz, 1H), 7.33 (d, J=8.4 Hz, 3H), 7.37-7.41 (m, 3H), 7.44-7.48 (m, 3H), 7.76 (d, J=7.6 Hz, 2H), 8.55 (t, J=6.0 Hz, 1H)
139	1H NMR (400 MHz, DMSO-d6): δ ppm 2.84-2.93 (m, 3 H), 3.15-3.20 (m, 1 H), 3.44-3.51 (m, 2 H), 3.90(s, 3 H), 7.15-7.23 (m, 3 H), 7.32-7.37 (m, 3 H), 7.43-7.47 (m, 2 H), 7.67 (d, J=7.2 Hz, 2 H), 7.76 (d, J=8.0Hz, 2 H), 8.50 (t, J=5.6 Hz, 1 H)
140	1H NMR (400 MHz, DMSO-d6): δ ppm 1.26 (s, 9 H) 2.80 (t, J=7.5 Hz, 2 H) 3.16 (d, J=6.5 Hz, 2H) 3.40 - 3.51 (m, 2 H) 4.17 - 4.28 (m, 1 H) 7.16 (d, J=8.3 Hz, 2 H) 7.27 - 7.38 (m, 4 H) 7.81 (d, J=8.3 Hz,2 H) 8.37 (d, J=3.5 Hz, 3 H) 8.58 (t, J=5.6 Hz, 1 H)
141	1H NMR (400 MHz, DMSO-d6): δ ppm 0.82 (dd, J=15.57, 6.64 Hz, 12 H) 2.30 - 2.43 (m, 2 H) 3.12 (d, J=6.25 Hz, 2 H) 3.95 (t, J=5.34 Hz, 2 H) 4.14 (br. s., 1 H) 7.27 - 7.35 (m, 3 H) 7.36 - 7.51 (m, 4 H) 7.51 - 7.77 (m, 7 H) 8.38 (br. s., 3 H)
142	ND (not determined)
143	1H NMR (400 MHz, DMSO-d6): δ ppm 3.22 (dd, J=5.9, 4.2 Hz, 2 H) 3.31 (t, J=7.5 Hz, 2 H) 3.53- 3.61 (m, 2 H) 4.13 - 4.20 (m, 1 H) 7.40 (dd, J=16.4, 8.1 Hz, 4 H) 7.49 - 7.61 (m, 2 H) 7.80 (d, J=7.6 Hz, 1 H) 7.84 (d, J=8.2 Hz, 2 H) 7.93 (d, J=8.1 Hz, 1 H) 8.30 (d, J=8.5 Hz, 1 H) 8.61 (d, J=4.0 Hz, 3 H) 8.84 (t, J=5.6 Hz, 1 H)
144	ND (not determined)
145	ND (not determined)
146	1H NMR (400 MHz, MeOH-d4): δ ppm 7.74-7.76 (d, J = 8.5 Hz, 2H), 7.56-7.58 (d, J = 7.5 Hz, 2H),7.51-7.53 (d, J = 7.0 Hz, 2H),7.29-7.42 (m, 7H),4.26-4.31 (m, 2H) ,3.32-3.39 (m, 1H), 3.18-3.23 (m, 1H), 2.96-3.00(dd, J = 13.5, 5.5 Hz, 1H), 2.87-2.92 (dd, J = 13.0, 8.0 Hz, 1H), 1.74-1.78 (m, 1H), 1.64-1.66 (m, 1H), 1.50 (m, 3H)
147	1H NMR (400 MHz, DMSO-d6): δ ppm 3.02 - 3.09 (m, 1 H) 3.19 (dd, J=14.3, 5.6 Hz, 1 H) 3.85 (t, J=6.3 Hz, 1 H) 4.56 (d, J=5.9 Hz, 2 H) 7.30 (d, J=7.7 Hz, 1 H) 7.37 (d, J=8.3 Hz, 3 H) 7.39 -7.42 (m, 1 H), 7.46 (t, J=7.6 Hz, 2 H) 7.53 (d, J=7.9 Hz, 1 H) 7.59 - 7.64 (m, 3 H) 7.87 (d, J=8.3 Hz, 2 H) 9.09 (t, J=6.0 Hz, 1 H)
148	1H NMR (400 MHz, MeOH-d4): δ ppm 1H NMR 8.18 (s, 1H), 7.74 – 7.66 (m, 7H),

	7.57 (t, J = 7.9 Hz, 2H), 7.46 – 7.31 (m, 5H), 3.66 (t, J = 7.3 Hz, 3H), 3.47 (dd, J = 7.9, 4.9 Hz, 2H), 3.13 (dd, J = 13.4, 4.9 Hz, 2H), 3.06 (t, J = 7.3 Hz, 3H), 2.84 (dd, J = 13.4, 7.9 Hz, 2H)
149	1H NMR (400 MHz, MeOH-d4): δ ppm 7.78 (d, J = 7.8 Hz, 2H), 7.65 (d, J = 7.7 Hz, 2H), 7.43 – 7.31 (m, 4H), 7.30 (s, 1H), 7.21 (t, J = 7.5 Hz, 1H), 3.80 (dd, J = 8.6, 4.6 Hz, 1H), 3.75 (t, J = 7.1 Hz, 2H), 3.39 – 3.31 (m, 2H), 3.30 (s, 2H), 3.08 (q, J = 8.1, 7.2 Hz, 3H), 1.28 (s, 1H)
150	1H NMR (400 MHz, DMSO-d6): δ ppm 8.53 (d, J = 6.6 Hz, 1H), 8.28 (s, 2H), 7.78 (d, J = 7.8 Hz, 2H), 7.34 (q, J = 7.6 Hz, 4H), 7.23 (d, J = 8.1 Hz, 2H), 6.93 (dd, J = 11.6, 8.2 Hz, 4H), 4.22 (s, 1H), 3.50-3.42 (m, 2H), 3.13 (d, J = 5.1 Hz, 2H), 2.81 (t, J = 7.4 Hz, 2H)
151	1H NMR (400 MHz, MeOH-d4): δ ppm 7.55 (dd, *J* = 19.2, 7.7 Hz, 3H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.29 (dd, *J* = 20.6, 7.7 Hz, 4H), 3.93 – 3.85 (m, 2H), 3.76 – 3.68 (m, 1H), 3.31 (s, 3H), 2.99 (dt, *J* = 11.0, 6.2 Hz, 2H), 1.01 (s, 6H)
152	1H NMR (400 MHz, DMSO-d6): δ ppm 7.65 (d, J = 8.0 Hz, 2H), 7.56 (t, J = 8.3 Hz, 3H), 7.44 – 7.22 (m, 9H), 7.16 (t, J = 7.2 Hz, 2H), 4.50 – 4.33 (m, 3H), 4.23 – 4.07 (m, 6H), 3.91 (d, J = 8.1 Hz, 2H), 3.09 (d, J = 6.6 Hz, 2H), 3.01 (s, 1H), 1.19 (s, 1H)
152a	1H NMR (400 MHz, DMSO-d6): δ ppm 8.34 (dd, *J* = 12.1, 6.5 Hz, 4H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.65 – 7.52 (m, 4H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 5H), 4.25 (m, 2H), 3.13 (d, *J* = 6.4 Hz, 2H), 2.92 (dd, *J* = 13.4, 7.8 Hz, 1H), 2.77 (dd, *J* = 13.5, 6.2 Hz, 1H), 1.17 (d, *J* = 6.6 Hz, 3H)

Example 153: (S)-2-amino-3-(4-((3-(2-(isoquinolin-7-yl)phenyl)propyl) carbamoyl)phenyl)propanoic acid



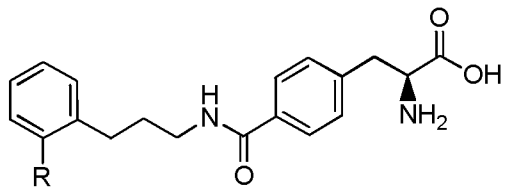
Step 1: A solution of (S)-2-amino-3-(4-((3-(2-bromophenyl)propyl) carbamoyl) phenyl)propanoic acid (Example 145, 140 mg, 0.27 mmol), CsOAc (99 mg, 0.51 mmol), $Pd(dppf)Cl_2$ (38 mg, 0.051 mmol) and isoquinolin-7-ylboronic acid (88 mg, 0.51 mmol) in THF (3 mL) was purged with N_2 and then heated to 90 °C for 3 h. After this time, the reaction was cooled to RT and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexanes:ethyl acetate/4:1) provided (S)-ethyl 2-((tert-butoxycarbonyl)amino)-3-(4-((3-(2-(isoquinolin-7-yl)phenyl)propyl)carbamoyl)phenyl)propanoate as an off-white solid.

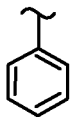
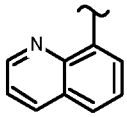
Step 2: To a 0 °C solution of (S)-ethyl 2-((tert-butoxycarbonyl)amino)-3-(4-((3-(2-(isoquinolin-7-yl)phenyl)propyl)carbamoyl)phenyl)propanoate (100 mg, 0.17 mmol) in CH_2Cl_2 (5 mL), was added dropwise TFA (1.2 mL). The reaction was warmed to RT for 3 h, then concentrate *in vacuo*. To the resulting residue was added saturated aqueous solution of $NaHCO_3$ to adjust the pH to ~7.5 and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide (S)-ethyl 2-amino-3-(4-((3-(2-(isoquinolin-7-yl)phenyl)propyl)carbamoyl)phenyl)propanoate as an off-white solid that was used without further purification.

Step 3: To a 0 °C solution of (S)-ethyl 2-amino-3-(4-((3-(2-(isoquinolin-7-yl)phenyl)propyl)carbamoyl)phenyl)propanoate (75 mg, 0.16 mmol) in MeOH (6 mL), was added dropwise 5 N NaOH (2 mL) and then the reaction mixture was warmed to RT for 3 h. After this time, the reaction mixture was acidified with 3N HCl to adjust the pH to 6-7, the MeOH was removed *in vacuo* and the resultant solid was filtered, washed with H_2O, and dried *in vacuo* to provide the title compound as a white solid. LCMS (M+H): 453.53.

The following compounds in Table 6a were prepared as described above for Example 153 using the appropriate boronic acid. NMR data is provided in Table 6b.

Table 6a



Ex. No.	R	Name	LCMS (MH+)
154		(S)-3-(4-((3-([1,1'-biphenyl]-2-yl)propyl)carbamoyl)phenyl)-2-aminopropanoic acid	402.49
155		(S)-2-amino-3-(4-((3-(2-(quinolin-8-yl)phenyl)propyl)carbamoyl)phenyl)propanoic acid	453.53

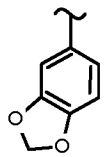
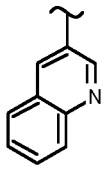
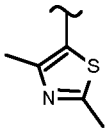
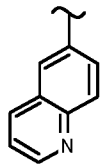
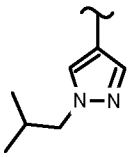
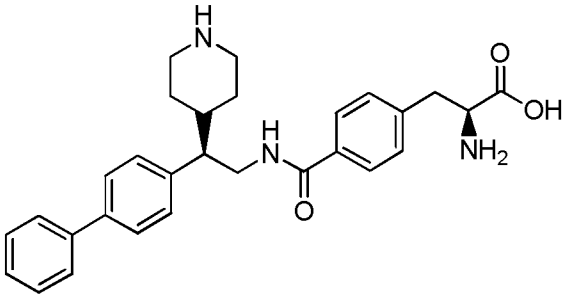
156		(S)-2-amino-3-(4-((3-(2-(benzo[d][1,3]dioxol-5-yl)phenyl)propyl)carbamoyl)phenyl)propanoic acid	446.50
157		(S)-2-amino-3-(4-((3-(2-(quinolin-3-yl)phenyl)propyl)carbamoyl)phenyl)propanoic acid	453.53
158		(S)-2-amino-3-(4-((3-(2-(2,4-dimethylthiazol-5-yl)phenyl)propyl)carbamoyl)phenyl)propanoic acid	438.55
159		(S)-2-amino-3-(4-((3-(2-(quinolin-6-yl)phenyl)propyl)carbamoyl)phenyl)propanoic acid	454.53
160		(S)-2-amino-3-(4-((3-(2-(1-isobutyl-1H-pyrazol-4-yl)phenyl)propyl)carbamoyl)phenyl)propanoic acid	449.56

Table 6b

Ex. No.	^{1}H NMR
154	1H NMR (400 MHz, DMSO-d6): δ ppm 1.68 (quin, J=7.6 Hz, 2 H) 2.57 (d, J=8.1 Hz, 2 H) 3.15 (dd, J=12.5, 6.1 Hz, 4 H) 4.21 (br. s., 1 H) 7.15 (dd, J=7.5, 1.0 Hz, 1 H) 7.23 - 7.28 (m, 2 H) 7.29 (d, J=1.7 Hz, 2 H) 7.34 (dd, J=4.1, 2.3 Hz, 4 H) 7.36 - 7.41 (m, 2 H) 7.74 (d, J=8.3 Hz, 2 H) 8.33 - 8.46 (m, 4 H) 13.87 (br. s., 1 H)

Example 160: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(piperidin-4-yl)ethyl) carbamoyl)phenyl)-2-aminopropanoic acid



Step 1: To a solution of ethyl 2-(4-bromophenyl)acetate (CAS#: 77143-76-1, 38 g, 0.16 mol) in DMF (380 mL), NaH (6.9 g,0.173 mol, 60% in oil) was added at -20 °C over 1 h and then the mixture was stirred at the same temperature for 2 h. After this time, tert-butyl 4-iodopiperidine-1-carboxylate (CAS#: 301673-14-3, 53.5 g,0.17 mol) was added dropwise at -10 °C. After addition, the mixture was stirred at RT for 12 h, then poured into ice/water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated, then purified by silica gel chromatography to provide tert-butyl 4-(1-(4-bromophenyl)-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (60 g) as an off-white solid.

Step 2: To a solution of tert-butyl 4-(1-(4-bromophenyl)-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (65 g, 0.15 mol) in ethanol //water (600 mL,v/v=1:1), KOH (25.70 g,0.458 mol) was added at RT and then the mixture was stirred at the same temperature for 12 h. The mixture was concentrated and adjusted pH=2. The solid was filtered, washed with water and dried under vacuum to provide 2-(4-bromophenyl)-2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid as a white solid.

Step 3: To a solution of 2-(4-bromophenyl)-2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid (10 g, 0.025 mol) in DMF (100 mL) was added (R)-1-phenylethanamine (1.52 g, 0.013 mol) and the mixture was stirred at RT for 1h. The solid was filtered, washed with water and dried under vacuum to provide (R)-1-phenylethanamine (R)-2-(4-bromophenyl)-2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetate. The salt was dissolved in water, and the pH adjusted to 2 by the slow addition of HCl, and then then extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum to provide (R)-2-(4-bromophenyl)-2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid as a white solid (98% ee by HPLC).

Step 4: To a solution of (R)-2-(4-bromophenyl)-2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid (4.5 g, 11.2 mmol) in THF (400 mL) was added a solution of $(Boc)_2O$ (3.20 g,14.7

mmol) in THF (50 mL) at 0°C over 30 min and then pyridine (581 mg,7.3 mmol) and NH_4CO_3 (1.16 g, 14.6 mmol) was added at 0°C. The mixture was warmed to RT and stirred for 12 h, then poured into water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to provide (R)-tert-butyl 4-(2-amino-1-(4-bromophenyl)-2-oxoethyl)piperidine-1-carboxylate as an off-white solid.

Step 5: To a solution of (R)-tert-butyl 4-(2-amino-1-(4-bromophenyl)-2-oxoethyl)piperidine-1-carboxylate (2 g, 5.1 mmol) in CH_2Cl_2 (20 mL) was added TFA (5 mL) dropwise at 0°C. The mixture was warmed to RT and then stirred for 2h, and then concentrated and dissolved in acetonitrile (2 mL).To the mixture was added sequenatlly K_2CO_3 (2.1 g , 15.1 mmol) and BnBr (0.95 g,5.5 mmol) and the resulting mixture was warmed to RT and stirred for 12 h. After this time the mixture was diluted with water and extracted with ethyl acetate, the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to provide (R)-2-(1-benzylpiperidin-4-yl)-2-(4-bromophenyl)acetamide as a white solid.

Step 6: A solution of (R)-2-(1-benzylpiperidin-4-yl)-2-(4-bromophenyl)acetamide (1.8 g,, 3.5 mmol) in THF (18 mL) was cooled to 0°C and a solution of borane in THF (1M/20 mL) was added dropwise. The resulting mixture was warmed to RT and then heated at reflux for 12 h. After this time, the reaction was cooled to RT and concentrated *in vacuo*. The residue was dissolved in 6 N HCl (20 mL), and then heated at 70°C for 3 h after which the reaction was cooled to RT and concentrated *in vacuo*. The residue was dissolved in methanol and then triethyl amine (1.7 g ,17.4 mmol) and $(Boc)_2O$ (3.8 g,17.431) were added. The mixture was stirred at RT for 12 h, then diluted with water and extracted with CH_2Cl_2.The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to provide (R)-tert-butyl (2-(1-benzylpiperidin-4-yl)-2-(4-bromophenyl)ethyl) carbamate as a light yellow semi-solid.

Step 7: To a solution of (R)-tert-butyl (2-(1-benzylpiperidin-4-yl)-2-(4-bromophenyl)ethyl) carbamate (700 mg, 1.5 mmol) in CH_2Cl_2, was added TFA (2 mL) and the reaction was stirred for 2 h. After this time the mixture was concentrated *in vacuo* and the residue was dissolved in DMF cooled to 0°C followed by the sequential addition of Intermediate A (500 mg, 1.5 mmol), triethyl amine (751 mg, 7.4 mmol) and HATU (1.13 g, 2.9 mmol). The mixture was stirred at RT for 12 h, then diluted with water and extracted with CH_2Cl_2. The

combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to provide (S)-ethyl 3-(4-(((R)-2-(1-benzylpiperidin-4-yl)-2-(4-bromophenyl)ethyl)carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate as a yellow solid.

Step 8: To a solution of (S)-ethyl 3-(4-(((R)-2-(1-benzylpiperidin-4-yl)-2-(4-bromophenyl) ethyl)carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (900 mg, 1.3 mmol) was added phenylboronic acid (317 mg, 2.6 mmol) and $Pd(dppf)Cl_2$ (95 mg, 0.13 mmol) in dioxane (9.0 mL) /aq.$NaCO_3$ (2M,3.0 mL) and refluxed for 3 h. After this time, the reaction was cooled to RT, diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to provide (S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(1-benzylpiperidin-4-yl)ethyl)carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate as an off-white solid.

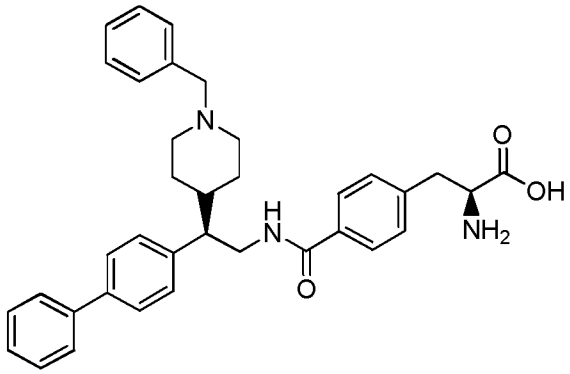
Step 9: A solution of (S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(1-benzylpiperidin-4-yl)ethyl)carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (600 mg, 0.87 mmol) in ethanol (6 mL) was heated at 50 °C under 50 psi H_2 for 12 h. After this time, the mixture was filtered, concentrated and purified by flash to provide 300 mg intermediate. The intermediate (150 mg) was dissolved in $CH_2Cl_2$and triethyl amine and $(Boc)_2O$ stirred at rt overnight. The mixture was concentrated and purified by silica gel chromatography to provide tert-butyl 4-((R)-1-([1,1'-biphenyl]-4-yl)-2-(4-((S)-2-((tert-butoxycarbonyl)amino)-3-ethoxy-3-oxopropyl) benzamido)ethyl)piperidine-1-carboxylate as a white solid.

Step 10: To a 0 °C solution of tert-butyl 4-((R)-1-([1,1'-biphenyl]-4-yl)-2-(4-((S)-2-((tert-butoxycarbonyl)amino)-3-ethoxy-3-oxopropyl)benzamido)ethyl)piperidine-1-carboxylate (170 mg, 0.243 mmol) in CH_2Cl_2 (4 mL), TFA(1 mL) was added dropwise at 0 °C for 1 h and then the mixture was concentrated, and the pH adjusted to ~6-7 with saturated aqueous $NaHCO_3$. The mixture was concentrated and purified by Prep-HPLC to afford (S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(piperidin-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoate as a yellow solid.

Step 11: The title compound was prepared as described for (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid (Example 1a, Step 4) via the hydrolysis of (S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(piperidin-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoate.

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.55 (d, J = 7.8 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 4.13 (s, 1H), 3.62 (d, J = 9.9 Hz, 1H), 3.49 (t, J = 11.6 Hz, 1H), 3.08 (d, J = 6.5 Hz, 1H), 2.81 (s, 1H), 1.62 (s, 1H), 1.40 (s, 1H), 1.17 (s, 2H), 1.09 (d, J = 7.5 Hz, 1H), 1.00 – 0.83 (m, 1H), 0.78 (s, 2H), 0.69 (s, 2H). LCMS (MH^+): 434.33.

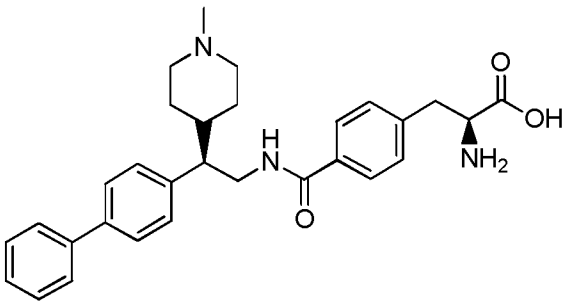
Example 161: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(1-benzylpiperidin-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid



The title compounds was prepared as described above starting from (S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(1-benzylpiperidin-4-yl)ethyl)carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino) propanoate (Example 160, Step 8) and following the procedure as outlined in (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid (Example 1a, Steps 3-4).

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.60 – 7.47 (m, 6H), 7.40 (t, J = 7.6 Hz, 7H), 7.36 – 7.22 (m, 3H), 7.20 (d, J = 8.0 Hz, 2H), 4.10 – 4.00 (m, 3H), 3.71 – 3.55 (m, 1H), 3.54 (s, 1H), 3.04 – 2.89 (m, 1H), 2.90 (s, 1H), 2.00 (d, J = 12.0 Hz, 2H), 1.49 (t, J = 13.9 Hz, 1H), 1.11 (t, J = 7.1 Hz, 1H). LCMS (MH^+): 471.59.

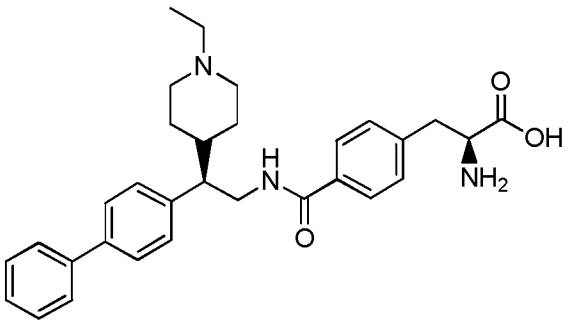
Example 162: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(1-methylpiperidin-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid



The title compound was prepared as described for the compound of Example 160 starting with 4-iodo-1-methylpiperidine (CAS#: 90485-32-8).

^{1}H NMR (400 MHz, MEOH-d4): δ ppm 7.63 – 7.47 (m, 6H), 7.47 – 7.36 (m, 2H), 7.30 (td, *J* = 8.5, 7.9, 1.5 Hz, 5H), 3.91 (dd, *J* = 13.3, 5.5 Hz, 1H), 3.76 – 3.57 (m, 1H), 3.26 (dd, *J* = 14.5, 4.6 Hz, 1H), 3.12 – 2.95 (m, 2H), 2.95 (s, 0H), 2.93 (s, 1H), 2.36 (s, 2H), 2.29 (t, *J* = 11.7 Hz, 1H), 2.21 – 2.05 (m, 2H), 1.76 (d, *J* = 8.3 Hz, 1H), 1.53 (t, *J* = 17.1 Hz, 2H), 1.26 (d, *J* = 18.3 Hz, 1H). LCMS (MH^+): 486.62.

Example 163: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(1-ethylpiperidin-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid

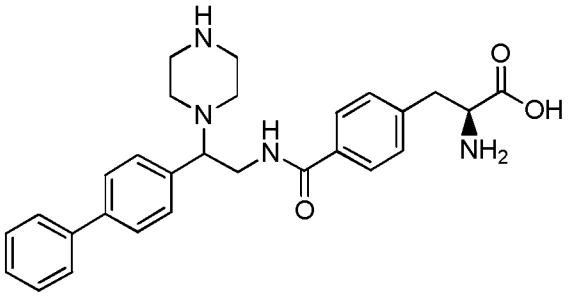


The title compound was prepared as described for the compound of Example 160 starting with 1-ethyl-4-bromopiperidine (CAS#: 90633-19-5).

^{1}H NMR (400 MHz, MEOH-d4): 7.56 (ddd, *J* = 8.1, 6.9, 1.4 Hz, 6H), 7.51 – 7.35 (m, 2H), 7.35 – 7.25 (m, 5H), 3.91 (dd, *J* = 13.3, 5.5 Hz, 1H), 3.68 – 3.57 (m, 1H), 3.22 (dd, *J* = 14.2, 4.7 Hz, 1H), 3.11 (d, *J* = 11.8 Hz, 1H), 3.00 – 2.87 (m, 1H), 2.47 (q, *J* = 7.1 Hz, 1H), 2.18 – 2.06 (m, 1H), 2.07 – 1.95 (m, 1H), 1.76 (d, *J* = 9.0 Hz, 1H), 1.52 (dd, *J* = 27.3, 12.9 Hz, 1H), 1.24 (dd, *J* = 24.3, 12.9 Hz, 1H), 1.09 (t, *J* = 7.2 Hz, 2H).

LCMS (MH^+): 500.64.

Example 164: (2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-(piperazin-1-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid



Step 1: To a 0 °C solution of ethyl 2-bromo-2-(4-bromophenyl)acetate (16.5 g, 93.8 mmol) and TEA (12.3 g, 121.9 mmol) in THF (300 mL), was added 1-benzylpiperazine (30 g, 93.2 mmol). After addition, the mixture was warmed to room temperature and stirred for 12 h, after which time, the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate and washed with aq. $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, concentrated and the residue was purified by silica gel chromatography to provide ethyl 2-(4-benzylpiperazin-1-yl)-2-(4-bromophenyl)acetate as a yellow solid.

Step 2: A solution of ethyl 2-(4-benzylpiperazin-1-yl)-2-(4-bromophenyl)acetate (22 g, 52.8 mmol), phenylboronic acid (7.66 g, 63.3 mmol) and Pd (dppf)Cl_2 (3.86 g, 5.28 mmol) in dioxane (100 mL)/aq. $NaCO_3$ (2.0M, 100 mL) was heated at 80 °C for 12 h, then cooled to room temperature. After this time, the mixture was diluted with water, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to provide ethyl 2-([1,1'-biphenyl]-4-yl)-2-(4-benzylpiperazin-1-yl)acetate as light yellow oil.

Step 3: A solution of ethyl 2-([1,1'-biphenyl]-4-yl)-2-(4-benzylpiperazin-1-yl)acetate (20 g, 48.3 mmol), KOH (8.12 g, 145 mmol) in EtOH/water (60 mL/ 20 mL) was heated at 80 °C for 2 h. After this time, the reaction was cooled to room temperature and the mixture was concentrated, diluted with water and adjusted pH=6-7 with 3 N HCl and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to provide 2-([1,1'-biphenyl]-4-yl)-2-(4-benzylpiperazin-1-yl)acetic acid as a light yellow solid that was used without further purification.

Step 4: To a solution of 2-([1,1'-biphenyl]-4-yl)-2-(4-benzylpiperazin-1-yl)acetic acid (1 g, 2.6 mmol) in CH_2Cl_2 (10 mL) was added $(COCl)_2$ (0.66 g, 5.2 mmol) dropwise at 0 °C. After

the addition, the mixture was stirred at room temperature for 2 h after which time the solvent was removed *in vacuo* to provide 2-([1,1'-biphenyl]-4-yl)-2-(4-benzylpiperazin-1-yl)acetyl chloride as a yellow oil used without further purification.

Step 5: A solution of 2-([1,1'-biphenyl]-4-yl)-2-(4-benzylpiperazin-1-yl)acetyl chloride (1 g, 2.5 mmol) in CH_2Cl_2 (10 mL) was added to 30% aqueous NH_4OH (10 mL).The mixture was stirred for 30 min and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to provide 2-([1,1'-biphenyl]-4-yl)-2-(4-benzylpiperazin-1-yl)acetamide as yellow oil used without further purification.

Step 6: To a solution of 2-([1,1'-biphenyl]-4-yl)-2-(4-benzylpiperazin-1-yl)acetamide (0.8 g, 2.1 mmol) in THF (10 mL) was added BH_3-THF (1N, 15 mL) dropwise at 0 °C. The reaction mixture was warmed to room temperature and then heated to reflux for 12 h. After this time, the reaction mixture was cooled to room temperature, 6N HCl (5 mL) was added and then the reaction mixture was refluxed for 2 h. The mixture was then cooled and concentrated *in vacuo* diluted with water, adjusted pH=7-8 with aqueous $NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, concentrated, and the residue was purified by silica gel chromatography to provide 2-([1,1'-biphenyl]-4-yl)-2-(4-benzylpiperazin-1-yl)ethanamine as a yellow oil.

Step 7: To a solution of 2-([1,1'-biphenyl]-4-yl)-2-(4-benzylpiperazin-1-yl) (400 mg, 1.1 mmol), TEA (222 mg, 2.2 mmol) and Intermediate A (371 mg, 1.1 mmol) in DMF (10 mL) was added HATU (630 mg, 1.6 mmol) at 5 °C. The mixture was stirred at room temperature for 12 h, then diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over Na_2SO_4, concentrated and purified by flash column to provide (2S)-ethyl 3-(4-((2-([1,1'-biphenyl]-4-yl)-2-(4-benzylpiperazin-1-yl)ethyl)carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate as a yellow oil.

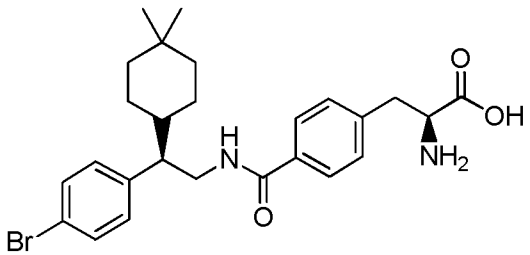
Step 8: A mixture of (2S)-ethyl 3-(4-((2-([1,1'-biphenyl]-4-yl)-2-(4-benzylpiperazin-1-yl)ethyl)carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (450 mg, 0.65 mmol) and 10% $Pd(OH)_2$ on activated carbon (20 mg) in MeOH (10mL) was stirred at room temperature under a hydrogen atmosphere (50 psi) for 12 h. After this time, the reaction mixture was filtered through a Celite pad, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica-gel to provide (2S)-ethyl 3-(4-((2-([1,1'-biphenyl]-

4-yl)-2-(piperazin-1-yl)ethyl)carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate as yellow oil.

Step 9: The title compound was made as described for the compound of Example 1a, Steps 3-4, starting with (2S)-ethyl 3-(4-((2-([1,1'-biphenyl]-4-yl)-2-(piperazin-1-yl)ethyl)carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate.

^{1}H NMR (400 MHz, MEOH-d4): 7.74 – 7.56 (m, 6H), 7.45 – 7.29 (m, 7H), 4.24 (t, J = 6.7 Hz, 1H), 4.10 (dd, J = 13.5, 7.0 Hz, 1H), 3.96 (t, J = 7.4 Hz, 1H), 3.69 (dd, J = 13.5, 7.5 Hz, 1H), 3.21 (m, 4H), 2.89 – 2.81 (m, 6H). LCMS (MH^+): 473.58.

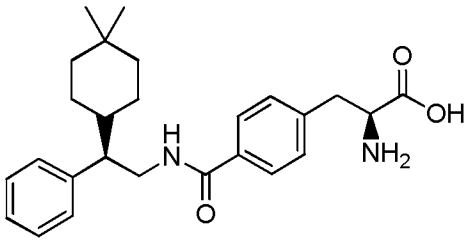
Example 165: (S)-2-amino-3-(4-(((R)-2-(4-bromophenyl)-2-(4,4-dimethylcyclohexyl)ethyl)carbamoyl)phenyl)propanoic acid



The title compound was made as described for the compound of Example 1a starting with (R)-2-(4-bromophenyl)-2-(4,4-dimethylcyclohexyl)ethanamine (Intermediate 50).

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.64 (d, J = 7.9 Hz, 3H), 7.57 (dd, J = 12.6, 7.8 Hz, 6H), 7.40 (t, J = 7.6 Hz, 3H), 4.64 – 4.49 (m, 1H), 4.46 – 4.26 (m, 2H), 4.13 (t, J = 6.4 Hz, 2H), 3.86 – 3.64 (m, 2H), 3.54 (dd, J = 13.3, 8.8 Hz, 2H), 3.24 (d, J = 12.0 Hz, 2H), 3.13 (s, 3H), 3.19 – 3.04 (m, 2H), 2.96 – 2.66 (m, 4H), 2.00 (d, J = 13.2 Hz, 1H), 1.93 – 1.86 (m, 1H), 1.57 (d, J = 13.5 Hz, 2H), 1.47 – 1.33 (m, 1H), 1.27 – 1.15 (m, 1H). LCMS (MH^+): 472.59.

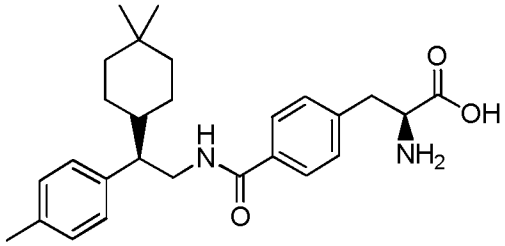
Example 166: (S)-2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-phenylethyl) carbamoyl)phenyl)propanoic acid



The title compound was made as described for the compound of (Example 1a, starting with (R)-2-(4,4-dimethylcyclohexyl)-2-phenylethanamine (Intermediate 55).

^{1}H NMR (400 MHz, DMSO-d6) δ 7.57 (d, J = 8.0 Hz, 2H), 7.28 – 7.18 (m, 4H), 7.13 (dd, J = 7.5, 4.7 Hz, 2H), 5.00 (d, J = 5.7 Hz, 1H), 4.15 (t, J = 6.4 Hz, 1H), 3.67 (dd, J = 13.3, 5.9 Hz, 1H), 3.52 (dd, J = 13.2, 9.5 Hz, 1H), 3.10 (d, J = 6.5 Hz, 1H), 2.83 (q, J = 7.3 Hz, 1H), 1.63 (s, 1H), 1.44 (d, J = 9.4 Hz, 1H), 1.32 (d, J = 8.4 Hz, 1H), 1.21 (d, J = 11.3 Hz, 1H), 1.12 (s, 1H), 0.96 (ddd, J = 28.2, 18.3, 11.1 Hz, 1H), 0.79 (s, 3H), 0.69 (s, 3H). LCMS (MH^+): 423.56.

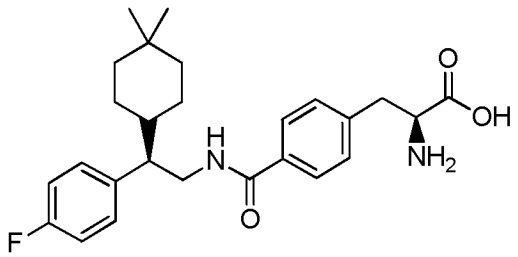
Example 167: (S)-2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(p-tolyl)ethyl) carbamoyl)phenyl)propanoic acid



The title compound was made as described for the compound of Example 1a, starting with (R)-2-(4,4-dimethylcyclohexyl)-2-(p-tolyl)ethanamine (Intermediate 56).

^{1}H NMR (400 MHz, Methanol-d4) δ 7.59 – 7.52 (m, 5H), 7.35 – 7.24 (m, 2H), 7.11 – 6.98 (m, 2H), 2.27 (s, 3H), 1.78 (d, J = 12.5 Hz, 1H), , 1.42 (dd, J = 12.4, 9.0 Hz, 1H), 1.36 – 1.16 (m, 2H), 0.79 (s, 3H), 0.69 (s, 3H)LCMS (MH^+): 437.59

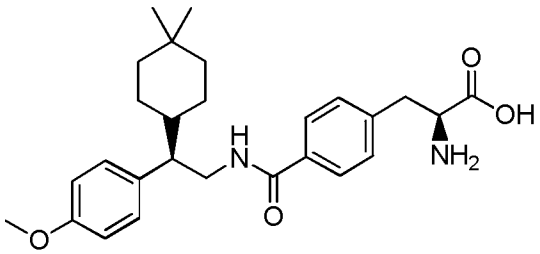
Example 168: (S)-2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(4-fluorophenyl)ethyl)carbamoyl)phenyl)propanoic acid



The title compound was made as described for the compound of Example 1a starting with (R)-2-(4,4-dimethylcyclohexyl)-2-(4-fluorophenyl)ethanamine (Intermediate 57).

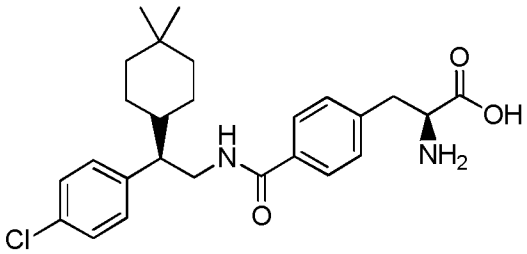
^{1}H NMR (400 MHz, Methanol-d4) δ 7.49 (d, J = 8.3 Hz, 2H), 7.25 – 7.13 (m, 2H), 7.04 – 6.94 (m, 2H), 4.08 (q, J = 7.1 Hz, 1H), 3.85 (dd, J = 13.3, 5.5 Hz, 1H), 3.69 (t, J = 6.7 Hz, 1H), 3.53 (dd, J = 13.3, 10.3 Hz, 1H), 2.99 (td, J = 12.9, 12.2, 6.8 Hz, 1H), 2.96 – 2.78 (m, 1H), 1.80 (d, J = 10.9 Hz, 1H), 1.56 – 1.50 (m, 1H), 1.28 (s, 3H), 1.32 – 1.10 (m, 2H), 1.14 – 0.96 (m, 1H), 0.87 (s, 3H), 0.82 (s, 3H). LCMS (MH^+): 441.55

Example 169: (S)-2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)phenyl)propanoic acid



The title compound was made as described for the compound of Example 1a, starting with (R)-2-(4,4-dimethylcyclohexyl)-2-(4-methoxyphenyl)ethanamine (Intermediate 58). ^{1}H NMR (400 MHz, Methanol-d4) δ 7.49 (d, J = 8.3 Hz, 2H), 7.25 – 7.13 (m, 4H), 7.04 – 6.94 (m, 2H), 4.2 (t, J = 7.1 Hz, 2H), 3.85 (dd, J = 13.3, 5.5 Hz, 1H), 3.69 (t, J = 6.7 Hz, 1H), 3.53 (dd, J = 13.3, 10.3 Hz, 1H), 2.99 (m, 3H), 2.96 – 2.78 (m, 1H), 1.80 (d, J = 10.9 Hz, 1H), 1.56 – 1.50 (t, 3H), 1.28 (s, 3H), 1.32 – 1.10 (m, 2H), 1.14 – 0.96 (m, 1H), 0.87 (s, 3H), 0.82 (s, 3H). LCMS (MH^+): 453.56.

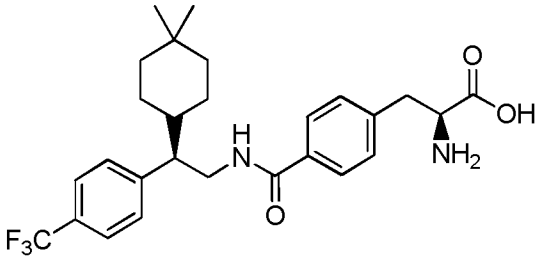
Example 170: (S)-2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(4-chlorophenyl)ethyl)carbamoyl)phenyl)propanoic acid



The title compound was made as described for the compound of Example 1a, starting with (R)-2-(4,4-dimethylcyclohexyl)-2-(4-chlorophenyl)ethanamine (Intermediate 59).

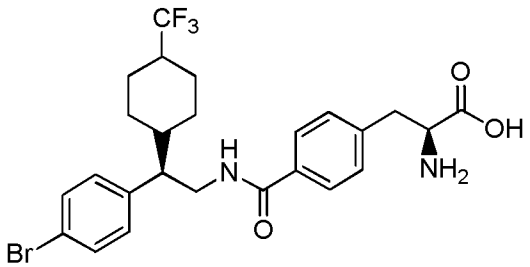
^{1}H NMR (400 MHz, DMSO-d6) δ 7.63 (d, J = 8.0 Hz, 2H), 7.29 (dd, J = 8.2, 5.6 Hz, 4H), 7.18 (d, J = 8.4 Hz, 2H), 3.68 (dd, J = 13.3, 5.6 Hz, 1H), 3.50 (ddd, J = 13.5, 9.2, 5.0 Hz, 1H), 3.15 (d, J = 11.6 Hz, 2H), 2.86 (dt, J = 9.1, 6.5 Hz, 1H), 1.22 (d, J = 12.4 Hz, 1H), 1.21 – 1.10 (m, 1H), 0.87 (s, 3H), 0.79 (s, 3H). LCMS (MH^+): 458.01.

Example 171: (S)-2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(4-trifluoromethylphenyl)ethyl)carbamoyl)phenyl)propanoic acid



The title compound was made as described for the compound of Example 1a, starting with (R)-2-(4,4-dimethylcyclohexyl)-2-(4-trifluoromethylphenyl)ethanamine (Intermediate 60). ^{1}H NMR (400 MHz, Methanol-d4) δ 7.57 (d, J = 8.0 Hz, 2H), 7.51 – 7.44 (m, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.24 – 7.17 (m, 1H), 3.73 – 3.54 (m, 1H), 3.05 – 2.89 (m, 1H), 1.60 (d, J = 9.6 Hz, 1H), 1.28 (dt, J = 22.5, 11.6 Hz, 1H), 0.97 (m, 3H), 0.85 (d, J = 19.3 Hz, 3H). LCMS (MH^+): 491.56.

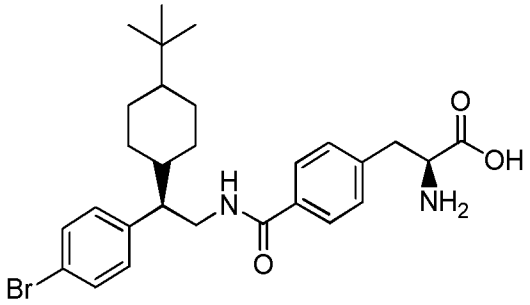
Example 172: (2S)-2-amino-3-(4-(((2R)-2-(4-bromophenyl)-2-(4-(trifluoromethyl)cyclohexyl)ethyl)carbamoyl)phenyl)propanoic acid



The title compound was made as described for the compound of Example 1a, starting with (2R)-2-(4-bromophenyl)-2-(4-(trifluoromethyl) cyclohexyl)ethanamine (Intermediate 62). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 7.69 – 7.65 (m, 1H), 7.42 (m, 5H), 7.25 (m, 2H), 3.72 (dd, J = 13.4, 6.1 Hz, 2H), 3.52 (dd, J = 13.3, 8.9 Hz, 1H), 3.08 (t, J = 5.8 Hz, 2H), 2.86 (q, J = 7.2 Hz, 1H), 2.11 (s, 1H), 2.00 (d, J = 10.0 Hz, 1H), 1.87 (d, J = 12.6 Hz, 1H), 1.78 (d, J = 12.8

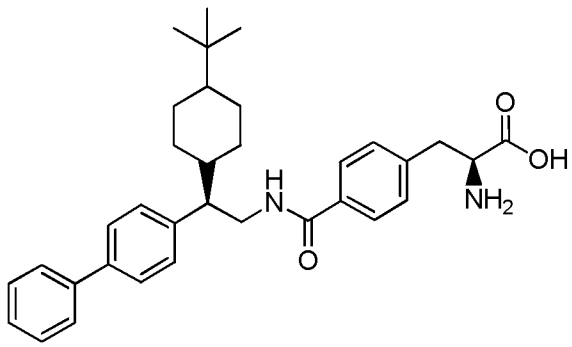
Hz, 1H), 1.61 (d, J = 11.6 Hz, 1H), 1.23 (d, J = 13.4 Hz, 2H), 1.07 (dt, J = 36.1, 11.8 Hz, 1H), 0.93 – 0.79 (m, 2H). LCMS (MH^+): 542.40.

Example 173: (2S)-2-amino-3-(4-(((2R)-2-(4-bromophenyl)-2-(4-(tert-butyl) cyclohexyl)ethyl)carbamoyl)phenyl)propanoic acid



The title compound was made as described for the compound of Example 1a, starting with (2R)-2-(4-bromophenyl)-2-(4-(tert-butyl)cyclohexyl)ethanamine (Intermediate 61). ^1H NMR (400 MHz, DMSO-d6) δ ppm 7 7.61 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 7.12 – 7.04 (m, 2H), 4.19 (t, J = 6.5 Hz, 1H), 3.63 (m, 2H), 3.08 (dd, J = 6.5, 3.9 Hz, 2H), 2.77 (dt, J = 9.3, 6.3 Hz, 1H), 1.90 (d, J = 11.5 Hz, 1H), 1.71 (d, J = 11.4 Hz, 1H), 1.62 (d, J = 10.2 Hz, 1H), 1.49 (d, J = 3.0 Hz, 1H), 1.47 (s, 2H), 1.43 (d, J = 7.5 Hz, 1H), 1.32 (s, 1H), 1.21 (d, J = 6.0 Hz, 1H), 0.97 – 0.75 (m, 14H). LCMS (MH^+): 530.51.

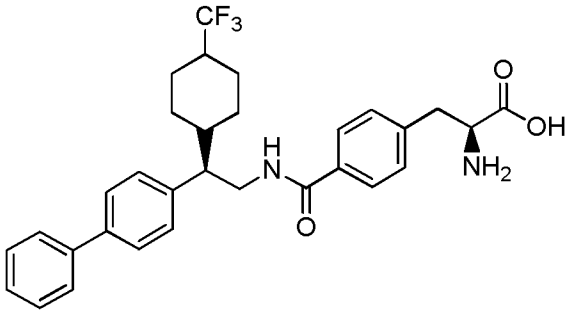
Example 174: (2S)-3-(4-(((2R)-2-([1,1'-biphenyl]-4-yl)-2-(4-(tert-butyl)cyclohexyl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid



The title compound was prepared as described for Example 1a starting with (2R)-2-(4-bromophenyl)-2-(4-(tert-butyl)cyclohexyl)ethanamine (Intermediate 61) and phenyl boronic acid.

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 8.25 (s, 1H), 7.68 – 7.56 (m, 4H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.36 – 7.18 (m, 5H), 3.88 (s, 1H), 3.71 (dt, *J* = 12.0, 5.6 Hz, 1H), 3.60 – 3.48 (m, 1H), 3.11 (dd, *J* = 14.3, 5.7 Hz, 1H), 2.99 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.85 (q, *J* = 7.1 Hz, 1H), 1.93 (s, 1H), 1.72 (s, 1H), 1.63 (s, 1H), 1.51 (s, 1H), 1.21 (s, 1H), 0.91 (dd, *J* = 19.8, 10.1 Hz, 1H), 0.81 (s, 1H), 0.76 (s, 12H). LCMS (MH$^+$): 528.71.

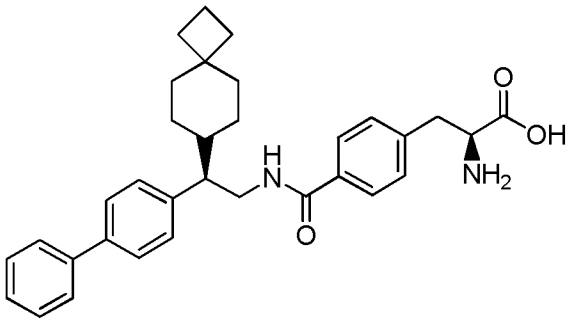
Example 175: (2S)-3-(4-(((2R)-2-([1,1'-biphenyl]-4-yl)-2-(4-(trifluoromethyl) cyclohexyl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid



The title compound was prepared as described for the compound of Example 1a starting with (2R)-2-(4-bromophenyl)-2-(4-(trifluoromethyl)cyclohexyl)ethanamine (Intermediate 62) and phenyl boronic acid.

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.69 – 7.53 (m, 4H), 7.42 (t, J = 7.7 Hz, 2H), 7.36 – 7.20 (m, 2H), 7.19 (m, 4H), 4.20 (t, J = 6.5 Hz, 1H), 3.72 (dd, J = 13.4, 6.1 Hz, 1H), 3.52 (dd, J = 13.3, 8.9 Hz, 1H), 3.08 (t, J = 5.8 Hz, 2H), 2.86 (q, J = 7.2 Hz, 1H), 2.11 (s, 1H), 2.00 (d, J = 10.0 Hz, 1H), 1.87 (d, J = 12.6 Hz, 1H), 1.78 (d, J = 12.8 Hz, 1H), 1.61 (d, J = 11.6 Hz, 1H), 1.23 (d, J = 13.4 Hz, 2H), 1.07 (dt, J = 36.1, 11.8 Hz, 1H), 0.93 – 0.79 (m, 2H). LCMS (MH$^+$): 540.60.

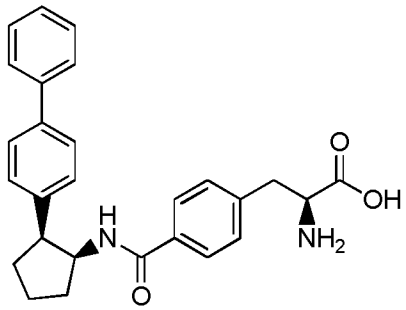
Example 176: (S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(spiro[3.5]nonan-7-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid



The title compound was prepared as described for the compound of Example 1a starting with (R)-2-(4-bromophenyl)-2-(spiro[3.5]nonan-7-yl)ethanamine (Intermediate 63)

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 1H NMR (400 MHz, DMSO-d6) δ 7.62 – 7.50 (m, 6H), 7.41 (t, J = 7.6 Hz, 2H), 7.34 – 7.18 (m, 5H), 4.18 (t, J = 6.4 Hz, 1H), 3.70 (dd, J = 13.2, 5.6 Hz, 1H), 3.48 (dd, J = 13.3, 9.4 Hz, 1H), 3.07 (t, J = 5.2 Hz, 2H), 2.82 (q, J = 7.6 Hz, 1H), 1.72 (q, J = 7.0, 6.2 Hz, 4H), 1.65 – 1.52 (m, 5H), 1.50 (m, 3H), 1.32 – 1.14 (m, 2H), 1.02 (m, 2 H).LCMS (MH^+): 511.67.

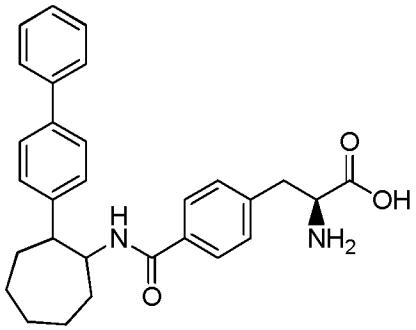
Example 177: (S)-3-(4-(((1S,2S)-2-([1,1'-biphenyl]-4-yl)cyclopentyl) carbamoyl)phenyl)-2-aminopropanoic acid



The title compound was prepared as described for the compound of Example 1a starting with (1S, 2S)-2-(4-bromo)cyclopentylamine (CAS# 1388847-75-3).

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.52 (d, J = 7.9 Hz, 2H), 7.40 (ddd, J = 20.9, 16.1, 7.7 Hz, 6H), 7.27 (d, J = 8.1 Hz, 3H), 7.16 (d, J = 7.7 Hz, 2H), 4.59 (q, J = 6.9 Hz, 1H), 4.08 (d, J = 6.5 Hz, 1H), 3.33 (q, J = 8.3 Hz, 1H), 3.04 (d, J = 6.6 Hz, 2H), 2.04 (dt, J = 17.3, 8.7 Hz, 4H), 1.72 (dq, J = 13.9, 7.6, 7.0 Hz, 2H). LCMS (MH^+): 429.52.

Example 178: (2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)cycloheptyl)carbamoyl)-phenyl)-2-aminopropanoic acid

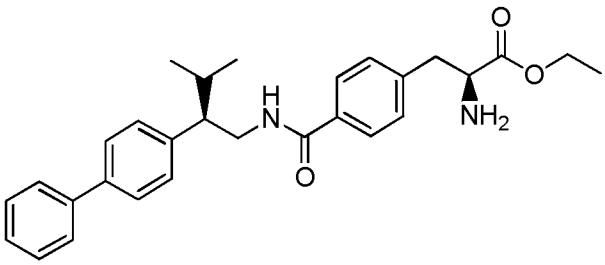


The title compound was prepared as described for the compound of Example 1a starting with 2-(4-chlorophenyl)cyclohexylamine (CAS# 1249261-65-1).

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 7.64 – 7.46 (m, 6H), 7.46 (d, J = 2.4 Hz, 2H), 7.38 (q, J = 9.4, 8.5 Hz, 3H), 7.35 – 7.19 (m, 2H), 4.43 (d, J = 6.3 Hz, 1H), 4.17 (t, J = 6.5 Hz, 1H), 3.94 (m, 1H), 3.17 (m, 2H), 2.32 – 2.21 (m, 1H), 1.89 – 1.78 (m, 6H), 1.48 (s, 2H), 1.45 (m, 3H). LCMS (MH^+): 485.63.

Preparation of prodrugs:

Example P1a: (S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoate



Step 1: To a solution of (S)-4-(2-((tert-butoxycarbonyl)amino)-3-ethoxy-3-oxopropyl)benzoic acid (Intermediate A, 200 mg, 0.82 mmol) in DMF (10 mL) was added (R)-2-(4-bromophenyl)-3-methylbutan-1-amine (Intermediate 44, 278 mg, 1.24 mmol), HATU (623 mg, 1.64 mmol), and TEA (166 mg, 1.64 mmol). The reaction was stirred for 48 h at RT. After this time, the reaction was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexanes:ethyl acetate/4:1 v/v) provided (S)-ethyl 3-(4-

(((R)-2-(4-bromophenyl)-3-methylbutyl)carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate as a white solid.

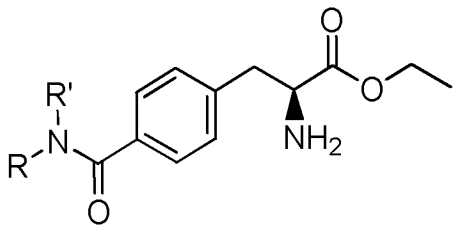
Step 2: To a solution of (S)-ethyl 3-(4-(((R)-2-(4-bromophenyl)-3-methylbutyl) carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (200 mg, 0.36 mmol) in dioxane (5.0 mL)/Na_2CO_3 (2.5 mL, 2.0 M, aq.) was added phenyl boronic acid (66 mg, 0.54 mmol) followed by $Pd(dppf)Cl_2$ (26 mg, 0.036 mmol). The reaction was purged with N_2 and then heated to 90 °C for 3 h. After this time, the reaction was cooled to RT and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via normal phase column chromatography (hexanes:ethyl acetate/4:1 v/v) provided (S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate as an off-white solid.

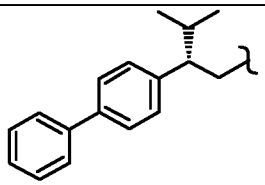
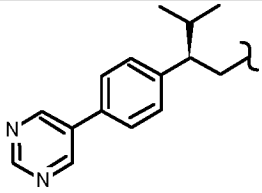
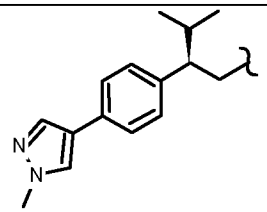
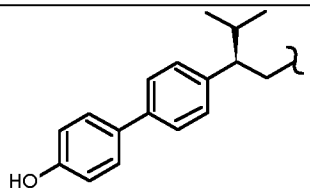
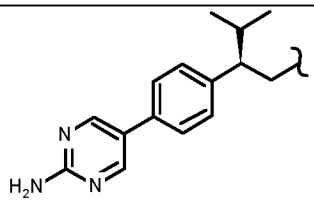
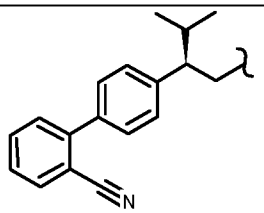
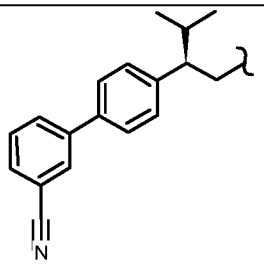
Step 3: To a 0 °C solution of (S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (150 mg, 0.27 mmol) in CH_2Cl_2 (6 mL), was added dropwise TFA (1.5 mL). The reaction was warmed to RT for 3 h, then concentrated *in vacuo*. To the resulting residue was added saturated aqueous solution of $NaHCO_3$ to adjust the pH to ~7.5 and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide (S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoate as an off-white solid.

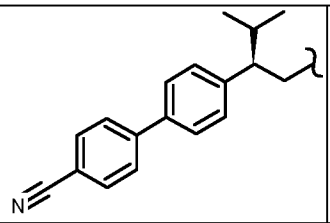
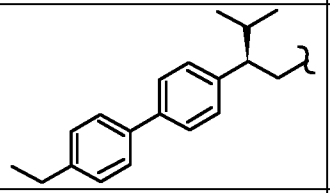
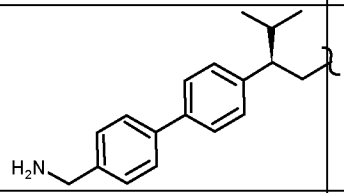
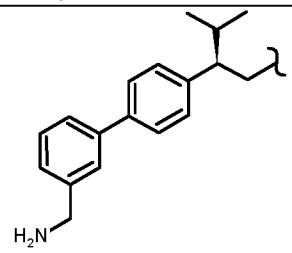
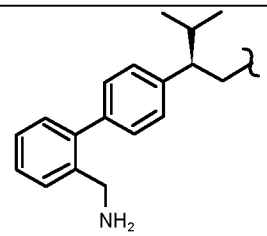
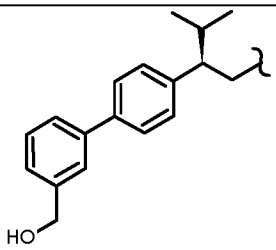
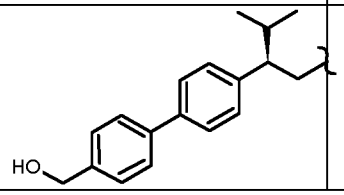
1H NMR (400 MHz, MeOH-d4): δ ppm 7.62 – 7.46 (m, 5H), 7.40 (t, J = 7.7 Hz, 2H), 7.34 – 7.24 (m, 3H), 7.19 (d, J = 8.3 Hz, 2H), 4.05 (qd, J = 7.1, 1.2 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.72 – 3.54 (m, 2H), 3.04 – 2.78 (m, 3H), 2.00 (dq, J = 13.7, 6.9 Hz, 1H), 1.16 – 1.05 (m, 5H), 0.82 (d, J = 6.7 Hz, 2H). LCMS (M+H): 459.59.

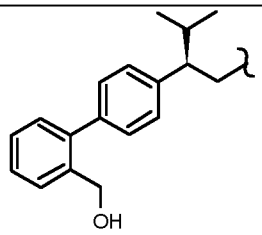
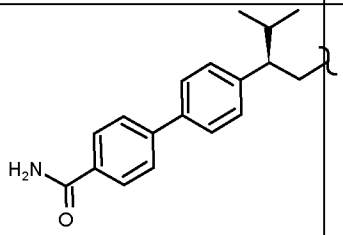
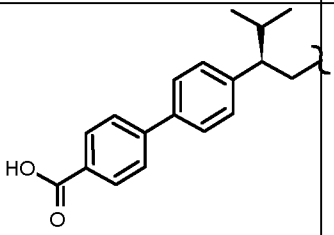
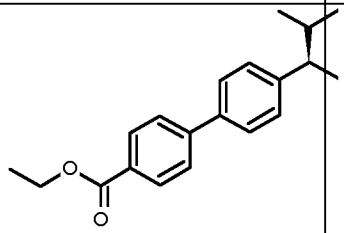
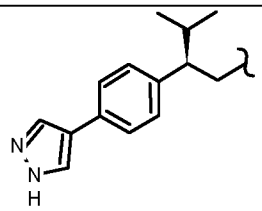
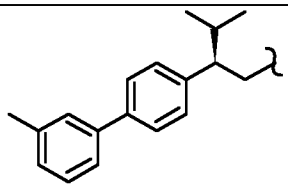
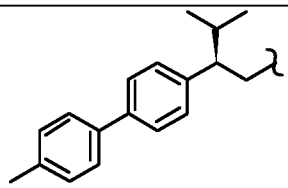
The compounds shown in Table 7a were made using the method described above starting with the appropriate ethyl ester. NMR data is provided in Table 7b.

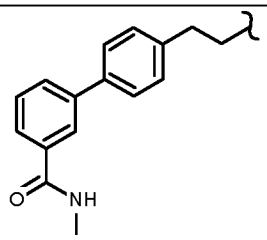
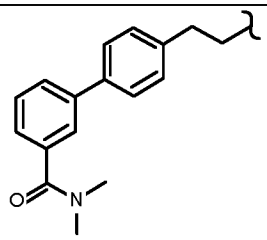
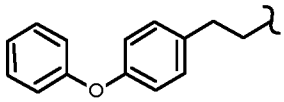
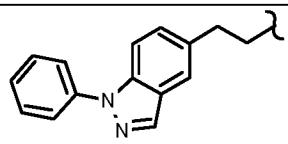
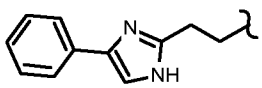
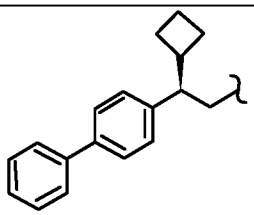
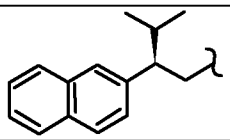
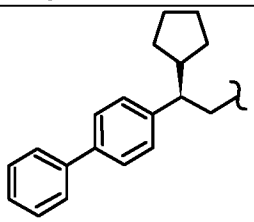
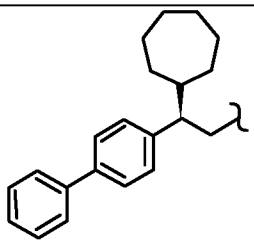
Table 7a

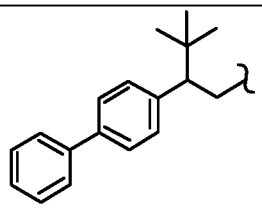
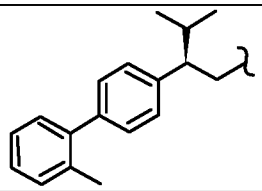
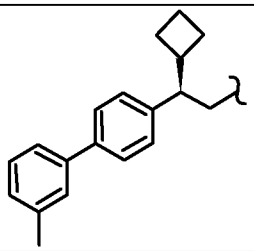
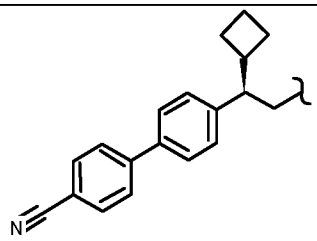
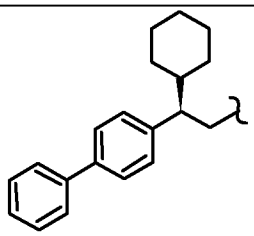
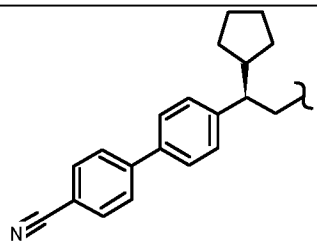
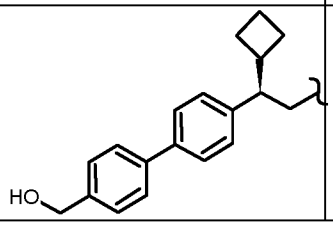


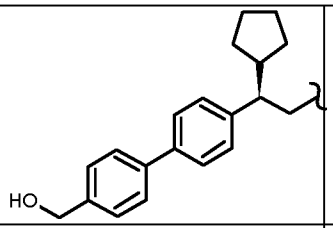
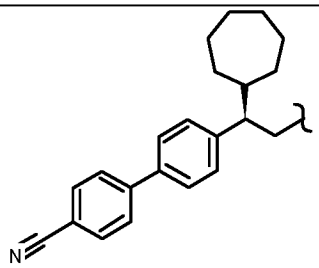
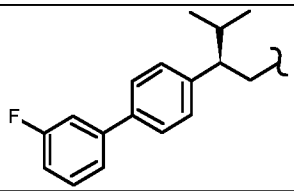
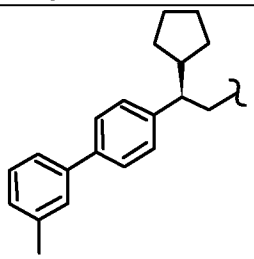
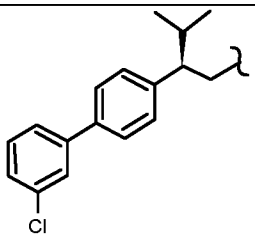
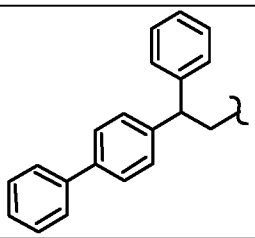
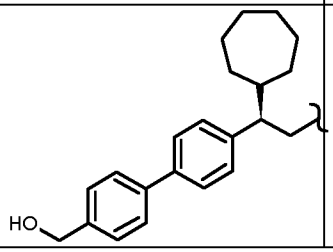
Ex. No.	R	R'	Name	LCMS (MH+)
P1b		H	(S)-ethyl 3-(4-(((S)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoate	459.59
P2		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4-(pyrimidin-5-yl)phenyl)butyl)carbamoyl)phenyl)-propanoate	461.57
P3		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)butyl)carbamoyl) phenyl)propanoate	463.58
P4		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-hydroxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	475.59
P5		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4-(2-aminopyrimidin-5-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	476.58
P6		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(2'-cyano-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	484.60
P7		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-cyano-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	484.60

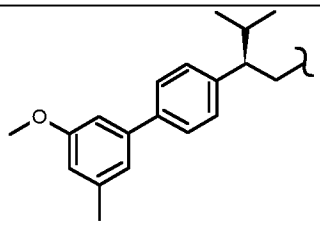
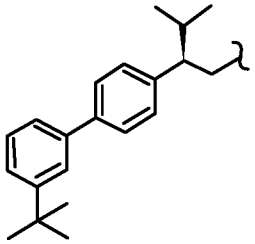
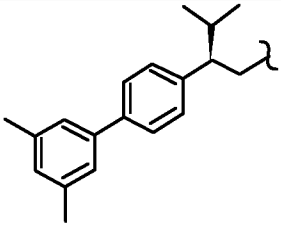
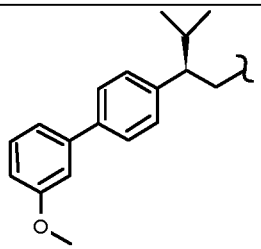
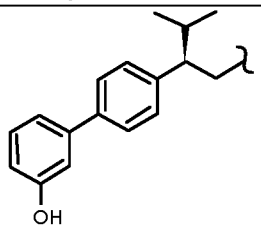
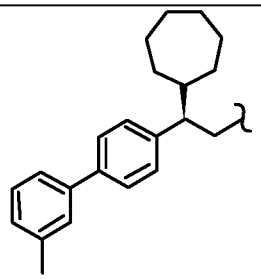
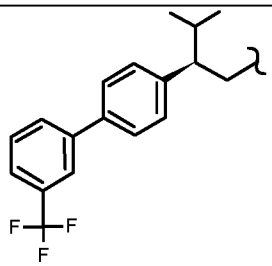
P8		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	484.60
P9		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-ethyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	487.64
P22		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-(aminomethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoate	488.63
P16		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-(aminomethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoate	488.63
P23		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(2'-(aminomethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoate	488.63
P10		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoate	489.61
P11		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoate	489.61

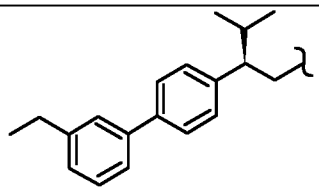
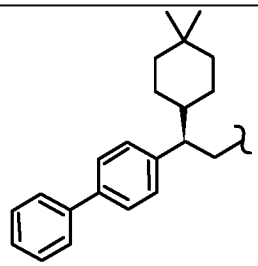
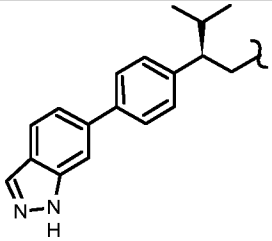
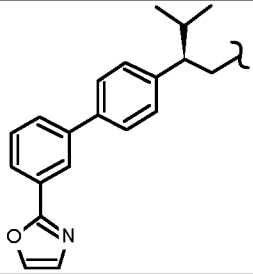
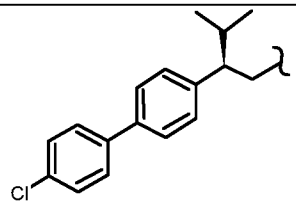
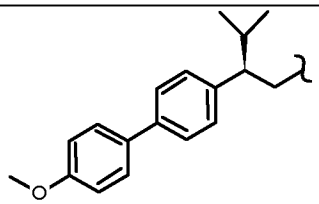
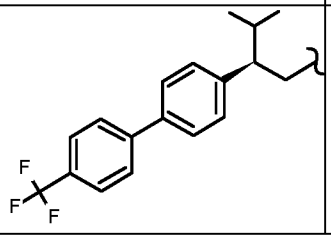
P17		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(2'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoate	489.61
P12		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-carbamoyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	502.62
P13		H	4'-((R)-1-(4-((S)-2-amino-3-ethoxy-3-oxopropyl)benzamido)-3-methylbutan-2-yl)-[1,1'-biphenyl]-4-carboxylic acid	503.60
P14		H	ethyl 4'-((R)-1-(4-((S)-2-amino-3-ethoxy-3-oxopropyl)benzamido)-3-methylbutan-2-yl)-[1,1'-biphenyl]-4-carboxylate	531.65
P15		H	(S)-ethyl 3-(4-(((R)-2-(4-(1H-pyrazol-4-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoate	449.56
P20		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl) propanoate	473.62
P21		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4'-methyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl) propanoate	473.62

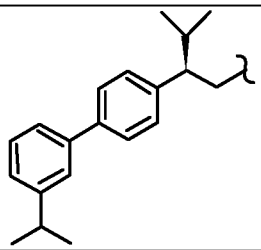
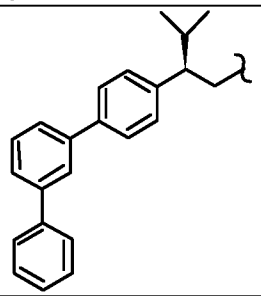
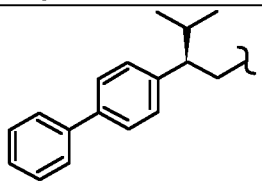
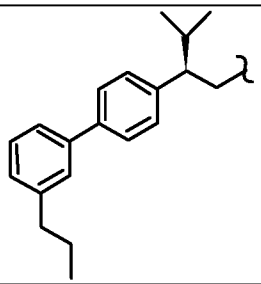
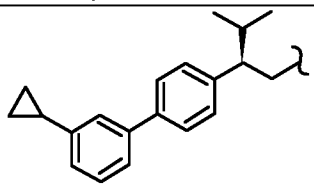
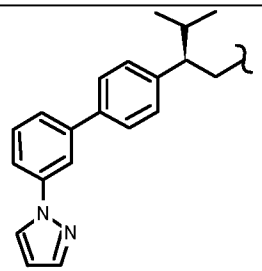
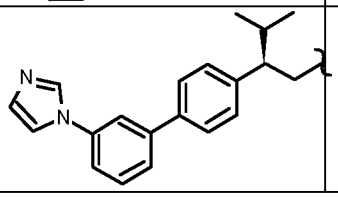
P106		H	(S)-ethyl 2-amino-3-(4-((2-(3'-(methylcarbamoyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)propanoate	473.56
P107		H	(S)-ethyl 2-amino-3-(4-((2-(3'-(dimethylcarbamoyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)propanoate	488.59
P150		H	(S)-ethyl 2-amino-3-(4-((4-phenoxyphenethyl)carbamoyl) phenyl)propanoate	433.51
P148		H	(S)-ethyl 2-amino-3-(4-((2-(1-phenyl-1H-indazol-5-yl)ethyl)carbamoyl) phenyl)propanoate	457.54
P149		H	(S)-ethyl 2-amino-3-(4-((2-(4-phenyl-1H-imidazol-2-yl)ethyl) carbamoyl)phenyl)propanoate	407.47
P73		H	(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl] -4-yl)-2-cyclobutylethyl)carbamoyl) phenyl)-2-aminopropanoate	443.55
P88		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(naphthalen-2-yl)butyl) carbamoyl)phenyl)propanoate	433.56
P80		H	(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cyclopentylethyl) carbamoyl)phenyl)-2-aminopropanoate	485.63
P84		H	(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cycloheptylethyl) carbamoyl)phenyl)-2-aminopropanoate	513.68

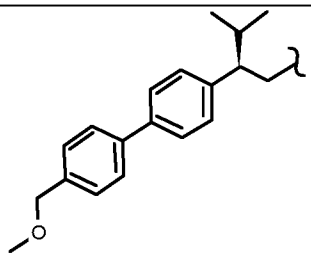
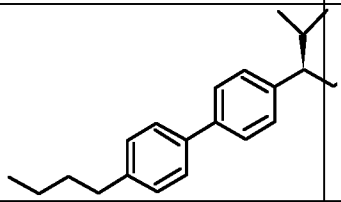
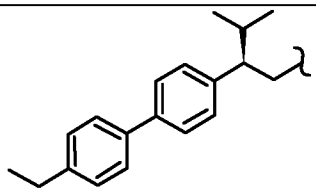
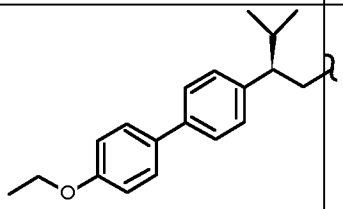
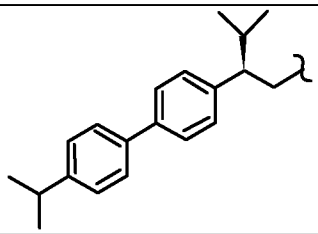
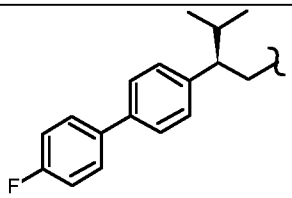
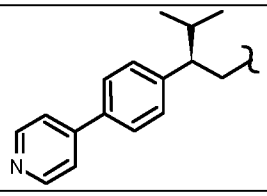
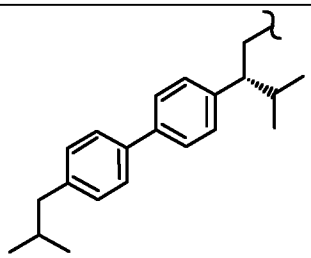
P151		H	(2S)-ethyl 3-(4-((2-([1,1'-biphenyl]-4-yl)-3,3-dimethylbutyl) carbamoyl)phenyl)-2-aminopropanoate	473.62
P24		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(2'-methyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl) phenyl)propanoate	473.62
P75		H	(S)-ethyl 2-amino-3-(4-(((R)-2-cyclobutyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)propanoate	485.63
P76		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-2-cyclobutylethyl)carbamoyl)phenyl)-propanoate	495.61
P78		H	(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cyclohexylethyl)carbamoyl)phenyl)-2-aminopropanoate	498.66
P81		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-2-cyclopentylethyl)carbamoyl)phenyl)-propanoate	510.64
P77		H	(S)-ethyl 2-amino-3-(4-(((R)-2-cyclobutyl-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)propanoate	501.63

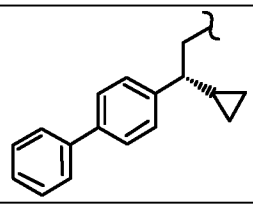
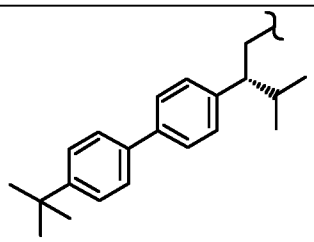
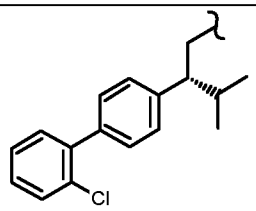
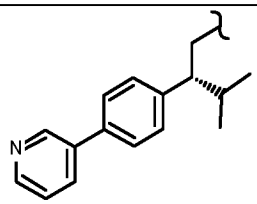
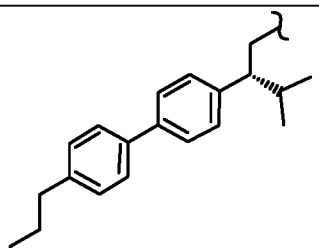
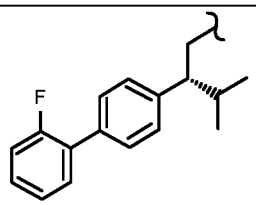
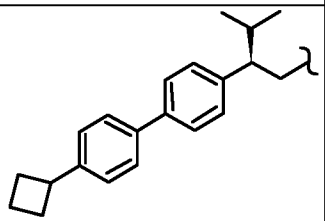
P82		H	(S)-ethyl 2-amino-3-(4-(((R)-2-cyclopentyl-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)propanoate	515.66
P85		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-2-cycloheptylethyl)carbamoyl)phenyl)-propanoate	538.69
P25		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-fluoro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	477.58
P83		H	(S)-ethyl 2-amino-3-(4-(((R)-2-cyclopentyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)propanoate	499.66
P26		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-chloro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl) propanoate	494.04
P152		H	(S)-ethyl 3-(4-((2-([1,1'-biphenyl]-4-yl)-2-phenylethyl)carbamoyl)phenyl)-2-aminopropanoate	493.61
P86		H	(S)-ethyl 2-amino-3-(4-(((R)-2-cycloheptyl-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)ethyl) carbamoyl)phenyl)propanoate	534.71

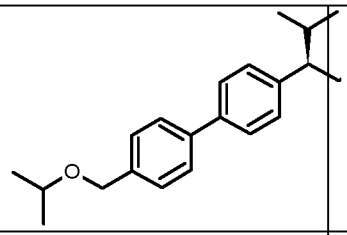
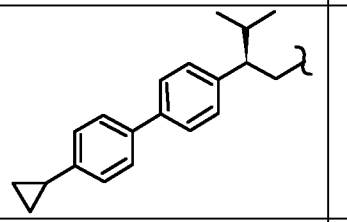
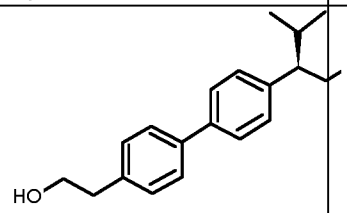
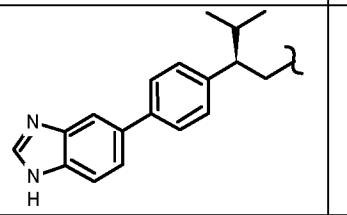
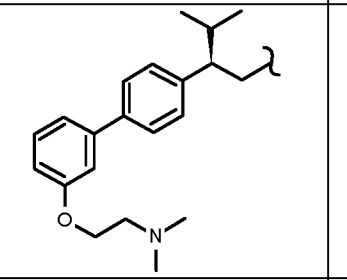
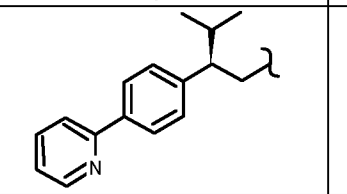
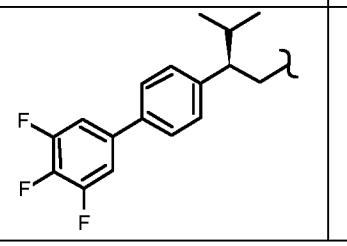
P27		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-methoxy-5'-methyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoate	503.64
P28		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-(tert-butyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	475.59
P29		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(3',5'-dimethyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	487.65
P30		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-methoxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	489.62
P31		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-hydroxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	447.54
P87		H	(S)-ethyl 2-amino-3-(4-(((R)-2-cycloheptyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)ethyl) carbamoyl)phenyl)propanoate	527.71
P32		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)butyl)carbamoyl) phenyl)propanoate	527.59

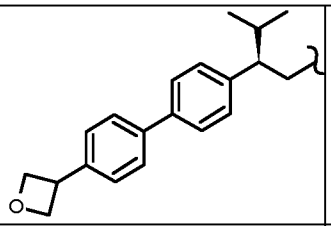
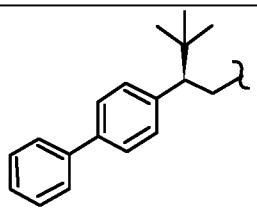
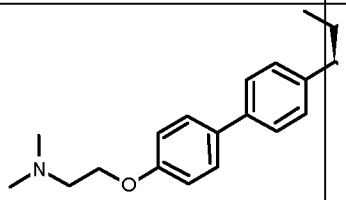
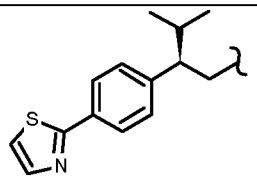
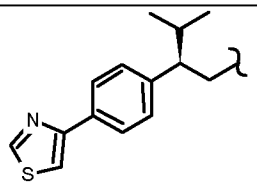
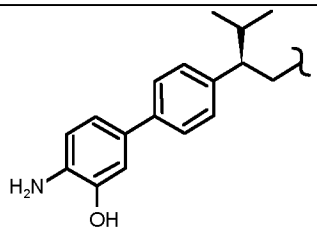
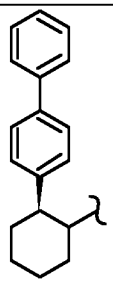
P33		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-ethyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	486.65
P79		H	(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(4,4-dimethylcyclohexyl)ethyl)carbamoyl) phenyl)-2-aminopropanoate	527.71
P34		H	(S)-ethyl 3-(4-(((R)-2-(4-(1H-indazol-6-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoate	499.62
P39		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(3'-(oxazol-2-yl)-[1,1'-biphenyl]-4-yl)butyl)carbamoyl) phenyl)propanoate	526.64
P43		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-chloro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	494.04
P35		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-methoxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	489.62
P40		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)butyl) carbamoyl)phenyl)propanoate	527.59

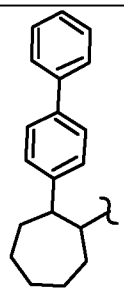
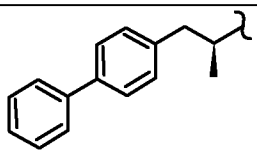
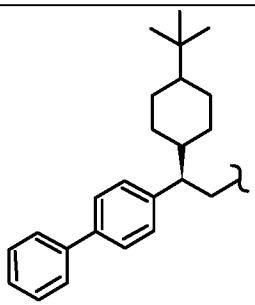
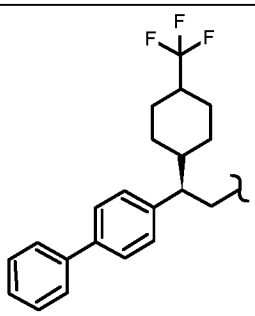
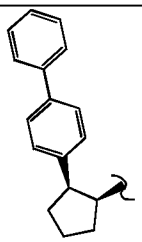
P36		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-isopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	501.67
P56		H	(S)-ethyl 3-(4-(((R)-2-([1,1':3',1''-terphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoate	535.69
P91		Me	(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)(methyl)carbamoyl)phenyl)-2-aminopropanoate	473.62
P53		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(3'-propyl-[1,1'-biphenyl]-4-yl)butyl) carbamoyl)phenyl)propanoate	501.67
P37		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-cyclopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoate	499.66
P38		H	(S)-ethyl 3-(4-(((R)-2-(3'-(1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)-2-aminopropanoate	525.65
P46		H	(S)-ethyl 3-(4-(((R)-2-(3'-(1H-imidazol-1-yl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoate	525.65

P51		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-(methoxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoate	503.65
P54		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-butyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl) propanoate	515.7
P44		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-ethyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl) propanoate	487.65
P41		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-ethoxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl) propanoate	503.65
P55		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-isopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl) propanoate	501.67
P42		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl) propanoate	477.58
P48		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4-(pyridin-4-yl)phenyl)butyl)carbamoyl) phenyl)propanoate	460.58
P45		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-isobutyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	515.70

P72		H	(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cyclopropylethyl)carbamoyl)phenyl)-2-aminopropanoate	457.58
P47		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-(tert-butyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	515.70
P59		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(2'-chloro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	494.04
P49		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4-(pyridin-3-yl)phenyl)butyl)carbamoyl)phenyl)-propanoate	450.58
P50		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4'-propyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)-propanoate	501.67
P52		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(2'-fluoro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	477.58
P58		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-cyclobutyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	513.68

P60		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-(isopropoxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	531.69
P61		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-cyclopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	499.66
P63		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-(2-hydroxyethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	503.64
P62		H	(S)-ethyl 3-(4-(((R)-2-(4-(1H-benzo[d]imidazol-5-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoate	499.61
P65		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-(2-(dimethylamino)ethoxy)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	546.71
P90		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4-(pyridin-2-yl)phenyl)butyl)carbamoyl)phenyl)-propanoate	460.59
P66		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(3',4',5'-trifluoro-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)-propanoate	513.56

P68		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4'-(oxetan-3-yl)-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)-propanoate	515.66
P74		H	(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3,3-dimethylbutyl)carbamoyl)pheny)-2-aminopropanoate	445.56
P67		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-(2-(dimethylamino)ethoxy)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-propanoate	546.71
P69		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4-(thiazol-2-yl)phenyl)butyl)carbamoyl) phenyl)propanoate	466.61
P70		H	(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4-(thiazol-4-yl)phenyl)butyl)carbamoyl) phenyl)propanoate	466.61
Q1		H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-amino-3'-hydroxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoate	490.61
P92		H	(S)-ethyl 3-(4-(((1S,2S)-2-([1,1'-biphenyl]-4-yl)cyclohexyl)carbamoyl)pheny)-2-aminopropanoate	471.60

P178		H	(2S)-ethyl 3-(4-((2-([1,1'-biphenyl]-4-yl)cycloheptyl)carbamoyl)phenyl)-2-aminopropanoate	485.63
P152a		H	(S)-ethyl 3-(4-(((S)-1-([1,1'-biphenyl]-4-yl)propan-2-yl)carbamoyl)phenyl)-2-aminopropanoate	431.54
P174		H	(2S)-ethyl 3-(4-(((2R)-2-([1,1'-biphenyl]-4-yl)-2-(4-(tert-butyl)cyclohexyl)ethyl)carbamoyl)phenyl)-2-aminopropanoate	555.76
P175		H	(2S)-ethyl 3-(4-(((2R)-2-([1,1'-biphenyl]-4-yl)-2-(4-(trifluoromethyl)cyclohexyl)ethyl)carbamoyl)phenyl)-2-aminopropanoate	567.65
P177		H	(S)-ethyl 3-(4-(((1S,2S)-2-([1,1'-biphenyl]-4-yl)cyclopentyl)carbamoyl)phenyl)-2-aminopropanoate	457.57

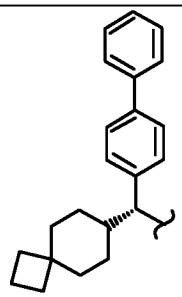
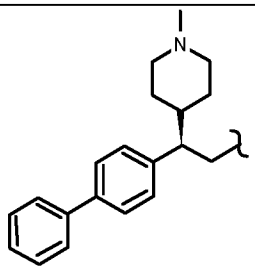
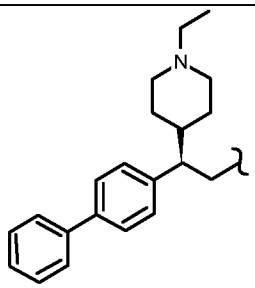
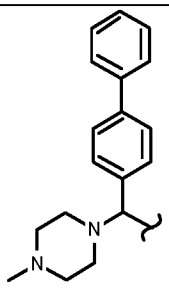
P176		H	(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(spiro[3.5]nonan-7-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoate	539.72
P162		H	(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(1-methylpiperidin-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoate	514.67
P163		H	(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(1-ethylpiperidin-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoate	527.69
Q2		H	(2S)-ethyl 3-(4-((2-([1,1'-biphenyl]-4-yl)-2-(4-methylpiperazin-1-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoate	515.66

Table 7b

Ex. No.	^{1}H NMR
P1b	1H NMR (400 MHz, MeOH-d4): δ ppm 7.62 – 7.47 (m, 5H), 7.40 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.34 – 7.24 (m, 3H), 7.23 – 7.16 (m, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.89 (dd, *J* = 13.3, 5.5 Hz, 1H), 3.70 (t, *J* = 6.7 Hz, 1H), 3.59 (dd, *J* = 13.3, 10.2

	Hz, 1H), 2.97 (qd, *J* = 13.5, 6.8 Hz, 3H), 1.99 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.16 – 1.05 (m, 5H), 0.82 (d, *J* = 6.7 Hz, 3H)
P2	1H NMR (400 MHz, MeOH-d4): δ ppm 9.10 (s, 1H), 9.04 (d, *J* = 1.4 Hz, 3H), 7.66 (d, *J* = 7.9 Hz, 3H), 7.51 (d, *J* = 7.9 Hz, 3H), 7.39 (d, *J* = 7.9 Hz, 3H), 7.20 (d, *J* = 7.9 Hz, 3H), 4.79 (s, 1H), 4.06 (q, *J* = 7.2 Hz, 3H), 3.87 (dd, *J* = 13.4, 5.4 Hz, 2H), 3.71 – 3.60 (m, 4H), 2.97 (td, *J* = 14.6, 14.0, 6.6 Hz, 4H), 2.90 (d, *J* = 8.6 Hz, 2H), 2.07 – 1.97 (m, 2H), 1.18 – 1.06 (m, 9H), 0.82 (d, *J* = 6.6 Hz, 5H)
P3	1H NMR (400 MHz, MeOH-d4): δ ppm 7.89 (s, 1H), 7.76 (s, 1H), 7.48 (dd, *J* = 16.8, 7.3 Hz, 4H), 7.22 – 7.15 (m, 4H), 4.05 (d, *J* = 7.2 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 1H), 3.66 (s, 1H), 2.95 (dd, *J* = 13.7, 6.3 Hz, 2H), 2.78 (s, 1H), 1.96 (s, 1H), 1.17 – 1.03 (m, 6H), 0.79 (d, *J* = 6.4 Hz, 3H)
P4	^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 7.48 (t, *J* = 8.6 Hz, 2H), 7.45 – 7.38 (m, 1H), 7.21 (dd, *J* = 10.8, 8.2 Hz, 2H), 6.86 – 6.79 (m, 1H), 4.05 (qd, *J* = 7.2, 1.6 Hz, 1H), 3.88 (dd, *J* = 13.2, 5.6 Hz, 1H), 3.70 – 3.52 (m, 2H), 2.95 (qd, *J* = 13.6, 6.9 Hz, 2H), 2.81 (q, *J* = 8.0 Hz, 1H), 1.99 (dd, *J* = 14.0, 7.0 Hz, 1H), 1.29 (s, 1H), 1.16 – 1.05 (m, 3H), 0.81 (d, *J* = 6.7 Hz, 2H)
P5	1H NMR (400 MHz, MeOH-d4): δ ppm 8.51 (s, 1H), 7.49 (dd, *J* = 10.7, 7.9 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 4.12 – 4.01 (m, 1H), 3.86 (dd, *J* = 13.3, 5.4 Hz, 1H), 3.71 – 3.55 (m, 2H), 2.96 (qd, *J* = 13.4, 6.6 Hz, 2H), 2.04 – 1.94 (m, 1H), 1.18 – 1.04 (m, 3H), 0.80 (d, *J* = 6.6 Hz, 2H)
P6	1H NMR (400 MHz, MeOH-d4): δ ppm 7.81 (d, *J* = 7.9 Hz, 1H), 7.60 – 7.45 (m, 5H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.24 – 7.14 (m, 2H), 4.82 (s, 6H), 4.07 (q, *J* = 7.8, 7.4 Hz, 2H), 3.91 (dd, *J* = 13.4, 5.5 Hz, 2H), 3.71 – 3.54 (m, 3H), 3.29 – 3.23 (m, 6H), 2.96 (qd, *J* = 13.4, 6.7 Hz, 4H), 2.00 (s, 1H), 1.18 – 1.08 (m, 5H), 0.83 (d, *J* = 6.7 Hz, 3H)
P7	1H NMR (400 MHz, MeOH-d4): δ ppm 7.98 – 7.88 (m, 2H), 7.70 – 7.55 (m, 3H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.87 (dd, *J* = 13.4, 5.3 Hz, 1H), 3.71 – 3.57 (m, 2H), 2.96 (qd, *J* = 13.8, 7.2 Hz, 3H), 2.87 (s, 1H), 1.17 – 1.06 (m, 5H), 0.82 (d, *J* = 6.8 Hz, 3H)
P8	1H NMR (400 MHz, MeOH-d4): δ ppm 7.78 (d, *J* = 2.6 Hz, 4H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 7.7 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.87 (dd, *J* = 13.4, 5.4 Hz, 1H), 3.64 (dt, *J* = 13.3, 8.2 Hz, 2H), 2.96 (dp, *J* = 13.4, 6.5 Hz, 2H), 2.88 (d, *J* = 8.1 Hz, 1H), 1.17 – 1.05 (m, 6H), 0.81 (d, *J* = 6.7 Hz, 3H)
P9	1H NMR (400 MHz, MeOH-d4): δ ppm 7.58 – 7.46 (m, 4H), 7.25 (dd, *J* = 8.0, 5.5 Hz, 4H), 4.19 – 4.03 (m, 2H), 3.88 (dd, *J* = 13.3, 5.4 Hz, 1H), 3.61 (dd, *J* = 13.3, 10.3 Hz, 1H), 3.12 (qd, *J* = 14.0, 6.9 Hz, 2H), 2.83 (td, *J* = 10.0, 9.4, 5.9 Hz, 1H), 2.66 (q, *J* = 7.7 Hz, 2H), 1.99 (h, *J* = 6.9 Hz, 1H), 1.25 (d, *J* = 7.6 Hz, 2H), 1.24 – 1.11 (m, 3H), 1.09 (d, *J* = 6.7 Hz, 2H), 0.82 (d, *J* = 6.7 Hz, 2H)
P22	1H NMR (400 MHz, MeOH-d4): δ ppm 7.60 – 7.47 (m, 6H), 7.39 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.88 (dd, *J* = 13.3, 5.3 Hz, 1H), 3.83 (s, 2H), 3.70 – 3.60 (m, 2H), 3.30 (s, 3H), 2.95 (qd, *J* = 13.4, 6.7 Hz, 3H), 2.84 (d, *J* = 7.0 Hz, 1H), 2.00 (q, *J* = 7.2 Hz, 1H), 1.28 (s, 1H), 1.16 – 1.05 (m, 6H), 0.82 (d, *J* = 6.7 Hz, 3H)

P16	1H NMR (400 MHz, MeOH-d4): δ ppm 7.64 – 7.47 (m, 4H), 7.30 (t, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 1H), 4.88 (s, 4H), 4.10 – 4.00 (m, 1H), 3.94 – 3.82 (m, 2H), 3.70 – 3.57 (m, 2H), 3.04 – 2.79 (m, 3H), 2.00 (q, *J* = 6.8 Hz, 1H), 1.28 (s, 1H), 1.17 – 1.05 (m, 4H), 0.82 (d, *J* = 6.7 Hz, 2H)
P23	1H NMR (400 MHz, MeOH-d4): δ ppm 7.61 (d, *J* = 7.9 Hz, 1H), 7.53 (s, 1H), 7.49 – 7.42 (m, 1H), 7.37 – 7.23 (m, 4H), 4.19 (q, *J* = 7.3 Hz, 2H), 4.06 (s, 1H), 3.85 (dd, *J* = 13.1, 5.4 Hz, 1H), 3.70 (t, *J* = 11.5 Hz, 1H), 3.18 (s, 1H), 2.88 (d, *J* = 9.8 Hz, 1H), 2.05 (d, *J* = 7.9 Hz, 1H), 1.29 (s, 1H), 1.19 (t, *J* = 7.2 Hz, 2H), 1.09 (d, *J* = 6.6 Hz, 2H), 0.84 (d, *J* = 6.7 Hz, 2H)
P10	1H NMR (400 MHz, $CDCl_3$): δ ppm 7.63 – 7.49 (m, 7H), 7.42 (dd, *J* = 8.0, 5.8 Hz, 5H), 7.34 (s, 2H), 7.25 (d, *J* = 7.3 Hz, 4H), 7.15 (d, *J* = 7.9 Hz, 3H), 5.81 (s, 1H), 4.75 (s, 3H), 4.14 (dq, *J* = 20.9, 7.1, 6.5 Hz, 5H), 3.65 (dd, *J* = 7.8, 5.3 Hz, 2H), 3.04 (dd, *J* = 13.6, 5.3 Hz, 2H), 2.90 (s, 1H), 2.83 (dd, *J* = 13.5, 7.9 Hz, 4H), 1.97 (dd, *J* = 14.1, 6.9 Hz, 3H), 1.28 – 1.16 (m, 8H), 1.10 (d, *J* = 6.6 Hz, 5H), 0.82 (d, *J* = 6.6 Hz, 5H)
P11	1H NMR (400 MHz, MeOH-d4): δ ppm 7.61 – 7.47 (m, 6H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 4.62 (s, 2H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.88 (dd, *J* = 13.3, 5.3 Hz, 1H), 3.71 – 3.60 (m, 2H), 3.30 (s, 3H), 3.04 – 2.87 (m, 3H), 2.83 (d, *J* = 8.3 Hz, 1H), 2.00 (d, *J* = 6.9 Hz, 1H), 1.16 – 1.05 (m, 6H), 0.82 (d, *J* = 6.6 Hz, 3H)
P17	1H NMR (400 MHz, $CDCl_3$): δ ppm 7.56 (d, *J* = 7.4 Hz, 2H), 7.46 – 7.15 (m, 17H), 5.77 (d, *J* = 6.7 Hz, 1H), 4.54 (s, 2H), 4.15 (q, *J* = 7.4 Hz, 4H), 3.44 (d, *J* = 9.5 Hz, 2H), 3.09 (dd, *J* = 13.6, 5.3 Hz, 2H), 2.67 (d, *J* = 11.7 Hz, 2H), 2.03 – 1.94 (m, 2H), 1.27 – 1.19 (m, 6H), 1.12 (d, *J* = 6.6 Hz, 4H), 0.98 (s, 1H), 0.84 (d, *J* = 6.6 Hz, 4H)
P12	1H NMR (400 MHz, MeOH-d4): δ ppm 7.96 – 7.89 (m, 2H), 7.70 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 7.8 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.88 (dd, *J* = 13.2, 5.3 Hz, 1H), 3.70 – 3.56 (m, 2H), 2.95 (dq, *J* = 13.4, 6.7 Hz, 2H), 2.86 (s, 1H), 1.16 – 1.06 (m, 5H), 0.82 (d, *J* = 6.7 Hz, 3H)
P13	1H NMR (400 MHz, DMSO-d6): δ ppm 8.23 (s, 1H), 7.96 (d, *J* = 7.9 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.59 (dd, *J* = 24.7, 7.8 Hz, 4H), 7.26 (d, *J* = 7.7 Hz, 2H), 7.17 (d, *J* = 7.7 Hz, 2H), 3.96 (d, *J* = 7.4 Hz, 2H), 2.82 (s, 2H), 1.93 (d, *J* = 6.6 Hz, 1H), 1.03 (t, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.72 (d, *J* = 6.5 Hz, 3H)
P14	1H NMR (400 MHz, MeOH-d4): δ ppm 8.09 – 8.01 (m, 2H), 7.74 – 7.67 (m, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.54 – 7.46 (m, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.22 – 7.15 (m, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.04 (qd, *J* = 7.1, 1.3 Hz, 2H), 3.88 (dd, *J* = 13.3, 5.5 Hz, 1H), 3.72 – 3.56 (m, 2H), 3.05 – 2.80 (m, 3H), 2.00 (h, *J* = 6.7 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.28 (s, 1H), 1.16 – 1.05 (m, 5H), 0.81 (d, *J* = 6.7 Hz, 3H)
P15	1H NMR (400 MHz, MeOH-d4): δ ppm 7.90 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 4H), 7.19 (d, *J* = 7.8 Hz, 4H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.86 (dd, *J* = 13.3, 5.5 Hz, 1H), 3.70 – 3.52 (m, 3H), 2.95 (qd, *J* = 13.4, 6.7 Hz, 3H), 2.79 (q, *J* = 8.6 Hz, 2H), 1.17 – 1.04 (m, 6H), 0.80 (d, *J* = 6.7 Hz, 3H)

P20	1H NMR (400 MHz, $CDCl_3$): δ ppm 7.57 (d, J = 7.8 Hz, 2H), 7.49 – 7.30 (m, 7H), 7.21 (dd, J = 32.2, 7.7 Hz, 7H), 5.79 (s, 1H), 4.15 (dq, J = 18.8, 7.6, 7.2 Hz, 4H), 3.06 (dd, J = 13.5, 5.3 Hz, 2H), 2.84 (dd, J = 13.5, 7.9 Hz, 2H), 2.64 (s, 1H), 2.42 (s, 4H), 2.03 – 1.92 (m, 2H), 1.28 – 1.05 (m, 10H), 0.82 (d, J = 6.6 Hz, 5H)
P21	1H NMR (400 MHz, MeOH-d4): δ ppm 7.54 (dd, J = 11.3, 7.9 Hz, 3H), 7.42 – 7.23 (m, 5H), 7.12 (d, J = 7.2 Hz, 1H), 3.88 (dd, J = 13.2, 5.4 Hz, 1H), 3.77 – 3.69 (m, 1H), 3.67 – 3.56 (m, 1H), 3.30 (s, 5H), 3.01 (dd, J = 14.4, 8.6 Hz, 1H), 2.82 (d, J = 13.3 Hz, 1H), 2.38 (s, 2H), 2.05 – 1.94 (m, 1H), 1.09 (d, J = 6.6 Hz, 2H), 0.82 (d, J = 6.7 Hz, 3H)
P106	1H NMR (400 MHz, Methanol-d4) δ 8.05 (s, 1H), 7.74 (dd, J = 15.8, 7.5 Hz, 4H), 7.61 (d, J = 7.8 Hz, 2H), 7.51 (t, J = 7.8 Hz, 1H), 7.37 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 7.8 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 3.72 (q, J = 7.7, 7.0 Hz, 1H), 3.63 (t, J = 7.5 Hz, 3H), 3.09 – 2.91 (m, 7H), 2.15 (s, 1H), 1.17 (t, J = 7.2 Hz, 3H)
P107	1H NMR (400 MHz, MeOH-d4): δ ppm 9.31 (s, 1H), 8.52 (t, J = 9.0 Hz, 3H), 8.42 (d, J = 6.1 Hz, 3H), 8.30 (t, J = 7.8 Hz, 1H), 8.14 (d, J = 7.6 Hz, 3H), 8.06 (d, J = 7.8 Hz, 2H), 4.31 (d, J = 7.1 Hz, 2H), 4.11 (s, 9H), 3.79 (s, 3H), 3.72 (d, J = 11.5 Hz, 4H), 3.69 – 3.56 (m, 4H), 3.29 (s, 3H), 2.79 (s, 1H), 1.90 (t, J = 7.2 Hz, 3H)
P150	1H NMR (400 MHz, MeOH-d4): δ ppm 7.71 (d, J = 7.8 Hz, 2H), 7.35 – 7.20 (m, 5H), 6.92 (t, J = 9.8 Hz, 3H), 4.10 (d, J = 7.2 Hz, 2H), 3.75 – 3.67 (m, 1H), 3.58 (t, J = 7.5 Hz, 2H), 3.30 (s, 2H), 3.09 – 2.85 (m, 4H), 1.17 (t, J = 7.3 Hz, 3H)
P148	1H NMR (400 MHz, Methanol-d4) δ 7.70 (ddd, J = 6.3, 3.2, 1.6 Hz, 3H), 7.56 (t, J = 7.9 Hz, 1H), 7.45 – 7.35 (m, 1H), 7.28 (d, J = 8.0 Hz, 1H), 4.09 (q, J = 7.1 Hz, 1H), 3.68 (dt, J = 18.3, 7.0 Hz, 2H), 3.10 – 2.91 (m, 3H), 1.16 (t, J = 7.1 Hz, 2H)
P149	1H NMR (400 MHz, MeOH-d4): δ ppm 7.74 (d, J = 7.9 Hz, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.39 – 7.25 (m, 3H), 7.21 (t, J = 7.4 Hz, 1H), 4.10 (q, J = 7.1 Hz, 1H), 3.74 (td, J = 6.9, 3.9 Hz, 2H), 3.02 (dp, J = 20.4, 7.0, 6.5 Hz, 3H), 1.29 (d, J = 4.2 Hz, 1H), 1.17 (t, J = 7.1 Hz, 2H)
P73	1H NMR (400 MHz, MeOH-d4): δ ppm 7.68 (d, J = 8.0 Hz, 2H), 7.57 (dd, J = 22.4, 7.8 Hz, 3H), 7.42 (t, J = 7.6 Hz, 2H), 7.28 (dt, J = 16.1, 7.6 Hz, 4H), 4.18 (t, J = 6.5 Hz, 1H), 3.48 (dd, J = 13.3, 6.1 Hz, 2H), 3.36 (dd, J = 13.1, 8.4 Hz, 2H), 3.09 (dd, J = 6.6, 3.2 Hz, 2H), 2.97 (q, J = 8.4, 7.9 Hz, 2H), 2.63 – 2.53 (m, 2H), 2.12 (s, 1H), 1.80 (dt, J = 17.7, 8.9 Hz, 3H), 1.66 (s, 1H), 1.52 (q, J = 9.5 Hz, 2H)
P88	1H NMR (400 MHz, MeOH-d4): δ ppm 7.78 (t, *J* = 7.9 Hz, 3H), 7.64 (d, *J* = 1.7 Hz, 1H), 7.47 – 7.34 (m, 5H), 7.16 – 7.09 (m, 2H), 4.86 (s, 6H), 4.09 – 3.90 (m, 4H), 3.72 – 3.57 (m, 3H), 3.00 – 2.90 (m, 3H), 2.90 – 2.83 (m, 1H), 2.06 (s, 1H), 1.15 – 1.05 (m, 6H), 0.80 (d, *J* = 6.7 Hz, 3H)
P80	1H NMR (400 MHz, MeOH-d4): δ ppm 7.61 – 7.49 (m, 4H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.29 (dd, *J* = 8.0, 3.1 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 1H), 3.85 (dd, *J* = 13.3, 4.8 Hz, 1H), 3.68 (t, *J* = 6.7 Hz, 1H), 3.52 (dd, *J* = 13.3, 10.3 Hz, 1H), 3.05 – 2.78 (m, 3H), 2.24 – 2.13 (m, 1H), 2.06 (qd, *J* = 7.6, 3.8 Hz, 1H), 1.73 (d, *J* = 11.0 Hz, 1H), 1.69 – 1.37 (m, 5H), 1.29 (s, 1H), 1.11 (q, *J* = 8.9, 8.0 Hz, 3H)

P84	1H NMR (400 MHz, MeOH-d4): δ ppm 7.62 – 7.45 (m, 5H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.29 (dd, *J* = 7.9, 6.1 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.88 (dd, *J* = 13.3, 5.5 Hz, 1H), 3.70 – 3.54 (m, 2H), 2.96 (ddq, *J* = 27.2, 13.5, 6.8 Hz, 3H), 1.94 (dt, *J* = 24.0, 8.1 Hz, 2H), 1.68 (d, *J* = 21.1 Hz, 2H), 1.60 (s, 1H), 1.50 (d, *J* = 7.8 Hz, 2H), 1.31 – 1.07 (m, 4H)
P151	1H NMR (400 MHz, MeOH-d4): δ ppm 7.62 – 7.50 (m, 3H), 7.40 (dt, *J* = 7.6, 3.6 Hz, 3H), 7.30 (dd, *J* = 13.4, 7.4 Hz, 3H), 7.15 (d, *J* = 8.0 Hz, 2H), 4.07 – 3.96 (m, 2H), 3.87 (d, *J* = 8.0 Hz, 2H), 3.63 (t, *J* = 6.7 Hz, 1H), 3.02 – 2.84 (m, 3H), 1.29 (s, 1H), 1.09 (td, *J* = 7.2, 1.9 Hz, 3H), 1.01 (s, 8H)
P24	1H NMR (400 MHz, MeOH-d4): δ ppm 7.49 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.08 (m, 7H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.88 (dd, *J* = 13.3, 5.6 Hz, 1H), 3.72 – 3.56 (m, 2H), 3.05 – 2.75 (m, 4H), 2.19 (s, 2H), 2.00 (dp, *J* = 14.1, 7.0 Hz, 2H), 1.29 (d, *J* = 4.7 Hz, 1H), 1.19 – 1.02 (m, 5H), 0.84 (d, *J* = 6.7 Hz, 2H)
P75	1H NMR (400 MHz, MeOH-d4): δ 7.64 – 7.47 (m, 4H), 7.41 – 7.31 (m, 2H), 7.31 – 7.14 (m, 6H), 7.11 (d, *J* = 7.5 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.73 – 3.62 (m, 2H), 3.42 (dd, *J* = 13.4, 9.0 Hz, 1H), 3.07 – 2.88 (m, 4H), 2.77 – 2.61 (m, 2H), 2.38 (s, 3H), 2.23 (ddd, *J* = 13.4, 8.4, 5.1 Hz, 2H), 2.03 – 1.72 (m, 6H), 1.63 (p, *J* = 8.8 Hz, 2H), 1.14 (t, *J* = 7.2 Hz, 3H)
P76	1H NMR (400 MHz, MeOH-d4): δ ppm 7.77 (s, 2H), 7.60 (dd, *J* = 8.2, 3.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 1H), 3.72 – 3.61 (m, 1H), 3.46 (dd, *J* = 13.3, 9.0 Hz, 1H), 2.98 (ddt, *J* = 28.6, 13.5, 7.2 Hz, 2H), 2.70 (q, *J* = 8.9 Hz, 1H), 2.04 – 1.73 (m, 3H), 1.63 (q, *J* = 9.4 Hz, 1H), 1.14 (t, *J* = 7.1 Hz, 2H)
P78	1H NMR (400 MHz, MeOH-d4): δ ppm 7.61 – 7.46 (m, 5H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.33 – 7.15 (m, 4H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.90 (dd, *J* = 13.3, 5.5 Hz, 1H), 3.71 – 3.52 (m, 2H), 3.03 – 2.80 (m, 3H), 2.00 (d, *J* = 12.9 Hz, 1H), 1.79 (d, *J* = 13.1 Hz, 1H), 1.73 – 1.52 (m, 4H), 1.40 – 1.26 (m, 2H), 1.26 – 1.03 (m, 6H), 0.88 (td, *J* = 12.2, 9.1 Hz, 1H)
P81	1H NMR (400 MHz, MeOH-d4): δ ppm 7.77 (d, *J* = 1.7 Hz, 9H), 7.64 – 7.45 (m, 10H), 7.35 (d, *J* = 8.3 Hz, 5H), 7.29 (s, 1H), 7.20 (d, *J* = 8.0 Hz, 5H), 4.06 (q, *J* = 7.1 Hz, 5H), 3.83 (dd, *J* = 13.3, 4.8 Hz, 3H), 3.66 (t, *J* = 6.7 Hz, 3H), 3.56 (dd, *J* = 13.3, 10.3 Hz, 3H), 3.04 – 2.81 (m, 9H), 2.18 (h, *J* = 8.9 Hz, 4H), 1.77 – 1.68 (m, 3H), 1.60 (s, 2H), 1.57 – 1.36 (m, 11H), 1.17 – 1.01 (m, 10H)
P77	1H NMR (400 MHz, MeOH-d4): δ ppm 7.64 – 7.50 (m, 5H), 7.40 (d, *J* = 7.9 Hz, 2H), 7.25 (dd, *J* = 14.3, 7.9 Hz, 4H), 4.63 (s, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.68 (dt, *J* = 14.2, 6.4 Hz, 2H), 3.43 (dd, *J* = 13.3, 8.9 Hz, 1H), 2.98 (qd, *J* = 13.8, 7.2 Hz, 3H), 2.69 (h, *J* = 8.4, 7.6 Hz, 1H), 2.26 – 2.19 (m, 1H), 2.04 – 1.83 (m, 3H), 1.78 (d, *J* = 10.1 Hz, 2H), 1.63 (p, *J* = 8.2, 7.2 Hz, 2H), 1.14 (t, *J* = 7.1 Hz, 2H)
P82	1H NMR (400 MHz, MeOH-d4): δ ppm 7.60 – 7.49 (m, 6H), 7.40 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 4.63 (s, 2H), 4.05 (q, *J* = 7.3 Hz, 2H), 3.84 (dd, *J* = 13.5, 4.6 Hz, 1H), 3.65 (d, *J* = 6.8 Hz, 1H), 3.31 (s, 1H), 3.04 – 2.78 (m, 4H), 2.17 (q, *J* = 8.6 Hz, 1H), 2.10 – 1.99 (m, 2H), 1.71 (s, 1H), 1.67 – 1.51 (m, 3H), 1.46 (s, 2H), 1.11 (q, *J* = 14.3, 10.8 Hz, 4H)
P85	1H NMR (400 MHz, MeOH-d4): δ ppm 7.82 – 7.72 (m, 2H), 7.61 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 4.06 (q, J = 7.1 Hz, 1H), 3.64 (dt, J = 13.3, 8.5 Hz, 1H), 3.31 (s, 3H), 3.07 – 2.87

	(m, 2H), 1.92 (d, J = 12.7 Hz, 1H), 1.72 – 1.56 (m, 2H), 1.56 – 1.46 (m, 2H), 1.38 (t, J = 10.6 Hz, 1H), 1.31 – 1.08 (m, 3H)
P25	1H NMR (400 MHz, MeOH-d4): δ ppm 7.59 – 7.50 (m, 2H), 7.50 – 7.36 (m, 2H), 7.36 – 7.26 (m, 2H), 7.20 (d, J = 8.2 Hz, 1H), 7.08 – 6.98 (m, 1H), 4.11 – 4.00 (m, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.71 – 3.55 (m, 2H), 3.04 – 2.79 (m, 3H), 2.01 (q, J = 6.9 Hz, 1H), 1.29 (s, 1H), 1.17 – 1.06 (m, 4H), 0.82 (d, J = 6.7 Hz, 2H)
P83	1H NMR (400 MHz, MeOH-d4): δ ppm 7.52 (d, J = 7.9 Hz, 5H), 7.42 – 7.32 (m, 3H), 7.27 (dd, J = 7.9, 5.9 Hz, 4H), 7.20 (d, J = 7.9 Hz, 3H), 7.12 (d, J = 7.5 Hz, 2H), 4.05 (q, J = 7.1 Hz, 3H), 3.85 (dd, J = 13.2, 4.8 Hz, 2H), 3.66 (t, J = 6.7 Hz, 2H), 3.52 (dd, J = 13.2, 10.2 Hz, 2H), 3.04 – 2.78 (m, 6H), 2.38 (s, 4H), 2.18 (q, J = 8.4, 7.9 Hz, 2H), 1.72 (s, 1H), 1.60 (s, 1H), 1.47 (s, 3H), 1.29 (s, 1H), 1.12 (t, J = 7.1 Hz, 5H)
P26	1H NMR (400 MHz, MeOH-d4): δ ppm 7.62 – 7.46 (m, 4H), 7.43 – 7.26 (m, 3H), 7.24 – 7.16 (m, 1H), 4.05 (qd, J = 7.1, 1.2 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.70 – 3.55 (m, 2H), 3.04 – 2.79 (m, 3H), 2.00 (h, J = 6.7 Hz, 1H), 1.16 – 1.05 (m, 4H), 0.82 (d, J = 6.7 Hz, 2H)
P152	1H NMR (400 MHz, MeOH-d4): δ ppm 7.61 – 7.52 (m, 6H), 7.43 – 7.28 (m, 6H), 7.27 – 7.20 (m, 4H), 4.49 (m, 1), 4.11 – 3.99 (m, 3H), 3.67 (d, J = 8.2 Hz, 1H), 3.03 – 2.92 (m, 2H), 1.14 (s, 2H)
P86	1H NMR (400 MHz, MeOH-d4): δ ppm 7.61 – 7.47 (m, 5H), 7.40 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 4.62 (s, 2H), 4.06 (q, J = 7.1 Hz, 2H), 3.88 (dd, J = 13.3, 5.4 Hz, 1H), 3.68 (t, J = 6.7 Hz, 1H), 3.59 (dd, J = 13.4, 10.1 Hz, 1H), 2.96 (qd, J = 13.8, 6.7 Hz, 3H), 2.00 – 1.84 (m, 2H), 1.72 – 1.62 (m, 2H), 1.59 (s, 2H), 1.55 – 1.45 (m, 3H), 1.44 – 1.31 (m, 2H), 1.31 – 1.19 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H)
P27	1H NMR (400 MHz, MeOH-d4): δ ppm 7.51 (t, J = 8.0 Hz, 4H), 7.23 (dd, J = 23.8, 8.1 Hz, 5H), 6.99 (s, 1H), 6.90 (t, J = 1.9 Hz, 1H), 6.71 (s, 1H), 4.05 (qd, J = 7.1, 1.5 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.81 (s, 3H), 3.70 – 3.54 (m, 2H), 3.04 – 2.77 (m, 3H), 2.35 (s, 3H), 1.99 (dt, J = 13.9, 6.8 Hz, 1H), 1.29 (s, 3H), 1.16 – 1.05 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P28	1H NMR (400 MHz, MeOH-d4): δ ppm 7.62 – 7.44 (m, 3H), 7.41 – 7.30 (m, 2H), 7.33 – 7.23 (m, 2H), 7.20 (d, J = 8.0 Hz, 2H), 4.13 – 3.99 (m, 1H), 3.72 – 3.54 (m, 1H), 3.04 – 2.74 (m, 2H), 2.00 (dp, J = 12.3, 6.5 Hz, 1H), 1.36 (s, 5H), 1.29 (s, 1H), 1.19 – 1.02 (m, 4H), 0.80 (dd, J = 23.6, 6.7 Hz, 2H)
P29	1H NMR (400 MHz, MeOH-d4): δ ppm 7.54 – 7.46 (m, 4H), 7.28 – 7.15 (m, 6H), 4.05 (qd, J = 7.2, 5.9 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.70 – 3.53 (m, 2H), 3.04 – 2.77 (m, 3H), 2.34 (s, 5H), 1.99 (h, J = 6.6 Hz, 1H), 1.29 (s, 1H), 1.16 – 1.05 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P30	1H NMR (400 MHz, MeOH-d4): δ ppm 7.57 – 7.46 (m, 4H), 7.36 – 7.08 (m, 8H), 6.87 (dd, J = 8.1, 2.5 Hz, 1H), 4.05 (qd, J = 7.1, 1.4 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.83 (s, 3H), 3.71 – 3.54 (m, 2H), 3.06 – 2.92 (m, 2H), 2.96 – 2.78 (m, 2H), 2.00 (h, J = 6.9 Hz, 1H), 1.19 – 1.02 (m, 7H), 0.85 – 0.73 (m, 3H)
P31	1H NMR (400 MHz, MeOH-d4): δ ppm 7.50 (dd, J = 8.0, 5.4 Hz, 4H), 7.29 – 7.16 (m, 5H), 7.08 – 6.97 (m, 2H), 6.77 – 6.69 (m, 1H), 4.11 – 4.00 (m, 2H), 3.88

	(dd, J = 13.3, 5.5 Hz, 1H), 3.67 (s, 1H), 3.59 (dd, J = 13.2, 10.2 Hz, 1H), 3.04 – 2.83 (m, 2H), 2.82 (s, 1H), 1.16 – 1.05 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P87	1H NMR (400 MHz, MeOH-d4): δ ppm 7.56 – 7.45 (m, 4H), 7.43 – 7.33 (m, 2H), 7.28 (dd, J = 7.8, 5.2 Hz, 3H), 7.20 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 7.5 Hz, 1H), 4.11 – 4.00 (m, 2H), 3.88 (dd, J = 13.2, 5.4 Hz, 1H), 3.71 – 3.53 (m, 2H), 2.95 (tt, J = 13.4, 6.8 Hz, 2H), 2.79 (s, 3H), 2.38 (s, 3H), 1.96 (s, 1H), 1.70 (s, 1H), 1.60 (s, 3H), 1.49 (s, 4H), 1.39 (t, J = 10.0 Hz, 1H), 1.31 – 1.07 (m, 4H)
P32	1H NMR (400 MHz, MeOH-d4): δ ppm 7.85 (d, J = 3.1 Hz, 2H), 7.66 – 7.55 (m, 4H), 7.51 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 7.9 Hz, 2H), 4.05 (q, J = 7.2 Hz, 2H), 3.88 (dd, J = 13.4, 5.5 Hz, 1H), 3.70 – 3.53 (m, 2H), 3.04 – 2.81 (m, 3H), 2.01 (h, J = 6.8 Hz, 1H), 1.23 – 1.02 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P33	1H NMR (400 MHz, MeOH-d4): δ ppm 7.52 (dd, J = 11.3, 8.0 Hz, 4H), 7.43 – 7.34 (m, 2H), 7.39 – 7.23 (m, 3H), 7.17 (dd, J = 18.1, 7.7 Hz, 3H), 4.04 (q, J = 7.0 Hz, 2H), 3.89 (dd, J = 13.3, 5.5 Hz, 1H), 3.70 – 3.54 (m, 2H), 3.03 – 2.78 (m, 3H), 2.69 (q, J = 7.6 Hz, 2H), 2.00 (h, J = 6.8 Hz, 1H), 1.26 (t, J = 7.6 Hz, 4H), 1.10 (q, J = 6.8 Hz, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P79	1H NMR (400 MHz, MeOH-d4): δ ppm 7.62 – 7.51 (m, 4H), 7.53 – 7.45 (m, 2H), 7.40 (dd, J = 8.4, 6.9 Hz, 2H), 7.34 – 7.23 (m, 3H), 7.19 (d, J = 8.2 Hz, 2H), 4.05 (qd, J = 7.1, 1.2 Hz, 2H), 3.70 – 3.52 (m, 2H), 3.04 – 2.85 (m, 3H), 1.84 (d, J = 12.2 Hz, 1H), 1.51 – 1.43 (m, 1H), 1.30 (dtd, J = 26.5, 12.8, 6.2 Hz, 4H), 1.19 – 1.05 (m, 5H), 0.86 (d, J = 17.2 Hz, 6H)
P34	1H NMR (400 MHz, MeOH-d4): δ ppm 7.65 – 7.51 (m, 6H), 7.41 (t, J = 7.6 Hz, 2H), 7.28 (dd, J = 24.5, 6.9 Hz, 3H), 7.23 (d, J = 6.1 Hz, 2H), 4.15 (t, J = 6.5 Hz, 1H), 3.71 (dd, J = 13.0, 5.8 Hz, 1H), 3.58 – 3.47 (m, 1H), 3.08 (d, J = 6.5 Hz, 2H), 2.89 (q, J = 7.6 Hz, 1H), 1.38 – 1.10 (m, 5H), 1.00 (p, J = 12.7 Hz, 2H), 0.81 (s, 3H), 0.72 (s, 3H)
P39	1H NMR (400 MHz, MeOH-d4): δ ppm 8.25 (d, J = 1.8 Hz, 1H), 8.02 – 7.92 (m, 2H), 7.74 (dt, J = 7.8, 1.5 Hz, 1H), 7.65 – 7.47 (m, 5H), 7.35 – 7.28 (m, 3H), 7.19 (d, J = 8.0 Hz, 2H), 4.04 (q, J = 7.1 Hz, 2H), 3.89 (dd, J = 13.4, 5.5 Hz, 1H), 3.69 – 3.56 (m, 2H), 3.03 – 2.81 (m, 3H), 2.01 (h, J = 6.8 Hz, 1H), 1.15 – 1.06 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P43	1H NMR (400 MHz, MeOH-d4): δ ppm 7.61 – 7.46 (m, 6H), 7.44 – 7.36 (m, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 4.05 (qd, J = 7.1, 1.3 Hz, 2H), 3.87 (dd, J = 13.3, 5.5 Hz, 1H), 3.70 – 3.55 (m, 2H), 3.04 – 2.79 (m, 3H), 1.16 – 1.05 (m, 6H), 0.81 (d, J = 6.7 Hz, 3H)
P35	1H NMR (400 MHz, MeOH-d4): δ ppm 7.56 – 7.46 (m, 6H), 7.27 – 7.16 (m, 4H), 7.01 – 6.93 (m, 2H), 4.10 – 4.00 (m, 2H), 3.93 – 3.79 (m, 4H), 3.70 – 3.53 (m, 2H), 2.95 (qd, J = 13.4, 6.7 Hz, 2H), 1.99 (hept, J = 6.5 Hz, 1H), 1.16 – 1.05 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P40	1H NMR (400 MHz, MeOH-d4): δ ppm 7.79 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.65 – 7.58 (m, 2H), 7.54 – 7.47 (m, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 4.05 (qd, J = 7.1, 1.4 Hz, 2H), 3.88 (dd, J = 13.3, 5.4 Hz, 1H), 3.71 – 3.57 (m, 2H), 3.04 – 2.81 (m, 3H), 2.01 (h, J = 6.8 Hz, 1H), 1.16 – 1.06 (m, 5H), 0.82 (d, J = 6.7 Hz, 3H)

P36	1H NMR (400 MHz, MeOH-d4): δ ppm 7.67 (d, J = 7.9 Hz, 2H), 7.55 (d, J = 7.9 Hz, 2H), 7.48 – 7.38 (m, 2H), 7.38 – 7.25 (m, 2H), 7.28 – 7.11 (m, 4H), 4.19 (t, J = 6.5 Hz, 1H), 3.71 – 3.57 (m, 2H), 3.70 (dd, J = 13.3, 6.0 Hz, 1H), 3.54 (dd, J = 13.4, 9.0 Hz, 1H), 3.16 – 3.05 (m, 2H), 3.04 – 2.81 (m, 3H), 2.99 – 2.79 (m, 2H), 1.95 (td, J = 13.8, 13.2, 6.9 Hz, 2H), 1.22 (d, J = 6.8 Hz, 8H), 0.95 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.6 Hz, 3H)
P56	1H NMR (400 MHz, MeOH-d4): δ ppm 7.79 (t, J = 1.8 Hz, 1H), 7.69 – 7.40 (m, 11H), 7.39 – 7.27 (m, 3H), 7.19 (d, J = 8.2 Hz, 2H), 4.03 (q, J = 7.1 Hz, 2H), 3.89 (dd, J = 13.3, 5.5 Hz, 1H), 3.69 – 3.56 (m, 2H), 3.03 – 2.80 (m, 3H), 2.01 (h, J = 6.8 Hz, 1H), 1.10 (t, J = 6.9 Hz, 6H), 0.83 (d, J = 6.7 Hz, 3H)
P91	1H NMR (400 MHz, MeOH-d4): δ ppm 7.60 (t, J = 7.6 Hz, 5H), 7.52 – 7.27 (m, 6H), 7.20 (d, J = 7.5 Hz, 1H), 4.08 (dd, J = 26.5, 13.9 Hz, 2H), 3.83 – 3.70 (m, 3H), 3.62 (dq, J = 14.1, 7.0 Hz, 2H), 2.93 (s, 5H), 2.65 (s, 3H), 2.04 – 1.98 (m, 1H), 1.26 – 1.07 (m, 6H), 0.91 (d, J = 6.3 Hz, 2H), 0.83 (d, J = 6.6 Hz, 3H), 0.62 (d, J = 6.6 Hz, 1H)
P53	1H NMR (400 MHz, MeOH-d4): δ ppm 7.52 (dd, J = 11.7, 7.9 Hz, 2H), 7.42 – 7.35 (m, 4H), 7.35 – 7.23 (m, 4H), 7.16 (dd, J = 26.8, 7.6 Hz, 2H), 4.05 (q, J = 7.0 Hz, 1H), 3.89 (dd, J = 13.3, 5.5 Hz, 1H), 3.71 – 3.54 (m, 1H), 2.96 (qd, J = 13.5, 6.7 Hz, 1H), 2.84 (t, J = 7.9 Hz, 1H), 2.64 (t, J = 7.6 Hz, 1H), 1.67 (p, J = 7.5 Hz, 1H), 1.20 (s, 2H), 1.16 – 1.06 (m, 3H), 0.96 (t, J = 7.3 Hz, 2H), 0.82 (d, J = 6.7 Hz, 2H)
P37	1H NMR (400 MHz, MeOH-d4): δ ppm 7.62 – 7.47 (m, 5H), 7.44 – 7.16 (m, 7H), 4.05 (q, J = 7.1 Hz, 2H), 3.88 (dd, J = 13.4, 5.4 Hz, 1H), 3.72 – 3.54 (m, 2H), 3.05 – 2.78 (m, 3H), 2.05 – 1.91 (m, 2H), 1.31 (d, J = 15.7 Hz, 1H), 1.18 – 1.03 (m, 6H), 1.02 – 0.92 (m, 2H), 0.82 (d, J = 6.7 Hz, 3H), 0.80 – 0.67 (m, 2H)
P38	1H NMR (400 MHz, MeOH-d4): δ ppm 8.29 (d, J = 2.5 Hz, 1H), 7.98 (d, J = 2.3 Hz, 1H), 7.74 (d, J = 1.8 Hz, 1H), 7.71 – 7.47 (m, 7H), 7.32 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.54 (t, J = 2.2 Hz, 1H), 4.04 (q, J = 7.1 Hz, 2H), 3.89 (dd, J = 13.4, 5.5 Hz, 1H), 3.70 – 3.57 (m, 2H), 2.93 (dtd, J = 26.5, 13.8, 6.8 Hz, 3H), 1.16 – 1.06 (m, 6H), 0.83 (d, J = 6.7 Hz, 3H)
P46	1H NMR (400 MHz, MeOH-d4): δ ppm 8.19 (s, 1H), 7.77 (t, J = 2.0 Hz, 1H), 7.68 – 7.54 (m, 5H), 7.57 – 7.46 (m, 3H), 7.32 (d, J = 8.0 Hz, 2H), 7.23 – 7.13 (m, 3H), 4.05 (q, J = 7.1 Hz, 2H), 3.87 (dd, J = 13.4, 5.4 Hz, 1H), 3.70 – 3.59 (m, 2H), 3.03 – 2.81 (m, 3H), 2.01 (h, J = 6.8 Hz, 1H), 1.16 – 1.06 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P51	1H NMR (400 MHz, MeOH-d4): δ ppm 7.57 (ddd, J = 12.4, 8.3, 1.9 Hz, 4H), 7.50 (dd, J = 8.3, 1.8 Hz, 2H), 7.42 – 7.35 (m, 2H), 7.31 – 7.24 (m, 2H), 7.19 (P37dd, J = 8.3, 1.8 Hz, 2H), 4.48 (s, 2H), 4.05 (qd, J = 7.1, 1.1 Hz, 2H), 3.88 (dd, J = 13.4, 5.5 Hz, 1H), 3.70 – 3.54 (m, 2H), 3.39 (d, J = 1.7 Hz, 2H), 3.04 – 2.78 (m, 3H), 1.16 – 1.05 (m, 5H), 0.82 (d, J = 6.8 Hz, 3H)
P54	1H NMR (400 MHz, MeOH-d4): δ ppm 7.56 – 7.46 (m, 6H), 7.29 – 7.16 (m, 6H), 4.05 (q, J = 7.1 Hz, 2H), 3.88 (dd, J = 13.3, 5.4 Hz, 1H), 3.72 – 3.53 (m, 2H), 2.96 (qd, J = 13.5, 6.7 Hz, 2H), 2.82 (s, 1H), 2.63 (t, J = 7.6 Hz, 2H), 2.00 (q, J = 6.8 Hz, 1H), 1.63 (d, J = 7.5 Hz, 1H), 1.60 (s, 2H), 1.38 (q, J = 7.7 Hz, 2H), 1.16 – 1.05 (m, 6H), 0.94 (q, J = 7.2 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H)
P44	1H NMR (400 MHz, MeOH-d4): δ ppm 7.51 (dd, J = 10.9, 7.9 Hz, 6H), 7.29 –

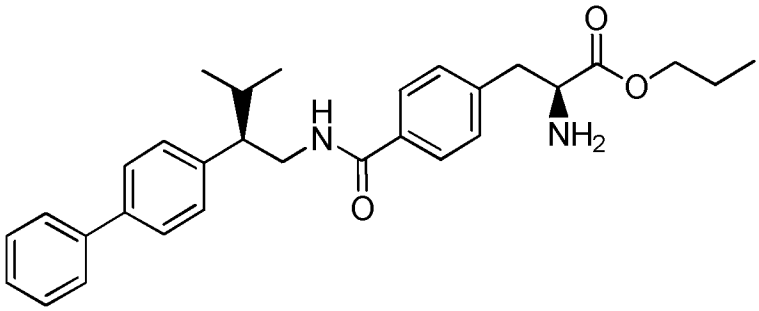
	7.13 (m, 6H), 4.05 (q, J = 7.0 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.71 – 3.53 (m, 2H), 3.04 – 2.77 (m, 3H), 2.66 (q, J = 7.6 Hz, 2H), 2.00 (h, J = 6.9 Hz, 1H), 1.24 (t, J = 7.6 Hz, 3H), 1.16 – 1.05 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P41	1H NMR (400 MHz, MeOH-d4): δ ppm 7.54 – 7.46 (m, 6H), 7.27 – 7.16 (m, 4H), 6.98 – 6.91 (m, 2H), 4.13 – 3.99 (m, 4H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.70 – 3.53 (m, 2H), 2.95 (qd, J = 13.5, 6.7 Hz, 2H), 1.99 (h, J = 6.8 Hz, 1H), 1.39 (t, J = 7.0 Hz, 3H), 1.16 – 1.05 (m, 6H), 0.81 (d, J = 6.7 Hz, 3H)
P55	1H NMR (400 MHz, MeOH-d4): δ ppm 7.57 – 7.44 (m, 6H), 7.31 – 7.16 (m, 6H), 4.86 – 4.79 (m, 1H), 4.05 (qd, J = 7.1, 1.4 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.71 – 3.53 (m, 2H), 3.04 – 2.77 (m, 4H), 2.00 (dq, J = 13.7, 6.8 Hz, 1H), 1.27 (d, J = 6.9 Hz, 6H), 1.18 – 1.02 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P42	1H NMR (400 MHz, MeOH-d4): δ ppm 7.59 (ddd, J = 8.5, 5.4, 2.6 Hz, 2H), 7.55 – 7.47 (m, 4H), 7.31 – 7.23 (m, 2H), 7.23 – 7.16 (m, 2H), 7.18 – 7.08 (m, 2H), 4.05 (dq, J = 10.4, 4.8, 3.4 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.71 – 3.55 (m, 2H), 3.04 – 2.78 (m, 5H), 2.00 (h, J = 6.8 Hz, 1H), 1.17 – 1.05 (m, 5H), 0.81 (d, J = 6.7 Hz, 3H)
P48	1H NMR (400 MHz, MeOH-d4): δ ppm 8.55 (d, J = 5.2 Hz, 2H), 7.74 – 7.67 (m, 4H), 7.51 (d, J = 7.9 Hz, 2H), 7.37 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.9 Hz, 2H), 4.07 (q, J = 7.2 Hz, 2H), 3.88 (dd, J = 13.4, 5.4 Hz, 1H), 3.76 – 3.59 (m, 2H), 2.98 (qd, J = 13.3, 6.5 Hz, 2H), 2.89 (s, 1H), 2.03 (dt, J = 14.0, 6.7 Hz, 1H), 1.17 – 1.06 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P45	1H NMR (400 MHz, MeOH-d4): δ ppm 7.57 – 7.46 (m, 6H), 7.22 (dd, J = 25.4, 8.2 Hz, 6H), 4.04 (qd, J = 7.2, 1.1 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.70 – 3.53 (m, 2H), 3.04 – 2.77 (m, 3H), 2.50 (d, J = 7.2 Hz, 2H), 1.10 (q, J = 6.9 Hz, 6H), 0.92 (d, J = 6.6 Hz, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P72	1H NMR (400 MHz, MeOH-d4): δ ppm 7.68 – 7.61 (m, 2H), 7.62 – 7.51 (m, 4H), 7.45 – 7.22 (m, 8H), 4.08 (q, J = 7.1 Hz, 2H), 3.80 (dd, J = 13.3, 7.0 Hz, 1H), 3.68 (dt, J = 14.2, 7.5 Hz, 2H), 2.99 (qd, J = 13.5, 6.8 Hz, 2H), 2.29 (q, J = 8.3 Hz, 1H), 1.15 (t, J = 7.1 Hz, 4H), 0.70 – 0.61 (m, 1H), 0.45 – 0.33 (m, 2H), 0.09 (dt, J = 9.5, 5.1 Hz, 1H)
P47	1H NMR (400 MHz, MeOH-d4): δ ppm 7.57 – 7.41 (m, 8H), 7.29 – 7.16 (m, 4H), 4.04 (qd, J = 7.1, 1.5 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.70 – 3.53 (m, 2H), 3.04 – 2.77 (m, 3H), 2.00 (h, J = 6.8 Hz, 1H), 1.34 (s, 9H), 1.10 (q, J = 6.9 Hz, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P59	1H NMR (400 MHz, MeOH-d4): δ ppm 7.47 (dd, J = 8.4, 6.9 Hz, 3H), 7.38 – 7.23 (m, 7H), 7.19 (d, J = 8.2 Hz, 2H), 4.07 (q, J = 7.1 Hz, 2H), 3.89 (dd, J = 13.3, 5.6 Hz, 1H), 3.71 – 3.54 (m, 2H), 3.05 – 2.81 (m, 3H), 2.08 – 1.94 (m, 1H), 1.20 – 1.07 (m, 6H), 0.83 (d, J = 6.7 Hz, 3H)
P49	1H NMR (400 MHz, MeOH-d4): δ ppm 8.77 (dd, J = 2.4, 0.9 Hz, 1H), 8.48 (dd, J = 4.9, 1.6 Hz, 1H), 8.07 (dt, J = 7.9, 2.0 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.50 (ddt, J = 8.2, 5.8, 2.2 Hz, 3H), 7.35 (dd, J = 8.5, 2.1 Hz, 2H), 7.23 – 7.16 (m, 2H), 4.86 (s, 3H), 4.11 – 4.00 (m, 2H), 3.88 (dd, J = 13.4, 5.4 Hz, 1H), 3.71 – 3.58 (m, 2H), 3.04 – 2.82 (m, 3H), 1.12 (td, J = 8.8, 7.9, 5.4 Hz, 5H), 0.82 (d, J = 6.7 Hz, 3H)
P50	1H NMR (400 MHz, MeOH-d4): δ ppm 7.57 – 7.45 (m, 6H), 7.34 – 7.08 (m, 7H), 4.06 (qd, J = 7.1, 1.2 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.71 (t, J =

	6.8 Hz, 1H), 3.59 (dd, J = 13.2, 10.3 Hz, 1H), 2.97 (qd, J = 13.6, 6.7 Hz, 2H), 2.83 (ddd, J = 10.1, 7.9, 5.5 Hz, 1H), 2.65 – 2.56 (m, 2H), 1.99 (dp, J = 15.1, 8.0, 7.3 Hz, 1H), 1.71 – 1.61 (m, 2H), 1.22 – 1.02 (m, 6H), 0.95 (t, J = 7.4 Hz, 3H), 0.79 (dd, J = 20.6, 6.7 Hz, 3H)
P52	1H NMR (400 MHz, MeOH-d4): δ ppm 7.53 – 7.40 (m, 5H), 7.38 – 7.20 (m, 4H), 7.24 – 7.10 (m, 4H), 4.11 – 4.01 (m, 2H), 3.89 (dd, J = 13.3, 5.5 Hz, 1H), 3.72 – 3.54 (m, 2H), 3.05 – 2.80 (m, 3H), 2.01 (h, J = 6.9 Hz, 1H), 1.17 – 1.06 (m, 6H), 0.83 (d, J = 6.7 Hz, 3H)
P58	1H NMR (400 MHz, MeOH-d4): 7.56 – 7.46 (m, 6H), 7.30 – 7.15 (m, 7H), 4.04 (q, J = 7.1 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.70 – 3.50 (m, 3H), 3.03 – 2.77 (m, 3H), 2.41 – 2.29 (m, 2H), 2.24 – 2.09 (m, 2H), 2.11 – 1.94 (m, 2H), 1.87 (q, J = 9.4 Hz, 1H), 1.29 (s, 1H), 1.20 – 1.05 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P60	1H NMR (400 MHz, MeOH-d4): δ ppm 7.61 – 7.43 (m, 6H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 4.54 (s, 2H), 4.05 (qd, *J* = 7.1, 1.1 Hz, 2H), 3.88 (dd, *J* = 13.3, 5.5 Hz, 1H), 3.72 (dt, *J* = 14.6, 6.4 Hz, 2H), 3.60 (dd, *J* = 13.4, 10.2 Hz, 1H), 3.05 – 2.78 (m, 3H), 2.00 (h, *J* = 6.8 Hz, 1H), 1.21 (d, *J* = 6.1 Hz, 5H), 1.18 – 1.03 (m, 6H), 0.82 (d, *J* = 6.7 Hz, 3H)
P61	1H NMR (400 MHz, MeOH-d4): δ 7.60 – 7.42 (m, 6H), 7.30 – 7.15 (m, 4H), 7.15 – 7.07 (m, 2H), 4.15 – 3.98 (m, 1H), 3.70 – 3.53 (m, 1H), 3.03 – 2.77 (m, 2H), 2.06 – 1.86 (m, 1H), 1.19 (s, 1H), 1.18 – 1.05 (m, 3H), 1.01 – 0.92 (m, 1H), 0.81 (d, J = 6.7 Hz, 2H), 0.73 – 0.64 (m, 1H)
P63	1H NMR (400 MHz, MeOH-d4): δ ppm 7.56 – 7.46 (m, 6H), 7.28 (d, J = 8.4 Hz, 3H), 7.29 – 7.16 (m, 2H), 4.05 (qd, J = 7.1, 1.2 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.81 – 3.54 (m, 4H), 2.97 (td, J = 13.5, 6.7 Hz, 2H), 2.94 – 2.77 (m, 3H), 2.00 (dq, J = 13.8, 6.9 Hz, 1H), 1.16 – 1.05 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P62	1H NMR (400 MHz, MeOH-d4): δ ppm 7.80 (s, 1H), 7.69 – 7.47 (m, 6H), 7.29 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 4.09 – 3.99 (m, 2H), 3.90 (dd, J = 13.3, 5.5 Hz, 1H), 3.71 – 3.56 (m, 2H), 3.04 – 2.79 (m, 3H), 2.01 (h, J = 6.8 Hz, 1H), 1.15 – 1.06 (m, 6H), 0.84 (d, J = 6.7 Hz, 3H)
P65	1H NMR (400 MHz, MeOH-d4): δ ppm 7.58 – 7.47 (m, 4H), 7.36 – 7.24 (m, 3H), 7.23 – 7.12 (m, 4H), 6.91 (ddd, J = 8.2, 2.5, 0.9 Hz, 1H), 4.16 (t, J = 5.4 Hz, 2H), 4.05 (qd, J = 7.1, 1.2 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.71 – 3.55 (m, 2H), 2.95 (qd, J = 13.5, 6.9 Hz, 2H), 2.81 (t, J = 5.5 Hz, 2H), 2.37 (s, 6H), 1.99 (dt, J = 13.7, 7.0 Hz, 2H), 1.29 (s, 5H), 1.22 – 1.05 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P90	1H NMR (400 MHz, MeOH-d4): δ ppm 8.57 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H), 7.92 – 7.78 (m, 4H), 7.54 – 7.47 (m, 2H), 7.38 – 7.29 (m, 3H), 7.19 (d, J = 8.3 Hz, 2H), 4.05 (qd, J = 7.2, 1.1 Hz, 2H), 3.89 (dd, J = 13.3, 5.4 Hz, 1H), 3.71 – 3.57 (m, 3H), 3.04 – 2.83 (m, 4H), 2.02 (h, J = 6.8 Hz, 2H), 1.29 (s, 2H), 1.18 – 1.06 (m, 5H), 0.82 (d, J = 6.7 Hz, 3H)
P66	1H NMR (400 MHz, MeOH-d4): δ ppm 7.57 – 7.47 (m, 4H), 7.41 – 7.33 (m, 2H), 7.33 – 7.27 (m, 2H), 7.19 (d, J = 8.2 Hz, 2H), 4.06 (qd, J = 7.2, 1.2 Hz, 2H), 3.86 (dd, J = 13.3, 5.5 Hz, 1H), 3.70 – 3.57 (m, 2H), 3.04 – 2.80 (m, 3H), 2.00 (dq, J = 13.7, 6.8 Hz, 1H), 1.20 – 1.02 (m, 5H), 0.80 (d, J = 6.7 Hz, 3H)

P68	1H NMR (400 MHz, MeOH-d4): δ ppm 7.65 – 7.43 (m, 8H), 7.27 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 5.10 (dd, J = 8.4, 5.9 Hz, 2H), 4.77 (dd, J = 6.7, 5.9 Hz, 2H), 4.30 (tt, J = 8.3, 6.7 Hz, 1H), 4.05 (qd, J = 7.1, 1.2 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.70 – 3.55 (m, 2H), 3.04 – 2.78 (m, 3H), 2.00 (dq, J = 13.7, 6.8 Hz, 1H), 1.18 – 1.01 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P74	1H NMR (400 MHz, MeOH-d4): δ 7.62 – 7.50 (m, 4H), 7.44 – 7.35 (m, 4H), 7.35 – 7.24 (m, 3H), 7.15 (d, J = 8.2 Hz, 2H), 4.02 (qd, J = 7.1, 1.6 Hz, 2H), 3.91 – 3.83 (m, 2H), 3.64 (t, J = 6.7 Hz, 1H), 3.02 – 2.85 (m, 3H), 1.08 (t, J = 7.1 Hz, 3H), 1.01 (s, 9H)
P67	1H NMR (400 MHz, MeOH-d4): δ ppm 7.51 (dd, J = 11.2, 8.4 Hz, 6H), 7.22 (dd, J = 18.5, 8.2 Hz, 4H), 7.04 – 6.97 (m, 2H), 4.15 (t, J = 5.4 Hz, 2H), 4.05 (qd, J = 7.1, 1.3 Hz, 2H), 3.88 (dd, J = 13.3, 5.5 Hz, 1H), 3.71 – 3.53 (m, 2H), 2.96 (qd, J = 13.5, 6.7 Hz, 2H), 2.86 (t, J = 5.4 Hz, 2H), 2.41 (s, 6H), 1.28 (s, 2H), 1.16 – 1.05 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H)
P69	1H NMR (400 MHz, MeOH-d4): δ ppm 7.90 – 7.80 (m, 3H), 7.59 – 7.46 (m, 3H), 7.33 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 4.05 (qd, J = 7.1, 0.9 Hz, 4H), 3.87 (dd, J = 13.3, 5.4 Hz, 2H), 3.72 – 3.57 (m, 4H), 3.04 – 2.82 (m, 6H), 2.00 (dt, J = 13.6, 6.8 Hz, 3H), 1.29 (d, J = 3.9 Hz, 7H), 1.18 – 1.06 (m, 12H), 0.94 – 0.85 (m, 1H), 0.81 (d, J = 6.7 Hz, 6H)
P70	1H NMR (400 MHz, MeOH-d4): δ ppm 9.03 (dd, J = 2.0, 0.9 Hz, 1H), 7.89 – 7.79 (m, 3H), 7.50 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 4.84 – 4.74 (m, 1H), 4.59 (s, 1H), 4.10 – 4.00 (m, 3H), 3.88 (dd, J = 13.3, 5.5 Hz, 2H), 3.70 – 3.55 (m, 4H), 2.95 (qd, J = 13.5, 6.8 Hz, 3H), 2.84 (s, 2H), 2.00 (dd, J = 13.9, 7.1 Hz, 3H), 1.29 (s, 6H), 1.16 – 1.06 (m, 10H), 0.81 (d, J = 6.7 Hz, 5H)
Q1	1H NMR (400 MHz, MeOH-d4): δ ppm 7.53 – 7.40 (m, 4H), 7.23 – 7.16 (m, 4H), 6.99 – 6.88 (m, 2H), 6.77 (d, J = 8.0 Hz, 1H), 4.05 (qd, J = 7.1, 1.5 Hz, 2H), 3.87 (dd, J = 13.3, 5.5 Hz, 1H), 3.66 (t, J = 6.7 Hz, 1H), 3.57 (dd, J = 13.3, 10.2 Hz, 1H), 2.95 (qd, J = 13.5, 6.8 Hz, 2H), 2.79 (ddd, J = 10.3, 7.9, 5.5 Hz, 1H), 2.04 – 1.91 (m, 1H), 1.16 – 1.04 (m, 6H), 0.81 (d, J = 6.7 Hz, 3H)
P92	1H NMR (400 MHz, MeOH-d4): δ ppm 7.56 – 7.31 (m, 10H), 7.31 – 7.12 (m, 3H), 4.22 (td, *J* = 11.0, 3.9 Hz, 1H), 4.01 (qd, *J* = 7.1, 1.5 Hz, 2H), 3.63 (t, *J* = 6.8 Hz, 1H), 3.01 – 2.85 (m, 2H), 2.77 (td, *J* = 11.7, 3.5 Hz, 1H), 2.09 (d, *J* = 11.5 Hz, 1H), 1.95 (t, *J* = 13.1 Hz, 2H), 1.87 (d, *J* = 15.9 Hz, 2H), 1.73 – 1.42 (m, 3H), 1.06 (t, *J* = 7.2 Hz, 3H)
P178	1H NMR (400 MHz, MeOH-d4): δ ppm 7.56 – 7.43 (m, 4H), 7.44 – 7.20 (m, 7H), 7.16 (d, J = 8.0 Hz, 2H), 4.66 – 4.51 (m, 1H), 4.09 – 3.98 (m, 2H), 3.69 (q, J = 6.6 Hz, 1H), 3.36 (d,m, 1H), 3.03 – 2.88 (m, 2H), 2.26 (q, J = 11.7, 11.0 Hz, 1H), 1.97 (m, 6H), 1.88 (s, 3H), 1.23 – 1.03 (m, 3H)
P152a	1H NMR (400 MHz, MeOH-d4): δ ppm 7.72 – 7.65 (m, 2H), 7.60 – 7.48 (m, 4H), 7.39 (s, 2H), 7.40 – 7.28 (m, 5H), 4.39 (h, J = 6.8 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.71 (t, J = 6.7 Hz, 1H), 3.09 – 2.81 (m, 3H), 2.95 (m, 1H), 2.01 (t, J = 10.0 Hz, 1H), 1.26 (d, J = 6.7 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H).
P174	1H NMR (400 MHz, MeOH-d4): δ ppm 7.62 – 7.44 (m, 5H), 7.45 – 7.35 (m, 5H), 7.34 – 7.13 (m, 2H), 4.07 (qd, J = 7.2, 1.1 Hz, 1H), 3.90 (dd, J = 13.3, 5.5 Hz, 1H), 3.77 (t, J = 6.7 Hz, 1H), 3.59 (dd, J = 13.3, 10.3 Hz, 1H), 2.99 (qd, J =

	13.6, 6.7 Hz, 2H), 2.90 – 2.79 (m, 1H), 2.11 (d, J = 7.9 Hz, 1H), 1.87 (d, J = 7.4 Hz, 1H), 1.61 (t, J = 12.9 Hz, 1H), 1.12 (t, J = 7.1 Hz, 5H), 0.92 (t, J = 11.9 Hz, 1H), 0.83 (s, 9H).
P175	1H NMR (400 MHz, MeOH-d4): δ ppm 7.62 – 7.51 (m, 5H), 7.54 – 7.47 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 3H), 7.20 (d, *J* = 8.3 Hz, 2H), 4.05 (qd, *J* = 7.1, 1.1 Hz, 2H), 3.92 (dd, *J* = 13.3, 5.6 Hz, 1H), 3.71 – 3.54 (m, 2H), 2.95 (dtd, *J* = 18.2, 12.5, 11.6, 5.6 Hz, 4H), 2.00 (d, *J* = 12.8 Hz, 2H), 1.87 (d, *J* = 13.2 Hz, 1H), 1.69 (d, *J* = 11.6 Hz, 1H), 1.45 – 1.31 (m, 1H), 1.28 (s, 1H), 1.26 – 1.11 (m, 1H), 1.11 (d, *J* = 7.2 Hz, 1H), 0.96 (q, *J* = 11.5, 10.8 Hz, 2H).
P177	1H NMR (400 MHz, MeOH-d4): δ ppm 7.56 – 7.44 (m, 4H), 7.49 – 7.34 (m, 2H), 7.38 – 7.27 (m, 5H), 7.25 (d, *J* = 23.0 Hz, 2H), 4.70 (q, *J* = 7.4 Hz, 1H), 4.13 – 3.93 (m, 2H), 3.63 (t, *J* = 6.7 Hz, 1H), 3.52 (q, *J* = 8.2 Hz, 1H), 2.99 – 2.84 (m, 2H), 2.23 – 2.10 (m, 4H), 1.90 – 1.68 (m, 2H), 1.22 – 1.03 (t, J = 7.4 Hz, 3H)
P176	1H NMR (400 MHz, MeOH-d4): δ ppm 7.62 – 7.50 (m, 5H), 7.52 – 7.45 (m, 2H), 7.40 (t, J = 7.7 Hz, 1H), 7.34 – 7.15 (m, 4H), 4.04 (qd, J = 7.1, 1.2 Hz, 2H), 4.01 (m, 1H), 3.90 (dd, J = 13.3, 5.5 Hz, 1H), 3.67 (t, J = 6.7 Hz, 1H), 2.96 (qd, J = 13.5, 6.7 Hz, 2H), 2.84 (s, 1H), 1.83 (m, 4H), 1.88 – 1.76 (m, 4H), 1.74 – 1.61 (m, 1H), 1.41 – 1.26 (m, 2H), 1.11 (t, J = 7.1 Hz, 2H), 1.00 – 0.86 (m, 3H)
P162	1H NMR (400 MHz, MeOH-d4): δ ppm δ 7.63 – 7.51 (m, 6H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.36 – 7.26 (m, 3H), 7.23 (d, *J* = 8.3 Hz, 2H), 4.07 (qd, *J* = 7.1, 1.2 Hz, 1H), 3.95 (dd, *J* = 13.4, 5.7 Hz, 1H), 3.74 (t, *J* = 6.7 Hz, 1H), 3.59 (dd, *J* = 13.4, 9.6 Hz, 1H), 3.40 (d, *J* = 12.4 Hz, 1H), 3.25 (s, 0H), 2.99 (qd, *J* = 13.6, 6.8 Hz, 2H), 2.83 (t, *J* = 12.4 Hz, 1H), 2.77 – 2.63 (m, 1H), 2.68 (s, 2H), 2.25 (d, *J* = 14.3 Hz, 1H), 1.73 (d, *J* = 14.7 Hz, 1H), 1.60 (q, *J* = 12.2 Hz, 1H), 1.42 – 1.23 (m, 1H), 1.14 (t, *J* = 7.1 Hz, 2H).
P163	1H NMR (400 MHz, MeOH-d4): δ ppm 7.61 – 7.47 (m, 6H), 7.45 – 7.35 (m, 2H), 7.34 – 7.25 (m, 3H), 7.24 – 7.17 (m, 2H), 4.05 (qd, *J* = 7.1, 1.1 Hz, 1H), 3.90 (dd, *J* = 13.3, 5.6 Hz, 0H), 3.70 – 3.57 (m, 1H), 3.09 (d, *J* = 11.6 Hz, 1H), 2.96 (qd, *J* = 13.5, 6.7 Hz, 1H), 2.45 (q, *J* = 7.1 Hz, 1H), 2.04 (dq, *J* = 38.6, 12.0 Hz, 1H), 1.50 (dt, *J* = 25.3, 11.4 Hz, 1H), 1.31 – 1.19 (m, 0H), 1.10 (dt, *J* = 13.4, 7.2 Hz, 3H).
Q2	1H NMR (400 MHz, MeOH-d4): δ ppm 7.60 (ddd, J = 8.1, 5.1, 1.2 Hz, 6H), 7.46 – 7.29 (m, 4H), 7.33 – 7.18 (m, 3H), 4.05 (dq, J = 20.4, 7.0 Hz, 3H), 3.73 – 3.62 (m, 1H), 3.5 (m, 2H), 2.98 (qd, J = 13.5, 6.7 Hz, 2H), 2.62 (m, 8H), 2.49 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H).

Example R1a: **(S)-propyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoate**

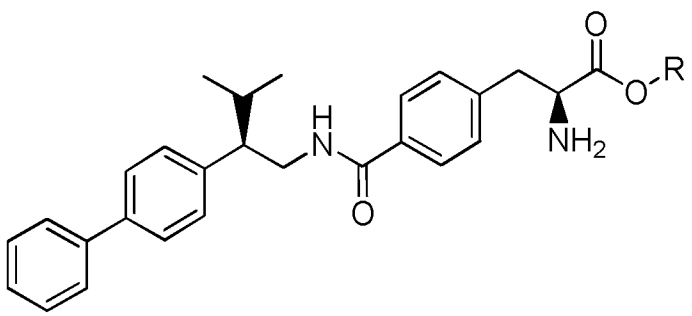


Step 1: To a 0°C solution of (S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (Example 1a, Step 2, 800 mg, 1.51 mmol) in DMF (8 mL) was added TEA (762 mg, 7.536 mmol) and HATU (1.15 g, 3.026 mmol) and the reaction mixture was warmed to RT and stirred for 12 h. The reaction was then diluted with water (10 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. Purification via normal phase column chromatography (hexanes:ethyl acetate/4:1 v/v) provided (S)-propyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate as a yellow solid.

Step 2: To a 0°C solution of (S)-propyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl) phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (1.0 g, 1.7 mmol) in dioxane (4 mL), was added HCl in dioxane (1 M, 10 mL). The reaction mixture was stirred for 2 h 0 °C and then an additional 2 h at RT. After this time, the reaction mixture was concentrated *in vacuo* and the resulting solid was washed with ether to provide the title compound as a white solid.

The compounds shown in Table 8a were made using the method described above for Example R1a starting with the appropriate alcohol. NMR data is provided in Table 8b.

Table 8a



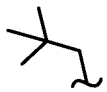
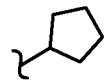
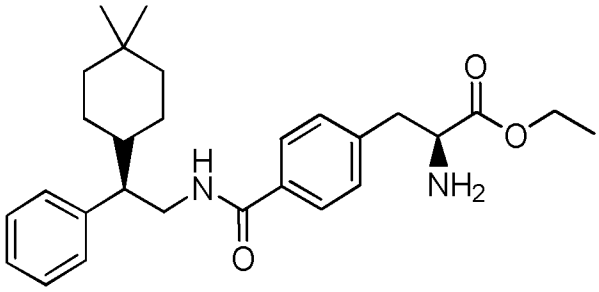
Ex. No.	R	Name	LCMS (MH+)
R1a		(S)-propyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoate	473.62
S1a		(S)-neopentyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoate	501.67
T1a		(S)-butyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoate	487.65
U1a		(S)-cyclopentyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoate	499.66

Table 8b

Ex. No.	^{1}H NMR
R1a	1H NMR (400 MHz, MeOH-d4): δ ppm 8.20 (d, J = 6.0 Hz, 2H), 7.62 – 7.51 (m, 4H), 7.40 (dd, J = 8.4, 7.0 Hz, 2H), 7.35 – 7.23 (m, 3H), 4.30 (t, J = 7.0 Hz, 1H), 4.15 – 4.04 (m, 1H), 3.88 (dt, J = 13.1, 5.2 Hz, 1H), 3.28 – 3.09 (m, 3H), 2.85 (s, 1H), 2.00 (dq, J = 13.9, 6.9 Hz, 1H), 1.78 (q, J = 5.7 Hz, 1H), 1.61 – 1.50 (m, 1H), 1.09 (d, J = 6.7 Hz, 2H), 0.86 – 0.77 (m, 4H)
S1a	1H NMR (400 MHz, MeOH-d4): δ ppm 7.63 – 7.51 (m, 6H), 7.40 (t, J = 7.7 Hz, 2H), 7.34 – 7.24 (m, 4H), 4.37 (d, J = 7.2 Hz, 2H), 3.92 – 3.82 (m, 1H), 3.77 – 3.52 (m, 2H), 3.28 – 3.16 (m, 1H), 2.91 – 2.78 (m, 1H), 1.97 (s, 1H), 1.09 (d, J = 6.6 Hz, 1H), 0.85 – 0.74 (m, 5H)
T1a	1H NMR (400 MHz, MeOH-d4): δ ppm 7.62 – 7.51 (m, 6H), 7.40 (t, J = 7.7 Hz, 2H), 7.34 – 7.24 (m, 6H), 4.30 (td, J = 7.0, 1.3 Hz, 1H), 4.18 – 4.07 (m, 1H), 3.88 (dtd, J = 13.3, 5.2, 3.1 Hz, 1H), 3.64 (s, 1H), 3.20 (dd, J = 7.0, 5.5 Hz, 1H), 2.86 (ddd, J = 10.3, 7.8, 5.5 Hz, 1H), 2.00 (dq, J = 13.7, 6.8 Hz, 1H), 1.50 (td, J = 7.0, 3.3 Hz, 1H), 1.28 – 1.17 (m, 1H), 1.09 (d, J = 6.6 Hz, 2H), 0.91 – 0.73 (m, 4H)
U1a	1H NMR (400 MHz, MeOH-d4): δ ppm 8.20 (s, 1H), 7.62 – 7.51 (m, 4H), 7.40 (t, J = 7.7 Hz, 1H), 7.35 – 7.23 (m, 3H), 5.15 (dq, J = 6.1, 3.7, 3.1 Hz, 1H), 4.23 (td, J = 7.2, 1.3 Hz, 1H), 3.88 (dt, J = 13.4, 5.2 Hz, 1H), 3.71 – 3.56 (m, 1H), 3.16 (d, J = 7.3 Hz, 1H), 2.91 – 2.80 (m, 1H), 2.00 (h, J = 6.7 Hz, 1H), 1.83 – 1.56 (m, 1H), 1.49 (s, 3H), 1.55 – 1.37 (m, 1H), 1.10 (d, J = 6.6 Hz, 2H), 0.82 (d, J = 6.7 Hz, 2H)

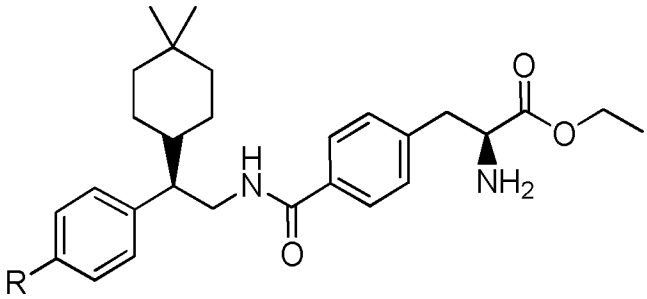
Example P166: (S)-ethyl 2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-phenylethyl)carbamoyl)phenyl)propanoate



The title compound was prepared as described for the compound of Example R1a starting with (R)-2-(4,4-dimethylcyclohexyl)-2-phenylethanamine (Interrmediate 55).

The compounds shown in Table 9a were made using the method according to Example P166 above starting with the appropriate intermediate.

Table 9a



Ex. No.	R	Name	LCMS (MH+)
P166	H	(S)-ethyl 2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-phenylethyl) carbamoyl) phenyl)propanoate	451.61
P167		(S)-ethyl 2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(p-tolyl)ethyl)carbamoyl) phenyl)propanoate	465.64
P168		(S)-ethyl 2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(4-fluorophenyl)ethyl)carbamoyl) phenyl) propanoate	469.60

P169		(S)-ethyl 2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(4-methoxyphenyl)ethyl)carbamoyl) phenyl)propanoate	481.64
P170		(S)-ethyl 2-amino-3-(4-(((R)-2-(4-chlorophenyl)-2-(4,4-dimethylcyclohexyl)ethyl) carbamoyl)phenyl)propanoate	486.06
P171		(S)-ethyl 2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(4-(trifluoromethyl)phenyl)ethyl) carbamoyl)phenyl)propanoate	519.61

Table 9b

Ex. No.	^{1}H NMR
P166	1H NMR (400 MHz, MeOH-d4): δ ppm 7.47 (d, J = 8.2 Hz, 4H), 7.31 – 7.11 (m, 5H), 4.08 (q, J = 7.1 Hz, 1H), 3.88 (dd, J = 13.2, 5.6 Hz, 1H), 3.68 (t, J = 6.7 Hz, 1H), 3.54 (dd, J = 13.2, 10.2 Hz, 1H), 3.05 – 2.80 (m, 2H), 1.84 – 1.75 (m, 1H), 1.49 – 1.39 (m, 1H), 1.38 – 1.18 (m, 3H), 1.19 – 0.96 (m, 3H), 0.84 (d, J = 22.6 Hz, 4H)
P167	1H NMR (400 MHz, MeOH-d4): δ ppm 7.48 (d, J = 8.2 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.12 – 7.02 (m, 3H), 4.08 (q, J = 7.2 Hz, 1H), 3.86 (dd, J = 13.2, 5.6 Hz, 1H), 3.69 (t, J = 6.7 Hz, 1H), 3.56 – 3.48 (m, 0H), 2.97 (qd, J = 13.5, 6.7 Hz, 1H), 2.28 (s, 3H), 1.78 (d, J = 12.3 Hz, 1H), 1.34 – 1.20 (m, 3H), 1.15 (t, J = 7.1 Hz, 2H), 1.06 (q, J = 11.0, 10.2 Hz, 1H), 0.87 (s, 3H), 0.81 (s, 3H)
P168	1H NMR (400 MHz, Methanol-d4) δ ppm 7.49 (d, J = 8.3 Hz, 2H), 7.25 – 7.13 (m, 4H), 7.04 – 6.94 (m, 2H), 4.2 (t, J = 7.1 Hz, 2H), 3.85 (dd, J = 13.3, 5.5 Hz, 1H), 3.69 (t, J = 6.7 Hz, 1H), 3.53 (dd, J = 13.3, 10.3 Hz, 1H), 2.99 (m, 3H), 2.96 – 2.78 (m, 1H), 1.80 (d, J = 10.9 Hz, 1H), 1.56 – 1.50 (t, 3H), 1.28 (s, 3H), 1.32 – 1.10 (m, 2H), 1.14 – 0.96 (m, 1H), 0.87 (s, 3H), 0.82 (s, 3H)
P169	1H NMR (400 MHz, Methanol-d4) δ ppm 7.49 (d, J = 8.3 Hz, 2H), 7.25 – 7.13 (m, 4H), 7.04 – 6.94 (m, 2H), 4.2 (t, J = 7.1 Hz, 2H), 3.85 (dd, J = 13.3, 5.5 Hz, 1H), 3.69 (t, J = 6.7 Hz, 1H), 3.53 (dd, J = 13.3, 10.3 Hz, 1H), 2.99 (m, 3H), 2.96 – 2.78 (m, 1H), 1.80 (d, J = 10.9 Hz, 1H), 1.56 – 1.50 (t, 3H), 1.28 (s, 3H), 1.32 – 1.10 (m, 2H), 1.14 – 0.96 (m, 1H), 0.87 (s, 3H), 0.82 (s, 3H)
P170	1H NMR (400 MHz, Methanol-d4) δ ppm 7.49 (d, J = 8.2 Hz, 2H), 7.33 – 7.13 (m, 6H), 4.08 (q, J = 7.1 Hz, 1H), 3.85 (dd, J = 13.3, 5.4 Hz, 1H), 3.60 – 3.48 (m, 1H), 2.98 (tt, J = 13.4, 6.5 Hz, 2H), 2.94 – 2.78 (m, 2H), 1.80 (d, J = 11.5 Hz, 1H), 1.55 (dd, J = 13.7, 7.3 Hz, 8H), 1.49 (t, 3H), 0.80 (s, 3H), 0.75 (s, 3H)
P171	1H NMR (400 MHz, Methanol-d4) δ ppm 7.57 (d, J = 8.0 Hz, 2H), 7.51 – 7.44 (m, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.24 – 7.17 (m, 1H), 4.07 (q, J = 7.1 Hz, 2H),

	3.73 – 3.54 (m, 1H), 3.05 – 2.89 (m, 1H), 1.60 (d, J = 9.6 Hz, 1H), 1.50 – 1.42 (m, 3H), 1.28 (dt, J = 22.5, 11.6 Hz, 1H), 0.97 (m, 3H), 0.85 (d, J = 19.3 Hz, 3H)

Example A: *In vitro* Inhibition Assays

TPH1 Assay

Recombinant human TPH1 (rTPH1 GenBank TM accession no. NP_004179) was expressed by cloning full length human TPH1 cDNA in to a bacterial pMAL-c5E expression vector to produce maltose-binding protein (MBP) TPH1 fusion proteins. *E.coli* BL21 (DE3) containing pMAL-c5E-TPH1 was used for protein generation and the recombinant protein was purified utilizing standard column chromatography techniques. The MBP tagged TPH1 (MBP-TPH1) was used directly to screen compounds as described below.

TPH1 activities were measured in an assay containing 200 mM ammonium sulfate, 7 mM DTT, 50 μg/mL catalase, 25 μM ammonium iron sulfate, 50 mM MES, pH 7.1. Test compounds were diluted in 100% DMSO and added to the assay plate in 1 μL aliquots at 100x final concentration. Fifty microliters of assay buffer containing 30 nM TPH1 enzyme (MBP tagged) were added to the plate wells containing the test compound by the use of an Eppendorf repeater pipette. The reaction was initiated by the addition of 50 μL of assay buffer containing 60 μM tryptophan and 72 μM 6-6-methyltetra-hydropterin (2x final concentration) by the use of a Multidrop (LabSystems). Final reaction conditions were 15 nM TPH1 enzyme, 30 μM tryptophan, 36 μM 6-methyltetra-hydropterin, 200 mM ammonium sulfate, 7 mM DTT, 25 μg/mL catalase, 25 μM ferrous ammonium sulfate, 50 mM MES, pH 7.1, with atmospheric oxygen at room temperature. The plate was immediately placed onto an M5 plate reader (Molecular Devices) for kinetic fluorescence measurement using an excitation setting of 300 nm and an emission setting of 335 nm. Fluorescence reads are recorded in kinetic mode for 300 seconds (5 minutes).

Kinetic assay data for compounds at specific concentrations was translated into slopes using the Softmax Pro software on a Spectramax reader, and compound inhibition slopes were compared with wells containing enzyme, substrate and cofactor in the absence of inhibitor (100%), and wells containing substrate and cofactor in the absence of enzyme (0%). DMSO concentration in the assay was 1%. Typically, in the absence of enzyme, reaction slopes were

~0. IC_{50}'s were determined using Graphpad Prism.

Compounds having an IC_{50} of 10,000 nM or less were considered active.

Data related to TPH1 inhibition activity of the compounds of the invention according to this assay is provided below in Table 10. Compounds that inhibit TPH1 with an IC_{50} from 3,000 nM to 10,000 nM are indicated by +. Compounds that inhibit TPH1 with an IC_{50} of less than 3,000 nM but more than 300 nM are indicated by ++. Compounds that inhibit TPH1 from 50 nM to 300 nM are indicated by +++. Compounds that inhibit TPH1 with an IC_{50} less than 50 nM are indicated by ++++.

Table 10. TPH1 Inhibition Data

Ex. No.	IC_{50}
1a	++++
1b	++
2	++
3	++
4	+++
5	++
6	+++
7	+++
8	++++
9	++++
10	++++
11	++++
12	+++
13	+
14	+++
15	++
16	+++
17	+++
18	+++
20	++++

21	++++
22	++
23	++
24	+++
25	++++
26	++++
27	++++
28	++++
29	++++
30	++++
31	++++
32	++++
33	++++
34	++++
35	++++
36	++++
37	++++
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39	++++
40	++++
41	++++
42	++++
43	++++
44	+++
46	++++
47	++
48	+++
49	+++
50	++
51	+++

52	++++
53	++++
54	++
55	+++
56	++++
57	++++
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61	+++
62	++++
63	++
64	++
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66	++++
67	+
68	+++
69	+++
70	++++
71	+
72	+++
73	++++
74	++++
75	++++
76	++++
77	++++
78	++++
79	++++
80	++++
81	++++

82	++++
83	++++
84	++++
85	++++
86	++++
87	+++
88	++++
89	++
90	+++
91	+++
92	+++
93	++
94	+++
95	++
96	++
97	++
98	++
99	+
100	+
101	+
102	+
103	+
104	+
105	+
106	++
107	+
108	++
109	++
110	++++
111	++++

112	+++
113	+++
114	+++
115	+++
116	+++
117	+++
118	+++
119	+++
120	+++
121	+++
122	+++
123	+++
124	+++
125	++
126	++
127	++
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129	++
130	++
131	++
132	++
133	++
134	++
135	++
136	++
137	++
138	++
139	+
140	+
141	+

142	+
143	+
144	+
145	+
146	+
147	+
148	++
149	+
150	+
151	++++
152	+++
153	++
154	++
155	++
156	++
157	+
158	+
159	+
160	+
178	+++
152a	+++
174	++++
175	++++
172	+++
173	++++
160	+++
161	++++
177	++++
176	++++
162	++++

163	++++
164	++
165	++++
166	+++
167	+++
168	+++
169	+++
170	++++
171	+++

Example B: Intestinal 5-HT depletion assay

The efficacy of the TPH1 inhibitors of the invention can be assessed for the ability to decrease intestinal serotonin concentration in mice. Mice (C57 BL6) are administered a single 150 mg/kg dose of test article by oral gavage. Each animal is euthanized by exsanguination under isoflurane anesthesia. Jejunal intestinal mucosa is isolated and homogenized in 300 μL of a buffer containing 0.3M trichloroacetic acid, 0.1M sodium acetate, 10 mM EDTA, 20 mM sodium bisulfate and 50 mM ascorbic acid. Following centrifugation the 5-HT levels in the supernatants are measured by HPLC. The remaining mucosal pellet is solubilized overnight at 37 °C in a 0.1% sodium dodecyl sulfate buffer in 0.1N NaOH followed by determination of protein concentrations using a BCA protein assay (Pierce, Rockford, Il. 5-HT levels were normalized to protein and data were expressed as mean percent reduction of mucosal 5-HT levels relative to vehicle control ± SEM (percent 5-HT reduction). All animal studies are carried out with protocols approved by the Institutional Animal Care and Use Committee.

Example C: Reduction of mucosal 5-HT concentrations

The efficacy of the TPH1 inhibitors of the invention can be assessed for the ability to decrease intestinal serotonin concentration in mice. Mice (C57 BL6) are administered an oral dose of 10 or 50 mg/kg of the test article in the evening. Approximately 16 h following the first dose, mice are administered a second oral dose of 50 mg/kg of the appropriate compound. A third oral dose of 50 mg/kg of the appropriate test article is administered 12 h after dose

2. Following an overnight fast, each animal is euthanized by exsanguination under isoflurane anesthesia. Jejunal intestinal mucosa is isolated and homogenized in 300 mL of a buffer containing 0.3 M trichloroacetic acid, 0.1 M sodium acetate, 10 mM EDTA, 20 mM sodium bisulfate and 50 mM ascorbic acid. Following centrifugation the 5-HT levels in the supernatants are measured by HPLC. The remaining mucosal pellet is solubilized overnight at 37 °C in a 0.1% sodium dodecyl sulfate buffer in 0.1N NaOH followed by determination of protein concentrations using a BCA protein assay (Pierce, Rockford, IL). 5-HT levels are normalized to protein and data are expressed as mean percent reduction of mucosal 5-HT levels relative to vehicle control ± SEM (percent 5-HT reduction). All animal studies are carried out with protocols approved by the Institutional Animal Care and Use Committee.

Certain compounds of the invention were tested in the above assay and found to be active in decreasing intestinal serotonin concentration. Tested compounds are indicated in Table 11 showing statistical significance (P-values) of the obtained data (ANOVA): * refers to P<0.05, ** refers to P<0.01, *** refers to P<0.005, and **** refers to P<0.0005.

Table 11.

Example No.	Statistical Significance	Example No.	Statistical Significance
P197	*	P1a	***
U1a	***	S1a	****
P175	***	P79	****
R1a	***	P174	****

Example D: *In vivo* assay for inflammatory bowel diseases

The utility of the compounds of the invention for the treatment of inflammatory bowel diseases can be measured, for example, using the experimental models of colitis induced by trinitrobenzene sulfonic acid (TNBS), dinitrobenzene sulfonic acid (DNBS), and dextran sodium sulfate (DSS), as described by Ghia, J.-E. et al. in *Gastroenterol.* **137**, 1649–60 (2009).

Example E: *In vivo* assay for low bone mass diseases

The utility of the compounds of the invention for the treatment of low bone mass diseases, such as osteoporosis, can be measured, for example, using the ovariectomy–induced osteopenia rat model, as described by Yadav, V. K. et al. in *Nature Med.* **16**, 308–12 (2010).

Example F: *In vivo* assay for PAH

The utility of the compounds of the invention for the treatment or prevention of pulmonary arterial hypertension (PAH), can be measured, for example, using the hypoxia mouse model, as described by Abid, S. et al. in *Am. J. Physiol., Lung Cellular and Molecular Physiology* **303**, L500–8 (2012), or using the rat monocrotaline-induced PAH or the rat chronic hypoxia model, as described by Kay, J. M. et al. *Respiration* 47, 48–56 (1985).

Example G: *In vivo* assay for allergic airway inflammation

The utility of the compounds of the invention for the treatment of allergic airway inflammation, can be measured, for example, using the mouse model of allergic asthma, as described by Dürk, T. et al. in *Am. J. Respir. Crit. Care Med.* **187**, 476–485 (2013).

Example H: *In vivo* assay for gastrointestinal disorders

The utility of the compounds of the invention for the treatment of gastrointestinal disorders associated with dysregulation of the GI serotonergic system, such as chemotherapy-induced emesis and irritable bowel syndrome, can be measured, for example, using the a ferret model of chemotherapy-induced emesis, as described by Liu, Q. et al. in *J. Pharmacol. Exp. Ther.* **325**, 47–55 (2008).

Example I: *In vivo* assay for tumor growth

The utility of the compounds of the invention for the treatment of tumor growth, can be measured, for example, using the the xenograft model of cholangiocarcinoma tumor growth, as described by Alpini, G. et al. in *Cancer Res.* **68**, 9184–93 (2008).

Example J: *In vivo* assay for leukemia

The utility of the compounds of the invention for the treatment and prevention of leukemia and other cancers of the blood, can be measured, for example, using the mouse

leukemia model, the osteoblast-deficient mouse model, or the murine model of acute myeloid leukemia, as described in WO 2013/074889.

Example K: *In vivo* assay for atherosclerosis

The utility of the compounds of the invention for the treatment or prevention of atherosclerosis, and the reduction of plasma cholesterol and triglyceride levels, can be measured, for example, using the Apo E -/- or LDLR -/- mouse models of atherosclerotic plaque development, as described in WO 2012/058598.

Example L: *In vivo* assay for necrotizing enterocolitis

The utility of the compounds of the invention for the treatment or prevention of of necrotizing enterocolitis can be assessed, for example, using SERT knockout mice, as described in WO 2013/148978.

Example M: *In vivo* assay for pulmonary fibrosis

The utility of the compounds of the invention for the treatment or prevention of pulmonary fibrosis (e.g., IPF) can be assessed, for example, using a bleomycin mouse model, as described in Fabre, A. et al. "Modulation of bleomycin-induced lung fibrosis by serotonin receptor antagonists in mice." *Eur. Respir. J.* 2008; 32; 426-436. Additional useful preclinical models and methods for testing the compounds of the invention for usefulness in the treatment or prevention of IPF are described in Moeller, A. et al. "The bleomycin animal model: a useful tool to investigate treatment options for idiopathic pulmonary fibrosis?" *Int. J. Biochem. Cell Biol.* 40, 362–82 (2008) and Mouratis, et al. "Modeling pulmonary fibrosis with bleomycin." *Curr. Opin. Pulm. Med.* 17, 355–61 (2011).

Example M: Preclinical model for systemic sclerosis (scleroderma)

The utility of the compounds of the invention for the treatment or prevention of scleroderma can be assessed, for example, according to the preclinical models and methods described in Derrett-Smith, E. C. et al. "Animal models of scleroderma: lessons from transgenic and knockout mice." *Curr. Opin. Rheumatol.* 21, 630–5 (2009) and Artlett, C. M. "Animal models of scleroderma: fresh insights." *Curr. Opin. Rheumatol.* 22, 677–82 (2010).

Example N: Preclinical model for liver fibrosis

The utility of the compounds of the invention for the treatment or prevention of liver fibrosis can be assessed, for example, according to the preclinical models and methods described in Liedtke, C. et al. "Experimental liver fibrosis research: update on animal models, legal issues and translational aspects." *Fibrogenesis Tissue Repair* 6, 19 (2013) and Iredale, J. P. "Models of liver fibrosis: exploring the dynamic nature of inflammation and repair in a solid organ." *J. Clin. Invest.* 117, 539–48 (2007).

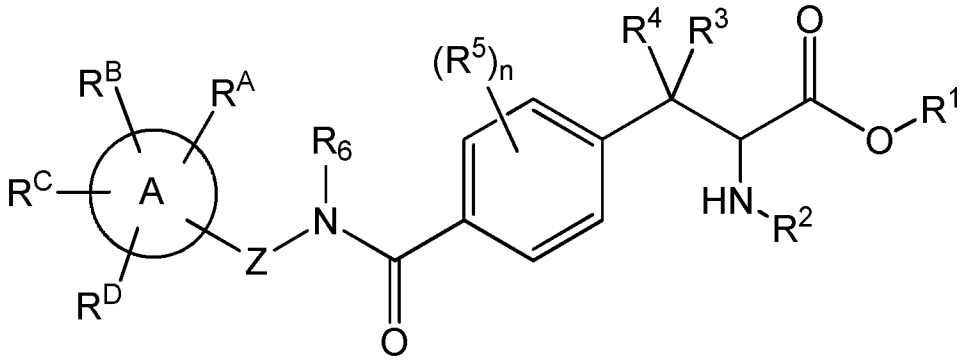
Example O: Preclinical model for renal fibrosis

The utility of the compounds of the invention for the treatment or prevention of renal fibrosis can be assessed, for example, using the preclinical *in vivo* animal model and methods described in Johnson, T.S., *J Clin Invest.* Jun 15, 1997; 99(12): 2950–2960.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

What is claimed is:

1. A compound of Formula I:



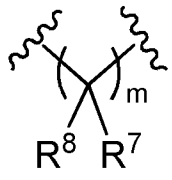
I

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is C_{3-14} cycloalkyl, C_{6-10} aryl, 4 to 14-membered heterocycloalkyl, or 5 to 10-membered heteroaryl;

Z is a bridging C_{3-14} cycloalkyl group, a bridging C_{6-10} aryl group, a bridging 4 to 14-membered heterocycloalkyl group, or a bridging 5 to 10-membered heteroaryl group, each optionally substituted by 1, 2, or 3 substituents independently selected from R^Z;

or Z is:



;

R^1 is H, C_{1-10} alkyl, C_{3-10} cycloalkyl, phenyl, $-(CR^9R^{10})_pOC(O)R^{11}$, $-(C\ R^9R^{10})_pNR^{11}R^{12}$, or $-(C\ R^9R^{10})_pC(O)NR^{11}R^{12}$, wherein said C_{1-10} alkyl, C_{3-10} cycloalkyl, and phenyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from F, Cl, Br, CN, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^2 is H, C_{1-4} alkyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, or $C(O)OR^{a1}$;

R^3 and R^4 are each independently selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, OH, and C_{1-4} alkoxy;

each R^5 is independently selected from halo, C_{1-4} alkyl, and C_{1-4} alkoxy;

R^6 is H or C_{1-4} alkyl;

or R^6 and Z, together with the N atom to which they are both attached, form a 4-7 membered heterocycloalkyl group optionally substituted by 1, 2, or 3 substituents independently selected from R^Z;

each R^7 is independently selected from H, halo, and C_{1-4} alkyl;

each R^8 is independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{8a}, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

or R^7 and R^8, when taken together with the single carbon atom to which they are both attached, form a C_{3-7} cycloalkyl group optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

each R^{8a} is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, 5-10 membered heteroaryl-C_{1-6} alkyl, and 4-10 membered heterocycloalkyl-C_{1-6} alkyl, each of which is optionally substituted by 1 or 2 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

R^9 are each independently selected from H and C_{1-4} alkyl;

R^{10} is C_{1-6} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from C_{1-6} haloalkyl, C_{3-10} cycloalkyl, OR^{a3}, and $NR^{c3}R^{d3}$;

R^{11} and R^{12} are each independently selected from H and C_{1-6} alkyl;

R^A is H, Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, or $S(O)_2NR^{c4}R^{d4}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$;

R^B is H, Cy^2, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}S(O)R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, or $S(O)_2NR^{c5}R^{d5}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from Cy^2, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}S(O)R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^C and R^D are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a6}, SR^{a6}, $C(O)R^{b6}$, $C(O)NR^{c6}R^{d6}$, $C(O)OR^{a6}$, $OC(O)R^{b6}$, $OC(O)NR^{c6}R^{d6}$, $NR^{c6}R^{d6}$, $NR^{c6}C(O)R^{b6}$, $NR^{c6}C(O)OR^{a6}$, $NR^{c6}C(O)NR^{c6}R^{d6}$, $NR^{c6}S(O)R^{b6}$, $NR^{c6}S(O)_2R^{b6}$, $NR^{c6}S(O)_2NR^{c6}R^{d6}$, $S(O)R^{b6}$, $S(O)NR^{c6}R^{d6}$, $S(O)_2R^{b6}$, and $S(O)_2NR^{c6}R^{d6}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a6}, SR^{a6}, $C(O)R^{b6}$, $C(O)NR^{c6}R^{d6}$, $C(O)OR^{a6}$, $OC(O)R^{b6}$, $OC(O)NR^{c6}R^{d6}$, $NR^{c6}R^{d6}$, $NR^{c6}C(O)R^{b6}$, $NR^{c6}C(O)OR^{a6}$, $NR^{c6}C(O)NR^{c6}R^{d6}$, $NR^{c6}S(O)R^{b6}$, $NR^{c6}S(O)_2R^{b6}$, $NR^{c6}S(O)_2NR^{c6}R^{d6}$, $S(O)R^{b6}$, $S(O)NR^{c6}R^{d6}$, $S(O)_2R^{b6}$, and $S(O)_2NR^{c6}R^{d6}$;

each R^Z is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with a substituent selected from halo, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

Cy^1 and Cy^2 are each independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy};

each R^{Cy} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl, CN, NO_2, OR^{a7}, SR^{a7}, $C(O)R^{b7}$, $C(O)NR^{c7}R^{d7}$, $C(O)OR^{a7}$, $OC(O)R^{b7}$, $OC(O)NR^{c7}R^{d7}$, $NR^{c7}R^{d7}$, $NR^{c7}C(O)R^{b7}$, $NR^{c7}C(O)OR^{a7}$, $NR^{c7}C(O)NR^{c7}R^{d7}$, $NR^{c7}S(O)R^{b7}$, $NR^{c7}S(O)_2R^{b7}$, $NR^{c7}S(O)_2NR^{c7}R^{d7}$, $S(O)R^{b7}$, $S(O)NR^{c7}R^{d7}$, $S(O)_2R^{b7}$, and $S(O)_2NR^{c7}R^{d7}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, CN, NO_2, OR^{a7}, SR^{a7}, $C(O)R^{b7}$, $C(O)NR^{c7}R^{d7}$, $C(O)OR^{a7}$, $OC(O)R^{b7}$, $OC(O)NR^{c7}R^{d7}$, $NR^{c7}R^{d7}$, $NR^{c7}C(O)R^{b7}$, $NR^{c7}C(O)OR^{a7}$, $NR^{c7}C(O)NR^{c7}R^{d7}$, $NR^{c7}S(O)R^{b7}$, $NR^{c7}S(O)_2R^{b7}$, $NR^{c7}S(O)_2NR^{c7}R^{d7}$, $S(O)R^{b7}$, $S(O)NR^{c7}R^{d7}$, $S(O)_2R^{b7}$, and $S(O)_2NR^{c7}R^{d7}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl;

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6}, R^{a7}, R^{b2}, R^{b4}, R^{b5}, R^{b6}, R^{b7}, R^{c2}, R^{c3}, R^{c4}, R^{c5}, R^{c6}, R^{c7}, R^{d2}, R^{d3}, R^{d4}, R^{d5}, R^{d6}, and R^{d7} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6}

alkenyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-4} alkyl, halo, CN, OR^{a8}, $C(O)R^{b8}$, $C(O)NR^{c8}R^{d8}$, $C(O)OR^{a8}$, $OC(O)R^{b8}$, $OC(O)NR^{c8}R^{d8}$, $NR^{c8}R^{d8}$, $NR^{c8}C(O)R^{b8}$, $NR^{c8}C(O)NR^{c8}R^{d8}$, $NR^{c8}C(O)OR^{a8}$, $S(O)R^{b8}$, $S(O)NR^{c8}R^{d8}$, $S(O)_2R^{b8}$, $NR^{c8}S(O)_2R^{b8}$, $NR^{c8}S(O)_2NR^{c8}R^{d8}$, and $S(O)_2NR^{c8}R^{d8}$;

each R^{a8}, R^{b8}, R^{c8}, and R^{d8} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{3-7} cycloalkyl, phenyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl, wherein said C_{1-4} alkyl, C_{2-4} alkenyl, C_{3-7} cycloalkyl, phenyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl are each optionally substituted by 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, and di(C_{1-4} alkyl)amino;

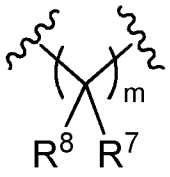
n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4; and

p is 1, 2, 3, or 4;

wherein:

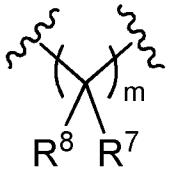
(3) when Z is:



,

R^2 is $C(O)OR^{a1}$, R^{a1} is C_{1-6} alkyl, m is 2, n is 0, R^3 is H, R^4 is H, R^6 is H, R^7 is H, R^8 is H, R^A is H, R^B is H, R^C is H, and R^D is H; then ring A is other than indolyl and naphthyl;

(4) when Z is:



,

R^2 is $C(O)OR^{a1}$, R^{a1} is C_{1-6} alkyl, m is 2, n is 0, R^3 is H, R^4 is H, R^6 is H, R^7 is H, R^8 is H, R^A is cyclohexyl or phenyl, R^B is H, R^C is H, and R^D is H; then ring A is other than phenyl;

(3) when Z is unsubstituted bridging furanyl, R^2 is H, n is 0, R^3 is H, R^4 is H, R^6 is H, and one of R^A, R^B, R^C, and R^D is methoxy; then ring A is other than phenyl; and

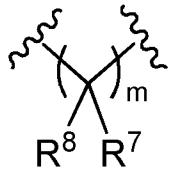
(4) when Z is bridging phenyl substituted by amino, R^2 is H, n is 0, R^3 is H, R^4 is H, and R^6 is H; then ring A is other than thienyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Ring A is C_{3-14} cycloalkyl, C_{6-10} aryl, 4 to 14-membered heterocycloalkyl, or 5 to 10-membered heteroaryl;

Z is a bridging C_{3-14} cycloalkyl group, a bridging C_{6-10} aryl group, a bridging 4 to 14-membered heterocycloalkyl group, or a bridging 5 to 10-membered heteroaryl group, each optionally substituted by 1, 2, or 3 substituents independently selected from R^Z;

or Z is:



;

R^1 is H, C_{1-10} alkyl, C_{3-10} cycloalkyl, phenyl, $-(CR^9R^{10})_pOC(O)R^{11}$, $-(C\ R^9R^{10})_pNR^{11}R^{12}$, or $-(C\ R^9R^{10})_pC(O)NR^{11}R^{12}$, wherein said C_{1-10} alkyl, C_{3-10} cycloalkyl, and phenyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from F, Cl, Br, CN, C_{1-4} alkyl, and C_{1-4} haloalkyl;

R^2 is H, C_{1-4} alkyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, or $C(O)OR^{a1}$;

R^3 and R^4 are each independently selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, OH, and C_{1-4} alkoxy;

each R^5 is independently selected from halo, C_{1-4} alkyl, and C_{1-4} alkoxy;

R^6 is H or C_{1-4} alkyl;

or R^6 and Z, together with the N atom to which they are both attached, form a 4-7 membered heterocycloalkyl group optionally substituted by 1, 2, or 3 substituents independently selected from R^Z;

each R^7 is independently selected from H, halo, and C_{1-4} alkyl;

each R^8 is independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

or R^7 and R^8, when taken together with the single carbon atom to which they are both attached, form a C_{3-7} cycloalkyl group optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

R^9 are each independently selected from H and C_{1-4} alkyl;

R^{10} is C_{1-6} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from C_{1-6} haloalkyl, C_{3-10} cycloalkyl, OR^{a3}, and $NR^{c3}R^{d3}$;

R^{11} and R^{12} are each independently selected from H and C_{1-6} alkyl;

R^A is H, Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, or $S(O)_2NR^{c4}R^{d4}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$,

$OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$;

R^B is H, Cy^2, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}S(O)R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, or $S(O)_2NR^{c5}R^{d5}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from Cy^2, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a5}, SR^{a5}, $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}S(O)R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^C and R^D are each independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a6}, SR^{a6}, $C(O)R^{b6}$, $C(O)NR^{c6}R^{d6}$, $C(O)OR^{a6}$, $OC(O)R^{b6}$, $OC(O)NR^{c6}R^{d6}$, $NR^{c6}R^{d6}$, $NR^{c6}C(O)R^{b6}$, $NR^{c6}C(O)OR^{a6}$, $NR^{c6}C(O)NR^{c6}R^{d6}$, $NR^{c6}S(O)R^{b6}$, $NR^{c6}S(O)_2R^{b6}$, $NR^{c6}S(O)_2NR^{c6}R^{d6}$, $S(O)R^{b6}$, $S(O)NR^{c6}R^{d6}$, $S(O)_2R^{b6}$, and $S(O)_2NR^{c6}R^{d6}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a6}, SR^{a6}, $C(O)R^{b6}$, $C(O)NR^{c6}R^{d6}$, $C(O)OR^{a6}$, $OC(O)R^{b6}$, $OC(O)NR^{c6}R^{d6}$, $NR^{c6}R^{d6}$, $NR^{c6}C(O)R^{b6}$, $NR^{c6}C(O)OR^{a6}$, $NR^{c6}C(O)NR^{c6}R^{d6}$, $NR^{c6}S(O)R^{b6}$, $NR^{c6}S(O)_2R^{b6}$, $NR^{c6}S(O)_2NR^{c6}R^{d6}$, $S(O)R^{b6}$, $S(O)NR^{c6}R^{d6}$, $S(O)_2R^{b6}$, and $S(O)_2NR^{c6}R^{d6}$;

each R^Z is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with a substituent selected from halo, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

Cy^1 and Cy^2 are each independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy};

each R^{Cy} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, (4-10 membered heterocycloalkyl)-C_{1-4} alkyl, CN, NO_2, OR^{a7}, SR^{a7}, $C(O)R^{b7}$, $C(O)NR^{c7}R^{d7}$, $C(O)OR^{a7}$, $OC(O)R^{b7}$, $OC(O)NR^{c7}R^{d7}$, $NR^{c7}R^{d7}$, $NR^{c7}C(O)R^{b7}$, $NR^{c7}C(O)OR^{a7}$, $NR^{c7}C(O)NR^{c7}R^{d7}$, $NR^{c7}S(O)R^{b7}$, $NR^{c7}S(O)_2R^{b7}$, $NR^{c7}S(O)_2NR^{c7}R^{d7}$, $S(O)R^{b7}$, $S(O)NR^{c7}R^{d7}$, $S(O)_2R^{b7}$, and $S(O)_2NR^{c7}R^{d7}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, CN, NO_2, OR^{a7}, SR^{a7}, $C(O)R^{b7}$, $C(O)NR^{c7}R^{d7}$, $C(O)OR^{a7}$, $OC(O)R^{b7}$, $OC(O)NR^{c7}R^{d7}$, $NR^{c7}R^{d7}$, $NR^{c7}C(O)R^{b7}$, $NR^{c7}C(O)OR^{a7}$, $NR^{c7}C(O)NR^{c7}R^{d7}$, $NR^{c7}S(O)R^{b7}$, $NR^{c7}S(O)_2R^{b7}$, $NR^{c7}S(O)_2NR^{c7}R^{d7}$, $S(O)R^{b7}$, $S(O)NR^{c7}R^{d7}$, $S(O)_2R^{b7}$, and $S(O)_2NR^{c7}R^{d7}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl;

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6}, R^{a7}, R^{b2}, R^{b4}, R^{b5}, R^{b6}, R^{b7}, R^{c2}, R^{c3}, R^{c4}, R^{c5}, R^{c6}, R^{c7}, R^{d2}, R^{d3}, R^{d4}, R^{d5}, R^{d6}, and R^{d7} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, (5-10 membered heteroaryl)-C_{1-4} alkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-4} alkyl, halo, CN, OR^{a8}, $C(O)R^{b8}$, $C(O)NR^{c8}R^{d8}$, $C(O)OR^{a8}$, $OC(O)R^{b8}$, $OC(O)NR^{c8}R^{d8}$, $NR^{c8}R^{d8}$, $NR^{c8}C(O)R^{b8}$, $NR^{c8}C(O)NR^{c8}R^{d8}$,

$NR^{c8}C(O)OR^{a8}$, $S(O)R^{b8}$, $S(O)NR^{c8}R^{d8}$, $S(O)_2R^{b8}$, $NR^{c8}S(O)_2R^{b8}$, $NR^{c8}S(O)_2NR^{c8}R^{d8}$, and $S(O)_2NR^{c8}R^{d8}$;

each R^{a8}, R^{b8}, R^{c8}, and R^{d8} is independently selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{3-7} cycloalkyl, phenyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl, wherein said C_{1-4} alkyl, C_{2-4} alkenyl, C_{3-7} cycloalkyl, phenyl, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl are each optionally substituted by 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, and di(C_{1-4} alkyl)amino;

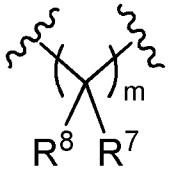
n is 0, 1, 2, 3, or 4;

m is 1, 2, 3, or 4; and

p is 1, 2, 3, or 4;

wherein:

(5) when Z is:



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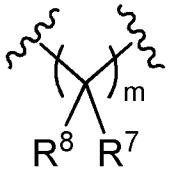
R^2 is $C(O)OR^{a1}$, R^{a1} is C_{1-6} alkyl, m is 2, n is 0, R^3 is H, R^4 is H, R^6 is H, R^7 is H, R^8 is H, R^A is H, R^B is H, R^C is H, and R^D is H; then ring A is other than indolyl and naphthyl;

(6) when Z is:



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R^2 is $C(O)OR^{a1}$, R^{a1} is C_{1-6} alkyl, m is 2, n is 0, R^3 is H, R^4 is H, R^6 is H, R^7 is H, R^8 is H, R^A is cyclohexyl or phenyl, R^B is H, R^C is H, and R^D is H; then ring A is other than phenyl;

(3) when Z is unsubstituted bridging furanyl, R^2 is H, n is 0, R^3 is H, R^4 is H, R^6 is H, and one of R^A, R^B, R^C, and R^D is methoxy; then ring A is other than phenyl; and

(4) when Z is bridging phenyl substituted by amino, R^2 is H, n is 0, R^3 is H, R^4 is H, and R^6 is H; then ring A is other than thienyl.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Ring A is C_{6-10} aryl or 5 to 10-membered heteroaryl.

4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Ring A is phenyl, naphthyl, pyridyl, indazolyl, or imidazolyl.

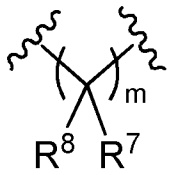
5. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Ring A is phenyl.

6. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Z is a bridging C_{3-14} cycloalkyl group, a bridging C_{6-10} aryl group, a bridging 4 to 14-membered heterocycloalkyl group, or a bridging 5 to 10-membered heteroaryl group, each optionally substituted by 1, 2, or 3 substituents independently selected from R^Z.

7. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Z is a bridging C_{3-7} cycloalkyl group.

8. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Z is a bridging cyclobutyl group or bridging cyclohexyl group.

9. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Z is:



10. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^6 and Z, together with the N atom to which they are both attached, form a 4-7 membered heterocycloalkyl group optionally substituted by 1, 2, or 3 substituents independently selected from R^Z.

11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^1 is H or C_{1-10} alkyl.

12. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^1 is H or C_{1-4} alkyl.

13. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^1 is H or ethyl.

14. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^1 is H.

15. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^1 is ethyl.

16. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^2 is H, C_{1-4} alkyl, $C(O)R^{b1}$, or $C(O)NR^{c1}R^{d1}$.

17. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^2 is H.

18. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each independently selected from H and C_{1-4} alkyl.

19. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are both H.

20. The compound of any one of claims 1 to 9 and 11 to 19, or a pharmaceutically acceptable salt thereof, wherein R^6 is H or methyl.

21. The compound of any one of 1 to 9 and 11 to 19, or a pharmaceutically acceptable salt thereof, wherein R^6 is H.

22. The compound of any one of claims 1 to 5, 9, and 11 to 21, or a pharmaceutically acceptable salt thereof, wherein each R^7 is independently selected from H and C_{1-4} alkyl.

23. The compound of any one of claims 1 to 5, 9, and 11 to 21, or a pharmaceutically acceptable salt thereof, wherein each R^7 is independently selected from H and methyl.

24. The compound of any one of claims 1 to 5, 9, and 11 to 21, or a pharmaceutically acceptable salt thereof, wherein R^7 is H.

25. The compound of any one of claims 1 to 5, 9, and 11 to 24, or a pharmaceutically acceptable salt thereof, wherein each R^8 is independently selected from H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

26. The compound of any one of claims 1 to 5, 9, and 11 to 24, or a pharmaceutically acceptable salt thereof, wherein each R^8 is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, and OR^{a2}, wherein said C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$,

$OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

27. The compound of any one of claims 1 to 5, 9, and 11 to 24, or a pharmaceutically acceptable salt thereof, wherein each R^8 is independently selected from H, C_{1-6} alkyl, or C_{3-10} cycloalkyl, wherein said C_{1-6} alkyl and C_{3-10} cycloalkyl, are each optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

28. The compound of any one of claims 1 to 5, 9, and 11 to 24, or a pharmaceutically acceptable salt thereof, wherein each R^8 is independently selected from H, C_{1-6} alkyl, or C_{3-7} cycloalkyl, wherein said C_{1-6} alkyl is optionally substituted by hydroxyl and said C_{3-7} cycloalkyl is optionally substituted by 1 or 2 methyl groups.

29. The compound of any one of claims 1 to 5, 9, and 11 to 24, or a pharmaceutically acceptable salt thereof, wherein each R^8 is independently selected from H and C_{1-6} alkyl.

30. The compound of any one of claims 1 to 5, 9, and 11 to 24, or a pharmaceutically acceptable salt thereof, wherein each R^8 is independently selected from H and C_{3-7} cycloalkyl.

31. The compound of any one of claims 1 to 5, 9, and 11 to 24, or a pharmaceutically acceptable salt thereof, wherein each R^8 is independently selected from H and 2-propyl.

32. The compound of any one of claims 1 to 5, 9, and 11 to 24, or a pharmaceutically acceptable salt thereof, wherein R^7 and R^8, when taken together with the single carbon atom to which they are both attached, form a C_{3-7} cycloalkyl group optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a2}, SR^{a2}, $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$,

$NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

33. The compound of any one of claims 1 to 5, 9, and 11 to 24, or a pharmaceutically acceptable salt thereof, wherein R^7 and R^8, when taken together with the single carbon atom to which they are both attached, form a C_{3-7} cycloalkyl group.

34. The compound of any one of claims 1 to 5, 9, and 11 to 24, or a pharmaceutically acceptable salt thereof, wherein R^7 and R^8, when taken together with the single carbon atom to which they are both attached, form a cyclopropyl group or a cyclobutyl group.

35. The compound of any one of claims 1 to 34, or a pharmaceutically acceptable salt thereof, wherein n is 0 or 1.

36. The compound of any one of claims 1 to 34, or a pharmaceutically acceptable salt thereof, wherein n is 0.

37. The compound of any one of claims 1 to 5, 9, and 11 to 36, or a pharmaceutically acceptable salt thereof, wherein m is 1.

38. The compound of any one of claims 1 to 5, 9, and 11 to 36, or a pharmaceutically acceptable salt thereof, wherein m is 2.

39. The compound of any one of claims 1 to 5, 9, and 11 to 36, or a pharmaceutically acceptable salt thereof, wherein m is 3.

40. The compound of any one of claims 1 to 5, 9, and 11 to 36, or a pharmaceutically acceptable salt thereof, wherein m is 4.

41. The compound of any one of claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein R^A is H, Cy^1, halo, C_{2-6} alkynyl, or OR^{a4}, wherein said C_{2-6} alkynyl is optionally

substituted with 1, 2, or 3 substituents independently selected from Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$.

42. The compound of any one of claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein R^A is Cy^1, halo, C_{2-6} alkynyl, or OR^{a4}, wherein said C_{2-6} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a4}, SR^{a4}, $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)OR^{a4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}S(O)R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, and $S(O)_2NR^{c4}R^{d4}$.

43. The compound of any one of claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein R^A is Cy^1.

44. The compound of any one of claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein Cy^1 is selected from phenyl, pyrazolyl, pyrimidinyl, pyridyl, cyclohexyl, cyclohexenyl, indazolyl, quinolyl, isoquinolyl, piperidinyl, thiazolyl, imidazolyl, benzimidazolyl, and benzo[d][1,3]dioxolyl, each of which is optionally substituted by 1, 2, or 3 substituents independently selected from R^{Cy}.

45. The compound of any one of claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein Cy^1 is phenyl optionally substituted by 1, 2, or 3 substituents independently selected from R^{Cy}.

46. The compound of any one of claims 1 to 45, or a pharmaceutically acceptable salt thereof, wherein each R^{Cy} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, OR^{a7}, $C(O)NR^{c7}R^{d7}$, $C(O)OR^{a7}$, and $NR^{c7}R^{d7}$, wherein said C_{1-6} alkyl is optionally substituted with 1 or 2 substituents independently selected from OR^{a7} and $NR^{c7}R^{d7}$.

47. The compound of any one of claims 1 to 45, or a pharmaceutically acceptable salt thereof, wherein each R^{Cy} is independently selected from F, Cl, methyl, ethyl, propyl, butyl, trifluoromethyl, phenyl, cyclopropyl, cyclobutyl, imidazolyl, oxazolyl, pyrazolyl, CN, hydroxy, methoxy, ethoxy, amino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methoxymethyl, hydroxymethyl, hydroxyethyl, isopropyloxymethyl, aminomethyl, carboxyl, carboxy ethyl ester, oxetanyl, dimethylaminoethyloxy, t-butoxy, cyclopropyloxy,

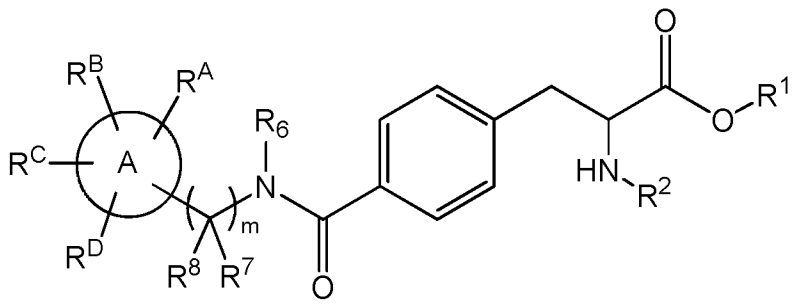
48. The compound of any one of claims 1 to 47, or a pharmaceutically acceptable salt thereof, wherein R^B is H, halo, or OR^{a5}.

49. The compound of any one of claims 1 to 47, or a pharmaceutically acceptable salt thereof, wherein R^B is H.

50. The compound of any one of claims 1 to 49, or a pharmaceutically acceptable salt thereof, wherein R^C is H.

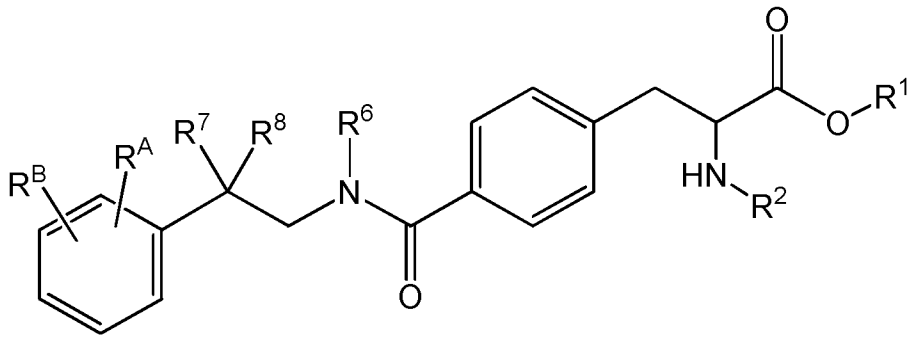
51. The compound of any one of claims 1 to 50, or a pharmaceutically acceptable salt thereof, wherein R^D is H.

52. The compound of any one of claims 1 to 5, 9, and 11 to 51, or pharmaceutically acceptable salt thereof, having Formula II:



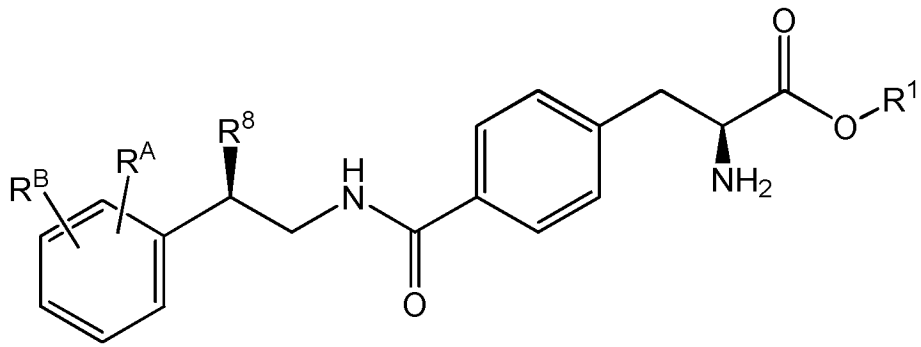
II.

53. The compound of any one of claims 1 to 5, 9, and 11 to 51, or pharmaceutically acceptable salt thereof, having Formula III:



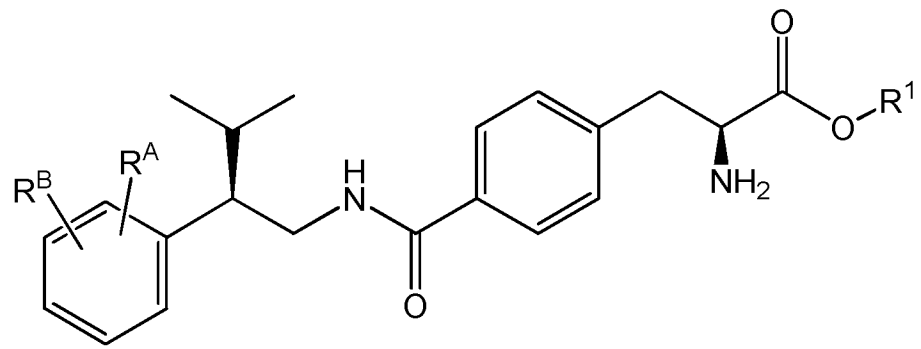
III.

54. The compound of any one of claims 1 to 5, 9, and 11 to 51, or pharmaceutically acceptable salt thereof, having Formula IV:



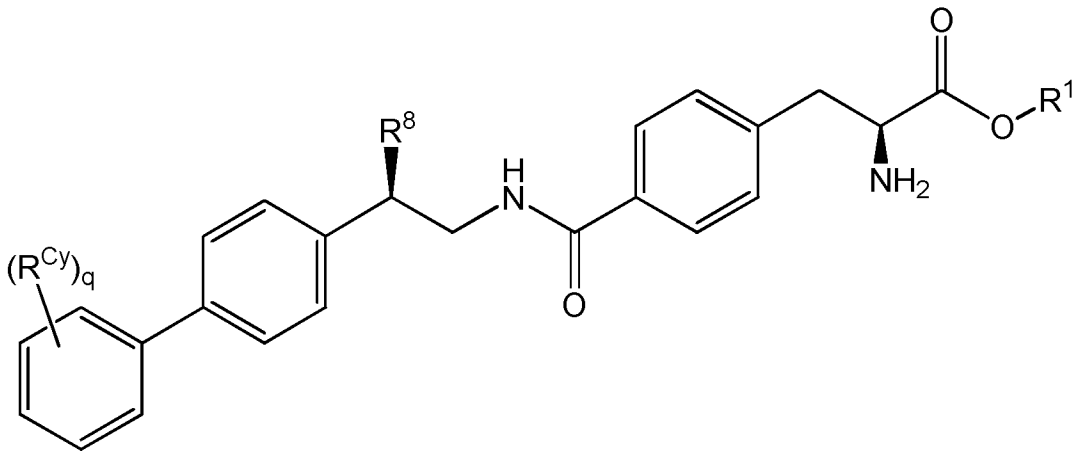
IV.

55. The compound of any one of claims 1 to 5, 9, and 11 to 51, or pharmaceutically acceptable salt thereof, having Formula V:



V.

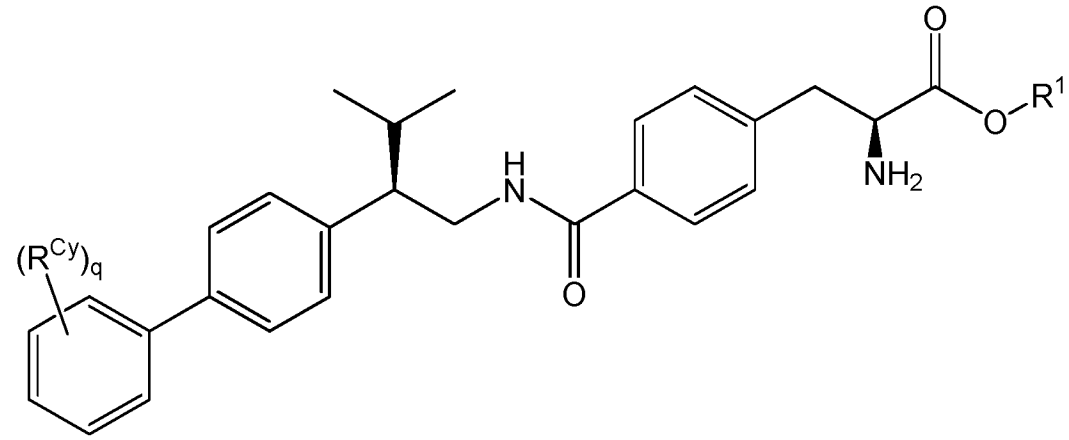
56. The compound of any one of claims 1 to 5, 9, and 11 to 51, or pharmaceutically acceptable salt thereof, having Formula VI:



VI

wherein q is 0, 1, 2, or 3.

57. The compound of any one of claims 1 to 5, 9, and 11 to 51, or pharmaceutically acceptable salt thereof, having Formula VII:



VII

wherein q is 0, 1, 2, or 3.

58. The compound of claim 1 selected from:

(S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-(((S)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(4-(pyrimidin-5-yl) phenyl)butyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)butyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-hydroxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4-(2-aminopyrimidin-5-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(2'-cyano-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(3'-cyano-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-ethyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(3'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-carbamoyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

4'-((R)-1-(4-((S)-2-amino-2-carboxyethyl)benzamido)-3-methylbutan-2-yl)-[1,1'-biphenyl]-4-carboxylic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-(ethoxycarbonyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid;

(S)-3-(4-(((R)-2-(4-(1H-pyrazol-4-yl)phenyl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-(((R)-2-(3'-(aminomethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(2'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(2',3',4',5'-tetrahydro-[1,1'-biphenyl]-4-yl)butyl)carbamoyl) phenyl) propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(4'-methyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-(aminomethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl) phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(2'-(aminomethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(2'-methyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(3'-fluoro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(3'-chloro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(3'-methoxy-5'-methyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(3'-(tert-butyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(3',5'-dimethyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(3'-methoxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(3'-hydroxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)butyl)carbamoyl) phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(3'-ethyl-[1,1'-biphenyl]-4-yl)-3-methyl butyl)carbamoyl)phenyl)propanoic acid;

(S)-3-(4-(((R)-2-(4-(1H-indazol-6-yl)phenyl)-3-methyl butyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-methoxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(3'-isopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(3'-cyclopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-3-(4-(((R)-2-(3'-(1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(3'-(oxazol-2-yl)-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-ethoxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-chloro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-ethyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-isobutyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-3-(4-(((R)-2-(3'-(1H-imidazol-1-yl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-(tert-butyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(4-(pyridin-4-yl)phenyl)butyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(4-(pyridin-3-yl)phenyl)butyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(4'-propyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-(methoxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(2'-fluoro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(3'-propyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-butyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-isopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid;

(S)-3-(4-(((R)-2-([1,1':3',1''-terphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-cyclopropoxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-cyclobutyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(2'-chloro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-(isopropoxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-cyclopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-3-(4-(((R)-2-(4-(1H-benzo[d]imidazol-5-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-(2-hydroxyethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-(tert-butoxy)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(3'-(2-(dimethylamino)ethoxy)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(3',4',5'-trifluoro-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-(2-(dimethylamino)ethoxy)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(4'-(oxetan-3-yl)-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(4-(thiazol-2-yl)phenyl) butyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(4-(thiazol-4-yl)phenyl)butyl) carbamoyl)phenyl)propanoic acid;

(S)-3-(4-(((R)-2-(4-(1H-imidazol-2-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoic acid; End Table 3

(S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cyclopropylethyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cyclobutylethyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3,3-dimethylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-(((R)-2-cyclobutyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-2-cyclobutylethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-cyclobutyl-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cyclohexylethyl)-carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(4,4-dimethylcyclohexyl) ethyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cyclopentylethyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-2-cyclopentylethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-cyclopentyl-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-cyclopentyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cycloheptylethyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-2-cycloheptylethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-cycloheptyl-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-cycloheptyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(naphthalen-2-yl)butyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-3-methyl-2-(4-(pyridin-2-yl)phenyl)butyl) carbamoyl)phenyl)propanoic acid;

(S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) (methyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-(((1S,2S)-2-([1,1'-biphenyl]-4-yl)cyclohexyl)carbamoyl) phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-((2-(4'-methoxy-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((2-(3'-chloro-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((2-(3'-methoxy-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((2-(2'-chloro-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((2-(2'-methoxy-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((4-(benzo[d][1,3]dioxol-5-yl)phenethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((4-(quinolin-8-yl)phenethyl)carbamoyl)phenyl) propanoic acid;

(S)-2-amino-3-(4-((4-(isoquinolin-5-yl)phenethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((4-(quinolin-3-yl)phenethyl)-carbamoyl)-phenyl) propanoic acid;

(S)-2-amino-3-(4-((4-(2-methoxypyridin-3-yl)phenethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((4-(1-methyl-1H-pyrazol-4-yl)phenethyl)carbamoyl) phenyl)propanoic acid;

(S)-2-amino-3-(4-((4-(pyridin-4-yl)phenethyl)carbamoyl)phenyl) propanoic acid;

(S)-2-amino-3-(4-((4-(isoquinolin-7-yl)phenethyl)carbamoyl)phenyl) propanoic acid;

S)-2-amino-3-(4-((2-(3'-(methylcarbamoyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)propanoic acid;

(S)-2-amino-3-(4-((2-(3'-(dimethylcarbamoyl)-[1,1'-biphenyl]-4-yl)ethyl) carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((2-(3'-carbamoyl-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-3-(4-((2-([1,1'-biphenyl]-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-5-hydroxy-3,3-dimethylhexyl)carbamoyl)phenyl)-2-aminopropanoic acid (Stereoisomer 1);

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-5-hydroxy-3,3-dimethylhexyl)carbamoyl)phenyl)-2-aminopropanoic acid (Stereoisomer 2);

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-5-hydroxy-3,3-dimethylhexyl)carbamoyl)phenyl)-2-aminopropanoic acid (Stereoisomer 3);

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-cycloheptylethyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-cyclohexylethyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-cyclopentylethyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-cyclobutylethyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-3-methylpentyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-4,4-dimethylpentyl) carbamoyl) phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-(tetrahydro-2H-pyran-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-4-methylpentyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-3,3,3-trifluoropropyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)hexyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-(((1-([1,1'-biphenyl]-4-yl)cyclobutyl)methyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)propyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)pentyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-(((1-([1,1'-biphenyl]-4-yl)cyclopropyl)methyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-((3-([1,1'-biphenyl]-2-yl)cyclobutyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((1-([1,1'-biphenyl]-4-yl)propan-2-yl)carbamoyl) phenyl)-2-aminopropanoic acid;

(S)-3-(4-((2-([1,1'-biphenyl]-3-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-((2-(naphthalen-2-yl)ethyl) carbamoyl)phenyl)propanoic acid;

(S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-methylpropyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-((3-([1,1'-biphenyl]-4-yl)propyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-((4-([1,1'-biphenyl]-2-yl)butyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-((2-(6-phenylpyridin-3-yl) ethyl)carbamoyl)phenyl)propanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-(2-hydroxyethoxy) ethyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-((2-(2-chloro-[1,1'-biphenyl]-4-yl) ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((2-(3-methoxy-[1,1'-biphenyl]-4-yl) ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((4-(tert-butyl)phenethyl)carbamoyl)phenyl)propanoic acid;

(S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-isopropyl-3-methyl butyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-((2-([1,1'-biphenyl]-2-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-((2-(naphthalen-1-yl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((2-(piperidin-1-yl)benzyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((3-(2-bromophenyl)propyl)carbamoyl)phenyl)propanoic acid;

(2S)-3-(4-((1-([1,1'-biphenyl]-4-yl)butan-2-yl) carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-(([1,1'-biphenyl]-3-ylmethyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-((2-(1-phenyl-1H-indazol-5-yl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((2-(4-phenyl-1H-imidazol-2-yl) ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((4-phenoxyphenethyl)carbamoyl)phenyl)propanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-3,3-dimethylbutyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-phenylethyl)carbamoyl) phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-((3-(2-(isoquinolin-7-yl)phenyl)propyl) carbamoyl)phenyl)propanoic acid;

(S)-3-(4-((3-([1,1'-biphenyl]-2-yl)propyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-((3-(2-(quinolin-8-yl)phenyl)propyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((3-(2-(benzo[d][1,3]dioxol-5-yl)phenyl)propyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((3-(2-(quinolin-3-yl)phenyl)propyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-((3-(2-(2,4-dimethylthiazol-5-yl)phenyl)propyl)carbamoyl)-phenyl)propanoic acid;

(S)-2-amino-3-(4-((3-(2-(quinolin-6-yl)phenyl)propyl)carbamoyl)phenyl)propanoic acid; and

(S)-2-amino-3-(4-((3-(2-(1-isobutyl-1H-pyrazol-4-yl)phenyl)propyl)-carbamoyl)phenyl)propanoic acid;

or a pharmaceutically acceptable salt of any of the aforementioned.

59. A compound of claim 1 selected from:

(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 3-(4-(((S)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4-(pyrimidin-5-yl)phenyl)butyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)butyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-hydroxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4-(2-aminopyrimidin-5-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(2'-cyano-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-cyano-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-ethyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-(aminomethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-(aminomethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(2'-(aminomethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(2'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-carbamoyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

4'-((R)-1-(4-((S)-2-amino-3-ethoxy-3-oxopropyl)benzamido)-3-methylbutan-2-yl)-[1,1'-biphenyl]-4-carboxylic acid;

ethyl 4'-((R)-1-(4-((S)-2-amino-3-ethoxy-3-oxopropyl)benzamido)-3-methylbutan-2-yl)-[1,1'-biphenyl]-4-carboxylate;

(S)-ethyl 3-(4-(((R)-2-(4-(1H-pyrazol-4-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4'-methyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-((2-(3'-(methylcarbamoyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-((2-(3'-(dimethylcarbamoyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-((4-phenoxyphenethyl)carbamoyl)phenyl)propanoate

(S)-ethyl 2-amino-3-(4-((2-(1-phenyl-1H-indazol-5-yl)ethyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-((2-(4-phenyl-1H-imidazol-2-yl)ethyl) carbamoyl)phenyl)propanoate;

(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl] -4-yl)-2-cyclobutylethyl)carbamoyl) phenyl)-2-aminopropanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(naphthalen-2-yl)butyl) carbamoyl)phenyl)propanoate;

(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cyclopentylethyl) carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cycloheptylethyl) carbamoyl)phenyl)-2-aminopropanoate;

(2S)-ethyl 3-(4-((2-([1,1'-biphenyl]-4-yl)-3,3-dimethylbutyl) carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(2'-methyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-cyclobutyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-2-cyclobutylethyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cyclohexylethyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-2-cyclopentylethyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-cyclobutyl-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-cyclopentyl-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-cyano-[1,1'-biphenyl]-4-yl)-2-cycloheptylethyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-fluoro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-cyclopentyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)ethyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-chloro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 3-(4-((2-([1,1'-biphenyl]-4-yl)-2-phenylethyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-cycloheptyl-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)ethyl) carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-methoxy-5'-methyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-(tert-butyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(3',5'-dimethyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-methoxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-hydroxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-cycloheptyl-2-(3'-methyl-[1,1'-biphenyl]-4-yl)ethyl) carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)butyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-ethyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(4,4-dimethylcyclohexyl)ethyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 3-(4-(((R)-2-(4-(1H-indazol-6-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(3'-(oxazol-2-yl)-[1,1'-biphenyl]-4-yl)butyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-chloro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-methoxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)butyl) carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-isopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 3-(4-(((R)-2-([1,1':3',1''-terphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)(methyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(3'-propyl-[1,1'-biphenyl]-4-yl)butyl) carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-cyclopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 3-(4-(((R)-2-(3'-(1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)-2-aminopropanoate;

(S)-ethyl 3-(4-(((R)-2-(3'-(1H-imidazol-1-yl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-(methoxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-butyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-ethyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-ethoxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-isopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4-(pyridin-4-yl)phenyl)butyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-isobutyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-cyclopropylethyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-(tert-butyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(2'-chloro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4-(pyridin-3-yl)phenyl)butyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4'-propyl-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(2'-fluoro-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-cyclobutyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-(isopropoxymethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-cyclopropyl-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-(2-hydroxyethyl)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 3-(4-(((R)-2-(4-(1H-benzo[d]imidazol-5-yl)phenyl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(3'-(2-(dimethylamino)ethoxy)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4-(pyridin-2-yl)phenyl)butyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(3',4',5'-trifluoro-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4'-(oxetan-3-yl)-[1,1'-biphenyl]-4-yl)butyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3,3-dimethylbutyl)carbamoyl)pheny)-2-aminopropanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-(2-(dimethylamino)ethoxy)-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4-(thiazol-2-yl)phenyl)butyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-3-methyl-2-(4-(thiazol-4-yl)phenyl)butyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4'-amino-3'-hydroxy-[1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl) phenyl)propanoate; and

(S)-ethyl 3-(4-(((1S,2S)-2-([1,1'-biphenyl]-4-yl)cyclohexyl)carbamoyl)pheny)-2-aminopropanoate;

or a pharmaceutically acceptable salt of any of the aforementioned.

60. A compound of claim 1 selected from:

(S)-3-(4-(((S)-1-([1,1'-biphenyl]-4-yl)propan-2-yl) carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(piperidin-4-yl)ethyl) carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(1-benzylpiperidin-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(1-methylpiperidin-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(1-ethylpiperidin-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)-2-(piperazin-1-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4-bromophenyl)-2-(4,4-dimethylcyclohexyl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-phenylethyl) carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(p-tolyl)ethyl) carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(4-fluorophenyl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(4-chlorophenyl)ethyl)carbamoyl)phenyl)propanoic acid;

(S)-2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(4-trifluoromethylphenyl)ethyl)carbamoyl)phenyl)propanoic acid;

(2S)-2-amino-3-(4-(((2R)-2-(4-bromophenyl)-2-(4-(trifluoromethyl)cyclohexyl)ethyl)carbamoyl)phenyl)propanoic acid;

(2S)-2-amino-3-(4-(((2R)-2-(4-bromophenyl)-2-(4-(tert-butyl) cyclohexyl)ethyl)carbamoyl)phenyl)propanoic acid;

(2S)-3-(4-(((2R)-2-([1,1'-biphenyl]-4-yl)-2-(4-(tert-butyl)cyclohexyl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(2S)-3-(4-(((2R)-2-([1,1'-biphenyl]-4-yl)-2-(4-(trifluoromethyl) cyclohexyl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(spiro[3.5]nonan-7-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoic acid;

(S)-3-(4-(((1S,2S)-2-([1,1'-biphenyl]-4-yl)cyclopentyl) carbamoyl)phenyl)-2-aminopropanoic acid; and

(2S)-3-(4-((2-([1,1'-biphenyl]-4-yl)cycloheptyl)carbamoyl)-phenyl)-2-aminopropanoic acid;

or a pharmaceutically acceptable salt of any of the aforementioned.

61. A compound of claim 1 selected from:

(2S)-ethyl 3-(4-((2-([1,1'-biphenyl]-4-yl)cycloheptyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 3-(4-(((S)-1-([1,1'-biphenyl]-4-yl)propan-2-yl)carbamoyl)phenyl)-2-aminopropanoate;

(2S)-ethyl 3-(4-(((2R)-2-([1,1'-biphenyl]-4-yl)-2-(4-(tert-butyl)cyclohexyl)ethyl)carbamoyl) phenyl)-2-aminopropanoate;

(2S)-ethyl 3-(4-(((2R)-2-([1,1'-biphenyl]-4-yl)-2-(4-(trifluoromethyl)cyclohexyl)ethyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 3-(4-(((1S,2S)-2-([1,1'-biphenyl]-4-yl)cyclopentyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(spiro[3.5]nonan-7-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(1-methylpiperidin-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-2-(1-ethylpiperidin-4-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoate;

(2S)-ethyl 3-(4-((2-([1,1'-biphenyl]-4-yl)-2-(4-methylpiperazin-1-yl)ethyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-propyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoate;

(S)-neopentyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoate;

(S)-butyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl) carbamoyl)phenyl)-2-aminopropanoate;

(S)-cyclopentyl 3-(4-(((R)-2-([1,1'-biphenyl]-4-yl)-3-methylbutyl)carbamoyl)phenyl)-2-aminopropanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-phenylethyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(p-tolyl)ethyl)carbamoyl) phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(4-fluorophenyl)ethyl)carbamoyl) phenyl) propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)phenyl)propanoate;

(S)-ethyl 2-amino-3-(4-(((R)-2-(4-chlorophenyl)-2-(4,4-dimethylcyclohexyl)ethyl)carbamoyl)phenyl)propanoate; and

(S)-ethyl 2-amino-3-(4-(((R)-2-(4,4-dimethylcyclohexyl)-2-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)phenyl)propanoate;

or a pharmaceutically acceptable salt of any of the aforementioned.

62. A pharmaceutical composition comprising a compound of any one of claims 1 to 61, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

63. A method of inhibiting TPH1 comprising contacting said TPH1 with a compound of any one of claims 1 to 61, or a pharmaceutically acceptable salt thereof.

64. A method of lowering peripheral serotonin in a patient comprising administering to said patient a compound of any one of claims 1 to 61, or a pharmaceutically acceptable salt thereof.

65. A method of treating or preventing a disease in a patient, wherein said disease is selected from bone disease, cardiovascular disease, metabolic disease, pulmonary disease, gastrointestinal disease, liver disease, cancer, inflammatory disease, and fibrotic disease comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1 to 61, or a pharmaceutically acceptable salt thereof.

66. The method of claim 65 wherein said bone disease is osteoporosis, osteoporosis pseudoglioma syndrome (OPPG), osteopenia, osteomalacia, renal osteodystrophy, Paget's disease, bone fracture, and bone metastasis.

67. The method of claim 65 wherein said osteoporosis is primary type 1 osteoporosis.

68. The method of claim 65 wherein said cardiovascular disease is pulmonary arterial hypertension (PAH).

69. The method of claim 68 wherein said PAH is associated pulmonary arterial hypertension (APAH).

70. The method of claim 65 wherein said metabolic disease is diabetes or hyperlipidemia.

71. The method of claim 65 wherein said pulmonary disease is chronic obstructive pulmonary disease (COPD) or pulmonary embolism.

72. The method of claim 65 wherein said gastrointestinal disease is irritable bowel disease (IBD).

73. The method of claim 65 wherein said liver disease is hepatitis.

74. The method of claim 65 wherein said cancer is liver cancer, breast cancer, cholangiocarcinoma, colon cancer, colorectal cancer, neuroendocrine tumors, pancreatic cancer, prostate cancer, bone cancer, or blood cancer.

75. The method of claim 65 wherein said inflammatory disease is allergic airway inflammation.

76. The method of claim 65 wherein said fibrotic disease is scleroderma, idiopathic pulmonary fibrosis (IPF), heart valve fibrosis, kidney fibrosis, or liver fibrosis.

77. A method of treating or preventing Raynaud's syndrome in a patient comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1 to 61, or a pharmaceutically acceptable salt thereof.

78. A method of treating or preventing carcinoid syndrome in a patient comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1 to 61, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/067815

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/14 C07D217/02 C07D317/58 C07D231/12 C07D231/56
C07D233/61 C07D235/14 C07D239/26 C07C229/00 C07D263/32
C07D277/28 C07D211/26 C07D295/13 C07D213/30 C07D213/40

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07C

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IRENA BEREZOWSKA ET AL: "Agonist vs Antagonist Behavior of [delta] Opioid Peptides Containing Novel Phenylalanine Analogues in Place of Tyr 1", JOURNAL OF MEDICINAL CHEMISTRY, vol. 52, no. 21, 12 November 2009 (2009-11-12), pages 6941-6945, XP055255383, US ISSN: 0022-2623, DOI: 10.1021/jm9004913 figure 1 -/--	1-5, 9-36,38, 41-46, 48-54, 56,62

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 March 2016	16/03/2016

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

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	LIANG OUYANG ET AL: "Combined Structure-Based Pharmacophore and 3D-QSAR Studies on Phenylalanine Series Compounds as TPH1 Inhibitors", INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES, vol. 13, no. 12, 2 December 2012 (2012-12-02), pages 5348-5363, XP055168454, ISSN: 1661-6596, DOI: 10.3390/ijms13055348 the whole document	1-78

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/067815

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