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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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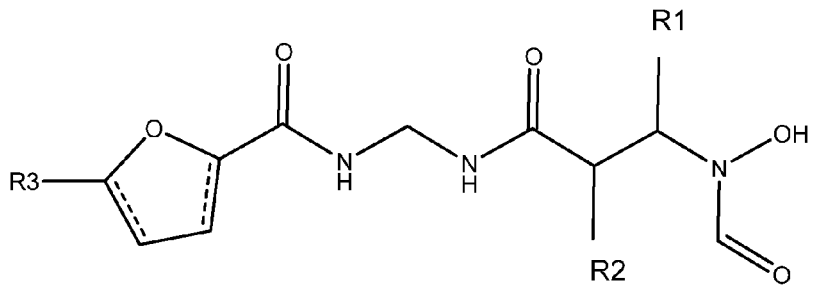
[Continued on next page]

(54) **Title**: HYDROXY FORMAMIDE DERIVATIVES AND THEIR USE



(I)

(57) **Abstract**: Disclosed are compounds having the formula (I): wherein R1, R2 and R3 are as defined herein, and methods of making and using the same, including use as inhibitors of BMP1, TLL1 and/or TLL2 and in treatment of diseases associated with BMP1, TLL1 and/or TLL2 activity.

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HYDROXY FORMAMIDE DERIVATIVES AND THEIR USE

FIELD OF THE INVENTION

The present invention relates to compounds that inhibit BMP1 (also known as BMP-1, bone morphogenic protein 1, bone morphogenetic protein 1, procollagen C-proteinase, and procollagen C-endopeptidase), Tolloid-like 1 (TLL1) and/or Tolloid-like 2 (TLL2) metalloproteases, inclusive of isoforms, in particular multiple isoforms encoded by RNA splice variants, and methods of making and using the same. Specifically, the present invention relates to reverse hydroxamate compounds as BMP1, TLL1 and/or TLL2 inhibitors.

BACKGROUND OF THE INVENTION

Fibrous collagens are integral parts of the extracellular matrix that support tissue integrity and maintain the cellular microenvironment for normal physiological functions. Collagens I-III, the major isoforms of the fibrous collagen protein family, are synthesized as procollagen precursors containing N-terminal and C-terminal propeptides. The procollagens are post-translationally modified by proline hydroxylation, and secreted into the peri-vascular space for further processing. N-terminal propeptides of the collagens are subsequently cleaved by proteinases of the ADAMTS (A Distintegrin And Metalloproteinase with ThromboSpondin repeats) family, while the C-terminal propeptides are processed by the Tolloid family of metalloproteases, which include BMP1, TLL1 and TLL2 (Hopkins, D.R. et al., Matrix Biology, 2007, 26, 508-523). The cleavage of both N-terminal and C-terminal propeptides allows further maturation of the collagen, leading to cross-linking at lysine residues and formation of insoluble fibrillar structures (Shoulders, M.D. et al., Annual Review of Biochemistry, 2009, 78, 929-958).

Whereas the BMP1, TLL1 and TLL2 proteins are encoded by separate genes, this family also includes isoforms of BMP1, including multiple isofoms of BMP1 that result from alternative splicing of the same gene product (see e.g.,Takahara, K., et al., The Journal of Biological Chemistry, 1994, 269. 32572-32578; and Cvetjeticanin, B. et al., Medical Hypotheses, 2014, 83, 656-658). The originally discovered form of BMP1 is designated BMP-1-1 or BMP1-1. Other BMP1 isoforms encoded by splice variant RNA transcripts have been described at the transcriptional level and designated with sequential suffixes, e.g., as BMP-1-2, BMP-1-3, BMP-1-4, BMP-1-5, BMP-1-6, and BMP-1-7 (see, e.g., Wozney et al., Science (1988), 242: 1528-1534; Kessler et al., Science, (1996) 271: 360-362; Li et al., Proc. Natl. Acad. Sci. USA (1996), 93: 5127-5130; Janitz et al., J. Mol. Med. (1998), 76: 141-146; Takahara et al., J. Biol. Chem. (1994), 269: 32572-

32578; and Ge and Greenspan, Birth Defect Res. (2006), 78: 47-68).

A number of BMP1 isoforms have also been confirmed at the protein level as circulating in the blood of patients with various diseases and in healthy humans (see, e.g., International Patent publication Nos. WO2008/011193 A2 and WO2013/163479 A1, and Grgurevic et al., J. Am. Soc. Nephrol. (2011), 21:681-692). In addition, the role of BMP1 in processing procollagen leading to fibrosis and scar tissue in a variety of diseases as well as the discovery of blood profiles comprising individual BMP1 isoforms in patients with various diseases has made BMP1 an attractive target for developing new therapies (see, e.g. WO2008/011193 A2; WO2013/163479 A1; Grgurevic et al., J. Am. Soc. Nephrol. (2011), 21:681-692, Cvetjeticanin, B. et al., Medical Hypotheses, 2014, 83, 656-658; and Turtle et al., Expert Opin. Ther. Patents (2004), 14(8):1185-1197).

Excessive production of extracellular matrix (ECM) proteins, including collagen, can lead to fibrotic pathologies in various organs or tissues that may be associated with increased tissue rigidity, parenchymal replacement, aberrant electrical conductance, sclerotic wound healing (e.g. infarction and burns), and/or abnormal cell-cell interactions. For example, increased fibrosis and collagen production are consistently observed in patients with acute and chronic cardiac diseases, e.g., heart failure, arrhythmias, hypertrophic cardiomyopathy, and myocardial infarction (Lopez, B. et al., Circulation, 2010, 121, 1645-1654; Ho, C.Y., et al., New England Journal of Medicine, 2010, 363, 552-563; Kostin, S. et al., Cardiovascular Research, 2002, 54, 361–379; See, F., et al., Current Pharmaceutical Design, 2005, 11, 477-487; Cvetjeticanin, B. et al. Medical Hypotheses, 2014, 83, 656-658), chronic obstructive pulmonary disease (“COPD”) (Salazar, L.M., et al., Lung, 2011, 189, 101-109), liver cirrhosis and nonalcoholic steatohepatitis (“NASH”) (Bataller, R., et al., Journal of Clinical Investigation, 2005, 115, 209-218), idiopathic pulmonary fibrosis (Chakraborty, S, et al., Expert Opin Investig Drugs, 2014, 23, 893-910), collagen vascular diseases, e.g. systemic lupus erythematosus, rheumatoid arhthritis and scleroderma (Eckes, B., et al., J Mol Med, 2014, 92, 913-924), muscular dystrophies (e.g., Serrano, A.C., et al., Experimental Cell Research, 2010, 316, 3050-3058; Klingler, W., et al., Acta Myoligica, XXXI, 2012, 184-195), chronic kidney disease (Liu, Y., Nature Reviews Nephrology, 2011, 7, 684-696), acute kidney injury (Molitoris, B., The Journal of clinical Investigation, 2014, 124, 2355-2363; Venkatachalam, M.A. et al., Am J Physiol Renal Physiol 298: F1078–F1094, 2010), diabetic nephropathy (Sun, Y.M., et a., Biochemical and Biophysical Research Communications, 2013, 433, 359-361), keloids, wound healing, adhesions, hypertrophic and other scarring associated with, e.g. burns, surgery and other trauma (Meier K., et al., Expert Opinion on Emerging Drugs, 2006, 11, 39-47; Malecaze, F., et al., Investigative

Opthalmology and Visual Science, 2014, 55, 6712-6721; van der Weer, W. et al., Burns, 2009, 35,15-29), stroke, multiple sclerosis and spinal cord injury (Fernández-Klett, F. and Piller, J. Brain Pathology, 2014, 24, 404-13; Rimar, D. et al., Arthritis & Rheumatology, Vol. 66, No. 3, March 2014, 726-730). Therefore, reducing excessive collagen production and maturation by targeting the BMP1, TLL1 and/or TLL2 pathway(s) can be an effective therapeutic strategy for treating fibrotic pathologies such as these diseases. This is supported by recent published studies using pharmacological agents that inhibit BMP1, TLL1 and/or TLL2 activity in cardiac and kidney disease models in small animals (Grgurevic, L., et al., Journal of the AmericanSociety of Nephrology, 2011, 21, 681-692; He, W., et al., Proceedings of the National Academy of Sciences, 2010, 107, 21110-21115; Cvetjeticanin, B. et al., Medical Hypotheses, 2014, 83, 656-658; International Patent publication Nos. WO2008/011193 A2 and WO2013/163479 A1).

The Tolloid family of metalloproteases (BMP1, TLL1 and TLL2) has additional substrates beyond collagens that may also contribute to its role in promoting ECM protein production. For example, the pro-form of lysyl oxidase 1 (LOX1) has been shown to be a substrate of BMP1, and cleavage by BMP1 enhances the LOX enzyme activity and thereby induces collagen cross-linking (Uzel, M.I., et al., Journal of Biological Chemistry, 2001, 276, 22537-22543). Thus, BMP1 also has a role in the development of pathological tissue stiffness via this mechanism, for example in glaucoma (Tovar-Vidales, T., et al., Investigative Ophthalmology & Visual Science, 2013, 54, 4741-4748) and in diastolic dysfunction in the heart (López, B., et al., American Journal of Physiology – Heart and Circulatory Physiology, 2010, 299, H1-H9). TGF-beta binding protein (LTBP) has also been shown to be cleaved by BMP1, allowing enhanced TGF-beta action to induce further collagen production (Ge, G., et al., Journal of Cell Biology, 2006, 175, 111-120). Regulation of TGF-beta by BMP1 may also play roles in other pathologies, such as control of cancer cell metastasis and invasion (Wu, X., et al. Oncogene, 2014, 33, 1506-1514). Similarly, BMP1, TLL1 and/or TLL2 also activate a broader range of other TGF-beta like molecules, such as BMPs 2 and 4, by proteolytically processing interacting proteins (Hopkins, D.R. et al., Matrix Biology, 2007, 26, 508-523). The combined actions of BMP1 and its various substrates suggest that BMP1, TLL1 and TLL2 are key regulators of tissue ECM production/maturation and that the members of the tolloid family of metalloproteases are particularly effective targets for anti-fibrosis therapeutic intervention.

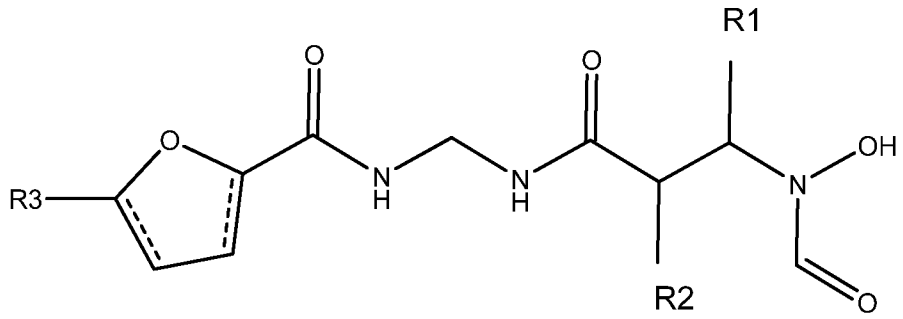
BMP1, TLL1 and TLL2 may also affect other biological pathways via additional substrate processing. In particular, they may affect muscle biology via promoting activation of myostatin. Myostatin is a hormone that negatively regulates muscle growth

(Lee, S. J., 2004, Annual Review of Cell & Developmental Biology, 20, 61-86). BMP1 has been demonstrated to cleave an inhibitory pro-peptide of myostatin and thus enhance myostatin activity (Wolfman N.M., et al., Proceedings of the National Academy of Sciences, 2003, 100, 15842-15846). Knockout of TLL2 in mice demonstrated enhanced muscle mass, thereby providing support for the connection between tolloid metalloprotease and myostatin (Lee, S.J., PLoS one, 2008, 3, e1628). An inhibitor of BMP1, TLL1 and/or TLL2 could therefore be beneficial in diseases where muscle function or muscle mass is diminished, including muscular dystrophy, sarcopenia, and cachexia associated with, e.g., heart failure, CKD, COPD, cancer or old age.

Taken together, the biology of BMP1, TLL1 and TLL2 lends strong support for their key roles in collagen processing, assembly and cross-linking, leading to the formation of a fibrillar collagen network that maintains tissue integrity and proper cellular microenvironment. This family of proteins may also play important roles in the etiology of fibrotic conditions, for example in the heart, lung, skeletal muscle, kidney, liver, skin, vasculature, nervous system, and eye, and inhibitors of these metalloproteases may provide broad benefits as anti-fibrotic agents for the treatment of diseases associated with fibrosis, such as myocardial infarction, heart failure, cardiac arrhythmias, hypertrophic cardiomyopathy, chronic kidney disease (CKD), post-acute kidney injury, diabetic nephropathy, delayed graft function post-transplantation, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), liver cirrhosis, non-alcoholic steatohepatitis (NASH), muscular dystrophies (e.g., Duchenne, Becker, limb-girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery-Dreifuss), glaucoma, corneal scarring, keloids, wound healing, adhesions, hypertrophic scarring, other scarring, e.g. associated with burns, surgery or other trauma, stroke, collagen vascular diseases such as systemic lupus erythematosus, rheumatoid arthritis and scleroderma, spinal cord injury and multiple sclerosis. Furthermore, BMP1, TLL1 and TLL2 inhibitors may have additional therapeutic applications in muscular disease based on their impact on myostatin biology, in particular muscular dystrophies (e.g., Duchenne, Becker, limb-girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery-Dreifuss), sarcopenia, and cachexia associated with, e.g., heart failure, CKD, COPD, cancer or old age.

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to compounds of Formula (I):



(I)

wherein:

R1 is selected from the group consisting of H, (C_1-C_4) straight chain alkyl, and (C_1-C_4) straight chain alkyl substituted with a hydroxy group;

R2 is selected from H, (C_1-C_{11})alkyl, (C_1-C_3)alkyl-(C_3-C_6)cycloalkyl, (C_1-C_3)alkyl-phenyl, (C_1-C_3)alkyl-naphthyl and (C_1-C_3)alkyl-heterocyclyl, wherein heterocyclyl is a monocyclic ring having 5-6 ring atoms wherein 1-2 of the ring atoms are selected from nitrogen, oxygen and sulfur, and wherein said (C_1-C_{11})alkyl, cycloalkyl, phenyl, naphthyl and heterocyclyl may be optionally substituted with 1-2 groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo,and cyano; and

R3 is selected from:

a) phenyl, optionally substituted with 1-3 groups independently selected from:

(C_1-C_6)alkyl, optionally substituted with 1-3 groups independently selected from: fluoro (e.g., -CF_3); -CO_2H; -P(O)R^fR^g; NR^aR^b wherein R^a is selected from H and (C_1-C_4)alkyl and R^b is selected from (C_1-C_4)alkyl substituted with -CO_2H or -P(O)R^fR^g, and -C(O)NR^aR^b wherein R^a and R^b are independently selected from H and (C_1-C_4)alkyl, wherein the (C_1-C_4)alkyl is optionally substituted with 1-3 groups independently selected from hydroxy, -CO_2H, -C(O)O(C_1-C_4)alkyl and -P(O)R^fR^g;

cyclopropyl, optionally substituted with 1 -CO_2H;

-C(O)NR^aR^b wherein R^a and R^b are independently selected from H and (C_1-C_4)alkyl, wherein the (C_1-C_4)alkyl is optionally substituted with 1-3 groups independently selected from hydroxy, -CO_2H, -C(O)O(C_1-C_4)alkyl, -P(O)R^fR^g, NR^cR^d and N^+ $R^cR^dR^e$;

(C_1-C_6)alkoxy, optionally substituted with 1-3 substituents independently selected from

halo, hydroxy, $-CO_2H$, (C_3-C_6)cycloalkyl, $C(O)NH_2$ and pyrrolidinyl;

(C_3-C_6)cycloalkoxy, optionally substituted with 1-3 substituents independently selected from halo, hydroxy, and $-CO_2H$;

$-NR^aR^b$ wherein R^a and R^b are independently selected from H and (C_1-C_4)alkyl, wherein the (C_1-C_4)alkyl is optionally substituted with 1-3 groups independently selected from oxo and $-CO_2H$;

$-SR^a$ wherein R^a is selected from H and (C_1-C_4)alkyl;

$-CO_2H$; $-C(NOH)NH_2$; cyano; $-C(O)O(C_1-C_4)$alkyl; $-C(O)CO_2H$; $-P(O)R^fR^g$; $-OP(O)R^fR^g$; halo; hydroxy; nitro; $-NHSO_2(C_1-C_2)$alkyl; $-SO_3H$; $-SO_2(C_1-C_2)$alkyl; $-SO_2NR^cR^d$; $-SO_2NHC(O)(C_1-C_2)$alkyl; and $-B(OH)_2$;

and

b) heteroaryl, optionally substituted with 1-2 groups independently selected from:

(C_1-C_4)alkyl, (C_1-C_4)alkoxy, oxo, $-CO_2H$, $-P(O)R^fR^g$, and $-OP(O)R^fR^g$;

wherein in each occurrence: R^c, R^d and R^e are independently selected from H and (C_1-C_2)alkyl; and R^f and R^g are independently selected from hydroxy, (C_1-C_2)alkyl and (C_1-C_2)alkoxy;

and salts, particularly pharmaceutically acceptable salts, thereof.

This invention is also directed to compounds of Formula (I) as represented above, wherein:

R1 is selected from H, (C_1-C_4) straight chain alkyl, and (C_1-C_4) straight chain alkyl substituted with a hydroxy group;

R2 is selected from H, (C_1-C_{11})alkyl, (C_1-C_3)alkyl-(C_3-C_6)cycloalkyl, (C_1-C_3)alkyl-phenyl and (C_1-C_3)alkyl-heterocyclyl, wherein heterocyclyl is a monocyclic ring having 5-6 ring atoms wherein 1-2 of the ring atoms are selected from nitrogen, oxygen and sulfur, and wherein said (C_1-C_{11})alkyl, cycloalkyl, phenyl and heterocyclyl may be optionally substituted with 1-2 groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo,and cyano; and

R3 is selected from:

a) phenyl, optionally substituted with 1-3 groups independently selected from:

$(C_1$-$C_6)$alkyl, optionally substituted with 1-3 groups independently selected from: fluoro (e.g., $-CF_3$); $-CO_2H$; $-P(O)R^fR^g$; and $-C(O)NR^aR^b$ wherein R^a and R^b are independently selected from H and $(C_1$-$C_4)$alkyl, wherein the $(C_1$-$C_4)$alkyl is optionally substituted with 1-3 groups independently selected from hydroxy, $-CO_2H$, $-C(O)O(C_1$-$C_4)$alkyl and $-P(O)R^fR^g$;

cyclopropyl, optionally substituted with 1 $-CO_2H$;

$-C(O)NR^aR^b$ wherein R^a and R^b are independently selected from H and $(C_1$-$C_4)$alkyl, wherein the $(C_1$-$C_4)$alkyl is optionally substituted with 1-3 groups independently selected from hydroxy, $-CO_2H$, $-C(O)O(C_1$-$C_4)$alkyl, $-P(O)R^fR^g$, NR^cR^d and $N^+R^cR^dR^e$;

$(C_1$-$C_6)$alkoxy, optionally substituted with 1-3 substituents independently selected from halo, hydroxy, $-CO_2H$, $(C_3$-$C_6)$cycloalkyl and pyrrolidinyl;

$(C_3$-$C_6)$cycloalkoxy, optionally substituted with 1-3 substituents independently selected from halo, hydroxy, and $-CO_2H$;

$-NR^aR^b$ wherein R^a and R^b are independently selected from H and $(C_1$-$C_4)$alkyl, wherein the $(C_1$-$C_4)$alkyl is optionally substituted with 1-3 groups independently selected from oxo and $-CO_2H$;

$-SR^a$ wherein R^a is selected from H and $(C_1$-$C_4)$alkyl;

$-CO_2H$; $-C(NOH)NH_2$; cyano; $-C(O)O(C_1$-$C_4)$alkyl; $-C(O)CO_2H$; $-P(O)R^fR^g$; $-OP(O)R^fR^g$; halo; hydroxy; nitro; $-NHSO_2(C_1$-$C_2)$alkyl; $-SO_3H$; $-SO_2(C_1$-$C_2)$alkyl; $-SO_2NR^cR^d$; $-SO_2NHC(O)(C_1$-$C_2)$alkyl; and $-B(OH)_2$;

and

b) heteroaryl, optionally substituted with 1-2 groups independently selected from:

$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, oxo, $-CO_2H$, $-P(O)R^fR^g$, and $-OP(O)R^fR^g$;

wherein in each occurrence: R^c, R^d and R^e are independently selected from H and $(C_1$-$C_2)$alkyl; and R^f and R^g are independently selected from hydroxy, $(C_1$-$C_2)$alkyl and $(C_1$-$C_2)$alkoxy;

and salts, particularly pharmaceutically acceptable salts, thereof.

The compounds according to Formula (I), or salts, particularly pharmaceutically acceptable salts, thereof, are inhibitors of BMP1, TLL1 and/or TLL2.

Accordingly, the present invention is also directed to a method of inhibiting BMP1, TLL1 and/or TLL2 which method comprises contacting a biological material comprising the protein(s) with a compound according to Formula (I), or a salt, particularly a pharmaceutically acceptable salt, thereof.

The invention is further directed to a method of treating a disease associated with BMP1, TLL1 and/or TLL2 activity in a subject (e.g., a human or other mammal, particularly a human) in need thereof, including for example treatment of a disease where inhibition of BMP1, TLL1 and/or TLL2 is of therapeutic benefit, which comprises administering to the subject a therapeutically effective amount of a compound according to Formula (I), or a salt thereof, particularly a pharmaceutically acceptable salt thereof. This invention also provides a compound of Formula (I), or a salt thereof, particularly a pharmaceutically acceptable salt thereof, for use in therapy, e.g. as an active therapeutic substance in the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity. The invention also provides for the use of a compound of Formula (I), or a salt thereof, particularly a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity.The present invention is further directed to a pharmaceutical composition comprising a compound according to Formula (I), or a salt thereof, particularly a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. Particularly, this invention is directed to a pharmaceutical composition for the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity, where the composition comprises a compound according to Formula (I), or a salt thereof, particularly a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

In some embodiments, the disease associated with BMP1, TLL1 and/or TLL2 activity is selected from those associated with pathological fibrotic conditions in body organs or tissues, e.g., such conditions of the: heart (e.g., myocardial infarction ("MI"), heart failure (e.g., heart failure with reduced ejection fraction, heart failure with preserved ejection fraction), cardiac arrhythmias (e.g., atrial fibrillation), hypertrophic cardiomyopathy), lung (e.g. chronic obstructive pulmonary disease ("COPD"), idiopathic pulmonary fibrosis ("IPF")), kidney (e.g. diabetic nephropathy, post-acute kidney injury, chronic kidney disease ("CKD"), delayed graft function post-transplantation), liver (e.g. liver cirrhosis, non-alcoholic steatohepatitis ("NASH")), eye (e.g. glaucoma, corneal scarring), skeletal muscle (e.g. muscular dystrophies, including Duchenne, Becker, limb-

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girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery-Dreifuss), skin (e.g. keloids, wound healing, adhesions, hypertrophic scarring and other scarring, e.g., associated with burns, surgery or other trauma), the vasculature (e.g. stroke, and collagen vascular diseases such as systemic lupus erythematosus, rheumatoid arthritis and scleroderma), and the nervous system (e.g. spinal cord injury, multiple sclerosis). In some embodiments, the disease associated with BMP1, TLL1 and/or TLL2 activity is selected from muscular diseases characterized by reduced muscle function and/or mass, e.g., muscular dystrophy (e.g., Duchenne, Becker, limb-girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery-Dreifuss), sarcopenia, and cachexia associated with, e.g., heart failure, CKD, COPD, cancer, or old age.

Other aspects of the present invention will be understood in light of this disclosure.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

DETAILED DESCRIPTION OF THE INVENTION

The alternative definitions for the various groups and substituent groups of Formula (I) provided throughout the specification are intended to particularly describe each compound species disclosed herein, individually, as well as groups of one or more compound species. The scope of this invention includes any combination of these group and substituent group definitions. The compounds of the invention are only those which are contemplated to be "chemically stable" as will be appreciated by those skilled in the art.

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As used herein, the term "alkyl" represents a saturated hydrocarbon moiety which, unless otherwise stated, may be straight or branched. The terms "C_1-C_2 alkyl", "C_1-C_3 alkyl", "C_1-C_4 alkyl", "C_1-C_6 alkyl" , and "C_1-C_{11} alkyl" refer to an alkyl group or moiety containing 1-2, 1-3, 1-4, 1-6, or 1-11 carbon atoms respectively. Exemplary alkyls include, but are not limited to methyl (Me), ethyl (Et), n-propyl, isopropyl, n-butyl, s-butyl, isobutyl, t-butyl, pentyl (also known as n-pentyl), and 2-ethylbutyl, as well as hexyl, heptyl, octyl, nonyl, decyl and undecyl, including the branched isomers of these groups.

As used herein, the term “cycloalkyl” refers to a non-aromatic, saturated, cyclic hydrocarbon ring moiety. The term “(C_3-C_6)cycloalkyl” refers to a non-aromatic cyclic hydrocarbon ring moiety having three to six ring carbon atoms. Exemplary “(C_3-C_6)cycloalkyl” groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

“Alkoxy” refers to an alkyl radical attached through an oxygen linking atom. The terms “(C_1-C_4)alkoxy” and “(C_1-C_6)alkoxy” refer to a straight- or branched-chain hydrocarbon radical containing 1-4 or 1-6 carbon atoms respectively, attached through an oxygen linking atom. “(C_1-C_4)alkoxy” and “(C_1-C_6)alkoxy” may be alternatively

designated as –O(C_1-C_4 alkyl) and –O(C_1-C_6 alkyl) respectively. Exemplary alkoxy groups include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, s-butoxy, isobutoxy, t-butoxy, pentoxy, and hexoxy, including the branched isomers of these groups.

"Cycloalkoxy" refers to a cycloalkyl radical attached through an oxygen linking atom. The term "(C_3-C_6)cycloalkoxy" refers to a cycloalkyl radical having 3 to 6 ring carbon atoms, attached through an oxygen linking atom. "(C_3-C_6)cycloalkoxy" may be alternatively designated as -O(C_3-C_6)cycloalkyl. Exemplary cycloalkoxy groups include cyclopropyloxy, cyclobutyloxy, cyclpentyloxy, and cyclohexyloxy.

A heterocyclic (alternatively referred to as heterocyclyl) group or moiety is a mono- or bi-cyclic group or moiety having as ring members atoms of at least two different elements (carbon and one or more of nitrogen, oxygen and/or sulfur). The ring(s) may be saturated or partially unsaturated (non-aromatic) or fully unsaturated (aromatic). Heterocyclic encompasses heterocycloalkyl and heteroaryl. For example, heterocyclyl may be a cyclic group or moiety having 5-10 ring atoms (i.e. "5-10 membered") wherein 1-4 of the ring atoms are heteroatoms selected from nitrogen, oxygen and sulfur, e.g., a monocyclic ring having 5-6 ring atoms wherein 1-2 of the ring atoms are heteroatoms selected from nitrogen, oxygen and sulfur, or a bicyclic ring having 9-10 ring atoms wherein 1-4 of the ring atoms are heteroatoms selected from nitrogen, oxygen and sulfur.

"Heterocycloalkyl" represents a group or moiety which is a non-aromatic, monocyclic radical, which is saturated or partially unsaturated, having 5-6 ring atoms wherein 1-2 of the ring atoms are heteroatoms selected from nitrogen, oxygen and sulfur. Illustrative examples of heterocycloalkyl groups include, but are not limited to, piperidyl (or piperidinyl), piperazinyl, morpholinyl, tetrahydrofuryl (or tetrahydrofuranyl), tetrahydropyranyl, tetrahydrothienyl, and thiomorpholinyl, including the various position isomers of the foregoing moieties.

"Heteroaryl" refers to a mono- or bi-cyclic group or moiety wherein at least one ring is aromatic, having 5- 10 ring atoms wherein 1-4 of the ring atoms are heteroatoms selected from nitrogen, oxygen and sulfur. In bicyclic heteroaryl, at least one ring is aromatic and the other ring may be aromatic, or saturated or unsaturated non-aromatic, and at least one ring is heterocyclic and the other ring may be heterocyclic or carbocyclic. Thus, this term encompasses but is not limited to bicyclic heterocyclic compounds containing at least one aromatic carbocyclic or heterocylic ring moiety, e.g., a phenyl ring moiety fused to a heterocycloalkyl ring moiety. Illustrative examples of heteroaryls include, but are not limited to, thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl (or furanyl), isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridyl (or pyridinyl), pyrazinyl,

pyrimidinyl, pyridazinyl, triazinyl, triazolyl, tetrazolyl, indazolyl, benzothienyl, benzofuranyl, benzothiazolyl, benzimidazolyl, benzoxazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, 2,3-dihydrobenzoisothiazolyl, and 1,1-dioxido-2,3-dihydrobenzoisothiazolyl (e.g., 1,1-dioxido-2,3-dihydrobenzo[d]isothiazolyl), including the various position isomers of the foregoing moieties.

In some embodiments, compounds of the invention comprise a 5-membered or 6-membered monocyclic heteroaryl group comprising at least one nitrogen ring atom, e.g., such groups as particularly disclosed herein. Selected 5-membered heteroaryl groups contain one nitrogen, and optionally contain one oxygen ring atom or 1, 2 or 3 additional nitrogen ring atoms. Selected 6-membered heteroaryl groups contain 1, 2, or 3 nitrogen ring heteroatoms.

In other embodiments, compounds of the invention comprise a 9-membered or 10-membered bicyclic heteroaryl group, e.g. such groups as particularly disclosed herein. Selected 9-10 membered heteroaryl groups contain one nitrogen, oxygen or sulfur ring heteroatom, and optionally contain 1, 2, or 3 additional nitrogen ring atoms.

It is to be understood that the terms heterocyclic, heteroaryl, and heterocycloalkyl are intended to encompass stable heterocyclic groups where a ring nitrogen heteroatom is optionally oxidized (e.g., heterocyclic groups containing an N-oxide, e.g., pyridine-N-oxide), or where a ring sulfur heteroatom is optionally oxidized (e.g., heterocyclic groups containing sulfones or sulfoxide moieties, e.g., tetrahydrothienyl-1-oxide [a tetrahydrothienyl sulfoxide], tetrahydrothienyl-1,1-dioxide [a tetrahydrothienyl sulfone], or 1,1-dioxido-2,3-dihydrobenzoisothiazolyl [e.g., 1,1-dioxido-2,3-dihydrobenzo[d]isothiazolyl]).

When the term "alkyl" is used in combination with other groups, e.g., "(C_1-C_3)alkyl-(C_3-C_6)cycloalkyl", "(C_1-C_3)alkyl-phenyl" and "(C_1-C_3)alkyl-heterocyclyl", the alkyl moiety is intended to encompass a divalent straight or branched-chain hydrocarbon radical and the cycloalkyl, phenyl, and heterocyclyl moieties are as defined herein. For example, in "(C_1-C_3)alkyl-phenyl " the (C_1-C_3)alkyl moiety thereof is a divalent straight or branched-chain carbon radical linked to the aryl group phenyl, and is represented by the bonding arrangement present in a benzyl group (-CH_2-phenyl). Particular examples of such groups include (cyclopentyl)methyl, 2-phenylethyl, 3-phenylpropyl, and 2-naphthylethyl.

"Oxo" represents a double-bonded oxygen moiety; for example, if attached directly to a carbon atom forms a carbonyl moiety (C = O). The terms "halogen" and "halo" represent chloro, fluoro, bromo or iodo substituents. "Hydroxy" or "hydroxyl" is intended to mean the radical -OH. "Cyano" means the radical –CN. "Nitro" means the radical –NO_2.

Where a numerical range is indicated, e.g., a carbon number range or a heteroatom number range, the range is intended to encompass particular embodiments corresponding to the particular integers within the range, and well as any range of integers within the most broadly stated range.

As used herein, the terms "compound(s) of the invention" or "compound(s) of this invention" mean a compound of Formula (I), as defined above (including more particular embodiments), in any form, i.e., any salt or non-salt form (e.g., as a free acid or base form, or as a salt, particularly a pharmaceutically acceptable salt thereof) and any physical form thereof (e.g., including non-solid forms (e.g., liquid or semi-solid forms), and solid forms (e.g., amorphous or crystalline forms, specific polymorphic forms, solvate forms, including hydrate forms (e.g., mono-, di- and hemi- hydrates)), and mixtures of various forms.

Accordingly, included within the present invention are compounds of Formulas (I), as defined herein (including more particular embodiments), in any salt or non-salt form and any physical form thereof, and mixtures of various forms. While such are included within the present invention, it will be understood that the compounds of Formulas (I), as defined herein, in any salt or non-salt form, and in any physical form thereof, may have varying levels of activity, different bioavailabilities and different handling properties for formulation purposes.

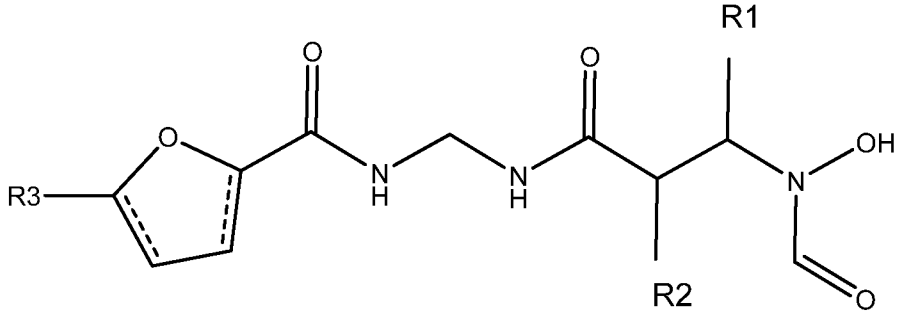
As used herein, the term “optionally substituted” indicates that a group, ring or moiety (such as an alkyl, cycloalkyl, alkoxy, cycloalkoxy, heterocycloalkyl, phenyl, heteroaryl, carbocyclic or heterocyclic group, ring or moiety) may be unsubstituted, or the group, ring or moiety may be substituted with one or more substituent(s) as defined. In the case where more than one group, ring or moiety may be substituted with a number of alternative substituent(s), the selected substituent(s) for each group, ring or moiety may be the same or different, i.e. the substituent(s) are selected independently for each group, ring or moiety. In the case where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different, i.e. the substituents are selected independently.

As used herein, the terms “a” and “an” are intended to include one or more of the indicated moiety, unless otherwise indicated.

As used herein, “BMP1, TLL1 and/or TLL2” encompasses one or more of BMP1, TLL1 and TLL2, including isoforms thereof (including particularly isoforms encoded by RNA splice variants). Thus, for example, as used herein BMP1 may include one or more of the isoforms BMP-1-1, BMP-1-2, BMP-1-3, BMP-1-4, BMP-1-5, BMP-1-6, and BMP-1-7.

All references/publications are hereby incorporated by reference into this disclosure in their entirety.

In one aspect, the present invention is directed to a compound of Formula (I):



(I)

or a salt thereof,

wherein:

R1 is selected from the group consisting of H, (C_1-C_4) straight chain alkyl, and (C_1-C_4) straight chain alkyl substituted with a hydroxy group;

R2 is selected from H, (C_1-C_{11})alkyl, (C_1-C_3)alkyl-(C_3-C_6)cycloalkyl, (C_1-C_3)alkyl-phenyl, (C_1-C_3)alkyl-naphthyl and (C_1-C_3)alkyl-heterocyclyl, wherein heterocyclyl is a monocyclic ring having 5-6 ring atoms wherein 1-2 of the ring atoms are selected from nitrogen, oxygen and sulfur, and wherein said (C_1-C_{11})alkyl, cycloalkyl, phenyl, naphthyl and heterocyclyl may be optionally substituted with 1-2 groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo,and cyano; and

R3 is selected from:

c) phenyl, optionally substituted with 1-3 groups independently selected from:

(C_1-C_6)alkyl, optionally substituted with 1-3 groups independently selected from: fluoro (e.g., $-CF_3$); $-CO_2H$; $-P(O)R^fR^g$; NR^aR^b wherein R^a is selected from H and (C_1-C_4)alkyl and R^b is selected from (C_1-C_4)alkyl substituted with $-CO_2H$ or $-P(O)R^fR^g$, and $-C(O)NR^aR^b$ wherein R^a and R^b are independently selected from H and (C_1-C_4)alkyl, wherein the (C_1-C_4)alkyl is optionally substituted with 1-3 groups independently selected from hydroxy, $-CO_2H$, $-C(O)O(C_1$-$C_4)$alkyl and $-P(O)R^fR^g$;

cyclopropyl, optionally substituted with 1 $-CO_2H$;

$-C(O)NR^aR^b$ wherein R^a and R^b are independently selected from H and (C_1-C_4)alkyl, wherein the (C_1-C_4)alkyl is optionally substituted with 1-3 groups independently selected from hydroxy, $-CO_2H$, $-C(O)O(C_1$-$C_4)$alkyl, $-P(O)R^fR^g$, NR^cR^d and N^+ $R^cR^dR^e$;

(C_1-C_6)alkoxy, optionally substituted with 1-3 substituents independently selected from halo, hydroxy, -CO_2H, (C_3-C_6)cycloalkyl, $C(O)NH_2$ and pyrrolidinyl;

(C_3-C_6)cycloalkoxy, optionally substituted with 1-3 substituents independently selected from halo, hydroxy, and -CO_2H;

-NR^aR^b wherein R^a and R^b are independently selected from H and (C_1-C_4)alkyl, wherein the (C_1-C_4)alkyl is optionally substituted with 1-3 groups independently selected from oxo and -CO_2H;

-SR^a wherein R^a is selected from H and (C_1-C_4)alkyl;

-CO_2H; -$C(NOH)NH_2$; cyano; -$C(O)O(C_1$-$C_4)$alkyl; -$C(O)CO_2H$; -$P(O)R^fR^g$; -$OP(O)R^fR^g$; halo; hydroxy; nitro; -$NHSO_2(C_1$-$C_2)$alkyl; -SO_3H; -$SO_2(C_1$-$C_2)$alkyl; -$SO_2NR^cR^d$; -$SO_2NHC(O)(C_1$-$C_2)$alkyl; and -$B(OH)_2$;

and

d) heteroaryl, optionally substituted with 1-2 groups independently selected from:

(C_1-C_4)alkyl, (C_1-C_4)alkoxy, oxo, -CO_2H, -$P(O)R^fR^g$, and -$OP(O)R^fR^g$;

wherein in each occurrence: R^c, R^d and R^e are independently selected from H and (C_1-C_2)alkyl; and

R^f and R^g are independently selected from hydroxy, (C_1-C_2)alkyl and (C_1-C_2)alkoxy.

In some embodiments of the compound of Formula (I):

R1 is selected from the group consisting of H, (C_1-C_4) straight chain alkyl, and (C_1-C_4) straight chain alkyl substituted with a hydroxy group;

R2 is selected from H, (C_1-C_{11})alkyl, (C_1-C_3)alkyl-(C_3-C_6)cycloalkyl, (C_1-C_3)alkyl-phenyl, and (C_1-C_3)alkyl-heterocyclyl, wherein heterocyclyl is a monocyclic ring having 5-6 ring atoms wherein 1-2 of the ring atoms are selected from nitrogen, oxygen and sulfur, and wherein said (C_1-C_{11})alkyl, cycloalkyl, phenyl, and heterocyclyl may be optionally substituted with 1-2 groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo,and cyano; and

R3 is selected from:

a) phenyl, optionally substituted with 1-3 groups independently selected from:

(C_1-C_6)alkyl, optionally substituted with 1-3 groups independently selected from: fluoro

(e.g., $-CF_3$); $-CO_2H$; $-P(O)R^fR^g$; and $-C(O)NR^aR^b$ wherein R^a and R^b are independently selected from H and (C_1-C_4)alkyl, wherein the (C_1-C_4)alkyl is optionally substituted with 1-3 groups independently selected from hydroxy, $-CO_2H$, $-C(O)O(C_1-C_4)$alkyl and $-P(O)R^fR^g$;

cyclopropyl, optionally substituted with 1 $-CO_2H$;

$-C(O)NR^aR^b$ wherein R^a and R^b are independently selected from H and (C_1-C_4)alkyl, wherein the (C_1-C_4)alkyl is optionally substituted with 1-3 groups independently selected from hydroxy, $-CO_2H$, $-C(O)O(C_1-C_4)$alkyl, $-P(O)R^fR^g$, NR^cR^d and $N^+ R^cR^dR^e$;

(C_1-C_6)alkoxy, optionally substituted with 1-3 substituents independently selected from halo, hydroxy, $-CO_2H$, (C_3-C_6)cycloalkyl, and pyrrolidinyl;

(C_3-C_6)cycloalkoxy, optionally substituted with 1-3 substituents independently selected from halo, hydroxy, and $-CO_2H$;

$-NR^aR^b$ wherein R^a and R^b are independently selected from H and (C_1-C_4)alkyl, wherein the (C_1-C_4)alkyl is optionally substituted with 1-3 groups independently selected from oxo and $-CO_2H$;

$-SR^a$ wherein R^a is selected from H and (C_1-C_4)alkyl;

$-CO_2H$; $-C(NOH)NH_2$; cyano; $-C(O)O(C_1-C_4)$alkyl; $-C(O)CO_2H$; $-P(O)R^fR^g$; $-OP(O)R^fR^g$; halo; hydroxy; nitro; $-NHSO_2(C_1-C_2)$alkyl; $-SO_3H$; $-SO_2(C_1-C_2)$alkyl; $-SO_2NR^cR^d$; $-SO_2NHC(O)(C_1-C_2)$alkyl; and $-B(OH)_2$;

and

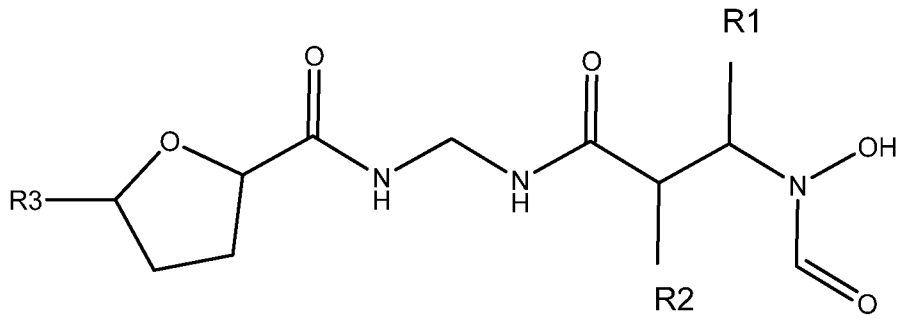
b) heteroaryl, optionally substituted with 1-2 groups independently selected from:

(C_1-C_4)alkyl, (C_1-C_4)alkoxy, oxo, $-CO_2H$, $-P(O)R^fR^g$, and $-OP(O)R^fR^g$;

wherein in each occurrence: R^c, R^d and R^e are independently selected from H and (C_1-C_2)alkyl; and

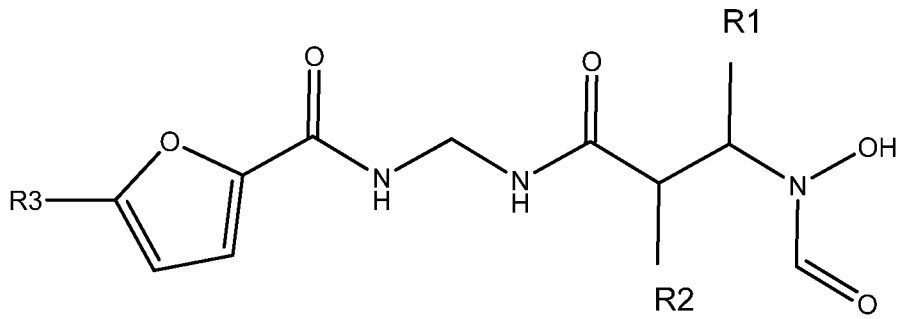
R^f and R^g are independently selected from hydroxy, (C_1-C_2)alkyl and (C_1-C_2)alkoxy.

In some embodiments, the compound according to Formula (I) has the Formula (I)(a):



(I)(a).

In other embodiments, the compound according to Formula (I) has the Formula (I)(b):



(I)(b).

In some embodiments of the compounds of the invention (e.g. compounds of Formula (I)), R1 is H, methyl, ethyl, or -CH_2OH; in more particular embodiments H, ethyl or –CH_2OH, more particularly H or ethyl and especially ethyl. In some embodiments, R1 is (C_1-C_4) straight chain alkyl substituted with one hydroxy group.

In some embodiments of the compounds of the invention (e.g. compounds of Formula (I)), R2 is H, n-pentyl, 2-ethylbutyl, (cyclopentyl)methyl, benzyl, 2-phenylethyl, or 3-phenylpropyl (in more particular embodiments n-pentyl, (cyclopentyl)methyl, 2-phenylethyl, or 3-phenylpropyl, even more particularly n-pentyl), where such groups are optionally substituted as defined above in accordance with Formula (I). In some embodiments of the compounds of the invention (e.g. compounds of Formula (I)), R2 is 2-naphthylethyl, optionally substituted as defined above in accordance with Formula (I). In some embodiments such groups are unsubstituted. In some embodiments, R2 is n-pentyl.

In some embodiments of the compounds of the invention (e.g. compounds of Formula (I)), R1 and R2 have (R) stereochemistry.

In some embodiments of the compounds of the invention (e.g. compounds of Formula (I)), R3 is phenyl, pyridyl, pyridazinyl, pyrimidinyl, oxazolyl, tetrazolyl, pyrazolyl, indazolyl, or 1,1-dioxido-2,3-dihydrobenzo[d]isothiazolyl (in more particular embodiments, phenyl, pyridyl, indazolyl, or 1,1-dioxido-2,3-dihydrobenzo[d]isothiazolyl), including the various position isomers thereof, where such groups are optionally substituted as defined above in accordance with Formula (I), including more particular embodiments of Formula (I).

In more particular embodiments, R3 is phenyl optionally substituted in accordance with the definition of Formula (I), including more particular embodiments of Formula (I). In more particular embodiments of compounds of the invention (e.g. compounds of Formula (I)), R3 is 3,4- or 3,5- disubstituted phenyl wherein the substituent groups are selected in accordance with the definition of Formula (I), including more particular embodiments of Formula (I). In some embodiments, R3 is phenyl substituted with ethoxy in the 3-position and $-P(O)(OH)_2$ or $-CO_2H$ in the 4- or 5- position (said positions relative to the point of attachment of the phenyl ring to the remainder of the compound of Formula (I)). In some embodiments, R3 is phenyl substituted with ethoxy in the 3-position $-OCH_2CO_2H$, or $-C(O)NHCH(CO_2H)(CH_2CO_2H)$ in the 4- or 5- position (said positions relative to the point of attachment of the phenyl ring to the remainder of the compound of Formula (I)).

In some embodiments of the compounds of the invention (e.g. a compound of Formula (I)), R3 is phenyl substituted with 1-3 groups selected from: $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCH_2CHF_2$, $-OC_2H_4$ – pyrrolidine, $-OCH_2CO_2H$, $-OCH_2C(O)NH_2$, $-CO_2H$, $-CH_3$, cyclopropane-1-carboxylic acid, $-CH_2CO_2H$, $-C(CH_3)_2CO_2H$, $-CH(CH_3)CO_2H$, $-CF_2CO_2H$, $-CH_2C(O)NHCH(CO_2H)(CH_2CO_2H)$, $-CH_2P(O)(OH)_2$,$-CH_2N(CH_3)(CH_2CO_2H)$, $-CH_2NHCH_2P(O)(OH)_2$, $-C(NH_2)(NOH)$, cyano, nitro, hydroxy, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, $-SO_2NH(CH_3)$, $-SO_2CH_3$, $-SO_2NHC(O)C_2H_5$, $-SCH_3$, $-SC_2H_5$, $-C(O)OCH_3$, $-C(O)OC(CH_3)_3$, $-C(O)NHCH_3$, $-C(O)NH(C_2H_4NH_2)$, $-C(O)NHC_2H_4N^+(CH_3)_3$, $-C(O)NHCH(CO_2H)(CH_2CO_2H)$, $-C(O)NHCH(CO_2H)(C_2H_4CO_2H)$, $-C(O)NHCH_2CO_2H$, $-C(O)N(CH_2CO_2H)_2$, $-C(O)NHCH_2P(O)(OH)_2$, $-C(O)NHC(CH_2OH)_3$, fluoro, $-NH_2$, $-N(CH_3)_2$, $-P(O)(CH_3)(OC_2H_5)$, $-P(O)(OCH_3)_2$, $-P(O)(CH_3)(OH)$, $-P(O)(OH)(OCH_3)$, and $-P(O)(OH)_2$. In some embodiments, R3 is phenyl substituted with 1-3 groups selected from: $-OC_2H_5$, hydroxy, $-CO_2H$, $-OCH_2CO_2H$, $-P(O)(OH)_2$, $-C(O)NHCH(CO_2H)(CH_2CO_2H)$ and $-C(O)NHCH_2P(O)(OH)_2$.

In some embodiments of the compounds of the invention (e.g. a compound of Formula (I)), R3 is optionally substituted pyridyl, pyridazinyl, pyrimidinyl, oxazolyl,

tetrazolyl, pyrazolyl, indazolyl, or 1,1-dioxido-2,3-dihydrobenzo[d]isothiazolyl. In some embodiments, R3 is optionally substituted pyridyl, indazolyl, or 1,1-dioxido-2,3-dihydrobenzo[d]isothiazolyl (including particularly pyridin-3-yl, pyridin-2-yl, 1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl, and indazol-6-yl). In these embodiments such R3 groups may be optionally substituted as defined in accordance with Formula (I), including more particular embodiments of Formula (I). In some embodiments, such R3 groups are substituted with 1-2 groups independently selected from: $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, $-CO_2H$, $-CH_3$, $-P(O)(CH_3)(OC_2H_5)$, $-P(O)(OCH_3)_2$, $-P(O)(CH_3)(OH)$, $-P(O)(OH)(OCH_3)$, and $-P(O)(OH)_2$. In some embodiments, such R3 groups are substituted with 1-2 groups independently selected from: $-OCH_3$, $-CH_3$, and $-CO_2H$.

Accordingly, a compound of the invention includes a compound of Formula (I), or a salt thereof, particularly a pharmaceutically acceptable salt thereof. Representative compounds of this invention include the specific compounds described herein, e.g., the compounds of the Examples, as well as any free acid/base forms, salt forms, and alternative salt forms thereof (particularly pharmaceutically acceptable salt or alternative salt forms thereof), as applicable.

Accordingly, in some embodiments the compound of the invention is a compound selected from the group consisting of:

2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzoic acid

(R)-N-((3-cyclopentyl-2-((N-hydroxyformamido)methyl)propanamido)methyl)-5-phenylfuran-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)-5-phenylpentanamido)methyl)-5-phenylfuran-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)-4-phenylbutanamido)methyl)-5-phenylfuran-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(2-methoxyphenyl)furan-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-methoxyphenyl)furan-2-carboxamide

(R)-5-(3-cyanophenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(2-hydroxyphenyl)furan-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(5-methoxypyridin-3-yl)furan-2-carboxamide

(R)-5-(4-cyanophenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-sulfamoylphenyl)furan-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(trifluoromethoxy)phenyl)furan-2-carboxamide

(R)-5-(3-ethoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(6-methoxypyridin-2-yl)furan-2-carboxamide

(R)-methyl 3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate

(R)-5-(4-fluoro-3-methoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(4-methoxypyridin-2-yl)furan-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(methylcarbamoyl)phenyl)furan-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)-4-phenylbutanamido)methyl)-5-(3-(methylsulfonyl)phenyl)furan-2-carboxamide

(R)-5-(3-(N,N-dimethylsulfamoyl)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(N-methylsulfamoyl)phenyl)furan-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(2,2,2-trifluoroethoxy)phenyl)furan-2-carboxamide

N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-isopropoxyphenyl)furan-2-carboxamide

(R)-methyl 3-ethoxy-5-(5-(((2-((N-

hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate
(R)-5-(3-(dimethylamino)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(N-propionylsulfamoyl)phenyl)furan-2-carboxamide
(R)-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-methoxybenzoic acid
(R)-3-ethoxy-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
ethyl (3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)(methyl)phosphinate
N-(((R)-2-((S)-2-hydroxy-1-(N-hydroxyformamido)ethyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide
(R)-5-(3-((2-aminoethyl)carbamoyl)-5-methoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide
(R)-5-(3-((2-aminoethyl)carbamoyl)-5-ethoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide
(R)-5-(3-(difluoromethoxy)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide
(R)-dimethyl (3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate
(R)-5-(1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(2-(pyrrolidin-1-yl)ethoxy)phenyl)furan-2-carboxamide
3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)benzoic acid
5-(3-((2-aminoethyl)carbamoyl)-5-ethoxyphenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)furan-2-carboxamide
2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid
2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid
2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)-2-methylpropanoic acid

1-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)cyclopropanecarboxylic acid

(S)-5-(tert-butoxy)-4-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl) heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)-5-oxopentanoic acid

5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)nicotinic acid

(S)-4-(tert-butoxy)-3-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)-4-oxobutanoic acid

(S)-dimethyl 2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)pentanedioate

2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)-2,2-difluoroacetic acid

dimethyl (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate

(R)-methyl 2-fluoro-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl) furan-2-yl)benzoate

(R)-5-(3,5-dimethoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide

(R)-5-(2,5-dimethoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide

(R)-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzoic acid

(R)-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methoxybenzoic acid

(R)-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methoxybenzoic acid

(R)-methyl 2-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate

(R)-methyl 4-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate

(R)-2-fluoro-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

(R)-2-(3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid

(R)-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzoic acid

(R)-2-hydroxy-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

(R)-tert-butyl 3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate

(R)-2-amino-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)-N,N,N-trimethylethanaminium hydroxide

5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methoxybenzoic acid

2-(3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)-2-methylpropanoic acid

5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzoic acid

N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)-5-(3-propoxyphenyl)furan-2-carboxamide

2-(2-fluoro-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid

4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid

5-(3-ethoxy-5-hydroxyphenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)furan-2-carboxamide

(S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid

(S)-2-(2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetamido)succinic acid

2-(3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-

yl)phenyl)propanoic acid
(S)-2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid
(R)-2,6-difluoro-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
3-ethoxy-5-(5-(((3-(N-hydroxyformamido)propanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
1-(3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)cyclopropanecarboxylic acid
5-ethoxy-2-hydroxy-3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-propoxybenzoic acid
(S)-2-(3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid
(R)-2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid
2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)acetic acid
2,2'-((2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetic acid
2,2'-((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetic acid
5-(3-((1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl)carbamoyl)-5-ethoxyphenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)furan-2-carboxamide
(R)-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
(R)-2-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

(R)-2-fluoro-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

(R)-4-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

(S)-2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)pentanedioic acid

(3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)(methyl)phosphinic acid

methyl hydrogen (3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl) carbamoyl)furan-2-yl)phenyl)phosphonate

(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid

(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl) tetrahydrofuran-2-yl)phenyl)phosphonic acid

(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid

(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzyl)phosphonic acid

((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonic acid

methyl hydrogen (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido) methyl)carbamoyl)furan-2-yl)phenyl)phosphonate

(R)-5-(3-(2,2-difluoroethoxy)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide

(R)-5-(3-(ethylthio)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl) furan-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(methylthio)phenyl)furan-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-nitrophenyl)furan-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(1-methyl-1H-indazol-6-yl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(2-methyl-2H-indazol-6-yl)furan-2-carboxamide
(R)-(3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid
5-(3-((Z)-N'-hydroxycarbamimidoyl)phenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido) methyl)furan-2-carboxamide and
N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)-5-phenyltetrahydrofuran-2-carboxamide;

or a salt thereof (in more particular embodiments, a pharmaceutically acceptable salt thereof).

In some embodiments the compound of the invention is a compound selected from the group consisting of:
(3-ethoxy-2-fluoro-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
3-hydroxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
3-(carboxymethoxy)-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
2-(carboxymethyl)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
5-ethoxy-2-hydroxy-3-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
(S)-2-(2-ethoxy-4-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-(2-(naphthalen-2-yl)ethyl)pentanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid
5-(carboxymethoxy)-3-(5-((((2R,3R)-2-(2,4-difluorophenethyl)-3-(N-hydroxyformamido)pentanamido)methyl)carbamoyl)furan-2-yl)-2-hydroxybenzoic acid
(S)-2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid
(S)-2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-

methylbenzamido)succinic acid
5-(carboxymethoxy)-2-hydroxy-3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
2,2'-((3-(5-((((2R,3R)-2-(2,4-difluorophenethyl)-3-(N-hydroxyformamido)pentanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoyl)azanediyl)diacetic acid
(S)-2-(4-(5-((((2R,3R)-2-(2,4-difluorophenethyl)-3-(N-hydroxyformamido)pentanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)succinic acid
2,2'-((2-ethoxy-4-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetic acid
(S)-2-(3-(carboxymethoxy)-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid
(S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid
(S)-2-(2-ethoxy-4-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid
2-ethoxy-6-hydroxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phthalic acid
2-((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzyl)(methyl)amino)acetic acid
3-(2-amino-2-oxoethoxy)-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
(R)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid
((R)-2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid
(S)-2-(4-(5-((((R)-2-((R)-1-(N-

hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)pentanedioic acid

(S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)pentanedioic acid

2,2'-((4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetic acid

(((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzyl)amino)methyl)phosphonic acid,

(3-hydroxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid

((2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonic acid

(3-ethoxy-5-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid

(3-ethoxy-5-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-(2-(naphthalen-2-yl)ethyl)pentanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid

((2-hydroxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonic acid

((4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonic acid

((4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzamido)methyl)phosphonic acid

2-(3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-phosphonophenoxy)acetic acid and

2-hydroxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid;

or a salt thereof (in more particular embodiments a pharmaceutically acceptable salt thereof).

In some embodiments the compound of the invention is a compound selected from the group consisting of:

2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzoic acid

3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)benzoic acid

(S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid

(S)-2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid

5-ethoxy-2-hydroxy-3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid

(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid

3-(carboxymethoxy)-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

(S)-2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid

(S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid

4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phthalic acid

(3-hydroxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid

((2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonic acid and
(3-ethoxy-5-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid;

or a salt thereof (in more particular embodiments a pharmaceutically acceptable salt thereof).

In some embodiments, the compound of the invention is (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid. In some embodiments, the compound of the invention is a salt (e.g., pharmaceutically acceptable salt) of (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid.

In some embodiments, the compound of the invention is (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid. In some embodiments, the compound of the invention is a salt (e.g., a pharmaceutically acceptable salt) of (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid.

In some embodiments, the compound of the invention is (S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid. In some embodiments, the compound of the invention is a salt (e.g., a pharmaceutically acceptable salt) of (S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid.

In some embodiments, the invention is directed to a method of inhibiting BMP1, TLL1 and/or TLL2 comprising contacting a biological material comprising the protein(s) with a compound of the invention. In some embodiments the contact is made in-vitro, and the biological material is, e.g., cell culture or cellular tissue. In other embodiments, the contact is made in-vivo.

In other embodiments, the invention is directed to a method of treating a disease associated with BMP1, TLL1 and/or TLL2 activity in a subject (e.g., a human or other mammal) in need thereof, comprising administering to the subject a therapeutically

effective amount of a compound of the invention (particularly a compound of Formula (I) or a pharmaceutically acceptable salt thereof). The invention is still further directed to the use of a compound of the invention or a pharmaceutical composition comprising a compound of the invention (particularly a compound of Formula (I) or a pharmaceutically acceptable salt thereof) to treat a disease associated with BMP1, TLL1 and/or TLL2 activity. The invention is further directed to a compound of the invention ((particularly a compound of Formula (I) or a pharmaceutically acceptable salt thereof) for use in therapy, particularly as an active therapeutic substance in the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity. The invention is further directed to the use of a compound of the invention (particularly a compound of Formula (I) or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for use in treating a disease associated with BMP1, TLL1 and/or TLL2 activity.

In some embodiments, the disease associated with BMP1, TLL1 and/or TLL2 activity is selected from those associated with pathological fibrotic conditions in body organs or tissues, e.g., such conditions of the heart, lung, kidney, liver, eye, skeletal muscle, skin, the vasculature, and the nervous system, e.g., myocardial infarction ("MI"), heart failure (e.g., heart failure with reduced ejection fraction, heart failure with preserved ejection fraction), cardiac arrhythmias (e.g., atrial fibrillation), hypertrophic cardiomyopathy, chronic obstructive pulmonary disease ("COPD"), idiopathic pulmonary fibrosis ("IPF"), diabetic nephropathy, post-acute kidney injury, chronic kidney disease ("CKD"), delayed graft function post-transplantation, liver cirrhosis, non-alcoholic steatohepatitis ("NASH"), glaucoma, corneal scarring, muscular dystrophies (including Duchenne, Becker, limb-girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery-Dreifuss), keloids, wound healing, adhesions, hypertrophic scarring and other scarring, e.g., associated with burns, surgery or other trauma, stroke, collagen vascular diseases (such as systemic lupus erythematosus, rheumatoid arthritis and scleroderma), spinal cord injury, and multiple sclerosis.

In some embodiments, the disease associated with BMP1, TLL1 and/or TLL2 activity is selected from muscular diseases characterized by reduced muscle function and/or mass, e.g., muscular dystrophy (e.g., Duchenne, Becker, limb-girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery-Dreifuss), sarcopenia, and cachexia associated with, e.g., heart failure, CKD, COPD, cancer, or old age.

The compounds according to Formula (I) may contain one or more asymmetric center(s) (also referred to as a chiral center(s)) and may, therefore, exist as individual enantiomers, diastereomers, or other stereoisomeric forms, or as mixtures thereof. Chiral

centers, such as a chiral carbon, sulfur or phosphorus, may also be present in the compounds of this invention. Where the stereochemistry of a chiral center present in a compound of this invention (e.g., compound name or in any chemical structure illustrated herein) is not specified, the compound, compound name, or structure is intended to encompass all individual stereoisomers and all mixtures thereof. Thus, compounds according to Formula (I) containing one or more chiral center(s) may be present as racemic mixtures, enantiomerically enriched mixtures, or as enantiomerically pure individual stereoisomers.

Individual stereoisomers of a compound according to Formula (I) which contain one or more asymmetric center(s) may be resolved by methods known to those skilled in the art. For example, such resolution may be carried out (1) by formation of diastereoisomeric salts, complexes or other derivatives; (2) by selective reaction with a stereoisomer-specific reagent, for example by enzymatic oxidation or reduction; or (3) by gas-liquid or liquid chromatography in a chiral environment, for example, on a chiral support such as silica with a bound chiral ligand or in the presence of a chiral solvent. The skilled artisan will appreciate that where the desired stereoisomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired form. Alternatively, specific stereoisomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

It is to be understood that a solid form of a compound of the invention may exist in crystalline forms, non-crystalline forms or a mixture thereof. Such crystalline forms may also exhibit polymorphism (i.e. the capacity to occur in different crystalline forms). These different crystalline forms are typically known as “polymorphs.” Polymorphs have the same chemical composition but differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state. Polymorphs, therefore, may have different physical properties such as shape, density, hardness, deformability, stability, and dissolution properties. Polymorphs typically exhibit different melting points, IR spectra, and X-ray powder diffraction patterns, which may be used for identification. One of ordinary skill in the art will appreciate that different polymorphs may be produced, for example, by changing or adjusting the conditions used in crystallizing/recrystallizing the compound.

Because of their potential use in medicine, the salts of the compounds of Formula (I) are preferably pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts include those described by Berge, S.M. et al., Journal of Pharmaceutical Sciences, 1977, 66, 1-19.

When a compound of the invention is a base (contains a basic moiety), a desired salt form may be prepared by any suitable method known in the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, trifluoroacetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, and the like, or with a pyranosidyl acid, such as glucuronic acid or galacturonic acid, or with an alpha-hydroxy acid, such as citric acid or tartaric acid, or with an amino acid, such as aspartic acid or glutamic acid, or with an aromatic acid, such as benzoic acid or cinnamic acid, or with a sulfonic acid, such as *p*-toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid or the like.

Suitable acid addition salts include acetate, p-aminobenzoate, ascorbate, aspartate, benzenesulfonate, benzoate, bicarbonate, bismethylenesalicylate, bisulfate, bitartrate, borate, calcium edetate, camsylate, carbonate, clavulanate, citrate, cyclohexylsulfamate, edetate, edisylate, estolate, esylate, ethanedisulfonate, ethanesulfonate, formate, fumarate, gluceptate, gluconate, glutamate, glycollate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, dihydrochloride, hydrofumarate, hydrogen phosphate, hydroiodide, hydromaleate, hydrosuccinate, hydroxynaphthoate, isethionate, itaconate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, *N*-methylglucamine, oxalate, oxaloacetate, pamoate (embonate), palmate, palmitate, pantothenate, phosphate/diphosphate, pyruvate, polygalacturonate, propionate, saccharate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, triethiodide, trifluoroacetate and valerate.

Other exemplary acid addition salts include pyrosulfate, sulfite, bisulfite, decanoate, caprylate, acrylate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, suberate, sebacate, butyne-1,4-dioate, hexyne-1,6-dioate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, phenylacetate, phenylpropionate, phenylbutrate, lactate, γ-hydroxybutyrate, mandelate, and sulfonates, such as xylenesulfonate, propanesulfonate, naphthalene-1-sulfonate and naphthalene-2-sulfonate.

If an inventive basic compound is isolated as a salt, the corresponding free base form of that compound may be prepared by any suitable method known to the art, including treatment of the salt with an inorganic or organic base, suitably an inorganic or organic base having a higher pK_a than the free base form of the compound.

When a compound of the invention is an acid (contains an acidic moiety), a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, tertiary or quaternary), an alkali metal or alkaline earth metal hydroxide, alkoxide (e.g. (C_{1-4})alkoxide), alkyl ester (e.g., (C_{1-4})alkyl ester, e.g. acetate), or the like. Illustrative examples of suitable salts include organic salts derived from amino acids such as glycine, lysine, and arginine, ammonia, primary, secondary, tertiary, and quaternary amines, cyclic amines, and amino sugars, e.g., 2-amino-2-deoxysugars, such as *N*-methyl-D-glucamine, diethylamine, isopropylamine, trimethylamine, ethylene diamine, dicyclohexylamine, ethanolamine, choline, piperidine, morpholine, piperazine, Tris (also known as THAM, or tris(hydroxymethyl)aminomethane), 2-amino-2-hydroxymethyl-propane-1,3-diol, and 2-amino-2-(hydroxymethyl)-1,3-propanediol), meglumine (also known as 1-Deoxy-1-(methylamino)-D-glucitol), galactosamine, glucosamine, and N-acetylglucosamine, as well as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium (e.g., hydroxides, (C_{1-4})alkoxides, and (C_{1-4})alkyl esters of such alkali and alkaline earth metals).

Treatment of a compound of Formula (I) containing a free acid with an inorganic or organic base, or containing a free base with an acid, to form a salt of the compound of Formula (I) may be done by methods known in the art. For example, the free acid may be admixed with a suitable solvent (e.g.in which the free acid is soluble) and treated with the base, with stirring, and optionally with heating and/or temperature cycling. Analogously, for a compound of Formula (I) containing a free base, the free base may be admixed with a suitable solvent (e.g.in which the free base is soluble) and treated with the acid, with stirring, and optionally with heating and/or temperature cycling.Certain of the compounds of the invention may form salts with one or more equivalents of an acid (if the compound contains a basic moiety) or a base (if the compound contains an acidic moiety). The present invention includes within its scope all possible stoichiometric and non-stoichiometric salt forms.

Compounds of the invention having both a basic and acidic moiety may be in the form of zwitterions, acid-addition salts of the basic moiety or base salts of the acidic moiety.

This invention also provides for the conversion of one pharmaceutically acceptable salt of a compound of this invention into another pharmaceutically acceptable salt of a compound of this invention.

In some embodiments, the compound of the invention is a salt, e.g., a pharmaceutically acceptable salt, of (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-

hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid. In some embodiments, the compound of the invention is a meglumine salt, Tris salt, or calcium salt of (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid, including all possible stoichiometric and non-stoichiometric forms of such salts.

In some embodiments, the compound of the invention is a salt, e.g., a pharmaceutically acceptable salt, of (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid.

In some embodiments, the compound of the invention is a salt, e.g., a pharmaceutically acceptable salt, of (S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid.

The compounds of Formula (I) and salts (including pharmaceutically acceptable salts) thereof may be in the form of a solvate. For solvates of the compounds of Formula (I), including solvates of salts of the compounds of Formula (I), that are in crystalline form, the skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed wherein solvent molecules are incorporated into the crystalline lattice during crystallization. Solvates may involve nonaqueous solvents such as ethanol, isopropanol, dimethylsulfoxide, acetic acid, ethanolamine, and ethyl acetate, or they may involve water as the solvent that is incorporated into the crystalline lattice. Solvates wherein water is the solvent that is incorporated into the crystalline lattice are typically referred to as "hydrates." Solvates include stoichiometric solvates as well as compositions containing variable amounts of the incorporated solvent(s), e.g. a hydrate includes stoichiometic hydrates and compositions containing variable amounts of water. The invention includes all such solvates, particularly hydrates. It is to be understood that the term “a salt, particularly a pharmaceutically acceptable salt, thereof, or solvate thereof” and the like in reference to a compound of Formula (I) encompasses a salt of a compound of Formula (I), a pharmaceutically acceptable salt of a compound of Formula (I), a solvate of a compound of Formula (I), a solvate of a salt of a compound of Formula (I), and a solvate of a pharmaceutically acceptable salt of a compound of Formula (I) (for example, where water is the incorporated solvent, said solvates are hydrates).

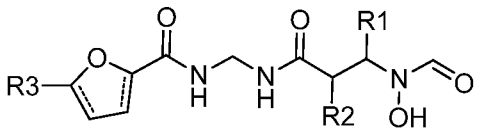
Because the compounds of the invention, particularly compounds of Formula (I), and pharmaceutically acceptable salts thereof, or a solvate (e.g., hydrate) thereof, are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more

suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

General Methods of Preparation:

The compounds of Formula (I) may be obtained by using synthetic procedures illustrated in the Schemes below or by drawing on the knowledge of a skilled organic chemist. The syntheses provided in these Schemes are applicable for producing compounds of the invention having a variety of different R1, R2 and R3 groups employing appropriate precursors. Those skilled in the art will appreciate that in the preparation of compounds of the invention (e.g., compounds of Formula (I), salts thereof, and/or solvates thereof) it may be necessary and/or desirable to protect one or more sensitive groups in the molecule or the appropriate intermediate to prevent undesirable side reactions. Suitable protecting groups for use according to the present invention are well know to those skilled in the art and may be used in a conventional manner. See for example, "Protective groups in organic synthesis" by T.W. Green and P.G.M Wuts (Wiley & Sons, 1991) or "Protecting Groups" by P.J.Kocienski (Georg Thieme Verlag, 1994). Subsequent deprotection, where needed, affords compounds of the nature generally disclosed. While the Schemes are shown with compounds of Formula (I), they are illustrative of processes that may be used to make the compounds of the invention.

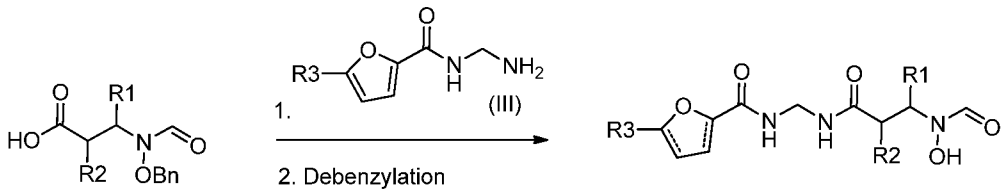
Compound names were generated using the software naming program Chem Draw Ultra v12.0 available from Perkin Elmer, 940 Winter Street, Waltham, Massachusetts, 02451, USA. (http://www.perkinelmer.com/).



(I)

In a general process, compounds of Formula (I) may be prepared according to reaction Schemes 1, 2 or 3:

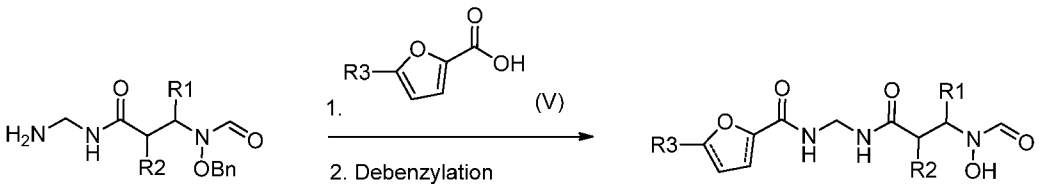
Scheme 1



(II) (III) (I)

1. React (II) and (III) in the presence of an amide coupling reagent (e.g. EDC/HOBT, HATU or HBTU) in the presence of a base (e.g. triethylamine or DIPEA) in a solvent such as DCM, DMF or THF either at room temperature or at an elevated temperature such as 50 °C. **2.** Debenzylation may be achieved via hydrogenation using a catalyst such as Pd/C and a hydrogen source (e.g. hydrogen gas or ammonium formate) at atmospheric pressure and temperature. Alternatively deprotection may be achieved using BCl_3 in a solvent such as DCM at 0 °C to room temperature. **3.** If required, re-formylation may be achieved utilizing a pre-mixed solution of CDI/formic acid in a solvent such as DCM at room temperature. Alternatively re-formylation may be achieved via reaction with 5-methyl-2-thioxo-1,3,4-thiadiazole-3(2H)-carbaldehyde (Yazawa, H., et al., Tetrahedron Letters, 1985, 26(31), 3703-6) in a solvent such as DCM at room temperature. As appreciated by those skilled in the art the order of the synthetic steps may be varied or omitted if unnecessary.

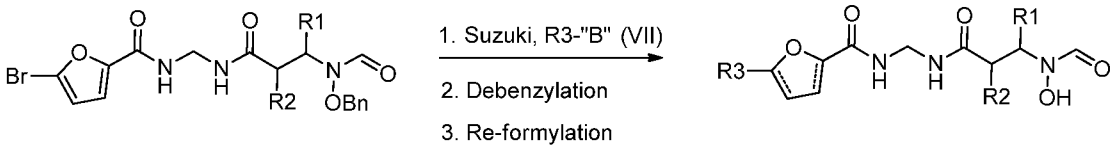
Scheme 2



(IV) (V) (I)

1. React (IV) and (V) in the presence of an amide coupling reagent (e.g. EDC/HOBT, HATU or HBTU) in the presence of a base (e.g. triethylamine, DIPEA or NMO) in a solvent such as DCM or DMF at room temperature or at an elevated temperature such as 50 °C. **2.-3.** Debenzylation and re-formylation (if required) may be achieved as described in Step 2 and Step 3 of Scheme 1. As appreciated by those skilled in the art the order of the synthetic steps may be varied or omitted if unnecessary.

Scheme 3

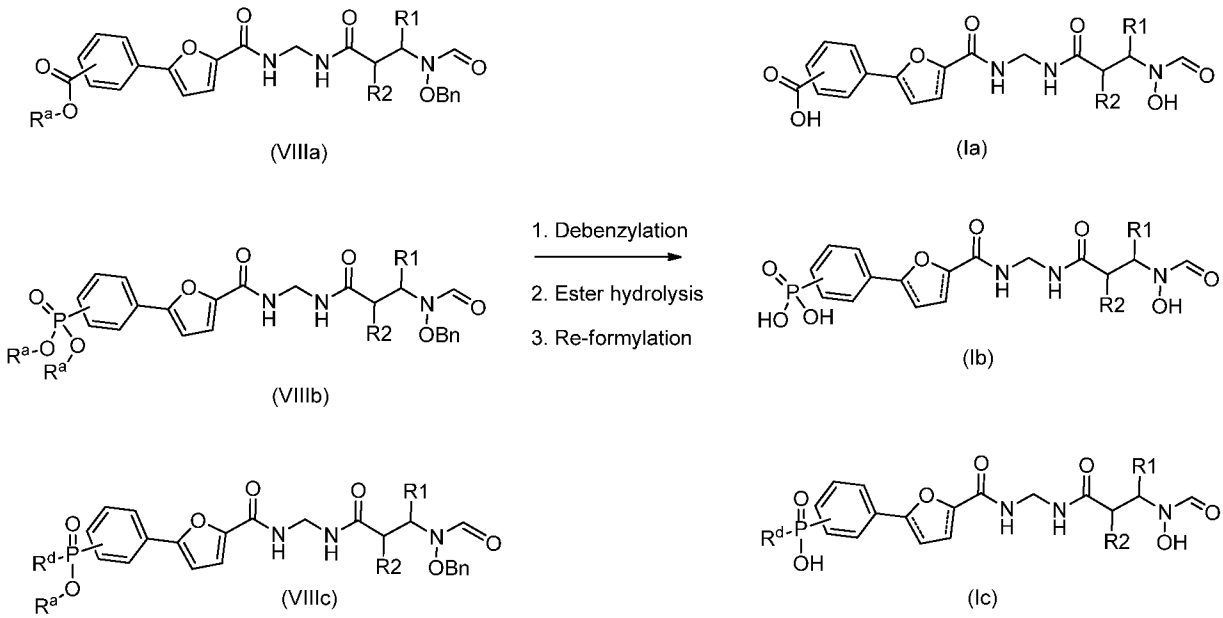


(VI) (I)

1. React (VI) with the appropriate boronic acid or boronate ester (R3-"B") derivative (VII) in the presence of a catalyst (e.g. $Pd(PPh_3)_4$ or $Pd(dppf)Cl_2$) in the presence of an inorganic base (e.g. potassium carbonate or aqueous sodium carbonate) in a suitable solvent (e.g. 1,4-dioxane or DME/water) at elevated temperature (50-150 °C) under microwave irradiation or by classical heating. **2.-3.** Debenzylation and re-formylation (if required) may be achieved as described in Step 2 and Step 3 of Scheme 1. As appreciated by those skilled in the art the order of the synthetic steps may be varied or omitted if unnecessary.

In a general process, compounds of Formula (I) wherein R3 contains a carboxylic acid (e.g., Formula (Ia)), phosphonic acid (e.g., Formula (Ib)) or phosphinic acid (e.g., Formula (Ic)) may be prepared according to Schemes 1, 2, 3 or as outlined in Scheme 4 from their corresponding ester functionalities (VIIIa), (VIIIb) and (VIIIc). The transformations in Scheme 4 are illustrated with a phenyl ring R3 however Scheme 4 applies analogously to preparation of corresponding molecules of Formula (1a-c) with all embodiments of R3 disclosed herein (including, e.g., where R3 is heteroaryl and/or optionally further substituted).

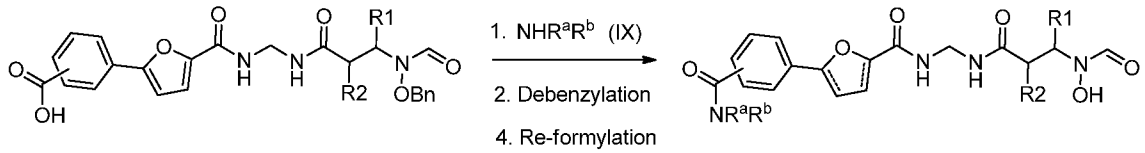
Scheme 4



1. Debenzylation may be achieved as described in Step 2 of Scheme 1. **2.** Ester hydrolysis may be achieved by reaction with lithium hydroxide in a suitable solvent such as a THF/water mixture or alcoholic solvent (e.g. ethanol or methanol/water mixture). For compounds of Formula (VIIIb) and (VIIIc), hydrolysis may be alternatively achieved by reaction with TMS-Br in a suitable solvent such as DCM at 0 °C to room temperature. **3.** If required, re-formylation can be achieved as described in Step 3 of Scheme 1. As appreciated by those skilled in the art the order of the synthetic steps may be varied or omitted if unecessary.

In a general process, compounds of Formula (I) wherein R3 contains an amide (e.g., Formula (1d)) may be prepared according to Scheme 1, 2, 3 or may be prepared according to reaction Scheme 5. The transformations in Scheme 5 are illustrated with a phenyl ring R3 however Scheme 5 applies analogously to preparation of corresponding molecules of Formula (1d) with all embodiments of R3 disclosed herein (including, e.g., where R3 is heteroaryl and/or optionally further substituted).

Scheme 5

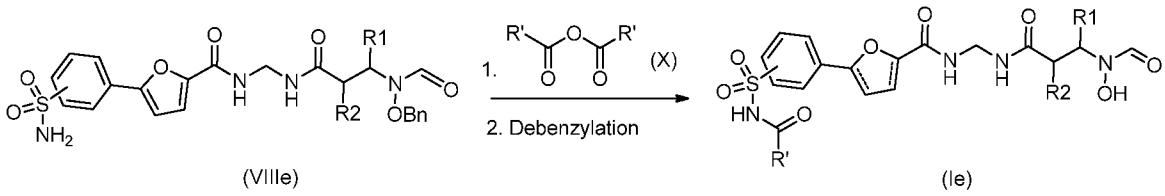


(VIIId) (Id)

1. React a compound of Formula (VIIId) and the appropriate amine NHR^aR^b (IX) in the presence of an amide coupling reagent (e.g. EDC/HOBT, HATU, HBTU or T3P®) in the presence of a base (e.g. triethylamine, DIPEA or NMO) in a solvent such as DCM or DMF at room temperature. **2.-3.** Debenzylation and re-formylation (if required) may be achieved as described in Step 2 and Step 3 of Scheme 1. As appreciated by those skilled in the art the order of the synthetic steps may be varied or omitted if uneccessary.

In a general process, compounds of Formula (I) wherein R3 contains an acyl sulphonamide (e.g., Formula (Ie)) may be prepared from compounds of Formula (VIIIe) wherein R3 contains a primary sulphonamide according to reaction Scheme 6. The transformations in Scheme 6 are illustrated with a phenyl ring R3 however Scheme 6 applies analogously to preparation of corresponding molecules of Formula (1e) with all embodiments of R3 disclosed herein (including, e.g., where R3 is heteroaryl and/or optionally further substituted).

Scheme 6

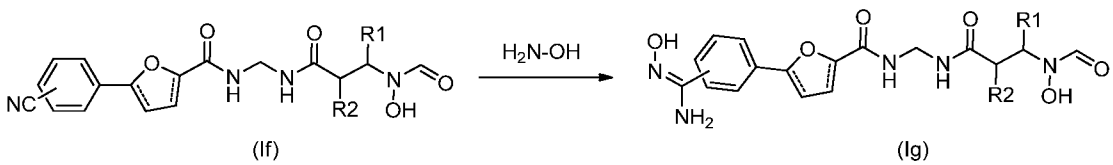


1. React a compound of Formula (VIIIe) with the appropriately substituted symmetrical anhydride (X) wherein R' is selected from C_{1-2} alkyl in the presence of a base such as triethylamine in a suitable solvent such as DCM at elevated temperature, such as 50 °C.

2. Debenzylation may be achieved as described in Step 2 of Scheme 1.

In a general process, compounds of Formula (I) wherein R3 contains an amide oxime (e.g., Formula (Ig)) may be prepared from compounds of Formula (If) wherein R3 contains a nitrile according to reaction Scheme 7. The transformation in Scheme 7 is illustrated with a phenyl ring R3 however Scheme 7 applies analogously to preparation of corresponding molecules of Formula (1g) with all embodiments of R3 disclosed herein (including, e.g., where R3 is heteroaryl and/or optionally further substituted).

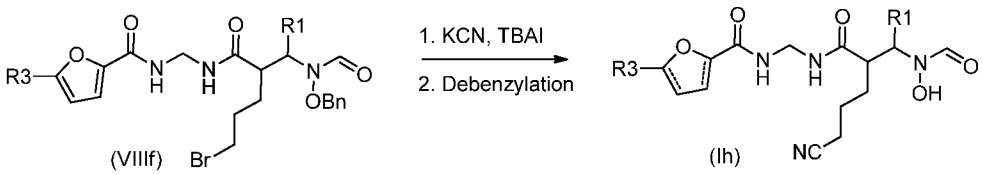
Scheme 7



React a compound of Formula (If) with hydroxylamine in a suitable solvent such as ethanol at an elevated temperature such as 75 °C.

In a general process, compounds of Formula (I) wherein R2 contains a nitrile functionality (e.g., Formula (Ih)) may be prepared from compounds of Formula (VIIIf) wherein R2 contains a bromide (Formula (VIIIf)) according to reaction Scheme 8. The transformations in Scheme 8 are illustrated with a propyl R2 however Scheme 8 applies analogously to preparation of corresponding molecules of Formula (1h) with all embodiments of R2 disclosed herein, including (C_1-C_{11})alkyl, (C_1-C_3)alkyl-(C_3-C_6)cycloalkyl, (C_1-C_3)alkyl-phenyl and (C_1-C_3)alkyl-heterocyclyl and/or optionally further substituted.

Scheme 8



1. React with potassium cyanide in the presence of catalytic TBAI in a suitable solvent such as acetonitrile at elevated temperature such as 80 °C. **2.** Debenzylation may be achieved as described in Step 2 of Scheme 1.

With regard to the above Schemes 1-8:

Compounds of Formula (II) may be prepared according to Schemes 9-14.

Compounds of Formula (III) may be prepared according to Schemes 15-17.

Compounds of formula (IV) may be prepared according to Scheme 18.

Compounds of Formula (VI) may be prepared according to Scheme 1 or 2 where the R3 of (III) or (V) is replaced by a bromide and by omitting the debenzylation step.

Compounds of Formula (VIIIa-c), (VIIId), and (VIIIe), and corresponding compounds with other R3; and compounds of Formula (VIIIf) and corresponding compounds with other R2, may be prepared according to Scheme 1, 2 or 3 by omitting the debenzylation step.

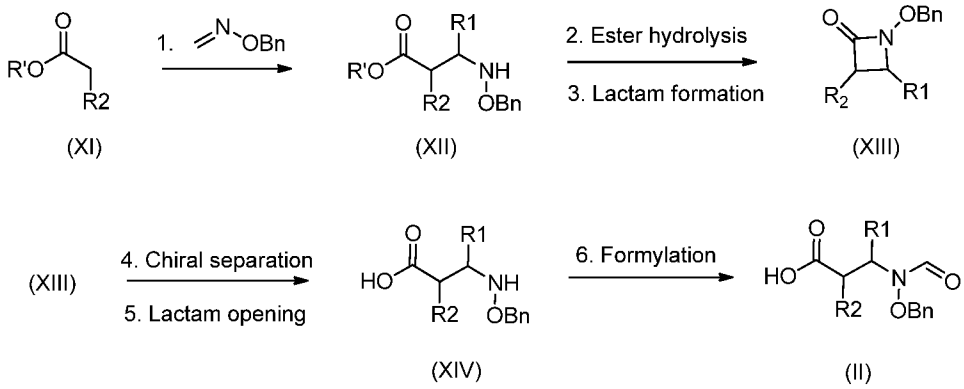
Compounds of Formula (If) and corresponding compounds with other R3 may be prepared according to Schemes 1, 2 or 3.

Compounds of Formula (V), (VII), and (X) may be sourced commercially or may be prepared by methods known in the literature or by processes known to those skilled in the art.

Compounds of Formula (IX) are commercially available.

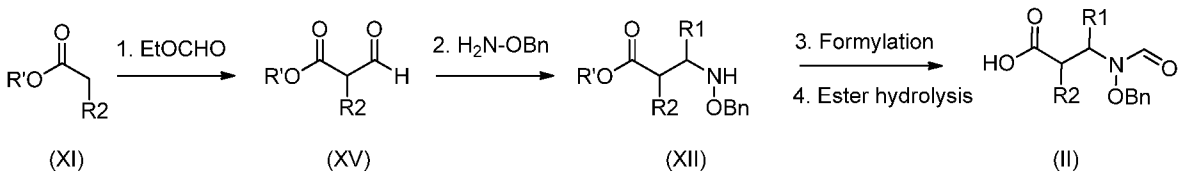
In a general process, compounds of Formula (II), wherein R1 is H, may be prepared according to the following reaction Schemes 9, 10, 11 or 14. In a general process, compounds of Formula (II) may be alternatively prepared according to the following reaction Schemes 12 or 13.

Scheme 9



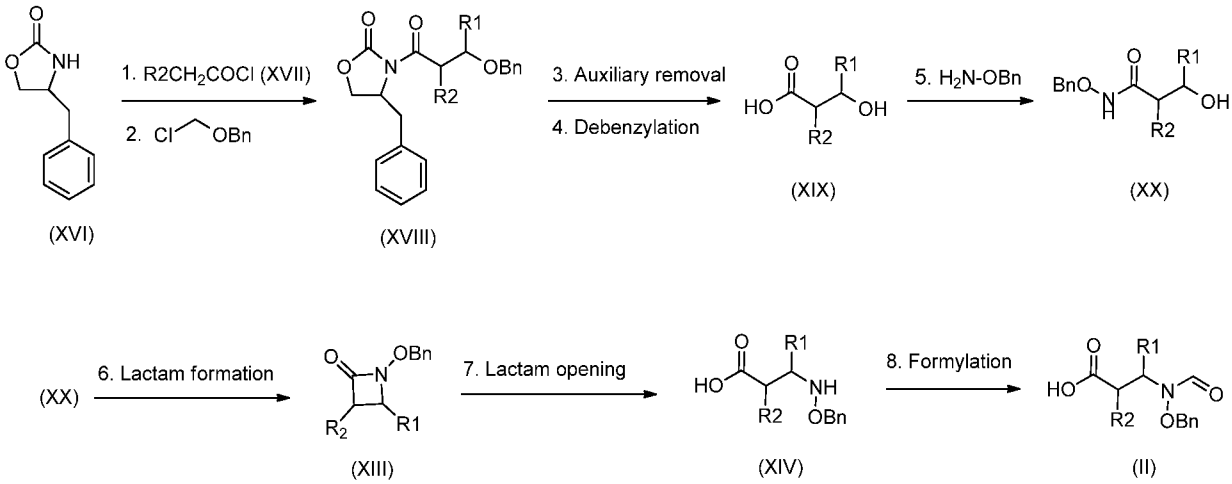
1.React formaldehyde O-benzyl oxime with a pre-mixed solution of NaI and TMS-Cl or TMS-OTf and then treat with a base such as triethylamine and a compound of Formula (XI) in a suitable solvent such as acetonitrile or DCM. **2.** In instances where R' is not H but selected from C_{1-2} alkyl, ester hydrolysis can be achieved by reaction with lithium hydroxide in a suitable solvent such as an ethanol/water mixture. **3.** Lactam formation may be achieved by reaction with phosphoryl trichloride in the presence of a base such as 2,6-dimethylpyridine in a suitable solvent such as toluene at an elevated temperature, such as at 50 °C. **4.** Chiral separation may be conducted at this stage using techniques known to those skilled in the art. **5.** Lactam ring opening may be achieved by reaction with lithium hydroxide in a suitable solvent such as a THF/water mixture. **6.** Formylation may be achieved as described in Step 3 of Scheme 1. As appreciated by those skilled in the art synthetic steps may be omitted if unnecessary.

Scheme 10



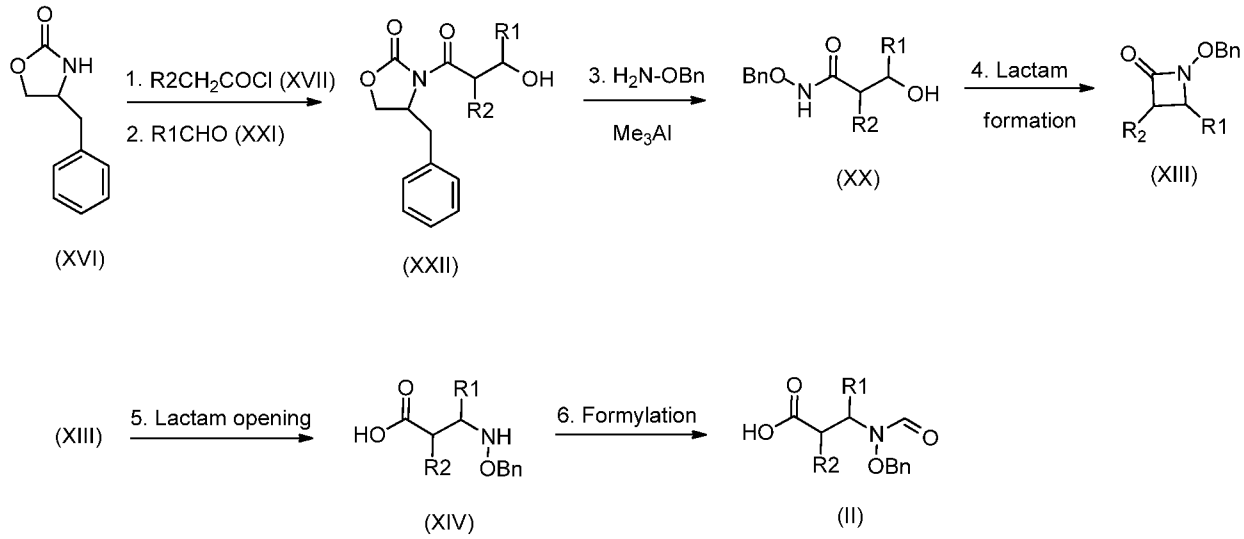
1. React a compound of Formula (XI) with a base such as LDA followed by reaction with ethyl formate in a suitable solvent such as THF at -78 °C to 0 °C. **2.** Conduct a reductive amination with O-benzylhydroxylamine hydrochloride in the presence of a reducing agent such as sodium triacetoxyborohydride in suitable solvent system such as a DCM/acetic acid mixture. **3.** Formylation may be achieved utilizing a mixture of CDI/formic acid in a solvent such as DCM at room temperature. **4.** Ester hydrolysis may be achieved by reaction with lithium hydroxide in a suitable solvent such as a THF/methanol/water mixture. As appreciated by those skilled in the art the order of the synthetic steps may be varied.

Scheme 11



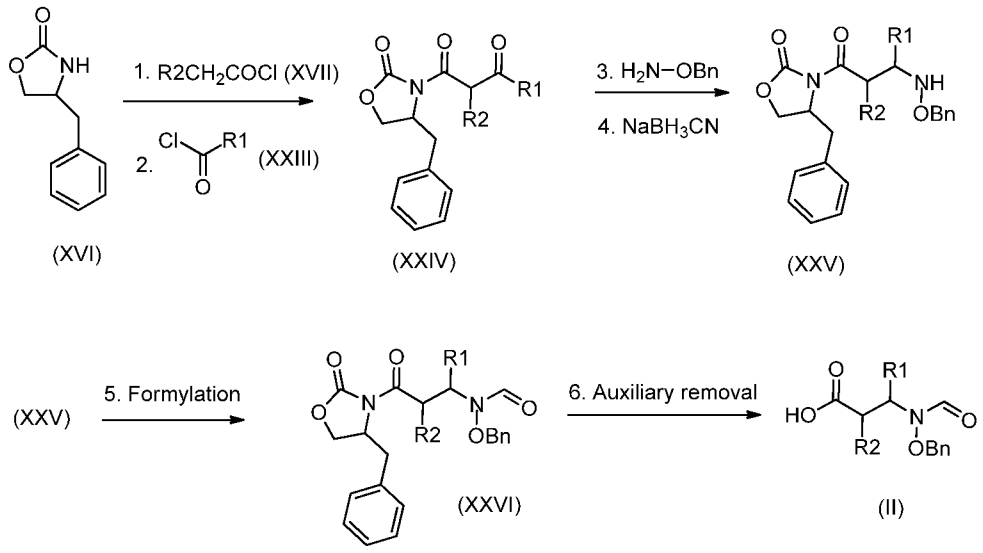
1. React the appropriate enantiomer of (XVI) with a base such as butyl lithium followed by the appropriate acyl chloride (XVII) in a suitable solvent such as THF at -78 °C to 0 °C. **2.** React with $TiCl_4$ in the presence of a suitable base such as DIPEA in a suitable solvent such as DCM followed by reaction with ((chloromethoxy)methyl)benzene. **3.** React with hydrogen peroxide and lithium hydroxide in a suitable solvent such as a mixture of THF and water at 0 °C. **4.** Debenzylation may be achieved via hydrogenation using Pd/C catalyst and a hydrogen source (e.g. hydrogen gas or ammonium formate) at room temperature. **5.** React with O-benzylhydroxylamine hydrochloride in the presence of a coupling agent such as EDC and DMAP in a suitable solvent such as DCM. **6.** Lactam formation may be achieved by reaction with DIAD and triphenylphosphine in a suitable solvent such as THF. **7.** Lactam ring opening may be achieved by reaction with lithium hydroxide in a suitable solvent such as a methanol/water mixture. **8.** Formylation may be achieved utilizing a mixture of CDI/formic acid in a solvent such as DCM at room temperature.

Scheme 12



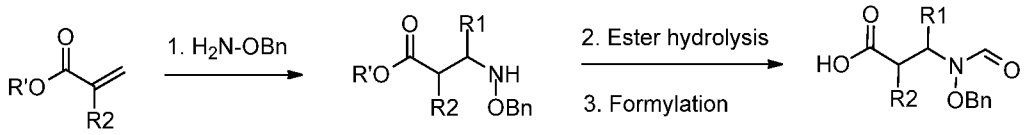
1. React the appropriate enantiomer of (XVI) with a base such as butyl lithium followed by the appropriate acyl chloride (XVII) in a suitable solvent such as THF. **2.** React with $TiCl_4$ in the presence of a suitable base such as DIPEA with a suitable additive such as NMP in a suitable solvent such as DCM followed by reaction with the appropriate aldehyde (XXI). **3.** React with O-benzylhydroxylamine hydrochloride in a suitable solvent such as THF in the presence of trimethylaluminium. **4.** React with methanesulfonyl chloride using a suitable base such as pyridine as the solvent. **5.** React with tetrabutylammonium hydroxide in a suitable solvent such as 2-methyl tetrahydrofuran. **6.** Formylation may be achieved utilizing a mixture of CDI/formic acid in a solvent such as DCM at room temperature.

Scheme 13



1. React the appropriate enantiomer of (XVI) with a base such as butyl lithium followed by the appropriate acyl chloride (XVII) in a suitable solvent such as THF. **2.** React with a suitable base such as NaHMDS in a suitable solvent such as THF at -78 °C followed by the appropriate acyl chloride (XXIII). **3.** React with O-benzylhydroxylamine hydrochloride in the presence of sodium acetate in a suitable solvent such as methanol. **4.** React with sodium cyanoborohydride in a suitable solvent mixture such as dichloroethane and acetic acid. **5.** Formylation may be achieved utilizing a mixture of CDI/formic acid in a solvent such as DCM at room temperature. **6.** React with hydrogen peroxide and lithium hydroxide in a suitable solvent such as a mixture of methanol and water at 0 °C.

Scheme 14



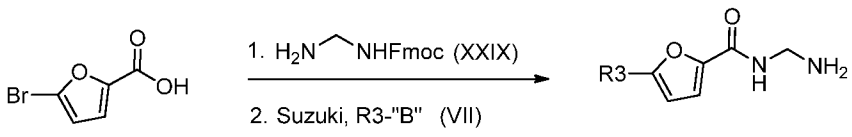
(XXVII) (XXVIII) (II)

1. React a compound of Formula (XXVII), wherein R' is C_{1-2} alkyl, with O-benzylhydroxylamine hydrochloride in the presence of (a) a suitable base such as triethylamine in a suitable solvent such as ethanol, or (b) $MgBr_2$ in a suitable solvent such as methanol at an elevated temperature such as 100 °C. **2.** Ester hydrolysis may be achieved by reaction with lithium hydroxide in a suitable solvent such as a THF/water mixture. **3.** Formylation may be achieved utilizing a mixture of CDI/formic acid in a solvent such as DCM at room temperature.

With regard to the above Schemes 9-14, compounds of Formula (XI), (XVI), (XVII), (XXI), (XXIII), and (XXVII) are commercially available or may be prepared by methods known in the literature or by processes known to those skilled in the art.

In a general process, compounds of Formula (III) may be prepared according to reaction Scheme 15, 16 or 17:

Scheme 15

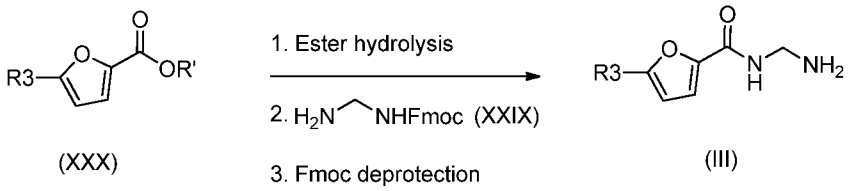


(III)

1. React 5-bromofuran-2-carboxylic acid with (XXIX) in the presence of a coupling reagent such as HATU in the presence of a base such as DIPEA in a suitable solvent such as DCM. **2.** React with the appropriate boronic acid or boronate ester (R3-"B")

derivative (VII) in the presence of a catalyst (e.g. $Pd(dppf)Cl_2$) in the presence of an inorganic base (e.g aqueous sodium carbonate) in a suitable solvent such as 1,4-dioxane or DME at an elevated temperature such as 100-105 °C under microwave irradiation. **3.** Fmoc deprotection may be achieved by reaction with a secondary amine such as piperidine, or pyrollidine in a suitable solvent such as DCM or acetonitrile. As appreciated by those skilled in the art the order of the synthetic steps may be varied.

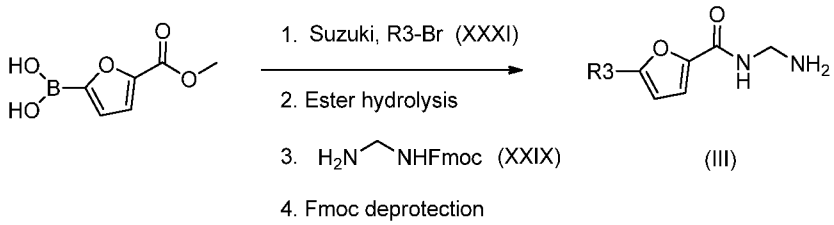
Scheme 16



(XXX) (III)

1. In instances where R' is not H but selected from C_{1-2} alkyl, ester hydrolysis may be achieved by reaction of a compound of Formula (XXX) with lithium hydroxide in a suitable solvent such as a mixture of methanol and water. **2.** Amide formation may be achieved by reaction with oxalyl chloride in a suitable solvent such as DMF at room temperature followed by reaction with a compound of Formula (XXIX) in the presence of a base such as DIPEA in a suitable solvent such as DCM. Alternatively, amide formation may be achieved by reaction (XXIX) in the presence of a coupling reagent such as HATU in the presence of a base such as DIPEA in a suitable solvent such as DCM. **3.** Fmoc deprotection may be achieved by reaction with a secondary amine such as pyrollidine or morpholine in a suitable solvent such as DCM or acetonitrile.

Scheme 17



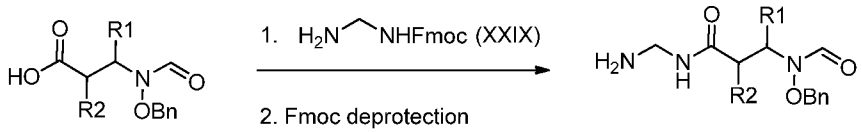
(III)

1. React (5-(methoxycarbonyl)furan-2-yl)boronic acid with the appropriate bromide, R^3-Br (XXXI), in the presence of a catalyst (e.g. $Pd(dppf)Cl_2$) in the presence of an inorganic base (e.g. aqueous sodium carbonate) in a suitable solvent (e.g. 1,4-dioxane) at elevated temperature (e.g. 100 °C) under microwave irradiation. **2.** Ester hydrolysis may be achieved by reaction with lithium hydroxide in a suitable solvent such as a THF/water mixture at room temperature. **3.** React with (XXIX) in the presence of a coupling reagent such as HBTU in the presence of a base such as DIPEA in a suitable solvent such as DMF at room temperature. **4.** Fmoc deprotection may be achieved by reaction with a secondary amine such as piperidine, or pyrollidine in a suitable solvent such as DCM or

acetonitrile.

In a general process, compounds of Formula (IV) may be prepared according to reaction Scheme 18.

Scheme 18



(II) (IV)

1. React compound of Formula (II) with (XXIX) in the presence of a coupling reagent such as HATU in the presence of a base such as DIPEA in a suitable solvent such as DMF at room temperature. **2.** Fmoc deprotection may be achieved by reaction with a secondary amine such as morpholine in a suitable solvent such as acetonitrile.

With regard to the above Schemes 15-18:

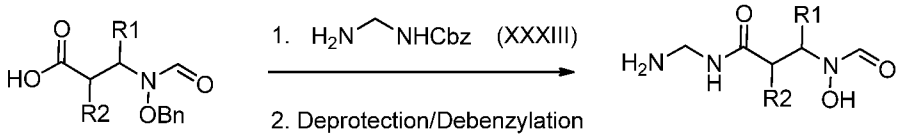
Compound (XXIX) may be prepared by processes known to those skilled in the art.

Compounds of Formula (VII) and (XXX) are commercially available, may be prepared by methods known in the literature or by processes known to those skilled in the art.

Compounds of Formula (XXXI) may be sourced commercially or prepared by methods known to those skilled in the art.

In a general process, compounds of Formula (XXXII) may be prepared according to reaction Scheme 19.

Scheme 19

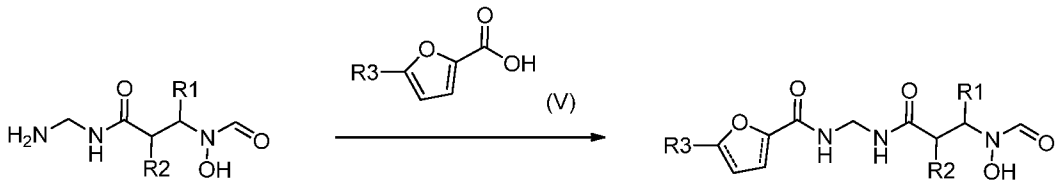


(II) (XXXII)

1. React compound of Formula (II) with (XXXIII) in the presence of a coupling reagent such as HATU in the presence of a base such as DIPEA in a suitable solvent such as DMF at room temperature. **2.** Deprotection of the Cbz group and debenzylation may be achieved under similar conditions described in Step 2 of Scheme 1 to yield the amine (XXXII).

In a general process, compounds of Formula I) may be prepared according to reaction Scheme 20.

Scheme 20

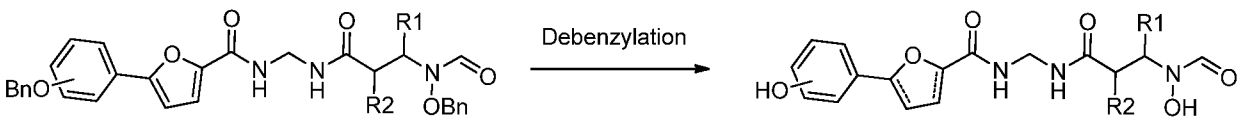


(XXXII) (I)

React (XXXII) and (V) in the presence of an amide coupling reagent (e.g. EDC/HOBT, HATU or HBTU) in the presence of a base (e.g. triethylamine, DIPEA or NMO) in a solvent such as DCM or DMF in the presence of TMSCl at room temperature or at an elevated temperature such as 50 °C to yield the final product (I).

In a general process, compounds of Formula (I) wherein R3 contains a phenol (e.g., Formula (Ii) may be prepared from compounds of Formula (XXXIV) wherein R3 contains a benzylether according to reaction Scheme 21. The transformation in Scheme 21 is illustrated with a phenyl ring R3 however Scheme 21 applies analogously to preparation of corresponding molecules of Formula (Ii) with all embodiments of R3 disclosed herein (including, e.g., where R3 is heteroaryl and/or optionally further substituted).

Scheme 21



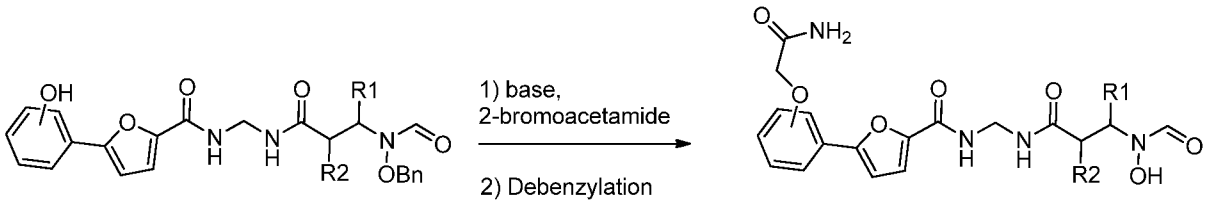
(XXXIV) (Ii)

React a compound of Formula (XXXIV) under debenzylation conditions similar to those described in Step 2 of Scheme 1 to yield the phenol (Ii).

In a general process, compounds of Formula (I) wherein R3 contains an amide (e.g., Formula (Ij) may be prepared from compounds of Formula (XXXV) wherein R3 contains a phenol according to reaction Scheme 22. The transformation in Scheme 22 is illustrated with a phenyl ring R3 however Scheme 22 applies analogously to preparation of corresponding molecules of Formula (Ij) with all embodiments of R3 disclosed herein

(including, e.g., where R3 is heteroaryl and/or optionally further substituted).

Scheme 22



(XXXV) (Ij)

1. React compound of Formula (XXXV) with an alkyl bromide such as 2-bromoacetamide in the presence of a base such as K_2CO_3 in a suitable solvent such as CH_3CN at elevated temperatures such as 80 ºC. **2.** Debenzylation may be achieved under similar conditions described in Step 2 of Scheme 1 to yield the product (Ij).

Further details for the preparation of compounds of the invention are found in the Intermediates and Examples section hereinafter.

Use of Compounds of the Invention:

The compounds of this invention are inhibitors of BMP1, TLL1 and/or TLL2 activity, and may be particularly useful for treatment of diseases associated with BMP1, TLL1 and/or TLL2 activity, including for example treatment of diseases where inhibition of BMP1, TLL1 and/or TLL2 is of therapeutic benefit. For example, compounds of the invention may be particularly useful for treatment of diseases where inhibition of tissue ECM (extracellular matrix) production and/or maturation would be beneficial, or where inhibition of myostatin activity would be beneficial.

In some embodiments, the disease associated with BMP1, TLL1 and/or TLL2 activity is selected from diseases associated with pathological fibrotic conditions in body organs or tissues, e.g., such conditions of the:

heart (e.g., myocardial infarction ("MI"), heart failure (e.g., heart failure with reduced ejection fraction, heart failure with preserved ejection fraction), cardiac arrhythmias (e.g., atrial fibrillation), hypertrophic cardiomyopathy),

lung (e.g. chronic obstructive pulmonary disease ("COPD"), idiopathic pulmonary fibrosis ("IPF")),

kidney (e.g. diabetic nephropathy, post-acute kidney injury, chronic kidney disease ("CKD"), delayed graft function post-transplantation),

liver (e.g. liver cirrhosis, non-alcoholic steatohepatitis ("NASH")),

eye (e.g. glaucoma, corneal scarring),

skeletal muscle (e.g. muscular dystrophies, including Duchenne, Becker, limb-girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery-Dreifuss),

skin (e.g. keloids, wound healing, adhesions, hypertrophic scarring and other scarring, e.g., associated with burns, surgery or other trauma),

the vasculature (e.g. stroke, and collagen vascular diseases such as systemic lupus erythematosus, rheumatoid arthritis and scleroderma), and

the nervous system (e.g. spinal cord injury, multiple sclerosis).

In some embodiments, the disease associated with BMP1, TLL1 and/or TLL2 activity is selected from muscular diseases characterized by reduced muscle function and/or mass, e.g., muscular dystrophy (e.g., Duchenne, Becker, limb-girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery-Dreifuss), sarcopenia, and cachexia associated with, e.g., heart failure, CKD, COPD, cancer, or old age.

Accordingly, this invention provides a method of treating a disease associated with BMP1, TLL1 and/or TLL2 activity in a subject in need thereof (e.g. a human or other mammal, particularly a human), for example the diseases recited herein, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a salt thereof, particularly a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of the invention is administered post-MI (i.e. to a subject who has suffered an MI), e.g. to treat fibrosis associated with myocardial infarction. In some embodiments, a compound of the invention is administered post-MI, e.g. to prevent fibrosis associated with myocardial infarction.

In some embodiments, the method of treating comprises administering a specific compound described herein, e.g., a compound of the Examples, or any free acid/base form, salt form, or alternative salt form (particularly pharmaceutically acceptable salts or alternative pharmaceutically acceptable salt forms) thereof, as applicable.

In some embodiments, the method of treating comprises administering (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid. In some embodiments, the method of treating comprises administering a pharmaceutically acceptable salt of (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid. In some embodiments, the method of treating comprises administering a meglumine salt, Tris salt, or calcium salt of (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-

hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid.

In some embodiments, the method of treating comprises administering (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid. In some embodiments, the method of treating comprises administering a pharmaceutically acceptable salt of (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid.

In some embodiments, the method of treating comprises administering (S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid. In some embodiments, the method of treating comprises administering a pharmaceutically acceptable salt of (S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid.

This invention also provides a compound of Formula (I), or a salt thereof, particularly a pharmaceutically acceptable salt thereof, for use in therapy. This invention specifically provides for the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as an active therapeutic substance in the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity, for example the diseases recited herein.

In some embodiments, the compound for use in therapy, e.g. for use in the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity, is a specific compound described herein, e.g., a compound of the Examples, or any free acid/base form, salt form, or alternative salt form (particularly pharmaceutically acceptable salts or alternative pharmaceutically acceptable salt forms) thereof, as applicable.

In some embodiments, the compound for use in therapy is (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid. In some embodiments, the compound for use in therapy is a pharmaceutically acceptable salt of (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid. In some embodiments, the compound for use in therapy is a meglumine salt, Tris salt, or calcium salt of (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid.

In some embodiments, the compound for use in therapy is (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid. In some embodiments, the compound for use in therapy is a pharmaceutically acceptable salt of (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid.

In some embodiments, the compound for use in therapy is (S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid. In some embodiments, the compound for use in therapy is a pharmaceutically acceptable salt of (S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid.

The invention also provides for the use of a compound of Formula (I), or a salt thereof, particularly a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity, for example the diseases recited herein.

In some embodiments, the invention provides for the use of a specific compound described herein, e.g., a compound of the Examples, or any free acid/base form, salt form, or alternative salt form (particularly pharmaceutically acceptable salts or alternative pharmaceutically acceptable salt forms) thereof, as applicable, in the manufacture of a medicament for use in the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity.

In some embodiments, the invention provides for the use of (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid, in the manufacture of a medicament for use in the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity. In some embodiments, the invention provides for the use of a pharmaceutically acceptable salt of (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid, in the manufacture of a medicament for use in the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity. In some embodiments, the invention provides for the use of a meglumine salt, Tris salt, or calcium salt of (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid, in the manufacture of a medicament for use in the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity.

In some embodiments, the invention provides for the use of (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid, in the manufacture of a medicament for use in the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity. In some embodiments, the invention provides for the use of a pharmaceutically acceptable salt of (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid, in the manufacture of a medicament for use in the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity.

In some embodiments, the invention provides for the use (S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid, in the manufacture of a medicament for use in the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity. In some embodiments, the invention provides for the use of a pharmaceutically acceptable salt of (S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid, in the manufacture of a medicament for use in the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity.

Treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity may be achieved using a compound of this invention as a monotherapy, or in dual or multiple combination therapy. For example, the compounds of this invention may be administered in combination with one or more therapeutically active agents selected from the group consisting of: anticoagulants, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta("β")-blockers, aldosterone antagonists, diuretics, vasodilators, cholesterol-lowering drugs (e.g., statins, fibrates, niacin, resins), statins, platelet antagonists, anti-arrhythmics, calcium channel blockers, erythropoiesis-stimulating agents (ESAs), iron, beta agonists, inhaled or oral steroids, anticholinergics, theophylline, PDE4 inhibitors, antibiotics, other antifibrotic agents, PDE5 inhibitors, immune modulators, neprilysin inhibitors, and digitalis preparations, e.g., any such agents as are known in the art, and combinations thereof. Particular therapeutic agents in these classes include those in the United States Pharmacopeia (USP). It will be understood that a particular active agent may fall within one or more of the foregoing classes. Such agents may be administered in therapeutically effective amounts, e.g., as is known in the art, or lesser or greater amounts than known in the art provided that the amount administered is therapeutically effective.

For example, treatment of cardiac diseases may include administration of one or more agents selected from the group: anticoagulants, ACE inhibitors, ARBs, β-blockers,

aldosterone antagonists, diuretics, vasodilators (e.g. nitrates), cholesterol lowering drugs (e.g., statins, fibrates, niacin, resins), platelet antagonists, anti-arrhythmics, calcium channel blockers, neprilysin inhibitors, digitalis preparations, and combinations thereof. In particular embodiments, treatment of atrial fibrillation, heart failure, or hypertrophic cardiomyopathy may comprise administration of one or more such agents.

As another example, treatment of CKD may include administration of one or more agents selected from ESAs, iron, ACE inhibitors, ARBs, β-blockers, diuretics, calcium channel blockers, statins, and combinations thereof.

In other exemplary embodiments, treatment of COPD may include administration of one or more agents selected from the group: beta agonists, inhaled or oral steroids, anticholinergics, theophylline, PDE4 inhibitors, antibiotics, and combinations thereof.

For example, idiopathic pulmonary fibrosis may include administration of one or more agents selected from the group: antifibrotics, PDE5 inhibitors, immune modulators, and combinations thereof.

Particular examples of other therapeutically active agents which may be used in combination with one or more compounds of the invention, for example to treat cardiac diseases, include:

anticoagulants such as: dalteparin (FRAGMIN), danaparoid (ORGARAN), enoxaparin (LOVENOX), heparin, tinzaparin (INNOHEP), warfarin (COUMADIN), alteplase, aspirin, ardeparin, fondaparinux, lepirudin, desirudin, bivalirudin, urokinase, rivaroxaban, apixaban, dabigatran, argatroban;

ACE inhibitors such as benazepril (LOTENSIN), captopril (CAPOTEN), enalapril (VASOTEC), fosinopril (MONOPRIL), lisinopril (PRINIVIL, ZESTRIL), moexipril (UNIVASC), perindopril (ACEON), quinapril (ACCUPRIL), Ramipril (ALTACE), trandolapril (MAVIK), imidapril;

ARBs such as candesartan (ATACAND), eprosartan (TEVETEN), irbesartan (AVAPRO), losartan (COZAAR), telmisartan (MICARDIS), valsartan (DIOVAN), olmesartan, azilsartan;

beta-blockers such as acebutolol (SECTRAL), atenolol (TENORMIN), betaxolol (KERLONE), bisoprolol/hydrochlorothiazide (ZIAC), bisoprolol (ZEBETA), carteolol (CARTROL), metoprolol (LOPRESSOR, TOPROL XL), nadolol (CORGARD), propranolol (INDERAL), sotalol (BETAPACE), timolol (BLOCADREN);

aldosterone antagonists such as spironolactone, eplerenone, Canrenone (canrenoate potassium), Prorenone (prorenoate potassium), Mexrenone (mexrenoate potassium);

diuretics such as amiloride (MIDAMOR), bumetanide (BUMEX), chlorothiazide (DIURIL), chlorthalidone (HYGROTON), furosemide (LASIX), hydro-chlorothiazide (ESIDRIX, HYDRODIURIL), indapamide (LOZOL), spironolactone (ALDACTONE), metolazone, torsemide, triamterene;

vasodilators such as nitroglycerin, isosorbide dinitrate (ISORDIL), isosorbide mononitrate, nesiritide (NATRECOR), hydralazine (APRESOLINE)

cholesterol-lowering drugs, e.g., statins, such as atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, including combination products, such as ADVICOR (lovastatin/niacin extended-release), SIMCOR (simvastatin/niacin extended-release), and VYTORIN (simvastatin/ezetimibe); nicotinic acid (niacin), fibrates such as gemfibrozil (LOPID), fenofibrate (TRICOR, FIBRICOR), clofibrate;

platelet antagonists such as aspirin, ticlopidine, clopidogrel (PLAVIX), dipyridamole;

anti-arrhythmics such as quinidine, procainamide, disopyramide, lidocaine, phenytoin, mexiletine, tocainide, encainide, flecainide, propafenone, moricizine, carvedilol, propranolol, esmolol, timolol, metoprolol, atenolol, bisoprolol, amiodarone, sotalol, ibutilide, dofetilide, dronedarone, verapamil, diltiazem, adenosine, digoxin, magnesium sulfate;

calcium channel blockers, such as amlodipine (NORVASC, LOTREL), bepridil (VASCOR), diltiazem (CARDIZEM, TIAZAC), felodipine (PLENDIL), nifedipine (ADALAT, PROCARDIA), nimodipine (NIMOTOP), nisoldipine (SULAR), verapamil (CALAN, ISOPTIN, VERELAN), isradipine, nicardipine;

neprilysin inhibitors such as sacubitril, including, e.g., a combination of sacubitril and valsartan, such as LCZ696;

digitalis preparations such as digoxin, digitoxin.

Combination therapy includes administration of the therapeutically active agents in separate dosage forms or together in a single dosage form. Combination therapy may involve simultaneous administration or separate administration of the therapeutically active agents, which may be substantially simultaneous or substantially separate administration. Typically, combination therapy will involve administration of each agent such that therapeutically effective amounts of each agent are present in the subject's body in at least an overlapping period.

In some embodiments, combination therapy comprises administering a specific compound described herein, e.g., a compound of the Examples, or any free acid/base

form, salt form, or alternative salt form (particularly pharmaceutically acceptable salts or alternative pharmaceutically acceptable salt forms) thereof, as applicable, and one or more additional therapeutically active agents.

In some embodiments, combination therapy comprises administering (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid, and one or more additional therapeutically active agents. In some embodiments, combination therapy comprises administering a pharmaceutically acceptable salt of (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid, and one or more additional therapeutically active agents. In some embodiments, combination therapy comprises administering a meglumine salt, Tris salt, or calcium salt of (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid, and one or more additional therapeutically active agents.

In some embodiments, combination therapy comprises administering (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid, and one or more additional therapeutically active agents. In some embodiments, combination therapy comprises administering a pharmaceutically acceptable salt of (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid, and one or more additional therapeutically active agents.

In some embodiments, combination therapy comprises administering (S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid, and one or more additional therapeutically active agents. In some embodiments, combination therapy comprises administering a pharmaceutically acceptable salt of (S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid, and one or more additional therapeutically active agents.

Accordingly, the present invention provides a composition comprising a) a compound of formula (I) or a pharmaceutically acceptable salt thereof and b) a combination partner. As used herein, suitable combination partners include one or more other therapeutically active agents such as those described above by classification or more particularly.

The present invention further provides a method for treating a disease associated with BMP1, TLL1 and/or TLL2 activity in a subject (e.g. a human or other mammal,

particularly a human) in need thereof comprising administering to said subject a therapeutically effective amount of a) a compound of formula (I) or a pharmaceutically acceptable salt thereof and b) a combination partner. The individual components of the combination may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations by any convenient route.

The invention further provides a combination of a) a compound of formula (I) or a pharmaceutically acceptable salt thereof and b) a combination partner.

In the compositions, methods and combinations of the invention comprising a combination partner, suitable combination partners include other therapeutically active agents such as described above by classification or more particularly.

In some embodiments of the compositions, methods and combinations of the inventions comprising a combination partner, the compound of formula (I) or a pharmaceutically acceptable salt thereof is a specific compound described herein, e.g., a compound of the Examples, or any free acid/base form, pharmaceutically acceptable salt form or alternative pharmaceutically acceptable salt form thereof, as applicable; in various more particular embodiments the compound of formula (I) or a pharmaceutically acceptable salt thereof is (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid, a pharmaceutically acceptable salt thereof, or a meglumine salt, Tris salt, or calcium salt thereof; in other various more particular embodiments the compound of formula (I) or a pharmaceutically acceptable salt thereof is (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid, or a pharmaceutically acceptable salt thereof; in other various more particular embodiments the compound of formula (I) or a pharmaceutically acceptable salt thereof is (S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid, or a pharmaceutically acceptable salt thereof.

A “therapeutically effective amount" is intended to mean that amount of a compound that, when administered to a subject in need of such treatment, is sufficient to effect treatment, as defined herein. Thus, for example, a therapeutically effective amount of a compound of the invention, e.g. a compound of Formula (I) or a pharmaceutically acceptable salt thereof, is a quantity of such agent that, when administered to a subject (e.g., human) in need thereof, is sufficient to modulate or inhibit the activity of BMP1, TLL1 and/or TLL2 such that a disease condition which is mediated or inhibited by that activity is reduced, alleviated or prevented. The amount of a given compound that will correspond to such an amount will vary depending upon factors such as the particular

compound (e.g., the potency (pIC_{50}) and the biological half-life of the particular compound), disease condition and its severity, and the identity (e.g., age, size and weight) of the subject in need of treatment, but can nevertheless be routinely determined by one skilled in the art. Likewise, the duration of treatment and the time period of administration (time period between dosages and the timing of the dosages, e.g., before/with/after meals) of the compound will vary according to the identity of the subject in need of treatment (e.g., weight), the particular compound and its properties (e.g., pharmaceutical characteristics), disease and its severity and the specific composition and method being used, but can nevertheless be determined by one of skill in the art.

In some embodiments, 0.1 mg to 1000 mg (e.g., 0.1 – 500 mg, or 0.1 – 100 mg) of a compound of the invention, particularly a compound of Formula (I) or a pharmaceutically acceptable salt thereof, is administered at a frequency of twice a day, once a day, once a week, or frequencies therebetween. In some embodiments, a compound of the invention, particularly a compound of Formula (I) or a pharmaceutically acceptable salt thereof, is administered sub-cutaneously in an amount of less than 100 mg per dose (e.g., 0.1 - <100 mg per dose).

“Treat”, "treating" or "treatment" is intended to mean at least the mitigation of a disease in a subject. The methods of treatment for mitigation of a disease include the use of the compounds in this invention in any conventionally acceptable manner, for example for prevention, retardation, prophylaxis, therapy, improvement or cure of a disease. Thus, treatment may involve at least the mitigation of one or more symptoms of a disease. Specific diseases that may be particularly susceptible to treatment using a compound of this invention include those described herein.

The compounds of the invention may be administered by any suitable route of administration, including both systemic administration and topical administration. Systemic administration includes oral administration, parenteral administration, transdermal administration, rectal administration, and administration by inhalation. Oral administration includes enteral (digestive tract) and buccal or sublingual administration. Parenteral administration refers to routes of administration other than enteral, transdermal, or by inhalation, and is typically by injection or infusion into tissue or blood. Parenteral administration includes intravenous, intramuscular, subcutaneous, intradermal, and transdermal implant injection or infusion. Inhalation refers to administration into the subject's lungs whether inhaled through the mouth or through the nasal passages. Topical administration includes application to the skin.

For use in therapy, the compounds of the invention will be normally, but not necessarily, formulated into a pharmaceutical composition prior to administration to a

subject. Accordingly, the invention also is directed to pharmaceutical compositions comprising a compound of the invention, particularly a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

The pharmaceutical compositions of the invention may be prepared and packaged in bulk form wherein an effective amount of a compound of the invention can be extracted and then given to the subject such as with powders, syrups, and solutions for injection. Alternatively, the pharmaceutical compositions of the invention may be prepared and packaged in unit dosage form. For oral application, for example, one or more tablets or capsules may be administered. A dose of the pharmaceutical composition contains at least a therapeutically effective amount of a compound of this invention (i.e., a compound of Formula (I), or a salt, particularly a pharmaceutically acceptable salt, thereof). When prepared in unit dosage form, the pharmaceutical compositions may contain from 0.1 mg to 1000 mg (e.g., 0.1 - 500 mg, or 0.1 - 100 mg) of a compound of this invention.

The pharmaceutical composition may include one or more compounds of the invention and/or one or more pharmaceutically acceptable excipients. The pharmaceutical compositions of the invention typically contain one compound of the invention. However, in certain embodiments, the pharmaceutical compositions of the invention contain more than one compound of the invention. In addition, the pharmaceutical compositions of the invention may optionally further comprise one or more additional pharmaceutically active compounds, e.g., the therapeutically active agents described above by classification or more particularly.

In some embodiments, the pharmaceutical composition comprises a) 0.01-100 mg of a compound of formula (I) or a pharmaceutically acceptable salt thereof and b) 0.001-900 mg of one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition comprises a) 0.01-100 mg/mL of a compound of formula (I) or a pharmaceutically acceptable salt thereof and b) 0.001-900 mg/mL of one or more pharmaceutically acceptable excipients.

In some embodiments, the pharmaceutical composition comprises a specific compound described herein, e.g., a compound of the Examples, or any free acid/base form, pharmaceutically acceptable salt form, or alternative pharmaceutically acceptable salt form thereof, as applicable.

In some embodiments, the pharmaceutical composition comprises (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid, and one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition comprises a pharmaceutically

acceptable salt of (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid, and one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition comprises a meglumine salt, Tris salt, or calcium salt of (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid, and one or more pharmaceutically acceptable excipients.

In some embodiments, the pharmaceutical composition comprises (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid, and one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable salt of (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid, and one or more pharmaceutically acceptable excipients.

In some embodiments, the pharmaceutical composition comprises (S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid, and one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable salt of (S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid, and one or more pharmaceutically acceptable excipients.

As used herein, "pharmaceutically acceptable excipient" means a material, composition or vehicle other than a pharmaceutical active ingredient(s) intended for treating a disease (e.g., a compound of the invention). Pharmaceutically acceptable excipients are involved in providing a property or function useful to a pharmaceutical composition, for example an excipient may be involved in modifying physical, sensory, stability, or pharmaco-kinetic properties of the composition, for example in giving form or consistency to the composition, in bulking up the active ingredient (e.g. for convenient and accurate dispensation), in enhancing therapy (e.g. facilitating drug absorption or solubility, or other pharmacokinetic properties), in the manufacturing process (e.g. as a handling or processing aid), in stabilizing the composition, or in enhancing subject compliance (e.g., enhancing palatability or appearance of the composition). Each excipient must be compatible with the other ingredients of the pharmaceutical composition when commingled such that interactions which would substantially reduce the efficacy of the compound of the invention (or any other active ingredient, if present)

when administered to a subject and interactions which would result in pharmaceutical compositions that are sufficiently high purity to render it pharmaceutically acceptable.

The compounds of the invention and the pharmaceutically acceptable excipient or excipients will typically be formulated into a dosage form adapted for administration to the subject by the desired route of administration. Conventional dosage forms include those adapted for (1) oral administration such as tablets, capsules, caplets, pills, lozenges, troches, powders, syrups, elixirs, suspensions, solutions, emulsions, sachets, and cachets; (2) parenteral administration such as sterile solutions, suspensions, lyophiles, microparticles, nanocarriers, implants, preformed implants and powders for reconstitution; (3) transdermal administration such as transdermal patches; (4) rectal administration such as suppositories; (5) inhalation such as aerosols and solutions; and (6) topical administration such as creams, ointments, lotions, solutions, pastes, sprays, foams, gels, dermal patches, and transdermal patches or sprays.

Suitable pharmaceutically acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically acceptable excipients may be chosen for their ability to: facilitate the production of uniform dosage forms, to facilitate the production of stable dosage forms, to facilitate the carrying or transporting the compound or compounds of the invention once administered to the subject from one organ, or portion of the body, to another organ, or portion of the body, and/or to enhance subject compliance.

Suitable pharmaceutically acceptable excipients include the following types of excipients: diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavoring agents, flavor masking agents, coloring agents, anti-caking agents, humectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, carriers, and buffering agents. The skilled artisan will appreciate that certain pharmaceutically acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other ingredients are present in the formulation.

Skilled artisans possess the knowledge and skill in the art to enable them to select suitable pharmaceutically acceptable excipients in appropriate amounts for use in the invention. In addition, there are a number of resources that are available to the skilled artisan which describe pharmaceutically acceptable excipients and may be useful in selecting suitable pharmaceutically acceptable excipients. Examples include

Remington's Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press), including current and past editions.

The pharmaceutical compositions of the invention are prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

In one aspect, the invention is directed to a solid oral dosage form such as a tablet or capsule comprising an effective amount of a compound of the invention and a diluent or filler, and optionally a binder, disintegrant, and/or lubricant. Suitable diluents and fillers include lactose, sucrose, dextrose, mannitol, sorbitol, starch (e.g. corn starch, potato starch, and pre-gelatinized starch), cellulose and its derivatives (e.g. microcrystalline cellulose), calcium sulfate, and dibasic calcium phosphate. Suitable binders include starch (e.g. corn starch, potato starch, and pre-gelatinized starch), gelatin, acacia, sodium alginate, alginic acid, tragacanth, guar gum, povidone, and cellulose and its derivatives (e.g. microcrystalline cellulose). Suitable disintegrants include crospovidone, sodium starch glycolate, croscarmelose, alginic acid, and sodium carboxymethyl cellulose. Suitable lubricants include stearic acid, magnesium stearate, calcium stearate, and talc.

In another aspect, the invention is directed to a parenteral formulation, e.g., in-situ gels, microspheres, nanospheres, nanosuspensions, or lyophilized products to control the release of a compound following subcutaneous administration, comprising a compound of the invention, a surfactant and/or a polymeric carrier and/or a solubilising excipient and/or an excipient to control osmolality. Suitable surfactants include polysorbates, polyvinyl alcohol, polyvinyl pyrrolidone and combinations thereof. Suitable polymeric carriers include polyethylene glycol, polymethacrylate, ethylene vinyl acetate copolymer, polyglactin, polyoxyethylene fatty acid esters, poly(lactic-co-glycolic acid), poly(epsilon-caprolactone), poly(p-dioxanone), poly(anhydride esters) and combinations thereof. Suitable solubilising excipients include n-methyl pyrollidone, polyethoxylated castor oil (e.g., CREMOPHOR such as CREMOPHOR EL), polysorbates, Solutol® (Macrogol 15 Hydroxystearate Ph.Eur; Polyoxyl 15 Hydroxystearate USP), ethanol and combinations thereof. Suitable excipients to control osmolality (and in the case of lyophiles, to bulk the lyophilized material) include mannitol, sucrose, glycine, and polyvinyl pyrrolidone.

In-situ gels can be prepared by solubilising a compound of the invention in solvent phase and water-insoluble polymeric carrier(s). The solution is then sterilized, e.g., by gamma irradiation.

Nanosuspensions can be prepared by combining a compound of the invention, a surfactant, a polymeric carrier and an excipient to control osmolality in aqueous phase, then bead milling or microfluidising the combination in aqueous phase to deliver particles of the compound between 100nm to less than 1µm. The nanosuspension is sterilized, e.g., by utilizing terminal heat sterilization or gamma irradiation techniques.

Microspheres and nanospheres can be prepared by various methods known in the art including water/oil/water emulsion methods, solvent/oil/water emulsion methods, oil/water emulsion methods, organic phase separation or melt extrusion/cryomilling techniques which involve inclusion of the compound of the invention and polymer(s) to control drug delivery. The particles are delivered to less than 100µm for microspheres and between 100nm to less than 1µm for nanospheres. The microspheres and nanospheres can go through further processing, including lyophilization, and require sterilization, e.g., through gamma irradiation.

A lyophilized product may suitably include a compound of the invention in a concentration of from 0.01 – 100 mg/mL, a surfactant, a polymeric carrier, and a solubilizing excipient. General conditions to provide a lyophilized product involve forming a solution of the product ingredients, reducing the solution below the glass transition, providing differential pressure to pull off aqueous and/or solvent phase, and slowly increasing temperature to form a lyophilized cake.

EXAMPLES

The following examples illustrate the invention. These examples are not intended to limit the scope of the present invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the present invention. While particular embodiments of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention.

In the following experimental descriptions, the following abbreviations may be used:

Abbreviation	Meaning
AcOH	acetic acid
aq.	aqueous
BBr_3	boron tribromide
BCl_3	boron trichloride
BH_3	borane

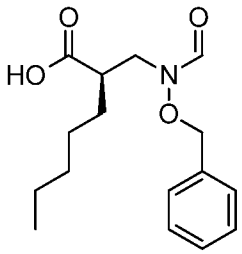
Bn	benzyl
brine	saturated aqueous sodium chloride
BuLi	butyl lithium
CDI	carbonyldiimidazole
CH_2Cl_2	methylene chloride
CH_3CN	acetonitrile
$COCl_2$	oxalyl chloride
DCC	dicyclohexylcarbodiimide
DCM	methylene chloride
DEAD	Diethyl azodicarboxylate
DEAP	diethyl aminopyridine
DIAD	diisopropyl azodicarboxylate
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DME	dimethoxyethane
DMSO	dimethylsulfoxide
EDC	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
Et	ethyl
Et_3N (also TEA)	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
Fmoc	fluorenylmethyloxycarbonyl
h	hour(s)
H_2	hydrogen
H_2O_2	hydrogen peroxide
H_2O	water

H_2SO_4	sulfuric acid
HATU	(O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate)
HBTU	2-(1H-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V)
HCl	hydrochloric acid
HCO_2H	formic acid
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
I_2	Iodine
JLR	jacketed lab reactor
K_2CO_3	potassium carbonate
$KHSO_4$	potassium hydrogen sulfate
KOAc	potassium acetate
LAH	Lithium aluminum hydride
LCMS	liquid chromatography-mass spectroscopy
LDA	lithium diisopropyl amide
LiOH	lithium hydroxide
LHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
MeOH	methanol
$MgBr_2$	magnesium bromide
$MgSO_4$	magnesium sulfate
min	minute(s)
MS	mass spectrum
MTBE	Methyl tert-butyl ether
μw	microwave
N_2	nitrogen
$Na(CN)BH_3$	sodium cyanoborohydride
NaCl	sodium chloride

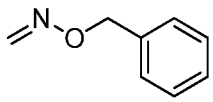
Na_2CO_3	sodium carbonate
$NaHCO_3$	sodium bicarbonate
NaHMDS	sodium bis(trimethylsilyl)amide
$NaHSO_3$	sodium bisulfite
NaH	sodium hydride
NaI	sodium iodide
NaOH	sodium hydroxide
Na_2SO_3	sodium sulfite
Na_2SO_4	sodium sulfate
NH_4Cl	ammonium chloride
$HCO_2{\bullet}NH_4$	ammonium formate
NH_4OH	ammonium hydroxide
NMO	4-methylmorpholine N-oxide
NMP	N-methyl-2-pyrrolidone
Pd/C	palladium on carbon
$PdCl_2$(dbpf)	1,1'-bis(di-tert-butylphosphino)ferrocene dichloropalladium
Pd(dppf)Cl_2/ $PdCl_2$(dppf)	[1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II)
$Pd(Ph_3)_4$	tetrakis(triphenylphosphine)palladium(0)
$Pd(OAc)_2$	palladium acetate
$Pd(OH)_2$	palladium hydroxide
Ph	phenyl
PL HCO_3 MP	macroporus polystyrene supported carbonate
$POCl_3$	phosphoryl chloride
PTFE	polytetrafluoroethylene
rt	room temperature
sat.	saturated
SFC	supercritical fluid chromatography
Si	silica
SPE	solid phase extraction

T3P®	propylphosphonic anhydride
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDMSCl	tert-butyldimethylsilyl chloride
TBME	tert-butylmethyl ether
TFA	trifluoroacetic acid
THF	tetrahydrofuran
$TiCl_4$	titanium tetrachloride
TMS-Br	trimethylsilyl bromide
TMS-Cl	trimethylsilyl chloride
TMS-OTf	trimethylsilyl triflate
tR	retention time
UPLC	ultra performance liquid chromatography

INTERMEDIATE 1: (R)-2-((N-(benzyloxy)formamido)methyl)heptanoic acid



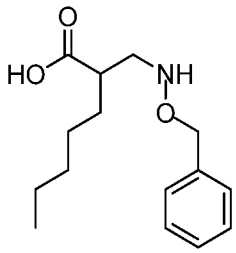
Step 1: formaldehyde O-benzyl oxime



A suspension of O-benzylhydroxylamine, hydrochloride (308 g, 1930 mmol) in t-butylmethyl ether (1800 ml) was added to a solution of sodium hydroxide (93 g, 2316 mmol) in water (570 ml) via an addition funnel. The funnel was rinsed with water (15 ml) and the reaction stirred for 10 minutes. Formaldehyde (37 % wt in water, 150 ml, 2015 mmol) was then added via an addition funnel slowly over ~20 minutes. The funnel was rinsed with water (15 ml) and the reaction mixture was stirred at 25 °C for 3 hours. The layers were then separated and the organic phase washed with 0.2 N HCl (480 ml), 5 % $NaHCO_3$ solution (300 ml), and 10 % brine solution (480 ml). The organics were separated and concentrated to give the title compound as a colorless oil (247 g, 90 %

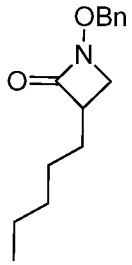
yield). MS (m/z) 136.1 ($M+H^+$)

Step 2: 2-(((benzyloxy)amino)methyl)heptanoic acid



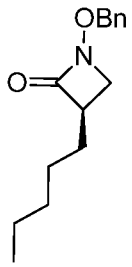
Acetonitrile (1250 ml) and sodium iodide (931 g, 6213 mmol) were charged to a 6 l reactor vessel under nitrogen at room temperature. The mixture was stirred vigorously for 10 minutes and chlorotrimethylsilane (790 ml, 6224 mmol) was then added. After stirring at room temperature for 15 minutes, the reaction was cooled to 15 ºC. Triethylamine (870 ml, 6242 mmol) was added. Heptanoic acid (264 ml, 1864 mmol) was then added slowly, maintaining the temperature below 35 ºC. The addition funnel was rinsed with CH_3CN (50 ml). The mixture was stirred at room temperature for 15 minutes and formaldehyde O-benzyl oxime (247 g, 1827 mmol) was added. The addition funnel was rinsed with CH_3CN (120 ml). The reaction was stirred at room temperature for 17 hours. The reaction mixture was then cooled to 12 ºC and quenched with a freshly prepared solution of sodium thiosulfate (491 g, 3107 mmol) in water (2250 ml) maintaining the temperature below 30 ºC. The reaction was stirred for 20 minutes and the pH of the reaction was then adjusted with 6N HCl (330 ml, 1980 mmol) to pH ~4. After stirring for 10 minutes EtOAc (500 ml) was added. The mixture was stirred for 5 minutes and then the layers were separated. The aqueous layer was back extracted with EtOAc (1750 ml). The combined organic solutions were washed with water (2 x 1250 ml) and 5 % brine (1250 ml) and then separated and concentrated to give 620 g of the crude product as a yellow oil. The crude residue was preabsorbed on silica and purified by flash chromatography (ISCO Torrent, 1.5 kg RediSep column, 1-5 % CH_2Cl_2/MeOH (6 runs)) to give three batches of the title compound as a colorless oil (176 g, 35 % yield), as a white solid (206 g, 41 % yield) and as a colorless oil (8 g, 2 % yield). MS (m/z) 266.1 ($M+H^+$)

Step 3: 1-(benzyloxy)-3-pentylazetidin-2-one



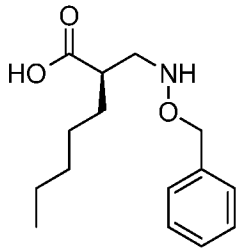
A 6 l reactor was charged with toluene (1750 ml) and 2,6-dimethylpyridine (232 ml, 1990 mmol) under a stream of nitrogen. Phosphoryl trichloride (99 ml, 1061 mmol) was added and the mixture was heated to 50 ºC. A solution of 2-(((benzyloxy)amino)methyl)heptanoic acid (176 g, 663 mmol) in toluene (1050 ml) was added over 40 minutes while maintaining the temperature below 55 ºC. The addition funnel was rinsed with toluene (100 ml). The reaction mixture was then stirred at 50°C for 1 hour. The reaction mixture was then cooled to 20 ºC and then drained. The reactor was rinsed with toluene (400 ml) and combined with the reaction mixture. The reactor was then charged with water (1600 ml) and Na_2CO_3 (239 g, 2255 mmol). The reaction mixture was slowly added to the Na_2CO_3 solution while maintaining the temperature below 35 ºC. The addition vessel was rinsed with toluene (400 ml). The biphasic mixture was stirred at 35 ºC for 30 minutes. The layers were left to separate, and the aqueous layer was drained. The organic phase was held at 3 ºC overnight and warmed up to 35 ºC the next morning before proceeding with the workup. The organic phase was washed sequentially with a mixed solution of concentrated HCl (123 ml) and 10% brine (1400 ml) to prevent emulsion formation, 10 % brine solution (900 ml), 5 % $NaHCO_3$ solution (900 ml) stirring for 10 minutes and then 10 % brine solution (900 ml). The organic phase was separated and concentrated to give the crude product as a yellow oil. The crude residue was preabsorbed on silica and purified by flash chromatography (ISCO Torrent 1.5 kg RediSep column, CH_2Cl_2/MeOH 0-5 %) to afford the title compound as a yellow oil. (87 g, 52 % yield). MS (m/z) 248.1 ($M+H^+$)

Step 4: (R)-1-(benzyloxy)-3-pentylazetidin-2-one



1-(benzyloxy)-3-pentylazetidin-2-one (220 g, 889 mmol) was subjected to chiral separation utilizing a SFC-70 Thar prep system. (Chiralpak AS-H column at room temperature, 15 % isopropanol, 50 g/min, 5 minute run time at a concentration of 250 mg/ml). Concentration of the appropriate fractions yielded two batches of the the title compound (13.5 g, 6.01 % yield, >96 % ee) and (87 g, 38.8 % yield, 96 % ee). MS (m/z) 248.1 ($M+H^+$)

Step 5: (R)-2-(((benzyloxy)amino)methyl)heptanoic acid



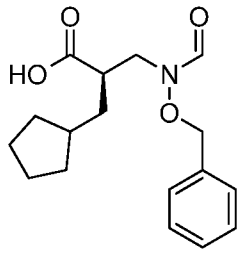
To a suspension of (R)-1-(benzyloxy)-3-pentylazetidin-2-one (10 g, 40.4 mmol) in tetrahydrofuran (108 ml) and water (53.9 ml) was added a freshly prepared solution of lithium hydroxide (4.84 g, 202 mmol) in water (53.9 ml) in a dropwise fashion. The reaction was then stirred at room temperature for 18 hours. The reaction was then cooled to -5 ºC and 1 M HCl was added dropwise until pH 5 was obtained. The reaction was extracted twice with ethyl acetate and the combined organics washed with brine, dried and concentrated to give the title compound as a thick clear oil which was used without further purification or characterization.

Step 6: (R)-2-((N-(benzyloxy)formamido)methyl)heptanoic acid

Formic acid (4.65 ml, 121 mmol) was added dropwise to a solution of CDI (19.67 g, 121 mmol) in dichloromethane (79 ml) and stirred at room temperature for 45 minutes. A solution of (R)-2-(((benzyloxy)amino)methyl)heptanoic acid (10.73 g, 40.4 mmol) in dichloromethane (79 ml) was then added and the reaction stirred at room temperature for 2 hours. The reaction was partitioned with 1 M HCl and the organic was collected via hydrophobic frit and concentrated to give a thick yellow oil which was dissolved in the minimum amount of DCM and passed through a Si plug (250 g Silica, DCM, 50:50 DCM: ether and ether in 250 ml fractions). Concentration of the cleanest fractions yielded the title compound as a clear oil (3.65 g, 97 % ee). Concentration of additional fractions yielded 8 g of an orange oil which was purified by flash chromatography (ISCO Companion, 120 g, 15-100 % ethyl acetate/hexanes) to give additional batches of the title compound as an orange oil (2.38 g, 97 % ee and 1.38 g, 97 % ee). MS (m/z) 294.1

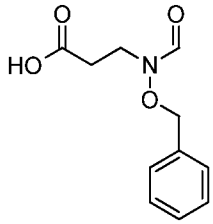
$(M+H^+)$

INTERMEDIATE 2: (R)-3-(N-(benzyloxy)formamido)-2-(cyclopentylmethyl)propanoic acid

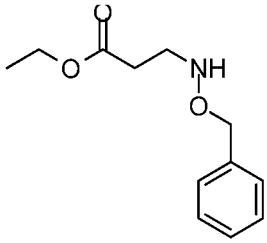


Intermediate 2 may be prepared according to procedures detailed for Intermediate A in WO2009061879, page 55.

INTERMEDIATE 3: 3-(N-(benzyloxy)formamido)propanoic acid

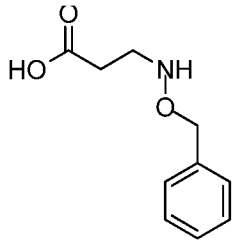


Step 1: ethyl 3-((benzyloxy)amino)propanoate



A solution of ethyl acrylate (13.67 ml, 125 mmol) in ethanol (150 ml) was cooled to -78 ºC. A solution of O-benzylhydroxylamine, hydrochloride (10.0 g, 62.7 mmol) and triethylamine (10.48 ml, 75 mmol) in ethanol (150 ml) was added dropwise via addition funnel. The reaction mixture was allowed to warm to room temperature and stirred for 24 hours. The reaction was then concentrated and the residue purified via flash chromatography (ISCO Combiflash Rf, 330 g column, 0-100 % ethyl acetate/hexanes) to give two batches of the title compound (4.67 g, 33 % yield) and (6.27 g, 45 % yield). MS (m/z) 224.1 $(M+H^+)$.

Step 2: 3-((benzyloxy)amino)propanoic acid

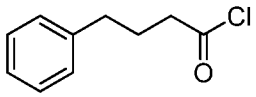


Ethyl 3-((benzyloxy)amino)propanoate (6.27 g, 28.1 mmol, 44.8 % yield) was dissolved in ethanol (100 ml) and water (25 ml) and lithium hydroxide (3.00 g, 125 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours. The ethanol was removed *in vacuo* and the mixture extracted with DCM. The aqueous was adjusted to ~pH 3 via addition of 6 N HCl and extracted with EtOAc (2 x 50 ml). The ethyl acetate layer was passed through a phase separator, concentrated and dried under vacuum over 4 days to give the title compound (609 mg). The aqueous layer was concentrated and combined with the aqueous layer isolated from a second hydrolysis reaction (4.67 g scale, conducted utilizing the same procedure) and extracted with ethyl acetate (4 x 50 ml). The ethyl acetate layer was passed through a phase separator, concentrated and dried under house vacuum overnight to give the title compound (6.91 g).The combined batches of the title compound were then triturated with ether/DCM. The solid was washed with ether, collected and dried under vacuum overnight to give the title compound (720 mg). The filtrate and residual solid from the trituration were recombined to give an additional batch of the title compound as a yellow oil (5.17 g, 70 % purity) which was used without further purification. MS (m/z) 196.0 ($M+H^+$).

Step 3: 3-(N-(benzyloxy)formamido)propanoic acid

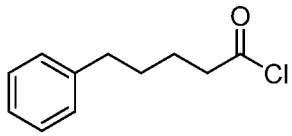
To a solution of CDI (1.50 g mg, 9.23 mmol) in dichloromethane (20 ml) was added formic acid (0.35 ml, 9.23 mmol) dropwise. The reaction mixture was stirred at room temperature for 1 hour. A solution of 3-((benzyloxy)amino)propanoic acid (721 mg, 3.69 mmol) in dichloromethane (5 ml) was then added dropwise. The reaction mixture was stirred at room temperature for 3 hours. The reaction was then cooled in a water bath and 1 N HCl (15 ml) added. The layers were separated and the organic layer washed with water, collected via hydrophobic frit and concentrated to give the title compound (570 mg, 69 % yield) which was dried under vacuum overnight and used without further purification. MS (m/z) 224.0 ($M+H^+$).

INTERMEDIATE 4: 4-phenylbutanoyl chloride

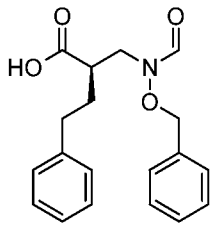


Oxalyl chloride (6 ml, 68.5 mmol) was added to a solution of 4-phenylbutanoic acid (7 g, 42.6 mmol) in dichloromethane (207 ml) and a few drops of DMF at 0 °C. The reaction was allowed to warm to room temperature overnight then concentrated to give the title compound as a yellow oil which was used without further purification or characterization.

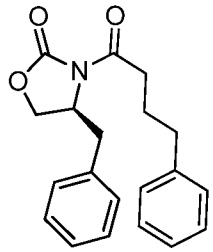
INTERMEDIATE 5 was prepared from 5-phenylpentanoic acid by methods analogous to that described for Intermediate 4.

#	Name	Structure	MS (m/z) ($M+H^+$)
5	5-phenylpentanoyl chloride		used without further purification or characterization

INTERMEDIATE 6: (R)-2-((N-(benzyloxy)formamido)methyl)-4-phenylbutanoic acid



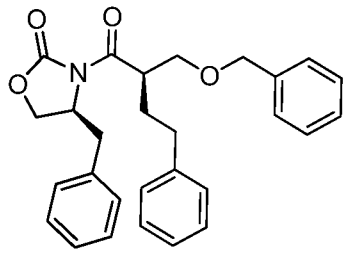
Step 1: (S)-4-benzyl-3-(4-phenylbutanoyl)oxazolidin-2-one



N-butyllithium (2.7 M in heptanes, 16.73 ml, 45.2 mmol) was added dropwise to a solution of (S)-4-benzyloxazolidin-2-one (7.28 g, 41.1 mmol) in tetrahydrofuran (91 ml) at -78 °C under N_2. After stirring for 30 minutes at -78 °C, 4-phenylbutanoyl chloride (7.5 g, 41.1 mmol) was added and the reaction was stirred at -78 °C for 1.5 hours and then at 0 °C for 2 hours. Aqueous NH_4Cl (150 ml) was then added and the mixture extracted with EtOAc (2 x). The combined organic layers were dried over Na_2SO_4 and concentrated to

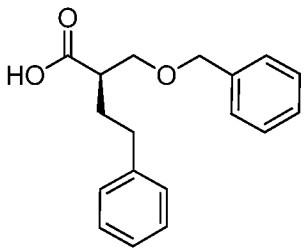
give the title compound as white crystals (13.15 g, 99 % yield). MS (m/z) 324.2 ($M+H^+$).

Step 2: (S)-4-benzyl-3-((R)-2-((benzyloxy)methyl)-4-phenylbutanoyl)oxazolidin-2-one



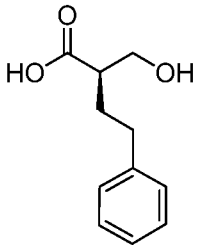
DIPEA (8.28 ml, 47.4 mmol) was added dropwise to a solution of (S)-4-benzyl-3-(4-phenylbutanoyl)oxazolidin-2-one (13.94 g, 43.1 mmol) and $TiCl_4$ (4.99 ml, 45.3 mmol) in dichloromethane (122 ml) at 0 °C. After stirring at 0 °C for 1.5 hours ((chloromethoxy)methyl)benzene (11.99 ml, 86 mmol) was added and the reaction was stirred at 0 °C for 3 hours . The reaction was then quenched with H_2O (150 ml), extracted with DCM (2 x) and the organics dried over $MgSO_4$ and concentrated. The residue was purified via flash chromatography (ISCO, 320 g column, hexanes: 5 minutes; 0-10 % hexanes/EtOAc: 15 minutes; 10-30 %: EtOAc/DCM: 5 minutes) to give the title compound as a clear oil (14.65 g, 77 % yield). MS (m/z) 444.2 ($M+H^+$).

Step 3: (R)-2-((benzyloxy)methyl)-4-phenylbutanoic acid



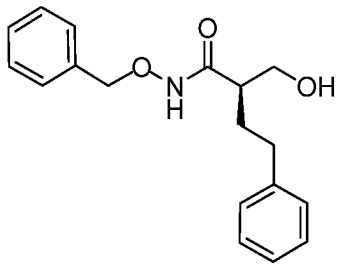
A mixture of (S)-4-benzyl-3-((R)-2-((benzyloxy)methyl)-4-phenylbutanoyl)oxazolidin-2-one (14.65 g, 33.0 mmol) in tetrahydrofuran (78 ml) and water (25.9 ml) was treated with hydrogen peroxide (30 % in H_2O, 27.0 ml, 264 mmol) followed by lithium hydroxide (1.58 g, 66.1 mmol) at 0 °C. The reaction was allowed to warm to room temperature overnight. The THF was removed under reduced pressure and the residue was extracted with DCM. The DCM layer was washed with H_2O (2 x). The combined aqueous layers were then acidified to pH 3 via addition of with 6N HCl and then extracted with EtOAc (4 x). The combined ethyl acetate extracts were dried over Na_2SO_4 and concentrated to give the title compound as a clear oil (9.5 g). MS (m/z) 267.1 ($M-17^+$).

Step 4: (R)-2-(hydroxymethyl)-4-phenylbutanoic acid



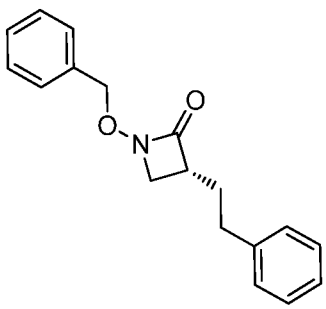
A solution of (R)-2-((benzyloxy)methyl)-4-phenylbutanoic acid (9.5 g, 33.4 mmol) in ethanol (130 ml) was added to Pd/C (2.94 g, 2.76 mmol) under N_2 and the reaction was subjected to hydrogenation in a Parr shaker at ~ 35 psi at room temperature overnight. The reaction was then filtered through a pad of Celite® and the filtrate concentrated to give the title compound as a clear oil (6.65 g). MS (m/z) 177.1 ($M-17^+$).

Step 5: (R)-N-(benzyloxy)-2-(hydroxymethyl)-4-phenylbutanamide



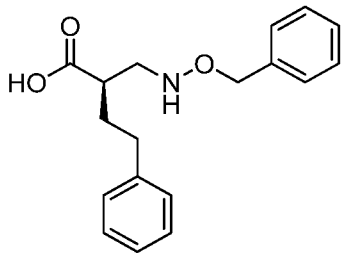
EDC (6.56 g, 34.2 mmol) was added to a solution of (R)-2-(hydroxymethyl)-4-phenylbutanoic acid (6.65 g, 34.2 mmol), O-benzylhydroxylamine hydrochloride (5.46 g, 34.2 mmol), and DMAP (8.37 g, 68.5 mmol) in dichloromethane (143 ml) at 0 ^oC and the reaction was allowed to warm to room temperature overnight. 1 N HCl (55 ml) was then added and the reaction was extracted with DCM (2 x) dried over Na_2SO_4 and concentrated to give the title compound as a white solid (9.52 g, 93 % yield). MS (m/z) 300.1 ($M+H^+$).

Step 6: (R)-1-(benzyloxy)-3-phenethylazetidin-2-one



DIAD (7.42 ml, 38.2 mmol) was added to a solution of (R)-N-(benzyloxy)-2-(hydroxymethyl)-4-phenylbutanamide (9.52 g, 31.8 mmol) and triphenylphosphine (10.01 g, 38.2 mmol) in tetrahydrofuran (200 ml) at 0 ^{o}C and the reaction was allowed to warm to room temperature over 3.5 hours. Water (100 ml) was then added and the reaction was extracted with DCM (2 x). The organics were separated, dried over $MgSO_4$ and concentrated. The residue was triturated with Et_2O (3 x) and the solid removed by filtration. The filtrate was concentrated and purifed via flash chromatography (ISCO, 220 g column, 0-20 % EtOAc/hexanes: 15 minutes, 20 % EtOAc/hexanes: 10 minutes) to give the title compound as a clear oil (5.06 g, 57 % yield). MS (m/z) 282.1 ($M+H^+$).

Step 7: (R)-2-(((benzyloxy)amino)methyl)-4-phenylbutanoic acid

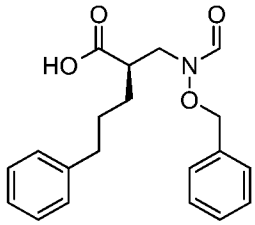


(R)-1-(benzyloxy)-3-phenethylazetidin-2-one (5.06 g, 17.97 mmol) in tetrahydrofuran (54 ml), methanol (18 ml) and water (18 ml) was treated with lithium hydroxide (4.30 g, 180 mmol) at room temperature for 1.5 days. The volatiles were removed under reduced pressure and the residue was acidified to ~ pH 5-6 via addition of 6 N HCl. The mixture was extracted with EtOAc (2 x), dried over Na_2SO_4 and concentrated to give the title compound as a clear oil (5.7 g). MS (m/z) 300.1 ($M+H^+$).

Step 8: (R)-2-((N-(benzyloxy)formamido)methyl)-4-phenylbutanoic acid

Formic acid (1.5 ml, 39.1 mmol) was added dropwise to a solution of CDI (6.3 g, 38.9 mmol) in dichloromethane (320 ml) and the reaction was stirred for 40 minutes before a solution of (R)-2-(((benzyloxy)amino)methyl)-4-phenylbutanoic acid (5 g, 16.70 mmol) in dichloromethane (40 ml) was added dropwise. The reaction was stirred at room temperature for 2 hours and then washed quickly with 1 N HCl. The organic layer was washed with H_2O, dried over Na_2SO_4 and concentrated to give the title compound as a sticky yellow oil (5.8 g). MS (m/z) 328.1 ($M+H^+$).

INTERMEDIATE 7: (R)-2-((N-(benzyloxy)formamido)methyl)-5-phenylpentanoic acid

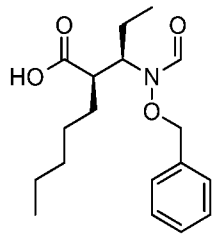


Intermediate 7 was prepared from 5-phenylpentanoyl chloride by methods analogous to that described for Intermediate 6.

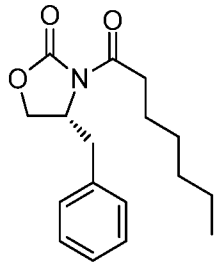
Step	Name	MS (m/z)
1	(S)-4-benzyl-3-(5-phenylpentanoyl)oxazolidin-2-one	338.2 ($M+H^+$)
2	(S)-4-benzyl-3-((R)-2-((benzyloxy)methyl)-5-phenylpentanoyl)oxazolidin-2-one	458.2 ($M+H^+$)
3	(R)-2-((benzyloxy)methyl)-5-phenylpentanoic acid	281.1 ($M-17^+$)
4	(R)-2-(hydroxymethyl)-5-phenylpentanoic acid	191.1 ($M-17^+$)
5	(R)-N-(benzyloxy)-2-(hydroxymethyl)-5-phenylpentanamide	314.2 ($M+H^+$)
6	(R)-1-(benzyloxy)-3-(3-phenylpropyl)azetidin-2-one	296.1 ($M+H^+$)
7	(R)-2-(((benzyloxy)amino)methyl)-5-phenylpentanoic acid	314.2 ($M+H^+$)
8	(R)-2-((N-(benzyloxy)formamido)methyl)-5-phenylpentanoic acid	342.2 ($M+H^+$)

5

INTERMEDIATE 8: (R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanoic acid

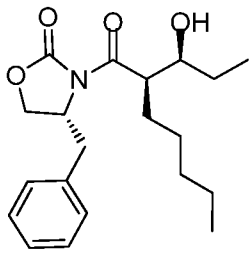


Step 1: (R)-4-benzyl-3-heptanoyloxazolidin-2-one



(R)-4-benzyloxazolidin-2-one (9.95 g, 56.2 mmol) was dissolved in dry tetrahydrofuran (100 ml) and the mixture cooled in a dry-ice acetone bath. BuLi (2.7 M in hexanes, 20.80 ml, 56.2 mmol) was added over 5 minutes under nitrogen resulting in a color change to dark yellow. The color was titrated out by addition of HCl in dioxane, then re-treated with enough BuLi to turn the mixture slightly yellow. Heptanoyl chloride (8.87 ml, 57.3 mmol) was then added. The mixture was stirred for ~ 30 minutes and then additional heptanoyl chloride (3 ml) was added. The reaction was then quenched by slow addition of water (10 ml). Solid formation was noted, additional water was added to obtain a solution. EtOAc (300 ml) was added and the layers separated. The organic was washed with sat. aq sodium carbonate then dried over sodium sulfate, filtered and concentrated. The residue was dissolved in heptane, and then concentrated to a thick oil. The residue was dissolved in heptane (100 ml) and the mixture cooled in an acetone/dry ice bath with stirring. The resultant precipitate was collected by filtration and dried under vacuum overnight to give the title compound as a white solid (15.1g, 93 % yield).

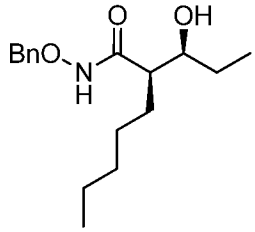
Step 2: (R)-4-benzyl-3-((R)-2-((S)-1-hydroxypropyl)heptanoyl)oxazolidin-2-one



To a solution of (R)-4-benzyl-3-heptanoyloxazolidin-2-one (15 g, 51.8 mmol) in DCM (300 ml) under N_2 in a ice-acetone bath was added $TiCl_4$ (6.00 ml, 54.4 mmol). DIPEA (9.96 ml, 57.0 mmol) was then slowly added followed by NMP (9.98 ml, 104

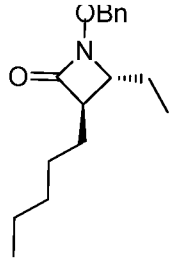
mmol) and the mixture stirred for 15 minutes. Propionaldehyde (7 ml, 95 mmol) was then added and the reaction stirred for 1.5 hours. The reaction was then quenched by addition of a solution of AcOH in DCM (15 ml of a 50:50 mix by volume). Aqueous Rochelles salt was added followed by aq HCl (50 % v/v) to dissolve any solids. The layers were then separated and the aqueous extracted with additional DCM. The combined organics were treated with aq $NaHSO_3$ for 30 minutes then the layers allowed to settle in a separation funnel overnight. The organic was then separated and filtered through a plug of silica (~3 cm). The filtrates were combined, concentrated and dried under vacuum to give the title compound (19 g, 87 % yield) which was used without further purification.

Step 3: (R)-N-(benzyloxy)-2-((S)-1-hydroxypropyl)heptanamide



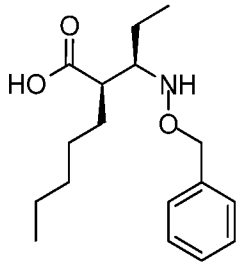
THF was boiled out of a 2l JLR and the reactor purged with N_2 whilst cooling to room temperature. O-benzylhydroxylamine, hydrochloride (15.96 g, 100 mmol) was added and the vessel purged with N_2. THF (800 ml) was then added and the mixture cooled to 0 °C. Trimethylaluminum (50 ml, 2 M in toluene, 100 mmol) was then added slowly. The white slurry was stirred for 15 minutes to obtain a clear solution. A solution of (R)-4-benzyl-3-((R)-2-((S)-1-hydroxypropyl)heptanoyl)oxazolidin-2-one (18 g, 51.8 mmol) in THF (200 ml) was then added over 5 minutes via cannula and the mixture stirred for 1.5 hours at 0 °C. The reaction mixture was warmed to 5 °C. Separately, O-benzylhydroxylamine, hydrochloride (5 g, 31 mmol) was dissolved in THF (100 ml) and treated with trimethylaluminum (17 ml, 2 M in toluene, 34 mmol) at 0 °C. The mixture was stirred until a solution was obtained and then added to primary reaction via cannula. The reaction was then quenched by the addition of sat.aq $KHSO_4$. A HCl solution (500 ml water, 500 ml conc HCl) was added and the layers separated. The organics were reduced in volume and re-combined with the aqueous, the volatiles were removed via rotovap and a white precipitate formed. The solids were collected by filtration and washed with 10 % HCl then water. The filter cake was then washed with toluene (2 x 100 ml) and air dried to give the title compound (10.65 g, 70 % yield). MS (m/z) 294.3 ($M+H^+$).

Step 4: (3R,4R)-1-(benzyloxy)-4-ethyl-3-pentylazetidin-2-one



(R)-N-(benzyloxy)-2-((S)-1-hydroxypropyl)heptanamide (4.61 g, 15.7 mmol) was dissolved in pyridine (14 ml) and cooled in an ice bath. Methanesulfonyl chloride (2.45 ml, 31.4 mmol) was then added dropwise maintaining the internal temperature below 10 °C. The reaction was then stirred for 2 hours. The reaction was diluted by the addition of TBME (23 ml) and 1 M HCl (46 ml) was added while cooling was applied. The layers were separated and the organic was washed with 1 M HCl (23 ml), sat. aq $NaHCO_3$ (9 ml) and brine (9 ml) and then concentrated to minimum volume then dissolved in acetone (46 ml). K_2CO_3 (6.51 g, 47.1 mmol) was added and the reaction heated at 50 °C for 1 hour. The reaction was then cooled to room temperature and filtered. The flask and filter cake were rinsed with acetone (2 x 23 ml). The filtrate was concentrated give the title compound (4.26 g).

Step 5: (R)-2-((R)-1-((benzyloxy)amino)propyl)heptanoic acid



(3R,4R)-1-(benzyloxy)-4-ethyl-3-pentylazetidin-2-one (356 g, 1.27 mol) was dissolved in 2-methyltetrahydrofuran (3560 ml). Tetrabutylammonium hydroxide (40 % aqueous solution, 1245 ml, 1.90 mol) was added. The reaction was heated to 50 °C for 2 hours and then cooled to room temperature. The reaction was diluted with water (1780 ml) and acidified with 6 M HCl (338 ml) to pH 3-4. The phases were separated and the organic phase was concentrated down to 5 volumes (1780 ml) and was used without further purification MS (m/z) 322 ($M+H^+$).

Step 6: (R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanoic acid

Carbonyldiimidazole (822 g, 5.07 mol) was suspended in 2-

methyltetrahydrofuran (5340 ml) and cooled to 0 °C. Formic acid (88 %, 276 ml, 6.33 mol) was added dropwise via addition funnel. The reaction was stirred at 5 °C for 10 minutes and then warmed to room temperature for an additional 30 minutes. The reaction was cooled back to 5 °C and (R)-2-((R)-1-((benzyloxy)amino)propyl)heptanoic acid in 2-methyltetrahydrofuran (1780 ml solution from previous step) was added. The reaction was warmed to room temperature and stirred for 40 minutes. In a separate vessel, carbonyldiimidazole (279 g, 1.72 mol) was suspended in 2-methyltetrahydrofuran (1500 ml) and cooled to 0 °C. Formic acid, (88 %, 93.8 ml, 2.16 mol) was added dropwise via addition funnel and stirred at 5 °C for 10 minutes and then warmed to room temperature for an additional 30 minutes. This mixture was then added dropwise via addition funnel to the original reaction at 5 °C. The reaction was warmed to room temperature and stirred for 60 minutes. The reaction was then cooled to 10 °C and quenched by addition of NaOH (4 M, 2122 ml) to pH 9. The phases were separated and the organic phase was washed with a 1:1 mixture (v/v) of 6 M HCl and saturated aqueous brine (4561 ml). The phases were separated and the organic phase was concentrated to 3.5 volumes (1246 ml) to give the title compound as a 30 % by weight solution in 2-methyltetrahydrofuran (1.15 kg, equates to 346 g of crude title product).

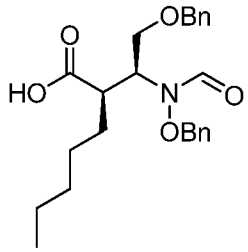
Steps 2 and 3 were repeated on 365 g scale to provide a second batch of the title compound as a 36 % by weight solution in 2-methyltetrahydrofuran (1.09 kg, equates to 363 g of crude title product) and on 20 g scale to provide the title compound as a 30 % by weight solution in 2-methyltetrahydrofuran (66 g, equates to 19.8 g of crude title product).

The 30 % by weight solution of crude title compound in 2-methyltetrahydrofuran (1.15 kg, 346 g crude) was concentrated, azeotroped three times with hexanes and then diluted with hexanes (2500 ml). The solution was seeded with crystals obtained from a previous SFC purification. Nitrogen was then passed over the solution with stirring overnight. The resulting crystalline material was broken up, diluted with hexanes and stirred at room temperature for 30 minutes then filtered to give the title compound as a light yellow crystalline solid (275 g).

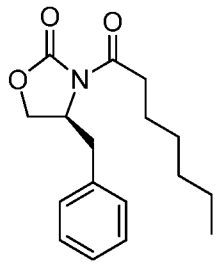
The 36 % (1.09 kg, 363 g crude) and 30 % (66.04 g, 19.8 g crude) by weight solutions of crude title compound were concentrated, azeotroped three times with methanol and combined with the filtrate from the initial 30 % by weight batch. The residue was diluted with methanol to a concentration of 200 mg/ml and purified by SFC (Thar SFC-70, DEAP column, 5 µM, 30 x 250 mm, i.d., eluting with 35 % isocratic methanol co-solvent, 60 g/min, 7 minute run) to give the title compound as a yellow oil. The oil was diluted with hexanes (2500 ml) and the solution seeded with crystals obtained from previous isolates. Nitrogen was passed over the solution with stirring overnight. The

resulting crystalline material was broken up, diluted with hexanes, and stirred at room temperature for 30 minutes then filtered to give the title compound as a light yellow crystalline solid (360 g). MS (m/z) 322.0 ($M+H^+$).

INTERMEDIATE 9: (R)-2-((S)-2-(benzyloxy)-1-(N-(benzyloxy)formamido)ethyl)heptanoic acid

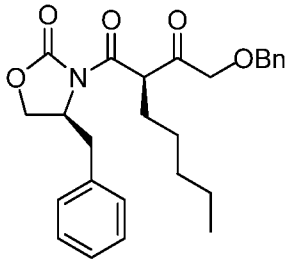


Step 1: (S)-4-benzyl-3-heptanoyloxazolidin-2-one



To a solution of (S)-4-benzyloxazolidin-2-one (5.0 g, 28.2 mmol) in dry THF (60 ml) at -78 °C was added dropwise n-BuLi (11.28 ml, 2.5 M in Hexane, 28.2 mmol). After stirring for 30 minutes at -78 °C, the reaction mixture was then treated with heptanoyl chloride (4.34 ml, 28.2 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was then quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (1-20 % EtOAc/cyclohexane) to to give the title compound (7.5 g, 51 % yield). MS (m/z) 290.1 ($M+H^+$).

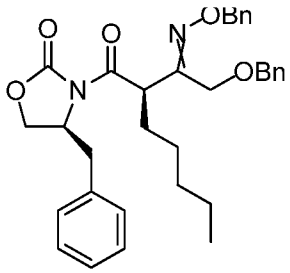
Step 2: (R)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-4-(benzyloxy)-2-pentylbutane-1,3-dione



Sodium bis(trimethylsilyl)amide (29.02 ml, 1 M in THF) was added dropwise to a

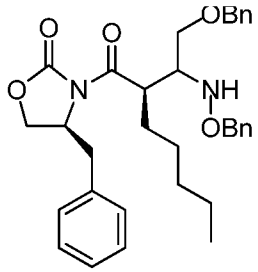
stirred solution of (S)-4-benzyl-3-heptanoyloxazolidin-2-one(7.0 g, 24.2 mmol) in THF (150 ml) at -78 ºC. After addition was complete the mixture was allowed to stir at -78 ºC for 30 minutes then 1-(benzyloxy)-3-chloropropan-2-one (5.72 ml, 36.3 mmol) was added. The reaction mixture was stirred at -78 ºC for 1 hour then quenched with saturated ammonium chloride solution (200 ml). The mixture was warmed to room temperature and extracted with EtOAc (2 x 250 ml). The combined organic phases were washed with brine (200 ml), dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by flash chromatography (SNAP 340 g column, 5-15 % EtOAc/cyclohexane) to give the title compound as a colorless oil (5.43 g, containing ~ 40 % (S)-4-benzyl-3-heptanoyloxazolidin-2-one) which was used without further purification. MS (m/z) 460.0 ($M+23^+$).

Step 3: (S)-4-benzyl-3-((R)-2-(2-(benzyloxy)-1-((benzyloxy)imino)ethyl)heptanoyl)oxazolidin-2-one



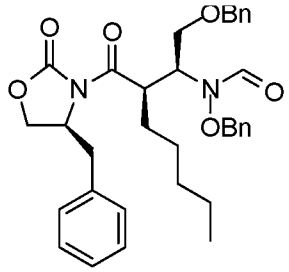
Sodium acetate (2.04 g, 24.8 mmol) was added to a stirred solution of (R)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-4-(benzyloxy)-2-pentylbutane-1,3-dione (5.43 g, 12.4 mmol) in MeOH (100 ml) followed by O-benzylhydroxylamine hydrochloride (3.96 g, 24.8 mmol) and the mixture stirred at room temperature for 18 hours. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between water (200 ml) and EtOAc (300 ml). The phases were separated and the organic washed with sodium hydrogen carbonate solution (100 ml) and brine (100 ml), dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by flash chromatography (SNAP 340 g column, 5-10 % EtOAc/cyclohexane) to give the title compound as a colorless oil which solidified on standing (5.06 g). MS (m/z) 565.1 (M+23).

Step 4: (4S)-4-benzyl-3-((2R)-2-(2-(benzyloxy)-1-((benzyloxy)amino)ethyl)heptanoyl)oxazolidin-2-one



Sodium cyanoborohydride (2.18 g, 34.5 mmol) was added portionwise over a period of 1 hour to a stirred solution of (S)-4-benzyl-3-((R)-2-(2-(benzyloxy)-1-((benzyloxy)imino)ethyl) heptanoyl)oxazolidin-2-one (4.72 g, 8.7 mmol) in dichloroethane (60 ml) and acetic acid (20 ml) at 0 °C. After addition the mixture was allowed to stir for 1 hour. Further sodium cyanoborohydride (1.09 g, 17.3 mmol) was added portionwise at 0 °C and the reaction stirred for 2 hours. The reaction mixture was evaporated under reduced pressure and the residue was treated with water (300 ml) and adjusted to pH 9 by addition of 2 M NaOH solution. The aqueous was extracted with EtOAc (1 x 200 ml, 1 x 100 ml). The combined organic phases were washed with sodium hydrogen carbonate solution (200 ml) and brine (100 ml), dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by flash chromatography (SNAP 340 g column, 5-10 % EtOAc/cyclohexane) to give the title compound as a ~ 3:1 mixture of diastereoisomers as a colorless oil (4.48 g). MS (m/z) 545.1 ($M+H^+$).

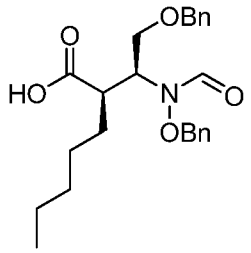
Step 5: N-((2S,3R)-3-((S)-4-benzyl-2-oxooxazolidine-3-carbonyl)-1-(benzyloxy)octan-2-yl)-N-(benzyloxy)formamide



Formic acid (0.46 ml, 12.3 mmol) was added dropwise to a suspension of CDI (1.99 g, 12.3 mmol) in dichloromethane (75 ml) at 0 ºC. After addition was complete the mixture was allowed to warm to room temperature and stirred for 30 minutes to give a clear solution. This mixture was then added to a solution of (4S)-4-benzyl-3-((2R)-2-(2-(benzyloxy)-1-((benzyloxy)amino)ethyl)heptanoyl)oxazolidin-2-one (4.47 g, 8.2 mmol) in dichloromethane (25 ml) at 0 ºC and the resulting mixture was stirred at 0 ºC for 30

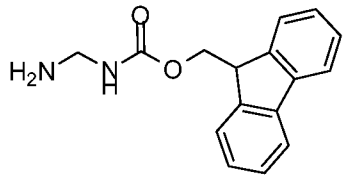
minutes then at room temperature overnight. The reaction mixture was warmed to 40 °C for 4 hours but no further conversion was observed. In a separate flask formic acid (0.23 ml, 5 mmol) was added dropwise to a suspension of CDI (0.99 g, 5 mmol) in dichloromethane (25 ml) and this mixture was stirred for 30 minutes then added to the main reaction mixture. The reaction was stirred for a further 2 hours at 40 °C. The reaction mixture was then diluted with EtOAc (500 ml) and washed with pH 3 buffer solution (300 ml), sodium bicarbonate solution (300 ml), and brine (300 ml). The organic phase was dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by flash chromatography (SNAP 340 g column, 5-30 % EtOAc/cyclohexane). Impure fractions from this column were purified by flash chromatography (SNAP 25 g column, 10-20 % EtOAc/cyclohexane). Combination of the appropriate fractions from both columns were concentrated to give the title compound as a white solid (0.68 g). MS (m/z) 573.1 ($M+H^+$).

Step 6: (R)-2-((S)-2-(benzyloxy)-1-(N-(benzyloxy)formamido)ethyl)heptanoic acid

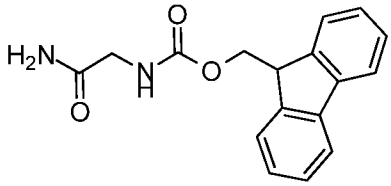


A solution of N-((2S,3R)-3-((S)-4-benzyl-2-oxooxazolidine-3-carbonyl)-1-(benzyloxy)octan-2-yl)-N-(benzyloxy)formamide (680 mg, 1.2 mmol) in a 3:1 mixture of THF (15 ml) and H_2O (5 ml) was treated with H_2O_2 (30 %, 0.55 ml, 4.8 mmol) followed by LiOH (75 mg, 1.8 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with aqueous sodium sulphite solution, diluted with pH 3 buffer (50 ml) and brought to pH 3 by addition of 1 M HCl solution. The aqueous phase was then extracted with EtOAc (2 x 50 ml) and the combined organic phases were washed with brine (30 ml), dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by flash chromatography (SNAP 50 g column, 1-4 % MeOH in a 25:75 mixture of EtOAc/dichloromethane) to give impure product which was then purified by Isolute NH_2 cartridge (2 g, eluted with 30 % EtOAc/dichloromethane and then 30 % EtOAc in dichloromethane + 1 % formic acid) to give the title compound (383 mg) as a colorless oil. MS (m/z) 414.1 ($M+H^+$).

INTERMEDIATE 10: (9H-fluoren-9-yl)methyl (aminomethyl)carbamate, trifluoroacetic acid salt

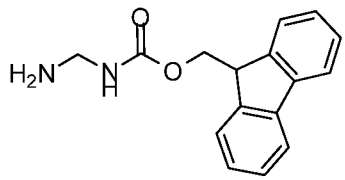


Step 1: (9H-fluoren-9-yl)methyl (2-amino-2-oxoethyl)carbamate



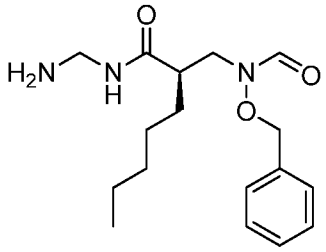
A mixture of 2-aminoacetamide, hydrochloride (231 g, 2.09 mol) in DCM (4 l) at 0 °C was treated with DIPEA (1.1 l, 6.27 mol) and then portionwise with (9H-fluoren-9-yl)methyl carbonochloridate (541 g, 2.09 mol). This mixture was stirred for 1 hour and was warmed to room temperature and then treated with water (2 l). The white precipitate was collected by filtration, then washed thoroughly with water, DCM, water and Et_2O and then air dried to give the title compound (618 g, 80 % yield) as a white solid. MS (m/z) 297.0 ($M+H^+$).

Step 2: (9H-fluoren-9-yl)methyl (aminomethyl)carbamate, trifluoroacetic acid salt

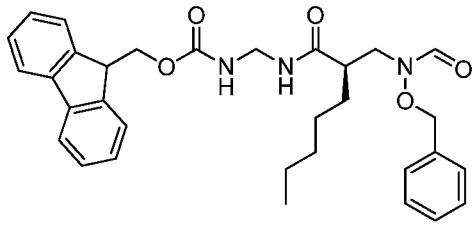


To a solution of [bis(trifluoroacetoxy)iodo]benzene (109 g, 253 mmol), water (800 ml), and THF (800 ml) was added (9H-fluoren-9-yl)methyl (2-amino-2-oxoethyl)carbamate (50 g, 169 mmol) and the mixture was stirred with an overhead stirrer for 60 minutes. Diethyl ether (1 l) and hexane (250 ml) were added and the layers were separated. The aqueous layer was washed with diethyl ether (600 ml). The organics were collected and concentrated to 350 ml of total volume, hexanes (600 ml) was then added with stirring. The mixture was stirred for an additional 1.5 hours then the precipitate was collected via filtration to yield the title compound as an off white solid (32.8 g, 51 % yield). MS (m/z) 269.1 ($M+H^+$).

INTERMEDIATE 11: (R)-N-(aminomethyl)-2-((N-(benzyloxy)formamido)methyl)heptanamide

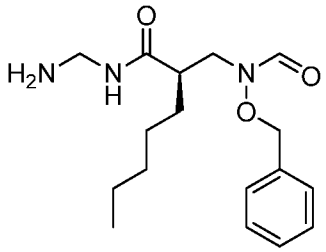


Step 1: (R)-(9H-fluoren-9-yl)methyl ((2-((N-(benzyloxy)formamido)methyl)heptanamido) methyl)carbamate



(R)-2-((N-(benzyloxy)formamido)methyl)heptanoic acid (1.13 g, 3.84 mmol) was dissolved in N,N-dimethylformamide (10.79 ml) and treated with HATU (1.46 g, 3.84 mmol). 9H-fluoren-9-yl)methyl (aminomethyl)carbamate, hydrochloride (1.17 g, 3.84 mmol) was added followed by DIPEA (2.01 ml, 11.52 mmol). The reaction was allowed to stir at room temperature for 18 hours. The reaction was then diluted with EtOAc (100 ml) and water (50 ml). The layers were separated, and the aqueous layer was washed with EtOAc (50 ml). The combined organics were washed with brine (1 x 20 ml), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (120 g silica gel column, 30 % EtOAc/hexanes: 10 minutes, 30-50 % EtOAc/hexanes: 3 minutes, 50 % EtOAc/hexanes: 15 minutes) to yield the title compound as a white solid (1.4 g, 67.1 % yield). MS (m/z) 544.3 ($M+H^+$).

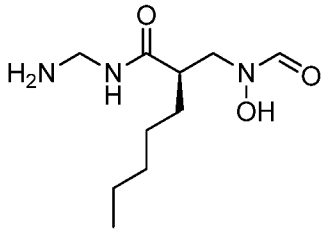
Step 2: (R)-N-(aminomethyl)-2-((N-(benzyloxy)formamido)methyl)heptanamide



(R)-(9H-fluoren-9-yl)methyl((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl) carbamate (1.4 g, 2.6 mmol) was suspended in acetonitrile (12 ml) and treated at room temperature with morpholine (6 ml,

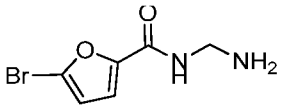
68.9 mmol). The reaction was allowed to stir at room temperature for 2 hours. The reaction was then filtered, washing with ether. The combined filtrates were concentrated and the residue was purified by flash chromatography (40 g column, 100 % DCM: 5 minutes, 0-10 % MeOH/DCM: 12 minutes, 10 % MeOH/DCM: 5 minutes) to yield the title compound as a clear, colorless oil (663 mg, 80 % yield).

INTERMEDIATE 12: (R)-N-(aminomethyl)-2-((N-hydroxyformamido)methyl)heptanamide

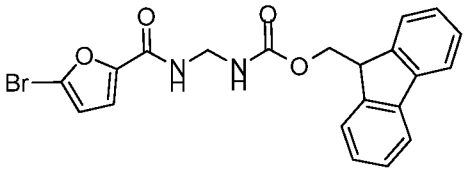


To a solution of (R)-N-(aminomethyl)-2-((N-(benzyloxy)formamido)methyl)heptanamide (55 mg, 0.17 mmol) in EtOH (10 ml) was added Pd/C (10 % wt, Degussa wet, 30 mg). The reaction mixture was hydrogenated at room temperature for 30 minutes. The catalyst was filtered off and washed with EtOH. The filtrate was was concentrated under reduced pressure to give the title compound as a grey solid (40 mg, 80 % purity) which was used without further purification.

INTERMEDIATE 13: N-(aminomethyl)-5-bromofuran-2-carboxamide



Step 1: (9H-fluoren-9-yl)methyl ((5-bromofuran-2-carboxamido)methyl)carbamate

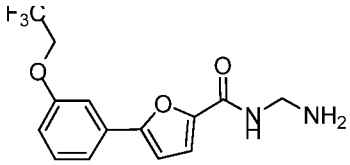


To a suspension of 5-bromofuran-2-carboxylic acid (25 g, 131 mmol) in DCM (367 ml) was added HATU (54.7 g, 144 mmol) followed by DIPEA (68.5 ml, 392 mmol) then (9H-fluoren-9-yl)methyl (aminomethyl)carbamate, trifluoroacetic acid salt (50 g, 131 mmol). The reaction mixture was stirred at room temperature for ~ 10 minutes. The precipitate was then collected via filtration to yield the title compound as an off white solid (40.8 g, 64 % yield). Additional precipitates could be obtained from the filtrate to yield additional batches of the title compound (8.8 g, 12 % yield and 1.1 g, 2 % yield). MS (m/z) 443.0 ($M+2^+$).

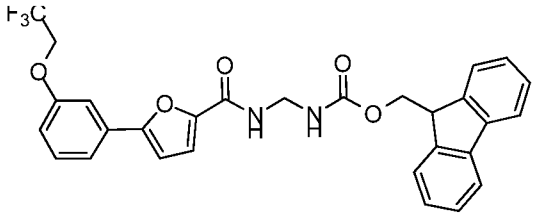
Step 2: N-(aminomethyl)-5-bromofuran-2-carboxamide

A suspension of (9H-fluoren-9-yl)methyl((5-bromofuran-2-carboxamido)methyl) carbamate (46.5 g, 84 mmol) in acetonitrile (198 ml) was treated with piperidine (83 ml, 843 mmol) and stirred at room temperature. After ~ 10 minutes, a thick precipitate formed and the reaction mixture was filtered. The filtrate was concentrated and the residue suspended in acetonitrile (100 ml) and filtered. The filtrate was collected and concentrated and the residue was suspended in DCM (100 ml) and a white precipitate formed. The precipitate was collected by filtration to give the title compound (10.6 g, 57 % yield). MS (m/z) 191.9 ($M-28^+$). The filtrates were combined, concentrated, and purified by flash chromatography (ISCO Combiflash, 330 g colum, 0-20 % methanol in DCM). Concentration of the appropriate fractions yielded a yellow solid (12.4 g) which was then suspended in DCM and filtered to yield an additional batch of the title compound as a white solid (2.83 g, 15 % yield). MS (m/z) 191.9 ($M-28^+$).

INTERMEDIATE 14: N-(aminomethyl)-5-(3-(2,2,2-trifluoroethoxy)phenyl)furan-2-carboxamide



Step 1: (9H-fluoren-9-yl)methyl ((5-(3-(2,2,2-trifluoroethoxy)phenyl)furan-2-carboxamido) methyl)carbamate

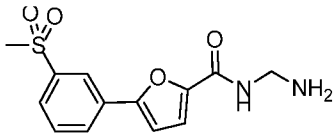


$PdCl_2(dppf)-CH_2Cl_2$ adduct (278 mg, 0.34 mmol) was added to a microwave vial containing sodium carbonate (1 M, 6.80 ml, 6.80 mmol) 1,2-dimethoxyethane (12 ml), (3-(2,2,2-trifluoroethoxy)phenyl)boronic acid (598 mg, 2.72 mmol), and (9H-fluoren-9-yl)methyl ((5-bromofuran-2-carboxamido)methyl)carbamate (1000 mg, 2.27 mmol) and the reaction irradiated at 105 °C for 5 minutes in a Biotage Initiator. The reaction was poured into brine and the mixture extracted with EtOAc. The organics were collected, dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography (1-1.5 % MeOH/DCM). Concentration of the appropriate fractions yielded material which was then triturated with ether to give the title compound as an off-white solid (700 mg, 58 % yield). MS (m/z) 537.1 ($M+H^+$).

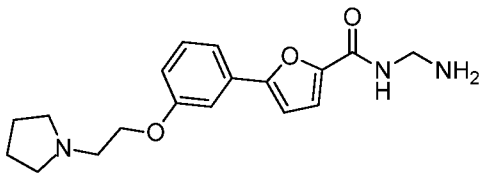
Step 2: N-(aminomethyl)-5-(3-(2,2,2-trifluoroethoxy)phenyl)furan-2-carboxamide

Pyrrolidine (2.16 ml, 26.1 mmol) was added to a mixture of (9H-fluoren-9-yl)methyl ((5-(3-(2,2,2-trifluoroethoxy)phenyl)furan-2-carboxamido)methyl)carbamate (700 mg, 1.31 mmol) in acetonitrile (5 ml) and the reaction was stirred for 2 hours. The reaction was concentrated and the residue was purified by flash chromatography (1-5 % $MeOH/CH_2Cl_2$) to give the title compound (350 mg, 85 % yield). MS (m/z) 315.0 ($M+H^+$).

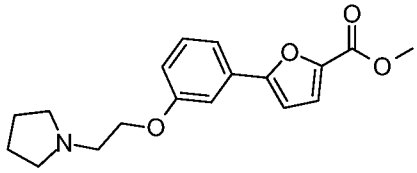
INTERMEDIATE 15 was prepared from (9H-fluoren-9-yl)methyl ((5-bromofuran-2-carboxamido)methyl)carbamate and (3-(methylsulfonyl)phenyl)boronic acid by methods analogous to that described for Intermediate 14.

#	Name	Structure	MS (m/z)	Name Step 1	MS (m/z) ($M+H^+$) Step 1
15	N-(aminomethyl)-5-(3-(methylsulfonyl)phenyl)furan-2-carboxamide		560.1 ($2M-28^+$)	(9H-fluoren-9-yl)methyl ((5-(3-(methylsulfonyl)phenyl)furan-2-carboxamido)methyl)carbamate	517.1

INTERMEDIATE 16: N-(aminomethyl)-5-(3-(2-(pyrrolidin-1-yl)ethoxy)phenyl)furan-2-carboxamide



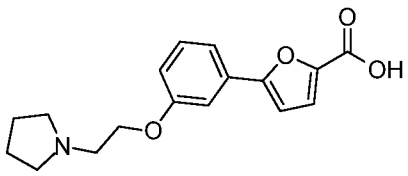
Step 1: methyl 5-(3-(2-(pyrrolidin-1-yl)ethoxy)phenyl)furan-2-carboxylate



A mixture of 1-(2-(3-bromophenoxy)ethyl)pyrrolidine, hydrochloride (0.71 ml, 1.96 mmol), (5-(methoxycarbonyl)furan-2-yl)boronic acid (0.40 g, 2.35 mmol), $PdCl_2$(dppf)-

CH_2Cl_2 adduct (0.16 g, 0.20 mmol) and sodium carbonate (1 M, 5.5 ml, 5.50 mmol) in 1,4-dioxane (3.57 ml) was irradiated for 5 minutes at 100 °C. The reaction was extracted with DCM (3 x). The organic extracts were passed through a phase separator and concentrated. The residue was purified by flash chromatography (ISCO, 40 g column, 0-100 % EtOAc/DCM: 15 minutes, 100 % EtOAc: 15 minutes) to give the title compound as a thick yellow oil (331 mg, 54 % yield). MS (m/z) 316.2 ($M+H^+$).

Step 2: 5-(3-(2-(pyrrolidin-1-yl)ethoxy)phenyl)furan-2-carboxylic acid

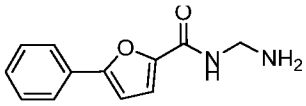


Methyl 5-(3-(2-(pyrrolidin-1-yl)ethoxy)phenyl)furan-2-carboxylate (331 mg, 1.05 mmol) in methanol (6.56 ml) and water (3.94 ml) was treated with lithium hydroxide (101 mg, 4.20 mmol) at room temperature for 4 hours. The volatiles were removed and the residue was acidified to ~ pH 4 by the addition of 1 N HCl. The mixture was extracted with EtOAc (2 x). The aqueous layer was concentrated to give the title compound as a brown solid (316 mg, 99 % yield). MS (m/z) 302.1 (M+H+).

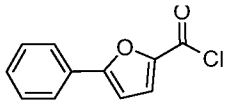
Step 3: N-(aminomethyl)-5-(3-(2-(pyrrolidin-1-yl)ethoxy)phenyl)furan-2-carboxamide

A solution of (9H-fluoren-9-yl)methyl (aminomethyl)carbamate, trifluoroacetic acid salt (381 mg, 1 mmol), 5-(3-(2-(pyrrolidin-1-yl)ethoxy)phenyl)furan-2-carboxylic acid (300 mg, 1 mmol), HBTU (453 mg, 1.2 mmol), DIPEA (0.52 ml, 3 mmol) in N,N-dimethylformamide (5 ml) was stirred at room temperature overnight. Water was then added and the reaction was stirred for 30 minutes. The grey precipitate was collected by filtration, washed with water and air dried. The solid was suspended in acetonitrile (4 ml) and treated with pyrrolidine (2.47 ml, 29.9 mmol) for 1 hour. The reaction was concentrated and the residue purified via flash chromatography (ISCO, 40 g silica gel column, 0-5 % MeOH/DCM: 10 minutes, 5 % MeOH/DCM: 10 minutes, 5-15 % MeOH/DCM: 5 minutes, 15 % MeOH/DCM: 7 minutes, 20 % MeOH (+0.1 % TEA)/DCM: 30 minutes) to give the title compound (110 mg, 34 % yield). MS (m/z) 330.1 ($M+H^+$).

INTERMEDIATE 17: N-(aminomethyl)-5-phenylfuran-2-carboxamide

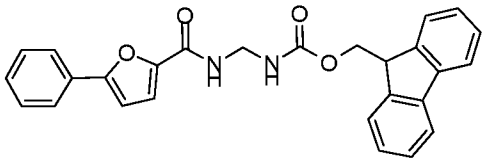


Step 1: 5-phenylfuran-2-carbonyl chloride



A mixture of 5-phenylfuran-2-carboxylic acid (16 g, 85 mmol) in dichloromethane (300 ml) at 25 °C was treated with DMF (0.07 ml, 0.85 mmol) and then oxalyl chloride (11.16 ml, 128 mmol) and stirred overnight before being concentrated to give the title compound as a pale yellow solid (17.6 g, 100 % yield). MS (m/z) 206.9 $(M)^+$

Step 2: (9H-fluoren-9-yl)methyl ((5-phenylfuran-2-carboxamido)methyl)carbamate

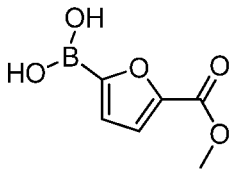


To a mixture of 5-phenylfuran-2-carbonyl chloride (17.6 g, 85 mmol) in dichloromethane (300 ml) at 25 °C was added (9H-fluoren-9-yl)methyl (aminomethyl)carbamate, trifluoroacetic acid salt (35.8 g, 94 mmol) followed by DIPEA (59.5 ml, 341 mmol) and the reaction stirred for 15 minutes before being treated with water and extracted with CH_2Cl_2. The organic extract was concentrated to give a tan solid, which was triturated with water and Et_2O and then air dried to give the title compound as a tan solid (33 g, 88 % yield). MS (m/z) 439.1 $(M+H^+)$.

Step 3: N-(aminomethyl)-5-phenylfuran-2-carboxamide

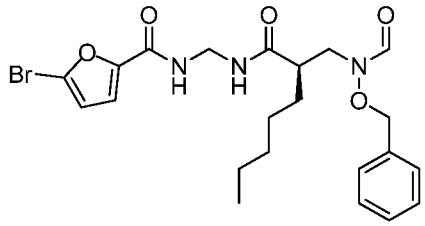
A mixture of (9H-fluoren-9-yl)methyl ((5-phenylfuran-2-carboxamido)methyl)carbamate (35 g, 80 mmol) in acetonitrile (300 ml) at 25 °C was treated with morpholine (160 ml, 1836 mmol) and stirred for 2 hours before being filtered, washing with acetonitrile. The filtrate was concentrated and the residue was purified by flash chromatography (2-10 % MeOH/CH_2Cl_2) to give pure product. Impure product was also isolated and purified by flash chromatography (2-5 % MeOH/CH_2Cl_2). Combination of the pure batches yielded a brown oil which was dissolved in CH_2Cl_2 and concentrated under reduced pressure, then placed under high vacuum for 20 hours, then under a stream of nitrogen for 24 hours to give the title compound as a brown oil (13.2 g, 69 % yield). MS (m/z) 188.1 $(M-28^+)$.

INTERMEDIATE 18: (5-(methoxycarbonyl)furan-2-yl)boronic acid



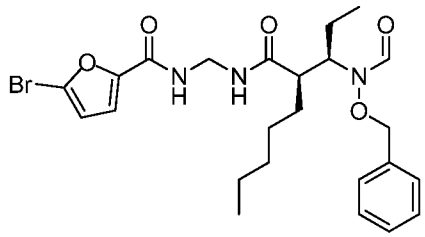
Isopropylmagnesium chloride (2 M in THF) (14.36 ml, 28.7 mmol) was added to a solution of 2,2'-oxybis(N,N-dimethylethanamine) (5.47 ml, 28.7 mmol) in tetrahydrofuran (130 ml) at 15 °C. After stirring for 25 minutes, methyl 5-bromofuran-2-carboxylate (3.27 g, 15.95 mmol) was added and the reaction was stirred at room temperature for 35 minutes. The reaction was cooled to 0 °C in an ice bath and trimethyl borate (8.91 ml, 80 mmol) was added and the reaction stirred at 0 °C for 10 minutes and then quenched with 1 N HCl to ~ pH 6 and then with 6 N HCl until ~ pH 2. The mixture was extracted with EtOAc (2 x). The organic layers were dried over Na_2SO_4 filtered and concentrated. The resultant brown solid was triturated with hexanes/EtOAc to give the title compound as a beige solid (2.15 g, 79 % yield). MS (m/z) 171.1 ($M+H^+$).

INTERMEDIATE 19: ((R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-bromofuran-2-carboxamide



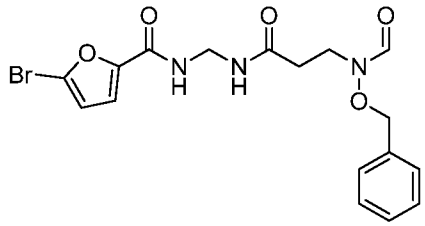
A solution of N-(aminomethyl)-5-bromofuran-2-carboxamide (0.75 g, 3.4 mmol) in DCM (4.8 ml) was added to a suspension of (R)-2-((N-(benzyloxy)formamido)methyl)heptanoic acid (1 g, 3.41 mmol), EDC (0.72 g, 3.75 mmol) and DIPEA (1.79 ml, 10.23 mmol) in DCM (4.8 ml). After stirring overnight, the reaction mixture was diluted with water and the organics were collected via hydrophobic frit and concentrated. The residue was then dissolved in the minimum amount of DCM and purified by flash chromatography (20 g Si SPE, eluted with DCM, 50:50 DCM: ether, ether), concentration of the appropriate fractions yielded the title compound as a white solid (1.03 g, 61 % yield). MS (m/z) 496.0 ($M+2^+$).

INTERMEDIATE 20: N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)-5-bromofuran-2-carboxamide



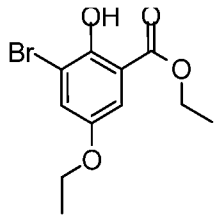
(R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanoic acid (8.26 ml, 22.1 mmol) was dissolved in N,N-dimethylformamide (91 ml) and treated with N-(aminomethyl)-5-bromofuran-2-carboxamide (4.84 g, 22.1 mmol), HBTU (8.80 g, 23.2 mmol) and DIPEA (11.57 ml, 66.3 mmol). The reaction mixture was stirred at room temperature for 4 hours. The reaction was then diluted with water and EtOAc. The layers were separated, and the organics were washed with brine, concentrated and the residue purified by flash chromatography (ISCO, 330 g column, 0-100 % EtOAc/hexanes over 30 minutes) to give the title compound as a white foam (9.9 g, 86 % yield). MS (m/z) 522.2 (M^+).

INTERMEDIATE 21: N-((3-(N-(benzyloxy)formamido)propanamido)methyl)-5-bromofuran-2-carboxamide

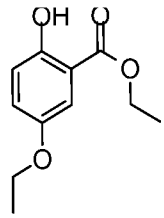


A mixture of N-(aminomethyl)-5-bromofuran-2-carboxamide, hydrochloride (200 mg, 0.78 mmol), 3-(N-(benzyloxy)formamido)propanoic acid (0.19 ml, 0.78 mmol), EDC (300 mg, 1.57 mmol), HOBT (144 mg, 0.94 mmol), and N-methylmorpholine (0.26 ml, 2.35 mmol) in dichloromethane (4 ml) was stirred at room temperature overnight. 1 N HCl (10 ml) and DCM (5 ml) were then added and the mixture stirred for 20 minutes. The layers were then separated and the organic passed through a phase separator and concentrated. The residue was purified by flash chromatography (ISCO Combiflash Rf, 25 g column, 0-100 % ethyl acetate/dichloromethane) to give the title compound (295 mg, 89 % yield) which was dried under vacuum overnight and then used without further purification. MS (m/z) 424.0 (M^+).

INTERMEDIATE 22: ethyl 3-bromo-5-ethoxy-2-hydroxybenzoate



Step 1: ethyl 5-ethoxy-2-hydroxybenzoate

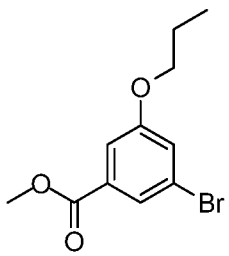


A mixture of 5-ethoxy-2-hydroxybenzoic acid (3.2 g, 17.6 mmol) in EtOH (35 ml), toluene (11 ml) and c.H_2SO_4 (0.88 ml) was heated at reflux for 12 hours. The reaction was then concentrated. The solid was dissolved in EtOAC (100 ml), washed with sat. $NaHCO_3$ dried ($MgSO_4$) and concentrated to give the title compound as a white solid (2.75 g).

Step 2: ethyl 3-bromo-5-ethoxy-2-hydroxybenzoate

Ethyl 5-ethoxy-2-hydroxybenzoate (500 mg, 2.4 mmol) was dissolved in glacial acetic acid (2.5 ml) and treated with sodium acetate (213 mg, 2.6 ml) and the mixture cooled in an ice bath. The mixture was then removed from the ice bath and a solution of bromine (125 µl, 2.45 mmol) in acetic acid (1 ml) was added dropwise. The reaction was stirred at room temperature for 1 hour and then concentrated. Water (20 ml) and sat. aq. $NaHCO_3$ solution (50 ml) were then added and the mixture extracted with ethyl acetate (50 ml). The reaction was repeated under the same conditions on a 2 g scale and the combined ethyl acetate extracts were dried over $MgSO_4$ and concentrated. The residue was crystallized from hexanes to give the title compound as a pink solid (2 g).

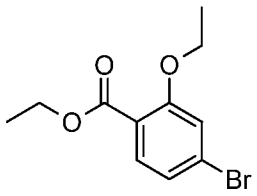
INTERMEDIATE 23: methyl 3-bromo-5-propoxybenzoate



A mixture of methyl 3-bromo-5-hydroxybenzoate (200 mg, 0.87 mmol) and K_2CO_3

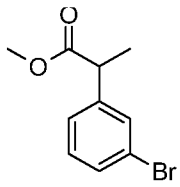
(598 mg, 4.33 mmol) in acetonitrile (8.54 ml) was treated with 1-iodopropane (0.12 ml, 1.21 mmol) and the reaction mixture heated to 70 ºC overnight. The reaction was cooled to room temperature and then filtered. The filtrate was concentrated and the residue partitioned between DCM (10 ml) and water (5 ml). The organic phase was passed through a hydrophobic frit and concentrated to give the title compound (203 mg, 86 % yield). MS (m/z) 274.9 ($M+2^+$).

INTERMEDIATE 24: ethyl 4-bromo-2-ethoxybenzoate



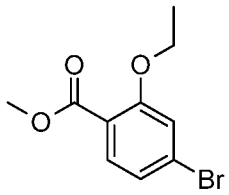
Iodoethane (17.20 ml, 213 mmol) was added dropwise to a mixture of 4-bromo-2-hydroxybenzoic acid (22 g, 101 mmol) and potassium carbonate (70.1 g, 507 mmol) in acetonitrile (659 ml) and the reaction mixture heated to 80 ºC. After 3.5 hours DMF (300 ml) was added. The temperature was lowered to 50 °C and the reaction stirred overnight. The reaction mixture was then cooled to room temperature and combined with another reaction conducted on a 5 g scale using the same conditions (exceptthe 5g scale reaction was stirred overnight at 40 °C), and filtered. The volatiles were removed *in vacuo* and ethyl acetate (500 ml) added. The organic layer was washed twice with water, separated and concentrated to give the title compound (34 g, 100 % yield). MS (m/z) 273.0 ($M+H^+$).

INTERMEDIATE 25: methyl 2-(3-bromophenyl)propanoate



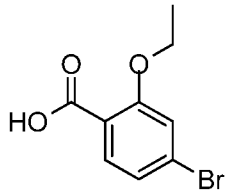
2-(3-bromophenyl)propanoic acid (1 g, 4.36 mmol) was dissolved in methanol (50 ml) and conc. H_2SO_4 (0.1 ml) was added and the solution stirred over the weekend. The reaction was then neutralized by the addition of aq. $NaHCO_3$ and concentrated. The residue was partitioned between water and ethyl acetate. The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (996 mg, 94 % yield). MS (m/z) 243.0 (M^+).

INTERMEDIATE 26: methyl 4-bromo-2-ethoxybenzoate



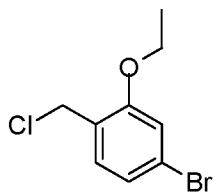
Iodoethane (6.12 ml, 76 mmol) was added dropwise to a mixture of methyl 4-bromo-2-hydroxybenzoate (5 g, 21.6 mmol) and potassium carbonate (8.97 g, 64.9 mmol) in N,N-dimethylformamide (80 ml) and the reaction mixture stirred at room temperature overnight. The mixture was then filtered, diluted with EtOAc and the organic layer washed twice with water. The organic layer was separated and then concentrated to give the title compound (5.61 g, 100 % yield). MS (m/z) 261.0 ($M+2^+$).

INTERMEDIATE 27: 4-bromo-2-ethoxybenzoic acid

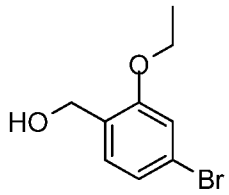


To a mixture of methyl 4-bromo-2-ethoxybenzoate (5.6 g, 21.6 mmol) in ethanol (25 ml) and tetrahydrofuran (25 ml) was added NaOH (2 M, 10.25 ml, 20.5 mmol) and the reaction stirred for 2 hours. Similarly, to a mixture of ethyl 4-bromo-2-ethoxybenzoate (33.9 g, 124 mmol) in ethanol (146 ml) and tetrahydrofuran (146 ml) was added NaOH (2 M, 62.1 ml, 124 mmol) and the reaction stirred at room temperature for 2 hours. The two reactions were then combined for workup, the volatiles were removed *in vacuo* and the residual aqueous extracted with DCM. The aqueous layer was then adjusted to ~pH 4 via addition of 6 N HCl. The mixture was then stirred and the light yellow solid collected by filtration, washed with water and air dried to give the title compound (33 g, 92 % yield) which was used without further purification. MS (m/z) 513.0 (2M+23).

INTERMEDIATE 28: 4-bromo-1-(chloromethyl)-2-ethoxybenzene



Step 1: (4-bromo-2-ethoxyphenyl)methanol

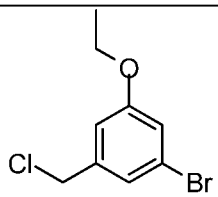


To a 250 ml flask was added 4-bromo-2-ethoxybenzoic acid (10.25g, 41.8 mmol) and tetrahydrofuran (50 ml). The solution was cooled to 0 ^{0}C in an ice-bath and then BH_3.THF (1 M, 46.0 ml, 46.0 mmol) was added dropwise over ~15 minutes while keeping the temperature below 20 ^{o}C. The reaction mixture was then stirred for 5 hours at room temperature and then carefully added to a saturated aq. K_2CO_3 solution (50 ml). The suspension was diluted with water (100 ml) and the THF layer separated and concentrated. The aqueous layer was extracted with EtOAc (3 x). The residue from the concentrated THF layer was combined with the organic layer which was washed with brine and then dried (Na_2SO_4), filtered and concentrated to give the title compound as a yellow solid (9.68 g). MS (m/z) 213.0 (M-17$^+$).

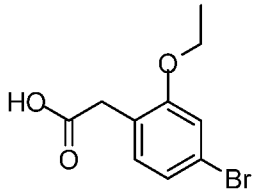
Step 2: 4-bromo-1-(chloromethyl)-2-ethoxybenzene

To a 100 ml flask was added (4-bromo-2-ethoxyphenyl)methanol (9.68g, 41.9 mmol) and thionyl chloride (13.76 ml, 189 mmol). The solution was heated to reflux for 15 minutes and then cooled to room temperature. The reaction was then concentrated and the residue dissolved in EtOAc, washed with saturated aq. $NaHCO_3$ and the layers separated. The aqueous layer was extracted with additional EtOAc and the combined organics were dried (Na_2SO_4), filtered and concentrated to give the title compound as a yellow solid (9.8 g). MS (m/z) 212.2 (fragment corresponding to loss of chlorine).

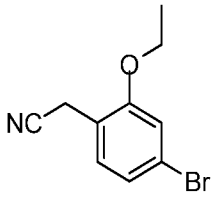
INTERMEDIATE 29 was prepared from 3-bromo-5-ethoxybenzoic acid by methods analogous to those described for Intermediate 28.

#	Name	Structure	MS (m/z) (M+H$^+$)	Name Step 1	Step 1 MS (m/z) (M+H$^+$)
29	1-bromo-3-(chloromethyl)-5-ethoxybenzene			(3-bromo-5-ethoxyphenyl) Methanol	

INTERMEDIATE 30: 2-(4-bromo-2-ethoxyphenyl)acetic acid



Step 1: 2-(4-bromo-2-ethoxyphenyl)acetonitrile

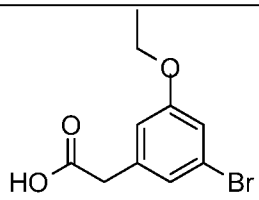


To a 100 ml flask was added 4-bromo-1-(chloromethyl)-2-ethoxybenzene (6.01 ml, 39.3 mmol), N,N-dimethylformamide (33.3 ml) and sodium cyanide (2.18 g, 43.2 mmol). The solution was stirred at room temperature overnight under nitrogen. The reaction was then diluted by the addition of NH_4Cl and EtOAc. The biphasic solution was diluted with water, the EtOAc layer separated and the aqueous extracted with additional EtOAc. The combined organic layers were washed with brine (2 x), dried (Na_2SO_4), filtered and concentrated to give the title compound as a dark oil (9.4 g) which was used without further purification or characterization.

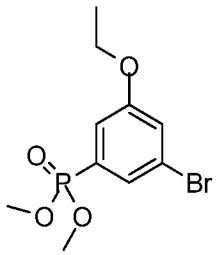
Step 2: 2-(4-bromo-2-ethoxyphenyl)acetic acid

To a 250 ml flask was added 2-(4-bromo-2-ethoxyphenyl)acetonitrile (5.79 ml, 39.3 mmol) followed by a solution of NaOH (11.5 g, 288 mmol) dissolved in water (140 ml). The reaction was heated to reflux for 5 hours, then cooled to room temperature and stirred for 7 hours. The reaction was extracted with DCM, and while stirring rapidly was acidified via addition of 6 N HCl. The resulting suspension was stirred at room temperature for 15 minutes and then filtered. The solids were dried under reduced pressure to give the title compound as a light yellow solid (8.9 g). MS (m/z) 278.0 ($M+18^+$).

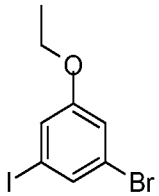
INTERMEDIATE 31 was prepared from 3-bromo-5-ethoxybenzoic acid by methods analogous to those described for Intermediate 30.

#	Name	Structure	MS (m/z)	Name Step 1	MS (m/z) ($M+H^+$) Step 1
31	2-(3-bromo-5-ethoxyphenyl)acetic acid		261.0 ($M+2^+$)	2-(3-bromo-5-ethoxyphenyl)acetonitrile	

INTERMEDIATE 32: dimethyl (3-bromo-5-ethoxyphenyl)phosphonate



Step 1: 1-bromo-3-ethoxy-5-iodobenzene



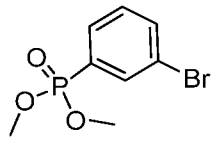
To a 250 ml flask was added CH_3CN (158 ml), 3-bromo-5-iodophenol (12.1 g, 40.5 mmol), potassium carbonate (28.0 g, 202 mmol), and iodoethane (3.60 ml, 44.5 mmol). The mixture was heated to 80 °C overnight and then cooled to room temperature. The reaction was filtered and the solids washed with CH_3CN. The filtrate was concentrated and the residue was stirred with hexanes, then filtered and the solid washed with hexanes. The hexanes was concentrated to to give the title compound as a yellow oil (13.2 g, 100 % yield). MS (m/z) 328.9 ($M+2^+$).

Step 2: dimethyl (3-bromo-5-ethoxyphenyl)phosphonate

To a 250 ml flask was added 1-bromo-3-ethoxy-5-iodobenzene (13.24 g, 40.5 mmol), $Pd(OAc)_2$ (0.91 g, 4.05 mmol) and trimethyl phosphate (10.77 ml, 92 mmol). The reaction was heated to 105 °C for 1 h. Additional $Pd(OAc)_2$ (0.91 g, 4.05 mmol) was added. After an additional 1.5 h, $Pd(OAc)_2$ (0.91 g, 4.05 mmol) was added along with trimethyl phosphite (4.79 ml, 40.5 mmol) and the reaction temperature increased to ~110

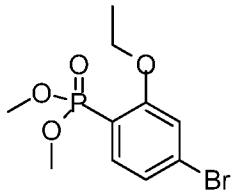
°C. Additional trimethyl phosphite (5.98 ml, 50.63 mmol) was added and the reaction observed to go to completion in 1 hour. The reaction was cooled to room temperature, diluted with Et_2O and then filtered. The filtrate was concentrated, and the residue stirred with hexanes. The hexanes was decanted and the process repeated twice with additional hexanes. The combined hexanes decants were washed with water, dried over Na_2SO_4, filtered and concentrated to give the title compound as an orange oil. (7.56 g, 60 % yield). MS (m/z) 309.0 (M^+).

INTERMEDIATE 33: Dimethyl (3-bromophenyl)phosphonate

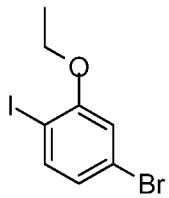


A mixture of 1-bromo-3-iodobenzene (5 g, 17.70 mmol), trimethyl phosphite (2.19 ml, 18.55 mmol) and palladium acetate (0.31 g, 1.38 mmol) was stirred in a sealed vial at 90 °C overnight. Further trimethyl phosphite (1.4 ml, 11.86 mmol) was added and the reaction heated for an additional 5 hours. After cooling, diethyl ether was added and the black mixture was filtered over Celite ®. The solvent was evaporated and the residue was purified by flash chromatography (Biotage SP1, SNAP silica column, 0-10 % methanol/DCM) to give the title compound (4.68 g, 99.8 % yield). MS (m/z) 266.8 ($M+H^+$).

INTERMEDIATE 34: dimethyl (4-bromo-2-ethoxyphenyl)phosphonate



Step 1: 4-bromo-2-ethoxy-1-iodobenzene



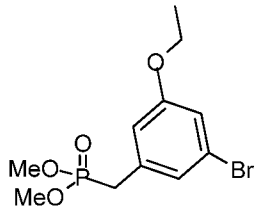
To a solution of 4-bromo-2-ethoxyaniline (8.78 g, 40.6 mmol) in acetonitrile (105 ml) at °C was added dropwise a solution of I_2 (20.63 g, 81 mmol) and tert-butyl nitrite (5.79 ml, 48.8 mmol) in acetonitrile (400 ml) over 30 minutes and the reaction stirred for 1.5 hours. The mixture was then quenched with aqueous Na_2SO_3 while maintaining the temperature below 10 °C and then extracted with hexanes (3 x 500 ml). The combined

hexane extracts were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (ISCO, 330 g column, 0-5 % EtOAc/hexanes over 30 minutes) to give the title compound as a clear oil (6 g, 45 % yield). MS (m/z) 327.2 ($M+H^+$).

Step 2: dimethyl (4-bromo-2-ethoxyphenyl)phosphonate

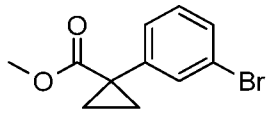
To a 50 ml flask was added 4-bromo-2-ethoxy-1-iodobenzene (6 g, 18.35 mmol), $Pd(OAc)_2$ (1.03 g, 4.59 mmol) and trimethyl phosphite (3.69 ml, 31.2 mmol). The mixture was heated to 90 °C. After 1 hour, additional $Pd(OAc)_2$ (1.03 g, 4.59 mmol) was added along with trimethyl phosphite (1.08 ml, 9.2 mmol). The temperature was increased to 105 °C and the reaction stirred at this temperature for 2.25 hour. The reaction mixture was cooled to room temperature, Et_2O was then added and the reaction was filtered through a plug of Celite®, washing with ethyl acetate. The filtrate was concentrated and the residue purified by flash chromatography (ISCO, 120 g column, 0-100 % EtOAc in DCM over 30 minutes) to give the title compound as a light orange oil (5.1 g, 90 % yield) which was used without further purification. MS (m/z) 311.0 ($M+2^+$).

INTERMEDIATE 35: dimethyl 3-bromo-5-ethoxybenzylphosphonate



NaH (0.08 g, 2.1 mmol) was added to a solution of dimethyl phosphonate (0.23 g, 2.1 mmol) in DMF (5 ml) at 0 °C. The reaction was stirred for 20 minutes, and then a solution of 1-bromo-3-(chloromethyl)-5-ethoxybenzene (0.5 g, 2 mmol) in DMF (2 ml) was added. The reaction was heated to 80 °C for 1 hour. The reaction mixture was then poured into water. The layers were separated and the aqueous layer extracted with EtOAc (3 x 15 ml). The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (ISCO, 25 g column, 0 – 5 % MeOH/DCM: 15 minutes, 5 -10 %: 10 minutes) to give the title compound (0.25 g, 80 % yield). MS (m/z) 325.0 ($M+2^+$).

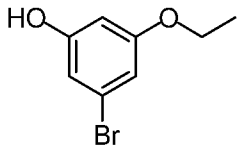
INTERMEDIATE 36: methyl 1-(3-bromophenyl)cyclopropanecarboxylate



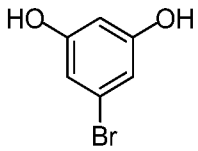
A mixture of 1-(3-bromophenyl)cyclopropanecarboxylic acid (250 mg, 1.037 mmol)

and K_2CO_3 (717 mg, 5.18 mmol) in acetonitrile (10.3 ml) was treated with iodomethane (0.08 ml, 1.24 mmol) and the reaction mixture heated at 50 ºC overnight. The reaction mixture was filtered and the filtrate concentrated. The residue was partitioned between DCM (10 ml) and water (5 ml). The organic was collected via hydrophobic frit and concentrated, the residue was placed under vacuum overnight to give the title compound (168 mg, 64 % yield). MS (m/z) 256.9 ($M+2^+$).

INTERMEDIATE 37: 3-bromo-5-ethoxyphenol



Step 1: 5-bromobenzene-1,3-diol



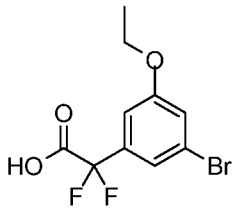
To a mixture of 1-bromo-3,5-dimethoxybenzene (15 g, 69.1 mmol) in dichloromethane (500 ml) at 0 ºC was added BBr_3 (14.37 ml, 152 mmol) dropwise over 5 minutes at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred for 5 hours. The reaction was then cooled to 0 ºC and BBr_3 (7.2 ml, 76 mmol) added dropwise. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction was again cooled to 0 ºC and BBr_3 (3.6 ml, 38 mmol) added dropwise. The reaction mixture was allowed to warm up to room temperature and stirred for 4 hours. The mixture was then poured slowly onto ice. When the ice melted, DCM (200 ml) was added and the layers separated. The aqueous was extracted with EtOAc (500 ml) and the layers separated. The combined organics were passed through a through a hydrophobic frit and concentrated. The residue was purified via flash chromatography (ISCO Combiflash Rf, 220 g column, 0-100 % ethyl acetate/hexanes) to give the title compound as a yellow oil (19.5 g, 70 % purity). MS (m/z) 189.0 (M^+).

Step 2: 3-bromo-5-ethoxyphenol

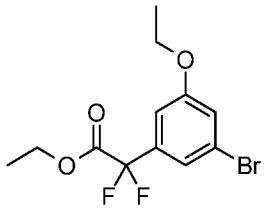
To a solution of 5-bromobenzene-1,3-diol (19.5 g, 69.1 mmol) in acetonitrile (200 ml) was added potassium carbonate (11.46 g, 83 mmol). Iodoethane (5.58 ml, 69.1 mmol) was then added dropwise to the reaction and the mixture stirred at 70 ºC for 3 hours. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue dissolved in DCM (250 ml) and washed with water.

The organic was passed through a phase separator and concentrated. The residue was purified via flash chromatography (ISCO Combiflash Rf, 220 g column, 0-100 % ethyl acetate/hexanes) to give the title compound as a clear oil (6.2 g, 41 % yield). MS (m/z) 219.0 ($M+2^+$).

INTERMEDIATE 38: 2-(3-bromo-5-ethoxyphenyl)-2,2-difluoroacetic acid



Step 1: ethyl 2-(3-bromo-5-ethoxyphenyl)-2,2-difluoroacetate

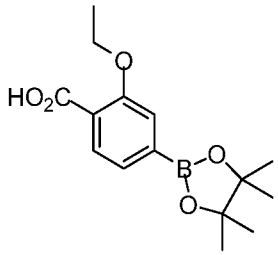


Ethyl 2-bromo-2,2-difluoroacetate (0.87 g, 4.28 mmol) was added to a suspension of copper (0.54 g, 8.56 mmol) in DMSO (7.14 ml) under N_2 and the reaction stirred for 1 hour at room temperature. 1-bromo-3-ethoxy-5-iodobenzene (0.7 g, 2.14 mmol) was added and the reaction was heated at 60 ^oC overnight. The reaction was then quenched by addition of sat. NH_4Cl, extracted with DCM (2 x) dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (ISCO, 80 g column,100 % hexanes: 4 minutes, 0-30 % DCM/hexanes: 15 minutes) to give the title compound as a clear oil (540 mg, 78 % yield). MS (m/z) 296.1 (fragment corresponding to acid).

Step 2: 2-(3-bromo-5-ethoxyphenyl)-2,2-difluoroacetic acid

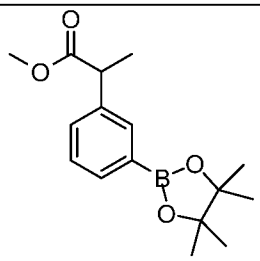
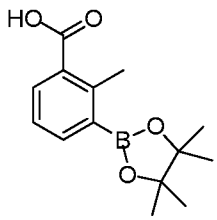
A solution of ethyl 2-(3-bromo-5-ethoxyphenyl)-2,2-difluoroacetate (0.6 g, 1.86 mmol) in methanol (3.5 ml) and THF (3.5 ml) was treated with sodium hydroxide (1.02 ml, 2.04 mmol) for 1.5 hours. The solvents were removed under reduced pressure and the residue was acidified with 6 N HCl. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated to give the title compound as a white solid (533 mg, 97 % yield). MS (m/z) 294.8 ($M+H^+$).

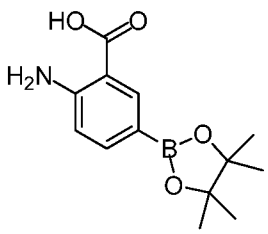
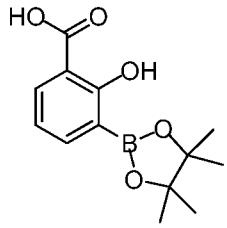
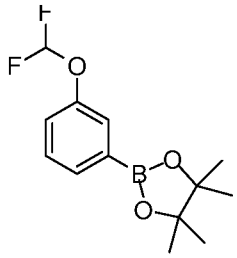
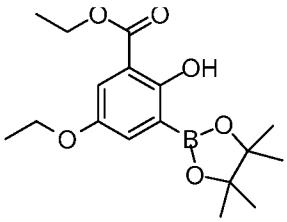
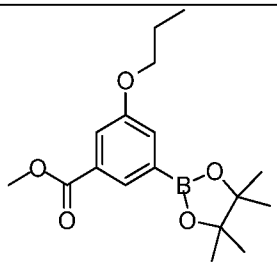
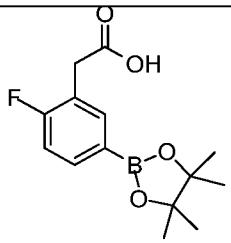
INTERMEDIATE 39: 2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid

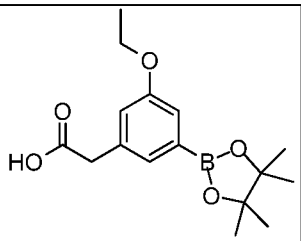
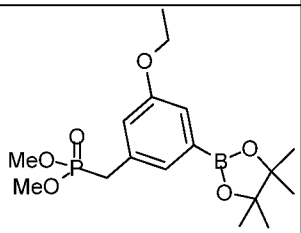
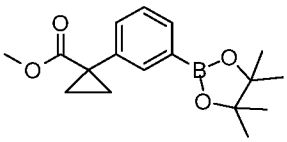
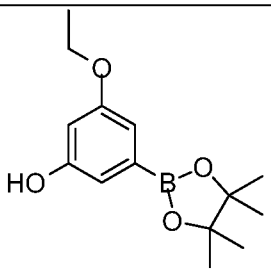
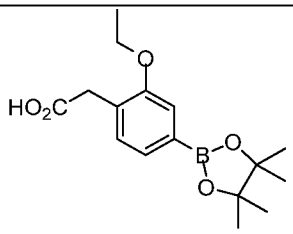
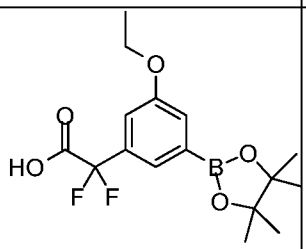


$PdCl_2(dppf)$-CH_2Cl_2 adduct (0.53 g, 0.64 mmol was added to a mixture of 4-bromo-2-ethoxybenzoic acid (3.15 g, 12.85 mmol), bis(pinacolato)diboron (4.90 g, 19.28 mmol), and potassium acetate (6.31 g, 64.3 mmol) in 1,4-dioxane (51.4 ml) and the reaction heated at 100 ºC for 4 hours. The reaction was then diluted with EtOAc and washed with NaOH (2 N, 50 ml). The layers were separated and the organic washed with water (2 x 50 ml). The aqueous layer was then acidified to pH 4 via addition of 6 N HCl and extracted with ethyl acetate. The EtOAc was concentrated to give a brown oil which was purified by flash chromatography (ISCO Rf, 120 g column, 0-100 % EtOAc/DCM) to give the title compound as an off white solid (2.5 g, 67 % yield). MS (m/z) 211.1 (fragment corresponding to mass of boronic acid).

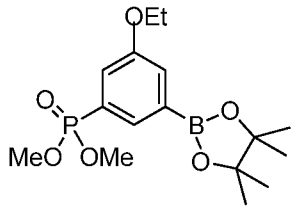
INTERMEDIATES 40-55 were prepared from the indicated bromide by methods analogous to those described for Intermediate 39.

#	Name	Structure	MS (m/z)	Bromide
40	methyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate		291.1 ($M+H^+$)	methyl 2-(3-bromophenyl)propanoate
41	2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid		263.1 ($M+H^+$)	3-bromo-2-methylbenzoic acid

42	2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid		264.1 ($M+H^+$)	2-amino-5-bromobenzoic acid
43	2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid		265.1 ($M+H^+$)	5-bromo-2-hydroxybenzoic acid
44	2-(3-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane		271.1 ($M+H^+$)	1-bromo-3-(difluoromethoxy)benzene
45	ethyl 5-ethoxy-2-hydroxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate		337.1 ($M+H^+$)	ethyl 3-bromo-5-ethoxy-2-hydroxybenzoate
46	methyl 3-propoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate		321.1 ($M+H^+$)	methyl 3-bromo-5-propoxybenzoate
47	2-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid		281.1 ($M+H^+$)	2-(5-bromo-2-fluorophenyl)acetic acid

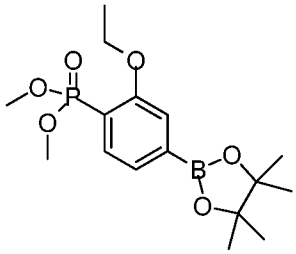
48	2-(3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid			2-(3-bromo-5-ethoxyphenyl)acetic acid
49	dimethyl 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylphosphonate		317.1 ($M+H^+$)	dimethyl 3-bromo-5-ethoxybenzylphosphonate
50	methyl 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarboxylate		303.1 ($M+H^+$)	methyl 1-(3-bromophenyl)cyclopropanecarboxylate
51	3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol		265.2 ($M+H^+$)	3-bromo-5-ethoxyphenol
52	2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid			2-(4-bromo-2-ethoxyphenyl)acetic acid
53	2-(3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2,2-difluoroacetic acid		360.0 ($M+18^+$)	2-(3-bromo-5-ethoxyphenyl)-2,2-difluoroacetic acid

INTERMEDIATE 54: dimethyl (3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonate



$PdCl_2(dppf)$-CH_2Cl_2 adduct (1.00 g, 1.22 mmol) was added to a mixture of dimethyl (3-bromo-5-ethoxyphenyl)phosphonate (7.56 g, 24.46 mmol), bis(pinacolato)diboron (9.32 g, 36.7 mmol), and potassium acetate (9.60 g, 98 mmol) in 1,4-dioxane (48.9 ml) and the reaction heated at 105 ºC for 3 hours. The reaction was then cooled to room temperature and diluted by the addition of Et_2O and water. The mixture was stirred for 5 minutes and then the layers were separated. The aqueous layer was extracted with additional ether. The combined ether extracts were filtered and concentrated to give a dark residue. Hexanes was added to the residue and the solution stirred for 5 minutes. The hexanes was decanted off and the process repeated twice more. The combined hexanes decants were dried over Na_2SO_4, filtered and concentrated to give an orange oil which was purified by flash chromatography (ISCO, 330 g column, 0-100 % EtOAc/DCM over 20 minutes and then 0-20 % MeOH/DCM over 20 minutes) to give the title compound as an orange oil (6.5 g, 60 % yield) that crystallized on standing. MS (m/z) 275.1 (mass of boronic acid).

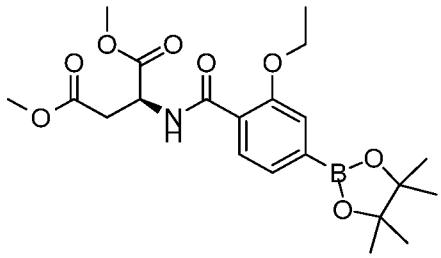
INTERMEDIATE 55: dimethyl (2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonate



To a mixture of dimethyl (4-bromo-2-ethoxyphenyl)phosphonate (5 g, 16.18 mmol), bis(pinacolato)diboron (6.16 g, 24.26 mmol), and potassium acetate (7.94 g, 81 mmol) in 1,4-dioxane (48 ml) was added $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.66 g, 0.81 mmol) and the reaction heated at 105 ºC for 3.5 hours. The reaction was diluted with EtOAc, cooled to room temperature with stirring and then filtered over Celite®. The filtrate was concentrated and the residue purified via flash chromatography (ISCO Rf, 220 g column, 0-100 % EtOAc/DCM over 25 minutes, 0-20 % MeOH/DCM over 15 minutes) to give ~

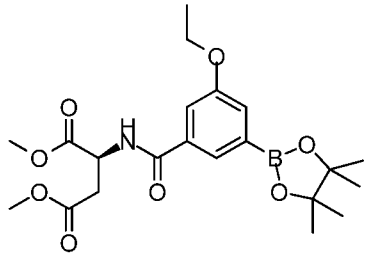
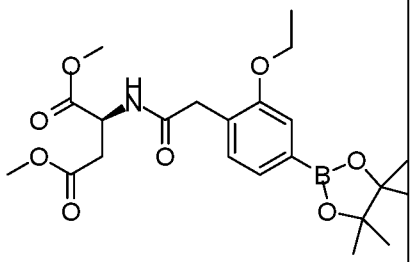
3.4 g of a dark material. Et_2O was added to the mixture resulting in precipitation of solids. The ether was decanted and concentrated to give 2.2 g of a dark oil which was purified via flash chromatography (ISCO, 80 g column, 0-20 % MeOH/DCM over 30 minutes) to give the title compound (1.4 g, 24 % yield). The remaining solids were dissolved in EtOAc and then concentrated to give 1.2 g of a black residue which was purified via flash chromatography (ISCO, 80 g column, 0-20 % MeOH/DCM over 30 minutes) to give an additional batch of the title compound (1.2 g). MS (m/z) 275.1 (mass of boronic acid).

INTERMEDIATE 56: (S)-dimethyl 2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)succinate

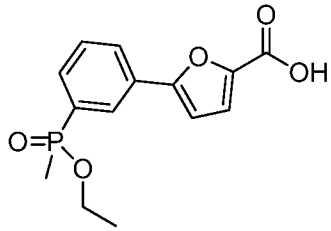


To a mixture of 2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (500 mg, 1.71 mmol) and (S)-dimethyl 2-aminosuccinate, hydrochloride (406 mg, 2.05 mmol) in dichloromethane (5.95 ml) was added DIPEA (0.90 ml, 5.13 mmol) and added HATU (781 mg, 2.05 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction was washed with water and the layers separated. The DCM layer was concentrated and the residue was purified via flash chromatography (ISCO Combiflash Rf, 80 g column, 20-100 % ethyl acetate/hexanes) to yield the title compound as a light yellow solid (638 mg, 86 % yield). MS (m/z) 436.2 ($M+H^+$).

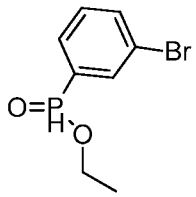
INTERMEDIATES 57 and 58 were prepared from (S)-dimethyl 2-aminosuccinate, hydrochloride and the indicated acid by methods analogous to those described for Intermediate 56.

#	Name	Structure	MS (m/z) ($M+H^+$)	Acid
57	S)-dimethyl 2-(3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)succinate		436.1	3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
58	(S)-dimethyl 2-(2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamido)succinate		450.2	2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid

INTERMEDIATE 59: 5-(3-(ethoxy(methyl)phosphoryl)phenyl)furan-2-carboxylic acid



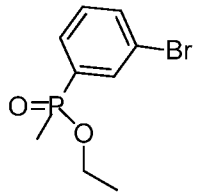
Step 1: ethyl (3-bromophenyl)phosphinate



n-BuLi (2.65 ml, 1.6 M in hexanes, 4.24 mmol) was added dropwise to a solution of 1,3-dibromobenzene (0.51 ml. 4.24 mmol) in THF (15 ml) at -78 °C. After stirring for 30 minutes at -78 °C the reaction mixture was cannulated into a stirred solution of diethyl chlorophosphite (0.61 ml, 8.48 mmol) in THF (5 ml) at -78 °C. The reaction mixture was stirred -78 °C for 1 hour then quenched with saturated aqueous NH_4Cl solution (20 ml).

The reaction mixture was extracted with EtOAc (100 ml). The organic layer was washed with brine (25 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (50 g SNAP silica column, 20-100% EtOAc/cyclohexane) to give the title compound as a colorless oil (420 mg, 40 % yield). MS (m/z) 250.8 ($M+H^+$).

Step 2: ethyl (3-bromophenyl)(methyl)phosphinate



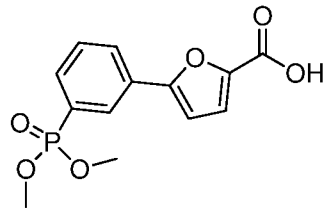
A solution of ethyl (3-bromophenyl)phosphinate (0.41 g, 1.64 mmol) in THF (5 ml) was cooled to -78 °C and deoxygenated by stirring under vacuum for 5 minutes. The flask was then back-filled with nitrogen and LHMDS (1.64 ml, 1.0 M in hexanes, 1.64 mmol) was added dropwise. After stirring for 10 minutes at -78 °C, iodomethane (107 µl, 1.72 mmol) was added and the reaction mixture stirred at -78 °C for 1 hour and then allowed to warm to room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 ml) and brine (10 ml) and extracted with EtOAc (40 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (25 g SNAP silica column, 50-100 % EtOAc/cyclohexanes) to give the title compound as a colorless oil (268 mg, 62 % yield). MS (m/z) 264.9 ($M+H^+$).

Step 3: 5-(3-(ethoxy(methyl)phosphoryl)phenyl)furan-2-carboxylic acid

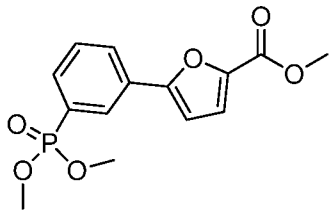
A flask charged with DME, water and EtOH was degassed with N_2 for 5 minutes. Ethyl (3-bromophenyl)(methyl)phosphinate (263 mg, 1.00 mmol), monobasic potassium phosphate (136 mg, 1.00 mmol), tribasic potassium phosphate (212 mg. 1.00 mmol) and 5-boronofuran-2-carboxylic acid (203 mg, 1.30 mmol) were then added. The reaction was degassed with N_2 and $PdCl_2$(dbpf) (24 mg, 0.05 mmol) then added. The reaction was then stirred at room temperature for 2 hours. Further $PdCl_2$(dbpf) (24 mg, 0.05 mmol) was added and the reaction stirred overnight. The organics were evaporated and the mixture then diluted with pH 3 buffer solution (50 ml) and brine (50 ml) and extracted with EtOAc (3 x 50 ml) and dichloromethane (2 x 50 ml). The combined organic phases were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (30 g SNAP C_{18} column, 0-30 % CH_3CN in water modified with

0.1% formic acid). Fractions containing product were partially evaporated to remove the CH_3CN then saturated with solid NaCl and extracted with dichloromethane (3 x 50 ml). The combined organic phases were dried over Na_2SO_4, filtered and evaporated under reduced pressure to give the title compound as a light brown gum (164 mg, 56 % yield). MS (m/z) 295.0 ($M+H^+$).

INTERMEDIATE 60: 5-(3-(dimethoxyphosphoryl)phenyl)furan-2-carboxylic acid



Step 1: methyl 5-(3-(dimethoxyphosphoryl)phenyl)furan-2-carboxylate



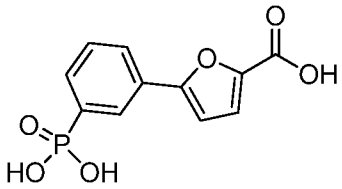
A mixture of (5-(methoxycarbonyl)furan-2-yl)boronic acid (1.5 g, 5.66 mmol, prepared according to Ishiyama, T., et al., Organic Synthesis, 2005, 82, 126-133, dimethyl (3-bromophenyl)phosphonate (1.25 g, 7.36 mmol), monobasic potassium phosphate (0.77 g, 5.66 mmol), tribasic potassium phosphate (1.2 g, 0.57 mmol) and 1,1'-Bis(di-tert-butylphosphino)ferrocene palladium (134 mg, 0.28 mmol) in DME (25 ml) and water (18.5 ml) was degassed with N_2 for 10 minutes and then stirred at room temperature overnight. The solvent was evaporated, the mixture was then diluted with DCM, washed with water, brine, dried over Na_2SO_4 and filtered. The solvent was evaporated and the residue was purified by flash chromatography (Biotage SP1, SNAP silica column, 50-75 % EtOAc/cyclohexanes) to give the title compound as an orange oil (1.06 g, 60 % yield). MS (m/z) 311.0 ($M+H^+$).

Step 2: 5-(3-(dimethoxyphosphoryl)phenyl)furan-2-carboxylic acid

A solution of methyl 5-(3-(dimethoxyphosphoryl)phenyl)furan-2-carboxylate (1.06 g, 3.42 mmol) in MeOH (13 ml) and water (4 ml) at room temperature was treated with LiOH monohydrate (155 mg, 3.76 mmol) and stirred overnight. Additional LiOH monohydrate was added (60 mg, 1.46 mmol) and the reaction stirred for 4 hours. The reaction mixture was evaporated, the residue was taken up into Et_2O and acidified with

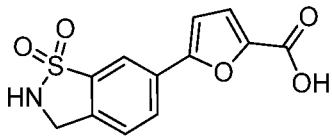
1N HCl to pH 2. The aqueous was extracted with Et_2O (3 x). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (Biotage SP1, SNAP silica column, 0-5 % MeOH + 5 % AcOH/DCM) to yield the title compound (0.66 g, 65 % yield). MS (m/z) 297.0 ($M+H^+$).

INTERMEDIATE 61: 5-(3-phosphonophenyl)furan-2-carboxylic acid

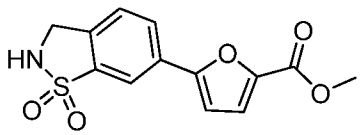


To a stirred solution of 5-(3-(dimethoxyphosphoryl)phenyl)furan-2-carboxylic acid (22 mg, 0.07 mmol) in dichloromethane (1.0 ml) was added bromotrimethyl silane (0.1 ml, 0.74 mmol) and the reaction mixture was stirred at room temperature for 1 hour. The reaction was quenched with 1 M NaOH solution (1 ml) and diluted with water (2 ml) and dichloromethane (5 ml). The organic phase was discarded and the aqueous phase was acidified to pH 1 via addition of 3 M HCl solution. The aqueous phase was then saturated with solid NaCl and dichloromethane (5 ml) added, resulting in emulsion formation. Addition of EtOAc (15 ml) and a few drops of MeOH failed to resolve the emulsion. The emulsion was filtered and and the solid collected to give the title compound as a white solid (14 mg, 71 5 yield). MS (m/z) 269.0 ($M+H^+$).

INTERMEDIATE 62: 5-(1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl)furan-2-carboxylic acid



Step 1: methyl 5-(1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl)furan-2-carboxylate



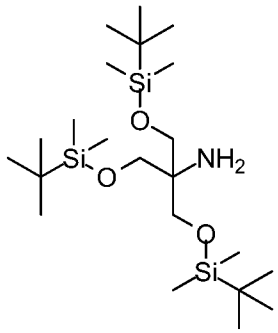
A mixture of 6-bromo-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (300 mg, 1.21 mmol), (5-(methoxycarbonyl)furan-2-yl)boronic acid (267 mg, 1.57 mmol, prepared according to Ishiyama, T., et al., Organic Synthesis, 2005, 82, 126-133, monobasic potassium phosphate (164 mg, 1.21 mmol), tribasic potassium phosphate (256 mg, 1.21 mmol) and 1,1'-Bis(di-tert-butylphosphino)ferrocene palladium (29 mg, 0.06 mmol) in DME (5.5 ml), water (4 ml) and EtOH (1.4 ml) was degassed with N_2 for 10 minutes. The

reaction was then stirred at room temperature for 5 hours. The reaction was diluted with DCM, washed with water, brine, dried over Na_2SO_4, filtered and the solvent evaporated. The residue was purified by flash chromatography (Biotage SP1, SNAP silica column, 25-50 % EtOAc/cyclohexanes) to give the title compound (230 mg, 65 % yield). MS (m/z) 293.9 ($M+H^+$).

Step 2: 5-(1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl)furan-2-carboxylic acid

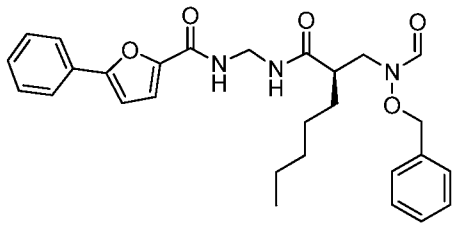
A solution of methyl 5-(1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl)furan-2-carboxylate (230 mg, 0.78 mmol) in MeOH (8 ml) and water (2 ml) was treated with LiOH monohydrate (39 mg, 0.940 mmol) and stirred at room temperature for 5 hours. The reaction was concentrated and the residue taken into Et_2O and acidified to pH 2 via addition of 1 N HCl. The aqueous was extracted with Et_2O (3 x). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the title compound (210 mg, 97 % yield). MS (m/z) 280.1 ($M+H^+$).

INTERMEDIATE 63: 6-(((tert-butyldimethylsilyl)oxy)methyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-amine



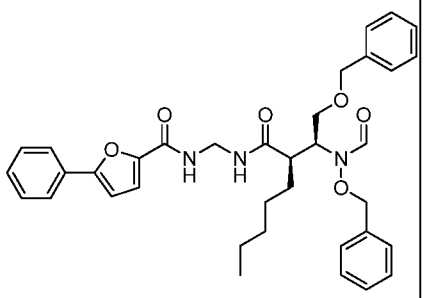
A mixture of 2-amino-2-(hydroxymethyl)propane-1,3-diol (100 mg, 0.83 mmol), TBDMSCl (622 mg, 4.13 mmol) and imidazole (562 mg, 8.26 mmol) in N,N-dimethylformamide (0.5 ml) was stirred at room temperature overnight. The reaction was then reduced in volume and diluted with EtOAc (5 ml) and washed with water (3 x 10 ml). The organic layer was separated, passed through a phase separator and concentrated to give the title compound (491 mg) which was used without further purification.

INTERMEDIATE 64: (R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide

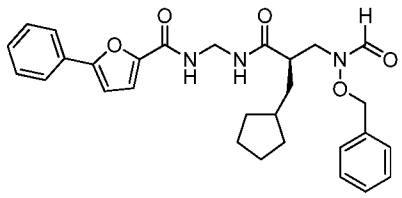
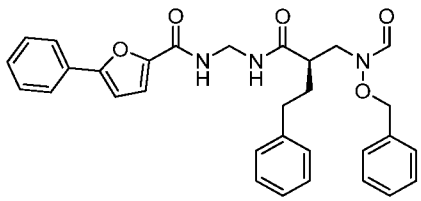
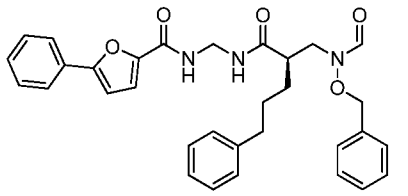


A mixture of N-(aminomethyl)-5-phenylfuran-2-carboxamide (1.62 g, 7.50 mmol), (R)-2-((N-(benzyloxy)formamido)methyl)heptanoic acid (2 g, 6.82 mmol), HOBt (1.15 g, 7.50 mmol), and Et_3N (2.85 ml, 20.45 mmol) in N,N-dimethylformamide (40 ml) was treated with EDC (1.44 g, 7.50 mmol) and stirred at 25 °C for 4 hours before being quenched with the addition of water and extracted with EtOAc. The organic extracts were washed with 1 N HCl, saturated aq. $NaHCO_3$, brine and then dried (sodium sulfate), and concentrated. The was subjected to flash chromatography (50-100 % EtOAc/hexanes, sample loaded as a CH_2Cl_2 solution) to give a colorless oil, which crystallized upon addition of Et_2O. The solid was collected by filtration, washed with Et_2O, and dried to give the title compound (1.5 g, 41% yield) as a white solid. MS (m/z) 492.2 ($M+H^+$).

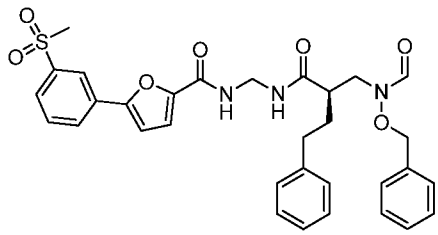
INTERMEDIATE 65 was prepared from N-(aminomethyl)-5-phenylfuran-2-carboxamide and the indicated acid by methods analogous to those described for Intermediate 64 utilizing DIPEA as the base instead of Et_3N.

#	Name	Structure	MS (m/z) ($M+H^+$)	Acid
65	N-(((R)-2-((S)-1-(N-(benzyloxy)formamido)-2-hydroxyethyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide		612.1	(R)-2-((S)-2-(benzyloxy)-1-(N-(benzyloxy)formamido)ethyl)heptanoic acid

INTERMEDIATES 66-68 were prepared from N-(aminomethyl)-5-phenylfuran-2-carboxamide and the indicated acid by methods analogous to those described for Intermediate 64 using DIPEA as the base instead of Et_3N and conducting the reaction at 50 °C instead of at room temperature. Intermediates 67and 68 used THF as solvent instead of DMF.

	Name	Structure	MS (m/z) ($M+H^+$)	Acid
66	(R)-N-((3-(N-(benzyloxy)formamido)-2-(cyclopentylmethyl)propanamido)methyl)-5-phenylfuran-2-carboxamide		504.0	(R)-3-(N-(benzyloxy)formamido)-2-(cyclopentylmethyl)propanoic acid
67	(R)-N-((2-((N-(benzyloxy)formamido)methyl)-4-phenylbutanamido)methyl)-5-phenylfuran-2-carboxamide		526.2	(R)-2-((N-(benzyloxy)formamido)methyl)-4-phenylbutanoic acid
68	(R)-N-((2-((N-(benzyloxy)formamido)methyl)-5-phenylpentanamido)methyl)-5-phenylfuran-2-carboxamide		540.3	(R)-2-((N-(benzyloxy)formamido)methyl)-5-phenylpentanoic acid

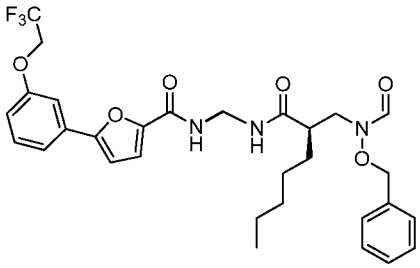
INTERMEDIATE 69: (R)-N-((2-((N-(benzyloxy)formamido)methyl)-4-phenylbutanamido)methyl)-5-(3-(methylsulfonyl)phenyl)furan-2-carboxamide



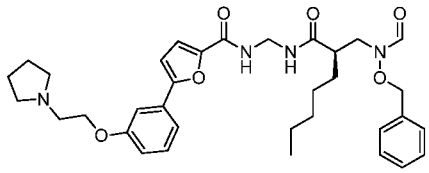
A solution of N-(aminomethyl)-5-(3-(methylsulfonyl)phenyl)furan-2-carboxamide (0.11 g, 0.36 mmol), (R)-2-((N-(benzyloxy)formamido)methyl)-4-phenylbutanoic acid (0.12 g, 0.36 mmol), HATU (0.16 g, 0.43 mmol), and DIPEA (0.19 ml, 1.07 mmol) in N,N-

dimethylformamide (2 ml) was stirred at room temperature overnight. Water was added and the reaction was extracted twice with EtOAc. The combined organic extracts were washed with water (3 x), dried over Na_2SO_4, filtered and concentrated. The residue was purified via flash chromatography (ISCO, 24 g silica column, 0-60 % EtOAc/DCM: 15 minutes, 60 % EtOAc: 6 minutes, 60-100 % EtOAc/DCM: 5 minutes, 100 % EtOAc: 5 minutes) to give the title compound as a sticky white solid (0.143 g, 66.4 % yield). MS (m/z) 604.2 ($M+H^+$).

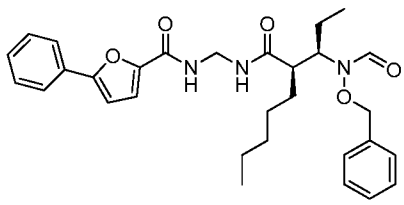
INTERMEDIATE 70 was prepared from N-(aminomethyl)-5-(3-(2,2,2-trifluoroethoxy)phenyl)furan-2-carboxamide and the indicated acid by methods analogous to those described for Intermediate 69.

#	Name	Structure	MS (m/z) ($M+H^+$)	Acid
70	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(2,2,2-trifluoroethoxy)phenyl)furan-2-carboxamide		590.2	(R)-2-((N-(benzyloxy)formamido)methyl)heptanoic acid

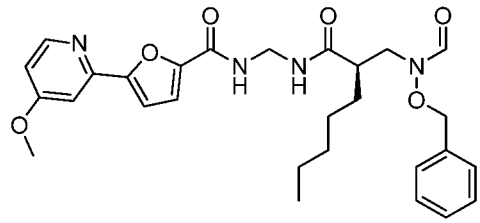
INTERMEDIATE 71 was prepared from N-(aminomethyl)-5-(3-(2-(pyrrolidin-1-yl)ethoxy) phenyl)furan-2-carboxamide and the indicated acid by methods analogous to those described for Intermediate 69 utilizing HBTU as the coupling reagent instead of HATU and DCM as the solvent instead of DMF.

#	Name	Structure	MS (m/z) ($M+H^+$)	Acid
71	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(2-(pyrrolidin-1-yl)ethoxy)phenyl)furan-2-carboxamide		605.4	(R)-2-((N-(benzyloxy)formamido)methyl) heptanoic acid

INTERMEDIATE 72 was prepared from N-(aminomethyl)-5-phenylfuran-2-carboxamide and the indicated acid by methods analogous to those described for Intermediate 69 utilizing HBTU as the coupling reagent instead of HATU.

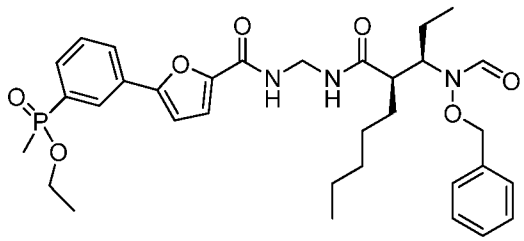
#	Name	Structure	MS (m/z) ($M+H^+$)	Acid
72	N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide		520.3	(R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanoic acid

INTERMEDIATE 73: (R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(4-methoxypyridin-2-yl)furan-2-carboxamide



(R)-N-(aminomethyl)-2-((N-(benzyloxy)formamido)methyl)heptanamide (0.1 g, 0.31 mmol) in dichloromethane (1 ml) was added to a solution of 5-(4-methoxypyridin-2-yl)furan-2-carboxylic acid (0.07 g, 0.31 mmol), HATU (0.13 g, 0.34 mmol), and DIPEA (0.16 ml, 0.93 mmol) in N,N-dimethylformamide (1 ml) and the reaction was stirred at room temperature overnight. The reaction was then extracted with EtOAc (2 x). The combined organic extracts were washed with water, dried over Na_2SO_4 and concentrated. The residue was treated with a pre-mixed solution of CDI (0.04 g, 0.23 mmol) and formic acid (0.01 ml, 0.31 mmol) in DCM (2 ml), and the reaction was stirred at room temperature overnight. The reaction was washed with 1N HCl, and then with water, dried over Na_2SO_4 and concentrated. The residue was purified by reverse phase HPLC (Waters, Sunfire C_{18} OBD column, 20-60 % CH_3CN/water (+ 0.1 % TFA), 16 minute gradient). The fractions containing desired product were combined and neutralized with sat. $NaHCO_3$, extracted with DCM, dried over Na_2SO_4 and concentrated to give the title compound as a thick oil (57 mg, 35 % yield). MS (m/z) 523.2 ($M+H^+$).

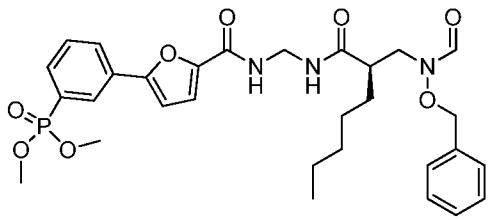
INTERMEDIATE 74: ethyl (3-(5-((((R)-2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)(methyl)phosphinate



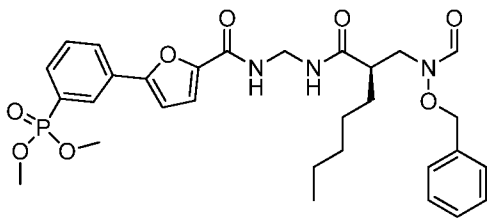
To a mixture of 5-(3-(ethoxy(methyl)phosphoryl)phenyl)furan-2-carboxylic acid (160 mg, 0.54 mmol), DIPEA (0.19 ml, 1.09 mmol), HOBt (96 mg, 0.71 mmol) and (R)-N-(aminomethyl)-2-((N-(benzyloxy)formamido)methyl)heptanamide (175 mg, 0.54 mmol) in DCM (5 ml) was added EDC (135 mg, 0.71 mmol). The reaction mixture was stirred overnight. The reaction mixture was then diluted with EtOAc (50 ml), washed with

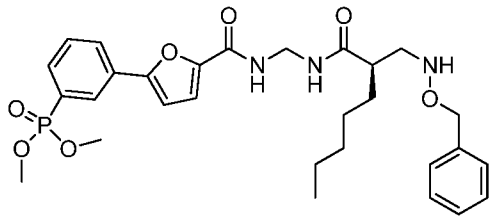
saturated $NaHCO_3$ solution (50 ml) and brine (25 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in DCM (5 ml) and treated with a solution of CDI (31 mg, 0.19 mmol) and formic acid (8 µl) in DCM (2 ml) that had been pre-stirred for 30 minutes at room temperature. The reaction was stirred for 1 hour. The reaction was then diluted with EtOAc (50 ml) and washed with pH 3 buffer solution (50 ml), saturated $NaHCO_3$ solution (50 ml) and brine (25 ml). The organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (25 g SNAP column, 0-15 % MeOH/EtOAc) to give the title compound as a pale yellow foam (274 mg, 84 % yield). MS (m/z) 598.1 ($M+H^+$).

INTERMEDIATE 75: (R)-dimethyl (3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate



Step 1: (R)-dimethyl (3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl) carbamoyl)furan-2-yl)phenyl)phosphonate and (R)-dimethyl (3-(5-(((2-(((benzyloxy)amino) methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate



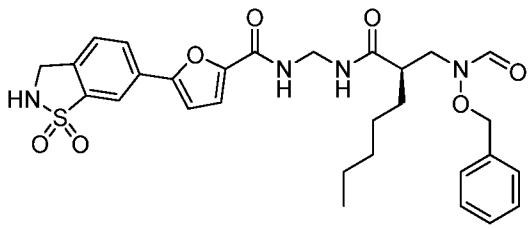


To a mixture of 5-(3-(dimethoxyphosphoryl)phenyl)furan-2-carboxylic acid (0.20 g, 0.68 mmol) , DIPEA (0.22 ml, 1.24 mmol), HOBt (0.10 g, 0.75 mmol) and EDC (0.16 g, 0.81 mmol) in DCM (4 ml) under nitrogen was added dropwise a solution of (R)-N-(aminomethyl)-2-((N-(benzyloxy)formamido)methyl)heptanamide (0.20 g, 0.62 mmol) in DCM (4 ml) and the reaction stirred for 1 hour. Additional (R)-N-(aminomethyl)-2-((N-(benzyloxy)formamido)methyl) heptanamide (0.05 g, 0.16 mmol in 1 ml of DCM) was added and the reaction stirred at room temperature overnight. The reaction was then diluted with DCM, washed with saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4, filtered and concentrated to afford a mixture of the the title compounds (440 mg) which was used without further purification. MS (m/z) 600.0 ($M+H^+$) and 572.3 ($M+H^+$).

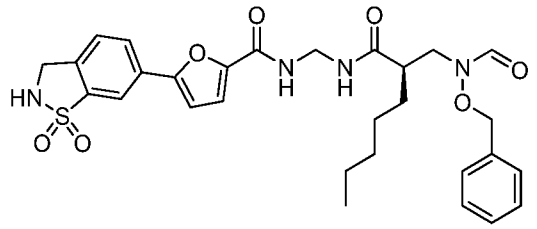
Step 2: (R)-dimethyl (3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate

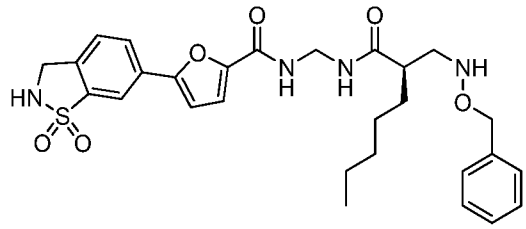
To a suspension of CDI (40 mg, 0.25 mmol) in DCM (3 ml) at 0 °C was added formic acid (12 µl, 0.31 mmol). The solution was stirred at room temperature for 20 minutes then added dropwise to a solution of (R)-dimethyl (3-(5-(((2-((N-(benzyloxy)formamido)methyl) heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate and (R)-dimethyl (3-(5-(((2-(((benzyloxy)amino)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate (440 mg) in DCM (6 ml) at 0 °C. The reaction was stirred at room temperature for 6 hours. The reaction was then diluted with DCM and quenched by addition of $NaHCO_3$. The organic phase was separated via hydrophobic frit and and concentrated. The residue was purified by flash chromatography (SNAP silica column, 0-6 % methanol/DCM) to give the title compound (310 mg). MS (m/z) 600.2 ($M+H^+$).

INTERMEDIATE 76: (R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl)furan-2-carboxamide



Step 1: (R)-N-((2-(((benzyloxy)amino)methyl)heptanamido)methyl)-5-(1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl)furan-2-carboxamide and (R)-N-((2-((N-(benzyloxy)formamido) methyl)heptanamido)methyl)-5-(1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl)furan-2-carboxamide





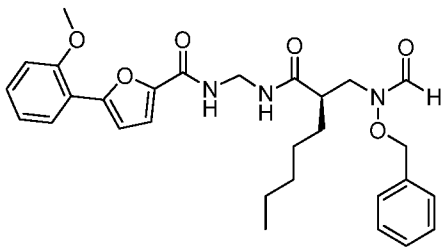
To a mixture 5-(1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl)furan-2-carboxylic acid (210 mg, 0.75 mmol), DIPEA (0.26 ml, 1.5 mmol), HOBt (122 mg, 0.9 mmol) and EDC.HCl (172 mg, 0.9 mmol) in dichloromethane (4 ml) under nitrogen was added dropwise a solution of (R)-N-(aminomethyl)-2-((N-

(benzyloxy)formamido)methyl)heptanamide (240 mg, 0.75 mmol) in DCM (4 ml). After 1 hour, additional (R)-N-(aminomethyl)-2-((N-(benzyloxy)formamido)methyl) heptanamide (50 mg, 0.16 mmol) dissolved in DCM (1 ml) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with DCM and the layers separated. The organic was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a mixture of the the title compounds (400 mg) which was used without further purification. MS (m/z) 583.0 ($M+H^+$) and 555.0 ($M+H^+$).

Step 2: (R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl)furan-2-carboxamide

To a suspension of CDI (36 mg, 0.22 mmol) in DCM (2 ml) at 0°C was added formic acid (9 µl) and the solution was stirred at room temperature for 20 minutes then added dropwise to a solution of (R)-N-((2-(((benzyloxy)amino)methyl)heptanamido)methyl)-5-(1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl)furan-2-carboxamide and (R)-N-((2-((N-(benzyloxy)formamido) methyl)heptanamido)methyl)-5-(1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl)furan-2-carboxamide (400 mg) in DCM (6 ml) at 0°C. The reaction was then warmed to room temperature and stirred for 2 hours. The reaction was then diluted with DCM and quenched by addition of sat aq. $NaHCO_3$. The organic phase was separated via hydrophobic frit and concentrated. The residue was purified by flash chromatography (SNAP silica cartridge, 0-5 % MeOH/DCM) to give the title compound (80 mg). MS (m/z) 583.2 ($M+H^+$).

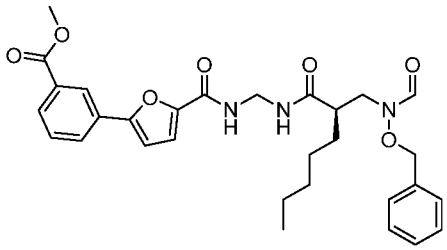
INTERMEDIATE 77: (R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(2-methoxyphenyl)furan-2-carboxamide



To a microwave vial charged with 1,2-dimethoxyethane (1 ml), water (0.1 ml), (R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-bromofuran-2-carboxamide (150 mg, 0.30 mmol), K_2CO_3 (84 mg, 0.61 mmol), and (2-methoxyphenyl)boronic acid (69.2 mg, 0.46 mmol) was addedTetrakis (35.1 mg, 0.03

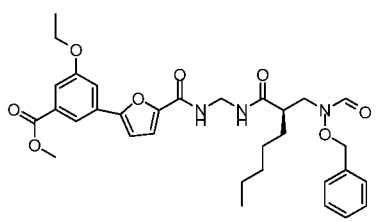
mmol) and the vial irradiated at 150 °C for 30 minutes in a microwave reactor (Biotage Initiator). The reaction was then poured into water and the mixture extracted with EtOAc. The organic was collected, dried (Na_2SO_4), filtered, concentrated, and the residue purified by flash chromatography (50 % EtOAc/hexanes) to give the title compound (80 mg, 51 % yield). MS (m/z) 522.2 ($M+H^+$).

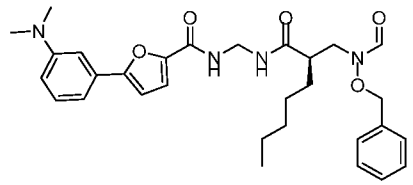
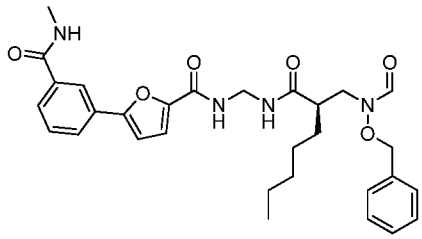
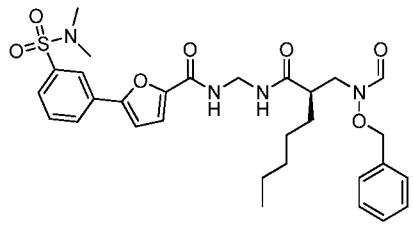
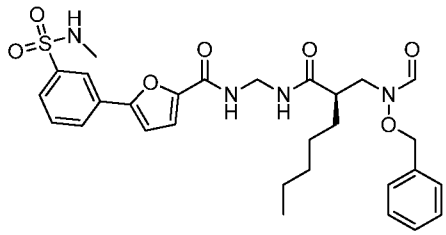
INTERMEDIATE 78: (R)-methyl 3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl) furan-2-yl)benzoate

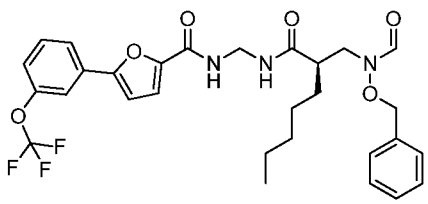
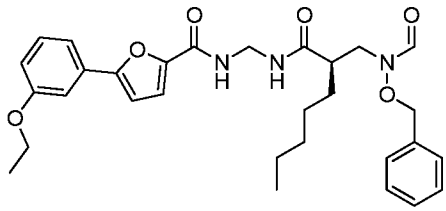
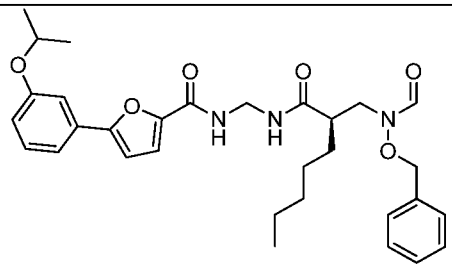
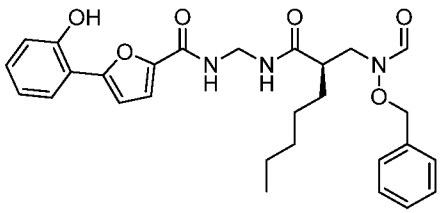
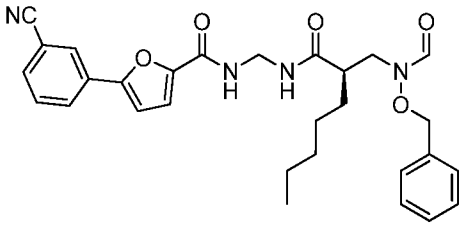
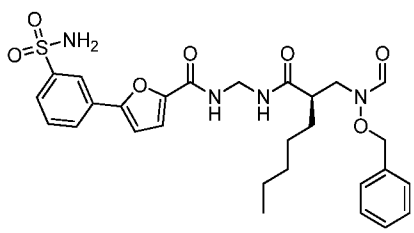


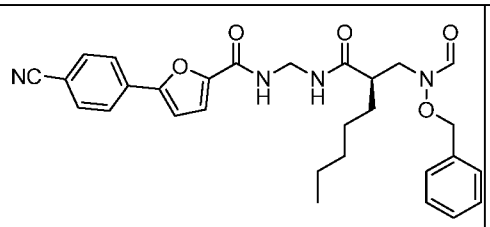
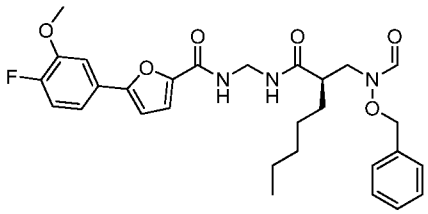
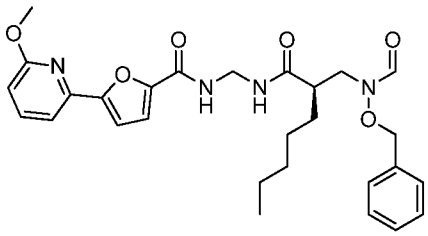
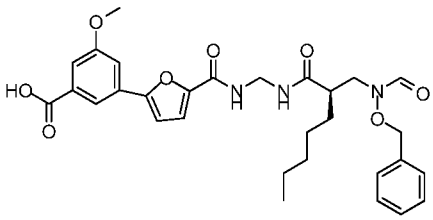
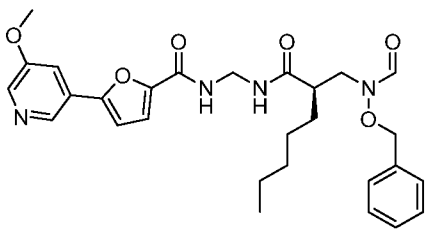
To a microwave reaction vessel charged with (R)-N-((2-((N-(benzyloxy) formamido)methyl)heptanamido)methyl)-5-bromofuran-2-carboxamide (150 mg, 0.30 mmol) and (3-(methoxycarbonyl)phenyl)boronic acid (65.5 mg, 0.36 mmol) and 1,4-dioxane (1.75 ml), was added $PdCl_2$(dppf)-CH_2Cl_2 adduct (24.78 mg, 0.03 mmol) and sodium carbonate (1M, 0.91 ml, 0.91 mmol). The reaction vessel was sealed and irradiated in a microwave reactor (Biotage Initiator) for 5 minutes at 100 ºC. The reaction mixture was concentrated and the residue purified by flash chromatography (ISCO Combiflash, 24 g column , 0-60 % EtOAc/DCM, over 15 minutes) to yield the title compound (167 mg, 60 % yield). (MS (m/z) 550.3 ($M+H^+$).

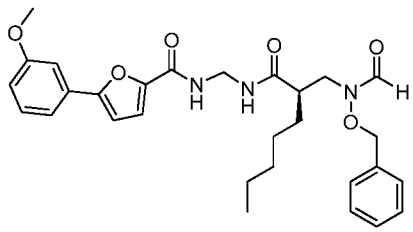
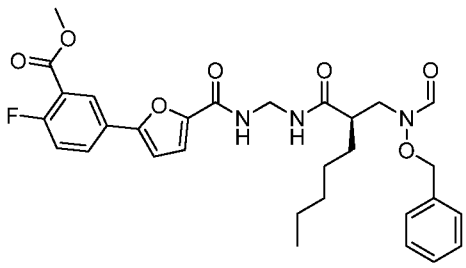
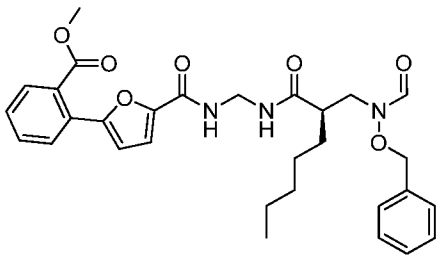
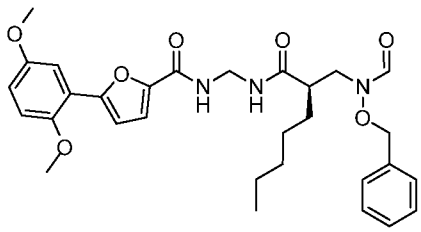
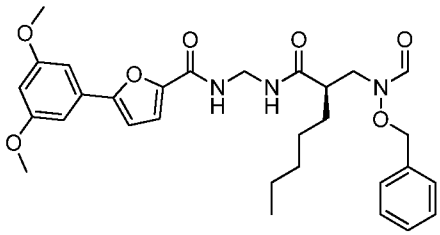
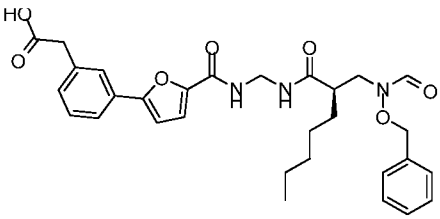
INTERMEDIATES 79-118 were prepared from ((R)-N-((2-((N-(benzyloxy)formamido) methyl)heptanamido)methyl)-5-bromofuran-2-carboxamide and the indicated boronic acid or boronate by methods analogous to those described for Intermediate 78.

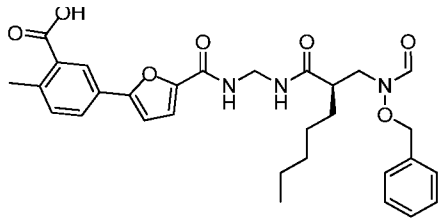
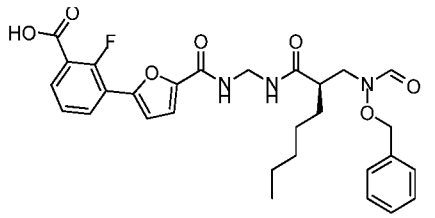
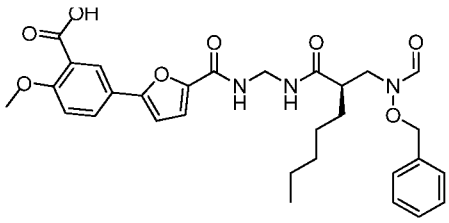
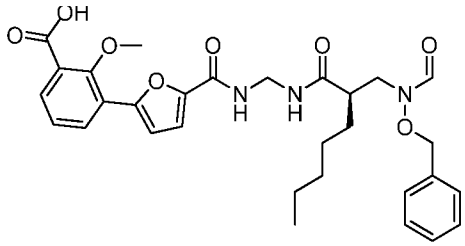
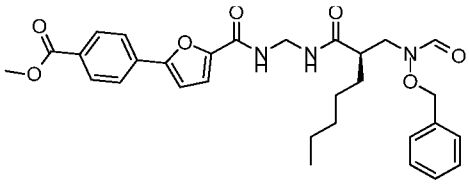
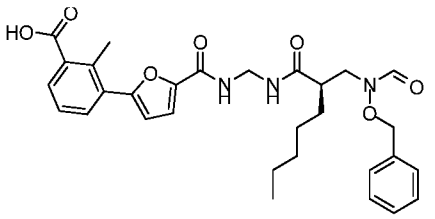
#	Name	Structure	MS (m/z) ($M+H^+$)	Boronic acid/ Boronate
79	(R)-methyl 3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-		594.2	methyl 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

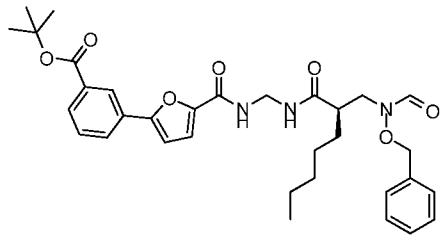
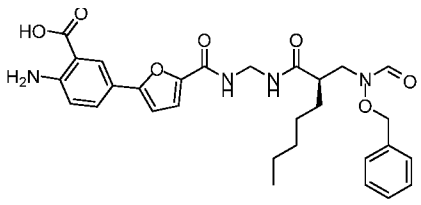
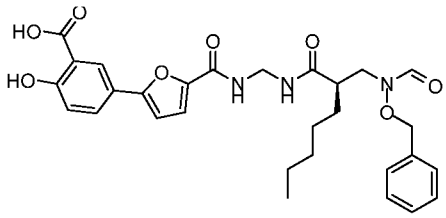
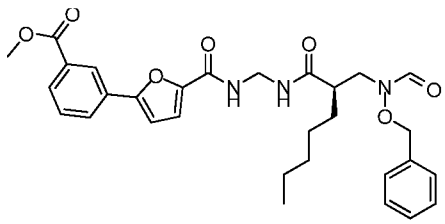
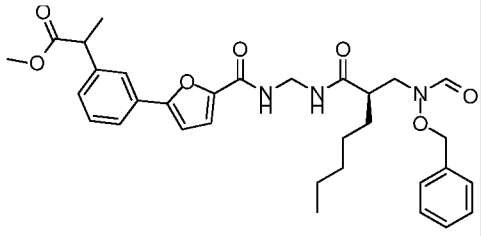
	ethoxybenzoate			
80	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(dimethylamino)phenyl)furan-2-carboxamide		535.2	(3-(dimethylamino)phenyl)boronic acid
81	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(methylcarbamoyl)phenyl)furan-2-carboxamide		549.3	(3-(methylcarbamoyl)phenyl)boronic acid
82	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(N,N-dimethylsulfamoyl)phenyl)furan-2-carboxamide		599.2	(3-(N,N-dimethylsulfamoyl)phenyl)boronic acid
83	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(N-methylsulfamoyl)phenyl)furan-2-carboxamide		585.3	(3-(N-methylsulfamoyl)phenyl)boronic acid

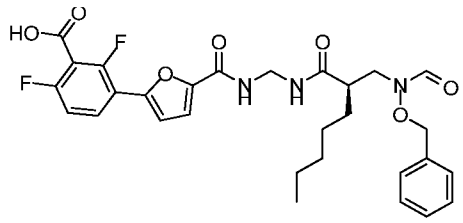
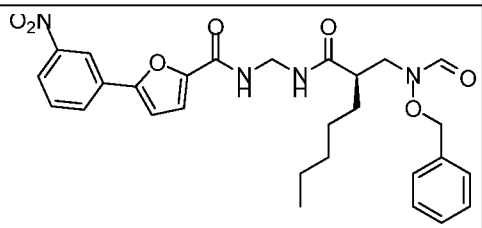
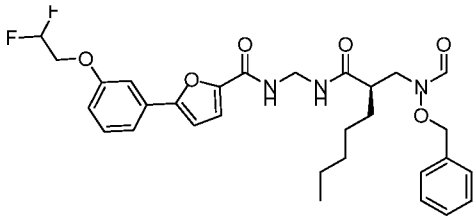
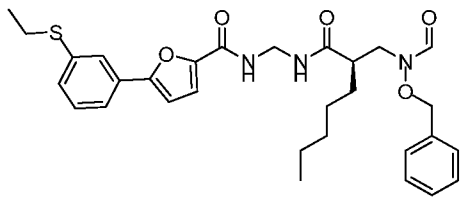
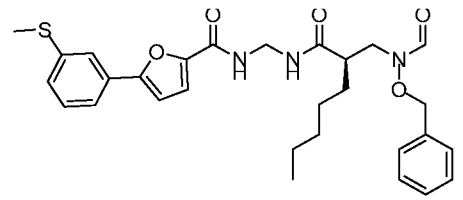
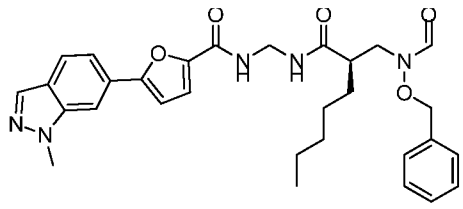
84	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(trifluoromethoxy)phenyl)furan-2-carboxamide		576.2	(3-(trifluoromethoxy)phenyl)boronic acid
85	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-ethoxyphenyl)furan-2-carboxamide		536.3	(3-ethoxyphenyl)boronic acid
86	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-isopropoxyphenyl)furan-2-carboxamide		550.3	(3-isopropoxyphenyl)boronic acid
87	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(2-hydroxyphenyl)furan-2-carboxamide		508.2	(2-hydroxyphenyl)boronic acid
88	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-cyanophenyl)furan-2-carboxamide		517.2	(3-cyanophenyl)boronic acid
89	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-sulfamoylphenyl)furan-2-carboxamide		571.2	(3-sulfamoylphenyl)boronic acid

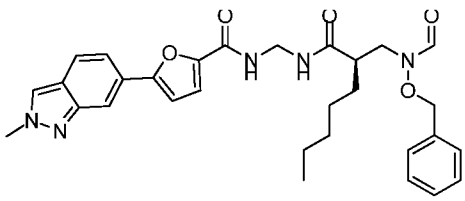
90	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(4-cyanophenyl)furan-2-carboxamide		517.3	(4-cyanophenyl)boronic acid
91	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(4-fluoro-3-methoxyphenyl)furan-2-carboxamide		540.3	(4-fluoro-3-methoxyphenyl)boronic acid
92	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(6-methoxypyridin-2-yl)furan-2-carboxamide		523.3	(6-methoxypyridin-2-yl)boronic acid
93	(R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-methoxybenzoic acid		566.2	3-borono-5-methoxybenzoic acid
94	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(5-methoxypyridin-3-yl)furan-2-carboxamide		523.2	3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

95	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-methoxyphenyl)furan-2-carboxamide		522.3	(3-methoxyphenyl) boronic acid
96	R)-methyl 5-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl) furan-2-yl)-2-fluorobenzoate		568.2	(4-fluoro-3-(methoxycarbonyl)phenyl)boronic acid
97	(R)-methyl 2-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate		550.2	(2-(methoxycarbonyl)phenyl)boronic acid
98	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(2,5-dimethoxyphenyl)furan-2-carboxamide		552.2	(2,5-dimethoxyphenyl)boronic acid
99	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3,5-dimethoxyphenyl)furan-2-carboxamide		552.2	(3,5-dimethoxyphenyl)boronic acid
100	(R)-2-(3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid		550.2	2-(3-boronophenyl)acetic acid

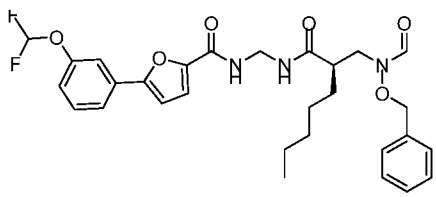
101	(R)-5-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzoic acid		550.2	5-borono-2-methylbenzoic acid
102	(R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-fluorobenzoic acid		554.2	3-borono-2-fluorobenzoic acid
103	(R)-5-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methoxybenzoic acid		566.2	5-borono-2-methoxybenzoic acid
104	(R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methoxybenzoic acid		566.2	3-borono-2-methoxybenzoic acid
105	(R)-methyl 4-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate		550.2	methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
106	(R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzoic acid		550.2	2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid

107	(R)-tert-butyl 3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate		592.3	(3-(tert-butoxycarbonyl)phenyl)boronic acid
108	(R)-2-amino-5-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		551.2	2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
109	(R)-5-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-hydroxybenzoic acid		552.2	2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid
110	(R)-methyl 3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate		550.2	(3-(methoxycarbonyl)phenyl)boronic acid
111	methyl 2-(3-(5-((((R)-2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)propanoate		578.3	methyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate

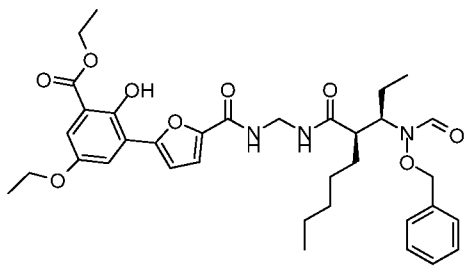
112	(R)-methyl 3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2,6-difluorobenzoate		586.2	(2,4-difluoro-3-(methoxycarbonyl)phenyl)boronic acid
113	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-nitrophenyl)furan-2-carboxamide		537.2	(3-nitrophenyl)boronic acid
114	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(2,2-difluoroethoxy)phenyl)furan-2-carboxamide		572.2	2-(3-(2,2-difluoroethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
115	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(ethylthio)phenyl)furan-2-carboxamide		552.2	(3-(ethylthio)phenyl)boronic acid
116	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(methylthio)phenyl)furan-2-carboxamide		538.2	(3-(methylthio)phenyl)boronic acid
117	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(1-methyl-1H-indazol-6-yl)furan-2-		546.2	(1-methyl-1H-indazol-6-yl)boronic acid

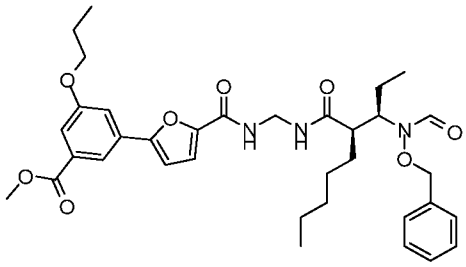
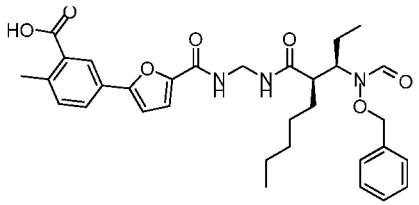
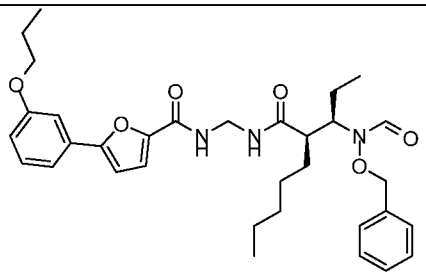
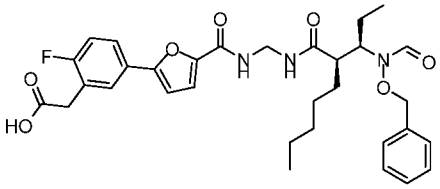
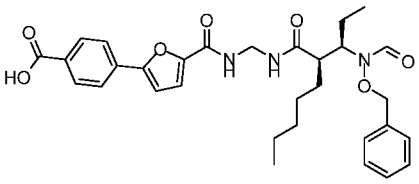
	carboxamide			
118	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(2-methyl-2H-indazol-6-yl)furan-2-carboxamide		546.2	(2-methyl-2H-indazol-6-yl)boronic acid

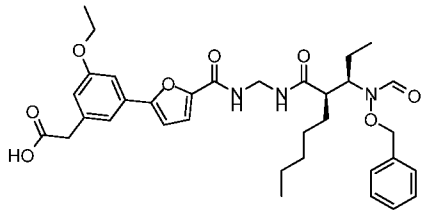
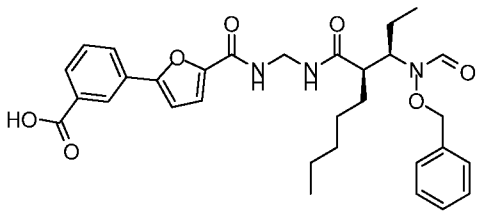
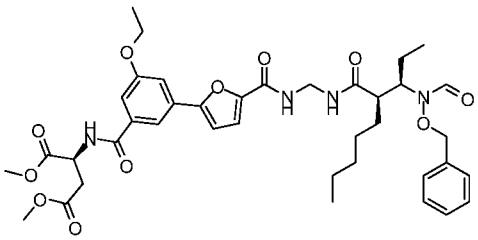
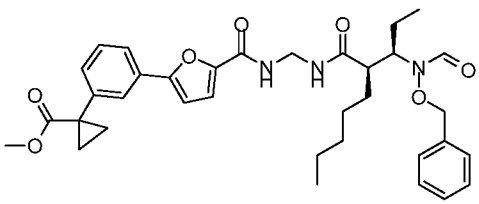
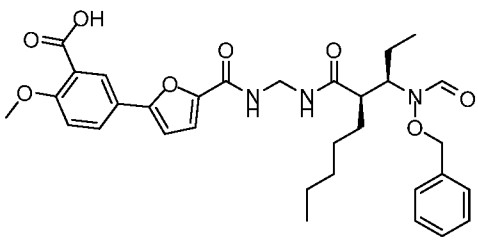
INTERMEDIATE 119 was prepared from ((R)-N-((2-((N-(benzyloxy)formamido)methyl) heptanamido)methyl)-5-bromofuran-2-carboxamide using the indicated boronate by methods analogous to those described in Intermediate 78 irradiating for 35 minutes at 110 °C, 15 minutes at 115 °C and then 15 minutes at 120 °C.

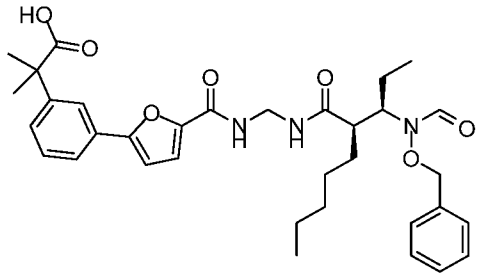
	Name	Structure	MS (m/z) ($M+H^+$)	Boronate
119	(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(difluoromethoxy)phenyl)furan-2-carboxamide		558.3	2-(3-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

INTERMEDIATES 120-131 were prepared from N-(((R)-2-((R)-1-(N-(benzyloxy)formamido) propyl)heptanamido)methyl)-5-bromofuran-2-carboxamide and the indicated boronate by methods analogous to those described for Intermediate 78.

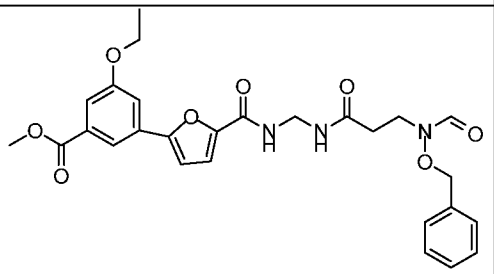
#	Name	Structure	MS (m/z) ($M+H^+$)	Boronate
120	ethyl 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxy-2-		652.2	ethyl 5-ethoxy-2-hydroxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

	hydroxybenzoate			
121	methyl 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-propoxybenzoate		636.3	methyl 3-propoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
122	5-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzoic acid		578.3	5-borono-2-methylbenzoic acid
123	N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)-5-(3-propoxyphenyl)furan-2-carboxamide		578.3	(3-propoxyphenyl)boronic acid
124	2-(5-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-fluorophenyl)acetic acid		596.3	2-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid
125	4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		564.3	4-boronobenzoic acid

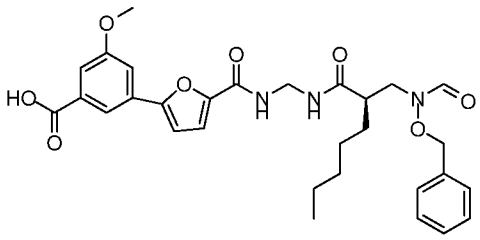
126	2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxyphenyl)acetic acid		532.3	2-(3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid
127	3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		564.3	3-boronobenzoic acid
128	(S)-dimethyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)succinate		751.3	(S)-dimethyl 2-(3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)succinate
129	methyl 1-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)cyclopropanecarboxylate		618.3	methyl 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarboxylate
130	5-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methoxybenzoic acid		594.2	5-borono-2-methoxybenzoic acid

131	2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)-2-methylpropanoic acid		606.3	2-(3-boronophenyl)-2-methylpropanoic acid

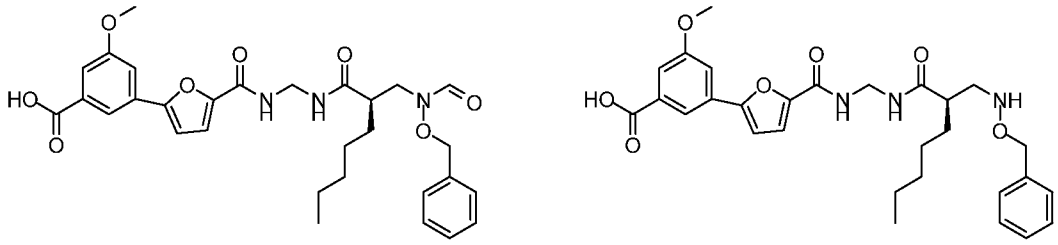
INTERMEDIATE 132 was prepared from N-((3-(N-(benzyloxy)formamido) propanamido)methyl)-5-bromofuran-2-carboxamide and the indicated boronate by methods analogous to those described for Intermediate 78.

#	Name	Structure	MS (m/z) ($M+H^+$)	Boronate
132	methyl 3-(5-(((3-(N-(benzyloxy)formamido)propanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoate		524.1	methyl 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

INTERMEDIATE 133: (R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-methoxybenzoic acid



Step 1: (R)-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-methoxybenzoic acid and (R)-3-(5-(((2-(((benzyloxy)amino)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-methoxybenzoic acid

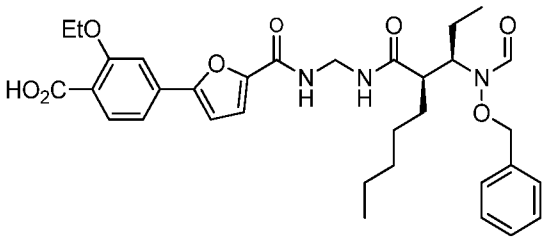


A mixture of 3-borono-5-methoxybenzoic acid (404 mg, 2.06 mmol), (R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-bromofuran-2-carboxamide (850 mg, 1.72 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (140 mg, 0.17 mmol) and Na_2CO_3 (1 M, 5.16 ml, 5.16 mmol) in 1,4-dioxane (4.5 ml) was irradiated in a microwave for 5 minutes at 100 ºC. Water and DCM were added to the reaction mixture and the pH adjusted to 5 by the addition of 1 M HCl. The DCM layer was collected and the aqueous extracted with ethyl acetate. The combined organics were concentrated and the residue purified by flash chromatography (ISCO CombiFlash, 40 g silica column, 0-20 % MeOH/DCM) to yield a beige solid which was purified by flash chromatography (20 g Si SPE, DCM, diethyl ether, ethyl acetate, acetone and 10 % MeOH/DCM) to give a mixture of the title compounds (531 mg). MS (m/z) 566.2 ($M+H^+$) and 538.2 ($M+H^+$).

Step 2: (R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-methoxybenzoic acid

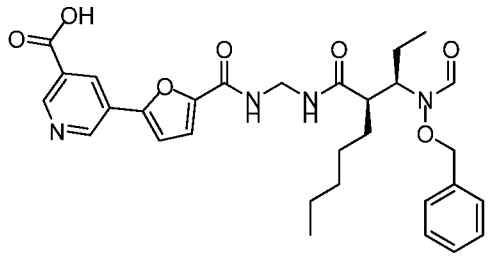
5-methyl-2-thioxo-1,3,4-thiadiazole-3(2H)-carbaldehyde (e.g., Yazawa, H., et al., Tetrahedron Letters, 1985, 26 (31), 3703-3706) (31.9 mg, 0.20 mmol) was added to a solution of ((R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-methoxybenzoic acid and (R)-3-(5-(((2-(((benzyloxy)amino)methyl) heptanamido)methyl)carbamoyl)furan-2-yl)-5-methoxybenzoic acid (530 mg, 0.80 mmol) in dichloromethane (2 ml) and the reaction stirred at room temperature for 45 minutes. The reaction mixture was concentrated, the residue dissolved in the minimum amount of DCM and purified by flash chromatography (10 g Si SPE, DCM, diethyl ether, ethyl acetate, acetone and 10 % MeOH/DCM) to give the title compound as an off white solid (482 mg). MS (m/z) 566.2 ($M+H^+$).

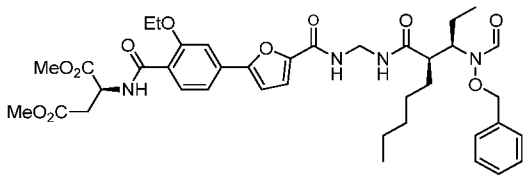
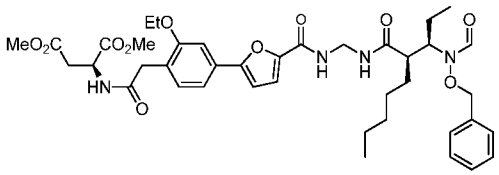
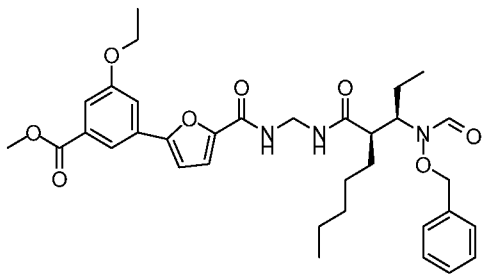
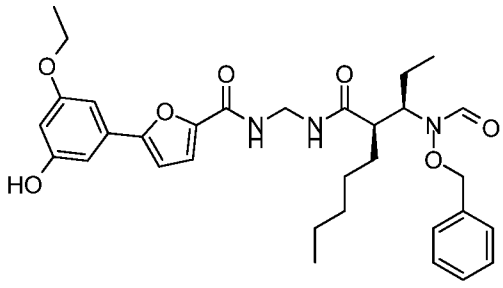
INTERMEDIATE 134: 4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzoic acid

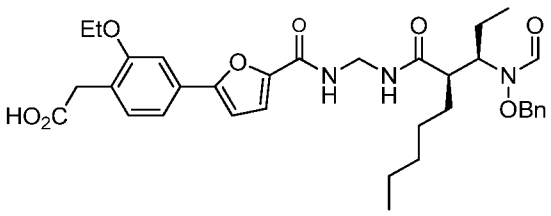
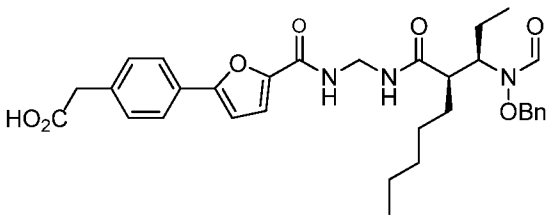
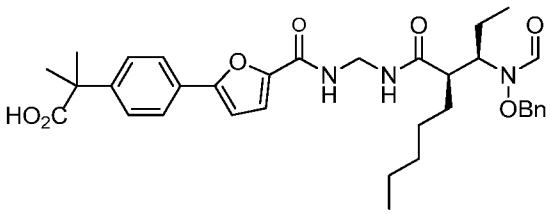
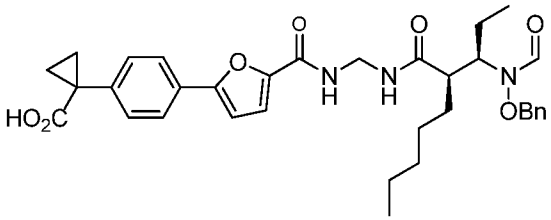


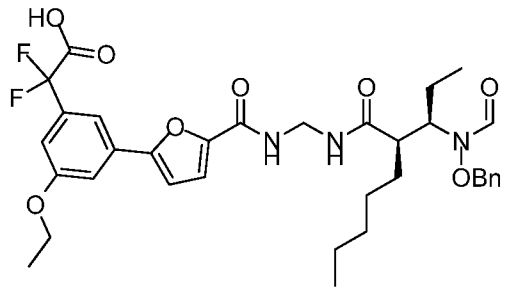
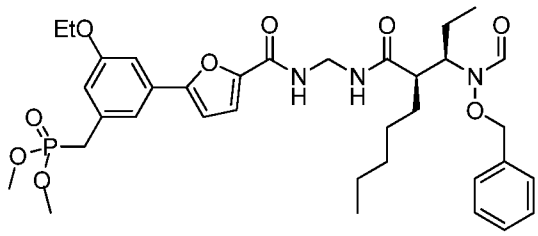
A mixture of 2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (151 mg, 0.52 mmol), N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl) heptanamido)methyl)-5-bromofuran-2-carboxamide (250 mg, 0.47 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (28.7 mg, 0.04 mmol) and Na_2CO_3 (1 M in water, 1.4 ml, 1.4 mmol) in 1,4-dioxane (3.6 ml) was stirred at 70 ºC for 60 mins. The reaction was then cooled to room temperature and slowly diluted with water (5 ml) and DCM (5 ml) and acidified via addition of HCl. The layers were separated and the DCM layer filtered and then concentrated to give the title compound as a yellow solid. MS (m/z) 608.3 ($M+H^+$).

INTERMEDIATES 135-146 were prepared from N-(((R)-2-((R)-1-(N-(benzyloxy)formamido) propyl)heptanamido)methyl)-5-bromofuran-2-carboxamide and the indicated boronic acid or boronate by methods analogous to those described for Intermediate 134.

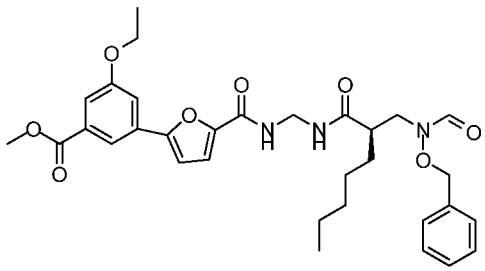
#	Name	Structure	MS (m/z) ($M+H^+$)	Boronoic Acid/ Boronate
135	5-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl) carbamoyl) furan-2-yl)nicotinic acid		565.2	5-brononicotinic acid

136	(S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)succinate		751.4	(S)-dimethyl 2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)succinate
137	(S)-dimethyl 2-(2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxyphenyl)acetamido)succinate		765.3	(S)-dimethyl 2-(2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamido)succinate
138	methyl-3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoate		622.3	3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
139	N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)-5-(3-ethoxy-5-hydroxyphenyl)furan-2-carboxamide		580.4	3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

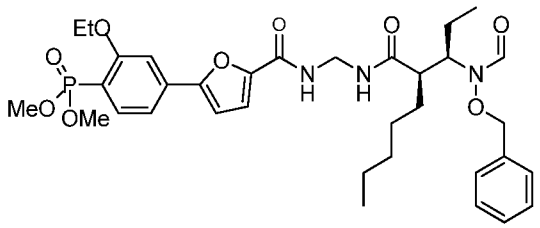
140	2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxyphenyl)acetic acid		622.3	2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid
141	2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid		578.3	2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid
142	2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)-2-methylpropanoic acid		606.3	2-(4-boronophenyl)-2-methylpropanoic acid
143	1-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)cyclopropanecarboxylic acid		604.3	1-(4-boronophenyl)cyclopropanecarboxylic acid

144	2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxyphenyl)-2,2-difluoroacetic acid		658.0	2-(3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2,2-difluoroacetic acid
145	dimethyl 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzylphosphonate		686.3	dimethyl 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylphosphonate

INTERMEDIATE 146 was prepared from (R)-N-((2-((N-(benzyloxy)formamido) methyl)heptanamido)methyl)-5-bromofuran-2-carboxamide and the indicated boronate by methods analogous to those described for Intermediate 134.

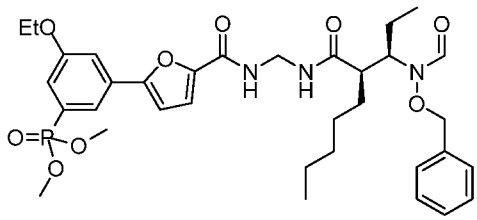
#	Name	Structure	MS (m/z) ($M+H^+$)	Boronate
146	(R)-methyl 3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoate		594.2	methyl 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

INTERMEDIATE 147: dimethyl (4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxyphenyl)phosphonate



A mixture of dimethyl (2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) phosphonate (409 mg, 1.15 mmol), N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl) heptanamido)methyl)-5-bromofuran-2-carboxamide (500 mg, 0.96 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (19.6 mg, 0.02 mmol) and Na_2CO_3 (1 M in water, 2.87 ml, 2.87 mmol) in 1,4-dioxane (6.7 ml) was stirred at 50 ºC for 30 minutes. The reaction was then cooled to room temperature and slowly diluted with water and DCM. The layers were separated and the aqueous layer extracted twice with DCM. The combined DCM extracts were combined and concentrated. The residue was purified by flash chromatography (ISCO, 120 g silica column, 0-10 % MeOH/DCM over 30 minutes) to give the title compound (600 mg, 93 % yield). MS (m/z) 672.3 ($M+H^+$).

INTERMEDIATE 148: dimethyl (3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido) methyl)carbamoyl)furan-2-yl)-5-ethoxyphenyl)phosphonate



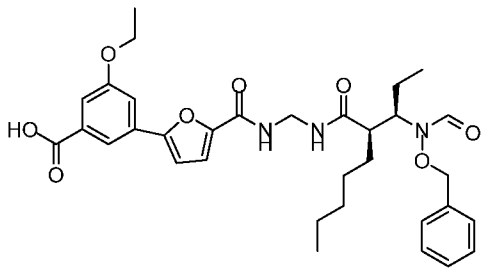
A mixture of dimethyl (3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonate (6.44 g, 14.65 mmol), N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)-5-bromofuran-2-carboxamide (6.95 g, 13.30 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.38 g, 0.47 mmol) and Na_2CO_3 (1 M in water, 39.9 ml, 39.9 mmol) in 1,4-dioxane (93 ml) was stirred at 50 ºC for 60 minutes. The reaction was then cooled to room temperature and slowly diluted with Et_2O and water. The layers were separated and the aqueous layer extracted twice with Et_2O. The combined ether extracts were dried over Na_2SO_4, filtered and concentrated to give a dark residue. To this residue was added Et_2O (until it became cloudy), the solution was stirred

and additional ether was added (~ 200 ml). After 10 minutes, the slurry was filtered. The filtrate was concentrated to give ~ 3 g of impure material. The gray solids were azeotroped with DCM to give 7.8 g of a gray material.

The 3 g of material obtained from the filtrate was purified via flash chromatography (ISCO, 330 g column, 0-10 % MeOH/DCM over 30 minutes) to give 1.6 g of the desired product containing some impurities. To this residue was added Et_2O (until it became cloudy), the solution was stirred and additional ether was added (~ 200 ml). After 10 minutes, the slurry was filtered. The filtrate was purified by reverse phase HPLC (Waters, Sunfire, 30 x 150 mm, 30-80 % CH_3CN/water (+ 0.1 % TFA) over 14 minutes). Fractions containing product were diluted with EtOAc and water. The water was extracted a total of 3 times and the combined extracts were concentrated to give the title compound as an off white solid (0.4 g, 5 % yield).

The gray solid (7.8 g) was purified by flash chromatography (ISCO, 220 g, 0-10 % MeOH/DCM over 30 minutes), fractions containing product were combined with the solids obtained from the 1.6 g crystallization and the material azeotroped with EtOAc (3 x). The resulting solids were then suspended in EtOAc (~100 ml) and the mixture heated to 60 °C then allowed to cool to room temperature with stirring, which was continued overnight. The slurry was then cooled to 0 °C and the solids collected by filtration, washed with hexanes and dried to give the desired product as a light gray solid. The filtrate was concentrated to dryness and re-crystalized from Et_2O and combined with the light gray solid from the EtOAc crystallization to give an additional batch of the title compound (7.25 g, 81 % yield). The filter funnel from the ether filtration was washed with DCM and the filtrate concentrated to give an additional batch of the title compound (0.9 g, 10 % yield). MS (m/z) 672.3 ($M+H^+$).

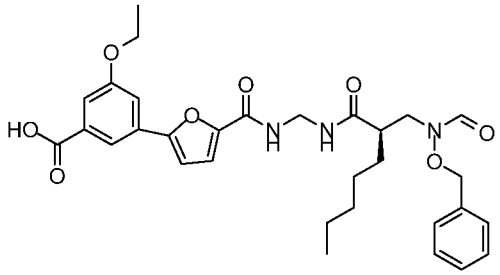
INTERMEDIATE 149: 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)-5-ethoxybenzoic acid



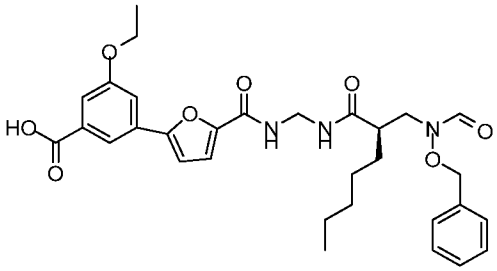
Lithium hydroxide hydrate (26.3 mg, 0.627 mmol) was added to a solution of methyl 3-(5-((((R)-2-((R)-1-(N-

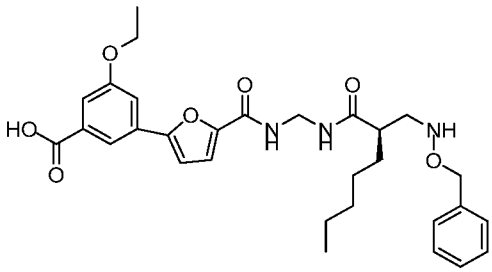
(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoate (260 mg, 0.314 mmol) in water (0.84 ml) and tetrahydrofuran (3.35 mll) and stirred at room temperature for 18 hours. The reaction was diluted with a small amount of CH_3CN, filtered, and purified via reverse phase HPLC (Waters, XBridge Prep Shield RP C_{18} 5 µm OBD 30 x 150 mm column, 20-60 % CH_3CN/water + 0.1 % NH_4OH over 14 minutes). Fractions containing product were combined, diluted with water, acidified by the addition of HCl and extracted with DCM. The DCM was passed through a phase separator and concentrated to give the title compound (162 mg, 85 % yield). MS (m/z) 608.3 ($M+H^+$).

INTERMEDIATE 150: (R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoic acid



Step 1: (R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoic acid and (R)-3-(5-(((2-(((benzyloxy)amino)methyl)heptanamido)methyl) carbamoyl)furan-2-yl)-5-ethoxybenzoic acid

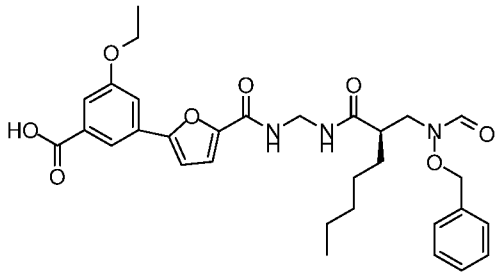




(R)-methyl 3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl) furan-2-yl)-5-ethoxybenzoate (572 mg, 0.87 mmol), was dissolved in methanol (2.5 ml) and tetrahydrofuran (2.5 ml) and sodium hydroxide (2 M, 2.17 ml, 4.34 mmol) was added and the reaction stirred at room temperature for 30 minutes. The reaction mixture was then concentrated and the residue adjusted to pH 5 via addition of 1 M HCl and extracted with EtOAc (2 x) and DCM (1 x). The combined organic layers were concentrated to give a

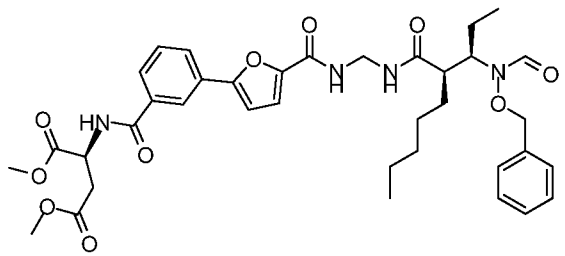
mixture of the title compounds as a pale yellow solid (424 mg). MS (m/z) 580.3 ($M+H^+$) and 552.3 ($M+H^+$).

Step 2: (R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoic acid



5-methyl-2-thioxo-1,3,4-thiadiazole-3(2H)-carbaldehyde (103 mg, 0.646 mmol) was added to a solution of (R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl) carbamoyl)furan-2-yl)-5-ethoxybenzoic acid and (R)-3-(5-(((2-(((benzyloxy)amino)methyl) heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoic acid(312 mg, 0.538 mmol) in dichloromethane (4 ml) and the reaction stirred at room temperature for 1 hour. The reaction mixture was concentrated and the residue purified by flash chromatography (10 g Si SPE, DCM, diethyl ether, ethyl acetate, acetone and 10 % MeOH/DCM) to yield the title compound as an off white solid (402 mg, 80 % yield). MS (m/z) 580.2 ($M+H^+$).

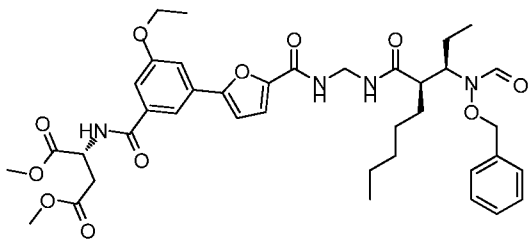
INTERMEDIATE 151: (S)-dimethyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido) methyl)carbamoyl)furan-2-yl)benzamido)succinate



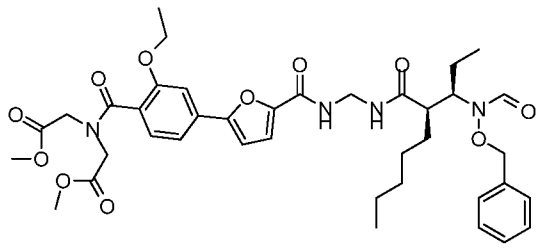
To a mixture of (S)-dimethyl 2-aminosuccinate, hydrochloride (56.1 mg, 0.28 mmol), 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid (160 mg, 0.28 mmol) and triethylamine (0.12 ml, 0.85 mmol) in dichloromethane (2.38 ml) was added T3P® (50 % wt in EtOAc, 0.34 ml, 0.57 mmol) and the reaction stirred for

2 hours at room temperature. The reaction was then diluted by the addition of DCM (7 ml) and water (5 ml). The layers were separated and the organic washed with water (5 ml), additional water (20 ml) was added to the emulsion that formed. The organic was then collected via hydrophobic frit and concentrated. The residue was purified via flash chrmoatography (ISCO Combiflash Rf, 25 g, column, 20-100 % ethyl acetate/hexanes) to give the title compound (98 mg, 49 % yield). MS (m/z) 707.3 ($M+H^+$).

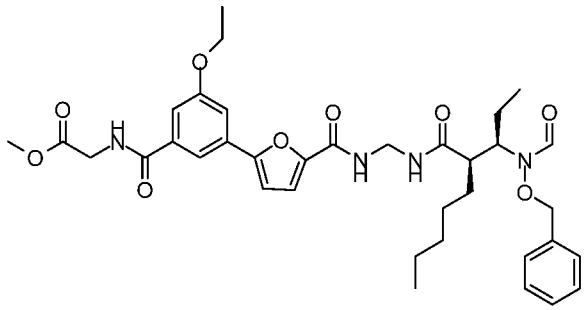
INTERMEDIATE 152 was prepared from 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido) propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoic acid and the indicated amine by methods analogous to those described for Intermediate 151.

#	Name	Structure	MS (m/z) ($M+H^+$)	Amine
152	(R)-dimethyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)succinate		751.3	(R)-dimethyl 2-aminosuccinate, hydrochloride

INTERMEDIATE 153 was prepared from 4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido) propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzoic acid and the indicated amine by methods analogous to those described for Intermediate 151.

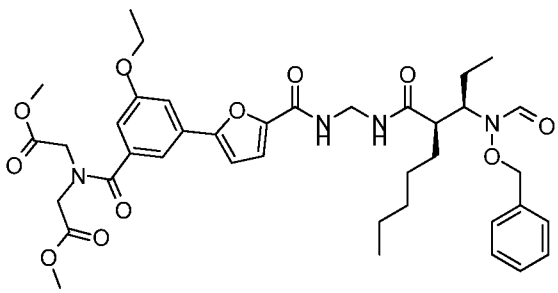
#	Name	Structure	MS (m/z) ($M+H^+$)	Amine
153	dimethyl 2,2'-((4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzoyl)azanediyl)diacetate		751.4	dimethyl 2,2'-azanediyldiacetate

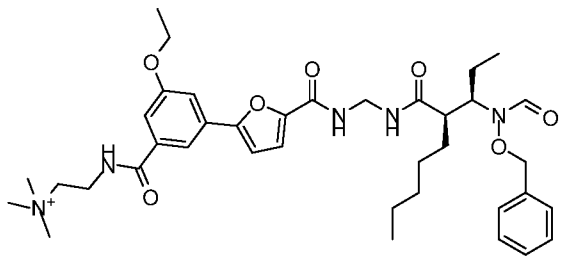
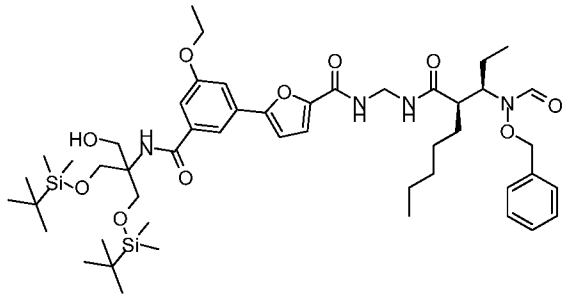
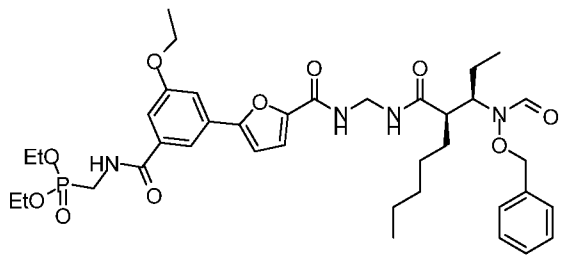
INTERMEDIATE 154: methyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido) methyl)carbamoyl) furan-2-yl)-5-ethoxybenzamido)acetate



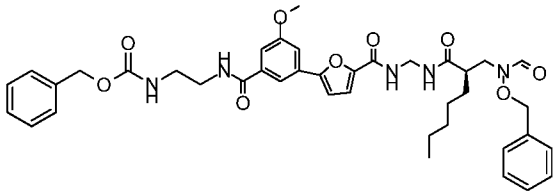
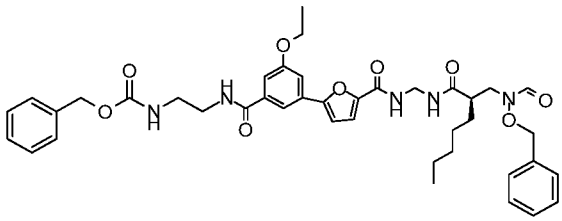
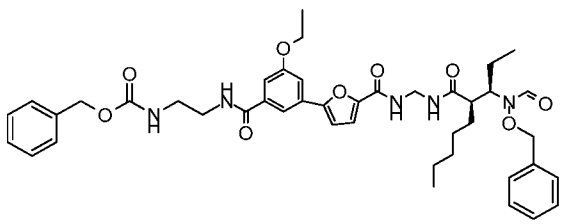
To a solution of 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl) heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoic acid (185 mg, 0.30 mmol), glycine methyl ester hydrochloride (38.2 mg, 0.30 mmol) and HATU (133 mg, 0.35 mmol) in dichloromethane (1.55 ml) was added DIPEA (0.17 ml, 0.94 mmol) and the reaction stirred at room temperature for 1 hr 15 minutes. The reaction was then concentrated and water (10 ml) and DCM (10 ml) were added to the residue. The organic was collected via hydrophobic frit and concentrated. The residue was purified via flash chromatography (ISCO Combiflash Rf, 25 g column, 20-100 % ethyl acetate/hexanes) to give the title compound (83.6 mg, 41 % yield). MS (m/z) 679.3 ($M+H^+$).

INTERMEDIATES 155-158 were prepared from 3-(5-((((R)-2-((R)-1-(N-(benzyloxy) formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoic acid and the indicated amine by methods analogous to those detailed for Intermediate 154.

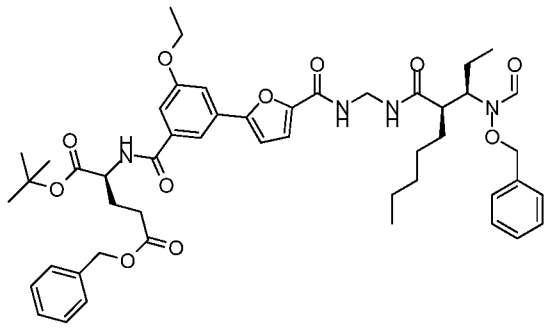
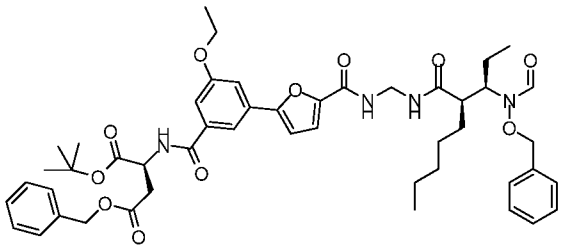
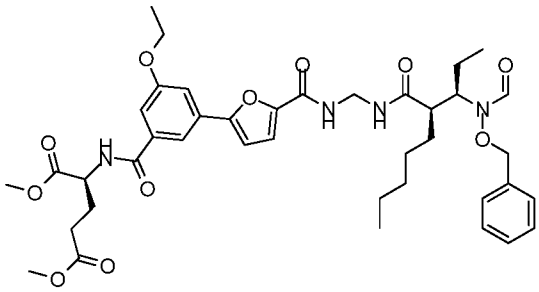
#	Name	Structure	MS (m/z)	Amine
155	dimethyl 2,2'-((3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)-5-ethoxybenzoyl)azanediyl)diacetate			dimethyl 2,2'-azanediyldiacetate, hydrochloride

156	2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)-N,N,N-trimethylethanaminium		692.3 (M+)	2-amino-N,N,N-trimethylethanaminium, chloride· hydrochloride
157	N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)-5-(3-ethoxy-5-((6-(hydroxymethyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)carbamoyl)phenyl)furan-2-carboxamide		940.5 ($M+H^+$)	6-(((tert-butyldimethylsilyl)oxy)methyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-amine
158	diethyl ((3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)methyl)phosphonate		757.3 ($M+H^+$)	diethyl (aminomethyl)phosphonate

INTERMEDIATES 159-161 were prepared from benzyl (2-aminoethyl)carbamate, hydrochloride and the indicated acid by methods analogous to those described for Intermediate 154. Intermediates 159 and 161 used DMF as solvent instead of DCM.

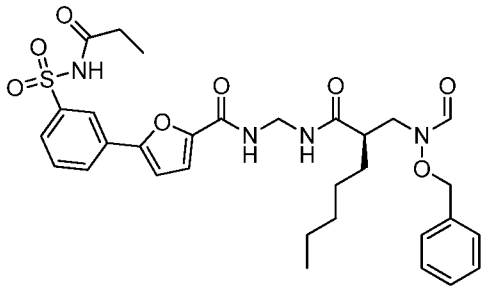
#	Name	Structure	MS (m/z) ($M+H^+$)	Acid
159	(R)-benzyl (2-(3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-methoxybenzamido)ethyl)carbamate		742.3	(R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-methoxybenzoic acid
160	(R)-benzyl (2-(3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)ethyl)carbamate		756.3	(R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoic acid
161	benzyl (2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)ethyl)carbamate		784.3	3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoic acid

INTERMEDIATES 162-164 were prepared from 3-(5-((((R)-2-((R)-1-(N-(benzyloxy) formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoic acid and the indicated amine by methods analogous to those detailed for Intermediate 154 utilizing triethylamine as the base instead of DIPEA.

	Name	Structure	MS (m/z) ($M+H^+$)	Amine
162	(S)-5-benzyl 1-tert-butyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl) heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)pentanedioate		883.5	(S)-5-benzyl 1-tert-butyl 2-aminopentanedioate, hydrochloride
163	(S)-4-benzyl 1-tert-butyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)-5-ethoxybenzamido)succinate		869.3	(S)-4-benzyl 1-tert-butyl 2-aminosuccinate, hydrochloride
164	(S)-dimethyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl) heptanamido)methyl)carbamoyl)furan-2-yl)-5-		765.3	(S)-dimethyl 2-aminopentanedioate, hydrochloride

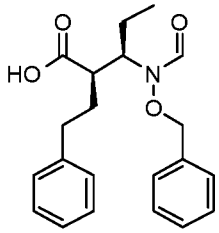
	ethoxybenzamido)pentanedioate			

INTERMEDIATE 165: (R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(N-propionylsulfamoyl) phenyl)furan-2-carboxamide



(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-sulfamoylphenyl) furan-2-carboxamide (103 mg, 0.180 mmol) in DCM (723 µl) was treated with triethylamine (75 µl, 0.541 mmol) for 20 minutes. Propionic anhydride (69.4 µl, 0.541 mmol) was added and the reaction was heated to 50 °C overnight. The reaction was then cooled to room temp and ice added. The reaction was then extracted with DCM, the organic layer was passed through a phase separator and concentrated. The residue was purified by flash chromatography (ISCO, 24 g silica gel column. 0-100 % EtOAc/DCM: 10 minutes,100 % EtOAc: 20 minutes) to give the title compound as a sticky solid (59 mg, 52.2 % yield). MS (m/z) 627.3 ($M+H^+$).

INTERMEDIATE 166: (2R,3R)-3-(N-(benzyloxy)formamido)-2-phenethylpentanoic acid

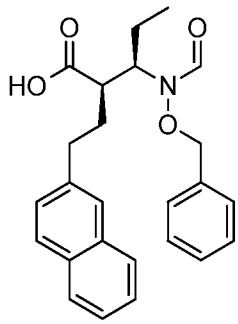


Intermediate 166 was prepared from 4-phenylbutanoyl chloride by methods analogous to that described for Intermediate 8.

Step	Name	MS (m/z)
1	(R)-4-benzyl-3-(4-phenylbutanoyl)oxazolidin-2-one	324.1

2	(R)-4-benzyl-3-((2R,3S)-3-hydroxy-2-phenethylpentanoyl)oxazolidin-2-one	382.1
3	(2R,3S)-N-(benzyloxy)-3-hydroxy-2-phenethylpentanamide	328.1
4	(3R,4R)-1-(benzyloxy)-4-ethyl-3-phenethylazetidin-2-one	310.1
5	(2R,3R)-3-((benzyloxy)amino)-2- phenethylpentanoic acid	328.1
6	(2R,3R)-3-(N-(benzyloxy)formamido)-2-phenethylpentanoic acid	356.1

INTERMEDIATE 167: (2R,3R)-3-(N-(benzyloxy)formamido)-2-(2-(naphthalen-2-yl)ethyl)pentanoic acid



Intermediate 167 was prepared from 4-(naphthalen-2-yl)butanoyl chloride by methods analogous to that described for Intermediate 8, except for Step 4' which is outlined below.

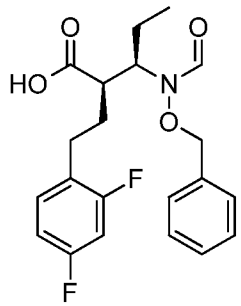
Step 4': (3R,4R)-1-(benzyloxy)-4-ethyl-3-(2-(naphthalen-2-yl)ethyl)azetidin-2-one

To a cooled solution at 0 °C of (2R,3S)-N-(benzyloxy)-3-hydroxy-2-(2-(naphthalen-2-yl)ethyl)pentanamide (20 g, 28.1 mmol) in tetrahydrofuran (THF) (150 ml) was added triphenylphosphine (8.84 g, 33.7 mmol) and DEAD (5.34 mL, 33.7mmol). The reaction stirred for 2 hours allowing to warm to RT. The reaction was monitored by TLC (SiO_2). Upon completion water (80 ml) was added to the reaction mixture and extracted with ethyl

acetate (2 x 150 ml). The combined organic layers were washed with water (150 ml) and concentrated in-vacuo to afford a yellow oil. The residue was purified by flash column chromatography (10% EtOAc/ Hexanes) to give the title compound (7 g, 55 % yield). MS (*m/z*) 360.2 ($M+H^+$).

Step	Name	MS (m/z)
1	(R)-4-benzyl-3-(4-(naphthalen-2-yl)butanoyl)oxazolidin-2-one	374.1
2	(R)-4-benzyl-3-((2S,3S)-3-hydroxy-2-(2-(naphthalen-2-yl)ethyl)pentanoyl)oxazolidin-2-one	N/A
3	(2R,3S)-N-(benzyloxy)-3-hydroxy-2-(2-(naphthalen-2-yl)ethyl)pentanamide	378.3
4*	(3R,4R)-1-(benzyloxy)-4-ethyl-3-(2-(naphthalen-2-yl)ethyl)azetidin-2-one	360.2
5	(2R,3R)-3-((benzyloxy)amino)-2-(2-(naphthalen-2-yl)ethyl)pentanoic acid	N/A
6	2R,3R)-3-(N-(benzyloxy)formamido)-2-(2-(naphthalen-2-yl)ethyl)pentanoic acid	406.1

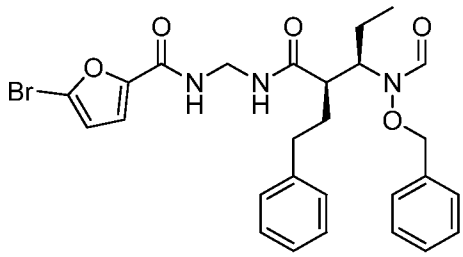
INTERMEDIATE 168: (2R,3R)-3-(N-(benzyloxy)formamido)-2-(2,4-difluorophenethyl)pentanoic acid



Intermediate 168 was prepared from 4-(2,4-difluorophenyl)butanoyl chloride by methods analogous to that described for Intermediate 167.

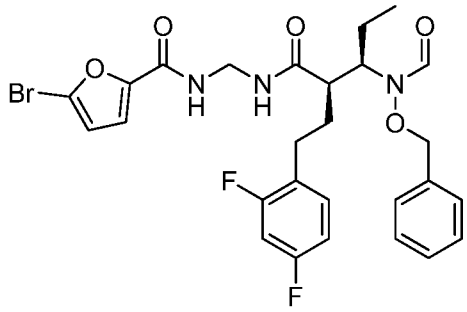
Step	Name	MS (m/z)
1	(R)-4-benzyl-3-(4-(2,4-difluorophenyl)butanoyl)oxazolidin-2-one	360.3
2	(R)-4-benzyl-3-((2S,3S)-2-(2,4-difluorophenethyl)-3-hydroxypentanoyl)oxazolidin-2-one	417.9
3	(2R,3S)-N-(benzyloxy)-2-(2,4-difluorophenethyl)-3-hydroxypentanamide	363.9
4	(3R,4R)-1-(benzyloxy)-3-(2,4-difluorophenethyl)-4-ethylazetidin-2-one	346.1
5	(2R,3R)-3-((benzyloxy)amino)-2-(2,4-difluorophenethyl)pentanoic acid	364.2
6	(2R,3R)-3-(N-(benzyloxy)formamido)-2-(2,4-difluorophenethyl)pentanoic acid	392.2

INTERMEDIATE 169: N-(((2R,3R)-3-(N-(benzyloxy)formamido)-2-phenethylpentanamido)methyl)-5-bromofuran-2-carboxamide



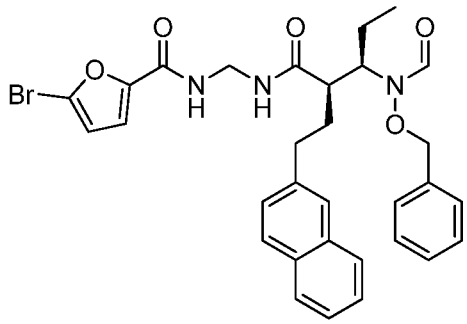
N-(aminomethyl)-5-bromofuran-2-carboxamide (0.600 g, 2.74 mmol) was added to a solution of (2R,3R)-3-(N-(benzyloxy)formamido)-2-phenethylpentanoic acid (0.97 g, 2.74 mmol), HATU (1.15 g, 3.01 mmol) and DIPEA (1.44 ml, 8.22 mmol) in DCM (12.26 ml). The reaction mixture was stirred at room temperature for 15 minutes. The reaction was then diluted with water. The layers were separated and the organic was passed through a hydrophobic frit, concentrated and the residue purified by flash chromatography (ISCO Companion, 40 g column, 20-80% ethylacetate/hexanes). The residue was dissolved in DCM and partitioned with water and stirred for 3 hours. The layers were separated and the organic was passed through a hydrophobic frit and concentrated to give the title compound as a white solid (1.23 g, 72.6% yield). MS (m/z) 558.1 (M^+).

INTERMEDIATE 170: N-(((2R,3R)-3-(N-(benzyloxy)formamido)-2-(2,4-difluorophenethyl)pentanamido)methyl)-5-bromofuran-2-carboxamide



(2R,3R)-3-(N-(benzyloxy)formamido)-2-(2,4-difluorophenethyl)pentanoic acid (3.00 g, 7.67 mmol), N-(aminomethyl)-5-bromofuran-2-carboxamide (1.68 g, 7.67 mmol), EDC (2.06 g, 10.74 mmol), 1-hydroxybenzotriazole hydrate (1.64 g, 10.74 mmol) and 4-methylmorpholine (3.37 ml, 30.7 mmol) were dissolved in DMF (40 ml). The reaction mixture was stirred for 2 hours at 25 °C. The reaction was then diluted with water and EtOAc. The layers were separated and the organics were washed with water three times, dried, concentrated and the residue purified by flash chromatography (ISCO, 80 g column, 0-40% hexanes/EtOAc) to give the title compound as a colorless oil (4.37 g, 91 % yield). MS (m/z) 594.1 (M^+).

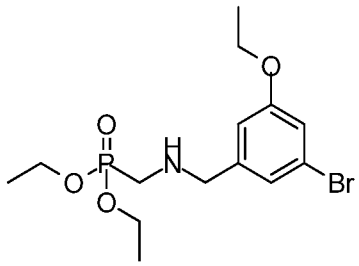
INTERMEDIATE 171: N-(((2R,3R)-3-(N-(benzyloxy)formamido)-2-(2-(naphthalen-2-yl)ethyl)pentanamido)methyl)-5-bromofuran-2-carboxamide



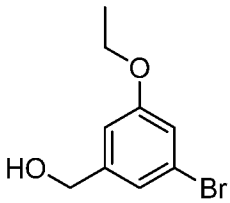
(2R,3R)-3-(N-(benzyloxy)formamido)-2-(2-(naphthalen-2-yl)ethyl)pentanoic acid (3.56 g, 8.79 mmol), N-(aminomethyl)-5-bromofuran-2-carboxamide (2.75 g, 8.79 mmol), EDC (2.190 g, 11.43 mmol) and HOBt (1.750 g, 11.43 mmol) were dissolved in DCM (60 ml) with N-methylmorpholine (3.86 ml, 35.2 mmol). The reaction mixture was stirred at 25 °C for 2.5 hours. A gummy residue formed on the edges of the flask, and the solution was decanted away from the gummy residue. The solution was diluted with water (60 ml) and DCM (50 ml) and stirrred for 30 minutes. The layers were separated, and the

organics were washed with brine and passed through a hydrophobic frit. The gummy residue was dissolved in MeOH and filtered. The filtrate was combined with the organic layer from the solution work up, concentrated and the residue purified by flash chromatography (ISCO Combiflash Rf, 80 g column, 0 to 100% Ethyl Acetate/hexanes over 40 minutes) to give the title compound as a yellow oil (2.28 g, 29.9 % yield). MS (m/z) 606.3 (M^+).

INTERMEDIATE 172: diethyl (((3-bromo-5-ethoxybenzyl)amino)methyl)phosphonate

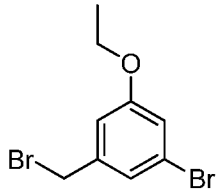


Step 1: (3-bromo-5-ethoxyphenyl)methanol



To a solution of methyl 3-bromo-5-ethoxybenzoate (5.6 g, 21.6 mmol) in toluene (108 ml) was added LAH (1.6 g, 43.2 mmol) upon which the reaction mixture was heated to 65 °C for 3 hours. 1N HCl was added slowly after cooling the reaction mixture in an ice bath. A slurry was formed. EtOAc was added and the layers were separated. The aq. layer was extracted with EtOAc (2 x 100 ml). The organics were washed with brine, dried over Na_2SO_4,filtered and concentrated to afford the title product as a colorless oil. MS (m/z) 230.9 ($M+H^+$).

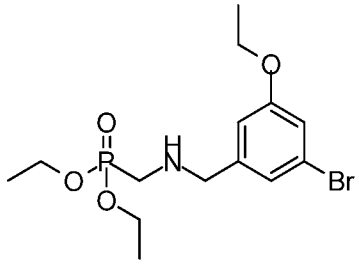
Step 2: 1-bromo-3-(bromomethyl)-5-ethoxybenzene



(3-bromo-5-ethoxyphenyl)methanol (4.6 g, 20 mmol) was dissolved in Et_2O(100 ml) and cooled to 0 °C before the addition of phosphorous tribromide (2.1 ml, 22 mmol). The mixture was allowed to stir at rt overnight. It was then poured into an ice water: ether solution. The aq. layer was extracted with ether (3 x 50 ml). The combined organic layers

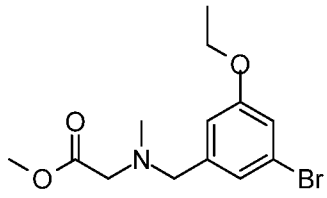
were dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified via flash column chromatography (0 - 15% EtOAc/hexanes) to afford the title compound as colorless oil (4.52 g, 71 % yield). MS (m/z) 293.0 ($M+H^+$).

Step 3: diethyl (((3-bromo-5-ethoxybenzyl)amino)methyl)phosphonate

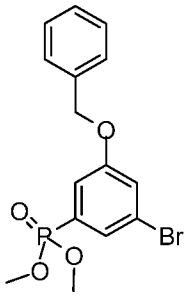


A solution of diethyl(aminomethyl)phosphonate, oxalic acid salt (1.1 g, 4.3 mmol), and TEA (1.35 ml, 9.7 mmol) was stirred in DMF (5 ml) for 15 minutes, upon which 1-bromo-3-(bromomethyl)-5-ethoxybenzene (1.14 g, 3.9 mmol) in DMF (1 mL) was added to the reaction mixture and stirred for 18 hours at rt. The reaction was poured into water and extracted into EtOAc (3 x 50 ml). The combined organic layers were washed with water, brine, and dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash column chromatography (0 - 10% MeOH/EtOAc) to afford the title compound as a white solid (0.755 g, 51 % yield). MS (m/z) 380.1 ($M+H^+$).

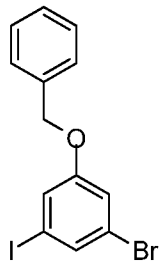
INTERMEDIATE 173 was prepared from the indicated amine by methods analogous to those described for Intermediate 172.

#	Name	Structure	MS (m/z) ($M+H^+$)	Amine
173	methyl 2-((3-bromo-5-ethoxybenzyl)(methyl)amino)acetate		364.1	methyl 2-(methylamino)acetate

INTERMEDIATE 174: dimethyl (3-(benzyloxy)-5-bromophenyl)phosphonate

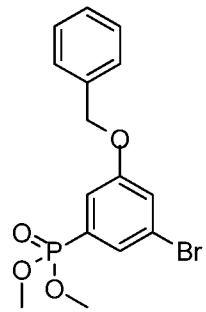


Step 1: 1-(benzyloxy)-3-bromo-5-iodobenzene



To a solution of 3-bromo-5-iodophenol (1.5 g, 5 mmol) in DMF (10 ml) was added K_2CO_3 (0.83 g, 6 mmol). The reaction mixture was then heated at 50 °C for 30 minutes before the addition of KI (0.08 g, 0.5 mmol) and (bromomethyl)benzene (0.93 g, 5.4 mmol). The reaction continued to stir for 18 hours at 65 °C. The mixture was poured into water and extracted with EtOAc (3 x 100 ml). The combined organic layers were washed with water (3 x 50 ml), brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant residue was purified via flash column chromatography (0-10 % EtOAc:Hexane) to afford the title compound as a yellow oil (1.3 g, 50 % yield). MS (m/z) 391.3 ($M+H^+$).

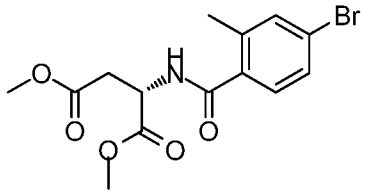
Step 2: dimethyl (3-(benzyloxy)-5-bromophenyl)phosphonate



To a solution of dimethyl (3-(benzyloxy)-5-bromophenyl)phosphonate (1.39 g, 3.57. mmol) in 1,4-dioxane (16 ml) were added trimethyl phosphite (0.99 g, 8.04 mmol) and diacetoxypalladium (0.12 g, 0.54 mmol). The reaction was heated at 105 °C for 5 hours. The reaction was monitored via LCMS to show the reaction was complete. The reaction mixture was filtered, concentrated and purified by flash column chromatography

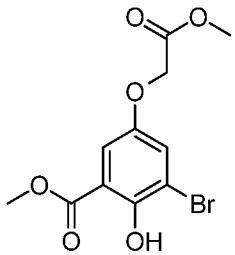
(0-5 % MeOH/DCM) to afford the title compound as a white solid (1.0 g, 75 % yield). MS (m/z) 371.9 ($M+H^+$).

INTERMEDIATE 175: (S)-dimethyl 2-(4-bromo-2-methylbenzamido)succinate

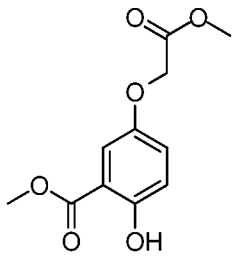


To a solution containing (S)-dimethyl 2-aminosuccinate hydrochloride (5.51 g, 27.9 mmol) and 4-bromo-2-methylbenzoic acid (5 g, 23.25 mmol) in N,N-dimethylformamide (100 ml) was added HATU (10.61 g, 27.9 mmol) followed by DIPEA (12.18 ml, 69.8 mmol). The reaction stirred for 18 hours. The reaction mixture was diluted with NH_4Cl aq. solution, extracted with ethyl ether (3 x 100 ml), dried over $MgSO_4$, filtered and concentrated onto SiO_2. Purification via flash column chromatography (0-50% EtOAc/Hexanes) afforded the titled compound as a colorless solid (6.0 g, 74 % yield). MS (m/z) 360.0 ($M+H^+$).

INTERMEDIATE 176: methyl 3-bromo-2-hydroxy-5-(2-methoxy-2-oxoethoxy)benzoate



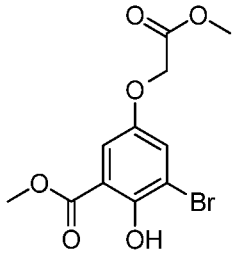
Step 1: methyl 2-hydroxy-5-(2-methoxy-2-oxoethoxy)benzoate



To a solution containing methyl 2,5-dihydroxybenzoate (25 g, 149 mmol) in acetone (600 ml) was added potassium carbonate (41.1 g, 297 mmol) followed by methyl 2-bromoacetate (14.07 mL, 149 mmol). The reaction was stirred for 18 hours at 55 °C. The mixture was filtered, concentrated and redissolved in DCM, then washed with water and brine. The organic phase was separated and passed through a hydrophobic frit,

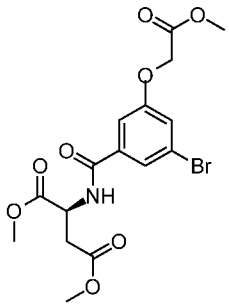
concentrated onto SiO_2 and purified by flash chromatography (Isco, 120 g column, 0-2% EtOAc/DCM) to afford the title compound as a colorless solid (16.2 g, 45.2 % yield). MS (m/z) 242.0 ($M+H^+$).

Step 2: methyl 3-bromo-2-hydroxy-5-(2-methoxy-2-oxoethoxy)benzoate

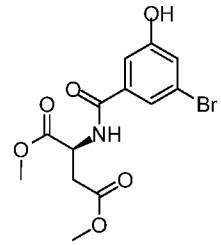


To a solution containing methyl 2-hydroxy-5-(2-methoxy-2-oxoethoxy)benzoate (5 g, 20.82 mmol) in acetic acid (50 mL) was added bromine (1.180 mL, 22.90 mmol) and the mixture stirred for 5 hours. Additional bromine (0.590 mL, 11.45 mmol) was added and the reaction stirred for 18 hours. The reaction mixture was poured into water upon which precipitation was formed. The precipitate was collected via filtration of the mixture. The solid was dissolved in DCM and concentrated onto SiO_2. Purification by flash chromatography (Isco, 40 g column, 0-30% EtOAc/hexane) afforded the title product as a yellow oil (4.0 g, 63 % yield). MS (m/z) 320.9 ($M+H^+$).

INTERMEDIATE 177: (S)-dimethyl 2-(3-bromo-5-(2-methoxy-2-oxoethoxy)benzamido)succinate



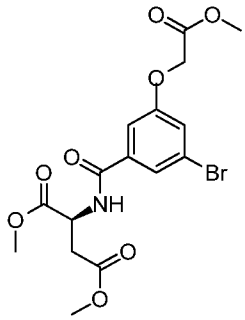
Step 1: (S)-dimethyl 2-(3-bromo-5-hydroxybenzamido)succinate



To a solution containing (S)-dimethyl 2-aminosuccinate hydrochloride (5.46 g, 27.6 mmol) and 3-bromo-5-hydroxybenzoic acid (5 g, 23.04 mmol) in N,N-

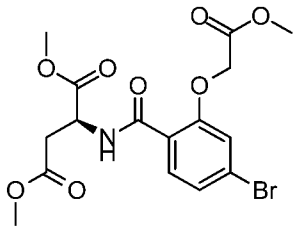
dimethylformamide (100 ml) was added DIPEA (12.07 ml, 69.1 mmol) followed by HATU (10.51 g, 27.6 mmol). The reaction was stirred for 18 hours. The reaction mixture was diluted with NH_4Cl aq. soln., extracted with ethyl ether (3 x 50 mL), dried over $MgSO_4$, filtered and concentrated onto SiO_2. Purification by flash chromatography (Isco, 80 g column, 0-50% EtOAc/hexanes) afforded the title compound as a colorless glass (6.0 g, 79 % yield). MS (m/z) 361.9 ($M+H^+$).

Step 2: (S)-dimethyl 2-(3-bromo-5-(2-methoxy-2-oxoethoxy)benzamido)succinate

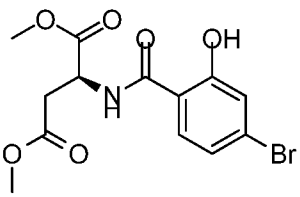


To a solution of (S)-dimethyl 2-(3-bromo-5-hydroxybenzamido)succinate (6.54 g, 18.16 mmol) in acetone (65 mL) was added potassium carbonate (5.02 g, 36.3 mmol) and methyl 2-bromoacetate (1.891 ml, 19.97 mmol). The reaction stirred for 18 hours. The reaction was diluted with water and extracted with EtOAc (3 x 100 ml). The organic layers were collected, dried over $MgSO_4$, filtered and concentrated onto SiO_2. Purification by flash chromatography (Isco, 80 g column, 0-70% EtOAc/hexanes) afforded the title compound as a colorless glass (7.3 g, 93 % yield). MS (m/z) 432.0 ($M+H^+$).

INTERMEDIATE 178: (S)-dimethyl 2-(4-bromo-2-(2-methoxy-2oxoethoxy)benzamido)succinate

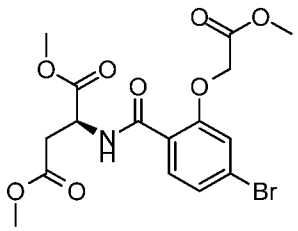


Step 1: (S)-dimethyl 2-(4-bromo-2-hydroxybenzamido)succinate



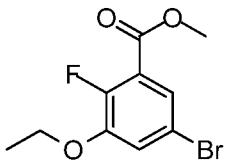
To a solution of (S)-dimethyl 2-aminosuccinate hydrochloride (5.46 g, 27.6 mmol) and 4-bromo-2-hydroxybenzoic acid (5 g, 23.04 mmol) in N,N-dimethylformamide (50 ml) was added DIPEA (12.07 ml, 69.1 mmol) followed by 1H-benzo[d][1,2,3]triazol-1-ol (3.74 g, 27.6 mmol) and EDC (5.30 g, 27.6 mmol). The reaction mixture was stirred for 18 hours. The reaction mixture was diluted with NH_4Cl aq. soln. and extracted with ethyl ether (3 x 50 ml). The organics were collected, dried over $MgSO_4$, filtered and concentrated onto SiO_2. Purification by flash chromatography (Isco, 80 g column, 0-50% EtOAc/hexanes) afforded the title compound as a yellow glass (3.1 g, 37.2 % yield). MS (m/z) 362.0 ($M+H^+$).

Step 2: (S)-dimethyl 2-(4-bromo-2-(2-methoxy-2oxoethoxy)benzamido)succinate

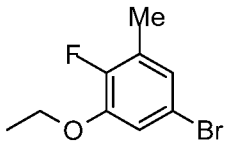


To a solution containing (S)-dimethyl 2-(4-bromo-2-hydroxybenzamido)succinate (3.09 g, 8.58 mmol) in acetone (40 ml) was added methyl 2-bromoacetate (0.893 ml, 9.44 mmol) and potassium carbonate (2.371 g, 17.16 mmol). The reaction mixture was stirred for 3 hours. The reaction was diluted with water and extracted with EtOAc (3 x 50 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated onto SiO_2. Purification by flash chromatography (Isco, 40g column, 0-70% ethyl EtOAc/hexanes) afforded the title compound as a colorless glass (3.5 g, 95 % yield). MS (m/z) 434.1 ($M+H^+$).

INTERMEDIATE 179: methyl 5-bromo-3-ethoxy-2-fluorobenzoate



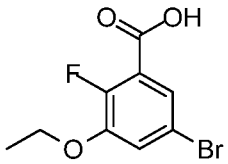
Step 1: 5-bromo-1-ethoxy-2-fluoro-3-methylbenzene



5-bromo-2-fluoro-3-methylphenol (2 g, 9.75 mmol) was dissolved in tetrahydrofuran (31.6 ml) and treated at RT with sodium hydride (0.429 g, 10.73 mmol).

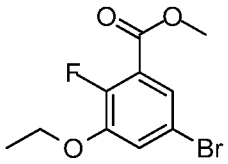
The reaction mixture was stirred for 30 minutes and then treated with iodoethane (0.867 ml, 10.73 mmol). The reaction was heated to 55 °C for 3 days. The reaction mixture was then cooled to RT, quenched with sat. aq. ammonium chloride solution, and allowed to stir for 15 minutes. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 ml). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The resultant oil was purified via flash column chromatography (10% EtOAc/hexanes). The desired fractions were combined and concentrated to afford the title compound (77 mg, 34 % yield). MS (m/z) 230.1($M+H^+$).

Step 2: 5-bromo-3-ethoxy-2-fluorobenzoic acid



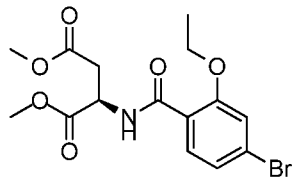
5-bromo-1-ethoxy-2-fluoro-3-methylbenzene (777 mg, 3.33 mmol) was dissolved in pyridine (3334 µl) and water (3334 µl) and treated with potassium permanganate (2213 mg, 14.00 mmol) at 90 °C for 18 hours. The reaction was cooled to rt, filtered through celite, and acidified to pH <4. A white precipitate formed which was collected via filtration. The white solid was dissolved in EtOAc, dried over $MgSO_4$, filtered, and concentrated to afford the title compound as a white solid (132 mg, 15 % yield). The product was used directly in the next reaction without further purification.

Step 3: methyl 5-bromo-3-ethoxy-2-fluorobenzoate



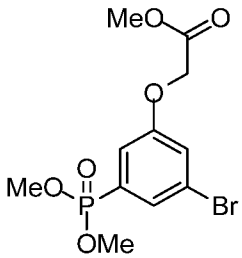
5-bromo-3-ethoxy-2-fluorobenzoic acid (132 mg, 0.50 mmol) was dissolved in acetonitrile (2.5 ml), treated with potassium carbonate (208 mg, 1.51 mmol), and heated to 80 °C for 18 hours. The reaction was cooled to RT, diluted with ether, and filtered through celite. The residual solid was washed with ether, and the filtrates were combined and purified via flash column chromatography (10-20% EtOAc/Hexanes) to afford the title compound as a white solid (103 mg, 74% yield). MS (m/z) 276.9 ($M+H^+$).

INTERMEDIATE 180: (R)-dimethyl 2-(4-bromo-2-ethoxybenzamido)succinate

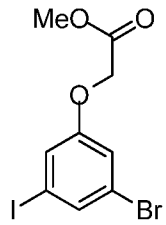


2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (3.39 ml, 5.69 mmol) was added to a suspension of (R)-dimethyl 2-aminosuccinate (0.61 g, 3.79 mmol), 4-bromo-2-ethoxybenzoic acid (0.93 g, 3.79 mmol) and triethylamine (1.59 ml, 11.38 mmol) in DCM (15 ml) at 25 °C. After 2 hours, the reaction was diluted with DCM and washed with water, 1N HCl and saturated $NaHCO_3$ solution. The organic layer was separated, concentrated and purified via flash column chromatography (12 g column, 0-30% EtOAC:EtOH 3:1/Hexanes) to obtain the title compound as a white solid (0.56 g, 34.2 % yield). MS (m/z) 388.0 ($M+H^+$).

INTERMEDIATE 181: methyl 2-(3-bromo-5-(dimethoxyphosphoryl)phenoxy)acetate

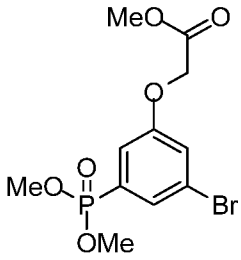


Step 1: methyl 2-(3-bromo-5-iodophenoxy)acetate



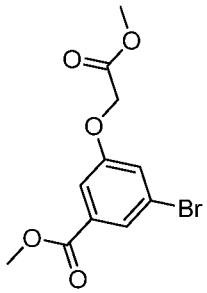
To a round bottom flask equipped with a teflon stir bar was added 3-bromo-5-iodophenol (2.06 g, 6.89 mmol), methyl 2-bromoacetate (0.979 ml, 10.34 mmol), acetonitrile (15.0 ml), and K_2CO_3 (4.76 g, 34.5 mmol). A water cooled-condenser, attached to a N_2 outlet was attached to the flask and the reaction heated to 80 ºC. The reaction was cooled to room temperature and quenched with water (40 ml). The solution was extracted with EtOAc (2 x 40 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford the titled compound (2.0 g, 78 % yield crude). MS (m/z) 372.7 ($M+H^+$).

Step 2: methyl 2-(3-bromo-5-(dimethoxyphosphoryl)phenoxy)acetate



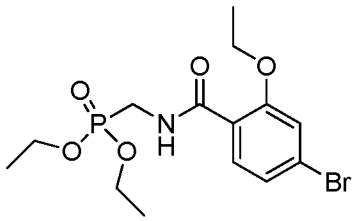
To a round bottomed flask equipped with a teflon stir bar was added methyl 2-(3-bromo-5-iodophenoxy)acetate (2.0 g, 5.39 mmol), trimethyl phosphite (1.4 ml, 13.47 mmol), 1,4-dioxane (12.77 ml), and $Pd(OAc)_2$ (0.242 g, 1.08 mmol). A water cooled condenser with a N_2 outlet was attached to the top of the flask and the reaction heated to reflux for 18 hours. The reaction was poured into water and extracted with EtOAc (3 x 50 ml). The combined organic layers were washed with water, brine, then dried over sodium sulfate, filtered and concentrated. The resultant orange residue was purified by flash chromatography (ISCO, 80 g, 0% to 10% MeOH/DCM) to afford the titled compound as a yellow solid (2.3 g, 109 % yield). MS (m/z) 354.9 ($M+H^+$).

INTERMEDIATE 182: methyl 3-bromo-5-(2-methoxy-2-oxoethoxy)benzoate



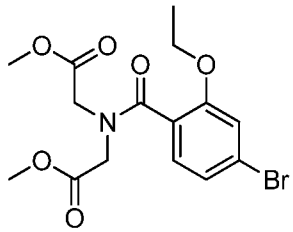
To a solution of methyl 3-bromo-5-hydroxybenzoate (34 g, 147 mmol), K_2CO_3 (61 g, 441 mmol), in N,N-Dimethylformamide (DMF) (340 mL) was added methyl 2-bromoacetate (22.5 g, 147 mmol). The reaction stirred at RT under nitrogen for 2 hours upon which the reaction was poured into ice water. A white precipitate formed which was filtered, washed with water, and dried to afford the title compound as a white solid (36 g, 81 % yield) MS (m/z) 304.2 ($M+H^+$).

INTERMEDIATE 183: diethyl ((4-bromo-2-ethoxybenzamido)methyl)phosphonate



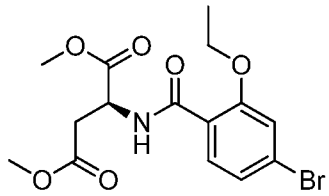
4-bromo-2-ethoxybenzoic acid (3 g, 12.24 mmol), EDC (2.82 g, 14.69 mmol), diethyl(aminomethyl)phosphonate, oxalic acid salt (3.15 g, 12.24 mmol), 1-hydroxy-7-azabenzotriazole (2.0 g, 14.69 mmol) and N-methylmorpholine (5.38 ml, 49.0 mmol) were dissolved in DCM (76 ml). The reaction mixture was stirred at room temperature for 1 hour. The reaction was then concentrated and the residue purified by flash chromatography (ISCO, 120 g column, 0-100% ethyl acetate/hexanes over 45 minutes) to give the title compound as an off white solid (3.0 g, 62.2% yield). MS (m/z) 395.9 (M^+).

INTERMEDIATE 184: dimethyl 2,2'-((4-bromo-2-ethoxybenzoyl)azanediyl)diacetate



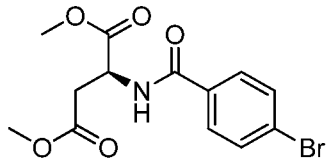
4-bromo-2-ethoxybenzoic acid (0.5 g, 2.040 mmol), dimethyl 2,2'-azanediyldiacetate (0.33 g, 2.040 mmol), EDC (0.39 g, 2.040 mmol),1-hydroxy-7-azabenzotriazole (0.31 g, 2.04 mmol) and N-methylmorpholine (0.22 ml, 2.04 mmol) were dissolved in DMF. The reaction mixture was stirred at room temperature for 18 hours. The reaction was then poured into water and diluted with ethyl acetate (50 ml). The layers were separated and the aqueous layer was washed twice with DCM (50 ml each). The layers were separated, and the organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (ISCO, 0-50% ethyl acetate/hexanes) to give the title compound (0.64 g, 81% yield). MS (m/z) 390.3 (M^+).

INTERMEDIATE 185: (S)-dimethyl 2-(4-bromo-2-ethoxybenzamido)succinate



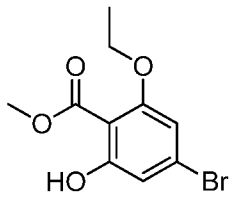
T3P, 50% wt in EtOAc (150 ml, 252 mmol) was added dropwise (in 1hr 10 minutes) to a suspension of 4-bromo-2-ethoxybenzoic acid (43.27 g, 177 mmol), (S)-dimethyl 2-aminosuccinate, hydrochloride (36.6 g, 185 mmol), and triethylamine (73.8 ml, 530 mmol) in DCM (420 ml) in a water bath to prevent warming. After addtion completed, the reaction mixture was stirred at room temperature for 2 hours. The reaction was then diluted with DCM and water. The layers were separated and the organics washed with 1N HCl and then sat. $NaHCO_3$. The layers were separated, the organic layer was dried over $MgSO_4$, concentrated and the residue split in half and purified by flash chromatography (ISCO, 330 g column, 0-50% EtOAc/hexanes) to obtain the title compound as a yellow oil (62.7 g, 91 % yield). MS (m/z) 390.0 (M^+).

INTERMEDIATE 186: (S)-dimethyl 2-(4-bromobenzamido)succinate



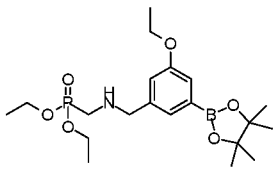
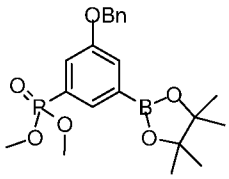
2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (4.40 ml, 7.39 mmol) was added to a suspension of (S)-dimethyl 2-aminosuccinate (1.0 g, 4.92 mmol), 4-bromobenzoic acid (1.0 g, 4.92 mmol) and TEA (2.06 ml, 14.77 mmol) in DCM (10 ml) in a water bath to prevent warming. The reaction mixture was stirred for 2 hours at 25 °C. The reaction was diluted with DCM and water. The layers were separated and the organic layer was washed with 1N HCl and then saturated $NaHCO_3$ solution, dried, and concentrated to obtain the title compound as a white solid (1.67 g, 98 % yield). MS (m/z) 344.0 (M^+).

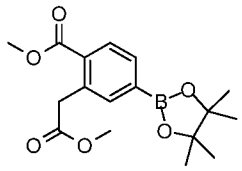
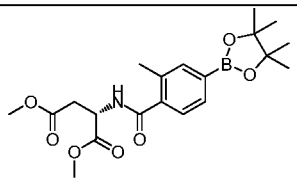
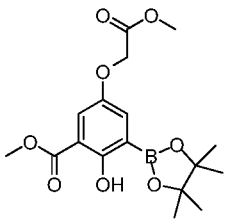
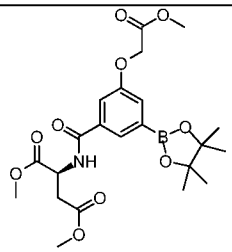
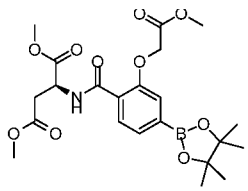
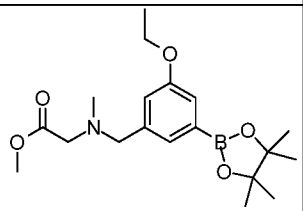
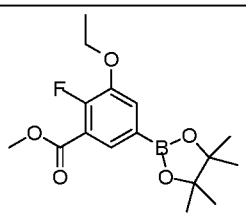
INTERMEDIATE 187: methyl 4-bromo-2-ethoxy-6-hydroxybenzoate

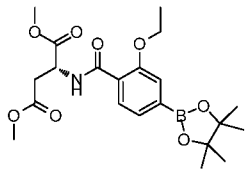
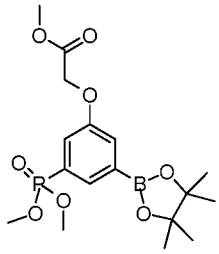
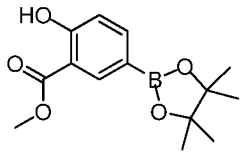
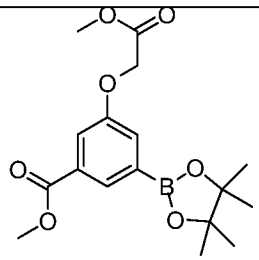


Methyl 4-bromo-2-ethoxybenzoate (3.0 g, 11.58 mmol), potassium persulfate (3.44 g, 12.74 mmol), and dichloro(p-cymene)ruthenium(II) dimer (177 mg, 0.29 mmol) were combined in TFA (20.26 ml) and trifluoroacetic anhydride (8.68 ml). The reaction mixture was stirred overnight at 80 °C under nitrogen. The reaction was cooled to room temperature and added dropwise to a solution of 10% sodium carbonate cooled to 0 °C. The neutral solution was warmed to room temperature and diluted with DCM (200 ml). The layers were separated and the aqueous layer was back extracted twice more with DCM (200 ml). The combined organics were dried over sodium sulfate, filtered, concentrated half-way and the residue was purified by flash chromatography (ISCO, 5-50% EtOAc/Hexanes over 35 minutes) to obtain the title compound as a white solid (250 mg, 7.85% yield).

INTERMEDIATES 188-200 were prepared from the indicated bromide in general by methods analogous to those described for Intermediate 55. Reaction times vary from 3.5 hours to 12 hours.

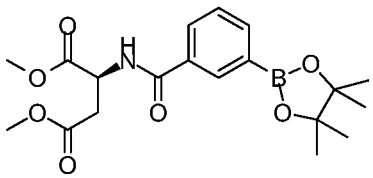
#	Name	Structure	MS (m/z)	Bromide
188	diethyl (((3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)amino)methyl) phosphonate		428.1	diethyl (((3-bromo-5-ethoxybenzyl)amino)methyl)phosphonate
189	dimethyl (3-(benzyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonate		419.1	dimethyl (3-(benzyloxy)-5-bromophenyl)phosphonate

190**	methyl 2-(2-methoxy-2-oxoethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate		335.1	methyl 4-bromo-2-(2-methoxy-2-oxoethyl)benzoate
191	(S)-dimethyl 2-(2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)succinate		406.4	(S)-dimethyl 2-(4-bromo-2-methylbenzamido)succinate
192	methyl 2-hydroxy-5-(2-methoxy-2-oxoethoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate		367.1	methyl 3-bromo-2-hydroxy-5-(2-methoxy-2-oxoethoxy)benzoate
193	methyl 2-hydroxy-5-(2-methoxy-2-oxoethoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate		480.2	(S)-dimethyl 2-(3-bromo-5-(2-methoxy-2-oxoethoxy)benzamido)succinate
194	(S)-dimethyl 2-(2-(2-methoxy-2-oxoethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)succinate		480.2	(S)-dimethyl 2-(4-bromo-2-(2-methoxy-2-oxoethoxy)benzamido)succinate
195	methyl 2-((3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)(methyl)amino)acetate		364.1	methyl 2-((3-bromo-5-ethoxybenzyl)(methyl)amino)acetate
196	methyl 3-ethoxy-2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate		325.1	methyl 5-bromo-3-ethoxy-2-fluorobenzoate

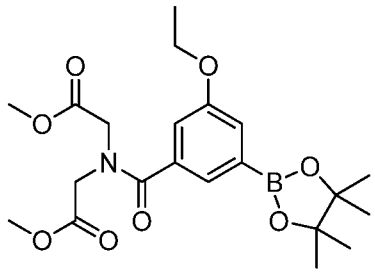
197	(R)-(4-((1,4-dimethoxy-1,4-dioxobutan-2-yl)carbamoyl)-3-ethoxyphenyl)boronic acid		436.2	(R)-dimethyl 2-(4-bromo-2-ethoxybenzamido)succinate
198	methyl 2-(3-(dimethoxyphosphoryl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)acetate		401.1	methyl 2-(3-bromo-5-(dimethoxyphosphoryl)phenoxy)acetate
199**	methyl 2-hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate		279.0	methyl 4-bromo-2-hydroxybenzoate
200	methyl 3-(2-methoxy-2-oxoethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate		351.2	methyl 3-bromo-5-(2-methoxy-2-oxoethoxy)benzoate

** Reaction performed in Biotage microwave reactor for 30 minutes versus thermally.

INTERMEDIATE 201 was prepared from (S)-dimethyl 2-aminosuccinate, hydrochloride and the indicated acid by methods analogous to those described for Intermediate 56.

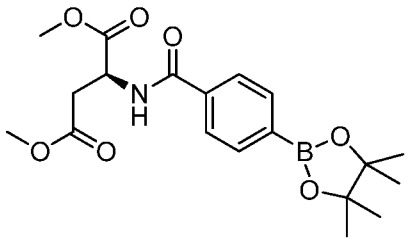
#	Name	Structure	MS (m/z) ($M+H^+$)	Acid
201	(S)-dimethyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)succinate		392.4	3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid

INTERMEDIATE 202: Dimethyl 2,2'-((3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl)azanediyl)diacetate



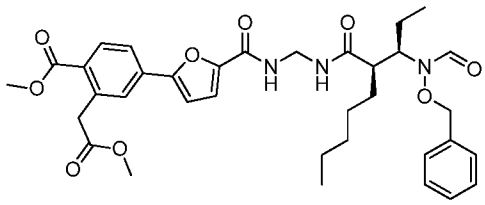
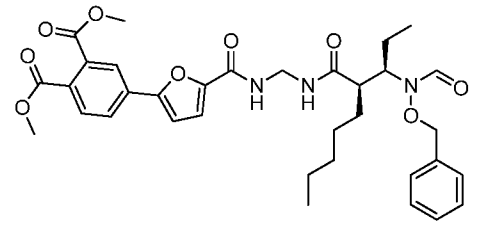
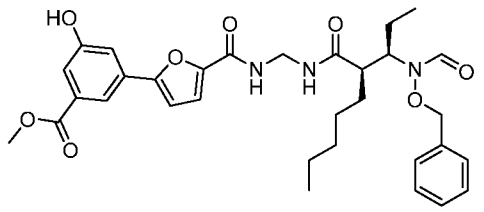
3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoicacid (350 mg, 1.198 mmol), dimethyl 2,2'-azanediyldiaceate, hydrochloride (237 mg, 1.2 mmol), EDC (276 mg, 1.438 mmol), 1-hydroxy-7- azabenzotriazole (196 mg, 1.44 mmol) and N-methylmorpholine (527 µl, 4.79 mmol) were dissolved in DMF (7.46 ml). The reaction mixture was stirred at room temperature for 18 hours. The reaction was poured slowly into cold stirring water and diluted with ethyl acetate. The layers were separated and the aqueous layer was back extracted twice more with ethyl acetate. The combined organics were washed with brine, dried over sodium sulfate, filtered, concentrated and the residue purifed by flash chromatography (ISCO, 12 g column, 10-70% EtOAc/Hexanes over 15 min) to obtain the title compound as a colorless oil (216 mg, 41.4% yield). MS (m/z) 436.3 (M^+).

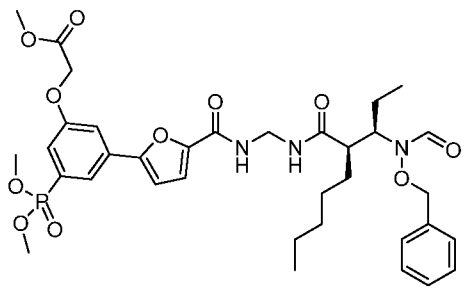
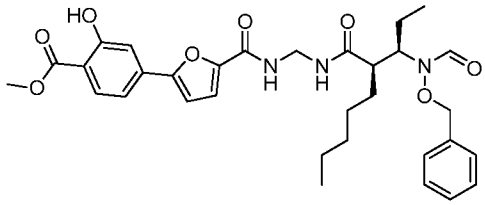
INTERMEDIATE 203: (S)-Dimethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)succinate



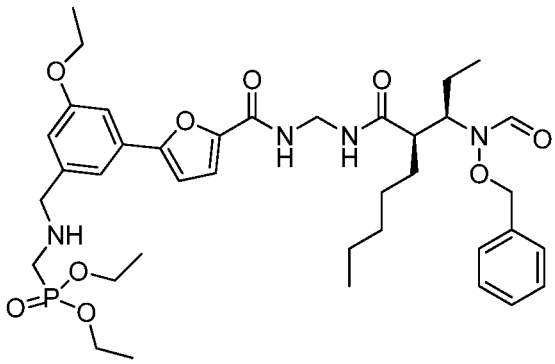
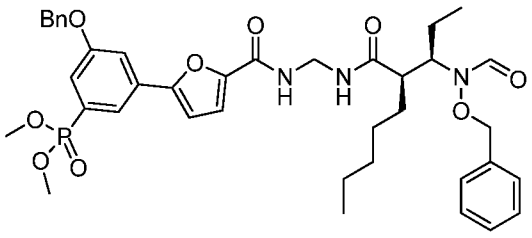
(S)-dimethyl 2-(4-bromobenzamido)succinate (1.67 g, 4.85 mmol) was dissolved in 1,4-dioxane (24.26 ml) and followed by addition of bis(pinacolato)diboron (1.51 g, 5.82 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.16 g, 0.19 mmol) and potassium acetate (1.91 g, 19.41 mmol). The reaction mixture was heated to 100 °C overnight. The reaction was diluted with EtOAc and water and then filtered. The layers of the filtrate were separated and the aqueous layer was back extracted with EtOAc three times. The combined organics were dried and concentrated to obtain the title compound as a black oil (0.53 g, 28 % yield). MS (m/z) 392.1 (M^+).

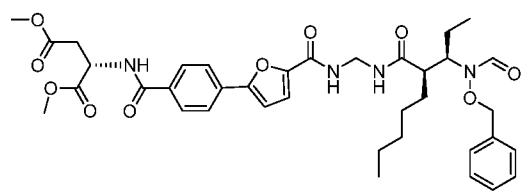
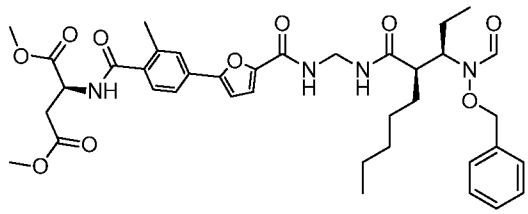
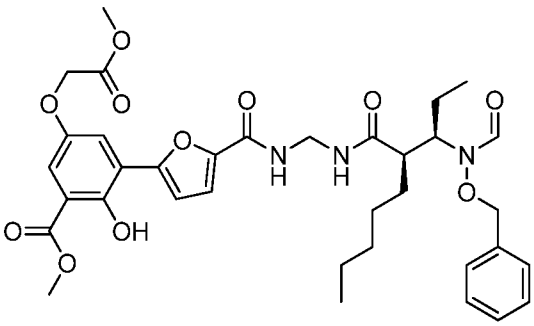
INTERMEDIATES 204-208 were prepared from N-(((R)-2-((R)-1-(N-(benzyloxy)formamido) propyl)heptanamido)methyl)-5-bromofuran-2-carboxamide and the indicated boronate by methods analogous to those described for Intermediate 78.

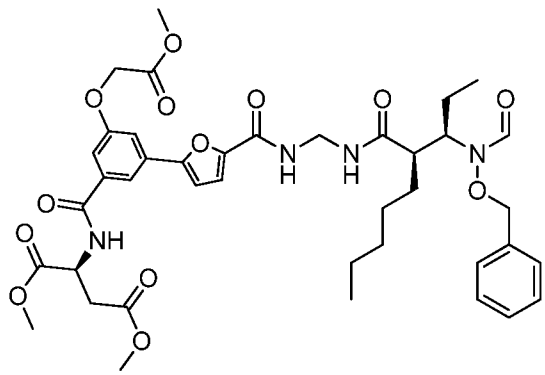
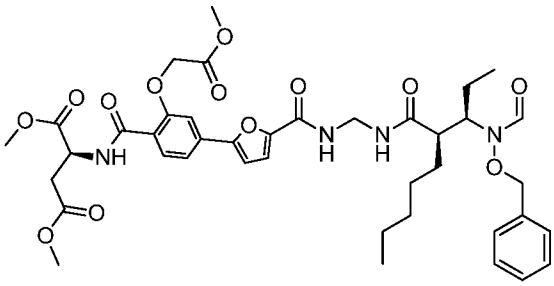
#	Name	Structure	MS (m/z) ($M+H^+$)	Boronate
204	methyl 4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)-2-(2-methoxy-2-oxoethyl)benzoate		650.2	methyl 2-(2-methoxy-2-oxoethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
205	dimethyl 4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phthalate		634.2	(3,4-bis(methoxycarbonyl)phenyl)boronic acid
206	methyl 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-hydroxybenzoate		594.2	methyl 3-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

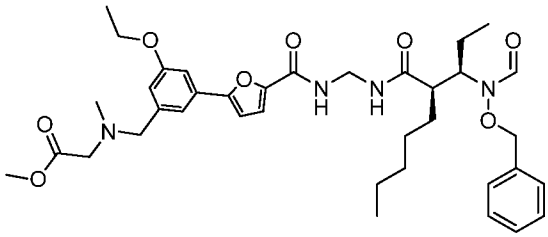
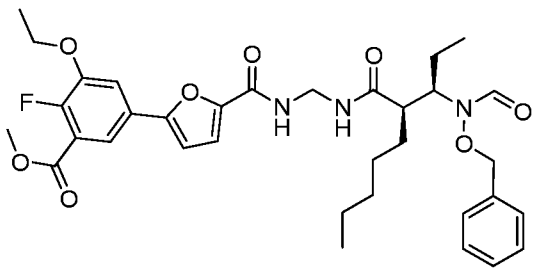
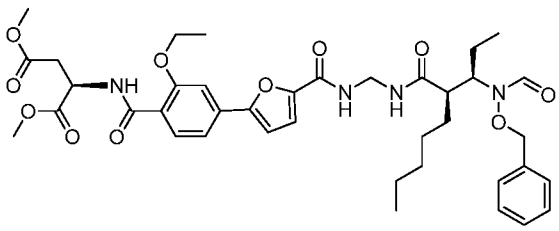
207	methyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-(dimethoxyphosphoryl)phenoxy)acetate		716.2	methyl 2-(3-(dimethoxyphosphoryl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)acetate
208	methyl 4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-hydroxybenzoate		594.2	methyl 2-hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

INTERMEDIATES 209-218 were prepared from N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)-5-bromofuran-2-carboxamide and the indicated boronate by methods analogous to those described for Intermediate 147.

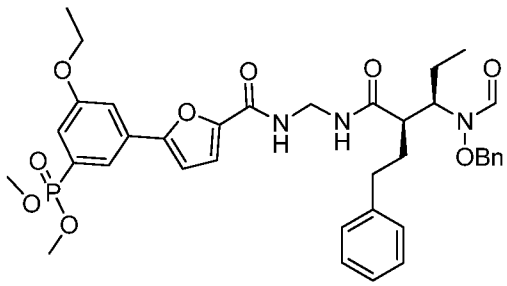
#	Name	Structure	MS (m/z) ($M+H^+$)	Boronate
209	diethyl (((3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzyl)amino)methyl)phosphonate		743.2	diethyl (((3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)amino)methyl)phosphonate
210	dimethyl (3-(benzyloxy)-5-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate		N/A	dimethyl (3-(benzyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonate

211	(S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinate		707.4	(S)-dimethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)succinate
212	(S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzamido)succinate		721.2	(S)-dimethyl 2-(2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)succinate
213	methyl 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-hydroxy-5-(2-methoxy-2-oxoethoxy)benzoate		682.3	methyl 2-hydroxy-5-(2-methoxy-2-oxoethoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

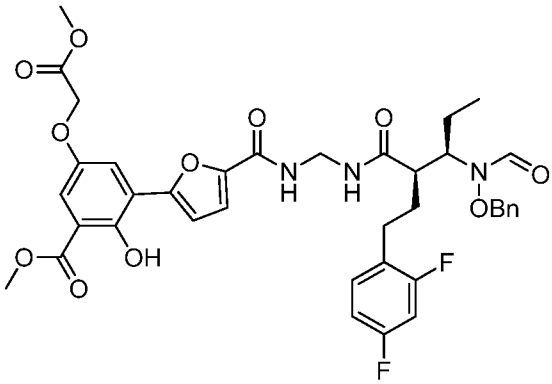
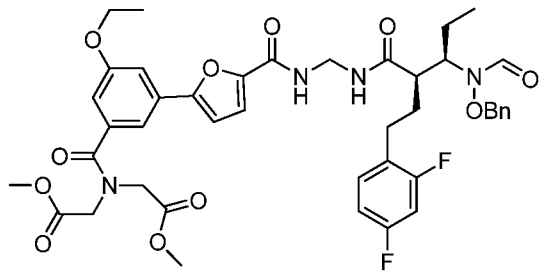
214	(S)-dimethyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-(2-methoxy-2-oxoethoxy)benzamido)succinate		795.3	methyl 2-hydroxy-5-(2-methoxy-2-oxoethoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
215	(S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-(2-methoxy-2-oxoethoxy)benzamido)succinate		795.3	(S)-dimethyl 2-(2-(2-methoxy-2-oxoethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)succinate

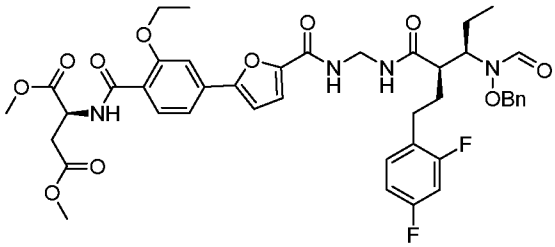
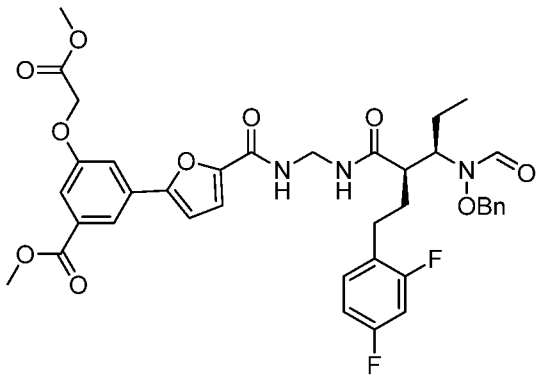
216	methyl 2-((3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzyl)(methyl)amino)acetate		679.2	methyl 2-((3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)(methyl)amino)acetate
217	methyl 5-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-3-ethoxy-2-fluorobenzoate		640.3	methyl 3-ethoxy-2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
218	(R)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)succinate		752.4	(R)-(4-((1,4-dimethoxy-1,4-dioxobutan-2-yl)carbamoyl)-3-ethoxyphenyl)boronic acid

INTERMEDIATE 219 was prepared from N-(((2R,3R)-3-(N-(benzyloxy)formamido)-2-phenethylpentanamido)methyl)-5-bromofuran-2-carboxamide and the indicated boronate by methods analogous to those described for Intermediate 147.

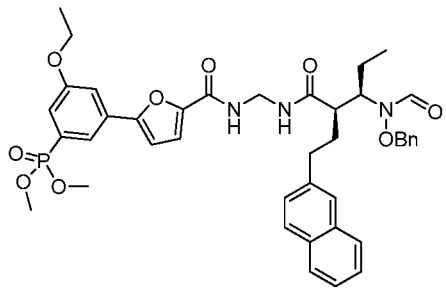
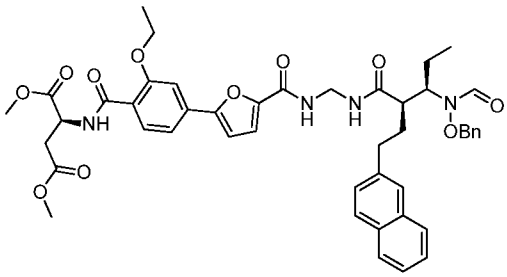
#	Name	Structure	MS (m/z) ($M+H^+$)	Boronate
219	dimethyl (3-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxyphenyl) phosphonate		706.4	dimethyl (3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonate

INTERMEDIATES 220-223 were prepared from N-(((2R,3R)-3-(N-(benzyloxy)formamido)-2-(2,4-difluorophenethyl)pentanamido)methyl)-5-bromofuran-2-carboxamide and the indicated boronate by methods analogous to those described for Intermediate 147.

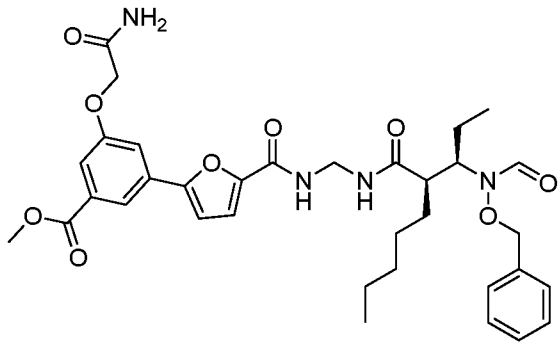
#	Name	Structure	MS (m/z) ($M+H^+$)	Boronate
220	methyl 3-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-(2,4-difluorophenethyl)pentanamido)methyl)carbamoyl)furan-2-yl)-2-hydroxy-5-(2-methoxy-2-oxoethoxy)benzoate		752.4	(2-hydroxy-5-(2-methoxy-2-oxoethoxy)-3-(methoxycarbonyl)phenyl)boronic acid
221	dimethyl 2,2'-((3-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-(2,4-difluorophenethyl)pentanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoyl)azanediyl)diacetate		821.3	dimethyl 2,2'-((3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl)azanediyl)diacetate

222	(S)-dimethyl 2-(4-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-(2,4-difluorophenethyl)pentanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)succinate		821.3	(S)-dimethyl 2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)succinate
223	methyl 3-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-(2,4-difluorophenethyl)pentanamido)methyl)carbamoyl)furan-2-yl)-5-(2-methoxy-2-oxoethoxy)benzoate		736.3	methyl 3-(2-methoxy-2-oxoethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

INTERMEDIATES 224-225 were prepared from N-(((2R,3R)-3-(N-(benzyloxy)formamido)-2-(2-(naphthalen-2-yl)ethyl)pentanamido)methyl)-5-bromofuran-2-carboxamide and the indicated boronate by methods analogous to those described for Intermediate 147.

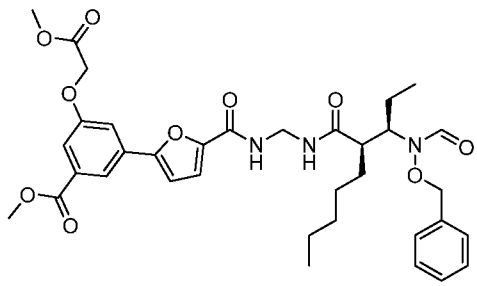
#	Name	Structure	MS (m/z) ($M+H^+$)	Boronate
224	dimethyl (3-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-(2-(naphthalen-2-yl)ethyl)pentanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxyphenyl)phosphonate		756.3	dimethyl (3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonate
225	(S)-dimethyl 2-(4-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-(2-(naphthalen-2-yl)ethyl)pentanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)succinate		835.4	(S)-dimethyl 2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)succinate

INTERMEDIATE 226: methyl 3-(2-amino-2-oxoethoxy)-5-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate

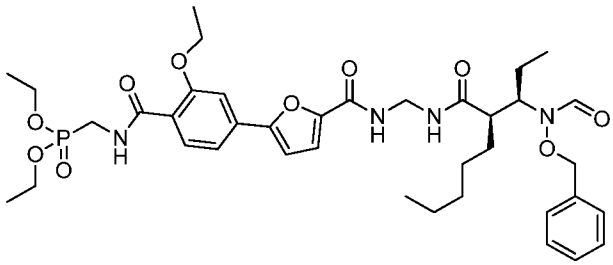


A mixture of methyl 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-hydroxybenzoate (0.25 g, 0.42 mmol), 2-bromoacetamide (0.116 g, 0.842 mmol), and K_2CO_3 (0.29 g, 2.106 mmol) in acetonitrile (1.50 ml) was heated at 80 ºC for 1 hour. The reaction was then cooled to RT and concentrated in-vacuo. The residue was partitioned between H_2O and EtOAc and the organic layer was separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to afford a white solid. The solid was purified by flash column chromotography (20-100%EtOAc:Hexane) to afford the titled compound.(0.22 g, 80 % yield) as white solid. MS (m/z) 651.2 (M+H+).

INTERMEDIATE 227 was prepared from N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)-5-bromofuran-2-carboxamide and the indicated bromide by the methods analogous to those described for Intermediate 226.

#	Name	Structure	MS (m/z) ($M+H^+$)	Bromide
227	methyl 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-(2-methoxy-2-oxoethoxy)benzoate		666.3	methyl 2-bromoacetate

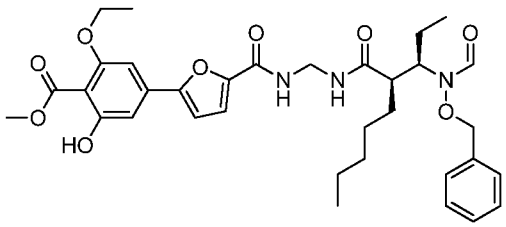
INTERMEDIATE 228: diethyl ((4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)methyl)phosphonate



A solution of diethyl ((4-bromo-2-ethoxybenzamido)methyl)phosphonate (1.8 g, 4.57 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (1.39 g, 5.48 mmol), potassium acetate (1.79 g, 18.26 mmol), and $PdCl_2$(dppf)-CH_2Cl_2 (0.15 g, 0.18 mmol) refluxed in 1,4-dioxane (11.42 ml) for 15 hour under nitrogen with a condensor. The reaction was cooled to RT and to the solution was added N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)-5-bromofuran-2-carboxamide (2.39 g, 4.57 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.37 g, 0.46 mmol), and 2M Na_2CO_3 (11.42 ml). The reaction stirred at 50 °C for 1 hour equipped with a condensor. The reaction was

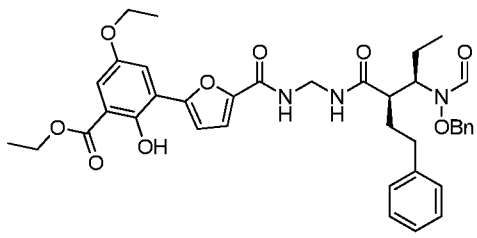
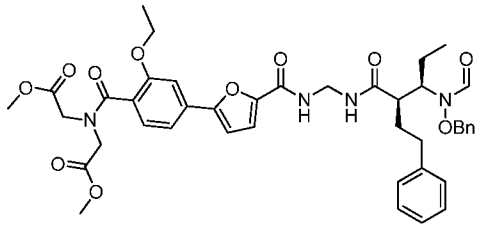
cooled to RT, poured into water and extracted into EtOAc (4 x 100 ml). The combined organic layers were collected, washed with brine, dried over sodium sulfate and decolorizing carbon, filtered thru a plug of celite and concentrated to an orange residue. The residue was redissolved in DCM and purified via flash column chromatography (120 g column, 0-10%MeOH/EtoAc over 45minutes)to afford an off-white solid as the title compound (2.0 g, 58 % yield). MS (m/z) 757.2 (M+H+).

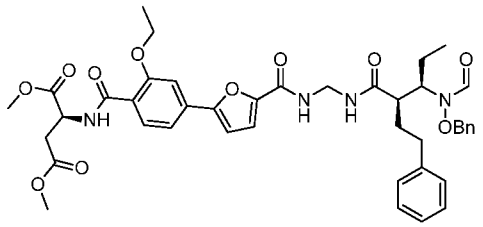
INTERMEDIATE 229 was prepared from N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)-5-bromofuran-2-carboxamide and the indicated bromide by the methods analogous to those described for Intermediate 228.

#	Name	Structure	MS (m/z) ($M+H^+$)	Bromide
229	methyl 4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxy-6-hydroxybenzoate		638.2	methyl 4-bromo-2-ethoxy-6-hydroxybenzoate

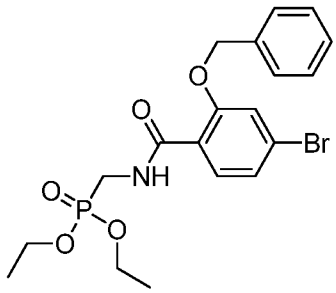
INTERMEDIATES 230-232 were prepared from N-(((2R,3R)-3-(N-(benzyloxy)formamido)-2-phenethylpentanamido)methyl)-5-bromofuran-2-carboxamide and the indicated bromide by the methods analogous to those described for Intermediate 228.

5

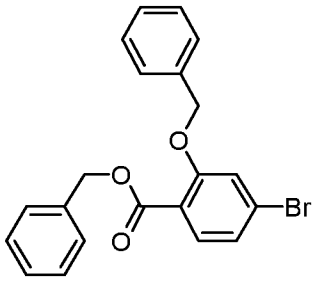
#	Name	Structure	MS (m/z) ($M+H^+$)	Bromide
230	ethyl 3-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxy-2-hydroxybenzoate		686.8	bromo-5-ethoxy-2-hydroxybenzoate
231	dimethyl 2,2'-((4-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzoyl)azanediyl)diacetate		785.7	(dimethyl 2,2'-((4-bromo-2-ethoxybenzoyl)azanediyl)diacetate

232	(S)-dimethyl 2-(4-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)succinate		785.4	(S)-dimethyl 2-(4-bromo-2-ethoxybenzamido)succinate

INTERMEDIATE 233: diethyl ((2-(benzyloxy)-4-bromobenzamido)methyl)phosphonate

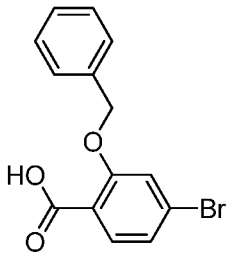


Step 1: benzyl 2-(benzyloxy)-4-bromobenzoate



Benzyl bromide (6.03 ml, 50.7 mmol) was added to a mixture of 4-bromo-2-hydroxybenzoic acid (5.00 g, 23.04 mmol) and potassium carbonate (10.51 g, 76 mmol) in DMF (23.04 ml). The mixture was stirred at room temperature for 2 days. Water and EtOAc were added and the organic layer was washed with brine (3x). The combined aqueous layer was extracted with EtOAc and the organics were combined and dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (0-40% EtOAc/Hex) to give the title compound (8.24 g, 90 % yield). MS (*m/z*) 397.0 $(M+H)^+$

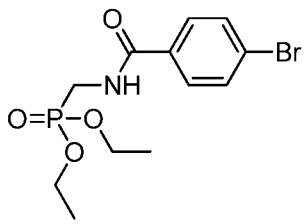
Step 2: 2-(benzyloxy)-4-bromobenzoic acid



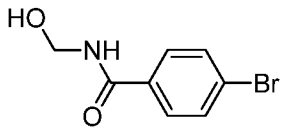
Sodium hydroxide (2 M, 31.3 ml, 62.5 mmol) was added to a stirring solution of benzyl 2-(benzyloxy)-4-bromobenzoate (8.28 g, 20.84 mmol) in MeOH (20.84 ml) and THF (20.84 ml). The resulting mixture was stirred at 50 °C for 2 hr and concentrated to an aqueous mixture. The mixture was neutralized with HCl (3.47 ml, 20.84 mmol) and then concentrated to dryness. The concentrate was triturated with a 1% MeOH/EtOAc solution to give the title compound (8.73 g, 28.4 mmol, 136 % yield). MS (*m/z*) 306.9 $(M+H)^+$

Step 3: diethyl ((2-(benzyloxy)-4-bromobenzamido)methyl)phosphonate
Diethyl (aminomethyl)phosphonate oxalate (2.51 g, 9.77 mmol) was free based using a Silicycle carbonate cartridge eluting with MeOH. After the solution was concentrated to dryness, it was combined with DMF (24.42 ml), 2-(benzyloxy)-4-bromobenzoic acid (1.50 g, 4.88 mmol), EDC (1.40 g, 7.33 mmol) and HOAt (0.80 g, 5.86 mmol) at RT. Next, N-methylmorpholine (1.611 ml, 14.65 mmol) was added to this mixture and it was stirred for 18 hr at RT. Water was added, and the organics were extracted with EtOAc (3x). The combined organic phase was washed with brine (3x), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (0-5% MeOH/EtOAc) to afford the title compound (1.55 g, 3.36 mmol, 68.9 % yield) as a colorless solid. MS (*m/z*) 456.1 $(M+H)^+$

INTERMEDIATE 234: diethyl ((4-bromobenzamido)methyl)phosphonate



Step 1: 4-bromo-N-(hydroxymethyl)benzamide

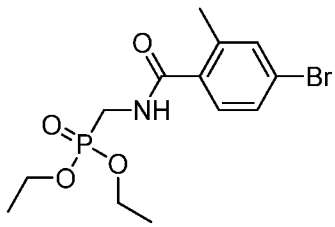


Formaldehyde (24.79 ml, 333 mmol) was added to a stirring mixture of 4-bromobenzamide (4.00 g, 20.00 mmol) and potassium carbonate (0.50 g, 3.62 mmol) in methanol (40.0 ml). The resulting mixture was stirred at RT for 2 days. SiO_2 was then added to the reaction mixture, the mixture was concentrated to dryness, and purified by flash chromatography (0-10% MeOH/DCM) to afford the title compound (2.5 g, 10.8 mmol, 54.0 % yield). MS (*m/z*) 251.9 $(M+Na)^+$

Step 2: diethyl ((4-bromobenzamido)methyl)phosphonate

Phosphorus trichloride (0.64 ml, 7.28 mmol) and triethyl phosphite (19.01 ml, 109 mmol) were added to a N_2 flushed round bottom flask equipped with a reflux condenser. 4-bromo-N-(hydroxymethyl)benzamide (2.50 g, 10.87 mmol) was added portion-wise to the reaction mixture and the mixture stirred at 65 °C for 1 hr. The resulting mixture was evaporated and recrystallized from ether to afford the title compound (2.65 g, 7.49 mmol, 68.9 % yield) as a colorless solid. MS (*m/z*) 350.0 $(M+H)^+$

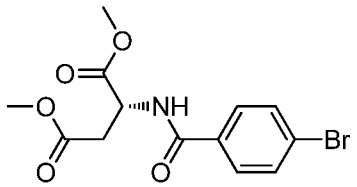
INTERMEDIATE 235: diethyl ((4-bromo-2-methylbenzamido)methyl)phosphonate



Diethyl (aminomethyl)phosphonate oxalate (2.39 g, 9.30 mmol) was free based using a Silicycle carbonate cartridge eluting with MeOH. After the solution was concentrated to dryness, it was combined with DMF (23.25 ml), EDC (1.34 g, 6.98 mmol), and HOAt (0.76 g, 5.58 mmol) and 4-bromo-2-methylbenzoic acid (1.00 g, 4.65 mmol) at RT. Next, N-methylmorpholine (1.53 ml, 13.95 mmol) was added to the stirring mixture and it was stirred for 18 hr at RT. Water was added and the organics were extracted with EtOAc

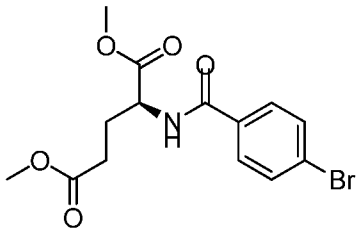
(3x). The combined organic phase was washed with brine (3x), dried over $MgSO_4$, filtered, and concentrated. Purification using ISCO Rf (0-5% MeOH/EtOAc) afforded the title compound (1.62 g, 4.40 mmol, 95 % yield) as a colorless solid. MS (*m/z*) 364.0 $(M+H)^+$

INTERMEDIATE 236: (R)-dimethyl 2-(4-bromobenzamido)succinate



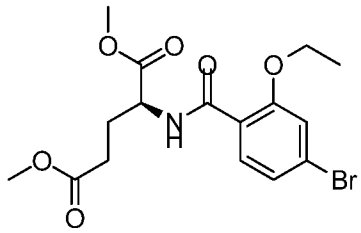
HATU (10.55 g, 27.8 mmol) was added to a stirring mixture of 4-bromobenzoic acid (4.65 g, 23.13 mmol) and (R)-dimethyl 2-aminosuccinate hydrochloride (5.49 g, 27.8 mmol) in DMF (46.3 ml) at RT. Triethylamine (9.67 ml, 69.4 mmol) was then added and the mixture was stirred for 18 h. EtOAc and brine were added and the organic phase was washed with brine (2x), and then the combined aqueous layers were back extracted with EtOAc (1x). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography (0-60% EtOAc/Hexanes) to afford the title compound (7.66 g, 22.02 mmol, 95 % yield). MS (*m/z*) 344.0 $(M+H)^+$

INTERMEDIATE 237: (S)-dimethyl 2-(4-bromobenzamido)pentanedioate



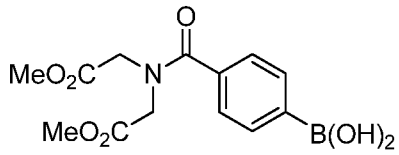
To a solution containing (S)-dimethyl 2-aminopentanedioate, hydrochloride (4.63 g, 21.89 mmol) and 4-bromobenzoic acid (4.0 g, 19.90 mmol) in DMF (75 ml) was added HATU (7.45 g, 19.59 mmol) followed by DIPEA (8.55 ml, 49.0 mmol). The reaction was stirred for 18 hr and then was diluted with NH_4Cl aq. solution, extracted with ethyl ether, dried over $MgSO_4$, filtered and concentrated onto SiO_2. Purification by flash chromatography (0-50% ethyl acetate/hexanes) afforded the title compound (4.01g, 11.2 mmol, 56%) as a colorless solid. MS (*m/z*) 357.9 $(M+H)^+$

INTERMEDIATE 238: (S)-dimethyl 2-(4-bromo-2-ethoxybenzamido)pentanedioate



To a solution containing (S)-dimethyl 2-aminopentanedioate, hydrochloride (3.80 g, 17.95 mmol) and 4-bromo-2-ethoxybenzoic acid (4.0 g, 16.32 mmol) in DMF (75 ml) was added HATU (7.45 g, 19.59 mmol) followed by DIPEA (8.55 ml, 49.0 mmol). The reaction was stirred for 18 hr and then was diluted with NH_4Cl aq. solution, extracted with ethyl ether, dried over $MgSO_4$, filtered and concentrated onto SiO_2. Purification by flash chromatography (0-50% ethyl acetate/hexanes) afforded the title compound (5.33 g, 13.3 mmol, 81% yield) as a colorless solid. MS (*m/z*) 402.1 $(M+H)^+$

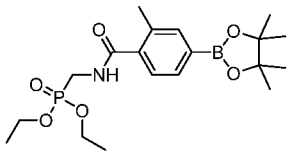
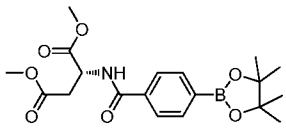
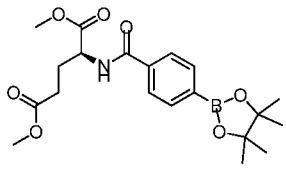
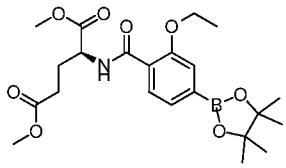
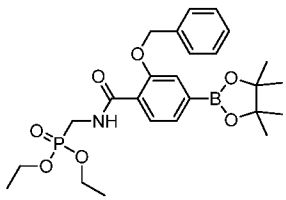
INTERMEDIATE 239: (4-(bis(2-methoxy-2-oxoethyl)carbamoyl)phenyl)boronic acid

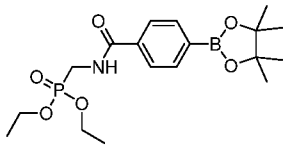


To a mixture of 4-boronobenzoic acid (0.10 g, 0.603 mmol) and DMF (1.21 ml) at 0°C was added HATU (0.25 g, 0.66 mmol) and DIPEA (0.316 ml, 1.81 mmol). The mixture stirred for 30 min, then dimethyl 2,2'-azanediyldiacetate, hydrochloride (0.155 g, 0.78 mmol) was added. The reaction stirred for 72 hours. The reaction was diluted with 1N HCl and extracted with EtOAc (4 X). The organic layers were combined, passed through a phase separator, concentrated, and purified via flash chromatography (ISCO, 12 g silica column, 0-40 % MeOH:EtOAc) to give the title compound (0.143 g, 66.4 % yield). MS (m/z) 310.0 $(M+H^+)$.

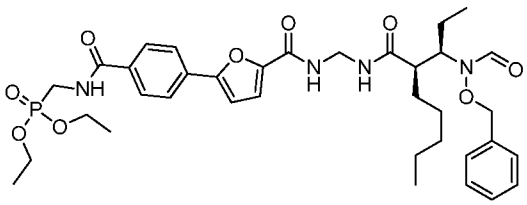
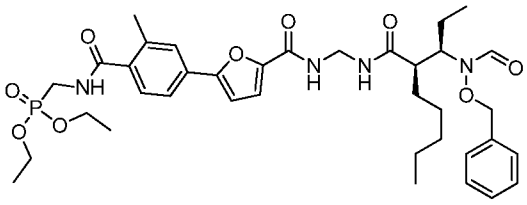
INTERMEDIATES 240-245 were prepared from the indicated bromide in general by methods analogous to those described for Intermediate 55. Reactions were heated to 90 ºC and reaction times vary from 12 hours to 18 hours.

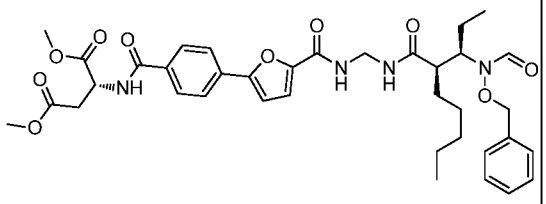
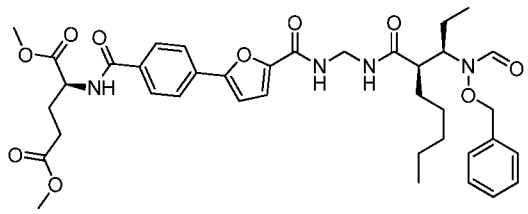
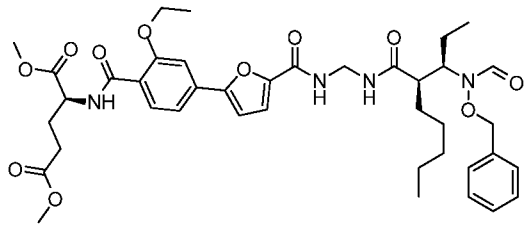
5

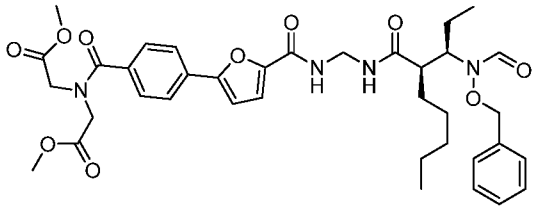
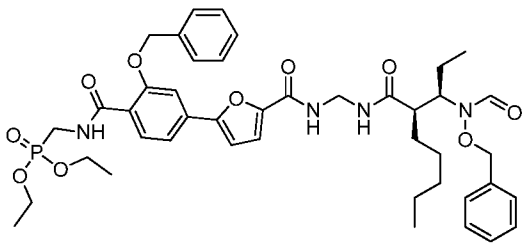
#	Name	Structure	MS (m/z)	Bromide
240	diethyl ((2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)methyl)phosphonate		412.2	diethyl ((4-bromo-2-methylbenzamido)methyl)phosphonate
241	(R)-dimethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)succinate		392.2	(R)-dimethyl 2-(4-bromobenzamido)succinate
242	(S)-dimethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)pentanedioate		406.4	(S)-dimethyl 2-(4-bromobenzamido)pentanedioate
243	(S)-dimethyl 2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)pentanedioate		450.1	(S)-dimethyl 2-(4-bromo-2-ethoxybenzamido)pentanedioate
244	diethyl ((2-(benzyloxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)methyl)phosphonate		504.3	diethyl ((2-(benzyloxy)-4-bromobenzamido)methyl)phosphonate

245	diethyl ((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)methyl)phosphonate		398.1	diethyl ((4-bromobenzamido)methyl)phosphonate

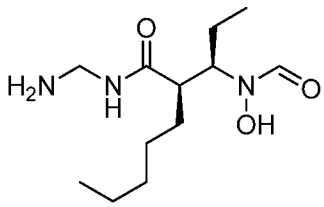
INTERMEDIATES 246-252 were prepared from N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)-5-bromofuran-2-carboxamide and the indicated boronate by methods analogous to those described for Intermediate 147. For Intermediates 246-250 and 252, reaction times vary from 2 hours to 4 hours. For Intermediate 251 the reaction was heated to 80 °C and reaction time was 5 minutes.

#	Name	Structure	MS (m/z) ($M+H^+$)	Boronate
246	diethyl ((4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonate		713.4	diethyl ((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)methyl)phosphonate
247	diethyl ((4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzamido)methyl)phosphonate		727.4	diethyl ((2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)methyl)phosphonate

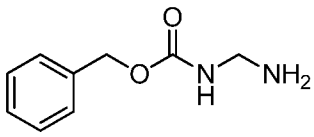
248	(R)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinate		707.3	(R)-dimethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido) succinate
249	(S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)pentanedioate		721.5	(S)-dimethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido) pentanedioate
250	(S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)pentanedioate		765.7	(S)-dimethyl 2-(2-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)pentanedioate

251	dimethyl 2,2'-((4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetate		707.3	(4-(bis(2-methoxy-2-oxoethyl)carbamoyl)phenyl)boronic acid
252	diethyl ((2-(benzyloxy)-4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonate		819.4	diethyl ((2-(benzyloxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)methyl)phosphonate

INTERMEDIATE 253: (R)-N-(aminomethyl)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamide

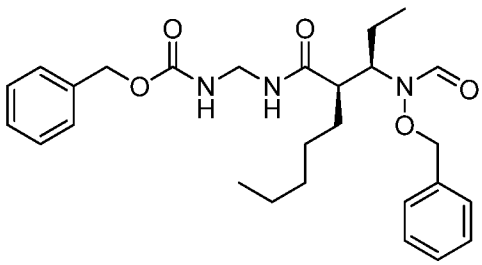


Step 1: benzyl (aminomethyl)carbamate, trifluoroacetic acid salt



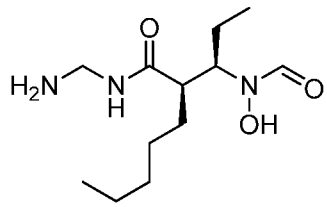
To a 4 neck, 2-L round bottom flask under nitrogen, benzyl (2-amino-2-oxoethyl)carbamate (300 g, 1442 mmol) and DCM (8400 ml) were charged, followed by water (26 ml). To the reaction mixture, PIFA (682 g, 1586 mmol) was added and the mixture was maintained at 23 °C for 1 hour. Seeding material of product (2 wt %) was added and the reaction mixture was maintained for an additional 1 hour. The mixture was cooled to 18-20 °C for 1 hour and then the suspension was filtered and washed with 20% DCM:n-heptane (3000 ml) and then air dried to give the title compound (389 g, 91% yield) as a white solid.

Step 2: benzyl (((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamate



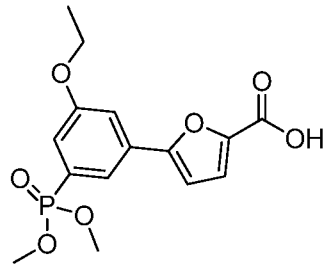
To a 4 neck round bottom flask (R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanoic acid (190 g, 592 mmol) and acetonitrile (1900 ml) were charged, followed by triethylamine (175 ml, 1256 mmol). The reaction mixture was cooled to 0-5 °C and HATU (247 g, 650 mmol) was added. The reaction mixture was warmed to 23 °C and maintained for 1 hour to form the HATU-acid adduct. In a separate round bottom flask, combined benzyl (aminomethyl)carbamate, trifluoroacetic acid salt (365 g, 1184 mmol) and acetonitrile (3800 ml) and cooled to 10-15 °C. Triethylamine (963 ml, 6909 mmol) was added slowly to the reaction mixture. The prepared HATU-acid adduct mixture was then added to the benzyl (aminomethyl)carbamate solution. The combined mixture was warmed to 23 °C and maintained for 1 hour. The reaction mixture was concentrated under reduced pressure. MTBE (3420 ml) and water (2375 ml) were added to the residue and stirred for 15 minutes. The layers were separated and the organic layer was passed through 60-120 silica gel. The filtrate was concentrated under reduced pressure and the residue was diluted with MTBE (950 ml) and cooled to 0-5 °C. The slurry was maintained for 1 hour and filtered to obtain title compound (170 g, 65% yield) as a white solid.

Step 3: (R)-N-(aminomethyl)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamide



To a 5L pressure reaction vessel, benzyl (((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamate (180 g, 372 mmol) and ethanol (3600 ml) were charged. Palladium on carbon, 10 wt% (18 g, 16.9 mmol) was added and the reaction vessel was purged with nitrogen and degassed. The reaction mixture was pressurized with 5.0 kg/cm^2 hydrogen gas at 20-25 °C for 4 hours. The mixture was then filtered through celite and the celite plug was washed with ethanol (900 ml). The filtrate was concentrated under reduced pressure at 40-45 °C. The crude product was slurried with n-heptane (900 ml), filtered, and dried at 35-40 °C for 6 hours to obtain the title compound (89 g, 90% yield) as a white solid.

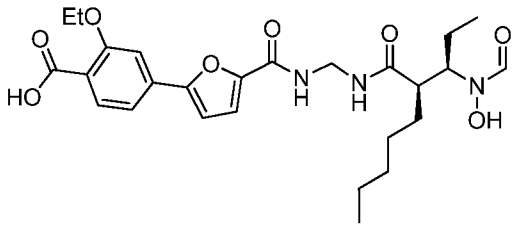
INTERMEDIATE 254: 5-(3-(dimethoxyphosphoryl)-5-ethoxyphenyl)furan-2-carboxylic acid



To a 500 ml round bottom flask was added dimethyl (3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonate (5.0 g, 14.04 mmol) in toluene (35 ml) and 5-bromo-2-furoic acid (2.68 g, 14.03 mmol), followed by THF (30 ml) and water (35 ml). Sodium bicarbonate (3.5 g, 41.7 mmol) was added to the reaction mixture and the mixture was purged with nitrogen. $Pd(Ph_3)_4$ (0.32 g, 0.28 mmol) was added and the reaction mixture was heated to 60-70 °C for 5 hours. The reaction was cooled to 45-50 °C and concentrated under reduced vacuum. The residue was diluted with water (25 ml) and ethyl acetate (25 ml). The layers were separated and the aqueous layer was adjusted to pH 3.0-3.5 using 1N HCl. The suspension was filtered and washed with water (25 ml). The crude solid was purified by flash chromatography (100% EtOAc followed by 2-5% MeOH/DCM). The pure fractions were combined and concentrated under reduced presure to give the title compound (5.5 g, 61%) as a brown solid.

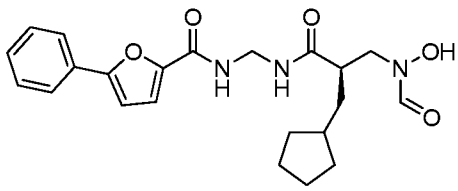
EXAMPLE 1

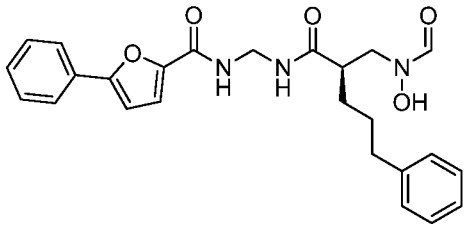
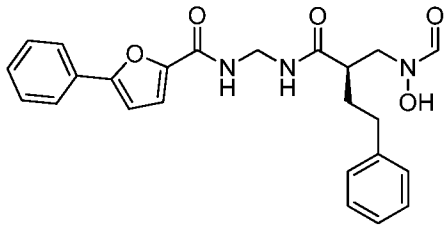
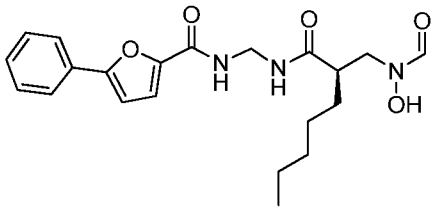
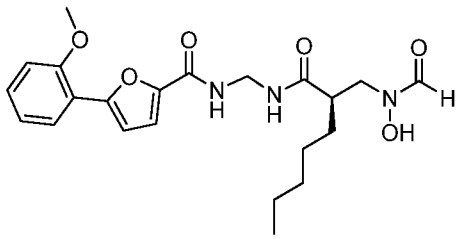
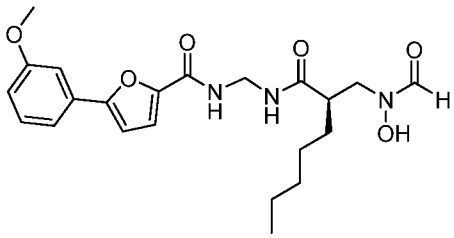
2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzoic acid

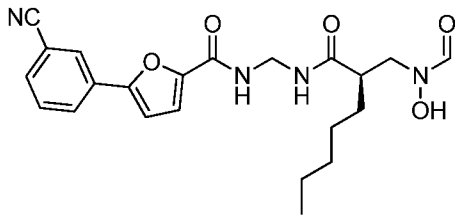
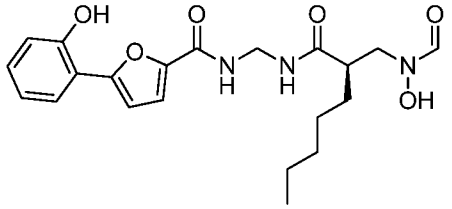
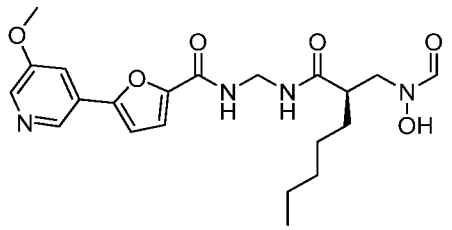
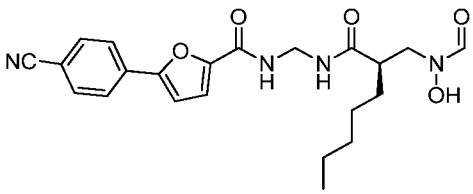
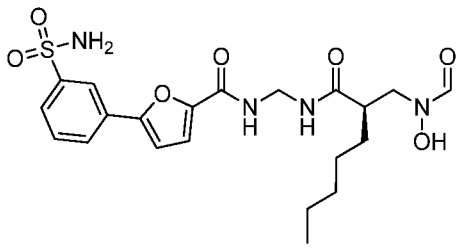
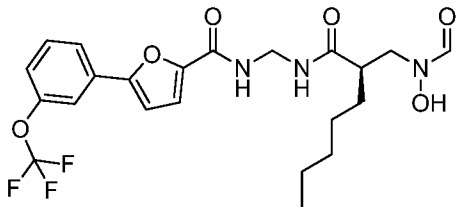


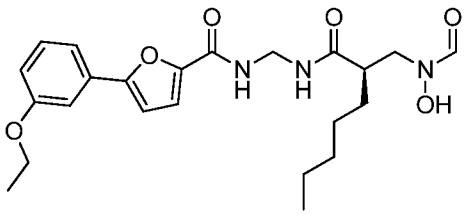
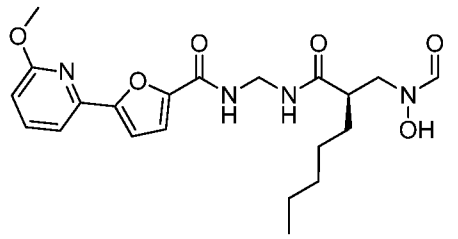
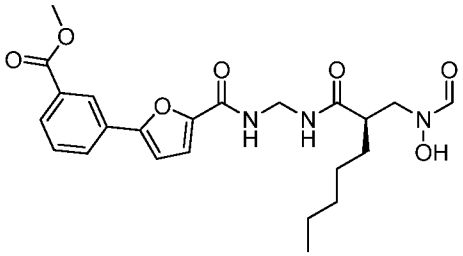
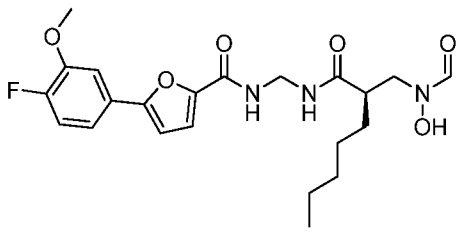
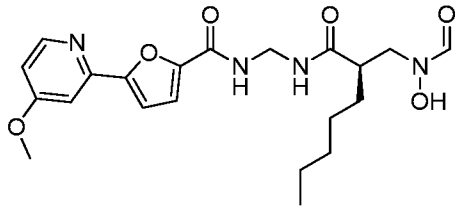
4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)-2-ethoxybenzoic acid (285 mg, 0.47 mmol), was dissolved in ethanol and the reaction flushed with nitrogen. Pd/C (125 mg, 0.12 mmol) was then added and the reaction placed under hydrogen atmosphere (balloon) and stirred for 5.5 hours. The reaction was then filtered through a PTFE frit and the filtrate concentrated. The residue was dissolved in methanol and purified by reverse phase HPLC (Waters, XBridge PrepShield RP C_{18}, 5 µM, 30 x 150 mm, 10-50 % CH_3CN/water + 0.1 % NH_4OH over 14 minutes). Fractions containing product were combined, made slightly acidic and extracted with DCM and then EtOAc. The combined organic extracts were concentrated to give the title compound as an off white solid (115 mg, 47 % yield).

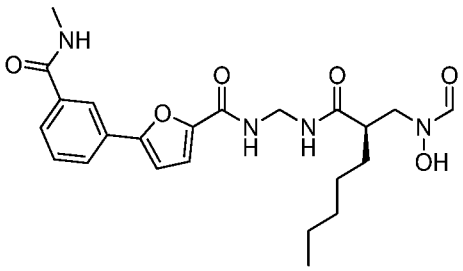
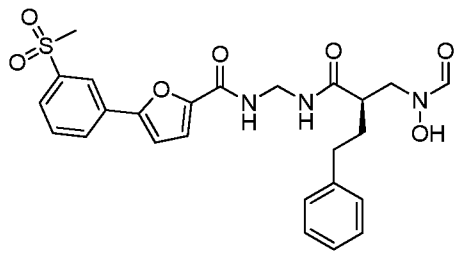
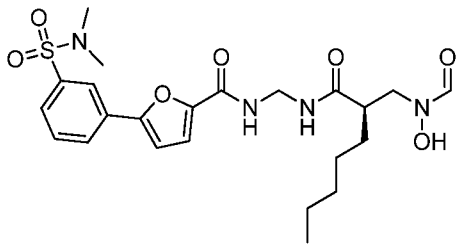
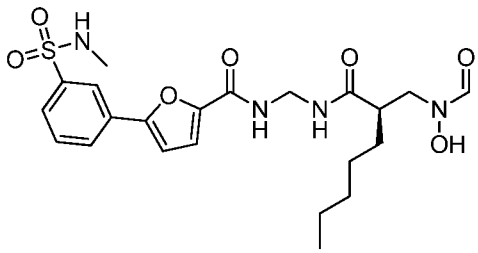
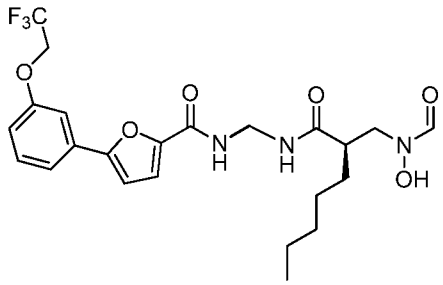
Examples 2-49 were prepared from the indicated intermediate by methods analogous to those described for Example 1. For Examples 5, 16, 21, 22, 25, 26, 27, 29, 30, 33, 34, 35, 40, 47 and 48 methanol was used as the solvent instead of ethanol. For Examples 12 and 46 a mixture of methanol and ethanol was used as the solvent instead of ethanol. For Example 45 a mixture of DCM and methanol was used as the solvent instead of ethanol.

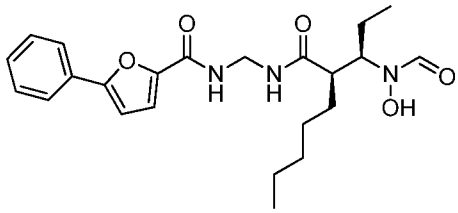
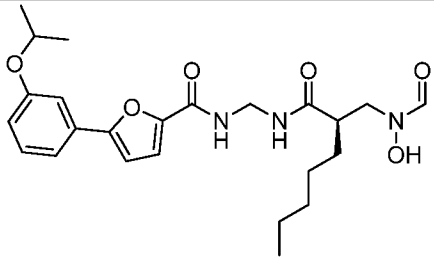
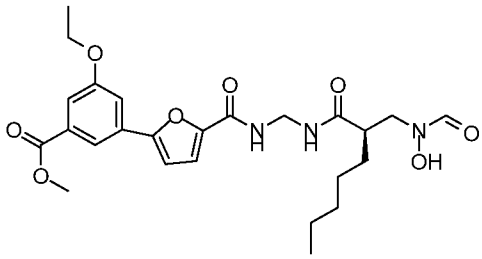
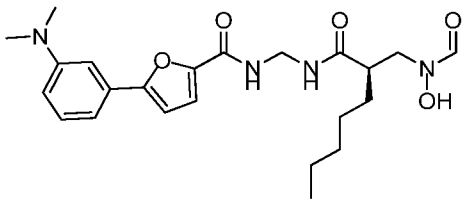
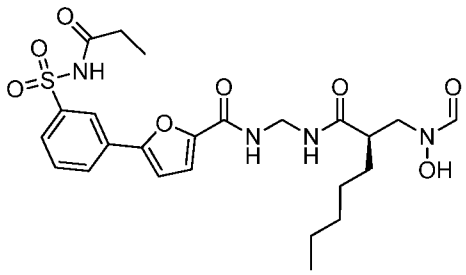
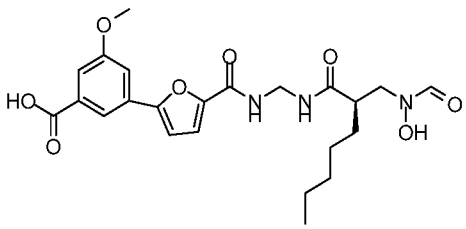
Ex.	Name	Structure	Intermediate
2	(R)-N-((3-cyclopentyl-2-((N-hydroxyformamido)methyl)propanamido)methyl)-5-phenylfuran-2-carboxamide		R)-N-((3-(N-(benzyloxy)formamido)-2-(cyclopentylmethyl)propanamido)methyl)-5-phenylfuran-2-carboxamide

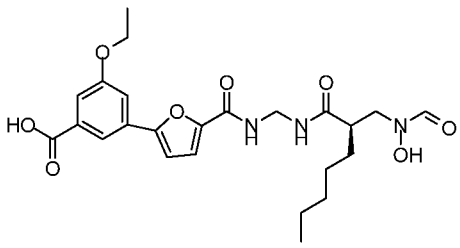
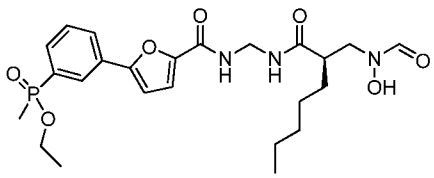
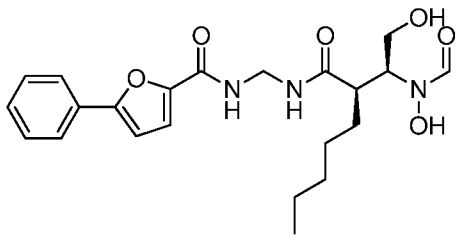
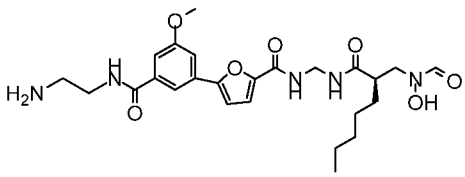
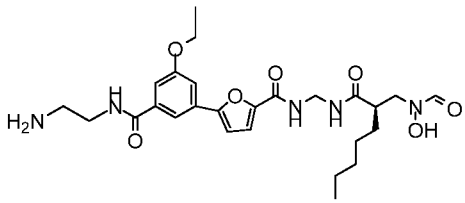
3	(R)-N-((2-((N-hydroxyformamido)methyl)-5-phenylpentanamido)methyl)-5-phenylfuran-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)-5-phenylpentanamido)methyl)-5-phenylfuran-2-carboxamide
4	(R)-N-((2-((N-hydroxyformamido)methyl)-4-phenylbutanamido)methyl)-5-phenylfuran-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)-4-phenylbutanamido)methyl)-5-phenylfuran-2-carboxamide
5	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide
6	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(2-methoxyphenyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(2-methoxyphenyl)furan-2-carboxamide
7	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-methoxyphenyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-methoxyphenyl)furan-2-carboxamide

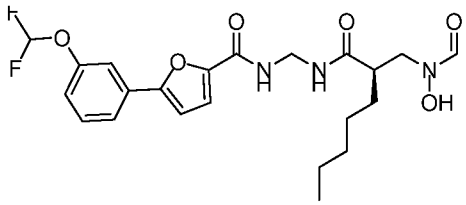
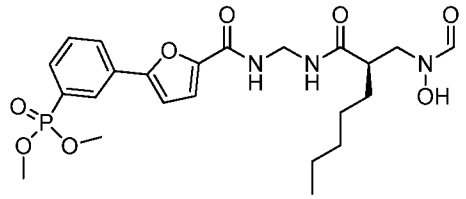
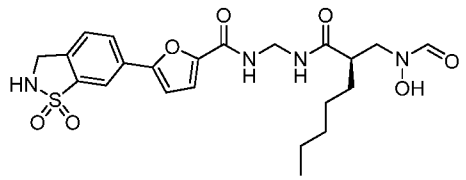
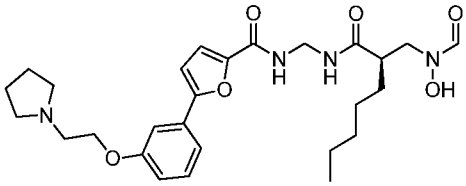
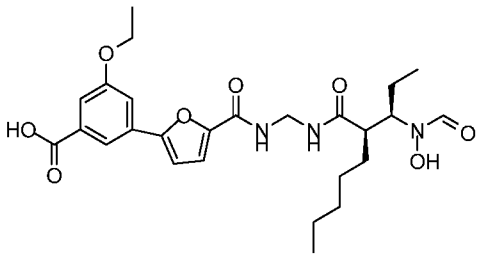
8	(R)-5-(3-cyanophenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-cyanophenyl)furan-2-carboxamide
9	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(2-hydroxyphenyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(2-hydroxyphenyl)furan-2-carboxamide
10	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(5-methoxypyridin-3-yl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(5-methoxypyridin-3-yl)furan-2-carboxamide
11	(R)-5-(4-cyanophenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(4-cyanophenyl)furan-2-carboxamide
12	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-sulfamoylphenyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-sulfamoylphenyl)furan-2-carboxamide
13	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(trifluoromethoxy)phenyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(trifluoromethoxy)phenyl)furan-2-carboxamide

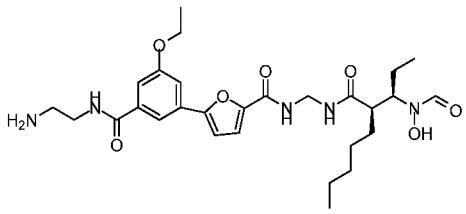
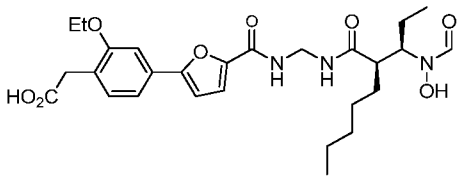
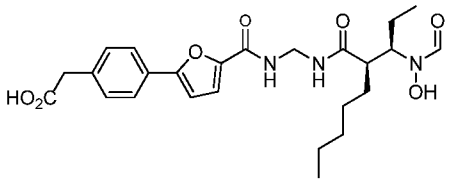
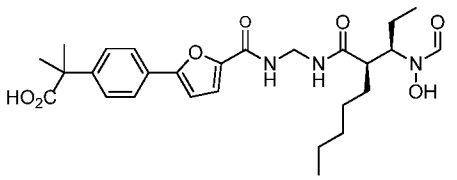
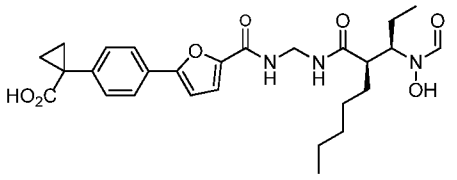
14	(R)-5-(3-ethoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-ethoxyphenyl)furan-2-carboxamide
15	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(6-methoxypyridin-2-yl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(6-methoxypyridin-2-yl)furan-2-carboxamide
16	(R)-methyl 3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate		(R)-methyl 3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate
17	(R)-5-(4-fluoro-3-methoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(4-fluoro-3-methoxyphenyl)furan-2-carboxamide
18	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(4-methoxypyridin-2-yl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(4-methoxypyridin-2-yl)furan-2-carboxamide

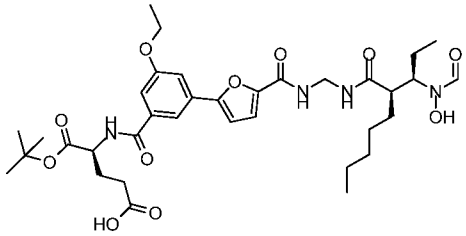
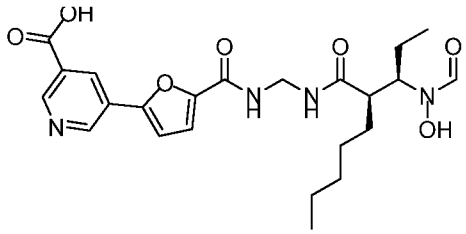
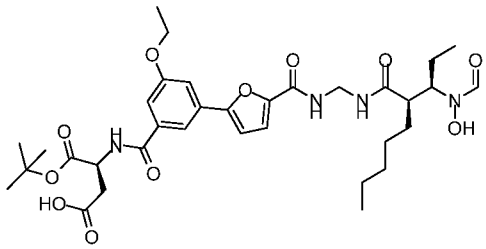
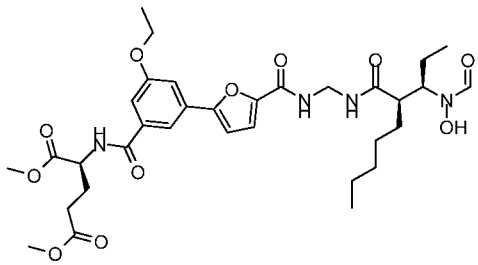
19	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(methylcarbamoyl)phenyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(methylcarbamoyl)phenyl)furan-2-carboxamide
20	(R)-N-((2-((N-hydroxyformamido)methyl)-4-phenylbutanamido)methyl)-5-(3-(methylsulfonyl)phenyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)-4-phenylbutanamido)methyl)-5-(3-(methylsulfonyl)phenyl)furan-2-carboxamide
21	(R)-5-(3-(N,N-dimethylsulfamoyl)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(N,N-dimethylsulfamoyl)phenyl)furan-2-carboxamide
22	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(N-methylsulfamoyl)phenyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(N-methylsulfamoyl)phenyl)furan-2-carboxamide
23	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(2,2,2-trifluoroethoxy)phenyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(2,2,2-trifluoroethoxy)phenyl)furan-2-carboxamide

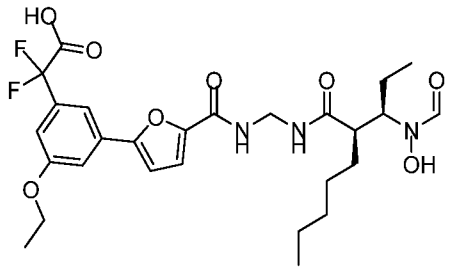
24	N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide		N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide
25	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-isopropoxyphenyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-isopropoxyphenyl)furan-2-carboxamide
26	(R)-methyl 3-ethoxy-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate		(R)-methyl 3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoate
27	(R)-5-(3-(dimethylamino)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(dimethylamino)phenyl)furan-2-carboxamide
28	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(N-propionylsulfamoyl)phenyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(N-propionylsulfamoyl)phenyl)furan-2-carboxamide
29	(R)-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-methoxybenzoic acid		(R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-methoxybenzoic

			acid
30	(R)-3-ethoxy-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		(R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoic acid
31	ethyl (3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)(methyl)phosphinate		ethyl (3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)(methyl)phosphinate
32	N-(((R)-2-((S)-2-hydroxy-1-(N-hydroxyformamido)ethyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide		N-(((R)-2-((S)-2-(benzyloxy)-1-(N-(benzyloxy)formamido)ethyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide
33	(R)-5-(3-((2-aminoethyl)carbamoyl)-5-methoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide		(R)-benzyl (2-(3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-methoxybenzamido)ethyl)carbamate
34	(R)-5-(3-((2-aminoethyl)carbamoyl)-5-ethoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide		(R)-benzyl (2-(3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)ethyl)carbamate

35	(R)-5-(3-(difluoromethoxy)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(difluoromethoxy)phenyl)furan-2-carboxamide
36	(R)-dimethyl (3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate		(R)-dimethyl (3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate
37	(R)-5-(1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl)furan-2-carboxamide
38	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(2-(pyrrolidin-1-yl)ethoxy)phenyl)furan-2-carboxamide		R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(2-(pyrrolidin-1-yl)ethoxy)phenyl)furan-2-carboxamide
39	3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)benzoic acid		3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)-5-ethoxybenzoic acid

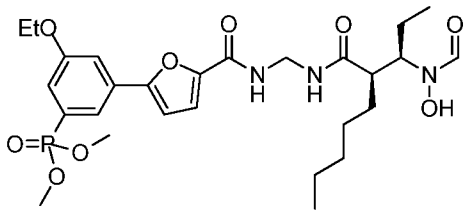
40	5-(3-((2-aminoethyl)carbamoyl)-5-ethoxyphenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)furan-2-carboxamide		benzyl (2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)ethyl)carbamate
41	2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid		2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxyphenyl)acetic acid
42	2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid		2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid
43	2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)-2-methylpropanoic acid		2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)-2-methylpropanoic acid
44	1-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)cyclopropanec		1-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-

	arboxylic acid		yl)phenyl)cyclopropanecarboxylic acid
45	(S)-5-(tert-butoxy)-4-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl) heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)-5-oxopentanoic acid		(S)-5-benzyl 1-tert-butyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl) heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)pentanedioate
46	5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)nicotinic acid		5-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)nicotinic acid
47	(S)-4-(tert-butoxy)-3-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)-4-oxobutanoic acid		(S)-4-benzyl 1-tert-butyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)succinate
48	(S)-dimethyl 2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)pentanedioate		(S)-dimethyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl) heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)pentanedioate

49	2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)phenyl)-2,2-difluoroacetic acid		2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxyphenyl)-2,2-difluoroacetic acid

EXAMPLE 50

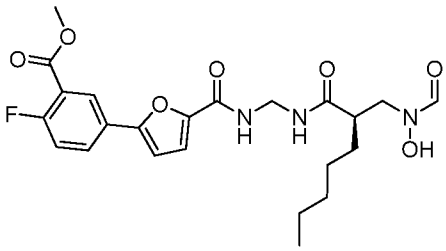
dimethyl (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate



Dimethyl (3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)-5-ethoxyphenyl)phosphonate (900 mg, 1.27 mmol), was dissolved in ethanol (2.5 ml) and flushed with nitrogen. Pd/C (271 mg, 0.26 mmol) was then added followed by methanol (2.5 ml) and the reaction placed under hydrogen atmosphere (balloon). The mixture was stirred at room temperature for 3.5 hours and then filtered through Celite®, washing with MeOH. The filtrate was concentrated and the residue was purified by flash chromatography (ISCO, 80 g column, 0-20 % MeOH/DCM over 30 minutes) to give the title compound as an off white solid (645 mg, 87 % yield).

EXAMPLE 51

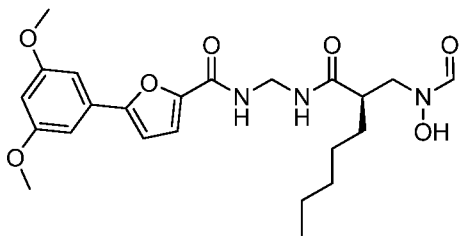
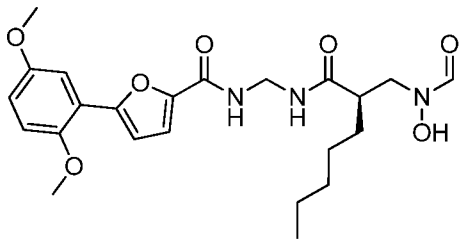
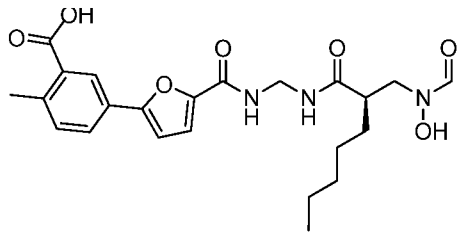
(R)-methyl 2-fluoro-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl) furan-2-yl)benzoate

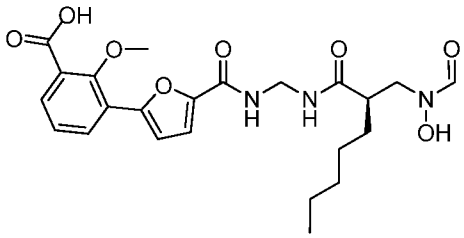
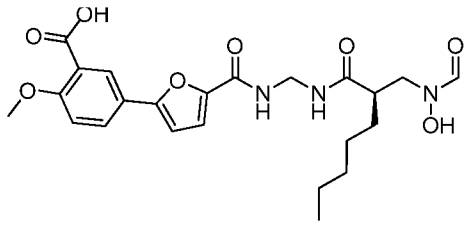
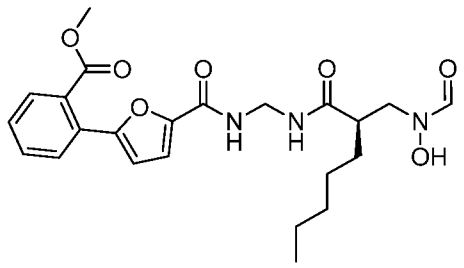
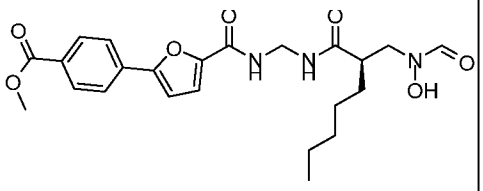


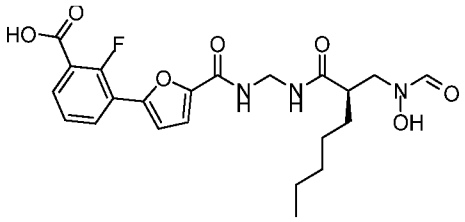
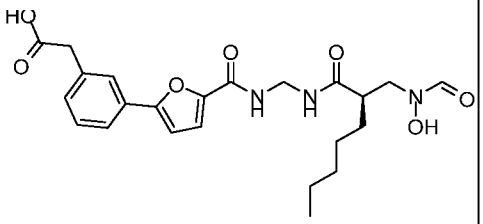
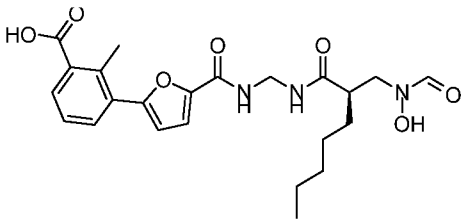
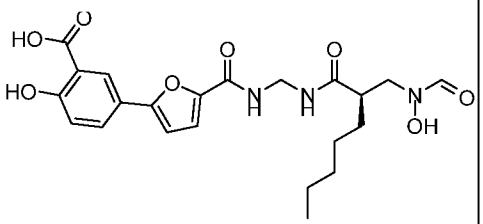
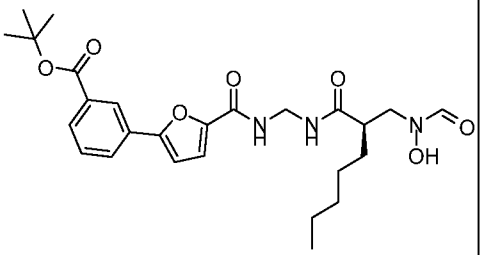
Dichloromethane (0.25 ml) was added to a nitrogen purged flask containing Pd/C

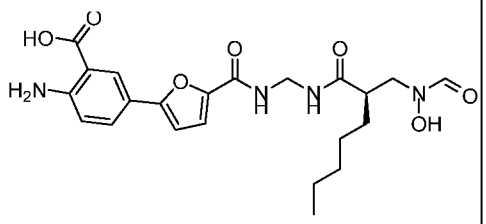
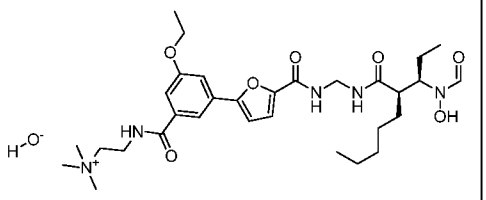
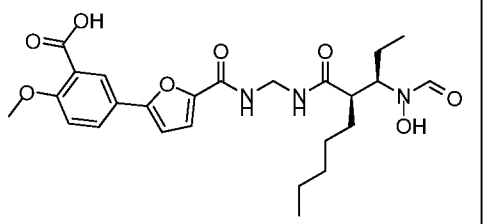
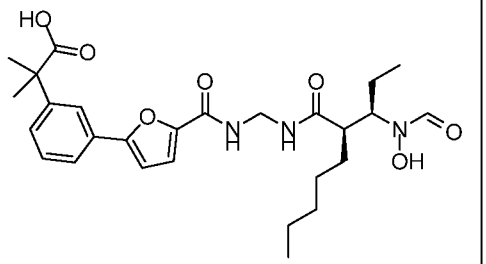
(8.23 mg, 7.73 µmol) followed by a solution of (R)-methyl 2-(5-(((2-((N-(benzyloxy)formamido) methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate (85 mg, 0.16 mmol) in methanol (2 ml) and ammonium formate (48.8 mg, 0.77 mmol). The reaction was stirred at room temperature for 4 hours then filtered through a plug of Celite® which was washed with methanol (10 ml) and the filtrate collected and concentrated. The residue was purified via flash chromatography (ISCO Combiflash Rf, 25 g column, 0–15 % methanol/DCM) to give the title compound (51 mg, 66 % yield).

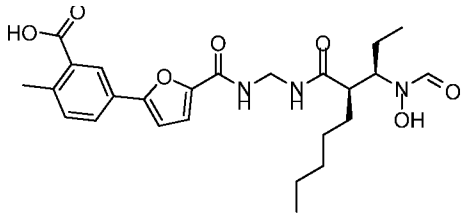
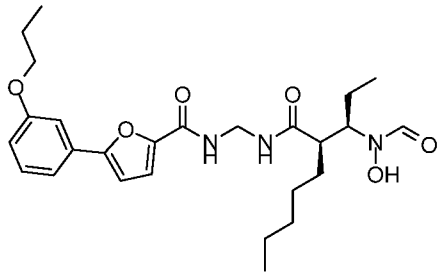
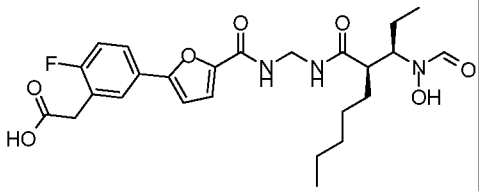
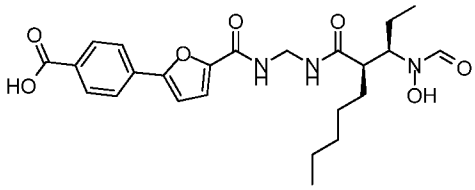
Examples 52-73 were prepared from the indicated intermediate by methods analogous to those described for Example 51. Purification methods may vary.

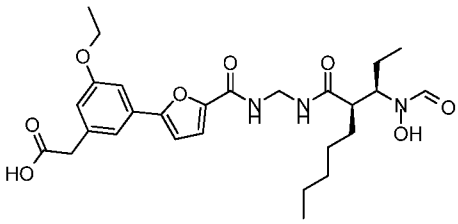
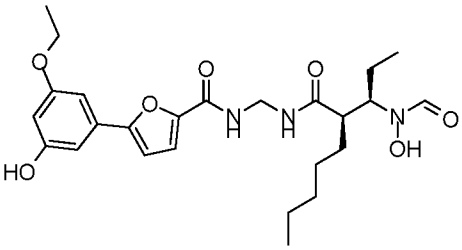
Ex.	Name	Structure	Intermediate
52	(R)-5-(3,5-dimethoxyphenyl)-N-((2-((N-hydroxyformamido) methyl)heptanamido)methyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3,5-dimethoxyphenyl)furan-2-carboxamide
53	(R)-5-(2,5-dimethoxyphenyl)-N-((2-((N-hydroxyformamido) methyl)heptanamido)methyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(2,5-dimethoxyphenyl)furan-2-carboxamide
54	(R)-5-(5-(((2-((N-hydroxyformamido) methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzoic acid		(R)-5-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzoic acid

55	(R)-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methoxybenzoic acid		(R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methoxybenzoic acid
56	(R)-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methoxybenzoic acid		(R)-5-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methoxybenzoic acid
57	(R)-methyl 2-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate		(R)-methyl 2-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate
58	(R)-methyl 4-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate		(R)-methyl 4-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate

59	(R)-2-fluoro-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		(R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-fluorobenzoic acid
60	(R)-2-(3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid		(R)-2-(3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid
61	(R)-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzoic acid		(R)-3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzoic acid
62	(R)-2-hydroxy-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		(R)-5-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-hydroxybenzoic acid
63	(R)-tert-butyl 3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate		(R)-tert-butyl 3-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate

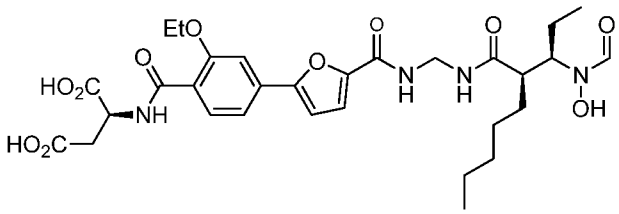
64	(R)-2-amino-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		(R)-2-amino-5-(5-(((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
65	2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)-N,N,N-trimethylethanaminium hydroxide		2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)-N,N,N-trimethylethanaminium
66	5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methoxybenzoic acid		5-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methoxybenzoic acid
67	2-(3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)-2-		2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)-

	methylpropanoic acid		2-methylpropanoic acid
68	5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzoic acid		5-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzoic acid
69	N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)-5-(3-propoxyphenyl)furan-2-carboxamide		N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)-5-(3-propoxyphenyl)furan-2-carboxamide
70	2-(2-fluoro-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid		2-(5-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-fluorophenyl)acetic acid
71	4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

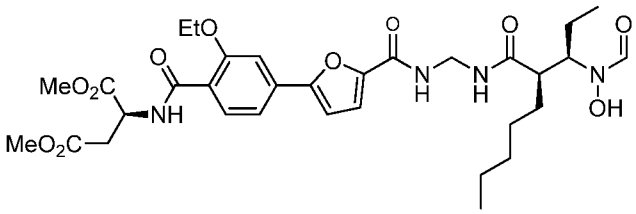
72	2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid		2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxyphenyl)acetic acid
73	5-(3-ethoxy-5-hydroxyphenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)furan-2-carboxamide		N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)-5-(3-ethoxy-5-hydroxyphenyl)furan-2-carboxamide

EXAMPLE 74

(S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid



Step 1: (S)-dimethyl 2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido) methyl)carbamoyl)furan-2-yl)benzamido)succinate



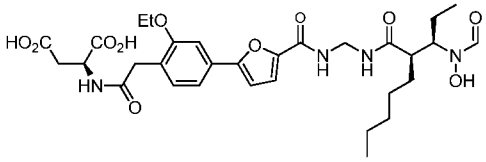
(S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido) methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)succinate (418 mg, 0.56 mmol), was

dissolved in ethanol (20 ml) and the reaction flushed with nitrogen. Pd/C (118 mg, 0.11 mmol) was then added followed by methanol (20 ml) and the reaction placed under hydrogen atmosphere and stirred at room temperature. After 2 hours, additional Pd/C (148 mg, 0.14 mmol) was added and the mixture stirred for another 2 hours. The reaction was then filtered through a PTFE frit and the filtrate concentrated. The residue was purified by flash chromatography (ISCO Rf, 80 g column, 0-100 % EtOAc/DCM over 20 minutes) to give the title compound (301 mg, 82 % yield). MS (m/z) 661.3 ($M+H^+$).

Step 2: (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid

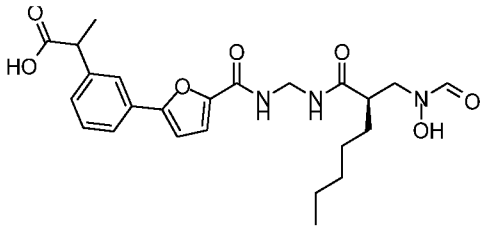
To a 20 ml vial was added (S)-dimethyl 2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinate (301 mg, 0.46 mmol), methanol (6 ml) and water (2 ml) followed by LiOH (70.3 mg, 2.93 mmol). The mixture was stirred at room temperature for 4 hours. The reaction volume was then reduced to ~ 5 ml and then extracted with EtOAc. The aqueous was then adjusted to acidic pH via dropwise addition of 6 N HCl and extracted twice with EtOAc. The organic layer was concentrated and the resultant solid suspended in EtOAc and stirred at room temperature for 1 hour and then collected by filtration to give the title compound as a light brown/orange solid (200 mg, 70 % yield).

Example 75 was prepared from (S)-dimethyl 2-(2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxyphenyl) acetamido)succinate by methods analogous to those described for Example 74.

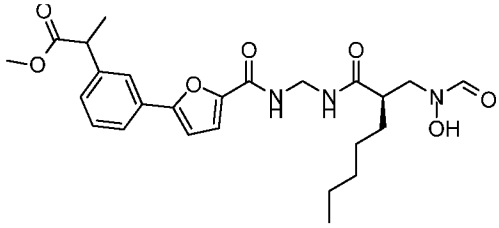
Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step1
75	(S)-2-(2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido) propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetamido)succinic acid		(S)-dimethyl 2-(2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetamido)succinate	675.3

EXAMPLE 76

2-(3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)propanoic acid



Step 1: methyl 2-(3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)propanoate



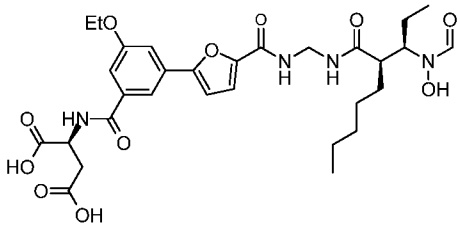
To a nitrogen purged vial was added Pd/C (7.53 mg, 7.08 µmol) and

dichloromethane (0.25 ml). Methyl 2-(3-(5-((((R)-2-((N-(benzyloxy)formamido)methyl)heptanamido) methyl) carbamoyl)furan-2-yl)phenyl)propanoate (161 mg, 0.28 mmol) in methanol (2 ml) was added followed by ammonium formate (44.6 mg, 0.71 mmol). The reaction was stirred at room temperature for 6 hours. Additional Pd/C (7.53 mg, 7.08 µmol) and ammonium formate (44.6 mg, 0.71 mmol) were added and the reaction stirred at room temperature overnight. The reaction mixture was filtered through a plug of Celite®, which was washed with methanol (10 ml). The filtrate was concentrated and the residue was purified via flash chromatography (ISCO Combiflash Rf, 25 g column, 0-15 % methanol/DCM) to give impure product which was purified via flash chromatography (ISCO Combiflash Rf, 12 g column, 0-10 % methanol/DCM) to give the title compound (64 mg). MS (m/z) 488.2 ($M+H^+$).

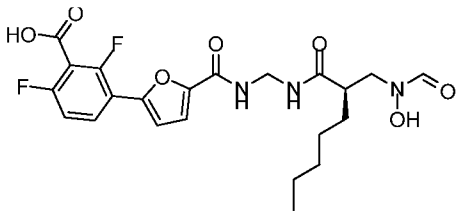
Step 2: 2-(3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)propanoic acid

Methyl 2-(3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)propanoate (64 mg, 0.13 mmol) and lithium hydroxide (9.43 mg, 0.39 mmol) were combined in ethanol (1 ml) and water (0.33 ml) and the reaction stirred at room temperature for 3 hours. The ethanol was removed *in vacuu* and the residual solution extracted with DCM. The aqueous layer was then adjusted to ~pH 3 via addition of 1 N HCl and extracted with EtOAc (2 x 5 ml). The organic was passed through a phase separator and concentrated. The residue was purified via flash chromatography (ISCO Combiflash Rf, 12 g column, 0-100 % ethyl acetate/DCM) to give the title compound (25 mg, 36.2 % yield).

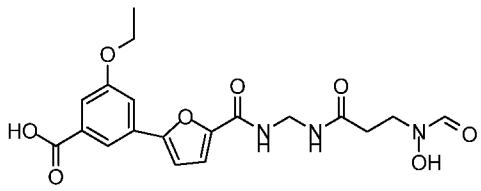
Example 77 was prepared from (S)-dimethyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido) succinate by methods analogous to those described for Example 76.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
77	(S)-2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido) propyl)heptanamid o)methyl)carbamoyl)furan-2-yl)benzamido)succi nic acid		(S)-dimethyl 2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido) propyl)heptanamid o)methyl)carbamoyl)furan-2-yl)benzamido)succi nate	661.2

Example 78 was prepared from (R)-methyl 3-(5-(((2-((N-(benzyloxy)formamido) methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2,6-difluorobenzoate by methods analogous to those described for Example 76.

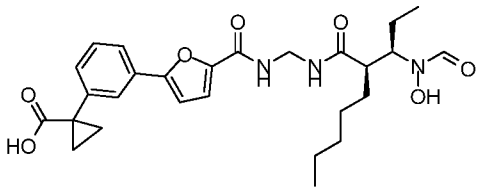
Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
78	R)-2,6-difluoro-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		(R)-methyl 2,6-difluoro-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate	496.1

Example 79 was prepared from methyl 3-(5-(((3-(N-(benzyloxy)formamido) propanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoate by methods analogous to those described for Example 76.

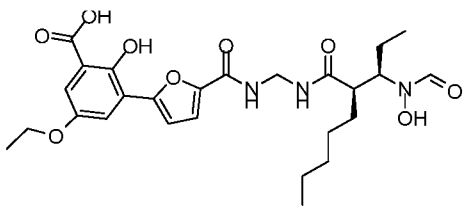
Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
79	3-ethoxy-5-(5-(((3-(N-hydroxyformamido)propanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		methyl 3-ethoxy-5-(5-(((3-(N-hydroxyformamido) propanamido)methyl)carbamoyl)furan-2-yl)benzoate	434.1

Example 80 was prepared from methyl 1-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy) formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)cyclopropanecarboxylate by methods analogous to those described for Example 76. In Step 2 a mixture of methanol and water was used as the solvent instead

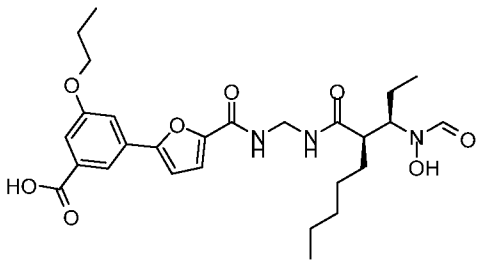
of a mixture of ethanol and water.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
80	1-(3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)cyclopropanecarboxylic acid		methyl 1-(3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)cycloprop anecarboxylate	528.2

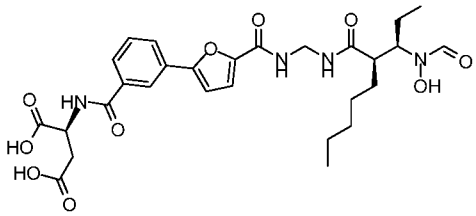
Example 81 was prepared from ethyl 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido) propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxy-2-hydroxybenzoate by methods analogous to those described for Example 76. In Step 2 a mixture of methanol, THF and water was used as the solvent instead of a mixture of ethanol and water.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
81	5-ethoxy-2-hydroxy-3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		ethyl 5-ethoxy-2-hydroxy-3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate	562.2

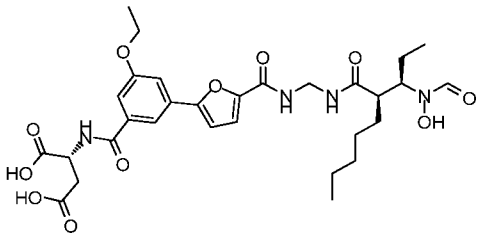
Example 82 was prepared from methyl 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido) propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-propoxybenzoate by methods analogous to those described for Example 76. In Step 2 a mixture of THF and water was used as the solvent instead of a mixture of ethanol and water.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
82	3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-propoxybenzoic acid		methyl 3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-propoxybenzoate	546.3

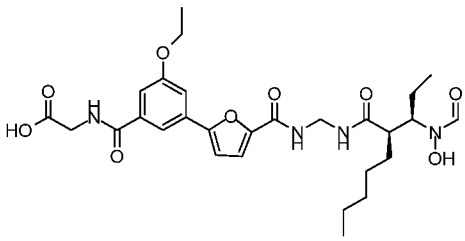
Example 83 was prepared from (S)-dimethyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy) formamido)propyl)heptanamido) methyl)carbamoyl)furan-2-yl)benzamido)succinate by methods analogous to those described for Example 76. In Step 2 a mixture of THF and water was used as the solvent instead of a mixture of ethanol and water.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
83	(S)-2-(3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid		(S)-dimethyl 2-(3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinate	617.3

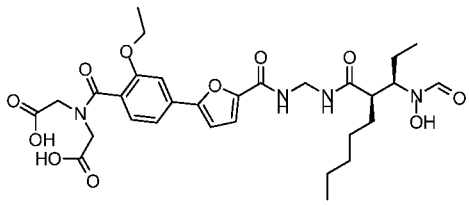
Example 84 was prepared from (R)-dimethyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy) formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)succinate by methods analogous to those described for Example 76.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
84	(R)-2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid		(R)-dimethyl 2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinate	661.2

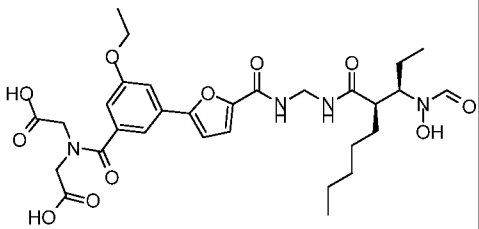
Example 85 was prepared from methyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy) formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)acetate in procedures analogous to those exemplified in Example 76. In Step 2 a mixture of THF and water was used as the solvent instead of a mixture of ethanol and water.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
85	2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)acetic acid		methyl 2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)acetate	589.2

Example 86 was prepared from dimethyl 2,2'-((4-(5-((((R)-2-((R)-1-(N-(benzyloxy) formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzoyl)azanediyl) diacetate by methods analogous to those described for Example 76. In Step 2 a mixture of THF and water was used as the solvent instead of a mixture of ethanol and water.

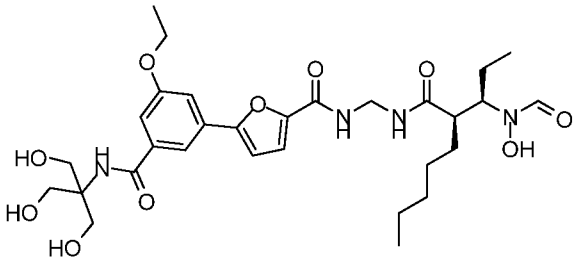
Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
86	2,2'-((2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetic acid		dimethyl 2,2'-((2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetate	661.3

Example 87 was prepared from dimethyl 2,2'-((3-(5-((((R)-2-((R)-1-(N-(benzyloxy) formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoyl)azanediyl) diacetate by methods analogous to those described for Example 76. In Step 2 a mixture of methanol and water was used as the solvent instead of a mixture of ethanol and water.

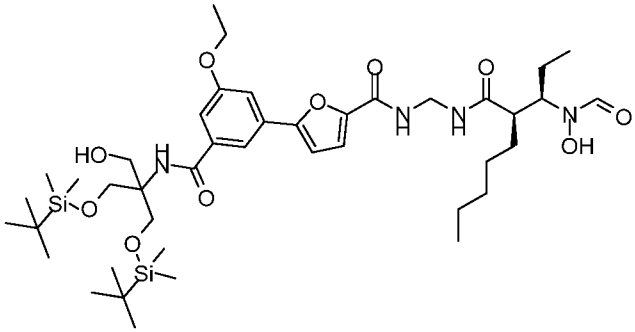
Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
87	2,2'-((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetic acid		dimethyl 2,2'-((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetate	661.2

EXAMPLE 88

5-(3-((1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl)carbamoyl)-5-ethoxyphenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)furan-2-carboxamide



Step 1: 5-(3-ethoxy-5-((6-(hydroxymethyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)carbamoyl)phenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl) heptanamido)methyl)furan-2-carboxamide



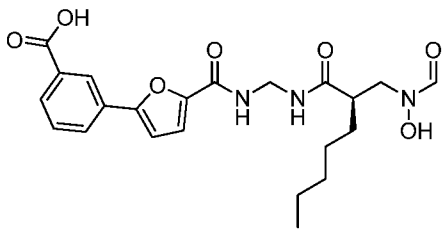
Dichloromethane (0.25 ml) was added to Pd/C (10 % wt, 8.76 mg, 8.23 µmol) in a nitrogen purged vial. A solution of N-(((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl) heptanamido)methyl)-5-(3-ethoxy-5-((6-(hydroxymethyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)carbamoyl)phenyl)furan-2-carboxamide (173 mg, 0.18 mmol) in methanol (1 ml) was added followed by ammonium formate (51.9 mg, 0.82 mmol) and the reaction mixture stirred at room temperature for 6 hours. Additional Pd/C, (10 % wt, 8.76 mg, 8.23 µmol) and ammonium formate (51.9 mg, 0.82 mmol) were added and the reaction stirred at room temperature overnight. The reaction was then filtered through a plug of Celite® which was washed with MeOH (10 ml). The filtrate was concentrated and the residue dissolved in DCM, filtered and then purified by flash chromatography (ISCO Combiflash Rf, 25 g column, 0-20 % methanol/DCM) to give the title compound as an orange oil (116 mg, 83 % yield). MS (m/z) 849.5 ($M+H^+$).

Step 2: 5-(3-((1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl)carbamoyl)-5-ethoxyphenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)furan-2-carboxamide

To a solution of 5-(3-ethoxy-5-((6-(hydroxymethyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)carbamoyl)phenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl) heptanamido)methyl)furan-2-carboxamide (116 mg, 0.14 mmol) in THF (1 ml) cooled to 0 ºC was added dropwise a solution of TBAF (1 M in THF, 0.82 ml, 0.82 mmol). The reaction was warmed to room temperature and stirred for 1 hour. Hexanes was then added to the reaction mixture, the hexanes were decanted from the resultant yellow oil. The oil was then dissolved in DCM and washed with water. The organic was collected via hydrophobic frit and concentrated. The residue was purified using reverse phase HPLC (Waters, XBridge Prep Shield RP C_{18} 5 µm OBD 30 X 150 mm column, 50-90 % CH_3CN/water + 0.1 % NH_4OH over 15 minutes) to give the title compound as a yellow solid (36 mg, 32 % yield).

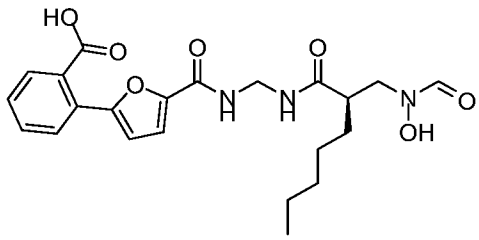
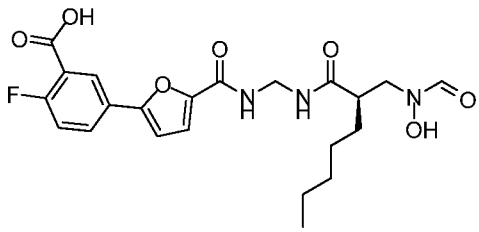
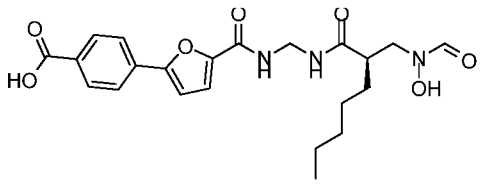
EXAMPLE 89

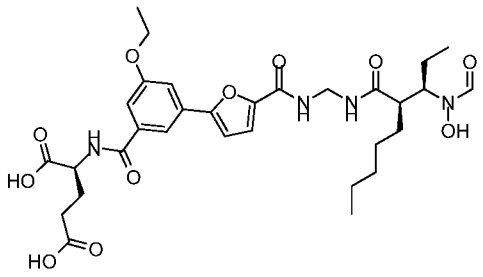
(R)-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid



(R)-methyl 3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl) furan-2-yl)benzoate (50 mg, 0.11 mmol) in methanol (1 ml) and water (0.3 ml) was treated with lithium hydroxide (7.82 mg, 0.33 mmol) for 3 days. The reaction was concentrated and acidified to ~pH 3 via addition of 1 N HCl. The reaction was extracted with EtOAc (3 x) and then with DCM (2 x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified via flash chromatography (ISCO, 4 g silica gel column, 0-100 % EtOAC/DCM: 5 minutes, 100 % EtOAC: 5 minutes, 5 % MeOH/DCM: 5 minutes, 5-10 % MeOH/DCM: 5 minutes, 10 % MeOH/DCM: 5 minutes) to give the title compound as a tan solid (41 mg, 95 % yield).

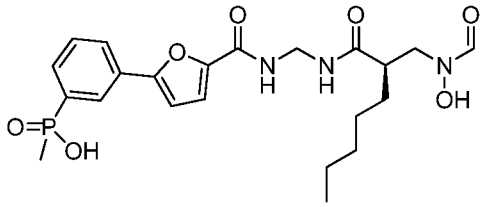
Examples 90-93 were prepared from the indicated ester by methods analogous to those described for Example 89. For Examples 90-92 a mixture of ethanol and water was used as the solvent instead of a mixture of methanol and water.

Ex.	Name	Structure	Ester
90	(R)-2-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		(R)-methyl 2-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate
91	(R)-2-fluoro-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		(R)-methyl 2-fluoro-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate
92	(R)-4-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		(R)-methyl 4-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate

93	(S)-2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)pentanedioic acid		(S)-dimethyl 2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)pentanedioate

EXAMPLE 94

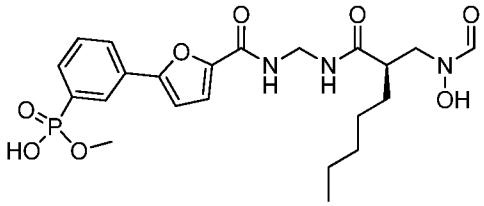
(3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)(methyl)phosphinic acid



To a solution of ethyl (3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)(methyl)phosphinate (100 mg, 0.20 mmol) in THF (5 ml) and water (1 ml) was added LiOH monohydrate (12 mg, 0.30 mmol) at 0 °C. The reaction was stirred for 2 hours at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred overnight. Additional LiOH monohydrate (6 mg, 0.15 mmol) was added and the reaction mixture stirred for a further 3 hours. The reaction mixture was then cooled to 0 °C and adjusted to pH 3 by addition of 1 M HCl solution (~0.4 ml). The reaction mixture was evaporated under reduced pressure. The residue was chromatographed (12 g, C_{18} SNAP reversed phase silica gel column, 0-50 % CH_3CN in water modified with 0.2 % formic acid) to give the title compound as a colorless oil (79 mg, 74 % yield).

EXAMPLE 95

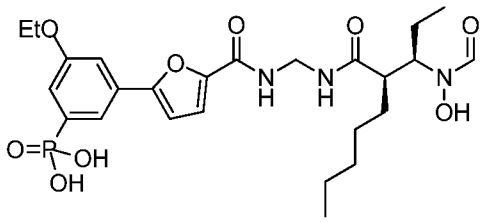
methyl hydrogen (3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl) carbamoyl)furan-2-yl)phenyl)phosphonate



A solution of (R)-dimethyl (3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido) methyl)carbamoyl)furan-2-yl)phenyl)phosphonate (86 mg, 0.17 mmol) in THF (1 ml) and water (1 ml) was treated with LiOH monohydrate (15 mg, 0.36 mmol) and stirred at room temperature for 3 hours. Additional LiOH monohydrate (15 mg, 0.36 mmol) was added and the reaction stirred overnight. The reaction was then diluted with DCM and acidified with 1 N HCl to pH 2. The aqueous was extracted with DCM (3 x). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the title compound as a white solid (75 mg, 89.7 % yield).

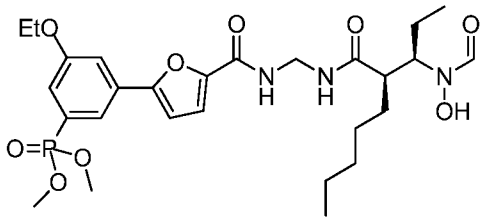
EXAMPLE 96

(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid



PREPARATION 1:

Step 1: dimethyl (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido) methyl)carbamoyl)furan-2-yl)phenyl)phosphonate



Dimethyl (3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)-5-

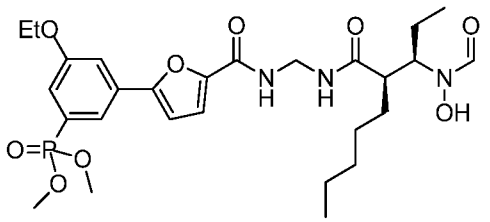
ethoxyphenyl)phosphonate (7.65 g, 11.39 mmol), was dissolved in ethanol (207 ml) and flushed with nitrogen. Pd/C (2.42 g, 2.28 mmol) was then added followed by methanol (20.71 ml) and the reaction then placed under hydrogen atmosphere (balloon). The mixture was stirred at room temperature for 1 hour and then filtered through Celite®, the Celite® was washed with MeOH and EtOAc. Concentration of the filtrates gave an orange residue which was azeotroped with EtOAc and then DCM to give the title compound as an orange residue (6.62 g) which was used without further purification. MS (m/z) 582.3 ($M+H^+$).

Step 2: (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)phenyl)phosphonic acid

Dimethyl (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido) methyl)carbamoyl)furan-2-yl)phenyl)phosphonate (6.62 g, 11.38 mmol) was dissolved in dichloromethane (224 ml). The mixture was cooled to 0 °C and then TMSBr (3.32 ml, 25.6 mmol) was added and the mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction was then concentrated and azeotroped with DCM, and then MeOH/EtOAc. The residue was dried under high vacuum and then diluted with ~250 ml of EtOAc and a minimal amount of MeOH to help dissolve the solids. To this solution was added ~200 ml water + 0.1 % TFA. The solution was shaken and the layers separated. The aqueous layer was extracted twice with EtOAc. The combined EtOAc extracts were concentrated to dryness and the residue suspended with ~200 ml EtOAc, sonicated and spun on a rotary vaporator in a water bath at 60 °C. The resulting suspension was cooled to room temperature and allowed to stir. At this time 400 mg of material similarly prepared was added. The light pink suspension was stirred for 1 hour at room temperature and then filtered. The solids were dried to give ~6 g of a light pink solid. This was then stirred in CH_3CN and heated to 60 °C, then cooled to room temperature and stirred for 1 hour before being filtered. The resulting solids were suspended in EtOAc/hexanes, stirred at room temperature for 1 hour and then filtered. The resulting light pink solids were dried under reduced pressure to give the title compound (5.52 g, 85 % yield). The filtrate was utilised to isolate Example 97.

PREPARATION 2:

Step 1: dimethyl (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido) methyl)carbamoyl)furan-2-yl)phenyl)phosphonate



To a 4 neck 1L round bottom flask, 5-(3-(dimethoxyphosphoryl)-5-ethoxyphenyl)furan-2-carboxylic acid (10 g, 29.4 mmol) and acetonitrile (200 ml) was added and the reaction mixture was cooled to 0-5 ºC. To the reaction mixture, triethylamine (5.74 ml, 41.2 mmol) and then HATU (10 g, 28.6 mmol) was added and the reaction mixture was warmed to 23-25 ºC and stirred for 1 hour to form the HATU-acid adduct. To a separate round bottom flask, (R)-N-(aminomethyl)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamide (7.6 g, 29.3 mmol) and acetonitrile (200 ml) was combined. This mixture was cooled to 0-5 ºC and then triethylamine (5.74 ml, 41.2 mmol) and TMS-Cl (7.5 ml, 59.1 mmol) was added and the mixture was stirred at 0-5 ºC for 1 hour. After 1 hour, the HATU-acid adduct was added to the second reaction mixture and the mixture was warmed to 23-25 ºC over 1 hour. The reaction mixture was concentrated under reduced vacuum at 35-40 ºC and the residue was diluted with ethyl acetate (100 ml) and water (50 ml). The layers were separated and the organic layer was washed with 5% sodium bicarbonate solution and then water. The organic layer was collected, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (1-3% MeOH/DCM). The pure fractions were combined and concentrated under reduced presure to give the title compound (14 g, 82%) as a brown foam.

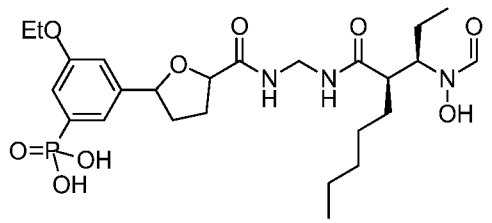
Step 2: (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)phenyl)phosphonic acid

Dimethyl (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido) methyl)carbamoyl)furan-2-yl)phenyl)phosphonate (6.62 g, 11.38 mmol) was dissolved in dichloromethane (224 ml). The mixture was cooled to 0 ºC and then TMSBr (3.32 ml, 25.6 mmol) was added and the mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction was then concentrated and azeotroped with DCM, and then

MeOH/EtOAc. The residue was dried under high vacuum and then diluted with ~250 ml of EtOAc and a minimal amount of MeOH to help dissolve the solids. To this solution was added ~200 ml water + 0.1 % TFA. The solution was shaken and the layers separated. The aqueous layer was extracted twice with EtOAc. The combined EtOAc extracts were concentrated to dryness and the residue suspended with ~200 ml EtOAc, sonicated and spun on a rotary vaporator in a water bath at 60 ºC. The resulting suspension was cooled to room temperature and allowed to stir. At this time 400 mg of material that was similarly prepared was added. The light pink suspension was stirred for 1 hour at room temperature and then filtered. The solids were dried to give ~6 g of a light pink solid. This was then stirred in CH_3CN and heated to 60 ºC, then cooled to room temperature and stirred for 1 hour before being filtered. The resulting solids were suspended in EtOAc/hexanes, stirred at room temperature for 1 hour and then filtered. The resulting light pink solids were dried under reduced pressure to give the title compound (5.52 g, 85 % yield).

EXAMPLE 97

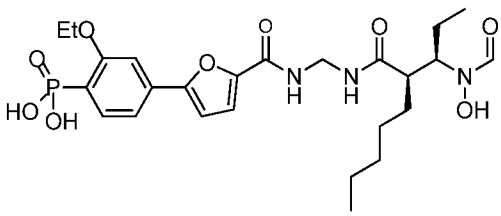
(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl) tetrahydrofuran-2-yl)phenyl)phosphonic acid



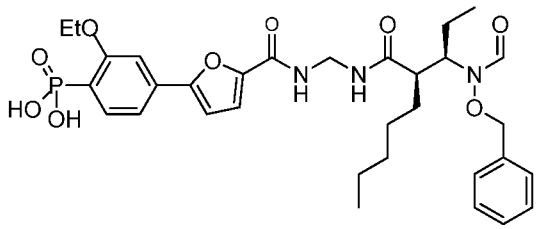
The filtrate from Example 96 was concentrated and purified by reverse phase HPLC (Waters, Starise, 30 x 150 mm, 20-60 % CH_3CN/water (+ 0.1 % TFA) over 14 minutes). The fractions were extracted with EtOAc and concentrated to give the title compound (30 mg).

EXAMPLE 98

(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid



Step 1: (4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)-2-ethoxyphenyl)phosphonic acid

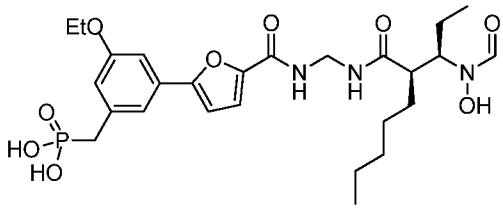


Dimethyl (4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)-2-ethoxyphenyl)phosphonate (600 mg, 0.89 mmol) was dissolved in dichloromethane (8.6 ml). The mixture was cooled to 0 °C and then bromotrimethylsilane (290 µl, 2.23 mmol) was added. The mixture was allowed to warm to room temperature, stirred for 1 hour and then concentrated. The residue was azeotroped twice with DCM to give the title compound as a dark residue which was used without further purification. MS (m/z) 672.3 ($M+H^+$).

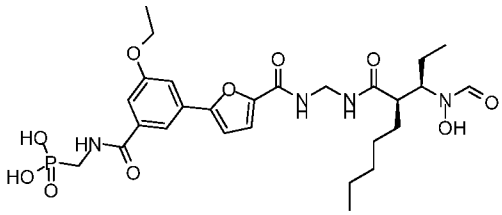
Step 2: (2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)phenyl)phosphonic acid

(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)-2-ethoxyphenyl)phosphonic acid (575 mg, 0.89 mmol), was dissolved in ethanol (20 ml) and the reaction flushed with nitrogen. Pd/C (238 mg, 0.22 mmol) was then added followed by methanol (20 ml) and the reaction was then placed under a hydrogen atmosphere (balloon). The mixture was stirred at room temperature for 1.5 hours then filtered through a PTFE filter, the filtrate was concentrated and purified via reverse phase HPLC (Waters, SunfirePrep C_{18} OBD, 5 µM 30 x 150 mm, 20-60 % CH_3CN/water (+ 0.1 % TFA) over 14 minutes). Fractions containing product were combined, diluted with EtOAc and the solution extracted with EtOAc (3 x). The combined EtOAc extracts were concentrated to give the title compound as an off white solid (245 mg, 50 % yield).

Example 99 was prepared from dimethyl 3-(5-((((R)-2-((R)-1-(N-(benzyloxy) formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzylphosphonate by methods analogous to those described in Example 98. In Step 2 methanol was used as the solvent instead of a mixture of methanol and ethanol.

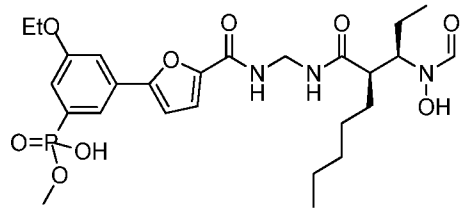
Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
99	(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzyl)phosphonic acid		(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzyl)phosphonic acid	659.4

Example 100 was prepared from diethyl ((3-(5-((((R)-2-((R)-1-(N-(benzyloxy) formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)methyl) phosphonate by methods analogous to those described in Example 98.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
100	((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonic acid		((3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzamido)methyl)phosphonic acid	701.2

EXAMPLE 101

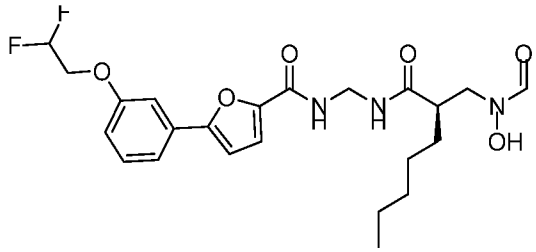
methyl hydrogen (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido) methyl)carbamoyl)furan-2-yl)phenyl)phosphonate



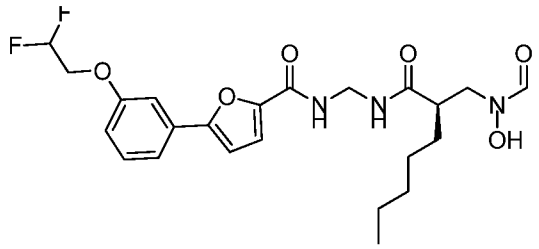
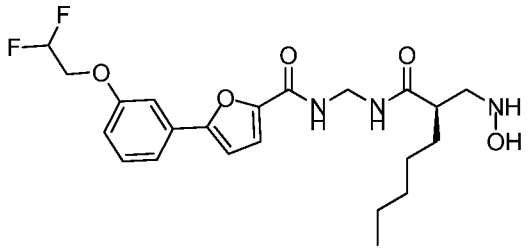
Dimethyl (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido) methyl)carbamoyl)furan-2-yl)phenyl)phosphonate (115 mg, 0.2 mmol) was dissolved in dichloromethane (1.95 ml). The mixture was cooled to 0 °C and then bromotrimethylsilane (25.7 µl, 0.2 mmol) was added and the mixture was allowed to warm to room temperature and stirred for 1 hour and then concentrated. The residue was purified by reverse phase HPLC (Waters, Starise 30 x1 50 mm, 20-60 % CH_3CN/water (+ 0.1% TFA)). The fractions containing product were passed through a StratoSpheres PL-HCO_3 MP SPE cartridge (500 mg/6 ml) and then concentrated to dryness via nitrogen blowdown at 50 °C. The residue was then dissolved in acetonitrile (250 µl) and water (600 µl) and lyopholized overnight to yield the title compound (19 mg, 17 % yield)

EXAMPLE 102

(R)-5-(3-(2,2-difluoroethoxy)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide



Step 1: (R)-5-(3-(2,2-difluoroethoxy)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido) methyl)furan-2-carboxamide and (R)-5-(3-(2,2-difluoroethoxy)phenyl)-N-((2(hydroxyamino) methyl)heptanamido)methyl)furan-2-carboxamide

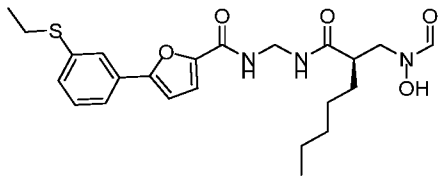
(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(2,2-difluoroethoxy)phenyl)furan-2-carboxamide (103.54 mg, 0.18 mmol) was dissolved in methanol (0.91 ml) under nitrogen. Pd/C (19.28 mg, 0.18 mmol) was added and the reaction placed under hydrogen atmosphere. The reaction was stirred for 4 hours and then filtered and concentrated. The residue was dissolved in DMF and purified by reverse phase HPLC (Gilson, Sunfire Prep C_{18} column, 5 µM, 30 x 150 mm, 20-80 % CH_3CN/water (+ 0.1 % TFA) over a 30 minute gradient) to give a mixture of the title compounds (180 mg) which was used without further purification. MS (m/z) 482.1 ($M+H^+$) and 454.2 ($M+H^+$).

Step 2: (R)-5-(3-(2,2-difluoroethoxy)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido) methyl)furan-2-carboxamide

CDI (96 mg, 0.6 mmol) was dissolved in DCM and formic acid (22.80 µl, 0.6 mmol) was added. The mixture was stirred for 45 minutes before being added to a solution of (R)-5-(3-(2,2-difluoroethoxy)phenyl)-N-((2-((hydroxyamino)methyl)heptanamido)methyl)furan-2-carboxamide and (R)-5-(3-(2,2-difluoroethoxy)phenyl)-N-((2-((hydroxyamino)methyl)heptanamido)methyl) furan-2-carboxamide (180 mg, 0.4 mmol) in DCM. The reaction mixture was then washed quickly with 0.6 N HCl. The aqueous layer was extracted with DCM. The combined organic layers were washed with H_2O, dried over Na_2SO_4 and concentrated to give the title compound (76.8 mg, 46.3 % yield).

EXAMPLE 103

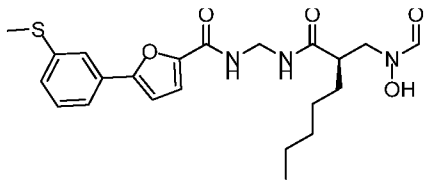
(R)-5-(3-(ethylthio)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl) furan-2-carboxamide



(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(ethylthio)

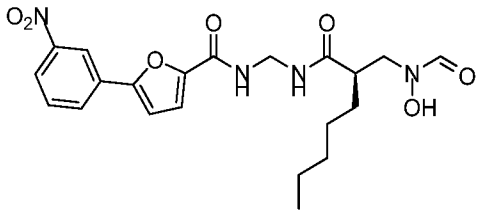
phenyl)furan-2-carboxamide (152.4 mg, 0.28 mmol) was dissolved in dichloromethane (0.55 ml) and boron trichloride (1 M, 0.83 ml , 0.83 mmol) was added and the reaction was stirred for 4 hours. The reaction was then quenched by addition of methanol. After stirring for 5 minutes the reaction was concentrated. Formic acid (20.57 µl, 0.54 mmol) was added to a solution of CDI (87 mg, 0.54 mmol) in dichloromethane (1.77 ml) and the reaction was stirred for 45 minutes before being added to the isolated residue. The reaction was allowed to stir overnight. The reaction was then washed quickly with 0.6 N HCl. The aqueous layer was extracted with DCM. The combined organic layers were washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was purified by mass directed reverse phase HPLC (Waters, Sunfire 30 x 150 mm, 30-70 % CH_3CN/water (+ 0.1 % TFA)). The fractions containing product were passed through a StratoSpheres PL-HCO_3 MP SPE cartridge (500 mg/6 ml) and then concentrated to dryness via nitrogen blowdown at 50 °C. The residue was then dissolved in acetonitrile (250 µl) and water (600 µl) and lyopholized overnight to yield the title compound (12.1 mg, 9.49 % yield).

Example 104 was prepared from the indicated intermediate by methods analogous to those described for Example 103.

Ex.	Name	Structure	Intermediate
104	(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(methylthio)phenyl)furan-2-carboxamide		(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-(methylthio)phenyl)furan-2-carboxamide

EXAMPLE 105

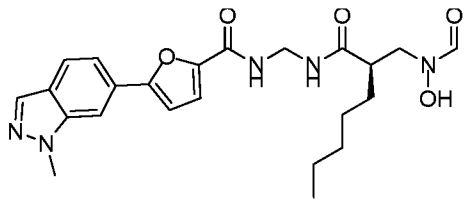
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-nitrophenyl)furan-2-carboxamide



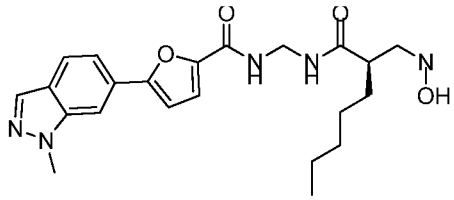
A solution of (R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(3-nitrophenyl)furan-2-carboxamide (150 mg, 0.28 mmol) in dichloromethane (0.28 ml) was cooled to 0 ºC and then treated with boron trichloride (1 M in DCM, 0.84 ml, 0.84 mmol). The reaction was then allowed to warm to room temperature and stirred for 4 hours. The reaction was diluted by the addition of water and the organic collected via hydrophobic frit and concentrated. The residue was then dissolved in dichloromethane (0.28 ml) and treated with 5-methyl-2-thioxo-1,3,4-thiadiazole-3(2H)-carbaldehyde Yazawa, H., et al., Tetrahedron Letters, 1985, 26 (31), 3703-3706 (44.8 mg, 0.28 mmol) and the reaction stirred at room temperature overnight. The reaction was then diluted by the addition of water and the organic collected via hydrophobic frit and concentrated. The residue was purified by flash chromatography (10 g Si SPE, DCM, ether, ethyl acetate, acetone). Fractions containing desired product were concentrated and the residue was dissolved in the minimum amount of DCM and ether added dropwise to achieve precipitate formation. The solid was then collected to yield the title compound as a yellow solid (26 mg, 19.8 % yield).

EXAMPLE 106

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(1-methyl-1H-indazol-6-yl)furan-2-carboxamide



Step 1: (R)-N-((2-((hydroxyamino)methyl)heptanamido)methyl)-5-(1-methyl-1H-indazol-6-yl)furan-2-carboxamide



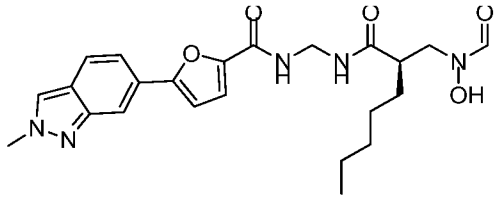
(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(1-methyl-1H-indazol-6-yl)furan-2-carboxamide (208.6 mg, 0.38 mmol) was dissolved in methanol (0.38 ml) under nitrogen. Pd/C (2.03 mg, 0.02 mmol) was added and the reaction placed under H_2 atmosphere. The reaction was stirred for 6 hours however LCMS indicated no formation of desired mass. The reaction mixture was filtered and concentrated. Dichloromethane (0.38 ml) was added to the residue followed by boron trichloride (1 M, 1.15 ml, 1.15 mmol). The reaction was stirred for 3 hours then quenched by the addition of MeOH and concentrated to give the title compound (191.3 mg) which was used without further purification. MS (m/z) 428.2 ($M+H^+$).

Step 2: (R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(1-methyl-1H-indazol-6-yl)furan-2-carboxamide

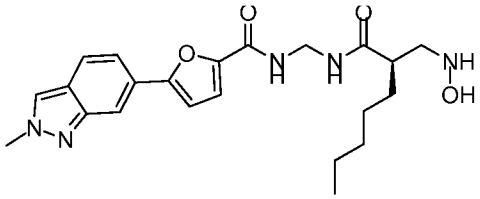
Formic acid (17.16 µl, 0.45 mmol) was added to a solution of CDI (72.6 mg, 0.45 mmol) in DCM (2.22 ml) and the reaction was stirred for 45 minutes before a solution of (R)-N-((2-((hydroxyamino)methyl)heptanamido)methyl)-5-(1-methyl-1H-indazol-6-yl)furan-2-carboxamide (191.3 mg, 0.45 mmol) in DCM was added. The reaction was stirred overnight. The reaction mixture was then washed quickly with 0.6 N HCl. The aqueous layer was extracted with DCM. The combined organic layers were washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was dissolved in DMF and purified by reverse phase HPLC (Gilson, Sunfire Prep C_{18} column, 5 µM, 30 x 150 mm, 20-60 % CH_3CN/water (+ 0.1 % TFA) 45 ml/min over a 30 minute gradient) to yield the title compound (22.7 mg, 11.1 % yield).

EXAMPLE 107

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(2-methyl-2H-indazol-6-yl)furan-2-carboxamide



Step 1: (R)-N-((2-((hydroxyamino)methyl)heptanamido)methyl)-5-(2-methyl-2H-indazol-6-yl)furan-2-carboxamide



(R)-N-((2-((N-(benzyloxy)formamido)methyl)heptanamido)methyl)-5-(2-methyl-2H-indazol-6-yl)furan-2-carboxamide (276.3 mg, 0.51 mmol) was dissolved in dichloromethane (0.51 ml) and then boron trichloride (1 M, 1.52 ml, 1.52 mmol) was added and the reaction was stirred for 7 hours. Additional boron trichloride (1 M, 1.01 ml, 1.01 mmol) was added and the reaction was stirred overnight. LCMS indicated no formation of desired mass. The reaction mixture was quenched with MeOH and concentrated. The residue was dissolved in methanol (0.51 ml) and placed under nitrogen atmosphere. Pd/C (53.9 mg, 0.51 mmol) was added and the reaction placed under hydrogen atmosohere and stirred for 6 hours. The reaction was then filtered and concentrated. The residue was dissolved in DMF and purified by reverse phase HPLC (Gilson, Sunfire Prep C_{18} column, 5 µM, 30 x 150 mm, 0-60 % CH_3CN/water (+ 0.1 % TFA) over a 30 minute gradient) to give the title compound (75.1 mg, 32.6 % yield). MS (m/z) 428.2 ($M+H^+$).

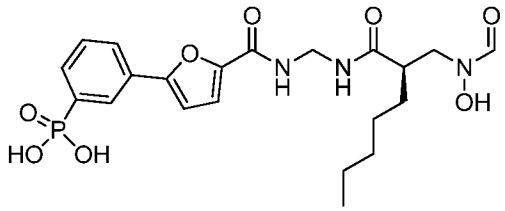
Step 2: (R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(2-methyl-2H-indazol-6-yl)furan-2-carboxamide

CDI (42.7 mg, 0.26 mmol) was dissolved in DCM and formic acid (10.11 µl, 0.26 mmol) was added. The mixture was stirred for 45 minutes before being added to a solution of (R)-N-((2-((hydroxyamino)methyl)heptanamido)methyl)-5-(2-methyl-2H-indazol-6-yl)furan-2-carboxamide (75.1 mg, 0.18 mmol) in DCM. The reaction was stirred overnight. The reaction mixture was then washed quickly with 0.6 N HCl. The aqueous layer was extracted with DCM. The combined organic layers were washed with H_2O,

dried over Na_2SO_4, filtered and concentrated. The residue was purified by mass directed reverse phase HPLC (Waters, Sunfire, 30 x 150 mm, 20-60 % CH_3CN/water (+ 0.1 % TFA)). The fractions containing product were passed through a StratoSpheres PL-HCO_3 MP SPE cartridge (500 mg/6 ml) and then concentrated to dryness via nitrogen blowdown at 50 °C. The residue was then dissolved in acetonitrile (250 µl) and water (600 µl) and lyopholized overnight to give the title compound (5.6 mg, 7 % yield).

EXAMPLE 108

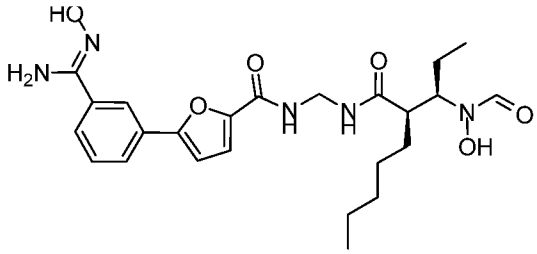
(R)-(3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid



To a mixture of 5-(3-phosphonophenyl)furan-2-carboxylic acid (176 mg, 0.66 mmol), DIPEA (0.23 ml, 1.32 mmol), HOBt (116 mg, 0.86 mmol) in dichloromethane (3 ml) and NMP (3 ml) was added EDC (164 mg, 0.86 mmol) and the reaction mixture stirred for 10 minutes. A solution of (R)-N-(aminomethyl)-2-((N-hydroxyformamido)methyl)heptanamide (152 mg, 0.66 mmol) in dichloromethane (3 ml) and NMP (3 ml) was then added and the reaction stirred for 4 nights. The reaction mixture was diluted with dichloromethane (25 ml) and water (25 ml), an emulsion formed, NaOH (100 mg) was added and the phases separated. The organic phase was washed with aqueous NaOH (100 mg in 20 ml of water). The aqueous phase was then washed with dichloromethane (7 x 50 ml) then treated with 1 M HCl (2.5 ml). The aqueous phase was loaded directly onto a 30 g SNAP C_{18} column and eluted with water containing 0.1 % formic acid and then 0-95 % CH_3CN in water containing 0.1 % formic acid. Product containing fractions were concentrated to give 14 mg and 59 mg of impure product which were then recombined and purified by mass directed reverse phase HPLC (Waters, Phenomenex Luna C_{18} , 10 µm, 250 x 21.2 mm, 15-80 % CH_3CN/water + 0.1 % HCOOH) to give the title compound as a pale pink glass (27 mg, 8 % yield, containing 13 % of (R)-(3-(5-(((2-((hydroxyamino)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid).

EXAMPLE 109

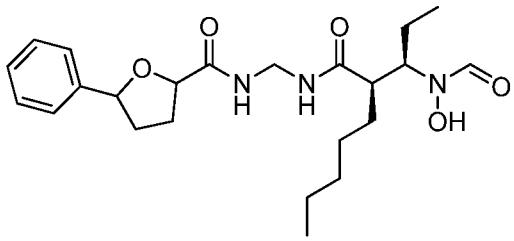
5-(3-((Z)-N'-hydroxycarbamimidoyl)phenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido) methyl)furan-2-carboxamide



5-(3-cyanophenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) furan-2-carboxamide (132 mg, 0.29 mmol) was dissolved in ethanol (1.45 ml) and treated with hydroxylamine (50 mg, 0.76 mmol) and the reaction mixture heated at 75 °C for 2 hours. The reaction was then cooled to room temperature, filtered through a syringe filter, and purified by reverse phase HPLC (Waters, Starise 30 x 150 mm, 10-50 % CH_3CN/water (+ 0.1 % TFA), 50 ml/min). The fractions containing product were passed through a StratoSpheres PL-HCO_3 MP SPE cartridge (500 mg/6 ml) and then concentrated to dryness via nitrogen blowdown at 50 °C. The residue was then dissolved in acetonitrile (250 µl) and water (600 µl) and lyopholized overnight to give the title compound as an off white solid (76 mg, 54 % yield).

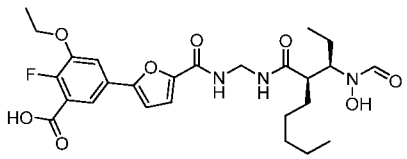
EXAMPLE 110

N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)-5-phenyltetrahydrofuran-2-carboxamide

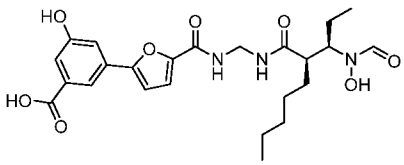


The title compound (400 mg) was isolated as a hydrogenation by-product following column chromatography of N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide.

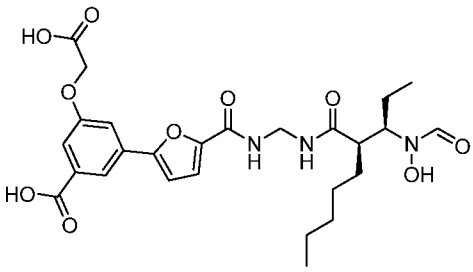
Example 111 was prepared from methyl 5-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-3-ethoxy-2-fluorobenzoate by methods analogous to those described for Example 74 using a 4:1 ratio of methanol:ethanol in Step 1 and a 3:1:1 ratio of THF:MeOH:H_2O in Step 2.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step1
111	3-ethoxy-2-fluoro-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		methyl 3-ethoxy-2-fluoro-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate	551.2

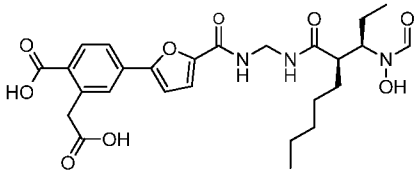
Example 112 was prepared from methyl 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-hydroxybenzoate by methods analogous to those described for Example 74 using $Pd(OH)_2$ instead of Pd/C in Step 1.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step1
112	3-hydroxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		methyl 3-hydroxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate	504.1

Example 113 was prepared from (methyl 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-(2-methoxy-2-oxoethoxy)benzoate by methods analogous to those described for Example 74 using $Pd(OH)_2$ instead of Pd/C in Step 1.

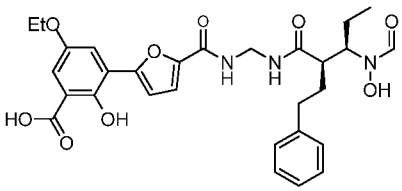
Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step1
113	3-(carboxymethoxy)-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		methyl 3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-(2-methoxy-2-oxoethoxy)benzoate	576.3

Example 114 was prepared from methyl 4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-(2-methoxy-2-oxoethyl)benzoate by methods analogous to those described for Example 76 using CH_3CN instead of ethanol and water in Step 2. Additionally, reaction times and amount of Pd/C may vary slightly in the Examples 114-132.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
114	2-(carboxymethyl)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		methyl 4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-(2-methoxy-2-oxoethyl)benzoate	560.2

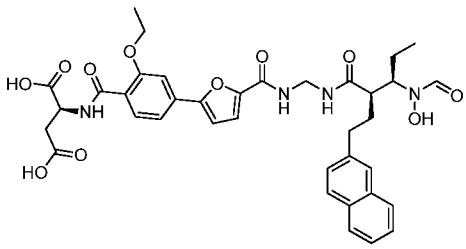
Example 115 was prepared from ethyl 3-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxy-2-hydroxybenzoate by methods analogous to those described for Example 76.

.

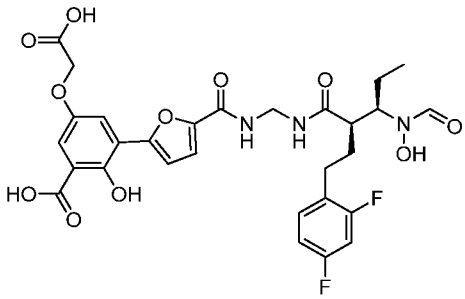
Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
115	5-ethoxy-2-hydroxy-3-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		ethyl 5-ethoxy-2-hydroxy-3-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)benzoate	596.4

Example 117 was prepared from (S)-dimethyl 2-(4-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-(2-(naphthalen-2-yl)ethyl)pentanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)succinate by methods analogous to those described for Example 76 using THF and water instead of ethanol and water in Step 2.

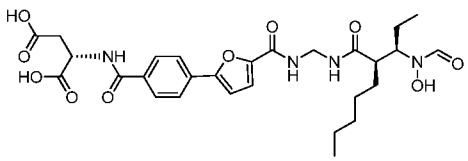
.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
117	(S)-2-(2-ethoxy-4-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-(2-(naphthalen-2-yl)ethyl)pentanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid		(S)-dimethyl 2-(2-ethoxy-4-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-(2-(naphthalen-2-yl)ethyl)pentanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinate	745.2

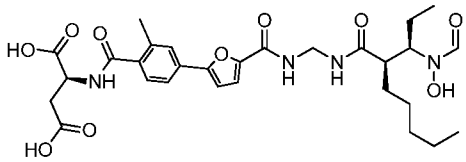
Example 118 was prepared from methyl 3-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-(2,4-difluorophenethyl)pentanamido)methyl)carbamoyl)furan-2-yl)-2-hydroxy-5-(2-methoxy-
2-oxoethoxy) by methods analogous to those described for Example 76 using THF and water instead of ethanol and water in Step 2.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
118	5-(carboxymethoxy)-3-(5-((((2R,3R)-2-(2,4-difluorophenethyl)-3-(N-hydroxyformamido)pentanamido)methyl)carbamoyl)furan-2-yl)-2-hydroxybenzoic acid		methyl 3-(5-((((2R,3R)-2-(2,4-difluorophenethyl)-3-(N-hydroxyformamido)pentanamido)methyl)carbamoyl)furan-2-yl)-2-hydroxy-5-(2-methoxy-2-oxoethoxy)benzoate	662.2

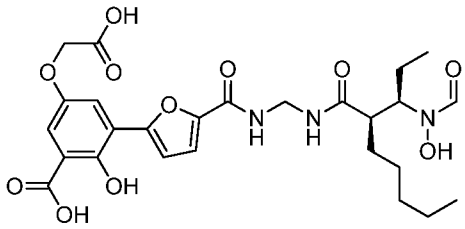
Example 119 was prepared from (S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinate by methods analogous to those described for Example 76 using MeOH instead of MeOH and DCM in Step 1.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
119	(S)-2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid		(S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinate	617.3

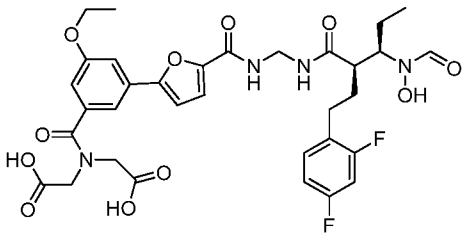
Example 120 was prepared from (S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzamido)succinate by methods analogous to those described for Example 76 using MeOH and water instead of ethanol and water in Step 2.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
120	(S)-2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzamido)succinic acid		(S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzamid)succinate	631.8

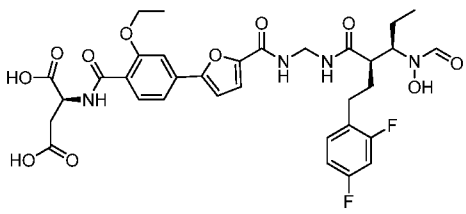
Example 121 was prepared from methyl 3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-hydroxy-5-(2-methoxy-2-oxoethoxy)benzoate by methods analogous to those described for Example 76 using MeOH and water instead of ethanol and water in Step 2.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
121	5-(carboxymethoxy)-2-hydroxy-3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		methyl 2-hydroxy-3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-(2-methoxy-2-oxoethoxy)benzoate	592.2

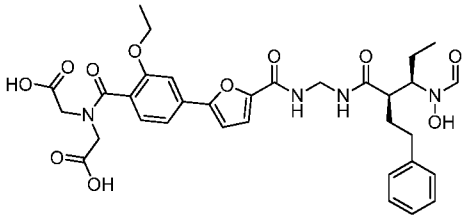
Example 122 was prepared from dimethyl 2,2'-((3-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-(2,4-difluorophenethyl)pentanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoyl)azanediyl)diacetate by methods analogous to those described for Example 76 using THF and water instead of ethanol and water in Step 2.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
122	2,2'-((3-(5-((((2R,3R)-2-(2,4-difluorophenethyl)-3-(N-hydroxyformamido)pentanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoyl)azanediyl)diacetic acid		dimethyl 2,2'-((3-(5-((((2R,3R)-2-(2,4-difluorophenethyl)-3-(N-hydroxyformamido)pentanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoyl)azanediyl)diacetate	731.3

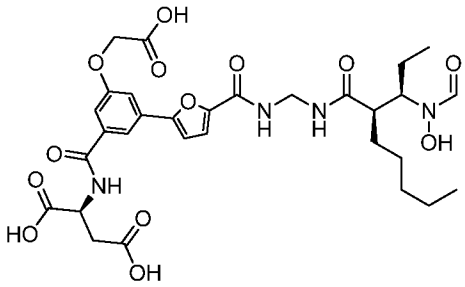
Example 123 was prepared from (S)-dimethyl 2-(4-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-(2,4-difluorophenethyl)pentanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)succinate by methods analogous to those described for Example 76 using THF and water instead of ethanol and water in Step 2.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
123	(S)-2-(4-(5-((((2R,3R)-2-(2,4-difluorophenethyl)-3-(N-hydroxyformamido)pentanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)succinic acid		(S)-dimethyl 2-(4-(5-((((2R,3R)-2-(2,4-difluorophenethyl)-3-(N-hydroxyformamido)pentanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)succinate	731.3

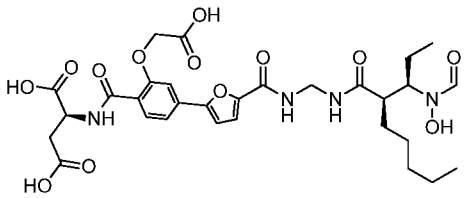
Example 124 was prepared from dimethyl 2,2'-((4-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzoyl)azanediyl)diacetate by methods analogous to those described for Example 76.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
124	2,2'-((2-ethoxy-4-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetic acid		2,2'-((2-ethoxy-4-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetic acid	667.2

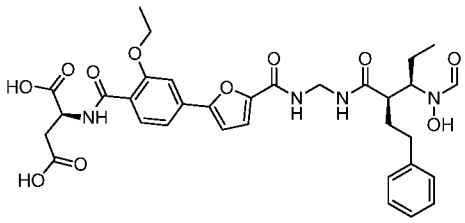
Example 125 was prepared from (S)-dimethyl 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-(2-methoxy-2-oxoethoxy)benzamido)succinate by methods analogous to those described for Example 76 using MeOH and water instead of ethanol and water in Step 2.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
125	(S)-2-(3-(carboxymethoxy)-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid		(S)-dimethyl 2-(3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-(2-methoxy-2-oxoethoxy)benzamido)succinate	705.3

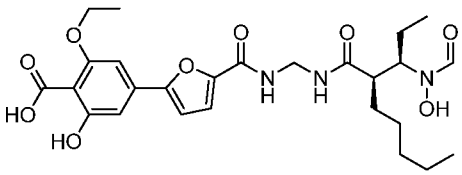
Example 126 was prepared from (S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-(2-methoxy-2-oxoethoxy)benzamido)succinate by methods analogous to those described for Example 76 using MeOH and water instead of ethanol and water in Step 2.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
126	(S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid		(S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-(2-methoxy-2-oxoethoxy)benzamido)succinate	705.3

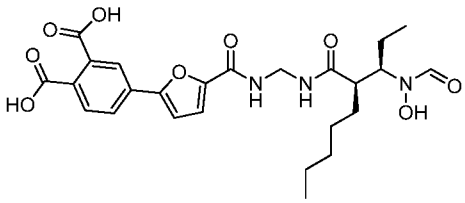
Example 127 was prepared from (R)-dimethyl 2-(4-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)succinate by methods analogous to those described for Example 76 using MeOH and water instead of ethanol and water in Step 2.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
127	(S)-2-(2-ethoxy-4-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid		(S)-dimethyl 2-(2-ethoxy-4-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinate	695.3

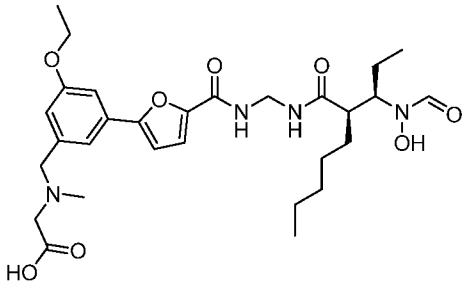
Example 128 was prepared from methyl 4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxy-6-hydroxybenzoate by methods analogous to those described for Example 76 using DCM and methanol instead of ethanol and water in Step 1.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
128	2-ethoxy-6-hydroxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		methyl 2-ethoxy-6-hydroxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate	548.3

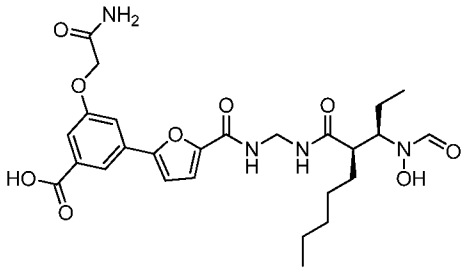
Example 129 was prepared from dimethyl 4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phthalate by methods analogous to those described for Example 76 using MeOH instead of MeOH and DCM in Step 1 and using acetonitrile and water instead of ethanol and water in Step 2.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
129	4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phthalic acid		dimethyl 4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phthalate	546.1

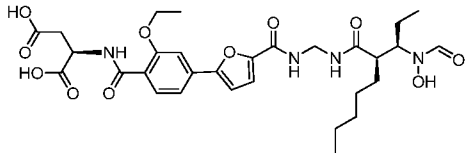
Example 130 was prepared from methyl 2-((3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzyl)(methyl)amino)acetate by methods analogous to those described for Example 76 using MeOH instead of MeOH and DCM in Step 1.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
130	2-((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzyl)(methyl)amino)acetic acid		methyl 2-((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzyl)(methyl)amino)acetate	589.2

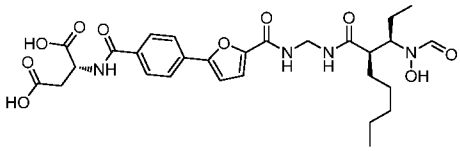
Example 131 was prepared from methyl 3-(2-amino-2-oxoethoxy)-5-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate by methods analogous to those described for Example 76.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
131	3-(2-amino-2-oxoethoxy)-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid		methyl 3-(2-amino-2-oxoethoxy)-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate	561.2

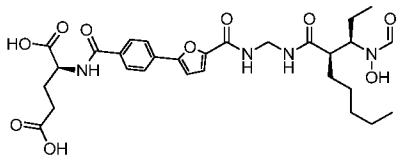
Example 132 was prepared from R)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)succinate by methods analogous to those described for Example 76 using THF and water instead of ethanol and water in Step 2.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
132	(R)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid		(R)-dimethyl 2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinate	561.2

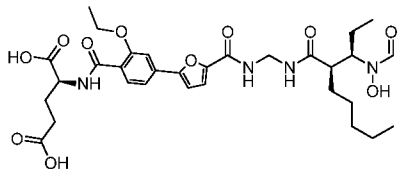
Example 133 was prepared from (R)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinate by methods analogous to those described for Example 76 using THF and a 1M solution of LiOH instead of ethanol/water mixture and solid LiOH in step 2.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
133	((R)-2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid		(R)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinate	617.3

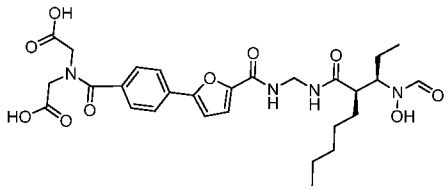
Example 134 was prepared from (S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)pentanedioate by methods analogous to those described for Example 76 using MeOH/water mixture and a 1M solution of LiOH instead of ethanol/water mixture and solid LiOH in step 2.

Ex.	Name	Structure	Name Step 1	MS (m/z) (M+H+) Step 1
134	(S)-2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)pentanedioic acid		(S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)pentanedioate	631.8

Example 135 was prepared from (S)-dimethyl 2-(4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)pentanedioate by methods analogous to those described for Example 76 using MeOH/water mixture and a 1M solution of LiOH instead of ethanol/water mixture and solid LiOH in step 2.

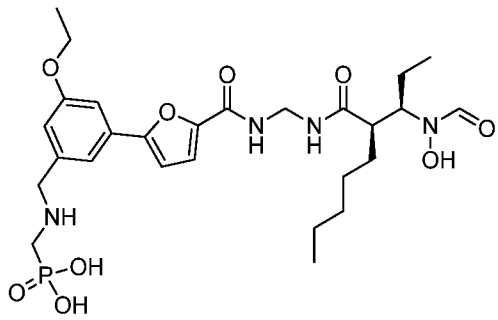
Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
135	(S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)pentanedioic acid		(S)-dimethyl 2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)pentanedioate	675.7

Example 136 was prepared from dimethyl 2,2'-((4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetate by methods analogous to those described for Example 76 using methanol and water instead of ethanol and water in step 2.

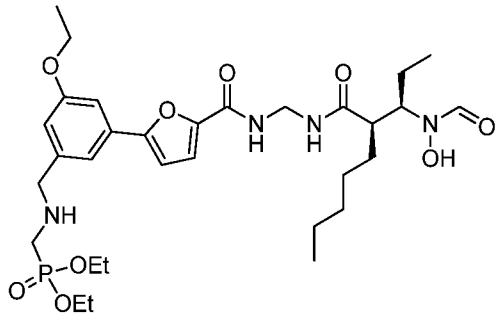
Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
136	2,2'-((4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetic acid		dimethyl 2,2'-((4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetate	617.4

Example 137

(((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzyl)amino)methyl)phosphonic acid, trifluoroacetic acid salt



Step 1: Diethyl (((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido) propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzyl)amino)methyl)phosphonate

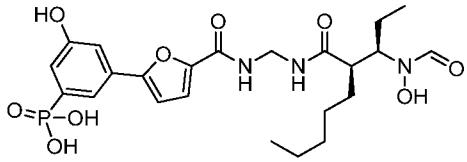


Diethyl (((3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)hexanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzyl)amino)methyl)phosphonate (0.6 g, 0.8 mmol) was dissolved in MeOH. 10% Pd/C (0.09 g, 0.08 mmol) followed by ammonium formate (0.26 g, 4.12 mmol) were added. The reaction was stirred for 2 h then Pd/C (0.09 g, 0.08 mmol and ammonium formate (0.26 g, 4.12 mmol) were added. The reaction mixture was filtered through celite, and the filtrate was concentrated, suspended in DCM and filtered. After the filtrate was concentrated, it was redissolved in MeOH and resubjected to the same conditions. The reaction mixture was filtered through celite and the filtrate was concentrated to obtain the title compound (0.25 g, 46%) as a yellow oil. MS (m/z) 653.2 ($M+H^+$).

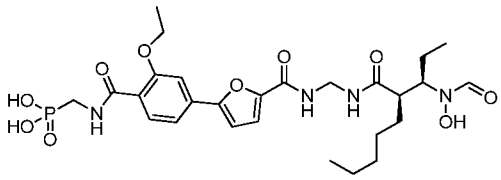
Step 2: (((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido) propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzyl)amino)methyl)phosphonic acid, trifluoroacetic acid salt

Diethyl (((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido) propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzyl)amino)methyl)phosphonate (0.26 g, 0.4 mmol) was dissolved in DCM and treated with TMS-Br (154 ul, 1.2 mmol). The reaction stirred for 4 hours and 3 more eq of TMS-Br was added and the reaction was stirred for another 8 hours. The material was then purified via reverse phase HPLC (Sunfire 30x150mm Acetonitrile:Water TFA 20-60%, flow rate 50 ml/min, gradient 16 min) to obtain the title compound as a white solid (0.035g, 12%). MS (m/z) 597.2 ($M+H^+$).

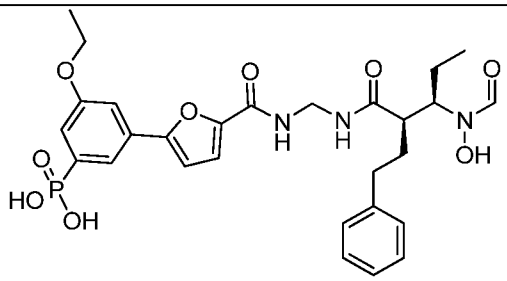
Example 138 was prepared from dimethyl (3-(benzyloxy)-5-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate by methods analogous to those described in Example 137.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
138	(3-hydroxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid		dimethyl (3-hydroxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate	554.2

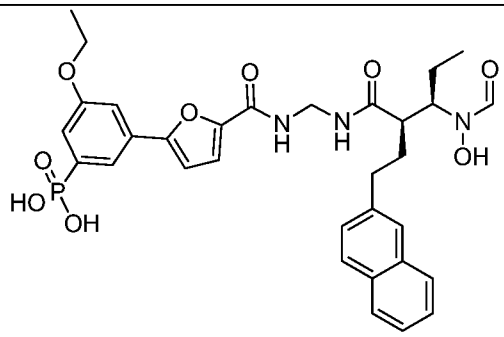
Example 139 was prepared from diethyl ((4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)methyl)phosphonate by methods analogous to those described in Example 137 using DCM and MeOH instead of MeOH in Step 1.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
139	((2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonic acid		diethyl ((2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonate	667.5 (M+H)

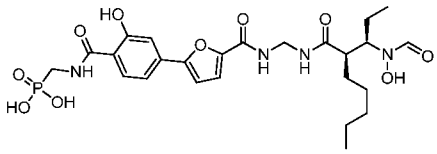
Example 140 was prepared from dimethyl (3-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxyphenyl)phosphonate by methods analogous to those described in Example 137 using DCM and MeOH instead of MeOH in Step 1 and using acetonitrile instead of DCM in Step 2.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
140	(3-ethoxy-5-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid		dimethyl (3-ethoxy-5-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate	616.3

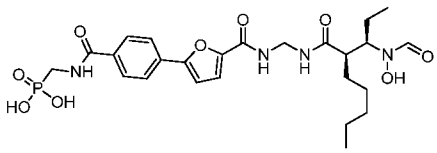
Example 141 was prepared from dimethyl (3-(5-((((2R,3R)-3-(N-(benzyloxy)formamido)-2-(2-(naphthalen-2-yl)ethyl)pentanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxyphenyl)phosphonate by methods analogous to those described in Example 137 using DCM and MeOH instead of MeOH in Step 1.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
141	(3-ethoxy-5-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-(2-(naphthalen-2-yl)ethyl)pentanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid		dimethyl (3-ethoxy-5-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-(2-(naphthalen-2-yl)ethyl)pentanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate	666.1

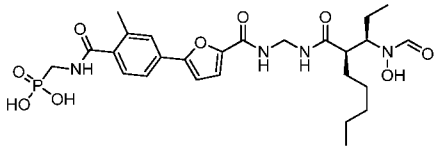
Example 142 was prepared from diethyl ((2-(benzyloxy)-4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonate by methods analogous to those described in Example 137 using DCM and MeOH instead of MeOH in Step 1.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
142	((2-hydroxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonic acid		diethyl ((2-hydroxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonate	639.3

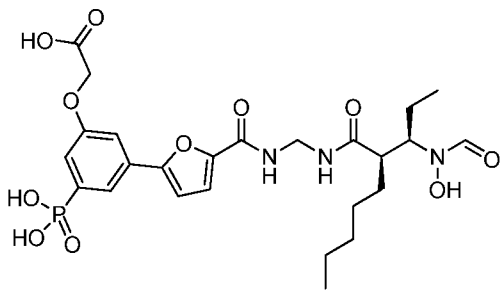
Example 143 was prepared from diethyl ((4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonate by methods analogous to those described in Example 137 using DCM and MeOH instead of MeOH in Step 1.

Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
143	((4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonic acid		diethyl ((4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonate	623.3

Example 144 was prepared from diethyl ((4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzamido)methyl)phosphonate by methods analogous to those described in Example 137 using DCM and MeOH instead of MeOH in Step 1.

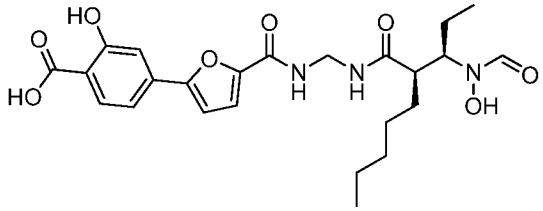
Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
144	((4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzamido)methyl)phosphonic acid		diethyl ((4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzamido)methyl)phosphonate	637.3

Example 145 was prepared from 2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-(dimethoxyphosphoryl)phenoxy)acetic acid by methods analogous to those described in Example 98 using $Pd(OH)_2$ instead of Pd/C and ethanol instead of an ethanol/methanol mixture in Step 2 and a DCM and acetonitrile mixture instead of DCM in Step 1.

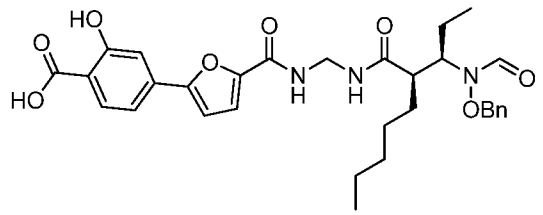
Ex.	Name	Structure	Name Step 1	MS (m/z) ($M+H^+$) Step 1
145	2-(3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-phosphonophenoxy)acetic acid		2-(3-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-phosphonophenoxy)acetic acid	674.1

EXAMPLE 146

2-hydroxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid



Step 1: 4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-hydroxybenzoic acid



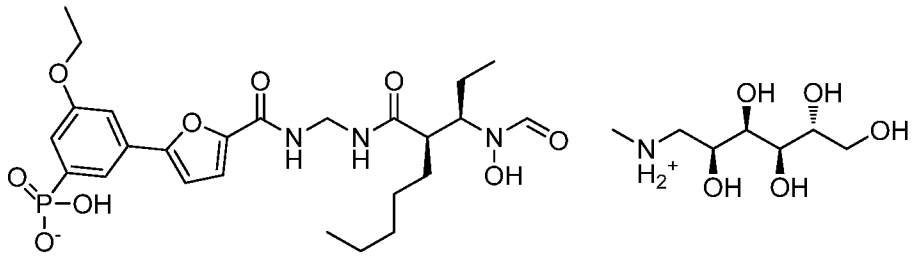
To a 20 ml microwave vial equipped with a teflon stir bar was added methyl 4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-hydroxybenzoate (300 mg, 0.51 mmol),1,1,1-trifluoro-2-iodoethane (125 µl, 1.26 mmol), and K_2CO_3 (349 mg, 2.53 mmol), sequentially at 25 ºC. Acetonitrile (2402 µl) was added and the reaction heated in the microwave at 150 ºC for 1/2 hour. The material was then redissolved in DCM and the material was cooled at -20 °C for 5 days. The organic solvents were evaporated in vacuo. The organic layer was extracted with 2M NaOH (2 X 10 mL). The aq layers were combined, cooled to 0 ºC with ice, then quenched with HCl (2.0 M) to pH < 4. The organic layer was dried over Na_2SO_4, filtered, and solvents removed in vacuo. The crude material (300 mg) was collected and purified by HPLC (Waters Sunfire 30x150mm Acetonitrile:Water TFA 50-100%) to give the title compound as a white solid (55 mg, 0.090 mmol, 17.84 % yield). MS (m/z) 580.2 (M+H+).

Step 2: 2-hydroxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

To a 250 mL round-bottomed-flask equipped with a teflon stir bar was added $Pd(OH)_2$ (6.66 mg, 9.49 µmol). A solution of 4-(5-((((R)-2-((R)-1-(N-(benzyloxy)formamido)propyl) heptanamido)methyl)carbamoyl)furan-2-yl)-2-hydroxybenzoic acid (55 mg, 0.095 mmol) in ethanol (1.9 ml) was added. An atmosphere of H_2 was applied and the reaction stirred vigorously at 25 ºC for 5 h. The reaction mixture was filtered through a plug of Celite ®, eluting with DCM. The filtrate was concentrated in vacuo to provide a crude material which was placed in the freezer ~48h. The semi-pure solid was dissolved in 20 ml EtOAc. 20 ml 2N NaOH was added with ca. 1 ml MeOH to aid in dissolution. After the solid was fully dissolved, the organic solvents were removed by rotary evaporation. The aq layer was extracted with DCM (3 X 5 ml).The aq. layer was separated, cooled to 0 ºC, and brought to a pH of < 4.0, and the aq. layer was extracted with 20 ml EtOAc. The layers were separated, the organic layer was dried with Na_2SO_4, filtered and solvents evaporated to provide the title compound (30 mg, 0.058 mmol, 61.4 % yield) as an off-white solid.

EXAMPLE 147

(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid, (-)-1-Deoxy-1-(methylamino)-D-glucitol salt

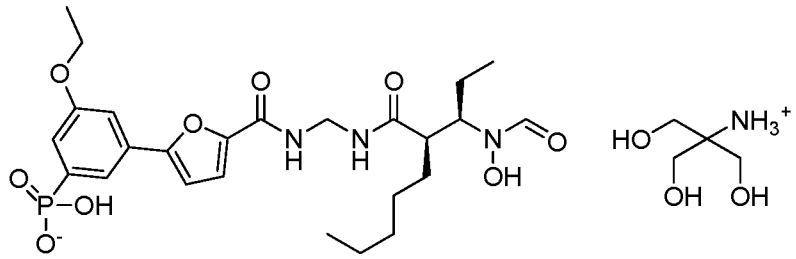


Step 1: (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid,(-)-1-Deoxy-1-(methylamino)-D-glucitol salt

(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid (265 mg, 0.479 mmol) was slurried in ethyl acetate (2.65 ml) and tetrahydrofuran (27 ml). (2R,3R,4R,5S)-6-(methylamino)hexane-1,2,3,4,5-pentaol (93 mg, 0.48 mmol) was added. The resulting slurry was stirred at 23 °C for 15 minutes and the slurry was seeded with seed crystals of title compound and then temperature cycled from 40 °C to 5 °C at 1 hour increments for 6 hours, followed by 18 hours at 23 °C. The slurry was then temperature cycled from 40 °C to 5 °C at 1 hour increments for 6 hours, followed by 18 hours at 23 °C, followed by temperature cycling from 45 °C to 5 °C at 1 hour increments for 6 hours, followed by 18 hours at 23 °C, followed by temperature cycling from 45 °C to 5 °C at 1 hour increments for 6 hours, followed by 18 hours at 23 °C, followed by temperature cycling from 45 °C to 5 °C at 1 hour increments for 6 hours. After the last 5 °C cycle, the slurry was filtered, rinsed with ethyl acetate, and the solid collected and dried under vacuum for 72 hours to the title compound (330 mg, 0.44 mmol, 92 % yield) as a white solid.

EXAMPLE 148

(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid, 2-amino-2-(hydroxymethyl)-1,3-propanediol salt

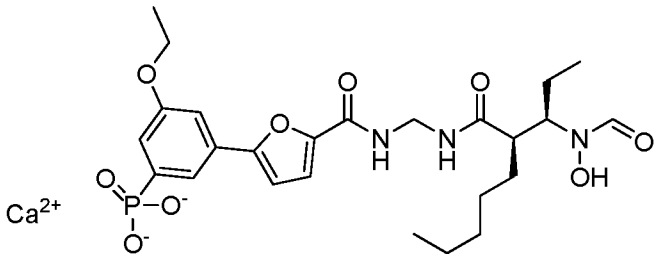


Step 1: (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid, 2-amino-2-(hydroxymethyl)-1,3-propanediol salt

(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid (390 mg, 0.71 mmol) was slurried in ethyl acetate (7.82 ml). 2-amino-2-(hydroxymethyl)propane-1,3-diol (86 mg, 0.71 mmol) was added. The resulting slurry was stirred at 23 °C for 15 minutes and the slurry was seeded with seed crystals of title compound and then temperature cycled from 40 °C to 5 °C at 1 hour increments for 6 hours, followed by 18 hours at 23 °C. The slurry was then temperature cycled from 40 °C to 5 °C at 1 hour increments for 6 hours, followed by 18 hours at 23 °C, followed by temperature cycling from 45 °C to 5 °C at 1 hour increments for 6 hours, followed by 18 hours at 23 °C, followed by temperature cycling from 45 °C to 5 °C at 1 hour increments for 6 hours, followed by 18 hours at 23 °C, followed by temperature cycling from 45 °C to 5 °C at 1 hour increments for 6 hours. After the last 5 °C cycle, the slurry was filtered, rinsed with ethyl acetate, and the solid collected and dried under vacuum for 72 hours to obtain the title compound (375 mg, 0.56 mmol, 79 % yield) as a white solid.

EXAMPLE 149

(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid, calcium salt



Step 1: (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid, calcium salt

(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid (381 mg, 0.688 mmol) was slurried in ethyl acetate (7.6 ml). Calcium acetate (110 mg, 0.69 mmol) was added. The resulting slurry was stirred at 23 °C for 15 minutes and then temperature cycled from 45 °C to 5 °C at 1 hour increments for 6 hours, followed by 88 hours at -20 °C. The slurry was then temperature cycled from 45 °C to 5 °C at 1 hour increments for 6 hours, followed by 18 hours at -20 °C, followed by temperature cycling from 45 °C to 5 °C at 1 hour increments for 6 hours, followed by 18 hours at -20 °C, followed by temperature cycling from 45 °C to 5 °C at 1 hour increments for 6 hours, followed by 186 hours at -20 °C, followed by temperature cycling from 45 °C to 5 °C at 1 hour increments for 6 hours, followed by 18 hours at 23 °C. The slurry was filtered, rinsed with ethyl acetate, and the solid collected and dried under vacuum for 72 hours to obtain the title compound (478 mg, 0.77 mmol) as a white solid.

Tabulated spectroscopic data for Examples 1 - 149:

Ex.	^{1}H NMR	tR (min)	MS (m/z)
1	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 12.64 (br. s., 1H), 9.60 (s, 0.3H), 9.28 (s, 0.7H), 9.11 - 9.22 (m, 0.3H), 8.98 - 9.09 (m, 0.7H), 8.71 - 8.83 (m, 0.3H), 8.46 - 8.59 (m, 0.7H), 8.29 (s, 0.3H), 7.76 (s, 0.7H), 7.71 (d, J = 8.0 Hz, 1H), 7.56 (s, 2H), 7.28 (br. s., 2H), 4.47 - 4.79 (m, 2H), 4.13 - 4.30 (m, J = 6.8, 6.8, 6.8 Hz, 2.3H), 3.48 - 3.66 (m, 0.7H), 2.55 - 2.67 (m, 1H), 1.46 - 1.60 (m, 2H), 1.30 - 1.46 (m, 5H), 1.15 (d, J = 6.0 Hz, 6H), 0.78 (br. s., 6H)	6.23 [a]	518.3 ($M+H^+$)
2	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.96 (br. s., 0.4H), 9.56 (br. s., 0.6H), 9.08 (br. s., 1H), 8.63 (br. s., 1H), 8.23 (s, 0.4H), 7.92 (d, J = 7.3 Hz, 2H), 7.82(s, 0.6H), 7.44 - 7.51 (m, 2H), 7.37 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 3.5 Hz, 1H), 7.11 (d, J = 3.5 Hz, 1H), 4.63 (m, 2H), 3.47 - 3.64 (m, 2H), 2.63 - 2.79 (m, 1H), 1.20 - 1.80 (m, 9H), 1.00 (br. s., 2H).	6.42 [a]	414.0 ($M+H^+$)
3	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.11 (br. s., 1H), 8.81 (br. s., 1H), 8.19 (s, 0.4H), 7.93 (d, J = 7.0 Hz, 2H), 7.77 (s, 0.6H), 7.44 - 7.51 (m, 2H), 7.34 - 7.42 (m, 1H), 7.25 (d, J = 3.5 Hz, 1H), 7.04 - 7.18 (m, 7H), 4.52 - 4.74 (m, 2H), 3.43 - 3.65 (m, 2H), 3.22 - 3.31 (m, 1H), 2.64 - 2.87 (m, 1H), 2.41 - 2.48 (m, 1H), 1.21 - 1.60 (m, 4H)	7.38 [a]	450.2 ($M+H^+$)
4	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.15 (br. s., 1H), 8.83 (br. s., 1H), 8.20 (s, 0.5H), 7.93 (d, J = 6.8 Hz, 2H), 7.80 (s, 0.5H), 7.42 - 7.52 (m, 2H), 7.34 - 7.40 (m, 1H), 7.26 (d, J = 3.5 Hz, 1H), 7.16 - 7.23 (m, 2H), 7.07 - 7.15 (m, 4H), 4.54 - 4.80 (m, 2H), 3.48 - 3.70 (m, 2H), 3.36 - 3.47 (m, 1H), 2.64 - 2.92 (m, 1H), 2.39 - 2.48 (m, 1H), 1.53 - 1.80 (m, 2H)	6.37 [a]	436.1 ($M+H^+$)
5	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.95 (br.s., 0.3H), 9.50 - 9.57 (m, 0.5H), 9.04 - 9.13 (m, 1H), 8.55 - 8.62 (m, 1H), 8.23 (s, 0.3H), 7.93 (d, J = 7.3 Hz, 2H), 7.83 (s, 0.6H), 7.44 - 7.50 (m, 2H), 7.35 - 7.41 (m, 1H), 7.25 (d, J = 3.8 Hz, 1H), 7.11 (d, J = 3.8 Hz, 1H), 4.52 - 4.70 (m, 2H), 3.52 - 3.68 (m, 1H), 3.34 (1H excluded by solvent), 2.59 - 2.76 (m, 1H), 1.27 - 1.45 (m, 2H), 1.07 - 1.25 (m, 6H), 0.69 - 0.81 (m, 3H)	2.48 [b]	402.1 ($M+H^+$)

6	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.13 (s, 0.4H), 7.96 (d, J = 7.5 Hz, 1H), 7.78 (s, 0.6H), 7.50 - 7.59 (m, 0.6H), 7.47 (dd, J = 6.9, 2.9 Hz, 0.4H), 7.21 - 7.29 (m, 1H), 7.12 (d, J = 3.5 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.92 - 6.98 (m, 2H), 4.62 - 4.70 (m, 1H), 3.86 (s, 3H), 3.67 (dd, J = 14.2, 8.9 Hz, 1H), 3.56 - 3.62 (m, 1H), 3.34 (dd, J = 14.2, 4.9 Hz, 1H), 2.73 (dt, J = 9.0, 4.4 Hz, 0.6H), 2.57 (d, J = 8.0 Hz, 0.4H), 1.39 - 1.54 (m, 1H), 1.28 - 1.39 (m, 1H), 1.06 - 1.26 (m, 6H), 0.68 (d, J = 4.3 Hz, 3H)	2.54[b]	432.2 ($M+H^+$)
7	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.22 - 8.32 (m, 0.5H), 8.03 (s, 0.5H), 7.82 - 7.92 (m, 1H), 7.45 (d, J = 12.8 Hz, 2H), 7.33 - 7.40 (m, 1H), 7.24 (d, J = 3.5 Hz, 1H), 6.95 (d, J = 4.0 Hz, 2H), 4.74 - 4.82 (m, 2H), 4.63 (br. s., 1H), 3.88 (s, 3H), 3.62 - 3.81 (m, 1H), 3.46 (dd, J = 14.1, 5.0 Hz, 1H), 2.76 - 2.90 (m, 1H), 2.62 - 2.75 (m, 0.5H), 2.10 - 2.23 (m, 0.5H), 1.50 - 1.68 (m, 1H), 1.39 - 1.51 (m, 1H), 1.28 (m, 6H), 0.73 - 0.98 (m, 3H)	2.53[b]	432.2 ($M+H^+$)
8	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.56 (br. s., 1H), 9.17 (br. s., 1H), 8.40 - 8.51 (m, 1H), 8.17 - 8.29 (m, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.62 - 7.70 (m, 1H), 7.60 (s, 1H), 7.20 - 7.29 (m, 2H), 4.52 - 4.76 (m, 2H), 3.22 - 3.58 (m, 2H), 2.61 - 2.89 (m, 1H), 1.34 - 1.55 (m, 2H), 0.99 - 1.32 (m, 6H), 0.65 - 0.82 (m, 3H)	6.89[a]	427.2 ($M+H^+$)
9	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 8.86 (br. s., 1H), 8.71 (br. s., 1H), 8.20 (s, 0.5H), 7.81 - 7.95 (m, 1H), 7.78 (s, 0.5H), 7.08 - 7.24 (m, 2H), 6.99 - 7.08 (m, 1H), 6.77 - 6.88 (m, 1H), 6.54 - 6.67 (m, 1H), 4.47 - 4.73 (m, 2H), 3.43 - 3.62 (m, 1H), 3.26 - 3.38 (m, 1H), 2.62 - 2.84 (m, 1H), 1.26 - 1.52 (m, 2H), 1.00 - 1.26 (m, 6H), 0.66 - 0.87 (m, 3H)	6.30[a]	418.2 ($M+H^+$)
10	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.66 (br. s., 1H), 8.27 (s, 0.6H), 8.21 (s, 1H), 7.95 (s, 1H), 7.88 (s, 0.4H), 7.29 (br. s., 1H), 7.16 (br. s., 1H), 4.72 - 4.87 (m, 2H), 3.98 (s, 3H), 3.39 - 3.87 (m, 2H), 2.62 - 2.96 (m, 1H), 1.36 - 1.68 (m, 2H), 1.14 - 1.35 (m, 6H), 0.81 (m, 3H)	2.03[b]	433.3 ($M+H^+$)
11	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.28 - 9.35 (m, 0.5H) 9.17 - 9.27 (m, 0.5H), 8.84 - 8.93 (m, 0.5H), 8.74 - 8.84 (m, 0.5H), 8.19 (s, 0.5H), 8.14 (d, J = 7.5 Hz, 2H), 7.95 (d, J = 8.3 Hz, 2H), 7.80 (s, 0.5H), 7.36 (d, J = 3.8 Hz, 1H), 7.29 (d, J = 3.5 Hz, 1H), 4.52 - 4.76 (m, 2H), 3.43 - 3.64 (m, 2H), 2.61 - 2.80 (m, 1H), 1.25 - 1.52 (m, 2H), 1.05 - 1.25 (m, 6H), 0.65 - 0.81 (m, 3H)	6.83[a]	449.1 (M+23) ($M+H^+$)

12	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.10 (br. s., 1H), 8.90 (br. s., 1H), 8.23 - 8.31 (m, 1H), 8.15 (s, 0.4H), 8.08 (d, J = 7.0 Hz, 1H), 7.72 - 7.81 (m, 1.6H), 7.59 - 7.67 (m, 1H), 7.29 (d, J = 3.0 Hz, 1H), 7.15 - 7.22 (m, 1H), 4.51 - 4.71 (m, 2H), 3.23 - 3.65 (m, 2H), 2.55 - 2.83 (m, 1H), 1.22 - 1.52 (m, 2H), 0.98 - 1.22 (m, 6H), 0.60 - 0.88 (m, 3H)	5.93[a]	961.3 ($2M+H^+$)
13	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 8.90 - 9.37 (m, 2H), 8.14 (s, 0.4H), 7.90 - 8.03 (m, 2H), 7.70 (s, 0.6H), 7.59 (t, J = 7.9 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.21 - 7.30 (m, 2H), 4.52 - 4.75 (m, 2H), 3.20 - 3.64 (m, 2H), 2.60 - 2.84 (m, 1H), 1.22 - 1.52 (m, 2H), 0.94 - 1.22 (m, 6H), 0.63 - 0.85 (m, 3H)	8.09[a]	486.2 ($M+H^+$)
14	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 8.99 - 9.26 (m, 1H), 8.66 - 8.87 (m, 1H), 8.19 (s, 0.4H), 7.79 (s, 0.6H), 7.43 - 7.53 (m, 2H), 7.36 (t, J = 7.9 Hz, 1H), 7.22 (d, J = 3.5 Hz, 1H), 7.11 (d, J = 3.5 Hz, 1H), 6.93 (dd, J = 8.2, 1.6 Hz, 1H), 4.62 (m, 2H), 4.10 (q, J = 6.9 Hz, 2H), 3.45 - 3.63 (m, 1H), 3.19 - 3.33 (m, 1H), 2.58 - 2.80 (m, 1H), 1.36 (t, J = 7.03 Hz, 3H), 1.25 - 1.49 (m, 2H), 1.06 - 1.26 (m, 6H), 0.65 - 0.89 (m, 3H)	7.67[a]	446.2 ($M+H^+$)
15	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.25 (br. s., 1H), 9.05 (br. s., 1H), 8.10 (s, 0.4H), 7.82 (m, 0.6H), 7.76 - 7.85 (m, 1H), 7.63 - 7.69 (m, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.23 - 7.30 (m, 1H), 7.07 - 7.15 (m, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.52 - 4.75 (m, 2H), 3.91 (s, 3H), 3.43 - 3.30 (m, 2H), 2.59 - 2.85 (m, 1H), 1.33 - 1.55 (m, 1H), 1.01 - 1.31 (m, 7H), 0.68 - 0.89 (m, 3H)	7.09[a]	433.2 ($M+H^+$)
16	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.03 - 9.29 (m, 1H), 8.69 - 9.01 (m, 1H), 8.33 - 8.47 (m, 1H), 8.10 - 8.27 (m, 1.3H), 7.90 - 8.02 (m, 1H), 7.71 - 7.81 (m, 0.7H), 7.56 - 7.66 (m, 1H), 7.25 - 7.35 (m, 1H), 7.19 - 7.25 (m, 1H), 4.52 - 4.80 (m, 2H), 3.91 (s, 3H), 3.22 - 3.61 (m, 2H), 2.55 - 2.85 (m, 1H), 1.23 - 1.52 (m, 1H), 1.01 - 1.23 (m, 7H), 0.75 (d, J = 3.5 Hz, 3H)	7.14[a]	460.2 ($M+H^+$)
17	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 8.79 - 9.22 (m, 2H), 8.15 (s, 0.4H), 7.72 (s, 0.6H), 7.57 - 7.69 (m, 1H), 7.46 - 7.57 (m, 1H), 7.27 - 7.36 (m, 1H), 7.23 (d, J = 3.5 Hz, 1H), 7.09 - 7.14 (m, 1H), 4.52 - 4.73 (m, 2H), 3.93 (s, 3H), 3.47 - 3.60 (m, 1H), 3.22 - 3.47 (m, 1H), 2.58 - 2.83 (m, 1H), 1.34 - 1.55 (m, 1H), 1.05 - 1.34 (m, 7H), 0.76 (m, 3H)	7.31[a]	472.2 (M+23)
18	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.85 (br. s., 1H), 9.16 (br. s., 1H), 8.33 - 8.47 (m, 1H), 8.04 (s, 0.5H), 7.71 (s, 0.5H), 7.60 - 7.67	5.15[a]	433.2 ($M+H^+$)

	(m, 1H), 7.57 (br. s., 1H), 7.21 - 7.32 (m, 1H), 7.11 - 7.20 (m, 1H), 6.88 - 7.01 (m, 1H), 4.45 - 4.80 (m, 2H), 3.90 (s, 3H), 3.20 - 3.52 (m, 2H), 2.59 - 2.87 (m, 1H), 1.34 - 1.55 (m, 1H), 0.99 - 1.31 (m, 7H), 0.61 - 0.88 (m, 3H)		
19	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.34 - 8.39 (m, 1H), 8.15 (s, 0.3H), 8.00 - 8.08 (m, 1H), 7.79 - 7.87 (m, 1H), 7.69 (s, 0.7H), 7.57 (t, J = 7.8 Hz, 1H), 7.24 - 7.30 (m, 1H), 7.01 - 7.06 (m, 1H), 4.74 - 4.88 (m, 2H), 3.35 - 3.86 (m, 2H), 2.96 - 3.00 (m, 3H), 2.88 - 2.96 (m, 1H), 1.35 - 1.71 (m, 2H), 1.11 - 1.35 (m, 6H), 0.81 (m, 3H)	5.52[a]	459.2 ($M+H^+$)
20	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.75 (br. s., 1H), 9.24 (br. s., 1H), 8.35 - 8.44 (m, 1H), 8.21 - 8.32 (m, 1H), 8.09 (s, 0.3H), 7.89 (d, J = 8.0 Hz, 1H), 7.69 - 7.77 (m, 1H), 7.64 (s, 0.7H), 7.24 - 7.35 (m, 2H), 7.15 - 7.24 (m, 2H), 7.03 - 7.15 (m, 3H), 4.67 (m, 2H), 3.2 - 3.75 (m, 3H), 3.28 (s, 3H), 2.71 - 2.98 (m, 1H), 2.39 - 2.49 (m, 1H), 1.48 - 1.85 (m, 2H)	6.29[a]	514.2 ($M+H^+$)
21	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.20 (br. s., 1H), 8.83 (br. s., 1H), 8.22 - 8.30 (m, 1H), 8.16 (d, J = 8.8 Hz, 1.6H), 7.69 - 7.79 (m, 3H), 7.29 - 7.37 (m, 2.3H), 4.53 - 4.74 (m, 2H), 3.40 - 3.62 (m, 2H), 2.71 - 2.80 (m, 1H), 2.65 (s, 6H), 1.34 - 1.50 (m, 1H), 1.22 - 1.34 (m, 1H), 1.09 - 1.22 (m, 6H), 0.74 (m, 3H)	6.87[a]	509.2 ($M+H^+$)
22	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.16 (br. s., 1H), 8.81 (br. s., 1H), 8.12 - 8.26 (m, 2.4H), 7.66 - 7.78 (m, 2.6H), 7.21 - 7.36 (m, 2H), 4.50 - 4.77 (m, 2H), 3.24 - 3.64 (m, 2H), 2.57 - 2.83 (m, 1H), 2.44 (s, 3H), 1.24 - 1.51 (m, 2H), 1.08 - 1.24 (m, 6H), 0.75 (d, J = 5.0 Hz, 3H)	6.35[a]	495.2 ($M+H^+$)
23	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.96 (br. s., 0.4H), 9.55 (br. s., 0.6H), 9.10 - 9.20 (m, 1H), 8.55 - 8.64 (m, 1H), 8.23 (s, 0.4H), 7.82 (br. s., 0.6H), 7.57 - 7.67 (m, 2H), 7.44 (t, J = 8.0 Hz, 1H), 7.24 (d, J = 3.5 Hz, 1H), 7.18 (d, J = 3.5 Hz, 1H), 7.08 (dd, J = 8.3, 1.8 Hz, 1H), 4.85 (q, J = 8.8 Hz, 2H), 4.62 (dd, J = 15.8, 5.5 Hz, 2H), 4.36 - 4.50 (m, 1H), 3.49 - 3.67 (m, 1H), 2.72 (br. s., 1H), 1.27 - 1.46 (m, 2H), 1.10 - 1.26 (m, 6H), 0.67 - 0.88 (m,3H)	2.73[b]	500.2 ($M+H^+$)
24	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.61 (s, 0.3H), 9.30 (s, 0.7H), 9.15 (t, J = 5.9 Hz, 0.3H), 9.00 (t, J = 5.9 Hz, 0.7H), 8.79 (t, J = 5.5 Hz, 0.3H), 8.53 (t, J = 5.6 Hz, 0.7H), 8.30 (s, 0.3H), 7.92 (d, J = 8.0 Hz, 2H), 7.76 (s, 0.7H), 7.44 - 7.50 (m, 2H), 7.35 - 7.41 (m, 1H), 7.23 - 7.27 (m, 1H), 7.07 - 7.14 (m, 1H), 4.47 - 4.73 (m, 0.2H), 4.22	7.79[a]	430.2 ($M+H^+$)

	(q, J = 7.3 Hz, 0.3H), 3.58 (td, J = 9.3, 4.8 Hz, 0.7H), 3.41 - 3.49 (m, 0.2H), 2.55 - 2.64 (m, 1H), 1.46 - 1.57 (m, 2H), 1.35 - 1.44 (m, 2H), 1.08 - 1.23 (m, 6H), 0.66 - 0.82 (m, 6H)		
25	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.26 (s, 0.4H), 7.90 (s, 0.6H), 7.38 - 7.48 (m, 2H), 7.34 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 2.3 Hz, 1H), 6.87 - 6.98 (m, 2H), 4.61 - 4.85 (m, 3H), 3.39 - 3.89 (m, 2H), 2.62 - 2.97 (m, 1H), 1.40 - 1.70 (m, 2H), 1.35 (d, J = 5.8 Hz, 6H), 1.15 - 1.33 (m, 6H), 0.72 - 0.88 (m, 3H)	7.98[a]	460.2 ($M+H^+$)
26	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.94 - 9.98 (m, 0.3H), 9.53 - 9.58 (m, 0.5H), 9.19 - 9.27 (m, 1H), 8.56 - 8.62 (m, 1H), 8.23 - 8.25 (m, 0.4H), 8.00 - 8.03 (m, 1H), 7.83 - 7.85 (m, 0.6H), 7.78 - 7.80 (m, 1H), 7.43 (br. s., 1H), 7.29 (d, J = 3.5 Hz, 1H), 7.26 (d, J = 3.8 Hz, 1H), 4.54 - 4.69 (m, 2H), 4.14 - 4.20 (m, 2H), 3.90 (s, 3H), 3.54 - 3.67 (m, 1H), 3.4 (1H excluded by solvent), 1.38 (t, J = 6.9 Hz, 3H), 1.29 - 1.35 (m, 2H), 1.13 - 1.21 (m, 6H), 0.72 - 0.77 (m, 3H)	2.64[b]	504.2 ($M+H^+$)
27	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.95 (s, 0.4H), 8.94 - 9.06 (m, 1H), 8.23 (s, 0.4H), 8.57 (d, J = 5.5 Hz, 1H), 7.83 (s, 0.6H), 7.25 - 7.30 (m, 1H), 7.18 - 7.25 (m, 3H), 7.07 (d, J = 3.5 Hz, 1H), 6.76 (d, J = 7.8 Hz, 1H), 4.62 - 4.72 (m, 1H), 4.51 - 4.62 (m, 1H), 3.53 - 3.67 (m, 1H), 3.28 - 3.44 (m, 1H), 2.59 - 2.77 (m, 1H), 1.26 - 1.46 (m, 2H), 1.17 (br. s., 6H), 0.67 - 0.84 (m, 3H)	1.42[c]	445.3 ($M+H^+$)
28	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.40 (br. s., 1H), 8.24 (s, 0.3H), 7.99 (d, J = 7.5 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.83 (s, 0.7H), 7.54 (t, J = 7.7 Hz, 1H), 7.26 (d, J = 3.0 Hz, 1H), 7.03 (d, J = 2.8 Hz, 1H), 4.72 - 4.88 (m, 2H), 3.40 - 3.88 (m, 2H), 2.61 - 2.99 (m, 1H), 2.17 (q, J = 7.5 Hz, 2H), 1.37 - 1.70 (m, 2H), 1.21 - 1.37 (m, 6H), 1.03 (t, J = 7.5 Hz, 3H), 0.69 - 0.86 (m, 3H)	6.45[a]	537.3 ($M+H^+$)
29	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.54 (br. s., 0.3H), 9.14 - 9.24 (m, 1H), 8.53 - 8.62 (m, 1H), 8.23 (s, 0.3H), 8.02 (s, 1H), 7.83 (s, 0.5H), 7.70 - 7.75 (m, 1H), 7.40 - 7.46 (m, 1H), 7.26 (s, 2H), 4.53 - 4.71 (m, 2H), 3.89 (s, 3H), 3.54 - 3.67 (m, 1H), 3.4 (1H excluded by solvent) 2.59 - 2.76 (m, 1H), 1.27 - 1.45 (m, 2H), 1.11 - 1.25 (m, 6H), 0.71 - 0.79 (m, 3H)	1.74[c]	476.2 ($M+H^+$)

30	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.12 (m, 0.5H), 8.91 - 8.98 (m, 0.3H), 8.62 (m, 1H), 8.22 (s, 0.3H), 7.93 (s, 1H), 7.83 (s, 0.5H), 7.55 (br. s., 1H), 7.40 (s, 1H), 7.23 (s, 1H), 7.13 (s, 1H), 4.62 (br. s., 2H), 4.11 (q, J = 6.8 Hz, 2H), 3.53 - 3.68 (m, 1H), 3.4 (1H excluded by solvent) 2.61 - 2.76 (m, 1H), 1.28 - 1.42 (m, 5H), 1.13 - 1.22 (m, 6H), 0.72 - 0.79 (m, 3H)	2.36[b]	490.1 ($M+H^+$)
31	^{1}H NMR (CHLOROFORM-d) δ ppm: 8.33 - 8.56 (m, 1H), 8.07 - 8.18 (m, 1H), 7.63 - 7.76 (m, 1H), 7.57 (m, 1H), 7.50 (m, 1H), 6.81 (m, 1H), 6.61 (br. s., 0.4H), 6.47 (br. s., 0.6H), 5.07 (m, 1H), 4.65 - 4.95 (m, 1H), 3.67 - 4.29 (m, 4H), 3.50 (dt, 3.5, 14.5 Hz, 1H), 2.87 (m, 0.6H), 2.59 (m, 0.4H), 2.05 (d, 1H, J = 14.5 Hz), 1.65 - 1.80 (m, 3H), 1.43 (t, J = 14.5 Hz, 1.5H), 1.27 - 1.37 (m, 6H), 1.22 (t, J = 14.5 Hz, 1.5H), 0.90 (m, 3H)	0.77[d]	508.1 ($M+H^+$)
32	^{1}H NMR (CHLOROFORM-d) δ ppm: 9.58 (br.s., 0.5H), 9.07-9.12 (t, 0.1 H), 8.98-9.04 (t, J= 2 Hz, 0.9H), 8.67-8.72 (t, 0.2 H), 8.50-8.56 (t, J= 2 Hz, 0.8H), 8.28 (s, 0.2H), 7.90-7.95 (d, J = 4 Hz, 2 H), 7.76 (s, 0.8H), 7.45-7.51 (t, J= 4 Hz, 2H), 7.36-7.41 (m, 1H), 7.24-7.26 (d, J= 1 Hz, 1H), 7.09-7.12 (d, J=1.5 Hz, 1H), 4.61-4.73 (m, 2H), 4.50-4.58 (m, 0.7H), 4.32-4.39 (m, 0.3H), 3.63-3.70 (m, 1 H), 3.48-3.54 (m, 2H), 2.60-2.67 (m, 1 H), 1.37 - 1.46 (m, 6H), 1.08-1.22 (m, 6H), 0.69-0.77 (m, 3H)	0.86[d]	432.2 ($M+H^+$)
33	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.07 - 9.15 (m, 1H), 8.60 (br. s., 1H), 8.54 (br. s., 1H), 8.21 - 8.25 (m, 0.4H), 7.91 (s, 1H), 7.81 - 7.85 (m, 0.5H), 7.64 (s, 1H), 7.38 (s, 1H), 7.26 (d, J = 3.5 Hz, 1H), 7.18 (d, J = 3.5 Hz, 1H), 4.55 - 4.71 (m, 2H), 3.88 (s, 3H), 3.54 - 3.67 (m, 1H), 3.4 (3H excluded by solvent), 2.72 (t, J = 6.4 Hz, 2H), 2.59 - 2.68 (m, 1H), 1.28 - 1.44 (m, 2H), 1.13 - 1.23 (m, 6H), 0.72 - 0.80 (m, 3H)	1.89[b]	518.2 ($M+H^+$)
34	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.14 (br. s., 1H), 8.55 - 8.63 (m, 1H), 8.46 - 8.53 (m, 1H), 8.24 (s, 0.3H), 7.89 (s, 1H), 7.83 (s, 0.5H), 7.65 (s, 1H), 7.37 (s, 1H), 7.26 (d, J = 3.3 Hz, 1H), 7.18 (d, J = 3.0 Hz, 1H), 4.55 - 4.70 (m, 2H), 4.16 (q, J = 6.4 Hz, 2H), 3.54 - 3.67 (m, 1H), 3.4 (3H excluded by solvent), 2.71 (t, J = 6.1 Hz, 2H), 2.60 - 2.67 (m, 1H), 1.29 - 1.44 (m, 5H), 1.18 (br. s., 6H), 0.70 - 0.81 (m, 3H)	1.95[b]	532.3 ($M+H^+$)

35	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.85 - 8.93 (m, 1H), 8.72 - 8.65 (m, 1H), 8.13 (s, 0.4H), 7.78 (s, 0.6H), 7.62 (d, J = 7.5 Hz, 1H), 7.58 (br. s., 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.13 (br. s., 1H), 7.04 (d, J = 7.5 Hz, 1H), 6.90 (br. s., 1H), 6.82 (t, J = 74.0 Hz, 1H), 4.66 (br. s., 2H), 3.56 - 3.70 (m, 1.4H), 3.34 (d, J = 10.3 Hz, 0.6H), 2.75 (m, 0.6H), 2.58 (m, 0.4H), 1.28 - 1.56 (m, 2H), 1.09 - 1.22 (m, 6H), 0.54 - 0.74 (m, 3H)	2.58[b]	468.1 ($M+H^+$)
36	^{1}H NMR (CHLOROFORM-d) δ ppm: 8.23 - 8.37 (m, 2H), 7.99 (s, 0.7H), 7.80-7.90 (m, 1H), 7.67 (m, 1H), 7.52 (m, 1H), 7.44 (s, 0.3H), 7.23 (d, J = 3.5 Hz, 0.3H), 7.03 (d, J = 3.5 Hz, 0.7H), 6.81 (d, J = 3.5 HZ, 0.3H), 6.68 (d, J = 3.5 Hz, 0.7H), 4.77 - 5.03 (m, 2H), 3.89 (d, J = 11.0 Hz, 3H), 3.80 (m, 1H), 3.76 (d, J = 11.0 Hz, 3H), 3.50 (m, 1H), 2.83 (m, 0.7H), 2.64 (m, 0.3H), 1.71 (m, 2H), 1.29 (m, 6H), 0.87 (m, 3H)	0.77[d]	510.0 ($M+H^+$)
37	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.35 (d, J = 5.6 Hz, 1H), 8.26 (s, 0.4H), 8.15 (dd, J = 1.6, 8.8 Hz, 1H), 7.89 (s, 0.6H), 7.61 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 5.0 Hz, 1H), 7.12 (d, J = 5.0 Hz, 1H), 4.78 (m, 2H), 4.49 (s, 2H), 3.69 - 3.82 (m, 1.4H), 3.45 (dd, J = 4.8, 14.0 Hz, 0.6H), 2.84 (m, 0.6H), 2.68 (m, 0.4H), 1.58 (m, 1H), 1.45 (m, 1H), 1.21 - 1.34 (m, 6H), 0.80 (m, 3H)	0.72[d]	493.0 ($M+H^+$)
38	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.26 (s, 0.4H), 7.90 (s, 0.6H), 7.50 - 7.55 (m, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.24 (d, J = 3.5 Hz, 1H), 6.97 - 7.02 (m, 1H), 6.96 (d, J = 3.5 Hz, 1H), 4.70 - 4.84 (m, 2H), 4.15 - 4.40 (m, 2H), 3.41 - 3.87 (m, 2H), 3.18 (t, J = 5.3 Hz, 2H), 2.89 - 3.03 (m, 4H), 2.64 - 2.91 (m, 1H), 1.80 - 2.05 (m, 4H), 1.37 - 1.64 (m, 2H), 1.12 - 1.35 (m, 6H), 0.71 - 0.91 (m, 3H)	5.69[a]	515.3 ($M+H^+$)
39	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 13.24 (br. s., 1H), 9.62 (s, 0.3H), 9.23 - 9.32 (m, 1H), 9.14 (t, J = 5.9 Hz, 0.7H), 8.78 (d, J = 5.3 Hz, 0.3H), 8.52 (t, J = 5.5 Hz, 0.7H), 8.30 (s, 0.3H), 8.00 (s, 1H), 7.75 (d, J = 5.8 Hz, 1.7H), 7.41 (br. s., 1H), 7.22 - 7.28 (m, 2H), 4.47 - 4.74 (m, 2H), 4.09 - 4.27 (m, 2.3H), 3.53 - 3.63 (m, 0.7H), 2.54 - 2.64 (m, 1H), 1.46 - 1.57 (m, 2H), 1.38 (t, J = 6.9 Hz, 5H), 1.07 - 1.22 (m, 6H), 0.66 - 0.82 (m, 6H)	7.29[a]	518.3 ($M+H^+$)

40	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.20 (br. s., 0.3H), 8.99 (br. s., 1H), 8.75 - 8.82 (m, 0.3H), 8.51 (br. s., 2H), 8.29 (s, 0.3H), 7.90 (br. s., 1H), 7.77 (s, 0.6H), 7.64 (br. s., 1H), 7.37 (br. s., 1H), 7.26 (d, J = 2.5 Hz, 1H), 7.18 (s, 1H), 4.49 - 4.73 (m, 2H), 4.09 - 4.22 (m, J = 6.5 Hz, 2H), 3.48 - 3.63 (m, 1H), 3.4 (2H excluded by solvent) 2.66 - 2.76 (m, 2H), 2.55 - 2.64 (m, 1H), 1.46 - 1.58 (m, 2H), 1.34 - 1.44 (m, 5H), 1.07 - 1.23 (m, 6H), 0.67 - 0.83 (m, 6H)	2.05[b]	560.2 ($M+H^+$)
41	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 12.19 (s, 1H), 9.61 (s, 0.3H), 9.29 (s, 0.7H), 9.03 - 9.14 (m, 0.3H), 8.88 - 9.00 (m, 0.7H), 8.70 - 8.82 (m, 0.3H), 8.45 - 8.57 (m, 0.7H), 8.30 (s, 0.3H), 7.77 (s, 0.7H), 7.38 - 7.52 (m, 2H), 7.20 - 7.33 (m, 2H), 7.11 (d, J = 3.3 Hz, 1H), 4.47 - 4.80 (m, 2H), 4.19 - 4.30 (m, 0.5H), 4.13 (q, J = 6.8 Hz, 2H), 3.57 - 3.71 (m, 0.9H), 2.54 - 2.76 (m, 1.5H), 1.34 (t, J = 6.8 Hz, 8H), 1.15 (d, J = 5.8 Hz, 6H), 0.59 - 0.93 (m, 6H)	6.29[a]	532.3 ($M+H^+$)
42	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 12.39 (br. s., 1H), 9.61 (s, 0.3H), 9.29 (br. s., 0.7H), 9.07 - 9.18 (m, 0.3H), 8.91 - 9.03 (m, 0.7H), 8.74 - 8.83 (m, 0.3H), 8.45 - 8.57 (m, 0.7H), 8.30 (s, 0.3H), 7.86 (d, J = 7.8 Hz, 2H), 7.77 (s, 0.7H), 7.36 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 3.0 Hz, 1H), 7.07 (d, J = 3.3 Hz, 1H), 4.45 - 4.76 (m, 2H), 4.14 - 4.29 (m, 0.3H), 3.60 - 3.71 (1H, concealed under solvent peak), 3.53 - 3.59 (m, 0.7H), 3.37 (none, 0.3H), 2.56 - 2.64 (m, 1H), 2.53 - 2.56 (m, 0.3H), 1.28 - 1.62 (m, 4H), 1.01 - 1.28 (m, 6H), 0.57 - 0.89 (m, 6H)	5.90[a]	488.3 ($M+H^+$)
43	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 12.39 (br. s., 1H), 9.61 (s, 0.3H), 9.29 (s, 0.7H), 9.04 - 9.18 (m, 0.3H), 8.89 - 9.03 (m, 0.7H), 8.72 - 8.84 (m, 0.3H), 8.46 - 8.60 (m, 0.7H), 8.29 (s, 0.3H), 7.86 (d, J = 8.0 Hz, 2H), 7.76 (s, 0.7H), 7.43 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 3.0 Hz, 1H), 7.06 (d, J = 3.5 Hz, 1H), 4.45 - 4.77 (m, 2H), 4.15 - 4.29 (m, 0.3H), 3.96 - 4.11 (m, 0.8H), 3.51 - 3.67 (m, 0.7H), 2.53 - 2.66 (m, 1.4H), 2.00 (s, 1H), 1.50 (s, 6H), 1.29 - 1.45 (m, 2H), 1.17 (d, J = 7.0 Hz, 6H), 0.78 (br. s., 6H)	6.47[a]	516.3 ($M+H^+$)
44	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.51 - 9.73 (m, 0.2H), 9.07 - 9.20 (m, 0.3H), 8.91 - 9.06 (m, 0.7H), 8.71 - 8.84 (m, 0.3H), 8.45 - 8.60 (m, 0.7H), 8.29 (s, 0.3H), 7.83 (d, J = 8.0 Hz, 2H), 7.76 (s, 0.7H), 7.41 (d, J = 8.0 Hz, 2H), 7.25 (br. s., 1H), 7.07 (d, J = 3.3 Hz, 1H), 4.44 - 4.79 (m, 2H), 4.14 - 4.31 (m, 0.3H), 3.46 - 3.67 (m, 0.7H), 3.21 - 3.29 (m, 0.2H), 2.53 - 2.67 (m, 1.5H), 1.47 (br. s., 6H), 1.18 (br. s., 7H), 0.55 - 0.92 (m, 6H)	6.31[a]	514.3 ($M+H^+$)

45	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 12.04 - 12.21 (m, 0.5H), 9.35 - 9.49 (m, 0.4H), 9.17 (t, J = 5.1 Hz, 0.3H), 9.07 (t, J = 5.8 Hz, 0.7H), 8.83 - 8.99 (m, 0.7H), 8.57 - 8.68 (m, 0.5H), 8.27 - 8.31 (m, 0.3H), 7.93 - 7.99 (m, 1H), 7.76 (s, 0.6H), 7.67 (s, 1H), 7.41 (s, 1H), 7.26 (d, J = 3.3 Hz, 1H), 7.17 - 7.21 (m, 1H), 4.68 - 4.80 (m, 1H), 4.45 - 4.61 (m, 1H), 4.32 - 4.40 (m, 1H), 4.17 (q, J = 7.0 Hz, 2H), 3.53 - 3.61 (m, 1H), 2.54 - 2.62 (m, 1H), 2.38 (m, 2H), 2.04 - 2.15 (m, 1H), 1.91 - 2.02 (m, 1H), 1.48 - 1.57 (m, 2H), 1.43 (s, 9H), 1.39 (t, J = 6.9 Hz, 5H), 1.10 - 1.21 (m, 6H), 0.69 - 0.81 (m, 6H)	2.78[b]	703.3 ($M+H^+$)
46	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.60 - 9.72 (m, 0.3H), 9.34 - 9.51 (m, 1.7H), 9.27 (t, J = 6.0 Hz, 1H), 9.08 (s, 1H), 8.80 - 8.86 (m, 0.3H), 8.78 (s, 1H), 8.57 (t, J = 5.8 Hz, 0.7H), 8.35 (s, 0.3H), 7.82 (s, 0.7H), 7.43 - 7.51 (m, 1H), 7.30 - 7.38 (m, 1H), 4.50 - 4.82 (m, 2H), 4.21 - 4.34 (m, 0.3H), 3.57 - 3.72 (m, 0.7H), 2.59 - 2.71 (m, 1H), 1.51 - 1.65 (m, 2H), 1.37 - 1.51 (m, 2H), 1.10 - 1.27 (m, 6H), 0.80 - 0.87 (m, 3H), 0.70 - 0.80 (m, 3H)	5.88[a]	475.0 ($M+H^+$)
47	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 12.45 (br. s., 0.7H), 9.58 - 9.65 (m, 0.2H), 9.25 - 9.33 (m, 0.5H), 9.17 - 9.22 (m, 0.3H), 9.02 - 9.08 (m, 0.6H), 8.84 (d, J = 7.5 Hz, 1H), 8.75 - 8.80 (m, 0.3H), 8.48 - 8.55 (m, 0.6H), 8.29 - 8.33 (m, 0.3H), 7.88 (s, 1H), 7.77 (s, 0.6H), 7.68 (s, 1H), 7.38 (s, 1H), 7.25 - 7.30 (m, 1H), 7.15 - 7.20 (m, 1H), 4.64 - 4.76 (m, 2H), 4.50 - 4.59 (m, 1H), 4.17 (q, J = 6.8 Hz, 2H), 3.54 - 3.62 (m, 1H), 2.80 - 2.89 (m, 1H), 2.67 - 2.77 (m, 1H), 2.56 - 2.64 (m, 1H), 1.49 - 1.58 (m, 2H), 1.36 - 1.47 (m, 14H), 1.10 - 1.23 (m, 6H), 0.67 - 0.84 (m, 6H)	2.69[b]	689.3 ($M+H^+$)
48	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.60 (s, 0.3H), 9.28 (s, 0.7H), 9.20 (d, J = 12.5 Hz, 0.3H), 9.05 (t, J = 5.6 Hz, 0.6H), 8.84 (d, J = 7.3 Hz, 1H), 8.73 - 8.79 (m, 0.3H), 8.50 (t, J = 5.6 Hz, 0.7H), 8.30 (s, 0.3H), 7.90 (s, 1H), 7.77 (s, 0.6H), 7.69 (s, 1H), 7.42 (s, 1H), 7.25 - 7.29 (m, 1H), 7.17 - 7.21 (m, 1H), 4.64 - 4.73 (m, 1H), 4.46 - 4.58 (m, 2H), 4.18 (q, J = 6.8 Hz, 2H), 3.67 (s, 3H), 3.53 - 3.64 (m, 4H), 2.56 - 2.64 (m, 1H), 2.5 (2H excluded by solvent) 2.10 - 2.21 (m, 1H), 1.99 - 2.10 (m, 1H), 1.47 - 1.58 (m, 2H), 1.35 - 1.44 (m, 5H), 1.11 - 1.22 (m, 6H), 0.68 - 0.83 (m, 6H)	2.65[b]	675.3 ($M+H^+$)
49	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.98 - 9.23 (m, 0.3H), 8.72 - 8.95 (m, 0.7H), 8.26 - 8.37 (m, 0.3H), 7.81 - 7.93 (m, 0.7H), 7.63 - 7.71 (m, 1H), 7.56 - 7.63 (m, 1H), 7.22 - 7.31 (m, 1H), 7.08 - 7.16 (m, 1H), 6.94 - 7.08 (m, 1H), 4.63 - 4.87 (m, 2H), 4.15 - 4.22 (q, J = 8 Hz, 2H), 3.51 - 3.75 (m, 1H), 2.51 - 2.82 (m, 1H), 1.49 - 1.77 (m,	7.43[a]	568.0 ($M+H^+$)

	4H), 1.47 (t, J = 8.0 Hz, 3H), 1.13 - 1.34 (m, 6H), 0.84 - 0.97 (m, 3H), 0.78 (m, 3H)		
50	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.60 (s, 0.3H), 9.27 (s, 0.7H), 9.20 - 9.26 (m, 0.3H), 9.10 (t, J = 6.0 Hz, 0.7H), 8.76 (t, J = 5.9 Hz, 0.3H), 8.50 (t, J = 5.6 Hz, 0.7H), 8.30 (s, 0.3H), 7.70 - 7.79 (m, J = 5.3 Hz, 2.7H), 7.28 - 7.33 (m, 1H), 7.24 - 7.28 (m, 1H), 7.16 (d, J = 14.3 Hz, 1H), 4.47 - 4.78 (m, 2H), 4.21 - 4.27 (m, 0.3H), 4.17 (q, J = 7.0 Hz, 2H), 3.72 (s, 3H), 3.69 (s, 3H), 3.53 - 3.63 (m, 0.8H), 2.54 - 2.66 (m, 1H), 1.47 - 1.59 (m, 2H), 1.38 (t, 5H), 1.04 - 1.27 (m, 6H), 0.64 - 0.85 (m, 6H)	6.55[a]	582.3 ($M+H^+$)
51	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.99 (br. s., 0.4H), 9.55 (br. s., 0.5H), 9.09 - 9.30 (m, 1H), 8.51 - 8.70 (m, 1H), 8.35 (dd, J = 6.8, 2.3 Hz, 1H), 8.17 - 8.27 (m, 1.3H), 7.83 (s, 0.6H), 7.51 (dd, J = 10.5, 8.8 Hz, 1H), 7.26 (d, J = 3.5 Hz, 1H), 7.21 (d, J = 3.8 Hz, 1H), 4.50 - 4.76 (m, 2H), 3.91 (s, 3H), 3.47 - 3.72 (m, 1H), 3.29 - 3.45 (1H, excluded by solvent), 2.59 - 2.82 (m, 1H), 1.26 - 1.49 (m, 2H), 1.07 - 1.25 (m, 6H), 0.69 - 0.80 (m, 3H)	2.46[b]	478.1 ($M+H^+$)
52	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.99 (br. s., 0.3H), 9.55 (br. s., 0.5H), 8.97 - 9.20 (m, 1H), 8.58 (t, J = 4.3 Hz, 1H), 8.23 (s, 0.4H), 7.83 (s, 0.6H), 7.23 (d, J = 3.5 Hz, 1H), 7.15 (d, J = 3.8 Hz, 1H), 7.09 (d, J = 2.3 Hz, 2H), 6.53 (t, J = 2.3 Hz, 1H), 4.49 - 4.75 (m, 2H), 3.82 (s, 6H), 3.48 - 3.70 (m, 1H), 3.29 - 3.46 (1H, excluded by solvent), 2.59 - 2.78 (m, 1H), 1.26 - 1.53 (m, 2H), 1.11 - 1.22 (6H, excluded by ethyl acetate), 0.71 - 0.80 (m, 3H)	2.52[b]	462.2 ($M+H^+$)
53	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 10.01 (s, 0.4H), 9.56 (br. s., 0.6H), 8.99 - 9.28 (m, J = 6.3, 6.3 Hz, 1H), 8.58 (t, J = 5.0 Hz, 1H), 8.23 (s, 0.4H), 7.83 (s, 0.6H), 7.68 (d, J = 3.0 Hz, 1H), 7.22 (d, J = 3.5 Hz, 1H), 7.08 (d, J = 9.0 Hz, 1H), 7.04 (d, J = 3.5 Hz, 1H), 6.97 (d, J = 3.0 Hz, 0.6H), 6.95 (d, J = 3.3 Hz, 0.4H), 4.48 - 4.76 (m, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 3.49 - 3.68 (m, 1H), 3.28 - 3.45 (1H, excluded by solvent), 2.57 - 2.79 (m, 1H), 1.25 - 1.47 (m, 2H), 1.08 - 1.25 (m, 6H), 0.68 - 0.81 (m, J = 2.3 Hz, 3H)	2.52[b]	462.1 ($M+H^+$)
54	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.11 (t, J = 6.5 Hz, 0.6H), 9.04 (t, J = 6.7 Hz, 0.4H), 8.61 (t, J = 5.8 Hz, 1H), 8.29 (s, 0.5H), 8.22 (s, 0.4H), 8.19 (d, J = 1.5 Hz, 1H), 7.90 (dd, J = 7.8, 1.5 Hz, 1H), 7.83 (s, 0.7H), 7.34 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 3.5 Hz, 1H), 7.09 (d, J = 3.5 Hz, 1H), 4.45 - 4.75 (m, 2H), 3.28 - 3.67 (2H, excluded by solvent), 3.17 (s, 3H), 2.58 - 2.79 (m, 1H), 1.27 - 1.48 (m, 2H), 1.08 - 1.22 (m, 6H), 0.75 (t, J = 5.5 Hz, 3H)	2.29[b]	460.2 ($M+H^+$)

55	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 13.05 - 13.82 (m, 1H), 10.00 (s, 0.2H), 9.55 (br. s., 0.4H), 9.06 - 9.23 (m, 1H), 8.48 - 8.67 (m, 1H), 8.20 - 8.31 (m, J = 8.0 Hz, 1H), 7.92 - 8.02 (m, 0.5H), 7.79 - 7.86 (m, 0.5H), 7.67 (dd, J = 7.5, 1.5 Hz, 1H), 7.26 - 7.33 (m, 2H), 7.08 (d, J = 3.8 Hz, 1H), 4.45 - 4.75 (m, 2H), 3.79 (s, 3H), 3.50 - 3.69 (m, 1H), 3.07 - 3.45 (1H, excluded by solvent), 2.58 - 2.80 (m, 1H), 1.26 - 1.47 (m, 2H), 1.07 - 1.23 (m, 6H), 0.69 - 0.80 (m, 3H)	2.16[b]	476.2 ($M+H^+$)
56	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.10 (t, J = 6.0 Hz, 0.6H), 8.99 - 9.07 (m, J = 5.8 Hz, 0.4H), 8.59 (t, J = 5.6 Hz, 1H), 8.19 - 8.30 (m, 1H), 8.03 (d, J = 2.3 Hz, 1H), 7.99 (br. s., 0.3H), 7.96 (dd, J = 8.5, 2.0 Hz, 1H), 7.83 (s, 0.5H), 7.22 (d, J = 3.5 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 3.8 Hz, 1H), 4.45 - 4.74 (m, 2H), 3.85 (s, 3H), 3.28 - 3.68 (2H, excluded by solvent), 2.58 - 2.80 (m, 1H), 1.26 - 1.50 (m, 2H), 1.17 (br. s., 6H), 0.75 (t, J = 5.5 Hz, 3H)	2.16[b]	476.1 ($M+H^+$)
57	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.99 (br. s., 0.4H), 9.55 (br. s., 0.6H), 8.79 - 9.00 (m, 1H), 8.56 - 8.73 (m, 1H), 8.23 (s, 0.4H), 7.86 (d, J = 7.5 Hz, 1H), 7.83 (s, 0.6H), 7.61 - 7.70 (m, J = 7.5 Hz, 2H), 7.46 - 7.56 (m, J = 8.0 Hz, 1H), 7.30 (d, J = 3.5 Hz, 1H), 6.86 (d, J = 3.5 Hz, 1H), 4.45 - 4.70 (m, 2H), 3.81 (s, 3H), 3.49 - 3.70 (m, 1H), 3.29 - 3.44 (1H, excluded by solvent), 2.58 - 2.78 (m, 1H), 1.26 - 1.49 (m, 2H), 1.08 - 1.23 (m, 6H), 0.76 (t, 3H)	2.42[b]	460.1 ($M+H^+$)
58	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 10.01 (m, 0.3H), 9.52 - 9.60 (m, 0.5H), 9.17 - 9.27 (m, 1H), 8.58 - 8.66 (m, 1H), 8.24 (s, 0.4H), 8.01 - 8.10 (m, 4H), 7.83 (s, 0.5H), 7.27 - 7.32 (m, 2H), 4.55 - 4.71 (m, 2H), 3.88 (s, 3H), 3.54 - 3.67 (m, 1H), 3.37 - 3.45 (m, 1H), 2.60 - 2.75 (m, 1H), 1.28 - 1.44 (m, 2H), 1.11 - 1.25 (m, 6H), 0.70 - 0.79 (m, 3H)	2.49[b]	460.2 ($M+H^+$)
59	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.15 - 9.23 (m, 0.5H), 9.12 (t, J = 6.0 Hz, 0.5H), 8.59 - 8.72 (m, 1H), 8.35 (s, 1H), 8.22 (s, 0.4H), 8.04 (t, J = 6.5 Hz, 1H), 7.82 (s, 0.6H), 7.48 - 7.59 (m, 1H), 7.26 (br. s., 1H), 7.19 (t, J = 7.8 Hz, 1H), 6.92 (br. s., 1H), 4.50 - 4.76 (m, 2H), 3.29 - 3.63 (2H, excluded by solvent), 2.60 - 2.81 (m, 1H), 1.27 - 1.53 (m, 2H), 1.17 (br. s., 6H), 0.75 (t, 3H)	2.17[b]	464.2 ($M+H^+$)
60	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 12.48 (s, 0.9H), 9.57 (br. s., 0.5H), 8.97 - 9.21 (m, 1H), 8.50 - 8.65 (m, 1H), 8.23 (s, 0.4H), 7.82 (d, J = 8.0 Hz, 1H), 7.80 (s, 1.6H), 7.42 (t, J = 7.8 Hz, 1H), 7.22 - 7.31 (m, 2H), 7.08 (d, J = 3.5 Hz, 1H), 4.48 - 4.75 (m, 2H), 3.62 - 3.69 (m, 2H), 3.51 - 3.62 (m, 1H), 3.29 - 3.44 (1H, excluded by solvent), 2.58 - 2.80 (m, 1H), 1.26 - 1.49 (m, 2H), 1.08 - 1.26 (m,	2.22[b]	460.2 ($M+H^+$)

	6H), 0.76 (t, 3H)		
61	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 13.10 (br. s., 0.7H), 10.00 (s, 0.2H), 9.56 (br. s., 0.5H), 8.91 - 9.12 (m, J = 5.5 Hz, 1H), 8.52 - 8.67 (m, 1H), 8.23 (s, 0.4H), 7.89 (d, J = 7.8 Hz, 1H), 7.83 (s, 0.6H), 7.69 (d, J = 7.5 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 3.5 Hz, 1H), 6.87 (d, J = 3.5 Hz, 1H), 4.45 - 4.74 (m, 2H), 3.49 - 3.72 (m, 1H), 3.28 - 3.44 (1H, excluded by solvent), 2.58 - 2.77 (m, 1H), 2.55 (s, 3H), 1.26 - 1.48 (m, 2H), 1.16 (br. s., 6H), 0.70 - 0.81 (m, 3H)	2.21[b]	460.1 ($M+H^+$)
62	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.99 (s, 0.4H), 9.56 (s, 0.6H), 8.84 - 8.99 (m, 1H), 8.45 - 8.62 (m, 1H), 8.24 (s, 0.4H), 8.14 (d, J = 2.5 Hz, 1H), 7.83 (s, 0.6H), 7.74 (dd, J = 8.3, 1.8 Hz, 1H), 7.20 (d, J = 3.5 Hz, 1H), 6.78 (d, J = 3.5 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H), 4.46 - 4.73 (m, 2H), 3.49 - 3.74 (m, 1H), 3.23 - 3.44 (1H, excluded by solvent), 2.58 - 2.78 (m, 1H), 1.26 - 1.48 (m, 2H), 1.08 - 1.23 (m, 6H), 0.76 (t, 3H)	2.27[b]	462.1 ($M+H^+$)
63	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.97 (br. s., 0.4H), 9.55 (br. s., 0.6H), 9.17 (dt, J = 12.5, 6.0 Hz, 1H), 8.61 (d, J = 4.5 Hz, 1H), 8.34 (s, 1H), 8.20 - 8.27 (m, 0.5H), 8.17 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.83 (s, 0.6H), 7.60 (t, J = 7.8 Hz, 1H), 7.29 (d, J = 3.5 Hz, 1H), 7.23 (d, J = 3.5 Hz, 1H), 4.49 - 4.73 (m, 2H), 3.51 - 3.70 (m, 1H), 3.30 - 3.40 (1H, excluded by solvent), 2.59 - 2.79 (m, 1H), 1.58 (s, 9H), 1.26 - 1.48 (m, 2H), 1.09 - 1.25 (m, 6H), 0.69 - 0.79 (m, 3H)	2.82[b]	502.2 ($M+H^+$)
64	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 10.08 (s, 0.1H), 9.38 - 9.77 (m, 0.6H), 8.89 - 8.98 (m, J = 5.3, 5.3 Hz, 0.6H), 8.82 - 8.90 (m, 0.4H), 8.56 (t, J = 5.5 Hz, 1H), 8.23 (s, 0.4H), 8.16 (d, J = 2.3 Hz, 1H), 7.83 (s, 0.6H), 7.74 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 3.5 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.77 (d, J = 3.5 Hz, 1H), 4.46 - 4.73 (m, 2H), 3.50 - 3.73 (m, 1H), 3.24 - 3.45 (1H, excluded by solvent), 2.58 - 2.79 (m, 1H), 1.26 - 1.48 (m, 2H), 1.09 - 1.23 (m, 6H), 0.76 (t, 3H)	2.14[b]	461.1 ($M+H^+$)
65	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.35 - 9.82 (m, 0.9H), 8.49 - 8.76 (m, 0.6H), 8.13 - 8.29 (m, 0.6H), 7.63 (s, 1H), 7.58 (br. s., 0.7H), 7.40 (br. s., 1H), 7.17 (d, J = 12.8 Hz, 2H), 4.33 - 4.86 (m,	2.07[b]	602.3 (M^+)

	2H), 4.12 (d, J = 6.8 Hz, 2H), 3.66 - 3.87 (m, 2H), 3.59 (br. s., 2H), 3.23 - 3.49 (m, 2H), 3.17 (br. s., 9H), 2.56 - 2.70 (m, 0.8H), 1.53 - 1.84 (m, 1H), 1.36 (t, J = 6.8 Hz, 5H), 0.94 - 1.29 (m, 6H), 0.55 - 0.89 (m, 6H)		
66	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.02 - 9.10 (m, 0.3H), 8.91 - 8.99 (m, 0.7H), 8.84 - 8.91 (m, 0.3H), 8.52 - 8.66 (m, 0.7H), 8.23 - 8.33 (m, 0.3H), 7.87 (d, J = 2.0 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.76 (s, 0.7H), 7.21 (d, J = 3.5 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.89 - 6.99 (m, J = 3.5 Hz, 1H), 4.45 - 4.73 (m, 2H), 3.79 (s, 3H), 3.53 - 3.64 (m, 1H), 2.55 - 2.66 (m, 1H), 1.30 - 1.61 (m, 4H), 1.03 - 1.28 (m, 6H), 0.65 - 0.85 (m, 6H)	2.32[b]	504.1 ($M+H^+$)
67	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.33 (s, 0.2H), 7.90 (s, 1H), 7.87 (s, 0.7H), 7.73 (d, J = 5.0 Hz, 1H), 7.35 - 7.48 (m, 2H), 7.25 (d, J = 3.5 Hz, 1H), 6.93 (d, J = 3.3 Hz, 1H), 4.67 - 4.87 (m, 2H), 4.29 - 4.41 (m, 0.3H), 3.57 - 3.72 (m, 0.7H), 2.57 - 2.79 (m, 1H), 1.66 - 1.78 (m, 2H), 1.61 (s, 6H), 1.45 - 1.57 (m, 2H), 1.14 - 1.37 (m, 6H), 0.84 - 1.00 (m, 3H), 0.77 (none, 3H)	2.56[b]	516.2 ($M+H^+$)
68	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.33 (s, 0.3H), 8.15 (br. s., 1H), 7.87 (s, 0.7H), 7.82 (d, J = 7.5 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 3.5 Hz, 1H), 6.92 (br. s., 1H), 4.67 - 4.86 (m, J = 13.1 Hz, 2H), 4.27 - 4.42 (m, 0.3H), 3.56 - 3.72 (m, 0.8H), 2.60 - 2.78 (m, 1H), 2.56 (s, 3H), 1.43 - 1.79 (m, 4H), 1.27 (br. s., 6H), 0.69 - 0.97 (m, 6H)	2.46[b]	488.2 ($M+H^+$)
69	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.23 - 9.80 (m, 0.8H), 9.11 - 9.24 (m, 0.3H), 9.03 (br. s., 0.6H), 8.73 - 8.89 (m, 0.2H), 8.43 - 8.69 (m, 0.6H), 8.29 (s, 0.3H), 7.76 (br. s., 0.7H), 7.43 - 7.57 (m, 2H), 7.31 - 7.42 (m, 1H), 7.23 (d, J = 1.3 Hz, 1H), 7.13 (br. s., 1H), 6.90 - 7.00 (m, J = 7.3 Hz, 1H), 4.42 - 4.78 (m, 2H), 4.14 - 4.31 (m, 0.3H), 4.00 (t, J = 5.8 Hz, 2H), 3.49 - 3.66 (m, 0.7H), 2.55 - 2.65 (m, 1H), 1.68 - 1.86 (m, 2H), 1.51 (br. s., 2H), 1.39 (br. s., 2H), 1.06 - 1.27 (m, J = 6.0 Hz, 6H), 1.01 (t, J = 7.2 Hz, 3H), 0.62 - 0.84 (m, 6H)	2.99[b]	488.3 ($M+H^+$)
70	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.20 (s, 0.3H), 7.71 - 7.80 (m, J = 2.0 Hz, 1.7H), 7.57 - 7.68 (m, 1H), 7.11 (d, J = 3.8 Hz, 1H), 7.01 (t, J = 9.0 Hz, 1H), 6.69 - 6.80 (m, 1H), 4.55 - 4.72 (m, J = 10.8 Hz, 2H), 4.15 - 4.30 (m, 0.3H), 3.44 - 3.58 (m, 2.7H), 2.44 - 2.66 (m, 1H), 1.33 - 1.67 (m, 4H), 1.04 - 1.23 (m, 6H), 0.73 - 0.85 (m, 3H), 0.60 - 0.72 (m, 3H)	2.50[b]	506.2 ($M+H^+$)

71	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.40 - 8.41 (m, 0.1H), 8.20 - 8.22 (m, 0.2H), 8.00 - 8.05 (m, 0.1H), 7.94 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.76 (s, 0.5H), 7.15 (d, J = 3.3 Hz, 1H), 6.89 - 6.95 (m, 1H), 4.58 - 4.72 (m, J = 9.0 Hz, 2H), 4.18 - 4.27 (m, 0.2H), 3.86 - 3.93 (m, 0.11H), 3.48 - 3.57 (m, 0.6H), 2.56 - 2.65 (m, 0.7H), 2.48 - 2.55 (m, 0.3H), 2.33 (m, 0.2H), 1.35 - 1.63 (m, 4H), 1.06 - 1.20 (m, 6H), 0.75 - 0.83 (m, 3H), 0.59 - 0.72 (m, 3H)	2.42[b]	474.2 ($M+H^+$)
72	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.20 (s, 0.3H), 7.74 (s, 0.7H), 7.26 (s, 1H), 7.22 (s, 1H), 7.11 (d, J = 3.5 Hz, 1H), 6.78 - 6.83 (m, 1H), 6.76 (s, 1H), 4.53 - 4.72 (m, 2H), 4.00 (q, J = 7.1 Hz, 2H), 3.44 - 3.56 (m, 3H), 2.42 - 2.64 (m, 1H), 1.33 - 1.64 (m, 4H), 1.30 (t, J = 7.0 Hz, 3H), 1.01 - 1.21 (m, 6H), 0.71 - 0.82 (m, J = 7.0, 7.0 Hz, 3H), 0.60 - 0.71 (m, 3H)	2.57[b]	532.3 ($M+H^+$)
73	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.64 (s, 1H), 9.61 (s, 0.3H), 9.29 (s, 0.7H), 9.12 (t, J = 5.9 Hz, 0.3H), 8.98 (t, J = 6.0 Hz, 0.7H), 8.77 (t, J = 5.6 Hz, 0.3H), 8.51 (t, J = 5.8 Hz, 0.7H), 8.29 (s, 0.3H), 7.76 (s, 0.7H), 7.19 - 7.25 (m, J = 3.8 Hz, 1H), 6.98 - 7.04 (m, 1H), 6.91 - 6.97 (m, 1H), 6.84 - 6.89 (m, J = 1.5 Hz, 1H), 6.34 (q, J = 2.2 Hz, 1H), 4.44 - 4.72 (m, J = 11.9, 11.9, 5.8 Hz, 2H), 4.16 - 4.28 (m, 0.3H), 3.95 - 4.10 (m, 2H), 3.57 (td, J = 9.3, 5.0 Hz, 0.7H), 2.53 - 2.64 (m, 1H), 1.36 - 1.59 (m, 4H), 1.33 (t, J = 6.9 Hz, 3H), 1.05 - 1.23 (m, 6H), 0.67 - 0.83 (m, 6H)	2.54[b]	490.0 ($M+H^+$)
74	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 12.32 - 13.17 (m, 1H), 9.60 (s, 0.3H), 9.20 - 9.40 (m, 0.6H), 9.10 - 9.19 (m, 0.3H), 8.95 - 9.06 (m, 0.7H), 8.87 (d, J = 7.8 Hz, 1H), 8.72 - 8.80 (m, 0.3H), 8.46 - 8.57 (m, 0.7H), 8.30 (s, 0.3H), 8.01 (d, J = 8.0 Hz, 1H), 7.77 (s, 0.7H), 7.56 - 7.70 (m, 2H), 7.23 - 7.38 (m, 2H), 4.77 - 4.92 (m, 1H), 4.49 - 4.77 (m, 2H), 4.33 (q, J = 6.9 Hz, 2H), 4.17 - 4.28 (m, 0.3H), 3.52 - 3.66 (m, 0.7H), 2.74 - 3.01 (m, 2H), 2.54 - 2.67 (m, 1H), 1.49 (t, J = 6.9 Hz, 6H), 1.19 (s, 7H), 0.62 - 0.85 (m, 6H)	5.56[a]	633.3 ($M+H^+$)
75	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.21 (s, 0.2H), 7.94 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.75 (s, 0.7H), 7.15 (d, J = 3.5 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 4.57 - 4.72 (m, J = 9.0 Hz, 2H), 4.16 - 4.30 (m, 0.3H), 3.46 - 3.59 (m, 0.7H), 2.47 - 2.66 (m, 1H), 1.34 - 1.64 (m, J = 7.3 Hz, 4H), 1.03 - 1.22 (m, 6H), 0.73 - 0.85 (m, 3H), 0.60 - 0.72 (m, 3H)	5.66[a]	647.3 ($M+H^+$)

76	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 12.39 (br. s., 1H), 9.97 (s, 0.2H), 9.55 (br. s., 0.6H), 8.96 - 9.16 (m, 1H), 8.51 - 8.66 (m, 1H), 8.23 (s, 0.4H), 7.82 (d, J = 7.3 Hz, 1H), 7.80 (s, 1.6H), 7.43 (t, J = 7.8 Hz, 1H), 7.29 (d, J = 7.0 Hz, 1H), 7.25 (d, J = 3.5 Hz, 1H), 7.11 (d, J = 3.5 Hz, 1H), 4.49 - 4.76 (m, 2H), 3.69 - 3.81 (m, 1H), 3.50 - 3.69 (m, 1H), 3.27 - 3.45 (1H, excluded by solvent), 2.57 - 2.79 (m, 1H), 1.43 (d, J = 7.0 Hz, 3H), 1.27 - 1.39 (m, 2H), 1.17 (d, J = 7.0 Hz, 6H), 0.76 (t, 3H)	2.31[b]	474.1 ($M+H^+$)
77	^{1}H NMR (400 MHz, Deuteriumoxide) δ ppm: 7.83 (s, 0.1H), 7.75 (s, 1H), 7.49 (s, 1H), 7.41 (s, 0.9H), 7.27 (s, 1H), 7.18 (d, J = 3.8 Hz, 1H), 7.00 (d, J = 3.8 Hz, 1H), 4.74 - 4.83 (1H, concealed under solvent peak), 4.44 - 4.56 (m, 2H), 4.13 (q, J = 6.9 Hz, 2H), 3.26 - 3.37 (m, 1H), 2.46 - 2.73 (m, 3H), 1.36 - 1.63 (m, 3H), 1.31 (t, J = 7.0 Hz, 4H), 0.80 - 1.12 (m, 6H), 0.68 (t, J = 7.2 Hz, 3H), 0.37 - 0.49 (m, 3H)	2.33[b]	633.3 ($M+H^+$)
78	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 10.02 (s, 0.4H), 9.56 (s, 0.6H), 9.08 - 9.23 (m, 1H), 8.59 (q, J = 5.4 Hz, 1H), 8.23 (s, 0.4H), 7.86 - 7.98 (m, 1H), 7.83 (s, 0.6H), 7.25 (d, J = 3.8 Hz, 1H), 7.06 (t, J = 8.3 Hz, 1H), 6.86 (t, J = 3.6 Hz, 1H), 4.46 - 4.77 (m, 2H), 3.50 - 3.73 (m, 1H), 3.26 - 3.44 (1H, excluded by solvent), 2.59 - 2.82 (m, 1H), 1.26 - 1.48 (m, 2H), 1.09 - 1.26 (m, 6H), 0.75 (t, 3H)	2.20[b]	482.1 ($M+H^+$)
79	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 13.18 (br. s., 1H), 10.02 (br. s., 0.3H), 9.54 (br. s., 0.5H), 9.14 - 9.31 (m, 1H), 8.50 - 8.65 (m, 1H), 8.21 (s, 0.4H), 8.01 (s, 1H), 7.90 (s, 0.6H), 7.75 (s, 1H), 7.42 (s, 1H), 7.26 (s, 2H), 4.63 (t, J = 5.6 Hz, 2H), 4.16 (q, J = 6.8 Hz, 2H), 3.65 (dt, J = 14.2, 6.8 Hz, 2H), 2.37 - 2.48 (m, 2H), 1.38 (t, J = 6.9 Hz, 3H)	2.23[b]	420.1
80	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 8.86 (br. s., 1H), 7.69 - 7.94 (m, 1H), 7.60 (br. s., 2H), 7.21 (br. s., 3H), 6.98 (br. s., 1H), 4.61 (br. s., 2H), 4.13 (br. s., 1H), 1.61 - 1.89 (m, 1H), 1.30 - 1.59 (m, 4H), 1.20 (d, J = 13.8 Hz, 8H), 0.77 (br. s., 8H)	2.50[b]	514.2 ($M+H^+$)
81	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.47 (s, 0.3H), 8.34 (s, 0.2H), 7.87 (s, 0.8H), 7.72 (d, J = 2.3 Hz, 1H), 7.50 (d, J = 2.5 Hz, 1H), 7.25 - 7.29 (m, 1H), 7.24 (br. s., 0.8H), 4.68 - 4.87 (m, 2H), 4.29 - 4.41 (m, 0.3H), 4.09 (q, J = 6.9 Hz, 2H), 3.56 - 3.74 (m, 0.8H), 3.37 (s, 0.8H), 2.58 - 2.78 (m, 1H), 1.46 - 1.81 (m, 4H), 1.41 (t, J = 6.9 Hz, 3H), 1.14 - 1.35 (m, 6H), 0.85 - 1.00 (m, J = 7.2, 7.2 Hz, 3H), 0.72 - 0.85 (m, 3H)	2.57[b]	534.2 ($M+H^+$)

82	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 11.06 - 11.71 (m, 0.6H), 8.70 - 8.96 (m, 1H), 7.90 (br. s., 1H), 7.58 (br. s., 1H), 7.40 (d, J = 12.3 Hz, 2H), 7.21 (d, J = 2.5 Hz, 1H), 7.01 (br. s., 1H), 4.62 (br. s., 2H), 3.98 (t, J = 6.1 Hz, 2H), 3.18 (br. s., 1H), 2.38 - 2.48 (m, 1H), 1.71 - 1.85 (m, J = 6.0 Hz, 2H), 1.31 - 1.64 (m, 4H), 1.21 (br. s., 6H), 0.96 - 1.09 (m, J = 7.0 Hz, 3H), 0.78 (d, J = 7.3 Hz, 6H)	2.72[b]	532.2 ($M+H^+$)
83	^{1}H NMR (400 MHz, Deuteriumoxide) δ ppm: 8.17 (s, 1H), 7.95 (d, J = 7.5 Hz, 1H), 7.69 - 7.79 (m, 2H), 7.49 - 7.59 (m, 1H), 7.23 (d, J = 3.5 Hz, 1H), 7.00 (d, J = 3.5 Hz, 1H), 4.79 (d, J = 13.8 Hz, 1H), 4.53 - 4.63 (m, 2H), 4.09 - 4.28 (m, 0.2H), 3.56 (t, J = 8.7 Hz, 0.8H), 2.53 - 2.83 (m, 3H), 1.31 - 1.75 (m, 4H), 0.99 - 1.19 (m, 4H), 0.86 - 0.99 (m, 2H), 0.69 - 0.82 (m, 3H), 0.50 (t, 3H)	2.27[b]	589.2 ($M+H^+$)
84	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 12.17 - 12.93 (m, 2H), 9.59 (s, 0.3H), 9.25 (s, 0.7H), 9.17 (t, J = 5.5 Hz, 0.3H), 9.02 (t, J = 5.6 Hz, 0.7H), 8.83 (d, J = 8.0 Hz, 1H), 8.74 (t, J = 5.5 Hz, 0.3H), 8.47 (t, J = 5.6 Hz, 0.7H), 8.27 (s, 0.3H), 7.87 (s, 1H), 7.74 (s, 0.7H), 7.65 (s, 1H), 7.36 (s, 1H), 7.23 (d, J = 3.0 Hz, 1H), 7.14 (d, J = 3.3 Hz, 1H), 4.75 (q, J = 7.4 Hz, 1H), 4.44 - 4.70 (m, 2H), 4.17 - 4.25 (m, 0.3H), 4.14 (q, J = 7.0 Hz, 2H), 3.55 (td, J = 9.0, 5.5 Hz, 0.7H), 2.79 - 2.91 (m, J = 5.8 Hz, 1H), 2.69 (dd, J = 16.6, 8.3 Hz, 1H), 2.51 - 2.62 (m, 1H), 1.42 - 1.58 (m, 3H), 1.36 (t, J = 6.9 Hz, 4H), 1.03 - 1.23 (m, J = 13.1, 7.3 Hz, 6H), 0.63 - 0.81 (m, 6H)	2.33[b]	633.2 ($M+H^+$)
85	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.32 (s, 0.2H), 7.91 - 8.00 (m, 1H), 7.88 (s, 0.7H), 7.65 (s, 1H), 7.43 (s, 1H), 7.27 (d, J = 3.8 Hz, 1H), 7.00 - 7.08 (m, 1H), 4.72 - 4.82 (m, 2H), 4.20 (q, J = 7.5 Hz, 2H), 4.15 (s, 2H), 2.51 - 2.80 (m, 1H), 1.50 - 1.77 (m, 4H), 1.46 (t, J = 6.9 Hz, 4H), 1.15 - 1.35 (m, 6H), 0.85 - 0.97 (m, 3H), 0.74 - 0.85 (m, 3H)	2.38[b]	575.2 ($M+H^+$)
86	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 12.68 (br. s., 2H), 9.22 - 9.75 (m, 0.6H), 9.11 - 9.21 (m, 0.4H), 9.02 (t, J = 5.8 Hz, 0.7H), 8.73 - 8.86 (m, 0.3H), 8.55 (t, J = 5.5 Hz, 0.7H), 8.35 (s, 0.3H), 7.82 (s, 0.7H), 7.51 - 7.66 (m, 2H), 7.31 (d, J = 3.3 Hz, 1H), 7.27 (t, J = 3.5 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 4.50 - 4.85 (m, 2H), 4.14 - 4.43 (m, 4H), 4.04 - 4.14 (m, 0.3H), 3.96 (s, 2H), 3.54 - 3.73 (m, 0.5H), 2.60 - 2.75 (m, 1H), 1.52 - 1.67 (m, 2H), 1.42 - 1.51 (m, 2H), 1.38 (s, 3H), 1.10 - 1.28 (m, 6H), 0.68 - 0.89 (m, 6H)	2.26[b]	633.3 ($M+H^+$)
87	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.19 (s, 0.3H), 7.75 (s, 0.7H), 7.44 - 7.50 (m, 1H), 7.39 (t, J = 1.3 Hz, 1H), 7.13 (d, J = 3.5 Hz, 1H), 6.82 - 6.90 (m, 2H), 4.56 - 4.73 (m, 2H), 4.21 (s, 2H), 4.01 -	2.30[b]	633.3 ($M+H^+$)

	4.07 (m, 4H), 3.97 - 4.01 (m, 0.3H), 3.46 - 3.59 (m, 0.8H), 2.44 - 2.66 (m, 1H), 1.37 - 1.67 (m, 4H), 1.33 (s, 3H), 1.01 - 1.22 (m, 6H), 0.73 - 0.85 (m, 3H), 0.65 (s, 3H)		
88	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.17 - 9.26 (m, 0.4H), 8.99 - 9.15 (m, 0.7H), 8.72 - 8.88 (m, 0.3H), 8.55 (br. s., 0.7H), 8.29 (s, 0.2H), 7.82 (s, 1H), 7.76 (s, 0.8H), 7.66 (br. s., 1H), 7.41 (br. s., 1H), 7.32 (br. s., 1H), 7.26 (br. s., 1H), 7.19 (br. s., 1H), 4.75 (br. s., 2H), 4.45 - 4.72 (m, 1H), 4.17 (br. s., 2H), 3.72 (br. s., 6H), 3.49 - 3.64 (m, 1H), 2.55 - 2.69 (m, 1H), 1.46 - 1.63 (m, 2H), 1.39 (br. s., 4H), 1.16 (br. s., 6H), 0.61 - 0.90 (m, 6H)	2.28[b]	621.3 ($M+H^+$)
89	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.03 - 9.14 (m, 0.5H), 8.87 - 8.98 (m, 0.5H), 8.66 - 8.80 (m, 1H), 8.29 - 8.38 (m, 1H), 8.22 (s, 0.4H), 7.92 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.82 (s, 0.6H), 7.42 (t, J = 7.5 Hz, 1H), 7.26 (d, J = 3.3 Hz, 1H), 7.08 (d, J = 3.0 Hz, 1H), 4.48 - 4.81 (m, 2H), 3.19 - 3.70 (m, 2H), 2.53 - 2.80 (m, 1H), 1.26 - 1.49 (m, 2H), 0.90 - 1.26 (m, 6H), 0.63 - 0.79 (m, 3H)	6.17[a]	446.1 ($M+H^+$)
90	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 8.83 (br. s., 0.4H), 8.54 - 8.69 (m, 1H), 8.47 (br. s., 0.5H), 8.20 (s, 0.5H), 7.73 - 7.88 (m, 1.6H), 7.26 - 7.45 (m, 3.4H), 7.18 (dd, J = 8.4, 3.4 Hz, 1.3H), 6.87 - 6.99 (m, 1H), 4.47 - 4.73 (m, 2H), 3.51 - 3.77 (m, 1H), 3.29 - 3.49 (1H, excluded by solvent), 2.54 - 2.76 (m, 1H), 1.28 - 1.55 (m, 2H), 1.12 - 1.23 (m, 6H), 0.78 (q, 3H)	2.27[b]	446.3 ($M+H^+$)
91	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 10.18 (br. s., 0.3H), 9.60 (br. s., 0.5H), 9.11 (d, J = 1.3 Hz, 0.5H), 9.03 (t, J = 5.8 Hz, 0.5H), 8.61 (t, J = 5.6 Hz, 1H), 8.19 - 8.27 (m, 0.4H), 8.14 (br. s., 1H), 7.93 (br. s., 1H), 7.83 (s, 0.6H), 7.19 - 7.29 (m, J = 3.5 Hz, 2H), 7.07 (d, J = 3.5 Hz, 1H), 4.44 - 4.74 (m, 2H), 3.50 - 3.70 (m, 1H), 3.24 - 3.45 (1H, excluded by solvent), 2.58 - 2.81 (m, 1H), 1.27 - 1.48 (m, 2H), 1.08 - 1.22 (m, 6H), 0.74 (t, 3H)	2.22[b]	464.1 ($M+H^+$)
92	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 13.10 (br. s., 1H), 9.96 (br. s., 0.3H), 9.55 (br. s., 0.6H), 9.11 - 9.27 (m, 1H), 8.54 - 8.66 (m, 1H), 8.23 (s, 0.4H), 8.03 (q, J = 8.5 Hz, 4H), 7.84 (s, 0.6H), 7.23 - 7.32 (m, 2H), 4.51 - 4.76 (m, 2H), 3.49 - 3.71 (m, 1H), 3.28 - 3.44 (1H, excluded by solvent), 2.59 - 2.78 (m, 1H), 1.26 - 1.47 (m, 2H), 1.10 - 1.23 (m, 6H), 0.75 (t, 3H)	2.22[b]	446.2 ($M+H^+$)
93	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 12.45 (br.s., 1.6H), 9.58 - 9.64 (m, 0.3H), 9.28 (s, 0.6H), 9.17 - 9.23 (m, 0.3H), 9.02 - 9.09 (m, 0.6H), 8.75 - 8.80 (m, 0.3H), 8.70 (d, J = 7.3 Hz, 1H), 8.47 - 8.54 (m, 0.6H), 8.28 - 8.33 (m, 0.3H), 7.91 (s, 1H), 7.77 (s, 0.6H), 7.69	2.42[b]	647.3 ($M+H^+$)

	(s, 1H), 7.43 (s, 1H), 7.27 (s, 1H), 7.19 (s, 1H), 4.49 - 4.74 (m, 2H), 4.40 - 4.49 (m, 1H), 4.13 - 4.24 (m, 2H), 3.53 - 3.63 (m, 1H), 2.56 - 2.64 (m, 1H), 2.39 (t, J = 7.3 Hz, 2H), 2.07 - 2.19 (m, 1H), 1.94 - 2.04 (m, 1H), 1.47 - 1.59 (m, 2H), 1.34 - 1.46 (m, 5H), 1.11 - 1.23 (m, 6H), 0.67 - 0.84 (m, 6H)		
94	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.11 (m, 1H), 8.59 (m, 1H), 8.20 (m, 1.4H), 8.09 (d, J = 8.0 Hz, 1H), 7.84 (s, 0.6H), 7.72 (m, 1H), 7.61 (dt, J = 3.0, 8.0 Hz, 1H), 7.29 (d, J = 3.0 Hz, 1H), 7.20 (d, J = 3.0 Hz, 1H), 4.63 (m, 2H), 3.60 (m, 1H), 3.42 (m, 1H), 2.62 - 2.74 (m, 1H), 1.57 (d, J = 14.5 Hz, 3H), 1.41 (m, 1H), 1.33 (m, 1H), 1.14 - 1.24 (m, 6H), 0.77 (m, 3H)	0.65[d]	480.1 ($M+H^+$)
95	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.26 (s, 0.4H), 8.23 (d, J = 13.0 Hz, 1H), 7.96 (d, J = 13.0 Hz, 1H), 7.89 (s, 0.6H), 7.76 (dd, J = 7.4, 12.6 Hz, 1H), 7.50 (dt, J = 4.8, 8.0 Hz, 1H), 7.25 (d, J = 2.8 Hz, 1H), 6.98 (d, J = 2.8 Hz, 1H), 4.79 (m, 2H), 3.69 - 3.81 (m, 1.4H), 3.50 (d, J = 10.4 Hz, 3H), 3.46 (m, 0.6H), 2.84 (m, 0.6H), 2.69 (m, 0.4H), 1.57 (m, 1H), 1.45 (m, 1H), 1.21 - 1.34 (m, 6H), 0.81 (m, 3H)	0.61[d]	496.0 ($M+H^+$)
96	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 11.18 (br. s., 1.7H), 9.57 (br. s., 0.2H), 9.26 (br. s., 0.5H), 9.09 - 9.18 (m, 0.3H), 8.98 (t, J = 6.0 Hz, 0.7H), 8.72 (t, J = 5.4 Hz, 0.3H), 8.47 (t, J = 5.6 Hz, 0.7H), 8.26 (s, 0.3H), 7.72 (s, 0.7H), 7.65 (d, J = 13.3 Hz, 1H), 7.57 (s, 1H), 7.22 (d, J = 3.5 Hz, 1H), 7.06 - 7.17 (m, 2H), 4.43 - 4.70 (m, 2H), 4.14 - 4.24 (m, 0.3H), 4.09 (q, J = 6.8 Hz, 2H), 3.48 - 3.59 (m, 0.8H), 2.50 - 2.61 (m, 1H), 1.42 - 1.55 (m, 2H), 1.28 - 1.41 (m, 5H), 1.01 - 1.21 (m, 6H), 0.63 - 0.81 (m, 6H)	6.04[a]	554.0 ($M+H^+$)
97	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.75 (br. s., 0.3H), 9.44 (br. s., 0.4H), 8.96 - 9.11 (m, 0.3H), 8.73 - 8.88 (m, 0.7H), 8.40 - 8.54 (m, 0.5H), 8.32 (t, J = 6.3 Hz, 0.7H), 7.88 - 7.93 (m, 0.7H), 7.37 - 7.51 (m, 2H), 7.26 (d, J = 14.6 Hz, 1H), 5.05 - 5.16 (m, 1H), 4.49 - 4.74 (m, 3H), 4.35 - 4.45 (m, 0.3H), 4.26 (q, J = 6.8 Hz, 2H), 3.63 - 3.80 (m, 0.8H), 2.72 - 2.79 (m, 1H), 2.35 - 2.54 (m, 2H), 2.10 - 2.26 (m, 1H), 1.77 - 1.92 (m, 1H), 1.63 - 1.78 (m, 2H), 1.53 (s, 5H), 1.24 - 1.45 (m, 6H), 0.82 - 1.04 (m, 6H)	1.70[c]	558.0 ($M+H^+$)
98	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.60 (s, 0.3H), 9.27 (br. s., 0.5H), 9.12 (t, J = 6.3 Hz, 0.3H), 8.98 (t, J = 5.9 Hz, 0.7H), 8.76 (t, J = 5.4 Hz, 0.3H), 8.51 (t, J = 5.4 Hz, 0.7H), 8.30 (s, 0.3H), 7.77 (s, 0.7H), 7.71 (dd, J = 14.2, 7.9 Hz, 1H), 7.47 - 7.56 (m, J = 5.3 Hz, 2H), 7.21 - 7.30 (m, 2H), 4.47 - 4.79 (m, 2H), 4.20 (q, J = 6.9 Hz, 2.2H), 3.51 - 3.65 (m, 0.7H), 2.55 - 2.67 (m, 1H), 1.47 - 1.61 (m,	5.62[a]	554.3 ($M+H^+$)

	2H), 1.38 (t, 5H), 1.07 - 1.29 (m, 6H), 0.64 - 0.85 (m, 6H)		
99	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.19 (s, 0.3H), 7.75 (s, 0.7H), 7.29 (br. s., 1H), 7.22 (br. s., 1H), 7.12 (d, J = 3.5 Hz, 1H), 6.75 - 6.87 (m, J = 3.5 Hz, 2H), 4.56 - 4.72 (m, 2H), 4.16 - 4.28 (m, 0.3H), 4.02 (q, J = 6.9 Hz, 2H), 3.44 - 3.58 (m, 0.7H), 3.07 (s, 1H), 3.02 (s, 1H), 2.54 - 2.66 (m, 0.7H), 2.44 - 2.54 (m, 0.3H), 1.35 - 1.65 (m, 4H), 1.31 (t, J = 6.9 Hz, 3H), 1.02 - 1.22 (m, 6H), 0.72 - 0.84 (m, J = 7.2, 7.2 Hz, 3H), 0.61 - 0.72 (m, 3H)	2.41[b]	568.2
100	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.16 - 9.35 (m, 0.7H), 9.03 - 9.16 (m, 0.3H), 8.84 - 8.94 (m, 0.6H), 8.64 - 8.72 (m, 0.4H), 8.55 - 8.64 (m, 1H), 8.39 - 8.48 (m, 0.7H), 8.22 (s, 0.3H), 7.82 - 7.90 (m, 1H), 7.70 (s, 1H), 7.59 (d, J = 1.5 Hz, 1H), 7.35 (d, J = 1.0 Hz, 1H), 7.18 (d, J = 3.5 Hz, 1H), 7.09 (d, J = 3.0 Hz, 1H), 4.42 - 4.66 (m, 2H), 4.04 - 4.13 (m, 2H), 3.44 - 3.59 (m, 3H), 2.47 - 2.57 (m, 1H), 1.36 - 1.51 (m, 3H), 1.31 (t, J = 6.7 Hz, 4H), 1.01 - 1.15 (m, 6H), 0.60 - 0.75 (m, 6H)	6.06[a]	610.8 ($M+H^+$)
101	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.62 (br. s., 0.3H), 9.30 (br. s., 0.5H), 9.21 (t, J = 5.9 Hz, 0.3H), 9.05 (t, J = 5.6 Hz, 0.7H), 8.76 (t, J = 5.6 Hz, 0.3H), 8.51 (t, J = 5.5 Hz, 0.7H), 8.30 (s, 0.3H), 7.77 (s, 0.7H), 7.65 - 7.75 (m, J = 13.6 Hz, 2H), 7.26 (d, J = 2.5 Hz, 1H), 7.21 - 7.25 (m, 1H), 7.15 (d, J = 14.3 Hz, 1H), 4.47 - 4.77 (m, 2H), 4.19 - 4.28 (m, 0.4H), 4.15 (q, J = 6.8 Hz, 2H), 3.52 - 3.62 (m, J = 11.0 Hz, 3.7H), 2.55 - 2.66 (m, 1H), 1.48 - 1.59 (m, 2H), 1.38 (t, J = 6.9 Hz, 5H), 1.05 - 1.25 (m, 6H), 0.66 - 0.84 (m, 6H)	1.84[c]	568.0 ($M+H^+$)
102	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.14 (s, 0.4H), 7.78 (s, 0.6H), 7.41 (br. s., 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.26 (t, J = 7.9 Hz, 1H), 7.12 (d, J = 3.3 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.83 (br. s., 1H), 6.10 (tt, J = 3.6, 56.0 Hz, 1H), 4.58 - 4.72 (m, 2H), 4.21 (td, J = 13.6, 3.3 Hz, 2H), 3.52 - 3.74 (m, 1.4H), 3.34 (dd, J = 14.2, 4.9 Hz, 0.6H), 2.73 (m, 0.6H), 2.58 (m, 0.4H), 1.38 - 1.54 (m, 1H), 1.26 - 1.38 (m, 1H), 1.00 - 1.26 (m, 6H), 0.68 (br. s., 3H)	2.57[b]	482.1 ($M+H^+$)
103	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.95 (s, 0.4H), 9.55 (s, 0.6H), 9.08 - 9.20 (m, 1H), 8.51 - 8.64 (m, 1H), 8.24 (s, 0.4H), 7.86 (s, 1H), 7.83 (s, 0.6H), 7.73 (d, J = 7.8 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.24 (d, J = 3.5 Hz, 1H), 7.15 - 7.19 (m, 1H), 4.52 - 4.71 (m, 2H), 3.52 - 3.68 (m, 2H), 2.72 (br. s., 0.6H), 2.64 (br. s., 0.4H), 1.30 - 1.46 (m, 2H), 1.17 (br. s., 6H), 0.69 - 0.81 (m, 3H)	2.17[b]	462.2 ($M+H^+$)

104	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.14 (s, 0.4H), 7.78 (s, 0.6H), 7.67 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.21 - 7.32 (m, 1H), 7.15 (d, J = 8.3 Hz, 1H), 7.13 (d, J = 3.3 Hz, 1H), 6.85 (d, J = 3.0 Hz, 1H), 4.60 - 4.69 (m, 2H), 3.53 - 3.72 (m, 1.4H), 3.34 (dd, J = 14.1, 4.8 Hz, 0.6H), 2.65 - 2.79 (m, 0.4H), 2.52 - 2.65 (m, 0.6H), 2.44 (s, 3H), 1.25 - 1.50 (m, 2H), 1.11 - 1.18 (m, 6H), 0.68 (d, J = 2.0 Hz, 3H)	2.61[b]	448.2 ($M+H^+$)
105	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.95 (br.s., 0.3H), 9.50 - 9.57 (m, 0.5H), 9.26 - 9.36 (m, 1H), 8.75 (s, 1H), 8.57 - 8.65 (m, 1H), 8.38 (d, J = 7.8 Hz, 1H), 8.18 - 8.26 (m, 1.4H), 7.84 (s, 0.6H), 7.78 (t, J = 8.0 Hz, 1H), 7.40 (d, J = 3.8 Hz, 1H), 7.30 (d, J = 3.5 Hz, 1H), 4.55 - 4.72 (m, 2H), 3.54 - 3.67 (m, 1H), 3.4 (1H excluded by solvent), 2.60 - 2.76 (m, 1H), 1.28 - 1.44 (m, 2H), 1.13 - 1.23 (m, 6H), 0.70 - 0.77 (m, 3H)	2.47[b]	447.1 ($M+H^+$)
106	^{1}H NMR (CHLOROFORM-d) δ ppm: 8.22 (br. s., 0.6H), 7.97 (s, 0.4H), 7.94 (br. s., 1H), 7.85 (br. s., 0.6H), 7.65 - 7.82 (m, 3H), 7.35 - 7.47 (m, 1H), 6.75 (br. s., 1H), 4.80 (m, 2H), 3.67 - 3.82 (m, 1H), 3.26 - 3.46 (m, 1H), 2.70 - 2.81 (m, 1H), 2.63 (s, 3H), 1.65 (br. s., 2H), 1.17 (br. s., 6H), 0.82 (br. s., 3H)	2.34[b]	456.1 ($M+H^+$)
107	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.27 (s, 0.4H), 8.21 (s, 1H), 8.15 (s, 1H), 7.90 (s, 0.6H), 7.77 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.27 (d, J = 3.5 Hz, 1H), 6.99 (d, J = 3.5 Hz, 1H), 4.72 - 4.87 (m, 2H), 4.24 (s, 3H), 3.70 - 3.84 (m, 1.4H), 3.47 (dd, J = 14.2, 5.1 Hz, 0.6H), 2.81 - 2.92 (m, 0.6H), 2.70 (m, 0.4H), 1.51 - 1.67 (m, 1H), 1.38 - 1.51 (m, 1H), 1.18 - 1.38 (m, 6H), 0.64 - 0.86 (m, 3H)	1.70[c]	456.3 ($M+H^+$)
108	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.26 (m, 1.5H), 8.06 (m, 1.5H), 7.91 (s, 0.5H), 7.80 (m, 1H), 7.58 (m, 1H), 7.27 (d, J = 3.5 Hz, 1H), 7.01 (d, J = 3.5 Hz, 0.5H), 4.80 (m, 2H), 3.70 - 3.83 (m, 1.5H), 3.47 (dd, J = 5.2, 14.5 Hz, 0.5H), 2.86 (m, 0.5H), 2.71 (m, 0.5H), 1.58 (m, 1H), 1.47 (m, 1H), 1.21 - 1.36 (m, 6H), 0.82 (m, 3H)	0.58[d]	482.0 ($M+H^+$)
109	^{1}H NMR (400 MHz, methanol-d4) δ ppm: 8.25 (s, 1H), 8.15 (d, J = 6.8 Hz, 1H), 7.95 - 8.06 (m, 1H), 7.86 (s, 1H), 7.61 - 7.70 (m, 2H), 7.42 - 7.50 (m, 1H), 7.27 (d, J = 3.5 Hz, 1H), 7.05 - 7.13 (m, 1H), 4.69 - 4.81 (m, 2H), 3.57 - 3.67 (m, 1H), 2.65 - 2.76 (m, 1H), 1.44 - 1.74 (m, 6H), 1.13 - 1.33 (m, 4H), 0.89 (t, J = 7.4 Hz, 3H), 0.81 (t, J = 6.5 Hz, 3H)	5.60[a]	488.0 ($M+H^+$)

110	^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 9.54 - 9.64 (m, 0.3H), 9.24 - 9.32 (m, 0.7H), 8.81 - 8.95 (m, 0.3H), 8.64 (t, J = 5.8 Hz, 0.7H), 8.27 - 8.33 (m, 0.3H), 8.22 (t, J = 6.0 Hz, 0.3H), 8.08 (t, J = 6.3 Hz, 0.7H), 7.64 - 7.78 (m, 0.7H), 7.14 - 7.52 (m, 5H), 4.80 - 4.98 (m, 1H), 4.27 - 4.59 (m, 3H), 4.15 - 4.27 (m, 0.3H), 3.47 - 3.63 (m, 0.7H), 2.18 - 2.36 (m, 2H), 1.92 - 2.08 (m, 1H), 1.28 - 1.76 (m, 5.2H), 0.94 - 1.28 (m, 6.4H), 0.51 - 0.92 (m, 6.4H)	2.64[b]	434.2
111	1H NMR (METHANOL-d4) Shift: 8.32 (s, 0.3H), 7.90 (d, J=5.5 Hz, 1H), 7.87 (s, 0.7H), 7.82 (d, J=7.3 Hz, 1H), 7.26 (d, J=3.5 Hz, 1H), 7.00 (d, J=3.3 Hz, 1H), 4.69-4.84 (m, 2H), 4.35 (br. s., 0.3H), 4.21-4.31 (m, 2H), 3.56-3.69 (m, 0.7H), 2.67-2.77 (m, 0.7H), 2.62 (br. s., 0.3H), 1.63-1.73 (m, 2H), 1.50 (t, J=6.9 Hz, 5H), 1.13-1.36 (m, 6H), 0.84-0.97 (m, 3H), 0.71-0.84 (m, 3H)	7.15[a]	536.0 ($M+H^+$)
112	1H NMR (DMSO-d6) Shift: 10.01 (br. s., 0.1H), 9.67 (br. s., 0.1H), 9.33 (br. s., 0.5H), 9.14-9.23 (m, 0.3H), 9.05 (t, J=5.9 Hz, 0.7H), 8.79 (t, J=5.5 Hz, 0.3H), 8.53 (t, J=5.6 Hz, 0.7H), 8.29 (s, 0.3H), 7.85 (s, 1H), 7.76 (s, 0.7H), 7.51 (br. s., 1H), 7.35 (d, J=1.3 Hz, 1H), 7.21-7.29 (m, 1H), 7.09-7.17 (m, 1H), 4.43-4.75 (m, 2H), 4.22 (q, J=7.8 Hz, 0.3H), 3.57 (td, J=9.2, 4.9 Hz, 0.7H), 2.54-2.70 (m, 1H), 1.31-1.62 (m, 4H), 1.03-1.28 (m, 6H), 0.59-0.87 (m, 6H)	5.41[g]	490.2 ($M+H^+$)
113	1H NMR (DMSO-d6) Shift: 9.61 (s, 0.2H), 9.22-9.37 (m, 0.7H), 9.13 (t, J=5.9 Hz, 0.6H), 8.78 (t, J=5.9 Hz, 0.3H), 8.52 (t, J=5.9 Hz, 0.6H), 8.30 (s, 0.3H), 7.99-8.09 (m, 1H), 7.70-7.82 (m, 1.7H), 7.38 (t, J=2.0 Hz, 1H), 7.21-7.29 (m, 2H), 4.84 (s, 2H), 4.43-4.74 (m, 2H), 4.15-4.29 (m, 0.3H), 3.57 (td, J=9.4, 4.8 Hz, 0.7H), 2.54-2.67 (m, 1H), 1.32-1.62 (m, 4H), 1.00-1.29 (m, 6H), 0.59-0.84 (m, 6H)	5.39[g]	548.3 ($M+H^+$)
114	1H NMR (DMSO-d6) Shift: 9.61 (s, 0.3H), 9.29 (s, 0.7H), 9.20 (t, J=5.9 Hz, 0.3H), 9.06 (t, J=6.1 Hz, 0.7H), 8.79 (t, J=5.8 Hz, 0.3H), 8.54 (t, J=5.9 Hz, 0.7H), 8.29 (s, 0.3H), 7.95-8.02 (m, 1H), 7.85-7.94 (m, 2H), 7.76 (s, 0.7H), 7.26-7.32 (m, 1H), 7.20-7.25 (m, 1H), 4.47-4.78 (m, 2H), 4.22 (q, J=7.3 Hz, 0.3H), 3.99 (s, 2H), 3.58 (td, J=9.5, 4.6 Hz, 0.7H), 2.54-2.67 (m, 1H), 1.30-1.60 (m, 4H), 1.05-1.21 (m, 6H), 0.59-0.86 (m, 6H)	2.26[b]	532.1 (M+H+)
115	1H NMR (DMSO-d6) Shift: 9.61 (s, 0.3H), 9.26-9.43 (m, 0.8H), 8.76 (t, J=5.6 Hz, 0.2H), 8.53 (t, J=5.8 Hz, 0.7H), 8.30 (s, 0.3H), 7.96-8.08 (m, 1H), 7.79 (s, 0.7H), 7.29-7.38 (m, 1H), 7.23-7.28 (m, 1H), 7.04-7.21 (m, 6H), 4.50-4.88 (m, 2H), 4.29 (d, J=6.8 Hz, 0.1H), 4.06 (q, J=6.9 Hz, 2H), 3.49-3.76 (m, 0.6H), 2.58-2.75 (m, 1H), 2.39-2.54 (2H, under solvent peak), 1.63-1.87 (m, 2H), 1.45-1.59 (m, 2H),	0.89[e]	568.5 (M+H+)

	1.25-1.39 (m, 3H), 0.58-0.87 (m, 3H)		
117	1H NMR (DMSO-d6) Shift: 9.58 (s, 0.3H), 9.28 (s, 0.7H), 9.21 (t, J=5.8 Hz, 0.5H), 8.83 (d, J=7.8 Hz, 1H), 8.58 (t, J=5.9 Hz, 0.6H), 8.30 (s, 0.3H), 7.96 (d, J=8.0 Hz, 1.4H), 7.51-7.86 (m, 7H), 7.24-7.46 (m, 5H), 4.97 (dt, J=7.7, 5.3 Hz, 1.2H), 4.28 (dd, J=7.2, 2.1 Hz, 0.6H), 4.11 (q, J=5.1 Hz, 0.7H), 3.69 (s, 4H), 3.62 (s, 2H), 3.17 (d, J=5.0 Hz, 2H), 2.97 (dd, J=8.0, 5.3 Hz, 2H), 2.58-2.75 (m, 2H), 1.32-1.51 (m, 3H), 0.64-0.86 (m, 3H)	1.21[h]	717.2 (M+H+)
118	1H NMR (METHANOL-d4) Shift: 8.27 (s, 0.3H), 7.82-8.00 (m, 1.6H), 7.44 (d, J=3.3 Hz, 1H), 7.10-7.33 (m, 3H), 6.72-6.88 (m, 2H), 4.60-4.88 (m, 4H), 4.35-4.50 (m, 0.3H), 3.63-3.82 (m, 0.7H), 2.69-2.92 (m, 1H), 2.47-2.66 (m, 2H), 1.56-2.00 (m, 4H), 0.69-1.03 (m, 3H)	6.57[a]	634.2 (M+H+)
119	1H NMR (METHANOL-d4) Shift: 9.11 (t, J=6.0 Hz, 0.2H), 9.01 (t, J=6.0 Hz, 0.5H), 8.91 (t, J=5.9 Hz, 0.2H), 8.84 (t, J=6.0 Hz, 0.5H), 8.74 (d, J=7.8 Hz, 0.3H), 8.32 (s, 0.2H), 7.91-8.05 (m, 4H), 7.87 (s, 0.7H), 7.28 (d, J=3.5 Hz, 1H), 7.03-7.14 (m, 1H), 4.97-5.06 (m, 1H), 4.66-4.88 (m, 2H), 4.35 (ddd, J=10.0, 7.2, 5.1 Hz, 0.2H), 3.55-3.75 (m, 0.8H), 2.86-3.13 (m, 2H), 2.52-2.81 (m, 1H), 1.43-1.81 (m, 4H), 1.11-1.37 (m, 6H), 0.66-1.01 (m, 6H)	5.40[a]	589.3 (M+H+)
120	1H NMR (DMSO-d6) Shift: 9.61 (s, 0.3H), 9.29 (s, 0.7H), 9.17 (t, J=6.0 Hz, 0.2H), 9.03 (t, J=6.0 Hz, 0.7H), 8.78 (t, J=5.5 Hz, 0.2H), 8.64 (br. s., 0.6H), 8.53 (t, J=6.0 Hz, 0.7H), 8.29 (s, 0.3H), 7.72-7.86 (m, 2.8H), 7.39 (d, J=8.0 Hz, 1H), 7.23-7.30 (m, 1H), 7.13-7.20 (m, 1H), 4.46-4.78 (m, 3H), 4.22 (q, J=7.4 Hz, 0.2H), 3.58 (td, J=9.5, 4.8 Hz, 0.7H), 2.77-2.89 (m, 1H), 2.55-2.73 (m, 2H), 2.41 (s, 3H), 1.33-1.62 (m, 4H), 1.05-1.25 (m, 6H), 0.60-0.85 (m, 6H)	5.46[a]	603.3 (M+H+)
121	1H NMR (DMSO-d6) Shift: 9.62 (s, 0.3H), 9.26-9.41 (m, 0.7H), 9.21 (t, J=6.0 Hz, 0.6H), 8.79 (t, J=5.6 Hz, 0.3H), 8.52 (t, J=5.9 Hz, 0.7H), 8.30 (s, 0.3H), 7.97-8.07 (m, 1H), 7.76 (s, 0.7H), 7.27-7.34 (m, 1H), 7.22-7.26 (m, 1H), 7.15-7.19 (m, 1H), 4.73 (s, 2H), 4.45-4.71 (m, 2H), 4.14-4.29 (m, 0.2H), 3.58 (td, J=9.5, 5.1 Hz, 0.7H), 2.54-2.68 (m, 1H), 1.31-1.63 (m, 4H), 1.03-1.26 (m, 6H), 0.57-0.86 (m, 6H)	5.29[i]	564.1 (M+H+)

122	1H NMR (METHANOL-d4) Shift: 8.32 (s, 0.3H), 7.89 (s, 0.6H), 7.52 (d, J=18.3 Hz, 2H), 7.24 (d, J=3.5 Hz, 1H), 7.12-7.21 (m, 1H), 6.90-7.02 (m, 2H), 6.70-6.86 (m, 2H), 4.65-4.89 (m, 2H), 4.28-4.47 (m, 2.2H), 4.03-4.22 (m, 4H), 3.59-3.77 (m, 0.7H), 2.47-2.89 (m, 3H), 1.52-1.97 (m, 4H), 1.42 (t, J=6.9 Hz, 3H), 0.77-1.00 (m, 3H)	6.56[a]	703.2 (M+H+)
123	1H NMR (METHANOL-d4) Shift: 9.27 (d, J=7.5 Hz, 0.6H), 9.13 (t, J=6.0 Hz, 0.1H), 8.27 (s, 0.3H), 8.09 (d, J=8.3 Hz, 1H), 7.90 (s, 0.6H), 7.58-7.68 (m, 1H), 7.52 (d, J=8.3 Hz, 1H), 7.26-7.37 (m, 1H), 7.15-7.25 (m, 1H), 7.03-7.14 (m, 1H), 6.70-6.89 (m, 2H), 4.66-4.86 (m, 2H), 4.26-4.50 (m, 2.3H), 3.60-3.82 (m, 0.6H), 2.88-3.21 (m, 2H), 2.67-2.86 (m, 1H), 2.50-2.64 (m, 2H), 1.77-1.96 (m, 2H), 1.51-1.76 (m, 5H), 0.76-1.02 (m, 3H)	6.40[a]	703.2 (M+H+)
124	1H NMR (DMSO-d6) Shift: 9.63 (s, 0.3H), 9.31 (s, 0.6H), 9.20 (t, J=6.1 Hz, 0.3H), 9.12 (t, J=6.0 Hz, 0.6H), 8.78 (t, J=5.8 Hz, 0.3H), 8.56 (t, J=5.8 Hz, 0.6H), 8.30 (s, 0.3H), 7.79 (s, 0.7H), 7.49-7.62 (m, 2H), 7.26-7.31 (m, 1H), 7.22-7.25 (m, 1H), 7.07-7.20 (m, 6H), 4.48-4.87 (m, 2H), 4.28 (d, J=6.3 Hz, 0.1H), 4.13 (br. s., 2H), 3.89 (s, 2H), 3.57-3.73 (m, 0.7H), 3.26-3.46 (2H, under solvent peak), 2.56-2.76 (m, 1H), 2.40-2.54 (2H, under solvent peak), 1.63-1.83 (m, 2H), 1.43-1.60 (m, 2H), 1.17-1.38 (m, 3H), 0.65-0.85 (m, 3H)	5.47[a]	667.4 (M+H+)
125	1H NMR (DMSO-d6) Shift: 9.62 (s, 0.2H), 9.21-9.40 (m, 0.4H), 9.07 (br. s., 0.6H), 8.72-8.89 (m, 0.3H), 8.53 (t, J=5.6 Hz, 0.7H), 8.30 (s, 0.3H), 7.93 (s, 1H), 7.76 (s, 0.7H), 7.67-7.72 (m, 1H), 7.39 (s, 1H), 7.24-7.31 (m, 1H), 7.14-7.22 (m, 1H), 4.83 (s, 2H), 4.46-4.78 (m, 2H), 4.13-4.31 (m, 0.2H), 3.58 (td, J=9.5, 4.6 Hz, 0.7H), 3.28-3.42 (2H, under solvent peak), 2.79-2.96 (m, 1H), 2.56-2.75 (m, 0.8H), 1.33-1.62 (m, 4H), 0.96-1.26 (m, 6H), 0.61-0.85 (m, 6H)	5.27[a]	663.3 (M+H+)
126	1H NMR (DMSO-d6) Shift: 9.63 (br. s., 0.1H), 9.13-9.26 (m, 1H), 8.99 (t, J=6.0 Hz, 0.6H), 8.78 (t, J=5.8 Hz, 0.2H), 8.54 (t, J=5.9 Hz, 0.7H), 8.29 (s, 0.3H), 7.90-8.07 (m, 1H), 7.77 (s, 0.7H), 7.64-7.72 (m, 1H), 7.53-7.63 (m, 1H), 7.17-7.37 (m, 2H), 4.88-5.06 (m, 2H), 4.49-4.84 (m, 3H), 4.22 (q, J=7.4 Hz, 0.2H), 3.57 (td, J=9.6, 4.4 Hz, 0.7H), 2.71-2.92 (m, 2H), 2.54-2.65 (m, 1H), 1.32-1.64 (m, 4H), 1.00-1.24 (m, 6H), 0.64-0.83 (m, 6H)	5.38[a]	663.3 (M+H+)

127	1H NMR (DMSO-d6) Shift: 9.62 (s, 0.3H), 9.31 (s, 0.7H), 9.24 (t, J=5.8 Hz, 0.3H), 9.15 (t, J=6.1 Hz, 0.6H), 8.90 (d, J=7.3 Hz, 1H), 8.77 (t, J=5.5 Hz, 0.2H), 8.56 (t, J=5.8 Hz, 0.7H), 8.30 (s, 0.3H), 8.01 (d, J=8.3 Hz, 1H), 7.79 (s, 0.7H), 7.59-7.68 (m, 2H), 7.28-7.35 (m, 2H), 7.07-7.24 (m, 5H), 4.51-4.89 (m, 3H), 4.17-4.40 (m, 2.5H), 3.56-3.73 (m, 0.7H), 2.59-2.96 (m, 2H), 2.40-2.57 (2H, under solvent peak), 1.33-1.91 (m, 7H), 0.65-0.87 (m, 3H)	0.79[e]	667.6 (M+H+)
128	1H NMR (METHANOL-d4) d: 8.29-8.34 (m, 0.2H), 7.87 (s, 0.8H), 7.27 (d, J=3.8 Hz, 1H), 7.08-7.17 (m, J=17.1, 1.5 Hz, 3H), 4.69-4.85 (m, 2H), 4.37 (q, J=7.0 Hz, 2H), 4.20-4.33 (m, J=5.8, 5.8 Hz, 0.2H), 3.57-3.69 (m, 0.7H), 2.72 (td, J=9.8, 4.8 Hz, 0.7H), 2.62 (ddd, J=10.4, 7.2, 4.5 Hz, 0.3H), 1.43-1.77 (m, 7H), 1.12-1.36 (m, 6H), 0.85-0.97 (m, J=7.2, 7.2 Hz, 3H), 0.73-0.84 (m, 3H)	0.97[e]	534.1 (M+H+)
129	1H NMR (DMSO-d6) Shift: 9.61 (s, 0.3H), 9.26-9.36 (m, 0.6H), 9.20 (t, J=5.9 Hz, 0.6H), 8.72-8.82 (m, 0.1H), 8.53 (t, J=5.8 Hz, 0.7H), 8.29 (s, 0.3H), 8.17 (s, 1H), 8.10 (dd, J=8.3, 1.8 Hz, 1H), 7.83 (d, J=8.0 Hz, 1H), 7.76 (s, 0.7H), 7.31-7.38 (m, 1H), 7.25-7.30 (m, 1H), 4.45-4.77 (m, 2H), 4.14-4.29 (m, 0.1H), 3.58 (td, J=9.3, 4.9 Hz, 0.5H), 2.53-2.67 (m, 1H), 1.31-1.61 (m, 4H), 1.02-1.23 (m, 6H), 0.56-0.83 (m, 6H)	2.23[b]	519.0 (M+H+)
130	1H NMR (METHANOL-d4) Shift: 9.06 (t, J=5.9 Hz, 0.1H), 8.89 (dt, J=16.5, 5.9 Hz, 0.7H), 8.29 (s, 0.3H), 8.10 (s, 0.1H), 7.83-7.93 (m, 0.8H), 7.61-7.69 (m, 1H), 7.54-7.59 (m, 1H), 7.27 (d, J=3.8 Hz, 1H), 7.13 (d, J=1.5 Hz, 1H), 7.00-7.08 (m, 1H), 4.71-4.85 (m, 2H), 4.42 (s, 2H), 3.92 (s, 2H), 3.56-3.73 (m, 0.8H), 2.93 (s, 3H), 2.55-2.81 (m, 1H), 1.37-1.80 (m, 4H), 1.12-1.35 (m, 6H), 0.65-1.03 (m, 6H)	5.87[a]	575.2 (M+H+)
131	1H NMR (METHANOL-d4) Shift: 8.32 (s, 0.2H), 8.13-8.17 (m, 0.8H), 8.08-8.12 (m, 0.1H), 7.87 (s, 0.7H), 7.72-7.82 (m, 0.8H), 7.64 (t, J=1.9 Hz, 0.8H), 7.55-7.60 (m, 0.2H), 7.25-7.31 (m, 1H), 7.01-7.11 (m, 1H), 4.70-4.81 (m, 2H), 4.65-4.68 (m, 2H), 4.26-4.42 (m, 0.2H), 3.56-3.73 (m, 0.7H), 2.55-2.80 (m, 1H), 1.46-1.83 (m, 3H), 1.14-1.36 (m, 7H), 0.63-1.00 (m, 6H)	5.65[a]	547.3 (M+H+)
132	1H NMR (METHANOL-d4) Shift: 8.31 (s, 0.3H), 8.06 (d, J=8.3 Hz, 1H), 7.89 (s, 0.7H), 7.54-7.61 (m, 1H), 7.48 (d, J=8.0 Hz, 1H), 7.23-7.30 (m, 1H), 7.01-7.11 (m, 1H), 4.64-4.86 (m, 2H), 4.19-4.45 (m, 2.5H), 3.86-4.00 (m, 0.2H), 3.59-3.78 (m, 0.8H), 3.41-3.54 (m, 0.2H), 3.13 (dd, J=17.2, 4.4 Hz, 1H), 2.87-3.02 (m, 1H), 2.55-2.80 (m, 1H), 1.45-1.85 (m, 7H), 1.08-1.37 (m, 6H), 0.62-0.98 (m, 6H)	5.80[a]	633.4 (M+H+)

133	1H NMR (DMSO-d6) Shift: 12.82 (br. s., 1H), 12.42 (br. s., 1H), 9.61 (s, 0.3H), 9.30 (br. s., 0.6H), 9.24 (t, J=6.5 Hz, 0.3H), 9.09 (t, J=5.9 Hz, 0.7H), 8.86 (d, J=7.8 Hz, 1H), 8.79 (s, 0.3H), 8.54 (t, J=5.4 Hz, 0.7H), 8.29 (s, 0.3H), 7.93-8.06 (m, 4H), 7.77 (s, 0.7H), 7.24-7.30 (m, 2H), 4.74-4.80 (m, 1H), 4.49-4.72 (m, 2H), 4.19-4.26 (m, 0.3H), 3.54-3.68 (m, 0.7H), 2.87 (dd, J=16.4, 5.6 Hz, 1H), 2.73 (dd, J=16.8, 7.8 Hz, 1H), 2.54-2.64 (m, 1H), 1.34-1.56 (m, 4H), 1.04-1.22 (m, 6H), 0.63-0.81 (m, 6H)	2.15[b]	589.2
134	1H NMR (DMSO-d6) Shift: 12.50 (br. s., 1H), 9.61 (s, 0.3H), 9.30 (s, 0.7H), 9.24 (t, J=6.1 Hz, 0.3H), 9.09 (t, J=6.0 Hz, 0.7H), 8.79 (t, J=5.5 Hz, 0.3H), 8.70 (d, J=7.5 Hz, 1H), 8.54 (t, J=5.8 Hz, 0.7H), 8.29 (s, 0.3H), 7.96-8.06 (m, 4H), 7.77 (s, 0.7H), 7.24-7.31 (m, 2H), 4.49-4.72 (m, 2H), 4.43 (ddd, J=9.7, 7.8, 5.1 Hz, 1H), 4.22 (d, J=7.5 Hz, 0.3H), 3.58 (td, J=9.6, 4.6 Hz, 0.7H), 2.54-2.67 (m, 1H), 2.32-2.43 (m, 2H), 2.06-2.16 (m, 1H), 1.91-2.02 (m, 1H), 1.34-1.56 (m, 4H), 1.06-1.23 (m, 6H), 0.66-0.82 (m, 6H)	0.84[f]	603.3
135	1H NMR (DMSO-d6) Shift: 12.90 (br. s., 1H), 12.23 (br. s., 1H), 9.61 (s, 0.3H), 9.29 (s, 0.7H), 9.18 (t, J=5.9 Hz, 0.3H), 9.04 (t, J=6.0 Hz, 0.7H), 8.77 (t, J=5.6 Hz, 0.3H), 8.50-8.59 (m, 1.7H), 8.29 (s, 0.3H), 7.88 (d, J=8.0 Hz, 1H), 7.76 (s, 0.7H), 7.59-7.65 (m, 2H), 7.27-7.33 (m, 2H), 4.50-4.73 (m, 3H), 4.27-4.37 (m, 2H), 4.22 (q, J=6.6 Hz, 0.3H), 3.57 (td, J=9.6, 4.6 Hz, 0.7H), 2.53-2.63 (m, 1H), 2.26-2.40 (m, 2H), 2.09-2.18 (m, 1H), 1.89-1.99 (m, 1H), 1.35-1.56 (m, 7H), 1.07-1.23 (m, 6H), 0.66-0.82 (m, 6H)	5.773[a]	647.4
136	1H NMR (DMSO-d6) Shift: 12.77 (br. s., 2H), 9.61 (s, 0.3H), 9.29 (s, 0.7H), 9.24 (t, J=5.9 Hz, 0.3H), 9.09 (t, J=5.8 Hz, 0.7H), 8.79 (br. s., 0.3H), 8.54 (t, J=5.6 Hz, 0.7H), 8.29 (s, 0.3H), 7.93-8.06 (m, 2H), 7.76 (s, 0.7H), 7.41 (d, J=8.3 Hz, 2H), 7.18-7.32 (m, 2H), 4.48-4.72 (m, 2H), 4.18-4.27 (m, 0.4H), 4.15 (s, 2H), 4.00-4.08 (m, 2H), 3.58 (td, J=9.3, 4.8 Hz, 0.7H), 2.55-2.65 (m, 1H), 1.33-1.56 (m, 4H), 1.07-1.26 (m, 6H), 0.66-0.86 (m, 6H)	5.283[a]	589.3
137	1H NMR (DEUTERIUM OXIDE) Shift: 7.75 (s, 0.7H), 7.42 (s, 0.9H), 7.33 (s, 1H), 7.11-7.19 (m, 1H), 6.98 (s, 1H), 6.85-6.92 (m, 1H), 4.48-4.63 (m, 1H), 4.23 (s, 2H), 4.08 (q, J=7.0 Hz, 2.5H), 3.01 (d, J=12.5 Hz, 2H), 1.30 (t, J=7.0 Hz, 3.4H), 0.92-1.14 (m, 0.6H), 0.64-0.81 (m, 3H), 0.37-0.53 (m, 2H)	5.64[a]	597.2 ($(M+H^+)$)

138	1H NMR (DMSO-d6) Shift: 9.93 (br. s., 0.8H), 9.62 (br. s., 0.2H), 9.17 (t, J=6.0 Hz, 0.3H), 9.00 (t, J=6.0 Hz, 0.7H), 8.79 (t, J=5.9 Hz, 0.3H), 8.54 (t, J=5.9 Hz, 0.7H), 8.29 (s, 0.3H), 7.76 (s, 0.7H), 7.55 (dd, J=13.4, 1.1 Hz, 1H), 7.38-7.46 (m, 1H), 7.22-7.32 (m, 1H), 7.01-7.18 (m, 2H), 4.44-4.76 (m, 2H), 4.15-4.29 (m, 0.3H), 3.57 (td, J=9.5, 4.6 Hz, 0.7H), 2.53-2.68 (m, 1H), 1.31-1.61 (m, 4H), 1.04-1.26 (m, 6H), 0.62-0.86 (m, 6H)	4.93[a]	526.3 ($M+H^+$)
139	1H NMR (DMSO-d6) Shift: 9.61 (s, 0.2H), 9.29 (br. s., 0.6H), 9.17 (t, J=5.9 Hz, 0.3H), 9.03 (t, J=5.9 Hz, 0.7H), 8.77 (t, J=5.6 Hz, 0.3H), 8.53 (t, J=5.8 Hz, 0.7H), 8.38 (q, J=5.2 Hz, 1H), 8.29 (s, 0.3H), 8.02 (d, J=8.3 Hz, 1H), 7.76 (s, 0.7H), 7.57-7.68 (m, 2H), 7.22-7.36 (m, 2H), 4.48-4.79 (m, 2H), 4.32 (q, J=6.9 Hz, 2H), 4.22 (q, J=7.4 Hz, 0.3H), 3.50-3.66 (m, 2.8H), 2.54-2.68 (m, 1H), 1.31-1.65 (m, 7H), 1.12 (dt, J=17.8, 6.7 Hz, 6H), 0.61-0.83 (m, 6H)	0.76[f]	611.2 ($M+H^+$)
140	1H NMR (DMSO-d6) Shift: 9.62 (s, 0.2H), 9.27 (t, J=5.9 Hz, 0.2H), 9.17 (t, J=6.0 Hz, 0.6H), 8.77 (t, J=5.8 Hz, 0.3H), 8.55 (t, J=5.8 Hz, 0.7H), 8.30 (s, 0.3H), 7.79 (s, 0.7H), 7.56-7.75 (m, 2H), 7.29 (d, J=3.5 Hz, 1H), 7.02-7.24 (m, 7.4H), 4.50-4.88 (m, 2H), 4.22-4.36 (m, 0.2H), 4.12 (q, J=6.9 Hz, 2H), 3.65 (td, J=9.9, 3.9 Hz, 0.7H), 2.59-2.73 (m, 1H), 2.40-2.55 (2H, under solvent peak), 1.64-1.81 (m, 2H), 1.44-1.61 (m, 2H), 1.28-1.41 (m, 3H), 0.69-0.83 (m, 3H)	5.61[a]	588.2 ($M+H^+$)
141	1H NMR (DMSO-d6) Shift: 9.58 (s, 0.3H), 9.21-9.35 (m, 1.5H), 8.74 (s, 0.2H), 8.57 (t, J=5.5 Hz, 0.6H), 8.30 (s, 0.3H), 7.68-7.88 (m, 5.6H), 7.65 (s, 1H), 7.56 (s, 1H), 7.38-7.50 (m, 2H), 7.28-7.33 (m, 2H), 7.13-7.21 (m, 2H), 4.71-4.82 (m, 1H), 4.54-4.65 (m, 1H), 4.31 (br. s., 0.3H), 4.11 (q, J=6.9 Hz, 2H), 3.64-3.71 (m, 0.8H), 2.60-2.71 (m, 3H), 1.74-1.92 (m, 2H), 1.47-1.67 (m, 2H), 1.25-1.38 (m, 3H), 0.71-0.81 (m, 3H)	6.17[a]	638.3 ($M+H^+$)
142	1H NMR (DMSO-d6) Shift: 11.70 (s, 1H), 9.04-9.20 (m, 1.7H), 8.79 (s, 0.3H), 8.55 (br. s., 0.7H), 8.27 (s, 0.3H), 8.01 (d, J=8.3 Hz, 1H), 7.76 (s, 0.7H), 7.59 (br. s., 0.7H), 7.40 (d, J=8.5 Hz, 1H), 7.02-7.25 (m, 4H), 4.58-4.73 (m, 1H), 4.44-4.55 (m, 1H), 4.17-4.23 (m, 0.3H), 3.48-3.59 (m, 2.7H), 2.53-2.62 (m, 1H), 1.34-1.56 (m, 4H), 1.05-1.24 (m, 6H), 0.59-0.83 (m, 6H)	5.279[a]	583.2
143	1H NMR (DMSO-d6) Shift: 11.01 (s, 0.6H), 9.24 (s, 0.3H), 9.10 (t, J=6.0 Hz, 0.7H), 8.80 (s, 0.3H), 8.63 (br. s., 1H), 8.54 (t, J=5.6 Hz, 0.7H), 8.29 (s, 0.3H), 7.99 (s, 3.7H), 7.73-7.78 (m, 1H), 7.20-7.29 (m, 2H), 7.13 (d, J=3.5 Hz, 2H), 4.49-4.72 (m, 2H), 4.18-4.25 (m, 0.3H), 3.46-3.61 (m, 2.7H), 2.53-2.63 (m, 1H), 1.34-1.56 (m, 4H),	5.129[a]	567.3

	1.04-1.24 (m, 6H), 0.62-0.83 (m, 6H)		
144	1H NMR (DMSO-d6) Shift: 11.04 (s, 0.8H), 9.17 (t, J=5.9 Hz, 0.3H), 9.03 (t, J=5.8 Hz, 0.7H), 8.77-8.81 (m, 0.3H), 8.53 (t, J=5.6 Hz, 0.7H), 8.39 (s, 0.3H), 8.29 (s, 1H), 7.73-7.79 (m, 2.7H), 7.43 (d, J=8.0 Hz, 1H), 7.02-7.26 (m, 4H), 4.48-4.72 (m, 2H), 4.19-4.25 (m, 0.3H), 3.54-3.61 (m, 0.7H), 3.47 (dd, J=12.3, 5.8 Hz, 2H), 2.53-2.64 (m, 1H), 2.41 (s, 3H), 1.34-1.56 (m, 4H), 1.05-1.23 (m, 6H), 0.64-0.83 (m, 6H)	5.173[a]	581.3
145	1H NMR (DMSO-d6) Shift: 7.99-8.12 (m, 0.4H), 7.53 (br. s., 0.3H), 6.99-7.14 (m, 2H), 6.90 (br. s., 1H), 6.40-6.62 (m, 2.5H), 6.23 (br. s., 1H), 3.86-4.08 (m, 4H), 3.56 (br. s., 0.3H), 2.84 (br. s., 0.9H), 1.79-1.97 (m, 1H), 0.70-0.94 (m, 4H), 0.35-0.56 (m, 6H), -0.06-0.16 (m, 6H)	4.95[a]	584.1 ($M+H^+$)
146	1H NMR (DMSO-d6) Shift: 9.62 (s, 0.3H), 9.22-9.36 (m, 1H), 9.14 (t, J=6.0 Hz, 0.7H), 8.78 (t, J=5.4 Hz, 0.3H), 8.52 (t, J=5.9 Hz, 0.7H), 8.29 (s, 0.3H), 7.71-7.85 (m, 1.7H), 7.49 (s, 1H), 7.36 (d, J=8.3 Hz, 1H), 7.15-7.28 (m, 2H), 4.43-4.78 (m, 2H), 4.14-4.29 (m, 0.3H), 3.58 (td, J=9.3, 4.6 Hz, 0.7H), 2.53-2.66 (m, 1H), 1.30-1.64 (m, 4H), 1.01-1.28 (m, 6H), 0.59-0.88 (m, 6H)	2.43[b]	488.0 ($M+H^+$)
147	1H NMR (DMSO-d6) Shift: 7.68-8.16 (m, 1H), 7.62 (d, J=12.5 Hz, 1H), 7.34 (s, 1H), 7.09-7.20 (m, 2H), 6.97 (d, J=3.5 Hz, 1H), 4.68 (d, J=13.3 Hz, 1H), 4.41-4.55 (1H, under solvent peak), 4.06 (q, J=6.6 Hz, 2H), 3.87 (d, J=5.3 Hz, 1H), 3.38-3.66 (m, 8H), 2.89-3.06 (m, 3H), 2.50-2.60 (1H, under solvent peak), 1.29 (t, J=7.0 Hz, 3H), 0.90-1.08 (m, 1H), 0.64-0.77 (m, 3H), 0.46-0.60 (m, 3H)	5.68[a]	554.2
148	1H NMR (DMSO-d6) Shift: 7.69-8.18 (m, 1H), 7.62 (d, J=12.3 Hz, 1H), 7.35 (d, J=1.8 Hz, 1H), 7.11-7.21 (m, 2H), 6.92-7.00 (m, 1H), 4.67 (d, J=13.3 Hz, 1H), 4.41-4.55 (1H, under solvent peak), 4.06 (q, J=7.0 Hz, 2H), 3.38-3.58 (7H, under solvent peak), 2.53-2.59 (m, 1H), 1.23-1.62 (m, 7H), 0.88-1.16 (m, 6H), 0.71 (t, J=7.3 Hz, 3H), 0.45-0.63 (m, 3H)	5.67[a]	554.3
149	1H NMR (DMSO-d6) Shift: 7.68-8.18 (m, 1H), 7.62 (d, J=13.1 Hz, 1H), 7.36 (s, 1H), 7.08-7.22 (m, 2H), 6.97 (d, J=3.5 Hz, 1H), 4.67 (d, J=13.6 Hz, 1H), 4.39-4.58 (1H, under solvent peak), 4.07 (d, J=7.0 Hz, 2H), 2.39-2.50 (1H, under solvent peak), 1.29 (t, J=6.9 Hz, 6H), 0.64-0.77 (m, 3H), 0.52 (t, J=7.0 Hz, 4H)	5.63[a]	554.3

Analytical methods:

[a]LCMS Method: Agilent 1100 Series LC/MSD SL or VL using electrospray positive [ES+ve to give $M+H^+$] equipped with a Xorbax Eclipse XDB-C8 5.0 µm column (4.6 mm x 150 mm, i.d.), eluting with 0.05 % TFA in water (solvent A) and 0.05 % TFA in CH_3CN (solvent B), using the following elution gradient 10-100 % (solvent B) over 10.0 min and holding at 100 % for 1.6 min at a flow rate of 1.0 ml/min.

[b]LCMS Method: Agilent 1100 Series LC/MSD SL or VL using electrospray positive [ES+ve to give $M+H^+$] equipped with a Sunfire C18 5.0 µm column (3.0 mm x 50 mm, i.d.), eluting with 0.05 % TFA in water (solvent A) and 0.05 % TFA in CH_3CN (solvent B), using the following elution gradient: 10–100 % (solvent B) over 2.5 min and holding at 100 % for 1.7 min at a flow rate of 1.0 ml/min.

[c] LCMS Method: Agilent 1200 Series LC/MSD SL or VL using electrospray positive [ES+ve to give $M+H^+$] equipped with a Sunfire C18 5.0 µm column (3.0 mm x 50 mm, i.d.), eluting with 0.1 % TFA in water (solvent A) and 0.1 % TFA in CH_3CN (solvent B), using the following elution gradient: 10–100 % (solvent B) over 2.5 min and holding at 100 % for 1.7 min at a flow rate of 1.0 ml/min.

[d] UPLC Method: Acquity UPLC with SQD MSD using electrospray positive [ES+ve to give $M+H^+$] equipped with a BEH C18 1.7 µm column (2.1 mm x 50 mm i.d.) eluting with 0.1 % formic acid in water (solvent A) and 0.1 % formic acid in CH_3CN (solvent B), using the following elution gradient: 3–100 % (solvent B) over 1.5 min and holding at 100 % for 0.4 min at a flow rate of 1.0 ml/min.

[e] LCMS Method: Shimadzu 10Avp with Sedere Sedex 75C and PE Sciex Single Quadrupole 150EX using electrospray positive [ES+ve to give $M+H^+$] equipped with a Thermo Hypersil Gold C18 1.9 µm column (2.1 mm x 20 mm i.d.) eluting with 0.02 % TFA in water (solvent A) and 0.02 % TFA in CH_3CN (solvent B), using the following elution gradient: 4–95 % (solvent B) over 1.88 min and holding at 4 % for 0.9 min at a flow rate of 1.4 ml/min.

[f] LCMS Method: Shimadzu 10Avp with Sedere Sedex 75C and Waters ZQ Single Quadrupole using electrospray positive [ES+ve to give $M+H^+$] equipped with a Thermo Hypersil Gold C18 1.9 µm column (2.1 mm x 20 mm i.d.) eluting with 0.02 % TFA in water (solvent A) and 0.02 % TFA in CH_3CN (solvent B), using the following elution gradient: 4–95 % (solvent B) over 1.88 min and holding at 4 % for 0.9 min at a flow rate of 1.4 ml/min.

[g] LCMS Method: Agilent 1200 Series LC/MSD SL or VL using electrospray positive [ES+ve to give $M+H^+$] equipped with a Zorbax C18 5.0 µm column (4.6 mm x 150 mm, i.d.), eluting with 0.1 % TFA in water (solvent A) and 0.1 % TFA in CH_3CN (solvent B),

using the following elution gradient: 10–100 % (solvent B) over 12.5 min and holding at 100 % for 1.8 min at a flow rate of 1.0 ml/min.

[h] LCMS Method: Agilent 1200 Series LC/MSD SL or VL using electrospray positive [ES+ve to give $M+H^+$] equipped with a Sunfire C18 2.5 µm column (2.1 mm x 20 mm, i.d.), eluting with 0.05 % TFA in water (solvent A) and 0.05 % TFA in CH_3CN (solvent B), using the following elution gradient: 10–100 % (solvent B) over 2.5 min and holding at 100 % for 0.2 min at a flow rate of 1.3 ml/min.

[i] LCMS Method: Agilent 1200 Series LC/MSD SL or VL using electrospray positive [ES+ve to give $M+H^+$] equipped with an Agilent Eclipse XBD-C18 5.0 µm column (4.6 mm x 250 mm, i.d.), eluting with 0.05 % TFA in water (solvent A) and 0.05 % TFA in CH_3CN (solvent B), using the following elution gradient: 1–99 % (solvent B) over 10 min at a flow rate of 1.0 ml/min.

Pharmaceutical Compositions

Example A - Tablets are prepared using conventional methods and are formulated as follows:

Ingredient	Amount per tablet
Compound of the invention	5 mg
Microcrystalline cellulose	100 mg
Lactose	100 mg
Sodium starch glycollate	30 mg
Magnesium stearate	2 mg
Total	237 mg

Example B - Capsules are prepared using conventional methods and are formulated as follows:

Ingredient	Amount per tablet
Compound of the invention	15 mg
Dried starch	178 mg
Magnesium stearate	2 mg
Total	195 mg

Example C – Nanosuspensions are prepared using conventional aqueous bead milling methods and are formulated as follows:

Ingredient	Amount per nanosuspension
Compound of the invention	50 mg
Polysorbate 20	10 mg
Polyethylene Glycol 4000	20 mg
Mannitol	30 mg
Purified Water	qs
Total	110 mg

Example D – Melt Extrudates are prepared using conventional melt extrusion techniques and cryomilling to achieve adequate particle size as follows:

Ingredient	Amount per Melt Extrudate
Compound of the invention	67 mg
75:25 Poly(lactic-co-glycolic acid)	34 mg
Total	100 mg

Example E – A lyophilized product is prepared by conventional methods formulated as follows:

Ingredient	Amount per Lyophilized Formulation
Compound of the invention	20 mg
Sodium Hydroxide	qs
Glycine	30 mg
Polyethylene Glycol	50 mg
Polysorbate	2.5 mg

Biological Assays

Materials:

Buffer components were purchased from Sigma-Aldrich (St. Louis, MO) or an equivalent supplier. The promyostatin peptide substrate was custom synthesized by American Peptide Company (Sunnyvale, CA) using the myostatin protein sequence (Uniprot accession number O14793) surrounding the cleavage site reviewed in Hopkins,

D.R., et al., 2007 Matrix Biology, 26, 508-523. The procollagen peptide substrate used in the high enzyme BMP1 cleavage assay was custom synthesized by 21st Century Biochemicals (Marlboro, MA) using the procollagen Iα protein sequence (Uniprot accession number P02452) surrounding the cleavage site reviewed in Hopkins, D.R., et al., 2007 Matrix Biology, 26, 508-523.

Preparation of Human BMP1 Protein:

The DNA sequence encoding amino acids 23-721 of human BMP1 (NM_001190) with the human RAGE signal sequence (aa1-22 of NM_001136) at the N-terminus and FLAG-6xHis epitope tags at the C-terminus was amplified using PCR technology. The resultant Rgss-BMP1(23-721)-FLAG-6xHis fragment was subcloned into pCDN, a mammalian expression vector driven by the CMV promoter and containing the DHFR gene to allow selection in nucleoside-free cell culture media. This construct was electroporated into CHOE1a cells. After selection, conditioned media from individual clones were analyzed using a BMP1 assay for promyostatin-derived peptidase activity (see assay below). Conditioned media from several clones with the highest activity were analyzed via western blot to confirm expression. The clone with the highest expression and peptidase activity was used for protein expression.

The mature form of human BMP1 (121-721), secreted from the stably transfected CHO cell line, was purified. All purification steps were carried out at 4 °C. 10 l of conditioned medium was concentrated to 1.2 l with a Watson Marlow diafiltration system (A/G Technology Corpraton, Model # UFP-10-C-55) using a 10 kDa cut off cartridge. A subsequent buffer exchange was carried out on the same system with 5 l of 50 mM Tris buffer, pH 8.0, containing 0.5 M NaCl, 20% glycerol, 1 mM CHAPS, 5 mM $CaCl_2$, 10 μM $ZnCl_2$, and 20 mM imidazole. The diafiltrated medium was subjected to successive nickel NTA superflow chromatography (Qiagen, Valencia, CA) using 50 ml, 30 ml, and 15 ml resin volumes, each overnight at 4°C, and the unbound fraction containing most of the BMP1 was retained. 100 ml of this unbound fraction was diluted into 1000 ml of 50 mM Tris buffer, pH 8.0, containing 20% glycerol, 10 mM NaCl, 5 mM $CaCl_2$, 10 μM $ZnCl_2$, and 1 mM CHAPS and applied to 20 ml of Q Sepharose Fast Flow (GE Healthcare Life Sciences). The Q Sepharose unbound fraction, which contains BMP1, was further concentrated on a Viva Spin, 10 kDa cut off cartridge (Viviproducts, Littleton, MA).

Preparation of Human TLL1 Protein:

The DNA sequence encoding a natural variant of full length native human TLL1 (BD165892.1) containing three amino acid substitutions I156V, N221S, V284A was

amplified from human heart and brain cDNA and subcloned into the pCDN expression vector . The plasmid was electroporated into CHOE1A cells. After selection, a clone expressing high levels of TLL1 was scaled and used for protein purification.

All purification steps were carried out at 4 °C. CHO conditioned medium was diluted 3-fold with 5 mM Tris buffer, pH 8.4, and human TLL1 was captured by Source 30 Q resin (GE Healthcare Life Sciences). After an extensive wash with 50 mM Tris buffer, pH 8.0, human TLL1 was eluted with a linear gradient of 0 to 0.5 M NaCl in 50 mM Tris buffer, pH 8.0. Following a 3.6-fold dilution into 20 mM Tris buffer, pH 7.4, human TLL1 from the Source 30Q pool was then captured onto a Macro-prep ceramic hydroxyapatite (HA) type I 40 µm resin (BioRad, Hercules, CA). The HA resin was washed with 20 mM Tris buffer, pH 7.4, and human TLL1 was eluted with 0.5 M potassium phosphate buffer, pH 7.4, in a linear gradient from wash buffer. Human TLL1 from the HA pool was salt fractionated with 40% ammonium sulfate saturation and resolubilized with 20 mM Tris buffer, pH 7.0, containing 0.25 M NaCl and 7 mM $CaCl_2$.

Preparation of Human TLL2 Protein:

The DNA sequence encoding amino acids 26-1015 of human TLL2 (NM_0124565) was PCR amplified from DNA template with the human RAGE signal sequence at the N-terminus and Avi-6xHis epitope tags at the C-terminus (GGLNDIFEAQKIEWHEHHHHHH). The Rgss-TLL2 Avi-6xHis fragment was subcloned into a pCDN expression vector by Gateway™ recombination (Life Technologies, Grand Island, NY). DHFR deficient CHOE1a cells were maintained in MR1 media (Life Technologies) supplemented with nucleosides at 37°C in 5% CO2. Linearized plasmid DNA was electroporated into the cells and clones were generated in media without nucleosides. Clones were screened for TLL2 activity in the promyostatin-derived peptidase assay (see below) which allowed identification of clones that expressed optimal levels of the active form of TLL2.

Stably expressing TLL2 CHO cell conditioned medium was concentrated by diafiltration as described for BMP1. 325 ml of concentrated medium was purified by nickel NTA superflow chromatography (20 ml Ni-NTA SF, overnight at 4 °C). The resin was washed with a 15 mM to 100 mM imidazole linear gradient, and protein was eluted with 0.3 M imidazole in buffer A (50 mM Tris, pH 8.0, 0.5 M NaCl, 20% glycerol, 1 mM CHAPS, 5 mM $CaCl_2$, 10 µM $ZnCl_2$).

Enzyme Inhibition Assay for human BMP1:

(i) Low enzyme concentration

Inhibition of BMP1 peptidase activity by test compounds of the invention was measured by monitoring cleavage of a promyostatin peptide substrate by recombinant, mature BMP1 protein (BMP1(121-721)-Flag-His). FRET quenching of dual-labeled peptide ((5-FAM)-ELIDQYDVQRDDSSDGSLED-K(5,6 TAMRA)-$CONH_2$) is relieved by BMP1-catalyzed cleavage. This assay was run as a 10 µl endpoint assay in 384-well format where the reaction contains 0.5 nM BMP1 and 0.8 µM promyostatin peptide substrate in 25 mM HEPES buffer, pH 7.5, containing 0.01% Brij-35 detergent, 5 mM $CaCl_2$, and 1 µM $ZnCl_2$. The assay was run by adding 5 µl enzyme solution to a black, low volume assay plate (Greiner 784076) pre-dispensed with 100 nl test compound solutions in DMSO. After 10 minutes, 5 µl substrate were added and the reaction was incubated at ambient temperature for an additional 60 minutes. The reaction was quenched with 5 µl of 0.5 M EDTA and the plate was read on a ViewLux (PerkinElmer) multilabel plate reader using a 480 nm excitation filter and 540 nm emission filter. The test compounds were prepared in neat DMSO at a concentration of 10 mM. For inhibition curves, compounds were diluted in DMSO using a three-fold serial dilution and tested at 11 concentrations (100 µM – 1.7 nM, final 1% DMSO). Responses were normalized to the uninhibited and no-enzyme controls within each plate. Dose-response curves were analyzed using a four-parameter logistic fit in ActivityBase and results are expressed as pIC_{50} values.

The compounds of Examples 1-115 and 117-149 were tested and exhibited a $pIC_{50} > 6.9$ according to this assay.

(ii) High enzyme concentration

Use of a high enzyme concentration assay may be useful, e.g., as discussed in Habig, M., et al., Journal of Biomolecular Screening, 2009, 14, 679-689.

This assay was run as a 10 µl endpoint assay in 384-well format where the reaction contains 50 nM BMP1 enzyme and 6 µM procollagen I peptide substrate ((5-FAM)-DGGRYYRADDANVVRD-K(5,6-TAMRA)-$CONH_2$) in 25 mM HEPES buffer, pH 7.5, containing 0.01% Brij-35 detergent, 5 mM $CaCl_2$, and 1 µM $ZnCl_2$. The assay was run by adding 5 µl enzyme solution to a black, low volume assay plate (Greiner 784076) pre-dispensed with 100 nl test compound solutions in DMSO. After 10 minutes, 5 µl substrate were added and the reaction was incubated at ambient temperature for an additional 30 minutes. The reaction was quenched with 5 µl of 0.5 M EDTA and the plate was read on a ViewLux (Perkin Elmer) multilabel plate reader using a 480 nm excitation filter and 540

nm emission filter. Data fitting and compound preparations were performed as described above for the low enzyme concentration.

The compounds of Examples 1-115, 117-146 and 149 were tested and exhibited a pIC_{50} > 6.7 according to this assay.

Enzyme Inhibition Assay for human TLL1 and TLL2:

Inhibition of human TLL1 and TLL2 recombinant enzymes was measured in 10 ul endpoint assays in 384-well format using the same promyostatin peptide substrate employed in the above Enzyme Inhibition Assay for human BMP1. The TLL1 reaction contained 2 nM TLL1 and 0.8 µM promyostatin peptide substrate in 25 mM HEPES buffer, pH 7.5, containing 0.01% Brij-35 detergent, 5 mM $CaCl_2$, and 1 µM $ZnCl_2$. The TLL1 assay was run by adding 5 µl enzyme solution to a black, low volume assay plate (Greiner 784076) pre-dispensed with 100 nl test compound solutions in DMSO. Following a 10 minute preincubation of enzyme with inhibitor, 5 µl of substrate solution were added. TLL1 reactions were incubated at ambient temperature for an additional 60 minutes. The TLL2 reaction contained 18 nM TLL2 and 5 µM promyostatin peptide substrate in 25 mM HEPES buffer, pH 7.5, containing 0.01% Brij-35 detergent, 5 mM $CaCl_2$, and 1 µM $ZnCl_2$. The TLL2 assay was run without an enzyme-inhibitor preincubation by adding 5 µl enzyme and 5 µl substrate solutions to a black, low volume assay plate (Greiner 784076) pre-dispensed with 100 nl compound solutions in DMSO. TLL2 reactions were incubated at ambient temperature for 60 minutes. TLL1 and TLL2 reactions were quenched with 5 µl of 0.5 M EDTA and plates were read on a ViewLux (Perkin Elmer) multilabel plate reader using a 480 nm excitation filter and 540 nm emission filter. Data fitting and compound preparations were performed as described above for the Enzyme Inhibition Assay for human BMP1.

The compounds of Examples 1-33, 35-71, 73-84, 86-115, 117-140, and 142-146 were tested in the TLL1 enzyme inhibition assay and exhibited a pIC_{50} > 6.4 according to this assay.

The compounds of Examples 1-24, 26-33, 35-71, 73-78, 80-84, 86-115, 117-140, and 142-146 were tested in the TLL2 enzyme inhibition assay and exhibited a pIC_{50} > 6.1 according to this assay.

The above enzyme assay results indicate that the tested compounds are potent inhibitors of one or more of BMP1, TLL1 and TLL2 enzymatic activity. The tested compounds inhibited one or more of these metalloproteases in biochemical assays using isolated enzymes and peptide substrates.

Cell-based Inhibition Assay of Generation of Procollagen I C-terminal Propeptide (PICP)

and Mature Collagen:

An adaptation of the collagen deposition assay described by Chen, C.Z.C., et al., British Journal of Pharmacology, 2009, 158, 1196-1209 was used to examine effect of compounds on procollagen I processing and collagen deposition. In the adapted assay, human cardiac fibroblasts were utilized. Processing of procollagen I was determined by a PICP ELISA assay and deposition of mature collagen was determined by immunostaining.

Human cardiac fibroblasts were cultured and maintained until passage 6 in FGM-3 media (Lonza, #CC-3132) in a 37 °C humidified incubator with 5% CO_2. They were then seeded in 96-well black wall, clear bottom plates at 10,000 to 15,000 cells per well in eagle's minimum essential media (EMEM, ATCC # 30-2003) containing 10% fetal bovine serum (FBS, Life Technologies # 10082147), 1% Glutamax (Life Technologies #35050061) and 1% Penicillin and Streptomycin (Life Technologies # 15070063) . These cultures were placed in 37 °C incubator. The next day, media were removed by aspiration and cells were rinsed with phosphate buffered saline. Crowding media (also called ficoll media) was prepared by adding 112.5 mg/ml of ficoll70 and 75 mg/ml ficoll400 (GE healthcare # 17-0310-10 and 17-0300-10, respectively), 100 µM ascorbic acid, 1% Glutamax and 1% Penicillin and Streptomycin to EMEM media. Test compounds (dissolved in DMSO) were diluted into crowding media and then added to the cells. Final concentration of DMSO in crowding media was less than 0.3%. Cells were treated for 24 to 48 hr in a 37 °C incubator. At the end of the treatment period, cell media were collected. The level of PICP in the media were determined by a PICP ELISA assay (Quidel #8003) following the manufacturer's protocol. Potencies of test compounds were calculated by fitting PICP levels, relative to untreated controls, to log (inhibitor) vs. response equation using Graphpad Prism software 5.0 and expressed as pIC_{50}.

For some compounds, deposition of mature collagen was measured by immunostaining in addition to PICP levels. At the end of the treatment period, cells on culture plate were fixed with 100% methanol (prechilled to -20 °C) for 10 min. Then the cells were immunostained with mouse anti-mature collagen I antibody (1:500 dilution, Sigma#C2456), anti-mouse secondary antibody Alexa647 (1:500 dilution, Invitrogen#A21236) and Hoechst (for nuclei, 2 µg/ml, Invitrogen#H3596). Fluorescent image acquisition was done using the Operetta High Content Imaging system (Perkin Elmer). For each image field, the intensity of mature collagen staining was normalized with the number of nuclei. Normalized collagen levels were used to calculate the potency of test compounds with Graphpad Prism software, as described above.

The compounds of Examples 1, 5, 12-14, 16, 18, 22-30, 33-35, 39-45, 47-53, 55,

59-62, 64, 65, 67, 70-78, 80-89, 91-106, 108, 111-115, and 117-146 were tested in the PICP cellular inhibition assay and exhibited a pIC_{50} > 5.4 in this assay.

The compounds of Examples 5, 24, 39, 47, 74, 75, 77, 80-82, 86, 93, 96, 98, 99, 111-113, 121-124, 126-128, 132, and 139 were tested in the mature collagen cellular inhibition assay and exhibited a pIC_{50} > 6.0 in this assay.

The above cellular assay results demonstrate that the tested compounds inhibit the processing of procollagen substrate by native enzyme produced by the fibroblast, the cell type that drives fibrosis in vivo.

In view of the above, compounds of the invention should have benefit as anti-fibrotic agents across a wide variety of diseases driven by pathological fibrosis, and diseases related to other in vivo substrates for these enzymes, e.g., where muscle function or muscle mass is diminished.

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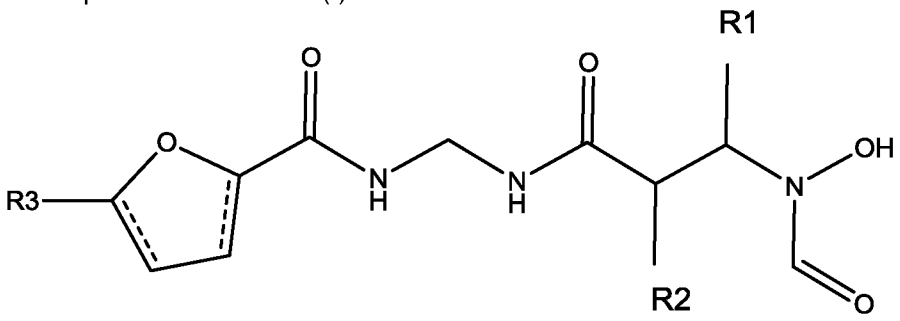
The claims defining the invention are as follows:

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

R1 is selected from the group consisting of H, (C_1-C_4) straight chain alkyl, and (C_1-C_4) straight chain alkyl substituted with a hydroxy group;

R2 is selected from H, (C_1-C_{11})alkyl, (C_1-C_3)alkyl-(C_3-C_6)cycloalkyl, (C_1-C_3)alkyl-phenyl, (C_1-C_3)alkyl-naphthyl and (C_1-C_3)alkyl-heterocyclyl, wherein heterocyclyl is a monocyclic ring having 5-6 ring atoms wherein 1-2 of the ring atoms are selected from nitrogen, oxygen and sulfur, and wherein said (C_1-C_{11})alkyl, cycloalkyl, phenyl, naphthyl and heterocyclyl are optionally substituted with 1-2 groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo, and cyano; and

R3 is selected from:

a) phenyl, optionally substituted with 1-3 groups independently selected from:

(C_1-C_6)alkyl, optionally substituted with 1-3 groups independently selected from: fluoro; -CO_2H; -P(O)R^fR^g; NR^aR^b wherein R^a is selected from H and (C_1-C_4)alkyl and R^b is selected from (C_1-C_4)alkyl substituted with -CO_2H or -P(O)R^fR^g, and -C(O)NR^aR^b wherein R^a and R^b are independently selected from H and (C_1-C_4)alkyl, wherein the (C_1-C_4)alkyl is optionally substituted with 1-3 groups independently selected from hydroxy, -CO_2H, -C(O)O(C_1-C_4)alkyl and -P(O)R^fR^g;

cyclopropyl, optionally substituted with 1 -CO_2H;

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-C(O)NR^aR^b wherein R^a and R^b are independently selected from H and (C_1-C_4)alkyl, wherein the (C_1-C_4)alkyl is optionally substituted with 1-3 groups independently selected from hydroxy, -CO_2H, -C(O)O(C_1-C_4)alkyl, -P(O)R^fR^g, NR^cR^d and N^+ $R^cR^dR^e$;

(C_1-C_6)alkoxy, optionally substituted with 1-3 substituents independently selected from halo, hydroxy, -CO_2H, (C_3-C_6)cycloalkyl, -C(O)NH_2 and pyrrolidinyl;

(C_3-C_6)cycloalkoxy, optionally substituted with 1-3 substituents independently selected from halo, hydroxy, and -CO_2H;

-NR^aR^b wherein R^a and R^b are independently selected from H and (C_1-C_4)alkyl, wherein the (C_1-C_4)alkyl is optionally substituted with 1-3 groups independently selected from oxo and -CO_2H;

-SR^a wherein R^a is selected from H and (C_1-C_4)alkyl;

-CO_2H; -C(NOH)NH_2; cyano; -C(O)O(C_1-C_4)alkyl; -C(O)CO_2H; -P(O)R^fR^g; -OP(O)R^fR^g; halo; hydroxy; nitro; -$NHSO_2$(C_1-C_2)alkyl; -SO_3H; -SO_2(C_1-C_2)alkyl; -$SO_2NR^cR^d$; -SO_2NHC(O)(C_1-C_2)alkyl; and -$B(OH)_2$;

and

b) heteroaryl, optionally substituted with 1-2 groups independently selected from:

(C_1-C_4)alkyl, (C_1-C_4)alkoxy, oxo, -CO_2H, -P(O)R^fR^g, and -OP(O)R^fR^g;

wherein in each occurrence: R^c, R^d and R^e are independently selected from H and (C_1-C_2)alkyl; and

R^f and R^g are independently selected from hydroxy, (C_1-C_2)alkyl and (C_1-C_2)alkoxy.

2. The compound or salt thereof according to claim 1, wherein in the compound of Formula (I):

R1 is selected from the group consisting of H, (C_1-C_4) straight chain alkyl, and (C_1-C_4) straight chain alkyl substituted with a hydroxy group;

R2 is selected from H, $(C_1\text{-}C_{11})$alkyl, $(C_1\text{-}C_3)$alkyl-$(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_3)$alkyl-phenyl, and $(C_1\text{-}C_3)$alkyl-heterocyclyl, wherein heterocyclyl is a monocyclic ring having 5-6 ring atoms wherein 1-2 of the ring atoms are selected from nitrogen, oxygen and sulfur, and wherein said $(C_1\text{-}C_{11})$alkyl, cycloalkyl, phenyl, and heterocyclyl are optionally substituted with 1-2 groups independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo, and cyano; and

R3 is selected from:

c) phenyl, optionally substituted with 1-3 groups independently selected from:

$(C_1\text{-}C_6)$alkyl, optionally substituted with 1-3 groups independently selected from: fluoro; $-CO_2H$; $-P(O)R^fR^g$; and $-C(O)NR^aR^b$ wherein R^a and R^b are independently selected from H and $(C_1\text{-}C_4)$alkyl, wherein the $(C_1\text{-}C_4)$alkyl is optionally substituted with 1-3 groups independently selected from hydroxy, $-CO_2H$, $-C(O)O(C_1\text{-}C_4)$alkyl and $-P(O)R^fR^g$;

cyclopropyl, optionally substituted with 1 $-CO_2H$;

$-C(O)NR^aR^b$ wherein R^a and R^b are independently selected from H and $(C_1\text{-}C_4)$alkyl, wherein the $(C_1\text{-}C_4)$alkyl is optionally substituted with 1-3 groups independently selected from hydroxy, $-CO_2H$, $-C(O)O(C_1\text{-}C_4)$alkyl, $-P(O)R^fR^g$, NR^cR^d and $N^+R^cR^dR^e$;

$(C_1\text{-}C_6)$alkoxy, optionally substituted with 1-3 substituents independently selected from halo, hydroxy, $-CO_2H$, $(C_3\text{-}C_6)$cycloalkyl, and pyrrolidinyl;

$(C_3\text{-}C_6)$cycloalkoxy, optionally substituted with 1-3 substituents independently selected from halo, hydroxy, and $-CO_2H$;

$-NR^aR^b$ wherein R^a and R^b are independently selected from H and $(C_1\text{-}C_4)$alkyl, wherein the $(C_1\text{-}C_4)$alkyl is optionally substituted with 1-3 groups independently selected from oxo and $-CO_2H$;

$-SR^a$ wherein R^a is selected from H and $(C_1\text{-}C_4)$alkyl;

$-CO_2H$; $-C(NOH)NH_2$; cyano; $-C(O)O(C_1\text{-}C_4)$alkyl; $-C(O)CO_2H$; $-P(O)R^fR^g$; $-OP(O)R^fR^g$; halo; hydroxy; nitro; $-NHSO_2(C_1\text{-}C_2)$alkyl; $-SO_3H$; $-SO_2(C_1\text{-}C_2)$alkyl; $-SO_2NR^cR^d$; $-SO_2NHC(O)(C_1\text{-}C_2)$alkyl; and $-B(OH)_2$;

and

d) heteroaryl, optionally substituted with 1-2 groups independently selected from:

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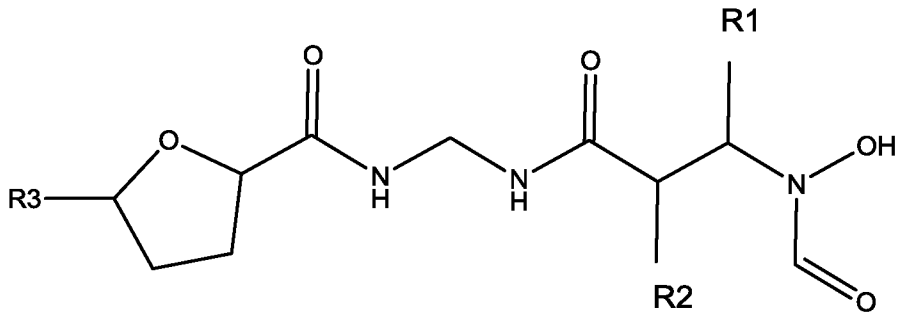
(C_1-C_4)alkyl, (C_1-C_4)alkoxy, oxo, -CO_2H, -P(O)R^fR^g, and -OP(O)R^fR^g;

wherein in each occurrence: R^c, R^d and R^e are independently selected from H and (C_1-C_2)alkyl; and

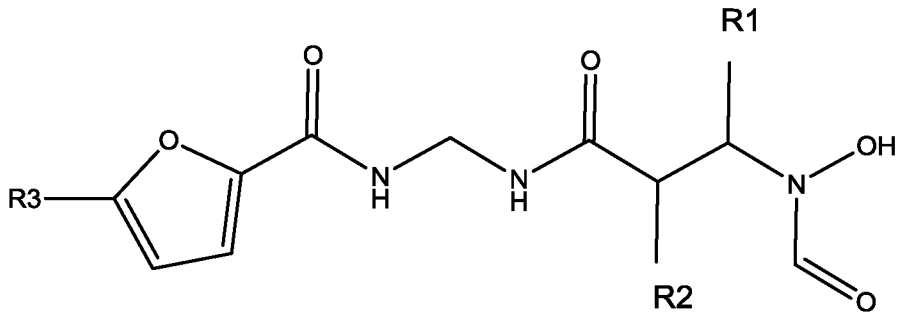
R^f and R^g are independently selected from hydroxy, (C_1-C_2)alkyl and (C_1-C_2)alkoxy.

3. The compound or salt thereof according to either claim 1 or 2, wherein the compound according to Formula (I) has the Formula (I)(a):



(I)(a).

4. The compound or salt thereof according to either claim 1 or 2, wherein the compound according to Formula (I) has the Formula (I)(b):



(I)(b).

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5. The compound or salt thereof according to any one of claims 1-4, wherein R1 is H, methyl, ethyl or –CH_2OH.

6. The compound or salt thereof according to any one of claims 1 to 5, wherein R2 is H or optionally substituted n-pentyl, 2-ethylbutyl, (cyclopentyl)methyl, benzyl, 2-phenylethyl, 3-phenylpropyl, or 2-naphthylethyl.

7. The compound or salt thereof according to any one of claims 1 to 6, wherein R1 and R2 have (R) stereochemistry.

8. The compound or salt thereof according to any one of claims 1 to 7, wherein R3 is optionally substituted phenyl.

9. The compound or salt thereof according to claim 8, wherein R3 is 3,4- or 3,5-disubstituted phenyl.

10. The compound or salt thereof according to claim 9, wherein R3 is phenyl substituted with ethoxy in the 3-position and -$P(O)(OH)_2$, -CO_2H, -OCH_2CO_2H, or –$C(O)NHCH(CO_2H)(CH_2CO_2H)$ in the 4- or 5- position.

11. The compound or salt thereof according to claim 8, wherein R3 is phenyl substituted with 1-3 groups selected from: -OCH_3, -OC_2H_5, -OC_3H_7, -$OCH(CH_3)_2$, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCH_2CHF_2, -OC_2H_4–pyrrolidine, -OCH_2CO_2H, -$OCH_2C(O)NH_2$, -CO_2H, -CH_3, cyclopropane-1-carboxylic acid, -CH_2CO_2H, -$C(CH_3)_2CO_2H$, -$CH(CH_3)CO_2H$, -CF_2CO_2H, -$CH_2C(O)NHCH(CO_2H)(CH_2CO_2H)$, -$CH_2P(O)(OH)_2$,-$CH_2N(CH_3)(CH_2CO_2H)$, -$CH_2NHCH_2P(O)(OH)_2$, -$C(NH_2)(NOH)$, cyano, nitro, hydroxy, -SO_2NH_2, -$SO_2N(CH_3)_2$, -$SO_2NH(CH_3)$, -SO_2CH_3, -$SO_2NHC(O)C_2H_5$, -SCH_3, -SC_2H_5, -$C(O)OCH_3$, -$C(O)OC(CH_3)_3$, -$C(O)NHCH_3$, -$C(O)NH(C_2H_4NH_2)$, -$C(O)NHC_2H_4N^+(CH_3)_3$, -$C(O)NHCH(CO_2H)(CH_2CO_2H)$, -$C(O)NHCH(CO_2H)(C_2H_4CO_2H)$, -$C(O)NHCH_2CO_2H$, -$C(O)N(CH_2CO_2H)_2$, -$C(O)NHCH_2P(O)(OH)_2$, -$C(O)NHC(CH_2OH)_3$, fluoro, -NH_2, -$N(CH_3)_2$, -$P(O)(CH_3)(OC_2H_5)$, -$P(O)(OCH_3)_2$, -$P(O)(CH_3)(OH)$, -$P(O)(OH)(OCH_3)$, and -$P(O)(OH)_2$.

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12. The compound or salt thereof according to claim 8, wherein R3 is phenyl substituted with 1-3 groups selected from: $-OC_2H_5$, hydroxy, $-CO_2H$, $-OCH_2CO_2H$, $-P(O)(OH)_2$, $-C(O)NHCH(CO_2H)(CH_2CO_2H)$ and $-C(O)NHCH_2P(O)(OH)_2$.

13. The compound or salt thereof according to any one of claims 1 to 7, wherein R3 is optionally substituted pyridyl, pyridazinyl, pyrimidinyl, oxazolyl, tetrazolyl, pyrazolyl, indazolyl, or 1,1-dioxido-2,3-dihydrobenzo[d]isothiazolyl.

14. The compound or salt thereof according to claim 13, wherein R3 is substituted with 1-2 groups independently selected from: $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, $-CO_2H$, $-CH_3$, $-P(O)(CH_3)(OC_2H_5)$, $-P(O)(OCH_3)_2$, $-P(O)(CH_3)(OH)$, $-P(O)(OH)(OCH_3)$, and $-P(O)(OH)_2$.

15. A compound selected from the group consisting of:

2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzoic acid

(R)-N-((3-cyclopentyl-2-((N-hydroxyformamido)methyl)propanamido)methyl)-5-phenylfuran-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)-5-phenylpentanamido)methyl)-5-phenylfuran-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)-4-phenylbutanamido)methyl)-5-phenylfuran-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(2-methoxyphenyl)furan-2-carboxamide

(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-methoxyphenyl)furan-2-carboxamide

(R)-5-(3-cyanophenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-

2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(2-hydroxyphenyl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(5-methoxypyridin-3-yl)furan-2-carboxamide
(R)-5-(4-cyanophenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-sulfamoylphenyl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(trifluoromethoxy)phenyl)furan-2-carboxamide
(R)-5-(3-ethoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(6-methoxypyridin-2-yl)furan-2-carboxamide
(R)-methyl 3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate
(R)-5-(4-fluoro-3-methoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(4-methoxypyridin-2-yl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(methylcarbamoyl)phenyl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)-4-phenylbutanamido)methyl)-5-(3-(methylsulfonyl)phenyl)furan-2-carboxamide
(R)-5-(3-(N,N-dimethylsulfamoyl)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(N-methylsulfamoyl)phenyl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(2,2,2-trifluoroethoxy)phenyl)furan-2-carboxamide

N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-isopropoxyphenyl)furan-2-carboxamide
(R)-methyl 3-ethoxy-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate
(R)-5-(3-(dimethylamino)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(N-propionylsulfamoyl)phenyl)furan-2-carboxamide
(R)-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-methoxybenzoic acid
(R)-3-ethoxy-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
ethyl (3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)(methyl)phosphinate
N-(((R)-2-((S)-2-hydroxy-1-(N-hydroxyformamido)ethyl)heptanamido)methyl)-5-phenylfuran-2-carboxamide
(R)-5-(3-((2-aminoethyl)carbamoyl)-5-methoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide
(R)-5-(3-((2-aminoethyl)carbamoyl)-5-ethoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide
(R)-5-(3-(difluoromethoxy)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide
(R)-dimethyl (3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate
(R)-5-(1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-6-yl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(2-(pyrrolidin-1-

yl)ethoxy)phenyl)furan-2-carboxamide
3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)benzoic acid
5-(3-((2-aminoethyl)carbamoyl)-5-ethoxyphenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)furan-2-carboxamide
2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid
2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid
2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)-2-methylpropanoic acid
1-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)cyclopropanecarboxylic acid
(S)-5-(tert-butoxy)-4-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl) heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)-5-oxopentanoic acid
5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)nicotinic acid
(S)-4-(tert-butoxy)-3-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)-4-oxobutanoic acid
(S)-dimethyl 2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)pentanedioate
2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)-2,2-difluoroacetic acid
dimethyl (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonate

(R)-methyl 2-fluoro-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl) furan-2-yl)benzoate

(R)-5-(3,5-dimethoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide

(R)-5-(2,5-dimethoxyphenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide

(R)-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzoic acid

(R)-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methoxybenzoic acid

(R)-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methoxybenzoic acid

(R)-methyl 2-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate

(R)-methyl 4-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate

(R)-2-fluoro-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

(R)-2-(3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid

(R)-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzoic acid

(R)-2-hydroxy-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

(R)-tert-butyl 3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoate

(R)-2-amino-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)-N,N,N-trimethylethanaminium hydroxide

5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methoxybenzoic acid

2-(3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)-2-methylpropanoic acid

5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzoic acid

N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)-5-(3-propoxyphenyl)furan-2-carboxamide

2-(2-fluoro-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid

4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetic acid

5-(3-ethoxy-5-hydroxyphenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)furan-2-carboxamide

(S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid

(S)-2-(2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)acetamido)succinic acid

2-(3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)propanoic acid

(S)-2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid

(R)-2,6-difluoro-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

3-ethoxy-5-(5-(((3-(N-hydroxyformamido)propanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

1-(3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)cyclopropanecarboxylic acid

5-ethoxy-2-hydroxy-3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-propoxybenzoic acid

(S)-2-(3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid

(R)-2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid

2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)acetic acid

2,2'-((2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetic acid

2,2'-((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetic acid

5-(3-((1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl)carbamoyl)-5-ethoxyphenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)furan-2-carboxamide

(R)-3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

(R)-2-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

(R)-2-fluoro-5-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

(R)-4-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-

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yl)benzoic acid
(S)-2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)pentanedioic acid
(3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)(methyl)phosphinic acid
methyl hydrogen (3-(5-((((R)-2-((N-hydroxyformamido)methyl)heptanamido)methyl) carbamoyl)furan-2-yl)phenyl)phosphonate
(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid
(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl) tetrahydrofuran-2-yl)phenyl)phosphonic acid
(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid
(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzyl)phosphonic acid
((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonic acid
methyl hydrogen (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido) methyl)carbamoyl)furan-2-yl)phenyl)phosphonate
(R)-5-(3-(2,2-difluoroethoxy)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)furan-2-carboxamide
(R)-5-(3-(ethylthio)phenyl)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl) furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-(methylthio)phenyl)furan-2-carboxamide

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(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(3-nitrophenyl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(1-methyl-1H-indazol-6-yl)furan-2-carboxamide
(R)-N-((2-((N-hydroxyformamido)methyl)heptanamido)methyl)-5-(2-methyl-2H-indazol-6-yl)furan-2-carboxamide
(R)-(3-(5-(((2-((N-hydroxyformamido)methyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid
5-(3-((Z)-N'-hydroxycarbamimidoyl)phenyl)-N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido) methyl)furan-2-carboxamide
N-(((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)-5-phenyltetrahydrofuran-2-carboxamide;

(3-ethoxy-2-fluoro-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
3-hydroxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
3-(carboxymethoxy)-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
2-(carboxymethyl)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
5-ethoxy-2-hydroxy-3-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
(S)-2-(2-ethoxy-4-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-(2-(naphthalen-2-yl)ethyl)pentanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid
5-(carboxymethoxy)-3-(5-((((2R,3R)-2-(2,4-difluorophenethyl)-3-(N-hydroxyformamido)pentanamido)methyl)carbamoyl)furan-2-yl)-2-hydroxybenzoic acid
(S)-2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid
(S)-2-(4-(5-((((R)-2-((R)-1-(N-

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hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzamido)succinic acid

5-(carboxymethoxy)-2-hydroxy-3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

2,2'-((3-(5-((((2R,3R)-2-(2,4-difluorophenethyl)-3-(N-hydroxyformamido)pentanamido)methyl)carbamoyl)furan-2-yl)-5-ethoxybenzoyl)azanediyl)diacetic acid

(S)-2-(4-(5-((((2R,3R)-2-(2,4-difluorophenethyl)-3-(N-hydroxyformamido)pentanamido)methyl)carbamoyl)furan-2-yl)-2-ethoxybenzamido)succinic acid

2,2'-((2-ethoxy-4-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetic acid

(S)-2-(3-(carboxymethoxy)-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid

(S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid

(S)-2-(2-ethoxy-4-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid

2-ethoxy-6-hydroxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phthalic acid

2-((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzyl)(methyl)amino)acetic acid

3-(2-amino-2-oxoethoxy)-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid

(R)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-

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yl)benzamido)succinic acid
((R)-2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid
(S)-2-(4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)pentanedioic acid
(S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)pentanedioic acid
2,2'-((4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoyl)azanediyl)diacetic acid
(((3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzyl)amino)methyl)phosphonic acid,
(3-hydroxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid
((2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonic acid
(3-ethoxy-5-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid
(3-ethoxy-5-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-(2-(naphthalen-2-yl)ethyl)pentanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid
((2-hydroxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonic acid
((4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-

yl)benzamido)methyl)phosphonic acid
((4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-2-methylbenzamido)methyl)phosphonic acid
2-(3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)-5-phosphonophenoxy)acetic acid
2-hydroxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid;

2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzoic acid
3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)benzoic acid
(S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid
(S)-2-(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid
5-ethoxy-2-hydroxy-3-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
(3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid
(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid
3-(carboxymethoxy)-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzoic acid
(S)-2-(4-(5-((((R)-2-((R)-1-(N-

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hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid

(S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid

4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phthalic acid

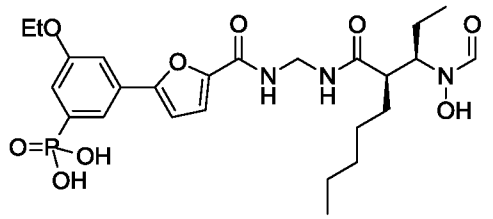
(3-hydroxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid

((2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)methyl)phosphonic acid and

(3-ethoxy-5-(5-((((2R,3R)-3-(N-hydroxyformamido)-2-phenethylpentanamido)methyl)carbamoyl)furan-2-yl)phenyl)phosphonic acid;

or a pharmaceutically acceptable salt thereof.

16. A compound which is (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid of formula:



or a pharmaceutically acceptable salt thereof.

17. A meglumine salt, Tris salt, or calcium salt of (3-ethoxy-5-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl) furan-2-yl)phenyl)phosphonic acid.

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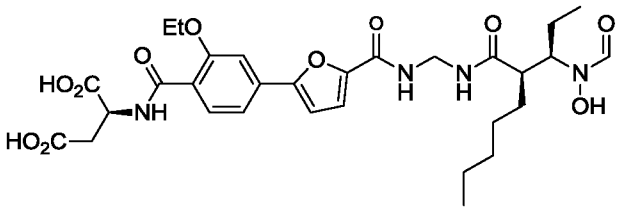
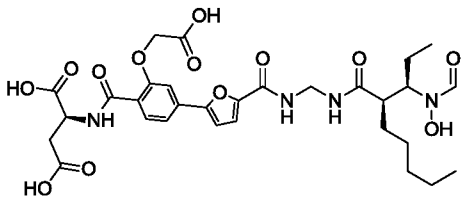
18. A compound which is (S)-2-(2-ethoxy-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl) carbamoyl)furan-2-yl)benzamido)succinic acid of formula:



or a pharmaceutically acceptable salt thereof.

19. A compound which is (S)-2-(2-(carboxymethoxy)-4-(5-((((R)-2-((R)-1-(N-hydroxyformamido)propyl)heptanamido)methyl)carbamoyl)furan-2-yl)benzamido)succinic acid of formula:



or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising the compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 19, and one or more pharmaceutically acceptable excipients.

21. A method of treating a disease associated with BMP1, TLL1 and/or TLL2 activity in a human in need thereof comprising administering to said human a therapeutically effective amount of the compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 19.

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22. Use of the compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1 to 19 in the manufacture of a medicament for the treatment of a disease associated with BMP1, TLL1 and/or TLL2 activity.

23. The method or use according to either claim 21 or claim 22, wherein the disease associated with BMP1, TLL1 and/or TLL2 activity is selected from diseases associated with pathological fibrotic conditions of the heart, lung, kidney, liver, eye, skin, skeletal muscle, vasculature, or nervous system.

24. The method or use according to claim 23, wherein the disease is selected from: myocardial infarction, heart failure, cardiac arrhythmia, hypertrophic cardiomyopathy, chronic obstructive pulmonary disease ("COPD"), idiopathic pulmonary fibrosis ("IPF"), diabetic nephropathy, post-acute kidney injury, chronic kidney disease ("CKD"), delayed graft function post-transplantation, liver cirrhosis, non-alcoholic steatohepatitis ("NASH"), glaucoma, corneal scarring, muscular dystrophy, keloids, wound healing, adhesions, hypertrophic scarring, scarring, stroke, collagen vascular diseases, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, spinal cord injury, and multiple sclerosis.

25. The method or use according to either claim 21 or claim 22, wherein the disease associated with BMP1, TLL1 and/or TLL2 activity is selected from muscular diseases characterized by reduced muscle function and/or mass.

26. The method or use according to claim 25, wherein the muscular disease is selected from: muscular dystrophy, sarcopenia, and cachexia.