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(54) Title: ANALOGUES OF N-LACTOYL-PHENYLALANINE, METHODS OF SYNTHESIS, AND METHODS OF USE

(57) Abstract: N-Lactoyl-Phenylalanine (Lac-Phe) analogues are disclosed having activity as appetite suppressants useful as therapeutics in the treatment of obesity and related secondary diseases. Methods of synthesis of the N-Lactoyl-Phenylalanine (Lac-Phe) analogues are also disclosed, as well as methods of use and treatment with the Lac-Phe analogues.



WO 2025/072489 A2

ANALOGUES OF N-LACTOYL-PHENYLALANINE, METHODS OF SYNTHESIS, AND METHODS OF USE

BACKGROUND

Field of the invention

[0001] The present disclosure relates to N-Lactoyl-Phenylalanine (Lac-Phe) analogues, methods of use, and methods of synthesis thereof.

Description of Related Art

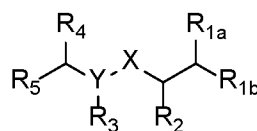
[0002] In the United States, nearly 1 in 3 adults are overweight, and more than 2 in 5 adults have obesity. These medical problems can be serious and life-threatening, causing secondary diseases such as diabetes, gallbladder disease, hypertension, elevated cholesterol, hyper triglyceride disease, dyslipidemia, non-alcoholic steatohepatitis, type 2 diabetes, coronary artery disease (CAD), CHD stroke, arthritis, and infertility.

[0003] Drugs approved by the FDA for weight loss include: Oral drugs: Naltrexone/bupropion, Benzphetamine, Amfepramone, Orlistat, Phendimetrazine, Phentermine/topiramate, Phentermine, Diethylpropion, and Injection drugs: Liraglutide, semaglutide, and setmelanotide.

[0004] Despite recent advancements in available therapies, current weight loss treatments are limited as the most effective treatments were not originally developed to treat obesity and many still may have undesirable side effects. For example, Glucagon-like peptide-1 (GLP-1s) receptor agonists are injectable therapeutics for diabetes and are used for weight-loss at higher doses, but have a high cost and might also have drawbacks regarding safety as there have been reports of issues with irreversible stomach paresis. The European Medicines Agency (EMA) is now currently surveilling GLP-1s for potential cancer risk. Taking GLP-1, GLP-1/GIP and triple agonist incretin drugs is not always accepted by patient as GI track issues (vomiting, nausea, diarrhea) at the treatment start are not always tolerated. Notably, treatment only works for as long as it is used. As soon as someone stops their regular course of GLP-1 treatment, weight is likely to begin again. There exists a need in the art for weight loss medication.

BRIEF SUMMARY

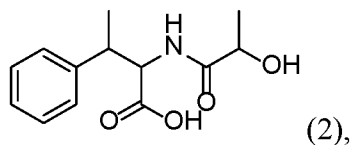
[0005] In an embodiment, a compound of Formula I



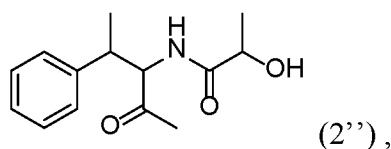
Formula I
(I)

wherein, X is a residue selected from the group consisting of -O-, carbonyl, and -NR, wherein R may be -H or alkyl, ; Y is a residue selected from -CH, -C=O, -SO₂ and -NH; wherein when Y is NH, then X is carbonyl and R³ is absent; wherein when Y is -SO₂, X is NH and R³ is absent; R^{1a} is a residue selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, silyl, phenyl, pentanyl, naphthalene-1-yl, naphthalene-2-yl, 3-phenyl-3-thioxopropanoic acid, and 3-(trimethylsilyl)propanoic acid; where R^{1b} is a residue selected from the group consisting of -H, alkyl, thiocarbonyl (C=S) and hydroxy; where R² is a residue selected from the group consisting of -COOR wherein R may be H, alkyl, sulfinic acid, 2-phenylethane-1-sulfinic acid, phosphinic acid, 2-phenylethylphosphinic acid, phosphonic acid, 2,2,2-trifluoromethyl-1-hydroxyethyl, and methyl 2-hydroxypropanoyl; wherein R³ is a residue selected from the group consisting of -H, hydroxy, =O, carbonyl (C=O), thiocarbonyl (C=S), and sulfinic acid; wherein R⁴ is a residue selected from the group consisting of hydroxyl, carbonyl (ketone), hydroxymethyl, and alkyl (e.g., methyl); and wherein R⁵ is a residue selected from alkyl, cycloalkyl, amine, hydroxy, butanoyl, hydroxybutanoyl, cyclopropanyl, ethyl (-CH₂CH₃), hydroxycyclopropane-1-carbonyl, amino, ethanol, and lactonyl; wherein optionally, R₂ and R₃ may combine to form a heterocycloalkyl group (e.g., oxazolidine).

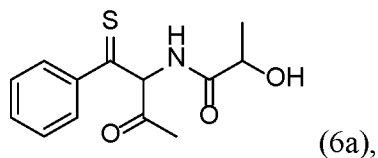
[0006] In an embodiment, the compound of Formula I can be 2-(2-hydroxypropanoylamino)-3-phenylbutanoic acid having structure (2)



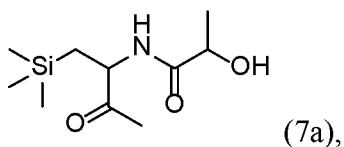
2-(2-hydroxypropanoylamino)-3-phenylmethylbutanone having structure (2'')



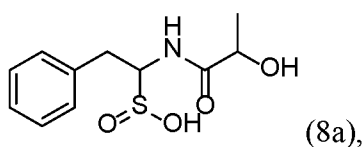
2-hydroxy-N-(3-oxo-1-phenyl-1-sulfanylidenebutan-2-yl)propanamide, having structure (6a)



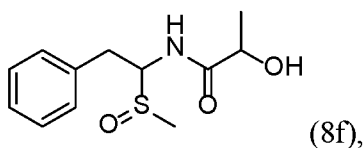
2-hydroxy-N-(3-oxo-1-trimethylsilylbutan-2-yl)propanamide having structure (7a)



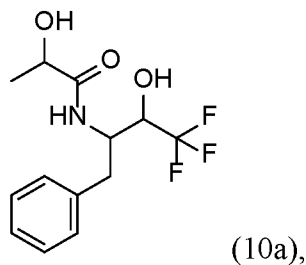
1-(2-hydroxypropanoylamino)-2-phenylethanesulfinic acid having structure (8)



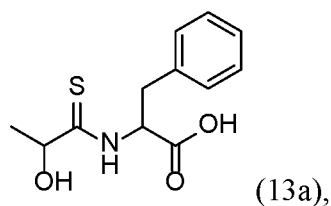
1-(2-hydroxypropanoylamino)-2-phenylethanemethylsulfoxide having structure (8f)



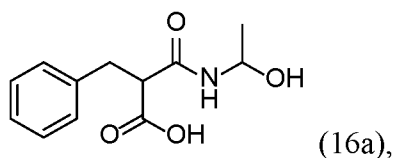
2-hydroxy-N-(4,4,4-trifluoromethyl-3-hydroxy-1-phenylbutan-2-yl)propanamide having structure (10)



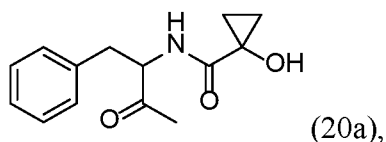
2-(2-hydroxypropanethioylamino)-3-phenylpropanoic acid having structure



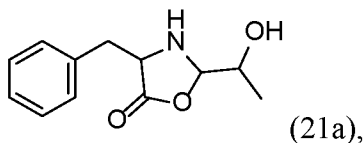
2-benzyl-5-hydroxyhex-3-enoic acid (15), 2-benzyl-3-(1-hydroxyethylamino)-3-oxopropanoic acid having structure



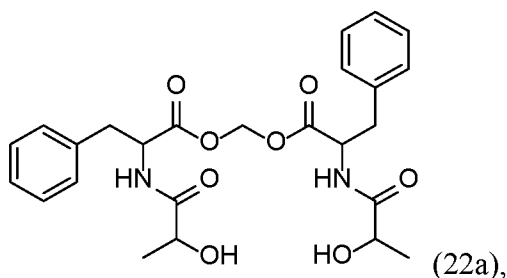
2-[(1-hydroxycyclopropanecarbonyl)amino]-3-phenylpropanoic acid having structure



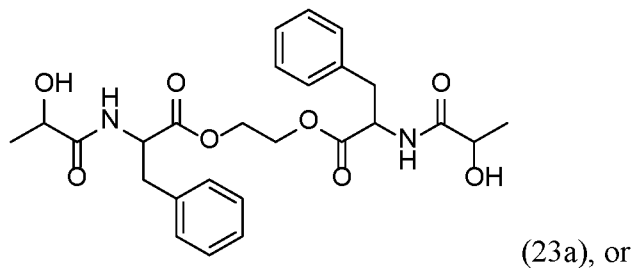
4-benzyl-2-(1-hydroxyethyl)-1,3-oxazolidin-5-one having structure



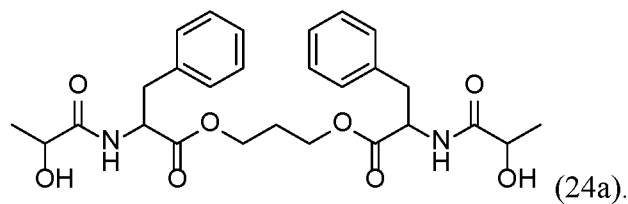
2-(2-hydroxypropanoylamino)-3-phenylpropanoyl]oxymethyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate having structure



2-[2-(2-hydroxypropanoylamino)-3-phenylpropanoyl]oxyethyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate having structure

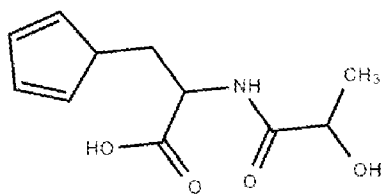


3-[2-(2-hydroxypropanoylamino)-3-phenylpropanoyl]oxypropyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate having structure



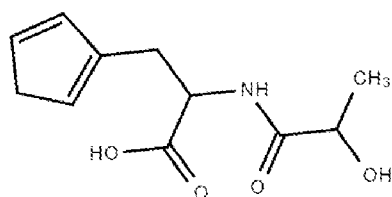
[0007] In an embodiment, the compound of Formula I can be

3-cyclopenta-2,4-dien-1-yl-2-(2-hydroxypropanoylamino)propanoic acid having structure



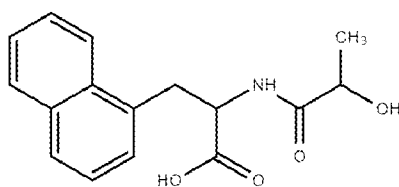
(3'),

3-cyclopenta-1,4-dien-1-yl-2-(2-hydroxypropanoylamino)propanoic acid having structure



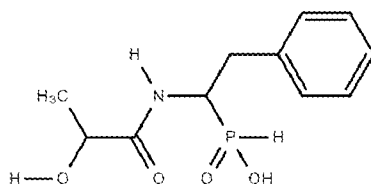
(4'),

2-(2-hydroxypropanoylamino)-3-naphthalen-1-ylpropanoic acid having structure



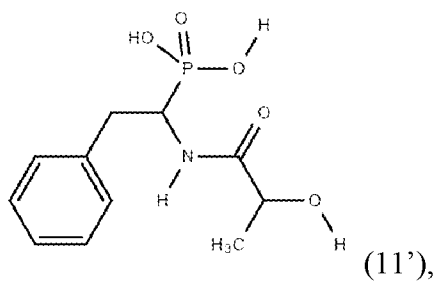
(5'),

[1-(2-hydroxypropanoylamino)-2-phenylethyl]phosphinic acid having structure



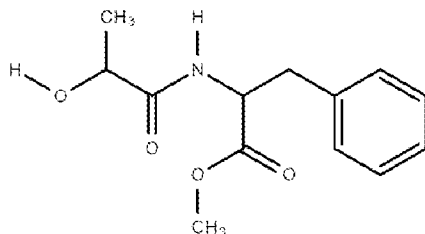
(9'),

[1-(2-hydroxypropanoylamino)-2-phenylethyl]phosphonic acid having structure



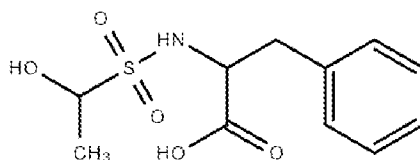
(11'),

methyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate having structure



(12'), or

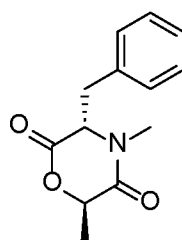
2-(1-hydroxyethylsulfonylamino)-3-phenylpropanoic acid having structure



(14').

[0008] In an embodiment, the compound of Formula I can be radio-labeled by an isotope, optionally ^{76}Br , ^{14}C , ^{13}C , ^2H , ^3H , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{15}N , ^{15}O , ^{18}F , or a combination thereof.

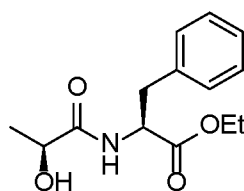
[0009] In an embodiment, the compound (3S,6S)-3-benzyl-4,6-dimethylmorpholine-2,5-dione can have the following structure



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(13b).

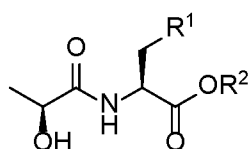
[0010] In an embodiment, the compound ethyl ((S)-2-hydroxypropanoyl)-L-phenylalaninate can have the structure



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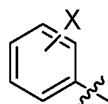
(14d).

[0011] In an embodiment, the compound of Formula I-a,

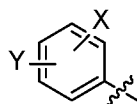


Formula I-a,

wherein R^1 is selected from the group consisting of methylcyclopentanyl, methylcyclohexanyl, a monosubstituted phenyl having structure

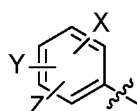


wherein X is selected from the group consisting of H, CN, CF_3 , F, Cl, OMe, Me, $CONH_2$, CF_3 , isopropyl, CF_2H , and Cyclopropyl, a di-substituted phenyl having structure

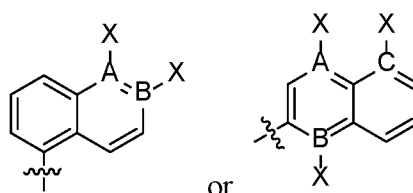


wherein X is selected from the group consisting of H, CN, CF_3 , F, Cl, OMe, Me, $CONH_2$, CF_3 , iPr, CF_2H , and Cyclopropyl, and where Y is selected from the group consisting of H, CN, CF_3 , F, Cl, OMe, Me, $CONH_2$, CF_3 , isopropyl, CF_2H , and Cyclopropyl,

a tri-substituted phenyl having structure

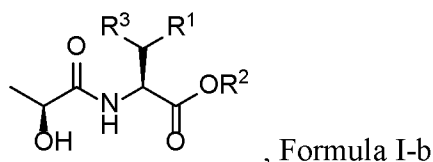


wherein X is selected from the group consisting of H, CN, CF_3 , F, Cl, OMe, Me, $CONH_2$, CF_3 , iPr, CF_2H , and Cyclopropyl, and where Y is selected from the group consisting of H, CN, CF_3 , F, Cl, OMe, Me, $CONH_2$, CF_3 , isopropyl, CF_2H , and Cyclopropyl, and Z is selected from the group consisting of H, CN, CF_3 , F, Cl, OMe, Me, $CONH_2$, CF_3 , isopropyl, CF_2H , and Cyclopropyl, a hetero-biphenyl compound having structure

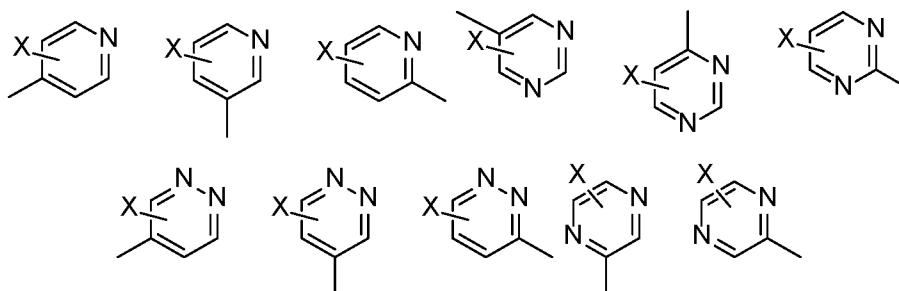


where A, B, or C is selected from the group consisting of N, and CX, where X is selected from the group consisting of Cl, H and Me, and R_2 is selected from the group consisting of ethyl, isopropanyl, ethylbenzene, and isopropyl acetate.

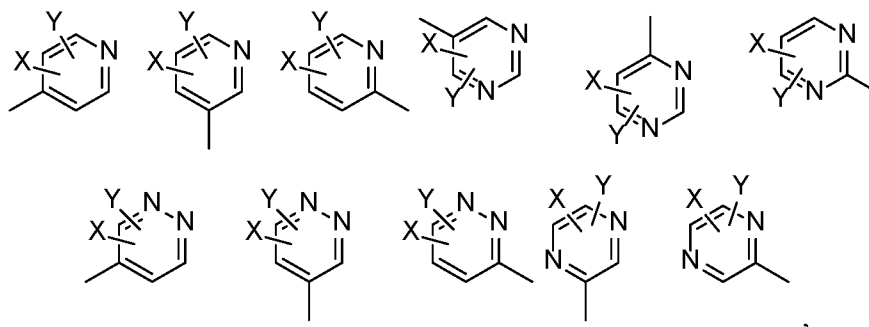
[0012] In an embodiment, the compound of Formula I-b can have the structure



where R^1 and R^3 have structure selected from

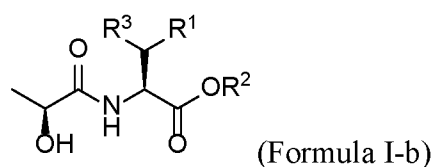


where X in R^1 and R^3 monosubstituted heteroaryl is selected from the group consisting of H, CN, CF_3 , F, Cl, OMe, Me, $CONH_2$, CF_3 , isopropyl, CF_2H , and Cyclopropyl, and optionally said R^1 and R^3 is a disubstituted heteroaryl compound of structure selected from

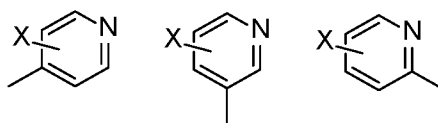


wherein X in said disubstituted heteroaryl is F or Cl, and Y is F or Cl.

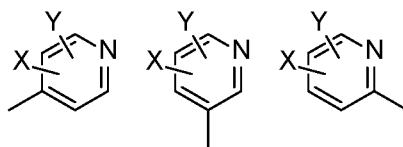
[0013] In an embodiment, the compound of Formula I-c can have the following structure



wherein R^1 is optionally a monosubstituted heteroaryl having structure selected from

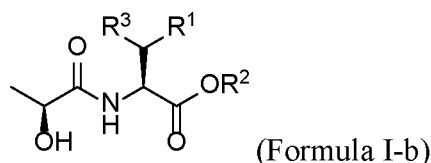


wherein X in said R^1 monosubstituted heteroaryl is selected from the group consisting of H, CN, CF_3 , F, Cl, OMe, Me, $CONH_2$, CF_3 , isopropyl, CF_2H , and Cyclopropyl, and optionally where R^1 is a disubstituted heteroaryl compound of structure selected from

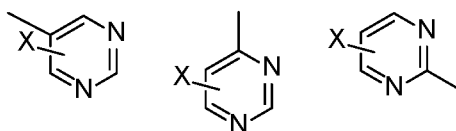


where X in said R¹ disubstituted heteroaryl is F or Cl, and Y is F or Cl.

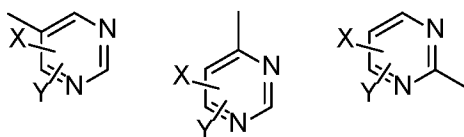
[0014] In an embodiment, the compound of Formula I-c can have the following structure



wherein R¹ is optionally a monosubstituted heteroaryl having structure selected from

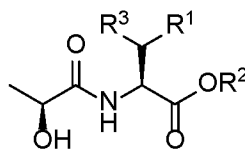


wherein X in said R¹ monosubstituted heteroaryl is selected from the group consisting of H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, isopropyl, CF₂H, and Cyclopropyl, and optionally where R¹ is a disubstituted heteroaryl compound of structure selected from

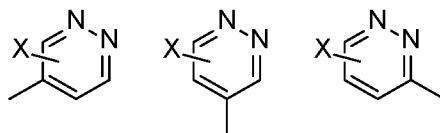


where X in said R¹ disubstituted heteroaryl is F or Cl, and Y is F or Cl.

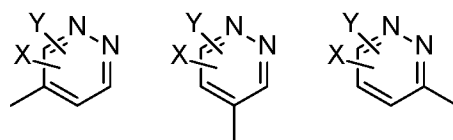
[0015] In an embodiment, the compound of Formula I-b can have the following structure



wherein R¹ is a monosubstituted heteroaryl having structure selected from

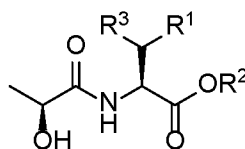


wherein X in said R¹ monosubstituted heteroaryl is selected from the group consisting of H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, isopropyl, CF₂H, and Cyclopropyl, and optionally R¹ is a disubstituted heteroaryl compound of structure selected from

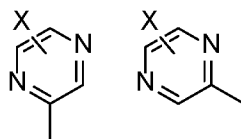


wherein X in said R¹ disubstituted heteroaryl is F or Cl, and Y is F or Cl.

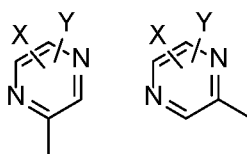
[0016] In an embodiment, the compound of Formula I-b can have the following structure



wherein R¹ is a monosubstituted heteroaryl having structure selected from

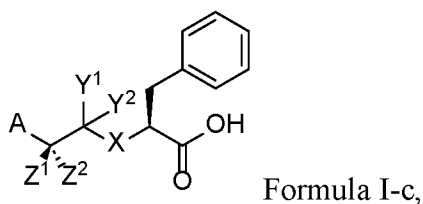


wherein X in said R¹ monosubstituted heteroaryl is selected from the group consisting of H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, isopropyl, CF₂H, and Cyclopropyl, and optionally R¹ is a disubstituted heteroaryl compound having structure selected from



wherein X in said R¹ disubstituted heteroaryl is F or Cl, and Y is F or Cl.

[0017] In an embodiment, the compound of Formula I-c can have the structure



where X is selected from the group consisting of O, NH, NCH₃, CH₂, and SO₂,

where Y¹ is selected from the group consisting of H, O, and OH,

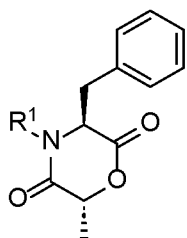
where Y² is selected from the group consisting of H, O, and OH,

where Z¹ is selected from the group consisting of H, D, OH, NH₂, Me, and Oxetane,

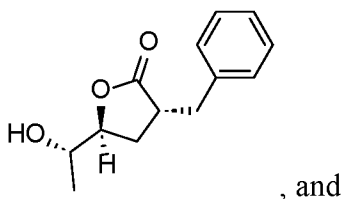
where Z² is selected from the group consisting of H, D, OH, NH₂, Me, and Oxetane and

where A is selected from the group consisting of CF₃, Me, Et, Pr, iPr, Aryl, CD₃, cyclopropane, cyclobutene.

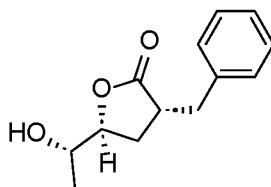
[0018] In an embodiment, the compound structure can be



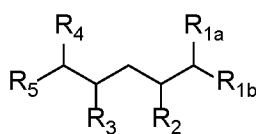
where R¹ is H or methyl,



, and



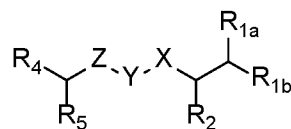
[0019] In an embodiment, the compound of Formula II can have the structure



Formula II

wherein, R^{1a} is a residue selected from alkyl, cycloalkyl (e.g., methylcyclopentanyl, methylcyclohexanyl), heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, silyl (e.g., trimethylsilyl), phenyl, pentanyl, 3-phenyl-3-thioxopropanoic acid, and 3-(trimethylsilyl)propanoic acid; where R^{1b} is a residue selected from -H, alkyl, thiocarbonyl (C=S) and hydroxy; where R² is a residue selected from -COOR where R may be H or alkyl, sulfinic acid, 2-phenylethane-1-sulfinic acid, phosphinic acid, 2-phenylethyl-phosphinic acid, phosphonic acid, 2,2,2-trifluoromethyl-1-hydroxyethyl, and methyl 2-hydroxypropanoyl; where R³ is a residue selected from -H, hydroxy, =O, carbonyl (C=O), thiocarbonyl (C=S), and sulfinic acid; where R⁴ is a residue selected from hydroxyl, carbonyl (ketone), hydroxy-methyl, and alkyl (e.g., methyl); and where R⁵ is a residue selected from alkyl, cycloalkyl, amine, hydroxy, butanoyl, hydroxybutanoyl, cyclopropanyl, ethyl (CH₂CH₃), hydroxycyclopropane-1-carbonyl, amino, ethanol, and lactonyl

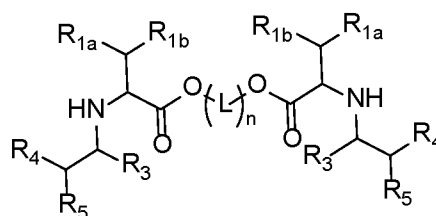
[0020] In an embodiment, the compound of Formula III can have the structure



Formula III

wherein, X and Z may be selected from NR, where R is H, C, or N; Y may be selected from carbonyl and CH; R^{1a} is a residue selected from alkyl, cycloalkyl (e.g., methylcyclopentanyl, methylcyclohexanyl), heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, silyl (e.g., trimethylsilyl), phenyl, pentanyl, 3-phenyl-3-thioxopropanoic acid, and 3-(trimethylsilyl)propanoic acid; where R^{1b} is a residue selected from -H, alkyl, thiocarbonyl (C=S) and hydroxy; where R² is a residue selected from -COOR where R may be H or alkyl, sulfinic acid, 2-phenylethane-1-sulfinic acid, phosphinic acid, 2-phenylethyl-phosphinic acid, phosphonic acid, 2,2,2-trifluoromethyl-1-hydroxyethyl, and methyl 2-hydroxypropanoyl; where R³ is a residue selected from -H, hydroxy, =O, carbonyl (C=O), thiocarbonyl (C=S), and sulfinic acid; where R⁴ (Group 4) is a residue selected from hydroxyl, carbonyl (ketone), hydroxy-methyl, and alkyl (e.g., methyl); and where R⁵ is a residue selected from alkyl, cycloalkyl, amine, hydroxy, butanoyl, hydroxybutanoyl, cyclopropanyl, ethyl (CH₂CH₃), hydroxycyclopropane-1-carbonyl, amino, ethanol, and lactonyl.

[0021] In an embodiment, the compound of Formula IV can have the structure



Formula IV

wherein, L is (CH₂)_n where n is 1, 2, or 3; R^{1a} is a residue selected from alkyl, cycloalkyl, heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, silyl (e.g., trimethylsilyl), phenyl, pentanyl, 3-phenyl-3-thioxopropanoic acid, and 3-(trimethylsilyl)propanoic acid; where R^{1b} is a residue selected from -H, alkyl, thiocarbonyl (C=S) and hydroxy; where R² is a residue

selected from -COOR where R may be H or alkyl, sulfinic acid, 2-phenylethane-1-sulfinic acid, phosphinic acid, 2-phenylethyl-phosphinic acid, phosphonic acid, 2,2,2-trifluoromethyl-1-hydroxyethyl, and methyl 2-hydroxypropanoyl; where R³ is a residue selected from -H, hydroxy, carbonyl, thiocarbonyl (C=S), and sulfinic acid; where R⁴ is a residue selected from hydroxyl, carbonyl (ketone), hydroxy-methyl, and alkyl (e.g., methyl); and where R⁵ is a residue selected from alkyl, cycloalkyl, amine, hydroxy, butanoyl, hydroxybutanoyl, cyclopropanyl, ethyl (CH₂CH₃), hydroxycyclopropane-1-carbonyl, amino, ethanol, and lactonyl.

[0022] In an embodiment, the compound is Methyl (S)-2-((S)-2-(benzyloxy)propanamido)-3-(2-fluorophenyl)propanoate.

[0023] In an embodiment, the compound is Methyl (S)-3-(2-fluorophenyl)-2-((S)-2-hydroxypropanamido) propanoate.

[0024] In an embodiment, the compound is (S)-3-(2-fluorophenyl)-2-((S)-2-hydroxypropanamido) propanoic acid.

[0025] In an embodiment, the compound is Methyl (S)-2-((S)-2-(benzyloxy)propanamido)-3-(3-fluorophenyl) propanoate.

[0026] In an embodiment, the compound is Methyl (S)-3-(3-fluorophenyl)-2-((S)-2-hydroxypropanamido) propanoate. In an embodiment, the compound is Methyl (S)-2-((S)-2-(benzyloxy)propanamido)-3-(4-fluorophenyl) propanoate.

[0027] In an embodiment, the compound is Methyl (S)-3-(4-fluorophenyl)-2-((S)-2-hydroxypropanamido) propanoate.

[0028] In an embodiment, the compound is (S)-3-(2-fluorophenyl)-2-((S)-2-hydroxypropanamido) propanoic acid.

[0029] In an embodiment, the compound is ((R)-2-hydroxypropyl)-L-phenylalanine.

[0030] In an embodiment, the compound is (R)-2-(benzyloxy) propanoyl)-D-phenylalanine methyl ester.

[0031] In an embodiment, the compound is ((R)-2-hydroxypropanoyl)-D-phenylalanine methyl ester.

[0032] In an embodiment, the compound is ((R)-2-hydroxypropanoyl)-D-phenylalanine.

[0033] In an embodiment, the compound is (((S)-2-hydroxypropyl) carbamoyl)-L-phenylalanine.

[0034] In an embodiment, the compound is Benzyl N-((S)-2-(benzyloxy)propanoyl)-N-methyl-L-phenylalaninate.

- [0035] In an embodiment, the compound is (3S,6S)-3-benzyl-4,6-dimethylmorpholine-2,5-dione.
- [0036] In an embodiment, the compound is Ethyl ((S)-2-hydroxypropanoyl)-L-phenylalaninate.
- [0037] In an embodiment, the compound is Benzyl N-((S)-2-acetoxypropanoyl)-N-methyl-L-phenylalaninate.
- [0038] In an embodiment, the compound is N-((S)-2-acetoxypropanoyl)-N-methyl-L-phenylalanine.
- [0039] In an embodiment, the compound is Potassium N-((S)-2-hydroxypropanoyl)-N-methyl-L-phenylalaninate. In an embodiment, the compound is Ethyl (E)-hex-4-enoate.
- [0040] In an embodiment, the compound is (S)-5-((S)-1-hydroxyethyl)dihydrofuran-2(3H)-one.
- [0041] In an embodiment, the compound is (S)-5-((S)-1-((tert butyldimethylsilyl)oxy)ethyl)dihydrofuran-2(3H)-one.
- [0042] In an embodiment, the compound is (3R,5S)-3-benzyl-5-((S)-1-((tert butyldimethylsilyl)oxy)ethyl)dihydrofuran-2(3H)-one.
- [0043] In an embodiment, the compound is (3R,5S)-3-benzyl-5-((S)-1-hydroxyethyl)dihydrofuran-2(3H)-one.
- [0044] In an embodiment, the compound is Sodium (4S,5S)-2-benzyl-4,5-dihydroxyhexanoate.
- [0045] In an embodiment, the compound is (3R,5S)-3-benzyl-5-((S)-1-(benzyloxy)ethyl)dihydrofuran-2(3H)-one.
- [0046] In an embodiment, the compound is Benzyl (2R,4S,5S)-2-benzyl-5-(benzyloxy)-4-hydroxyhexanoate.
- [0047] In an embodiment, the compound is Benzyl (5S)-2-benzyl-5-(benzyloxy)-4-oxohexanoate.
- [0048] In an embodiment, the compound is (5S)-2-benzyl-5-hydroxy-4-oxohexanoic acid.
- [0049] In an embodiment, the compound is Methyl (S)-2-(allyloxy)-3-phenylpropanoate.
- [0050] In an embodiment, the compound is Methyl (S)-2-(2-oxopropoxy)-3-phenylpropanoate.
- [0051] In an embodiment, the compound is Methyl (2S)-2-(2-hydroxypropoxy)-3-phenylpropanoate.
- [0052] In an embodiment, the compound is (2S)-2-(2-hydroxypropoxy)-3-phenylpropanoic acid.

[0053] In an embodiment, the compound is (2S,3R)-5-benzyl-2,6-bis(benzyloxy)-6-oxohexan-3-yl 4-nitrobenzoate.

[0054] In an embodiment, the compound is (5R)-3-benzyl-5-((S)-1-(benzyloxy)ethyl)dihydrofuran-2(3H)-one.

[0055] In an embodiment, the compound is (5R)-3-benzyl-5-((S)-1-hydroxyethyl)dihydrofuran-2(3H)-one.

[0056] In an embodiment, the compound is Sodium (4R,5S)-2-benzyl-4,5-dihydroxyhexanoate.

[0057] In an embodiment, a composition can comprise an effective amount of a compound of described herein. The composition can be a pharmaceutical composition. The composition can further comprise an excipient, lubricant, antioxidant, emulsifier, stabilizer, solvent, diluent, buffer, vehicle, or a combination thereof.

[0058] In an embodiment, composition can further comprise an antidiabetic drug selected from the group consisting of alpha-glucosidase inhibitors, acarbose, miglitol, amylin analogs, pramlintide, dipeptidyl peptidase 4 inhibitors, alogliptan, linagliptan, saxagliptin, sitagliptin, incretin mimetics, albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, tirzepatide, retatrutide, insulin, meglitinides, nateglinide, repaglinide), non-sulfonylureas, metformin, imeglimin, SGLT-2 inhibitors, canagliflozin, dapagliflozin, empagliflozin, sulfonylureas, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide, thiazolidinediones, rosiglitazone, pioglitazone, or a combination thereof.

[0059] In an embodiment, composition can further comprise a lipid lowering drug selected from the group consisting of a statin, a cholesterol absorption inhibitor, an antibody against PCSK9, an siRNA PCSK9, an anti-fibrotic agent, a thyroid hormone, a selective thyroid receptor- β agonist, apoptosis signal-regulating kinase 1 (ASK1) inhibitor, acetyl-CoA carboxylase (ACC) inhibitor, an integrin antagonist, a Semicarbazide Sensitive Amine Oxidase (SSAO) inhibitor, also known as Vascular Adhesion Protein-1 (VAP-1) inhibitor, a fibroblast growth factor mimetic 21 (FGF21), a Fatty acid synthase inhibitor, a non-steroidal Farnesoid X receptor (FXR) agonist, a long hydrocarbon chain diacid, a pantothenic acid analog, bempedoic acid, gemfibrozil, fenofibrate, bezafibrate, clofibrate, ciprofibrate, clinofibrate, etofylline, pirifibrate, simfibrate, tocofibrate, pemaefibrate, or a combination thereof. The statin can be selected from the group consisting of atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin, mevastatin, dalvastatin, dihydrocompactin, cerivastatin, or a combination thereof, optionally wherein said statin is a pharmaceutically acceptable salt or solvate thereof.

[0060] In an embodiment, a method of treating obesity and its secondary diseases in a subject in need thereof can comprise administering to a subject in need thereof an effective amount of a compound described herein or a composition described herein. The secondary disease related to obesity can be metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia, hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and/or neuro-disease.

[0061] In an embodiment, the subject can be a mammal, optionally human.

[0062] In an embodiment, the subject can be pediatric patient.

[0063] In an embodiment, the composition for the treatment of obesity or a secondary disease thereof can comprise an effective amount of a compound described herein.

[0064] In an embodiment, the use of a compound described herein can be used in the manufacture of a medicament for the treatment of obesity and secondary diseases related to obesity. The secondary disease related to obesity can be metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia, hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and/or neuro-disease.

[0065] In an embodiment, the medicament can further comprise alpha-glucosidase inhibitors, acarbose, miglitol, amylin analogs, pramlintide, dipeptidyl peptidase 4 inhibitors, alogliptan, linagliptan, saxagliptin, sitagliptin, incretin mimetics, albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, tirzepatide, retatrutide, insulin, meglitinides, nateglinide, repaglinide), non-sulfonylureas, metformin, imeglimin, SGLT-2 inhibitors, canagliflozin, dapagliflozin, empagliflozin, sulfonylureas, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide, thiazolidinediones, rosiglitazone, pioglitazone, or a combination thereof. In an embodiment, the antidiabetic drug can be in a pharmaceutically acceptable salt or solvate thereof.

[0066] In an embodiment, the medicament can further comprise a lipid lowering drug selected from the group consisting of a statin, a cholesterol absorption inhibitor, ezetimibe, an antibody against PCSK9, an siRNA PCSK9, an anti-fibrotic agent, a thyroid hormone, a selective thyroid receptor- β agonist, apoptosis signal-regulating kinase 1 (ASK1) inhibitor, acetyl-CoA carboxylase (ACC) inhibitor, an integrin antagonist, a Semicarbazide Sensitive Amine Oxidase (SSAO) inhibitor, also known as Vascular Adhesion Protein-1 (VAP-1) inhibitor, a fibroblast growth factor mimetic 21 (FGF21), a Fatty acid synthase inhibitor, a non-steroidal Farnesoid X receptor (FXR) agonist, a long hydrocarbon chain diacid, a pantothenic acid analog, bempedoic acid, gemfibrozil, fenofibrate, bezafibrate, clofibrate, ciprofibrate, clinofibrate, etofylline,

pirifibrate, simfibrate, tocofibrate, pemaifibrate, or a combination thereof, where said lipid lowering drug can be in a pharmaceutically acceptable salt or solvate thereof.

[0067] In an embodiment, a method for diagnostic testing of sensitivity to a compound described herein by a subject in need of treatment for obesity and secondary diseases related to obesity, said secondary disease related to obesity can be metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia, hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and neuro-disease, said method comprising the steps of administering incremental doses of said compound being test for sensitivity in said subject, and observing effects of said doses on said subject.

[0068] In an embodiment, a method of synthesizing a compound of Formula I-IV, can comprise the steps of:

diazotization of D-Phe with NaNO_2 ,

bromination with HBR of the diazotization reaction of D-Phe with NaNO_2 ,

nucleophilic displacement, and

deprotection of the protecting groups of the bromination reaction with MeOH and H_2SO_4 .

[0069] In an embodiment, a method of synthesizing a compound of Formula I-IV, comprising the steps of:

- EDC coupling of protected D-Lactic acid and a compound selected from D-Phe, N-methyl-phenylalanine, and solid supported Phe with carbonyl diimidazole; and
- deprotection of the products.

BRIEF DESCRIPTION OF THE DRAWINGS

[0070] **FIG. 1** depicts Lac-Phe analogue compounds of Formula I-IV. The figure includes (A) 6 possible areas for modification. The areas (surrounded by dotted lines) can be modified alone or in combination with another area. (B) Structure with Lac-Phe stereochemistry. (C) Lac-Phe analogue compounds of Formula I-IV.

[0071] **FIG. 2A** depicts method of synthesis of Lac-Phe analogues (Scheme I)

[0072] **FIG. 2B** shows alternate synthesis methods for compounds (5b) and (6b).

[0073] **FIG. 3** depicts average percent weight lost in mice following 14 days of treatment with Lac-Phe described herein.

[0074] **FIG. 4** depicts the percent food left (uneaten) weight shows higher weight of food left uneaten by treated mice.

[0075] **FIG. 5** depicts the feces weight decrease following 14 days of treatment.

[0076] FIG. 6 depicts the individual mouse weight following 14 days of treatment. A1-A12 each represent individual mice.

[0077] FIG. 7 depicts that LacPhe mimetics described herein have increased lipophilicity.

[0078] FIG. 8 depicts the median feces weight over 12 days of treatment with LacPhe. LacPhe decreases the median feces weight.

[0079] FIG. 9 depicts the amount of feed left during the course of treatment with LacPhe. LacPhe decreases the amount of feed the animal eats.

[0080] FIG. 10 depicts the mouse weight after 14 days of LacPhe treatment. LacPhe treatment causes a significant weight loss.

[0081] FIG. 11 depicts the mouse weight after 14 days of LacPhe treatment followed by days after LacPhe treatment. The data shows that the mouse begins to gain weight after cessation of LacPhe treatment.

DETAILED DESCRIPTION

[0082] Before the subject disclosure is further described, it is to be understood that the disclosure is not limited to the particular embodiments described below, as variations of the particular embodiments may be made and still fall within the scope of the appended claims. It is also to be understood that the terminology employed is for the purpose of describing particular embodiments, and is not intended to be limiting. Instead, the scope of the present disclosure will be established by the appended claims.

[0083] In this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural reference unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this disclosure belongs.

[0084] *Obesity Epidemic and Treatment*

[0085] Sympathomimetics are a class of drugs that include amphetamines and are known to suppress appetite. Most of these effects are believed to be due to their ability to stimulate the release of biogenic amines (norepinephrine and dopamine) from their storage sites in the nerve terminals. They are known for strong cardiovascular effects too. Amphetamine undergoes several routes of metabolism: hydroxylation, N- dealkylation, oxidative deamination, N-oxidation and conjugation of the nitrogen. Approximately 50% of the drug is excreted unchanged in the urine. For most amphetamines, the major route of metabolism is oxidative deamination. Amphetamines also have undesirable side effects.

N-Lactoyl-Phenylalanine (Lac-Phe)

[0086] N-lactoyl-amino acids are ubiquitous metabolites that can originate from enzymes such as carnosine dipeptidase 2 (CNDP2), which mediates reverse proteolysis of lactate and amino acids. Lac-Phe is a lactoyl-amino acid derivative formed by amide bond formation between lactic acid and phenylalanine. Lac-Phe was first described, along with other lactoyl-amino acid derivatives, as a ligand for the Calcium Sensing Receptor (CaSR) in the tongue and responsible for imparting the kokumi taste sensation to food.

[0087] N-Lactoyl-Phenylalanine (Lac-Phe) is an endogenous metabolite in humans and shows promise with distinct advantages regarding toxicity as it is hypothesized to act only on hunger and has been shown to not impact energy expenditure, unlike other drugs and currently available therapies. Furthermore, the mechanism of action has been studied and is safe because Lac-Phe is a natural metabolite found in human plasma.

[0088] N-Lactoyl-Phenylalanine (Lac-Phe) is abundant in many fermented foods like pickles or aged foods like cheeses. Lac-Phe is an abundant plasma metabolite formed shortly after aerobic exercise in both animal and human studies. Lac-Phe is produced enzymatically by reverse proteolysis by carnosine dipeptidase 2 (CNDP2), when levels of lactic acid build up in skeletal muscle after exercise. It is actively effluxed from cells by the ATP-binding cassette subfamily C member 5 (ABCC5) transporter into the plasma, where it mediates appetite suppression by an unknown mechanism. Diet-induced obese (DIO) mice given a single IP bolus of Lac-Phe (50 mg/kg) decreased their calorie consumption by approximately 50% over 12 hours, without affecting energy expenditure. Lac-Phe given orally was ineffective most likely due to its lability from proteolysis in the gastrointestinal (GI) tract.

[0089] *N-Lactoyl-Phenylalanine (Lac-Phe) analogues*

[0090] N-Lactoyl-Phenylalanine (Lac-Phe) analogues described herein have Lac-Phe-like activity as appetite suppressants and can be used as therapeutics in the treatment of obesity and related secondary diseases. Methods of synthesis of the Lac-Phe analogues described herein are also disclosed, as well as methods of use and treatment with the Lac-Phe analogues. The Lac-Phe analogues described herein can be used as therapeutics to suppress feeding and improve glucose homeostasis and obesity. The Lac-Phe analogues described herein are essentially mimetics of Lac-Phe including analogue, bio-isosteres and structurally modified Lactate and Phenylalanine, as well as mimetics of the amide bond link, to improve the properties of the compounds, most importantly regarding improved pharmacokinetics and degradation of the compounds.

[0091] The Lac-Phe analogues described herein retain structural similarity to Lac-Phe and retain anorexiant properties. The Lac-Phe analogues described herein have anorexiant properties (suppress appetite) or are anorectic without significant toxicity to a subject or patient at

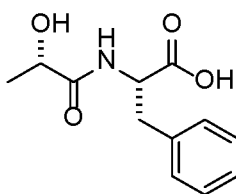
therapeutically effective doses. The Lac-Phe analogues described herein are anorectic without loss of efficacy or without adverse or undesirable side effects to a patient at therapeutically effective doses.

[0092] The Lac-Phe analogues described herein are designed to be resistant to digestion and degradation in the gastrointestinal system and therefore have increased bioavailability. GI tract hydrolysis results from secreted enzymes, acids, or from the action of the intestinal flora (digestion by intestinal bacteria).

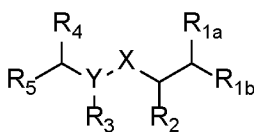
[0093] The Lac-Phe analogues described herein have a structural resemblance to compounds such as Levoamphetamine or Phentermine hydrochloride which also have the ability to suppress feeding and obesity through mechanisms like the inhibition of pro-neuropeptide Y. There is no evidence for neurological adverse effects of Lac-Phe and it is anticipated no adverse effect with the Lac-Phe analogues described herein.

[0094] Therapeutic applications of the Lac-Phe analogues described herein include but are not limited to treatment of metabolic disease: TG related diseases, hyper TG, dyslipidemia, NASH/NAFLD, and neuro-diseases. The chemical structure designs of the Lac-Phe analogues described herein can be applied to any N-lactoyl-amino acids that are but not limited to those originating from the CNDP2-mediated reverse proteolysis of lactate and amino acids for the treatment of metabolic diseases such as obesity, dyslipidemia, and hypertension, and associated secondary diseases.

[0095] The N-Lactoyl-Phenylalanine (Lac-Phe) analogues described herein can comprise Formula I having the structure



Lac-Phe

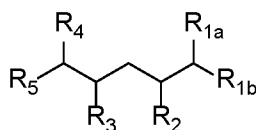


Formula I

wherein, X is a residue selected from -O-, -NR, where R may be -H or alkyl, and carbonyl; Y is a residue selected from -C-, -C=O, -SO₂ and -NH; where if Y = NH, then X = carbonyl and R³ is absent; where if Y = -SO₂, X = NH and R³ is absent; R^{1a} (Group 1) is a residue selected from

alkyl, cycloalkyl (e.g., methylcyclopentanyl, methylcyclohexanyl), heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, silyl (e.g., trimethylsilyl), phenyl, pentanyl, : naphthalene-1-yl, naphthalene-2-yl, 3-phenyl-3-thioxopropanoic acid, and 3-(trimethylsilyl)propanoic acid; where R^{1b} is a residue selected from -H, alkyl, thiocarbonyl (C=S) and hydroxy; where R^2 (Group 2) is a residue selected from -COOR where R may be H or alkyl, sulfinic acid, 2-phenylethane-1-sulfinic acid, phosphinic acid, 2-phenylethyl-phosphinic acid, phosphonic acid, 2,2,2-trifluoromethyl-1-hydroxyethyl, and methyl 2-hydroxypropanoyl; where R^3 (Group 3) is a residue selected from -H, hydroxy, =O, carbonyl (C=O), thiocarbonyl (C=S), and sulfinic acid; where R^4 (Group 4) is a residue selected from hydroxyl, carbonyl (ketone), hydroxy-methyl, and alkyl (e.g., methyl); and where R^5 (Group 5) is a residue selected from alkyl, cycloalkyl, amine, hydroxy, butanoyl, hydroxybutanoyl, cyclopropanyl, ethyl(CH₂CH₃), hydroxycyclopropane-1-carbonyl, amino, ethanol, and lactonyl; where optionally, R2 and R3 may combine to form a heterocycloalkyl group (e.g., oxazolidine, morpholine). Groups 1, 2, 3, 4, and 5 are in reference to FIG. 1.

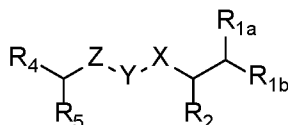
[0096] The N-Lactoyl-Phenylalanine (Lac-Phe) analogues described herein can comprise Formula II having the structure



Formula II

wherein, R^{1a} (Group 1) is a residue selected from alkyl, cycloalkyl (e.g., methylcyclopentanyl, methylcyclohexanyl), heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, silyl (e.g., trimethylsilyl), phenyl, pentanyl, 3-phenyl-3-thioxopropanoic acid, and 3-(trimethylsilyl)propanoic acid; where R^{1b} (Group 1) is a residue selected from -H, alkyl, thiocarbonyl (C=S) and hydroxy; where R^2 (Group 2) is a residue selected from -COOR where R may be H or alkyl, sulfinic acid, 2-phenylethane-1-sulfinic acid, phosphinic acid, 2-phenylethyl-phosphinic acid, phosphonic acid, 2,2,2-trifluoromethyl-1-hydroxyethyl, and methyl 2-hydroxypropanoyl; where R^3 is a residue selected from -H, hydroxy, =O, carbonyl (C=O), thiocarbonyl (C=S), and sulfinic acid; where R^4 (Group 4) is a residue selected from hydroxyl, carbonyl (ketone), hydroxy-methyl, and alkyl (e.g., methyl); and where R^5 (Group 5) is a residue selected from alkyl, cycloalkyl, amine, hydroxy, butanoyl, hydroxybutanoyl, cyclopropanyl, ethyl, hydroxycyclopropane-1-carbonyl, amino, ethanol, and lactonyl.

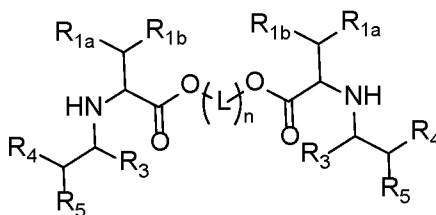
[0097] The N-Lactoyl-Phenylalanine (Lac-Phe) analogues described herein can comprise Formula III having the structure



Formula III

wherein, X and Z may be selected from NR, where R is H, C, or N; Y may be selected from carbonyl and CH; R^{1a} (Group 1) is a residue selected from alkyl, cycloalkyl (e.g., methylcyclopentanyl, methylcyclohexanyl), heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, silyl (e.g., trimethylsilyl), phenyl, pentanyl, 3-phenyl-3-thioxopropanoic acid, and 3-(trimethylsilyl)propanoic acid; where R^{1b} (Group 1) is a residue selected from -H, alkyl, thiocarbonyl (C=S) and hydroxy; where R² (Group 2) is a residue selected from -COOR where R may be H or alkyl, sulfinic acid, 2-phenylethane-1-sulfinic acid, phosphinic acid, 2-phenylethyl-phosphinic acid, phosphonic acid, 2,2,2-trifluoromethyl-1-hydroxyethyl, and methyl 2-hydroxypropanoyl; where R³ is a residue selected from -H, hydroxy, =O, carbonyl (C=O), thiocarbonyl (C=S), and sulfinic acid; where R⁴ (Group 4) is a residue selected from hydroxyl, carbonyl (ketone), hydroxy-methyl, and alkyl (e.g., methyl); and where R⁵ (Group 5) is a residue selected from alkyl, cycloalkyl, amine, hydroxy, butanoyl, hydroxybutanoyl, cyclopropanyl, ethyl, hydroxycyclopropane-1-carbonyl, amino, ethanol, and lactonyl.

[0098] The N-Lactoyl-Phenylalanine (Lac-Phe) analogues described herein can comprise Formula IV having the structure

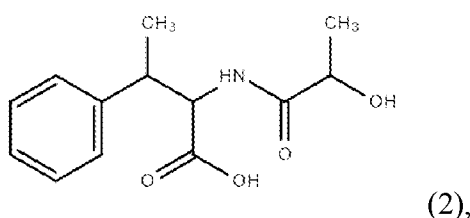


Formula IV

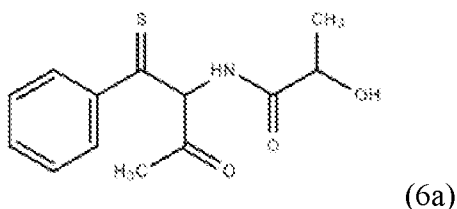
[0099] wherein, L is CH₂, where n is 1, 2, or 3; R^{1a} (Group 1) is a residue selected from alkyl, cycloalkyl, heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, silyl (e.g., trimethylsilyl), phenyl, pentanyl, 3-phenyl-3-thioxopropanoic acid, and 3-(trimethylsilyl)propanoic acid; where R^{1b} (Group 1) is a residue selected from -H, alkyl, thiocarbonyl (C=S) and hydroxy; where R² (Group 2) is a residue selected from -COOR where R

may be H or alkyl, sulfinic acid, 2-phenylethane-1-sulfinic acid, phosphinic acid, 2-phenylethyl-phosphinic acid, phosphonic acid, 2,2,2-trifluoromethyl-1-hydroxyethyl, and methyl 2-hydroxypropanoyl; where R^3 is a residue selected from -H, hydroxy, carbonyl, thiocarbonyl ($C=S$), and sulfinic acid; where R^4 (Group 4) is a residue selected from hydroxyl, carbonyl (ketone), hydroxy-methyl, and alkyl (e.g., methyl); and where R^5 (Group 5) is a residue selected from alkyl, cycloalkyl, amine, hydroxy, butanoyl, hydroxybutanoyl, cyclopropanyl, ethyl, hydroxycyclopropane-1-carbonyl, amino, ethanol, and lactonyl.

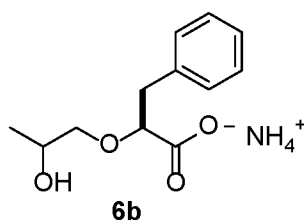
[0100] The N-Lactoyl-Phenylalanine (Lac-Phe) analogues described herein can comprise compounds of Formula I-IV, wherein said compound is selected from the group consisting of 2-(2-hydroxypropanoylamino)-3-phenylbutanoic acid having structure (2)



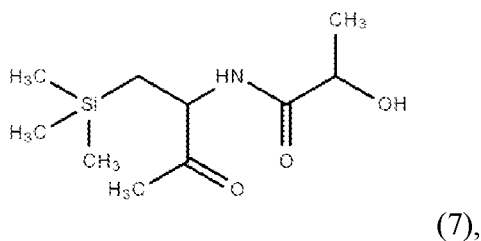
2-hydroxy-N-(3-oxo-1-phenyl-1-sulfanylidenebutan-2-yl)propanamide, having structure (6a)



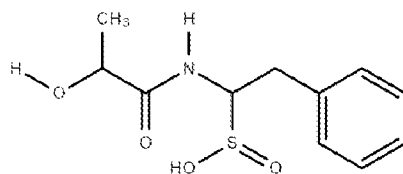
ammonium (2*S*)-2-(2-hydroxypropoxy)-3-phenylpropanoate (6b)



2-hydroxy-N-(3-oxo-1-trimethylsilylbutan-2-yl) propanamide having structure (7)

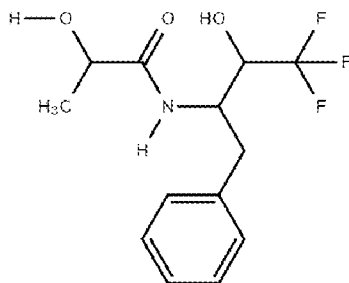


1-(2-hydroxypropanoylamino)-2-phenylethanesulfinic acid having structure (8)



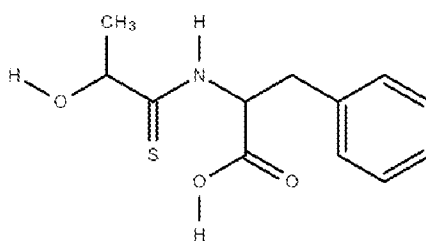
(8),

2-hydroxy-N-(4,4,4-trifluoro-3-hydroxy-1-phenylbutan-2-yl) propanamide having structure (10).



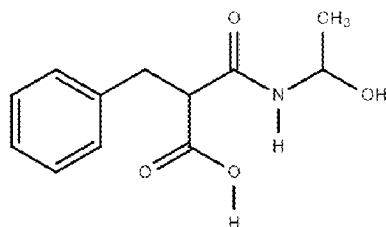
(10),

2-(2-hydroxypropanethioylamino)-3-phenylpropanoic acid having structure (13)



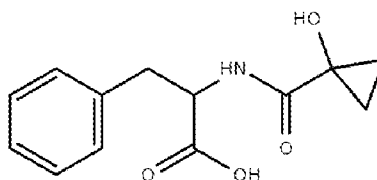
(13),

2-benzyl-5-hydroxyhex-3-enoic acid (15), 2-benzyl-3-(1-hydroxyethylamino)-3-oxopropanoic acid having structure (16)



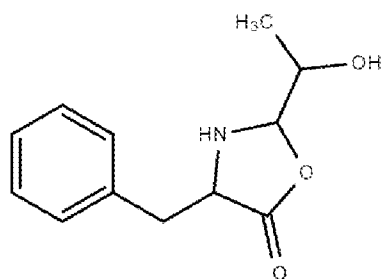
(16),

2-[(1-hydroxycyclopropanecarbonyl)amino]-3-phenylpropanoic acid having structure (20)



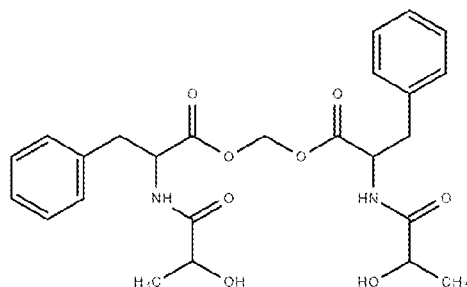
(20),

4-benzyl-2-(1-hydroxyethyl)-1,3-oxazolidin-5-one having structure (21)



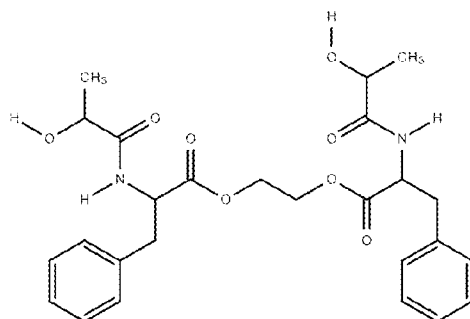
(21),

2-(2-(2-hydroxypropanoylamino)-3-phenylpropanoyl]oxymethyl 2-(2-(2-hydroxypropanoylamino)-3-phenylpropanoate having structure (22)



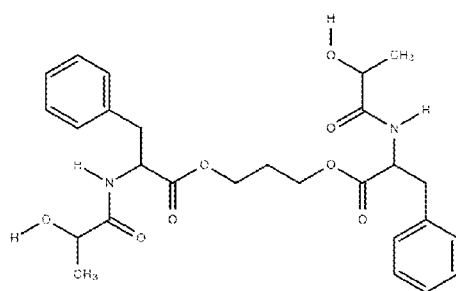
(22),

2-[2-(2-hydroxypropanoylamino)-3-phenylpropanoyl]oxyethyl 2-(2-(2-hydroxypropanoylamino)-3-phenylpropanoate having structure



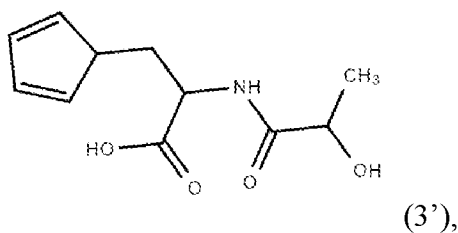
(23), and

3-[2-(2-hydroxypropanoylamino)-3-phenylpropanoyl]oxypropyl 2-(2-(2-hydroxypropanoylamino)-3-phenylpropanoate having structure (24)

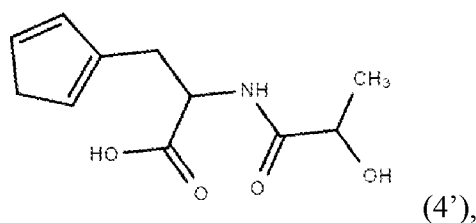


(24).

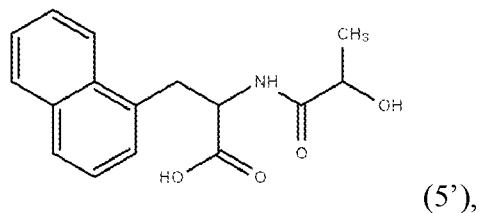
[0101] The Lac-Phe analogues described herein can comprise compounds of Formula I-IV, wherein said compound is selected from the group consisting of 3-cyclopenta-2,4-dien-1-yl-2-(2-hydroxypropanoylamino)propanoic acid having structure



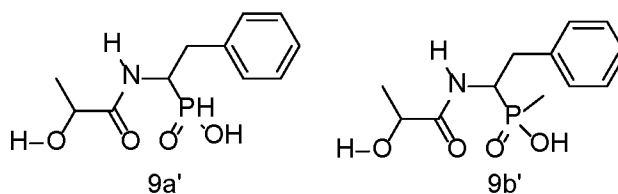
3-cyclopenta-1,4-dien-1-yl-2-(2-hydroxypropanoylamino)propanoic acid having structure



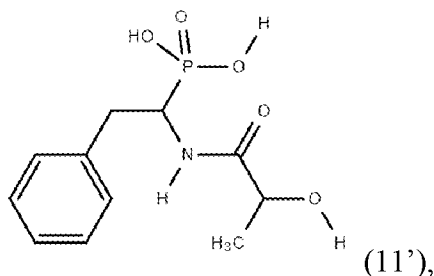
2-(2-hydroxypropanoylamino)-3-naphthalen-1-ylpropanoic acid having structure



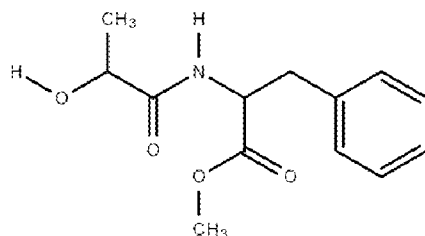
[1-(2-hydroxypropanoylamino)-2-phenylethyl]phosphinic acid (9a') and [1-(2-hydroxypropanoylamino)-2-phenylethyl] methyl phosphinic acid (9b') having structure



[1-(2-hydroxypropanoylamino)-2-phenylethyl]phosphonic acid having structure

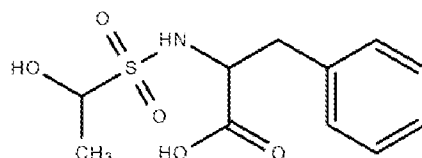


methyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate having structure



(12'), and

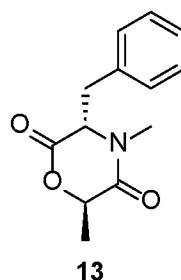
2-(1-hydroxyethylsulfonylamino)-3-phenylpropanoic acid having structure



(14').

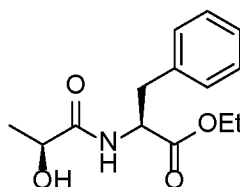
[00100] The Lac-Phe analogues described herein can comprise compounds of Formula I-IV, wherein said compound is radio-labeled by an isotope selected from the group consisting of ^{76}Br , ^{14}C , ^{13}C , ^2H , ^3H , ^{131}I , ^{123}I , ^{124}I , ^{125}I , ^{15}N , ^{15}O , and ^{18}F .

[0102] The Lac-Phe analogues described herein can comprise compounds of Formula I-IV, wherein said compound is (3S,6S)-3-benzyl-4,6-dimethylmorpholine-2,5-dione having structure



13

[0103] The Lac-Phe analogues described herein can comprise compounds of Formula I, where said compound is ((S)-2-hydroxypropanoyl)-L-phenylalaninate having structure



14

[0104] Methods of synthesizing a compound of Formula I can comprise the steps of: (Scheme 1 compounds 5b and 6) diazotization of D-Phe with NaNO_2 , bromination with HBR of the diazotization reaction of D-Phe with NaNO_2 , nucleophilic displacement, and deprotection of the protecting groups of the bromination reaction with MeOH and H_2SO_4 .

[0105] Methods of synthesizing a compound of Formula I-IV can comprise the steps of EDC coupling of protected D-Lactic acid and a compound selected from D-Phe, N-methyl-phenylalanine, and solid supported Phe with carbonyl diimidazole; and deprotection of the products. (Compounds 9, 10, and 11).

[0106] Methods of treating obesity and its secondary diseases in a subject in need thereof, said secondary disease related to obesity selected from the group consisting of metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia, hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and neuro-disease, said method comprising the step of administering to the subject an effective amount of a compound of Formula I-IV.

[0107] Methods of treating obesity and its secondary diseases in a subject in need thereof, said method can comprise administering an effective amount of a compound of Formula I-IV in combination with one or more antidiabetic drugs selected from the group consisting of alpha-glucosidase inhibitors, acarbose, miglitol, amylin analogs, pramlintide, dipeptidyl peptidase 4 inhibitors, alogliptan, linagliptan, saxagliptin, sitagliptin, incretin mimetics, albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, tirzepatide, retatrutide, insulin, meglitinides, nateglinide, repaglinide), non-sulfonylureas, metformin, imeglimin, SGLT-2 inhibitors, canagliflozin, dapagliflozin, empagliflozin, sulfonylureas, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide, thiazolidinediones, rosiglitazone, pioglitazone, or a combination thereof.

[0108] Methods of treating obesity and its secondary diseases in a subject in need thereof, said method comprising administering an effective amount of a compound of Formula I-IV in combination with one or more lipid lowering drugs selected from the group consisting of a statin, a cholesterol absorption inhibitor, an antibody against PCSK9, an siRNA PCSK9, an anti-fibrotic agent, a thyroid hormone, a selective thyroid receptor- β agonist, apoptosis signal-regulating kinase 1 (ASK1) inhibitor, acetyl-CoA carboxylase (ACC) inhibitor, an integrin antagonist, a Semicarbazide Sensitive Amine Oxidase (SSAO) inhibitor, also known as Vascular Adhesion Protein-1 (VAP-1) inhibitor, a fibroblast growth factor mimetic 21 (FGF21), a Fatty acid synthase inhibitor, a non-steroidal Farnesoid X receptor (FXR) agonist, a long hydrocarbon chain diacid, a pantothenic acid analog, bempedoic acid, gemfibrozil, fenofibrate, bezafibrate, clofibrate, ciprofibrate, clinofibrate, etofylline, pirifibrate, simfibrate, tocofibrate, pemafibrate, or combinations thereof.

[0109] Methods of treating obesity and its secondary diseases in a subject in need thereof, said method comprising administering an effective amount of a compound of Formula I-IV in

combination with one or more lipid lowering drugs selected from the group consisting of a statin, a cholesterol absorption inhibitor, an antibody against PCSK9, an siRNA PCSK9, an anti-fibrotic agent, a thyroid hormone, a selective thyroid receptor- β agonist, apoptosis signal-regulating kinase 1 (ASK1) inhibitor, acetyl-CoA carboxylase (ACC) inhibitor, an integrin antagonist, a Semicarbazide Sensitive Amine Oxidase (SSAO) inhibitor, also known as Vascular Adhesion Protein-1 (VAP-1) inhibitor, a fibroblast growth factor mimetic 21 (FGF21), a Fatty acid synthase inhibitor, a non-steroidal Farnesoid X receptor (FXR) agonist, a long hydrocarbon chain diacid, a pantothenic acid analog, bempedoic acid, gemfibrozil, fenofibrate, bezafibrate, clofibrate, ciprofibrate, clinofibrate, etofylline, pirifibrate, simfibrate, tocofibrate, and pemafibrate, where said statin is selected from the group consisting of atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin, mevastatin, dalvastatin, dihydrocompactin, cerivastatin, or a combination thereof, optionally wherein said statin is a pharmaceutically acceptable salt or solvate thereof.

[0110] Methods of treating obesity and its secondary diseases in a subject in need thereof, said condition is secondary to obesity is selected from the group consisting of metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia, hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and neuro-disease, said method comprising administering a effective amount of a compound of Formula I-IV.

[0111] Methods of treating obesity and its secondary diseases in a subject in need thereof, said condition is secondary to obesity is selected from the group consisting of metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia, hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and neuro-disease, said method comprising administering a effective amount of a compound of Formula I-IV in a therapeutically effective formulation, where said subject is a mammal, a patient, optionally a pediatric patient.

[0112] Use of a compound of Formula I-IV for the treatment in a subject in need thereof for obesity and secondary diseases related to obesity, said secondary disease related to obesity selected from the group consisting of metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia, hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and neuro-disease, can comprise administering to the subject an effective dose of a compound of Formula I-IV.

[0113] Use of a compound of Formula I-IV in the manufacture of a medicament for the treatment in a subject in need thereof for obesity and secondary diseases related to obesity, said

secondary disease related to obesity selected from the group consisting of metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia, hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and neuro-disease, comprising an effective dose of a compound of Formula I-IV, said method comprising administering an effective amount of a compound of Formula I-IV in combination with one or more antidiabetic drugs selected from the group consisting of alpha-glucosidase inhibitors, acarbose, miglitol, amylin analogs, pramlintide, dipeptidyl peptidase 4 inhibitors, alogliptan, linagliptan, saxagliptin, sitagliptin, incretin mimetics, albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, tirzepatide, retatrutide, insulin, meglitinides, nateglinide, repaglinide), non-sulfonylureas, metformin, imeglimin, SGLT-2 inhibitors, canagliflozin, dapagliflozin, empagliflozin, sulfonylureas, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide, thiazolidinediones, rosiglitazone, pioglitazone, or a combination thereof, wherein said antidiabetic drug is in a pharmaceutically acceptable salt or solvate thereof.

[0114] Use of a compound of Formula I-IV for the manufacture of a medicament for the treatment in a subject in need thereof for obesity and secondary diseases related to obesity, said secondary disease related to obesity selected from the group consisting of metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia, hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and neuro-disease, comprising effective dose of a compound of Formula I-IV, optionally in combination with one or more antidiabetic drugs selected from the group consisting of alpha-glucosidase inhibitors, acarbose, miglitol, amylin analogs, pramlintide, dipeptidyl peptidase 4 inhibitors, alogliptan, linagliptan, saxagliptin, sitagliptin, incretin mimetics, albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, tirzepatide, retatrutide, insulin, meglitinides, nateglinide, repaglinide), non-sulfonylureas, metformin, imeglimin, SGLT-2 inhibitors, canagliflozin, dapagliflozin, empagliflozin, sulfonylureas, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide, thiazolidinediones, rosiglitazone, pioglitazone, or a combination thereof, optionally wherein said antidiabetic drug is in a pharmaceutically acceptable salt or solvate thereof, said method comprising administering an effective amount of a compound of Formula I-IV in combination with one or more lipid lowering drugs selected from the group consisting of a statin, a cholesterol absorption inhibitor, ezetimibe, an antibody against PCSK9, an siRNA PCSK9, an anti-fibrotic agent, a thyroid hormone, a selective thyroid receptor- β agonist, apoptosis signal-regulating kinase 1 (ASK1) inhibitor, acetyl-CoA carboxylase (ACC) inhibitor, an integrin antagonist, a Semicarbazide Sensitive

Amine Oxidase (SSAO) inhibitor, also known as Vascular Adhesion Protein-1 (VAP-1) inhibitor, a fibroblast growth factor mimetic 21 (FGF21), a Fatty acid synthase inhibitor, a non-steroidal Farnesoid X receptor (FXR) agonist, a long hydrocarbon chain diacid, a pantothenic acid analog, bempedoic acid, gemfibrozil, fenofibrate, bezafibrate, clofibrate, ciprofibrate, clinofibrate, etofylline, pirifibrate, simfibrate, tocofibrate, pemafibrate, or a combination thereof, optionally wherein said lipid lowering drug is in a pharmaceutically acceptable salt or solvate thereof.

[0115] Use of a compound of Formula I-IV for the diagnostic testing of sensitivity to the compound by a subject in need of treatment for obesity and secondary diseases related to obesity, said secondary disease related to obesity selected from the group consisting of metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia, hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and neuro-disease can comprise testing a subject for a therapeutic response to an effective amount of a compound of Formula I-IV.

[0116] Use of a compound of Formula I-IV for experimental determination of the pharmacodynamics of compounds of Formula I-IV in the treatment of obesity and secondary diseases related to obesity, said secondary disease related to obesity selected from the group consisting of metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia, hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and neuro-disease can comprise testing a subject for a therapeutic response to an effective amount of a compound of Formula I-IV.

[0117] Use of a compound of Formula I-IV for experimental determination of the pharmacodynamics of compounds of Formula I-IV in the treatment of obesity and secondary diseases related to obesity, said secondary disease related to obesity selected from the group consisting of metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia, hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and neuro-disease, can comprise testing a subject for a therapeutic response to an effective amount of a compound of Formula I-IV, wherein said experimental use is performed on a mammal, a patient or optionally a pediatric patient.

[0118] Use of a compound of Formula I-IV for the diagnostic testing of sensitivity to the compound by a subject in need of treatment for obesity and secondary diseases related to obesity, said secondary disease related to obesity selected from the group consisting of metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia,

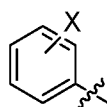
hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and neuro-disease, can comprise testing a subject for a therapeutic response to an effective amount of a compound of Formula I-IV, wherein said compound of Formula I-IV is optionally radiolabeled with a radio-isotope selected from the group consisting of ^{76}Br , ^{14}C , ^{13}C , ^2H , ^3H , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{15}N , ^{15}O , and ^{18}F .

N-Lactoyl-Phenylalanine (Lac-Phe) Analogue Compounds

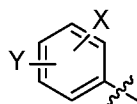
[0119] Alkyl refers to a straight or branched chain hydrocarbon group with only single carbon-carbon bonds and having 1 to 12 carbon atoms in the chain. Representative examples include methyl (which can be structurally depicted by the symbol “/”), ethyl, propyl, isopropyl, butyl, isobutyl, tertbutyl, pentyl, and hexyl. The term C_{x-y} alkyl as used here refers to a straight- or branched-chain alkyl group having from X to Y carbon atoms in the chain. For example, C_{1-6} alkyl refers to a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms in the chain, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl. Lower alkyl refers to $\text{C}_1\text{-C}_6$ alkyl. The term “Me” refers to methyl group ($-\text{CH}_3$), “Et” refers to ethyl group ($-\text{CH}_2\text{CH}_3$), “Pr” refers to n-propyl group ($-\text{CH}_2\text{CH}_2\text{CH}_3$), “iPr” refers to iso-propyl group ($-\text{CH}(\text{CH}_3)_2$).

[0120] Alkoxy refers to the group alkyl-O-. Lower alkoxy refers to a $\text{C}_1\text{-C}_6$ alkoxy group.

[0121] Aryl refers to a monocyclic or bicyclic aromatic carbocycle having 5-14 ring atoms (ring structure having ring atoms that are all carbon). Exemplary aryl groups include phenyl, tolyl, xylyl, naphthyl, pyridyl, and pyrimidinyl. The aryl group may be in the substituted or unsubstituted form. The substituted forms include, without limitation, a monosubstituted phenyl having structure

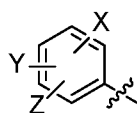


wherein X is selected from the group consisting of H, CN, CF_3 , F, Cl, OMe, Me, CONH_2 , CF_3 , isopropyl, CF_2H , and Cyclopropyl,
a di-substituted phenyl having structure



wherein X is selected from the group consisting of H, CN, CF_3 , F, Cl, OMe, Me, CONH_2 , CF_3 , iPr, CF_2H , and Cyclopropyl, and where Y is selected from the group consisting of H, CN, CF_3 , F, Cl, OMe, Me, CONH_2 , CF_3 , isopropyl, CF_2H , and Cyclopropyl,

a tri-substituted phenyl having structure

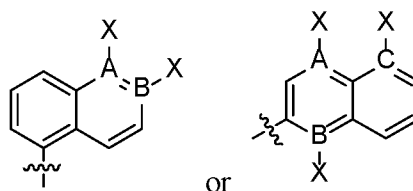


wherein X is selected from the group consisting of H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, iPr, CF₂H, and Cyclopropyl, and where Y is selected from the group consisting of H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, isopropyl, CF₂H, and Cyclopropyl, and Z is selected from the group consisting of H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, isopropyl, CF₂H, and Cyclopropyl.

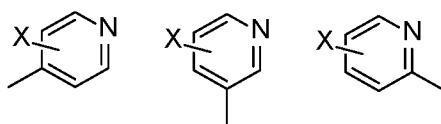
[0122] Cycloalkyl refers to a saturated or unsaturated monocyclic carbocycle. C₃-C₇ cycloalkyl refers to a saturated or unsaturated monocyclic carbocycle having from 3 to 7 ring atoms. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0123] Halogen refers to F, Cl, Br and I.

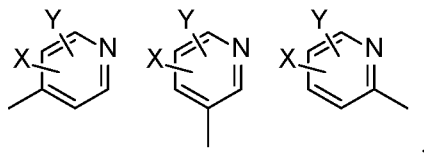
[0124] Heteroaryl refers to a monocyclic or fused bicyclic heterocycle having 5 to 14 ring atoms, where the ring atoms are selected from carbon atoms and up to four heteroatoms each individually selected from nitrogen, oxygen, sulfur, and selenium. Exemplary heteroaryl groups include furanyl, thienyl, pyridyl, pyrrolyl, pyrimidyl, pyrazinyl, imidazolyl, triazolyl, pyrazyl, quinolinyl, indolyl, furanyl, thiane, triazolinyl, thiazolyl, oxazolyl, isoxazolyl, benzopyridyl, benzopyrazolyl, benzofuranyl, and benzothiazolyl. The heteroaryl group may be unsubstituted or substituted. Exemplary substituted heteroaryl groups include, without limitation a hetero-biphenyl compound having structure



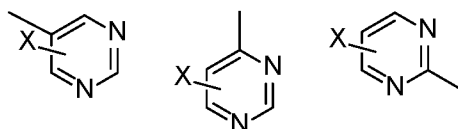
where A, B, or C is selected from the group consisting of N, and CX, where X is selected from the group consisting of Cl, H and Me.



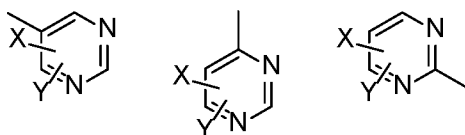
where X is selected from the group consisting of H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, isopropyl, CF₂H, and Cyclopropyl



where X is F or Cl, and Y is F or Cl.



where X is selected from the group consisting of H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, isopropyl, CF₂H, and cyclopropyl.



where X is F or Cl, and Y is F or Cl.

[0125] C₃-C₇ heterocycloalkyl refers to a saturated or unsaturated monocyclic ring structure having 3 to 7 ring atoms selected from carbon atoms and up to two heteroatoms selected from nitrogen, oxygen, and sulfur. Heterocycloalkyl groups may be attached through a heteroatom or through a carbon atom in the ring. Exemplary heterocycloalkyl groups include oxiranyl, oxetanyl, and azetidiny groups.

[0126] Methylene refers to -CH₂-. Substituted methylene refers to a methylene in which one or two of the hydrogens is replaced with -OH, halogen (*e.g.*, F), =O, =CH₂, C₁-C₆ alkyl (*e.g.*, methyl), or C₁-C₆ alkoxy (*e.g.*, methoxy).

[0127] The terms “isotopically labelled compounds” or “radio-labelled compounds”, especially ²H (deuterium) or ¹³C (carbon-13) labelled compounds, are compounds that differ only in that one or more atoms have each been replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. In ²H (deuterium) labelled compounds, at least one hydrogen atom of a compound is substituted with the heavier isotope ²H (deuterium). In ¹³C (carbon-13) labelled compounds, at least one carbon atom of a compound is substituted with the heavier isotope ¹³C (carbon-13). Other examples of isotopically labelled compounds can be ³H (tritium) or ¹⁴C (carbon-14) labelled compounds. Still other examples of radioisotopes for radio-labelling compounds are ⁷⁶Br, ¹²³I, ¹²⁴I, ¹²⁵I, ¹³¹I, ¹⁵N, ¹⁵O,

and ^{18}F . For the purposes of the present disclosure, the terms analogs, analogues, mimetics and the like are used interchangeably.

[0128] For the purposes of the present disclosure, designation of bonds without specification of stereochemistry is intended to include all possible stereochemistry.

[0129] Amino acid bio-isostere

[0130] Bio-isostere or isostere refers to substituents or groups with similar physical or chemical properties which produce broadly similar biological properties in a chemical compound.

[0131] Amino acids: As used herein the term “amino acid” encompasses any molecule containing both amino and carboxyl functional groups, wherein the amino and carboxylate groups are attached to the same carbon (the alpha carbon). The alpha carbon optionally may have one or two further organic substituents. For the purposes of the present disclosure designation of an amino acid without specifying its stereo-chemistry is intended to encompass either the L or D form of the amino acid, or a racemic mixture. However, in the instance where an amino acid is designated by its three letter code and includes a superscript number, the D form of the amino acid is specified by inclusion of a lower case d before the three letter code (e.g., dLys) wherein the designation lacking the lower case d (e.g., Lys) is intended to specify the native L form of the amino acid.

[0132] Uncanonical amino acids: In some instances, amino acids can be canonical amino acids such as the 20 proteinogenic L-amino acids. In some instances, amino acids can be uncanonical amino acids. An “uncanonical amino acid” as described herein can include any amino acid other than one of the 20 proteinogenic proteins in an L-configuration. Such amino acids can include amino acids with non-canonical side chains, D-amino acids, and the like. Exemplary amino acids described are depicted in the L-configuration, but can be a configuration other than an L-configuration. In some instances, an uncanonical amino acid can be an NMR-promoting agent. An uncanonical amino acid for use as an NMR promoting agent can comprise an amino acid with an NMR active side chain, or a side chain capable of becoming NMR active. In some instances, an NMR-promoting agent can be selected from the group consisting of a spin-labeled compound, a paramagnetic metal chelating compound, a compound comprising an NMR active isotope, and any combination thereof. A spin-labeled compound can be prepared through reaction of an amino acid such as p-acetylphenylalanine with a nitroxide compound.

[0133] Pharmaceutically acceptable salt refers to acid-addition salts or base-addition salts of the compounds described herein and are formed from pharmaceutically acceptable organic or inorganic acids or organic or inorganic bases. Exemplary acid-addition salts include those

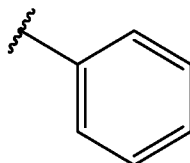
derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Exemplary base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. Salts can be prepared using organic bases, such as salts of primary, secondary and tertiary amines, substituted amines including naturally-occurring substituted amines, and cyclic amines including isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, *N*-alkylglucamines, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, and the like. Another exemplary salt described herein is a compound of any one of Formulas I-IV in salt form with 3-(diaminomethylidene)-1,1-dimethylguanidine (metformin). The chemical modification of a pharmaceutical compound into a salt is a well-known technique which can be used to improve properties involving physical or chemical stability, *e.g.*, hygroscopicity, flowability or solubility of compounds.

[0134] Pharmaceutically acceptable ester refers to an esterified compound described herein having a carboxyl group. Such esters can be cleaved *in vivo* to the corresponding carboxylic acid. Examples of ester groups which are cleaved (*e.g.*, hydrolyzed) *in vivo* to the corresponding carboxylic acids are those in which the hydrogen is replaced with lower alkyl which is unsubstituted or substituted, *e.g.*, with a heterocycle, cycloalkyl, etc. Examples of substituted lower alkyl esters are those in which lower alkyl is substituted with pyrrolidine, piperidine, morpholine, N-methylpiperazine, etc. The group which is cleaved *in vivo* can be, for example, ethyl, morpholino ethyl, or diethylamino ethyl. Pharmaceutically acceptable esters can comprise a compound described herein linked via an ester bond to a second active agent, for example a uric acid transporter inhibitor, for example as described in U.S. Patent No. 10,358,424, the contents of which are incorporated herein by reference in their entirety.

[0135] Pharmaceutically acceptable amide refers to a compound described herein having an amine or carboxylic acid group converted into an amide. Amides of compounds described herein can be prepared according to conventional methods. Pharmaceutically acceptable amides can be prepared from compounds containing primary or secondary amine groups by reaction of the compound that contains the amine group with an alkyl anhydride, aryl anhydride, acyl halide, or aroyl halide. In the case of compounds containing carboxylic acid groups, the pharmaceutically acceptable amides are prepared from compounds containing the carboxylic acid groups by

reaction of the compound with base such as triethylamine, a dehydrating agent such as dicyclohexyl carbodiimide or carbonyl diimidazole, and an alkyl amine, dialkylamine, for example with methylamine, diethylamine, and piperidine. They also can be prepared by reaction of the compound with an acid such as sulfuric acid and an alkylcarboxylic acid such as acetic acid, or with acid and an arylcarboxylic acid such as benzoic acid under dehydrating conditions such as with molecular sieves added.

[0136] Phenyl refers to the group



Prodrugs

[0137] The N-Lactoyl-Phenylalanine (Lac-Phe) analogues described herein can be in the form of a prodrug.

[0138] Prodrug refers to compounds, which undergo transformation prior to exhibiting their pharmacological effects. The chemical modification of drugs to overcome pharmaceutical problems has also been termed “drug latention.” Drug latention is the chemical modification of a biologically active compound to form a new compound, which upon *in vivo* enzymatic attack will liberate the parent compound. The chemical alterations of the parent compound are such that the change in physicochemical properties will affect the absorption, distribution and/or enzymatic metabolism. The definition of drug latention has also been extended to include nonenzymatic regeneration of the parent compound. Regeneration takes place as a consequence of hydrolytic, dissociative, and other reactions not necessarily enzyme mediated. The terms prodrugs, latented drugs, and bio-reversible derivatives are used interchangeably. By inference, latention implies a time lag element or time component involved in regenerating the bioactive parent molecule *in vivo*. The term prodrug is general in that it includes latented drug derivatives as well as those substances, which are converted after administration to the actual substance, which combines with receptors. The term prodrug is a generic term for agents, which undergo biotransformation prior to exhibiting their pharmacological actions.

[0139] When referring to any formula given herein, the selection of a particular species from a list of possible species for a specified variable is not intended to define the same choice of the species for the variable appearing elsewhere. In other words, where a variable appears more than once, the choice of a species from a specified list is independent of the choice of another species for the same variable elsewhere in the formula, unless stated otherwise.

[0140] Prodrugs can be formed by attaching a prodrug group to a functional group, *e.g.*, HO-, HS-, HOOC-, amine, that is present in a compound described herein. The prodrug group can be cleaved from the compound *in vivo*. Prodrugs include but are not limited to carboxylate esters where the group is alkyl, aryl, aralkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl as well as esters of hydroxyl, thiol and amines where the group attached is an acyl group, an alkoxycarbonyl, aminocarbonyl, phosphate or sulfate. The prodrug groups illustrated are exemplary, not exhaustive, and one skilled in the art can prepare other known varieties of prodrugs. Such prodrugs of the Lac-Phe analogues described herein fall within this scope. Prodrugs undergo some form of a chemical transformation to produce the compound that is biologically active or is a precursor of the biologically active compound. The prodrug can be biologically active or not, usually less than the drug itself, and serves to improve drug efficacy or safety through improved oral bioavailability, and/or pharmacodynamic half-life, etc. Prodrug forms of compounds can be utilized, for example, to improve bioavailability, improve subject acceptability such as by masking or reducing unpleasant characteristics such as bitter taste or gastrointestinal irritability, alter solubility such as for intravenous use, provide for prolonged or sustained release or delivery, improve ease of formulation, or provide site-specific delivery of the compound.

[0141] Prodrugs of carboxylic acid-containing compounds are convertible by solvolysis or under physiological conditions to the free carboxylic acids. Examples of prodrugs include carboxylic acid esters, *e.g.*, lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, aryl esters, mono- or di-substituted lower alkyl esters, *e.g.*, the ω -(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, and the α -(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxy-methyl ester.

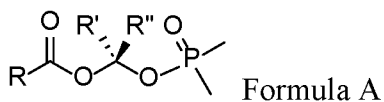
[0142] The Lac-Phe analogues described herein can be the form of a prodrug comprising a covalently attached phosphorus containing group. Attaching a phosphorus containing group (*e.g.*, to create a phosphonic acid) to a compound described herein can enhance its absorption and target the compound to the liver where it can be metabolized by a cytochrome (*e.g.*, CYP3A4). Such metabolism can result in a negatively charged active molecule that stays trapped in liver cells, thereby enhancing potency.

[0143] Prodrugs of phosphorus-containing prodrugs can breakdown chemically or enzymatically to a phosphonic acid or phosphinic acid group or a monoester thereof *in vivo*. As employed herein the term includes, but is not limited to, the following groups and combinations of these groups:

[0144] Acyloxyalkyl esters which are well described in the literature.

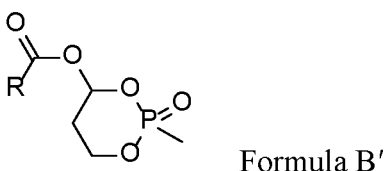
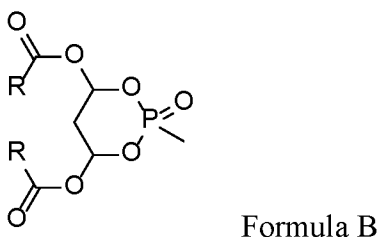
[0145] Other acyloxyalkyl esters are possible in which a cyclic alkyl ring is formed. These esters have been shown to generate phosphorus-containing nucleotides inside cells through a postulated sequence of reactions beginning with deesterification and followed by a series of elimination reactions.

[0146] Another class of these double esters known as alkyloxy- carbonyloxymethyl esters, as shown in formula A, where R is alkoxy, aryloxy, alkylthio, arylthio, alkylamino, or arylamino; R', and R'' are independently -H, alkyl, aryl, alkylaryl, or heterocycloalkyl have been studied in the area of lactam antibiotics.



[0147] Formula A, wherein R, R', and R'' are independently H, alkyl, aryl, alkylaryl, and alicyclic.

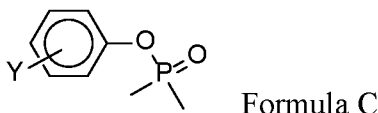
[0148] Other acyloxyalkyl esters are possible in which a cyclic alkyl ring is formed such as shown in Formula B. These esters have been shown to generate phosphorus-containing nucleotides inside cells through a postulated sequence of reactions beginning with deesterification and followed by a series of elimination reactions.



Formula B' wherein R is -H, alkyl, aryl, alkylaryl, alkoxy, aryloxy, alkylthio, arylthio, alkylamino, arylamino, or cycloalkyl.

[0149] Aryl esters have also been used as phosphonate prodrugs. Phenyl as well as mono and poly-substituted phenyl proesters have generated the parent phosphonic acid in studies conducted in animals and in man (Formula C).

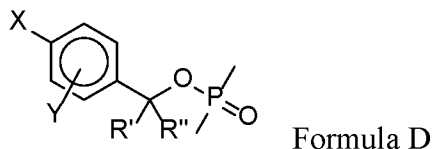
Formula C,



wherein Y is -H, alkyl, aryl, alkylaryl, alkoxy, acyloxy, halogen, amino, alkoxy carbonyl, hydroxy, cyano, or heterocycloalkyl.

[0150] Benzyl esters have also been reported to generate the parent phosphonic acid. Substituents at the para-position can accelerate the hydrolysis. Benzyl analogs with 4-acyloxy or 4-alkyloxy group [Formula D, X= -H, OR or O(CO)R or O(CO)OR] can generate the 4-hydroxy compound more readily through the action of enzymes, *e.g.*, oxidases, esterases, etc.

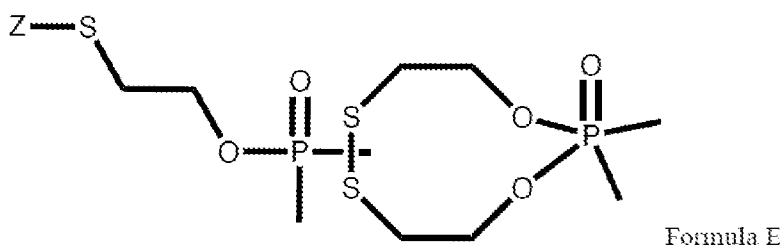
Formula D,



wherein X and Y are independently -H, alkyl, aryl, alkylaryl, alkoxy, acyloxy, hydroxy, cyano, nitro, perhaloalkyl, halo, or alkyloxycarbonyl; and R' and R'' are independently H, alkyl, aryl, alkylaryl, halogen, or cyclic alkyl.

[0151] Thia-containing phosphonate proesters can also be useful in the delivery of drugs to hepatocytes. These proesters contain a protected thioethyl moiety as shown in formula E. One or more of the oxygens of the phosphonate can be esterified. Since the mechanism that results in deesterification requires the generation of a free thiolate, a variety of thiol protecting groups are possible. For example, the disulfide is reduced by a reductase-mediated process. Thioesters will also generate free thiolates after esterase-mediated hydrolysis. Cyclic analogs are also possible and were shown to liberate phosphonate in isolated rat hepatocytes.

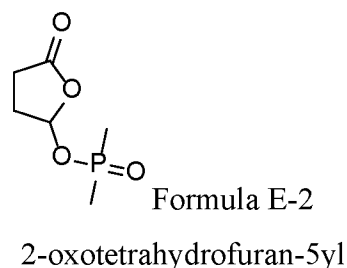
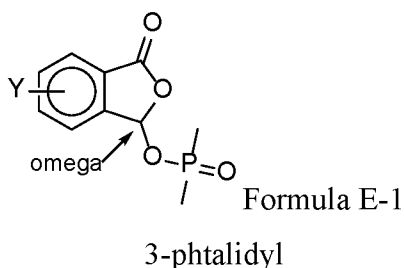
Formula E:



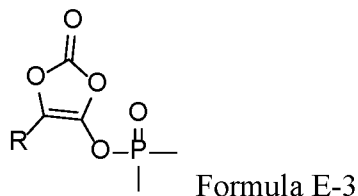
wherein Z is alkylcarbonyl, alkoxy carbonyl, arylcarbonyl, aryloxycarbonyl, or alkylthio.

[0152] Other examples of prodrugs include proester classes. Some of the structural classes described are optionally substituted, including fused lactones attached at the omega position (formulae E-1 and E-2) and optionally substituted oxo-1,3-dioxolenes attached through a methylene to the phosphorus oxygen (formula E-3) such as:

Formula E-1, and E-2



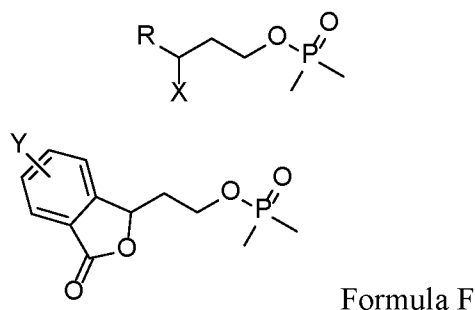
Formula E-3



wherein R is -H, alkyl, cycloalkyl, or heterocycloalkyl; and wherein Y is -H, alkyl, aryl, alkylaryl, cyano, alkoxy, acyloxy, halogen, amino, heterocycloalkyl, or alkoxy- carbonyl.

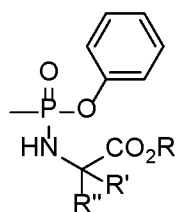
[0153] The prodrugs of Formula E-3 are an example of “optionally substituted heterocycloalkyl where the cyclic moiety contains a carbonate or thiocarbonate.

[0154] Propyl phosphonate proesters can also be used to deliver drugs into hepatocytes. These proesters can contain a hydroxyl and hydroxyl group derivatives at the 3-position of the propyl group as shown in formula F. The R and X groups can form a cyclic ring system as shown in formula F. One or more of the oxygens of the phosphonate can be esterified.

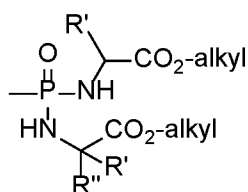


wherein R is alkyl, aryl, heteroaryl; X is hydrogen, alkylcarbonyloxy, or alkyloxycarbonyloxy; and Y is alkyl, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, halogen, hydrogen, hydroxy, acyloxy, or amino.

[0155] Phosphoramidate derivatives have been explored as phosphate prodrugs as shown in Formula G and H.



Formula G



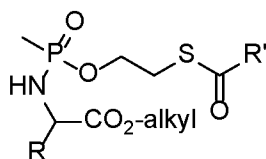
Formula H

where R, R' and R'' are as described elsewhere in this Section.

[0156] Cyclic phosphoramidates have also been studied as phosphonate prodrugs because of their speculated higher stability compared to non-cyclic phosphoramidates.

[0157] Another type of phosphoramidate prodrug was reported as the combination of S-acyl2-thioethyl ester and phosphoramidate for example, bis(trichloroethyl) esters, and the phenyl and benzyl combined nucleotide esters.

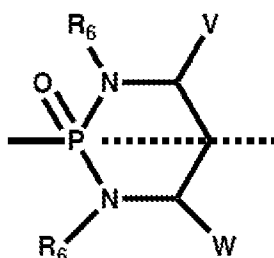
Formula J



Formula J

where R and R' are as described elsewhere in this Section.

[0158] Other prodrugs are possible based on literature reports such as substituted ethyls, for Formula K,



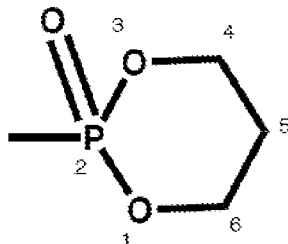
Formula K

has a plane of symmetry running through the phosphorus-oxygen double bond when $R^6=R^6$.

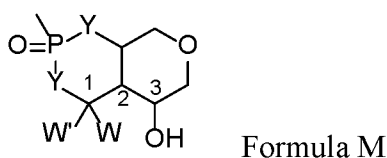
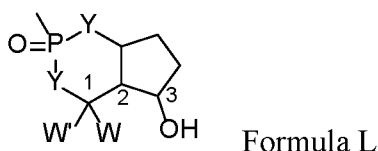
$V=W$ and W are either both pointing up or both pointing down. The same is true of structures where each $-NR^6$ is replaced with $-O-$. In the above structure, each R^6 is independently selected from the group consisting of hydrogen, halogen, optionally substituted $-C_1-C_4$ alkyl, optionally substituted $-S-C_1-C_3$ alkyl, optionally substituted $-C_2-C_4$ alkenyl, optionally substituted $-C_2-C_4$ alkynyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, optionally substituted $-O-C_1-C_3$ alkyl, hydroxy and cyano; and V and W are independently selected from hydrogen, optionally

substituted alkyl, optionally substituted aralkyl, heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, optionally substituted I-alkenyl, and optionally substituted I-alkynyl.

[0159] Another prodrug group includes the following:



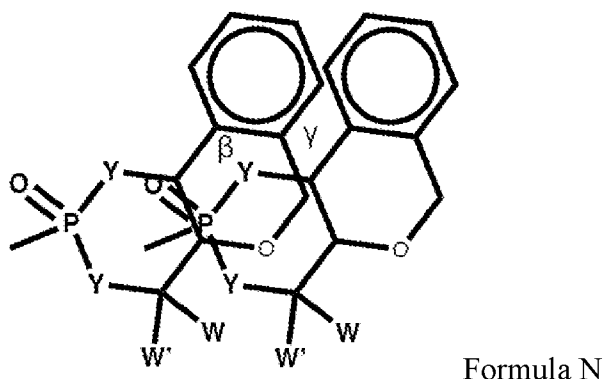
[0160] Further prodrug groups include the following, Formula L and Formula M



where each Y is independently -O- or NR^v-, where R^v is H, lower alkyl, acyloxyalkyl, alkoxy-carbonyloxyalkyl, or lower acyl; and W and W' are independently hydrogen, optionally substituted alkyl, optionally substituted aralkyl, heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, optionally substituted I-alkenyl, and optionally substituted I-alkynyl.

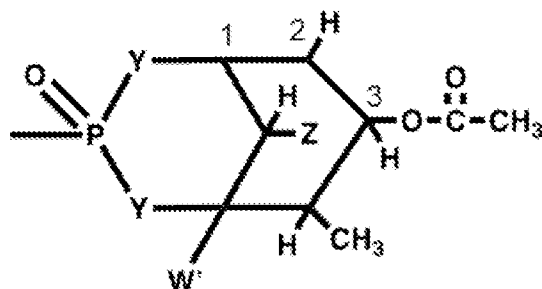
[0161] The structure shown in Formula L has an additional 3 carbon atoms that forms a five-member cyclic group. Such cyclic groups must possess the listed substitution to be oxidized.

[0162] Further prodrug groups include the following:



where Y, W, and W' are as described for Formulas L and M.

[0163] Further prodrug groups include the following:

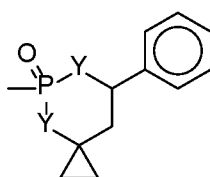


Formula O

wherein Y and W' are as described for Formulas L and N and Z is alkylcarbonyl, alkoxy carbonyl, arylcarbonyl, aryloxy carbonyl, or alkylthio.

[0164] The structure above has an acyloxy substituent that is three carbon atoms from a Y, and an optional substituent, ---CH₃, on the new 6-membered ring. There has to be at least one hydrogen at each of the following positions: the carbon attached to Z; both carbons alpha to the carbon labeled "3"; and the carbon attached to "OC(O)CH₃" above.

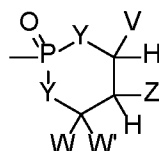
[0165] Further prodrug groups can comprise the following:



Formula P

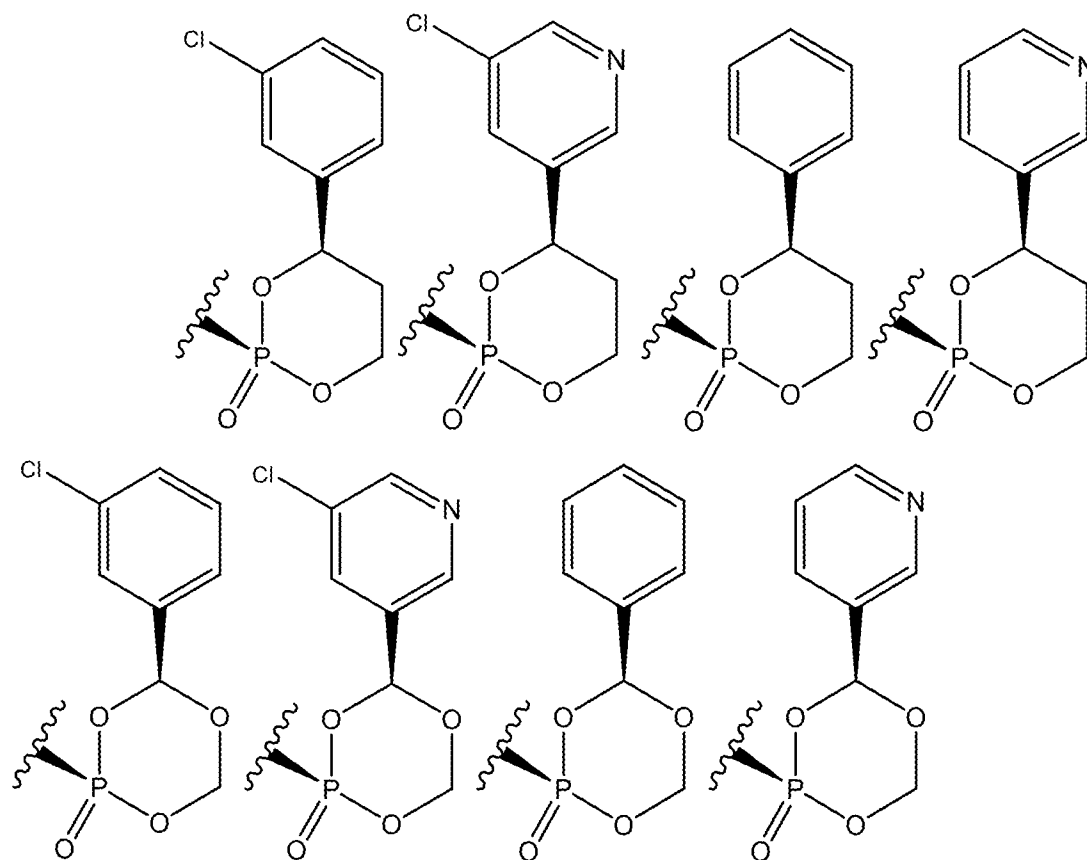
wherein Y is as described for Formulas L and N.

[0166] Further prodrug groups can comprise the following:



wherein Y, W, and W' are as described for formulas L and M.

[0167] Further exemplary prodrug groups can comprise the following moieties:



[0168] Further exemplary phosphorus containing prodrug groups that can be attached to compounds described herein to form a prodrug.

[0169] The groups described here can be attached to a compound described herein at the R^{2c} position of a Z^2 group described herein, although attachment at other positions of the compound described herein is within the scope of this disclosure.

[0170] Compositions, optionally pharmaceutically acceptable compositions can comprise Lac-Phe analogues of Formula I-IV as described herein. Methods of use and the treatment for obesity and secondary disease in subjects in need thereof can comprise administering compositions, optionally pharmaceutically acceptable compositions can comprise Lac-Phe analogues of Formula I-IV as described herein. Methods of synthesis of compounds of Formula I-IV, as well as therapeutically useful salts and prodrug compositions thereof, are described herein.

[0171] **Pharmaceutical compositions**

[0172] The disclosure further provides pharmaceutical compositions comprising a compound described herein. Pharmaceutical compositions described herein can comprise a single compound described herein or more than one compound described herein. Pharmaceutical compositions described herein typically comprise at least one pharmaceutically acceptable excipient (*e.g.*, one or more than one pharmaceutically acceptable excipient).

[0173] Administration and formulation

[0174] The appropriate dosages of the compounds of disclosure comprise therapeutically effective ranges, preferably between 0 and 1,000 mg/Kg in human subjects. In some embodiments, different dosage forms of the compounds of the invention comprise but are not limited to intravenous (IV), intraperitoneal (IP), intramuscular (IM), subcutaneous (SC), transdermic, parenteral and oral dosages form formulations. An “immediate release formulation” is one that has been formulated to allow to act as quickly as possible. Preferred immediate release formulations include, but are not limited to readily dissolvable formulations. A “controlled release formulation” includes a pharmaceutical formulation that has been adapted such that drug release rates and drug release profiles can be matched to physiological and chronotherapeutic requirements or alternatively, has been formulated to effect release of a drug at a programmed rate. Preferred controlled release formulations include, but are not limited to, granules, delayed release granules, hydrogels (synthetic or natural origin), other gelling agents (formulations comprising a polymeric material having at least one active ingredient dispersed therethrough), granules within a matrix, polymeric mixtures, granular masses, and the like.

[0175] A pharmaceutical composition described herein comprises at least one compound selected from compounds described herein. A pharmaceutical composition described herein comprises at least one compound selected from pharmaceutically acceptable salts of compounds described herein. A pharmaceutical composition described herein comprises at least one compound selected from esters of compounds described herein. A pharmaceutical composition described herein comprises at least one compound selected from amides of compounds described herein. A pharmaceutical composition described herein comprises at least one compound selected from active metabolites of compounds described herein. A pharmaceutical composition described herein comprises at least one compound selected from prodrugs of compounds described herein.

[0176] A pharmaceutical composition described herein comprises a compound in any of Tables 1 to 12 or a pharmaceutically acceptable salt, ester, amide active metabolite or prodrug or any of the foregoing.

[0177] The pharmaceutically acceptable excipient includes, but is not limited to, a binder, filler, diluent, disintegrant, wetting agent, lubricant, glidant, coloring agent, dyemigration inhibitor, sweetening agent, flavoring agent or a combination thereof.

[0178] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remains intact after compression. Binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (*e.g.*, STARCH 1500®); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as

acacia, alginic acid, alginates, extract of Irish moss, Panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof.

[0179] Fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder is hydroxypropylcellulose.

[0180] Diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The diluent is lactose monohydrate. The diluent is lactose monohydrate Fast-Flo 316 NF.

[0181] Disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrillin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of disintegrant in the compositions described herein can vary. The disintegrant is croscarmellose sodium. The disintegrant is croscarmellose sodium NF (Ac-Di-Sol).

[0182] Lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The lubricant is magnesium stearate.

[0183] Glidants include colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and talc, including asbestos-free talc.

[0184] Coloring agents include any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof.

[0185] Flavoring agents include natural flavors extracted from plants, such as fruits, and synthetic blends of compounds that provide a pleasant taste sensation, such as peppermint and methyl salicylate.

[0186] Sweetening agents include sucrose, lactose, mannitol, syrups, glycerin, sucralose, and artificial sweeteners, such as saccharin, stevioside (Stevia) and aspartame.

[0187] Emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suspending and dispersing agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether.

[0188] Solvents include but are not limited to glycerin, sorbitol, ethyl alcohol, and syrup.

[0189] Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate.

[0190] Pharmaceutical compositions can be formulated for administration by a variety of means including orally, parenterally, by inhalation spray, topically, or rectally in formulations containing pharmaceutically acceptable carriers, adjuvants and vehicles. The term “parenteral” as used here includes subcutaneous, intravenous, intramuscular, and intraarterial injections with a variety of infusion techniques. Intraarterial and intravenous injection as used herein includes administration through catheters.

[0191] Pharmaceutical compositions can be formulated in accordance with the routine procedures adapted for desired administration route. Accordingly, the compositions described herein can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The compositions described herein can be formulated as a preparation for implantation or injection. Thus, for example, the compositions described herein can be formulated with polymeric or hydrophobic materials (*e.g.*, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives (*e.g.*, as a sparingly soluble salt). The compounds described herein and the compositions described herein can be in powder form for constitution with a vehicle, *e.g.*,

sterile pyrogen-free water, before use. Formulations for each of these methods of administration can be found, for example, in Remington: The Science and Practice of Pharmacy, A. Gennaro, ed., 20th edition, Lippincott, Williams & Wilkins, Philadelphia, PA.

[0192] The compositions described herein can be formulated for oral administration. These compositions can comprise solid, semisolid, gelmatrix or liquid dosage forms. As used herein, oral administration includes buccal, lingual, and sublingual administration. Oral dosage forms include, without limitation, tablets, capsules, pills, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, granules, bulk powders, effervescent or non-effervescent powders or granules, solutions, emulsions, suspensions, solutions, wafers, sprinkles, elixirs, syrups or any combination thereof. The compositions described herein can be formulated for oral administration are in the form of a tablet or a capsule. The composition described herein is in a form of a tablet. The composition described herein is in a form of a capsule. The compound described herein is contained in a capsule.

[0193] The capsules are immediate release capsules. A non-limiting example of a capsule is a CONI-SNAP® hard gelatin capsule.

[0194] The compositions described herein can be in the form of compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenylsalicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which can be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. A film coating can impart the same general characteristics as a sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry coated tablets.

[0195] The coating is a film coating. The film coating comprises Opadry White and simethicone emulsion 30% USP.

[0196] The N-Lactoyl-Phenylalanine (Lac-Phe) compounds described herein can be contained in a tablet. The N-Lactoyl-Phenylalanine (Lac-Phe) compounds described herein can be contained in a compressed tablet. The compounds described herein can be contained in a film-

coated compressed tablet. A pharmaceutical composition described herein can be in the form of film-coated compressed tablet.

[0197] Pharmaceutical compositions described herein can be in the form of soft or hard capsules, which can be made, for example, from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), can comprise two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells can contain a preservative to prevent the growth of microorganisms. Preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein can be encapsulated in a capsule. Liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules can also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[0198] The pharmaceutical compositions described herein can be in liquid or semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion can be a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions can include a pharmaceutically acceptable non-aqueous liquids or solvent, emulsifying agent, and preservative. Suspensions can include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions can include a pharmaceutically acceptable acetal, such as a di-(lower alkyl)acetal of a lower alkyl aldehyde, *e.g.*, acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs can be clear, sweetened, and hydroalcoholic solutions. Syrups can be concentrated aqueous solutions of a sugar, for example, sucrose, and can comprise a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol can be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be measured conveniently for administration.

[0199] The pharmaceutical compositions described herein for oral administration can be also provided in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[0200] The pharmaceutical compositions described herein can be provided as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form.

Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders can include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders can include organic acids and a source of carbon dioxide.

[0201] Coloring and flavoring agents can be used in all of the above dosage forms. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[0202] The pharmaceutical compositions described herein can be formulated as immediate or modified release dosage forms, including delayed-, extended, pulsed-, controlled, targeted-, and programmed-release forms.

[0203] The pharmaceutical compositions described herein comprise a film coating.

[0204] The pharmaceutical compositions described herein can comprise another active ingredient that does not impair the composition's therapeutic or prophylactic efficacy or can comprise a substance that augments or supplements the composition's efficacy.

[0205] The pharmaceutical compositions described herein can be in a modified release or a controlled release dosage form. The compositions described herein can comprise particles exhibiting a particular release profile. For example, the composition described herein can comprise a compound described herein in an immediate release form while also comprising a statin or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof in a modified release form, both compressed into a single tablet. Other combination and modification of release profile can be achieved as understood by one skilled in the art. Examples of modified release dosage forms suited for pharmaceutical compositions of the instant disclosure are described, without limitation, in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500.

[0206] The compositions described herein are a matrix-controlled release dosage form. The release profile of the compound described herein and of the other pharmaceutically active agent is the same or different. Matrix-controlled release dosage forms are described, for example, in Takada *et al* in "Encyclopedia of Controlled Drug Delivery," Vol. 2, Mathiowitz ed., Wiley, 1999.

[0207] The erodible matrix of the matrix-controlled release form comprises chitin, chitosan, dextran, or pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum, or scleroglucan; starches, such as dextrin or

maltodextrin; hydrophilic colloids, such as pectin; phosphatides, such as lecithin; alginates; propylene glycol alginate; gelatin; collagen; cellulose, such as ethyl cellulose (EC), methylcellulose (MEC), carboxymethyl cellulose (CMC), carboxymethyl ethyl cellulose (CMEC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), or ethylhydroxy ethylcellulose (EHEC); polyvinyl pyrrolidone; polyvinyl alcohol; polyvinyl acetate; glycerol fatty acid esters; polyacrylamide; polyacrylic acid; copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®, Rohm America, Inc., Piscataway, NJ); poly(2-hydroxyethyl-methacrylate); polylactides; copolymers of L-glutamic acid and ethyl-L-glutamate; degradable lactic acid-glycolic acid copolymers; poly-D-(-)-3-hydroxybutyric acid; or other acrylic acid derivatives, such as homopolymers and copolymers of butylmethacrylate, methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, or (trimethylaminoethyl)methacrylate chloride; or any combination thereof.

[0208] The pharmaceutical compositions described herein are in a matrix-controlled modified release form comprising a non-erodible matrix. The statin, the compound described herein is dissolved or dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once administered. The non-erodible matrix of the matrix-controlled release form comprises an insoluble polymer, such as polyethylene, polypropylene, polyisoprene, polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated polyethylene, polyvinylchloride, a methyl acrylate-methyl methacrylate copolymer, an ethylene-vinylacetate copolymer, an ethylene/propylene copolymer, an ethylene/ethyl acrylate copolymer, a vinylchloride copolymer with vinyl acetate, a vinylidene chloride, an ethylene or a propylene, an ionomer polyethylene terephthalate, a butyl rubber epichlorohydrin rubber, an ethylene/vinyl alcohol copolymer, an ethylene/vinyl acetate/vinyl alcohol terpolymer, an ethylene/vinyloxyethanol copolymer, a polyvinyl chloride, a plasticized nylon, a plasticized polyethyleneterephthalate, a natural rubber, a silicone rubber, a polydimethylsiloxane, a silicone carbonate copolymer, or a hydrophilic polymer, such as an ethyl cellulose, a cellulose acetate, a crospovidone, or a cross-linked partially hydrolyzed polyvinyl acetate; a fatty compound, such as a carnauba wax, a microcrystalline wax, or a triglyceride; or any combination thereof.

[0209] The compositions described herein that are in a modified release dosage form can be prepared by methods known to those skilled in the art, including direct compression, dry or wet granulation followed by compression, melt-granulation followed by compression.

[0210] The compositions described herein comprise from about 1 mg to about 5000 mg of a compound described herein or any amount ranging from and to these values. The compositions described herein comprise from about 1 mg to about 4000 mg of a compound described herein or any amount ranging from and to these values. The compositions described herein comprise from about 1 mg to about 3000 mg of a compound described herein or any amount ranging from and to these values. The compositions described herein comprise from about 1 mg to about 2000 mg of a compound described herein or any amount ranging from and to these values. The compositions described herein comprise from about 1 mg to about 1000 mg of a compound described herein or any amount ranging from and to these values. The compositions described herein comprise from about 1 mg to about 500 mg of a compound described herein or any amount ranging from and to these values. The compositions described herein comprise from about 1 mg to about 400 mg of a compound described herein or any amount ranging from and to these values. The compositions described herein comprise from about 1 mg to about 200 mg of a compound described herein or any amount ranging from and to these values. The compositions described herein comprise from about 1 mg to about 100 mg of a compound described herein or any amount ranging from and to these values.

[0211] The compositions described herein comprise a compound described herein in an amount that is a molar equivalent to about 1 mg to about 1000 mg of a compound described herein or any amount ranging from and to these values. The compositions described herein comprise a compound described herein in an amount that is a molar equivalent to about 1 mg to about 500 mg of a compound described herein or any amount ranging from and to these values. The compositions described herein comprise a compound described herein in an amount that is a molar equivalent to about 1 mg to about 400 mg of a compound described herein or any amount ranging from and to these values.

[0212] The pharmaceutical compositions described herein comprise a compound described herein in an amount of about 10 wt% to about 99 wt% of the total weight of the composition described herein.

Uses of Compounds described herein: Methods of Treatment

[0213] Compounds described herein are useful for treating diseases such as obesity, dyslipidemia, atherosclerosis, and liver diseases, cachexia (wasting syndrome), obesity secondary diseases such as diabetes, gallbladder disease, hypertension, elevated cholesterol, hyper triglyceride disease, dyslipidemia, non-alcoholic steatohepatitis, type 2 diabetes, coronary artery disease (CAD), coronary heart disease (CHD) stroke, arthritis, infertility, as well as other

diseases. Such diseases include cardiovascular disease, stroke, peripheral vascular disease, dyslipidemia, dyslipoproteinemia, a disorder of glucose metabolism, Alzheimer's Disease, Parkinson's Disease, diabetic nephropathy, diabetic retinopathy, insulin resistance, a metabolic syndrome disorder (*e.g.*, Syndrome X), a peroxisome proliferator activated receptor-associated disorder, septicemia, a thrombotic disorder, obesity, pancreatitis, hypertension, renal disease, cancer, inflammation, an inflammatory muscle disease (*e.g.*, polymyalgia rheumatica, polymyositis, or fibrositis) impotence, gastrointestinal disease, irritable bowel syndrome, inflammatory bowel disease, an inflammatory disorder (*e.g.*, asthma, vasculitis, ulcerative colitis, Crohn's disease, Kawasaki disease, Wegener's granulomatosis, (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), or autoimmune chronic hepatitis), arthritis (*e.g.*, rheumatoid arthritis, juvenile rheumatoid arthritis, or osteoarthritis), osteoporosis, soft tissue rheumatism (*e.g.*, tendonitis), bursitis, a hyperlipidemia (*e.g.*, familial hypercholesterolemia (FH) or familial combined hyperlipidemia (FCH)), a lipoprotein lipase deficiency (*e.g.*, hypertriglyceridemia, hypoalphalipoproteinemia, or hypercholesterolemia), a lipoprotein abnormality associated with diabetes, a lipoprotein abnormality associated with obesity, or a lipoprotein abnormality associated with Alzheimer's Disease.

[0214] Methods for treating or preventing obesity can comprise administering to a subject in need thereof an effective amount of a compound described herein or a composition described herein. The obesity is abdominal obesity. The methods for treating or preventing obesity further comprise promoting weight reduction in the subject.

[0215] Diseases treatable by GLP-1, GLP-1/GIP, opiate antagonists (Bupropion-naltrexone), lipase inhibitors (Orlistat), sympathomimetic amines (Phentermine-topiramate), melanocortin 4 (MC4) receptor agonists (Setmelanotide), and include hypercholesterolemia and cardiovascular disease (CVD), obesity, diabetes, insulin resistance, fatty liver disease, metabolic syndrome. Further diseases treatable include diabetes-related disorders including Type 1 diabetes (insulin-dependent diabetes mellitus, IDDM) and Type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM), impaired glucose tolerance, hyperglycemia, diabetic complications, including, but not limited to atherosclerosis, coronary heart disease, stroke, peripheral vascular disease, nephropathy, hypertension, neuropathy and nephropathy; obesity comorbidities including but not limited to metabolic syndrome, dyslipidemia, Type III dyslipidemia, hypertension, insulin resistance, diabetes (including Type 1 and Type 2 diabetes), coronary artery disease, and heart failure.

[0216] Methods of treating a subject diagnosed with or at risk of a dyslipidemia can comprise to the subject a effective amount of a compound or pharmaceutical composition described herein.

[0217] Methods of treating a subject diagnosed with or at risk of a vascular or cardiovascular disease (*e.g.*, atherosclerosis or hyperlipidemia, such as hypercholesterolemia, homozygous familial hypercholesterolemia, heterozygous familial hypercholesterolemia hypertriglyceridemia, or familial combined hyperlipidemia) can comprise to the subject a effective amount of a compound or pharmaceutical composition described herein.

[0218] Methods of treating a subject diagnosed with or at risk of a liver disease (*e.g.*, liver fibrosis, fatty liver disease, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), or alcoholic steatohepatitis, primary biliary cirrhosis (PBC), or progressive familial intrahepatic cholestasis (PFIC)) comprising administering to the subject a effective amount of a compound or pharmaceutical composition described herein. Treating NAFLD or NASH can prevent cirrhosis and hepatocellular carcinoma, as NAFLD and NASH can precede cirrhosis and hepatocellular carcinoma.

[0219] Exemplary liver diseases that can be treated with a compound described herein include liver fibrosis, fatty liver disease, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) (*e.g.*, noncirrhotic NASH or NASH with cirrhosis), or alcoholic steatohepatitis, primary biliary cirrhosis (PBC), progressive familial intrahepatic cholestasis (PFIC) or hepatocellular adenomas and carcinomas.

[0220] Compounds described herein can be used to reduce or normalize (1) liver histopathology in the presence of steatohepatitis and/or (2) the NAFLD activity score (NAS score).

[0221] Compounds described herein can be used to reduce liver fibrosis associated with NAFLD/NASH.

[0222] Compounds described herein can be used to reduce or normalize at least one of the components of the NAFLD activity score (NAS score), namely, hepatic inflammation, hepatocellular ballooning, fibrosis, steatosis, or a combination thereof.

[0223] Compounds described herein can be used to reduce or normalize lipid hepatic content such as triglycerides, fatty acid, cholesterol, cholesterol esters, or a combination thereof.

[0224] Compounds described herein can be used to reduce or normalize non-invasive imaging biomarkers, such as liver fat content as measured by MRI.

[0225] The liver disorder treatable by compounds described herein involves pathological disruption, inflammation, degeneration, apoptosis, or proliferation of liver cells.

[0226] Compounds described herein can be used to for reduce or normalize expression of inflammatory markers such as tumor necrosis factor alpha (TNF alpha) and/or interleukin 6 (IL-6).

[0227] Compounds described herein can be used to treat or prevent dyslipidemia. The dyslipidemia is hyperlipidemia or an abnormally low concentration of high-density lipoprotein cholesterol (HDL-C) in the subject's blood plasma or blood serum. The term "dyslipidemia" refers to a disorder that leads to or is manifested by an aberrant level of circulating lipids.

[0228] Compounds described herein can be used to restore blood plasma or blood serum concentration of total-cholesterol, low density lipoprotein cholesterol (LDL-C), HDL-C, non-HDL-C or free triglycerides to a normal or recommended concentration or ratio. Accordingly, to the extent that levels of lipids in the blood plasma or blood serum are abnormally high, the compounds described herein or the compositions described herein can be administered to a subject to restore normal levels. Normal levels of lipids are well known to those skilled in the art. For example, normal blood levels of total cholesterol, low density lipoprotein cholesterol (LDL-C), HDL-C, non-HDL-C, free triglycerides and other parameters relating to lipid metabolism can be found at the web site of the American Heart Association, The National Lipid Association and that of the National Cholesterol Education Program of the National Heart, Lung and Blood Institute. A recommended concentration of HDL-C in the blood plasma or the blood serum is above 35 mg/dl. A recommended concentration of LDL-C in the blood plasma or the blood serum is below 100 mg/dl. A recommended LDL-C:HDL-C ratio in the blood plasma or in the blood serum is below 5:1, in some embodiments, 3.5:1. A recommended concentration of free triglycerides in the blood plasma or the blood serum is less than 200 mg/dl.

[0229] Compounds described herein can be used to treat or prevent hyperlipidemia. In some embodiments, hyperlipidemia is hypercholesterolemia, familial hypercholesterolemia, hypertriglyceridemia, or familial combined hyperlipidemia. In some embodiments, hyperlipidemia is characterized by an abnormally reduced or deficient lipoprotein lipase level or activity in the subject's blood plasma or blood serum, or an abnormally high concentration of ketone bodies, lipoprotein(a) cholesterol (Lp(a)-C), low density lipoprotein (LDL), very low density lipoproteins cholesterol (VLDLC) or non-esterified fatty acids (NEFA) in the subject's blood plasma or blood serum. The reduced or deficient lipoprotein lipase level or activity is a result of a lipoprotein lipase mutation. The reduced or deficient lipoprotein lipase level or activity is a result of a mutation in a gene encoding a lipoprotein lipase.

[0230] Non-limiting examples of ketone bodies include acetoacetate, beta-hydroxybutyrate, and acetone. An "abnormally high concentration" of ketone bodies in a subject's blood plasma or blood serum is 1 mg/dL or greater (< 0.1 mmol/L). Methods for reducing an abnormally high concentration of ketone bodies in a subject's blood plasma or blood serum, wherein the concentration is 1 mg/dL or greater. The reducing is to a normal level. The normal level is less

than 1 mg/dL (< 0.1 mmol/L). See Devkota, B. P. *et al.* Medscape emedicine, updated Oct. 30, 2015.

[0231] An “abnormally high concentration” of VLDL-C in a subject’s blood plasma or blood serum is greater than 30 mg/dL (1.7 mmol/L). Compounds described herein can be used to reduce VLDL-C concentration in a subject’s blood plasma or blood serum, wherein the VLDL-C concentration is greater than 30 mg/dL. The reducing is to a normal level. The normal level ranges from 2 mg/dL to 30 mg/dL (0.1 to 1.7 mmol/L).

[0232] An “abnormally high concentration” of NEFA is in a subject’s blood plasma or blood serum in a non-fasting state is 0.9 mM or greater. An “abnormally high concentration” of NEFA in a subject’s blood plasma or blood serum in a fasting state is greater than 1.8 mM at a fasting state. An “abnormally high concentration” of NEFA in a subject’s blood plasma or blood serum at 15-hour fasting is greater than 1.1 mM. An “abnormally high concentration” of NEFA in a subject’s blood plasma or blood serum at 20-hour fasting is greater than 1.3 mM. An “abnormally high concentration” of NEFA in a subject’s blood plasma or blood serum at 15-hour fasting is greater than 1.1 mM. An “abnormally high concentration” of NEFA in a subject’s blood plasma or blood serum at 24-hour fasting is greater than 1.8 mM. Compounds described herein can be used to reduce NEFA concentration in a subject’s blood plasma or blood serum, for example where the subject’s NEFA concentration is greater than 0.9 mM, greater than 1.1 mM, greater than 1.5 mM or greater than 1.8 mM. The reducing is to a normal level. The normal level is 1.8 mM or less, in some embodiments 1.5 mM or less, in some embodiments 1.1 mM or less and in some embodiments 0.9 mM or less. See Horowitz, G. L. *et al.* Medscape emedicine, updated July 25, 2019.

[0233] Compounds described herein can be used to treat or prevent dyslipoproteinemia. The dyslipoproteinemia is characterized by an abnormally high concentration of LDL, apolipoprotein (a) or VLDL in a subject’s blood plasma or blood serum, or an abnormally low concentration of high density lipoprotein (HDL) or lipoprotein lipase in a subject’s blood plasma or blood serum. The abnormally low concentration of the lipoprotein lipase is associated with: a lipoprotein lipase mutation, hypoalphalipoproteinemia, a lipoprotein abnormality associated with diabetes, a lipoprotein abnormality associated with obesity, a lipoprotein abnormality associated with Alzheimer’s disease, or familial combined hyperlipidemia. The term “dyslipoproteinemia” refers to a disorder that leads to or is manifested by an aberrant concentration of circulating lipoproteins in a subject’s blood plasma or blood serum. To the extent that the concentrations of lipoproteins in the blood plasma or blood serum are too high, the compounds described herein or the compositions described herein can be administered to the subject to restore to normal

concentrations of lipoproteins. Conversely, to the extent that the concentrations of lipoproteins in the blood plasma or blood serum are too low, the compounds described herein or the compositions described herein can be administered to the subject to restore to normal concentrations. Normal concentrations of lipoproteins are reported in medical treatises known to those of skill in the art.

[0234] Compounds described herein can be used to treat or prevent a disorder of glucose metabolism. The term “disorder of glucose metabolism” refers to a disorder that leads to or is manifested by aberrant glucose storage and/or utilization. To the extent that indicia of glucose metabolism (*e.g.*, insulin, glucose, or glycated hemoglobin in a subject’s blood plasma or blood serum) are too high, the compounds described herein or the compositions described herein can be administered to a subject to restore to normal levels. Normal indicia of glucose metabolism are reported in medical treatises known to those of skill in the art. *See* US 7,709,682 B2.

[0235] Compounds described herein can be used to reduce an abnormally high concentration of glucose in a subject’s blood plasma or blood serum. An “abnormally high concentration” of glucose in a subject’s blood plasma or blood serum at a fasted state (10-16 hours without eating) is greater than 5.6 mmol/L (100 mg/dL). The reducing is to a normal concentration. The normal concentration of glucose is less than 5.6 mmol/L at fasted state. A fasted glucose blood plasma or blood serum concentration in the range of 5.6 mmol/L to 6 mmol/L (100–109 mg/dL) may indicate prediabetes. A fasted glucose blood plasma or blood serum concentration in the range of 6.1 mmol/L to 6.9 mmol/L (110–125 mg/dL) can indicate diabetes. A fasted glucose blood plasma or blood serum concentration of 7 mmol/L (126 mg/dL) and above indicates diabetes.

[0236] The abnormally high concentration of glucose in a subject’s blood plasma or blood serum is measured in a glucose tolerance test (GTT).

[0237] An “abnormally high concentration” of glucose in a subject’s blood plasma or blood serum in a one-hour GTT is greater than 10 mmol/L (180 mg/dL). The reducing is to a normal concentration. The normal concentration in a one-hour GTT is less than 10 mmol/L (180 mg/dL).

[0238] An “abnormally high concentration” of glucose in a subject’s blood plasma or blood serum in a two-hour GTT with 75 g intake is greater than 7.8 mmol/L (140 mg/dL), which indicates hyperglycemia. The reducing is to a normal concentration. The normal concentration in two-hour GTT with 75 g intake is less than 7.8 mmol/L (140 mg/dL). A glucose concentration in a subject’s blood plasma or blood serum between 7.8 mmol/L (140 mg/dL) and 11.1 mmol/L (200 mg/dL) in two-hour GTT with 75 g intake indicates impaired glucose tolerance. A glucose concentration above 11.1 mmol/L in two hour GTT with 75 g intake indicates diabetes.

[0239] Compounds described herein can be used to increase abnormally low glucose metabolism in a subject, wherein the subject's glucose concentration in the subject's blood plasma or blood serum is greater than 7.8 mmol/L (140 mg/dL) in a two-hour GTT. Compounds described herein can be used to treat or prevent a disorder of glucose metabolism in a subject, wherein the subject's glucose concentration in the subject's blood plasma or blood serum is in the range of 7.8 mmol/L (140 mg/dL) to 11.1 mmol/L (200 mg/dL) in a two-hour GTT. Compounds described herein can be used to treat or prevent a disorder of glucose metabolism in a subject, wherein the subject's glucose concentration in the subject's blood plasma or blood serum is greater than 11.1 mmol/L (200 mg/dL) in a two-hour GTT.

[0240] Compounds described herein can be used to reduce an abnormally high level of HbA_{1c} in a subject's blood plasma or blood serum. An "abnormally high level" of hemoglobin A_{1c} (HbA_{1c}) in a subject's blood plasma or blood serum is 6.5% or greater (expressed in % NGSP units). The reducing is to a normal level. The normal levels of HbA_{1c} is in the range of about 4% to about 5.9%. Compounds described herein can be used to reduce HbA_{1c} level in a subject's blood plasma or blood serum, wherein the HbA_{1c} level is greater than 7%, greater than 8%, or greater than 9%. See Horowitz, G. L. *et al.* Medscape emedicine, updated July 25, 2019.

[0241] Compounds described herein can be used to increase abnormally low glucose metabolism in a subject, wherein the subject's HbA_{1c} level is 6.5% or greater and the subject's fasting glucose concentration is 126 mg/dL or greater (≥ 7.0 mmol/L), in the subject's blood plasma or blood serum. See Selvin, E. *et al.* *Ann Intern Med.* Published online June 18, 2018.

[0242] Compounds described herein can be used to treat or prevent a disorder of glucose metabolism in a subject, wherein the subject has HbA_{1c} greater than or equal to 6.5%. Compounds described herein can be used to treat or prevent a disorder of glucose metabolism in a subject, wherein the subject has HbA_{1c} greater than or equal to 6.5% and fasting glucose concentration greater than or equal to 126 mg/dL (7.0 mmol/L) in the subject's blood plasma or blood serum.

[0243] Compounds described herein can be used to reduce an abnormally high concentration of glucose in a subject's blood plasma or blood serum, for example where the subject is pregnant. An "abnormally high concentration" of glucose in a pregnant subject's blood plasma or blood serum at fasted state is greater than 5.3 mmol/L (95 mg/dL).

[0244] Compounds described herein can be used to reduce an abnormally high concentration of glucose in a subject's blood plasma or blood serum. A method of reducing an abnormally high concentration of glucose in a subject's blood plasma or blood serum can comprise administering to a subject in need thereof (i) a glucose solution as part of a two-step gestational diabetes test

and (ii) an effective amount of a compound described herein or a composition described herein. An “abnormally high concentration” of glucose in a subject’s blood plasma or blood serum at 1 hour after drinking the glucose solution in a two-step gestational diabetes test is greater than 10 mmol/L (180 mg/dL). In the twostep procedure, the first step is a 50 g glucose dose. If it results in a blood glucose level of more than 7.8 mmol/L (140 mg/dL), it is followed by a 100 g glucose dose. An “abnormally high concentration: of glucose in a subject’s blood plasma or blood serum at 2 hour after drinking the glucose solution in a two-step gestational diabetes test is greater than 8.6 mmol/L (155 mg/dL). An “abnormally high concentration: of glucose in a subject’s blood plasma or blood serum at 3 hour after drinking the glucose solution in a twostep gestational diabetes test is greater than 7.8 mmol/L (140 mg/dL).

[0245] Compounds described herein can be used to treat or prevent a disorder of glucose metabolism in a subject having impaired glucose tolerance. Compounds described herein can be used to treat or prevent a disorder of glucose metabolism in a subject having diabetes.

Compounds described herein can be used to treat or prevent a disorder of glucose metabolism in a subject having confirmed undiagnosed diabetes. Compounds described herein can be used to treat or prevent a disorder of glucose metabolism in a subject having gestational diabetes.

[0246] Compounds described herein can be used to reduce abnormally high concentration of insulin in a subject’s blood plasma or blood serum. An “abnormally high concentration” of insulin in a subject’s blood plasma or blood serum at a fasted state is greater than 25 mIU/L (>174 pmol/L). The reducing is to a normal concentration. The normal concentration of insulin in a subject’s blood plasma or blood serum at a fasted state is less than 25 mIU/L (<174 pmol/L). See Buppajarntham, S. *et al.* Medscape emedicine, updated Jan. 2, 2019.

[0247] Compounds described herein can be used to reduce abnormally high concentration of insulin in a subject’s blood plasma or blood serum. A method for reducing abnormally high concentration of insulin in a subject’s blood plasma or blood serum can comprise administering to a subject in need thereof an effective amount of a compound described herein or a composition described herein. The method further comprises administering glucose to the subject. The method does not comprise administering glucose to the subject. The subject is in a fasted state.

[0248] The subject has an abnormally high concentration of insulin in the subject’s blood plasma or blood glucose at 30 minutes after glucose administration. An “abnormally high concentration” of insulin in a subject’s blood plasma or blood serum at 30 minutes after glucose administration is greater than 230 mIU/L (>1597 pmol/L). The reducing is to a normal concentration. The normal concentration of insulin in a subject’s blood plasma or blood serum at

30 minutes after glucose administration is in the range of about 30 mIU/L to about 230 mIU/L (208-1597 pmol/L). See Buppajarntham, 2019.

[0249] The subject has an abnormally concentration of insulin in the subject's blood plasma or blood serum at 1 hour after glucose administration. An "abnormally high concentration" of insulin in a subject's blood plasma or blood serum at 1 hour after glucose administration is greater than 276 mIU/L (>1917 pmol/L). Methods for reducing abnormally high concentration of insulin in a subject's blood plasma or blood serum can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. The reducing is to a normal concentration. The normal concentration of insulin in a subject's blood plasma or blood serum at 1 hour after glucose administration is in the range of about 18 mIU/L to about 276 mIU/L (125-1917 pmol/L). See Buppajarntham, 2019.

[0250] The subject has an abnormally concentration of insulin in the subject's blood plasma or blood glucose at 2 hours after glucose administration. An "abnormally high concentration" of insulin in a subject's blood plasma or blood serum at 2 hour after glucose administration is greater than 166 mIU/L (>1153 pmol/L). Methods for reducing an abnormally high concentration of insulin in a subject's blood plasma or blood serum can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. The normal concentration of insulin in a subject's blood plasma or blood serum at 2 hours after glucose administration is in the range of about 16 mIU/L to about 166 mIU/L (111-1153 pmol/L). See Buppajarntham, 2019.

[0251] The subject has an abnormally concentration of insulin in the subject's blood plasma or blood glucose at 3 hours after glucose administration. An "abnormally high concentration" of insulin in a subject's blood plasma or blood serum at 3 hours after glucose administration is greater than 25 mIU/L (> 174 pmol/L). Methods for reducing an abnormally high concentration of insulin in a subject's blood plasma or blood serum can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. The normal concentration of insulin in a subject's blood plasma or blood serum at 3 hours or later after glucose administration is less than 25 mIU/L (< 174 pmol/L). See Buppajarntham, 2019.

[0252] Compounds described herein can be used to treat or prevent a disorder of glucose metabolism in a subject, wherein the subject has insulin concentration in the subject's blood plasma or blood serum above 25 mIU/L at a fasted state or after 3 hours after glucose administration. See Buppajarntham, 2019.

[0253] The disorder of glucose metabolism is an impaired glucose tolerance; an insulin resistance; an insulin resistance-related breast, colon or prostate cancer; diabetes; pancreatitis;

hypertension; polycystic ovarian disease; or an abnormally high concentration of blood insulin or glucose in the subject's blood plasma or blood serum. The diabetes is non-insulin dependent diabetes mellitus (NIDDM), insulin dependent diabetes mellitus (IDDM), gestational diabetes mellitus (GDM), or maturity onset diabetes of the young (MODY).

[0254] Compounds described herein can be used to treat or prevent a metabolic syndrome (Syndrome X). Compounds described herein can be used to treat or prevent a symptom of a metabolic syndrome (Syndrome X). The symptom is impaired glucose tolerance, hyper tension, dyslipidemia, or dyslipoproteinemia.

[0255] Compounds described herein can be used to treat or prevent a vascular disease or cardiovascular disease. The term "cardiovascular disease" refers to a disease of the heart or circulatory system. The vascular disease or the cardiovascular disease is a peripheral vascular disease, a coronary heart disease, stroke, restenosis, arteriosclerosis, ischemia, an endothelium dysfunction, an ischemia-reperfusion injury, a myocardial infarction, or a cerebral infarction.

[0256] The subject is a male subject. An "abnormally high concentration" of HDL in a male subject is greater than 75 mg/dL.

[0257] The subject is a female subject. An "abnormally high concentration" of HDL for a female subject is greater than 90 mg/dL.

[0258] Compounds described herein can be used to reduce an abnormally high concentration of HDL in a subject's blood plasma or blood serum. The reducing is to a normal concentration. The normal concentration for a male subject is less than 75 mg/dL. The normal concentration for a female subject is less than 90 mg/dL. Compounds described herein can be used to treat or prevent a PPAR-associated disorder in a male subject, wherein the subject has HDL concentration in the subject's blood plasma or blood serum greater than 75 mg/dL. Compounds described herein can be used to treat or prevent a PPAR-associated disorder in a female subject, wherein the subject has HDL concentration in the subject's blood plasma or blood serum greater than 90 mg/dL. See Hassan, M. et. al., 2016, Glob Cardiol Sci Pract. 2016(4): e201634.

[0259] Compounds described herein can be used to treat a muscle mass disorder. The muscle mass disorder is cachexia, cartilage degeneration, cerebral palsy, compartment syndrome, critical illness myopathy, inclusion body myositis, muscular atrophy (disuse), sarcopenia, steroid myopathy, or systemic lupus erythematosus.

[0260] Compounds described herein can be used to treat a metabolic disease. The metabolic disease is hyperlipidemia, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, HDL hypocholesterolemia, LDL hypercholesterolemia, HDL noncholesterolemia, VLDL hyperproteinemia, dyslipoproteinemia, apolipoprotein A-I hypoproteinemia, atherosclerosis, a

disease of arterial sclerosis, a disease of cardiovascular system, cerebrovascular disease, peripheral circulatory disease, metabolic syndrome, syndrome X, obesity, diabetes, type I diabetes, type II diabetes, hyperglycemia, insulin resistance, impaired glucose tolerance, hyperinsulinism, a diabetic complication, cardiac insufficiency, cardiac infarction, cardiomyopathy, hypertension, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), a thrombus, Alzheimer disease, a neurodegenerative disease, a demyelinating disease, multiple sclerosis, adrenal leukodystrophy, dermatitis, psoriasis, acne, skin aging, trichosis, inflammation, arthritis, asthma, hypersensitive intestine syndrome, ulcerative colitis, Crohn's disease, or pancreatitis.

[0261] Methods for treating or preventing diabetic nephropathy can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. The methods for treating or preventing diabetic nephropathy further comprise treating or preventing a kidney disease that develops as a result of diabetes mellitus. Methods for treating or preventing diabetes mellitus can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein.

[0262] Methods for treating or preventing diabetic retinopathy can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. The methods for treating or preventing diabetic retinopathy result in treating or preventing a complication of diabetes that can lead to or cause blindness.

[0263] Methods for treating or preventing a cerebrovascular disease can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. The cerebrovascular disease is cerebral ischemia.

[0264] Methods for treating or preventing hypertension can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein.

[0265] Methods for treating or preventing an inflammatory disease can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein.

[0266] Methods for treating or preventing cholestasis can comprise to a subject in need thereof an effective amount of the compound described herein or the composition described herein.

[0267] The cholestasis is intrahepatic cholestatic disease or extrahepatic cholestatic disease. The intrahepatic cholestatic disease is primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), progressive familial intrahepatic cholestasis (PFIC), or Alagille syndrome (AS). The methods for treating or preventing intrahepatic cholestatic disease result in preventing

or reducing the risk of developing an intrahepatic cholestatic disease, *e.g.*, causing the clinical symptoms of an intra hepatic cholestatic disease to not develop in a subject who may be predisposed to an intrahepatic cholestatic disease by who does not yet experience or display symptoms of the intrahepatic cholestatic disease (*i.e.*, prophylaxis). The methods for treating or preventing intrahepatic cholestatic disease comprise inhibiting an intrahepatic cholestatic disease, *e.g.*, arresting or reducing the development of the intrahepatic cholestatic disease or reducing the number, frequency, duration or severity of one or more of its clinical symptoms.

[0268] Methods for treating or preventing hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, or dyslipidemia can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. The hypercholesterolemia is homozygous or heterozygous familial hypercholesterolemia.

[0269] Methods for treating a subject having or preventing a subject from having an abnormally high concentration in a subject's blood plasma or blood serum of high low-density lipoprotein (LDL), apolipoprotein B (apo B), lipoprotein(a) (Lp(a)), apolipoprotein (a), or very low-density lipoprotein (VLDL) can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein.

[0270] An "abnormally high concentration" of lipoprotein-cholesterol can depend on the number of risk factors and whether the treatment is for a primary or a secondary prevention. As used herein a "primary prevention" refers to a treatment aimed to avoid a subject developing or getting a disease or a condition. As used herein a "secondary prevention" refers to a treatment aimed to detect a disease or a condition early and prevent the disease or condition from getting worse or advancing. Recommended lipoprotein-cholesterol concentrations can be found in guidelines published by the National Lipid Association or by the National Institute of Health National Heart, Lung, and Blood Institute such as the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III Final Report), 2002. The ATP III Final Report is hereby incorporated by reference in its entirety for all purposes.

[0271] Methods for reducing an abnormally high concentration of apo B in a subject's blood plasma or blood serum can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. An "abnormally high concentration" of apo B in a subject's blood plasma or blood serum is greater than 130 mg/dL. The reducing is to a normal concentration. The normal concentration of apo B in a subject's blood plasma or blood serum is less than 130 mg/dL. The subject is a male subject. The subject is

a female subject. Methods for treating a subject with apo B blood plasma or blood serum concentration of greater than 130 mg/dL. Methods for treating a subject with apo B blood plasma or blood serum concentration of greater than 130 mg/dL, when the subject is at low risk of coronary heart disease (CHD) having 0-1 CHD risk factors.

[0272] Compounds described herein can be used to treat a subject with apo B blood plasma or blood serum concentration of greater than 110 mg/dL, when the subject is at moderate risk of CHD having 2 or more CHD risk factors. An “abnormally high concentration” of apo B in a subject’s blood plasma or blood serum is greater than 110 mg/dL. The subject has 2 or more CHD risk factors. Compounds described herein can be used to treat a subject with apo B blood plasma or blood serum concentration of greater than 90 mg/dL, when the subject has a CHD or a CHD risk equivalent.

[0273] Methods for reducing an abnormally high concentration of Lp(a) in a subject’s blood plasma or blood serum can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. An “abnormally high concentration” of Lp(a) in a subject’s blood plasma or blood serum is greater than 10 mg/dL. The abnormally high concentration of Lp(a) is associated with an increase in cardiovascular risk. The reducing is to a normal concentration. The normal concentration of Lp(a) in a subject’s blood plasma or blood serum is less than 10 mg/dL. The normal concentration of Lp(a) in a subject’s blood plasma or blood serum is less than 50 mg/dL (*See*, Banach, M. J Am Heart Assoc. 2016 Apr; 5(4): e003597). Methods for treating a subject with Lp(a) blood plasma concentration of greater than 50 mg/dL can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein.

[0274] Methods for treating a subject having or preventing a subject from having an abnormally high apo B/apo A-I ratio in a subject’s blood plasma or blood serum can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. Methods for reducing an abnormally high apo B/apo A-I ratio in a subject’s blood plasma or blood serum can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. An “abnormally high” apo B/apo A-I ratio in a subject’s blood plasma or blood serum is greater than 0.9. The reducing is to a normal level. A normal apo B/apo A-I ratio in a subject’s blood plasma or blood serum is less than 0.9. The normal apo B/apo A-I ratio in a subject’s blood plasma or blood serum is less than 0.7. The subject has an apo B/apo A-I ratio in a subject’s blood plasma or blood serum of greater than 0.9. The subject has an apo B/apo A-I ratio in a subject’s blood plasma or blood serum of greater than 0.7. See Walldius, G. et al. 2006, J Intern Med. 259(5):493-519.

[0275] A male subject having an apo B/apo A-I ratio in the male subject's blood plasma or blood serum of greater than 0.7 is considered for a secondary prevention treatment. A female subject having an apo B/apo A-I ratio in the female subject's blood plasma or blood serum of greater than 0.6 is considered for a secondary prevention treatment. The subject is a male subject and has an apo B/apo A-I ratio in the subject's blood plasma or blood serum of greater than 0.7. The subject is a female subject and has an apo B/apo A-I ratio in the subject's blood plasma or blood serum of greater than 0.6. See Walldius, 2006.

[0276] Methods for treating a subject having or preventing a subject from having an abnormally low concentration in a subject's blood plasma or blood serum of high-density lipoprotein (HDL) can comprise to a subject in need thereof an effective amount of the compound described herein or the composition described herein.

[0277] Methods for treating a subject having or preventing a subject from having an abnormally reduced or deficient lipoprotein lipase concentration or activity in a subject's blood plasma or blood serum can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. The reduced or deficient lipoprotein lipase level or activity is a result of a lipoprotein lipase mutation. The reduced or deficient lipoprotein lipase level or activity is a result of a mutation in a gene encoding a lipoprotein lipase.

[0278] Methods for elevating an abnormally low concentration of lipoprotein lipase in a subject's blood plasma or blood serum can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. An "abnormally reduced concentration" of lipoprotein lipase in a subject's blood serum is less than 46 ng/mL. The subject has an increased risk for future coronary artery disease. The elevating is to a normal concentration. The normal concentration of lipoprotein lipase in a subject's blood serum is greater than 46 ng/mL. Methods for treating a subject with lipoprotein lipase blood plasma or blood serum concentration of less than 46 ng/mL can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. See Rip, J. *et al.* *Arterioscler Thromb Vasc Biol.* 2006 Mar;26(3):637-42. Epub 2005 Dec 22.

[0279] Methods for reducing in a subject's blood plasma or blood serum an abnormally high concentration of triglyceride, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), non-high-density lipoprotein cholesterol, (nonHDL-C), lipoprotein(a) (Lp(a)), apolipoprotein B, HDL/(VLDL+LDL) ratio, apolipoprotein C-II (apo C-II) or apolipoprotein C-III (apo C-III) can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein.

[0280] An “abnormally high concentration” of triglyceride in a subject’s blood serum is greater than 150 mg/dL. The reducing is to a normal concentration. The normal concentration of triglyceride in a subject’s blood serum is less than 150 mg/dL. Methods for reducing a subject’s blood serum triglyceride concentration, where the subject has a blood serum triglyceride concentration greater than or equal to 200 mg/dL. Methods for reducing a subject’s blood serum triglyceride concentration, where the subject has a blood serum triglyceride concentration greater than or equal to 500 mg/dL.

[0281] An “abnormally high concentration” of LDL-C in a subject’s blood plasma or blood serum for primary prevention is greater than 100 mg/dL. An “abnormally high concentration” of LDL-C in a subject’s blood plasma or blood serum for secondary prevention in a subject with risk factors is greater than 70 mg/dL. The reducing is to a normal concentration. The normal concentration of LDL-C in a subject’s blood plasma or blood serum is less than 100 mg/dL, wherein the subject is being considered for primary prevention. The normal concentration of LDL-C in a subject’s blood plasma or blood serum is less than 70 mg/dL. The subject has risk factors and is being considered for secondary prevention. See Walldius, 2006.

[0282] An “abnormally high concentration” of apo C-III concentration in a subject’s blood plasma or blood serum is greater than 7.87 mg/dL. The reducing is to a normal concentration. The normal concentration of apo C-III concentration in a subject’s blood plasma or blood serum is less than 7.87 mg/dL. Methods for treating a subject, where the subject has an apo C-III blood plasma or blood serum concentration greater than 8 mg/dL. Methods for treating a subject, where the subject has an apo C-III blood plasma or blood serum concentration greater than 7.9 mg/dL. Methods for treating a subject, where the subject has an apo C-III blood plasma or blood serum concentration greater than 7.87 mg/dL. The abnormally high concentration of apo C-III is associated with high risk of coronary artery disease. See Capelleveen *et al.* Arterioscler Thromb Vasc Biol. 2017 Jun; 37(6): 1206– 1212.

[0283] Methods for reducing in a subject’s blood plasma or blood serum an abnormally high LDL-C/HDL-C ratio can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein.

[0284] An “abnormally high ratio” of LDL-C/HDL-C in a male subject’s blood plasma or blood serum for primary prevention is greater than 3.0. The reducing is to a normal ratio. The normal ratio of LDL-C/HDL-C in a male subject’s blood plasma or blood serum is less than 3.0, wherein the subject is being considered for primary prevention. Methods for treating a male subject with an LDL-C/HDL-C ratio in a subject’s blood plasma or blood serum of greater than 3.0. In some embodiment, the method is for primary prevention.

[0285] Methods for reducing in a subject's blood plasma or blood serum an abnormally high concentration of non-HDL-C can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein.

[0286] An "abnormally high concentration" of non-HDL-C in a subject's blood plasma or blood serum is greater than 190 mg/dL. The reducing is to a normal concentration. The normal concentration of non-HDL-C in a subject's blood plasma or blood serum is less than 190 mg/dL. The subject has 0-1 CHD risk factors. Methods for reducing a subject's non-HDL-C concentration in the subject's blood plasma or blood serum, wherein the non-HDL-C concentration is greater than 190 mg/dL. The subject has 0-1 CHD risk factors.

[0287] An "abnormally high concentration" of non-HDL-C in a subject's blood plasma or blood serum is greater than 160 mg/dL. The subject has 2 or more CHD risk factors. The reducing is to a normal concentration. The normal concentration of non-HDL-C in a subject's blood plasma or blood serum is less than 160 mg/dL. In some embodiment, the subject has 2 or more CHD risk factors. Methods for reducing a subject's non-HDL-C concentration in the subject's blood plasma or blood serum, wherein the subject's non-HDL-C concentration is greater than 160 mg/dL. The subject has 2 or more CHD risk factors. See Walldius, 2006.

[0288] Methods for elevating in a subject's blood plasma or blood serum an abnormally low concentration of a high-density lipoprotein (HDL)-associated protein, HDLcholesterol (HDL-C), apolipoprotein A-I, or apolipoprotein E can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. The HDL-associated protein is apolipoprotein A-I (apo A-I), apolipoprotein A-II (apo A-II), apolipoprotein A-IV (apo A-IV) or apolipoprotein E (apo E).

[0289] An "abnormally low concentration" of HDL-C in a subject's blood plasma or blood serum is less than 40 mg/dL. The elevating is to a normal concentration. The normal concentration of HDL-C in a subject's blood plasma or blood serum is greater than 40 mg/dL. Methods for elevating HDL-C concentration in a subject's blood plasma or blood serum, where the subject's HDL-C concentration is less than 40 mg/dL. The subject is a male subject. The subject is a female subject.

[0290] Compounds described herein can be used to elevate HDL-C concentration in a subject's blood plasma or blood serum to 45 mg/dL or greater, where the subject's HDL-C concentration in a subject's blood plasma or blood serum is less than 40 mg/dL. Compounds described herein can be used to elevate HDL-C concentration in a subject's blood plasma or blood serum to 50 mg/dL or greater, where the subject's HDL-C concentration in a subject's blood plasma or blood serum is less than 40 mg/dL. Compounds described herein can be used to

elevate HDL-C concentration in a subject's blood plasma or blood serum to 55 mg/dL or greater, where the subject's HDL-C concentration in a subject's blood plasma or blood serum is less than 40 mg/dL.

[0291] Compounds described herein can be used to elevate HDL-C concentration in a male/female subject's blood plasma or blood serum to 50 mg/dL or greater, where the subject's HDLC concentration in a subject's blood plasma or blood serum is less than 45 mg/dL.

Compounds described herein can be used to elevate HDL-C concentration in a female subject's blood plasma or blood serum to 50 mg/dL or greater, where the subject's HDL-C concentration in a subject's blood plasma or blood serum is less than 50 mg/dL. Compounds described herein can be used to elevate HDL-C concentration in a female subject's blood plasma or blood serum to 55 mg/dL or greater, where the subject's HDL-C concentration in a subject's blood plasma or blood serum is less than 50 mg/dL.

[0292] Methods for promoting clearance of triglyceride from a subject's blood plasma or blood serum can comprise to a subject in need thereof an effective amount of the compound described herein or the composition described herein.

[0293] Methods for increasing an abnormally low glucose metabolism or increasing an abnormally low lipid metabolism in a subject can comprise to a subject in need thereof an effective amount of a compound described herein or a composition described herein. The method for increasing an abnormally low glucose metabolism increases insulin sensitivity or oxygen consumption in a subject. The method for increasing an abnormally low glucose metabolism reduces blood insulin, blood glucose, or glycated hemoglobin in a subject's blood plasma or blood serum. The methods for increasing an abnormally low lipid metabolism reduces a concentration of LDL or free triglyceride in a subject's blood plasma or blood serum, or inhibits saponified or non-saponified fatty acid synthesis.

[0294] A subject with abnormally low glucose metabolism has an abnormally high concentration of glucose or hemoglobin (Hb) in the subject's blood plasma or blood serum. Methods for reducing an abnormally high concentration of glucose or hemoglobin in a subject's blood plasma or blood serum. The method increases abnormally low glucose metabolism. An "abnormally high concentration" of glucose in a subject's blood plasma or blood serum in a two-hour GTT is greater than 7.8 mmol/L (140 mg/dL). In some embodiments, reducing is to a normal concentration. The normal concentration of glucose in a subject's blood plasma or blood serum in a two hour GTT is less than 7.8 mmol/L (140 mg/dL). Methods for increasing abnormally low glucose metabolism in a subject's blood plasma or blood serum, where the subject's glucose concentration in the subject's blood plasma or blood serum in a two-hour GTT

is greater than 7.8 mmol/L (140 mg/dL). Methods for increasing abnormally low glucose metabolism in a subject, where the subject's glucose concentration in the subject's blood plasma or blood serum in a two-hour GTT ranges from 7.8 mmol/L (140 mg/dL) to 11.1 mmol/L (200 mg/dL). Methods for increasing abnormally low glucose metabolism in a subject, where the subject's glucose concentration in the subject's blood plasma or blood serum in a two-hour GTT is above 11.1 mmol/L (200 mg/dL).

[0295] Methods for increasing abnormally low glucose metabolism in a subject, where the subject has impaired glucose tolerance. Methods for increasing abnormally low glucose metabolism in a subject, where the subject has diabetes. Methods for increasing abnormally low glucose metabolism in a subject, where the subject has gestational diabetes.

[0296] A low lipid metabolism can be characterized by dyslipidemia (using the LDL-C, TGs, nonHDL-cholesterol, apo B, apo C-III or apo C-II values) but also with elevated concentration of transaminases. The subject having a low lipid metabolism also has dyslipidemia.

[0297] Methods for reducing fat content of meat in livestock can comprise to livestock an effective amount of a compound described herein or a composition described herein.

[0298] Compounds described herein or the compositions described herein can be administered according to an administration regimen comprising hourly, daily, weekly, or monthly administration. The compounds and formulations of the present disclosure can be administered, for example, three times a day, twice a day or once a day. The compounds and compositions of the present disclosure can be administered with food or without food. An appropriate length of the treatment, dosages, and route of administration can be determined and/or adjusted by a physician.

[0299] The subject can be a mammal.

[0300] The subject can be a human subject.

[0301] The subject can be a pediatric subject.

[0302] In the methods described herein, a compound described herein can be as reference compound, for example to assess one or more biological activities of another compound (*e.g.*, an enantiomer of the reference compound) or to improve a structure-activity relationship algorithm.

[0303] Compounds described herein and the compositions described herein can be used as inhibitors or activators in preclinical models to study metabolic routes or screen other compounds. For instance, identification of redundant pathways can be identified after administration of compounds described herein.

[0304] Compounds described herein and the compositions described herein can be used as diagnostic agents. For example, the compounds and compositions can be used for molecular

imaging when a radionuclide is included in their structure (*e.g.*, ^{18}F , ^{76}Br , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{15}O , ^{13}C , ^{14}C or ^{15}N).

[0305] The compounds described herein can be used in combination with antidiabetic drugs such as alpha-glucosidase inhibitors (*e.g.*, acarbose, miglitol), amylin analogs (*e.g.*, pramlintide) dipeptidyl peptidase 4 inhibitors (*e.g.*, alogliptan, linagliptan, saxagliptin, sitagliptin), incretin mimetics (*e.g.*, albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, tirzepatide, retatrutide), insulin, meglitinides (*e.g.*, nateglinide, repaglinide), non-sulfonylureas (*e.g.*, metformin, imeglimin) SGLT-2 inhibitors (*e.g.*, canagliflozin, dapagliflozin, empagliflozin), sulfonylureas (*e.g.*, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide) and thiazolidinediones (*e.g.*, rosiglitazone, pioglitazone).

[0306] The compounds described herein can be used in combination with a lipid lowering drug, a statin, a cholesterol absorption inhibitor, an antibody against PCSK9, an siRNA PCSK9, an anti-fibrotic agent, a thyroid hormone, a selective thyroid receptor- β agonist, apoptosis signal-regulating kinase 1 (ASK1) inhibitor, acetyl-CoA carboxylase (ACC) inhibitor, an integrin antagonist, a Semicarbazide Sensitive Amine Oxidase (SSAO) inhibitor, also known as Vascular Adhesion Protein-1 (VAP-1) inhibitor, a fibroblast growth factor mimetic 21 (FGF21), a Fatty acid synthase inhibitor, a non-steroidal Farnesoid X receptor (FXR) agonist, a long hydrocarbon chain diacid (*e.g.*, a pantothenic acid analog) such as bempedoic acid.

[0307] The lipid lowering drug is gemfibrozil, fenofibrate, bezafibrate, clofibrate, ciprofibrate, clinofibrate, etofylline, pirifibrate, simfibrate, tocofibrate, or pemafibrate. The lipid lowering drug is gemfibrozil, fenofibrate, bezafibrate, or pemafibrate.

[0308] In some embodiments, statin is atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin, mevastatin, dalvastatin, dihydrocompactin, or cerivastatin, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, statin is atorvastatin, simvastatin, pravastatin or rosuvastatin, or a pharmaceutically acceptable salt or solvate thereof.

[0309] The cholesterol absorption inhibitor is ezetimibe.

EXAMPLES

EXAMPLE 1

N-Lactoyl-Phenylalanine (Lac-Phe) Analog Compounds

[0310] Exemplary N-Lactoyl-Phenylalanine (Lac-Phe) compounds described herein are listed in Tables 1-8. Pharmaceutically acceptable salts, esters, amides, and metabolites of compounds listed in Tables 1-8 and prodrugs of the compounds of Tables 1-8 can be used in methods of treating obesity.

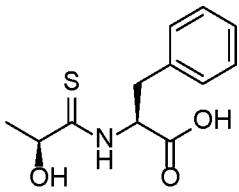
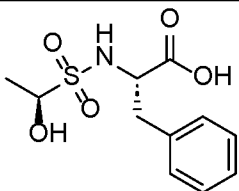
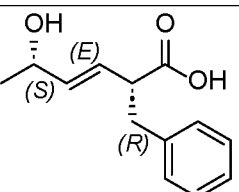
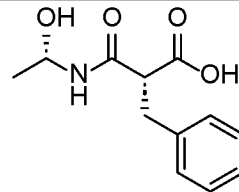
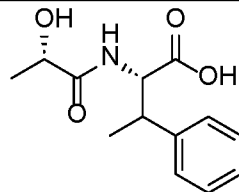
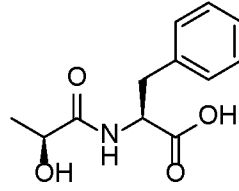
Table 1 - Compounds of Formula I-A (amide bond bio-isosteres)	
Structure	Name
	((<i>S</i>)-2-hydroxypropanethioyl)- <i>L</i> -phenylalanine
	(((<i>R</i>)-1-hydroxyethyl)sulfonyl)- <i>L</i> -phenylalanine
	(2 <i>R</i> ,5 <i>S</i> , <i>E</i>)-2-benzyl-5-hydroxyhex-3-enoic acid
	(<i>R</i>)-2-benzyl-3-(((<i>S</i>)-1-hydroxyethyl)amino)-3-oxopropanoic acid

Table 2 - Compounds of Formula II-A (Phenylalanine bio-isosteres and substitutions)	
Structure	Name
	(2 <i>S</i>)-2-(((<i>S</i>)-2-hydroxypropanamido)-3-phenylbutanoic acid
	(<i>S</i>)-3-(cyclopenta-2,4-dien-1-yl)-2-(((<i>S</i>)-2-hydroxypropanamido)propanoic acid

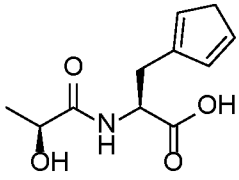
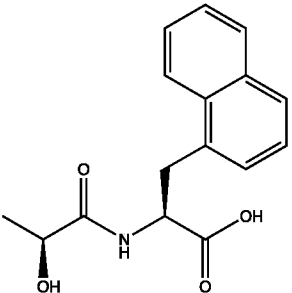
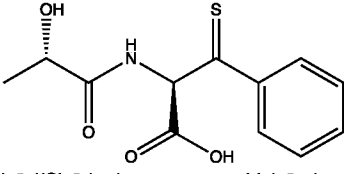
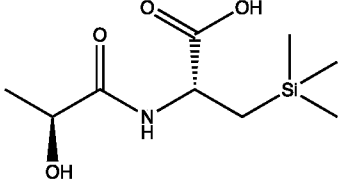
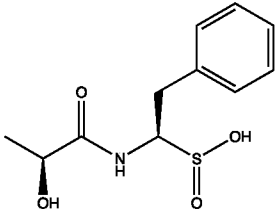
	(S)-3-(cyclopenta-1,4-dien-1-yl)-2-((S)-2-hydroxypropanamido)propanoic acid
 (S)-2-((S)-2-hydroxypropanamido)-3-(naphthalen-1-yl)propanoic acid	(S)-2-((S)-2-hydroxypropanamido)-3-(naphthalen-1-yl)propanoic acid
 (R)-2-((S)-2-hydroxypropanamido)-3-phenyl-3-thioxopropanoic acid	(R)-2-((S)-2-hydroxypropanamido)-3-phenyl-3-thioxopropanoic acid
 (R)-2-((S)-2-hydroxypropanamido)-3-(trimethylsilyl)propanoic acid	(R)-2-((S)-2-hydroxypropanamido)-3-(trimethylsilyl)propanoic acid

Table 3 - Compounds of Formula III-A (carboxyl group bio-isosteres)

Structure	Name
 (1R)-1-((S)-2-hydroxypropanamido)-2-phenylethane-1-sulfonic acid	(1R)-1-((S)-2-hydroxypropanamido)-2-phenylethane-1-sulfonic acid

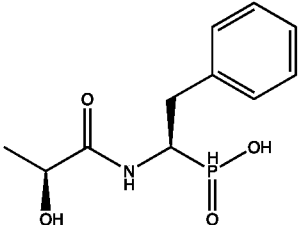
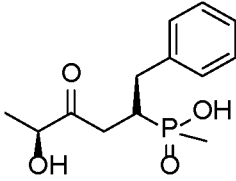
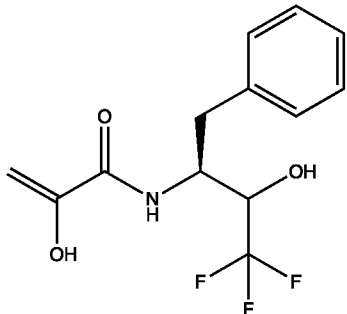
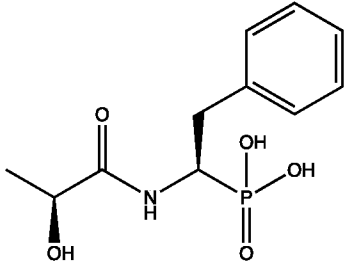
 ((R)-1-((S)-2-hydroxypropanamido)-2phenylethyl)phosphinic acid	((R)-1-((S)-2-hydroxypropanamido)-2phenylethyl)phosphinic acid
 ((R)-1-((S)-2-hydroxypropanamido)-2phenylethyl)methyl phosphinic acid	((R)-1-((S)-2-hydroxypropanamido)-2phenylethyl)methyl phosphinic acid
 (2S)-2-hydroxy-N-((2S)-4,4,4-trifluoro-3hydroxy-1-phenylbutan-2-yl)propenamide	(2S)-2-hydroxy-N-((2S)-4,4,4-trifluoromethyl-3-hydroxy-1-phenylbutan-2-yl) propenamide
 ((R)-1-((S)-2-hydroxypropanamido)-2phenylethyl)phosphonic acid	((R)-1-((S)-2-hydroxypropanamido)-2-phenylethyl) phosphonic acid

Table 4 - Compounds of Formula IV-A (protected carboxylic group)

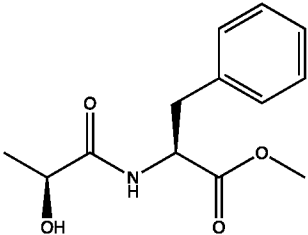
Structure	Name
 methyl ((S)-2-hydroxypropanoyl)-L-phenylalaninate	methyl ((S)-2-hydroxypropanoyl)-L-phenylalaninate

Table 5 - Compounds of Formula V-A (hydroxyl group)	
Structure	Name
(2-oxopropanoyl)-L-phenylalanine	(2-oxopropanoyl)-L-phenylalanine
((R)-3-hydroxy-2-methylpropanoyl)-L-phenylalanine	((R)-3-hydroxy-2-methylpropanoyl)-L-phenylalanine
((S)-2-hydroxybutanoyl)-L-phenylalanine	((S)-2-hydroxybutanoyl)-L-phenylalanine
(1-hydroxycyclopropane-1-carbonyl)-L-phenylalanine	(1-hydroxycyclopropane-1-carbonyl)-L-phenylalanine

Table 6 - Compounds of formula VI-A (Prodrugs)	
Structure	Name
Lactones	
(3S)-3-((2-(λ¹ oxidaneyl)propyl)amino)-4-phenylbutan-2-one	(3S)-3-((2-(λ ¹ oxidaneyl)propyl)amino)-4-phenylbutan-2-one
(4S)-4-benzyl-2-((S)-1-hydroxyethyl)oxazolidine-5-on	(4S)-4-benzyl-2-((S)-1-hydroxyethyl)oxazolidine-5-on

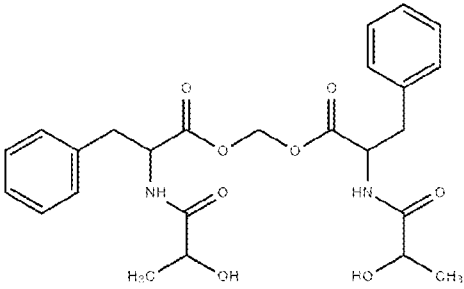
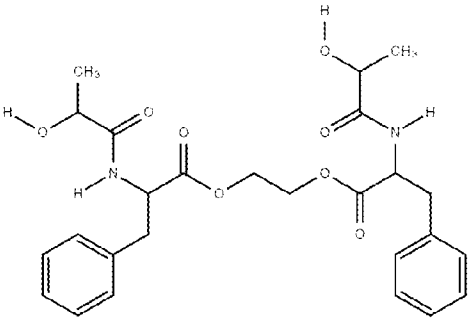
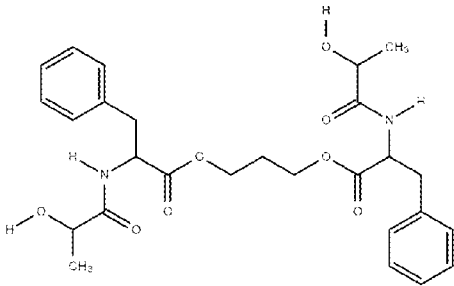
Dimers	
	2-(2-hydroxypropanoylamino)-3-phenylpropanoyl oxymethyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate
	2-[2-(2-hydroxypropanoylamino)-3-phenylpropanoyl]oxyethyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate
	3-[2-(2-hydroxypropanoylamino)-3-phenylpropanoyl]oxypropyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate.

Table 7 – Compounds of Formula I-IV

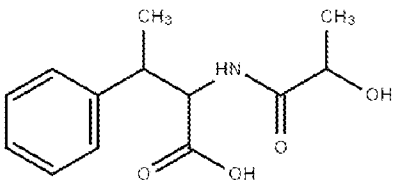
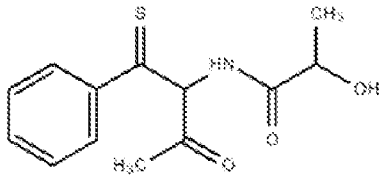
No.	Structure	IUPAC Name
2a		2-(2-hydroxypropanoylamino)-3-phenylbutanoic acid
6a		2-hydroxy-N-(3-oxo-1-phenyl-1-sulfanylidenebutan-2-yl)propanamide

Table 7 – Compounds of Formula I-IV

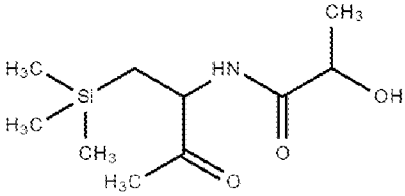
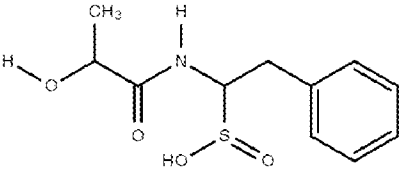
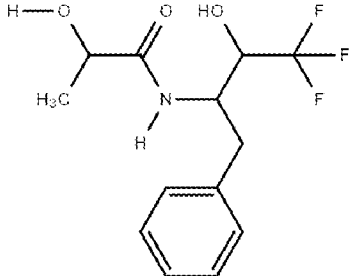
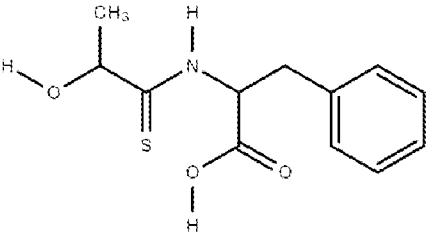
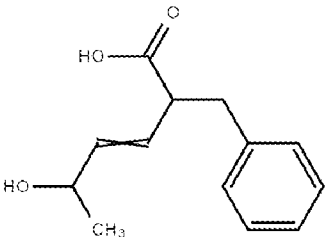
No.	Structure	IUPAC Name
7a		2-hydroxy-N-(3-oxo-1-trimethylsilylbutan-2-yl)propanamide
8a		1-(2-hydroxypropanoylamino)-2-phenylethanesulfinic acid
10a		2-hydroxy-N-(4,4,4-trifluoromethyl-3-hydroxy-1-phenylbutan-2-yl)propanamide
13a		2-(2-hydroxypropanethioylamino)-3-phenylpropanoic acid
15a		2-benzyl-5-hydroxyhex-3-enoic acid

Table 7 – Compounds of Formula I-IV

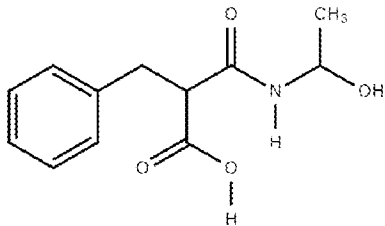
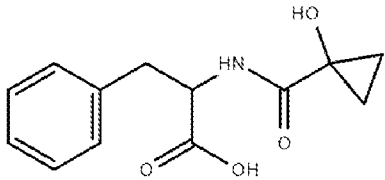
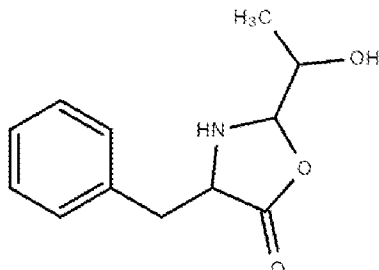
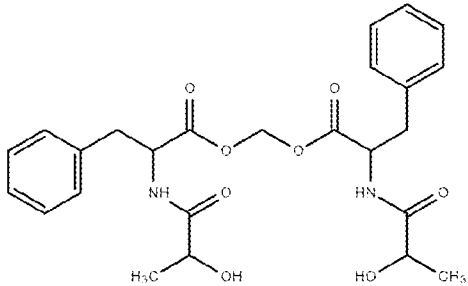
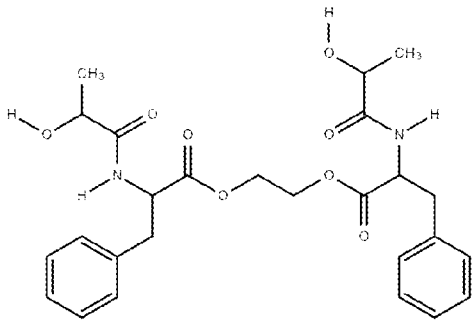
No.	Structure	IUPAC Name
16a		2-benzyl-3-(1-hydroxyethylamino)-3-oxopropanoic acid
20a		2-[(1-hydroxycyclopropanecarbonyl)amino]-3-phenylpropanoic acid
21a		4-benzyl-2-(1-hydroxyethyl)-1,3-oxazolidin-5-one
22a		2-(2-hydroxypropanoylamino)-3-phenylpropanoyl]oxymethyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate
23a		2-[2-(2-hydroxypropanoylamino)-3-phenylpropanoyl]oxyethyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate

Table 7 – Compounds of Formula I-IV

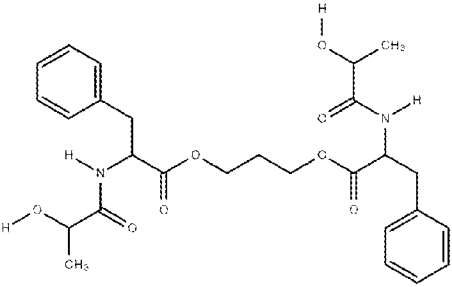
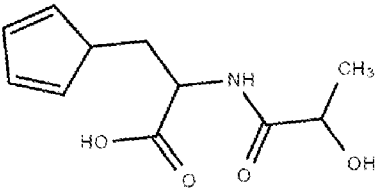
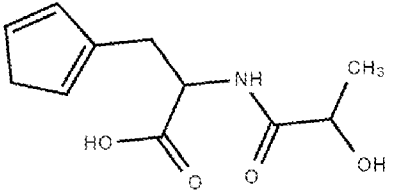
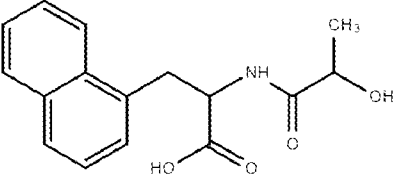
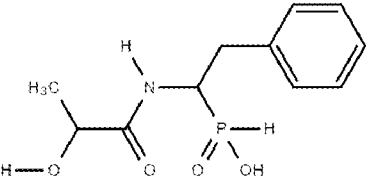
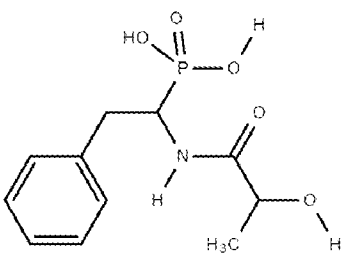
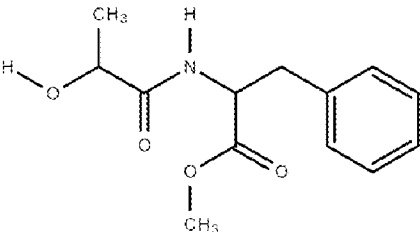
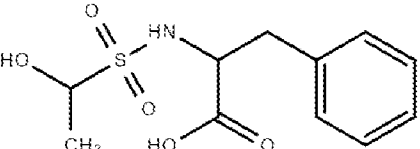
No.	Structure	IUPAC Name
24a		3-[2-(2-hydroxypropanoylamino)-3-phenylpropanoyl]oxypropyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate.

Table 8 – Compounds of Formula I-IV *bis*

No.	Structure	IUPAC Name
3'		3-cyclopenta-2,4-dien-1-yl-2-(2-hydroxypropanoylamino)propanoic acid
4'		3-cyclopenta-1,4-dien-1-yl-2-(2-hydroxypropanoylamino)propanoic acid
5'		2-(2-hydroxypropanoylamino)-3-naphthalen-1-ylpropanoic acid
9'		[1-(2-hydroxypropanoylamino)-2-phenylethyl]phosphinic acid

No.	Structure	IUPAC Name
11'		[1-(2-hydroxypropanoylamino)-2-phenylethyl]phosphonic acid
12'		methyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate
14'		2-(1-hydroxyethylsulfonylamino)-3-phenylpropanoic acid

EXAMPLE 2

Lac-Phe Study in Mice

[0311] A study of the effect of Lac-Phe analogues on mice was performed using controlled injection volume and concentration (50mg/kg at 5 μ L/g body weight). Mice were injected in the evening right before the night cycle (6:45 p.m.) and feces, weight, and food weight were measured in the morning at 6:45 a.m. and 6:45 p.m. daily using previously reported conditions and products. See Li *et al.* (2022) *Nature* 606: 785-801. The results of average percent weight loss are shown in Fig. 3. Following treatment of mice for 14 days, average percent weight lost, percent food left (uneaten), feces weight, and individual mouse weight were measured and shown in FIG. 3, 4, 5, and 6, respectively.

[0312] Functional Assays

[0313] Analogues and/or derivatives of the compounds described herein can be tested for metabolic stability: their ability to withstand incubation with several proteolytic enzymes (trypsins, pepsin, proteinase K, pancreatic enzyme mix, et cetera) that are present in the gastrointestinal system and/or in the blood compartment or tissues in the subject (human, mouse).

After incubation with the proteolytic enzyme we would measure the integrity of our compounds by performing tests such as but not limited to: commercially available L-lactate kit, MALDI-TOF spectrometry, TOF LC/MS et cetera.

[0314] Analogues and/or derivatives of the compounds described herein can be tested for activity: their ability to suppress appetite (suppress food intake) in a subject (DIO mice). And stimulation of intestinal CaSR (known to enhance GLP-1 secretion and inhibit gastric motility), could also be a measure of appetite suppression. Additionally, several *in vivo* parameters are to be included as a functional assay, blood parameters such as ketone bodies, glucose, lipid panels, and glucose tolerance test and also any hormone or metabolites related to metabolic disorders, obesity, weight, feeding, fasting such as FGF-21, adiponectin, leptin, ghrelin. Organ collection to measure parameters associated with metabolic disease or obesity (WAT, BAT, Liver, Kidneys, GI tract, etc.) are also a functional assay. Assay protocols are well described in the literature.

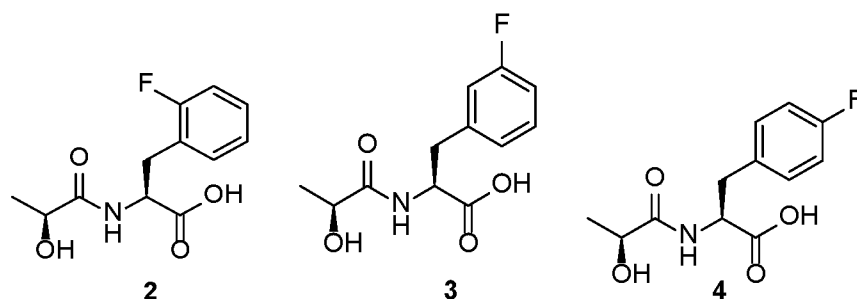
[0315] The brain plays an essential role in the regulation of appetite and body mass. Analogues and/or derivatives of the compounds described herein can be tested for their ability to act on orexigenic and anorexigenic centers or neurons. Compounds could be tested for activity using any assay able to assess their capacity to activate or inhibit neural circuits in the brain whether it be by electrophysiology or by another method. It has been previously shown that Lac-Phe acts on orexigenic Agouti-related peptide (AgRP) and anorexigenic proopiomelanocortin (POMC) expressing neurons. Therefore, whole-cell patch clamp slice electrophysiology can be used to determine the effect of described compounds on neuronal populations known to regulate food intake. Furthermore Neuronal Activity Assay for Sartorius and/or cell culture studies to measure the effect of compound on neurons in presence or not of other pharmacological agents such as DNQX, D-AP5 bicuculline or toxins such as TTX can be used as an *in vitro* test, in one aspect of the invention.

EXAMPLE 3

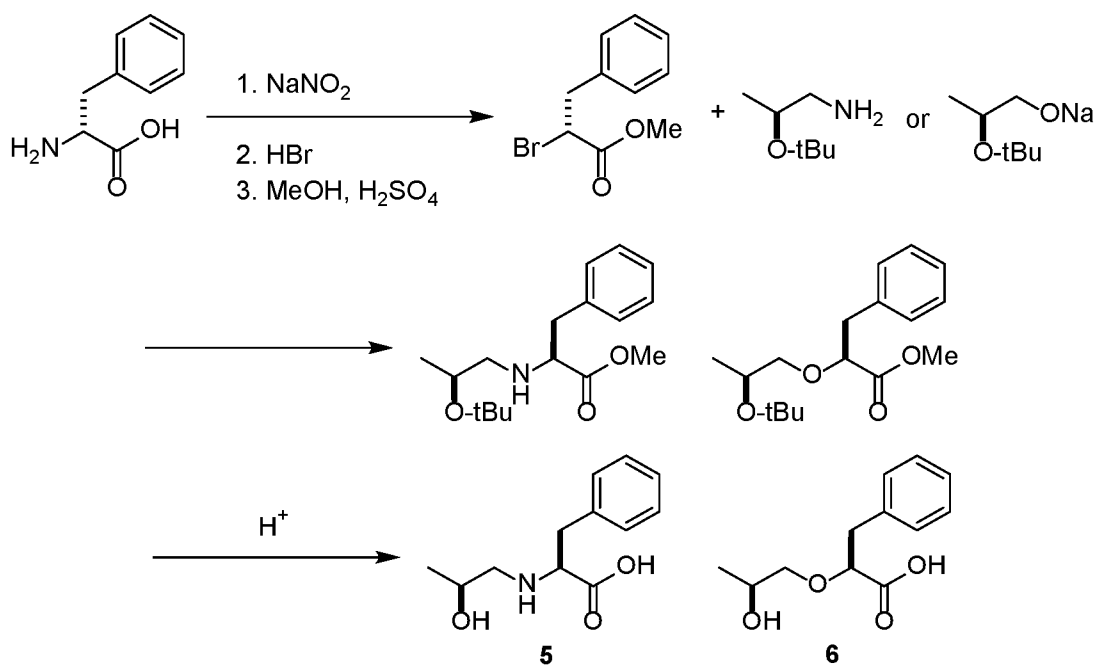
Methods of Synthesis

[0316] Preparation of fluorinated derivatives of the Lac-Phe analogues of the present disclosure

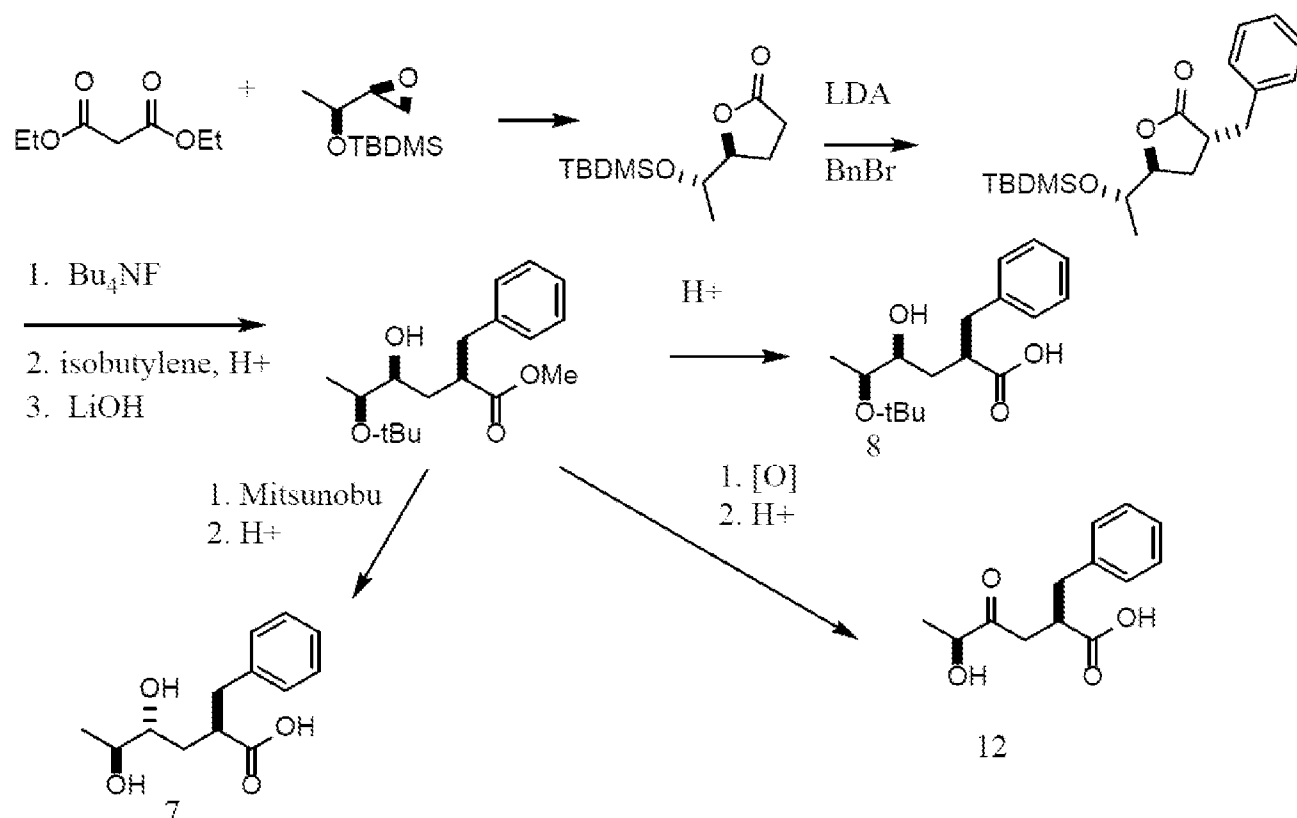
Compounds having structure 2, 3 and 4 for use as ¹⁸F-PET probes were prepared by amide coupling EDC of commercially available F-phenylalanine (Aldrich) and lactic acid.



[0317] Compounds of the Lac-Phe analogues of the present disclosure having structures 5 and 6 are prepared (Scheme I) by using diazotization of D-Phe, followed by bromination, nucleophilic displacement and deprotection of the protecting groups, per Scheme I below, and as shown in Fig. 2(A).



[0318] Lac-Phe analogues described herein having structures 7, 8, and 12 can be prepared using a strategy based on Merk's Indinaver's synthesis (Scheme II)

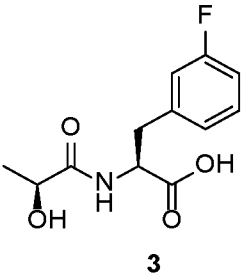
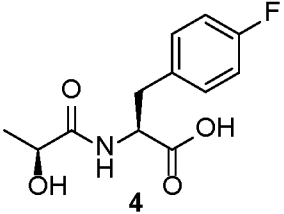


Scheme 2 for preparation of compounds 7, 8, and 12

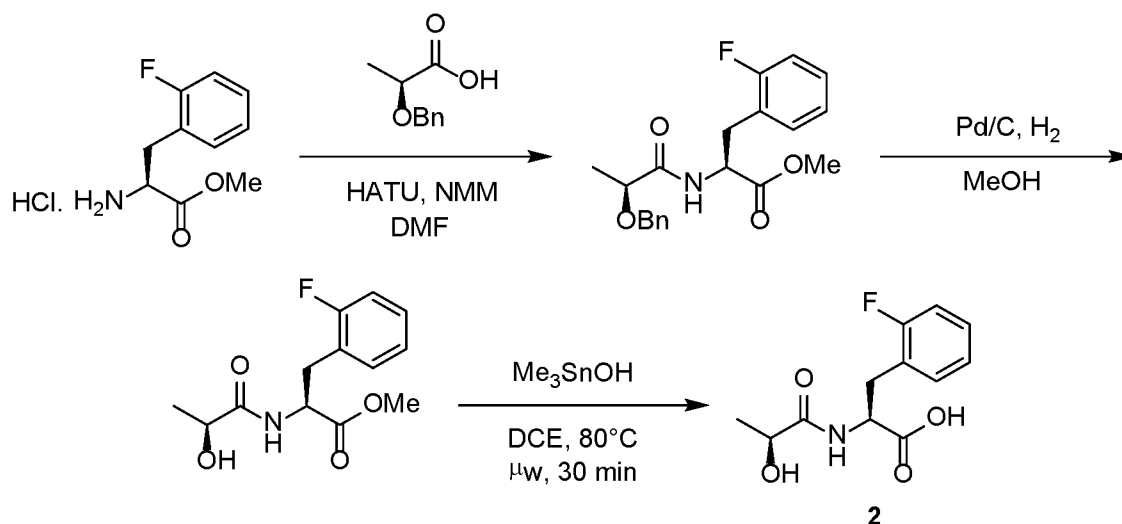
[0319] PET Probes Synthesis. To make a PET probe of Lac-Phe to perform mouse imaging studies, one of the hydrogens on the aromatic ring of Phe is replaced with a radioisotope of fluorine (^{18}F) to create a PET probe of Lac-Phe having structures set forth in Table 10, which we are used in mouse studies before and after exercise. This enables us to determine the tissues that bind Lac-Phe and mediate its anorexic effect. CaSRs are known to be expressed in the brain and also in the pancreas, where they stimulate insulin secretion. Binding of Lac-Phe to other possible receptors is also ascertained by this approach.

[0320] Table 10 – PET probes (^{18}F Cu-boronate method on bis-t-butyl protected precursor)

Table 10 – PET probes		
No.	Structure	IUPAC Name
2'	2	(S)-3-(2-fluorophenyl)-2-((S)-2-hydroxypropanamido)propanoic acid (2)

No.	Structure	IUPAC Name
3'	 3	(S)-3-(3-fluorophenyl)-2-((S)-2-hydroxypropanamido)propanoic acid (3)
4'	 4	(S)-3-(4-fluorophenyl)-2-((S)-2-hydroxypropanamido)propanoic acid (4)

[0321] Method of synthesis of (S)-3-(2-fluorophenyl)-2-((S)-2-hydroxypropanamido)propanoic acid (2)



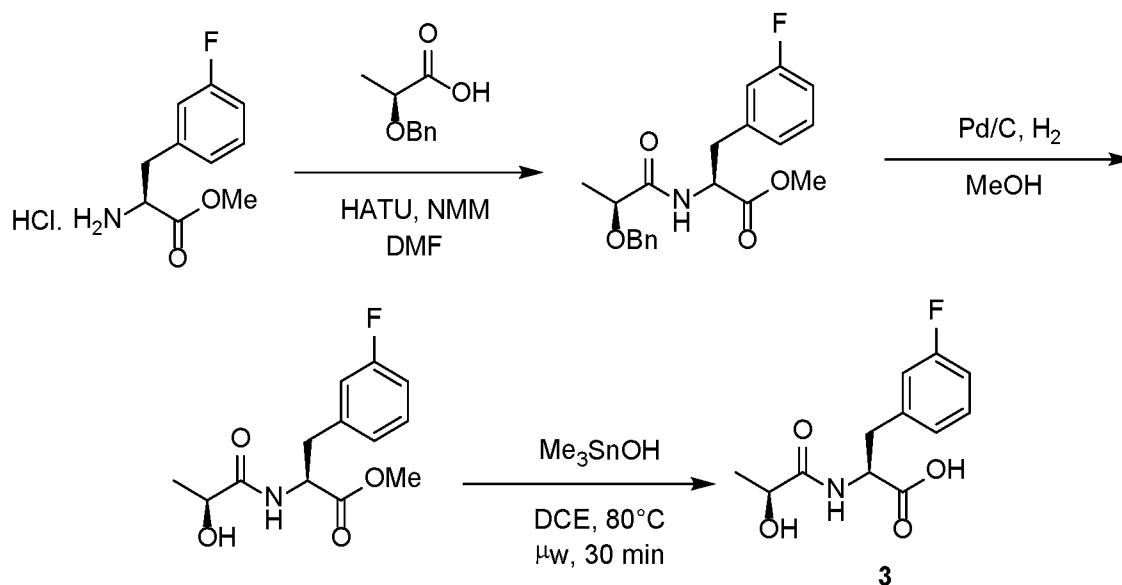
[0322] Method of synthesis of Methyl (S)-2-((S)-2-(benzyloxy)propanamido)-3-(2-fluorophenyl)propanoate: To an ice-cooled solution of methyl (S)-2-amino-3-(2-fluorophenyl)propanoate hydrochloride (500 mg, 1 Eq, 2.14 mmol), (S)-2-(benzyloxy)propanoic acid (386 mg, 1 Eq, 2.14 mmol), and N-methylmorpholine (476 mg, 518 μ L, 2.2 Eq, 4.71 mmol) in N,N-Dimethylformamide (7 mL) was added HATU (895 mg, 1.1 Eq, 2.35 mmol). After 10 minutes the ice-bath was removed and the reaction was left stirring for 3 hours at room temperature. The reaction mixture was diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate twice and the combined organic layers were washed with brine,

dried over sodium sulfate, filtered, and concentrated under reduced pressure. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.28 (m, 4H), 7.22 (dtd, $J = 7.4, 5.5, 2.7$ Hz, 1H), 7.13 (td, $J = 7.6, 1.9$ Hz, 2H), 7.08 – 6.97 (m, 2H), 4.90 (ddd, $J = 8.6, 6.9, 5.6$ Hz, 1H), 4.57 (d, $J = 11.4$ Hz, 1H), 4.47 (d, $J = 11.5$ Hz, 1H), 3.91 (q, $J = 6.8$ Hz, 1H), 3.76 (s, 3H), 3.25 (dd, $J = 14.0, 5.7$ Hz, 1H), 3.13 (dd, $J = 13.9, 7.0$ Hz, 1H), 1.30 (d, $J = 6.8$ Hz, 3H). LCMS: $[\text{M}+\text{H}]^+$; calculated: 360.160, found 360.000.

[0323] Method of synthesis of Methyl (S)-3-(2-fluorophenyl)-2-((S)-2-hydroxypropanamido)propanoate: To a solution of methyl (S)-2-((S)-2-(benzyloxy)propanamido)-3-(2-fluorophenyl)propanoate (600 mg, 1 Eq, 1.67 mmol) in methanol (10 mL) was added palladium on carbon (10%; 50% water) (178 mg). The mixture was then evacuated and purged with hydrogen. This was repeated twice and the reaction was left stirring at room temperature overnight. Celite was added to the reaction mixture, which was then filtered through celite and concentrated under reduced pressure and used without further purification. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.27 – 7.19 (m, 2H), 7.13 (m, 1H), 7.10 – 7.04 (m, 1H), 7.01 (m, 1H), 4.88 (ddt, $J = 8.6, 6.0, 2.8$ Hz, 1H), 4.19 (d, $J = 7.1$ Hz, 1H), 3.75 (s, 1H), 3.25 (ddt, $J = 14.0, 5.8, 1.7$ Hz, 1H), 3.20 – 3.06 (m, 1H), 1.36 – 1.32 (m, 3H). LCMS: $[\text{M}+\text{H}]^+$; calculated: 270.113, found 270.200.

[0324] Method of synthesis of (S)-3-(2-fluorophenyl)-2-((S)-2-hydroxypropanamido)propanoic acid (**2**): To a microwave vial was added methyl (S)-3-(3-fluorophenyl)-2-((S)-2-hydroxypropanamido)propanoate (222 mg, 1 Eq, 0.824 mmol), trimethyltinhydroxide (596 mg, 4 Eq, 3.30 mmol), and 1,2-Dichloroethane (3.5 mL). The vial was then sealed and heated in a microwave reactor for 30 minutes at 80 degrees Celsius. The reaction mixture was diluted with ethyl acetate and washed with 1N HCl, brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by rp-HPLC (H₂O/ACN with 0.05% TFA). The desired fractions were pooled and lyophilized to give the final product as a fluffy white solid (94 mg, 0.37 mmol, 45%). ^1H NMR (400 MHz, Deuterium Oxide) δ 7.37 (ddd, $J = 9.1, 7.5, 6.2$ Hz, 1H), 7.10 (dt, $J = 7.7, 1.2$ Hz, 1H), 7.10 – 7.01 (m, 2H), 4.72 (m, 1H), 4.19 (q, $J = 6.9$ Hz, 1H), 3.33 (dd, $J = 14.0, 5.1$ Hz, 1H), 3.06 (dd, $J = 13.9, 9.4$ Hz, 1H), 1.19 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (101 MHz, Deuterium Oxide) δ 177.08, 175.05, 162.48 (d, $J = 243.2$ Hz), 130.20 (d, $J = 8.6$ Hz), 125.14 (d, $J = 2.8$ Hz), 115.89 (d, $J = 21.4$ Hz), 113.70 (d, $J = 22.0$ Hz), 67.51, 53.27, 36.43, 19.38. LCMS: $[\text{M}+\text{H}]^+$; calculated: 256.098, found 256.00.

[0325] Method of synthesis of (S)-3-(3-fluorophenyl)-2-((S)-2-hydroxypropanamido)propanoic acid (**3**)



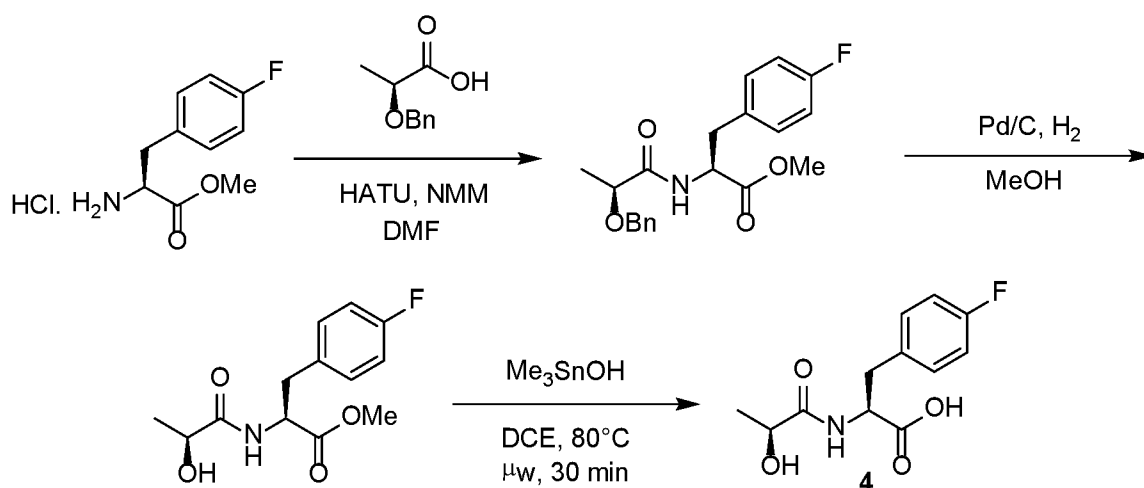
[0326] Method of synthesis of Methyl (S)-2-((S)-2-(benzyloxy)propanamido)-3-(3-fluorophenyl)propanoate: To an ice-cooled solution of methyl (S)-2-amino-3-(3-fluorophenyl)propanoate hydrochloride (500 mg, 1 Eq, 2.14 mmol), (S)-2-(benzyloxy)propanoic acid (386 mg, 1 Eq, 2.14 mmol), and N-methylmorpholine (476 mg, 518 μ L, 2.2 Eq, 4.71 mmol) in N,N-Dimethylformamide (7 mL) was added HATU (895 mg, 1.1 Eq, 2.35 mmol). After 10 minutes the ice-bath was removed and the reaction was left stirring for 3 hours at room temperature. The reaction mixture was diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate twice and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (0-50% EtOAc/Hexane) gave the product as a clear oil (685 mg, 2.14 mmol, 89%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.29 (m, 4H), 7.29 – 7.20 (m, 1H), 7.11 (d, J = 8.5 Hz, 1H), 7.00 – 6.89 (m, 2H), 6.88 – 6.81 (m, 1H), 4.92 (ddd, J = 8.5, 6.5, 5.6 Hz, 1H), 4.64 – 4.44 (m, 2H), 3.96 (q, J = 6.8 Hz, 1H), 3.78 (s, 3H), 3.22 (dd, J = 13.9, 5.6 Hz, 1H), 3.10 (dd, J = 13.9, 6.5 Hz, 1H), 1.37 (d, J = 6.8 Hz, 3H). LCMS: $[\text{M}+\text{H}]^+$; calculated: 360.160, found 360.000.

[0327] Method of synthesis of Methyl (S)-3-(3-fluorophenyl)-2-((S)-2-hydroxypropanamido)propanoate: To a solution of methyl (S)-2-((S)-2-(benzyloxy)propanamido)-3-(3-fluorophenyl)propanoate (657.7 mg, 1 Eq, 1.830 mmol) in methanol (10 mL) was added palladium on carbon (10%; 50% water) (194.7 mg). The mixture was then evacuated and purged with hydrogen. This was repeated twice and the reaction was left stirring at room temperature overnight. Another 60 mg of palladium on carbon (10%; 50% water) was added and the reaction mixture was purged with hydrogen and left stirring for another 16

hours. Celite was added to the reaction mixture, which was then filtered through celite and concentrated under reduced pressure. Purification by flash chromatography (0-100% EtOAc/Hexane) gave the product as a clear oil (413 mg, 1.83 mmol, 84 %). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.21 (m, 1H), 7.06 – 6.86 (m, 2H), 6.82 (dt, J = 9.5, 2.1 Hz, 1H), 4.87 (dt, J = 8.1, 6.1 Hz, 1H), 4.21 (q, J = 6.8 Hz, 1H), 3.74 (s, 3H), 3.19 (dd, J = 13.9, 5.7 Hz, 1H), 3.07 (dd, J = 13.9, 6.4 Hz, 1H), 1.36 (d, J = 6.8 Hz, 1H). LCMS: $[\text{M}+\text{H}]^+$; calculated: 270.113, found 270.200.

[0328] Method of synthesis of (S)-3-(3-fluorophenyl)-2-((S)-2-hydroxypropanamido)propanoic acid (3): To a microwave vial was added methyl (S)-3-(2-fluorophenyl)-2-((S)-2-hydroxypropanamido)propanoate (213 mg, 1 Eq, 791 μmol), trimethyltinhydroxide (572 mg, 4 Eq, 3.16 mmol), and 1,2-Dichloroethane (3.5 mL). The vial was then sealed and heated in a microwave reactor for 30 minutes at 80 degrees Celsius. The reaction mixture was diluted with ethyl acetate and washed with 1N HCl, brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by rp-HPLC (H₂O/ACN with 0.05% TFA). The desired fractions were pooled and lyophilized to give the final product as a fluffy white solid (98 mg, 0.79 mmol, 49%). ^1H NMR (400 MHz, Deuterium Oxide) δ 7.32 (m, 2H), 7.22 – 7.09 (m, 2H), 4.75 (m, 1H), 4.18 (q, J = 6.8 Hz, 1H), 3.39 (dd, J = 14.0, 5.1 Hz, 1H), 3.10 (dd, J = 14.0, 9.4 Hz, 1H), 1.17 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, Deuterium Oxide) δ 177.19, 174.78, 161.17 (d, J = 243.3 Hz), 131.81 (d, J = 4.5 Hz), 129.18 (d, J = 8.3 Hz), 124.38 (d, J = 3.5 Hz), 123.37 (d, J = 15.6 Hz), 115.23 (d, J = 21.9 Hz), 67.53, 52.35, 30.53, 19.32. LCMS: $[\text{M}+\text{H}]^+$; calculated: 256.098, found 256.000.

[0329] Method of synthesis of (S)-3-(4-fluorophenyl)-2-((S)-2-hydroxypropanamido)propanoic acid (4)



[0330] Method of synthesis of Methyl (S)-2-((S)-2-(benzyloxy)propanamido)-3-(4-fluorophenyl)propanoate: To an ice-cooled solution of methyl (S)-2-amino-3-(4-fluorophenyl)propanoate hydrochloride (500 mg, 1 Eq, 2.14 mmol), (S)-2-(benzyloxy)propanoic acid (386 mg, 1 Eq, 2.14 mmol), and N-methylmorpholine (476 mg, 518 μ L, 2.2 Eq, 4.71 mmol) in N,N-Dimethylformamide (7 mL) was added HATU (895 mg, 1.1 Eq, 2.35 mmol). After 10 minutes the ice-bath was removed and the reaction was left stirring for 3 hours at room temperature. The reaction mixture was diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate twice and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (0-45% EtOAc/Hexane) gave the product as a clear oil (725 mg, 2.02 mmol, 94%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.30 (m, 3H), 7.30 – 7.26 (m, 3H), 7.06 (ddd, J = 8.4, 5.4, 2.5 Hz, 3H), 7.00 – 6.89 (m, 2H), 4.88 (ddd, J = 8.6, 6.4, 5.7 Hz, 1H), 4.60 – 4.46 (m, 2H), 3.93 (q, J = 6.8 Hz, 1H), 3.75 (s, 3H), 3.15 (dd, J = 14.0, 5.7 Hz, 1H), 3.06 (dd, J = 14.0, 6.4 Hz, 1H), 1.33 (d, J = 6.8 Hz, 3H). LCMS: $[\text{M}+\text{H}]^+$; calculated: 360.160, found 360.000.

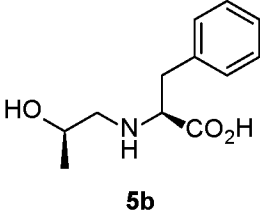
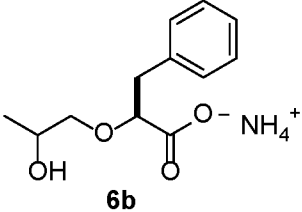
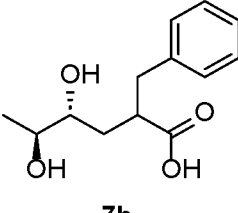
[0331] Method of synthesis of Methyl (S)-3-(4-fluorophenyl)-2-((S)-2-hydroxypropanamido)propanoate: To a solution of methyl (S)-2-((S)-2-(benzyloxy)propanamido)-3-(4-fluorophenyl)propanoate (657.7 mg, 1 Eq, 1.830 mmol) in Methanol (10 mL) was added palladium on carbon (10%; 50% water) (194.7 mg). The mixture was then evacuated and purged with hydrogen. This was repeated twice and the reaction was left stirring at room temperature overnight. Another 100 mg of palladium on carbon (10%; 50% water) was added and the reaction mixture was purged with hydrogen and left stirring overnight. Celite was added to the reaction mixture, which was then filtered through celite and concentrated under reduced pressure and used without further purification. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.10 – 7.04 (m, 2H), 6.97 (td, J = 8.5, 1.7 Hz, 3H), 4.84 (dt, J = 8.4, 6.1 Hz, 1H), 4.20 (qd, J = 6.9, 1.5 Hz, 1H), 3.72 (d, J = 1.4 Hz, 3H), 3.15 (dd, J = 14.1, 5.8 Hz, 1H), 3.05 (ddd, J = 14.1, 6.5, 1.6 Hz, 1H), 1.34 (dd, J = 6.8, 1.4 Hz, 3H). LCMS: $[\text{M}+\text{H}]^+$; calculated: 270.113, found 270.200.

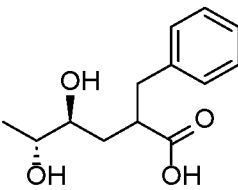
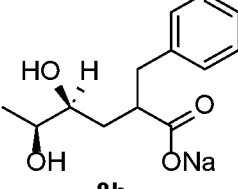
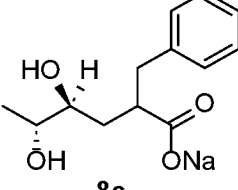
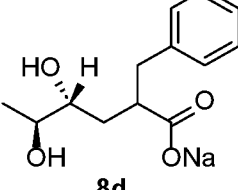
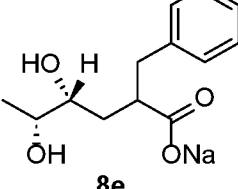
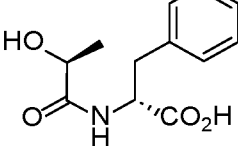
[0332] Method of synthesis of (S)-3-(4-fluorophenyl)-2-((S)-2-hydroxypropanamido)propanoic acid (4): To a microwave vial was added methyl (S)-3-(4-fluorophenyl)-2-((S)-2-hydroxypropanamido)propanoate (219.5 mg, 1 Eq, 815.2 μ mol), trimethyltinhydroxide (589.6 mg, 4 Eq, 3.261 mmol), and 1,2-Dichloroethane (3.5 mL). The vial was then sealed and heated in a microwave reactor for 30 minutes at 80 degrees Celsius. The reaction mixture was diluted with ethyl acetate and washed with 1N HCl, brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified

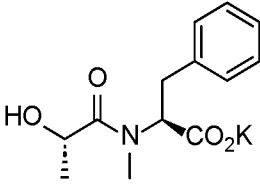
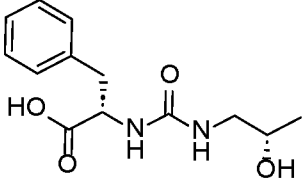
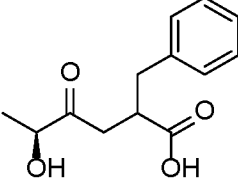
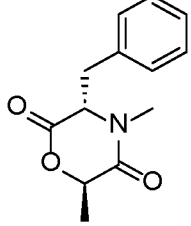
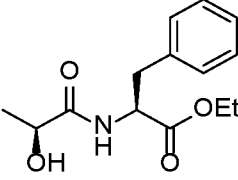
by rp-HPLC (H₂O/ACN with 0.05% TFA). The desired fractions were pooled and lyophilized to give the final product as a fluffy white solid (112 mg, 0.44 mmol, 54%). ¹H NMR (400 MHz, Deuterium Oxide) δ 7.33 – 7.23 (m, 2H), 7.16 – 7.05 (m, 2H), 4.69 (dd, J = 9.2, 5.1 Hz, 1H), 4.19 (q, J = 6.9 Hz, 1H), 3.30 (dd, J = 14.0, 5.1 Hz, 1H), 3.04 (dd, J = 14.0, 9.2 Hz, 1H), 1.19 (d, J = 6.9 Hz, 3H). LCMS: [M+H]⁺; calculated: 256.098, found 256.200.

[0333] Method of Synthesis of analogues of Lac-Phe.

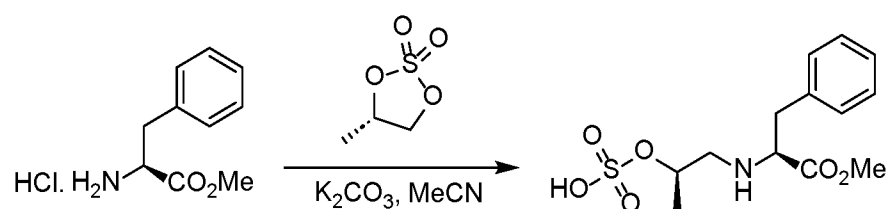
[0334] The designed Lac-Phe analogues in Table 11 have modifications around their amide bond to prevent proteolysis. These compounds are first screened using a CaSR reporter cell line (Thermo Fisher) before and after treatment with various proteases. Active compounds are then tested in mice housed in metabolic cages to monitor food consumption after IP and oral gavage. Stimulation of intestinal CaSR is also known to enhance GLP-1 secretion and inhibit gastric motility, which also contributes to appetite suppression. This potential peripheral effect of Lac-Phe on appetite suppression is also enhanced by the designed Lac-Phe stable analogues.

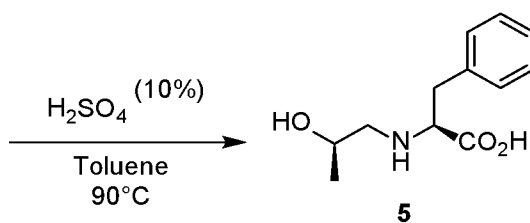
Table 11 – Stable Analogues of Lac-Phe		
No.	Structure	IUPAC Name
5b		((R)-2-hydroxypropyl)-L-phenylalanine (5)
6b		ammonium (2S)-2-(2-hydroxypropoxy)-3-phenylpropanoate
7b		(4R,5S)-2-benzyl-4,5-dihydroxyhexanoic acid

No.	Structure	IUPAC Name
7c	 7c	(4 <i>S</i> ,5 <i>R</i>)-2-benzyl-4,5-dihydroxyhexanoic acid
8b	 8b	sodium (4 <i>S</i> ,5 <i>S</i>)-2-benzyl-4,5-dihydroxyhexanoate
8c	 8c	sodium (4 <i>S</i> ,5 <i>R</i>)-2-benzyl-4,5-dihydroxyhexanoate
8d	 8d	sodium (4 <i>R</i> ,5 <i>S</i>)-2-benzyl-4,5-dihydroxyhexanoate
8e	 8e	sodium (4 <i>R</i> ,5 <i>R</i>)-2-benzyl-4,5-dihydroxyhexanoate
9b	 9b	((<i>R</i>)-2-hydroxypropanoyl)- <i>D</i> -phenylalanine (9)

No.	Structure	IUPAC Name
10b	 10b	Potassium N-((S)-2-hydroxypropanoyl)-N-methyl- <i>L</i> -phenylalaninate (10)
11b	 11b	(((S)-2-hydroxypropyl)carbamoyl)- <i>L</i> -phenylalanine (11)
12b	 12b	(5 <i>S</i>)-2-benzyl-5-hydroxy-4-oxohexanoic acid
13b	 13b	(3 <i>S</i> ,6 <i>S</i>)-3-benzyl-4,6-dimethylmorpholine-2,5-dione (13)
14b	 14b	Ethyl ((S)-2-hydroxypropanoyl)- <i>L</i> -phenylalaninate (14)

EXAMPLE 4

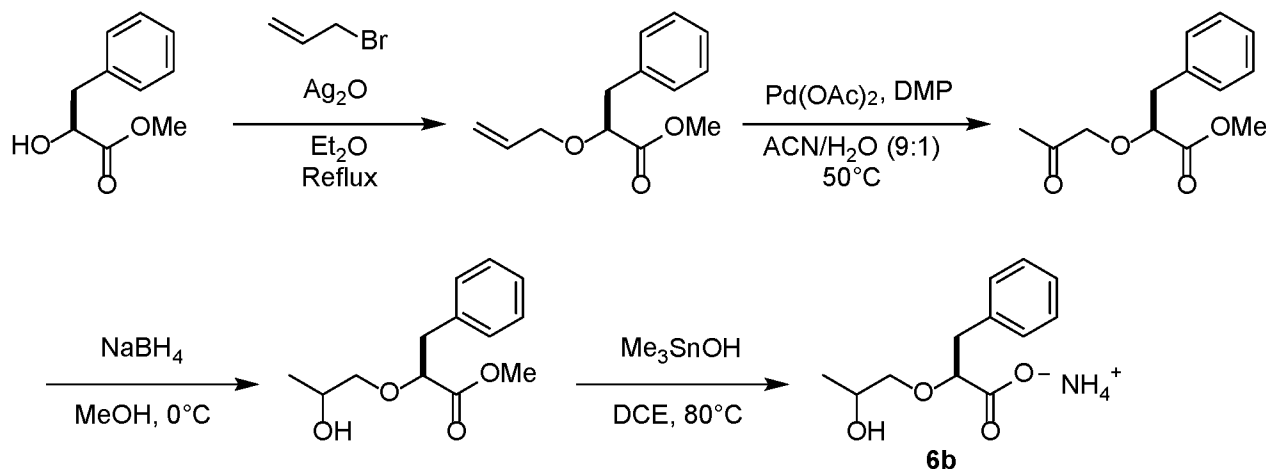
Method of synthesis of ((R)-2-hydroxypropyl)-*L*-phenylalanine (5)



[0335] Method of synthesis of ((*R*)-2-hydroxypropyl)-*L*-phenylalanine (**5**): To a solution of *L*-phenylalanine methyl ester hydrochloride (70 mg, 0.51 mmol, 1.0 eq.) and potassium carbonate (107 mg, 0.77 mmol, 1.6 eq.) dry acetonitrile (3 mL) was added (4*S*)-methyl-1-[1,3,2]dioxathiolane 2,2-dioxide (70 mg, 0.51 mmol, 1.1 eq.). The reaction stirred at room temperature overnight. The reaction was concentrated under reduced pressure and the residue was treated with 20% sulfuric acid and toluene and heated to 90° for 3.5 hours. The solution was concentrated and the residue was then subjected to reverse phase HPLC (H₂O and MeCN with 0.05% TFA). The desired fractions were combined and lyophilized, yielding the compound as a white sticky solid (66.4 mg, 59.8% yield). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.37 – 7.26 (m, 6H), 4.04 – 3.94 (m, 1H), 3.90 (t, *J* = 6.6 Hz, 1H), 3.33 (m, 1H) 3.18 (dd, *J* = 14.4, 7.1 Hz, 1H), 3.03 (dd, *J* = 12.6, 1.5 Hz, 1H), 2.77 (m, 1H), 1.15 (d, *J* = 6.3 Hz, 3H). LCMS: [M+H]⁺; calculated:224.13, found 224.20.

EXAMPLE 5

Method of synthesis of ammonium (2*S*)-2-(2-hydroxypropoxy)-3-phenylpropanoate (**6b**)



[0336] Method of synthesis of Methyl (*S*)-2-(allyloxy)-3-phenylpropanoate: To a solution of methyl (*S*)-2-hydroxy-3-phenylpropanoate (3.00 g, 1 Eq, 16.6 mmol) and allyl bromide (3.02 g, 2.2 mL, 1.5 Eq, 25.0 mmol) in dry Diethyl ether (50 mL) under argon was added silver oxide (7.72 g, 2 Eq, 33.3 mmol) and the reaction was refluxed for 3 days. The reaction was then filtered through celite, washed with ethyl acetate, and concentrated under reduced pressure. Flash chromatography (0-20% EtOAc/Hexane) gave methyl (*S*)-2-(allyloxy)-3-phenylpropanoate

(2.657 g, 12.06 mmol, 72.5 %) as a clear oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.17 (m, 5H), 5.86 – 5.72 (m, 1H), 5.26 – 5.07 (m, 2H), 4.17 – 4.06 (m, 2H), 3.88 (dd, J = 12.7, 6.2 Hz, 1H), 3.73 (s, 3H), 3.14 – 2.95 (m, 2H). LCMS: $[\text{M}+\text{NH}_4]^+$; calculated: 238.144, found 238.200.

[0337] Method of synthesis of Methyl (S)-2-(2-oxopropoxy)-3-phenylpropanoate: A 20 mL microwave vial was charged with methyl (S)-2-(allyloxy)-3-phenylpropanoate (650 mg, 1 Eq, 2.95 mmol), DMP (2.50 g, 2 Eq, 5.90 mmol), palladium(II) acetate (66.3 mg, 0.1 Eq, 295 μmol), Acetonitrile (12.9 mL), and Water (1.84 mL). The vial was capped and the solution was degassed and purged with argon. The reaction was heated in a microwave for 6 hours at 50 $^\circ\text{C}$. The reaction was diluted with ethyl acetate and filtered through a silica plug and the filtrate was washed with an aqueous solution of 5% sodium diethyldithiocarbamate, water, and brine, dried over sodium sulfate, and concentrated under reduced pressure. Flash chromatography (0-40% EtOAc/Hexane) gave methyl (S)-2-(2-oxopropoxy)-3-phenylpropanoate (332 mg, 1.41 mmol, 47.6 %) as a colorless oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.21 (m, 11H), 4.13 (d, J = 16.6 Hz, 1H), 3.87 (d, J = 16.6 Hz, 1H), 3.73 (s, 3H), 3.19 – 3.00 (m, 4H), 2.06 (s, 3H). LCMS: $[\text{M}+\text{NH}_4]^+$; calculated: 254.139, found 254.400.

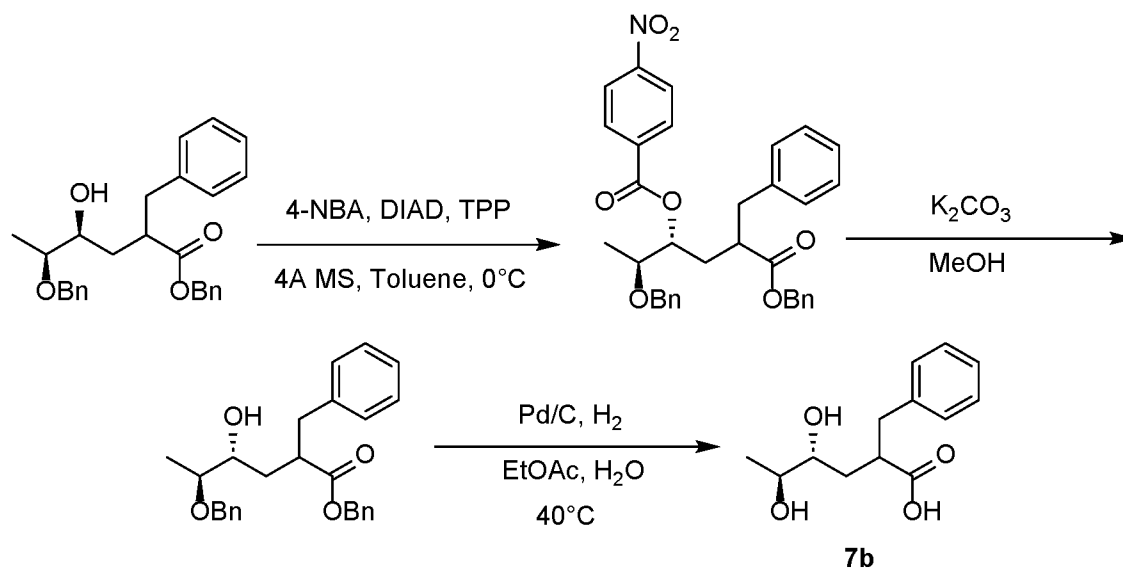
[0338] Method of synthesis of Methyl (2S)-2-(2-hydroxypropoxy)-3-phenylpropanoate: To an ice-cooled solution of methyl (S)-2-(2-oxopropoxy)-3-phenylpropanoate (234.9 mg, 1 Eq, 994.2 μmol) in methanol (8 mL) was added sodium borohydride (39.49 mg, 1.05 Eq, 1.044 mmol) in methanol (2 mL) dropwise. The acetic acid was added after 1.5 hours and the reaction was concentrated under reduced pressure. The residue was redissolved in ethyl acetate and washed with water, sodium bicarbonate, brine, dried over sodium sulfate, and concentrated under reduced pressure. Flash chromatography (0-50% EtOAc/Hexane) gave methyl (2S)-2-(2-hydroxypropoxy)-3-phenylpropanoate as a mix of diastereomers (157.1 mg, 659.3 μmol , 66.32 %) as a clear sticky oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.36-7.30 (m, 2H), 7.27 (m, 3H), 4.13-4.05 (m, 1H, mix of 2 isomers), 3.93 – 3.81 (m, 1H), 3.77 (s, 3H, two overlapping singlets from 2 isomers), 3.62 (dd, J = 9.6, 2.8 Hz, 1H, isomer 1), 3.39 (dd, J = 9.8, 2.9 Hz, 1H, isomer 2), 3.29 (dd, J = 9.8, 8.1 Hz, 1H, isomer 2), 3.17 – 3.12 (m, 1H), 3.11 (dd, J = 10.2, 4.1 Hz, 1H), 3.06 (dd, J = 9.6, 8.4 Hz, 1H, isomer 1), 3.00 (d, J = 9.3 Hz, 1H), 2.97 (d, J = 9.4 Hz, 1H), 1.06 (m, 3H, mix of isomers). ^{13}C NMR (101 MHz, CDCl_3) δ 172.94, 172.85, 137.20, 129.39, 129.33, 128.64, 128.57, 127.06, 126.99, 80.91, 80.33, 66.41, 66.16, 52.23, 52.21, 39.40, 39.36, 18.34, 18.09. LCMS: $[\text{M}+\text{NH}_4]^+$; calculated: 256.154, found 256.400.

[0339] Method of synthesis of ammonium (2S)-2-(2-hydroxypropoxy)-3-phenylpropanoate (6b): A microwave vial was loaded with methyl (2S)-2-(2-hydroxypropoxy)-3-phenylpropanoate

(157 mg, 1 Eq, 659 μ mol), Trimethyltin hydroxide (477 mg, 4 Eq, 2.64 mmol), and 1,2-Dichloroethane (6.59 mL). The vial was capped and heated in a Biotage microwave for 4 hours at 80°C. The suspension was then concentrated and loaded onto a redisepp Rf RP C18 column and purified by reverse phase flash chromatography (0-50% ACN (50 mM NH_4OAc , 0.2% AcOH) / Water (50 mM NH_4OAc , 0.2% AcOH). The combined fractions were lyophilized to give the desired product (2S)-2-(2-hydroxypropoxy)-3-phenylpropanoic acid (65.7 mg, 293 μ mol, 44.5 %) as a 6:4 mix of diastereomers. ^1H NMR (400 MHz, Acetonitrile- d_3) δ 7.43 – 7.11 (m, 5H), 4.59 (m, 1H, isomer 1), 4.54 (dd, J = 7.6, 4.3 Hz, 1H, isomer 1), 4.46 (m, 2H, isomer 2), 3.87 (dd, J = 12.6, 3.2 Hz, 1H, isomer 2), 3.82 (dd, J = 12.4, 3.1 Hz, 1H, isomer 1), 3.59 (dd, J = 12.5, 4.5 Hz, 1H, isomer 1), 3.44 (dd, J = 12.6, 10.0 Hz, 1H, isomer 2), 3.31 – 2.96 (m, 2H), 1.19 (d, J = 6.5 Hz, 3H, isomer 2), 1.16 (d, J = 6.5 Hz, 3H, isomer 1). LCMS: $[\text{M}+\text{NH}_4]^+$; calculated: 242.139, found 242.394.

EXAMPLE 6

Method of synthesis of Sodium (4R,5S)-2-benzyl-4,5-dihydroxyhexanoate (7b)



[0340] Method of synthesis of (2S,3R)-5-benzyl-2,6-bis(benzyloxy)-6-oxohexan-3-yl 4-nitrobenzoate: To an ice-cooled solution of benzyl (4S,5S)-2-benzyl-5-(benzyloxy)-4-hydroxyhexanoate (282 mg, 1 Eq, 674 μ mol), triphenylphosphine (353 mg, 2 Eq, 1.35 mmol), and 3A molecular sieves in dry Toluene (7 mL) under argon was added DIAD (272 mg, 262 μ L, 2 Eq, 1.35 mmol) dropwise. The reaction was left to slowly warm to room temperature and stirred overnight. The reaction mixture was diluted with diethyl ether and filtered through a celite/silica gel plug and poured into sat. NaHCO_3 , extracted x 2 with EtOAc, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was loaded onto a silica gel cartridge and purified by flash chromatography (0-20% diethyl ether / Hexane)

to give (2S,3R)-5-benzyl-2,6-bis(benzyloxy)-6-oxohexan-3-yl 4-nitrobenzoate (153 mg, 270 μ mol, 40.0 %) as a white solid (6:4 mix of diastereomers). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.26 – 8.20 (m, 2H), 8.12 (d, J = 8.8 Hz, 2H, isomer 1), 8.05 (d, J = 8.8 Hz, 2H, isomer 2), 7.32 – 6.93 (m, 15H), 5.36 (dt, J = 10.2, 3.4 Hz, 1H, isomer 1), 5.25 (dt, J = 9.5, 3.3 Hz, 1H, isomer 2), 5.01 (d, J = 12.3 Hz, 1H, isomer 2), 4.93 (d, J = 12.2 Hz, 1H, isomer 2), 4.85 (d, J = 12.4 Hz, 1H, isomer 1), 4.62 (d, J = 12.6 Hz, 1H, isomer 1), 4.55-4.48 (m, 2H), 3.75-3.63 (m, 1H), 3.06 – 2.74 (m, 3H), 2.34 (ddd, J = 14.8, 10.1, 7.9 Hz, 1H, isomer 1), 2.16-2.03 (m, 2H, isomer 2), 1.94 (ddd, J = 14.7, 5.3, 3.2 Hz, 1H, isomer 1), 1.22 (d, J = 6.4 Hz, 3H, isomer 1), 1.19 (d, J = 6.6 Hz, 3H, isomer 2). LCMS: $[\text{M}+\text{NH}_4]^+$; calculated: 585.260, found 585.400.

[0341] Method of synthesis of (5R)-3-benzyl-5-((S)-1-(benzyloxy)ethyl)dihydrofuran-2(3H)-one: To a solution of (2S,3R)-5-benzyl-2,6-bis(benzyloxy)-6-oxohexan-3-yl 4-nitrobenzoate (153 mg, 1 Eq, 270 μ mol) in Methanol (5 mL) was added sodium azide (52.6 mg, 3 Eq, 809 μ mol) and the reaction was heated to 45 °C overnight under argon. TLC and LCMS showed no hydrolysis. Reaction was cooled to room temperature and potassium carbonate (37.3 mg, 1 Eq, 270 μ mol) was added and the reaction was stirred under argon overnight. The reaction was then filtered and concentrated. The residue was loaded onto a C18 cartridge and purified by reverse phase flash chromatography (water (10 mM NH_4OAc), acetonitrile/water (9:1)(10 mM NH_4OAc))(0-100%) to give (5R)-3-benzyl-5-((S)-1-(benzyloxy)ethyl)dihydrofuran-2(3H)-one (37.5 mg, 121 μ mol, 44.8 mg) as a 1:1 mix of diastereomers. ^1H NMR (400 MHz, Acetonitrile-*d*₃) δ 7.31 – 7.19 (m, 7H), 7.15 (m, 3H), 4.51 (m, 1H), 4.35 (m, 1H), 4.24 (m, 1H), 3.70 – 3.60 (m, 1H), 3.03 (m, 1H), 2.96 – 2.85 (m, 1H), 2.64 (m, 1H), 2.18 – 2.02 (m, 2H), 1.90 – 1.84 (m, 1H), 1.77 (m, 1H), 1.04 (d, J = 2.6 Hz, 1H, isomer 2), 1.02 (d, J = 2.6 Hz, 1H, isomer 1). LCMS: $[\text{M}]^+$; calculated: 328.167, found 328.200.

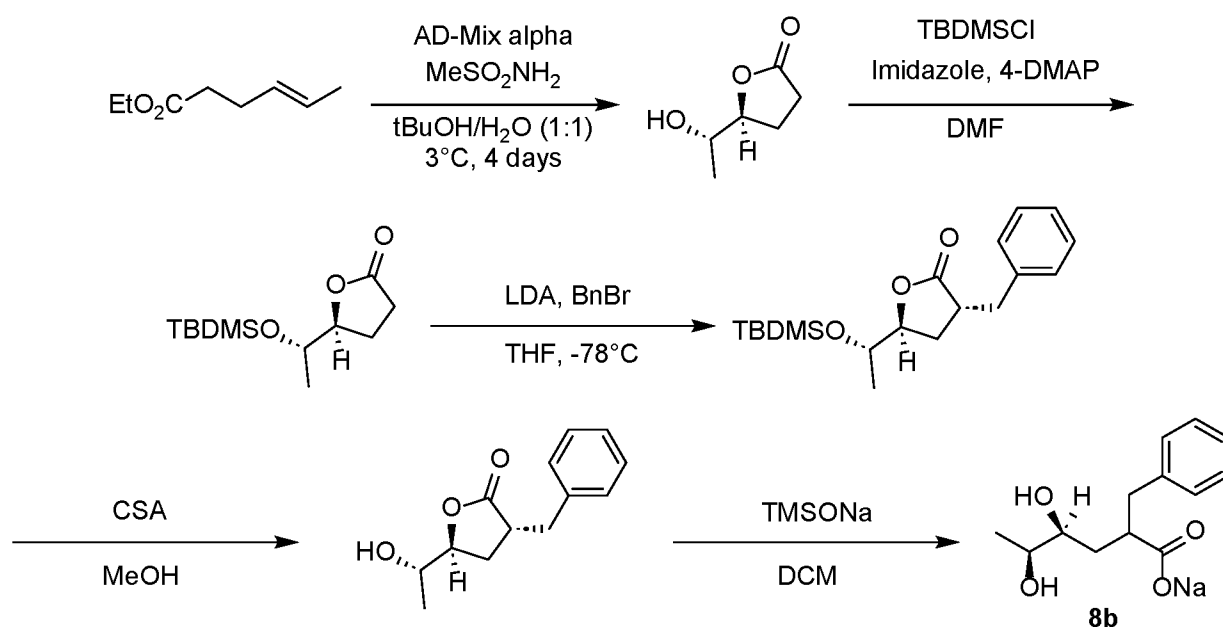
[0342] Method of synthesis of (5R)-3-benzyl-5-((S)-1-hydroxyethyl)dihydrofuran-2(3H)-one: To a solution of (5R)-3-benzyl-5-((S)-1-(benzyloxy)ethyl)dihydrofuran-2(3H)-one (37.5 mg, 1 Eq, 121 μ mol) in Methanol (5 mL) was added palladium on carbon (10% w/w)(50% water)(60 mg). The solution was purged with hydrogen and stirred overnight at 40 °C. The reaction mixture was filtered through slurried celite and concentrated under reduced pressure to give (5R)-3-benzyl-5-((S)-1-hydroxyethyl)dihydrofuran-2(3H)-one (26.4 mg, 120 μ mol, 99.2 %) as a clear oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.32-7.28 (m, 2H), 7.26 – 7.17 (m, 3H), 4.25 (ddd, J = 9.8, 6.1, 3.4 Hz, 1H, isomer 1), 4.16 (ddd, J = 8.2, 4.7, 3.4 Hz, 1H, isomer 2), 4.10-4.00 (m, 2H, isomer 1 & 2), 3.30 (dd, J = 13.9, 4.1 Hz, 1H, isomer 1), 3.17 (dd, J = 13.8, 4.6 Hz, 1H, isomer 2), 3.06 (m, 1H, isomer 2), 2.93 (m, 1H, isomer 1), 2.81 – 2.73 (m, 1H, isomer 2), 2.74 – 2.66 (m, 1H, isomer 1), 2.30 (ddd, J = 13.2, 9.7, 4.7 Hz, 1H, isomer 2), 2.12 (ddd, J = 12.6, 8.9,

6.1 Hz, 1H, isomer 1), 2.05 – 1.87 (m, 2H, isomer 1 & 2), 1.12 (d, $J = 6.6$ Hz, 3H, isomer 1 & 2). LCMS: $[M+H]^+$; calculated: 221.117, found 221.200.

[0343] Method of synthesis of Sodium (4R,5S)-2-benzyl-4,5-dihydroxyhexanoate (7b): To a solution of (5R)-3-benzyl-5-((S)-1-hydroxyethyl)dihydrofuran-2(3H)-one (26.4 mg, 1 Eq, 120 μ mol) in Water (0.380 mL) and 1,4-Dioxane (0.5 mL) was added sodium hydroxide (4.79 mg, 120 μ L, 1 molar, 1 Eq, 120 μ mol). After 3 hours the solution was lyophilized to yield sodium (4R,5S)-2-benzyl-4,5-dihydroxyhexanoate (31 mg, 0.12 mmol, 99 %) as a white solid. LCMS: $[M+Na]^+$; calculated: 261.110, found 261.200.

EXAMPLE 7

Method of synthesis of Sodium (4S,5S)-2-benzyl-4,5-dihydroxyhexanoate (8b)



[0344] Method of synthesis of Ethyl (E)-hex-4-enoate: A solution of but-3-en-2-ol (5.00 g, 6.0 mL, 1 Eq, 69.3 mmol) propionic acid (257 mg, 259 μ L, 0.05 Eq, 3.47 mmol) and triethyl orthoacetate (16.9 g, 19.1 mL, 1.5 Eq, 104 mmol) was refluxed for 16 hours. The reaction mixture was cooled to room temperature and 5 mL of aqueous saturated sodium bicarbonate solution was added. 50 mL of DCM and 50 mL of 1M HCl was then added and the reaction was stirred for 2 hours. The two phases were separated and the aqueous phase was extracted twice with DCM. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (0-20% DCM/Hexane) to give ethyl (E)-hex-4-enoate (4.9 g, 35 mmol, 50 %) as a clear oil. ^1H NMR (400 MHz, Chloroform- d) δ 5.52 – 5.37 (m, 3H), 4.12 (q, $J = 7.1$ Hz, 2H), 2.40 – 2.25 (m, 5H), 1.63 (d, $J = 5.8$ Hz, 5H), 1.25 (t, $J = 7.1$ Hz, 4H).

[0345] Method of synthesis of (S)-5-((S)-1-hydroxyethyl)dihydrofuran-2(3H)-one: To an solution of AD-mix alpha (35.45 g) in Water (126.6 mL) and tert-Butanol (126.6 mL) was added methanesulfonamide (2.483 g, 97% Wt, 1 Eq, 25.32 mmol) and the solution was stirred at 3°C for 30 minutes. ethyl (E)-hex-4-enoate (3600 mg, 4 mL, 1 Eq, 25.32 mmol) was added and the reaction was vigorously stirred at 3°C for 7 days. The reaction was quenched by addition of 38 g of sodium sulfite. The reaction was stirred at room temperature for an hour. The mixture was extracted with ethyl acetate (120 mL x 3) and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude was loaded onto a silica gel cartridge and purified by flash chromatography (0-20% EtOAc/Hexane) and MeOH/DCM (0-5%) to yield (S)-5-((S)-1-hydroxyethyl)dihydrofuran-2(3H)-one (2.1 g, 16 mmol, 65 %)(96:4 % ee) as a clear oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 4.34 (td, *J* = 7.4, 5.3 Hz, 1H), 3.78 (p, *J* = 6.4 Hz, 1H), 2.69 – 2.48 (m, 2H), 2.25 (dddd, *J* = 12.7, 9.4, 7.3, 5.3 Hz, 1H), 2.13 – 1.97 (m, 1H), 1.25 (d, *J* = 6.5 Hz, 3H). LCMS: [M]⁺; calculated: 130.063, found 130.200.

[0346] Method of synthesis of (S)-5-((S)-1-((tert butyldimethylsilyl)oxy)ethyl)dihydrofuran-2(3H)-one: To an ice-cooled solution of (S)-5-((S)-1-hydroxyethyl)dihydrofuran-2(3H)-one (1.8 g, 1 Eq, 14 mmol) in Dichloromethane (17 mL) was added imidazole (2.9 g, 3 Eq, 42 mmol), 4-dimethylaminopyridine (0.17 g, 0.1 Eq, 1.4 mmol), and TBDMS-Cl (3.2 g, 1.5 Eq, 21 mmol). After 5 minutes the ice-bath was removed and the reaction was left stirring overnight. The reaction mixture was diluted with dichloromethane and poured into water and the organic layer was further washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography (0-40% EtOAc/Hexane) to give (S)-5-((S)-1-((tert butyldimethylsilyl)oxy)ethyl)dihydrofuran-2(3H)-one (2.17 g, 8.88 mmol, 63 %) was a clear oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 4.29 (ddd, *J* = 7.8, 5.9, 4.0 Hz, 1H), 3.79 (qd, *J* = 6.4, 4.0 Hz, 1H), 2.55 – 2.31 (m, 2H), 2.13 (dddd, *J* = 12.9, 10.1, 7.9, 6.4 Hz, 1H), 2.01 – 1.89 (m, 2H), 1.11 (d, *J* = 6.4 Hz, 3H), 0.80 (s, 9H), 0.00 (s, 6H). LCMS: [M]⁺; calculated: 130.063, found 130.200.

[0347] Method of synthesis of (3R,5S)-3-benzyl-5-((S)-1-((tert-butyldimethylsilyl)oxy)ethyl)dihydrofuran-2(3H)-one: (S)-5-((S)-1-((tert-butyldimethylsilyl)oxy)ethyl)dihydrofuran-2(3H)-one (1880 mg, 1 Eq, 7.692 mmol) was co-evaporated with benzene (10 mL x 3). Dry Tetrahydrofuran (25 mL) was added under argon and the solution was cooled to -78 °C. LDA in THF/Hexanes (906.4 mg, 8.461 mL, 1 molar, 1.1 Eq, 8.461 mmol) was added dropwise and the solution was stirred for 30 minutes. Benzyl bromide

was then added dropwise and the reaction was stirred for 4 hours. The reaction was quenched by addition of 1 mL of 10% citric acid. The solution was then diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude was subjected to flash chromatography to yield (3R,5S)-3-benzyl-5-((S)-1-((tert-butyl)dimethylsilyl)oxy)ethyl) dihydrofuran-2(3H)-one (1.80 g, 5.38 mmol, 70.0 %) as a clear oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.16 (m, 5H), 4.18 – 4.03 (m, 1H), 3.72 (td, *J* = 6.5, 5.2 Hz, 1H), 3.19 (dd, *J* = 13.8, 4.5 Hz, 1H), 3.06 (tdd, *J* = 9.4, 7.3, 4.6 Hz, 1H), 2.79 (dd, *J* = 13.8, 9.3 Hz, 1H), 2.18 – 1.96 (m, 2H), 1.22 (d, *J* = 6.5 Hz, 3H). LCMS: [M+H]⁺; calculated: 335.204, found 335.200.

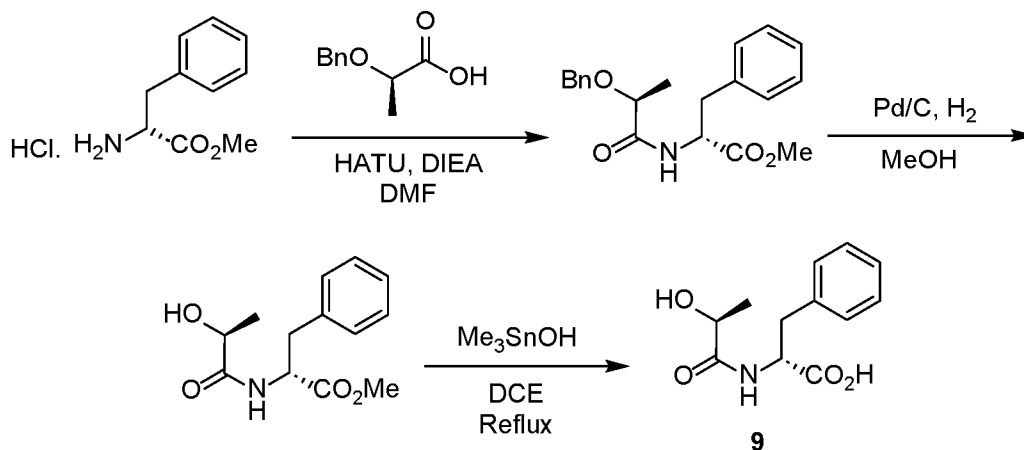
[0348] Method of synthesis of (3R,5S)-3-benzyl-5-((S)-1-hydroxyethyl) dihydrofuran-2(3H)-one: To an ice-cooled solution of (3R,5S)-3-benzyl-5-((S)-1-((tert-butyl)dimethylsilyl)oxy)ethyl) dihydrofuran-2(3H)-one (1.149 g, 1 Eq, 3.435 mmol) in methanol (17.17 mL) was added ((1R,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonic acid (119.7 mg, 0.15 Eq, 515.2 μmol) and the reaction was stirred overnight. The reaction was quenched with aqueous saturated sodium bicarbonate solution and diluted with dichloromethane. The layers were partitioned and the aqueous layer was extracted with dichloromethane twice. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Flash chromatography (0-100% EtOAc/Hexane) gave (3R,5S)-3-benzyl-5-((S)-1-hydroxyethyl) dihydrofuran-2(3H)-one (0.68 g, 3.1 mmol, 90 %) as a clear oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.16 (m, 5H), 4.18 – 4.03 (m, 1H), 3.72 (td, *J* = 6.5, 5.2 Hz, 1H), 3.19 (dd, *J* = 13.8, 4.5 Hz, 1H), 3.06 (tdd, *J* = 9.4, 7.3, 4.6 Hz, 1H), 2.79 (dd, *J* = 13.8, 9.3 Hz, 1H), 2.18 – 1.96 (m, 2H), 1.22 (d, *J* = 6.5 Hz, 3H). LCMS: [M+H]⁺; calculated: 221.117, found 221.200.

[0349] Method of synthesis of Sodium (4S,5S)-2-benzyl-4,5-dihydroxyhexanoate (8b): To a solution of (3R,5S)-3-benzyl-5-((S)-1-hydroxyethyl) dihydrofuran-2(3H)-one (200.4 mg, 1 Eq, 909.8 μmol) in Dichloromethane (9 mL) was added sodium trimethylsilanolate (107.2 mg, 1.05 Eq, 955.3 μmol) and the reaction was stirred at room temperature under argon for 3 days. The white precipitate was filtered, washed with hexane, and dried under vacuum to yield the product (150 mg, 576 μmol, 63.3%) as mixture between diastereomers (1.8:1) of sodium (2R,4S,5S)-2-benzyl-4,5-dihydroxyhexanoate and sodium (2S,4S,5S)-2-benzyl-4,5-dihydroxyhexanoate respectively. ¹H NMR (400 MHz, Deuterium Oxide) δ 7.39-7.33 (m, 2H), 7.31-7.25 (m, 3H), 3.72 (qd, *J* = 6.5, 4.6 Hz, 1H, isomer 2), 3.62 (m, 1H, isomer 1), 3.47 (dt, *J* = 8.1, 5.0 Hz, 1H,

isomer 2), 3.36 (ddd, $J = 10.5, 5.5, 2.4$ Hz, 1H, isomer 1), 2.92 – 2.63 (m, 3H), 1.81 – 1.64 (m, 1H), 1.47 (m, 1H), 1.15 (m, 3H). LCMS: $[M+H]^+$; calculated: 239.128, found 239.200.

EXAMPLE 8

Method of Synthesis of ((R)-2-hydroxypropanoyl)-D-phenylalanine (9b)



[0350] Method of Synthesis of (R)-2-(benzyloxy)propanoyl)-D-phenylalanine methyl ester: To a solution of *D*-phenylalanine methyl ester hydrochloride (500 mg, 2.59 mmol, 1 eq.) and (R)-2-(benzyloxy)propanoic acid (503 mg, 2.79 mmol, 1 eq.) in dimethylformamide (10 mL) was added diisopropylethylamine (0.97 mL, 5.58 mmol, 2 eq.) followed by (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (1.17 g, 3.07 mmol, 1.1 eq.). After 2 hours the reaction was quenched with water and the mixture was diluted with ethyl acetate and left stirring for 15 minutes. The layers were then partitioned, and the aqueous layer was further extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (0-40%; EtOAc/Hexane). The desired compound was obtained as a colorless oil (788 mg, 82.7%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.24 (m, 8H), 7.16 – 7.10 (m, 2H), 4.94 (m, 1H), 4.58 (d, $J = 11.4$ Hz, 1H), 4.49 (d, $J = 11.4$ Hz, 1H), 3.95 (q, $J = 6.8$ Hz, 1H), 3.77 (s, 3H), 3.21 (dd, $J = 13.9, 5.7$ Hz, 1H), 3.12 (dd, $J = 13.9, 6.5$ Hz, 1H), 1.35 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 174.56, 169.45, 129.26, 128.62, 128.56, 128.03, 127.96, 127.18, 76.14, 72.12, 52.36, 52.31, 37.99, 18.79. LCMS: $[M+H]^+$; calculated: 224.130, found 224.200.

[0351] Method of synthesis of ((R)-2-hydroxypropanoyl)-D-phenylalanine methyl ester: To a solution ((R)-2-(benzyloxy)propanoyl)-D-phenylalanine methyl ester (769 mg, 2.25 mmol) in methanol (10 mL) was added palladium on carbon (77 mg, 10%; 50% water (w/w)). The mixture was evacuated using house vacuum and purged with argon. This was repeated three times, after which a hydrogen balloon was fitted and the mixture was evacuated and purged with hydrogen

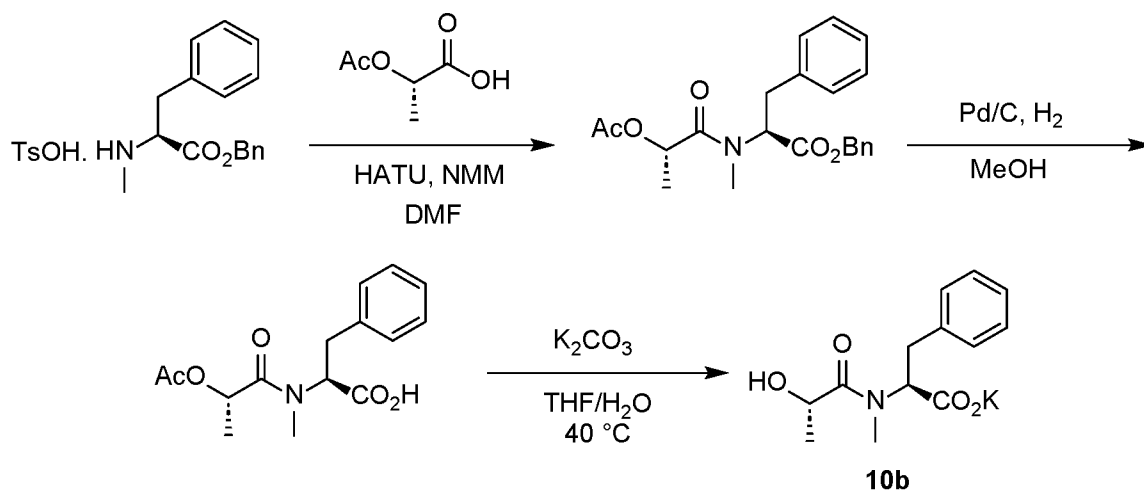
three times. The reaction was stirred overnight. Additional palladium on carbon was added (30 mg) and the reaction mixture was heated to 40°C. The reaction was removed from heating when LCMS indicated complete conversion. The mixture was diluted with ethyl acetate and slurried with celite and filtered through a pad of celite and silica gel. The filtrate was concentrated and the residue was purified by flash chromatography (0-50%; EtOAc/Hexane) to give the product as a colorless oil (465 mg, 1.85 mmol, 82%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.21 (m, 3H), 7.17 – 7.02 (m, 2H), 4.87 (m, 1H), 4.19 (m, 1H), 3.73 (s, 3H), 3.19 (dd, *J* = 13.9, 5.7 Hz, 1H), 3.09 (dd, *J* = 13.8, 6.6 Hz, 1H), 1.32 (d, *J* = 6.7 Hz, 3H). LCMS: [M+H]⁺; calculated: 252.123, found 252.200.

[0352] Method of synthesis of ((*R*)-2-hydroxypropanoyl)-*D*-phenylalanine (9b): To a solution ((*R*)-2-hydroxypropanoyl)-*D*-phenylalanine methyl ester (465 mg, 2.25 mmol, 1 eq.) in 1,2-dichloroethane (15 mL) was added trimethyltinhydroxide (1.62 g, 8.96 mmol, 4.8 eq.) and the reaction was heated to 80°C and stirred for 16 hours. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate and added to an aqueous solution of potassium bisulfate (0.02 M). The organic layers were separated and the aqueous layer was further extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The white solid was recrystallized from ethyl acetate/hexane to give the desired compound as a white solid (200 mg, 46%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.35 – 7.12 (m, 5H), 4.69 (dd, *J* = 7.7, 5.2 Hz, 1H), 4.06 (q, *J* = 6.9 Hz, 1H), 3.23 (dd, *J* = 13.9, 5.2 Hz, 1H), 3.06 (dd, *J* = 13.8, 7.7 Hz, 1H), 1.21 (d, *J* = 6.8 Hz, 3H). LCMS: [M+H]⁺; calculated: 238.110, found 238.200.

EXAMPLE 9

Method of Synthesis of

Potassium N-((*S*)-2-hydroxypropanoyl)-N-methyl-*L*-phenylalaninate (10b)



[0353] Method of Synthesis of Benzyl N-((S)-2-acetoxypropanoyl)-N-methyl-*L*-phenylalaninate: To a solution of benzyl methyl-*L*-phenylalaninate 4-methylbenzenesulfonate (1000 mg, 1 Eq, 2.265 mmol) and (S)-2-acetoxypropanoic acid (329.1 mg, 279 μ L, 1.1 Eq, 2.491 mmol) in N,N-Dimethylformamide (7 mL) was added 4-methylmorpholine (710.2 mg, 0.77 mL, 3.1 Eq, 7.021 mmol) and HATU (1.033 g, 1.2 Eq, 2.718 mmol). After an hour the reaction was quenched with dilute potassium bisulfate and diluted with ethyl acetate. The aqueous layer was extracted twice more with ethyl acetate. The combined organic extracts were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was loaded onto a silica cartridge and purified by COMBIFLASH chromatography (EtOAc/Hexane (0-50%)) to give the desired product as a colorless oil (709.5 mg, 1.85 mmol, 82%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.13 (m, 10H), 5.32 – 5.16 (m, 2H), 5.15 (d, J = 6.6 Hz, 2H), 3.37 (dd, J = 14.6, 6.1 Hz, 1H), 3.09 (dd, J = 14.6, 9.9 Hz, 1H), 2.82 (s, 3H), 2.02 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H). LCMS: $[\text{M}+\text{H}]^+$; calculated: 384.180, found 384.200.

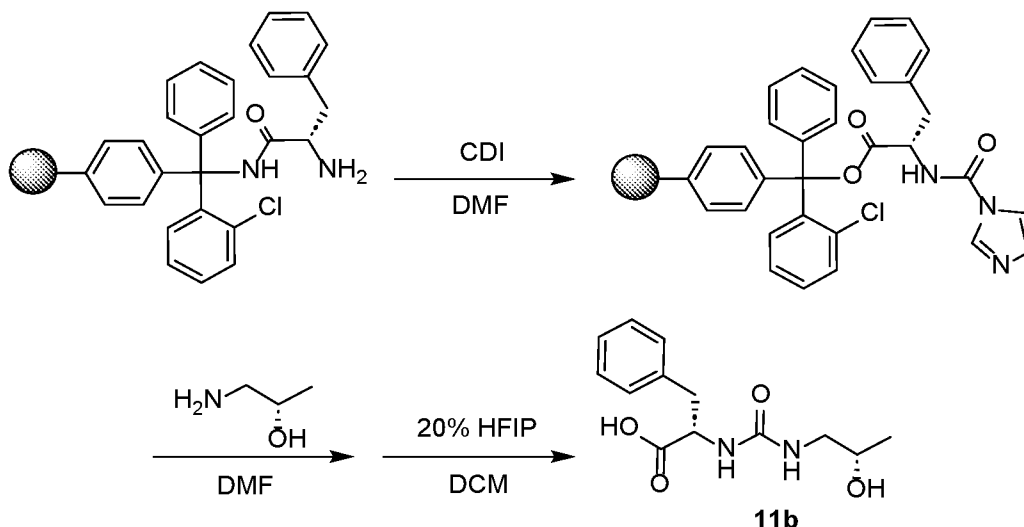
[0354] Method of Synthesis of N-((S)-2-acetoxypropanoyl)-N-methyl-*L*-phenylalanine: To a solution of benzyl N-((R)-2-acetoxypropanoyl)-N-methyl-*L*-phenylalaninate (699 mg, 1 Eq, 1.82 mmol) in methanol (5 mL) was added Pd/C (100 mg)(10%, 50% water). The mixture was then evacuated and purged with hydrogen. This was repeated twice and the reaction was stirred at room temperature overnight. Celite was added to the reaction mixture, which was then filtered through celite and concentrated under reduced pressure to give the product as a colorless oil (quantitative). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.10 (m, 5H), 5.27 (q, J = 6.8 Hz, 1H), 5.07 – 4.95 (m, 1H), 3.43 – 3.31 (m, 1H), 3.16 (dd, J = 14.5, 10.5 Hz, 1H), 2.85 (s, 3H), 2.04 (s, 3H), 1.36 (d, J = 6.7 Hz, 3H). LCMS: $[\text{M}+\text{H}]^+$; calculated: 294.133, found 294.200.

[0355] Method of Synthesis of Potassium N-((S)-2-hydroxypropanoyl)-N-methyl-*L*-phenylalaninate (10b): To solution of N-((R)-2-acetoxypropanoyl)-N-methyl-*L*-phenylalanine (230 mg, 1 Eq, 784 μ mol) in Tetrahydrofuran (5.88 mL) and Water (1.96 mL) was added potassium carbonate (1.08 g, 10 Eq, 7.84 mmol). The reaction mixture was heated to 40 $^{\circ}\text{C}$ and stirred for 3 days. The reaction was concentrated under reduced pressure and the residue was then dissolved in acetonitrile and filtered. The filtrate was diluted with water and loaded onto a RP-C18 column and purified by COMBIFLASH chromatography column using water/acetonitrile. The combined fractions gave the product as a glassy solid (135 mg, 0.54 mmol, 69%). LCMS: $[\text{M}+\text{H}]^+$; calculated: 252.123, measured 252.200. ^1H NMR (400 MHz, Deuterium Oxide). Mixture of isomers (Ratio: 1.5:1). Addition of a drop of DCl shifted the ratio to 2:1). ^1H NMR (400 MHz, Deuterium Oxide) δ 7.28 (m, J = 7.5 Hz, 2H), 7.24 – 7.14 (m, 3H), 4.77 (dd, J = 11.7,

4.7 Hz, 1H), 4.51 (m, 1H), 4.42 (q, $J = 6.5$ Hz, 1H, isomer 2), 4.23 (q, $J = 6.5$ Hz, 1H, isomer 1), 3.26 (m, 1H, isomer 1/2), 2.97 (m, 1H, isomer 1/2), 2.85 (s, 3H, isomer 1), 2.75 (s, 3H, isomer 2), 1.15 (d, $J = 6.6$ Hz, 3H, isomer 2), 0.50 (d, $J = 6.5$ Hz, 3H, isomer 1). ^{13}C NMR (101 MHz, Deuterium Oxide) δ 177.16, 176.59, 175.58, 138.57, 138.32, 129.17, 128.95, 128.86, 128.53, 126.90, 126.47, 64.63, 64.55, 63.54, 62.24, 35.39, 34.57, 32.77, 30.77, 18.65, 18.35.

EXAMPLE 10

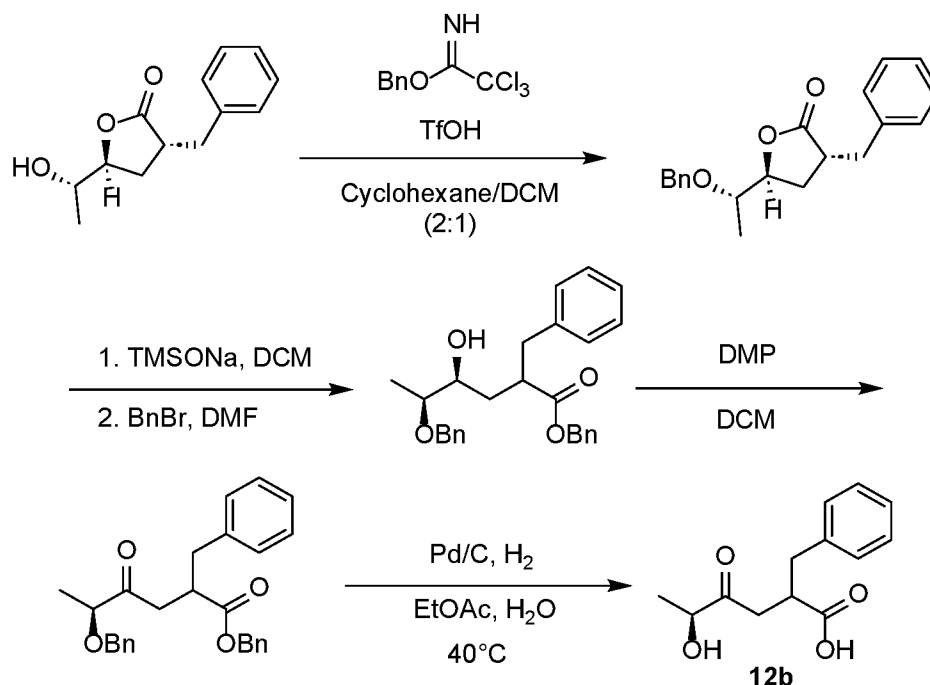
Method of synthesis of (((S)-2-hydroxypropyl)carbamoyl)-L-phenylalanine (11b)



[0356] Method of synthesis of (((S)-2-hydroxypropyl)carbamoyl)-L-phenylalanine (11b): 2-Chlorotrityl resin, preloaded with L-Phenylalanine (0.74 mmol/g resin, 354 mg, 0.48 mmol) was treated with a solution of CDI (631 mg, 5 Eq, 3.89 mmol) in N,N-Dimethylformamide (10 mL). The reaction was shaken at room temperature for 4 hours and the resin was then washed with DMF (x3) and DCM (x2), and diethyl ether (x1). The resin was swollen in THF (10 mL) and (S)-1-aminopropan-2-ol (584 mg, 10 Eq, 7.78 mmol) was added and the reaction was shaken at room temperature overnight. The next day the resin was washed with DMF (x3) and DCM (x2), diethyl ether (x1), and dried under argon. The resin was then treated with a solution of HFIP/DCM (1:4) for 1.5 hours, after which the reaction was filtered and the resin was washed with dcm once. This sequence further repeated twice and the combined filtrates were concentrated under reduced pressure. The residue was then purified by RP-HPLC to give the product as a white solid (115 mg, 0.43 mmol, 56%). ^1H NMR (400 MHz, Methanol- d_4) δ 7.31 – 7.24 (m, 2H), 7.24 – 7.16 (m, 3H), 4.55 (dd, $J = 7.7, 5.2$ Hz, 1H), 3.74 (pd, $J = 6.4, 4.5$ Hz, 1H), 3.14 (ddd, $J = 13.7, 4.9, 3.1$ Hz, 2H), 2.97 (ddd, $J = 13.9, 7.3, 3.4$ Hz, 2H), 1.09 (d, $J = 6.3$ Hz, 3H). LCMS: $[\text{M}+\text{H}]^+$; calculated: 267.134, found 267.200.

EXAMPLE 11

Method of synthesis of (5S)-2-benzyl-5-hydroxy-4-oxohexanoic acid (12b)



[0357] Method of synthesis of (3R,5S)-3-benzyl-5-((S)-1-(benzyloxy)ethyl)dihydrofuran-2(3H)-one: To a solution of (3R,5S)-3-benzyl-5-((S)-1-hydroxyethyl)dihydrofuran-2(3H)-one (668.5 mg, 1 Eq, 3.035 mmol) and benzyl 2,2,2-trichloroacetimidate (1.150 g, 845.9 μ L, 1.5 Eq, 4.552 mmol) in Dichloromethane (7.5 mL) and Cyclohexane (15 mL) was added trifluoromethanesulfonic acid (68.32 mg, 40.42 μ L, 0.15 Eq, 455.2 μ mol) and the reaction was stirred at ambient temperature for 2 days. The reaction was quenched with saturated aqueous sodium bicarbonate solution, extracted with dichloromethane, washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. Flash chromatography (0-40%, EtOAc/Hexane) yielded (3R,5S)-3-benzyl-5-((S)-1-(benzyloxy)ethyl)dihydrofuran-2(3H)-one (0.75 g, 2.4 mmol, 80 %) as a colorless oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.11 (m, 8H), 7.11 – 7.04 (m, 2H), 4.55 (d, J = 11.8 Hz, 1H), 4.32 (d, J = 11.8 Hz, 1H), 4.21 (dt, J = 8.0, 4.0 Hz, 1H), 3.43 (qd, J = 6.4, 3.7 Hz, 1H), 3.13 (dd, J = 13.9, 4.4 Hz, 1H), 3.00 (qd, J = 9.3, 4.4 Hz, 1H), 2.61 (dd, J = 13.9, 9.7 Hz, 1H), 1.99-1.86 (m, 2H), 1.15 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 179.18, 138.65, 138.20, 128.94, 128.77, 128.53, 127.84, 127.81, 126.78, 80.87, 76.08, 71.20, 41.17, 36.96, 30.12, 15.29. LCMS: $[\text{M}+\text{NH}_4]^+$; calculated: 328.191, found 328.400.

[0358] Method of synthesis of Benzyl (2R,4S,5S)-2-benzyl-5-(benzyloxy)-4-hydroxyhexanoate: To a solution of (3R,5S)-3-benzyl-5-((S)-1-(benzyloxy)ethyl)dihydrofuran-2(3H)-one (509.0 mg, 1 Eq, 1.640 mmol) in dichloromethane (8.199 mL) was added sodium trimethylsilanolate (193.2 mg, 1.05 Eq, 1.722 mmol) and the reaction was stirred for 5 days at

room temperature under argon. The reaction was concentrated under reduced pressure and dried under vacuum. The residue was dissolved in dry N,N-Dimethylformamide (7 mL) and benzyl bromide (280.5 mg, 195.1 μ L, 1 Eq, 1.640 mmol) was added and the reaction was stirred under argon overnight. The reaction was diluted with water and ethyl acetate and left stirring for 20 minutes. The layers were partitioned and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. Flash chromatography (0-50% EtOAc/Hexane) gave benzyl (2R,4S,5S)-2-benzyl-5-(benzyloxy)-4-hydroxyhexanoate (519.1 mg, 1.240 mmol, 75.63 %)(6:4 mix of diastereomers) as a sticky clear oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.10 (m, 15H), 5.11 – 4.96 (m, 2H), 4.64-4.60 (m, 1H), 4.39 (m, 1H), 3.54—3.46 (m, 1H, isomer 2), 3.43 – 3.27 (m, 3H), 3.17-3.07 (m, 1H, isomer 1), 3.03 – 2.76 (m, 3H), 1.98 – 1.88 (m, 1H, isomer 2), 1.83 (ddd, J = 13.4, 10.7, 2.3 Hz, 1H, isomer 1), 1.68 (ddd, J = 14.0, 5.6, 3.4 Hz, 1H, isomer 2), 1.60 (ddd, J = 13.8, 10.3, 3.4 Hz, 1H, isomer 1), 1.15 (d, J = 6.2 Hz, 1H, isomer 2), 1.12 (d, J = 6.1 Hz, 1H, isomer 1). LCMS: $[\text{M}+\text{H}]^+$; calculated: 419.222, found 419.400.

[0359] Method of synthesis of Benzyl (2R,4S,5S)-2-benzyl-5-(benzyloxy)-4-hydroxyhexanoate: To a solution of (3R,5S)-3-benzyl-5-((S)-1-(benzyloxy)ethyl)dihydrofuran-2(3H)-one (509.0 mg, 1 Eq, 1.640 mmol) in dichloromethane (8.199 mL) was added sodium trimethylsilanolate (193.2 mg, 1.05 Eq, 1.722 mmol) and the reaction was stirred for 5 days at room temperature under argon. The reaction was concentrated under reduced pressure and dried under vacuum. The residue was dissolved in dry N,N-Dimethylformamide (7 mL) and benzyl bromide (280.5 mg, 195.1 μ L, 1 Eq, 1.640 mmol) was added and the reaction was stirred under argon overnight. The reaction was diluted with water and ethyl acetate and left stirring for 20 minutes. The layers were partitioned and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. Flash chromatography (0-50% EtOAc/Hexane) gave benzyl (2R,4S,5S)-2-benzyl-5-(benzyloxy)-4-hydroxyhexanoate (519.1 mg, 1.240 mmol, 75.63 %)(6:4 mix of diastereomers) as a sticky clear oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.10 (m, 15H), 5.11 – 4.96 (m, 2H), 4.64-4.60 (m, 1H), 4.39 (m, 1H), 3.54—3.46 (m, 1H, isomer 2), 3.43 – 3.27 (m, 3H), 3.17-3.07 (m, 1H, isomer 1), 3.03 – 2.76 (m, 3H), 1.98 – 1.88 (m, 1H, isomer 2), 1.83 (ddd, J = 13.4, 10.7, 2.3 Hz, 1H, isomer 1), 1.68 (ddd, J = 14.0, 5.6, 3.4 Hz, 1H, isomer 2), 1.60 (ddd, J = 13.8, 10.3, 3.4 Hz, 1H, isomer 1), 1.15 (d, J = 6.2 Hz, 1H, isomer 2), 1.12 (d, J = 6.1 Hz, 1H, isomer 1). LCMS: $[\text{M}+\text{H}]^+$; calculated: 419.222, found 419.400.

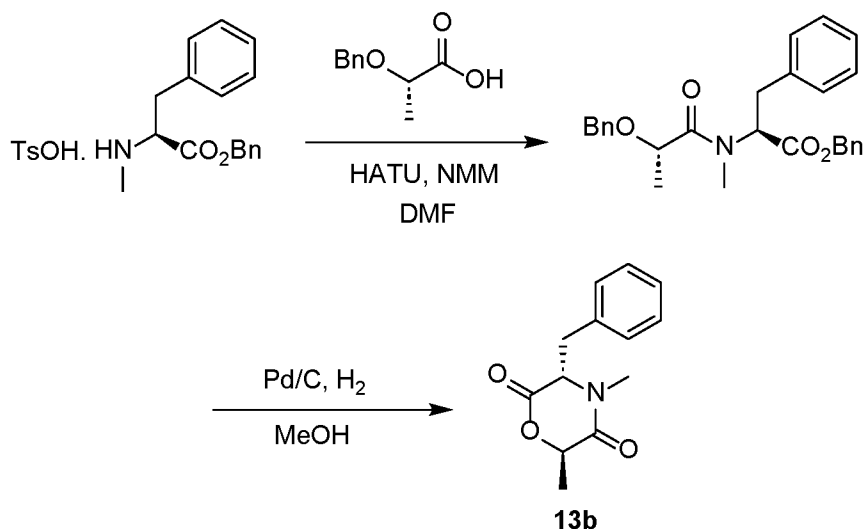
[0360] Method of synthesis of Benzyl (5S)-2-benzyl-5-(benzyloxy)-4-oxohexanoate: To an ice-cooled solution of benzyl (4S,5S)-2-benzyl-5-(benzyloxy)-4-hydroxyhexanoate (225 mg, 1

Eq, 538 μmol) in dichloromethane (6 mL) was added DMP (453 mg, 1.99 Eq, 1.07 mmol). The reaction was allowed to warm to room temperature. After 4.5 hours DMP (114 mg, 0.5 Eq, 269 μmol) was added. After another hour DMP (134 mg, 0.588 Eq, 316 μmol) was added. After 1 hour the reaction was diluted with dichloromethane and filtered through a celite and silica gel plug. The solution was concentrated under reduced pressure and diluted with ethyl acetate and a 1:1 mixture of aqueous saturated sodium bicarbonate and sodium thiosulfate. The layers were partitioned and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated sodium bicarbonate (x2) and brine, dried of magnesium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography (0-20% EtOAc/Hexane) gave benzyl (5S)-2-benzyl-5-(benzyloxy)-4-oxohexanoate (6:4 mix of diastereomers) as a clear oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.19 (m, 13H), 7.19 – 7.10 (m, 2H), 5.17 – 5.06 (m, 2H), 4.55 (d, J = 11.6 Hz, 1H), 4.44 (d, J = 11.8 Hz, 1H), 3.93-3.87 (m, 1H), 3.31-3.22 (m, 1H), 3.14 – 2.99 (m, 2H), 2.85-2.76 (m, 1H), 2.68 (dd, J = 18.7, 4.4 Hz, 1H, isomer 1), 2.60 (dd, J = 18.5, 4.2 Hz, 1H, isomer 2), 1.33 – 1.25 (m, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 175.91, 175.53, 139.07, 138.99, 138.37, 136.07, 129.16, 129.09, 128.60, 128.57, 128.55, 128.52, 128.32, 128.19, 128.15, 127.94, 127.90, 126.53, 78.54, 78.16, 77.36, 73.51, 72.93, 71.17, 71.12, 66.32, 66.29, 60.54, 44.84, 43.93, 39.32, 38.50, 35.47, 35.20, 21.20, 15.61, 15.59, 14.35. . LCMS: $[\text{M}+\text{NH}_4]^+$; calculated: 439.000, found: 439.188.

[0361] Method of synthesis of (5S)-2-benzyl-5-hydroxy-4-oxohexanoic acid (12b): A flask was charged with benzyl (5S)-2-benzyl-5-(benzyloxy)-4-oxohexanoate (191 mg, 1 Eq, 459 μmol), Ethyl acetate (3 mL), and Water (3 mL). The flask was purged with argon and palladium on carbon (10% (50% water)) (60 mg) was added. The flask was then fitted with a hydrogen balloon, purged, and heated to 40°C overnight. The reaction was then filtered through celite and concentrated under reduced pressure. The residue was loaded onto a C18 cartridge and purified by reverse phase flash chromatography (0-50% Acetonitrile/Water). Combined fractions were lyophilized to give the desired product (5S)-2-benzyl-5-hydroxy-4-oxohexanoic acid (70 mg, 0.30 mmol, 65 %), as a 6:4 mix of diastereomers. LCMS: $[\text{M}+\text{NH}_4]^+$; calculated: 254.139, found: 254.400.

EXAMPLE 12

Method of synthesis of Benzyl N-((S)-2-(benzyloxy)propanoyl)-N-methyl-L-phenylalaninate



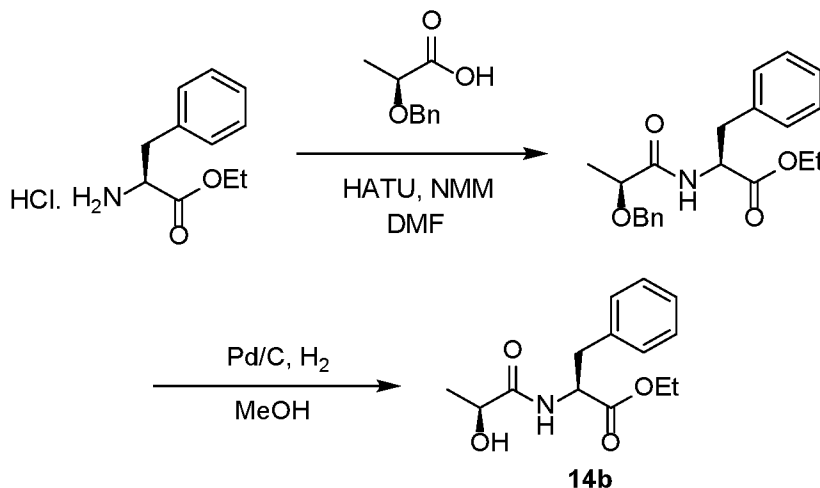
[0362] Method of synthesis of Benzyl N-((S)-2-(benzyloxy)propanoyl)-N-methyl-L-phenylalaninate: To an ice-cooled solution of benzyl methyl-L-phenylalaninate 4-methylbenzenesulfonate (1000 mg, 1 Eq, 2.265 mmol), (S)-2-(benzyloxy)propanoic acid (448.9 mg, 1.1 Eq, 2.491 mmol), and N-methylmorpholine (504.0 mg, 548 μ L, 2.2 Eq, 4.983 mmol) in N,N-Dimethylformamide (5 mL) was added HATU (1.033 g, 1.2 Eq, 2.718 mmol). After 10 minutes the ice-bath was removed and the reaction was left stirring for 1.5 hours at room temperature. The reaction mixture was diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate twice and the combined organic layers were washed with water, saturated sodium bicarbonate, brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (0-30% EtOAc/Hexane) gave the product as a clear oil (795 mg, 1.84 mmol, 81%). LCMS: $[M+H]^+$; calculated: 432.217, found 432.200.

[0363] Method of synthesis of (3S,6S)-3-benzyl-4,6-dimethylmorpholine-2,5-dione (13b): To a solution of benzyl N-((S)-2-(benzyloxy)propanoyl)-N-methyl-L-phenylalaninate (388 mg, 1 Eq, 899 μ mol) in Methanol (8 mL) was added Pd/C (96 mg) (10%, 50% water). The mixture was then evacuated and purged with hydrogen. This was repeated twice and the reaction was heated to 40°C and stirred overnight. Celite was added to the reaction mixture, which was then filtered through celite and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with aqueous saturated sodium bicarbonate, brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give (3S,6S)-3-benzyl-4,6-dimethylmorpholine-2,5-dione as a white solid. ^1H NMR (400 MHz, Chloroform- d) δ 7.38 – 7.25 (m, 3H), 7.16 – 7.09 (m, 2H), 4.72 (q, J = 7.2 Hz, 1H), 4.43 (t, J = 4.3 Hz, 1H), 3.34 (dd, J = 14.1, 4.1 Hz, 1H), 3.25 (dd, J = 14.1, 4.6 Hz, 1H), 3.07 (s, 3H), 0.64 (d, J = 7.2 Hz, 3H). ^{13}C

NMR (101 MHz, Chloroform-*d*) δ 165.76, 165.57, 134.29, 130.25, 129.38, 128.22, 75.81, 62.04, 37.43, 32.60, 19.39. LCMS: $[M+H]^+$; calculated: 234.112, found 234.200.

EXAMPLE 13

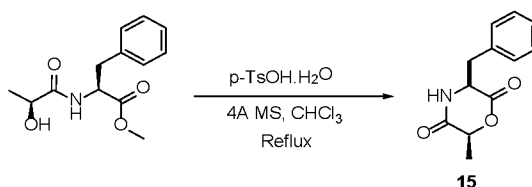
Method of synthesis of Ethyl ((S)-2-hydroxypropanoyl)-L-phenylalaninate (14b)



[0364] Method of synthesis of Ethyl ((S)-2-hydroxypropanoyl)-L-phenylalaninate (14): To an ice-cooled solution of ethyl *L*-phenylalaninate hydrochloride (1020 mg, 1 Eq, 4.441 mmol), (S)-2-(benzyloxy)propanoic acid (880.2 mg, 1.1 Eq, 4.885 mmol), and N-methylmorpholine (988.2 mg, 1.07 mL, 2.2 Eq, 9.769 mmol) in N,N-Dimethylformamide (10 mL) was added HATU (2.026 g, 1.2 Eq, 5.329 mmol). After 10 minutes the ice-bath was removed and the reaction was left stirring for 1 hour at room temperature. The reaction mixture was diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate twice and the combined organic layers were washed with water, saturated sodium bicarbonate, brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in methanol (7 mL) and Pd/C (10%; 50% water) (150 mg) was added. The mixture was then evacuated and purged with hydrogen. This was repeated twice and the reaction was stirred at 40°C overnight. Celite was added to the reaction mixture, which was then filtered through celite and concentrated under reduced pressure. Purification by flash chromatography (0-100% EtOAc/Hexane) gave the product as a clear oil (943 mg, 3.55 mmol, 80% over 2 steps). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.18 (m, 2H), 7.15 – 7.08 (m, 2H), 6.98 (s, 1H), 4.83 (dt, J = 8.4, 6.2 Hz, 1H), 4.22 – 4.06 (m, 3H), 3.21 – 3.03 (m, 2H), 1.32 (d, J = 6.8 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 174.26, 171.58, 135.76, 129.29, 128.51, 127.10, 68.33, 61.59, 52.69, 37.99, 21.00, 14.06. : $[M+H]^+$; calculated: 266.138, found 266.200.

EXAMPLE 14

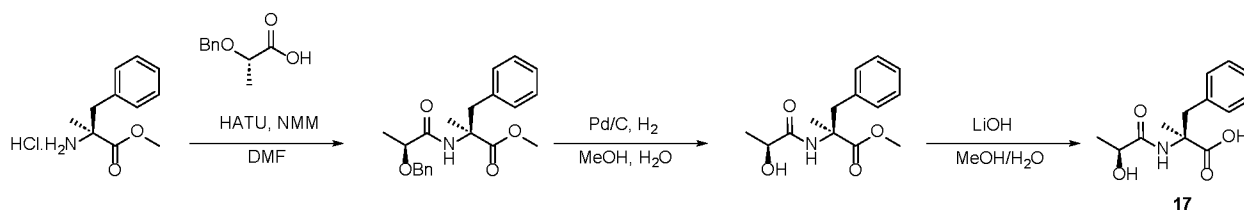
Method of synthesis of (3*S*,6*S*)-6-Methyl-3-(phenylmethyl)-2,5-morpholinedione (15)



[0365] To a solution of methyl ((S)-2-hydroxypropanoyl)-L-phenylalaninate (5.50 g, 21.9 mmol) chloroform (100 mL) was added p-Toluenesulfonic acid monohydrate. The reaction flask was fitted with a Soxhlet extractor (filled with activated 4A molecular sieves) and the reaction mixture was refluxed for 24 hours. The reaction mixture was washed with saturated NaHCO₃ solution, water, and brine. The organic layer was then dried over sodium sulfate and concentrated under reduced pressure. Recrystallization from ethyl acetate/hexane gave the desired product as a white solid (1.35 g, 21.9 mmol, 28%). ¹H NMR (400 MHz, cdcl₃) δ 7.33 (dd, *J* = 14.7, 7.0 Hz, 3H), 7.26 – 7.15 (m, 3H), 5.92 (s, 1H), 4.83 (q, *J* = 6.9 Hz, 1H), 4.40 (dd, *J* = 9.4, 4.0 Hz, 1H), 3.45 (dd, *J* = 14.4, 4.0 Hz, 1H), 2.97 (dd, *J* = 14.3, 9.4 Hz, 1H), 1.43 (d, *J* = 6.9 Hz, 3H). LCMS: [M+H]⁺; calculated: 220.097, found 220.200.

EXAMPLE 15

Method of synthesis of (S)-2-((S)-2-hydroxypropanamido)-2-methyl-3-phenylpropanoic acid (17)



[0366] Methyl (S)-2-((S)-2-hydroxypropanamido)-2-methyl-3-phenylpropanoate

[0367] To an ice-cooled solution of methyl (S)-2-amino-2-methyl-3-phenylpropanoate hydrochloride (890 mg, 1 Eq, 3.87 mmol) and (S)-2-(benzyloxy)propanoic acid (768 mg, 1.1 Eq, 4.26 mmol) in DMF (8 mL) was added N-methylmorpholine (862 mg, 937 μL, 2.2 Eq, 8.52 mmol) and HATU (1.77 g, 1.2 Eq, 4.65 mmol). The ice-bath was removed after 5 minutes and the reaction was stirred at room temperature for 1 hour. Water and ethyl acetate were added, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then dissolved in methanol (10 mL), flushed with argon and treated with palladium on carbon (200 mg) and fitted with a hydrogen balloon. The reaction was stirred overnight at 40 °C. The reaction mixture was filtered through a pad of celite and concentrated under reduced pressure.

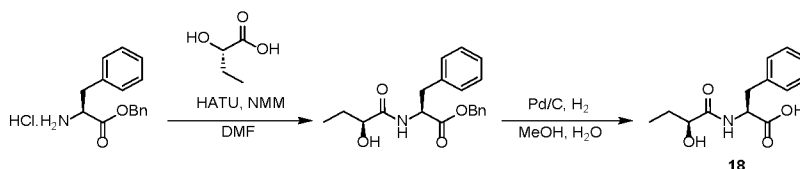
The residue was purified by combiflash chromatography (Ethyl acetate/Hexane (0-80%)) to give the desired product (0.86 g, 82.7% yield over 2 steps). ^1H NMR (400 MHz, cdcl_3) δ 7.34 (s, 1H), 7.31 – 7.22 (m, 2H), 7.11 – 7.02 (m, 2H), 4.14 (dq, J = 10.0, 7.0 Hz, 1H), 3.97 (s, 1H), 3.77 (s, 3H), 3.50 (d, J = 13.5 Hz, 1H), 3.23 (d, J = 13.5 Hz, 1H), 1.66 (s, 3H), 1.39 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, cdcl_3) δ 174.40, 174.16, 136.00, 129.89, 128.24, 127.04, 68.43, 60.65, 52.64, 41.69, 23.12, 20.91. LCMS: $[\text{M}+\text{H}]^+$; calculated: 356.186, found 356.200.

[0368] (S)-2-((S)-2-hydroxypropanamido)-2-methyl-3-phenylpropanoic acid (17)

[0369] To a solution of methyl (S)-2-((S)-2-hydroxypropanamido)-2-methyl-3-phenylpropanoate (0.86 g, 1 Eq, 3.2 mmol) in methanol (9.7 mL) was added a solution of lithium hydroxide (0.12 g, 1.5 Eq, 4.9 mmol) in water (1.1 mL). The reaction was stirred overnight and treated with 1M HCl and extracted with ethyl acetate thrice. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The white solid was recrystallized from ethyl acetate, dissolved in water/acetonitrile and lyophilized. ^1H NMR (500 MHz, DMSO) δ 7.58 (s, 1H), 7.29 – 7.18 (m, 3H), 7.05 (d, J = 7.2 Hz, 2H), 5.65 (dd, J = 4.9, 1.3 Hz, 1H), 3.97 – 3.88 (m, 1H), 3.43 (d, J = 13.3 Hz, 1H), 3.10 (d, J = 13.2 Hz, 1H), 1.53 (d, J = 1.2 Hz, 3H), 1.20 (dd, J = 6.9, 1.2 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 174.96, 173.70, 136.69, 129.83, 127.93, 126.64, 67.37, 59.41, 40.42, 23.11, 20.89. LCMS: $[\text{M}+\text{H}]^+$; calculated: 252.123, found 252.200.

EXAMPLE 16

Method of synthesis of ((S)-2-hydroxybutanoyl)-L-phenylalanine (18)



[0370] Benzyl ((S)-2-hydroxybutanoyl)-L-phenylalaninate

[0371] To an ice-cold solution of benzyl L-phenylalaninate hydrochloride (367 mg, 1 Eq, 1.26 mmol), (S)-2-hydroxybutanoic acid (131 mg, 1 Eq, 1.26 mmol), and N-methylmorpholine (280 mg, 304 μL , 2.2 Eq, 2.77 mmol) in DMF (5 mL) was added HATU (574 mg, 1.2 Eq, 1.51 mmol). After 5 minutes, the ice-bath was removed, and the reaction was left stirring at room temperature for 40 minutes. Water and ethyl acetate was added, and the layers were partitioned. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by combiflash chromatography (0-70% EtOAc/Hexane) to give the product, benzyl ((S)-

2-hydroxybutanoyl)-L-phenylalaninate (370 mg, 1.08 mmol, 86.2 %), as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.33 (m, 3H), 7.31-7.27 (m, 2H), 7.24-7.18 (m, 3H), 7.07 – 6.99 (m, 2H), 6.96 (d, *J* = 8.3 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 5.11 (d, *J* = 12.1 Hz, 1H), 4.94 (dt, *J* = 8.3, 6.2 Hz, 1H), 4.03 (dt, *J* = 7.3, 4.5 Hz, 1H), 3.15 (dd, *J* = 13.9, 5.9 Hz, 1H), 3.08 (dd, *J* = 13.9, 6.5 Hz, 1H), 1.81-1.72 (m, 1H), 1.58 (dp, *J* = 14.6, 7.3 Hz, 1H), 0.89 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 173.62, 171.55, 135.71, 135.16, 129.37, 128.74, 128.68, 128.66, 127.21, 73.11, 67.44, 52.80, 38.11, 27.88, 9.16. LCMS: [M+H]⁺; calculated: 342.170, found 342.200.

[0372] ((S)-2-hydroxybutanoyl)-L-phenylalanine (18)

[0373] To a solution of benzyl ((R)-2-hydroxybutanoyl)-L-phenylalaninate (370 mg, 1 Eq, 1.08 mmol) in Ethyl acetate (5 mL) was added palladium on carbon (115 mg, 10% Wt, 0.1 Eq, 108 μmol). The reaction flask was fitted with a balloon of hydrogen gas and the reaction was stirred at 30 °C for 2 days. The reaction mixture was then filtered through celite and concentrated under reduced pressure. The residue was then dissolved in water/acetonitrile and purified by rf C18 combiflash (0-50% ACN/H₂O (0.05% TFA)). The desired fractions were combined and lyophilized to give the final compound as a white solid (170 mg, 1.08 mmol, 62.4% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.35 (dd, *J* = 8.6, 7.1 Hz, 2H), 7.30 – 7.24 (m, 3H), 3.79 (s, 3H), 2.85 (dd, *J* = 9.6, 7.6 Hz, 1H), 1.86 (dd, *J* = 9.7, 5.0 Hz, 1H), 1.47 (dd, *J* = 7.6, 5.0 Hz, 1H). ¹³C NMR (126 MHz, MeOD) δ 176.75, 174.37, 138.01, 130.42, 129.46, 127.89, 73.80, 54.10, 38.46, 28.61, 9.58. LCMS: [M+H]⁺; calculated: 252.123, found 252.200.

EXAMPLE 17

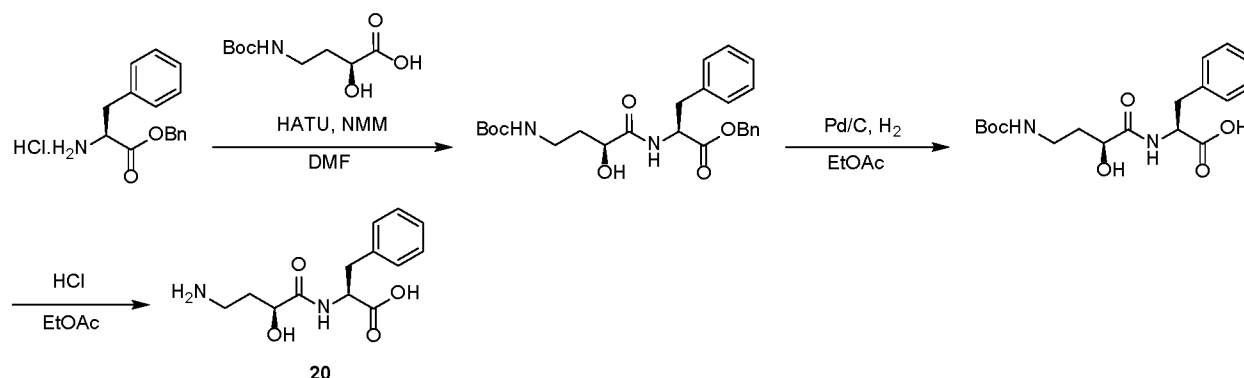
Method of synthesis of Benzyl ((S)-2-hydroxypropanoyl)-L-phenylalaninate (19)

[0374] To a solution of benzyl L-phenylalaninate hydrochloride (405 mg, 1 Eq, 1.39 mmol) in DMF (5 mL) was added (S)-2-hydroxypropanoic acid (150 mg, 1.2 Eq, 1.67 mmol), DIEA (161 mg, 218 μL, 0.9 Eq, 1.25 mmol), and HOBt (213 mg, 1 Eq, 1.39 mmol).dic (175 mg, 217 μL, 1 Eq, 1.39 mmol) was then added and the reaction was stirred at ambient temperature for 4 hours. The reaction was poured into water and the layers were partitioned, and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by combiflash chromatography (0-70% EtOAc/Hexane) to give the final compound as a

colorless oil (389.3 mg, 1.39 mmol, 85.8% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.39 – 7.33 (m, 3H), 7.30-7.27 (m, 2H), 7.24-7.19 (m, 3H), 7.06 – 7.00 (m, 2H), 5.17 (d, J = 12.2 Hz, 1H), 5.11 (d, J = 12.1 Hz, 1H), 4.91 (dt, J = 8.4, 6.2 Hz, 1H), 4.21 – 4.11 (m, 1H), 3.16 (dd, J = 13.9, 5.9 Hz, 1H), 3.08 (dd, J = 13.9, 6.4 Hz, 1H), 1.31 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 174.74, 171.61, 135.68, 135.11, 129.39, 128.73, 128.64, 127.20, 68.43, 68.41, 67.45, 52.78, 52.76, 37.97, 21.03. LCMS: $[\text{M}+\text{H}]^+$; calculated: 328.154, found 328.200.

EXAMPLE 18

Method of synthesis of ((S)-4-amino-2-hydroxybutanoyl)-L-phenylalanine (20)



[0375] Benzyl ((S)-4-((tert-butoxycarbonyl)amino)-2-hydroxybutanoyl)-L-phenylalaninate

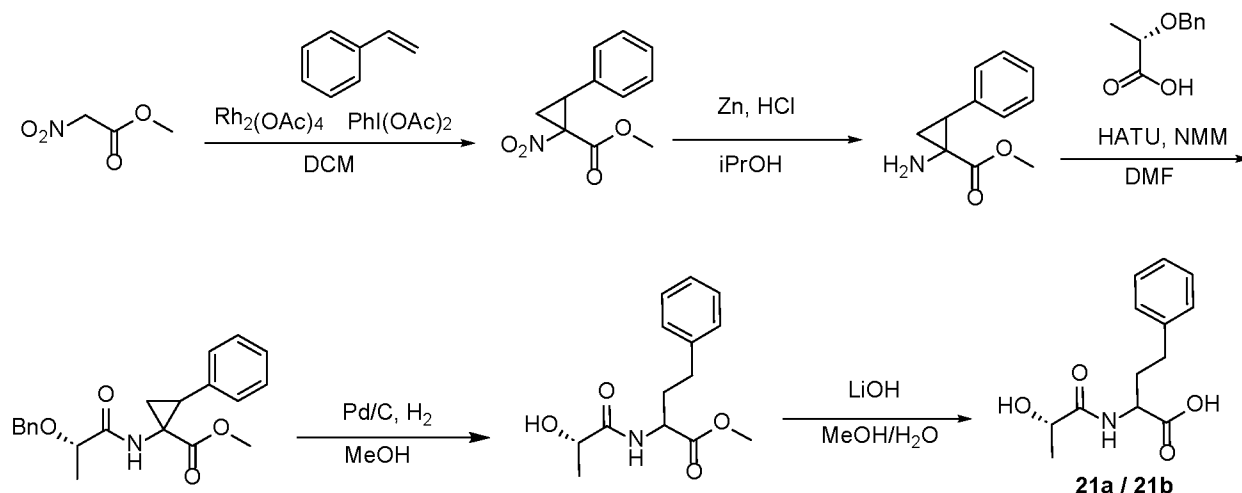
[0376] To a solution of benzyl L-phenylalaninate hydrochloride (133 mg, 1 Eq, 456 μmol) and (S)-4-((tert-butoxycarbonyl)amino)-2-hydroxybutanoic acid (100 mg, 1 Eq, 456 μmol) in DMF (5 mL) was added 4-methylmorpholine (102 mg, 0.11 mL, 2.2 Eq, 1.00 mmol) and 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate (208 mg, 1.2 Eq, 547 μmol). After an hour, the reaction was diluted with water and ethyl acetate and stirred for 5 minutes. The organic layers were then partitioned, and the aqueous layer was extracted with ethyl acetate twice. The combined organic extracts were then washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by combiflash chromatography (0-60% EtOAc/Hexane) gave the desired product as a clear oil (194 mg, 0.46 mmol, 93% yield). ^1H NMR (500 MHz, MeOD) δ 7.40 – 7.28 (m, 5H), 7.25-7.17 (m, 3H), 7.15 – 7.10 (m, 2H), 6.45 (s, 1H), 5.20 – 5.09 (m, 2H), 4.77 (dd, J = 8.0, 5.7 Hz, 1H), 4.00 (dd, J = 8.5, 3.9 Hz, 1H), 3.18 (dd, J = 13.9, 5.8 Hz, 1H), 3.13-3.02 (m, 3H), 1.79 (dtd, J = 14.4, 7.5, 3.9 Hz, 1H), 1.60-1.52 (dq, 1H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.71, 171.26, 157.49, 135.74, 135.10, 129.26, 128.54, 128.48, 128.43, 128.41, 126.98, 79.75, 68.90, 67.14, 52.86, 38.01, 36.42, 35.26, 28.34. LCMS: $[\text{M}-\text{Boc}+\text{H}]^+$; calculated: 357.181, found 357.200.

[0377] ((S)-4-amino-2-hydroxybutanoyl)-L-phenylalanine (20)

[0378] To a solution of benzyl ((S)-4-((tert-butoxycarbonyl)amino)-2-hydroxybutanoyl)-L-phenylalaninate (194 mg, 1 Eq, 425 μ mol) in Ethyl acetate (5 mL) was added palladium on carbon (90.4 mg, 10% Wt, 0.2 Eq, 85.0 μ mol). The reaction flask was fitted with a balloon of hydrogen gas and the reaction was stirred at ambient temperature overnight. The reaction mixture was then filtered through celite and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (3 mL) and treated with 1M HCl in EtOAc (1 mL) and the reaction was stirred at room temperature for 2 hours. The reaction mixture was then concentrated under reduced pressure to give a white solid. The solid was purified by rp C18 combiflash chromatography (H₂O/ACN (0.05% TFA)) to give the final product as a white solid (88.9 mg, 0.33 mmol, 73% yield over 2 steps) ¹H NMR (500 MHz, DMSO) δ 12.98 (s, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.70 (s, 3H), 7.28 (t, J = 7.4 Hz, 2H), 7.24 – 7.16 (m, 3H), 5.99 (s, 1H), 4.56-4.49 (m, 1H), 4.03-3.95 (m, 1H), 3.11 (dd, J = 13.9, 4.8 Hz, 1H), 3.01 (dd, J = 13.9, 8.6 Hz, 1H), 2.85 – 2.64 (m, 2H), 1.90 – 1.79 (m, 1H), 1.70-1.60 (m, 1H). ¹³C NMR (126 MHz, DMSO) δ 172.66, 172.59, 137.30, 129.17, 128.20, 126.51, 68.45, 52.58, 36.48, 35.90, 31.95. LCMS: [M+H]⁺; calculated: 267.134, found 267.200.

EXAMPLE 18

Method of synthesis of 2-((S)-2-hydroxypropanamido)-4-phenylbutanoic acid (21a/21b)



[0379] Methyl 1-nitro-2-phenylcyclopropane-1-carboxylate

[0380] To a solution of methyl 2-nitroacetate (1.29 g, 997 μ L, 1 Eq, 10.8 mmol) and Rhodium(II) Acetate Dimer (47.9 mg, 0.01 Eq, 108 μ mol) in Dichloromethane (12 mL) was added styrene (5.70 g, 6.27 mL, 99% Wt, 5 Eq, 54.2 mmol) followed by phenyl-1,3-iodanediyl diacetate (3.84 g, 1.1 Eq, 11.9 mmol) and the reaction was stirred overnight. The reaction was concentrated and purified via combiflash chromatography (0-10% EtOAc/Hexane) to give the product as a colorless oil (1.37 g, 10.8 mmol, 57.2 % yield). (75:25 E/Z ratio). ¹H NMR (500 MHz, CDCl₃) δ

7.37 – 7.27 (m, 3H), 7.25 – 7.17 (m, 2H), 3.77 (dd, $J = 10.7, 9.2$ Hz, 1H), 3.50 (s, 2H), 2.45 (dd, $J = 9.2, 6.6$ Hz, 1H), 2.22 (dd, $J = 10.7, 6.6$ Hz, 1H).

[0381] Methyl (1S,2R/1R,2S)-1-amino-2-phenylcyclopropane-1-carboxylate

[0382] To a solution of methyl 1-nitro-2-phenylcyclopropane-1-carboxylate (1.37 g, 6.19 mmol) (74:26 E/Z ratio) in isopropanol (12 mL) was added 1M hydrochloric acid (62 mL, 62 mmol), followed by zinc (8.10 g, 124 mmol) and the reaction was stirred for 2 hours at room temperature. The solution was then filtered over celite. The filtrate was extracted with dichloromethane (x 3) and the combined layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using combiflash chromatography (0-100% EtOAc/Hexane) to give the desired compounds: cis-isomers (184.5 mg, 0.96 mmol, 15.6 %) and trans-diastereomers (529.6 mg, 2.77 mmol, 44.7 %) as colorless oils. *Z*-Methyl 1-amino-2-phenyl-1-cyclopropanecarboxylate: ^1H NMR (500 MHz, CDCl_3) δ 7.36 – 7.22 (m, 5H), 3.77 (s, 3H), 2.83 (dd, $J = 9.5, 7.6$ Hz, 1H), 1.84 (dd, $J = 9.6, 5.0$ Hz, 1H), 1.58 (s (br), 2H), 1.45 (dd, $J = 7.6, 4.9$ Hz, 1H). *E*-Methyl 1-amino-2-phenyl-1-cyclopropanecarboxylate: ^1H NMR (500 MHz, CDCl_3) δ 7.29 – 7.21 (m, 2H), 7.21 – 7.14 (m, 3H), 3.29 (s, 2H), 2.65 (t, $J = 8.7$ Hz, 1H), 2.18 (s (br) 2H), 1.98 (dd, $J = 7.9, 5.0$ Hz, 1H), 1.46 (dd, $J = 9.5, 5.0$ Hz, 1H). LCMS: $[\text{M}+\text{H}]^+$; calculated: 192.102, found 192.200.

[0383] Methyl (1R,2S/1R,2S)-1-((S)-2-(benzyloxy)propanamido)-2-phenylcyclopropane-1-carboxylate

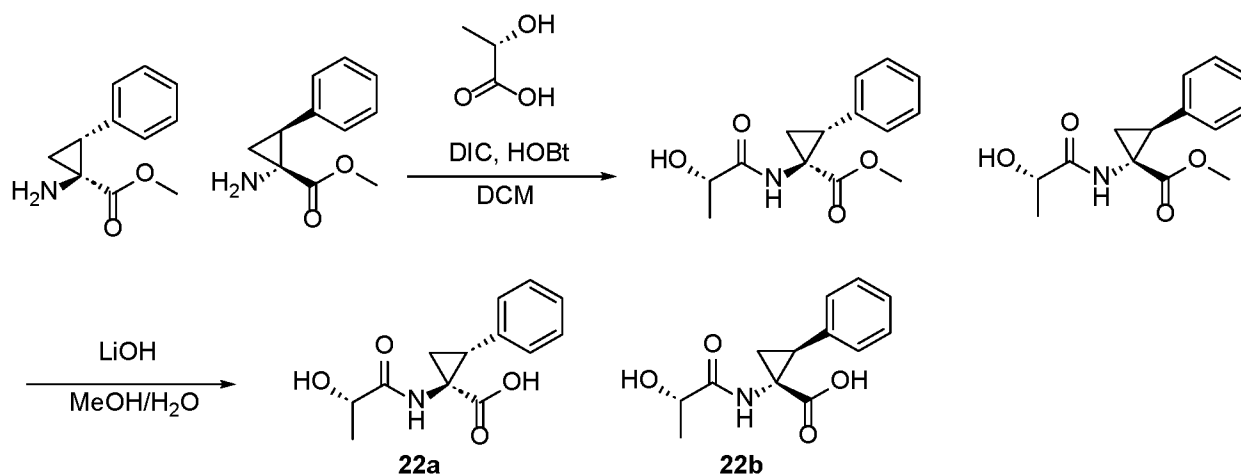
[0384] To a solution of methyl (1S,2R/1R,2S)-1-amino-2-phenylcyclopropane-1-carboxylate (41 mg, 0.21 mmol) and (S)-2-(benzyloxy)propanoic acid (42 mg, 1.1 Eq, 0.24 mmol) in DMF (1 mL) was added DIEA (55 mg, 75 μL , 2 Eq, 0.43 mmol) and HATU (98 mg, 1.2 Eq, 0.26 mmol). The reaction was stirred for one hour at room temperature after which water and ethyl acetate was added. The aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by combiflash chromatography (0-40% EtOAc/Hexane) to give the desired product (mixture of diastereomers) as a white solid (64 mg, 0.21 mmol, 85%). ^1H NMR (500 MHz, CDCl_3) δ 7.43 – 7.34 (m, 6H), 7.29 (dq, $J = 11.2, 5.7$ Hz, 3H), 7.23 (t, $J = 7.3$ Hz, 1H), 4.64 (s, 1H), 4.05 (p, $J = 6.7$ Hz, 1H), 3.36 (s, 2H), 2.84 (t, $J = 9.2$ Hz, 1H), 2.25 (ddd, $J = 11.1, 8.5, 5.6$ Hz, 1H), 1.58 (dt, $J = 9.7, 6.1$ Hz, 1H), 1.50-1.47 (m, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 174.65, 169.76, 169.74, 137.37, 135.31, 135.22, 129.38, 129.35, 128.71, 128.70, 128.25, 128.22, 128.06, 128.03, 128.00, 127.10, 127.08, 76.51, 76.45, 72.23, 72.17, 52.01, 52.00, 39.75, 39.68, 34.85, 34.83, 20.46, 20.28, 18.62, 18.57. LCMS: $[\text{M}+\text{H}]^+$; calculated: 354.170, found 354.200.

[0385] 2-((S)-2-hydroxypropanamido)-4-phenylbutanoic acid (21a/21b)

[0386] To a solution of methyl (1*S*,2*R*/1*R*,2*S*)-1-((*S*)-2-(benzyloxy)propanamido)-2-phenylcyclopropane-1-carboxylate (64 mg, 0.18 mmol) in methanol (12 mL) was added palladium on carbon (50 mg) and the reaction was stirred under hydrogen (1 atm) at 40 °C overnight. The reaction mixture was filtered over celite and concentrated under reduced pressure. The residue was dissolved in methanol (3 mL) and a solution of lithium hydroxide (6.5 mg, 0.27 mmol) in water (0.6 mL) was added and the reaction was stirred overnight at room temperature. The two isomers were separated and purified by rp-HPLC (0-50% ACN/H₂O (0.05% TFA)). Isomer 1: (12.8 mg 51 μmol) ¹H NMR (500 MHz, DMSO) δ 7.84 (d, *J* = 7.6 Hz, 1H), 7.29 - 7.25 (m, 2H), 7.20 - 7.16 (m, 3H), 4.23 - 4.17 (m, 1H), 4.05 (q, *J* = 6.7 Hz, 1H), 2.65 - 2.52 (m, 2H), 2.07 - 1.91 (m, 2H), 1.23 (d, *J* = 6.8 Hz, 3H). ¹³C NMR (126 MHz, DMSO) δ 174.56, 173.45, 141.13, 128.34, 128.32, 125.88, 115.71, 93.81, 67.11, 51.03, 32.95, 31.34, 21.01. LCMS: [M+H]⁺; calculated: 252.120, found 252.200. Isomer 2 (13.8 mg 55 μmol): ¹H NMR (500 MHz, DMSO) δ 7.81 (d, *J* = 7.7 Hz, 1H), 7.29-7.26 (m, *J* = 7.5 Hz, 2H), 7.20-7.16 (m, 3H), 4.23-4.18 (m, 1H), 4.03 (q, *J* = 6.8 Hz, 1H), 2.65 - 2.51 (m, 2H), 2.08 - 1.91 (m, 2H), 1.25 (d, *J* = 6.7 Hz, 3H). ¹³C NMR (126 MHz, DMSO) δ 174.51, 173.47, 141.17, 128.35, 125.90, 67.20, 51.00, 33.04, 31.31, 21.22. LCMS: [M+H]⁺; calculated: 252.120, found 252.200.

EXAMPLE 19

Method of synthesis of (1*R*,2*S*/1*S*,2*R*)-1-((*S*)-2-hydroxypropanamido)-2-phenylcyclopropane-1-carboxylic acid (**22a/b**)

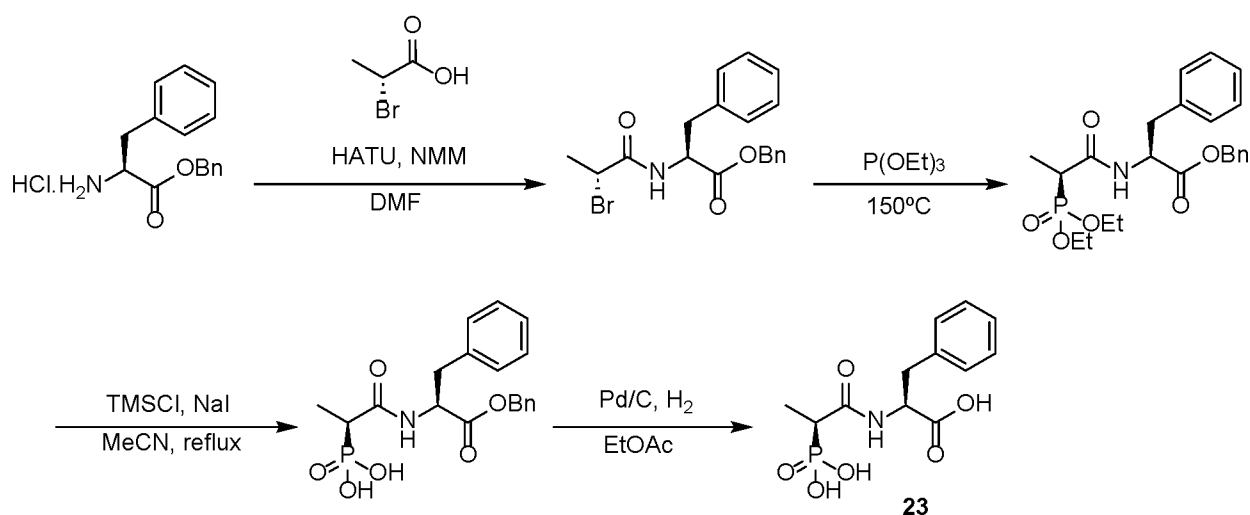


[0387] To a solution of methyl (1*S*,2*R*)-1-amino-2-phenylcyclopropane-1-carboxylate (115.0 mg, 1 Eq, 601.4 μmol), *L*-Lactic acid (67 mg, 57 μL, 1.2 Eq, 0.74 mmol), and HOBT (92.09 mg, 1 Eq, 601.4 μmol) in DMF (0.3 mL) and Dichloromethane (5 mL) was added DIC (75.89 mg, 94.2 μL, 1 Eq, 601.4 μmol) and the reaction was stirred at room temperature under argon for 2 days.

The reaction was diluted with dichloromethane and washed with sodium bicarbonate, water, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by combiflash chromatography (0-100% EtOAc/Hexane) gave products as a 1:1 mixture of the two diastereomers: methyl (1*R*,2*S*/*1S*,2*R*)-1-((*S*)-2-hydroxypropanamido)-2-phenylcyclopropane-1-carboxylic acid as a white solid (110 mg, 0.57 mmol, 75% yield). The solid was dissolved in methanol (5 mL) and an aqueous solution of lithium hydroxide (81 mg, 3.4 mmol, 1 mL). The reaction was stirred overnight and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, treated with 1M HCl. The layers were partitioned, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with water, brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase C18 combiflash chromatography (0-50% ACN/H₂O (0.05%)) and the desired fractions were combined and lyophilized to give the desired compounds (mix of trans-isomers) as a white solid. ¹H NMR (400 MHz, CD₃CN) δ 7.38 – 7.15 (m, 5H), 6.93 (d, *J* = 32.9 Hz, 1H), 3.88 (dq, *J* = 18.5, 6.8 Hz, 1H), 3.01 (ddd, *J* = 9.6, 8.0, 4.7 Hz, 1H), 1.92 – 1.88 (m, 1H), 1.72 (dd, *J* = 8.0, 5.8 Hz, 1H), 1.06 (d, *J* = 6.5 Hz, 3H). ¹³C NMR (101 MHz, CD₃CN) δ 176.97, 176.83, 173.67, 173.62, 135.96, 135.92, 129.87, 129.76, 129.00, 128.90, 127.96, 127.89, 68.62, 68.47, 42.59, 39.58, 39.52, 32.76, 32.71, 23.47, 21.15, 20.95, 20.93, 20.75. LCMS: [M+H]⁺; calculated: 250.107, found 250.200.

EXAMPLE 20

Method of synthesis of ((*S*)-2-phosphonopropanoyl)-*L*-phenylalanine (23)



[0388] Benzyl ((*R*)-2-bromopropanoyl)-*L*-phenylalaninate

[0389] To a solution of benzyl *L*-phenylalaninate hydrochloride (189 mg, 1 Eq, 647 μ mol) and (R)-2-bromopropanoic acid (99.0 mg, 1 Eq, 647 μ mol) in DMF (3 mL) was added DIEA (184 mg, 248 μ L, 2.2 Eq, 1.42 mmol) and HATU (320 mg, 1.3 Eq, 841 μ mol). The reaction was stirred for one hour at room temperature after which water and ethyl acetate was added. The aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by combiflash chromatography (0-30% EtOAc/Hexane) to give the desired product as a white solid (211.3 mg, 0.65 mmol, 84%).

[0390] **Benzyl ((S)-2-(diethoxyphosphoryl)propanoyl)-*L*-phenylalaninate**

[0391] A solution of benzyl ((R)-2-bromopropanoyl)-*L*-phenylalaninate (138 mg, 0.35 mmol) in triethyl phosphite (5 mL) was refluxed at 150 °C for 24 hours. The reaction was concentrated under reduced pressure and purified by combiflash chromatography (0-100% EtOAc/Hexane) to give the desired product as a colorless oil (100 mg, 0.22 mmol, 63% yield). LCMS: $[M+H]^+$; calculated: 448.188, found 448.200.

[0392] **((S)-2-phosphonopropanoyl)-*L*-phenylalanine (23)**

[0393] To a solution of benzyl ((S)-2-(diethoxyphosphoryl)propanoyl)-*L*-phenylalaninate (151.6 mg, 0.34 mmol) in dry acetonitrile (8 mL) under argon was added sodium iodide (50.8 mg, 0.34 mmol) and trimethylchlorosilane (184 mg, 1.69 mmol) and the reaction was refluxed for 48 hours. The reaction was filtered through celite and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (5 mL) and treated with palladium on carbon (10% wt, 50 mg) and fitted with a hydrogen balloon. The reaction was stirred at room temperature overnight. The reaction was filtered through celite and concentrated under reduced pressure. Purification by rp-HPLC (0-50% ACN/H₂O (0.05% TFA)) gave the final product as a white solid.

EXAMPLE 21

Method of synthesis of (1*S*,2*S*/1*R*,2*R*)-1-((*S*)-2-hydroxypropanamido)-2-phenylcyclopropane-1-carboxylic acid (23a/b)

[0394] To a solution of methyl (1S,2S/1R/2R)-1-amino-2-phenylcyclopropane-1-carboxylate (111.7 mg, 1 Eq, 584.1 μ mol), L-Lactic acid (63.14 mg, 54.15 μ L, 1.2 Eq, 700.9 μ mol), and HOBt (89.45 mg, 1 Eq, 584.1 μ mol) in Dichloromethane (5 mL) and DMF (0.3 mL) was added DIC (73.72 mg, 91.5 μ L, 1 Eq, 584.1 μ mol) and the reaction was stirred at room temperature under argon for 2 days. The reaction was diluted with dichloromethane and washed with sodium bicarbonate, water, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by combiflash chromatography (0-100% EtOAc/Hexane) gave the desired products as a 1:1 mixture of diastereomers methyl (1S,2S)-1-((S)-2-hydroxypropanamido)-2-phenylcyclopropane-1-carboxylate and methyl (1R,2R)-1-((S)-2-hydroxypropanamido)-2-phenylcyclopropane-1-carboxylate (130 mg, 84.5% 0.58 mmol). The cis-isomers were dissolved in methanol (5 mL) and an aqueous solution of lithium hydroxide (71 mg, 2.96 mmol, 1 mL) was added and the reaction was stirred at ambient temperature overnight and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, treated with 1M HCl. The layers were partitioned, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with water, brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase C18 combiflash chromatography (0-50% ACN/H₂O (0.05%)) and the desired fractions were combined and lyophilized to give the desired compounds ((1S,2S)-1-((S)-2-hydroxypropanamido)-2-phenylcyclopropane-1-carboxylic acid and (1R,2R)-1-((S)-2-hydroxypropanamido)-2-phenylcyclopropane-1-carboxylic acid) as a white solid. ¹H NMR (500 MHz, CD₃CN) δ 7.74 (s, 1H), 7.36 (d, J = 7.6 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 4.15 (qd, J = 6.9, 2.3 Hz, 1H), 2.79 (td, J = 9.1, 6.4 Hz, 1H), 2.11 (dd, J = 8.6, 5.6 Hz, 1H), 1.51 (ddd, J = 9.6, 5.6, 3.9 Hz, 1H), 1.33 (d, J = 6.7 Hz, 1H). ¹³C NMR (126 MHz, CD₃CN) δ 178.02, 177.98, 170.59, 136.70, 130.26, 128.94, 127.91, 68.74, 68.70, 41.22, 35.19, 35.15, 21.17, 21.03, 20.09. LCMS: [M+H]⁺; calculated: 250.107, found 250.200.

EXAMPLE 22**Method of synthesis of ((S)-2-phosphonopropanoyl)-L-phenylalanine (24)****[0395] Benzyl ((R)-2-bromopropanoyl)-L-phenylalaninate**

[0396] To a solution of benzyl L-phenylalaninate hydrochloride (189 mg, 1 Eq, 647 μ mol) and (R)-2-bromopropanoic acid (99.0 mg, 1 Eq, 647 μ mol) in DMF (3 mL) was added DIEA (184 mg, 248 μ L, 2.2 Eq, 1.42 mmol) and HATU (320 mg, 1.3 Eq, 841 μ mol). The reaction was stirred for one hour at room temperature after which water and ethyl acetate was added. The aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by combiflash chromatography (0-30% EtOAc/Hexane) to give the desired product as a white solid (211.3 mg, 0.65 mmol, 84%).

[0397] Benzyl ((S)-2-(diethoxyphosphoryl)propanoyl)-L-phenylalaninate

[0398] A solution of benzyl ((R)-2-bromopropanoyl)-L-phenylalaninate (138 mg, 0.35 mmol) in triethyl phosphite (5 mL) was refluxed at 150 °C for 24 hours. The reaction was concentrated under reduced pressure and purified by combiflash chromatography (0-100% EtOAc/Hexane) to give the desired product as a colorless oil (100 mg, 0.22 mmol, 63% yield). LCMS: [M+H]⁺ ; calculated: 448.188, found 448.200.

[0399] ((S)-2-phosphonopropanoyl)-L-phenylalanine (24)

[0400] To a solution of benzyl ((S)-2-(diethoxyphosphoryl)propanoyl)-L-phenylalaninate (151.6 mg, 0.34 mmol) in dry acetonitrile (8 mL) under argon was added sodium iodide (50.8 mg, 0.34 mmol) and trimethylchlorosilane (184 mg, 1.69 mmol) and the reaction was refluxed for 48 hours. The reaction was filtered through celite and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (5 mL) and treated with palladium on carbon (10% wt,

50 mg) and fitted with a hydrogen balloon. The reaction was stirred at room temperature overnight. The reaction was filtered through celite and concentrated under reduced pressure. Purification by rp-HPLC (0-50% ACN/H₂O (0.05% TFA)) gave the final product as a white solid. LCMS: [M+H]⁺; calculated: 302.079, found 302.000.

EXAMPLE 23

Method of synthesis of (S)-2-((S)-2-hydroxypropanamido)-3-(naphthalen-2-yl)propanoic acid (25)

[0401] To a solution of benzyl (S)-2-amino-3-(naphthalen-2-yl)propanoate 4-methylbenzenesulfonate (200 mg, 1 Eq, 419 μ mol), (S)-2-hydroxypropanoic acid (45.3 mg, 1.2 Eq, 503 μ mol), HOBt (64.1 mg, 1 Eq, 419 μ mol), and DIEA (54.1 mg, 72.9 μ L, 1 Eq, 419 μ mol) in Dichloromethane (5 mL) was added dic (63.4 mg, 78.7 μ L, 1.2 Eq, 503 μ mol) and the solution was stirred at ambient temperature under argon overnight. The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was loaded onto a silica gel cartridge and purified by combiflash chromatography (0-80% EtOAc/Hexane) to give benzyl (S)-2-((S)-2-hydroxypropanamido)-3-(naphthalen-2-yl)propanoate as a colorless oil. This residue was dissolved in methanol (5 mL) and treated with palladium on carbon (10 wt %, 50 mg) and the reaction was stirred under a hydrogen atmosphere overnight. The reaction was then filtered through celite, and concentrated under reduced pressure. The residue was then subjected to rp-HPLC (10-50% ACN/H₂O (0.05% TFA)) to give the final product as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.85 – 7.71 (m, 3H), 7.66 (s, 1H), 7.47 – 7.40 (m, 2H), 7.35 (d, J = 6.8 Hz, 1H), 4.81 (dd, J = 7.9, 5.1 Hz, 1H), 4.07 (q, J = 6.8 Hz, 1H), 3.42 (dd, J = 13.8, 4.8 Hz, 1H), 3.22 (dd, J = 13.8, 7.8 Hz, 1H), 1.17 (d, J = 6.8 Hz, 3H). ¹³C NMR (101 MHz, CD₃OD) δ 177.40, 174.09, 135.52, 134.85, 133.93, 129.12, 129.02, 128.58, 128.53, 127.05, 126.63, 68.97, 54.39, 38.56, 21.06. LCMS: [M+H]⁺; calculated: 288.123, found 288.200.

EXAMPLE 24

Method of synthesis of ((S)-oxirane-2-carbonyl)-L-phenylalanine (26)**[0402] Benzyl ((S)-oxirane-2-carbonyl)-L-phenylalaninate**

[0403] To an ice-cooled solution of Potassium-(S)-Oxirane-2-carboxylate (200 mg, 1 Eq, 1.59 mmol) in DMF (4 mL) was added HATU (723 mg, 1.2 Eq, 1.90 mmol) and the reaction was stirred for 15 minutes under argon. A solution of benzyl L-phenylalaninate hydrochloride (463 mg, 1 Eq, 1.59 mmol) and DIEA (410 mg, 552 μ L, 2 Eq, 3.17 mmol) in DMF (3 mL) was then added drop wise and the reaction was stirred for 2 hours. The reaction was then diluted with ethyl acetate and water and the layers were partitioned. The aqueous layer was further extracted with ethyl acetate twice and the combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was loaded onto a silica gel cartridge and subjected to combiflash chromatography (0-60% EtOAc/Hexane) to give the desired compound benzyl ((S)-oxirane-2-carbonyl)-L-phenylalaninate (221.2 mg, 679.9 μ mol, 42.9 %) as a light-yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.33 – 7.21 (m, 5H), 7.16 – 7.11 (m, 3H), 6.92 – 6.86 (m, 2H), 6.47 (d, J = 8.2 Hz, 1H), 5.12 (d, J = 12.1 Hz, 1H), 5.06 (d, J = 12.1 Hz, 1H), 4.80 (q, J = 6.9 Hz, 1H), 3.31 – 3.26 (m, 1H), 3.10 (dd, J = 14.0, 5.8 Hz, 1H), 2.93 (dd, J = 14.0, 6.8 Hz, 1H), 2.81 – 2.75 (m, 1H), 2.36 (ddd, J = 5.6, 2.6, 1.2 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 170.90, 168.31, 135.54, 135.07, 129.24, 128.71, 128.65, 128.62, 127.24, 67.48, 52.30, 49.43, 47.42, 37.73. LCMS: [M+H]⁺; calculated: 326.139, found 326.200.

[0404] ((S)-oxirane-2-carbonyl)-L-phenylalanine (26)

[0405] To a solution of benzyl ((S)-oxirane-2-carbonyl)-L-phenylalaninate (33.5 mg, 1 Eq, 103 μ mol) in Methanol (3 mL) was added palladium on carbon (15 mg, 10% Wt, 0.14 Eq, 14 μ mol) and the reaction was stirred under a hydrogen atmosphere for 1 hour. The reaction was then filtered through celite and concentrated under reduced pressure to give the desired product, ((S)-oxirane-2-carbonyl)-L-phenylalanine, as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.27 – 7.19 (m, 2H), 7.19 – 7.13 (m, 3H), 4.64 (t, J = 6.4 Hz, 1H), 3.31 – 3.28 (m, 1H), 3.19 (t, J = 5.4 Hz, 1H), 2.96 (dd, J = 14.0, 8.5 Hz, 1H), 2.80 (dd, J = 6.0, 4.4 Hz, 1H), 2.43 (dd, J = 6.1, 2.4 Hz, 1H). LCMS: [M+H]⁺; calculated: 236.092, found 236.200.

EXAMPLE 25

Method of synthesis of ((S)-3-amino-2-hydroxypropanoyl)-L-phenylalanine (27)**[0406] ((S)-3-azido-2-hydroxypropanoyl)-L-phenylalaninate**

[0407] To a solution of benzyl ((S)-oxirane-2-carbonyl)-L-phenylalaninate (116.8 mg, 1 Eq, 359.0 μ mol) in DMF (2.5 mL) was added sodium azide (116.7 mg, 5 Eq, 1.795 mmol) and the solution was heated to 80 °C and stirred for 2.5 hours. The reaction was then concentrated under reduced pressure and redissolved in ethyl acetate and washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was then loaded onto a silica gel cartridge and subjected to combiflash chromatography (0-80% EtOAc/Hexane) to give the desired compound benzyl ((S)-3-azido-2-hydroxypropanoyl)-L-phenylalaninate (47 mg, 0.13 mmol, 36 %) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.29 (d, J = 6.0 Hz, 3H), 7.23 (dd, J = 5.9, 3.1 Hz, 2H), 7.19 – 7.08 (m, 3H), 6.97 (q, J = 5.0 Hz, 2H), 5.11 (d, J = 12.1 Hz, 1H), 5.04 (d, J = 12.1 Hz, 1H), 4.89 – 4.79 (m, 1H), 4.16 – 4.08 (m, 1H), 3.50 – 3.33 (m, 2H), 3.15 – 2.97 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 171.30, 170.62, 135.45, 135.05, 129.43, 128.78, 128.74, 128.72, 127.34, 71.33, 67.60, 54.27, 53.01, 37.98. LCMS: [M+H]⁺ ; calculated: 369.156, found 369.200.

[0408] ((S)-3-amino-2-hydroxypropanoyl)-L-phenylalanine (27)

[0409] To a solution of benzyl ((S)-3-azido-2-hydroxypropanoyl)-L-phenylalaninate (47 mg, 1 Eq, 0.13 mmol) in THF (4 mL) and Water (0.4 mL) was added triphenylphosphine (67 mg, 2 Eq, 0.26 mmol) and the reaction was stirred overnight at ambient temperature. The reaction mixture was concentrated and loaded onto a c18 cartridge and purified by reverse phase combiflash (0-70% ACN/H₂O (0.05% TFA)) and the desired fractions were lyophilized. benzyl ((S)-3-amino-2-hydroxypropanoyl)-L-phenylalaninate (1 Eq) was dissolved in Ethyl acetate (4 mL) and Water (0.4 mL) and palladium on carbon (60 mg, 10% Wt, 1 Eq, 56 μ mol) was added. The reaction was stirred overnight under a hydrogen atmosphere. The reaction was filtered through celite and concentrated under reduced pressure to give the desired compound ((S)-3-amino-2-hydroxypropanoyl)-L-phenylalanine (26.8 mg, 106 μ mol, 82 % over 2 steps) as a white

solid. ¹H NMR (400 MHz, cd₃od) δ 7.31 – 7.14 (m, 5H), 4.57 – 4.48 (m, 1H), 4.28 – 4.20 (m, 1H), 3.27 (d, J = 4.7 Hz, 1H), 3.19 – 2.96 (m, 2H), 2.88 – 2.77 (m, 1H). ¹³C NMR (101 MHz, CD₃OD) δ 181.97, 178.75, 139.30, 130.52, 129.27, 127.52, 69.62, 56.90, 44.15, 38.83. LCMS: [M+H]⁺ ; calculated: 253.118, found 253.200.

EXAMPLE 26

Method of synthesis of ((S)-2,3-dihydroxypropanoyl)-L-phenylalanine (28)

[0410] ((S)-2,2-dimethyl-1,3-dioxolane-4-carbonyl)-L-phenylalaninate

[0411] To a solution of benzyl L-phenylalaninate hydrochloride (200 mg, 1 Eq, 685 μmol) and (S)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (105 mg, 1.05 Eq, 720 μmol) in DMF (5 mL) was added DIEA (195 mg, 263 μL, 2.2 Eq, 1.51 mmol) and HATU (313 mg, 1.2 Eq, 823 μmol) and the reaction was stirred at ambient temperature for 2 hours. The reaction mixture was then diluted with ethyl acetate and water. The layers were partitioned, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then loaded onto a silica gel cartridge and subjected to combiflash chromatography (0-100% EtOAc/Hexane) to give the desired compound benzyl ((S)-2,2-dimethyl-1,3-dioxolane-4-carbonyl)-L-phenylalaninate (148.6 mg, 387.5 μmol, 56.5 %) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.30 – 7.18 (m, 5H), 7.15 – 7.08 (m, 3H), 6.97 (d, J = 8.0 Hz, 1H), 6.94 – 6.86 (m, 2H), 5.08 (d, J = 12.2 Hz, 1H), 5.04 (d, J = 12.2 Hz, 1H), 4.80 (q, J = 6.5 Hz, 1H), 4.32 (ddd, J = 7.0, 5.3, 1.4 Hz, 1H), 4.16 – 4.08 (m, 1H), 3.85 (dd, J = 8.8, 5.2 Hz, 1H), 3.11 (dd, J = 14.0, 5.7 Hz, 1H), 2.99 (dd, J = 13.9, 6.3 Hz, 1H), 1.22 (s, 3H), 1.16 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 170.86, 170.80, 135.39, 135.01, 129.28, 128.55, 128.50, 128.48, 127.05, 110.90,

74.83, 67.60, 67.22, 52.54, 37.61, 25.78, 24.86. LCMS: $[M+H]^+$; calculated: 384.181, found 384.200.

[0412] Benzyl ((S)-2,3-dihydroxypropanoyl)-L-phenylalaninate

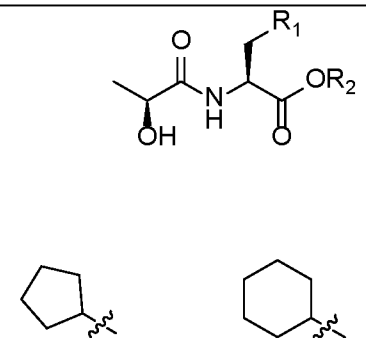
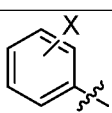
[0413] To a solution of benzyl ((S)-2,2-dimethyl-1,3-dioxolane-4-carbonyl)-L-phenylalaninate (148.6 mg, 1 Eq, 387.5 μ mol) in DCM (3 mL) was added TFA (44.19 mg, 29.86 μ L, 1 Eq, 387.5 μ mol) and a drop of water and the reaction was stirred at ambient temperature overnight. The reaction was concentrated under reduced pressure and loaded onto a silica gel cartridge and then subjected to combiflash chromatography (0-15% MeOH/DCM) to give the desired compound benzyl ((S)-2,3-dihydroxypropanoyl)-L-phenylalaninate (52.6 mg, 153 μ mol, 39.5 %) as a white solid. LCMS: $[M+H]^+$; calculated: 344.149, found 344.000.

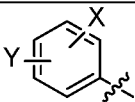
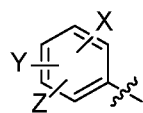
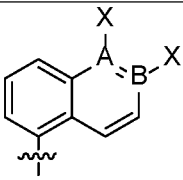
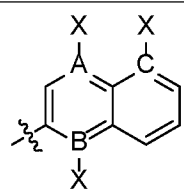
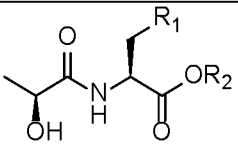
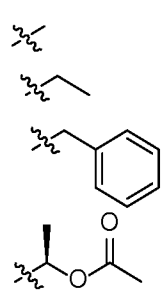
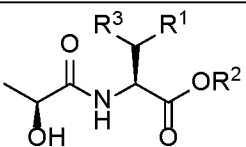
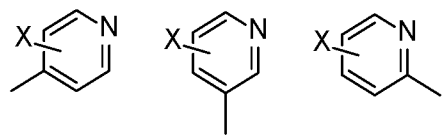
[0414] ((S)-2,3-dihydroxypropanoyl)-L-phenylalanine (28)

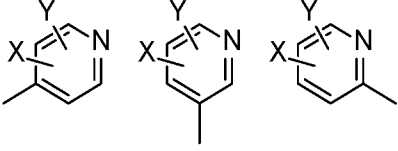
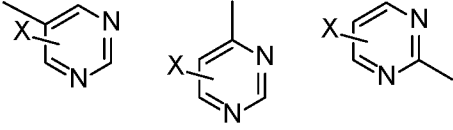
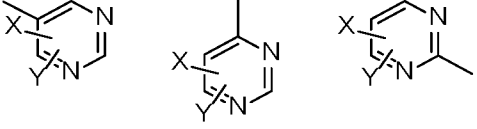
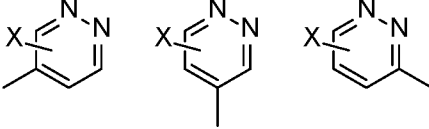
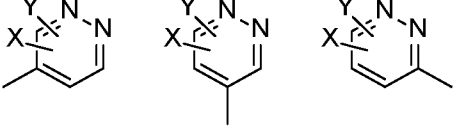
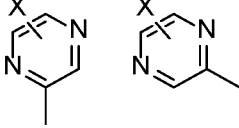
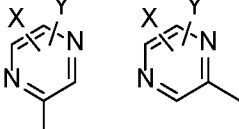
[0415] benzyl ((S)-2,3-dihydroxypropanoyl)-L-phenylalaninate (52.6 mg, 1 Eq, 153 μ mol) was dissolved in Methanol (5 mL) and Water (0.5 mL) and palladium on carbon (40 mg, 10% Wt, 0.25 Eq, 38 μ mol) was added. The reaction was stirred under a hydrogen atmosphere overnight. The reaction was filtered through celite and concentrated under reduced pressure to give the desired compound ((S)-2,3-dihydroxypropanoyl)-L-phenylalanine as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 7.58 (d, J = 7.2 Hz, 1H), 7.22 – 7.06 (m, 5H), 5.99 (d, J = 4.8 Hz, 1H), 5.01 (s, 1H), 4.29 – 4.22 (m, 1H), 3.88 – 3.79 (m, 1H), 3.57 (dd, J = 11.4, 3.3 Hz, 1H), 3.35 – 3.26 (m, 1H), 3.14 – 2.97 (m, 2H). LCMS: $[M+H]^+$; calculated: 254.102, found 254.200.

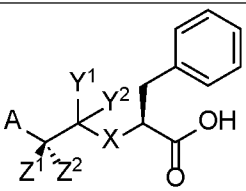
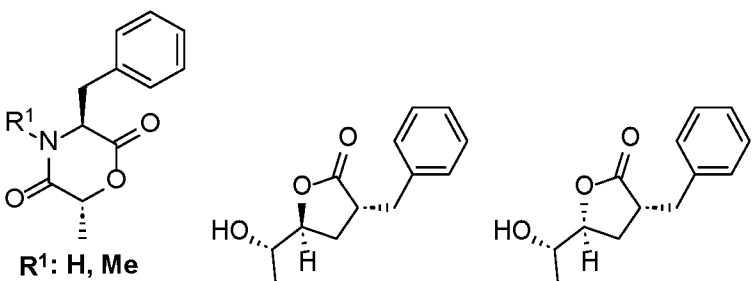
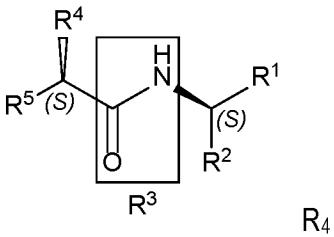
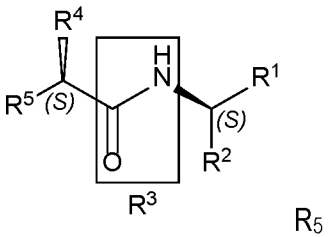
EXAMPLE 27

Table 12 – Exemplary N-Lactoyl-Phenylalanine (Lac-Phe) Analogues – Genus 1, 2, and 3

Table 12 - Lac-Phe Analogues – Genus 1, 2 and 3	
Genus 1	 R_1:
	 Mono substituted: X: H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, iPr, CF₂H, Cyclopropyl

	 Di substituted: X: H,CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, iPr, CF₂H, Cyclopropyl Y: H,CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, iPr, CF₂H, Cyclopropyl  Tri substituted: X: H,CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, iPr, CF₂H, Cyclopropyl Y: H,CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, iPr, CF₂H, Cyclopropyl Z: H,CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, iPr, CF₂H, Cyclopropyl
	  A/B/C: N, CX (X:Cl, H, Me)
	 R₂: 
	 R¹ and R³ selected from:  Mono substituted: X: H,CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, iPr, CF₂H, Cyclopropyl

	 X: F, Cl Y: F, Cl
	 Mono substituted: X: H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, iPr, CF₂H, Cyclopropyl  Disubstituted X: F, Cl Y: F, Cl
	 Mono substituted: X: H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, iPr, CF₂H, Cyclopropyl  Disubstituted X: F, Cl Y: F, Cl
	 Mono substituted: X: H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, iPr, CF₂H, Cyclopropyl  Disubstituted X: F, Cl

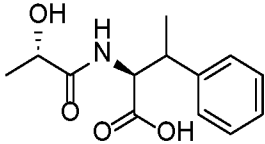
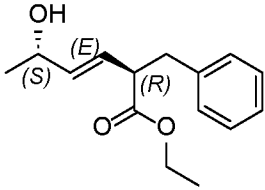
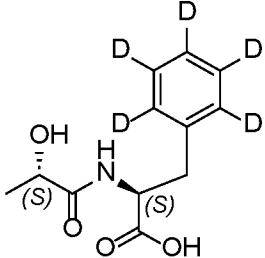
	Y: F, Cl
Genus 2	 X: O, NH, NMe, CH₂, SO₂ Y¹: H, O, OH Y²: H, O, OH Z¹: H, D, OH, NH₂, Me, Oxetane Z²: H, D, OH, NH₂, Me, Oxetane A: CF₃, Me, Et, Pr, iPr, Aryl, CD₃, cyclopropane, cyclobutane
Genus 3	Lactone – Prodrugs  R¹: H, Me
Genus 4	 R₄
Genus 5	 R₅

EXAMPLE 22

N-Lactoyl-Phenylalanine (Lac-Phe) Analogues: amide bond bioisosters

Table 13 - Lac-Phe Analogues: amide bond bioisosters	
Structure	Name

	(S)-2-(4-((S)-1-hydroxyethyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropanoic acid
	Compound 9 (retro-inverso)
	(2R,5S,E)-2-benzyl-5-hydroxyhex-3-enoic acid
	Compound 5
Phenylalanine bioisosteres	
	(S)-3-(cyclopenta-2,4-dien-1-yl)-2-((S)-2-hydroxypropanamido)propanoic acid
	(S)-2-((S)-2-hydroxypropanamido)-3-(naphthalen-1-yl)propanoic acid
Dimer prodrugs	
	methylene (2S,2'S)-bis(2-((S)-2-hydroxypropanamido)-3-phenylpropanoate)
Increasing logP	

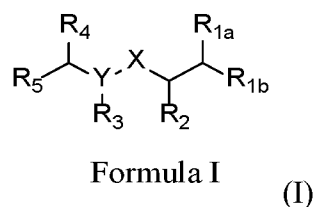
	(2S)-2-((S)-2-hydroxypropanamido)-3-phenylbutanoic acid
	ethyl (2R,5S,E)-2-benzyl-5-hydroxyhex-3-enoate
Other compounds	
	Deuterated Lac-Phe-D5

[0416] All references cited in this specification are herein incorporated by reference as though each reference was specifically and individually indicated to be incorporated by reference.

CLAIMS

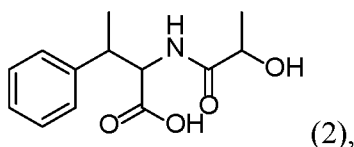
What is claimed is:

1. A compound of Formula I

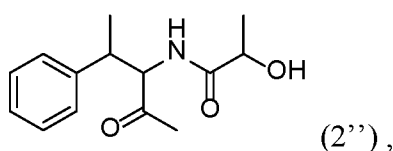


wherein, X is a residue selected from -O-, -NR, where R may be -H or alkyl, and carbonyl; Y is a residue selected from -CH-, -C=O-, -SO₂ and -NH; where if Y = NH, then X = carbonyl and R³ is absent; where if Y = -SO₂, X = NH and R³ is absent; R^{1a} is a residue selected from alkyl, cycloalkyl, heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, silyl, phenyl, pentanyl, naphthalene-1-yl, naphthalene-2-yl, 3-phenyl-3-thioxopropanoic acid, and 3-(trimethylsilyl)propanoic acid; where R^{1b} is a residue selected from -H, alkyl, thiocarbonyl (C=S) and hydroxy; where R² is a residue selected from -COOR where R may be H or alkyl, sulfinic acid, 2-phenylethane-1-sulfinic acid, phosphinic acid, 2-phenylethyl-phosphinic acid, phosphonic acid, 2,2,2-trifluoromethyl-1-hydroxyethyl, and methyl 2-hydroxypropanoyl; where R³ is a residue selected from -H, hydroxy, =O, carbonyl (C=O), thiocarbonyl (C=S), and sulfinic acid; where R⁴ is a residue selected from hydroxyl, carbonyl (ketone), hydroxymethyl, and alkyl (e.g., methyl); and where R⁵ is a residue selected from alkyl, cycloalkyl, amine, hydroxy, butanoyl, hydroxybutanoyl, cyclopropanyl, ethyl(CH₂CH₃), hydroxycyclopropane-1-carbonyl, amino, ethanol, and lactonyl; where optionally, R² and R³ may combine to form a heterocycloalkyl group (e.g., oxazolidine).

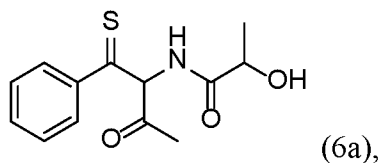
2. The compound of Formula I of claim 1, wherein said compound is 2-(2-hydroxypropanoylamino)-3-phenylbutanoic acid having structure (2)



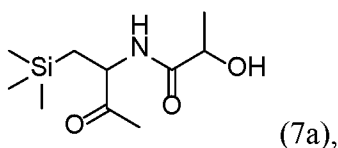
- 2-(2-hydroxypropanoylamino)-3-phenylmethylbutanone having structure (2'')



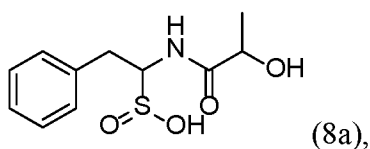
2-hydroxy-N-(3-oxo-1-phenyl-1-sulfanylidenebutan-2-yl)propanamide, having structure (6a)



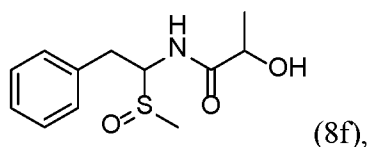
2-hydroxy-N-(3-oxo-1-trimethylsilylbutan-2-yl)propanamide having structure (7a)



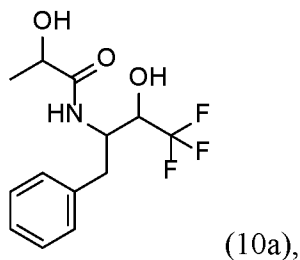
1-(2-hydroxypropanoylamino)-2-phenylethanesulfinic acid having structure (8)



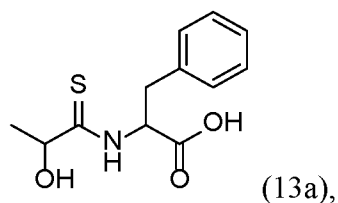
1-(2-hydroxypropanoylamino)-2-phenylethanemethylsulfoxide having structure (8f)



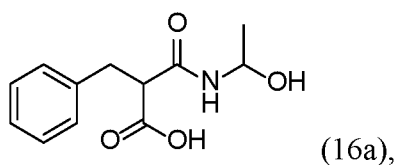
2-hydroxy-N-(4,4,4-trifluoromethyl-3-hydroxy-1-phenylbutan-2-yl)propanamide having structure (10)



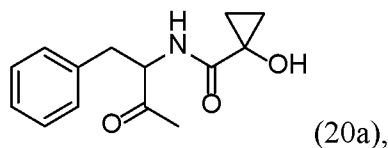
2-(2-hydroxypropanethioylamino)-3-phenylpropanoic acid having structure



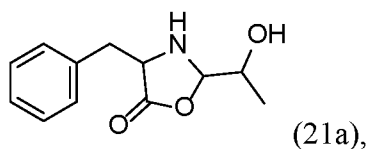
2-benzyl-5-hydroxyhex-3-enoic acid (15), 2-benzyl-3-(1-hydroxyethylamino)-3-oxopropanoic acid having structure



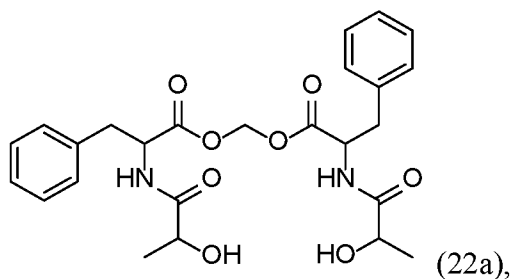
2-[(1-hydroxycyclopropanecarbonyl)amino]-3-phenylpropanoic acid having structure



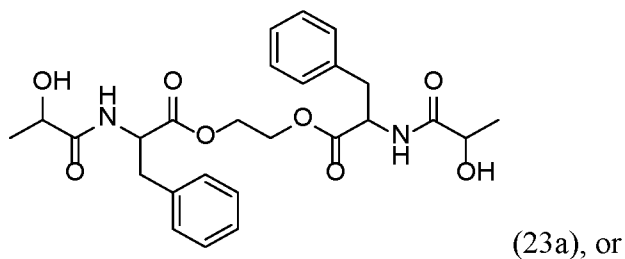
4-benzyl-2-(1-hydroxyethyl)-1,3-oxazolidin-5-one having structure



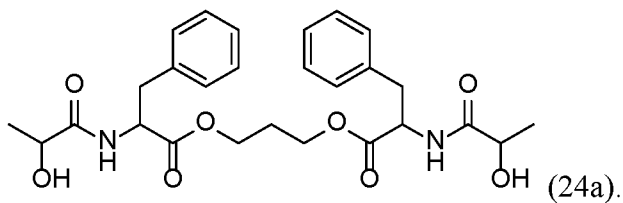
2-(2-hydroxypropanoylamino)-3-phenylpropanoyl]oxymethyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate having structure



2-[2-(2-hydroxypropanoylamino)-3-phenylpropanoyl]oxyethyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate having structure

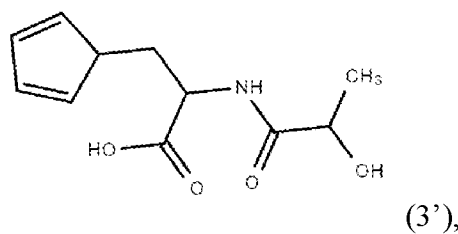


3-[2-(2-hydroxypropanoylamino)-3-phenylpropanoyl]oxypropyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate having structure

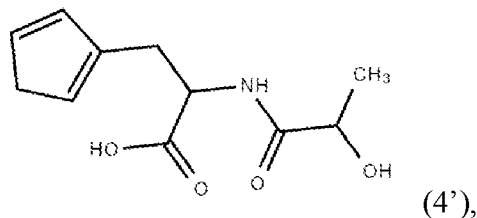


3. The compound of Formula I of claim 1, wherein said compound is

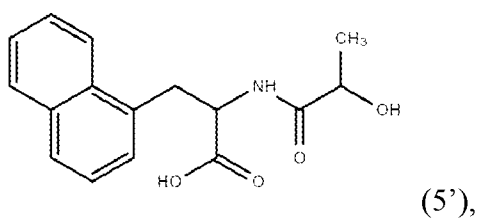
3-cyclopenta-2,4-dien-1-yl-2-(2-hydroxypropanoylamino)propanoic acid having structure



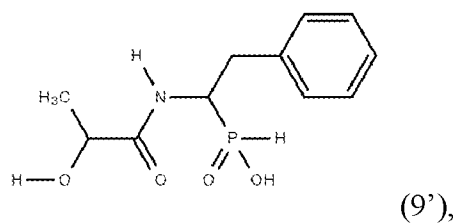
3-cyclopenta-1,4-dien-1-yl-2-(2-hydroxypropanoylamino)propanoic acid having structure



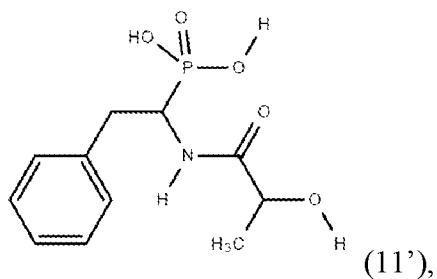
2-(2-hydroxypropanoylamino)-3-naphthalen-1-ylpropanoic acid having structure



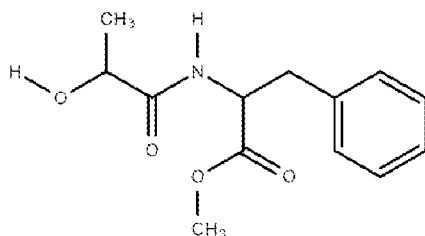
[1-(2-hydroxypropanoylamino)-2-phenylethyl]phosphinic acid having structure



[1-(2-hydroxypropanoylamino)-2-phenylethyl]phosphonic acid having structure

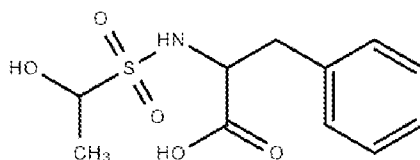


methyl 2-(2-hydroxypropanoylamino)-3-phenylpropanoate having structure



(12'), or

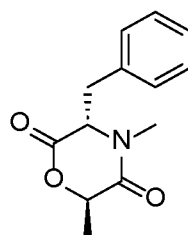
2-(1-hydroxyethylsulfonylamino)-3-phenylpropanoic acid having structure



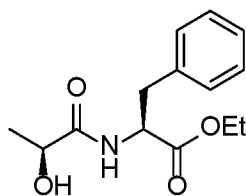
(14').

4. The compound of Formula I of claim 1, wherein said compound is radio-labeled by an isotope, optionally ^{76}Br , ^{14}C , ^{13}C , ^2H , ^3H , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{15}N , ^{15}O , ^{18}F , or a combination thereof.

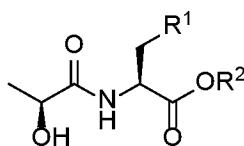
5. A compound (3S,6S)-3-benzyl-4,6-dimethylmorpholine-2,5-dione having structure

**13****(13b).**

6. A compound ethyl ((S)-2-hydroxypropanoyl)-L-phenylalaninate having structure

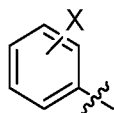
**14****(14d).**

7. A compound of Formula I-a,

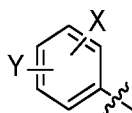


Formula I-a,

wherein R^1 is selected from the group consisting of methylcyclopentanyl,
methylcyclohexanyl,
a monosubstituted phenyl having structure

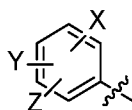


wherein X is selected from the group consisting of H, CN, CF_3 , F, Cl, OMe, Me, $CONH_2$,
 CF_3 , isopropyl, CF_2H , and Cyclopropyl,
a di-substituted phenyl having structure

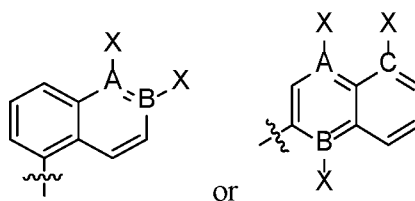


wherein X is selected from the group consisting of H, CN, CF_3 , F, Cl, OMe, Me,
 $CONH_2$, CF_3 , iPr, CF_2H , and Cyclopropyl, and where Y is selected from the group
consisting of H, CN, CF_3 , F, Cl, OMe, Me, $CONH_2$, CF_3 , isopropyl, CF_2H , and
Cyclopropyl,

a tri-substituted phenyl having structure



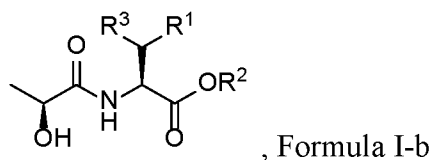
wherein X is selected from the group consisting of H, CN, CF_3 , F, Cl, OMe, Me,
 $CONH_2$, CF_3 , iPr, CF_2H , and Cyclopropyl, and where Y is selected from the group
consisting of H, CN, CF_3 , F, Cl, OMe, Me, $CONH_2$, CF_3 , isopropyl, CF_2H , and
Cyclopropyl, and Z is selected from the group consisting of H, CN, CF_3 , F, Cl, OMe, Me,
 $CONH_2$, CF_3 , isopropyl, CF_2H , and Cyclopropyl,
a hetero-biphenyl compound having structure



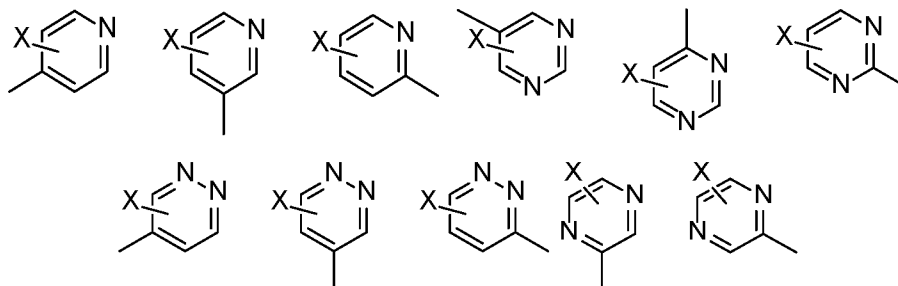
where A, B, or C is selected from the group consisting of N, and CX, where X is selected
from the group consisting of Cl, H and Me, and

R_2 is selected from the group consisting of ethyl, isopropyl, ethylbenzene, and
isopropyl acetate.

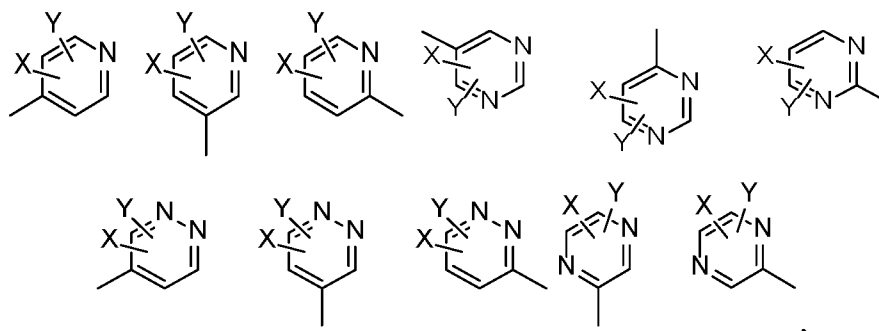
8. A compound of Formula I-b having structure



wherein R¹ and R³ have structure selected from

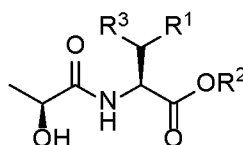


wherein X in R¹ and R³ monosubstituted heteroaryl is selected from the group consisting of H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, isopropyl, CF₂H, and Cyclopropyl, and optionally said R¹ and R³ is a disubstituted heteroaryl compound of structure selected from

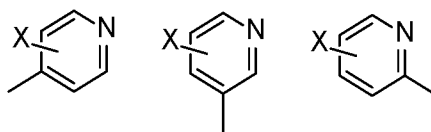


wherein X in said disubstituted heteroaryl is F or Cl, and Y is F or Cl.

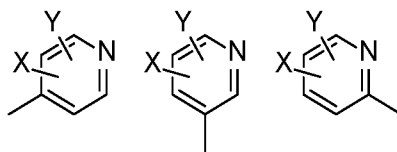
9. The compound of Formula I-b of claim 8, wherein the structure is



wherein R¹ is optionally a monosubstituted heteroaryl having structure selected from

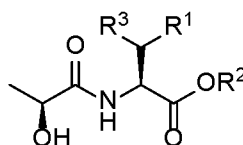


wherein X in R¹ and R³ monosubstituted heteroaryl is selected from the group consisting of H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, isopropyl, CF₂H, and Cyclopropyl, and optionally said R¹ and R³ is a disubstituted heteroaryl compound of structure selected from

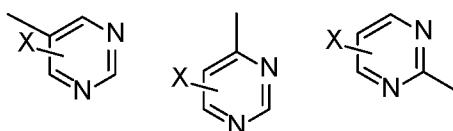


wherein X in said disubstituted heteroaryl is F or Cl, and Y is F or Cl.

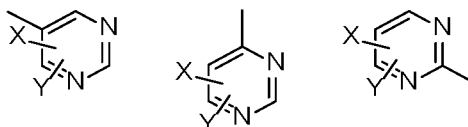
10. The compound of Formula I-b of claim 8, wherein the structure is



wherein R¹ is optionally a monosubstituted heteroaryl having structure selected from

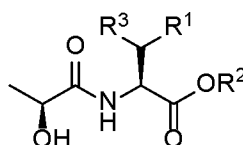


wherein X in said R¹ monosubstituted heteroaryl is selected from the group consisting of H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, isopropyl, CF₂H, and Cyclopropyl, and optionally wherein R¹ is a disubstituted heteroaryl compound of structure selected from

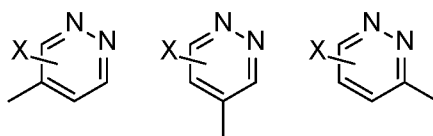


where X in said R¹ disubstituted heteroaryl is F or Cl, and Y is F or Cl.

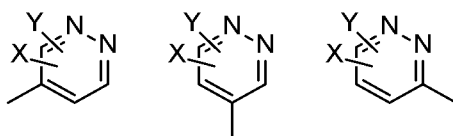
11. The compound of Formula I-b of claim 8, wherein the structure is



wherein R¹ is a monosubstituted heteroaryl having structure selected from

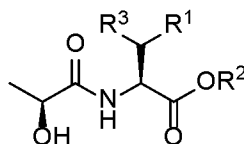


where X in said R¹ monosubstituted heteroaryl is selected from the group consisting of H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, isopropyl, CF₂H, and Cyclopropyl, and optionally R¹ is a disubstituted heteroaryl compound of structure selected from

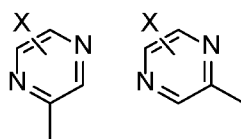


where X in said R¹ disubstituted heteroaryl is F or Cl, and Y is F or Cl.

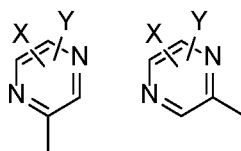
12. The compound of Formula I-c of claim 8, wherein the structure is



where R¹ is a monosubstituted heteroaryl having structure selected from

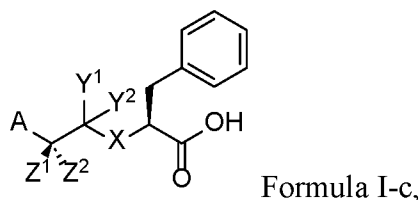


where X in said R¹ monosubstituted heteroaryl is selected from the group consisting of H, CN, CF₃, F, Cl, OMe, Me, CONH₂, CF₃, isopropyl, CF₂H, and Cyclopropyl, and optionally R¹ is a disubstituted heteroaryl compound having structure selected from



where X in said R¹ disubstituted heteroaryl is F or Cl, and Y is F or Cl.

13. A compound of Formula I-c having structure



where X is selected from the group consisting of O, NH, NCH₃, CH₂, and SO₂,

where Y¹ is selected from the group consisting of H, O, and OH,

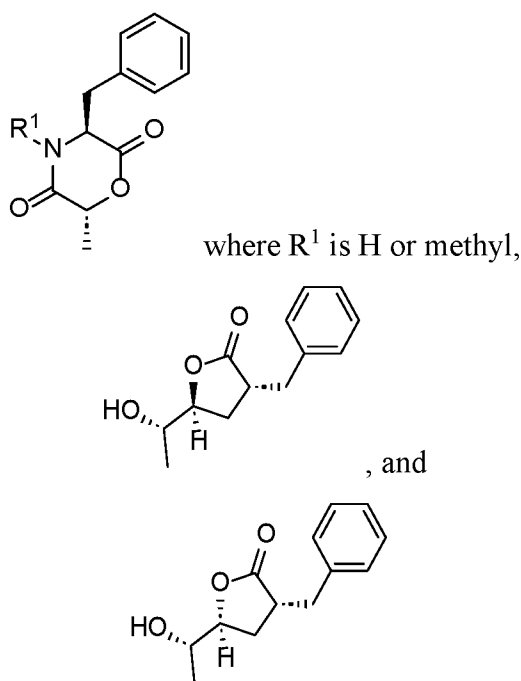
where Y² is selected from the group consisting of H, O, and OH,

where Z¹ is selected from the group consisting of H, D, OH, NH₂, Me, and Oxetane,

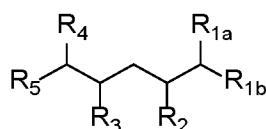
where Z² is selected from the group consisting of H, D, OH, NH₂, Me, and Oxetane and

where A is selected from the group consisting of CF₃, Me, Et, Pr, iPr, Aryl, CD₃, cyclopropane, cyclobutene.

14. A compound of structure selected from the group consisting of



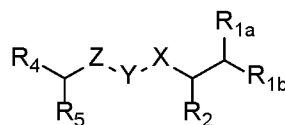
15. A compound of Formula II having the structure



Formula II

wherein, R^{1a} is a residue selected from alkyl, cycloalkyl (e.g., methylcyclopentanyl, methylcyclohexanyl), heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, silyl (e.g., trimethylsilyl), phenyl, pentanyl, 3-phenyl-3-thioxopropanoic acid, and 3-(trimethylsilyl)propanoic acid; where R^{1b} is a residue selected from -H, alkyl, thiocarbonyl ($C=S$) and hydroxy; where R^2 is a residue selected from -COOR where R may be H or alkyl, sulfinic acid, 2-phenylethane-1-sulfinic acid, phosphinic acid, 2-phenylethyl-phosphinic acid, phosphonic acid, 2,2,2-trifluoromethyl-1-hydroxyethyl, and methyl 2-hydroxypropanoyl; where R^3 is a residue selected from -H, hydroxy, =O, carbonyl ($C=O$), thiocarbonyl ($C=S$), and sulfinic acid; where R^4 is a residue selected from hydroxyl, carbonyl (ketone), hydroxy-methyl, and alkyl (e.g., methyl); and where R^5 is a residue selected from alkyl, cycloalkyl, amine, hydroxy, butanoyl, hydroxybutanoyl, cyclopropanyl, ethyl (CH_2CH_3), hydroxycyclopropane-1-carbonyl, amino, ethanol, and lactonyl

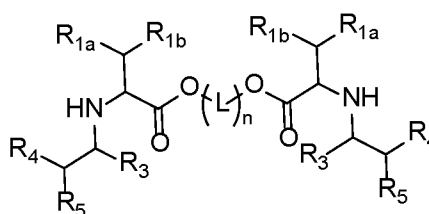
16. A compound of Formula III having the structure



Formula III

wherein, X and Z may be selected from NR, where R is H, C, or N; Y may be selected from carbonyl and CH; R^{1a} is a residue selected from alkyl, cycloalkyl (e.g., methylcyclopentanyl, methylcyclohexanyl), heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, silyl (e.g., trimethylsilyl), phenyl, pentanyl, 3-phenyl-3-thioxopropanoic acid, and 3-(trimethylsilyl)propanoic acid; where R^{1b} is a residue selected from -H, alkyl, thiocarbonyl (C=S) and hydroxy; where R² is a residue selected from -COOR where R may be H or alkyl, sulfinic acid, 2-phenylethane-1-sulfinic acid, phosphinic acid, 2-phenylethyl-phosphinic acid, phosphonic acid, 2,2,2-trifluoromethyl-1-hydroxyethyl, and methyl 2-hydroxypropanoyl; where R³ is a residue selected from -H, hydroxy, =O, carbonyl (C=O), thiocarbonyl (C=S), and sulfinic acid; where R⁴ (Group 4) is a residue selected from hydroxyl, carbonyl (ketone), hydroxy-methyl, and alkyl (e.g., methyl); and where R⁵ is a residue selected from alkyl, cycloalkyl, amine, hydroxy, butanoyl, hydroxybutanoyl, cyclopropanyl, ethyl (CH₂CH₃), hydroxycyclopropane-1-carbonyl, amino, ethanol, and lactonyl.

17. A compound of Formula IV having the structure



Formula IV

wherein, L is (CH₂)_n where n is 1, 2, or 3; R^{1a} is a residue selected from alkyl, cycloalkyl, heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, silyl (e.g., trimethylsilyl), phenyl, pentanyl, 3-phenyl-3-thioxopropanoic acid, and 3-(trimethylsilyl)propanoic acid; where R^{1b} is a residue selected from -H, alkyl, thiocarbonyl (C=S) and hydroxy; where R² is a residue

selected from -COOR where R may be H or alkyl, sulfinic acid, 2-phenylethane-1-sulfinic acid, phosphinic acid, 2-phenylethyl-phosphinic acid, phosphonic acid, 2,2,2-trifluoromethyl-1-hydroxyethyl, and methyl 2-hydroxypropanoyl; where R³ is a residue selected from -H, hydroxy, carbonyl, thiocarbonyl (C=S), and sulfinic acid; where R⁴ is a residue selected from hydroxyl, carbonyl (ketone), hydroxy-methyl, and alkyl (e.g., methyl); and where R⁵ is a residue selected from alkyl, cycloalkyl, amine, hydroxy, butanoyl, hydroxybutanoyl, cyclopropanyl, ethyl (CH₂CH₃), hydroxycyclopropane-1-carbonyl, amino, ethanol, and lactonyl.

18. The compound of claim 1, wherein the compound is Methyl (S)-2-((S)-2-(benzyloxy)propanamido)-3-(2-fluorophenyl)propanoate.
19. The compound of claim 1, wherein the compound is Methyl (S)-3-(2-fluorophenyl)-2-((S)-2-hydroxypropanamido) propanoate.
20. The compound of claim 1, wherein the compound is (S)-3-(2-fluorophenyl)-2-((S)-2-hydroxypropanamido) propanoic acid.
21. The compound of claim 1, wherein the compound is Methyl (S)-2-((S)-2-(benzyloxy)propanamido)-3-(3-fluorophenyl) propanoate.
22. The compound of claim 1, wherein the compound is Methyl (S)-3-(3-fluorophenyl)-2-((S)-2-hydroxypropanamido) propanoate.
23. The compound of claim 1, wherein the compound is Methyl (S)-2-((S)-2-(benzyloxy)propanamido)-3-(4-fluorophenyl) propanoate.
24. The compound of claim 1, wherein the compound is Methyl (S)-3-(4-fluorophenyl)-2-((S)-2-hydroxypropanamido) propanoate.
25. The compound of claim 1, wherein the compound is (S)-3-(2-fluorophenyl)-2-((S)-2-hydroxypropanamido) propanoic acid.
26. The compound of claim 1, wherein the compound is ((R)-2-hydroxypropyl)-L-phenylalanine.
27. The compound of claim 1, wherein the compound is (R)-2-(benzyloxy) propanoyl)-D-phenylalanine methyl ester.
28. The compound of claim 1, wherein the compound is ((R)-2-hydroxypropanoyl)-D-phenylalanine methyl ester.
29. The compound of claim 1, wherein the compound is ((R)-2-hydroxypropanoyl)-D-phenylalanine.

30. The compound of claim 1, wherein the compound is (((S)-2-hydroxypropyl) carbamoyl)-*L*-phenylalanine.
31. The compound of claim 1, wherein the compound is Benzyl N-((S)-2-(benzyloxy)propanoyl)-N-methyl-*L*-phenylalaninate.
32. The compound of claim 1, wherein the compound is (3S,6S)-3-benzyl-4,6-dimethylmorpholine-2,5-dione.
33. The compound of claim 1, wherein the compound is Ethyl ((S)-2-hydroxypropanoyl)-*L*-phenylalaninate.
34. The compound of claim 1, wherein the compound is Benzyl N-((S)-2-acetoxypropanoyl)-N-methyl-*L*-phenylalaninate.
35. The compound of claim 1, wherein the compound is N-((S)-2-acetoxypropanoyl)-N-methyl-*L*-phenylalanine.
36. The compound of claim 1, wherein the compound is Potassium N-((S)-2-hydroxypropanoyl)-N-methyl-*L*-phenylalaninate.
37. The compound of claim 1, wherein the compound is Ethyl (E)-hex-4-enoate.
38. The compound of claim 1, wherein the compound is (S)-5-((S)-1-hydroxyethyl)dihydrofuran-2(3H)-one.
39. The compound of claim 1, wherein the compound is (S)-5-((S)-1-((tert-butyl)dimethylsilyl)oxy)ethyl)dihydrofuran-2(3H)-one.
40. The compound of claim 1, wherein the compound is (3R,5S)-3-benzyl-5-((S)-1-((tert-butyl)dimethylsilyl)oxy)ethyl)dihydrofuran-2(3H)-one.
41. The compound of claim 1, wherein the compound is (3R,5S)-3-benzyl-5-((S)-1-hydroxyethyl)dihydrofuran-2(3H)-one.
42. The compound of claim 1, wherein the compound is Sodium (4S,5S)-2-benzyl-4,5-dihydroxyhexanoate.
43. The compound of claim 1, wherein the compound is (3R,5S)-3-benzyl-5-((S)-1-(benzyloxy)ethyl)dihydrofuran-2(3H)-one.
44. The compound of claim 1, wherein the compound is Benzyl (2R,4S,5S)-2-benzyl-5-(benzyloxy)-4-hydroxyhexanoate.
45. The compound of claim 1, wherein the compound is Benzyl (5S)-2-benzyl-5-(benzyloxy)-4-oxohexanoate.
46. The compound of claim 1, wherein the compound is (5S)-2-benzyl-5-hydroxy-4-oxohexanoic acid.

47. The compound of claim 1, wherein the compound is Methyl (S)-2-(allyloxy)-3-phenylpropanoate.
48. The compound of claim 1, wherein the compound is Methyl (S)-2-(2-oxopropoxy)-3-phenylpropanoate.
49. The compound of claim 1, wherein the compound is Methyl (2S)-2-(2-hydroxypropoxy)-3-phenylpropanoate.
50. The compound of claim 1, wherein the compound is (2S)-2-(2-hydroxypropoxy)-3-phenylpropanoic acid.
51. The compound of claim 1, wherein the compound is (2S,3R)-5-benzyl-2,6-bis(benzyloxy)-6-oxohexan-3-yl 4-nitrobenzoate.
52. The compound of claim 1, wherein the compound is (5R)-3-benzyl-5-((S)-1-(benzyloxy)ethyl)dihydrofuran-2(3H)-one.
53. The compound of claim 1, wherein the compound is (5R)-3-benzyl-5-((S)-1-hydroxyethyl)dihydrofuran-2(3H)-one.
54. The compound of claim 1, wherein the compound is Sodium (4R,5S)-2-benzyl-4,5-dihydroxyhexanoate.
55. A composition comprising an effective amount of a compound of any one of claims 1-54.
56. The composition of claim 55, wherein said composition is a pharmaceutical composition.
57. The composition of claim 55 or 56, wherein said composition further comprises an excipient, lubricant, antioxidant, emulsifier, stabilizer, solvent, diluent, buffer, vehicle, or a combination thereof.
58. The composition of any one of claims 55-57, wherein said composition further comprises an antidiabetic drug selected from the group consisting of alpha-glucosidase inhibitors, acarbose, miglitol, amylin analogs, pramlintide, dipeptidyl peptidase 4 inhibitors, alogliptan, linagliptan, saxagliptin, sitagliptin, incretin mimetics, albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, tirzepatide, retatrutide, insulin, meglitinides, nateglinide, repaglinide), non-sulfonylureas, metformin, imeglimin, SGLT-2 inhibitors, canagliflozin, dapagliflozin, empagliflozin, sulfonylureas, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide, thiazolidinediones, rosiglitazone, pioglitazone, or a combination thereof.
59. The composition of any one of claims 55-58, wherein said composition further comprises a lipid lowering drug selected from the group consisting of a statin, a cholesterol absorption inhibitor, an antibody against PCSK9, an siRNA PCSK9, an anti-fibrotic agent, a thyroid hormone, a selective thyroid receptor- β agonist, apoptosis signal-

regulating kinase 1 (ASK1) inhibitor, acetyl-CoA carboxylase (ACC) inhibitor, an integrin antagonist, a Semicarbazide Sensitive Amine Oxidase (SSAO) inhibitor, also known as Vascular Adhesion Protein-1 (VAP-1) inhibitor, a fibroblast growth factor mimetic 21 (FGF21), a Fatty acid synthase inhibitor, a non-steroidal Farnesoid X receptor (FXR) agonist, a long hydrocarbon chain diacid, a pantothenic acid analog, bempedoic acid, gemfibrozil, fenofibrate, bezafibrate, clofibrate, ciprofibrate, clinofibrate, etofylline, pirifibrate, simfibrate, tocofibrate, pemafibrate, or a combination thereof.

60. The composition of claim 59, wherein said statin is selected from the group consisting of atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin, mevastatin, dalvastatin, dihydrocompactin, cerivastatin, or a combination thereof, optionally wherein said statin is a pharmaceutically acceptable salt or solvate thereof.
61. A method of treating obesity and its secondary diseases in a subject in need thereof comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-54 or a composition of any one of claims 55-60.
62. The method of claim 61, wherein said secondary disease related to obesity is selected from the group consisting of metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia, hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and neuro-disease.
63. The method of claim 61 or 62, wherein said subject is a mammal.
64. The method of any one of claims 61-63, wherein said subject is pediatric patient.
65. A composition for the treatment of obesity or a secondary disease thereof comprising an effective amount of a compound of any one of claims 1-54.
66. Use of a compound of any one of claims 1-54 for the manufacture of a medicament for the treatment of obesity and secondary diseases related to obesity.
67. The use of claim 66, wherein said secondary disease related to obesity selected from the group consisting of metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia, hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and neuro-disease.
68. The use of claim 66 or 67, wherein said medicament further comprises one or more antidiabetic drugs selected from the group consisting of alpha-glucosidase inhibitors, acarbose, miglitol, amylin analogs, pramlintide, dipeptidyl peptidase 4 inhibitors,

alogliptan, linagliptan, saxagliptin, sitagliptin, incretin mimetics, albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, tirzepatide, retatrutide, insulin, meglitinides, nateglinide, repaglinide), non-sulfonylureas, metformin, imeglimin, SGLT-2 inhibitors, canagliflozin, dapagliflozin, empagliflozin, sulfonylureas, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide, thiazolidinediones, rosiglitazone, pioglitazone, or a combination thereof, wherein said antidiabetic drug is in a pharmaceutically acceptable salt or solvate thereof.

69. The use of any one of claims 66-68, wherein the medicament further comprises a lipid lowering drug selected from the group consisting of a statin, a cholesterol absorption inhibitor, ezetimibe, an antibody against PCSK9, an siRNA PCSK9, an anti-fibrotic agent, a thyroid hormone, a selective thyroid receptor- β agonist, apoptosis signal-regulating kinase 1 (ASK1) inhibitor, acetyl-CoA carboxylase (ACC) inhibitor, an integrin antagonist, a Semicarbazide Sensitive Amine Oxidase (SSAO) inhibitor, also known as Vascular Adhesion Protein-1 (VAP-1) inhibitor, a fibroblast growth factor mimetic 21 (FGF21), a Fatty acid synthase inhibitor, a non-steroidal Farnesoid X receptor (FXR) agonist, a long hydrocarbon chain diacid, a pantothenic acid analog, bempedoic acid, gemfibrozil, fenofibrate, bezafibrate, clofibrate, ciprofibrate, clinofibrate, etofylline, pirifibrate, simfibrate, tocofibrate, pemaifibrate, or a combination thereof, where said lipid lowering drug is in a pharmaceutically acceptable salt or solvate thereof.
70. A method for diagnostic testing of sensitivity to the compound of any one of claims 1-54 by a subject in need of treatment for obesity and secondary diseases related to obesity, said secondary disease related to obesity selected from the group consisting of metabolic disease, triglyceride related disease, diabetes, gallbladder disease, hypertension, hyperlipidemia, hypertriglyceridemia, dyslipidemia, Non-alcoholic steatohepatitis, steatohepatitis, Non-Alcoholic fatty liver disease, and neuro-disease, said method comprising the steps of administering incremental doses of said compound being test for sensitivity in said subject, and observing effects of said doses on said subject.
71. A method of synthesizing a compound of Formula I-IV, comprising the steps of:
- diazotization of D-Phe with NaNO_2 ,
 - bromination with HBR of the diazotization reaction of D-Phe with NaNO_2 ,
 - nucleophilic displacement, and

- deprotection of the protecting groups of the bromination reaction with MeOH and H₂SO₄.

72. A method of synthesizing a compound of Formula I-IV, comprising the steps of:

- EDC coupling of protected D-Lactic acid and a compound selected from D-Phe, N-methyl-phenylalanine, and solid supported Phe with carbonyl diimidazole; and
- deprotection of the products.

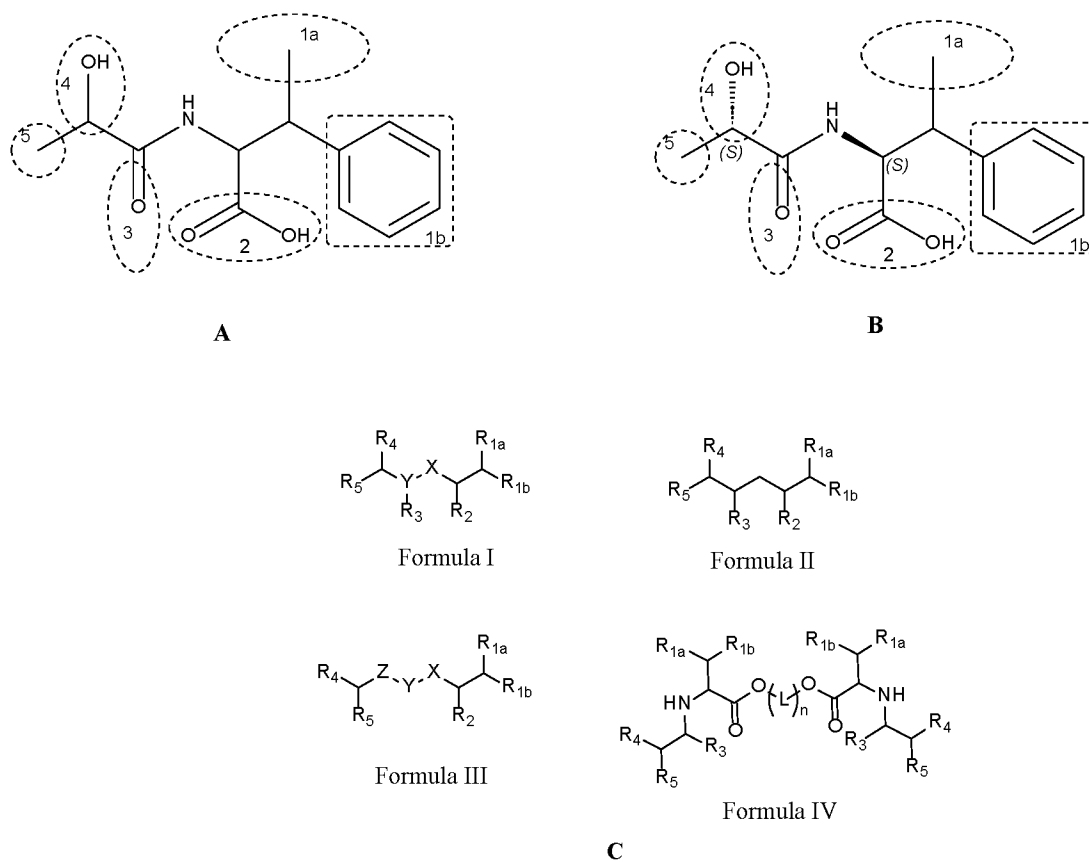


FIG. 1

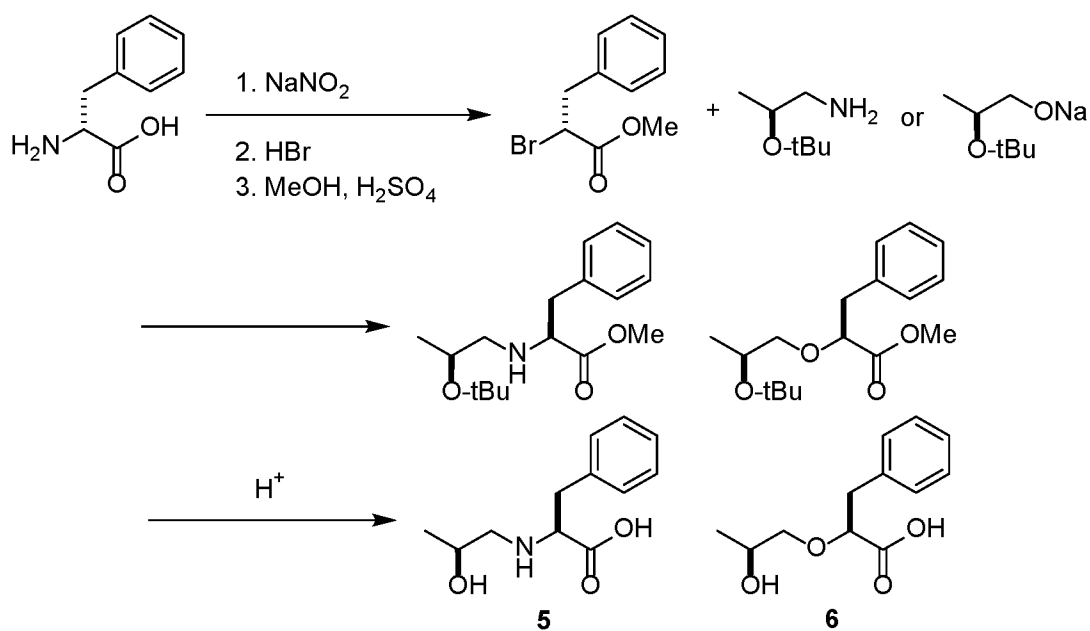


FIG. 2A

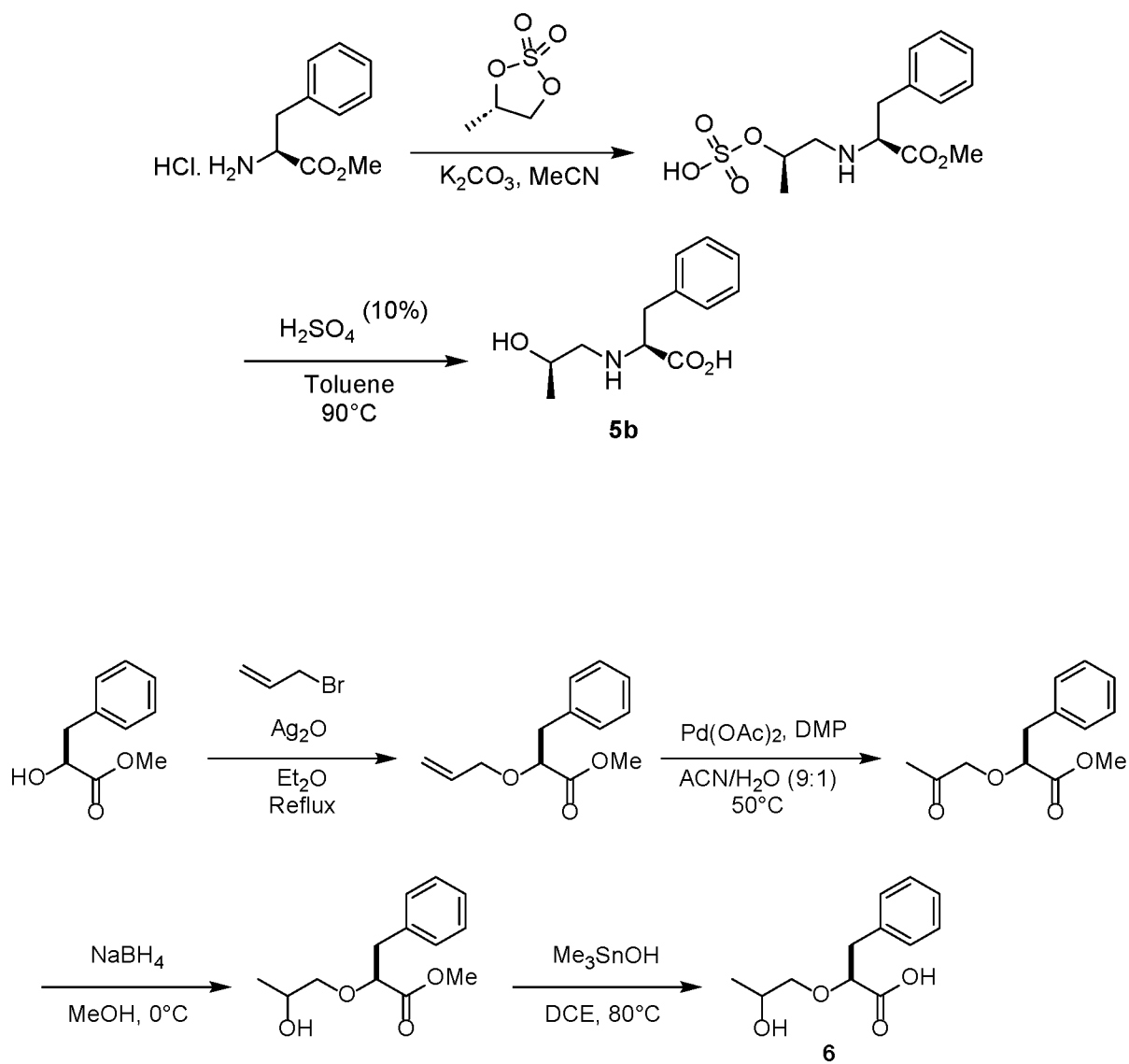


FIG. 2B

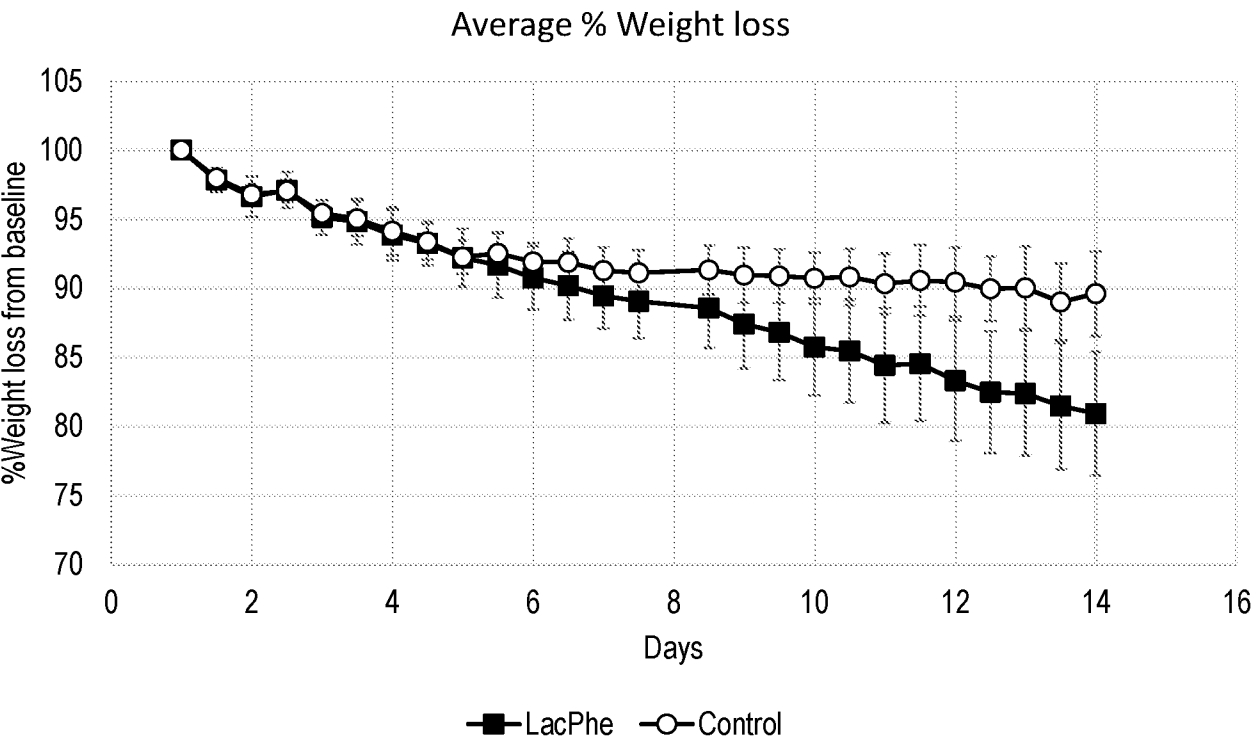


FIG. 3

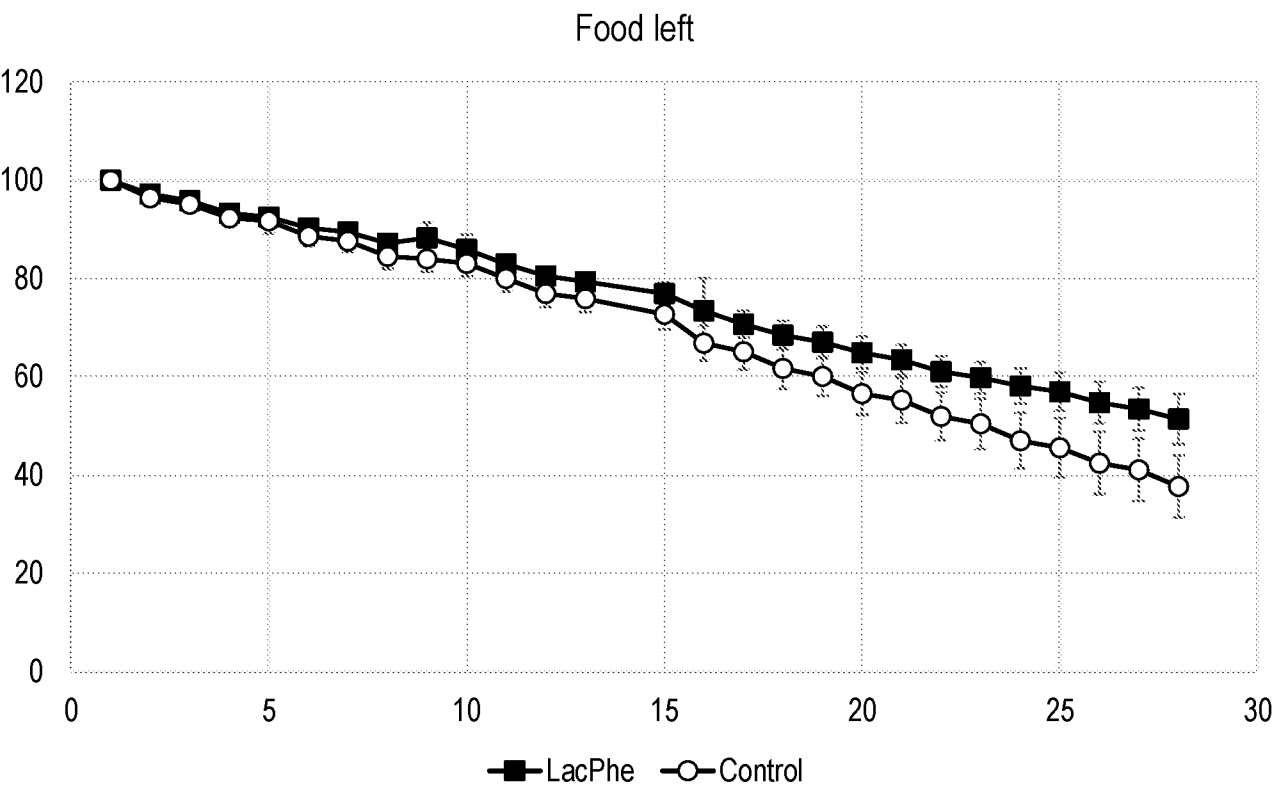


FIG. 4

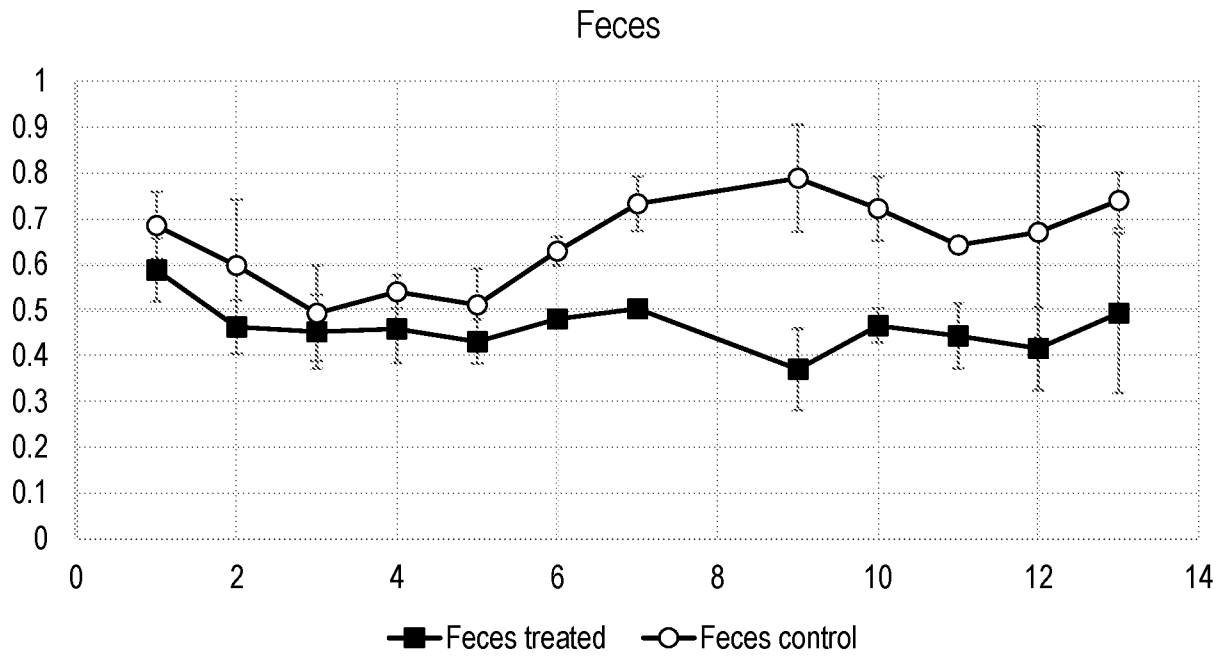


FIG. 5

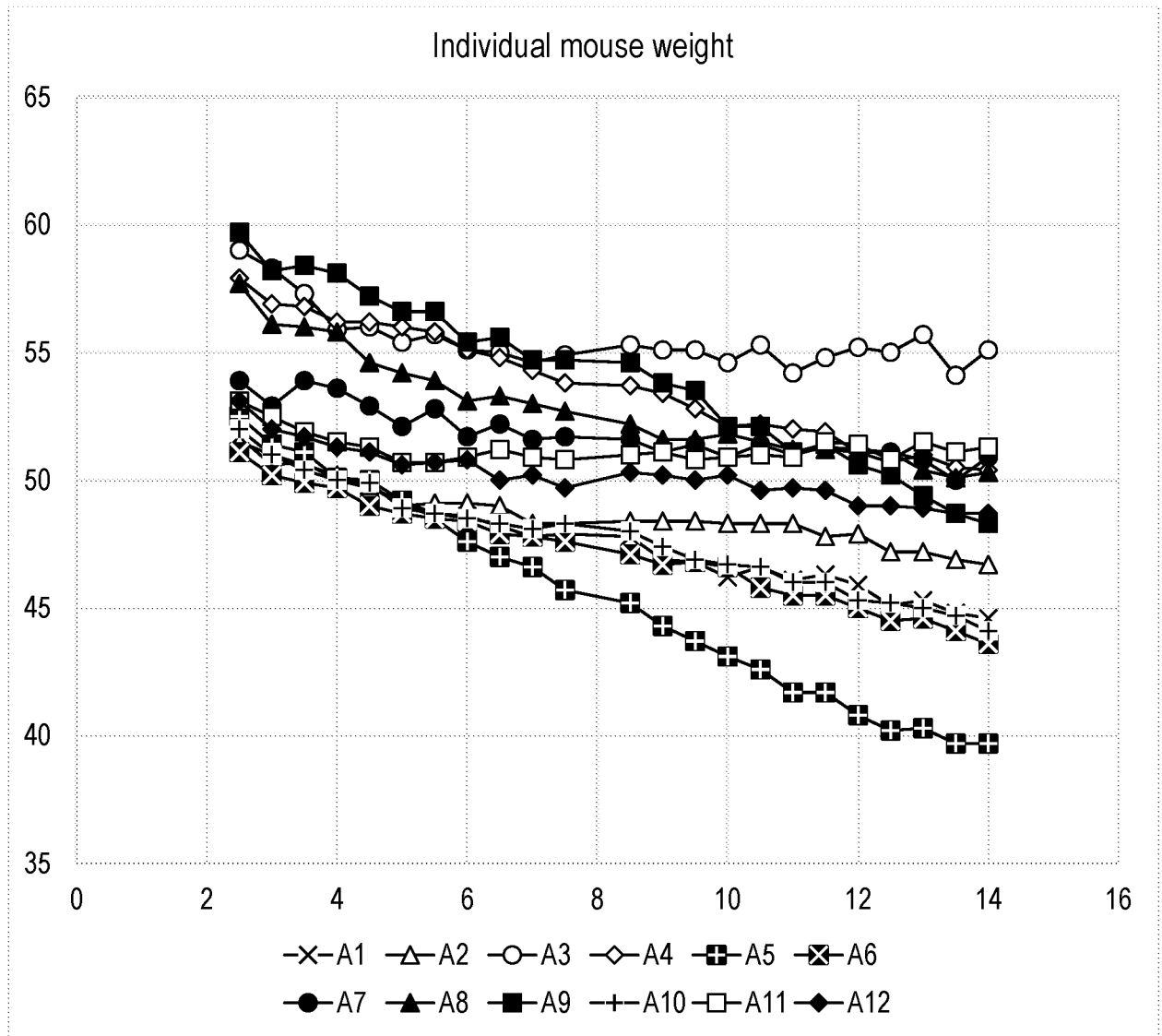


FIG. 6

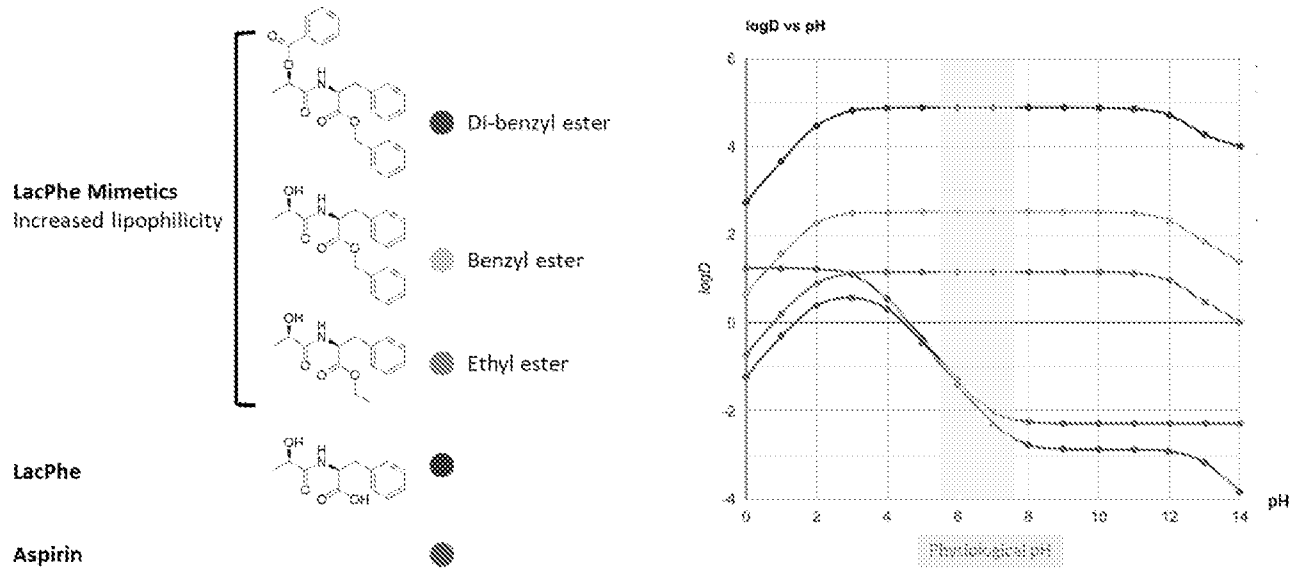


FIG. 7

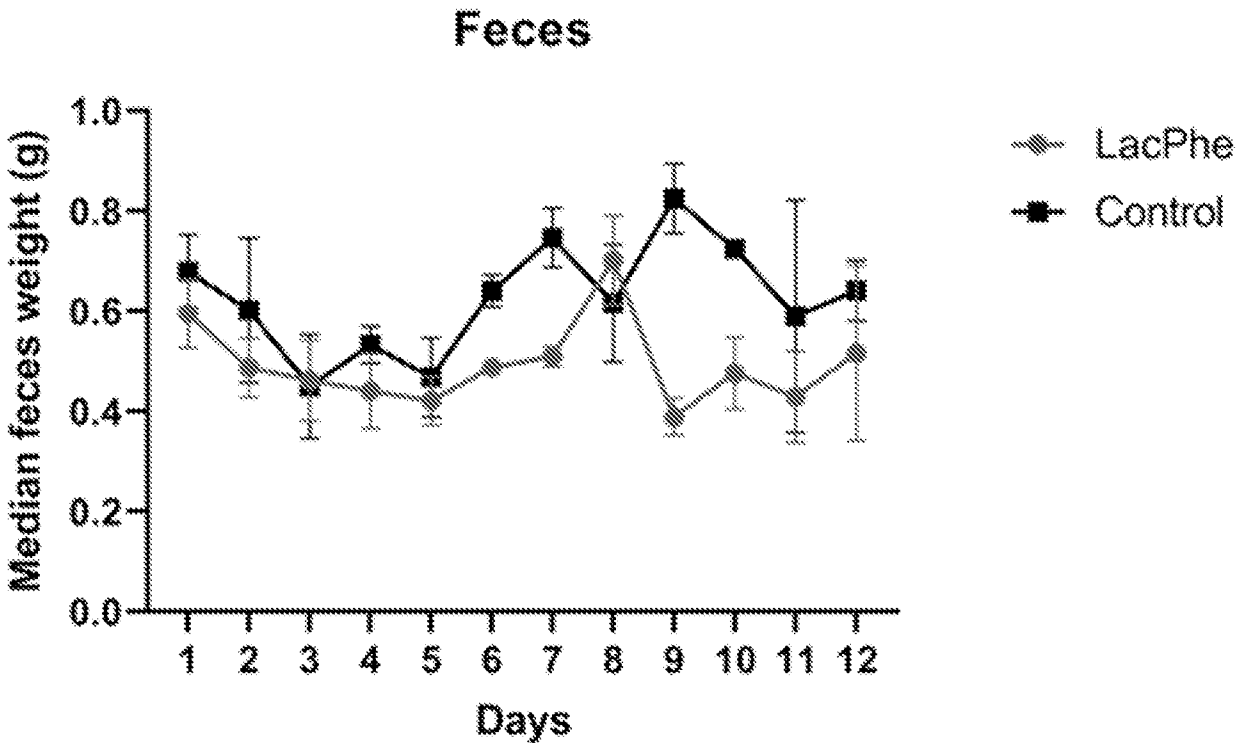


FIG. 8

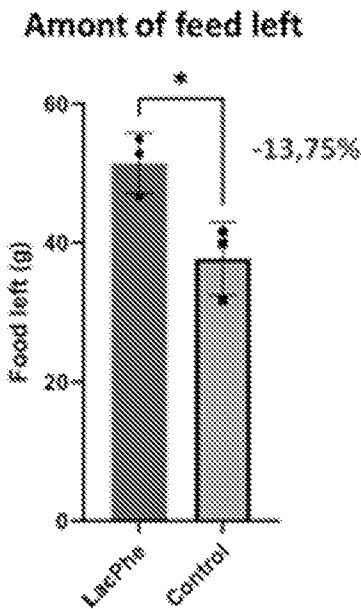


FIG. 9

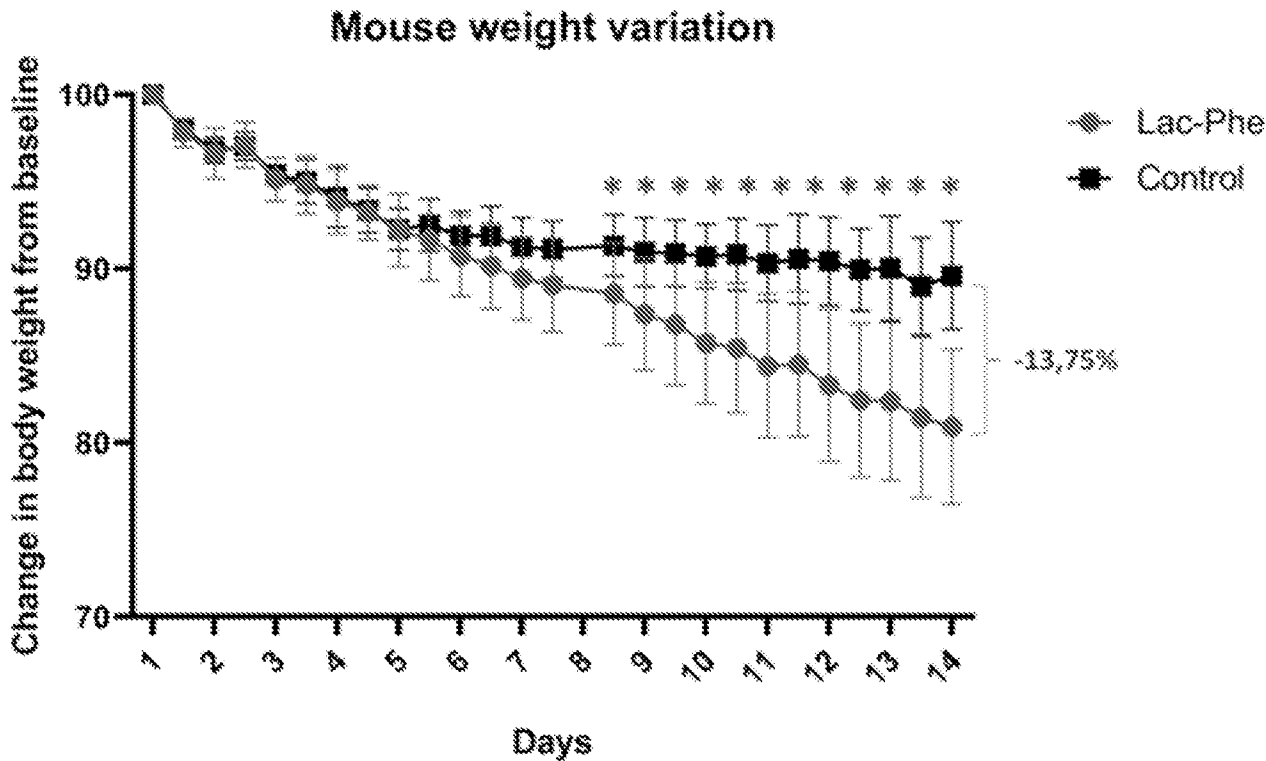


FIG. 10

Mouse weight continued

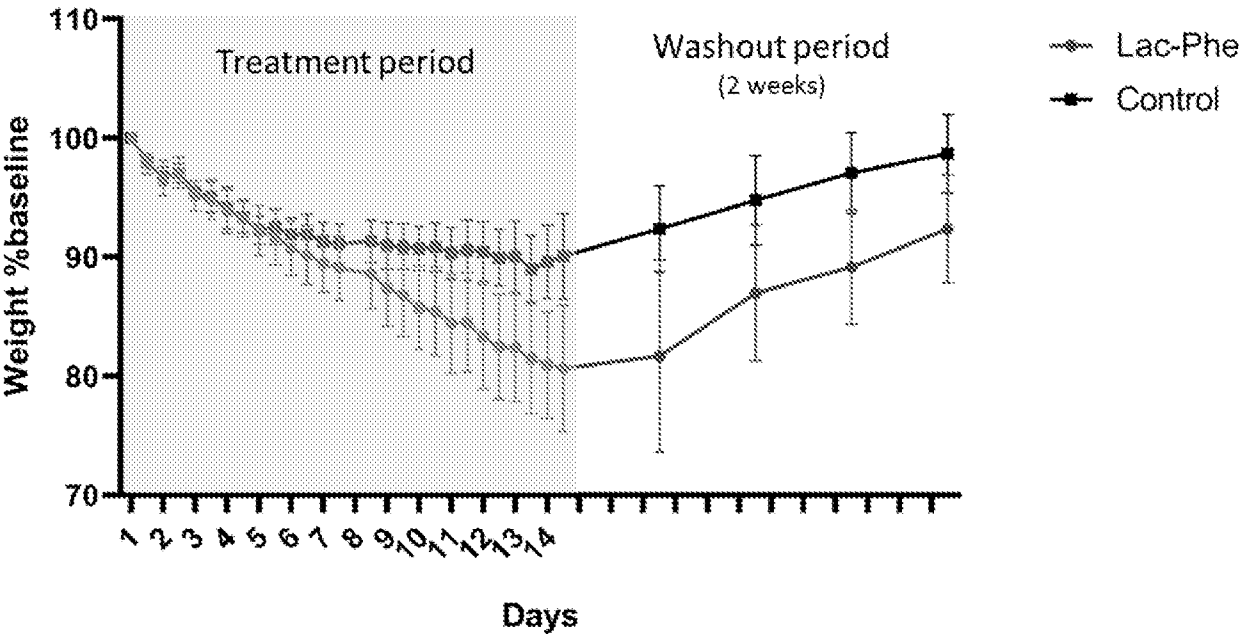


FIG. 11