(19) DANMARK

(10) DK/EP 3464336 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *C 07 K 5/065 (2006.01)* *A 61 K 38/00 (2006.01)* *A 61 K 38/22 (2006.01)*
C 07 K 5/02 (2006.01) *C 07 K 5/06 (2006.01)* *C 07 K 14/475 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2022-05-09**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2022-03-16**

(86) Europæisk ansøgning nr.: **17807519.8**

(86) Europæisk indleveringsdag: **2017-06-01**

(87) Den europæiske ansøgnings publiceringsdag: **2019-04-10**

(86) International ansøgning nr.: **US2017035547**

(87) Internationalt publikationsnr.: **WO2017210489**

(30) Prioritet: **2016-06-01 US 201662344305 P**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

(73) Patenthaver: **Athira Pharma, Inc., 18706 North Creek Parkway, Suite 104, Bothell, WA 98011, USA**

(72) Opfinder: **KAWAS, Leen, H., c/o M3 Biotechnology Inc., 4000 Mason Road Suite 300, Box 352141, Seattle, WA 98195, USA**
SINGH, Jasbir, c/o M3 Biotechnology Inc., 4000 Mason Road Suite 300, Box 352141, Seattle, WA 98195, USA
STEWART, Lansing Joseph, c/o M3 Biotechnology Inc., 4000 Mason Road Suite 300, Box 352141, Seattle, WA 98195, USA
BAKER, William, R., c/o M3 Biotechnology Inc., 4000 Mason Road, Suite 300, Box 352141, Seattle, WA 98195, USA

(74) Fuldmægtig i Danmark: **NORDIC PATENT SERVICE A/S, Bredgade 30, 1260 København K, Danmark**

(54) Benævnelse: **FORBINDELSER**

(56) Fremdragne publikationer:
WO-A1-97/08193
US-A1- 2005 118 643
US-A1- 2005 214 859
US-A1- 2013 165 392
US-A1- 2014 051 633
JIN-MI NOH ET AL: "Kojic acid-tripeptide amide as a new tyrosinase inhibitor", BIOPOLYMERS, vol. 88, no. 2, 1 January 2007 (2007-01-01), pages 300-307, XP55649603, US ISSN: 0006-3525, DOI: 10.1002/bip.20670
DEBORAH HEYL ET AL: "Peptide Inhibitors of a-Amylase Based on Tendamistat: Development of Analogues with [pi]-Amino Acids Linking Critical Binding Segments", PROTEIN AND PEPTIDE LETTERS: INTERNATIONAL JOURNAL FOR RAPID PUBLICATION OF SHORT PAPERS IN PROTEIN AND PEPTIDE SCIENCE, vol. 12, no. 3, 1 April 2005 (2005-04-01), pages 275-280, XP55649610, NL ISSN: 0929-8665, DOI: 10.2174/0929866053587110
DATABASE PUBCHEM [Online] 04 December 2007 XP055447500 Database accession no. 18232021

Fortsættes ...

GHOSH ET AL.: 'Organic Carbamates in Drug Design and Medicinal Chemistry' JOURNAL OF MEDICINAL CHEMISTRY vol. 58, 07 January 2015, pages 2895 - 2940, XP055425367

DESCRIPTION

1. BACKGROUND

[0001] The small molecule peptidic compound, N-hexanoic-L-tyrosine-L-isoleucine-(6)-aminohexanoic amide ("Base Structure"), has been shown or predicted to have potential as a neuroprotective/neuroregenerative agent, to protect from or reverse neurodegenerative disease, to prevent or reverse the symptoms of dementia, to facilitate repair of traumatic injury to the nervous system, and to enhance cognitive function. US2013165392A1 describes small molecule, peptidic hepatocyte growth factors mimics, which act as both mimetics and antagonists. Given Base Structure's therapeutic potential to treat Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, other dementias and neurodegenerative diseases, spinal cord injury, traumatic brain injury, and sensorineural hearing and vision loss, there is a need in the art for compounds that retain Base Structure's therapeutic activities while possessing optimized pharmacokinetic and pharmacodynamic properties.

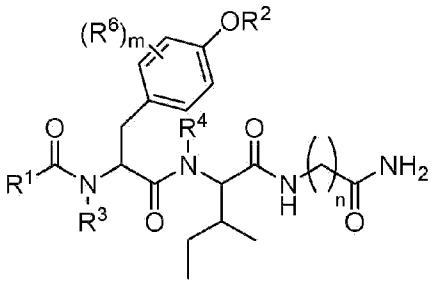
2. SUMMARY

[0002] Compounds have been synthesized that demonstrate increased stability in simulated intestinal fluid and simulated gastric fluid, but that can be hydrolyzed in plasma to produce Base Structure or Base Structure-like compounds that retain Base Structure's beneficial properties.

[0003] Accordingly, in a first aspect, compounds are provided, as defined in the appended claims 1 to 4.

[0004] In typical embodiments, the compounds possess a di-amino acid core structure and are substituted by one or more organic functional groups at the C-terminus, N-terminus, and/or the side-chain of the core.

[0005] The invention as set out by the language of the appended claims 1 or 4 provides a compound of formula II:



(II)

wherein:

n is 1, 2, 3, 4, 5, 6, 7, 8, or 9;

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

R^1 is selected from the group consisting of: C_1-C_{12} alkyl, C_1-C_{12} substituted alkyl, C_1-C_{12} alkenyl, C_1-C_{12} substituted alkenyl, C_1-C_{12} alkynyl, and C_1-C_{12} substituted alkynyl;

R^2 is selected from the group consisting of: hydrogen,

$PO(OY)_2$,

$PO(OH)_2$, -C(=O)-Y and -CO-U;

Y is -Z-$(CH_2)_q$-W-R^b, or alternatively -C(=O)-Y forms an amide bond through a nitrogen atom on Y in which case Y is selected from the group consisting of: glycine, sarcosine, N,N-dimethyl glycine, alanine, valine, leucine, isoleucine, lysine, ornithine, arginine, serine, and threonine;

q is 0-4;

Z and W are independently selected from the group consisting of: CH_2, O, S, NR^c and R^b, wherein optionally Z and W are taken together to form a C_3-C_8 heterocycloalkyl or C_4-C_{10} heteroaryl or bicyclic ring system in which one of the rings is a C_4-C_{10} heteroaryl;

R^c is selected from the group consisting of: hydrogen, C_1-C_4 alkyl, and C_3-C_6 cycloalkyl;

R^b is selected from the group consisting of: hydrogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyl, C_3-C_8 cycloalkyl, C_3-C_8 substituted cycloalkyl, C_3-C_8 heterocycloalkyl, and C_3-C_8 substituted heterocycloalkyl;

U is selected from the group consisting of: pyridine, 1,4-dihydropyridine, N-alkyl-1,4-dihydropyridine, and C-imidazole, or U is selected from aryl, heteroaryl or heterocycloalkyl;

R^3 and R^4 together are bonded to form a spirocyclic ring system;

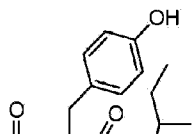
each R^6 is independently selected from the group consisting of: hydrogen, deuterium, CH_3, F, ^{19}F, and ^{18}F;

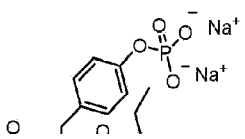
and wherein each heterocyclic and heteroaryl ring contains up to four heteroatoms selected from the group consisting of: O, N, and S;

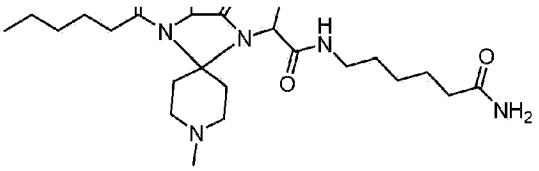
with the proviso that when both Z and W are heteroatoms, the value of q cannot be 1;

or a tautomer and/or a pharmaceutically acceptable salt thereof;

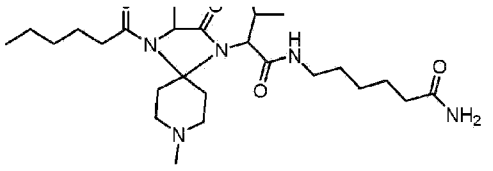
or a compound selected from the following structures:



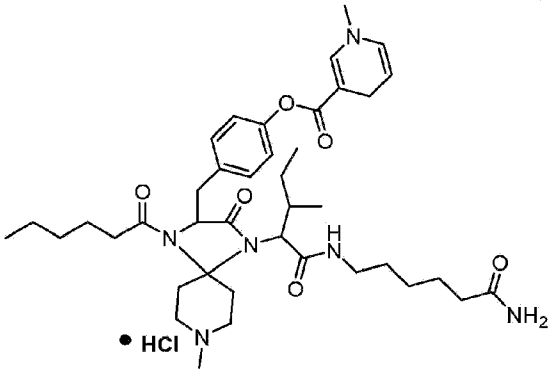




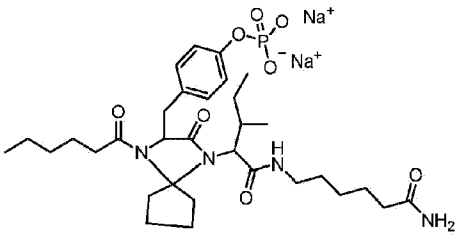
1



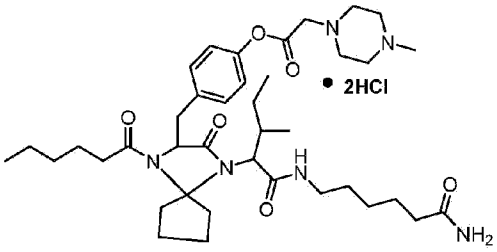
2



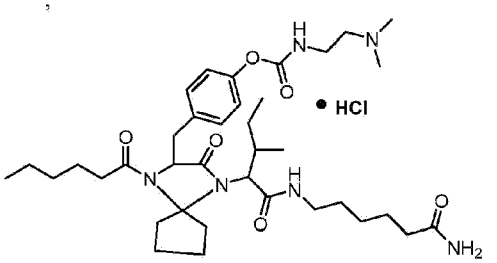
3



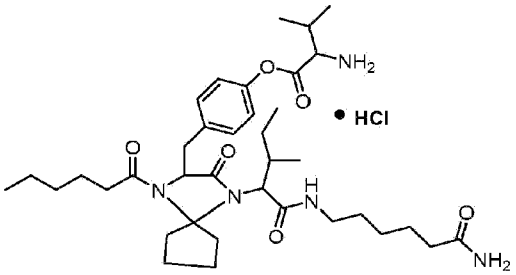
4



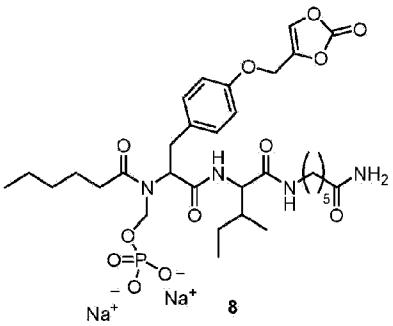
5



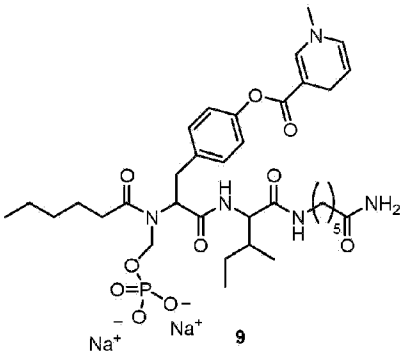
6



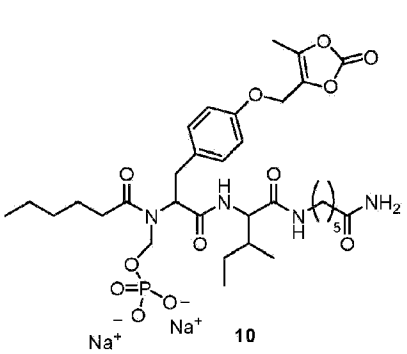
7



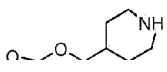
8

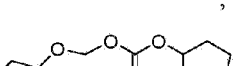


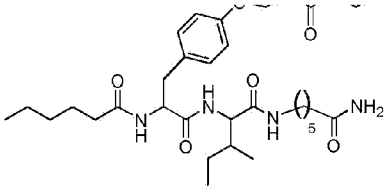
9



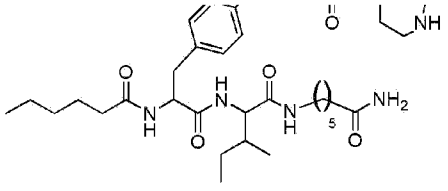
10



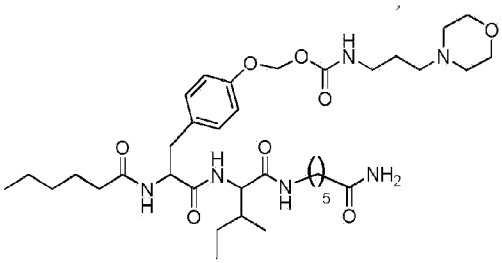




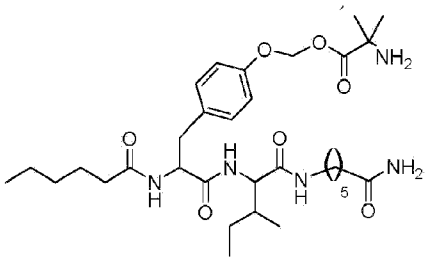
A17a



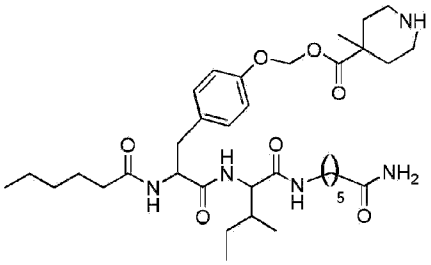
A17b



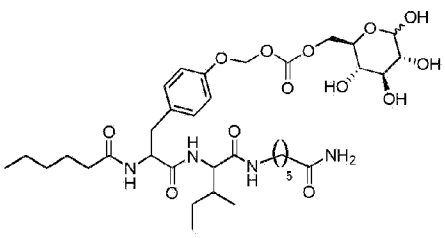
A17c



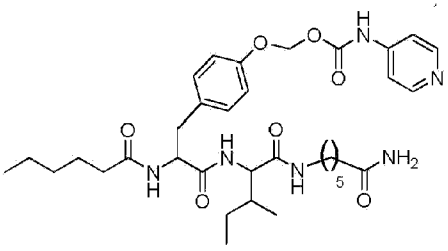
A17e



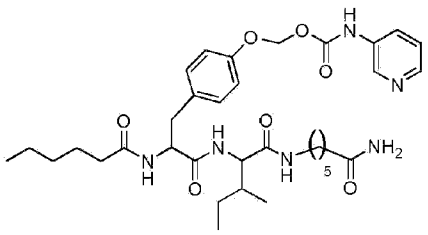
A17f



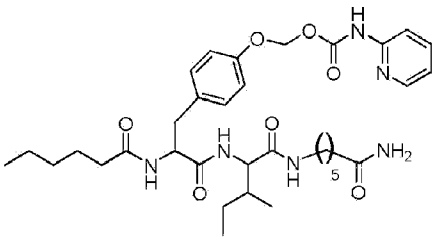
A17g



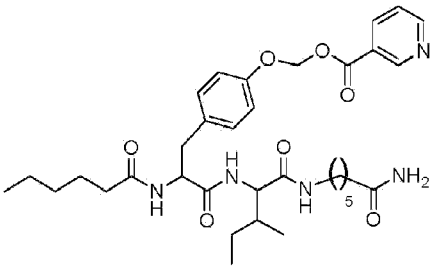
A17h



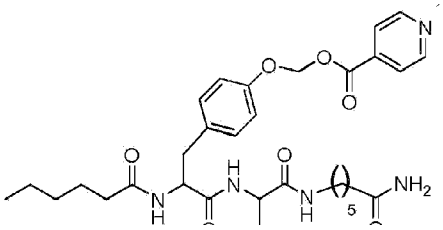
A17i

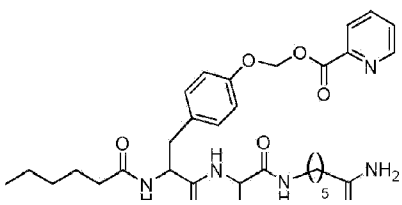


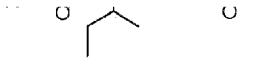
A17j



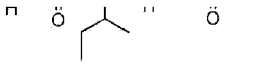
A17k



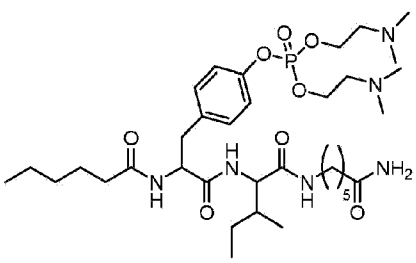




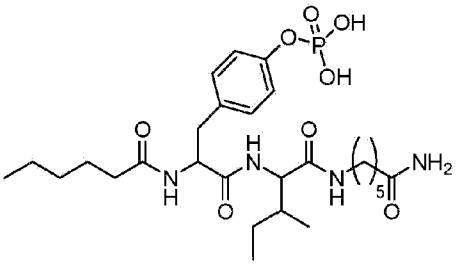
A17l ,



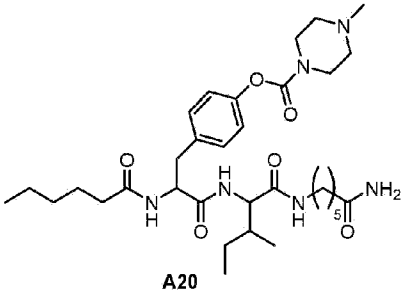
A17m ,



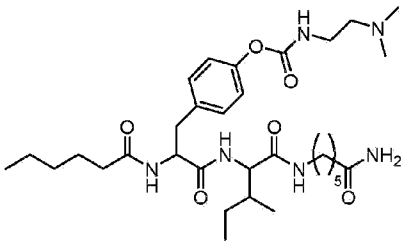
A18 ,



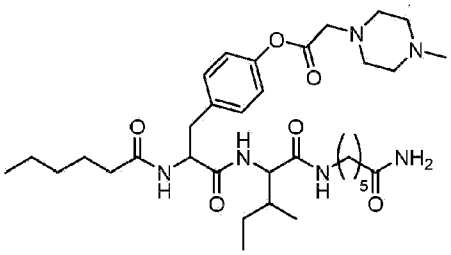
A19 ,



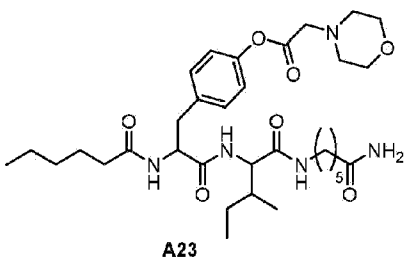
A20 ,



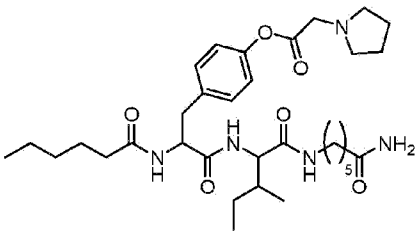
A21 ,



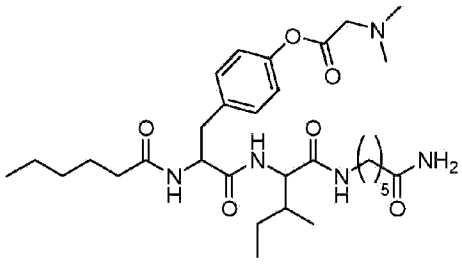
A22 ,



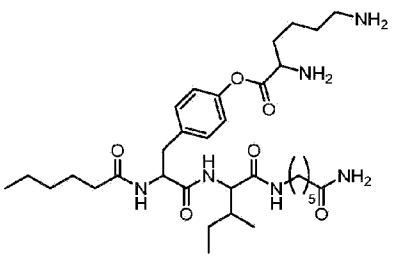
A23 ,



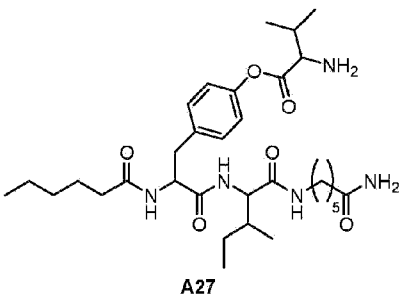
A24 ,



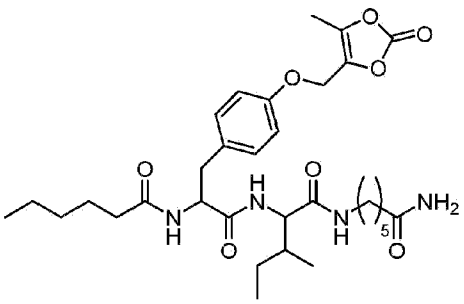
A25 ,



A26 ,



A27 , and



A28 ;

or a tautomer and/or a pharmaceutically acceptable salt thereof.

[0006] In various embodiments, the compound is selected from among certain specific compounds disclosed herein.

[0007] In another aspect, compositions comprising at least one of the compounds described herein are provided, as defined by the language of the appended claim 5.

[0008] In a further aspect, pharmaceutical compositions comprising at least one of the compounds described herein are provided, as defined by the language of the appended claim 6.

[0009] In a still further aspect, a compound for use in methods of treatment are provided, as defined by the language of the appended claims 8 and 9. The methods comprise administering at least one compound as described herein to a subject in an amount effective to treat, protect from, or reverse neurodegenerative disease, to prevent or reverse the symptoms of dementia, to facilitate repair of traumatic injury to the nervous system, or to enhance cognitive function. In various embodiments, the subject has a disease selected from Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, other dementias and neurodegenerative diseases, spinal cord injury, traumatic brain injury, and/or sensorineural hearing loss. In typical embodiments, the method comprises administering a pharmaceutical composition comprising at least one of the compounds described herein, as described herein.

[0010] In various embodiments, the compound is administered as the sole medical treatment. In various embodiments, the compound is administered in combination with other medical and/or surgical interventions according to the prevailing standards of care.

[0011] These and other embodiments are described in further detail herein.

3. BRIEF DESCRIPTION OF THE DRAWINGS

[0012] These and other features, aspects, and advantages of the present invention will become better understood with regard to the following description, and accompanying drawings, where:

FIG. 1 are graphs containing data from experiments testing stability of various compounds synthesized as potential prodrugs of Base Structure in the presence of Simulated Intestinal Fluid

(SIP), pH 6.8 (+/- Pancreatin) or Simulated Gastric Fluid (SGF), pH 1.2 (+/-Pepsin). The results demonstrate increased stability of some prodrugs even in the presence of enzymes native to either intestinal or gastric fluids over 240 minutes.

FIG. 2 are graphs showing data measuring the formation of Base Structure from various prodrugs in both human and rat plasma over 240 minutes, measured both as percent prodrug compound remaining (left y-axis).

4. DETAILED DESCRIPTION

4.1. Definitions

[0013] Various terms used in the specification and claims herein are defined as set forth below, unless otherwise specifically defined in this disclosure. All technical and scientific terms not defined herein have the meaning commonly understood by a person skilled in the art to which this invention belongs.

[0014] "Alkyl" refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 10 carbon atoms and preferably 1 to 6 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methyl (CH_3-), ethyl (CH_3CH_2-), *n*-propyl ($CH_3CH_2CH_2$-), isopropyl ($(CH_3)_2CH$-), *n*-butyl ($CH_3CH_2CH_2CH_2$-), isobutyl ($(CH_3)_2CHCH_2$-), *sec*-butyl ($(CH_3)(CH_3CH_2)CH$-), *t*-butyl ($(CH_3)_3C$-), *n*-pentyl ($CH_3CH_2CH_2CH_2CH_2$-), and neopentyl ($(CH_3)_3CCH_2$-). C_x alkyl refers to an alkyl group having x number of carbon atoms.

[0015] "Alkenyl" refers to straight or branched hydrocarbyl groups having from 1 to 6 carbon atoms and preferably 2 to 4 carbon atoms and having at least 1 and preferably from 1 to 2 sites of unsaturation (>C=C<). Such groups are exemplified, for example, by vinyl, allyl, and but-3-en-1-yl. Included within this term are the *cis* and *trans* isomers or mixtures of these isomers. C_x alkenyl refers to an alkenyl group having x number of carbon atoms.

[0016] "Alkynyl" refers to straight or branched monovalent hydrocarbyl groups having from 2 to 6 carbon atoms and preferably 2 to 3 carbon atoms and having at least 1 and preferably from 1 to 2 sites of acetylenic (-C≡ C-) unsaturation. Examples of such alkynyl groups include acetylenyl (-C≡ CH), and propargyl (-CH_2C≡ CH). C_x alkynyl refers to an alkynyl group having x number of carbon atoms.

[0017] "Substituted alkyl" refers to an alkyl group having from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, aminocarbonylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy,

aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein.

[0018] In some embodiments, the substituted alkyl groups include halogenated alkyl groups and particularly halogenated methyl groups such as trifluoromethyl, difluromethyl, and fluoromethyl.

[0019] "Alkyl aryl" refers to an alkyl group having from 1 to 8, preferably 1 to 5, or more preferably 1 to 3 carbon atoms in length and is substituted specifically at any one of the carbons along the chain with an aryl group. **"Alkenyl aryl"** refers to an alkenyl or alkene group having from 1 to 8, preferably 1 to 5, or more preferably 1 to 3 carbon atoms in length and is substituted specifically at any one of the carbons along the chain with an aryl group. The aryl group can include heteroatoms or not. **Alkynyl aryl"** refers to an alkynyl or alkyne group having from 1 to 8, preferably 1 to 5, or more preferably 1 to 3 carbon atoms in length and is substituted specifically at any one of the carbons along the chain with an aryl group. The aryl group can include heteroatoms or not.

[0020] "Cycloalkyl" or **"Cyclyl alkyl"** refers to a saturated or partially saturated, but not aromatic, group having from 3 to 10 ring carbon atoms and no heteroatoms. Cycloalkyl encompasses single ring systems.

[0021] "Substituted alkenyl" refers to alkenyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, aminocarbonylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein and with the proviso that any hydroxy or thiol substitution is not attached to a vinyl (unsaturated) carbon atom.

[0022] "Substituted alkynyl" refers to alkynyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, aminocarbonylamino, acyloxy, amino, substituted amino, aminocarbonyl,

aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein and with the proviso that any hydroxyl or thiol substitution is not attached to an acetylenic carbon atom.

[0023] "Ar" and/or "aryl" refers to any group which is aromatic. This group must be cyclic; and does not contain heteroatoms.

[0024] "Alkoxy" refers to the group -O-alkyl wherein alkyl is defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, *sec*-butoxy, and *n*-pentoxy.

[0025] "Substituted alkoxy" refers to the group -O-(substituted alkyl) wherein substituted alkyl is defined herein. Preferred substituted alkyl groups in -O-(substituted alkyl) include halogenated alkyl groups and particularly halogenated methyl groups such as trifluoromethyl, difluromethyl, and fluoromethyl.

[0026] "Acyl" refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, alkynyl-C(O)-, substituted alkynyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O)-, heterocyclic-C(O)-, and substituted heterocyclic-C(O)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein. Acyl includes the "acetyl" group $CH_3C(O)$-.

[0027] "Acylamino" refers to the groups -$NR^{30}C(O)$alkyl, -$NR^{30}C(O)$substituted alkyl, -$NR^{30}C(O)$cycloalkyl, -$NR^{30}C(O)$substituted cycloalkyl, -N $R^{30}C(O)$alkenyl, -$NR^{30}C(O)$substituted alkenyl, alkoxy, substituted alkoxy-$NR^{30}C(O)$alkynyl, -$NR^{30}C(O)$substituted alkynyl, -$NR^{30}C(O)$aryl, -$NR^{30}C(O)$substituted aryl, -$NR^{30}C(O)$heteroaryl, -$NR^{30}C(O)$substituted heteroaryl, -$NR^{30}C(O)$heterocyclic, and -$NR^{30}C(O)$substituted heterocyclic wherein R^{30} is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0028] "Aminoacyl" refers to the groups H-C(N)-, alkyl-C(N)-, substituted alkyl-C(N)-, alkenyl-C(N)-, substituted alkenyl-C(N)-, alkynyl-C(N)-, substituted alkynyl-C(N)-, cycloalkyl-C(N)-, substituted cycloalkyl-C(N)-, aryl-C(N)-, substituted aryl-C(N)-, heteroaryl-C(N)-, substituted

heteroaryl-C(N)-, heterocyclic-C(N)-, and substituted heterocyclic-C(N)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0029] "Acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, alkynyl-C(O)O-, substituted alkynyl-C(O)O-, aryl-C(O)O-, substituted aryl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, heteroaryl-C(O)O-, substituted heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O-wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0030] "Amino" refers to the group $-NH_2$.

[0031] "Substituted amino" refers to the group $-NR^{31}R^{32}$ where R^{31} and R^{32} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, and substituted sulfonyl and wherein R^{31} and R^{32} are optionally joined, together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that R^{31} and R^{32} are both not hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. When R^{31} is hydrogen and R^{32} is alkyl, the substituted amino group is sometimes referred to herein as alkylamino. When R^{31} and R^{32} are alkyl, the substituted amino group is sometimes referred to herein as dialkylamino. When referring to a monosubstituted amino, it is meant that either R^{31} or R^{32} is hydrogen but not both. When referring to a disubstituted amino, it is meant that neither R^{31} nor R^{32} are hydrogen.

[0032] "Aminocarbonyl" refers to the group $-C(O)NR^{33}R^{34}$ where R^{33} and R^{34} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{33} and R^{34} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0033] "Aminoacyl carbonyloxy" refers to the group $-C(NR^{33})OR^{34}$ where R^{33} and R^{34} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, aryl, substituted aryl,

cycloalkyl, substituted cycloalkyl heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{33} and R^{34} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0034] "Aminothiocarbonyl" refers to the group $-C(S)NR^{33}R^{34}$ where R^{33} and R^{34} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{33} and R^{34} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0035] "Aminocarbonylamino" refers to the group $-NR^{30}C(O)NR^{33}R^{34}$ where R^{30} is hydrogen or alkyl and R^{33} and R^{34} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{33} and R^{34} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0036] "Aminothiocarbonylamino" refers to the group $-NR^{30}C(S)NR^{33}R^{34}$ where R^{30} is hydrogen or alkyl and R^{33} and R^{34} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{33} and R^{34} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0037] "Aminocarbonyloxy" refers to the group $-O-C(O)NR^{33}R^{34}$ where R^{33} and R^{34} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{33} and R^{34} are optionally joined together with the nitrogen bound thereto

to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0038] "Aminosulfonyl" refers to the group $-SO_2NR^{33}R^{34}$ where R^{33} and R^{34} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{33} and R^{34} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0039] "Aminosulfonyloxy" refers to the group $-O-SO_2NR^{33}R^{34}$ where R^{33} and R^{34} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{33} and R^{34} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0040] "Aminosulfonylamino" refers to the group $-NR^{30}-SO_2NR^{33}R^{34}$ where R^{30} is hydrogen or alkyl and R^{33} and R^{34} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{33} and R^{34} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0041] "Amidino" refers to the group $-C(=NR^{35})NR^{33}R^{34}$ where R^{33}, R^{34}, and R^{35} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{33} and R^{34} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and

substituted heterocyclic are as defined herein.

[0042] "Substituted aryl" refers to aryl groups which are substituted with 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, aminocarbonylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, a monosaccharide (which may be covalently bonded to the aryl group thru any oxygen atom on the saccharide), and substituted alkylthio, wherein said substituents are defined herein.

[0043] "Aryloxy" refers to the group -O-aryl, where aryl is as defined herein, that includes, by way of example, phenoxy and naphthoxy.

[0044] "Substituted aryloxy" refers to the group -O-(substituted aryl) where substituted aryl is as defined herein.

[0045] "Arylthio" refers to the group -S-aryl, where aryl is as defined herein.

[0046] "Substituted arylthio" refers to the group -S-(substituted aryl), where substituted aryl is as defined herein.

[0047] "Carbonyl" refers to the divalent group -C(O)- which is equivalent to -C(=O)-.

[0048] "Carboxy" or **"carboxyl"** refers to -COOH or salts thereof.

[0049] "Carboxyl ester" or **"carboxy ester"** refers to the groups -C(O)O-alkyl, -C(O)O-substituted alkyl, -C(O)O-alkenyl, -C(O)O-substituted alkenyl, -C(O)O-alkynyl, -C(O)O-substituted alkynyl, -C(O)O-aryl, -C(O)O-substituted aryl, -C(O)O-cycloalkyl, -C(O)O-substituted cycloalkyl, -C(O)O-heteroaryl, -C(O)O-substituted heteroaryl, -C(O)O-heterocyclic, and -C(O)O-substituted heterocyclic wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0050] "(Carboxyl ester)amino" refers to the group $-NR^{30}$-C(O)O-alkyl, $-NR^{30}$-C(O)O-substituted alkyl, $-NR^{30}$-C(O)O-alkenyl, $-NR^{30}$-C(O)O-substituted alkenyl, $-NR^{30}$-C(O)O-alkynyl, $-NR^{30}$-C(O)O-substituted alkynyl, $-NR^{30}$-C(O)O-aryl, $-NR^{30}$-C(O)O-substituted aryl, $-NR^{30}$-C(O)O-

cycloalkyl, -NR^{30}-C(O)O-substituted cycloalkyl, -NR^{30}-C(O)O-heteroaryl, -NR^{30}-C(O)O-substituted heteroaryl, -NR^{30}-C(O)O-heterocyclic, and -NR^{30}-C(O)O-substituted heterocyclic wherein R^{30} is alkyl or hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0051] "(Carboxyl ester)oxy" refers to the group -O-C(O)O-alkyl, -O-C(O)O-substituted alkyl, -O-C(O)O-alkenyl, -O-C(O)O-substituted alkenyl, -O-C(O)O-alkynyl, -O-C(O)O-substituted alkynyl, -O-C(O)O-aryl, -O-C(O)O-substituted aryl, -O-C(O)O-cycloalkyl, -O-C(O)O-substituted cycloalkyl, -O-C(O)O-heteroaryl, -O-C(O)O-substituted heteroaryl, -O-C(O)O-heterocyclic, and -O-C(O)O-substituted heterocyclic wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0052] "Cyano" refers to the group -C=N.

[0053] "Cycloalkyl" refers to a saturated or unsaturated but nonaromatic cyclic alkyl groups of from 3 to 10 carbon atoms having single or multiple cyclic rings including fused, bridged, and spiro ring systems. C_x cycloalkyl refers to a cycloalkyl group having x number of ring carbon atoms. Examples of suitable cycloalkyl groups include, for instance, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclooctyl. One or more the rings can be aryl, heteroaryl, or heterocyclic provided that the point of attachment is through the non-aromatic, non-heterocyclic ring saturated carbocyclic ring. "Substituted cycloalkyl" refers to a cycloalkyl group having from 1 to 5 or preferably 1 to 3 substituents selected from the group consisting of oxo, thione, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, aminocarbonylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein.

[0054] "Cycloalkyloxy" refers to -O-cycloalkyl.

[0055] "Substituted cycloalkyloxy" refers to -O-(substituted cycloalkyl).

[0056] "Cycloalkylthio" refers to -S-cycloalkyl.

[0057] "Substituted cycloalkylthio" refers to -S-(substituted cycloalkyl).

[0058] "Ethylene glycol" refers to the group -O-CH2CH2-O-E, wherein E is either H or CH3.

[0059] "Guanidino" refers to the group -NHC(=NH)NH_2.

[0060] "Substituted guanidino" refers to -$NR^{36}C(=NR^{36})N(R^{36})_2$ where each R^{36} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and two R^{36} groups attached to a common guanidino nitrogen atom are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that at least one R^{36} is not hydrogen, and wherein said substituents are as defined herein.

[0061] "Halo" or **"halogen"** refers to fluoro, chloro, bromo and iodo and preferably is fluoro or chloro.

[0062] "Hydroxy" or **"hydroxyl"** refers to the group -OH.

[0063] "Heteroaryl" refers to an aromatic group of from 4 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within the ring. Such heteroaryl groups can have a single ring (e.g., pyridinyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl) wherein the condensed rings may or may not be aromatic and/or contain a heteroatom provided that the point of attachment is through an atom of the aromatic heteroaryl group. In one embodiment, the nitrogen and/or the sulfur ring atom(s) of the heteroaryl group are optionally oxidized to provide for the N-oxide (N→O), sulfinyl, or sulfonyl moieties. Preferred heteroaryls include 5 or 6 membered heteroaryls such as pyridinyl, pyrrolyl, indolyl, thiophenyl, and furanyl.

[0064] "Substituted heteroaryl" refers to heteroaryl groups that are substituted with from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of the same group of substituents defined for substituted aryl.

[0065] "Heteroaryloxy" refers to -O-heteroaryl.

[0066] "Substituted heteroaryloxy" refers to the group -O-(substituted heteroaryl).

[0067] "Heteroarylthio" refers to the group -S-heteroaryl.

[0068] "Substituted heteroarylthio" refers to the group -S-(substituted heteroaryl).

[0069] "Heterocycle" or **"heterocyclic"** or **"heterocycloalkyl"** or **"heterocyclyl"** refers to a saturated or partially saturated, but not aromatic, group having from 2 to 10 ring carbon atoms and from 1 to 4 ring heteroatoms selected from the group consisting of nitrogen, sulfur, or oxygen. C_x cycloalkyl or heterocycloalkyl refers to a group having x number of ring carbon atoms excluding the ring heteroatoms. Heterocycle encompasses single ring or multiple condensed

rings, including fused, bridged and spiro ring systems. In fused ring systems, one or more the rings can be cycloalkyl, aryl or heteroaryl provided that the point of attachment is through the non-aromatic ring. In one embodiment, the nitrogen and/or sulfur atom(s) of the heterocyclic group are optionally oxidized to provide for the N-oxide, sulfinyl, sulfonyl moieties.

[0070] "Substituted heterocyclic" or **"substituted heterocycloalkyl"** or **"substituted heterocyclyl"** refers to heterocyclyl groups that are substituted with from 1 to 5 or preferably 1 to 3 of the same substituents as defined for substituted cycloalkyl.

[0071] "Heterocyclyloxy" refers to the group -O-heterocycyl.

[0072] "Substituted heterocyclyloxy" refers to the group -O-(substituted heterocycyl).

[0073] "Heterocyclylthio" refers to the group -S-heterocycyl.

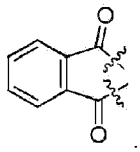
[0074] "Substituted heterocyclylthio" refers to the group -S-(substituted heterocycyl).

[0075] Examples of heterocycle and heteroaryl include, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, dihydroindole, dexahydroindole, dihydropyridine, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, imidazolinone, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene, benzo[b]thiophene, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), 1,1-dioxothiomorpholinyl, piperidinyl, pyrrolidine, and tetrahydrofuranyl.

[0076] "Nitro" refers to the group $-NO_2$.

[0077] "Oxo" refers to the atom (=O) or ($-O^-$).

[0078] "Phthalimido" refers to the group



[0079] Phthalimide functional groups are well known in the art and can be generated by covalently bonding a nitrogen atom to a $C_6H_4(CO)_2$ group.

[0080] "Polyethylene glycol" refers to the group $-O-(CH_2CH_2-O)_n-E$, wherein E is either H or CH_3, where n is between 2-20,000.

[0081] "Spirocyclic ring system" refers to a ring system with two rings that has a single ring

carbon atom in common to both rings. Herein used the term bicyclic can incorporate up to four heteroatoms in either ring.

[0082] "Bicyclic ring" or **"Bicyclic ring system"** refers to a ring system with two rings that has two ring carbon atoms in common, and which can located at any position along either ring. Herein used the term bicyclic ring system can incorporate up to four heteroatoms in either ring.

[0083] "Sulfinyl" refers to the divalent group -SO-.

[0084] "Sulfonyl" refers to the divalent group $-S(O)_2-$.

[0085] "Substituted sulfonyl" refers to the group $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-OH, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cylcoalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein. Substituted sulfonyl includes groups such as methyl-SO_2-, phenyl-SO_2-, and 4-methylphenyl-SO_2-. Preferred substituted alkyl groups on the substituted alkyl-SO_2- include halogenated alkyl groups and particularly halogenated methyl groups such as trifluoromethyl, difluromethyl, and fluoromethyl.

[0086] "Substituted sulfinyl" refers to the group -SO-alkyl, -SO-substituted alkyl, -SO-alkenyl, -SO-substituted alkenyl, -SO-cycloalkyl, -SO-substituted cylcoalkyl, -SO-aryl, -SO-substituted aryl, -SO-heteroaryl, -SO-substituted heteroaryl, -SO-heterocyclic, -SO-substituted heterocyclic, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein. Substituted sulfinyl includes groups such as methyl-SO-, phenyl-SO-, and 4-methylphenyl-SO-. Preferred substituted alkyl groups on the substituted alkyl-SO- include halogenated alkyl groups and particularly halogenated methyl groups such as trifluoromethyl, difluromethyl, and fluoromethyl.

[0087] "Sulfonyloxy" or **"substituted sulfonyloxy"** refers to the group $-OSO_2$-alkyl, $-OSO_2$-substituted alkyl, $-OSO_2$-OH, $-OSO_2$-alkenyl, $-OSO_2$-substituted alkenyl, $-OSO_2$-cycloalkyl, $-OSO_2$-substituted cylcoalkyl, $-OSO_2$-aryl, $-OSO_2$-substituted aryl, $-OSO_2$-heteroaryl, $-OSO_2$-substituted heteroaryl, $-OSO_2$-heterocyclic, $-OSO_2$-substituted heterocyclic, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0088] "Substitution" or **"substitution"** or **"substitutied"** generally refers groups which are covalently bonded to an atom to replace a hydrogen atom. The atom in this general context can be a carbon atom or a heteroatom, for example a nitrogen atom.

[0089] "Thioacyl" refers to the groups H-C(S)-, alkyl-C(S)-, substituted alkyl-C(S)-, alkenyl-

C(S)-, substituted alkenyl-C(S)-, alkynyl-C(S)-, substituted alkynyl-C(S)-, cycloalkyl-C(S)-, substituted cycloalkyl-C(S)-, aryl-C(S)-, substituted aryl-C(S)-, heteroaryl-C(S)-, substituted heteroaryl-C(S)-, heterocyclic-C(S)-, and substituted heterocyclic-C(S)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0090] "Mercapto" or **"thiol"** refers to the group -SH.

[0091] "Formyl" refers to the group -C(O)H.

[0092] "Tautomer" refers to alternate forms of a compound that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring NH moiety and a ring =N moiety such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

[0093] "Thiocarbonyl" refers to the divalent group -C(S)- which is equivalent to -C(=S)-.

[0094] "Thione" refers to the atom (=S).

[0095] "Alkylthio" refers to the group -S-alkyl wherein alkyl is as defined herein.

[0096] "Substituted alkylthio" refers to the group -S-(substituted alkyl) wherein substituted alkyl is as defined herein. Preferred substituted alkyl groups on -S-(substituted alkyl) include halogenated alkyl groups and particularly halogenated methyl groups such as trifluoromethyl, difluromethyl, and fluoromethyl.

[0097] The term **"ameliorating"** refers to any therapeutically beneficial result in the treatment of a disease state, e.g., an inflammatory disease state, including lessening in the severity or progression, remission, or cure thereof. In some embodiments, "ameliorating" includes prophylaxis of a disease state.

[0098] The term **"mammal"** as used herein includes both humans and non-humans and include humans, non-human primates, canines, felines, murines, bovines, equines, and porcines.

[0099] The term **"sufficient amount"** means an amount sufficient to produce a desired effect, e.g., an amount sufficient to modulate protein aggregation in a cell.

[0100] The term "**therapeutically effective amount**" is an amount that is effective to ameliorate a symptom of a disease. A therapeutically effective amount can, in some embodiments, be a "prophylactically effective amount" as prophylaxis can be considered therapy.

[0101] "Subject" refers to a mammalian organism treated using a compound of the present invention. The "subject" can be a human or non-human mammalian organism.

[0102] **"Treating"** or **"treatment"** of a disease or disorder in a subject refers to 1) preventing the disease or disorder from occurring in a subject that is predisposed or does not yet display symptoms of the disease or disorder; 2) binding the disease or disorder or arresting its development; or 3) ameliorating or alleviating the cause of the regression of the disease or disorder.

[0103] As used herein, an agent is said to be **"specific"** if it reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with a specified target than it does with alternative substances, especially as compared to substances that are structurally related to the target, e.g., an isoform of the target. In some embodiments, an agent is "specific" for a target if a concentration of the agent that produces a maximal effect in an *in vitro* or *in vivo* target assay (e.g., a binding assay or an enzyme activity assay) produces no measurable effect in a comparable assay carried out using another substance, especially one or more substances that are structurally related to the target.

[0104] As used herein, the term **"contacting,"** as used herein, includes both directly contacting cells, for example, *in vivo, in vitro,* or *ex vivo,* or indirectly contacting cells, such as, for example, by administering an agent to a subject. Further, "contacting" a cell with an agent includes administering or applying a prodrug version of the agent.

[0105] As used herein, the terms **"prevent," "preventing," "prevention,"** and **"prophylactic treatment"** refer to reducing the probability of developing a disease, disorder, or condition in a subject, who does not have, but is at risk of or susceptible to developing a disease, disorder, or condition. Thus, in some embodiments, an agent can be administered prophylactically to prevent the onset of a disease, disorder, or condition, or to prevent the recurrence of a disease, disorder, or condition.

4.2. Additional interpretational conventions

[0106] Generally, reference to or depiction of a certain element such as hydrogen or H is meant to include all isotopes of that element. For example, if an R group is defined to include hydrogen or H, it also includes deuterium and tritium. Compounds comprising radioisotopes such as tritium, ^{14}C, ^{32}P and ^{35}S are thus within the scope of the present technology. Procedures for inserting such labels into the compounds of the present technology will be readily apparent to those skilled in the art based on the disclosure herein.

[0107] Unless the specific stereochemistry is expressly indicated, all chiral, diastereomeric, and racemic forms of a compound are intended. Thus, compounds described herein include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions. Racemic mixtures, and d or 1 enriched stereomeric mixtures, as well as the individual optical isomers can be isolated or synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these stereoisomers are all within the scope of the present technology.

[0108] The compounds described herein may exist as solvates, especially hydrates, and unless otherwise specified, all such solvates and hydrates are intended. Hydrates may form during manufacture of the compounds or compositions comprising the compounds, or hydrates may form over time due to the hygroscopic nature of the compounds. Compounds of the present technology may exist as organic solvates as well, including DMF, ether, and alcohol solvates, among others. The identification and preparation of any particular solvate is within the skill of the ordinary artisan of synthetic organic or medicinal chemistry.

[0109] Herein any substituted functional group is substituted at from one to three different positions, and those one to three substituting groups are capable of each independently being substituted at one to three positions, wherein any and each substituting group is independently selected from the group consisting of: halogen, hydroxyl, C_1-C_8 alkyl, substituted C_1-C_8 alkyl, C_1-C_8 alkenyl, substituted C_1-C_8 alkenyl, C_1-C_8 alkynyl, substituted C_1-C_8 alkynyl, acyl, acylamino, aminocarbonylamino, aminoacyl, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminoacyl carbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, C_1-C_8 alkoxy, substituted C_1-C_8 alkoxy, C_3-C_7 aryl, substituted C_3-C_7 aryl, C_3-C_7 aryloxy, substituted C_3-C_7 aryloxy, C_3-C_7 arylthio, substituted C_3-C_7 arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, C_3-C_{10} cycloalkyl, substituted C_3-C_{10} cycloalkyl, C_3-C_7 heterocycloalkyl, guanidino, substituted guanidino, C_3-C_7 heteroaryloxy, C_3-C_7 substituted heteroaryloxy, C_3-C_7 heteroarylthio, C_3-C_7 substituted heteroarylthio, sulfonyl, substituted sulfonyl, sulfinyl, substituted sulfinyl, sulfonyloxy, substituted sulfonyloxy, thioacyl, alkylthio, substituted alkylthio, C_3-C_7 heteroaryl, and substituted C_3-C_7 heteroaryl.

[0110] Herein any and all heteroaryl and heterocycloalkyl substituents may contain up to four heteroatoms selected from the group consisting of: O, N, and S but may not contain a heteroatom-heteroatom bond such as: O-O, O-S, N-S, N-O and S-S bonds are not covered. It is understood that in all substituted groups defined above, polymers arrived at by defining substituents with further substituents to themselves (e.g., substituted aryl having a substituted aryl group as a substituent which is itself substituted with a substituted aryl group, etc.) are not intended for inclusion herein. In such cases, the maximum number of such substituents is three. That is to say that each of the above definitions is constrained by a limitation that each functional group is substituted (at from one to three positions) and that any and all of those substituent groups may be substituted one more time (at from one to three positions).

[0111] It is understood that the definitions presented herein are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluoro groups). Such impermissible substitution patterns are well known to the skilled artisan.

[0112] Throughout this application, the text refers to various embodiments of the present compounds, compositions, and methods. The various embodiments described are meant to provide a variety of illustrative examples and should not be construed as descriptions of alternative species. Rather, it should be noted that the descriptions of various embodiments provided herein may be of overlapping scope. The embodiments discussed herein are merely

illustrative and are not meant to limit the scope of the present technology. The scope of the invention is defined by the appended claims.

[0113] For the purposes of this specification and appended claims, unless otherwise indicated, all numbers expressing amounts, sizes, dimensions, proportions, shapes, formulations, parameters, percentages, parameters, quantities, characteristics, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about" even though the term "about" may not expressly appear with the value, amount or range. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are not and need not be exact, but may be approximate and/or larger or smaller as desired, reflecting tolerances, conversion factors, rounding off, measurement error, and other factors known to those of skill in the art depending on the desired properties sought to be obtained by the presently disclosed subject matter. For example, the term "about," when referring to a value can be meant to encompass variations of, in some aspects, ± 100% in some aspects ± 50%, in some aspects ± 20%, in some aspects ± 10%, in some aspects ± 5%, in some aspects ± 1%, in some aspects ± 0.5%, and in some aspects ± 0.1% from the specified amount, as such variations are appropriate to perform the disclosed methods or employ the disclosed compositions.

[0114] As used herein and in the appended claims, singular articles such as "a," "an" and "the" and similar referents in the context of describing the elements (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, including the upper and lower bounds of the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the embodiments and does not pose a limitation on the scope of the claims unless otherwise stated. No language in the specification should be construed as indicating any non-claimed element as essential.

[0115] Unless indicated otherwise, the nomenclature of substituents that are not explicitly defined herein are arrived at by naming the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. For example, the substituent "alkoxycarbonylalkyl" refers to the group (alkoxy)-C(O)-(alkyl)-.

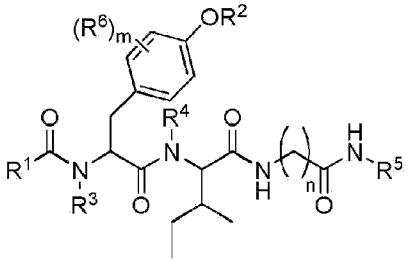
4.3. Compounds

[0116] In a first aspect, compounds are provided that demonstrate improved drug characteristics and enhanced solubility properties, improved DMPK properties demonstrated by increased stability in simulated intestinal fluid and simulated gastric fluid, but that can be hydrolyzed in plasma to produce Base Structure, or to produce Base Structure-like compounds that retain Base

Structure's therapeutic activity, are provided.

[0117] In typical embodiments, the compounds possess a di-amino acid core structure and are substituted by one or more organic functional groups at the C-terminus, N-terminus, and/or the side-chain of the core.

[0118] In some embodiments not according to the invention as defined by the language of appended claims 1 or 4, the compound is a compound of formula I:



(I)

wherein:

n is 1, 2, 3, 4, 5, 6, 7, 8, or 9;

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

R^1 is selected from the group consisting of: amino, substituted amino, alkoxy, substituted alkoxy, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyl, C_1-C_{12} alkenyl, C_1-C_{12} substituted alkenyl, C_1-C_{12} alkynyl, C_1-C_{12} substituted alkynyl, C_1-C_6 alkyl aryl, C_1-C_6 substituted alkyl aryl, C_1-C_6 alkenyl aryl, C_1-C_6 substituted alkenyl aryl, C_1-C_6 alkynyl aryl, C_1-C_6 substituted alkynyl aryl, norleucine, tyrosine, phenylalanine, aspartic acid, arginine, isoleucine, serine, threonine, histidine, glycine, cysteine, methionine, tryptophan, lysine norvaline, norleucine, ornithine, S-benzyl cysteine, O-benzyl serine, O-benzyl threonine, cyclohexylalanine, 4-tetrahydropyranyl-glycine, and azaleucine;

R^2 is selected from the group consisting of: hydrogen, $-CH(R^a)OPO(OH)_2$, -CO-Y, $PO(OY)_2$, $PO(OH)_2$, -C(=O)-Y, -CO-U, $-C(=O)-(CH_2)_rU$, and $-CH_2$-V, where R^a is hydrogen or CH_3, where Y is $-Z-(CH_2)_q-W-R^b$, q is 0-4, where Z and W are independently selected from the group consisting of: CH_2, O, S, NR^c and R^b, where R^c is selected from the group consisting of: hydrogen, C_1-C_4 alkyl, and C_3-C_6 cycloalkyl, R^b is selected from the group consisting of: hydrogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyl, C_1-C_{12} alkenyl, C_1-C_{12} substituted alkenyl, C_1-C_{12} alkynyl, C_1-C_{12} substituted alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 substituted cycloalkyl, C_6-C_{10} aryl, C_6-C_{10} substituted aryl, C_3-C_8 heterocycloalkyl, C_3-C_8 substituted heterocycloalkyl, C_4-C_{10} heteroaryl, and C_4-C_{10} substituted heteroaryl, where r is 0-5, U is selected from aryl, heteroaryl or heterocycloalkyl, where V is $-O-C(=O)-Q-(CH_2)_r-R^d$, where Q is selected from the group consisting of: a bond, O, and $N(R^c)$, where R^d is selected from the group consisting of: C_6-C_{10} aryl, C_4-C_{10} heteroaryl, C_3-C_8 heterocycloalkyl, a hexose, a pentose, and - (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl), or alternatively -C(=O)-Y forms an amide bond thru a nitrogen atom on Y in which case Y is a

selected from the group consisting of: glycine, sarcosine, N,N-dimethyl glycine, alanine, valine, leucine, isoleucine, lysine, ornithine, ariginine, serine, and threonine;

R^3 and R^4 are independently selected from the group consisting of: hydrogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyl, C_1-C_{12} alkenyl, C_1-C_{12} substituted alkenyl, C_1-C_{12} alkynyl, C_1-C_{12} substituted alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 substituted cycloalkyl, C_6-C_{10} aryl, C_6-C_{10} substituted aryl, C_3-C_8 heterocycloalkyl, C_3-C_8 substituted heterocycloalkyl, C_4-C_{10} heteroaryl, C_4-C_{10} substituted heteroaryl,

‡

$CH(R^a)OPO(OY)_2$,

‡

$CH(R^a)OPO(OY)(OH)$ and

‡

$CH(R^a)OPO_3H_2$, or optionally R^3 and R^4 together are bonded to form a fused bicyclic ring system or a spirocyclic ring system;

R^5 is selected from the group consisting of: hydrogen,

‡

CH_2-O-CO-Y, and

‡

$CH(R^a)$-O-PO_3H_2;

each R^6 is independently selected from the group consisting of: hydrogen, deuterium, CH_3, F, ^{19}F, and ^{18}F;

wherein optionally Z and W are taken together to form a C_3-C_8 heterocycloalkyl or C_4-C_{10} heteroaryl or fused bicyclic ring system in which one of the rings is a C_4-C_{10} heteroaryl;

and wherein the amino acid of R^1, if present, is covalently bonded either thru the nitrogen atom of the N-terminus of the amino acid to the carbon atom of the C(=O) in

,

or a carbon atom of the amino acid of R^1 is bonded to the C(=O) such that

taken together represents amino acid where the C(=O) of

is the carboxy-terminus of the amino acid;

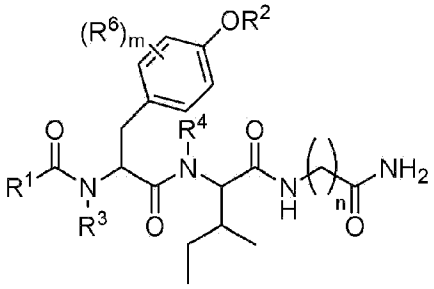
and wherein any and all heterocyclic and heteroaryl rings contain up to four heteroatoms selected from the group consisting of: O, N, and S;

with the proviso that when both Z and W are heteroatoms, the value of q cannot be 1;

and with the proviso that when both R^2 and R^5 are hydrogen and n is 5, at least one of the R^3 or R^4 groups is not hydrogen;

or a tautomer and/or a pharmaceutically acceptable salt thereof.

[0119] In some embodiments, the compound is a compound of formula II:



(II)
wherein:

n is 1, 2, 3, 4, 5, 6, 7, 8, or 9;

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

R^1 is selected from the group consisting of: C_1-C_{12} alkyl, C_1-C_{12} substituted alkyl, C_1-C_{12} alkenyl, C_1-C_{12} substituted alkenyl, C_1-C_{12} alkynyl, and C_1-C_{12} substituted alkynyl;

R^2 is selected from the group consisting of: hydrogen, $PO(OY)_2$, $PO(OH)_2$, -C(=O)-Y and -CO-U, where Y is -Z-$(CH_2)_q$-W-R^b, q is 0-4, where Z and W are independently selected from the group consisting of: CH_2, O, S, NR^c and R^b, where R^c is selected from the group consisting of: hydrogen, C_1-C_4 alkyl, and C_3-C_6 cycloalkyl, R^b is selected from the group consisting of: hydrogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyl, C_3-C_8 cycloalkyl, C_3-C_8 substituted cycloalkyl, C_3-C_8 heterocycloalkyl, and C_3-C_8 substituted heterocycloalkyl, or alternatively -C(=O)-Y forms an amide bond thru a nitrogen atom on Y in which case Y is a selected from the group consisting of: glycine, sarcosine, N,N-dimethyl glycine, alanine, valine, leucine, isoleucine, lysine, ornithine, ariginine, serine, and threonine and where U is selected from the group consisting of: pyridine, 1,4-dihydropyridine, N-alkyl-1,4-dihydropyridine, and C-imidazole or U is selected from aryl, heteroaryl or heterocycloalkyl;

R^3 and R^4 together are bonded to form a fused bicyclic ring system or a spirocyclic ring system;

each R^6 is independently selected from the group consisting of: hydrogen, deuterium, CH_3, F, ^{19}F, and ^{18}F;

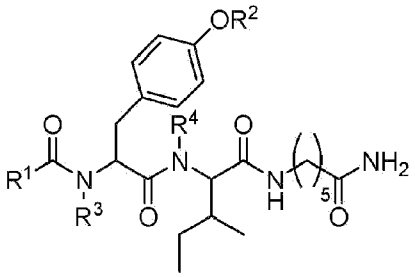
wherein optionally Z and W are taken together to form a C_3-C_8 heterocycloalkyl or C_4-C_{10} heteroaryl or bicyclic ring system in which one of the rings must be a C_4-C_{10} heteroaryl;

and wherein any and all heterocyclic and heteroaryl rings contain up to four heteroatoms selected from the group consisting of: O, N, and S;

with the proviso that when both Z and W are heteroatoms, the value of q cannot be 1;

or a tautomer and/or a pharmaceutically acceptable salt thereof.

[0120] In some embodiments, the compound is a compound of formula III:



(III)

wherein:

R^1 is a C_1-C_{12} alkyl or C_1-C_{12} substituted alkyl;

R^2 is selected from the group consisting of: hydrogen, $PO(OY)_2$, $PO(OH)_2$, and - C(=O)-Y, where Y is -Z-$(CH_2)_q$-W-R^b, q is 0-4, where Z and W are independently selected from the group consisting of: CH_2, O, S, NR^c and R^b, where R^c is selected from the group consisting of: hydrogen, C_1-C_4 alkyl, and C_3-C_6 cycloalkyl, R^b is selected from the group consisting of: hydrogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyl, C_3-C_8 cycloalkyl, C_3-C_8 substituted cycloalkyl, C_3-C_8 heterocycloalkyl, and C_3-C_8 substituted heterocycloalkyl;

R^3 and R^4 together are bonded to form a fused bicyclic ring system or a spirocyclic ring system, where the fused ring is a C_3-C_8 heterocycloalkyl or C_6-C_{10} aryl or C_4-C_{10} heteroaryl;

wherein optionally Z and W are taken together to form a C_3-C_8 heterocycloalkyl or C_4-C_{10} heteroaryl or bicyclic ring system in which one of the rings must be a C_4-C_{10} heteroaryl;

and wherein any and all heterocyclic and heteroaryl rings contain up to four heteroatoms selected from the group consisting of: O, N, and S;

with the proviso that when both Z and W are heteroatoms, the value of q cannot be 1;

or a tautomer and/or a pharmaceutically acceptable salt thereof.

[0121] In some embodiments, the compound is a compound of Formula II, where R^1 is C_1-C_{12} alkynyl.

[0122] In some embodiments, the compound is a compound of Formula II, where R^2 is a -

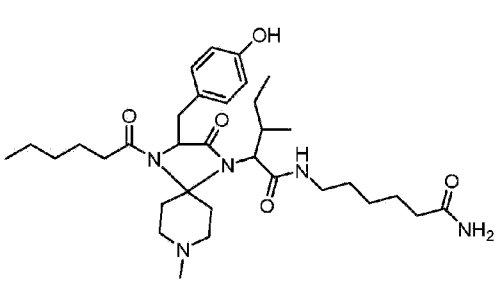
C(=O)-Y, where Z is CH_2, q is 0, W is N, and R^3 and R^4 together form a spirocyclic ring system where one ring is a C_4 heterocycle and the other is a C_5 cycloalkyl.

[0123] In some embodiments, the compound is a compound of Formula II, where m is 0, R^1 is a C_1-C_{12} alkyl, and R^3 and R^4 together form a spirocyclic ring system.

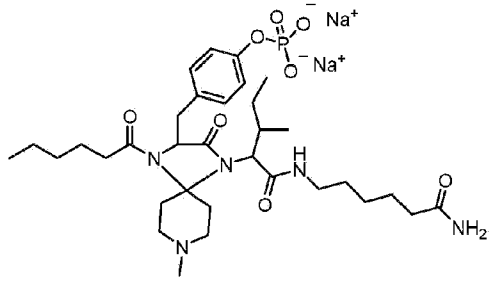
[0124] In some embodiments, the compound is a compound of Formula II, where m is 1 or 2, R^1 is a C_1-C_{12} alkyl, R^3 and R^4 together form a spirocyclic ring system, and R^6 is selected from the group consisting of: hydrogen, deuterium, F, ^{19}F, and ^{18}F.

[0125] In some embodiments, the compound is a compound of Formula III, where R^1 is a C_5 alkyl.

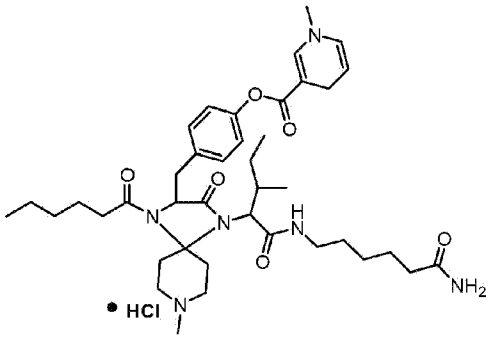
[0126] In some embodiments, the compound is a compound selected from the following structures:



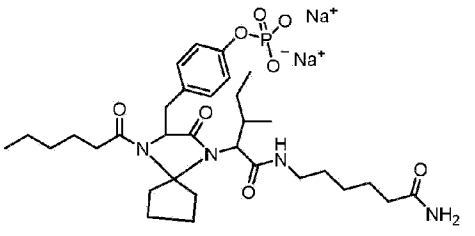
1 ,



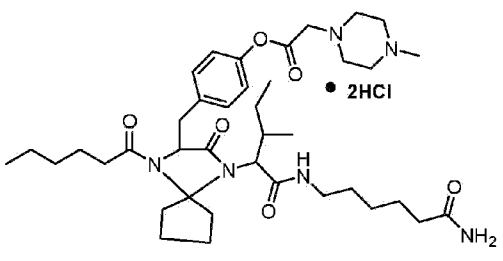
2 ,



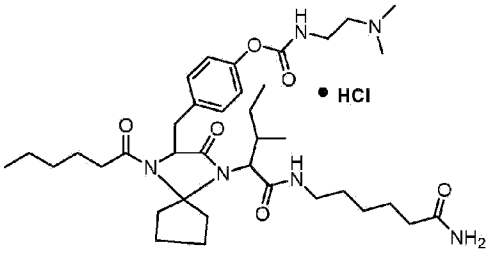
3 ,



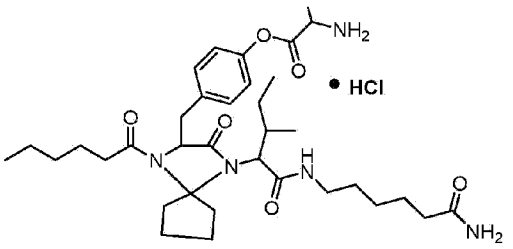
4 ,



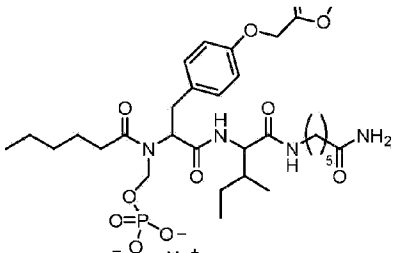
5 ,



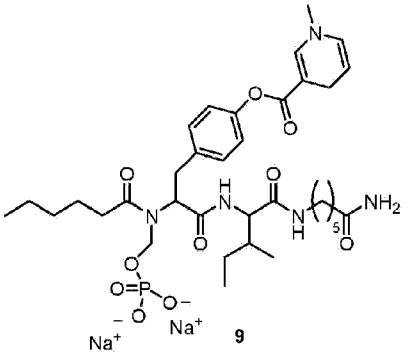
6 ,



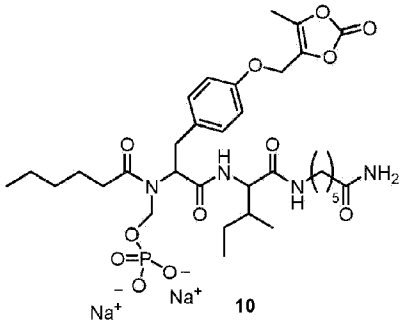
7 ,



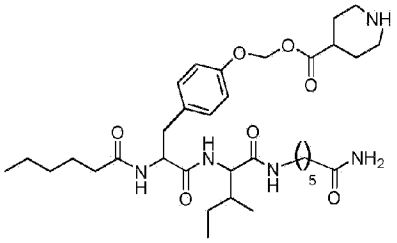
8 ,



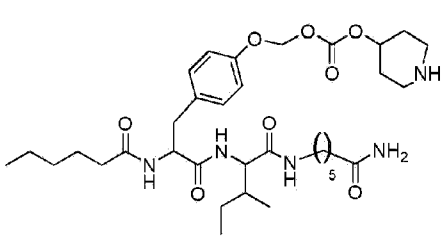
9 ,



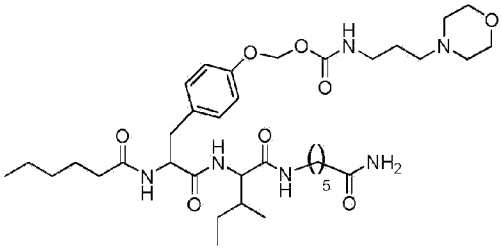
10 ,



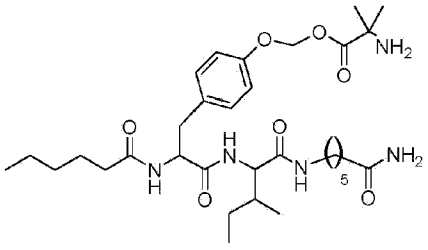
A17a ,



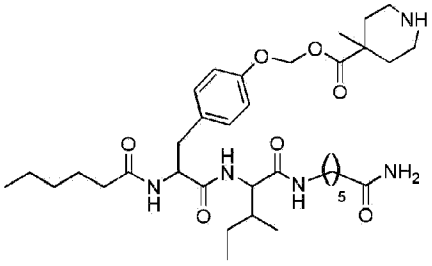
A17b .



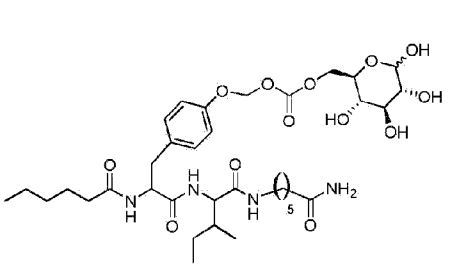
A17c ,



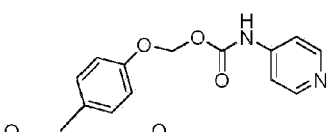
A17e ,

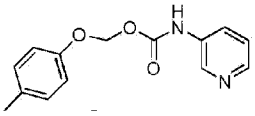


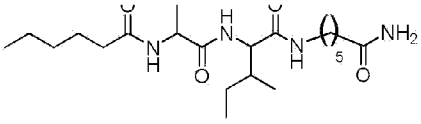
A17f ,



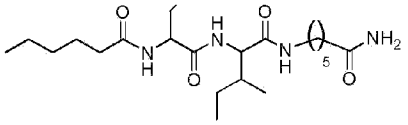
A17g ,



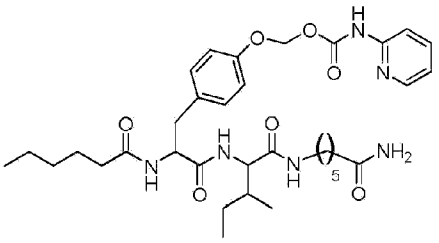




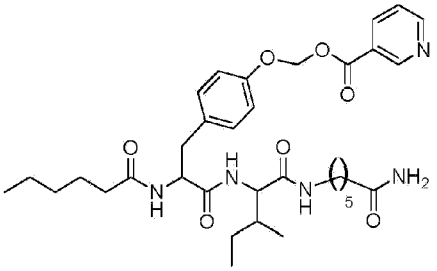
A17h ,



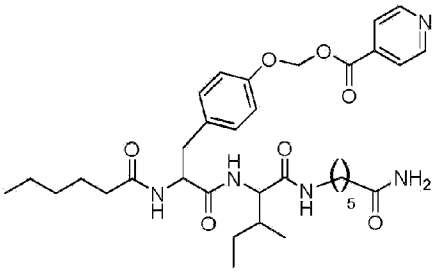
A17i ,



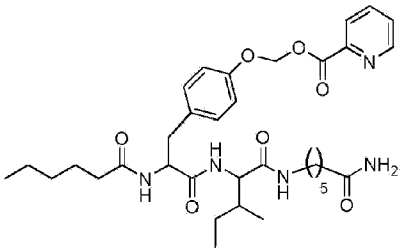
A17j ,



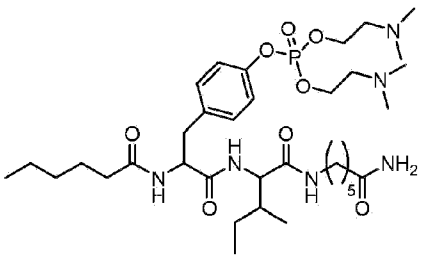
A17k ,



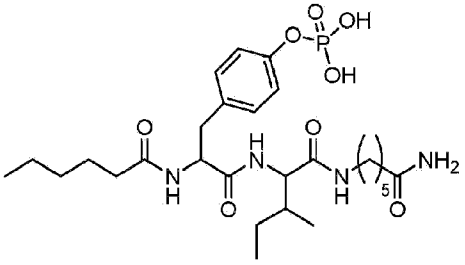
A17l ,



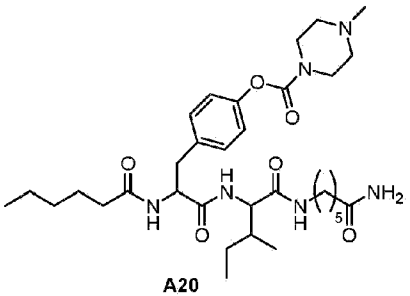
A17m ,



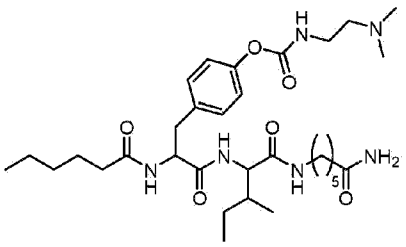
A18 ,



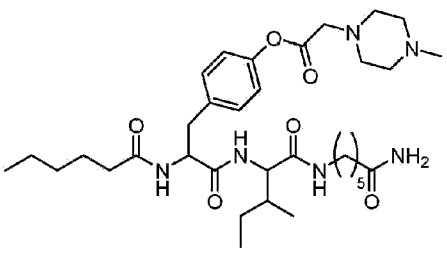
A19 ,

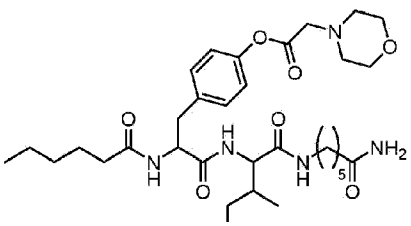


A20 ,

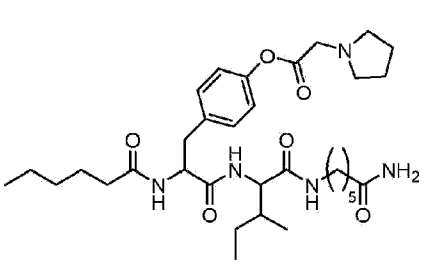


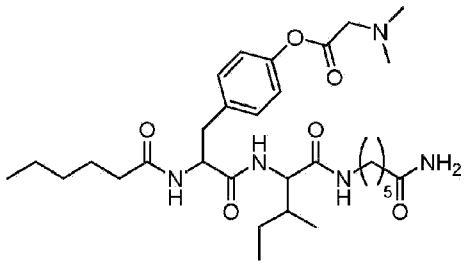
A21 ,



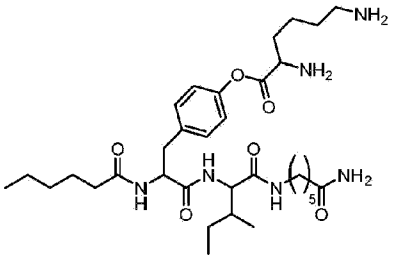


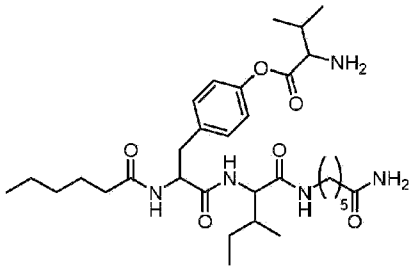
A22 , A23 ,



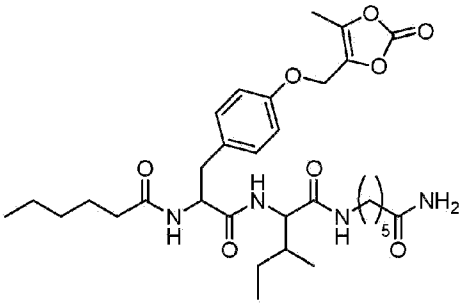


A24 , A25 ,



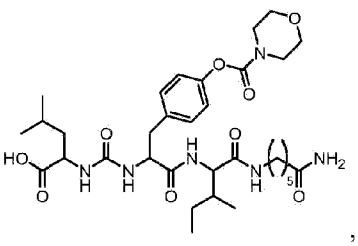


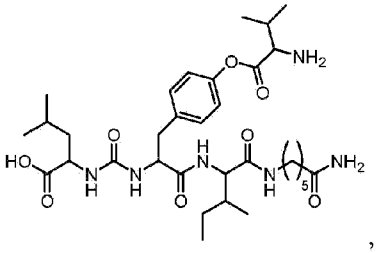
A26 , A27 , and



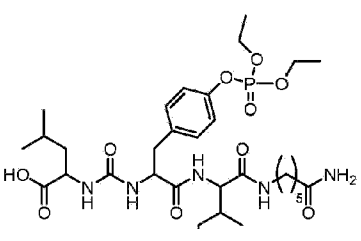
A28 .

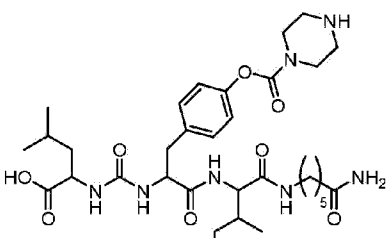
[0127] In some embodiments not according to the invention as defined by the language of appended claims 1 or 4, the compound is a compound selected from the following structures:





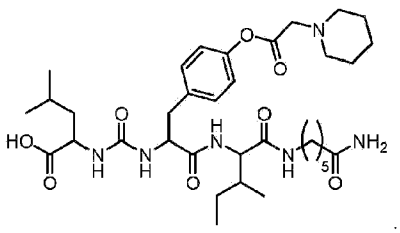
B1 , B2 ,





B3 B4

and



B5

Synthesis

4.3.1. General synthetic methods

[0128] The compounds described herein can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactant or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

[0129] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional group are well known in the art. For example, numerous protecting groups are described in T. W. Greene and P. G. M. Wuts, Protecting Groups in Organic Synthesis, Third Edition, Wiley, New York, 1999, and references cited therein.

[0130] If the compounds described herein contain one or more chiral centers, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or d(l) stereoisomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of the present technology, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, or chiral resolving agents.

[0131] The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co.

(Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemce or Sigma (St. Louis, Missouri, USA), CombiChem (SAN DIEGO, CA). Others may be prepared by procedures, or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley, and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5, and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley, and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley, and Sons, 5th Edition, 2001), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

4.3.2. Synthesis routes to described compounds

[0132] The following specific, non-limiting examples are illustrative of the invention.

[0133] In one general embodiment, the method comprises reacting an appropriately N-protected compound with nucleophilic coupling partner and HATU to give the desired amide. It is appreciated that other suitable coupling conditions and reagents, such as HOBt and/or DMAP, may be used to form a requisite amide. The skilled artisan will appreciate that there are many synthetic conditions or methods by which an amide functional group can be made, for example by reacting the starting carboxylate to synthesize a reactive derivative such as the corresponding acid chloride and then reacting that intermediate directly with the amine nucleophile to produce the desired amide. These synthetic methods are well within in the scope of the present technology disclosed.

[0134] On the other hand, it is generally known that the N-terminus of di-peptide derivatives can be produced by first protecting or blocking (i.e. putting on the desired amide group on the C-terminus if the functional groups are compatible so as to not interfere with the subsequent steps in the overall synthesis of the compound and thus, are "orthogonal") the C-terminus and reacting the free di-peptide amine with an activated electrophile such as an acid anhydride, acid chloride, phosphorus oxychloride or phosphonyl chloride.

[0135] Of course it is recognized that esterification reactions may be used to generate non-trivial groups on the tyrosine moiety. Such reactions can be accelerated by using anhydrides, or other acid catalysts, when reacting the free alcohol with a reactive carboxy compound. Functional groups which are appropriate for active carboxy compound include anhydrides, acid chlorides, Mitsunobu conditions or Steglich-type conditions or anhydrous acid conditions with the carboxylic acid.

[0136] In one general embodiment, the synthesis can include functionalizing the nitrogen atoms of the amides on the di-peptide derivative. Such reactions are commonly accomplished by protecting sensitive functional groups on the rest of the molecule whilst generating an anion on one or both of the nitrogen by adding a strong base such as sodium amide, LDA, a Grignard reagent, or $LiN(i\text{-}Pr)_2$. Of course this list of bases is not comprehensive. The next step would be to add the appropriate electrophile. In the case where the artisan would like to make a spirocyclic ring system with the two nitrogen atoms of the di-peptide derivative, one could add a di-

functionalized electrophile such as 1,1 di-bromo-cyclopentane, or even the requisite carbonyl compound under strong Lewis acidic conditions will work.

[0137] Herein it is understood that amino, keto, thio, hydroxyl, and any other necessary protecting groups and their methods of deprotection are known in the art, such as those described in T. W. Greene and P. G. M. Wuts, Protecting Groups in Organic Synthesis, Third Edition, Wiley, New York, 1999.

[0138] Alternatively, the skilled artisan will recognize that there is additional synthetic functional group modifications that one can use to prepare spirocyclic and other bicyclic or tricyclic compounds from dipeptide derivative intermediates.

4.4. Compositions

[0139] In another aspect, compositions are provided that comprise at least one compound as described herein.

[0140] In various embodiments, the compositions comprise one compound as described herein. In other embodiments, the compositions comprise a plurality of compounds as described herein. In certain of these latter embodiments, the compositions comprise 2, 3, 4, or 5 or more of the herein described compounds. In typical embodiments comprising a plurality of compounds, the compounds are selected to have pharmacokinetic properties different from one another.

[0141] In certain embodiments, the composition comprises at least one compound as described herein, and Base Structure. In various embodiments, the composition comprises 1, 2, 3, 4, or 5 compounds as described herein, and Base Structure. In typical embodiments, the compounds are selected to have pharmacokinetic properties different from Base Structure. In certain embodiments in which a plurality of compounds as described herein are included, the compounds are selected to have pharmacokinetic properties different from one another.

[0142] In various embodiments, the composition comprises at least one compound of Formula II, or tautomers, stereoisomers, salts, solvates or hydrates thereof.

[0143] In certain embodiments, the composition comprises at least one compound selected from the group consisting of Compound **1,** Compound **2,** Compound **3,** Compound **4,** Compound **5,** Compound **6,** Compound **7,** Compound **8,** Compound **9,** and Compound **10,** as described herein above, or tautomers, stereoisomers, salts, solvates or hydrates thereof.

[0144] In certain embodiments, the composition comprises at least one compound selected from the group consisting of compound 1-10, A2-A17, A17a-17m and A18-A34f, and optionally B1-B5 as described herein above, tautomers, stereoisomers, salts, solvates or hydrates thereof.

[0145] In various embodiments, the composition is a solid.

[0146] In various other embodiments, the composition is a liquid.

[0147] In various fluid embodiments, at least one of the at least one compound in the composition is present at a concentration of at least 10 ng/ mL, 50 ng/ mL, 100 ng/ mL, 500 ng/ mL, 1 ug/ mL, 10 ug/ mL, 50 ug/ mL, 75 ug/ mL, 0.1 mg/ml, 0.2 mg/ml, 0.3 mg/ml, 0.4 mg/ml, even at least 0.5 mg/ml. In some fluid embodiments, at least one of the at least one compound in the composition is present at a concentration of at least 1 mg/ml, 2 mg/ml, 3 mg/ml, 4 mg/ml or 5 mg/ml. In some fluid embodiments, at least one of the at least one compound in the composition is present at a concentration of at least 10 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml or 50 mg/ml. In some fluid embodiments, at least one of the compound in the composition is present at a concentration of at least 100 mg/ml, 125 mg/ml, 150 mg/ml, 175 mg/ml, or 200 mg/ml. In some fluid embodiments, at least one of the at least one compound in the composition is present at a concentration of at least 250 mg/ml.

[0148] In certain fluid embodiments, each of the at least one compound in the composition is present at a concentration of at least 0.1 mg/ml, 0.2 mg/ml, 0.3 mg/ml, 0.4 mg/ml, even at least 0.5 mg/ml. In some fluid embodiments, each of the at least one compound in the composition is present at a concentration of at least 1 mg/ml, 2 mg/ml, 3 mg/ml, 4 mg/ml or 5 mg/ml. In some fluid embodiments, each of the at least one compound in the composition is present at a concentration of at least 10 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml or 50 mg/ml. In some fluid embodiments, each of the at least one compound in the composition is present at a concentration of at least 100 mg/ml, 125 mg/ml, 150 mg/ml, 175 mg/ml, or 200 mg/ml. In some fluid embodiments, each of the at least one compound in the composition is present at a concentration of at least 250 mg/ml.

4.5. Pharmaceutical Compositions

[0149] In a further aspect, pharmaceutical compositions are provided that comprise at least one of the compounds described herein and a pharmaceutically acceptable carrier or excipient.

[0150] In various embodiments, the pharmaceutical compositions comprise one compound as described herein. In other embodiments, the pharmaceutical compositions comprise a plurality of compounds as described herein. In certain of these latter embodiments, the pharmaceutical compositions comprise 2, 3, 4, or 5 or more of the herein described compounds. In typical embodiments comprising a plurality of compounds, the compounds are selected to have pharmacokinetic properties different from one another.

[0151] In certain embodiments, the pharmaceutical composition comprises at least one compound as described herein, and Base Structure. In various embodiments, the pharmaceutical composition comprises 1, 2, 3, 4, or 5 compounds as described herein, and Base Structure. In typical embodiments, the compounds are selected to have pharmacokinetic properties different from Base Structure. In certain embodiments in which a plurality of compounds as described herein are included, the compounds are selected to have pharmacokinetic properties different from one another.

[0152] In various embodiments, the pharmaceutical composition comprises at least one compound of Formula I, or tautomers, stereoisomers, salts, solvates or hydrates thereof.

[0153] In various embodiments, the pharmaceutical composition comprises at least one compound of Formula II, or tautomers, stereoisomers, salts, solvates or hydrates thereof.

[0154] In certain embodiments, the pharmaceutical composition comprises at least one compound selected from the group consisting of Compound **1,** Compound **2,** Compound **3,** Compound **4,** Compound **5,** Compound **6,** Compound **7,** Compound **8,** Compound **9,** and Compound **10,** as described herein above, or tautomers, stereoisomers, salts, solvates or hydrates thereof.

[0155] In certain embodiments, the pharmaceutical composition comprises at least one compound selected from the group consisting of Compound 1-10, A2-A17, A17a-17m and A18-A34f, and optionally B1-B5, as described herein above, tautomers, stereoisomers, salts, solvates or hydrates thereof.

[0156] In various embodiments, the pharmaceutical composition is formulated for enteral route of administration.

[0157] Pharmaceutical compositions for enteral route of administration can be in tablet, capsule, powder or liquid form. A tablet can include a solid carrier such as gelatin or an adjuvant. Liquid pharmaceutical compositions generally include a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol can be included. A pharmaceutical composition can include a cyclodextrin. A pharmaceutical composition can contain poloxamer and/or Vitamin E TPGS.

[0158] In embodiments in which the pharmaceutical composition is formulated for enteral route of administration in a solid dosage form, the composition will contain, on a weight percent (wt %) basis, from about 0.01 - 99.99 wt % of the compound of the present technology based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Preferably, the compound is present at a level of about 1 - 80 wt %.

[0159] In other embodiments, the pharmaceutical composition is formulated for inhalation suspended in solutions or mixtures of excipients (e.g., preservatives, viscosity modifiers, emulsifiers, buffering agents) in non-pressurized or pressurized dispensers that deliver a spray containing a metered dose of at least one compound as described herein. In certain inhalation embodiments, the pharmaceutical composition is formulated for nasal or oral administration.

[0160] In other embodiments, the pharmaceutical composition is formulated for topical administration. In certain topical embodiments, the pharmaceutical composition is formulated for enepidermic route, Epidermic route, Instillation administration, or Painting/Swabbing.

[0161] In other embodiments, the pharmaceutical composition is formulated for parenteral administration. In certain parenteral embodiments, the pharmaceutical composition is formulated for intravenous, subcutaneous, or intradermal administration. In other embodiments, the pharmaceutical composition is formulated for intrathecal or intracerebroventricular administration.

[0162] In typical parenteral embodiments, the composition will be in the form of a parenterally acceptable aqueous solution that is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilizers, buffers, antioxidants and/or other additives can be included, as required.

[0163] In various fluid embodiments, at least one of the compound in the pharmaceutical composition is present at a concentration of at least 0.1 mg/ml, 0.2 mg/ml, 0.3 mg/ml, 0.4 mg/ml, even at least 0.5 mg/ml. In some fluid embodiments, at least one of the at least one compound in the pharmaceutical composition is present at a concentration of at least 1 mg/ml, 2 mg/ml, 3 mg/ml, 4 mg/ml or 5 mg/ml. In some fluid embodiments, at least one of the at least one compound in the pharmaceutical composition is present at a concentration of at least 10 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml or 50 mg/ml. In some fluid embodiments, at least one of the at least one compound in the pharmaceutical composition is present at a concentration of at least 100 mg/ml, 125 mg/ml, 150 mg/ml, 175 mg/ml, or 200 mg/ml. In some fluid embodiments, at least one of the at least one compound in the pharmaceutical composition is present at a concentration of at least 250 mg/ml.

[0164] In certain fluid embodiments, each of the at least one compound in the pharmaceutical composition is present at a concentration of at least 0.1 mg/ml, 0.2 mg/ml, 0.3 mg/ml, 0.4 mg/ml, even at least 0.5 mg/ml.

[0165] In some fluid embodiments, each of the at least one compound in the pharmaceutical composition is present at a concentration of at least 1 mg/ml, 2 mg/ml, 3 mg/ml, 4 mg/ml or 5 mg/ml. In some fluid embodiments, each of the at least one compound in the pharmaceutical composition is present at a concentration of at least 10 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml or 50 mg/ml. In some fluid embodiments, each of the at least one compound in the pharmaceutical composition is present at a concentration of at least 100 mg/ml, 125 mg/ml, 150 mg/ml, 175 mg/ml, or 200 mg/ml. In some fluid embodiments, each of the at least one compound in the pharmaceutical composition is present at a concentration of at least 250 mg/ml.

4.6. Methods of use

[0166] In another aspect, compounds for use in methods of treatment are provided.

[0167] The compounds may be for use in methods comprising administering at least one compound as described herein to a subject in an amount effective to treat, protect from, or reverse neurodegenerative disease, to prevent or reverse the symptoms of dementia, to facilitate

repair of traumatic injury to the nervous system, or to enhance cognitive function. In various embodiments, the subject has a disease selected from Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, other dementias and neurodegenerative diseases, spinal cord injury, traumatic brain injury, and/or sensorineural hearing and vision loss. In typical embodiments, the method comprises administering a pharmaceutical composition comprising at least one of the compounds described herein, as described above.

[0168] In some aspects, a method for treating a disease state or condition is described, the method comprising administration of an effective amount of one or more compounds of the formulae as disclosed herein or a pharmaceutical composition as disclosed herein to a subject in need thereof.

[0169] In some aspects, compound for use in a method for treating a disease state or condition is provided for, where the disease is neurodegenerative disease.

[0170] In some aspects, compound for use in a method for treating a disease state or condition is provided for, where the disease is selected from the group consisting of: Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, other dementias and neurodegenerative diseases, spinal cord injury, traumatic brain injury, sensorineural hearing and vision loss.

[0171] In some aspects, the disease is Alzheimer's disease.

[0172] In some aspects, the disease is Parkinson's disease.

[0173] In some aspects, the route of administration is selected from the group consisting of: enteral, parenteral, inhalation, and topical, including oral, intravenous, subcutaneous, intrathecal, and intracerebroventricular administration.

[0174] In some aspects, the administration is intravenous.

[0175] In some aspects, the subject is a mammal. In some aspects, the subject is a human.

[0176] In some aspects, the use of one or more compounds disclosed herein is provided for in the manufacture of a medicament for treating a disease state or condition described herein.

[0177] In various embodiments, the compound is administered as the sole medical treatment. In various embodiments, the compound is administered in combination with other medical and/or surgical interventions according to the prevailing standards of care.

[0178] In various embodiments, the dose is determined without regard to patient weight. In certain embodiments, the dose is between 0.1 mg to about 1000 mg, between 1 mg to about 500 mg, between 1 mg to about 300 mg, or between 1 mg to about 100 mg per day. Such doses can be administered once a day or more than once a day, for example 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day. Additionally, a dose can be administered daily or alternatively, a few times a week, where the subsequent dose is administered after 1, 2 or 3 day interval.

[0179] In some embodiments, the dose is determined based on patient weight. In certain embodiments, the dose is between 0.001 mg/kg patient weight to about 15 mg/kg per kg patient weight per administration, or 0.01 mg/kg to about 1.5 mg/kg.

[0180] The amount of compound administered will vary depending upon the disease treated, the route of administration, and the dosage schedule.

[0181] It will be understood, however, that the specific dose level for any particular subject will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs that have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those of skill in the area.

[0182] Therapy can extend for a number of days, a number of weeks or months, and in some cases, years.

[0183] A composition can be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated.

[0184] Dosage amount and dosage schedule may be adjusted individually to provide plasma levels of the active moiety that are sufficient to achieve the desired effects; i.e., the minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from, for example, in vitro data and animal experiments. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[0185] The amount of agent or composition administered may be dependent on a variety of factors, including the sex, age, and weight of the subject being treated, the severity of the affliction, the manner of administration, and the judgment of the prescribing physician.

5. EXAMPLES

[0186] The following synthetic and biological examples are offered to illustrate this the present technology and are not to be construed in any way as limiting the scope of this the present technology. Unless otherwise stated, all temperatures are in degrees Celsius.

[0187] The examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental error and deviation should, of course, be allowed for.

[0188] The practice of the present invention will employ, unless otherwise indicated, conventional methods of protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art. Such techniques are explained fully in the literature. See, e.g., T.E. Creighton, Proteins: Structures and Molecular Properties (W.H. Freeman and Company, 1993); A.L. Lehninger, Biochemistry (Worth Publishers, Inc., current addition); Sambrook, et al., Molecular Cloning: A Laboratory Manual (2nd Edition, 1989); Methods In Enzymology (S. Colowick and N. Kaplan eds., Academic Press, Inc.); Remington's Pharmaceutical Sciences, 18th Edition (Easton, Pennsylvania: Mack Publishing Company, 1990); Carey and Sundberg Advanced Organic Chemistry 3rd Ed. (Plenum Press) Vols A and B(1992), and Organic Reactions, Volumes 1-40 (John Wiley, and Sons, 1991).

[0189] The present technology is further understood by reference to the following examples, which are intended to be purely exemplary of the present technology. The exemplified embodiments are intended as illustrations of single aspects of the present technology only. Various modifications of the present technology in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures.

[0190] In the examples below, the following abbreviations have the following meanings. +If an abbreviation is not defined, it has its generally accepted meaning.

aq.	= aqueous
LC-MS	= liquid chromatography-mass spectrometry
MS	= mass spectrometry
THF	= tetrahydrofuran
$NaHCO_3$	= sodium bicarbonate
DIEA	= diisopropylethylamine
MS	= mass spectrometry
NaH	= sodium hydride
o/n	= overnight
HATU	= 1-[Bis(dimethylamino)methylene]-1H-1,2,3-trl zolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
r.t.	= room temperature
LAH	= lithium aluminum hydride
DCM	= dichloromethane
DMF	= dimethylformamide
DMSO	= dimethyl sulfoxide
equiv.	= equivalent
EtOAc	= ethyl acetate
EtOH	= ethanol
g	= gram
h	= hours

HCl	= hydrochloric acid
HPLC	= high-performance liquid chromatography
HOAc	= acetic acid
M	= molar
MeOH	= methanol
mg	= milligrams
mL	= milliliters
mmol	= millimols
mp	= melting point
m/z	= mass to charge ratio
NaCl	= sodium chloride
Na_2CO_3	= sodium carbonate
NMR	= nuclear magnetic resonance
NaOH	= sodium hydroxide
Na_2SO_4	= sodium sulfate
TLC	= thin layer chromatography
UV	= ultraviolet
wt %	= weight percent
µM	= micromolar

5.1. EXAMPLE 1: Syntheses

General experimental details:

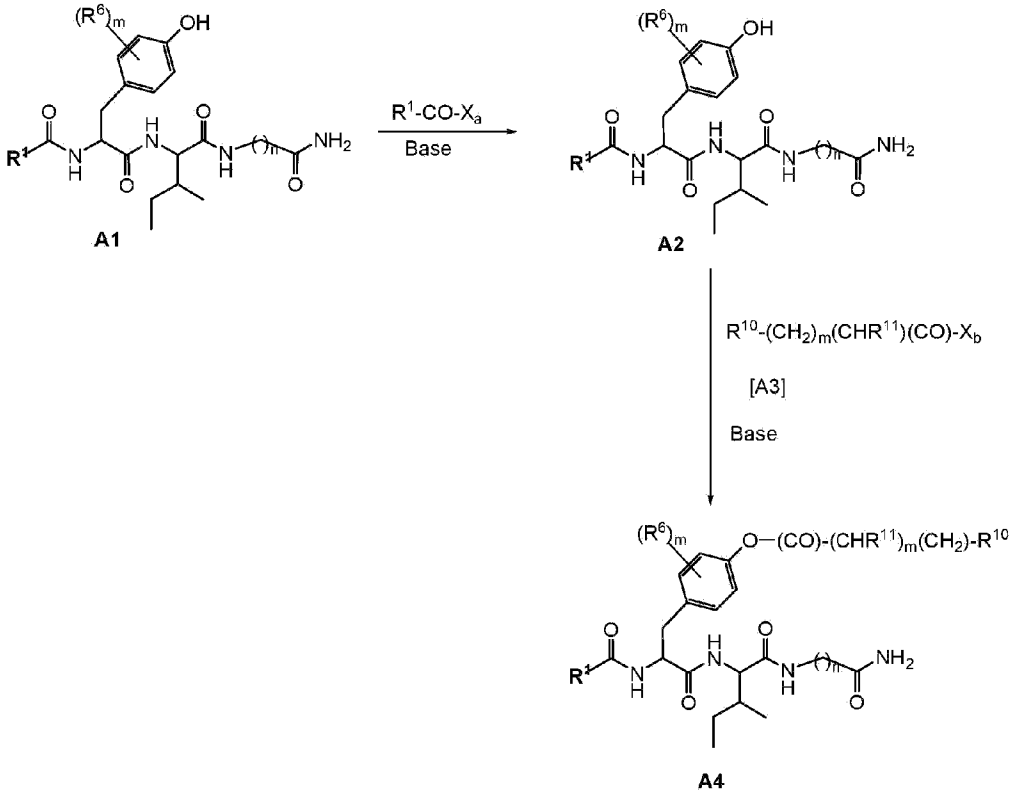
[0191] Final compounds were confirmed by HPLC/MS analysis and determined to be ≥ 90%. ^{1}H and ^{13}C NMR spectra were recorded in CDCW (residual internal standard CHCW = δ 7.26), DMSO-d_6 (residual internal standard CD_3SOCD_2H = δ 2.50), methanol-d_4 (residual internal standard CD_2HOD = δ 3.20), or acetone-d_6 (residual internal standard CD_3COCD_2H = δ 2.05). The chemical shifts (δ) reported are given in parts per million (ppm) and the coupling constants (*J*) are in Hertz (Hz). The spin multiplicities are reported as s = singlet, bs = broad singlet, bm = broad multiplet, d = doublet, t = triplet, q = quartet, p = pentuplet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet, td = triplet of doublet, tt = triplet of triplet, and m = multiplet.

[0192] HPLC-MS analysis was carried out with gradient elution. Medium pressure liquid chromatography (MPLC) was performed with silica gel columns in both the normal phase and

reverse phase.

[0193] In general, the compounds of the present invention may be prepared as illustrated in the general reaction schemes described below, or by modifications thereof, using readily available starting materials, reagents, and conventional synthesis procedures, or could be inferred by one skilled in the art. Generally, compounds of the Formula I, may be prepared by standard solution phase or solid-phase synthesis from commercially available inputs by procedures well established in the art. For example, acylation of the amino terminal would then provide a common intermediate A2. The tyrosyl hydroxyl group of A2 can be acylated with a carboxylic acid derivative (A3), which may be a N-BOC protected amino-acid (such as α, β, γ or ω amino acid, or a di-amino acid derivative such as Lys or Orn) followed by removal of the amine protecting group under acidic conditions to provide A4 (Scheme 1 below).

Scheme-I

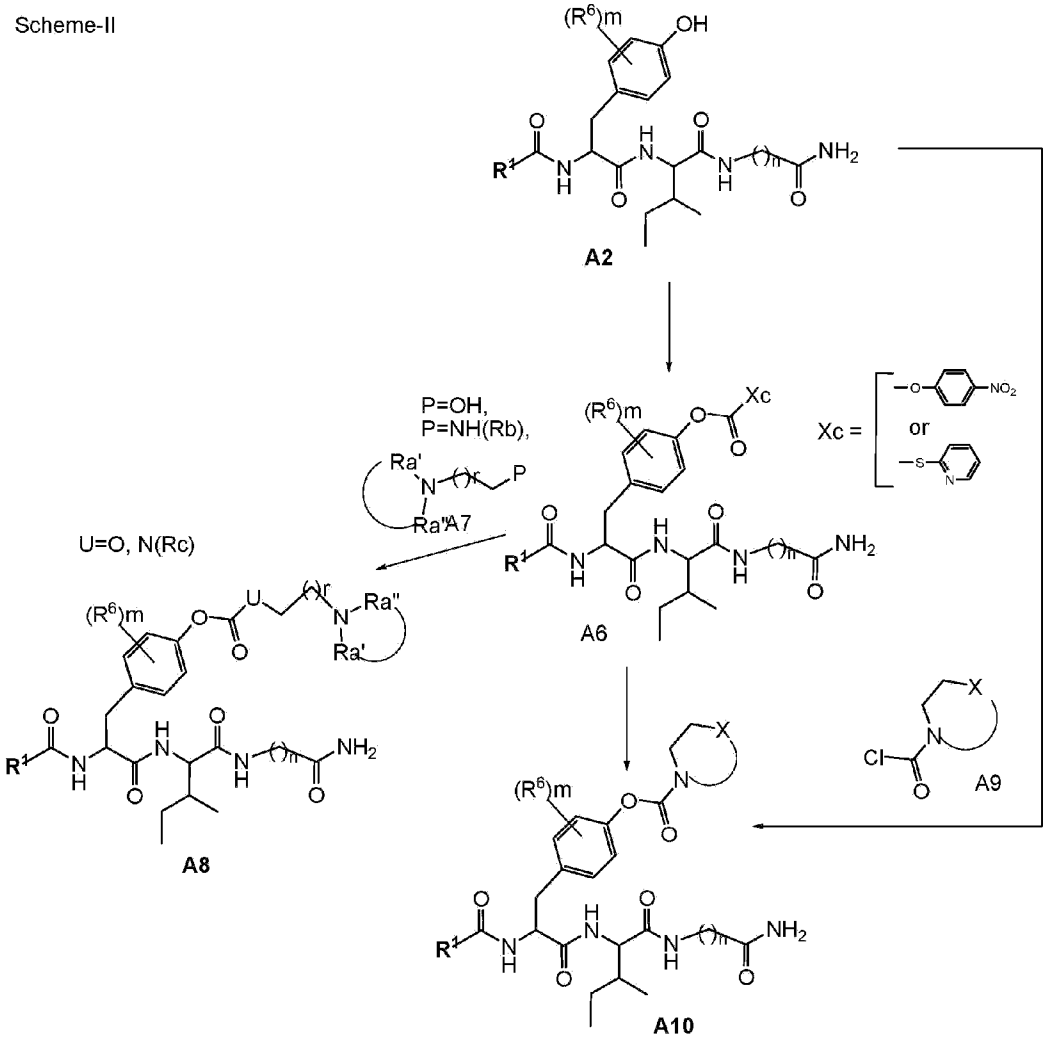


[0194] Alternatively, the carboxylic acid A3 may represent N-mono or N,N- dialkylated amino acid derivatives, as several such analogs are commercially available, and the final product can then be converted to corresponding amine salt, A4, as depicted in Scheme-I

[0195] Alternatively, the tyrosyl hydroxyl of A2 may be derivatized to provide a mixed carbonate derivative, A6, which could then be reacted with an alcohol or an amine derivative, A7, to provide the corresponding carbonate or carbamate derivatives such as A8 and A10, respectively (Scheme-II). A wide range of starting materials, alcohol or amine derivatives, represented by A7, are commercially available or could be prepared by short synthetic sequence reported in published literature. The carbamate derivatives, A10, could also be prepared directly from A2 via reaction with carbamoyl chlorides, A9. Some carbamoyl chlorides are commercially available and

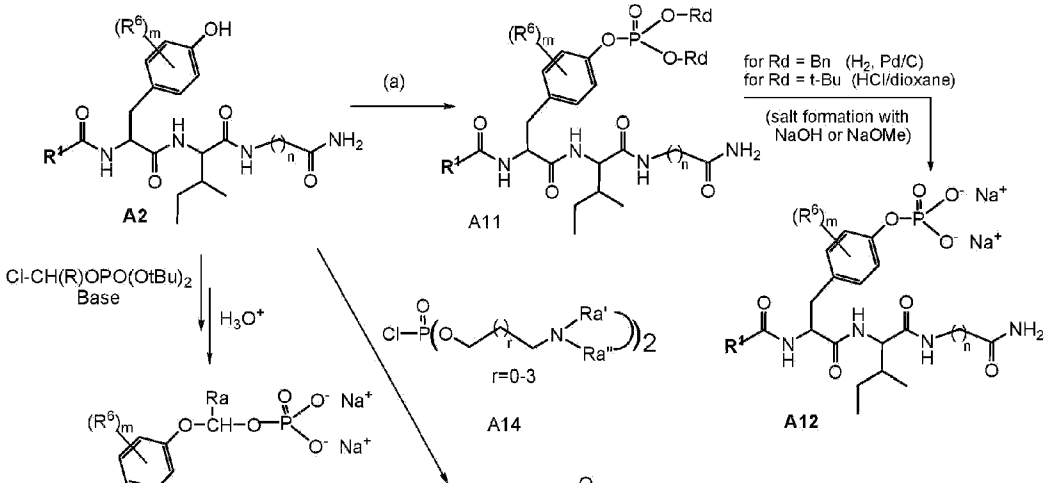
others could be prepared just prior to use from corresponding secondary amine and diphosgene.

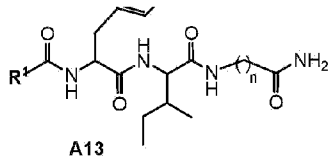
Scheme-II

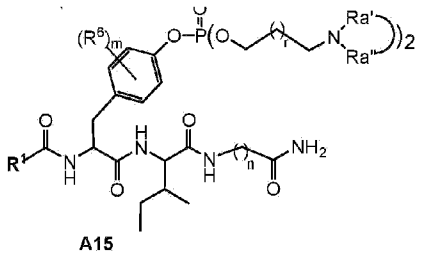


[0196] Tyrosyl hydroxyl could be converted to phosphate derivatives A12, A13, A15, as shown in Scheme-III. The reaction with 2-eq of appropriate alcohols with either POCl3 or 4-nitrophenyl phosphorodichloridate provides intermediate A14, which is then used to derivatize the phenolic hydroxyl of A2 to provide a desired product, A15.

Scheme-III

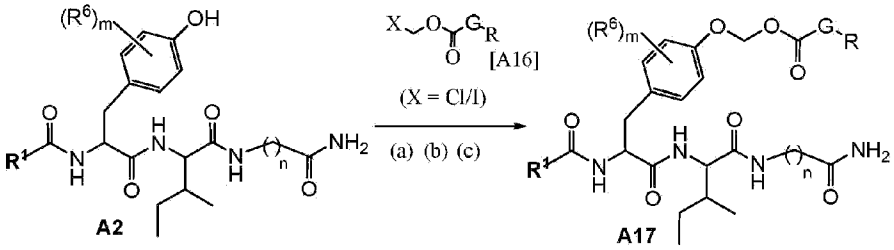




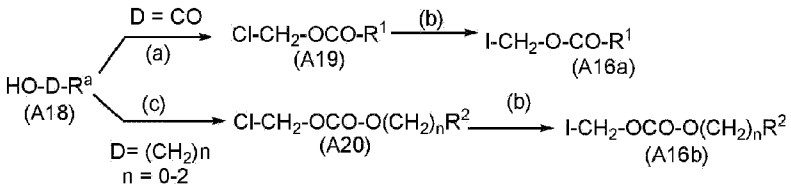


[0197] Another variant of R2 derivatives where the prodrug moiety represents alkoxy-carbonyl based-derivatives can be prepared by route and chemistries shown in Scheme IV. For alkylation of A2, the alkoxy-carbonyl reagents, A16, where the amine is protected with an acid labile BOC group can be prepared utilizing the chemistries, as outlined in Scheme V, or via commercially available reagents. Table 1 below represents some non-limiting examples of these derivatives as a R2 substituent, where A17g represents an example of non-amine based, polyhydroxyl solubility enhancing moiety.

Scheme-IV



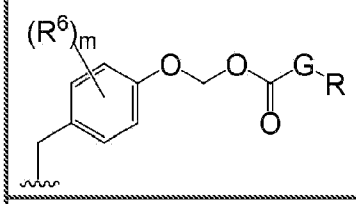
Scheme V: Preparation of Prodrug moiety (A16).

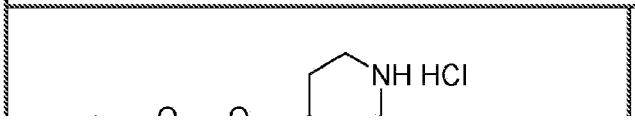


[0198] Reagents: (a) Cl-CH_2-OSO_2Cl, aq. NaHCO3, CH_2Cl_2 (b) Nal/acetone (if required), (c) Cl-CH_2-OCOCl, base,

Table 1

Representative Examples of Alkoxy-carbonyl-derived compounds, for simplicity shown for R^6=H





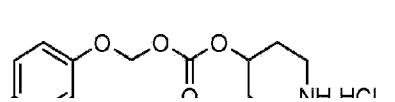
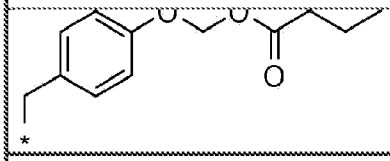
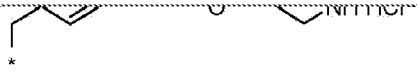
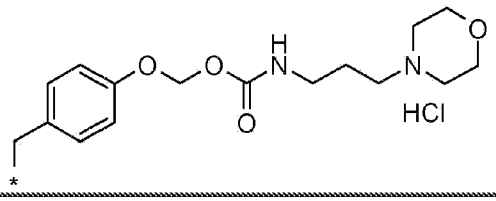
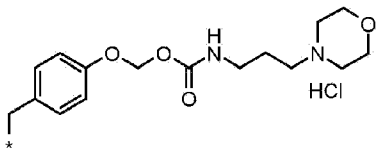
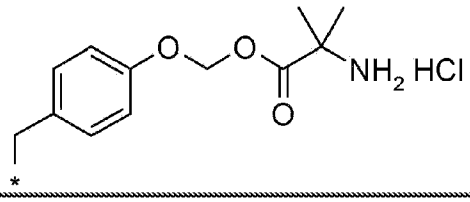
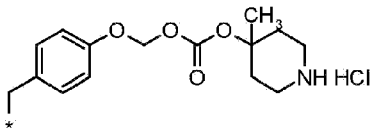
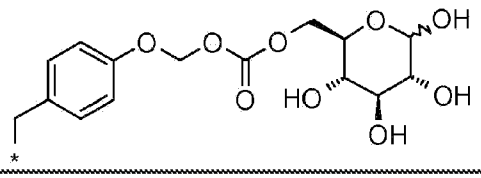
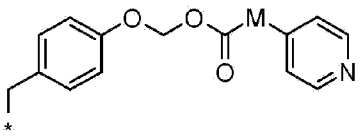


Table 1

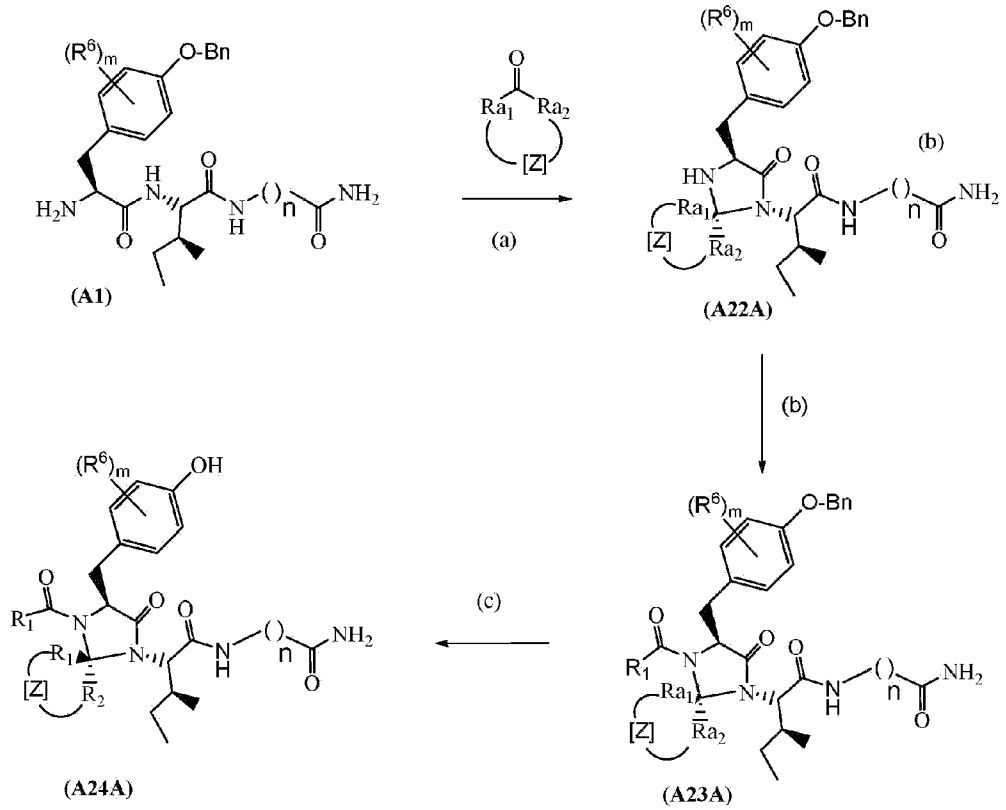
Representative Examples of Alkoxy-carbonyl-derived compounds, for simplicity shown for R^6=H

	
(A17a)	(A17b)
	
(A17c)	(A17d)
	
(A17e)	(A17f)
	
(A17g)	(A17h-m) [M=covalent bond or CH_2], also 2-Py, 3-Py

[0199] Chemistries for incorporation of R3-R4 bicyclic derivatives are shown in the Schemes below. When symmetrical acyclic or cyclic ketones are used for ring formation, no new chiral center will be produced. However, unsymmetrical ketone or aldehyde derived cyclization will generate a new chiral center. The cyclization is expected to proceed via the intermediacy of a Schiff's base, and since chirally pure peptide derivative will be used, one would expect to obtain a thermodynamically stable cyclic-aminal (imidazolidinone) product. A literature report by Lydie, H. et.al. Tett. Letters (2015) 6240-6243, provides an example of cyclization reaction using 2-pyridine carboxaldehyde with a dipeptide, which provides two diastereomers in 46% and 11% yield]. The R3-R4 bridged mono- and/or spirocyclic aminals can be prepared either under acidic or base catalyzed conditions such as similar to or variations of conditions reported in the literature, such as, by, Gomes, P. et.al. Tetrahedron, 2004, 5551-62, DeMong. D. et.al. J. Med. Chem. 2014, 57, 2601-10, and reference cited therein. Subsequent N-acylation of A23A, followed by hydrogenation and removal of the acid labile protecting group, where applicable, will provide the

target imidazolidinone derivatives A24A, Scheme VI.

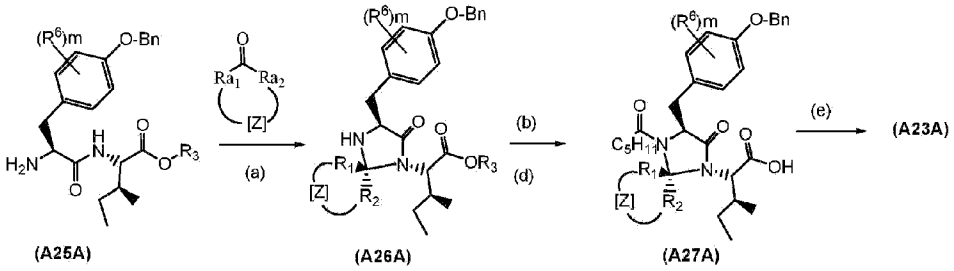
Scheme VI



Reagents: (a) Cat. acid (pTSA or HOAc), in ROH (MeOH, EtOH, IPA) rt or gentle heat, (b) R^1COCl or $(R^1\text{-}CO)_2O$, Et_3N, THF or DMF, (c) H_2-Pd/C EtOH/IPA or galc. HOAc, RT,

[0200] Alternatively, reaction of dipeptide (A25A) with a carbonyl compound could be used to prepare the cyclic aminals, A26A (Scheme VII). Subsequent N-acylation, followed by the coupling reaction shown, should provide the desired key intermediate (A23A), which would then be elaborated further as shown in Scheme VI.

Scheme VII

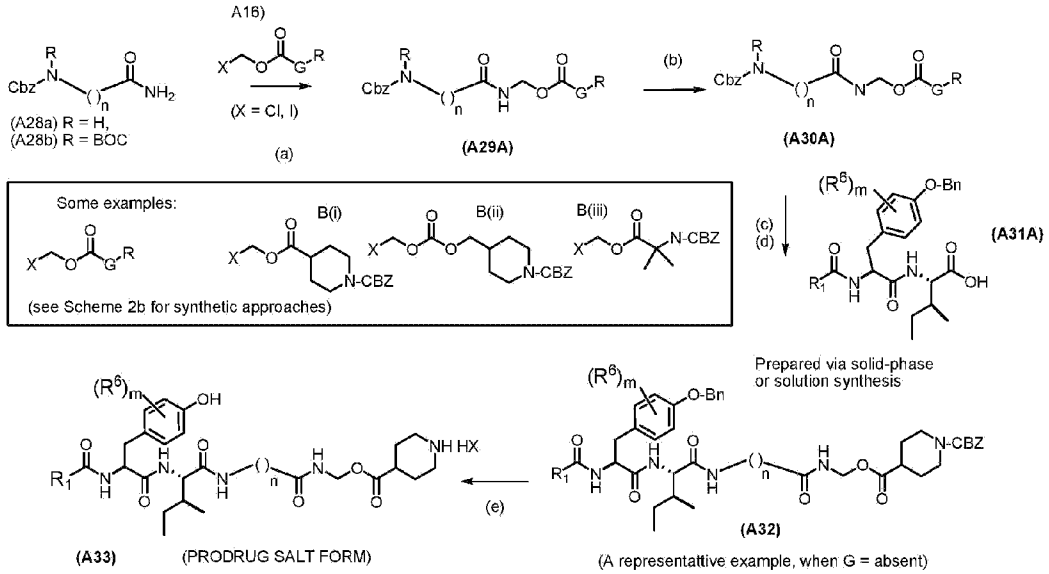


Reagents: (a) Cat. acid (pTSA or HOAc), in ROH (MeOH, EtOH, IPA) rt or gentle heat, (b) R_1COCl or $(R_rCO)_2O$, Et_3N, THF or DMF, (c) H_2-Pd/C EtOH/IPA or galc. HOAc, RT, (d) R_3 = TBDMS, 0.5-1 M aq HCl (e) EDCI, HOBt, $NH_2\text{-}(CH_2)n\text{-}CONH_2$

[0201] The alkoxy-carbonyl bearing an amino group can also be introduced at the C-terminal amide, which following esterase mediated bioconversion should regenerate A2. The chemistry to prepare reagents [A16] is similar to the one described above in Scheme V, except the prodrug generating reagents [A16] contains a CBZ protected amine. Some examples of the reagents

used are shown in the box (insert) in Scheme VIII. Following synthesis of the protected penultimate intermediate, the final hydrogenation step in the presence of an acid would provide the desired prodrug derivative A33A.

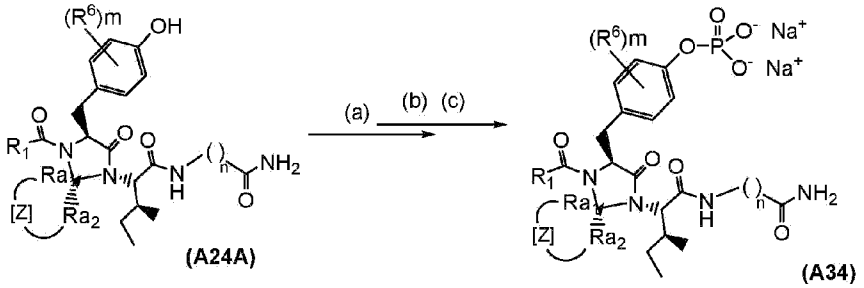
Scheme VIII, C-terminal Amide Prodrugs



Reagents: (a) Cs_2CO_3, DMF, (b) 4M HCl/p-dioxane, (C) H2/Pd/c, (d)HATU,HBOT, DMF or EDCI, HOBt, DMF, (e) H_2/Pd-C glac HOAc/aq. HCl (1-1.5 eq.)

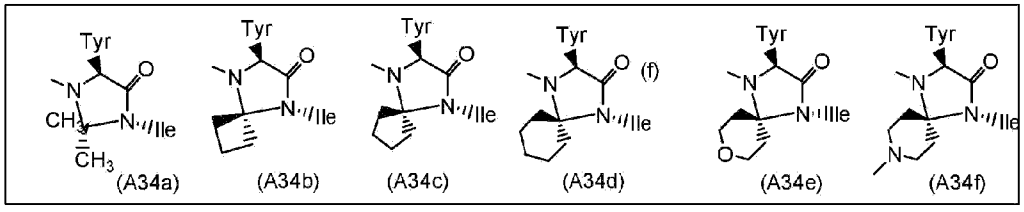
[0202] One may also be able to prepare derivatives incorporating dual prodrug moieties, one at the Tyr and other at the C-terminal amide, or at R3/R4 bridge and at R2, or some combination of the chemistries described above. As an example, dual prodrug analogs from one of these approaches, and corresponding proposed synthetic route, is shown in Scheme IX, below.

Scheme IX



(a) $(BnO)_2PO\text{-}O\text{-}PO(OBn)_2$/ (non-aq) Base/ DMF, (b) H_2/Pd-C, glac HOAc, (c) salt formation, (e.g. Ion-exchange resin)

[0203] Some Examples of (Cyclic Aminal) Imidazolidinone Fragments: CH(Ra)O

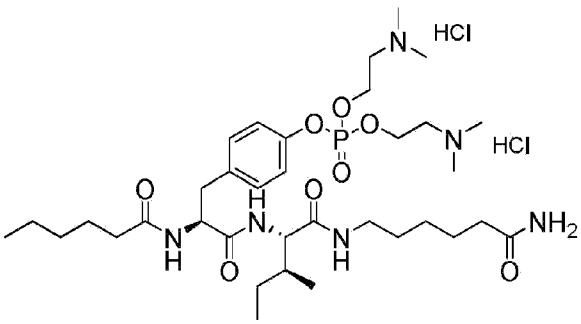


[0204] Furthermore, the tyrosine analogs with R6 variants such as F, ^{2}H and CH_3 are reported in the published primary literature and/or in the patents and references cited therein. [For $(R_6)_m$ as ^{2}H: 2,6-didetutero tyrosine, Nishiyama, B. et.al. J. Labeled Compounds and Radiopharmaceuticals, 1994, 34(9), 831-37; 2,3,4,6-tetradeutero tyrosine: Walker, T.E. etal.al J. Org Chem. 1986, 51(8), 1775-79; for (R_6)m as CH3: 2-methyl tyrosine, Schmidt, E.W. Tett. Letters, 2004, 3921-24; for 2,3-dimethyl tyrosine or 2,5-dimethyl tyrosine, Santagada, V. J. Med. Chem. 2006, 49(6), 1882-90, for 2,6-dimethyl tyrosine EP1481965A1 (2004) and EP2959918A1 (2015); and for $(R_6)_m$ as F: 2,6- or 2,3- or 2,4-difluoro and/or 2,3,5- or 2,3,6-trifluoro tyrosine, Seyedsayamdost, H. et.al. J. Am. Chem. Soc 2006, 49(6), 1882-90; and 2,3,5,6-tetrafuloro tyrosine is commercially available.] In addition, the derivative of A2 where R6 is 2-fluoro, such derivatives should be accessible via regiospecific electrophilic fluorination of the tyrosine-containing peptide or peptide mimetics utilizing *in-situ* generated CH3COOF, as described by Hebel, D., Tett. Letters, 1990, 31(5), 619-622. Other such R6 derivatives should be accessible from extension of these chemistries.

[0205] The following specific, non-limiting examples are illustrative of the invention.

Example-1A.

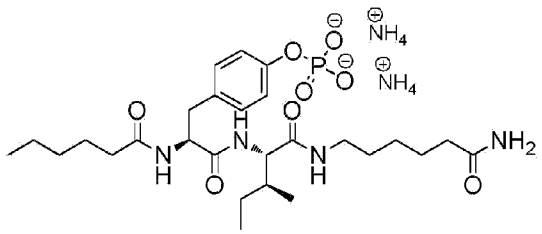
[0206]



[0207] To a mixture of 4-nitrophenyl phosphorodichloridate (504 mg, 1.98 mmol) in THF (30 mL) at 0 °C was added, 2-(dimethylamino)ethanol (397 µL, 3.97 mmol) and stirred for two hours at room temperature. THF was evaporated and crude product was dissolved in DMF (20 mL) followed by addition of Base Structure (500 mg, 0.992 mmol) and $LiOH.H_2O$ (208 mg, 4.96 mmol) and the mixture was stirred at room temperature overnight. Quenched with 4 Molar HCl, concentrated, washed (DCM/CH_3CN), and purified by preparative HPLC using Isocratic 40% MeOH vs 60% aqueous formic acid solution (0.1%), pure fractions were combined, (HCl Salt was formed by addition of 4 Molar HCl) to give the title compound, as a white solid, after lyophilization. [(obs) MH^{+}= 727.5]

Example-1B:

[0208]

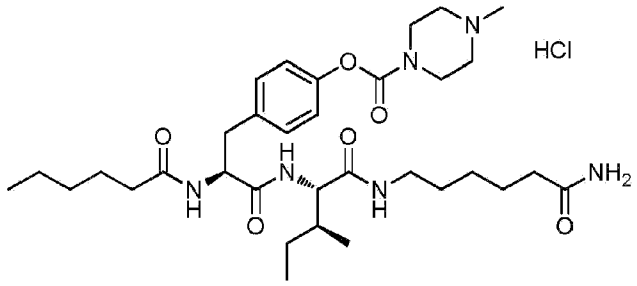


[0209] Step-1: A mixture of Base Structure (500 mg, 0.992 mmol) in DMF, tetrabenzyl diphosphate (587 mg, 1.09 mmol) and $LiOH.H_2O$ (46 mg, 1.09 mmol) was stirred at room temperature overnight. Concentrated, washed (DCM) and used in the next step without further purification.

[0210] Step-2: 4-((S)-3-((2S,3S)-1-(6-amino-6-oxohexylamino)-3-methyl-1-oxopentan-2-ylamino)-2-hexanamido-3-oxopropyl)phenyl dibenzyl phosphate was dissolved in acetic acid (15 mL) and 10% Pd/C 0.5 eq (w/w) was added and stirred for two hours under hydrogen atmosphere. Reaction mixture was filtered through a pad of celite. Filtrate was concentrated, washed (DCM) and purified by preparative HPLC (Isocratic 70% MeOH vs 30% ammonium acetate buffer (pH 8) to give the desired compound after lyophilization as a white solid (NH_4^+ Salt). [(obs) MH^+= 684.5]

Example-1C:

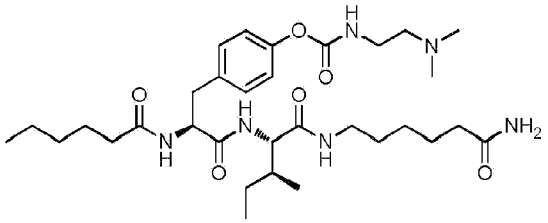
[0211]



[0212] Base Structure (564.9 mg, 1.119 mmol) was dissolved in dry DMF (12 mL) then $LiOH•H_2O$ (46.9 mg, 1.119 mmol) and bis(4-nitrophenyl)carbonate (374.6 mg, 1.231 mmol) were added. The solution was stirred at room temperature under nitrogen atmosphere for 17h. *N*-methylpiperazine hydrochloride (198.8 mg, 1.455 mmol) was added and the mixture stirred for another 6h then quenched with HCl and concentrated to dryness. The solid was washed (DCM, EtOAc) then purified by Biotage C-18 reverse phase flash chromatography (30%-100% MeOH vs 0.1% aqueous formic acid) to give the title compound Base Structure-C-PIPM (227.6 mg, 30%) after treatment with HCl and lyophilization. [(obs) MH^+= 631.4 and $M+Na^+$ = 653.4]

Example-ID:

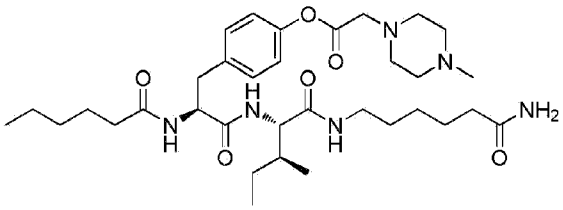
[0213]



[0214] Base Structure (508.1 mg, 1.007 mmol) was dissolved in dry DMF (8 mL) then $LiOH•H_2O$ (42.2 mg, 1.007 mmol) and bis(4-nitrophenyl)carbonate (336.9 mg, 1.107 mmol) were added. The solution was stirred at room temperature under nitrogen atmosphere overnight. *N,N*-dimethylethane-1,2-diamine hydrochloride (163.1 mg, 1.309 mmol) was added and the mixture stirred for another 4h then quenched with HCl and concentrated to dryness. The solid was washed (DCM, EtOAc) then purified by preparative HPLC (50%-70% MeOH vs 0.1% aqueous formic acid) to give the title compound (154.8 mg, 12%) after treatment with HCl and lyophilization. [(obs) MH^+= 619.5 and $M+Na^+$ = 641.6]

Example-IE:

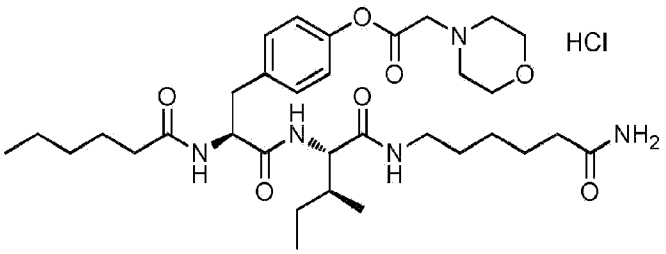
[0215]



[0216] To a solution of Base Structure (200 mg; 0.39 mmol) and 2-(4-methylpiperazin-1-yl)acetic acid (175.6 mg; 1.1 mmol) in anhydrous DMF (15 mL), EDC HCl (247.3 mg; 1.3 mmol) and HOBt (61 mg; 039 mmol) were added at 0° C. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with 4M HCl in 1,4-dioxane (0.5 mL). The solvent was evaporated in vacuum and the solid material was dissolved in methanol (2 mL). Product was precipitated by adding diethylether to the above solution, and was separated by filtration. Crude product was purified by reverse phase HPLC using methanol (B) : 0.1% formic acid in water (D), [gradient elution; 10 to 100% of B vs D in 20 min]. The combined fractions were acidified with HCl and lyophilized to offer the compound (206 mg, 82 %) as white solid. [(obs) MH^+= 645.4]

Example-IF:

[0217]

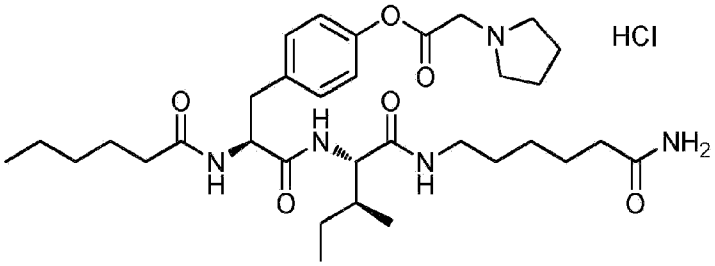


[0218] Step-1: A mixture of 2-morpholinoacetic acid (975 mg, 6.73 mmol), 4-nitrophenol (850 mg, 6.12 mmol), DCC (1386 mg, 6.73 mmol) and DMAP (40 mg, 0.306 mmol) in DCM (50 mL) was stirred at room temperature overnight. Reaction mixture was filtered, concentrated and washed with DCM gave 4-nitrophenyl 2-morpholinoacetate as a white solid which was used in the next step without further purification.

[0219] Step-2: A mixture of 4-nitrophenyl 2-morpholinoacetate (288 mg, 0.95 mmol), Base Structure (400 mg, 0.79 mmol), and $LiOH•H_2O$ (74 mg, 1.75 mmol) in DMF (10 mL) was stirred at room temperature overnight. Quenched with 4 molar HCl, Concentrated and washed (DCM/THF/CH_3CN) gave the desired compounds as a white solid (HCl Salt). [(obs) MH^+= 632.5, $M+Li^+$ = 638.5]

Example-1G:

[0220]



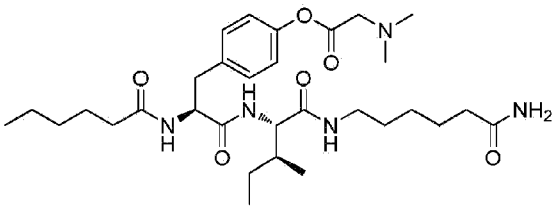
[0221] Step-1: A mixture of 2-(pyrrolidin-1-yl)acetic acid hydrochloride (1000 mg, 6.06 mmol), 4-nitrophenol (842 mg, 6.06 mmol), DCC (1500 mg, 7.27 mmol) and DMAP (39 mg, 0.30 mmol) in CH_3CN (50 mL) was stirred at room temperature overnight. Reaction mixture was filtered, concentrated and washed with DCM gave 4-nitrophenyl 2-(pyrrolidin-1-yl)acetate hydrochloride as yellow viscous oil which was used in the next step without further purification.

[0222] Step-2: A mixture of 4-nitrophenyl 2-(pyrrolidin-1-yl)acetate hydrochloride (187mg, 0.66 mmol), Base Structure (300 mg, 0.59 mmol), and $LiOH•H_2O$ (55 mg, 1.31 mmol) in DMF (10 mL) was stirred at room temperature overnight. Quenched with 4 molar HCl, concentrated, washed

(DCM/CH_3CN) and purified by preparative HPLC using isocratic 40% MeOH and 60% 0.1% aqueous formic acid solution gave the desired compounds as a white solid 4 molar HCl was added to make HCl Salt of the final product) after lyophilization. [(obs) MH^+= 616.5 and $M+Na^+$ = 638.4]

Example-1H:

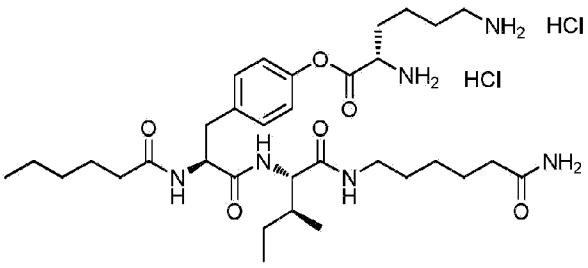
[0223]



[0224] To a solution of Base Structure (200 mg; 0.39 mmol) and 2-(dimethylamino) acetic acid (124.4 mg; 1.1 mmol) in anhydrous DMF (15 mL), EDC HCl (191.7 mg; 1 mmol) and HOBt (61.2 mg; 0.39 mmol) were added at 0 °C. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with 4M HCl in 1,4-dioxane (0.5 mL). The solvent was evaporated in vacuum and the solid material was dissolved in methanol (2 mL). Product was precipitated by adding diethylether to the above solution, and was separated by filtration. The crude product was purified by reverse phase HPLC using methanol (B) : 0.1% formic acid in water (D), [gradient elution; 10 to 100% of B vs D in 20 min]. The combined fractions were acidified with HCl and lyophilized to offer as white solid (94 mg 40 %). In addition, 63 mg of Base Structure was also recovered from this reaction. [(obs) MH^+= 590.4 and $M+Na^+$ = 612.4]

Example-1I:

[0225]



[0226] Step-1: A mixture of Boc-(*S*)-Lys(Boc)-OH (741 mg, 2.14 mmol), 4-nitrophenol (282.7 mg, 2.03 mmol), DCC (441.3 mg, 2.14 mmol) and DMAP (26.1 mg, 0.214 mmol) in dry acetonitrile (20 mL) was stirred at room temperature under nitrogen atmosphere overnight. Reaction mixture was filtered, concentrated and crude product was purified by flash chromatography (silica gel, hexanes/EtOAc) to provide (*S*)-4-nitrophenyl 2,6-bis(tert-butoxycarbonylamino) hexanoate (548.7

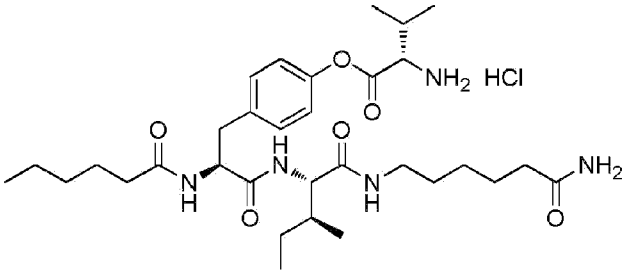
mg, 55%).

[0227] Step-2: (*S*)-4-nitrophenyl 2,6-bis(tert-butoxycarbonylamino)hexanoate (512.0 mg, 1.095 mmol) in solution in dry DMF (5 mL) was added to a solution of Base Structure (460.6 mg, 0.9127 mmol) and LiOH•H_2O (40.2 mg, 0.958 mmol). The mixture was stirred at room temperature under nitrogen atmosphere overnight. Concentration and washing (DCM, acetonitrile) gave bis(Boc-protected)- (578.2 mg, 76%).

[0228] Step-3: Bis(Boc-protected)- (307.1 mg, 0.369 mmol) was stirred in a DMF (1.5 mL) / 4N HCl in dioxane (8 mL) mixture at room temperature for 3.5h then concentrated, washed (DCM) and purified by preparative HPLC (40%-100% MeOH vs 0.1% aqueous formic acid), after treatment with HCl and lyophilisation provided the title compound (204.1 mg, 68%). [(obs) MH^+ = 633.5 and $M+Na^+$ = 655.6]

Example-1J:

[0229]



[0230] Step-1: To a solution of 4-nitrophenol (1 g, 7.2 mmol) and (*S*)-2-(tert-butoxycarbonylamino)-3-methylbutanoic acid (1.8 g, 8.6 mmol) in anhydrous acetonitrile (25 mL), was added DCC (1.8 g, 8.6 mmol) and DMAP (44 mg, 0.36 mmol). The mixture was stirred overnight under nitrogen atmosphere. The solvent evaporated in vacuum and crude mixture was purified by normal phase column chromatography using DCM (100%) as eluent to offer (S)-4-nitrophenyl-2-(tert-butoxycarbonylamino)-3-methylbutanoate (0.7g, 29 %).

[0231] (*S*)-4-nitrophenyl-2-(tert-butoxycarbonylamino)-3-methylbutanoate and Base Structure (300 mg; 0.59 mmol) was dissolved in anhydrous DMF (25 mL). LiOH H_2O (24.9 mg, 0.59 mmol) was added to the solution. The mixture was stirred at room temperature under nitrogen atmosphere overnight. The solvent was evaporated in vacuum, solid material was washed with DCM (100%) and then acetonitrile (100 %) to offer pure BOC-protected- product (300 mg), which was dissolved in a mixture of DMF (3 mL) and 1,4-dioxane (1 mL). 4 M HCl in 1,4-dioxane (10 mL) was added to the above solution. The mixture was stirred at room temperature for 4 h. The solvent was evaporated in vacuum and the crude product was purified by reverse phase HPLC using methanol (B): 0.1% formic acid in water (D), [gradient elution; 40 to 100% of B vs D in 20 min]. The combined fractions were acidified with HCl and lyophilized to offer the compound

(180mg, 50 %) as white solid. [(obs) MH^+ = 604.4, $M+Na^+$ = 626.5]

5.2. EXAMPLE 2: Stability in simulated intestinal fluid, simulated gastric fluid, and plasma | Permeability

[0232] Experiments were conducted to assess the metabolic stability of test compounds in the simulated intestinal fluid (SIF), simulated gastric fluid (SGF), and plasma.

Plasma Stability Study

[0233]

Assay Conditions

[Compound] = 1 µM

Time = 0, 60, 120, and 240 min

Temperature = 37°C

Experimental Protocol

Human and rat plasma (K2 EDTA) were obtained from Bioreclamation.

[0234] Compounds were dissolved as 0.3 mM DMSO stocks. Compounds were transferred to the plasma at 1 µM on a 96-well deep well plate. After mixing, samples were transferred to several 96-well plates (25 µL/well), and incubated at 37°C. The extent of metabolism was calculated as the disappearance of the test compound, compared to the 0-min control reaction incubations. Propantheline was included as a positive control to verify assay performance.

[0235] At each of the time points, 150 µL of quench solution (50% acetonitrile, 50% methanol with 0.05% formic acid) with internal standard (bucetin for positive ESI mode and warfarin for negative ESI mode) was transferred to each well. Plates were sealed and centrifuged at 4°C for 15 minutes at 4000 rpm. The supernatant was transferred to fresh plates for LC/MS/MS analysis.

[0236] All samples were analyzed on LC/MS/MS using an AB Sciex API 4000 instrument, coupled to a Shimadzu LC-20AD LC Pump system. Analytical samples were separated using a Waters Atlantis T3 dC18 reverse phase HPLC column (20 mm x 2.1 mm) at a flow rate of 0.5 mL/min. The mobile phase consisted of 0.1% formic acid in water (solvent A) and 0.1% formic acid in

100% acetonitrile (solvent B). Elution conditions are detailed in the table below.

Table 1: Gradient Conditions

Time (min)	Flow (µL/min)	%A	%B
0	500	98	2
0.30	500	98	2
1.40	500	2	98
2.00	500	2	98
2.01	500	98	2
2.50	500	98	2

[0237] Initial rates of the clearance of test compounds were calculated using linear regression of semi-log plot of % remaining of compounds versus time. The elimination rate constant (equals to -slope) of the linear regression was then used to determine t1/2 values.

Metabolic Stability in SIF and SGF (Simulated Intestinal and Gastric Fluid)

Assay Conditions

[0238]

[Drug] = 5 µM

Buffer 1 = SGF without enzyme

Buffer 2 = SGF with 0.32% pepsin

Buffer 3 = SIF without enzyme

Buffer 4 = SIF with 1% pancreatin

Time = 0, 60, 120, and 240 min

Temperature = 37°C

Experimental Protocol

[0239] SIF was prepared freshly with 8.7 mM NaOH, 28.65 mM NaH_2PO_4, 105.85 mM NaCl, with a final pH of 6.8. SGF was prepared freshly with 34.2 mM NaCl, with a final pH of 1.2. Enzymes such as pepsin or pancreatin were added to some buffers. Human and rat plasma (K2

EDTA) were purchased from BioreclamationIVT.

[0240] Compounds were dissolved as 1.5 mM DMSO stocks. Compounds were transferred to SIF, SGF, or plasma at 5 µM on a 96-well deep well plate. After mixing, samples were transferred to several 96-well plates (25 µL/well), and incubated at 37°C. The extent of metabolism was calculated as the disappearance of the test compound, compared to the 0-min control reaction incubations. Candesartan Cilexetil and omeprazole were included as positive controls for SIF and SGF, respectively, to verify assay performance.

[0241] At each of the time points, 150 µL of quench solution (100% acetonitrile with 0.1% formic acid) with internal standard (bucetin for positive ESI mode and warfarin for negative ESI mode) was transferred to each well. Plates were sealed and centrifuged at 4°C for 15 minutes at 4000 rpm. The supernatant was transferred to fresh plates for LC/MS/MS analysis.

[0242] All samples were analyzed on LC/MS/MS using an AB Sciex API 4000 instrument, coupled to a Shimadzu LC-20AD LC Pump system. Analytical samples were separated using a Waters Atlantis T3 dC18 reverse phase HPLC column (20 mm x 2.1 mm) at a flow rate of 0.5 mL/min. The mobile phase consisted of 0.1% formic acid in water (solvent A) and 0.1% formic acid in 100% acetonitrile (solvent B). Elution conditions are detailed in the table below.

Table 1: Gradient Conditions

Time (min)	Flow (µL/min)	%A	%B
0	500	98	2
0.30	500	98	2
1.40	500	2	98
2.00	500	2	98
2.01	500	98	2
2.50	500	98	2

[0243] Initial rates of the clearance of test compounds were calculated using linear regression of semi-log plot of % remaining of compounds versus time. The elimination rate constant (equals to -slope) of the linear regression was then used to determine t1/2 values.

Permeability Study

Caco Experiment Methods

<u>Assay Conditions</u>

[0244]

[Compound] = 10 µM

[GF120918] = 0 or 10 µM

Buffer = HBSS, pH 7.4 with 5 mM HEPES

Time = 1 hr

Controls = Digoxin

Experimental Protocol

[0245] Caco-2 cell plates were obtained commercially and were maintained for 21 days at 37°C with 5% CO2. Cells were washed with Hank's Balanced Salt Solution (HBSS) 30 min before starting the experiment. Test compound solutions were prepared by diluting from DMSO stock into HBSS buffer in the presence or absence of 10 µM of P-gp inhibitor GF120918. The final DMSO concentration is 0.2%. Prior to each experiment, cell monolayer integrity was verified by transendothelial electrical resistance (TEER). Transport experiment was initiated by adding test compounds to the apical (75 µL) side. Transport plates were incubated at 37°C in a humidified incubator with 5% CO2. Samples were taken from the donor and acceptor compartments after 1 hr and analyzed by liquid chromatography with tandem mass spectrometry (LC/MS/MS).

[0246] Apparent permeability (Papp) values were calculated using the following equation:

$$Papp = (dQ/dt)/A/C_0$$

where dQ/dt is the initial rate of amount of test compound transported across cell monolayer, A is the surface area of the filter membrane, and Co is the initial concentration of the test compound. Co is calculated for each condition using a 4-point calibration curve. To calculate Papp each pro-drug and MM-201 were monitored simultaneously and the concentrations were added up to determine the final compound concentration in the system.

[0247] Absorption quotient between the two assay conditions was calculated by the following equation:

Absorption quotient (AQ)=(Papp, A-B with inhibitor - Papp, A-B without inhibitor)/Papp, A-B with inhibitor where Papp, A-B with inhibitor and Papp, A-B without inhibitor represent the apparent permeability of test compound from the apical to basal side of the cellular monolayer in the presence and absence of 10 µM P-gp inhibitor GF120918, respectively.

[0248] All samples were analyzed on LC/MS/MS using an AB Sciex API 4000 instrument, coupled to a Shimadzu LC-20AD LC Pump system. Analytical samples were separated using a Waters Atlantis T3 dC18 reverse phase HPLC column (10 mm x 2.1 mm) at a flow rate of 0.5 mL/min. The mobile phase consisted of 0.1% formic acid in water (solvent A) and 0.1% formic acid in acetonitrile (solvent B).

Table 1: Gradient Conditions

Time (min)	Flow (µL/min)	%A	%B
0	500	98	2
0.30	500	98	2
1.40	500	2	98
2.00	500	2	98
2.01	500	98	2
2.50	500	98	2

5.3. EXAMPLE 3: In-Vivo Pharmacokinetics

Methods and Materials:

[0249]

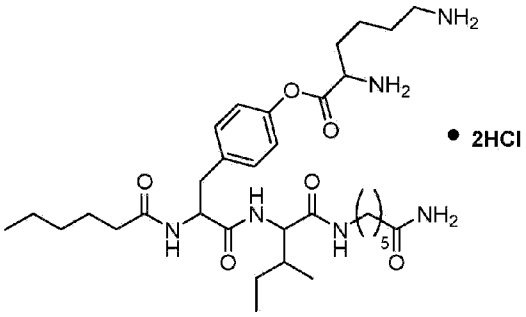
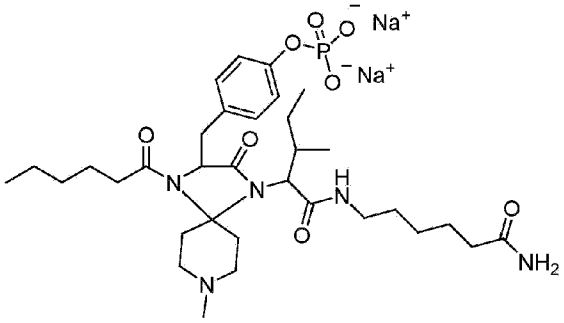
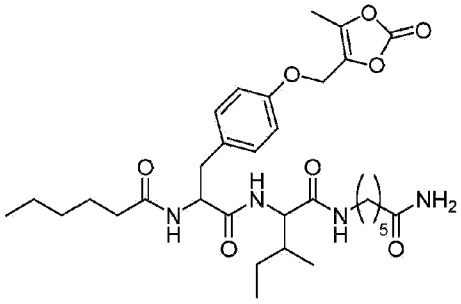
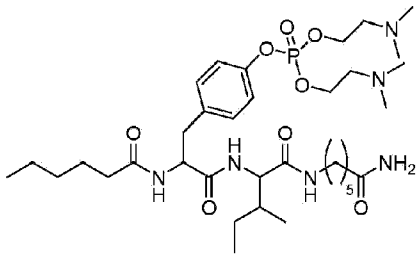
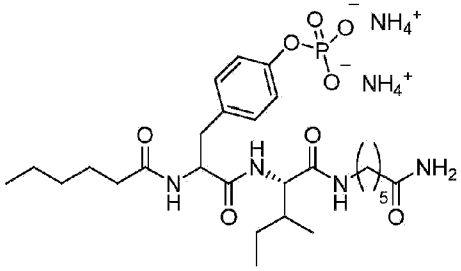
1. 1. Eighy (8) male JVC SD rats (purchased from Charles River Lab) were monitored daily for body condition and health status during the 3-5 days acclimation period. The rats were randomly assigned into one group (n=4).
2. 2. On Day 1,
   Rats are weighed and PO dosed with

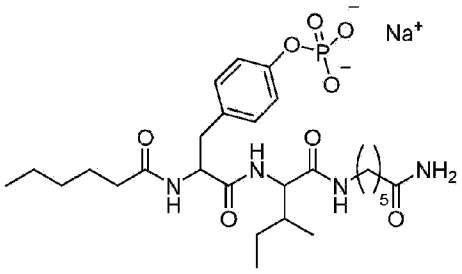
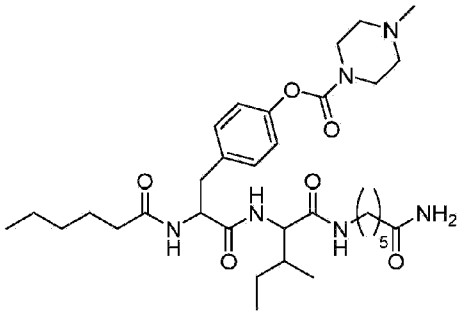
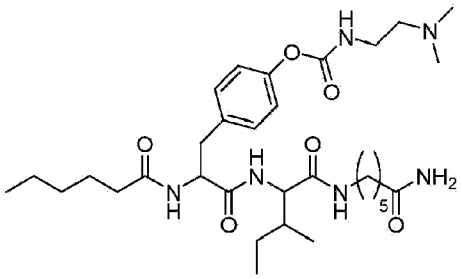
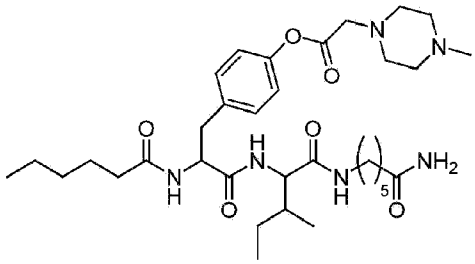
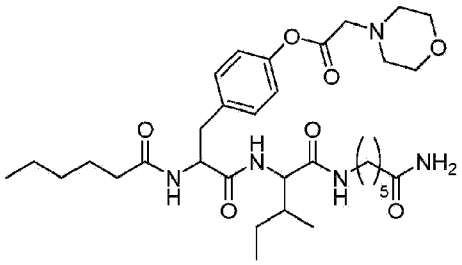
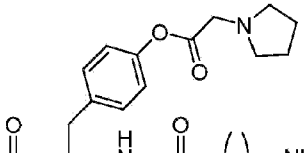
   -- Group 1: 13.2 mg/kg of A20 (10 mL/kg of 1.32 mg/mL)

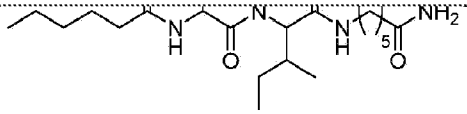
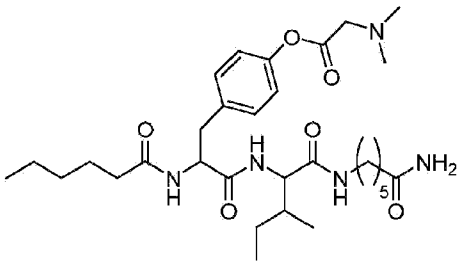
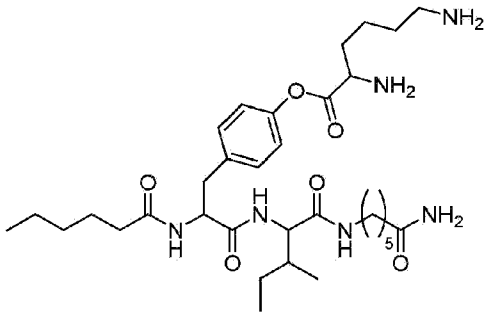
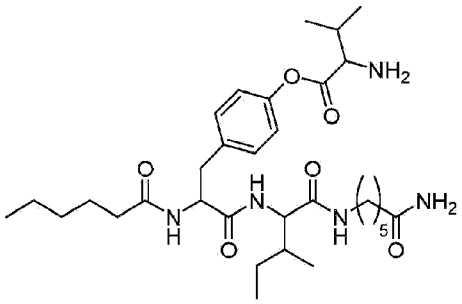
   -- Group 2: 14.2 mg/kg of A22 (10 mL/kg of 1.42 mg/mL).

3. 3. The dosed rats were individually placed into a metabolic cage, and have access to food and water at all times. The urine from each rat was collected daily from the metabolic cages, and kept in dry ice.
4. 4. At predose (0 min), 5 min, 15 min, 30 min, 1 hr, 2 hr, 8 hr, and 24 hr post dosing, approximately 200 ul blood samples were collected from each rat and transferred to EDTA tubes.
5. 5. The blood samples in EDTA vials were centrifuged at 4°C and 6,000 rpm for 10 minutes to generate ~100 µl of plasma per sample. Blood samples were processed as quickly as possible and remain no longer than 2 min at room temperature and no longer than 15 minutes at 4 °C prior to processing.
6. 6. All samples were transferred for bioanalytic assay using LCMS

[0250] Data for each study are shown below:

Compound ID	Structure
Base Structure	N-hexanoic-L-tyrosine-L-isoleucine-(6)-aminohexanoic amide
A26	
2	
A28	
A18	 A18
A29	

Compound ID	Structure
A30	
A20	
A21	
A22	
A23	
A24	

Compound ID	Structure
	
A25	
A26	
A27	

Compound ID	Plasma Stability (% Parent Remaining)									
	Human Plasm					Rat Plasma				
	0 min	60 min	120 min	240 min	Half-Life (min)	0 min	60 min	120 min	240 min	Half-Life (min)
Base Structure	100%	98%	102%	98%	12558.0	100%	87%	89%	83%	1095.1
A26	100%	106%	123%	109%	NA	100%	112%	117%	111%	NA
2	100%	113%	90%	72%	424.5	100%	82%	77%	83%	1083.6
A28	-	-	-	-	-	-	-	-	-	-
A18	-	-	-	-	-	-	-	-	-	-
A29	-	-	-	-	-	-	-	-	-	-
A30	100%	36%	20%	12%	84.2	100%	88%	87%	86%	1307.4
A20	100%	83%	87%	90%	2957.7	100%	73%	56%	34%	157.0

Compound ID	Plasma Stability (% Parent Remaining)									
	Human Plasm					Rat Plasma				
	0 min	60 min	120 min	240 min	Half-Life (min)	0 min	60 min	120 min	240 min	Half-Life (min)
A21	100%	59%	33%	11%	73.4	100%	61%	34%	9%	69.7
A22	100%	59%	37%	15%	87.9	100%	1%	0%	0%	8.7
A23	100%	29%	7%	1%	31.3	100%	1%	1%	0%	8.2
A24	100%	0%	0%	0%	7.3	100%	55%	27%	47%	64.2
A25	100%	2%	0%	0%	10.1	100%	1%	0%	0%	8.2
A26	100%	11%	7%	13%	18.8	100%	5%	10%	8%	13.5
A27	100%	4%	4%	5%	13.2	100%	27%	29%	37%	31.9

Compound ID	SIF Stability (pH 6.8)									
	-Pancreatin					+Pancreatin				
	0 min	60 min	120 min	240 min	Half-Life (min)	0 min	60 min	120 min	240 min	Half-Life (min)
BASE STRUCTURE	100%	119%	-	113%	Neg.	-	-	-	-	-
A26	Not in report	Not in report	Not in report	Not in report	Not in report	Not in report	Not in report	Not in report	Not in report	Not in report
2	100%	82%	82%	78%	801.5	100%	94%	51%	34%	142.4
A28										
A18	100%	25%	17%	8%	30.2	100%	40%	12%	25%	39.4
A29	100%	96%	97%	103%	Neg.	100%	94%	98%	104%	Neg.
A30	100%	43%	22%	8%	68.4	100%	70%	51%	34%	156.6
A20	100%	65%	57%	51%	95.4	100%	62%	54%	61%	86.6
A21	-	-	-	-	-	100%	95%	97%	93%	3006.4
A22	100%	74%	61%	59%	335.8	100%	69%	64%	63%	425.9
A23	100%	93%	95%	79%	744.0	100%	66%	41%	20%	104.5
A24	100%	62%	38%	14%	83.5	100%	13%	1%	0%	18.8
A25	-	-	-	-	-	100%	27%	7%	1%	34.7
A26	100%	11%	1%	0%	19.6	100%	78%	52%	37%	166.9
A27	100%	63%	59%	24%	122.6	100%	49%	24%	5%	57.1

Compound ID	SGF Stability (pH 1.2)									
	-Pepsin					+Pepsin				
	0 min	60 min	120 min	240 min	Half-Life (min)	0 min	60 min	120 min	240 min	Half-Life (min)
BASE STRUCTURE	100%	127%	-	122%	Neg.	100%	13%	-	0.2%	26.0
A26	Not in report	Not in report	Not in report	Not in report	Not in report	Not in report	Not in report	Not in report	Not in report	Not in report
2	100%	84%	78%	67%	430.2	100%	94%	89%	73%	517.4
A28	-	-	-	-	-	-	-	-	-	-
A18	100%	51%	14%	15%	42.6	100%	52%	17%	18%	46.4
A29	100%	117%	129%	123%	Neg.	100%	86%	63%	49%	225.0
A30	100%	95%	98%	89%	1713.6	100%	95%	64%	54%	248.3
A20	100%	70%	57%	60%	116.5	100%	57%	37%	26%	84.5
A21	-	-	-	-	-	100%	87%	74%	54%	265.1
A22	100%	70%	51%	55%	124.5	100%	52%	26%	10%	73.5
A23	100%	92%	85%	83%	892.2	100%	79%	65%	45%	211.0
A24	100%	97%	89%	84%	916.4	100%	74%	61%	43%	201.9
A25	-	-	-	-	-	100%	94%	91%	65%	389.4
A26	100%	63%	33%	115%	75.9	100%	88%	36%	120%	80.3
A27	100%	115%	107%	105%	Neg.	100%	102%	95%	71%	449.7

Compound ID	Caco-2 Cells Permeability				
	-GF120918		+GF120918		Abs. Quotient
	$P_{app\ A-B}$	Recovery Rate	$P_{app\ A-B}$	Recovery Rate	
BASE STRUCTURE	0.064	87%	0.41	83%	0.84
	0.1	91%	0.5	96%	0.82
A26	-	-	-	-	-
2	-	-	-	-	-
A28	-	-	-	-	-
A18	0.04	48%	0.08	90%	0.54
A29	0.028	86%	0.17	76%	0.83
A30	-	-	-	-	-
A20	0.06	71%	0.5	90%	0.88
A21	0.099	84%	0.2	84%	0.50
A22	0.1	107%	0.7	104%	0.78
A23	0.1	91%	0.4	96%	0.78

Compound ID	Caco-2 Cells Permeability				
	-GF120918		+GF120918		Abs. Quotient
	$P_{app\ A-B}$	Recovery Rate	$P_{app\ A-B}$	Recovery Rate	
BASE STRUCTURE	0.064	87%	0.41	83%	0.84
	0.1	91%	0.5	96%	0.82
A24	0.1	72%	0.6	72%	0.88
A25	0.092	91%	0.4	83%	0.77
A26	0.044	94%	0.29	89%	0.85
A27	0.117	90%	0.39	94%	0.70

Compound ID	Rat PK (PO Route, 10 mg/kg Equiv., n=4)				
	Parent (BASE STRUCTURE)				
	"AUC_{0-24} (ng·h/mL)"	"AUC_{0-inf} (ng·h/mL)"	"Cmax (ng/mL)"	"Tmax (h)"	"Half-Life (h)"
BASE STRUCTURE	0.4 ± 0.2	-	0.9 ± 0.5	0.4 ± 0.5	-
A26	-	-	-	-	-
2	-	-	-	-	-
A28	-	-	-	-	-
A18	4.1 ± 3.8	6.8 ± 4	3.1 ± 2.5	0.2 ± 0.1	3.5 ± 2.6
A29	35.9 ± 27.6	48.6 ± 26.5	39.7 ±74.2	2.1 ± 4	15.7 ± 14.3
A30					
A20	0.8 ±1	1.61	1.7 ± 1.3	0.3 ± 0	0.17
A21	7.4 ± 0.9	47.8 ± 1	0.6 ± 0.1	0.9 ± 0.8	81.7 ± 5.7
A22	25.1 ± 4.4	91.3	1.4 ± 0.1	15 ± 10.5	58.8
A23	5.1 ± 1.4	12.4 ± 8.8	5.5 ± 6.2	0.2 ± 0.2	22.1 ± 17.1
A24	0.4 ± 0.2	1.1 ± 0.9	0.3 ± 0.1	0.4 ± 0.4	5 ± 5.1
A25	10.9 ± 4	31 ± 26.1	3.1 ± 3.5	0.3 ± 0.2	42.5 ± 49.9
A26	14.1 ± 6.3	28 ± 12	6.8 ± 6.6	1.1 ± 1.9	8.9 ± 0.5
A27	29.6 ± 35	9.0	2.8 ± 2.7	18.1 ± 11.8	13.4

Compound ID	Rat PK (PO Route, 10 mg/kg Equiv., n=4)				
	Prodrug				
	"AUC0-24 (ng·h/mL)"	"AUC0-inf (ng·h/mL)"	"Cmax (ng/mL)"	"Tmax (h)"	"Half-Life (h)"
BASE STRUCTURE					
A26	-	-	-	-	-
2	-	-	-	-	-
A28	-	-	-	-	-
A18	4.9 ± 2.6	-	3.8 ± 0.1	1.5 ± 0.7	-
A29	0	0	0	0	0
A30					
A20	0	0	0	0	0
A21	2.8 ± 1.9	6.46	1.6 ± 0.5	0.8 ± 0.4	1.32
A22	0	0	0	0	0
A23	0	0	0	0	0
A24	0.2 ± 0.1	-	0.5 ± 0.1	0.9 ± 0.3	-
A25	91.2 ± 3.8	3709.5	4.2 ± 0.1	9.3 ± 10.2	667.8
A26	0	0	0	0	0
A27	0	0	0	0	0

Animal 2	Animal 3	Animal 4	Average	Std. Dev	Combined
0.25	1		0.4433333	0.4895236	0.4 ± 0.5
1.54	0.551		0.9266667	0.5356252	0.9 ± 0.5
0	0		0	0	0 ± 0
0.6	1		0.819255	0.2027616	0.8 ± 0.2
0.517525	0.206625		0.4468367	0.2138184	0.4 ± 0.2

Animal 2	Animal 3	Animal 4	Average	Std. Dev	Combined

' 0-t/0-inf_obs								
/IC 0-inf_obs	ng/ml*h^2							
[0-inf_obs	h							
' _obs	(mg/kg)/(ng/ml)							
_obs	(mg/kg)/(ng/ml)/h							
ed as A18 (10 mg/kg equivalent of : Structure) meters for nt (Base cture) wing dosing of								
meter	Unit	Animal 1	Animal 2	Animal 3	Animal 4	Average	Std. Dev.	Combined
bda_z	1/h	0.3302821	1.5184227	0.123071	0.1201033	0.5229698	0.6708888	0.5 ± 0.7
	h	2.0986519	0.4564916	5.6320917	5.7712605	3.4896239	2.641384	3.5 ± 2.6
ax	h	0.25	0.08	0.08	0.25	0.165	0.0981495	0.2 ± 0.1
ax	ng/ml	1.3	3.37	1.27	6.62	3.14	2.5196428	3.1 ± 2.5
	h	0	0	0	0	0	0	0 ± 0
t_obs/Cmax		0.4638462	0.0836795	0.7102362	0.026284	0.3210115	0.3240825	0.3 ± 0.3
' 0-t	ng/ml*h	1.663875	3.218	1.90263	9.77745	4.1404888	3.8195962	4.1 ± 3.8
' 0-inf_obs	ng/ml*h	3.4895869	3.403719	9.2317325	11.226203	6.8378105	3.999685	6.8 ± 4
' 0-t/0-inf_obs		0.4768114	0.9454364	0.2060967	0.8709489	0.6248234	0.3467035	0.6 ± 0.3
MC 0-inf_obs	ng/ml*h^2	10.678131	2.5861986	76.049072	97.479622	46.698256	47.200073	46.7 ± 47.2
[0-inf_obs	h	3.0599986	0.7598155	8.2377898	8.6832225	5.1852066	3.9010672	5.2 ± 3.9
'_obs	(mg/kg)/(ng/ml)	8.6764271	1.9348781	8.8015882	7.4167273	6.7074052	3.2425711	6.7 ± 3.2
'_obs	(mg/kg)/(ng/ml)/h	2.8656687	2.9379628	1.0832203	0.8907731	1.9444062	1.1087024	1.9 ± 1.1
ı for Prodrug								
meter	Unit	Animal 1	Animal 2	Animal 3	Animal 4	Average	Std. Dev.	Combined
bda_z	1/h	-	-					

	BASE STRUCTURE (20 mg/kg)		
	Dosed as Parent (Base Structure)		
	Parameter	Unit	Animal 1
5	Lambda_z	1/h	
6	t1/2	h	
7	Tmax	h	0.08
8	Cmax	ng/ml	0.685
9	Tlag	h	0
10	Clast_obs/Cmax		0.8577649
11	AUC 0-t	ng/ml*h	0.61636
12	AUC 0-inf_obs	ng/ml*h	
13	AUC 0-t/0-inf_obs		
14	AUMC 0-inf_obs	ng/ml*h^2	
15	MRT 0-inf_obs	h	
16	Vz/F_obs	(mg/kg)/(ng/ml)	
17	Cl/F_obs	(mg/kg)/(ng/ml)/h	
	Prodrug		
	Parameter	Unit	Animal 1
21	Lambda_z	1/h	
22	t1/2	h	
23	Tmax	h	
24	Cmax	ng/ml	
25	Tlag	h	
26	Clast_obs/Cmax		
27	AUC 0-t	ng/ml*h	
28	AUC 0-inf_obs	ng/ml*h	

22.480048	20.6 ± 22.5
6.8587039	6.6 ± 6.9
0.1007951	0.2 ± 0.1
Std. Dev.	Combined
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
Std. Dev.	Combined
	4.021864
	0.172345
0	0.3 ± 0

55	t1/2	h	-	-					
56	Tmax	h	2	1			1.5	0.7071068	1.5 ± 0.7
57	Cmax	ng/ml	3.84	3.68			3.76	0.1131371	3.8 ± 0.1
58	Tlag	h	0	0			0	0	0 ± 0
59	Clast_obs/Cmax		1	1			1	0	1 ± 0
60	AUC 0-t	ng/ml*h	6.8	3.09875			4.949375	2.617179	4.9 ± 2.6
61	AUC 0-inf_obs	ng/ml*h	-	-					
62	AUC 0-t/0-inf_obs		-	-					
63	AUMC 0-inf_obs	ng/ml*h^2	-	-					
64	MRT 0-inf_obs	h	-	-					
65	Vz/F_obs	(mg/kg)/(ng/ml)	-	-					
66	Cl/F_obs	(mg/kg)/(ng/ml)/h	-	-					
	Sample dosed as 2 (10 mg/kg, equivalent of Base Structure) Parameters for Parent (Base Structure) following dosing of **2**								
	Parameter	Unit	Animal 1	Animal 2	Animal 3	Animal 4	Average	Std. Dev.	Combined
71	Lambda_z	1/h	0.1912491	0.0584922	0.0219906	-	0.0905773	0.0890741	0.1 ± 0.1
72	t1/2	h	3.6243165	11.85024	31.520108	-	15.664888	14.333787	15.7 ± 14.3
73	Tmax	h	0.08	0.08	0.08	8	2.06	3.96	2.1 ± 4
74	Cmax	ng/ml	151	4.73	1.36	1.65	39.685	74.225665	39.7 ± 74.2
75	Tlag	h	0	0	0	0	0	0	0 ± 0
76	Clast_obs/Cmax		0.0042848	0.0501057	0.3117647	0.3369697	0.1757812	0.1728955	0.2 ± 0.2
77	AUC 0-t	ng/ml*h	75.7995	30.4074	12.9897	24.48944	35.92151	27.551283	35.9 ± 27.6
78	AUC 0-inf_obs	ng/ml*h	79.182523	34.459219	32.270635	-	48.637459	26.475426	48.6 ± 26.5
79	AUC 0-t/0-inf_obs		0.9572756	0.882417	0.4025238	-	0.7474055	0.3010124	0.7 ± 0.3
80	AUMC 0-inf_obs	ng/ml*h^2	284.76414	414.61785	1486.3623	-	728.58144	659.46145	728.6 ± 659.5

29	AUC
30	AUN
31	MRT
32	Vz/F
33	Cl/F
	Dose
	Base
	Para
	Pare
	Struc
	follo
	A18
	Para
38	Lam
39	t1/2
40	Tma
41	Cma
42	Tlag
43	Clas
44	AUC
45	AUC
46	AUC
47	AUN
48	MRT
49	Vz/F
50	Cl/F
	Data
	A18
	Para
54	Lam

		2.66	1.7125	1.3399674	1.7 ± 1.3
		0	0	0	0 ± 0
		0.0582707	0.5291353	0.6659032	0.5 ± 0.7
		1.5726	0.8309375	1.0488692	0.8 ± 1
		1.6111393	1.6111393		1.611139
		0.9760794	0.9760794		0.976079
		0.6699418	0.6699418		0.669942
		0.4158187	0.4158187		0.415819
		1.5432616	1.5432616		1.543262
		6.2067878	6.2067878		6.2067878
al 2	Animal 3	Animal 4	Average	Std. Dev.	Combined
			0		0
			0		0
			0		0
			0		0
			0		0
			0		0
			0		0
			0		0
			0		0
			0		0
			0		0
			0		0

81	MRT 0-inf_obs	h	3.5963005	12.032131	46.059284	-	20.562572
82	Vz/F_obs	(mg/kg)/(ng/ml)	0.6603457	4.9613088	14.091419	-	6.5710244
83	Cl/F_obs	(mg/kg)/(ng/ml)/h	0.1262905	0.2901981	0.3098792	-	0.2421226
	Data for Prodrug 2						
	Parameter	Unit	Animal 1	Animal 2	Animal 3	Animal 4	Average
87	Lambda_z	1/h	0				0
88	t1/2	h	0				0
89	Tmax	h	0				0
90	Cmax	ng/ml	0				0
91	Tlag	h	0				0
92	Clast_obs/Cmax		0				0
93	AUC 0-t	ng/ml*h	0				0
94	AUC 0-inf_obs	ng/ml*h	0				0
95	AUC 0-t/0-inf_obs		0				0
96	AUMC 0-inf_obs	ng/ml*h^2	0				0
97	MRT 0-inf_obs	h	0				0
98	Vz/F_obs	(mg/kg)/(ng/ml)	0				0
99	Cl/F_obs	(mg/kg)/(ng/ml)/h	0				0
	Dosed as A20 (10 mg/kg., equivalent of Base Structure) Parameters for Parent (Base Structure) following dosing of **A20**						
	Parameter	Unit	Animal 1	Animal 2	Animal 3	Animal 4	Average
104	Lambda_z	1/h	-			4.0218636	4.0218636
105	t1/2	h	-			0.1723448	0.1723448
106	Tmax	h	0.25			0.25	0.25

ng of								
	Unit	Animal 1	Animal 2	Animal 3	Animal 4	Average	Std. Dev.	Combined
	1/h	0.0080896	0.0089246	-	-	0.0085071	0.0005904	0 ± 0
	h	85.683945	77.667256	-	-	81.6756	5.6686552	81.7 ± 5.7
	h	0.25	0.25	1	2	0.875	0.8291562	0.9 ± 0.8
	ng/ml	0.744	0.604	0.555	0.577	0.62	0.0850608	0.6 ± 0.1
	h	0	0	0	0	0	0	0 ± 0
ax		0.4475806	0.5745033	0.8630631	0.9341421	0.7048223	0.2315052	0.7 ± 0.2
	ng/ml*h	7.284615	8.222465	6.27042	8.02234	7.44996	0.8837489	7.4 ± 0.9
s	ng/ml*h	48.448677	47.103872	-	-	47.776275	0.9509207	47.8 ± 1
_obs		0.1503574	0.1745603	-	-	0.1624588	0.017114	0.2 ± 0
obs	ng/ml*h^2	6167.4557	5387.4053	-	-	5777.4305	551.5789	5777.4 ± 551.6
s	h	127.29874	114.37288	-	-	120.83581	9.139968	120.8 ± 9.1
	(mg/kg)/(ng/ml)	25.514794	23.787888	-	-	24.651341	1.2211068	24.7 ± 1.2
	(mg/kg)/(ng/ml)/h	0.206404	0.2122968	-	-	0.2093504	0.0041668	0.2 ± 0
ug								
	Unit	Animal 1	Animal 2	Animal 3	Animal 4	Average	Std. Dev.	Combined
	1/h	0.5256781	-	-	-	0.5256781		0.525678
	h	1.3185771	-	-	-	1.3185771		1.318577
	h	0.25	1	1	1	0.8125	0.375	0.8 ± 0.4
	ng/ml	2.18	1.89	1.01	1.38	1.615	0.5215681	1.6 ± 0.5
	h	0	0	0	0	0	0	0 ± 0
ax		0.2027523	0.6296296	0.6049505	0.5862319	0.5058911	0.2028725	0.5 ± 0.2
	ng/ml*h	5.61855	2.381305	1.497735	1.885	2.8456475	1.8836413	2.8 ± 1.9
s	ng/ml*h	6.4593687	-	-	-	6.4593687		6.459369
_obs		0.8698296	-	-	-	0.8698296		0.86983
obs	ng/ml*h^2	13.688243	-	-	-	13.688243		13.68824

107	Cmax	ng/ml	0.765	
108	Tlag	h	0	
109	Clast_obs/Cmax		1	
110	AUC 0-t	ng/ml*h	0.089275	
111	AUC 0-inf_obs	ng/ml*h	-	
112	AUC 0-t/0-inf_obs		-	
113	AUMC 0-inf_obs	ng/ml*h^2	-	
114	MRT 0-inf_obs	h	-	
115	Vz/F_obs	(mg/kg)/(ng/ml)	-	
116	Cl/F_obs	(mg/kg)/(ng/ml)/h	-	
	Data for Prodrug **A20**			
	Parameter	Unit	Animal 1	Anim
120	Lambda_z	1/h	0	
121	t1/2	h	0	
122	Tmax	h	0	
123	Cmax	ng/ml	0	
124	Tlag	h	0	
125	Clast_obs/Cmax		0	
126	AUC 0-t	ng/ml*h	0	
127	AUC 0-inf_obs	ng/ml*h	0	
128	AUC 0-t/0-inf_obs		0	
129	AUMC 0-inf_obs	ng/ml*h^2	0	
130	MRT 0-inf_obs	h	0	
131	Vz/F_obs	(mg/kg)/(ng/ml)	0	
132	Cl/F_obs	(mg/kg)/(ng/ml)/h	0	
	Dosed as A21 (10 mg/kg, equivalent of Base Structure)			
	Parent (Base			

	0
	0
	0
	0
	0
	0
	0
	0
	0
	0
	Combined
32	0 ± 0
36	22.1 ± 17.1
73	0.2 ± 0.2
88	5.5 ± 6.2
0	0 ± 0
34	0.1 ± 0.1
86	5.1 ± 1.4
05	12.4 ± 8.8
81	0.5 ± 0.2
63	609 ± 848.2
89	35.2 ± 27.3
99	26.2 ± 8.2

163	MRT 0-inf_obs	h	2.1191302	-	-	-	2.1191302		2.11913
164	Vz/F_obs	(mg/kg)/(ng/ml)	2.9450319	-	-	-	2.9450319		2.945032
165	Cl/F_obs	(mg/kg)/(ng/ml)/h	1.5481389	-	-	-	1.5481389		1.5481389
	Dosed as A22 (10 mg/kg, equivalent of Base Structure) Parameters for Parent (Base Structure) following dosing of **A22**								
	Parameter	Unit	Animal 1	Animal 2	Animal 3	Animal 4	Average	Std. Dev.	Combined
170	Lambda_z	1/h	-	0.0117847	-	-	0.0117847		0.011785
171	t1/2	h	-	58.817694	-	-	58.817694		58.81769
172	Tmax	h	24	4	24	8	15	10.519823	15 ± 10.5
173	Cmax	ng/ml	1.51	1.32	1.35	1.55	1.4325	0.1144188	1.4 ± 0.1
174	Tlag	h	0	0	0	0	0	0	0 ± 0
175	Clast_obs/Cmax		1	0.6477273	1	0.4251613	0.7682221	0.2826374	0.8 ± 0.3
176	AUC 0-t	ng/ml*h	28.915155	18.755375	26.459875	26.3888	25.129801	4.408945	25.1 ± 4.4
177	AUC 0-inf_obs	ng/ml*h	-	91.307251	-	-	91.307251		91.30725
178	AUC 0-t/0-inf_obs		-	0.2054095	-	-	0.2054095		0.205409
179	AUMC 0-inf_obs	ng/ml*h^2	-	8134.3242	-	-	8134.3242		8134.324
180	MRT 0-inf_obs	h	-	89.087384	-	-	89.087384		89.08738
181	Vz/F_obs	(mg/kg)/(ng/ml)	-	9.2934564	-	-	9.2934564		9.293456
182	Cl/F_obs	(mg/kg)/(ng/ml)/h	-	0.1095203	-	-	0.1095203		0.1095203
	Data for Prodrug **A22**								
	Parameter	Unit	Animal 1	Animal 2	Animal 3	Animal 4	Average	Std. Dev.	Combined
186	Lambda_z	1/h	0				0		0
187	t1/2	h	0				0		0
188	Tmax	h	0				0		0

	Structure) following dosi **A21**
	Parameter
137	Lambda_z
138	t1/2
139	Tmax
140	Cmax
141	Tlag
142	Clast_obs/Cma
143	AUC 0-t
144	AUC 0-inf_ob
145	AUC 0-t/0-inf
146	AUMC 0-inf_
147	MRT 0-inf_ob
148	Vz/F_obs
149	Cl/F_obs
	Data for Prodr **A21**
	Parameter
153	Lambda_z
154	t1/2
155	Tmax
156	Cmax
157	Tlag
158	Clast_obs/Cma
159	AUC 0-t
160	AUC 0-inf_ob
161	AUC 0-t/0-inf
162	AUMC 0-inf_

0.8038705	0.4028208	1.1136077	0.6115504	1.1 ± 0.6

nimal 3	Animal 4	Average	Std. Dev.	Combined
		0		0
		0		0
		0		0
		0		0
		0		0
		0		0
		0		0
		0		0
		0		0
		0		0
		0		0
		0		0
		0		0

nimal 3	Animal 4	Average	Std. Dev.	Combined
0.6866692	0.0645992	0.3243095	0.3234895	0.3 ± 0.3
1.009434	10.729971	4.9554926	5.1117072	5 ± 5.1
0.08	0.08	0.415	0.4373786	0.4 ± 0.4
0.217	0.218	0.26825	0.0641632	0.3 ± 0.1
0	0	0	0	0 ± 0

189	Cmax	ng/ml	0				0	
190	Tlag	h	0				0	
191	Clast_obs/Cmax		0				0	
192	AUC 0-t	ng/ml*h	0				0	
193	AUC 0-inf_obs	ng/ml*h	0				0	
194	AUC 0-t/0-inf_obs		0				0	
195	AUMC 0-inf_obs	ng/ml*h^2	0				0	
196	MRT 0-inf_obs	h	0				0	
197	Vz/F_obs	(mg/kg)/(ng/ml)	0				0	
198	Cl/F_obs	(mg/kg)/(ng/ml)/h	0				0	
	Dosed as A23 (10 mg/kg, equivalent of Base Structure) Parameters for Parent (Base Structure) following dosing of **A23**							
	Parameter	Unit	Animal 1	Animal 2	Animal 3	Animal 4	Average	Std. Dev.
203	Lambda_z	1/h	0.0435952	0.0738764	0.0440852	0.014645	0.0440505	0.02418
204	t1/2	h	15.899634	9.3825196	15.722913	47.329796	22.083715	17.1015
205	Tmax	h	0.08	0.5	0.08	0.25	0.2275	0.19855
206	Cmax	ng/ml	2.51	3.48	14.6	1.28	5.4675	6.15452
207	Tlag	h	0	0	0	0	0	
208	Clast_obs/Cmax		0.0454183	0.0321839	0.0165753	0.2234375	0.0794038	0.09674
209	AUC 0-t	ng/ml*h	3.56898	4.61648	6.95044	5.29615	5.1080125	1.41893
210	AUC 0-inf_obs	ng/ml*h	6.1839488	6.1325248	12.439815	24.824934	12.395306	8.79964
211	AUC 0-t/0-inf_obs		0.5771361	0.7527862	0.5587253	0.2133399	0.5254969	0.22573
212	AUMC 0-inf_obs	ng/ml*h^2	156.19016	90.340465	316.30901	1873.3254	609.04125	848.180
213	MRT 0-inf_obs	h	25.257349	14.731366	25.427147	75.461445	35.219327	27.2904
214	Vz/F_obs	(mg/kg)/(ng/ml)	37.093326	22.072662	18.23449	27.505596	26.226518	8.18230

	0.3019943	0.158885	0.4046083	0.4284404	0.323482	0.1226806	0.3 ± 0.1
/ml*h	0.530985	0.35458	0.12241	0.616765	0.406185	0.2184112	0.4 ± 0.2
/ml*h	1.0091947	-	0.2502736	2.0626041	1.1073575	0.9101442	1.1 ± 0.9
	0.5261472	-	0.4891047	0.2990225	0.4380915	0.1218531	0.4 ± 0.1
/ml*h^2	4.9662575	-	0.3669321	36.618365	13.983852	19.736498	14 ± 19.7
	4.9210102	-	1.4661237	17.753463	8.0468655	8.5818169	8 ± 8.6
g/kg)/(ng/ml)	44.703091	-	58.188531	75.051126	59.31425	15.205303	59.3 ± 15.2
g/kg)/(ng/ml)/h	9.9088907	-	39.95627	4.8482401	18.2378	18.978184	18.2 ± 19
nit	Animal 1	Animal 2	Animal 3	Animal 4	Average	Std. Dev.	Combined
h	-	-	-	-			
	-	-	-	-			
	1	1	1	0.5	0.875	0.25	0.9 ± 0.3
/ml	0.503	0.678	0.513	0.503	0.54925	0.0859627	0.5 ± 0.1
	0	0	0	0	0	0	0 ± 0
	1	1	1	1	1	0	1 ± 0
/ml*h	0.188625	0.25425	0.192375	0.062875	0.1745313	0.0802895	0.2 ± 0.1
/ml*h	-	-	-	-			
	-	-	-	-			
/ml*h^2	-	-	-	-			
	-	-	-	-			
g/kg)/(ng/ml)	-	-	-	-			
g/kg)/(ng/ml)/h	-	-	-	-			
, equivalent of							

215	Cl/F_obs	(mg/kg)/(ng/ml)/h	1.6170897	1.6306497	
	Data for Prodrug **A23**				
	Parameter	Unit	Animal 1	Animal 2	A
219	Lambda_z	1/h	0		
220	t1/2	h	0		
221	Tmax	h	0		
222	Cmax	ng/ml	0		
223	Tlag	h	0		
224	Clast_obs/Cmax		0		
225	AUC 0-t	ng/ml*h	0		
226	AUC 0-inf_obs	ng/ml*h	0		
227	AUC 0-t/0-inf_obs		0		
228	AUMC 0-inf_obs	ng/ml*h^2	0		
229	MRT 0-inf_obs	h	0		
230	Vz/F_obs	(mg/kg)/(ng/ml)	0		
231	Cl/F_obs	(mg/kg)/(ng/ml)/h	0		
	Dosed as A24 (10 mg/kg, equivalent of Base Structure) Parameters for Parent (Base Structure) following dosing of **A24**				
	Parameter	Unit	Animal 1	Animal 2	A
236	Lambda_z	1/h	0.2216601	-	
237	t1/2	h	3.1270727	-	
238	Tmax	h	0.5	1	
239	Cmax	ng/ml	0.351	0.287	
240	Tlag	h	0	0	

	A25								
	Parameter	Unit	Animal 1	Animal 2	Animal 3	Animal 4	Average	Std. Dev.	Combined
269	Lambda_z	1/h	0.1243062	0.0152996	0.0061827	0.0980479	0.0609591	0.0590866	0.1 ± 0.1
270	t1/2	h	5.5761279	45.304992	112.11041	7.0694775	42.515252	49.907149	42.5 ± 49.9
271	Tmax	h	0.25	0.08	0.5	0.25	0.27	0.1730125	0.3 ± 0.2
272	Cmax	ng/ml	8.15	0.862	0.699	2.67	3.09525	3.4861992	3.1 ± 3.5
273	Tlag	h	0	0	0	0	0	0	0 ± 0
274	Clast_obs/Cmax		0.0342331	0.3422274	0.5035765	0.0700375	0.2375186	0.2244443	0.2 ± 0.2
275	AUC 0-t	ng/ml*h	16.15725	7.403555	11.877475	8.2102	10.91212	4.0022368	10.9 ± 4
276	AUC 0-inf_obs	ng/ml*h	18.401708	26.685135	68.810354	10.117432	31.003657	26.096229	31 ± 26.1
277	AUC 0-t/0-inf_obs		0.8780299	0.2774412	0.1726117	0.8114905	0.5348933	0.3613762	0.5 ± 0.4
278	AUMC 0-inf_obs	ng/ml*h^2	158.76057	1811.7945	10702.647	123.73178	3199.2334	5063.9044	3199.2 ± 5063.9
279	MRT 0-inf_obs	h	8.6274912	67.895273	155.53832	12.229564	61.072662	68.572231	61.1 ± 68.6
280	Vz/F_obs	(mg/kg)/(ng/ml)	4.3716877	24.49352	23.505348	10.08072	15.612819	9.9687179	15.6 ± 10
281	Cl/F_obs	(mg/kg)/(ng/ml)/h	0.5434278	0.3747405	0.145327	0.9883931	0.5129721	0.3564752	0.5 ± 0.4
	Data for Prodrug **A25**								
	Parameter	Unit	Animal 1	Animal 2	Animal 3	Animal 4	Average	Std. Dev.	Combined
285	Lambda_z	1/h	0.001038	-	-	-	0.001038		0.001038
286	t1/2	h	667.7753	-	-	-	667.7753		667.7753
287	Tmax	h	1	24	4	8	9.25	10.242884	9.3 ± 10.2
288	Cmax	ng/ml	4.23	4.21	4	4.28	4.18	0.1235584	4.2 ± 0.1
289	Tlag	h	0	0	0	0	0	0	0 ± 0
290	Clast_obs/Cmax		0.8888889	1	0.9625	0.885514	0.9342257	0.0564327	0.9 ± 0.1
291	AUC 0-t	ng/ml*h	87.1052	93.73835	88.82275	95.084	91.187575	3.8273909	91.2 ± 3.8
292	AUC 0-inf_obs	ng/ml*h	3709.4746	-	-	-	3709.4746		3709.475
293	AUC 0-t/0-inf_obs		0.0234818	-	-	-	0.0234818		0.023482
294	AUMC 0-inf_obs	ng/ml*h^2	3577773.1	-	-	-	3577773.1		3577773
295	MRT 0-inf_obs	h	964.49592	-	-	-	964.49592		964.4959

241	Clast_obs/Cmax	
242	AUC 0-t	ng
243	AUC 0-inf_obs	ng
244	AUC 0-t/0-inf_obs	
245	AUMC 0-inf_obs	ng
246	MRT 0-inf_obs	h
247	Vz/F_obs	(m
248	Cl/F_obs	(m
	Data for Prodrug **A24**	
	Parameter	Un
252	Lambda_z	1/h
253	t1/2	h
254	Tmax	h
255	Cmax	ng
256	Tlag	h
257	Clast_obs/Cmax	
258	AUC 0-t	ng
259	AUC 0-inf_obs	ng
260	AUC 0-t/0-inf_obs	
261	AUMC 0-inf_obs	ng
262	MRT 0-inf_obs	h
263	Vz/F_obs	(m
264	Cl/F_obs	(m
	Dosed as A25 (10 mg/kg Base Structure) Parameters for Parent (Base Structure) following dosing of	

	0		0
	0		0
	0		0
	0		0
	0		0
	0		0
	0		0
	0		0
	0		0

Animal 4	Average	Std. Dev.	Combined
-	0.0517028		0.051703
-	13.406364		13.40636
24	18.125	11.75	18.1 ± 11.8
6.68	2.77	2.6701186	2.8 ± 2.7
0	0	0	0 ± 0
1	0.7859677	0.4280645	0.8 ± 0.4
80.391315	29.552726	34.964384	29.6 ± 35
-	8.9995036		8.999504
-	0.5207393		0.520739
-	238.35106		238.3511
-	26.484912		26.48491
-	21.491512		21.49151
-	1.1111724		1.1111724

296	Vz/F_obs	(mg/kg)/(ng/ml)	2.5971228	-	-	-	2.5971228		2.5
297	Cl/F_obs	(mg/kg)/(ng/ml)/h	0.0026958	-	-	-	0.0026958		0.00
	Dosed as A26 (10 mg/kg, equivalent of Base Structure) Parameters for Parent (Base Structure) following dosing of **A26**								
	Parameter	Unit	Animal 1	Animal 2	Animal 3	Animal 4	Average	Std. Dev.	Combi
302	Lambda_z	1/h	0.074747	0.0804088	-	-	0.0775779	0.0040035	0.1 ± 0
303	t1/2	h	9.2732385	8.6202849	-	-	8.9467617	0.4617079	8.9 ± 0
304	Tmax	h	0.25	0.08	4	0.08	1.1025	1.9333283	1.1 ± 1
305	Cmax	ng/ml	15.5	8.31	1.5	1.84	6.7875	6.5995221	6.8 ± 6
306	Tlag	h	0	0	0	0	0	0	0 ± 0
307	Clast_obs/Cmax		0.0658065	0.07858	0.64	0.3625	0.2867216	0.2724423	0.3 ± 0
308	AUC 0-t	ng/ml*h	22.797	11.33965	14.321275	7.97054	14.107116	6.347608	14.1 ±
309	AUC 0-inf_obs	ng/ml*h	36.443024	19.460647	-	-	27.951836	12.008354	28 ± 1
310	AUC 0-t/0-inf_obs		0.6255518	0.5826965	-	-	0.6041241	0.0303033	0.6 ± 0
311	AUMC 0-inf_obs	ng/ml*h^2	724.50431	430.36668	-	-	577.43549	207.98671	577.4 ±
312	MRT 0-inf_obs	h	19.880466	22.114716	-	-	20.997591	1.5798534	21 ± 1
313	Vz/F_obs	(mg/kg)/(ng/ml)	3.6710606	6.3905596	-	-	5.0308101	1.9229761	5 ± 1.9
314	Cl/F_obs	(mg/kg)/(ng/ml)/h	0.2744009	0.5138575	-	-	0.3941292	0.1693214	0.4 ± 0
	Data for Prodrug **A26**								
	Parameter	Unit	Animal 1	Animal 2	Animal 3	Animal 4	Average	Std. Dev.	Combi
318	Lambda_z	1/h	0				0		
319	t1/2	h	0				0		
320	Tmax	h	0				0		
321	Cmax	ng/ml	0				0		

	Animal 1	Animal 2	Animal 3	Animal 4	Average	Std. Dev.	Combined
	0				0		0
	0				0		0
	0				0		0
	0				0		0
	0				0		0
	0				0		0
	0				0		0
	0				0		0
	0				0		0
	0				0		0
	0				0		0
	0				0		0
/h	0				0		0

322	Tlag	h	0		
323	Clast_obs/Cmax		0		
324	AUC 0-t	ng/ml*h	0		
325	AUC 0-inf_obs	ng/ml*h	0		
326	AUC 0-t/0-inf_obs		0		
327	AUMC 0-inf_obs	ng/ml*h^2	0		
328	MRT 0-inf_obs	h	0		
329	Vz/F_obs	(mg/kg)/(ng/ml)	0		
330	Cl/F_obs	(mg/kg)/(ng/ml)/h	0		
	Dosed as A27 (10 mg/kg, equivalent of Base Structure) Parameters for Parent (Base Structure) following dosing of **A27**				
	Parameter	Unit	Animal 1	Animal 2	Animal 3
335	Lambda_z	1/h	-	-	0.0517028
336	t1/2	h	-	-	13.406364
337	Tmax	h	24	24	0.5
338	Cmax	ng/ml	0.72	2.13	1.55
339	Tlag	h	0	0	0
340	Clast_obs/Cmax		1	1	0.143871
341	AUC 0-t	ng/ml*h	8.586975	24.54622	4.686395
342	AUC 0-inf_obs	ng/ml*h	-	-	8.9995036
343	AUC 0-t/0-inf_obs		-	-	0.5207393
344	AUMC 0-inf_obs	ng/ml*h^2	-	-	238.35106
345	MRT 0-inf_obs	h	-	-	26.484912
346	Vz/F_obs	(mg/kg)/(ng/ml)	-	-	21.491512
347	Cl/F_obs	(mg/kg)/(ng/ml)/h	-	-	1.1111724

	Data for Prodrug A27 Parameter	Unit
351	Lambda_z	1/h
352	t1/2	h
353	Tmax	h
354	Cmax	ng/ml
355	Tlag	h
356	Clast_obs/Cmax	
357	AUC 0-t	ng/ml*h
358	AUC 0-inf_obs	ng/ml*h
359	AUC 0-t/0-inf_obs	
360	AUMC 0-inf_obs	ng/ml*h^2
361	MRT 0-inf_obs	h
362	Vz/F_obs	(mg/kg)/(ng/ml)
363	Cl/F_obs	(mg/kg)/(ng/ml)

[0251] While some embodiments have been illustrated and described, a person with ordinary skill in the art, after reading the foregoing specification, can effect changes, substitutions of equivalents and other types of alterations to the compounds of the present technology or salts, pharmaceutical compositions, derivatives, prodrugs, metabolites, tautomers or racemic mixtures thereof as set forth herein. The scope of the invention is defined by the appended claims.

[0252] The embodiments, illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising," "including," "containing," etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the claimed technology. Additionally, the phrase "consisting essentially of" will be understood to include those elements specifically recited and those additional elements that do not materially affect the basic and novel characteristics of the claimed technology. The phrase "consisting of" excludes any element not specified.

[0253] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the present technology. This includes the generic description of the present technology with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0254] Definitions that are contained in publications, patent applications, issued patents, and other documents (for example, journals, articles and/or textbooks) referred to in this specification are excluded to the extent that they contradict definitions in this disclosure.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US2013165392A1 [0001]
- EP1481965A1 [0204]
- EP2959918A1 [0204]

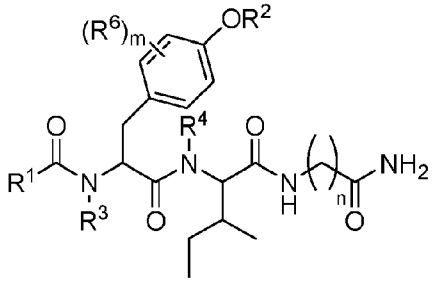
Non-patent literature cited in the description

- **T. W. GREENEP. G. M. WUTS**Protecting Groups in Organic SynthesisWiley19990000 [0129] [0137]
- Fieser and Fieser's Reagents for Organic SynthesisJohn Wiley, and Sons19910000vol. 1-15, [0131]
- Rodd's Chemistry of Carbon Compounds, vol. 1-5, [0131]
- SupplementalsElsevier Science Publishers19890000 [0131]
- Organic ReactionsJohn Wiley, and Sons19910000vol. 1-40, [0131] [0188]
- March's Advanced Organic ChemistryJohn Wiley, and Sons20010000 [0131]
- Larock's Comprehensive Organic TransformationsVCH Publishers Inc.19890000 [0131]
- **T.E. CREIGHTON**Proteins: Structures and Molecular PropertiesW.H. Freeman and Company19930000 [0188]
- **A.L. LEHNINGER**BiochemistryWorth Publishers, Inc. [0188]
- **SAMBROOK et al.**Molecular Cloning: A Laboratory Manual19890000 [0188]
- Methods In EnzymologyAcademic Press, Inc. [0188]
- Remington's Pharmaceutical SciencesMack Publishing Company19900000 [0188]
- **CAREYSUNDBERG**Advanced Organic ChemistryPlenum Press19920000vol. A,B, [0188]
- **LYDIE, H.**Tett. Letters, 2015, 6240-6243 [0199]
- **GOMES, P.**Tetrahedron, 2004, 5551-62 [0199]
- **DEMONG. D.**J. Med. Chem., 2014, vol. 57, 2601-10 [0199]
- **NISHIYAMA, B.**J. Labeled Compounds and Radiopharmaceuticals, 1994, vol. 34, 9831-37 [0204]
- **WALKER, T.E.**J. Org Chem., 1986, vol. 51, 81775-79 [0204]

- **SCHMIDT, E.W.**Tett. Letters, 2004, 3921-24 [0204]
- **SANTAGADA, V.**J. Med. Chem., 2006, vol. 49, 61882-90 [0204]
- **SEYEDSAYAMDOST, H.**J. Am. Chem. Soc, 2006, vol. 49, 61882-90 [0204]
- **HEBEL, D.**Tett. Letters, 1990, vol. 31, 5619-622 [0204]

Patentkrav

1. Forbindelse med formlen II:



(II)

hvor:

n er 1, 2, 3, 4, 5, 6, 7, 8 eller 9;

m er 0, 1, 2, 3 eller 4;

R^1 er valgt fra gruppen bestående af: C_1-C_{12}-alkyl, substitueret C_1-C_{12}-alkyl, C_1-C_{12}-alkenyl, substitueret C_1-C_{12}-alkenyl, C_1-C_{12}-alkynyl og substitueret C_1-C_{12}-alkynyl;

R^2 er valgt fra gruppen bestående af: hydrogen, $-PO(OY)_2$, $-PO(OH)_2$, -C(=O)-Y og -CO-U;

Y er $-Z-(CH_2)_q-W-R^b$, eller alternativt danner -C(=O)-Y en amidbinding via et nitrogenatom på Y, i hvilket tilfælde Y er valgt fra gruppen bestående af: glycin, sarcosin, N,N-dimethylglycin, alanin, valin, leucin, isoleucin, lysin, ornithin, arginin, serin og threonin;

q er 0-4;

Z og W er valgt uafhængigt fra gruppen bestående af: CH_2, O, S, NR^c og R^b, hvor Z og W eventuelt tages tilsammen for at danne en C_3-C_8-heterocycloalkyl eller en C_4-C_{10}-heteroaryl eller et bicyklisk ringsystem, i hvilket en af ringene er en C_4-C_{10}-heteroaryl;

R^c er valgt fra gruppen bestående af: hydrogen, C_1-C_4-alkyl og C_3-C_6-cycloalkyl;

R^b er valgt fra gruppen bestående af: hydrogen, C_1-C_{12}-alkyl, substitueret C_1-C_{12}-alkyl, C_3-C_8-cycloalkyl, substitueret C_3-C_8-cycloalkyl, C_3-C_8-heterocycloalkyl og substitueret C_3-C_8-heterocycloalkyl;

U er valgt fra gruppen bestående af: pyridin, 1,4-dihydropyridin, N-alkyl-1,4-dihydropyridin og C-imidazol, eller U er valgt blandt aryl, heteroaryl og heterocycloalkyl;

R^3 og R^4 tilsammen er bundet for at danne et spirocyklisk ringsystem;

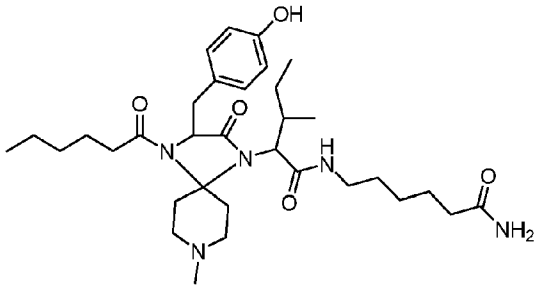
hver R^6 er valgt uafhængigt fra gruppen bestående af: hydrogen, deuterium, CH_3, F, ^{19}F og ^{18}F;

og hvor hver heterocyklisk ring og heteroarylring indeholder op til fire heteroatomer valgt fra gruppen bestående af: O, N og S;
med det forbehold, at når både Z og W er heteroatomer, kan værdien af q ikke være 1;
eller en tautomer og/eller et farmaceutisk acceptabelt salt deraf.

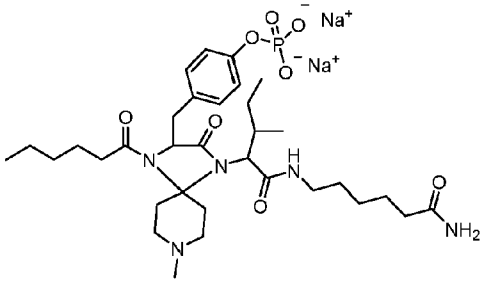
2. Forbindelse ifølge krav 1, hvor m er 0, R^1 er en C_1-C_{12}-alkyl, og R^3 og R^4 tilsammen danner et spirocyklisk ringsystem.

3. Forbindelse ifølge krav 1, hvor m er 1 eller 2, R^1 er en C_1-C_{12}-alkyl, R^3 og R^4 tilsammen danner et spirocyklisk ringsystem, og R^6 er valgt fra gruppen bestående af: hydrogen, deuterium, F, ^{19}F og ^{18}F.

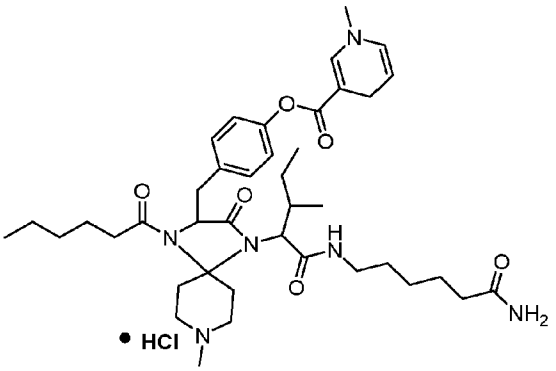
4. Forbindelse valgt blandt følgende strukturer:



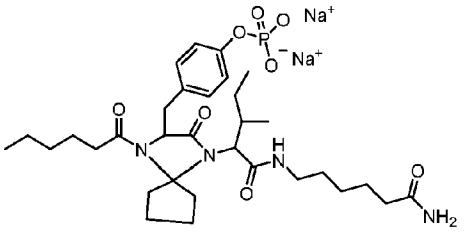
1 ,



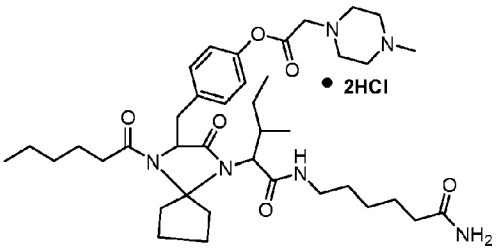
2 ,



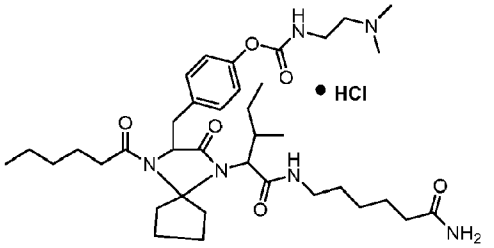
3



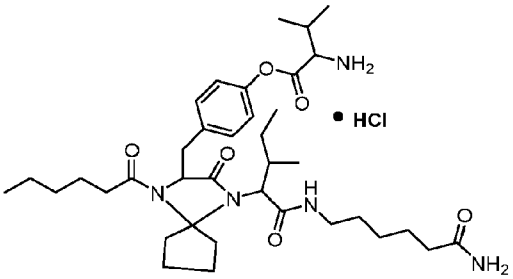
4



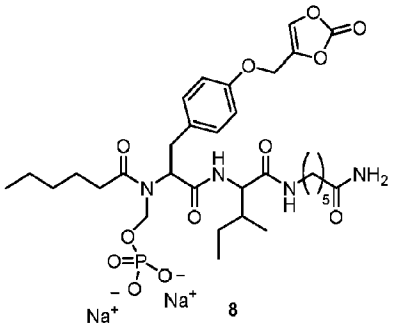
5



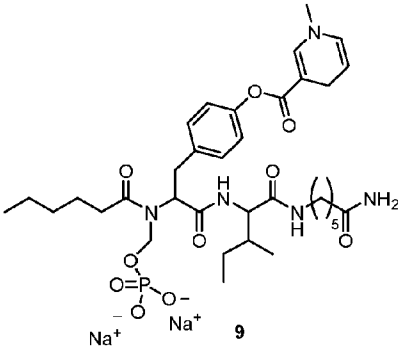
6



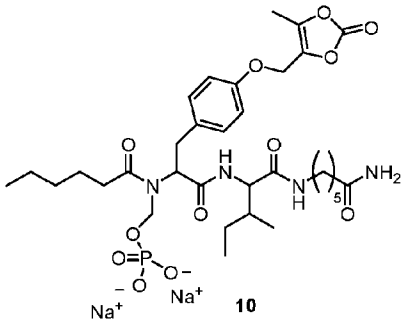
7



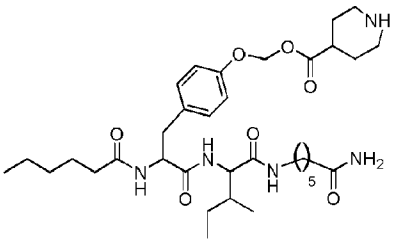
8



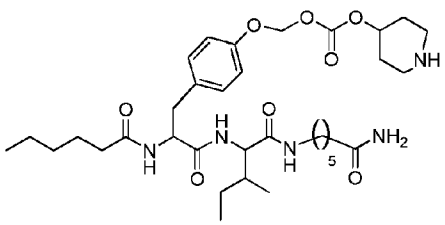
9



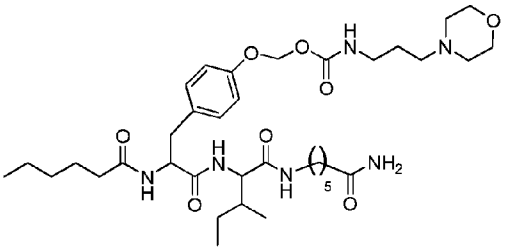
10



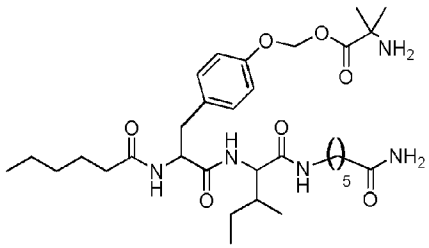
A17a ,



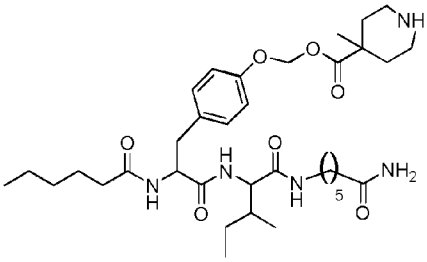
A17b ,



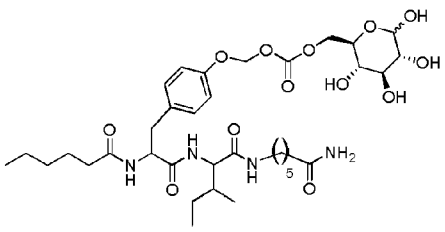
A17c ,



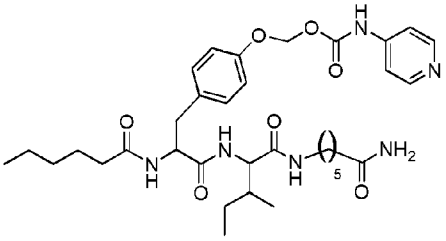
A17e ,



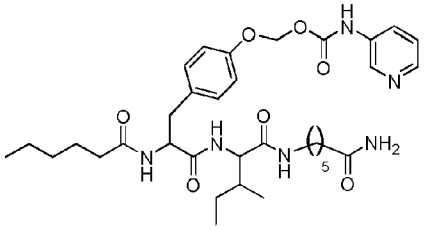
A17f ,



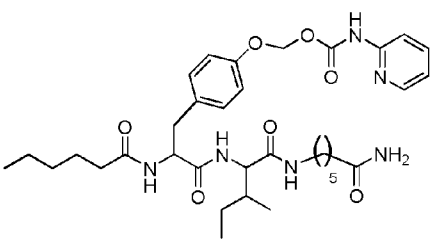
A17g ,



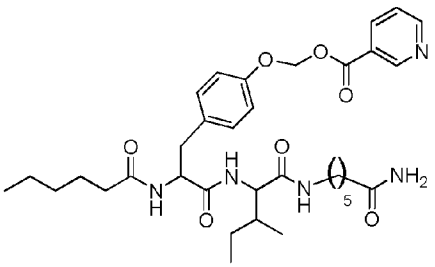
A17h ,



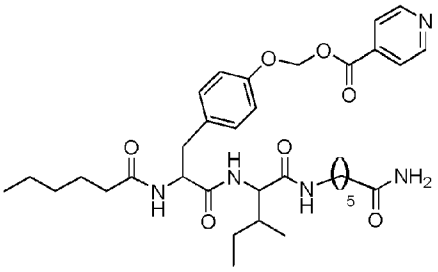
A17i ,



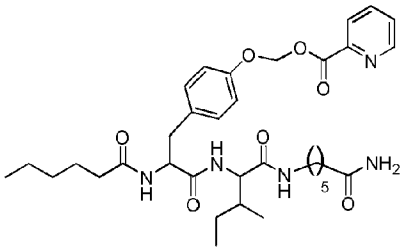
A17j ,



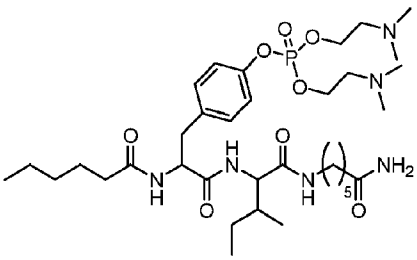
A17k ,



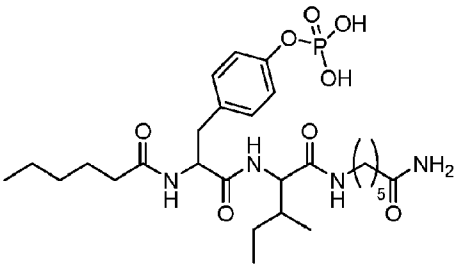
A17l



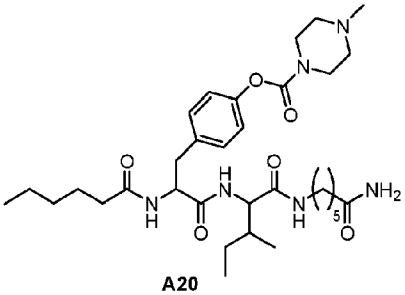
A17m



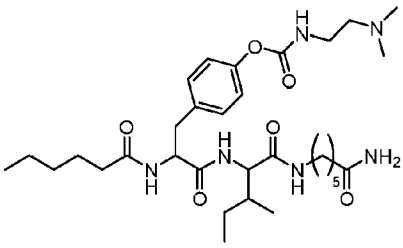
A18



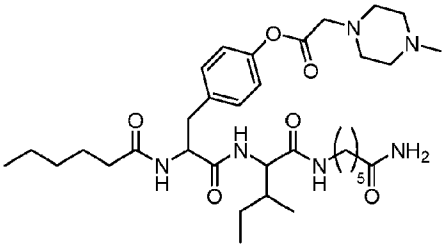
A19



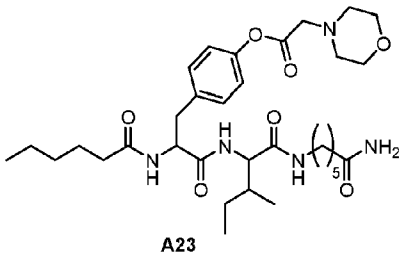
A20



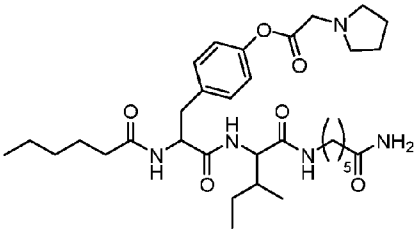
A21



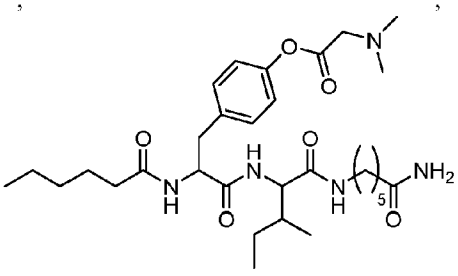
A22



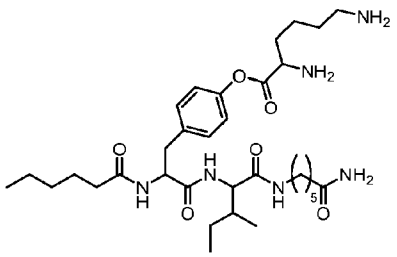
A23



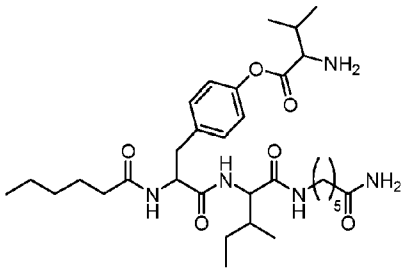
A24



A25

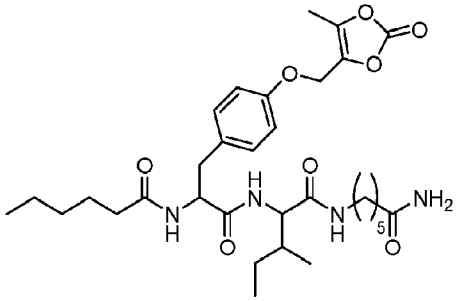


A26 ,



A27 ,

og



A28 .

eller en tautomer og/eller et farmaceutisk acceptabelt salt deraf.

5. Sammensætning, der omfatter mindst en forbindelse som beskrevet i et hvilket som helst af kravene 1-4 eller tautomerer, stereoisomerer, salte, solvater eller hydrater deraf.

6. Farmaceutisk sammensætning, der omfatter mindst en forbindelse som beskrevet i et hvilket som helst af kravene 1-4 eller tautomerer, stereoisomerer, salte, solvater eller hydrater deraf og et farmaceutisk acceptabelt bærestof eller hjælpestof.

7. Farmaceutisk sammensætning ifølge krav 6, der endvidere omfatter N-hexanoyl-L-tyrosin-L-isoleucin-(6)-aminohexanamid ("N-hexanoic-L-tyrosine-L-isoleucine-(6)-aminohexanoic amide").

8. Forbindelse ifølge et hvilket som helst af kravene 1-4 eller farmaceutisk sammensætning ifølge krav 6 eller 7 til anvendelse i en fremgangsmåde til behandling af en neurodegenerativ lidelse.

9. Forbindelse ifølge et hvilket som helst af kravene 1-4 eller farmaceutisk sammensætning ifølge krav 6 eller 7 til anvendelse ifølge krav 8, hvor den neurodegenerative lidelse er valgt fra gruppen bestående af: Alzheimers sygdom, Parkinsons sygdom, amyotrof lateralsklerose, andre typer demens og neurodegenerative lidelser, rygmarvsskader, traumatisk hjerneskade,

neurosensorisk høre- og synstab, fortrinsvis Alzheimers sygdom eller Parkinsons sygdom.

DRAWINGS

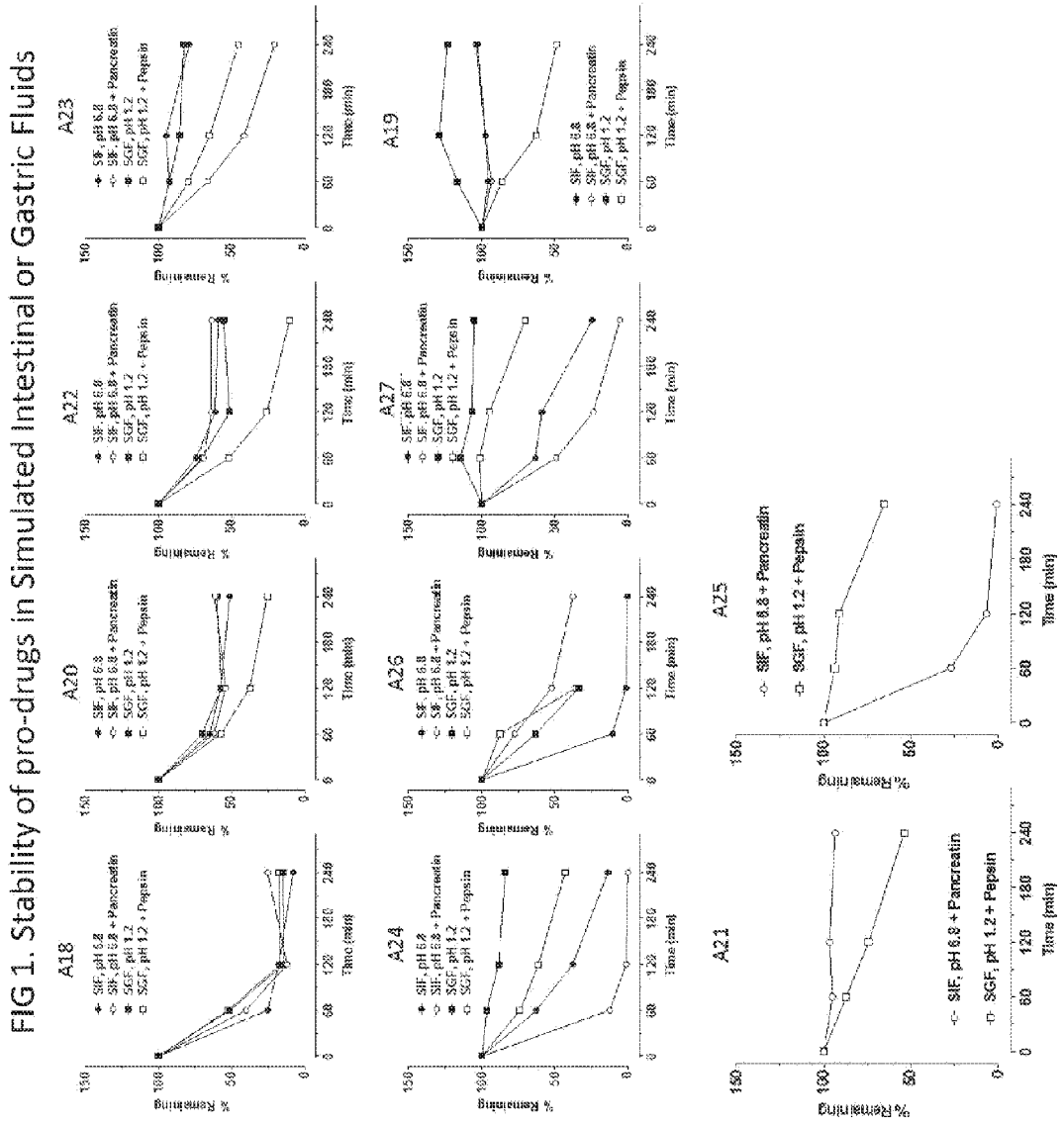


FIG 1. Stability of pro-drugs in Simulated Intestinal or Gastric Fluids
A18
A20
A22
A23
A19
A27
A26
A24
A25
A21
% Remaining
Time (min)
SIF, pH 6.8
SIF, pH 6.8 + Pancreatin
SGF, pH 1.2
SGF, pH 1.2 + Pepsin

FIG 2. Formation of active pro-drugs