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earlier application (Rule 4.17(iii))

(54) Title: LIPID-SUBSTITUTED AMINO 1,2-AND 1,3-DIOL COMPOUNDS AS MODULATORS OF TLR2 DIMERIZATION

(57) Abstract: The present invention relates to lipid-substituted amino 1,2- and 1,3-diol compounds, pharmaceutical compositions comprising such compounds, and use of such compounds in methods of treatment or in medicaments for treatment of inflammatory diseases and certain neurological disorders that are related to inflammatory signaling processes, including but not limited to misfolded proteins.



**LIPID-SUBSTITUTED AMINO 1,2- AND 1,3-DIOL COMPOUNDS AS MODULATORS
OF TLR2 DIMERIZATION**

Cross-Reference to Related Applications

[0001] This application claims priority to U.S. Provisional Application No. 62/370,637, filed August 3, 2016, which is hereby incorporated by reference in its entirety.

Technical Field

[0002] The present invention relates to lipid-substituted amino 1,2- and 1,3-diol compounds, pharmaceutical compositions comprising such compounds, and use of such compounds in methods of treatment or in medicaments for treatment of inflammatory diseases and certain neurological disorders that are related to inflammatory signaling processes, including but not limited to misfolded proteins.

Background

[0003] Toll-like receptors (TLRs) are sentinel receptors of the immune system. When these receptors are activated on cell surfaces, they initiate recruitment of a family of TIR-domain containing adapter proteins, which induce a signaling cascade that ultimately results in cell-type specific inflammatory responses, resulting in the elevation of pro-inflammatory mediators such as IL1, IL6, IL8 and TNF α . Of the different TLR receptors expressed on mammalian cells, TLR2 forms heterodimers with either TLR1 or TLR6 to initiate inflammatory responses with various microbial derived ligands. Among the various bacterial ligands are lipopolysaccharides (LPS), acylated lipopeptides, lipoglycans, peptidoglycans, porins, glycosylphosphatidyl-inosol anchors, and other bacterial cell wall components such as lipoteichoic acid (LTA) from streptococcus pneumonia. In addition to the microbial activation of TLR2, it has also been found that abnormal aggregation of neuron released oligomeric proteins such as alpha-synuclein (aSyn) can induce similar inflammatory responses in animal models of neurodegenerative diseases, including Parkinson's disease (PD), dementia with Lewy bodies, multiple system atrophy (MSA) and Alzheimer's disease (AD). *See, e.g.,* Kim et al., Nat. Commun. 2013, 4, 1562.

[0004] The ability of TLR2 to induce signaling via heterodimers allows discrimination between various recognition patterns, which allows for the design of ligands with specific inhibition patterns. Kajava *et al.*, *J. Biol. Chem.* 2010, 285, 6227. Inhibitors that compete primarily with a specific pathological agonist, such as oligomeric pathogenic alpha-synuclein, but do not affect other ligands involved in pro-inflammatory signaling of bacterial or viral infections, would therefore be useful as potential therapeutic agents. Described herein are compounds that function directly as inhibitors of TLR2 interaction with its heterodimer proteins, rather than as delivery vehicles for other therapeutic agents (such as liposomal delivery of active agents or as targeting agents for delivery of therapeutic moieties covalently bound to the polar heads of the lipid components).

[0005] The function of Toll-like receptors has been linked to various protein folding, protein dimerization, and inflammatory processes and to related diseases such as Alzheimer's disease (Gambuzza, M. *et al.*, "Toll-like receptors in Alzheimer's disease: a therapeutic perspective," *CNS Neurol. Disord. Drug Targets* 2014, 13(9), 1542-58), Parkinson's disease and Parkinson's disease with dementia (Beraud, D. *et al.*, "Misfolded α -synuclein and Toll-like receptors: therapeutic targets for Parkinson's disease," *Parkinsonism Relat. Disord.* 2012, 18 (Suppl. 1), S17-20), fronto-temporal dementia, dementia with Lewy bodies (Lewy body disease), multiple system atrophy (Vieira, B. *et al.*, "Neuroinflammation in multiple system atrophy: Response to and cause of α -synuclein aggregation," *Front. Cell Neurosci.* 2015, 9, 437), amyotrophic lateral sclerosis (Casula, M. *et al.*, "Toll-like receptor signaling in amyotrophic lateral sclerosis spinal cord tissue," *Neuroscience* 2011, 179, 233-43), Huntington's disease (Kalathur, R.K.R. *et al.*, "Huntington's disease and its therapeutic target genes: a global functional profile based on the HD Research Crossroads database," *BMC Neurology* 2012, 12, 47), inflammatory diseases, asthma and chronic obstructive pulmonary disease (COPD) (Zuo, L. *et al.*, "Molecular regulation of Toll-like receptors in asthma and COPD," *Front. Physiol.* 2016, 6, 312), chronic peptic ulcers (Smith, S., "Roll of Toll-like receptors in *Helicobacter pylori* infection and immunity," *World J. Gastrointest. Pathophysiol.* 2014, 5(3), 133-146), tuberculosis (Harding, C.V. *et al.*, "Regulation of antigen presentation by Mycobacterium tuberculosis: a role for Toll-like receptors," *Nat. Rev. Microbiol.* 2010, 8(4), 296-307), rheumatoid arthritis (Huang, Q.-Q. *et al.*, "Roll of Toll like receptors in rheumatoid arthritis," *Curr. Rheumatol. Rep.* 2009, 11(5),

357-364), chronic sinusitis (Zhang, Q. *et al.*, “Differential expression of Toll-like receptor pathway genes in chronic rhinosinusitis with or without nasal polyps,” *Acta Otolaryngol.* 2013, 133(2), 165-173), hepatitis (including hepatitis B and C) (Zhang, E. *et al.*, “Toll-like receptor (TLR)-mediated innate immune responses in control of hepatitis B virus (HBV) infection,” *Med. Microbiol. Immunol.* 2015, 204(1), 11-20; Howell, J. *et al.*, “Toll-like receptors in hepatitis C infection: implications for pathogenesis and treatment,” *J. Gastroenterol. Hepatol.* 2013, 28(5), 766-776), gout, lupus, psoriasis, psoriatic arthritis (Santegoets, K.C.M. *et al.*, “Toll-like receptors in rheumatic diseases: are we paying a high price for our defense against bugs?” *FEBS Letters* 2011, 585(23), 3660-3666), vasculitis, laryngitis, pleurisy (Chen, X. *et al.*, “Engagement of Toll-like receptor 2 on CD4(+) T cells facilitates local immune responses in patients with tuberculous pleurisy,” *J. Infect. Dis.* 2009, 200(3), 399-408), eczema (Miller, L.S., “Toll-like receptors in skin,” *Adv. Dermatol.* 2008, 24, 71-87), gastritis (Schmausser, B. *et al.*, “Toll-like receptors TLR4, TLR5 and TLR9 on gastric carcinoma cells: an implication for interaction with *Helicobacter pylori*,” *Int. J. Med. Microbiol.* 2005, 295(3), 179-85), vasculitis (Song, G.G. *et al.*, “Toll-like receptor polymorphisms and vasculitis susceptibility: meta-analysis and systematic review,” *Mol. Biol. Rep.* 2013, 40(2), 1315-23), laryngitis (King, S. N. *et al.*, “Characterization of the Leukocyte Response in Acute Vocal Fold Injury,” *PLoS One*, 2015; 10(10): e0139260), allergic reactions (Gangloff, S.C. *et al.*, “Toll-like receptors and immune response in allergic disease,” *Clin. Rev. Allergy Immunol.* 2004, 26(2), 115-25), multiple sclerosis (Miranda-Hernandez, S. *et al.*, “Role of toll-like receptors in multiple sclerosis,” *Am. J. Clin. Exp. Immunol.* 2013, 2(1), 75-93), Crohn’s disease (Cario, E., “Toll-like receptors in inflammatory bowel diseases: A decade later,” *Inflamm. Bowel Dis.* 2010, 16(9), 1583-1597), and traumatic brain injury (Hua, F. *et al.*, “Genomic profile of Toll-like receptor pathways in traumatically brain-injured mice: effect of exogenous progesterone,” *J. Neuroinflammation* 2011, 8, 42).

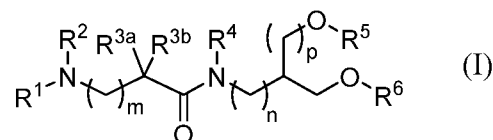
[0006] Patent publications that discuss aminoacid, cationic, and other modified lipids include: U.S. Pat. Publ. Nos. 2015/0030670, 2005/0113345, 2005/0175682, 2011/0091525, 2011/0152251, and 2015/0065414; PCT Publ. Nos. WO2002/0729068, WO2005/039504, WO2009/129385, WO2011/062955, WO2013/030678, and WO2013/135359; and U.S. Patent Nos. 7,803,397, 8,609,663, and 8,936,942. Other publications include: Long, E.M. *et al.*, “A

subclass of acylated anti-inflammatory mediators usurp Toll-like receptor 2 to inhibit neutrophil recruitment through peroxisome proliferator-activated receptor,” *PNAS* 2011, 103(39), 16357-16362; Kang, J.Y. *et al.*, “Recognition of Lipopeptide Patterns by Toll-like Receptor 2-Toll-like Receptor 6 Heterodimer,” *Immunity* 2009, 31(6), 873-884; Kajava, A.V. *et al.*, “A Network of Hydrogen Bonds on the Surface of TLR2 Controls Ligand Positioning and Cell Signaling,” *J. Biol. Chem.* 2010, 285, 6227-6234; Medel, I. *et al.* “VB-201, an oxidized phospholipid small molecule, inhibits CD14- and Toll-like receptor-2-dependent innate cell activation and constrains atherosclerosis,” *Clin. Exp. Immunol.* 2014, 175(1), 126-37; Kadl, A. *et al.*, “Oxidized phospholipid-induced inflammation is mediated by Toll-like receptor 2,” *Free Radic. Biol. Med.* 2011, 51(10), 1903-9.

[0007] Described herein are lipid-substituted amino 1,2- and 1,3-diol compounds that serve as antagonists of TLR2 heterodimer binding with high potency and selectivity.

Summary of the Invention

[0008] In one aspect, the invention relates to a compound of Formula (I):



wherein

R¹ is H, -CO₂-C₁₋₈alkyl, -CO₂-CHR^a-aryl, -CO₂-CHR^a-heteroaryl, -C(O)-C₁₋₄alkyl, -C(O)aryl, -C(O)-heteroaryl, -C(O)-CHR^b-NR^cR^d, -C(O)-CHR^a-heteroaryl, -CHR^a-aryl, -CHR^a-heteroaryl, -SO₂-C₁₋₄alkyl, -SO₂-aryl, or -SO₂-heteroaryl;

wherein R^a is H or C₁₋₁₅alkyl;

$$R^b \text{ is H or } -C_{1-5}\text{alkyl}-NR^eR^f;$$

where R^e is H or C₁₋₄alkyl and R^f is H, C₁₋₄alkyl, or -CO₂C₁₋₄alkyl;

R^c is H or C₁₋₄alkyl and R^d is H, C₁₋₄alkyl, or -CO₂C₁₋₄alkyl; and

each aryl or heteroaryl is optionally substituted with halo, C₁₋₄alkyl, C₁₋₄fluoroalkyl, -OH, -OC₁₋₄alkyl, -OC₁₋₄fluoroalkyl, -CN, phenyl, -OC₁₋₄alkyl-aryl, or -CO₂C₁₋₄alkyl;

R² is H or C₁₋₄alkyl;

R^{3a} is H, $-C_{6-14}alkyl$, $-CHR^g-aryl$, $-CHR^g-heteroaryl$, $-CHR^g-heterocycloalkyl$, $-C_{1-4}alkyl-NR^hR^i$, $-C_{1-4}alkyl-CO_2C_{1-4}alkyl$, $-C_{1-4}alkyl-CO_2H$, or $-C_{1-4}alkyl-CONR^jR^k$;

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

R^h is H, $C_{1-4}alkyl$, or $-CO_2C_{1-4}alkyl$;

R^i is H, $C_{1-4}alkyl$, or $-C(=NH)-NHR^m$;

wherein R^m is H, $-SO_2aryl$, or $-CO_2C_{1-4}alkyl$;

R^j is H or $C_{1-4}alkyl$; and

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

and wherein each aryl, heteroaryl, and heterocycloalkyl is optionally substituted with $-OH$,

$C_{1-4}alkyl$, $-CO_2C_{1-4}alkyl$, phenyl, or benzyloxy;

or R^2 and R^{3a} taken together with the atoms to which they are attached form $C_{2-4}alkylene$;

R^{3b} is H; or R^{3a} and R^{3b} taken together with the carbon to which they are attached form a 4- to 7-membered heterocycloalkyl, optionally substituted with $C_{1-4}alkyl$ or $-CO_2C_{1-4}alkyl$;

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

R^5 is $C_{8-16}alkyl$ or $C_{8-16}alkenyl$;

R^6 is $C_{8-16}alkyl$ or $C_{8-16}alkenyl$;

m is 0 or 1;

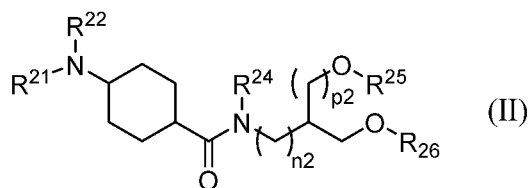
n is 0 or 1; and

p is 0 or 1;

wherein at least one of n and p is 1;

or a pharmaceutically acceptable salt thereof.

[0009] In another aspect, the invention relates to a compound of Formula (II):



wherein

R^{21} is H, $C_{1-4}alkyl$, or $-CO_2C_{1-4}alkyl$;

R^{22} is H or $C_{1-4}alkyl$;

R^{24} is H or $C_{1-4}alkyl$;

R^{25} is C_{8-16} alkyl or C_{8-16} alkenyl;

R^{26} is C_{8-16} alkyl or C_{8-16} alkenyl;

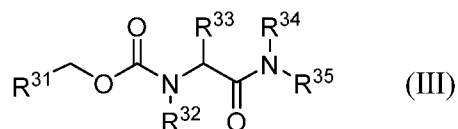
n_2 is 0 or 1; and

p_2 is 0 or 1;

wherein at least one of n_2 and p_2 is 1;

or a pharmaceutically acceptable salt thereof.

[0010] In another aspect, the invention relates to a compound of Formula (III):



wherein

R^{31} is phenyl or monocyclic heteroaryl;

R^{32} is H or C_{1-4} alkyl;

R^{33} is C_{1-4} alkyl- NR^xR^y ;

where R^x is H, C_{1-4} alkyl, or $-CO_2-C_{1-4}$ alkyl; and

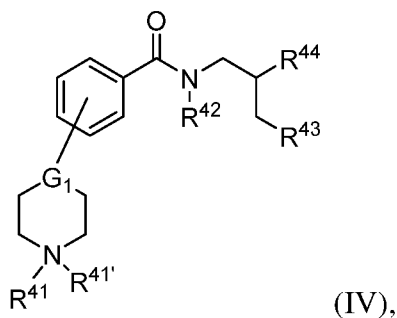
R^y is H or C_{1-4} alkyl;

R^{34} is H or C_{1-4} alkyl; and

R^{35} is C_{14-18} alkyl or C_{14-18} alkenyl;

or a pharmaceutically acceptable salt thereof.

[0011] In another aspect, the invention relates to a compound of Formula (IV):



wherein

G^1 is N or CH;

R^{41} is H, C_{1-4} alkyl, or $-CO_2C_{1-4}$ alkyl;

$R^{41'}$ is absent, H, or C_{1-4} alkyl; wherein when $R^{41'}$ is H or C_{1-4} alkyl, the nitrogen attached to $R^{41'}$ has a positive charge;

R^{42} is H or C_{1-4} alkyl;

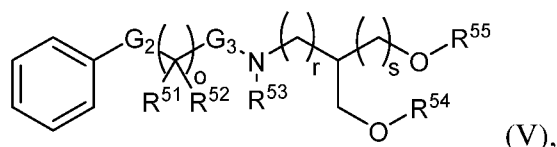
R^{43} is $-OC_{1-18}$ alkyl, $-OC_{1-18}$ alkenyl, $-C_{1-18}$ alkyl, or $-C_{1-18}$ alkenyl, each optionally substituted with $-OH$, $-OC_{1-4}$ alkyl, $-C(O)OH$, $-C(O)OC_{1-4}$ alkyl, $-C(O)NHR^{4b}$, or aryl; and

R^{44} is $-OC_{4-18}$ alkyl or $-OC_{4-18}$ alkenyl, each optionally substituted with $-OH$, $-OC_{1-4}$ alkyl, $-C(O)OH$, $-C(O)OC_{1-4}$ alkyl, $-C(O)NHR^{4c}$, or aryl;

wherein R^{4b} and R^{4c} are each independently H or C_{1-4} alkyl;

or a pharmaceutically acceptable salt thereof.

[0012] In another aspect, the invention relates to a compound of Formula (V):



wherein

G_2 is a bond, $-CH_2-$, $-CH_2NH-$, or $-CH_2NHCH_2-$;

G_3 is $-C(O)-$ or $-CH_2-$;

R^{51} is H, C_{1-4} alkyl, $-CO_2C_{1-4}$ alkyl, heterocycle, or $-C_{1-4}$ alkyl- $NR^{5a}R^{5b}$; where R^{5a} is H or C_{1-4} alkyl and R^{5b} is H, C_{1-4} alkyl, or $-CO_2C_{1-4}$ alkyl; and

R^{52} is H or C_{1-4} alkyl;

or R^{51} and R^{52} , together with the carbon to which they are attached, form a heterocycloalkyl optionally substituted with $-CO_2C_{1-4}$ alkyl;

R^{53} is H or C_{1-4} alkyl;

o is 0 or 1;

r is 0 or 1;

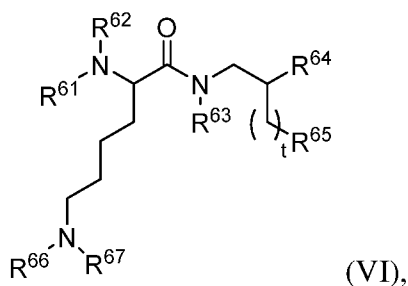
s is 0 or 1;

R^{54} is C_{8-18} alkyl or C_{8-18} alkenyl; and

R^{55} is C_{8-18} alkyl or C_{8-18} alkenyl;

or a pharmaceutically acceptable salt thereof.

[0013] In another aspect, the invention relates to a compound of Formula (VI):



wherein

R^{61} is H, $-\text{CO}_2\text{-C}_{1-8}\text{alkyl}$, $-\text{CO}_2\text{-CHR}^{6a}\text{-aryl}$, $-\text{CO}_2\text{-CHR}^{6a}\text{-heteroaryl}$, $-\text{C(O)-C}_{1-4}\text{alkyl}$, $-\text{C(O)aryl}$, $-\text{C(O)-heteroaryl}$, $-\text{C(O)-CHR}^{6b}\text{-NR}^{6c}\text{R}^{6d}$, $-\text{C(O)-CHR}^{6a}\text{-heteroaryl}$, $-\text{CHR}^{6a}\text{-aryl}$, $-\text{CHR}^{6a}\text{-heteroaryl}$, $-\text{SO}_2\text{-C}_{1-4}\text{alkyl}$, $-\text{SO}_2\text{-aryl}$, or $-\text{SO}_2\text{-heteroaryl}$;

where R^{6a} is H or $\text{C}_{1-15}\text{alkyl}$;

R^{6b} is H or $-\text{C}_{1-5}\text{alkyl-NR}^{6e}\text{R}^{6f}$;

R^{6c} is H or $\text{C}_{1-4}\text{alkyl}$;

R^{6d} is H, $\text{C}_{1-4}\text{alkyl}$, or $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$;

R^{6e} is H or $\text{C}_{1-4}\text{alkyl}$;

R^{6f} is H, $\text{C}_{1-4}\text{alkyl}$, or $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$; and

each aryl or heteroaryl is optionally substituted with halo, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{fluoroalkyl}$, $-\text{OH}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{OC}_{1-4}\text{fluoroalkyl}$, $-\text{CN}$, phenyl, or $-\text{OC}_{1-4}\text{alkyl-aryl}$;

R^{62} is H or $\text{C}_{1-4}\text{alkyl}$;

R^{66} is H, $\text{C}_{1-4}\text{alkyl}$, or $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$;

R^{67} is H, $\text{C}_{1-4}\text{alkyl}$, or $-\text{C(=NH)-NHR}^{6m}$;

where R^{6m} is H, $-\text{SO}_2\text{aryl}$, or $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$;

R^{63} is H or $\text{C}_{1-4}\text{alkyl}$;

R^{64} is H or $-\text{OH}$,

or R^{64} is $-\text{C}_{1-18}\text{alkyl}$, $-\text{C}_{1-18}\text{alkenyl}$, $-\text{OC}_{1-18}\text{alkyl}$, or $-\text{OC}_{1-18}\text{alkenyl}$, each of which is optionally substituted with $-\text{OH}$ or $-\text{OC}_{1-4}\text{alkyl}$;

R^{65} is H or $-\text{C}_{4-8}\text{cycloalkyl}$,

or R^{65} is $-\text{C}_{1-18}\text{alkyl}$, $-\text{C}_{1-18}\text{alkenyl}$, $-\text{OC}_{1-12}\text{alkyl}$, or $-\text{OC}_{1-12}\text{alkenyl}$, each of which is optionally substituted with $-\text{OH}$ or $-\text{OC}_{1-4}\text{alkyl}$; and

t is 0 or 1;

or a pharmaceutically acceptable salt thereof.

[0014] In certain embodiments, the compound of Formula (I), (II), (III), (IV), (V), or (VI) is a compound selected from those species described or exemplified herein.

[0015] In a further aspect, the invention relates to a pharmaceutical composition comprising at least one compound of Formula (I) or a pharmaceutically acceptable salt thereof. In a further aspect, the invention relates to a pharmaceutical composition comprising at least one compound of Formula (II) or a pharmaceutically acceptable salt thereof. In a further aspect, the invention relates to a pharmaceutical composition comprising at least one compound of Formula (III) or a pharmaceutically acceptable salt thereof. In a further aspect, the invention relates to a pharmaceutical composition comprising at least one compound of Formula (IV) or a pharmaceutically acceptable salt thereof. In a further aspect, the invention relates to a pharmaceutical composition comprising at least one compound of Formula (V) or a pharmaceutically acceptable salt thereof. In a further aspect, the invention relates to a pharmaceutical composition comprising at least one compound of Formula (VI) or a pharmaceutically acceptable salt thereof. In a further aspect, the invention relates to a pharmaceutical composition comprising at least one compound of any of Tables 1-6 or a pharmaceutically acceptable salt thereof. Pharmaceutical compositions according to the invention may further comprise a pharmaceutically acceptable excipient. The invention is also a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use as a medicament. The invention is also a compound of Formula (II) or a pharmaceutically acceptable salt thereof for use as a medicament. The invention is also a compound of Formula (III) or a pharmaceutically acceptable salt thereof for use as a medicament. The invention is also a compound of Formula (IV) or a pharmaceutically acceptable salt thereof for use as a medicament. The invention is also a compound of Formula (V) or a pharmaceutically acceptable salt thereof for use as a medicament. The invention is also a compound of Formula (VI) or a pharmaceutically acceptable salt thereof for use as a medicament. The invention is also a compound of any of Tables 1-6 or a pharmaceutically acceptable salt thereof for use as a medicament.

[0016] In another aspect, the invention is directed to a method of treating a disease or condition associated with TLR2 heterodimerization, comprising administering to a subject in need of such treatment an effective amount of at least one compound of Formula (I), (II), (III),

(IV), (V), or (VI), or a compound of any of Tables 1-6, or a pharmaceutically acceptable salt of any of the foregoing. In another aspect, described herein is a compound or composition for use in treating a disease or condition associated with TLR2 heterodimerization.

[0017] In another aspect, the invention is directed to a method of treating a disease or medical condition associated with TLR2 heterodimerization, comprising administering to a subject in need of such treatment an effective amount of at least one compound of Formula (I), (II), (III), (IV), (V), or (VI), or a compound of any of Tables 1-6, or a pharmaceutically acceptable salt of any of the foregoing. The invention is also directed to the use of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a compound of any of Tables 1-6, or a pharmaceutically acceptable salt of any of the foregoing for the treatment of, or for the preparation of a medicament for the treatment of, such diseases and medical conditions.

[0018] In yet another aspect, the invention relates to a method of interfering with the heterodimerization of TLR2 in a cell, or modulating, preventing, slowing, reversing, or inhibiting TLR2 heterodimerization in a cell, comprising contacting the cell with an effective amount of at least one compound of Formula (I), (II), (III), (IV), (V), or (VI), or a compound of any of Tables 1-6, or a salt of any of the foregoing, and/or with at least one pharmaceutical composition of the invention, wherein the contacting is *in vitro*, *ex vivo*, or *in vivo*.

[0019] Additional embodiments, features, and advantages of the invention will be apparent from the following detailed description and through practice of the invention.

[0020] For the sake of brevity, the disclosures of publications cited in this specification, including patents, are herein incorporated by reference.

Detailed Description of the Invention

[0021] Before the present invention is further described, it is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, as the scope of the present invention will be limited only by the specification taken as a whole, or by the appended claims.

[0022] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. All patents, applications, published applications and other publications referred to herein are incorporated by reference in their entireties. If a definition set forth in this section is contrary to or otherwise inconsistent with a definition set forth in a patent, application, or other publication that is herein incorporated by reference, the definition set forth in this section prevails over the definition incorporated herein by reference.

[0023] As used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as “solely,” “only” and the like in connection with the recitation of claim elements, or use of a “negative” limitation.

[0024] As used herein, the terms “including,” “containing,” and “comprising” are used in their open, non-limiting sense.

[0025] To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term “about”. It is understood that, whether the term “about” is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including equivalents and approximations due to the experimental and/or measurement conditions for such given value. Whenever a yield is given as a percentage, such yield refers to a mass of the entity for which the yield is given with respect to the maximum amount of the same entity that could be obtained under the particular stoichiometric conditions. Concentrations that are given as percentages refer to mass ratios, unless indicated differently.

[0026] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by

reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[0027] Except as otherwise noted, the methods and techniques of the present embodiments are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See, e.g., Loudon, Organic Chemistry, Fourth Edition, New York: Oxford University Press, 2002, pp. 360-361, 1084-1085; Smith and March, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Fifth Edition, Wiley-Interscience, 2001.

[0028] The nomenclature used herein to name the subject compounds is illustrated in the Examples herein. This nomenclature has generally been derived using the commercially-available ChemBioDraw Ultra software, Version 14.0.

[0029] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables are specifically embraced by the present invention and are disclosed herein just as if each and every combination was individually and explicitly disclosed, to the extent that such combinations embrace compounds that are stable compounds (i.e., compounds that can be isolated, characterized, and tested for biological activity). In addition, all subcombinations of the chemical groups listed in the embodiments describing such variables are also specifically embraced by the present invention and are disclosed herein just as if each and every such sub-combination of chemical groups was individually and explicitly disclosed herein.

Representative Embodiments

- Formula (I)

[0030] In some embodiments of Formula (I), R¹ is H, -CO₂-C₁₋₈alkyl, -CO₂-CHR^a-aryl, -CO₂-CHR^a-heteroaryl, -C(O)-C₁₋₄alkyl, -C(O)aryl, -C(O)-heteroaryl, -C(O)-CHR^b-NR^cR^d, -

C(O)-CHR^a-heteroaryl, -CHR^a-aryl, -CHR^a-heteroaryl, -SO₂-C₁₋₄alkyl, -SO₂-aryl, or -SO₂-heteroaryl; wherein R^a is H or C₁₋₁₅alkyl; R^b is H or -C₁₋₅alkyl-NR^eR^f; where R^e is H or C₁₋₄alkyl and R^f is H, C₁₋₄alkyl, or -CO₂C₁₋₄alkyl; R^c is H or C₁₋₄alkyl and R^d is H, C₁₋₄alkyl, or -CO₂C₁₋₄alkyl; and each aryl or heteroaryl is optionally substituted with halo, C₁₋₄alkyl, C₁₋₄fluoroalkyl, -OH, -OC₁₋₄alkyl, -OC₁₋₄fluoroalkyl, -CN, phenyl, or -OC₁₋₄alkyl-aryl.

[0031] In some embodiments of Formula (I), R¹ is H, -CO₂-C₁₋₈alkyl, -CO₂-CHR^a-aryl, -CO₂-CHR^a-heteroaryl, -C(O)-C₁₋₄alkyl, -C(O)aryl, -C(O)-heteroaryl, -C(O)-CHR^b-NR^cR^d, -C(O)-CHR^a-heteroaryl, -CHR^a-aryl, -CHR^a-heteroaryl, -SO₂-C₁₋₄alkyl, -SO₂-aryl, or -SO₂-heteroaryl. In some embodiments, R¹ is H, -CO₂-CHR^a-aryl, -CO₂-CHR^a-heteroaryl, -C(O)-C₁₋₄alkyl, -C(O)aryl, -C(O)-heteroaryl, -C(O)-CHR^a-heteroaryl, -CHR^a-aryl, -CHR^a-heteroaryl, -SO₂-C₁₋₄alkyl, -SO₂-aryl, or -SO₂-heteroaryl. In some embodiments, R¹ is H. In other embodiments, R¹ is -CO₂-C₁₋₈alkyl. In other embodiments, R¹ is -CO₂-CHR^a-aryl or -CO₂-CHR^a-heteroaryl. In other embodiments, R¹ is -C(O)-C₁₋₄alkyl, -C(O)aryl, or -C(O)-heteroaryl. In other embodiments, R¹ is -C(O)-CHR^b-NR^cR^d. In other embodiments, R¹ is -C(O)-CHR^a-heteroaryl. In other embodiments, R¹ is -CHR^a-aryl or -CHR^a-heteroaryl. In other embodiments, R¹ is -SO₂-C₁₋₄alkyl, -SO₂-aryl, or -SO₂-heteroaryl. In some embodiments, the R¹ aryl is phenyl. In other embodiments, the R¹ aryl is fluorenyl. In some embodiments, the R¹ heteroaryl is a bicyclic heteroaryl. In other embodiments, the R¹ heteroaryl is indolyl, benzofuranyl, benzothiophenyl, benzoxazolyl, or benzothiazolyl. In other embodiments, the R¹ heteroaryl is indolyl. In some embodiments, the R¹ aryl or heteroaryl is unsubstituted. In other embodiments, the R¹ aryl or heteroaryl is substituted with one or more substituents independently selected from the group consisting of halo, C₁₋₄alkyl, C₁₋₄fluoroalkyl, -OH, -OC₁₋₄alkyl, -OC₁₋₄fluoroalkyl, -CN, phenyl, and -OC₁₋₄alkyl-aryl. In other embodiments, the R¹ aryl or heteroaryl is substituted with one or more substituents independently selected from the group consisting of halo, C₁₋₄alkyl, C₁₋₄fluoroalkyl, -OH, -OC₁₋₄alkyl, -OC₁₋₄fluoroalkyl, -CN, phenyl, -OC₁₋₄alkyl-aryl, and -CO₂C₁₋₄alkyl. In some embodiments, the R¹ aryl or heteroaryl is substituted with methyl, fluoro, phenyl, or benzyloxy. In some embodiments, the R¹ aryl or heteroaryl is substituted with methyl, fluoro, phenyl, benzyloxy, or tert-butyloxycarbonyl.

[0032] In some embodiments, R^1 is $-\text{CO}_2\text{-CH}_2\text{-fluorenyl}$, acetyl, or carbobenzyloxy. In some embodiments, R^1 is tert-butyloxycarbonyl. In some embodiments, R^1 is substituted or unsubstituted benzyl. In some embodiments, R^1 is benzyl substituted with halo or phenyl.

[0033] In some embodiments, R^a is H. In other embodiments, R^a is $\text{C}_{1-15}\text{alkyl}$. In other embodiments, R^a is $\text{C}_{10-15}\text{alkyl}$.

[0034] In some embodiments, R^b is H. In some embodiments, R^b is $-\text{C}_{1-5}\text{alkyl-NR}^e\text{R}^f$. In some embodiments, R^e is H. In other embodiments, R^e is $\text{C}_{1-4}\text{alkyl}$. In some embodiments, R^f is H. In some embodiments, R^f is $\text{C}_{1-4}\text{alkyl}$. In other embodiments, R^f is $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$.

[0035] In some embodiments, R^c is H. In some embodiments, R^c is $\text{C}_{1-4}\text{alkyl}$. In some embodiments, R^d is H. In other embodiments, R^d is $\text{C}_{1-4}\text{alkyl}$. In other embodiments, R^d is $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$.

[0036] In some embodiments, R^2 is H. In other embodiments, R^2 is $\text{C}_{1-4}\text{alkyl}$.

[0037] In some embodiments, R^1 and R^2 are both hydrogen.

[0038] In some embodiments, R^{3a} is H. In other embodiments, R^{3a} is $-\text{C}_{6-14}\text{alkyl}$. In other embodiments, R^{3a} is $-\text{CHR}^g\text{-aryl}$, $-\text{CHR}^g\text{-heteroaryl}$, or $-\text{CHR}^g\text{-heterocycloalkyl}$. In some embodiments, the R^{3a} aryl is phenyl. In some embodiments, the R^{3a} heteroaryl is pyrrolyl, imidazolyl, indolyl, or benzimidazolyl. In other embodiments, the R^{3a} heteroaryl is pyrrolyl or indolyl. In other embodiments, the R^{3a} heterocycloalkyl is a monocyclic heterocycloalkyl. In some embodiments, the R^{3a} heterocycloalkyl is pyrrolidinyl or piperazinyl. In some embodiments, the R^{3a} aryl, heteroaryl, and heterocycloalkyl are unsubstituted. In other embodiments, the R^{3a} aryl, heteroaryl, and heterocycloalkyl are substituted with $-\text{OH}$, $\text{C}_{1-4}\text{alkyl}$, or $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$. In other embodiments, the R^{3a} aryl and heteroaryl are optionally substituted with phenyl or benzyloxy.

[0039] In some embodiments, R^{3a} is $-\text{C}_{1-4}\text{alkyl-NR}^h\text{R}^i$. In other embodiments, R^{3a} is $-\text{C}_{1-4}\text{alkyl-CO}_2\text{C}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkyl-CO}_2\text{H}$, or $-\text{C}_{1-4}\text{alkyl-CONR}^j\text{R}^k$.

[0040] In some embodiments, R^g is H. In other embodiments, R^g is $\text{C}_{1-4}\text{alkyl}$.

[0041] In some embodiments, R^h is H. In other embodiments, R^h is $\text{C}_{1-4}\text{alkyl}$. In other embodiments, R^h is $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$.

[0042] In some embodiments, R^i is H. In other embodiments, R^i is C_{1-4} alkyl. In further embodiments, R^i is $-C(=NH)-NHR^m$.

[0043] In some embodiments, R^m is H. In some embodiments, R^m is $-SO_2$ phenyl. In other embodiments, R^m is $-CO_2C_{1-4}$ alkyl.

[0044] In some embodiments, R^j is H. In some embodiments, R^j is C_{1-4} alkyl. In some embodiments, R^k is H. In some embodiments, R^k is C_{1-4} alkyl.

[0045] In some embodiments, R^2 and R^{3a} taken together form C_{2-4} alkylene. In some embodiments, R^2 and R^{3a} taken together form C_3 alkylene.

[0046] In some embodiments, R^{3b} is H. In some embodiments, R^{3a} and R^{3b} taken together with the carbon to which they are attached form a 4- to 7-membered heterocycloalkyl, optionally substituted with C_{1-4} alkyl or $-CO_2C_{1-4}$ alkyl. In some embodiments, the heterocycloalkyl is pyrrolidine or piperazine.

[0047] In some embodiments, R^{3a} is substituted or unsubstituted $-CH_2$ -phenyl. In some embodiments, R^{3a} is $-CH_2$ -phenyl substituted with benzyloxy, hydroxyl, or phenyl. In some embodiments, R^{3a} is $-CH_2$ -imidazolyl, optionally substituted with tert-butoxycarbonyl. In some embodiments, R^{3a} is $-CH_2$ -indolyl. In some embodiments, R^{3a} is $-CH_2$ -piperidine, optionally substituted with tert-butoxycarbonyl. In some embodiments, R^{3a} is butylamine, optionally substituted with tert-butoxycarbonyl. In some embodiments, R^{3a} is propylamine, optionally substituted with guanidinyl, wherein the guanidinyl is optionally substituted. In some embodiments, R^{3a} is carboxyethyl, optionally substituted with tert-butyl. In some embodiments, R^{3a} is carboxymethyl, optionally substituted with tert-butyl. In some embodiments, R^{3a} and R^{3b} are both hydrogen.

[0048] In some embodiments, R^4 is H. In some embodiments, R^4 is C_{1-4} alkyl.

[0049] In some embodiments, R^5 and R^6 are each independently C_{8-16} alkyl or C_{8-16} alkenyl. In some embodiments, R^5 and R^6 are each independently C_{8-16} alkyl. In some embodiments, R^5 and R^6 are the same. In other embodiments, R^5 and R^6 are different. In some embodiments, R^5 and R^6 are unbranched hydrocarbons. In some embodiments, R^5 and R^6 are each C_{14} alkyl.

[0050] In some embodiments, m is 0. In other embodiments, m is 1. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, p is 0. In other embodiments, p is 1. In some embodiments, n is 1 and p is 0. In other embodiments, n is 0 and p is 1.

[0051] In some embodiments, R⁵ and R⁶ are each independently C₁₃₋₁₆alkyl or C₁₃₋₁₆alkenyl. In some embodiments, R⁵ and R⁶ are each independently C₈₋₁₁alkyl, C₁₃₋₁₆alkyl, C₈₋₁₁alkenyl, or C₁₃₋₁₆alkenyl. In some embodiments, R⁵ and R⁶ are each independently C₈₋₁₁alkyl, C₁₃₋₁₆alkyl, C₈₋₁₁alkenyl, or C₁₃₋₁₆alkenyl, and R¹ is H, -CO₂-C₁₋₈alkyl, -CO₂-CHR^a-heteroaryl, -C(O)-C₁₋₄alkyl, -C(O)aryl, -C(O)-heteroaryl, -C(O)-CHR^b-NR^cR^d, -C(O)-CHR^a-heteroaryl, -CHR^a-aryl, -CHR^a-heteroaryl, -SO₂-C₁₋₄alkyl, -SO₂-aryl, or -SO₂-heteroaryl. In some embodiments, R⁵ and R⁶ are each independently C₈₋₁₁alkyl, C₁₃₋₁₆alkyl, C₈₋₁₁alkenyl, or C₁₃₋₁₆alkenyl, and R^{3a} is H, -C₆₋₁₄alkyl, -CHR^g-aryl, -CHR^g-heterocycloalkyl, -C₁₋₄alkyl-CO₂C₁₋₄alkyl, -C₁₋₄alkyl-CO₂H, or -C₁₋₄alkyl-CONR^jR^k. In some embodiments, R⁵ and R⁶ are each independently C₁₄alkyl or C₁₄alkenyl. In some embodiments, R⁵ and R⁶ are each independently C₁₆alkyl or C₁₆alkenyl.

[0052] In some embodiments, R¹ is -CO₂-C₁₋₈alkyl or -C(O)-CHR^b-NR^cR^d, and R^{3a} is -C₆₋₁₄alkyl, -CHR^g-aryl, -CHR^g-heteroaryl, -CHR^g-heterocycloalkyl, -C₁₋₄alkyl-NR^hRⁱ, -C₁₋₄alkyl-CO₂C₁₋₄alkyl, -C₁₋₄alkyl-CO₂H, or -C₁₋₄alkyl-CONR^jR^k. In some embodiments, R¹ is -CO₂-C₁₋₈alkyl and m is 1. In some embodiments, R¹ is -CO₂-C₁₋₈alkyl and R² is C₁₋₄alkyl.

[0053] In other embodiments, the compound of Formula (I) is selected from the group consisting of compounds of Table 1:

Table 1.

Ex. #	Structure	Chemical Name
1		tert-Butyl ((2S)-3-(4-(benzyloxy)phenyl)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxopropan-2-yl)carbamate

Ex. #	Structure	Chemical Name
2		(2S)-2-Amino-3-(4-(benzyloxy)phenyl)-N-(2,3-bis(tetradecyloxy)propyl)propanamide
3		tert-Butyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate
4		(2S)-2-Amino-N-(2,3-bis(tetradecyloxy)propyl)-3-(1H-indol-3-yl)propanamide
5		tert-Butyl (2S)-2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)pyrrolidine-1-carboxylate
6		(2S)-N-(2,3-Bis(tetradecyloxy)propyl)pyrrolidine-2-carboxamide
7		tert-Butyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate
8		(2S)-2-Amino-N-(2,3-bis(tetradecyloxy)propyl)-3-(4-hydroxyphenyl)propanamide
9		(9H-Fluoren-9-yl)methyl tert-butyl ((5S)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexane-1,5-diyl)dicarbamate

Ex. #	Structure	Chemical Name
10		(9H-Fluoren-9-yl)methyl ((2S)-6-amino-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxohexan-2-yl)carbamate
11		(9H-Fluoren-9-yl)methyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate
12		tert-Butyl ((2R)-1-((2,3-bis(tetradecyloxy)propyl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate
13		(2R)-2-Amino-N-(2,3-bis(tetradecyloxy)propyl)-3-(1H-indol-3-yl)propanamide
14		tert-Butyl (4S)-5-((2,3-bis(tetradecyloxy)propyl)amino)-4-((tert-butoxycarbonyl)amino)-5-oxopentanoate
15		(4S)-4-Amino-5-((2,3-bis(tetradecyloxy)propyl)amino)-5-oxopentanoic acid
16		tert-Butyl (2R)-2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)pyrrolidine-1-carboxylate
17		Bis(tetradecyloxy)propylpyrrolidine-2-carboxamide

Ex. #	Structure	Chemical Name
18		N-(2,3-Bis(tetradecyloxy)propyl)-2-((4-methylphenyl)sulfonamido)acetamide
19		tert-Butyl 4-((2S)-3-((2,3-bis(tetradecyloxy)propyl)amino)-2-((tert-butoxycarbonyl)amino)-3-oxopropyl)-1H-imidazole-1-carboxylate
20		(2S)-2-Amino-N-(2,3-bis(tetradecyloxy)propyl)-3-(1H-imidazol-4-yl)propanamide
21		tert-Butyl (3-((2,3-bis(tetradecyloxy)propyl)amino)-3-oxopropyl) carbamate
22		3-Amino-N-(2,3-bis(tetradecyloxy)propyl)propanamide
23		tert-Butyl (3S)-4-((2,3-bis(tetradecyloxy)propyl)amino)-3-((tert-butoxycarbonyl)amino)-4-oxobutanoate
24		(3S)-3-Amino-4-((2,3-bis(tetradecyloxy)propyl)amino)-4-oxobutanoic acid
25		tert-Butyl (2-((2,3-bis(tetradecyloxy)propyl)amino)-2-oxoethyl) (methyl)carbamate
26		N-(2,3-bis(tetradecyloxy)propyl)-2-(methylamino)acetamide

Ex. #	Structure	Chemical Name
27		tert-Butyl (3S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-((2,3-bis(tetradecyloxy)propyl)amino)-4-oxobutanoate
28		(3S)-3-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-4-((2,3-bis(tetradecyloxy)propyl)amino)-4-oxobutanoic acid
29		tert-Butyl (4S)-4-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-((2,3-bis(tetradecyloxy)propyl)amino)-5-oxopentanoate
30		(4S)-4-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-5-((2,3-bis(tetradecyloxy)propyl)amino)-5-oxopentanoic acid
31		Benzyl tert-butyl ((5R)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexan-1,5-diyl)dicarbamate
32		Benzyl ((2R)-6-amino-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxohexan-2-yl)carbamate

Ex. #	Structure	Chemical Name
33		tert-Butyl ((2R)-3-([1,1'-biphenyl]-4-yl)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxopropan-2-yl)carbamate
34		(2R)-3-([1,1'-Biphenyl]-4-yl)-2-amino-N-(2,3-bis(tetradecyloxy)propyl)propanamide
35		tert-Butyl ((2S)-3-([1,1'-biphenyl]-4-yl)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxopropan-2-yl)carbamate
36		(2S)-3-([1,1'-Biphenyl]-4-yl)-2-amino-N-(2,3-bis(tetradecyloxy)propyl)propanamide
37		Di-tert-butyl ((5S)-6-((2S)-2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)pyrrolidin-1-yl)-6-oxohexane-1,5-diyl)dicarbamate
38		(2S)-1-(L-Lysyl)-N-(2,3-bis(tetradecyloxy)propyl)pyrrolidine-2-carboxamide
39		tert-Butyl 2-((2S)-2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate
40		(2S)-N-(2,3-bis(tetradecyloxy)propyl)-1-glycylpyrrolidine-2-carboxamide

Ex. #	Structure	Chemical Name
41		3-(2-(5-(Benzyloxy)-1H-indol-3-yl)acetamido)-N-(2,3-bis(tetradecyloxy)propyl)propanamide
42		(9H-Fluoren-9-yl)methyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxo-5-(3-tosylguanidino)pentan-2-yl)carbamate
43		(9H-Fluoren-9-yl)methyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxo-5-(1,3-bis-(tert-butyl)oxy)guanidino)pentan-2-yl)carbamate
44		(9H-Fluoren-9-yl)methyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-5-guanidino-1-oxopentan-2-yl)carbamate
45		tert-Butyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxo-5-(3-tosylguanidino)pentan-2-yl)carbamate
46		(2S)-2-Amino-N-(2,3-bis(tetradecyloxy)propyl)-5-(3-tosylguanidino)pentanamide

Ex. #	Structure	Chemical Name
47		tert-Butyl ((2S)-4-amino-1-((2,3-bis(tetradecyloxy)propyl)amino)-1,4-dioxobutan-2-yl)carbamate
48		Di-tert-butyl ((5S)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexane-1,5-diyl)dicarbamate
49		(2S)-2,6-Diamino-N-(2,3-bis(tetradecyloxy)propyl)hexanamide
50		tert-Butyl ((5S)-5-acetamido-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexyl)carbamate
51		(2S)-2-Acetamido-6-amino-N-(2,3-bis(tetradecyloxy)propyl)hexanamide
52		tert-Butyl 4-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-((2,3-bis(tetradecyloxy)propyl)amino)-3-oxopropyl)piperidine-1-carboxylate
53		(9H-Fluoren-9-yl)methyl (1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxo-3-(piperidin-4-yl)propan-2-yl)carbamate hydrochloride

Ex. #	Structure	Chemical Name
54		tert-Butyl 4-(((benzyloxy)carbonyl)amino)-4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)peridine-1-carboxylate
55		Benzyl (4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)peridin-4-yl)carbamate
56		tert-Butyl ((5S)-5-([1,1'-biphenyl]-4-ylmethyl)amino)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexyl)carbamate
57		(2S)-2-([1,1'-Biphenyl]-4-ylmethyl)amino)-6-amino-N-(2,3-bis(tetradecyloxy)propyl)hexanamide
58		tert-Butyl ((5S)-6-((2,3-bis(tetradecyloxy)propyl)amino)-5-((4-fluorobenzyl)amino)-6-oxohexyl)carbamate
59		(2S)-6-Amino-N-(2,3-bis(tetradecyloxy)propyl)-2-((4-fluorobenzyl)amino)hexanamide
60		tert-Butyl ((5S)-5-(benzylamino)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexyl)carbamate
61		(2S)-6-Amino-2-(benzylamino)-N-(2,3-bis(tetradecyloxy)propyl)hexanamide

Ex. #	Structure	Chemical Name
62		tert-Butyl ((5R)-5-(benzylamino)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexyl)carbamate
63		((2R)-6-Amino-2-(benzylamino)-N-(2,3-bis(tetradecyloxy)propyl)hexanamide
72		tert-butyl 3-((((10S)-2,2-dimethyl-4,11-dioxo-14-(tetradecyloxy)-3,16-dioxo-5,12-diazatriacontan-10-yl)amino)methyl)-1H-indole-1-carboxylate
73		(2S)-2-((((1H-indol-3-yl)methyl)amino)-6-amino-N-(2,3-bis(tetradecyloxy)propyl)hexanamide dihydrochloride
74		tert-butyl 3-(2-((((10S)-2,2-dimethyl-4,11-dioxo-14-(tetradecyloxy)-3,16-dioxo-5,12-diazatriacontan-10-yl)amino)-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate
75		(2S)-6-amino-N-(2,3-bis(tetradecyloxy)propyl)-2-(2-(5-methoxy-1H-indol-3-yl)acetamido)hexanamide hydrochloride
76		tert-butyl 5-(benzyloxy)-3-(2-((((10S)-2,2-dimethyl-4,11-dioxo-14-(tetradecyloxy)-3,16-dioxo-5,12-diazatriacontan-10-yl)amino)-2-oxoethyl)-1H-indole-1-carboxylate

Ex. #	Structure	Chemical Name
77		(2S)-6-amino-2-(2-(5-(benzyloxy)-1H-indol-3-yl)acetamido)-N-(2,3-bis(tetradecyloxy)propyl)hexanamide hydrochloride
78		tert-butyl ((5S)-6-((2,3-bis(tetradecyloxy)propyl)amino)-5-((naphthalen-2-ylmethyl)amino)-6-oxohexyl)carbamate
79		(2S)-6-amino-N-(2,3-bis(tetradecyloxy)propyl)-2-((naphthalen-2-ylmethyl)amino)hexanamide dihydrochloride
136		N-(1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxotetradecan-2-yl)-5-fluoro-1H-indole-3-carboxamide
137		N-(2,3-bis(tetradecyloxy)propyl)-2-((1-(5-fluoro-1H-indol-3-yl)tetradecyl)amino)acetamide
138		3-((1-(1H-Indol-3-yl)tetradecyl)amino)-N-(2,3-bis(tetradecyloxy)propyl)propanamide
139		2-Amino-N-(1,3-bis(octadecyloxy)propan-2-yl)-3-guanidinopropanamide
140		2-Amino-N-(1,3-bis(octadecyloxy)propan-2-yl)-3-(1H-imidazol-5-yl)propanamide
141		2-Amino-N-(1,3-bis(octadecyloxy)propan-2-yl)-3-(1H-indol-2-yl)propanamide

Ex. #	Structure	Chemical Name
142		2,5-Diamino-N-(1,3-bis(octadecyloxy)propan-2-yl)pentanamide and
143		2,6-Diamino-N-(1,3-bis(octadecyloxy)propan-2-yl)hexanamide

and pharmaceutically acceptable salts thereof.

[0054] In some embodiments, the compound is not a compound of Table 1X.

Table 1X.

Ex. #	Structure
1x	
2x	
3x	
4x	
5x	

Ex. #	Structure
6x	
7x	
8x	
9x	
10x	
11x	

and pharmaceutically acceptable salts thereof.

- Formula (II)

[0055] In some embodiments of Formula (II), R^{21} is H. In other embodiments, R^{21} is C_{1-4} alkyl. In other embodiments, R^{21} is $-CO_2C_{1-4}$ alkyl. In other embodiments, R^{21} is H or $-CO_2$ -tert-butyl. In some embodiments, R^{22} is H. In other embodiments, R^{22} is C_{1-4} alkyl. In some embodiments, R^{24} is H. In other embodiments, R^{24} is C_{1-4} alkyl.

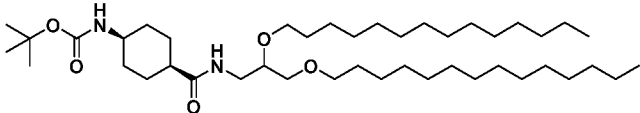
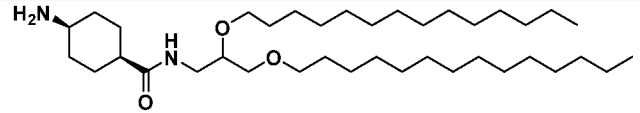
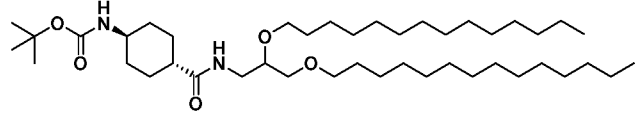
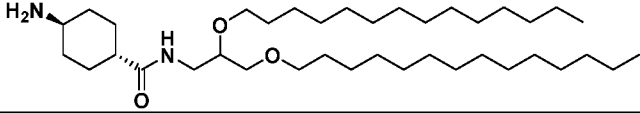
[0056] In some embodiments, R^{25} and R^{26} are each independently C_{8-16} alkyl or C_{8-16} alkenyl. In some embodiments, R^{25} and R^{26} are each independently C_{8-16} alkyl. In some embodiments, R^{25} and R^{26} are the same. In other embodiments, R^{25} and R^{26} are different. In some

embodiments, R^{25} and R^{26} are unbranched hydrocarbons. In some embodiments, R^{25} and R^{26} are each C_{14} alkyl.

[0057] In some embodiments, n_2 is 0. In some embodiments, n_2 is 1. In some embodiments, p_2 is 0. In other embodiments, p_2 is 1. In some embodiments, n_2 is 1 and p_2 is 0. In other embodiments, n_2 is 0 and p_2 is 1.

[0058] In other embodiments, the compound of Formula (II) is selected from the group consisting of compounds of Table 2:

Table 2.

Ex. #	Structure	Chemical Name
64		tert-Butyl ((<i>cis</i>)-4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)cyclohexyl)carbamate
65		(<i>cis</i>)-4-Amino-N-(2,3-bis(tetradecyloxy)propyl)cyclohexane-1-carboxamide
66		tert-Butyl ((<i>trans</i>)-4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)cyclohexyl)carbamate and
67		(<i>trans</i>)-4-Amino-N-(2,3-bis(tetradecyloxy)propyl)cyclohexane-1-carboxamide

and pharmaceutically acceptable salts thereof.

- Formula (III)

[0059] In some embodiments of Formula (III), R^{31} is phenyl or monocyclic heteroaryl. In some embodiments, R^{31} is phenyl. In some embodiments, R^{31} is monocyclic heteroaryl. In some embodiments, the R^{31} heteroaryl is pyrrolyl, imidazolyl, furanyl, or thiophenyl.

[0060] In some embodiments, R^{32} is H. In other embodiments, R^{32} is C_{1-4} alkyl.

[0061] In some embodiments, R^{33} is C_{1-4} alkyl- NR^xR^y . In some embodiments, R^x is H. In some embodiments, R^x is C_{1-4} alkyl. In some embodiments, R^x is $-CO_2-C_{1-4}$ alkyl. In some

embodiments, R^y is H. In other embodiments, R^y is C_{1-4} alkyl. In some embodiments, R^x and R^y are both H. In some embodiments, R^x is $-\text{CO}^2$ -tert-butyl and R^y is H.

[0062] In some embodiments, R^{34} is H. In some embodiments, R^{34} is C_{1-4} alkyl.

[0063] In some embodiments, R^{35} is C_{14-18} alkyl. In some embodiments, R^{35} is C_{14-18} alkenyl. In some embodiments, the C_{14-18} alkenyl has one double bond. In some embodiments, the C_{14-18} alkenyl has one cis double bond.

[0064] In other embodiments, the compound of Formula (III) is selected from the group consisting of compounds of Table 3:

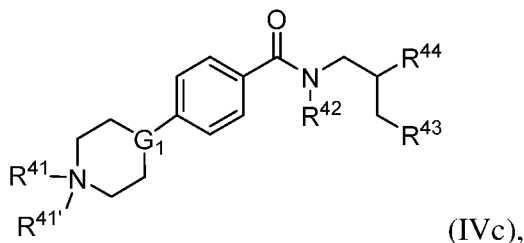
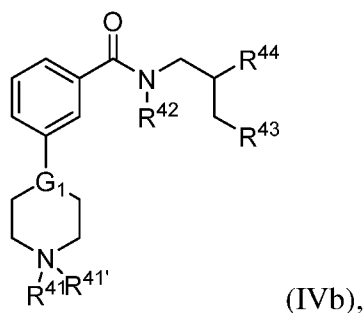
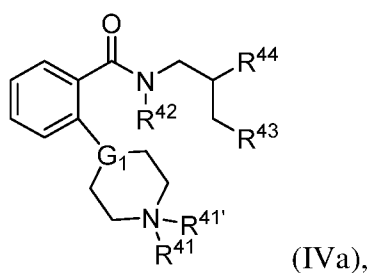
Table 3.

Ex. #	Structure	Chemical Name
68		Benzyl tert-butyl (6-(octadec-9-en-1-ylamino)-6-oxohexane-1,5-diyl)(R,Z)-dicarbamate
69		Benzyl (R,Z)-(6-amino-1-(octadec-9-en-1-ylamino)-1-oxohexan-2-yl)carbamate
70		Benzyl tert-butyl (6-oxo-6-(tetradecylamino)hexane-1,5-diyl)(R)-dicarbamate and
71		Benzyl (R)-(6-amino-1-oxo-1-(tetradecylamino)hexan-2-yl)carbamate

and pharmaceutically acceptable salts thereof.

- Formula (IV)

[0065] In some embodiments of Formula (IV), the compound is of the formula (IVa), (IVb), or (IVc):



wherein G^1 , R^{41} , $R^{41'}$, R^{42} , R^{43} and R^{44} are as defined for Formula (IV);

or a pharmaceutically acceptable salt thereof.

[0066] In some embodiments of Formula (IV), (IVa), (IVb), or (IVc), G^1 is N. In other embodiments, G^1 is CH.

[0067] In some embodiments of Formula (IV), (IVa), (IVb), or (IVc), R^{41} is H. In some embodiments, R^{41} is C_{1-4} alkyl. In some embodiments, R^{41} is $-CO_2C_{1-4}$ alkyl. In some embodiments, $R^{41'}$ is absent. In other embodiments, $R^{41'}$ is H or C_{1-4} alkyl, wherein the nitrogen attached to $R^{41'}$ has a positive charge. In some embodiments, $R^{41'}$ is H. In other embodiments, $R^{41'}$ is C_{1-4} alkyl. In some embodiments, R^{41} is H, methyl, or tert-butyloxycarbonyl.

[0068] In some embodiments of Formula (IV), (IVa), (IVb), or (IVc), R^{42} is H. In other embodiments, R^{42} is C_{1-4} alkyl, such as methyl.

[0069] In some embodiments of Formula (IV), (IVa), (IVb), or (IVc), R^{43} is $-OC_{1-18}$ alkyl or $-OC_{1-18}$ alkenyl, each optionally substituted with $-OH$, $-OC_{1-4}$ alkyl, $-C(O)OH$, $-C(O)OC_{1-4}$ alkyl, $-C(O)NHR^{4b}$, or aryl. In some embodiments, R^{43} is $-C_{1-18}$ alkyl, or $-C_{1-18}$ alkenyl, each optionally substituted with $-OH$, $-OC_{1-4}$ alkyl, $-C(O)OH$, $-C(O)OC_{1-4}$ alkyl, $-C(O)NHR^{4b}$, or aryl.

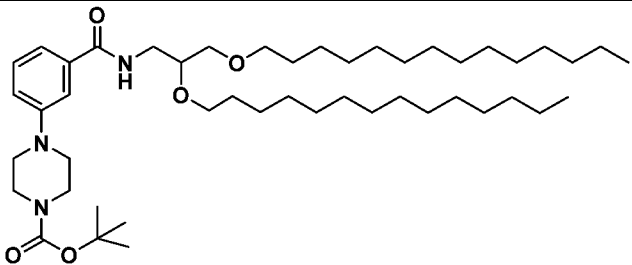
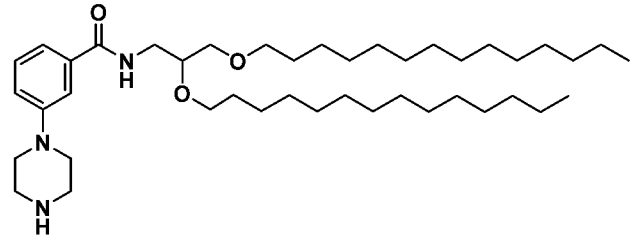
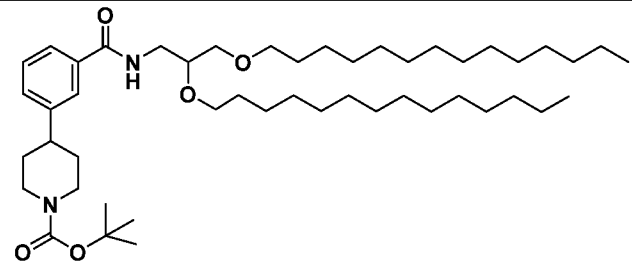
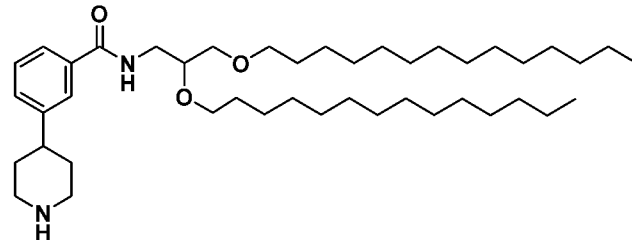
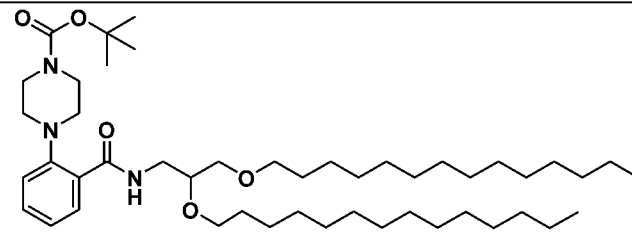
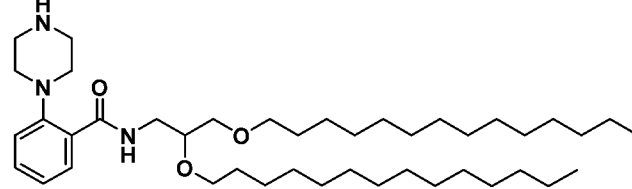
[0070] In some embodiments of Formula (IV), (IVa), (IVb), or (IVc), R^{44} is $-OC_{4-18}$ alkyl, optionally substituted with $-OH$, $-OC_{1-4}$ alkyl, $-C(O)OH$, $-C(O)OC_{1-4}$ alkyl, $-C(O)NH_2$, $-C(O)NHC_{1-4}$ alkyl, or aryl. In other embodiments, R^{44} is $-OC_{4-18}$ alkenyl, optionally substituted with $-OH$, $-OC_{1-4}$ alkyl, $-C(O)OH$, $-C(O)OC_{1-4}$ alkyl, $-C(O)NH_2$, $-C(O)NHC_{1-4}$ alkyl, or aryl.

[0071] In some embodiments of Formula (IV), (IVa), (IVb), or (IVc), R^{43} is $-OC_{1-18}$ alkyl and R^{44} is $-OC_{4-18}$ alkyl. In some embodiments, R^{43} is $-OC_{1-18}$ alkenyl and R^{44} is $-OC_{4-18}$ alkenyl. In some embodiments, R^{43} is $-OC_{13-18}$ alkyl and R^{44} is $-OC_{13-18}$ alkyl. In some embodiments, R^{43} is $-OC_{13-18}$ alkenyl and R^{44} is $-OC_{13-18}$ alkenyl. In some embodiments, R^{43} is $-OC_{1-12}$ alkyl and R^{44} is $-OC_{4-12}$ alkyl. In some embodiments, R^{43} is $-OC_{1-12}$ alkenyl and R^{44} is $-OC_{4-12}$ alkenyl, wherein R^{43} and R^{44} are each optionally substituted with $-OH$, $-OC_{1-4}$ alkyl, $-C(O)OC_{1-4}$ alkyl, $-C(O)NH_2$, $-C(O)NHC_{1-4}$ alkyl, or aryl. In some embodiments, R^{43} and R^{44} are each $-OC_7$ alkyl. In some embodiments, R^{43} and R^{44} are each $-OC_{14}$ alkyl or $-OC_{14}$ alkenyl. In some embodiments, R^{43} and R^{44} are each $-OC_{16}$ alkyl or $-OC_{16}$ alkenyl. In some embodiments, R^{43} and R^{44} are each $-OC_{18}$ alkyl or $-OC_{18}$ alkenyl.

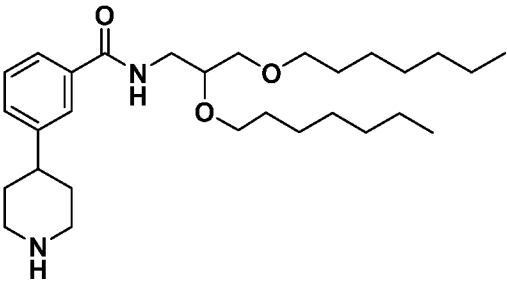
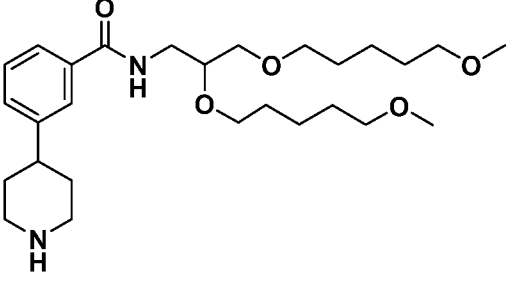
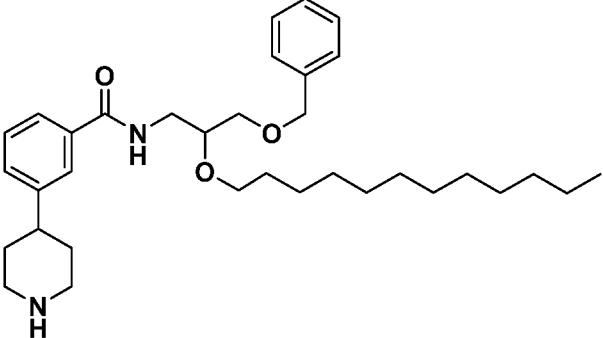
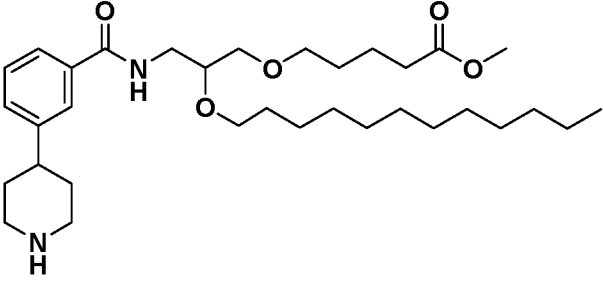
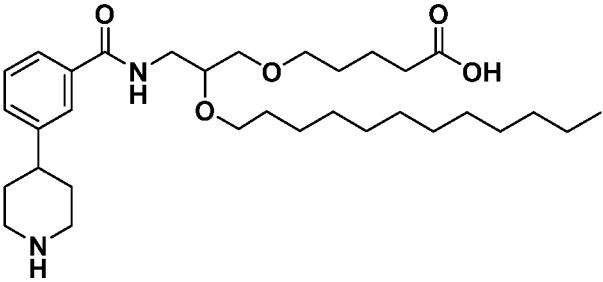
[0072] In other embodiments, the compound is selected from the group consisting of compounds of Table 4:

Table 4.

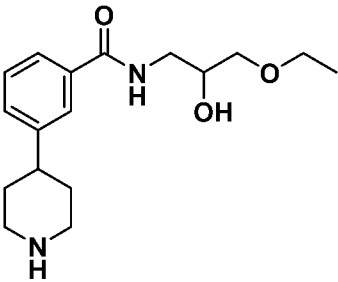
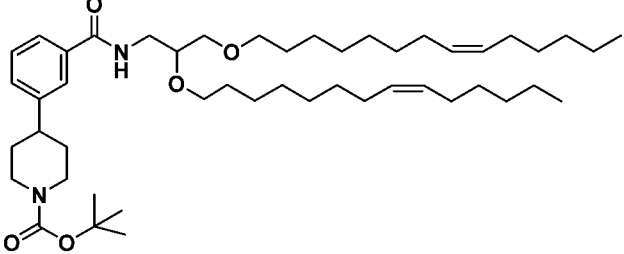
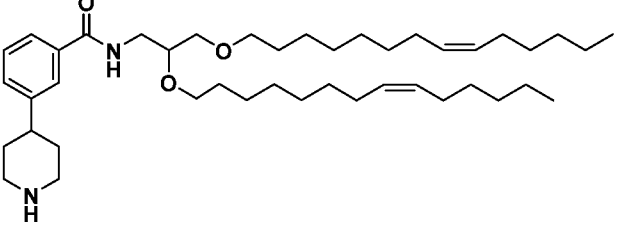
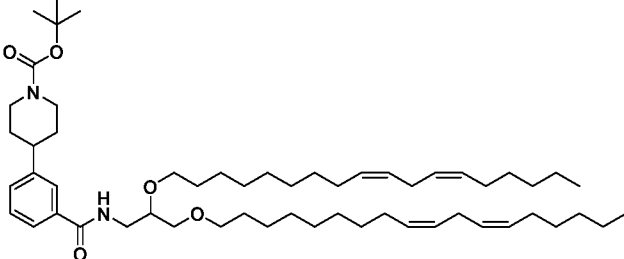
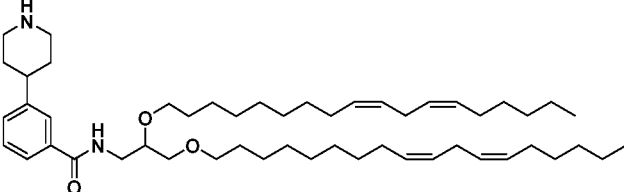
Ex. #	Structure	Chemical Name
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Ex. #	Structure	Chemical Name
80		tert-butyl 4-(3-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperazine-1-carboxylate
81		N-(2,3-bis(tetradecyloxy)propyl)-3-(piperazin-1-yl)benzamide hydrochloride
82		tert-butyl 4-(3-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate
83		N-(2,3-bis(tetradecyloxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride
84		tert-butyl 4-(2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperazine-1-carboxylate
85		N-(2,3-bis(tetradecyloxy)propyl)-2-(piperazin-1-yl)benzamide hydrochloride

Ex. #	Structure	Chemical Name
86		tert-butyl 4-(2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate
87		N-(2,3-bis(tetradecyloxy)propyl)-2-(piperidin-4-yl)benzamide hydrochloride
88		tert-butyl 4-(4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperazine-1-carboxylate
89		N-(2,3-bis(tetradecyloxy)propyl)-4-(piperazin-1-yl)benzamide hydrochloride
90		tert-butyl 4-(4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate
91		N-(2,3-bis(tetradecyloxy)propyl)-4-(piperidin-4-yl)benzamide hydrochloride
92		4-(3-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)-1,1-dimethylpiperidin-1-ium iodide

Ex. #	Structure	Chemical Name
93		N-(2,3-bis(heptyloxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride
94		N-(2,3-bis((5-methoxypentyl)oxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride
95		N-(3-(benzyloxy)-2-(dodecyloxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride
96		methyl 5-(2-(dodecyloxy)-3-(3-(piperidin-4-yl)benzamido)propoxy)pentanoate hydrochloride
97		5-(2-(dodecyloxy)-3-(3-(piperidin-4-yl)benzamido)propoxy)pentanoic acid hydrochloride

Ex. #	Structure	Chemical Name
98		N-(2-(dodecyloxy)-3-((5-(methylamino)-5-oxopentyl)oxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride
99		N-(3-((5-amino-5-oxopentyl)oxy)-2-(dodecyloxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride
100		N-(3-(octyloxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride
101		3-(piperidin-4-yl)-N-tetradecylbenzamide hydrochloride
102		N-(3-(2-methoxyethoxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride

Ex. #	Structure	Chemical Name
103		N-(3-ethoxy-2-hydroxypropyl)-3-(piperidin-4-yl)benzamide hydrochloride
113		tert-butyl 4-(3-((2,3-bis(((Z)-tetradec-8-en-1-yl)oxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate
114		N-(2,3-bis(((Z)-tetradec-8-en-1-yl)oxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride
115		tert-butyl 4-(3-((2,3-bis(((9Z,12Z)-octadeca-9,12-dien-1-yl)oxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate
116		N-(2,3-bis(((9Z,12Z)-octadeca-9,12-dien-1-yl)oxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride

and pharmaceutically acceptable salts thereof.

- Formula (V)

[0073] In some embodiments of Formula (V), G_2 is a bond. In some embodiments, G_2 is $-CH_2-$. In some embodiments, G_2 is $-CH_2NH-$. In other embodiments, G_2 is $-CH_2NHCH_2-$.

[0074] In some embodiments, G_3 is $-C(O)-$. In other embodiments, G_3 is $-CH_2-$.

[0075] In some embodiments, R^{51} is H. In some embodiments, R^{51} is C_{1-4} alkyl. In some embodiments, R^{51} is $-CO_2C_{1-4}$ alkyl. In some embodiments, R^{51} is a heterocycle, such as pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, or morpholinyl. In other embodiments, R^{51} is $-C_{1-4}$ alkyl- $NR^{5a}R^{5b}$; where R^{5a} is H or C_{1-4} alkyl and R^{5b} is H, C_{1-4} alkyl, or $-CO_2C_{1-4}$ alkyl.

[0076] In some embodiments, R^{52} is H. In other embodiments, R^{52} is C_{1-4} alkyl;

[0077] In some embodiments, R^{51} and R^{52} , together with the carbon to which they are attached, form a heterocycloalkyl; wherein the heterocycloalkyl is optionally substituted with $-CO_2C_{1-4}$ alkyl. In some embodiments, R^{51} and R^{52} , together with the carbon to which they are attached, form a heterocycloalkyl; wherein the heterocycloalkyl is optionally substituted with tert-butyloxycarbonyl. In some embodiments, R^{51} and R^{52} , together with the carbon to which they are attached, form a piperidinyl, optionally substituted with $-CO_2C_{1-4}$ alkyl, such as tert-butyloxycarbonyl.

[0078] In some embodiments, R^{53} is H. In other embodiments, R^{53} is C_{1-4} alkyl.

[0079] In some embodiments, o is 0. In some embodiments, o is 1. In some embodiments, r is 0. In some embodiments, r is 1. In some embodiments, s is 0. In some embodiments, s is 1.

[0080] In some embodiments, r is 1 and s is 1. In some embodiments, r is 1 and s is 0. In some embodiments, r is 0 and s is 1. In some embodiments G_2 is a bond, r is 1, and s is 0. In some embodiments G_2 is a bond, r is 1, s is 0, and R^{51} and R^{52} , together with the carbon to which they are attached, form a heterocycloalkyl; wherein the heterocycloalkyl is optionally substituted with $-CO_2C_{1-4}$ alkyl. In some embodiments G_2 is $-CH_2-$, r is 1, and s is 0. In some embodiments G_2 is $-CH_2-$, r is 1, s is 0, and R^{51} and R^{52} , together with the carbon to which they are attached, form a heterocycloalkyl; wherein the heterocycloalkyl is optionally substituted with $-CO_2C_{1-4}$ alkyl. In some embodiments G_2 is $-CH_2NH-$, r is 1, and s is 0. In some embodiments G_2 is $-CH_2NH-$, r is 1, s is 0, and R^{51} and R^{52} , together with the carbon to which they are attached, form a heterocycloalkyl; wherein the heterocycloalkyl is optionally substituted with $-CO_2C_{1-4}$ alkyl. In

some embodiments G_2 is $-\text{CH}_2\text{NHCH}_2-$, r is 1, and s is 0. In some embodiments G_2 is $-\text{CH}_2\text{NHCH}_2-$, r is 1, s is 0, and R^{51} and R^{52} , together with the carbon to which they are attached, form a heterocycloalkyl; wherein the heterocycloalkyl is optionally substituted with $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$. In some embodiments G_2 is $-\text{CH}_2\text{NHCH}_2-$, r is 1, and s is 0. In some embodiments, G_2 is $-\text{CH}_2-$ or $-\text{CH}_2\text{NH}-$, r is 1, s is 0, and R^{51} is a heterocycle. In some embodiments, R^{51} is a heterocycle and R^{52} is H.

[0081] In some embodiments, R^{53} is H. In some embodiments, R^{53} is $\text{C}_{1-4}\text{alkyl}$.

[0082] In some embodiments, R^{54} is $\text{C}_{8-18}\text{alkyl}$. In some embodiments, R^{54} is $\text{C}_{8-18}\text{alkenyl}$. In some embodiments, R^{55} is $\text{C}_{8-18}\text{alkyl}$. In some embodiments, R^{55} is $\text{C}_{8-18}\text{alkenyl}$. In some embodiments, R^{54} and R^{55} are each independently $\text{C}_{8-18}\text{alkyl}$ or $\text{C}_{8-18}\text{alkenyl}$. In some embodiments, R^{54} and R^{55} are each independently $\text{C}_{8-18}\text{alkyl}$. In some embodiments, R^{54} and R^{55} are each independently $\text{C}_{8-18}\text{alkenyl}$. In some embodiments, R^{54} and R^{55} are the same. In other embodiments, R^{54} and R^{55} are different. In some embodiments, R^{54} and R^{55} are unbranched hydrocarbons. In some embodiments, R^{54} and R^{55} are each $\text{C}_{14}\text{alkyl}$. In some embodiments, R^{54} and R^{55} are each $\text{C}_{14}\text{alkenyl}$. In some embodiments, R^{54} and R^{55} are each $\text{C}_{16}\text{alkyl}$ or $\text{C}_{16}\text{alkenyl}$. In some embodiments, R^{54} and R^{55} are each $\text{C}_{18}\text{alkyl}$ or $\text{C}_{18}\text{alkenyl}$.

[0083] In other embodiments, the compound of Formula (V) is selected from the group consisting of compounds of Table 5:

Table 5.

Ex. #	Structure	Chemical Name
104		tert-butyl 4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)-4-phenylpiperidine-1-carboxylate
105		N-(2,3-bis(tetradecyloxy)propyl)-4-phenylpiperidine-4-carboxamide hydrochloride

Ex. #	Structure	Chemical Name
106		3-amino-N-(2,3-bis(tetradecyloxy)propyl)-2-phenylpropanamide hydrochloride
107		tert-butyl 3-benzyl-3-((2,3-bis(tetradecyloxy)propyl)carbamoyl)piperidine-1-carboxylate
108		3-benzyl-N-(2,3-bis(tetradecyloxy)propyl)piperidine-3-carboxamide hydrochloride
109		2-(benzylamino)-N-(2,3-bis(tetradecyloxy)propyl)-2-(piperidin-4-yl)acetamide hydrochloride
110		4-((benzylamino)methyl)-N-(2,3-bis(tetradecyloxy)propyl)piperidine-4-carboxamide hydrochloride
111		N-benzyl-2,3-bis(tetradecyloxy)propan-1-amine
112		N-benzyl-N,N-dimethyl-2,3-bis(tetradecyloxy)propan-1-aminium iodide

and pharmaceutically acceptable salts thereof.

- Formula (VI)

[0084] In some embodiments of Formula (VI), R^{61} is H. In some embodiments, R^{61} is $-CO_2-C_{1-8}alkyl$. In some embodiments, R^{61} is $-CO_2-CHR^{6a}-aryl$ or $-CO_2-CHR^{6a}-heteroaryl$, where R^{6a} is H or $C_{1-15}alkyl$ and the aryl or heteroaryl is optionally substituted with halo, $C_{1-4}alkyl$, C_1 -

4fluoroalkyl, -OH, -OC₁₋₄alkyl, -OC₁₋₄fluoroalkyl, -CN, phenyl, or -OC₁₋₄alkyl-aryl. In some embodiments, R⁶¹ is -C(O)-C₁₋₄alkyl. In some embodiments, R⁶¹ is -C(O)aryl, or -C(O)-heteroaryl, each optionally substituted with halo, C₁₋₄alkyl, C₁₋₄fluoroalkyl, -OH, -OC₁₋₄alkyl, -OC₁₋₄fluoroalkyl, -CN, phenyl, or -OC₁₋₄alkyl-aryl. In some embodiments, R⁶¹ is -C(O)-CHR^{6b}-NR^{6c}R^{6d}, where R^{6b} is H or -C₁₋₅alkyl-NR^{6e}R^{6f}; R^{6e} is H or C₁₋₄alkyl and R^{6f} is H, C₁₋₄alkyl, or -CO₂C₁₋₄alkyl; R^{6c} is H or C₁₋₄alkyl and R^{6d} is H, C₁₋₄alkyl, or -CO₂C₁₋₄alkyl. In some embodiments, R⁶¹ is -C(O)-CHR^{6a}-heteroaryl, -CHR^{6a}-aryl, or -CHR^{6a}-heteroaryl, where R^{6a} is H or C₁₋₁₅alkyl and each aryl or heteroaryl is optionally substituted with halo, C₁₋₄alkyl, C₁₋₄fluoroalkyl, -OH, -OC₁₋₄alkyl, -OC₁₋₄fluoroalkyl, -CN, phenyl, or -OC₁₋₄alkyl-aryl. In some embodiments, R⁶¹ is -SO₂-C₁₋₄alkyl, -SO₂-aryl, or -SO₂-heteroaryl. In some embodiments, R⁶¹ is -CHR^{6a}-aryl, where R^{6a} is H or C₁₋₁₅alkyl and the aryl is optionally substituted with halo, C₁₋₄alkyl, C₁₋₄fluoroalkyl, -OH, -OC₁₋₄alkyl, -OC₁₋₄fluoroalkyl, -CN, phenyl, or -OC₁₋₄alkyl-aryl. In some embodiments, R⁶¹ is -CHR^{6a}-heteroaryl, where R^{6a} is H or C₁₋₁₅alkyl and the heteroaryl is optionally substituted with halo, C₁₋₄alkyl, C₁₋₄fluoroalkyl, -OH, -OC₁₋₄alkyl, -OC₁₋₄fluoroalkyl, -CN, phenyl, or -OC₁₋₄alkyl-aryl. In some embodiments, R⁶¹ is -CH₂-phenyl. In some embodiments, R⁶¹ is -CH₂-naphthyl.

[0085] In some embodiments, R⁶² is H. In some embodiments, R⁶² is C₁₋₄alkyl.

[0086] In some embodiments, R⁶¹ is -CHR^{6a}-aryl or -CHR^{6a}-heteroaryl, where R^{6a} is H or C₁₋₁₅alkyl and each aryl or heteroaryl is optionally substituted with halo, C₁₋₄alkyl, C₁₋₄fluoroalkyl, -OH, -OC₁₋₄alkyl, -OC₁₋₄fluoroalkyl, -CN, phenyl, or -OC₁₋₄alkyl-aryl; and R⁶² is H or methyl. In some embodiments, R⁶¹ is -CH₂-phenyl or -CH₂-naphthyl; and R⁶² is H.

[0087] In some embodiments, R⁶⁶ is H. In some embodiments, R⁶⁶ is C₁₋₄alkyl. In other embodiments, R⁶⁶ is -CO₂C₁₋₄alkyl. In some embodiments, R⁶⁷ is H. In some embodiments, R⁶⁷ is C₁₋₄alkyl. In some embodiments, R⁶⁷ is -C(=NH)-NHR^{6m}, where R^{6m} is H, -SO₂aryl, or -CO₂C₁₋₄alkyl. In some embodiments, R⁶⁶ is -CO₂C₁₋₄alkyl and R⁶⁷ is H. In some embodiments, R⁶⁶ is H and R⁶⁷ is C₁₋₄alkyl or -C(=NH)-NHR^{6m}, where R^{6m} is H, -SO₂aryl, or -CO₂C₁₋₄alkyl. In some embodiments, R⁶⁶ and R⁶⁷ are both H.

[0088] In some embodiments, R^{63} is H. In some embodiments, R^{63} is C_{1-4} alkyl. In some embodiments, R^{62} and R^{63} are both H. In other embodiments, one of R^{62} and R^{63} is H and the other is C_{1-4} alkyl.

[0089] In some embodiments, R^{64} is H. In some embodiments, R^{64} is -OH. In some embodiments, R^{64} is $-C_{1-18}$ alkyl or $-C_{1-18}$ alkenyl, each optionally substituted with -OH or $-OC_{1-4}$ alkyl. In some embodiments, R^{64} is $-OC_{1-18}$ alkyl or $-OC_{1-18}$ alkenyl, each optionally substituted with -OH or $-OC_{1-4}$ alkyl. In some embodiments, R^{65} is H. In some embodiments, R^{65} is $-C_{4-8}$ cycloalkyl. In some embodiments, R^{65} is $-C_{1-18}$ alkyl or $-C_{1-18}$ alkenyl, each of which is optionally substituted with -OH or $-OC_{1-4}$ alkyl. In some embodiments, R^{65} is $-OC_{1-18}$ alkyl or $-OC_{1-18}$ alkenyl, each of which is optionally substituted with -OH or $-OC_{1-4}$ alkyl.

[0090] In some embodiments, R^{64} is $-OC_{1-18}$ alkyl or $-OC_{1-18}$ alkenyl, each of which is optionally substituted with -OH or $-OC_{1-4}$ alkyl; and R^{65} is $-OC_{1-18}$ alkyl or $-OC_{1-18}$ alkenyl, each of which is optionally substituted with -OH or $-OC_{1-4}$ alkyl. In some embodiments, R^{64} and R^{65} are each $-OC_{18}$ alkenyl. In some embodiments, R^{64} is $-C_{1-18}$ alkyl or $-C_{1-18}$ alkenyl, optionally substituted with -OH or $-OC_{1-4}$ alkyl; and R^{65} is H. In some embodiments, R^{65} is $-OC_{1-18}$ alkyl or $-OC_{1-18}$ alkenyl, optionally substituted with -OH or $-OC_{1-4}$ alkyl; and R^{64} is H. In some embodiments, R^{65} is $-C_{4-8}$ cycloalkyl and R^{64} is H.

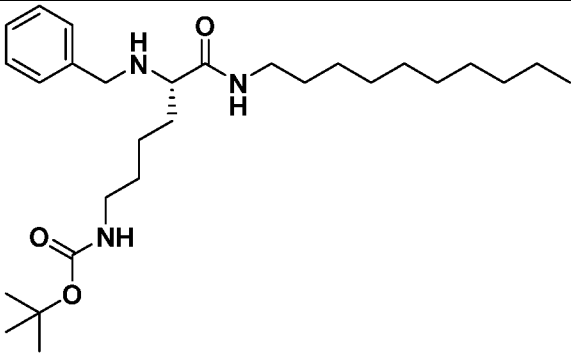
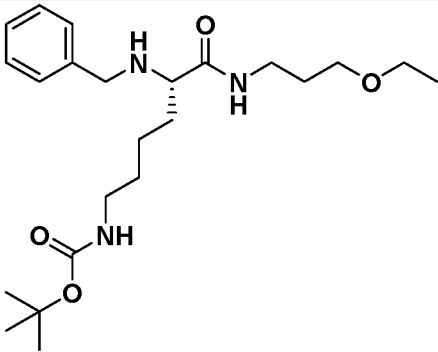
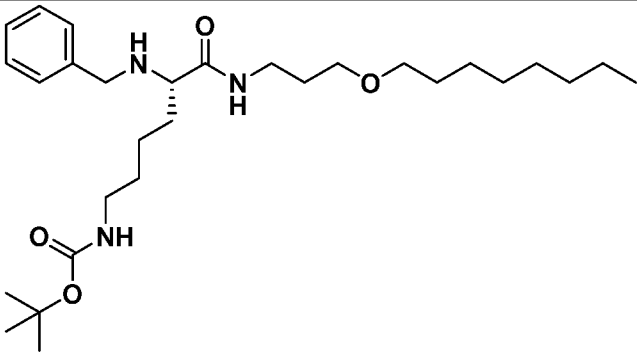
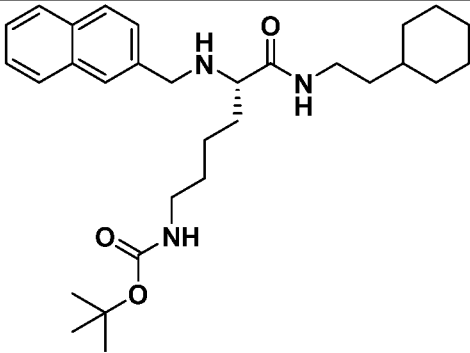
[0091] In some embodiments, t is 0. In some embodiments, t is 1. In some embodiments, t is 0 and R^{65} is $-C_{4-8}$ cycloalkyl. In some embodiments, t is 1; R^{64} is $-OC_{1-18}$ alkyl or $-OC_{1-18}$ alkenyl, each of which is optionally substituted with -OH or $-OC_{1-4}$ alkyl; and R^{65} is $-OC_{1-18}$ alkyl or $-OC_{1-18}$ alkenyl, each of which is optionally substituted with -OH or $-OC_{1-4}$ alkyl. In some embodiments, t is 1 and R^{64} and R^{65} are each $-OC_{18}$ alkenyl. In some embodiments, t is 1; R^{64} is $-C_{1-18}$ alkyl or $-C_{1-18}$ alkenyl, optionally substituted with -OH or $-OC_{1-4}$ alkyl; and R^{65} is H. In some embodiments, t is 1; R^{65} is $-OC_{1-18}$ alkyl or $-OC_{1-18}$ alkenyl, optionally substituted with -OH or $-OC_{1-4}$ alkyl; and R^{64} is H. In some embodiments, t is 0, R^{65} is $-C_{4-8}$ cycloalkyl, and R^{64} is H.

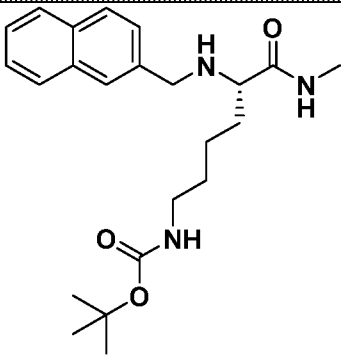
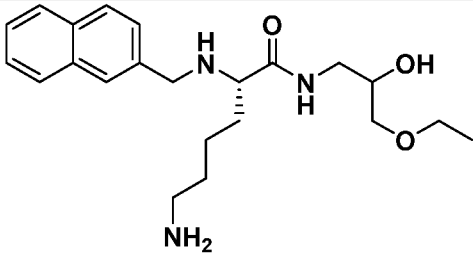
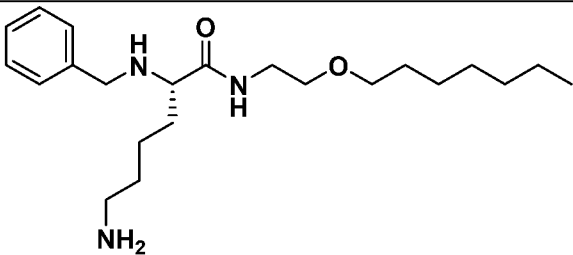
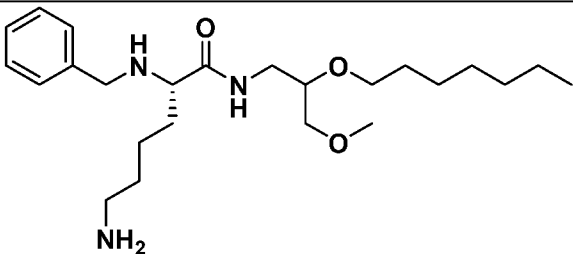
[0092] In other embodiments, the compound of Formula (VI) is selected from the group consisting of compounds of Table 6:

Table 6.

Ex. #	Structure	Chemical Name
117		tert-butyl ((5R)-5-(benzylamino)-6-((2,3-bis(((9Z,12Z)-octadeca-9,12-dien-1-yl)oxy)propyl)amino)-6-oxohexyl)carbamate
118		(2R)-6-amino-2-(benzylamino)-N-(2,3-bis(((9Z,12Z)-octadeca-9,12-dien-1-yl)oxy)propyl)hexanamide dihydrochloride
119		(S)-6-amino-2-(benzylamino)-N-tetradecylhexanamide dihydrochloride
120		(S)-6-amino-2-(benzylamino)-N-decylhexanamide dihydrochloride
121		(S)-6-amino-2-(benzylamino)-N-(3-ethoxypropyl)hexanamide dihydrochloride
122		(S)-6-amino-2-(benzylamino)-N-(3-(octyloxy)propyl)hexanamide dihydrochloride

Ex. #	Structure	Chemical Name
123		(S)-6-amino-N-(2-cyclohexylethyl)-2-((naphthalen-2-ylmethyl)amino)hexanamide dihydrochloride
124		(S)-6-amino-N-methyl-2-((naphthalen-2-ylmethyl)amino)hexanamide dihydrochloride
125		(2S)-6-amino-2-(benzylamino)-N-(2,3-bis(heptyloxy)propyl)hexanamide dihydrochloride
126		(2S)-6-amino-2-(benzylamino)-N-(2,3-bis((5-methoxypentyl)oxy)propyl)hexanamide dihydrochloride
127		tert-butyl (S)-(5-(benzylamino)-6-oxo-6-(tetradecylamino)hexyl)carbamate

Ex. #	Structure	Chemical Name
128		tert-butyl (S)-(5-(benzylamino)-6-(decylamino)-6-oxohexyl)carbamate
129		tert-butyl (S)-(5-(benzylamino)-6-((3-ethoxypropyl)amino)-6-oxohexyl)carbamate
130		tert-butyl (S)-(5-(benzylamino)-6-((3-(octyloxy)propyl)amino)-6-oxohexyl)carbamate
131		tert-butyl (S)-(6-((2-cyclohexylethyl)amino)-5-((naphthalen-2-ylmethyl)amino)-6-oxohexyl)carbamate

Ex. #	Structure	Chemical Name
132		tert-butyl (S)-6-((2-cyclohexylethyl)amino)-5-((naphthalen-2-ylmethyl)amino)-6-oxohexyl)carbamate
133		(2S)-6-amino-N-(3-ethoxy-2-hydroxypropyl)-2-((naphthalen-2-ylmethyl)amino) hexanamide dihydrochloride
134		(S)-6-amino-2-(benzylamino)-N-(2-(heptyloxy)ethyl)hexanamide dihydrochloride
135		(2S)-6-amino-2-(benzylamino)-N-(2-(heptyloxy)-3-methoxypropyl)hexanamide dihydrochloride

and pharmaceutically acceptable salts thereof.

[0093] Any formula or compound given herein, such as Formula (I), (II), (III), (IV), (V), or (VI), or compounds of Tables 1-6, is intended to represent compounds having structures depicted by the structural formula as well as certain variations or forms. In particular, compounds of any formula given herein may have asymmetric centers and therefore exist in different enantiomeric or diastereomeric forms. All optical isomers and stereoisomers of the compounds of the general formula, and mixtures thereof in any ratio, are considered within the

scope of the formula. Thus, any formula given herein is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms, and mixtures thereof in any ratio. Where a compound of Tables 1-6 is depicted with a particular stereochemical configuration, also provided herein is any alternative stereochemical configuration of the compound, as well as a mixture of stereoisomers of the compound in any ratio. Any compound of Tables 1-6 is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms, and mixtures thereof in any ratio. Furthermore, certain structures may exist as geometric isomers (i.e., *cis* and *trans* isomers), as tautomers, or as atropisomers. Additionally, any formula given herein is intended to refer to hydrates, solvates, and amorphous forms of such compounds, and mixtures thereof, even if such forms are not listed explicitly. In some embodiments, the solvent is water and the solvates are hydrates.

Chemical Definitions

[0094] The term “alkyl” refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain. Examples of alkyl groups include methyl (Me), ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

[0095] The term “alkenyl” refers to a straight- or branched-chain hydrocarbon group having from 2 to 12 carbon atoms in the chain, and having one or more double bonds. Examples of alkenyl groups include ethenyl (or vinyl), allyl, and but-3-en-1-yl. Included within this term are *cis* and *trans* isomers and mixtures thereof.

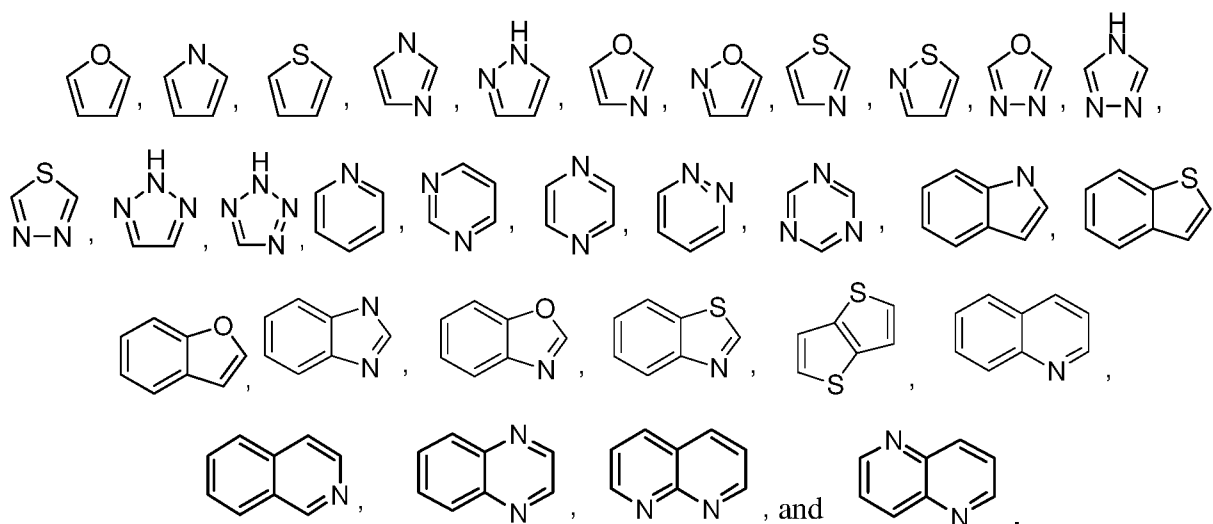
[0096] The term “alkylene” refers to a divalent group that is a radical of an alkane. The alkylene can be a straight- or branched-chain divalent alkyl radical. “C₁₋₄ alkylene” refers to alkylene groups with 1 to 4 carbon atoms.

[0097] The term “aryl” refers to a monovalent aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (a phenyl group) or a multiple condensed ring (such as naphthyl, anthracenyl, or indanyl), in which condensed rings are optionally aromatic, provided

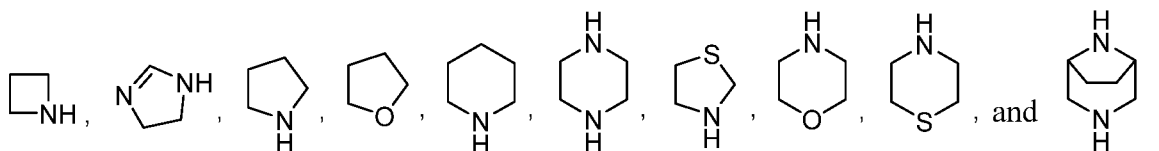
that the point of attachment of the aryl group to the parent structure is through an atom of an aromatic ring. “Aryl” as defined herein encompasses groups such as phenyl and fluorenyl.

[0098] The term “fluoroalkyl” refers to an alkyl group as defined above, substituted with one or more fluoro substituents. Examples of fluoroalkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, and trifluoroethyl.

[0099] The term “heteroaryl” refers to a monocyclic, fused bicyclic, or fused polycyclic aromatic heterocycle (ring structure having ring atoms selected from carbon atoms and up to four heteroatoms selected from nitrogen, oxygen, and sulfur) having from 3 to 12 ring atoms per heterocycle. Illustrative examples of heteroaryl groups include the following entities, in the form of properly bonded moieties:



[0100] The term “heterocycloalkyl” refers to a saturated or partially unsaturated group having a single ring or multiple condensed rings, including fused, bridged, or spiro ring systems, and having from 3 to 20 ring atoms, including 1 to 10 heteroatoms. These ring atoms are selected from the group consisting of carbon, nitrogen, sulfur, or oxygen. In certain embodiments, the nitrogen and/or sulfur atom(s) of the heterocyclic group are optionally oxidized to provide for N-oxide, -S(O)-, or -SO₂- moieties. Illustrative examples of heterocyclic groups include the following entities, in the form of properly bonded moieties:



[0101] The term “halogen” represents chlorine, fluorine, bromine, or iodine. The term “halo” represents chloro, fluoro, bromo, or iodo.

[0102] The term “oxo” represents a carbonyl oxygen. For example, a cyclopentyl substituted with oxo is cyclopentanone.

[0103] Those skilled in the art will recognize that the species listed or illustrated above are not exhaustive, and that additional species within the scope of these defined terms may also be selected.

[0104] The term “substituted” means that the specified group or moiety bears one or more substituents. The term “unsubstituted” means that the specified group bears no substituents. The term “optionally substituted” means that the specified group is unsubstituted or substituted by one or more substituents. Where the term “substituted” is used to describe a structural system, the substitution is meant to occur at any valency-allowed position on the system.

[0105] Any formula depicted herein is intended to represent a compound of that structural formula as well as certain variations or forms. For example, a formula given herein is intended to include a racemic form, or one or more enantiomeric, diastereomeric, or geometric isomers, or a mixture thereof. Additionally, any formula given herein is intended to refer also to a hydrate, solvate, or polymorph of such a compound, or a mixture thereof.

[0106] Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , and ^{125}I , respectively. Such isotopically labelled compounds are useful in metabolic studies (preferably with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques [such as positron emission tomography (PET) or single-photon

emission computed tomography (SPECT)] including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or ^{11}C labeled compound may be particularly preferred for PET or SPECT studies. PET and SPECT studies may be performed as described, for example, by Brooks, D.J., "Positron Emission Tomography and Single-Photon Emission Computed Tomography in Central Nervous System Drug Development," *NeuroRx* 2005, 2(2), 226-236, and references cited therein. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[0107] The nomenclature " C_{i-j} " with $j > i$, when applied herein to a class of substituents, is meant to refer to embodiments of this invention for which each and every one of the number of carbon members, from i to j including i and j , is independently realized. By way of example, the term C_{1-3} refers independently to embodiments that have one carbon member (C_1), embodiments that have two carbon members (C_2), and embodiments that have three carbon members (C_3).

[0108] Any disubstituent referred to herein is meant to encompass the various attachment possibilities when more than one of such possibilities are allowed. For example, reference to disubstituent $-\text{A}-\text{B}-$, where $\text{A} \neq \text{B}$, refers herein to such disubstituent with A attached to a first substituted member and B attached to a second substituted member, and it also refers to such disubstituent with A attached to the second substituted member and B attached to the first substituted member.

[0109] The invention also includes pharmaceutically acceptable salts of the compounds represented by Formula (I), (II), (III), (IV), (V), or (VI) or the compounds of any of Tables 1-6, preferably of those described above and of the specific compounds exemplified herein, and pharmaceutical compositions comprising such salts, and methods of using such salts.

[0110] A "pharmaceutically acceptable salt" is intended to mean a salt of a free acid or base of a compound represented herein that is non-toxic, biologically tolerable, or otherwise

biologically suitable for administration to the subject. See, generally, S.M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977, 66, 1-19. Preferred pharmaceutically acceptable salts are those that are pharmacologically effective and suitable for contact with the tissues of subjects without undue toxicity, irritation, or allergic response. A compound described herein may possess a sufficiently acidic group, a sufficiently basic group, both types of functional groups, or more than one of each type, and accordingly react with a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

[0111] Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, methylsulfonates, propylsulfonates, besylates, xylenesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ -hydroxybutyrates, glycolates, tartrates, and mandelates. Lists of other suitable pharmaceutically acceptable salts are found in Remington's Pharmaceutical Sciences, 17th Edition, Mack Publishing Company, Easton, Pa., 1985.

[0112] For a compound of Formula (I), (II), (III), (IV), (V), or (VI) or a compound of any of Tables 1-6 that contains a basic nitrogen, a pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, boric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, phenylacetic acid, propionic acid, stearic acid, lactic acid, ascorbic acid, maleic acid, hydroxymaleic acid, isethionic acid, succinic acid, valeric acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, oleic acid, palmitic acid, lauric acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an α -hydroxy acid, such as mandelic acid, citric acid, or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid, 2-acetoxybenzoic acid, naphthoic acid, or cinnamic acid,

a sulfonic acid, such as laurylsulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, or ethanesulfonic acid, or any compatible mixture of acids such as those given as examples herein, and any other acid and mixture thereof that are regarded as equivalents or acceptable substitutes in light of the ordinary level of skill in this technology.

[0113] The invention also relates to pharmaceutically acceptable prodrugs of the compounds of Formula (I), (II), (III), (IV), (V), or (VI), or the compounds of any of Tables 1-6, and treatment methods employing such pharmaceutically acceptable prodrugs. The term "prodrug" means a precursor of a designated compound that, following administration to a subject, yields the compound *in vivo* via a chemical or physiological process such as solvolysis or enzymatic cleavage, or under physiological conditions (e.g., a prodrug on being brought to physiological pH is converted to the formula compound). A "pharmaceutically acceptable prodrug" is a prodrug that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to the subject. Illustrative procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

[0114] The present invention also relates to pharmaceutically active metabolites of compounds of Formula (I), (II), (III), (IV), (V), or (VI), or the compounds of any of Tables 1-6, and uses of such metabolites in the methods of the invention. A "pharmaceutically active metabolite" means a pharmacologically active product of metabolism in the body of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or the compounds of any of Tables 1-6, or a salt of any of the foregoing. Prodrugs and active metabolites of a compound may be determined using routine techniques known or available in the art. See, e.g., Bertolini et al., *J. Med. Chem.* 1997, 40, 2011-2016; Shan et al., *J. Pharm. Sci.* 1997, 86 (7), 765-767; Bagshawe, *Drug Dev. Res.* 1995, 34, 220-230; Bodor, *Adv. Drug Res.* 1984, 13, 255-331; Bundgaard, *Design of Prodrugs* (Elsevier Press, 1985); and Larsen, *Design and Application of Prodrugs, Drug Design and Development* (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991).

Pharmaceutical Compositions

[0115] For treatment purposes, pharmaceutical compositions comprising the compounds described herein may further comprise one or more pharmaceutically-acceptable excipients. A pharmaceutically-acceptable excipient is a substance that is non-toxic and otherwise biologically suitable for administration to a subject. Such excipients facilitate administration of the compounds described herein and are compatible with the active ingredient. Examples of pharmaceutically-acceptable excipients include stabilizers, lubricants, surfactants, diluents, anti-oxidants, binders, coloring agents, bulking agents, emulsifiers, or taste-modifying agents. In preferred embodiments, pharmaceutical compositions according to the invention are sterile compositions. Pharmaceutical compositions may be prepared using compounding techniques known or that become available to those skilled in the art.

[0116] Sterile compositions are also contemplated by the invention, including compositions that are in accord with national and local regulations governing such compositions.

[0117] The pharmaceutical compositions and compounds described herein may be formulated as solutions, emulsions, suspensions, or dispersions in suitable pharmaceutical solvents or carriers, or as pills, tablets, lozenges, suppositories, sachets, dragees, granules, powders, powders for reconstitution, or capsules along with solid carriers according to conventional methods known in the art for preparation of various dosage forms. Pharmaceutical compositions of the invention may be administered by a suitable route of delivery, such as oral, parenteral, rectal, nasal, topical, or ocular routes, or by inhalation. Preferably, the compositions are formulated for intravenous or oral administration.

[0118] For oral administration, the compounds the invention may be provided in a solid form, such as a tablet or capsule, or as a solution, emulsion, or suspension. To prepare the oral compositions, the compounds of the invention may be formulated to yield a dosage of, *e.g.*, from about 0.01 to about 50 mg/kg daily, or from about 0.05 to about 20 mg/kg daily, or from about 0.1 to about 10 mg/kg daily. Additional dosages include from about 0.1 mg to 1 g daily, from about 1 mg to about 10 mg daily, from about 10 mg to about 50 mg daily, from about 50 mg to about 250 mg daily, or from about 250 mg to 1 g daily. Oral tablets may include the active ingredient(s) mixed with compatible pharmaceutically acceptable excipients such as diluents,

disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like. Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinyl-pyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are exemplary disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, may be magnesium stearate, stearic acid, or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating.

[0119] Capsules for oral administration include hard and soft gelatin capsules. To prepare hard gelatin capsules, active ingredient(s) may be mixed with a solid, semi-solid, or liquid diluent. Soft gelatin capsules may be prepared by mixing the active ingredient with water, an oil such as peanut oil or olive oil, liquid paraffin, a mixture of mono and di-glycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol.

[0120] Liquids for oral administration may be in the form of suspensions, solutions, emulsions, or syrups, or may be lyophilized or presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may optionally contain: pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, e.g., oil (for example, almond oil or fractionated coconut oil), propylene glycol, ethyl alcohol, or water; preservatives (for example, methyl or propyl p-hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if desired, flavoring or coloring agents.

[0121] The inventive compositions may be formulated for rectal administration as a suppository. For parenteral use, including intravenous, intramuscular, intraperitoneal, intranasal, or subcutaneous routes, the agents of the invention may be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity or in parenterally acceptable oil. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Such forms

may be presented in unit-dose form such as ampoules or disposable injection devices, in multi-dose forms such as vials from which the appropriate dose may be withdrawn, or in a solid form or pre-concentrate that can be used to prepare an injectable formulation. Illustrative infusion doses range from about 1 to 1000 $\mu\text{g/kg/minute}$ of agent admixed with a pharmaceutical carrier over a period ranging from several minutes to several days.

[0122] For nasal, inhaled, or oral administration, the inventive pharmaceutical compositions may be administered using, for example, a spray formulation also containing a suitable carrier.

[0123] For topical applications, the compounds of the present invention are preferably formulated as creams or ointments or a similar vehicle suitable for topical administration. For topical administration, the inventive compounds may be mixed with a pharmaceutical carrier at a concentration of about 0.1% to about 10% of drug to vehicle. Another mode of administering the agents of the invention may utilize a patch formulation to effect transdermal delivery.

[0124] As used herein, “treatment” or “treating” is an approach for obtaining a beneficial or desired result, including clinical results. For purposes of this invention, beneficial or desired results include, but are not limited to: reducing the severity of or suppressing the worsening of a disease, symptom, or condition, alleviating a symptom and/or diminishing the extent of a symptom and/or preventing a worsening of a symptom associated with a condition, arresting the development of a disease, symptom, or condition, relieving the disease, symptom, or condition, causing regression of the disease, disorder, or symptom (in terms of severity or frequency of negative symptoms), or stopping the symptoms of the disease or condition. Beneficial or desired results can also be slowing, halting, or reversing the progressive course of a disease or condition. For example, beneficial effects may include slowing the progression of Parkinson’s disease from an earlier stage (e.g., prodromal stage or stage 1, 2 or 3) to a later stage (e.g., stage 4 or 5), or halting Parkinson’s disease at a prodromal or early stage.

[0125] As used herein, “delaying” development of a disease or condition means to defer, hinder, slow, retard, stabilize and/or postpone development of the disease or condition. This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease or

condition. For example, a method that “delays” development of Parkinson’s disease (e.g., in a prodromal individual) is a method that reduces probability of disease development in a given time frame and/or reduces extent of the disease in a given time frame, when compared to not using the method.

[0126] The term “subject” refers to a mammalian patient in need of such treatment, such as a human. A “subject” may be a human, or may be a cat, dog, cow, rat, mouse, horse, or other domesticated mammal.

[0127] Exemplary diseases that are characterized by protein aggregation include Alzheimer’s disease, Parkinson’s disease, fronto-temporal dementia, dementia with Lewy bodies (Lewy body disease), Parkinson’s disease with dementia, multiple system atrophy, amyotrophic lateral sclerosis, and Huntington’s disease, as well inflammatory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), chronic peptic ulcers, tuberculosis, rheumatoid arthritis, chronic sinusitis, hepatitis (such as hepatitis B or C), gout, lupus, pleurisy, eczema, gastritis, psoriasis, psoriatic arthritis, vasculitis, laryngitis, allergic reactions, multiple sclerosis, Crohn’s disease, traumatic brain injury, CIDP (chronic inflammatory demyelinating polyneuropathy), atopic dermatitis, acne vulgaris, rosacea, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, corneal wounds, corneal disorders, Stargardt disease (Juvenile macular degeneration), age-related macular degeneration, sepsis, diabetic wounds, herpes simplex virus, and anti-fungal, anti-bacterial, antiviral and antitumor diseases or conditions.

[0128] In one aspect, the compounds and pharmaceutical compositions of the invention specifically target TLR2 protein dimers. Thus, these compounds and pharmaceutical compositions can be used to prevent, reverse, slow, or inhibit dimerization of TLR2 proteins with other natural protein ligands, and are used in methods of the invention to treat neurological and inflammatory diseases related to or caused by such dimerization. In preferred embodiments, methods of treatment target Parkinson’s disease, Alzheimer’s disease, Lewy body disease, multiple system atrophy, atopic dermatitis, traumatic brain injury, or multiple sclerosis. The compounds, compositions, and method of the present invention are also used to mitigate deleterious effects that are secondary to protein dimerization and/or misfolding, such as neuronal cell death.

[0129] In some aspects, the compounds, compositions, and methods of the invention are used to inhibit TLR2 dimerization. In alternative aspects, the compounds, compositions, and methods of the invention are used to inhibit TLR2 dimerization with TLR1, or with TLR6, or both.

[0130] In the inhibitory methods of the invention, an “effective amount” means an amount sufficient to reduce, slow the progression of, or reverse TLR2 dimerization. Measuring the amount of dimerization may be performed by routine analytical methods such as those described below. Such modulation is useful in a variety of settings, including *in vitro* assays. In such methods, the cell is preferably a nerve cell or an HEK or THP cell.

[0131] In treatment methods according to the invention, an “effective amount” means an amount or dose sufficient to generally bring about the desired therapeutic benefit in subjects needing such treatment. Effective amounts or doses of the compounds of the invention may be ascertained by routine methods, such as modeling, dose escalation, or clinical trials, taking into account routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the infection, the subject’s health status, condition, and weight, and the judgment of the treating physician. An exemplary dose is in the range of about 1 µg to 2 mg of active agent per kilogram of subject’s body weight per day, preferably about 0.05 to 100 mg/kg/day, or about 1 to 35 mg/kg/day, or about 0.1 to 10 mg/kg/day. In alternative embodiments an exemplary dose is in the range of about 1 mg to about 1 g per day, or about 1-500, 1-250, 1-100, 1-50, 50-500, or 250-500 mg per day. The total dosage may be given in single or divided dosage units (e.g., BID, TID, QID).

[0132] Once improvement of the patient’s disease has occurred, the dose may be adjusted for preventative or maintenance treatment. For example, the dosage or the frequency of administration, or both, may be reduced as a function of the symptoms, to a level at which the desired therapeutic or prophylactic effect is maintained. Of course, if symptoms have been alleviated to an appropriate level, treatment may cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms. Patients may also require chronic treatment on a long-term basis.

Drug Combinations

[0133] The inventive compounds described herein may be used in pharmaceutical compositions or methods in combination with one or more additional active ingredients in the treatment of neurodegenerative disorders. Further additional active ingredients for cancer applications include other cancer therapeutics or agents that mitigate adverse effects of cancer chemotherapeutic agents. Such combinations may serve to increase efficacy, ameliorate other disease symptoms, decrease one or more side effects, or decrease the required dose of an inventive compound. The additional active ingredients may be administered in a separate pharmaceutical composition from a compound of the present invention or may be included with a compound of the present invention in a single pharmaceutical composition. The additional active ingredients may be administered simultaneously with, prior to, or after administration of a compound of the present invention.

[0134] Combination agents include additional active ingredients are those that are known or discovered to be effective in treating the diseases, disorders, conditions, and symptoms discussed herein, including those active against another target associated with the disease, disorder, or symptom such as but not limited to, a) compounds that address protein misfolding (such as drugs which reduce the production of these proteins, which increase their clearance or which alter their aggregation and/or propagation); b) compounds that treat symptoms of such disorders (e.g., dopamine replacement therapies); and c) drugs that act as neuroprotectants by complementary mechanisms (e.g., those targeting autophagy, those that are anti-oxidants, and those acting by other mechanisms such as adenosine A2A antagonists).

[0135] For example, compositions and formulations of the invention, as well as methods of treatment, can further comprise other drugs or pharmaceuticals, e.g., other active agents useful for treating or palliative for a neurological or inflammatory diseases related to or caused by TLR2 dimerization, e.g., Parkinson's disease, Alzheimer's Disease (AD), Lewy body disease (LBD) and multiple system atrophy (MSA), or related symptoms or conditions. For example, the pharmaceutical compositions of the invention may additionally comprise one or more of such active agents, and methods of treatment may additionally comprise administering an effective amount of one or more of such active agents. In certain embodiments, additional active agents may be antibiotics (e.g., antibacterial or bacteriostatic peptides or proteins), e.g., those effective

against gram positive or negative bacteria, fluids, cytokines, immunoregulatory agents, anti-inflammatory agents, complement activating agents, such as peptides or proteins comprising collagen-like domains or fibrinogen-like domains (e.g., a ficolin), carbohydrate-binding domains, and the like and combinations thereof. Additional active agents include those useful in such compositions and methods include dopamine therapy drugs, catechol-O-methyl transferase (COMT) inhibitors, monamine oxidase inhibitors, cognition enhancers (such as acetylcholinesterase inhibitors or memantine), adenosine 2A receptor antagonists, beta-secretase inhibitors, or gamma-secretase inhibitors. In particular embodiments, at least one compound of the present invention may be combined in a pharmaceutical composition or a method of treatment with one or more drugs selected from the group consisting of: tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon) galantamine (Reminyl), physostigmine, neostigmine, Icopezil (CP-118954, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo-[4,5-f-]-1,2-benzisoxazol-6-one maleate), ER-127528 (4-[(5,6-dimethoxy-2-fluoro-1-indanon)-2-yl]methyl-1-(3-fluorobenzyl)piperidine hydrochloride), zanapezil (TAK-147; 3-[1-(phenylmethyl)piperidin-4-yl]-1-(2,3,4,5-tetrahydro-1H-1-benzazepin- 8-yl)-1-propane fumarate), Metrifonate (T-588; (-)-R-.alpha.-[[2-(dimethylamino)ethoxy]methyl] benzo[b]thiophene-5-methanol hydrochloride), FK-960 (N-(4-acetyl-1-piperazinyl)-p-fluorobenzamide-hydrate), TCH-346 (N-methyl-N-2-pyropinyldibenz[b,f]oxepine-10-methanamine), SDZ-220-581 ((S)-alpha-amino-5-(phosphonomethyl)-[1,1'-biphenyl]-3-propionic acid), memantine (Namenda/Exiba) and 1,3,3,5,5-pentamethylcyclohexan-1-amine (Neramexane), tarenflurbil (Flurizan), tramiprosate (Alzhemed), clioquinol, PBT-2 (an 8-hydroxyquinilone derivative), 1-(2-(2-Naphthyl)ethyl)-4-(3-trifluoromethylphenyl)-1, 2,3,6-tetrahydropyridine, Huperzine A, posatirelin, leuprolide or derivatives thereof, ispronicline, (3-aminopropyl)(n-butyl)phosphinic acid (SGS-742), N-methyl-5-(3-(5-isopropoxy-pyridinyl))-4-penten-2-amine (ispronicline), 1-decanaminium, N-(2-hydroxy-3-sulfopropyl)-N-methyl-N-octyl-, inner salt (zt-1), salicylates, aspirin, amoxiprin, benorilate, choline magnesium salicylate, diflunisal, faislamine, methyl salicylate, magnesium salicylate, salicyl salicylate, diclofenac, aceclofenac, acetmetacin, bromfenac, etodolac, indometacin, nabumetone, sulindac, tolmetin, ibuprofen, carprofen, fenbufen, fenoprofen, flurbiprofen, ketoprofen, ketorolac, loxoprofen, naproxen, tiaprofenic acid, suprofen, mefenamic acid, meclofenamic acid, phenylbutazone,

azapropazone, metamizole, oxyphenbutazone, sulfinprazone, piroxicam, lornoxicam, meloxicam, tenoxicam, celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, valdecoxib, nimesulide, arylalkanoic acids, 2-arylpropionic acids (profens), N-arylanthranilic acids (fenamic acids), pyrazolidine derivatives, oxicams, COX-2 inhibitors, sulphonanilides, essential fatty acids, and Minozac (2-(4-(4-methyl-6-phenylpyridazin-3-yl)piperazin-1-yl)pyrimidine dihydrochloride hydrate), or a combination thereof.

Methods of Use

[0136] The compounds and pharmaceutical compositions herein may be used to treat or prevent a disease or condition in an individual. In some embodiments, provided are methods of treating a disease or condition associated with TLR2 heterodimerization, comprising administering to the individual in need thereof a compound of Formula (I), (I), (III), (IV), (V), or (VI), or a compound of Tables 1, 2, 3, 4, 5, or 6, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, provided are methods of treating a disease or condition associated with TLR2 heterodimerization comprising administering to the subject a therapeutically effective amount of at least one chemical entity as described herein.

[0137] In some embodiments, provided are compositions containing one or more compounds of Formula (I), (I), (III), (IV), (V), or (VI), or a compound of Tables 1, 2, 3, 4, 5, or 6, or a pharmaceutically acceptable salt of any of the foregoing, for use in the treatment of a disease or condition associated with TLR2 heterodimerization. In some embodiments, provided are compositions containing at least one chemical entity as described herein for use in the treatment of a disease or condition associated with TLR2 heterodimerization.

[0138] Also provided herein is the use of a compound of Formula (I), (I), (III), (IV), (V), or (VI), or a compound of Tables 1, 2, 3, 4, 5, or 6, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treatment of a disease or condition associated with TLR2 heterodimerization. In some embodiments, provided is the use of at least one chemical entity as described herein in the manufacture of a medicament for treatment of a disease or condition associated with TLR2 heterodimerization.

[0139] In some embodiments, the disease or condition is selected from Alzheimer's disease, Parkinson's disease, fronto-temporal dementia, dementia with Lewy bodies (Lewy body disease), Parkinson's disease with dementia, multiple system atrophy, amyotrophic lateral sclerosis, Huntington's disease, inflammatory diseases, asthma, chronic obstructive pulmonary disease (COPD), chronic peptic ulcers, tuberculosis, rheumatoid arthritis, chronic sinusitis, hepatitis, hepatitis B, hepatitis C, gout, lupus, pleurisy, eczema, gastritis, psoriasis, psoriatic arthritis, vasculitis, laryngitis, allergic reactions, multiple sclerosis, Crohn's disease, and traumatic brain injury.

[0140] Also provided are methods for interfering with the heterodimerization of TLR2 in a cell, or modulating, preventing, slowing, reversing, or inhibiting TLR2 heterodimerization in a cell which involves contacting the cell with an effective amount of at least one compound of Formula (I), (I), (III), (IV), (V), or (VI), or a compound of Tables 1, 2, 3, 4, 5, or 6, or a pharmaceutically acceptable salt thereof. In some embodiments, provided are methods for interfering with the heterodimerization of TLR2 in a cell, or modulating, preventing, slowing, reversing, or inhibiting TLR2 heterodimerization in a cell which involves contacting the cell with an effective amount of at least one chemical entity as described herein.

[0141] Also provided herein are compositions containing one or more compounds of Formula (I), (I), (III), (IV), (V), or (VI), or a compound of Tables 1, 2, 3, 4, 5, or 6, or a pharmaceutically acceptable salt of any of the foregoing, for use in interfering with the heterodimerization of TLR2 in a cell, or modulating, preventing, slowing, reversing, or inhibiting TLR2 heterodimerization in a cell. In some embodiments, provided are compositions containing at least one chemical entity as described herein for use in interfering with the heterodimerization of TLR2 in a cell, or modulating, preventing, slowing, reversing, or inhibiting TLR2 heterodimerization in a cell.

[0142] Additionally provided herein is the use of at least one chemical entity as described herein, such as a compound of Formula (I), (I), (III), (IV), (V), or (VI), or a compound of Tables 1, 2, 3, 4, 5, or 6, or a pharmaceutically acceptable salt of any of the foregoing in the manufacture of a medicament for interfering with the heterodimerization of TLR2, or modulating, preventing, slowing, reversing, or inhibiting TLR2 heterodimerization.

Kits

[0143] Also provided are articles of manufacture and kits containing any of the compounds or pharmaceutical compositions provided herein. The article of manufacture may comprise a container with a label. Suitable containers include, for example, bottles, vials, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container may hold a pharmaceutical composition provided herein. The label on the container may indicate that the pharmaceutical composition is used for preventing, treating or suppressing a condition described herein, and may also indicate directions for either *in vivo* or *in vitro* use.

[0144] In one aspect, provided herein are kits containing a compound or composition described herein and instructions for use. The kits may contain instructions for use in the treatment of a disease or condition associated with TLR2 heterodimerization in an individual in need thereof. A kit may additionally contain any materials or equipment that may be used in the administration of the compound or composition, such as vials, syringes, or IV bags. A kit may also contain sterile packaging.

General Synthetic methods

[0145] The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter (such as the schemes provided in the Examples below). In the following process descriptions, the symbols when used in the formulae depicted are to be understood to represent those groups described above in relation to the formulae herein.

[0146] Where it is desired to obtain a particular enantiomer of a compound, this may be accomplished from a corresponding mixture of enantiomers using any suitable conventional procedure for separating or resolving enantiomers. Thus, for example, diastereomeric derivatives may be produced by reaction of a mixture of enantiomers, *e.g.*, a racemate, and an appropriate chiral compound. The diastereomers may then be separated by any convenient means, for example by crystallization and the desired enantiomer recovered. In another resolution process, a racemate may be separated using chiral High Performance Liquid

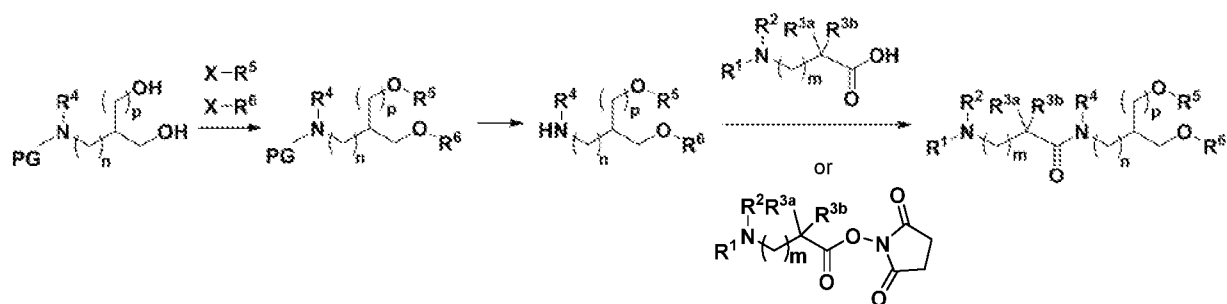
Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described.

[0147] Chromatography, recrystallization and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular isomer of a compound or to otherwise purify a product of a reaction.

[0148] Solvates of a compound provided herein or a pharmaceutically acceptable salt thereof are also contemplated. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol.

[0149] In some embodiments, compounds of the Formula (I) may be synthesized according to Scheme 1.

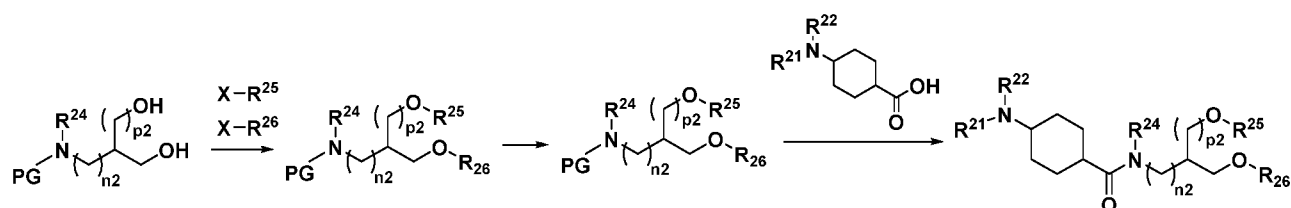
Scheme 1.



wherein R^1 , R^2 , R^{3a} , R^{3b} , R^4 , R^5 , R^6 , m , n , and p are as defined for Formula (I), or any variation thereof detailed herein; PG is a protecting group, and X is a halogen.

[0150] In some embodiments, compounds of the Formula (II) may be synthesized according to Scheme 2.

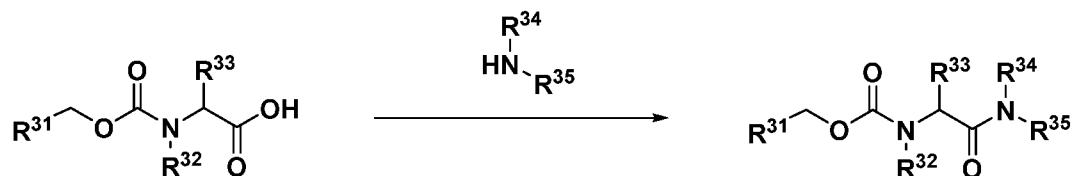
Scheme 2.



wherein R^{21} , R^{22} , R^{24} , R^{25} , R^{26} , $n2$, and $p2$ are as defined for Formula (II), or any variation thereof detailed herein; PG is a protecting group, and X is a halogen.

[0151] In some embodiments, compounds of the Formula (III) may be synthesized according to Scheme 3.

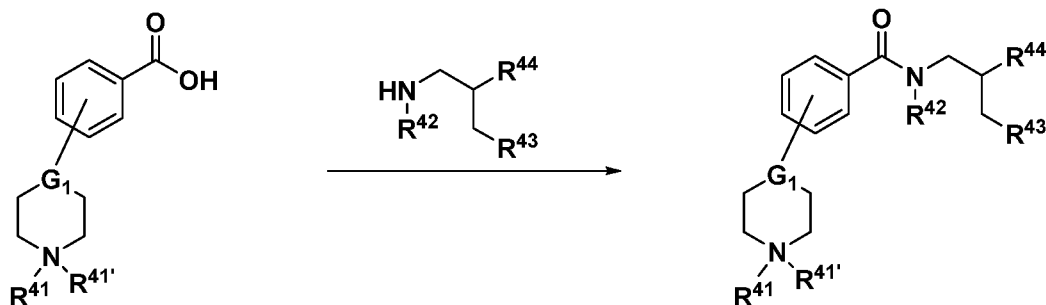
Scheme 3.



wherein R^{31} , R^{32} , R^{33} , R^{34} , and R^{35} are as defined for Formula (III), or any variation thereof detailed herein.

[0152] In some embodiments, compounds of the Formula (IV) may be synthesized according to Scheme 4.

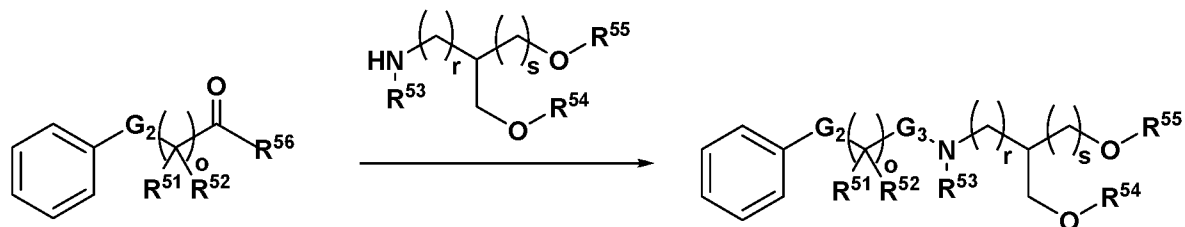
Scheme 4.



wherein R^{41} , $R^{41'}$, R^{42} , R^{43} , R^{44} , and G_1 are as defined for Formula (IV), or any variation thereof detailed herein.

[0153] In some embodiments, compounds of the Formula (V) may be synthesized according to Scheme 5.

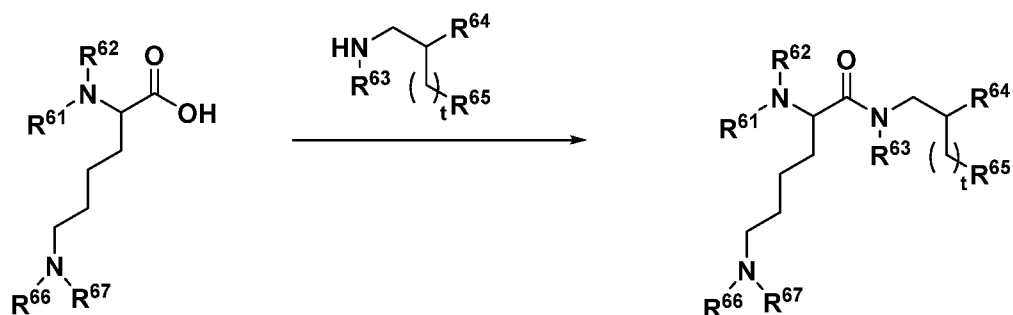
Scheme 5.



wherein R^{51} , R^{52} , R^{53} , R^{54} , R^{55} , G_2 , G_3 , o , r , and s are as defined for Formula (V), or any variation thereof detailed herein; and R^{56} is H or OH.

[0154] In some embodiments, compounds of the Formula (VI) may be synthesized according to Scheme 6.

Scheme 6.



wherein R^{61} , R^{62} , R^{63} , R^{64} , R^{65} , R^{66} , R^{67} , and t are as defined for Formula (VI), or any variation thereof detailed herein.

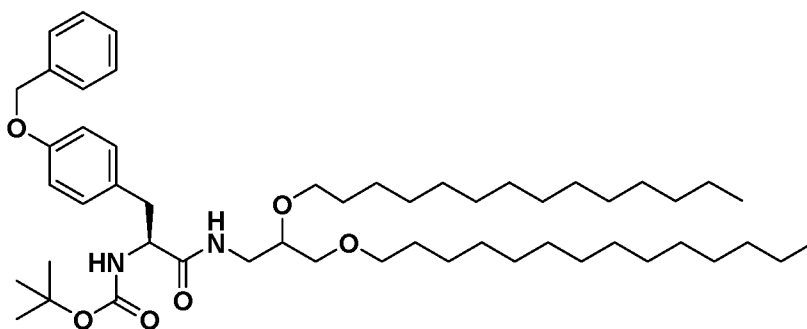
Chemical Synthesis

[0155] Exemplary chemical entities useful in methods of the invention will now be described by reference to the specific examples that follow. Artisans will recognize that, to obtain the various compounds herein, starting materials may be suitably selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent. Furthermore, one of skill in the art will recognize that the transformations shown in the schemes below may be performed in any order that is compatible with the functionality of the particular pendant groups. Each of the reactions depicted in the general schemes is preferably run at a temperature from about 0 °C to the reflux temperature of the organic solvent used. Isotopically labeled compounds as described herein are prepared according to the methods described below, using suitably labeled starting materials. Such materials are generally available from commercial suppliers of radiolabeled chemical reagents.

Examples

[0156] The following examples are offered to illustrate but not to limit the invention. One of skill in the art will recognize that the following synthetic reactions and schemes may be modified by choice of suitable starting materials and reagents in order to access other compounds of Formula (I), (II), (III), (IV), (V), or (VI). The compounds are prepared using the general methods described above.

Example 1: tert-Butyl ((2S)-3-(4-(benzyloxy)phenyl)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxopropan-2-yl)carbamate.



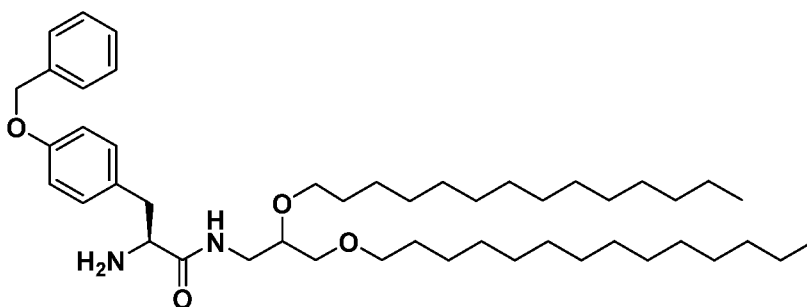
[0157] Step 1: tert-Butyl (2,3-bis(tetradecyloxy)propyl)carbamate. In a 50 mL sealed cap glass vial, a mixture of tert-butyl (2,3-dihydroxypropyl)carbamate (1.15 g, 6.0 mmol) in toluene (6.0 mL) was treated sequentially with 1-bromotetradecane (10.71 mL, 36 mmol), sodium hydroxide (50% aq.; 6.0 mL) and tetrabutylammonium bisulfate (1.02 g, 3.0 mmol). The vial was sealed and heated at 65 °C with vigorous stirring overnight. The mixture was cooled to room temperature (rt) and extracted with toluene (2 x 25 mL). The combined organic layers were washed with water, dried over sodium sulfate, and evaporated. The resulting colorless liquid was purified by silica gel column chromatography (hexane-ethyl acetate (0-25%)) to give the title compound as a colorless liquid (1.52 g, 44% yield). ¹H NMR (500 MHz, Chloroform-d) δ 4.88 (s, 1H), 3.57 (dt, *J* = 9.3, 6.7 Hz, 1H), 3.52 – 3.29 (m, 7H), 3.17 (dt, *J* = 12.1, 5.7 Hz, 1H), 1.63 – 1.48 (m, 5H), 1.44 (s, 9H), 1.25 (s, 44H), 0.88 (t, *J* = 6.9 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₃₆H₇₃NO₄, 585; found, 585.

[0158] Step 2: 2,3-Bis(tetradecyloxy)propan-1-amine. A solution of tert-butyl (2,3-bis(tetradecyloxy)propyl) carbamate (1.50 g, 2.57 mmol) was dissolved in tetrahydrofuran (10

mL) was treated with HCl (4 N in dioxane; 10 mL) and the resulting mixture was stirred at rt for 5 h. The mixture was concentrated, and then re-concentrated twice with 1:1 dichloromethane-diethyl ether. The resulting solid was lyophilized to obtain the title compound as a white powder (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 8.29 (s, 3H), 4.00 – 3.63 (m, 2H), 3.63 – 3.27 (m, 7H), 3.24 (s, 1H), 3.11 (s, 1H), 1.75 – 1.43 (m, 4H), 1.26 (s, 44H), 0.88 (t, J = 6.9 Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{31}\text{H}_{65}\text{NO}_2$, 485; found, 485.

[0159] Step 3. In a 30 mL sealed cap glass vial, 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) was suspended in 1:2 satd. aq. sodium bicarbonate/dioxane (21 mL) and treated with Boc-L-Tyr(O-Bn)-OSu (234 mg, 0.5 mmol), and the resulting mixture was stirred at rt overnight. The mixture was diluted with water and brine, and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were dried over sodium sulfate, and evaporated. The residue was purified by silica gel column (hexane-ethyl acetate (0-100%)) to give the title compound as a white solid (205 mg, 49% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.39 (dt, J = 14.8, 7.6 Hz, 4H), 7.32 (t, J = 7.1 Hz, 1H), 7.18 – 7.06 (m, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.12 (d, J = 21.0 Hz, 1H), 5.03 (d, J = 2.0 Hz, 2H), 4.25 (s, 1H), 3.47 (tdd, J = 10.9, 6.6, 3.3 Hz, 2H), 3.43 – 3.27 (m, 6H), 3.23 (dt, J = 12.8, 5.6 Hz, 1H), 2.98 (q, J = 12.9, 12.0 Hz, 2H), 1.50 (dq, J = 14.7, 6.7 Hz, 4H), 1.41 (s, 9H), 1.25 (s, 44H), 0.88 (t, J = 6.9 Hz, 6H); ESI-MS m/z $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{52}\text{H}_{88}\text{N}_2\text{O}_6$, 860; found, 860.

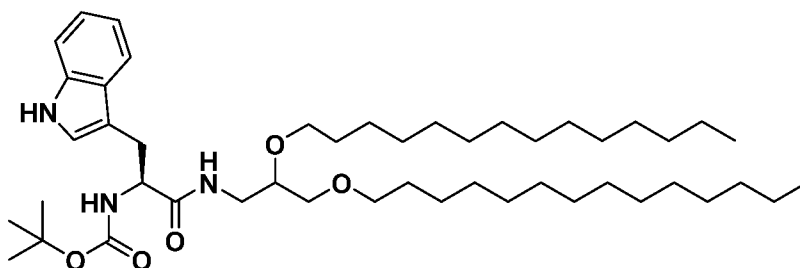
Example 2: (2S)-2-Amino-3-(4-(benzyloxy)phenyl)-N-(2,3-bis(tetradecyloxy)propyl)propanamide hydrochloride.



[0160] The title compound was prepared from tert-butyl ((2S)-3-(4-(benzyloxy)phenyl)-1-((2,3-bis(tetradecyloxy)propyl) amino)-1-oxopropan-2-yl)carbamate (167.5 mg, 0.2 mmol) as in Example 1, Step 2, to give an off-white solid (150 mg, 100% yield). ^1H NMR (500 MHz,

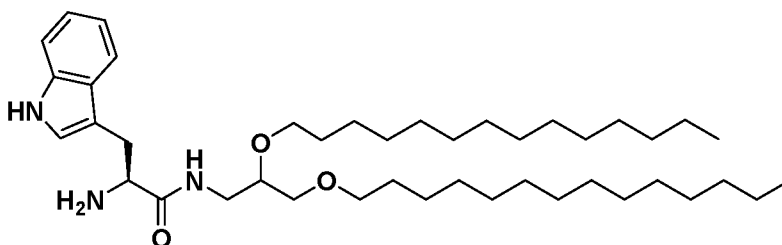
DMSO-*d*₆) δ 8.35 (dt, *J* = 11.5, 5.8 Hz, 1H), 8.17 (s, 3H), 7.53 – 7.24 (m, 6H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.03 – 6.87 (m, 2H), 5.06 (d, *J* = 3.0 Hz, 2H), 3.95 (t, *J* = 7.1 Hz, 1H), 3.81 – 3.68 (m, 1H), 3.69 – 3.59 (m, 1H), 3.44 (t, *J* = 6.5 Hz, 1H), 3.32 (m, 3H), 3.13 (dd, *J* = 10.6, 5.9 Hz, 1H), 3.04 (dt, *J* = 13.5, 5.2 Hz, 1H), 2.94 (tt, *J* = 13.0, 6.9 Hz, 2H), 2.01 – 1.67 (m, 1H), 1.44 (dq, *J* = 12.0, 6.5 Hz, 4H), 1.34 – 1.06 (m, 44H), 0.85 (t, *J* = 6.8 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₄₇H₈₀N₂O₄, 738; found, 738.

Example 3: tert-Butyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate.



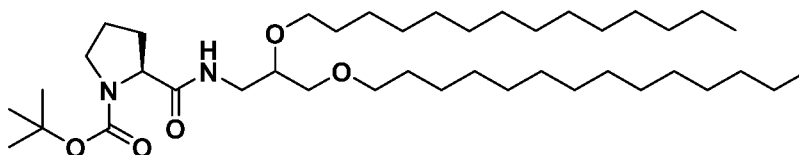
[0161] The title compound was prepared from 2,3-bis(tetradecyloxy) propan-1-amine hydrochloride (260 mg, 0.5 mmol) and activated Boc-L-Trp-OSu (201 mg, 0.5 mmol) as in Example 1, Step 3, to give a gummy solid (265 mg, 69% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.66 (dd, *J* = 8.0, 3.9 Hz, 1H), 7.34 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 2.3 Hz, 1H), 6.06 (d, *J* = 25.0 Hz, 1H), 5.13 (s, 1H), 4.41 (s, 1H), 3.39 (dt, *J* = 9.3, 6.7 Hz, 2H), 3.34 – 3.20 (m, 5H), 3.16 (dd, *J* = 14.1, 8.2 Hz, 3H), 1.66 – 1.45 (m, 4H), 1.42 (s, 9H), 1.25 (s, 44H), 0.88 (t, *J* = 6.8 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₄₇H₈₃N₃O₅, 771; found, 771.

Example 4: (2S)-2-Amino-N-(2,3-bis(tetradecyloxy)propyl)-3-(1H-indol-3-yl)propanamide hydrochloride.



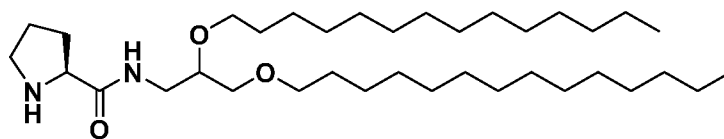
[0162] The title compound was prepared from tert-butyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate (154 mg, 0.2 mmol) as described in Example 1 to give a gummy solid (100% yield). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.02 (s, 1H), 8.49 (t, $J = 6.0$ Hz, 1H), 8.23 – 8.04 (m, 3H), 7.65 (d, $J = 7.9$ Hz, 1H), 7.35 (d, $J = 8.1$ Hz, 1H), 7.20 (d, $J = 2.2$ Hz, 1H), 7.08 (ddd, $J = 8.1, 6.9, 1.1$ Hz, 1H), 7.00 (t, $J = 7.4$ Hz, 1H), 3.98 (d, $J = 6.5$ Hz, 1H), 3.78 – 3.50 (m, 6H), 3.48 – 3.36 (m, 2H), 3.24 – 2.96 (m, 3H), 1.54 – 1.31 (m, 4H), 1.34 – 1.12 (m, 44H), 0.85 (t, $J = 6.8$ Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{42}\text{H}_{75}\text{N}_3\text{O}_3$, 671; found, 671.

Example 5: tert-Butyl (2S)-2-((2,3-bis(tetradecyloxy)propyl)carbamoyl) pyrrolidine-1-carboxylate.



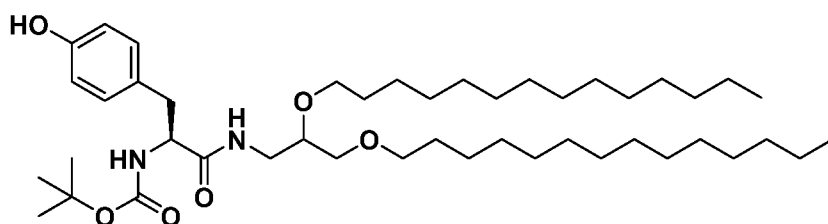
[0163] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and Boc-L-Pro-OSu (156 mg, 0.5 mmol) as in Example 1 to give a colorless liquid (252 mg, 74% yield). ^1H NMR (500 MHz, $\text{Chloroform}-d$) δ 4.39 – 4.12 (d, 1H), 3.56 (m, 1H), 3.52 – 3.35 (m, 7H), 3.32 (s, 1H), 2.08 (t, $J = 19.9$ Hz, 2H), 1.99 – 1.78 (m, 2H), 1.67 – 1.50 (m, 6H), 1.45 (s, 11H), 1.25 (s, 42H), 0.88 (t, $J = 6.8$ Hz, 6H); ESI-MS m/z $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{41}\text{H}_{80}\text{N}_2\text{O}_5$, 704; found, 704.

Example 6: (2S)-N-(2,3-Bis(tetradecyloxy)propyl)pyrrolidine-2-carboxamide hydrochloride.



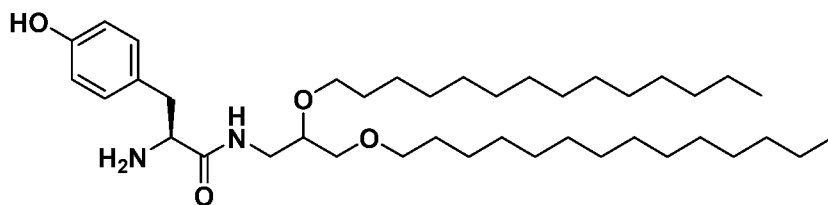
[0164] The title compound was prepared from tert-butyl (2S)-2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)pyrrolidine-1-carboxylate (136.2 mg, 0.2 mmol) as in Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, DMSO- d_6) δ 9.26 (s, 1H), 8.46 (s, 1H), 4.14 (dd, J = 10.2, 3.9 Hz, 1H), 3.79 – 3.69 (m, 3H), 3.68 – 3.57 (m, 2H), 3.56 – 3.34 (m, 4H), 3.28 – 3.14 (m, 2H), 1.93 – 1.80 (m, 3H), 1.53 – 1.39 (m, 4H), 1.24 (s, 44H), 0.88 (t, J = 6.8 Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{36}\text{H}_{72}\text{N}_2\text{O}_3$, 582; found, 582.

Example 7: tert-Butyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate.



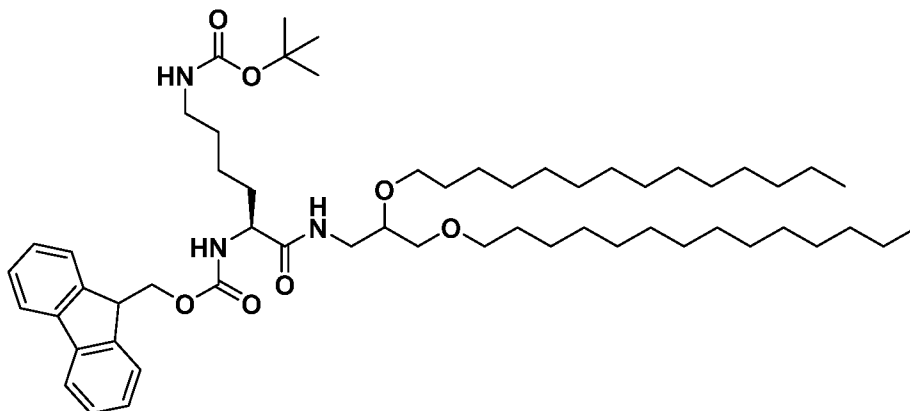
[0165] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and Boc-L-Tyr-OSu (189 mg, 0.5 mmol) as in Example 1 to give a white solid (163 mg, 44% yield). ^1H NMR (500 MHz, Chloroform- d) δ 7.10 – 7.00 (m, 2H), 6.80 – 6.65 (m, 2H), 6.16 (d, J = 18.5 Hz, 1H), 5.25 (s, 1H), 5.01 (s, 1H), 4.25 (s, 1H), 3.56 – 3.28 (m, 8H), 3.23 (d, J = 14.3 Hz, 1H), 2.97 (s, 2H), 1.51 (dp, J = 13.8, 7.0, 6.6 Hz, 4H), 1.41 (s, 9H), 1.25 (s, 44H), 0.88 (t, J = 6.9 Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{45}\text{H}_{82}\text{N}_2\text{O}_6$, 748; found, 748.

Example 8: (2S)-2-Amino-N-(2,3-bis(tetradecyloxy)propyl)-3-(4-hydroxyphenyl)propanamide hydrochloride.



[0166] The title compound was prepared from tert-butyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate (149.5 mg, 0.2 mmol) as for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, DMSO- d_6) δ 9.35 (s, 1H), 8.39 (dt, $J = 11.2, 5.4$ Hz, 1H), 8.15 (s, 3H), 7.15 – 6.90 (m, 2H), 6.81 – 6.53 (m, 2H), 3.91 (t, $J = 6.8$ Hz, 1H), 3.45 (t, $J = 6.5$ Hz, 1H), 3.40–3.11 (m, 7H), 3.06 (dt, $J = 13.6, 5.4$ Hz, 1H), 2.91 (m, $J = 7.4, 7.0$ Hz, 1H), 2.85 (ddd, $J = 13.8, 7.1, 3.7$ Hz, 1H), 1.54 – 1.36 (m, 4H), 1.23 (d, $J = 3.1$ Hz, 44H), 0.85 (t, $J = 6.8$ Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{40}\text{H}_{74}\text{N}_2\text{O}_4$, 648; found, 648.

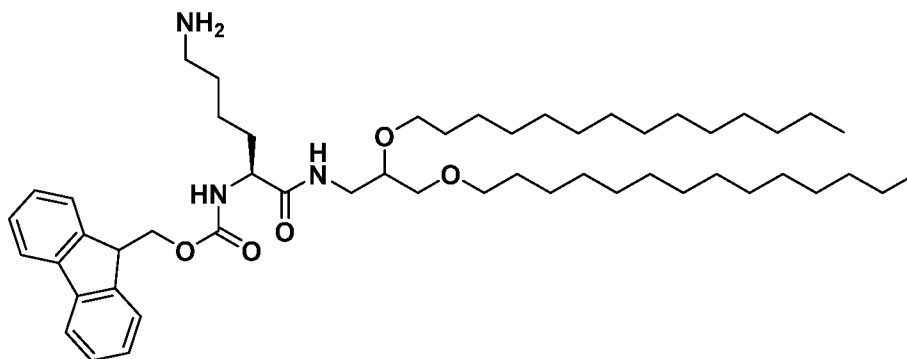
Example 9: (9H-Fluoren-9-yl)methyl tert-butyl ((5S)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexane-1,5-diyl)dicarbamate.



[0167] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and N^{α} -Fmoc- N^{ϵ} -Boc-L-Lys-OSu (283 mg, 0.5 mmol) as described in Example 1 to give a white solid (152 mg, 33% yield). ^1H NMR (500 MHz, Chloroform- d) δ 7.76 (d, $J = 7.6$ Hz, 2H), 7.59 (d, $J = 7.4$ Hz, 2H), 7.40 (t, $J = 7.5$ Hz, 2H), 7.31 (t, $J = 7.5$ Hz, 2H), 6.33 (s, 1H), 5.49 (s, 1H), 4.59 (s, 1H), 4.43 – 4.31 (m, 2H), 4.21 (t, $J = 7.0$ Hz, 1H), 4.11 (d, $J = 6.9$ Hz, 1H), 3.69 – 3.23 (m, 9H), 3.19 – 2.95 (m, 2H), 1.85 (s, 1H), 1.61

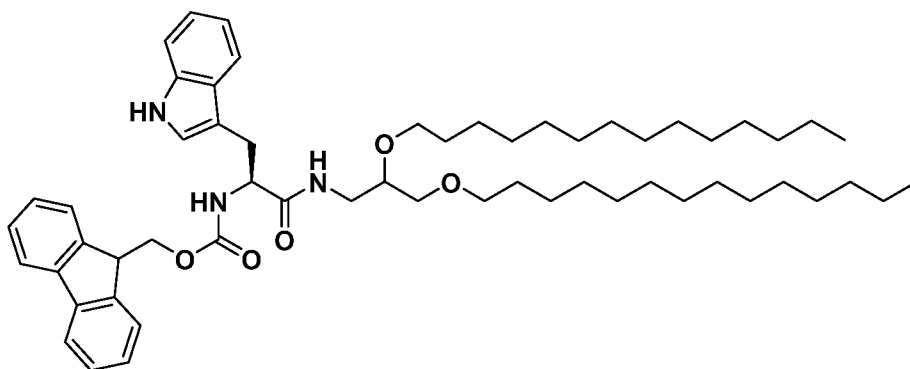
(s, 2H), 1.52 (dq, $J = 14.0, 6.4, 5.7$ Hz, 4H), 1.43 (s, 9H), 1.25 (q, $J = 6.8, 5.5$ Hz, 47H), 0.88 (t, $J = 6.8$ Hz, 6H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{57}H_{95}N_3O_7$, 935; found, 935.

Example 10: (9H-Fluoren-9-yl)methyl ((2S)-6-amino-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxohexan-2-yl)carbamate hydrochloride.



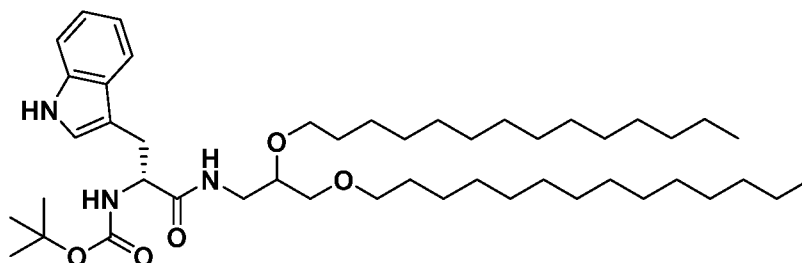
[0168] The title compound was prepared from (9H-fluoren-9-yl)methyl tert-butyl ((5S)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexane-1,5-diyl)dicarbamate (94 mg, 0.1 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, $DMSO-d_6$) δ 7.89 (d, $J = 7.5$ Hz, 2H), 7.84 – 7.74 (m, 4H), 7.71 (t, $J = 7.8$ Hz, 2H), 7.50 (dd, $J = 8.4, 3.6$ Hz, 1H), 7.41 (t, $J = 7.4$ Hz, 2H), 7.32 (t, $J = 7.4$ Hz, 2H), 4.32 – 4.12 (m, 3H), 3.95 (tt, $J = 9.3, 5.3$ Hz, 1H), 3.42 (qd, $J = 6.9, 2.9$ Hz, 3H), 3.34 (s, 4H), 3.11 (ddt, $J = 34.7, 13.1, 6.5$ Hz, 2H), 2.74 (s, 2H), 1.61 (d, $J = 9.6$ Hz, 1H), 1.57 – 1.47 (m, 3H), 1.46 – 1.34 (m, 4H), 1.21 (s, $J = 4.8$ Hz, 46H), 0.84 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{52}H_{87}N_3O_5$, 835; found, 835.

[0169] Example 11: (9H-Fluoren-9-yl)methyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate.



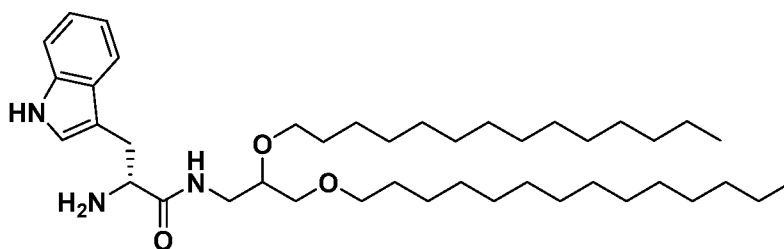
[0170] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and Fmoc-L-Trp-OSu (262 mg, 0.5 mmol) as described for Example 1 to give a white solid (185 mg, 42% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 8.05 (d, $J = 3.0$ Hz, 1H), 7.76 (d, $J = 7.6$ Hz, 2H), 7.70 (s, 1H), 7.55 (t, $J = 8.2$ Hz, 2H), 7.45 – 7.33 (m, 3H), 7.30 (td, $J = 7.5, 3.1$ Hz, 2H), 7.17 (dt, $J = 30.1, 7.5$ Hz, 2H), 7.08 – 7.00 (m, 1H), 5.99 (d, $J = 22.3$ Hz, 1H), 5.52 (s, 1H), 4.54 – 4.27 (m, 3H), 4.20 (t, $J = 7.1$ Hz, 1H), 3.51 – 3.21 (m, 6H), 3.21 – 3.07 (m, 3H), 1.46 (q, $J = 6.7$ Hz, 2H), 1.37 (q, $J = 7.0$ Hz, 2H), 1.33 – 1.06 (m, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{57}\text{H}_{85}\text{N}_3\text{O}_5$, 915; found, 915.

Example 12: tert-Butyl ((2R)-1-((2,3-bis(tetradecyloxy)propyl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate.



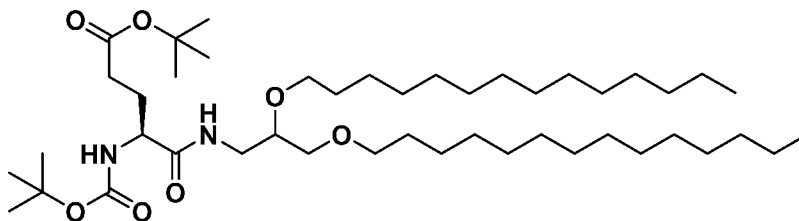
[0171] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and Boc-D-Trp-OSu (262 mg, 0.5 mmol) as described for Example 1 to give a white solid (175 mg, 46% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 8.06 (s, 1H), 7.66 (dd, $J = 8.0, 3.9$ Hz, 1H), 7.34 (dd, $J = 8.2, 1.9$ Hz, 1H), 7.23 – 7.16 (m, 1H), 7.12 (t, $J = 7.4$ Hz, 1H), 7.06 (d, $J = 2.3$ Hz, 1H), 6.06 (d, $J = 24.9$ Hz, 1H), 5.13 (s, 1H), 4.41 (s, 1H), 3.47 – 3.04 (m, 11H), 1.48 (q, $J = 6.6$ Hz, 2H), 1.42 (s, 11H), 1.26 (s, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{47}\text{H}_{83}\text{N}_3\text{O}_5$, 771; found, 771.

Example 13: (2R)-2-Amino-N-(2,3-bis(tetradecyloxy)propyl)-3-(1H-indol-3-yl)propanamide hydrochloride.



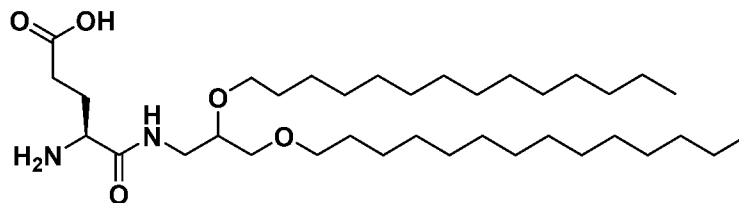
[0172] The title compound was prepared from tert-butyl ((2R)-1-((2,3-bis(tetradecyloxy)propyl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate (154 mg, 0.2 mmol) as described for Example 1 to give a gummy solid (100% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 9.42 (s, 3H), 8.01 (s, 1H), 7.26 (s, 3H), 7.17 – 6.71 (m, 2H), 4.55 – 4.04 (m, 1H), 3.33 (s, 11H), 1.45 (d, *J* = 20.1 Hz, 4H), 1.24 (t, *J* = 6.9 Hz, 44H), 0.88 (t, *J* = 6.8 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₄₂H₇₅N₃O₃, 671; found, 671.

Example 14: tert-Butyl (4S)-5-((2,3-bis(tetradecyloxy)propyl)amino)-4-((tert-butoxycarbonyl)amino)-5-oxopentanoate.



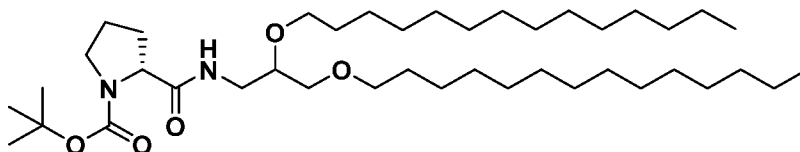
[0173] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and Boc-L-Glu(OtBu)-OSu (200 mg, 0.5 mmol) as described for Example 1 to give a white solid (230 mg, 60% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 6.51 (t, *J* = 5.4 Hz, 1H), 5.26 (s, 1H), 4.09 (s, 1H), 3.62 – 3.21 (m, 9H), 2.39 (dtd, *J* = 16.7, 7.3, 2.6 Hz, 1H), 2.28 (dt, *J* = 16.5, 7.0 Hz, 1H), 2.08 (dtd, *J* = 14.1, 7.1, 4.9 Hz, 1H), 1.96 – 1.78 (m, 1H), 1.56 (d, *J* = 8.2 Hz, 4H), 1.44 (d, *J* = 6.8 Hz, 18H), 1.26 (s, 44H), 0.88 (t, *J* = 6.9 Hz, 6H); ESI-MS *m/z* [M+Na]⁺ calc'd for C₄₅H₈₈N₂O₇, 792; found, 792.

Example 15: (4S)-4-Amino-5-((2,3-bis(tetradecyloxy)propyl)amino)-5-oxopentanoic acid hydrochloride.



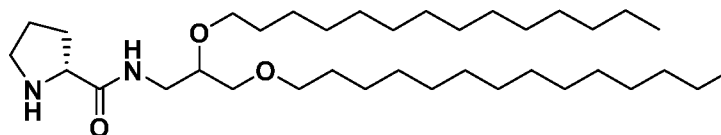
[0174] The title compound was prepared from tert-butyl (4S)-5-((2,3-bis(tetradecyloxy)propyl)amino)-4-((tert-butoxycarbonyl)amino)-5-oxopentanoate (154 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.48 – 7.93 (m, 4H), 4.01 – 3.13 (m, 9H), 2.65 (s, 2H), 1.87 (dddd, *J* = 18.6, 15.0, 10.6, 5.6 Hz, 2H), 1.72 (ddd, *J* = 14.6, 10.8, 6.4 Hz, 1H), 1.54 (s, 4H), 1.25 (s, 44H), 0.88 (t, *J* = 6.8 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₃₆H₇₂N₂O₅, 614; found, 614.

Example 16: tert-Butyl (2R)-2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)pyrrolidine-1-carboxylate.



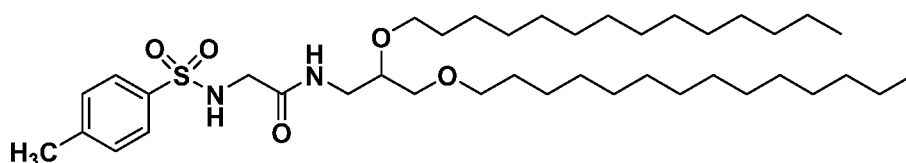
[0175] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and Boc-D-Pro-OSu (156 mg, 0.5 mmol) as described for Example 1 to give a white solid (275 mg, 81% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 4.45 – 4.10 (m, 1H), 3.67 – 3.16 (m, 12H), 2.47 – 2.00 (m, 2H), 1.86 (s, 2H), 1.54 (q, *J* = 6.9 Hz, 4H), 1.46 (s, 9H), 1.25 (s, 44H), 0.88 (t, *J* = 6.9 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₄₁H₈₀N₂O₅, 682; found, 682.

Example 17: (2R)-N-(2,3-Bis(tetradecyloxy)propyl)pyrrolidine-2-carboxamide hydrochloride.



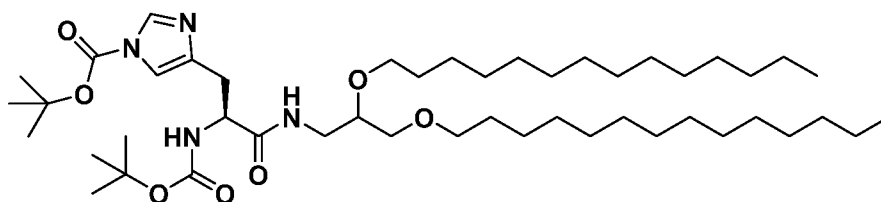
[0176] The title compound was prepared from tert-butyl (2R)-2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)pyrrolidine-1-carboxylate (204 mg, 0.3 mmol) as described for Example 1 to give a white solid (100% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 11.37 (s, 1H), 7.62 (d, *J* = 97.3 Hz, 2H), 3.94 – 3.21 (m, 11H), 2.63 – 2.42 (m, 1H), 2.22 – 1.95 (m, 2H), 1.95 – 1.61 (m, 2H), 1.62 – 1.45 (m, 4H), 1.25 (s, 44H), 0.87 (t, *J* = 6.8 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₃₆H₇₂N₂O₃, 582; found, 582.

Example 18: N-(2,3-Bis(tetradecyloxy)propyl)-2-((4-methylphenyl)sulfonamido)acetamide.



[0177] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and Tosyl-Gly-OSu (163 mg, 0.5 mmol) as described for Example 1 to give a white solid (115 mg, 33% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.87 – 7.68 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.50 (t, *J* = 5.6 Hz, 1H), 5.14 (t, *J* = 5.9 Hz, 1H), 3.66 – 3.13 (m, 11H), 2.43 (s, 3H), 1.56 (tt, *J* = 11.3, 7.1 Hz, 4H), 1.26 (s, 44H), 0.88 (t, *J* = 6.9 Hz, 6H); ESI-MS *m/z* [M+Na]⁺ calc'd for C₄₀H₇₄N₂O₅S, 718; found, 718.

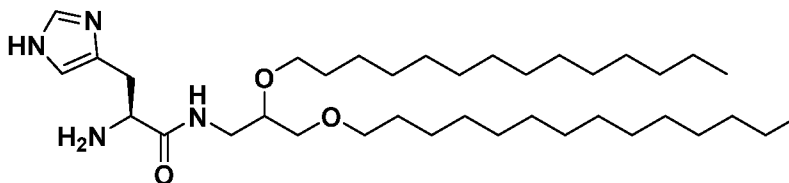
Example 19: tert-Butyl 4-((2S)-3-((2,3-bis(tetradecyloxy)propyl)amino)-2-((tert-butoxycarbonyl)amino)-3-oxopropyl)-1H-imidazole-1-carboxylate.



[0178] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and Boc-L-His(Boc)-OSu (226 mg, 0.5 mmol) as described for Example 1 to give a white solid (245 mg, 60% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.01 (t, *J* = 1.7 Hz, 1H), 7.17 (d, *J* = 1.9 Hz, 1H), 6.89 (s, 1H), 6.11 (s, 1H), 4.43 (s, 1H), 3.61 – 3.15 (m, 9H), 3.09 (s, 1H), 2.94 (dd, *J* = 14.9, 5.5 Hz, 1H), 1.60 (s, 9H), 1.53 (q, *J* = 7.1 Hz,

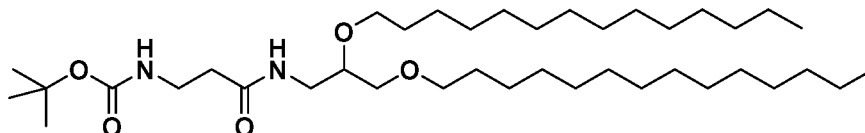
4H), 1.44 (s, 9H), 1.34 – 1.16 (m, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[M+Na]^+$ calc'd for $C_{47}H_{88}N_4O_7$, 844; found, 844.

Example 20: (2S)-2-Amino-N-(2,3-bis(tetradecyloxy)propyl)-3-(1H-imidazol-4-yl)propanamide dihydrochloride.



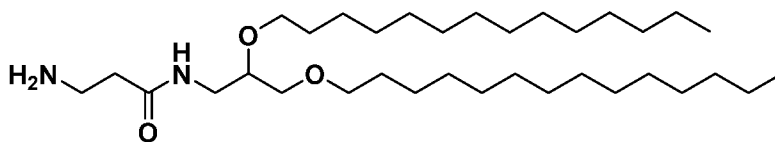
[0179] The title compound was prepared from tert-butyl 4-((2S)-3-((2,3-bis(tetradecyloxy)propyl)amino)-2-((tert-butoxycarbonyl)amino)-3-oxopropyl)-1H-imidazole-1-carboxylate (164 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, Chloroform- d) δ 8.89 (s, 1H), 8.21 (s, 4H), 7.62 (s, 1H), 4.70 (d, $J = 41.4$ Hz, 1H), 3.87 – 3.18 (m, 9H), 2.61 – 2.15 (m, 2H), 1.72 – 1.45 (m, 4H), 1.24 (d, $J = 7.3$ Hz, 44H), 0.88 (t, $J = 6.8$ Hz, 6H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{37}H_{72}N_4O_3$, 622; found, 622.

Example 21: tert-Butyl (3-((2,3-bis(tetradecyloxy)propyl)amino)-3-oxopropyl) carbamate.



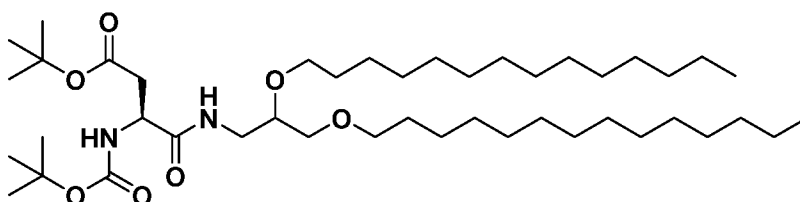
[0180] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and Boc- β -Ala-OSu (143 mg, 0.5 mmol) as described for Example 1 to give a white solid (255 mg, 78% yield). ^1H NMR (500 MHz, Chloroform- d) δ 5.97 (t, $J = 5.6$ Hz, 1H), 5.21 (s, 1H), 3.68 – 3.35 (m, 10H), 3.30 (dt, $J = 13.7, 5.2$ Hz, 1H), 2.37 (t, $J = 6.0$ Hz, 2H), 1.63 – 1.47 (m, 4H), 1.43 (s, 9H), 1.25 (s, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[M+Na]^+$ calc'd for $C_{39}H_{78}N_2O_5$, 678; found, 678.

Example 22: 3-Amino-N-(2,3-bis(tetradecyloxy)propyl)propanamide hydrochloride.



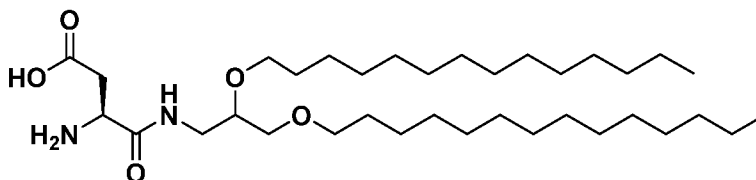
[0181] The title compound was prepared from tert-butyl (3-((2,3-bis(tetradecyloxy)propyl)amino)-3-oxopropyl)carbamate (196.5 mg, 0.3 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 8.43 (s, 3H), 6.54 (s, 1H), 3.60 – 3.19 (m, 11H), 2.76 (s, 2H), 1.96 (s, 2H), 1.55 (t, J = 6.6 Hz, 4H), 1.25 (s, 44H), 0.88 (t, J = 6.9 Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{34}\text{H}_{70}\text{N}_2\text{O}_3$, 556; found, 556.

Example 23: tert-Butyl (3S)-4-((2,3-bis(tetradecyloxy)propyl)amino)-3-((tert-butoxycarbonyl)amino)-4-oxobutanoate.



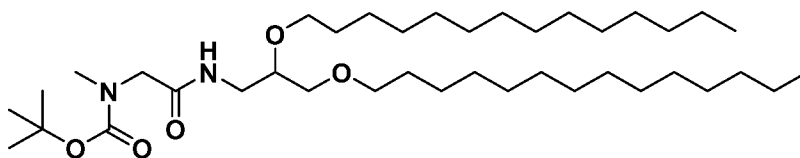
[0182] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and Boc-L-Asp(OtBu)-OSu (193 mg, 0.5 mmol) as described for Example 1 to give a white solid (160 mg, 42% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 6.79 (q, J = 5.2 Hz, 1H), 5.63 (d, J = 8.6 Hz, 1H), 4.43 (s, 1H), 3.63 – 3.21 (m, 9H), 2.89 (dd, J = 16.9, 4.7 Hz, 1H), 2.59 (dd, J = 16.9, 6.1 Hz, 1H), 1.56 (td, J = 14.2, 12.7, 5.7 Hz, 4H), 1.44 (d, J = 5.1 Hz, 18H), 1.25 (s, 44H), 0.88 (t, J = 6.9 Hz, 6H); ESI-MS m/z $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{44}\text{H}_{86}\text{N}_2\text{O}_7$, 778; found, 778.

Example 24: (3S)-3-Amino-4-((2,3-bis(tetradecyloxy)propyl)amino)-4-oxobutanoic acid hydrochloride.



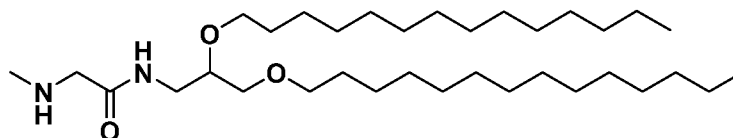
[0183] The title compound was prepared from tert-butyl (3S)-4-((2,3-bis(tetradecyloxy)propyl)amino)-3-((tert-butoxycarbonyl)amino)-4-oxobutanoate (151 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (499 MHz, Chloroform-*d*) δ 8.09 (d, $J = 111.7$ Hz, 4H), 3.92 – 3.20 (m, 10H), 3.08 (s, 2H), 1.55 (s, 4H), 1.26 (s, 44H), 0.88 (t, $J = 6.8$ Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{35}\text{H}_{70}\text{N}_2\text{O}_5$, 600; found, 600.

[0184] Example 25: tert-Butyl (2-((2,3-bis(tetradecyloxy)propyl)amino)-2-oxoethyl (methyl)carbamate.



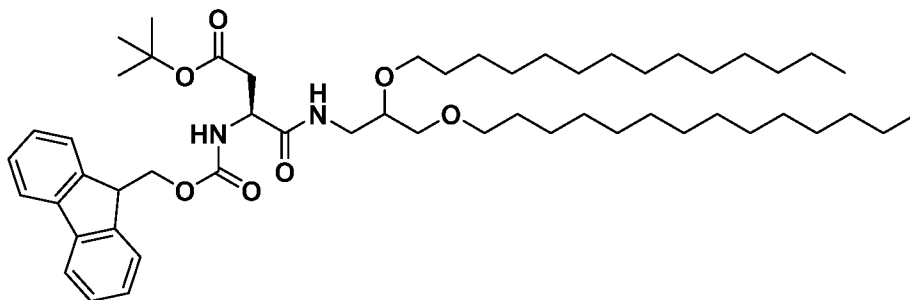
[0185] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and Boc-Sar-OSu (Sar = N-methylglycine; 143 mg, 0.5 mmol) as described for Example 1 to give a white solid (220 mg, 67% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 6.41 (s, 1H), 3.87 (s, 2H), 3.66 – 3.20 (m, 9H), 2.92 (s, 3H), 1.55 (td, $J = 7.2, 3.7$ Hz, 4H), 1.46 (s, 9H), 1.25 (s, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{39}\text{H}_{78}\text{N}_2\text{O}_5$, 678; found, 678.

Example 26: N-(2,3-bis(tetradecyloxy)propyl)-2-(methylamino)acetamide hydrochloride.



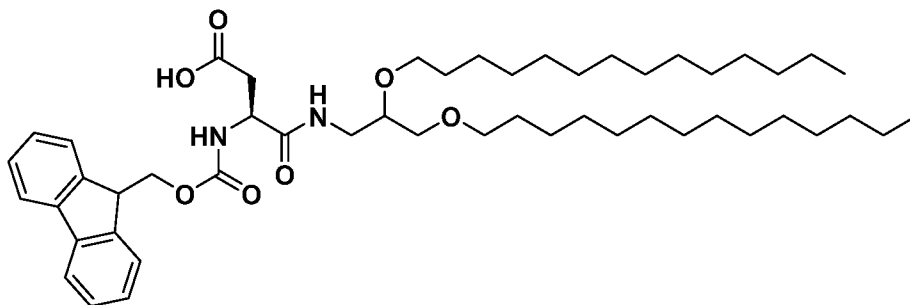
[0186] The title compound was prepared from tert-butyl (2-((2,3-bis(tetradecyloxy)propyl)amino)-2-oxoethyl (methyl)carbamate (196.5 mg, 0.3 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (499 MHz, Chloroform-*d*) δ 9.42 (s, 2H), 7.45 (d, $J = 12.9$ Hz, 1H), 3.88 (s, 2H), 3.72 – 3.19 (m, 9H), 2.82 (s, 3H), 1.54 (q, $J = 6.8$ Hz, 4H), 1.25 (s, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{34}\text{H}_{70}\text{N}_2\text{O}_3$, 556; found, 556.

Example 27: tert-Butyl (3S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-((2,3-bis(tetradecyloxy)propyl)amino)-4-oxobutanoate.



[0187] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and Fmoc-L-Asp(OtBu)-OSu (254 mg, 0.5 mmol) as described for Example 1 to give a white solid (280 mg, 64% yield). ^1H NMR (499 MHz, Chloroform-*d*) δ 7.76 (d, $J = 7.6$ Hz, 2H), 7.58 (d, $J = 7.5$ Hz, 2H), 7.40 (t, $J = 7.5$ Hz, 2H), 7.31 (t, $J = 7.5$ Hz, 2H), 6.89 – 6.64 (m, 1H), 5.96 (d, $J = 8.4$ Hz, 1H), 4.50 (s, 1H), 4.40 (tt, $J = 18.4$, 9.0 Hz, 2H), 4.22 (t, $J = 7.2$ Hz, 1H), 3.62 – 3.22 (m, 9H), 2.92 (dd, $J = 17.0$, 4.4 Hz, 1H), 2.61 (dd, $J = 17.1$, 6.6 Hz, 1H), 1.67 – 1.49 (m, 4H), 1.45 (s, 9H), 1.25 (q, $J = 7.3$, 5.2 Hz, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{54}\text{H}_{88}\text{N}_2\text{O}_7$, 878; found, 878.

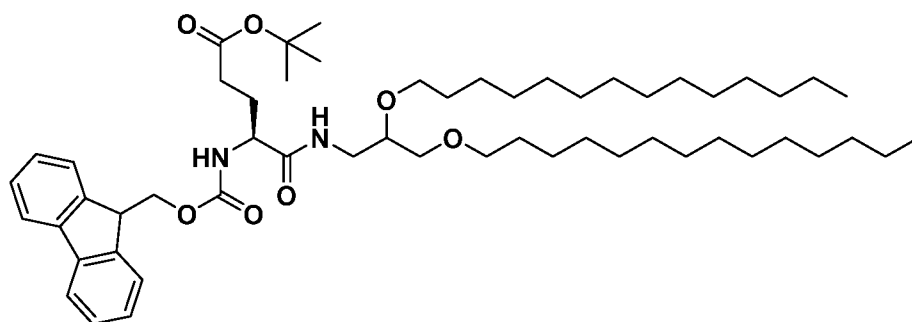
Example 28: (3S)-3-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-4-((2,3-bis(tetradecyloxy)propyl)amino)-4-oxobutanoic acid.



[0188] The title compound was prepared from tert-butyl (3S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-((2,3-bis(tetradecyloxy) propyl)amino)-4-oxobutanoate (175.4 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ^1H NMR

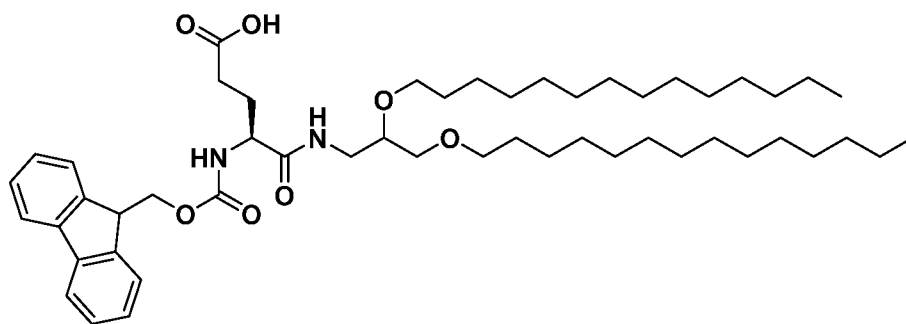
(499 MHz, Chloroform-*d*) δ 7.76 (dd, $J = 7.6, 3.0$ Hz, 2H), 7.58 (d, $J = 7.3$ Hz, 2H), 7.40 (td, $J = 7.5, 2.5$ Hz, 2H), 7.31 (td, $J = 7.5, 2.4$ Hz, 2H), 6.85 (dd, $J = 38.1, 6.0$ Hz, 1H), 5.96 (d, $J = 8.9$ Hz, 1H), 4.66 – 4.28 (m, 3H), 4.21 (q, $J = 7.1$ Hz, 1H), 3.77 (q, $J = 4.7, 3.8$ Hz, 2H), 3.64 (dt, $J = 7.4, 5.0$ Hz, 2H), 3.58 – 3.19 (m, 6H), 3.15 – 2.81 (m, 1H), 2.82 – 2.48 (m, 1H), 1.53 (p, $J = 6.7$ Hz, 4H), 1.38 – 1.11 (m, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[M-H]^+$ calc'd for $C_{50}H_{80}N_2O_7$, 820; found, 820.

Example 29: tert-Butyl (4S)-4-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-((2,3-bis(tetradecyloxy)propyl)amino)-5-oxopentanoate.



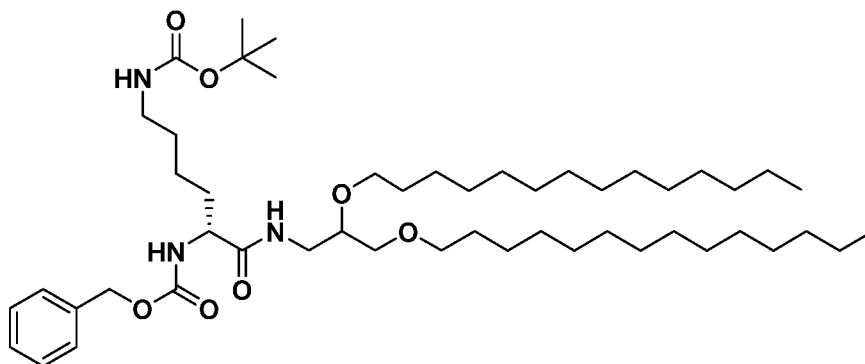
[0189] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and Fmoc-L-Glu(OtBu)-OSu (261 mg, 0.5 mmol) as described for Example 1 to give a white solid (265 mg, 60% yield). ^1H NMR (499 MHz, Chloroform-*d*) δ 7.76 (d, $J = 7.5$ Hz, 2H), 7.59 (d, $J = 7.5$ Hz, 2H), 7.40 (t, $J = 7.5$ Hz, 2H), 7.31 (t, $J = 7.4$ Hz, 2H), 6.54 (s, 1H), 5.74 (s, 1H), 4.52 – 4.27 (m, 2H), 4.21 (t, $J = 7.2$ Hz, 2H), 3.71 – 3.13 (m, 9H), 2.43 (d, $J = 16.7$ Hz, 1H), 2.35 – 2.19 (m, 1H), 2.09 (dd, $J = 14.3, 7.0$ Hz, 1H), 1.93 (dd, $J = 14.7, 7.4$ Hz, 1H), 1.65 – 1.49 (m, 4H), 1.46 (s, 9H), 1.25 (q, $J = 7.5, 5.7$ Hz, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[M+Na]^+$ calc'd for $C_{55}H_{90}N_2O_7$, 914; found, 914.

[0190] Example 30: (4S)-4-(((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-5-((2,3-bis(tetradecyloxy)propyl)amino)-5-oxopentanoic acid.



[0191] The title compound was prepared from tert-butyl (4S)-4-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-((2,3-bis(tetradecyloxy)propyl)amino)-5-oxopentanoate (178 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.75 (t, J = 6.3 Hz, 2H), 7.59 (t, J = 7.3 Hz, 2H), 7.39 (t, J = 7.1 Hz, 2H), 7.34 – 7.27 (m, 2H), 6.76 (s, 1H), 5.82 (d, J = 8.3 Hz, 1H), 4.47 – 4.24 (m, 3H), 4.20 (q, J = 7.1 Hz, 1H), 3.59 – 3.16 (m, 9H), 2.59 – 2.46 (m, 1H), 2.45 – 2.28 (m, 1H), 2.14 (s, 1H), 2.05 – 1.82 (m, 1H), 1.52 (h, J = 6.5 Hz, 4H), 1.24 (q, J = 6.7, 5.4 Hz, 44H), 0.88 (t, J = 6.9 Hz, 6H); ESI-MS m/z $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{51}\text{H}_{82}\text{N}_2\text{O}_7$, 858; found, 858.

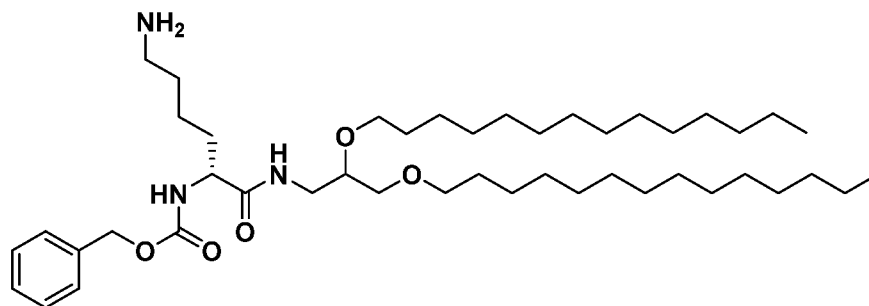
Example 31: Benzyl tert-butyl ((5R)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexane-1,5-diyl)dicarbamate.



[0192] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and $\text{N}^\alpha\text{-Z-N}^\epsilon\text{-Boc-D-Lys-OSu}$ (237 mg, 0.5 mmol) as described for Example 1 to give a white solid (280 mg, 66% yield). ^1H NMR (499 MHz, Chloroform-*d*) δ 7.44 – 7.29 (m, 5H), 6.36 (d, J = 6.7 Hz, 1H), 5.43 (s, 1H), 5.10 (d, J = 3.5 Hz, 2H), 4.57 (s, 1H), 4.11 (d, J = 6.9 Hz, 1H), 3.65 – 3.18 (m, 9H), 3.09 (d, J = 7.0 Hz, 2H), 1.97 – 1.74 (m, 1H), 1.73 – 1.59 (m, 2H), 1.54 (q, J = 6.7 Hz, 4H), 1.50-1.31 (m, 3H), 1.42 (s, 9H),

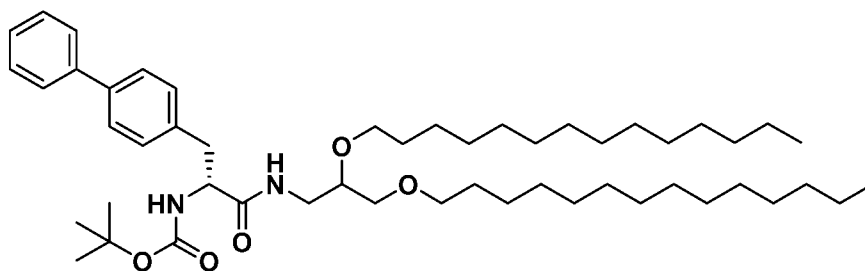
1.25 (s, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[M+Na]^+$ calc'd for $C_{50}H_{91}N_3O_7$, 869; found, 869.

Example 32: Benzyl ((2R)-6-amino-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxohexan-2-yl)carbamate hydrochloride.



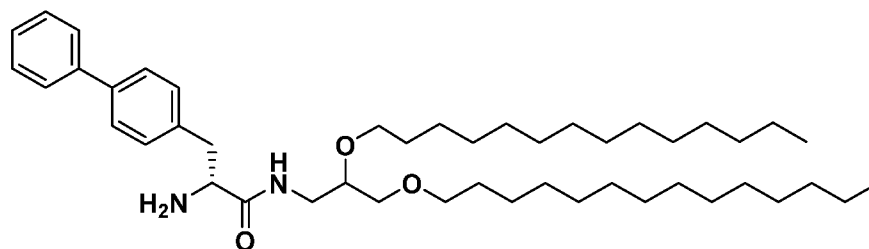
[0193] The title compound was prepared from benzyl tert-butyl ((5R)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexane-1,5-diyl)dicarbamate (169 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, Chloroform- d) δ 8.21 (s, 3H), 7.41 – 7.29 (m, 5H), 7.17 (s, 1H), 6.09 (s, 1H), 5.07 (s, 2H), 4.24 (s, 1H), 3.59 – 3.20 (m, 9H), 2.93 (m, 2H), 2.15 (s, 3H), 1.74 (m, 3H), 1.53 (t, $J = 6.8$ Hz, 4H), 1.24 (d, $J = 3.5$ Hz, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{45}H_{83}N_3O_5$, 747; found, 747.

Example 33: tert-Butyl ((2R)-3-([1,1'-biphenyl]-4-yl)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxopropan-2-yl)carbamate



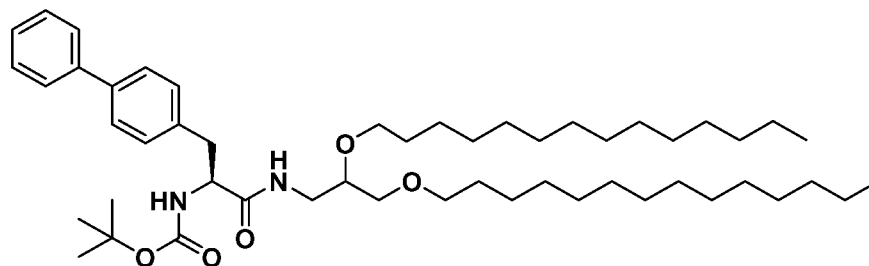
[0194] In a 30 mL sealed cap glass vial, a solution of Boc-4-Phe-D-Phenyl-Ala-OH (171 mg, 0.5 mmol) in DMF (5 mL) was treated with HATU (285 mg, 0.75 mmol) and diisopropyl ethylamine (174 μ L, 1.0 mmol). After stirring for 5 min at rt, 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) was added to the reaction vial, the cap was closed, and stirring was continued at rt for 5 h. The mixture was diluted with water (10 mL) and brine (10 mL), and extracted with ethyl acetate (2 x 25 mL), and the combined organic layers were dried over sodium sulfate and concentrated. The residue was purified on a silica gel column (hexane-ethyl acetate (0-100%)) to give the title compound as white solid (172 mg, 43% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.60 – 7.49 (m, 4H), 7.42 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 7.28 (dd, J = 8.7, 2.6 Hz, 2H), 6.15 (d, J = 30.8 Hz, 1H), 5.04 (d, J = 21.2 Hz, 1H), 4.34 (s, 1H), 3.80 (dt, J = 9.5, 6.5 Hz, 1H), 3.56 – 3.18 (m, 8H), 3.10 (dq, J = 8.1, 5.0, 4.2 Hz, 2H), 1.49 (dq, J = 14.5, 6.9 Hz, 4H), 1.41 (d, J = 1.4 Hz, 9H), 1.35 – 1.09 (m, 44H), 0.88 (t, J = 6.9 Hz, 6H); ESI-MS m/z $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{51}\text{H}_{86}\text{N}_2\text{O}_5$, 830; found, 830.

Example 34: (2R)-3-([1,1'-Biphenyl]-4-yl)-2-amino-N-(2,3-bis(tetradecyloxy)propyl)propanamide hydrochloride.



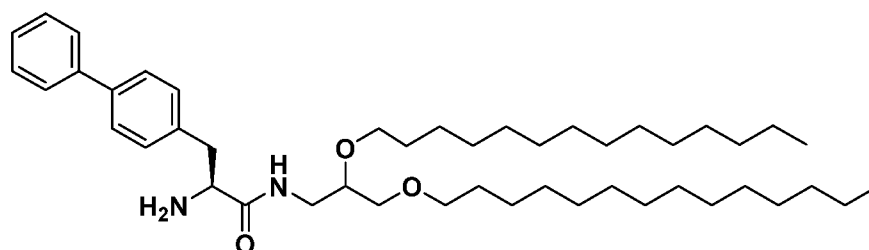
[0195] The title compound was prepared from tert-butyl ((2R)-3-([1,1'-biphenyl]-4-yl)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxopropan-2-yl)carbamate (162 mg, 0.2 mmol) as described for Example 1 to give a solid (100% yield). ^1H NMR (500 MHz, DMSO-*d*₆) δ 8.41 (dt, J = 14.0, 5.8 Hz, 1H), 8.26 (s, 3H), 7.70 – 7.55 (m, 4H), 7.45 (t, J = 7.6 Hz, 2H), 7.35 (dd, J = 11.5, 7.7 Hz, 3H), 4.08 (d, J = 34.4 Hz, 1H), 3.81 – 3.56 (m, 1H), 3.52 – 3.16 (m, 7H), 3.14 – 2.87 (m, 3H), 1.40 (ddd, J = 28.0, 13.0, 6.6 Hz, 4H), 1.32 – 1.02 (m, 44H), 0.85 (t, J = 6.8 Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{46}\text{H}_{78}\text{N}_2\text{O}_3$, 708; found, 708.

Example 35: tert-Butyl ((2S)-3-([1,1'-biphenyl]-4-yl)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxopropan-2-yl)carbamate.



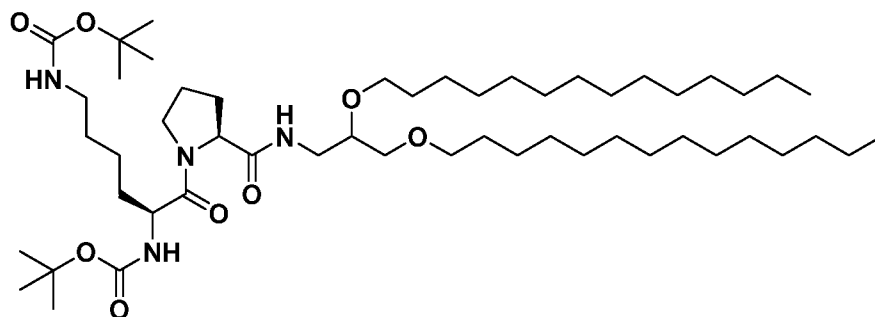
[0196] The title compound was prepared from Boc-4-Phe-L-Phenyl Ala-OH (171 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described in Example 33 to give a white solid (225 mg, 56% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.54 (dd, $J = 16.5, 7.8$ Hz, 4H), 7.42 (t, $J = 7.5$ Hz, 2H), 7.33 (t, $J = 7.4$ Hz, 1H), 7.28 (dd, $J = 8.7, 2.5$ Hz, 2H), 6.15 (d, $J = 30.9$ Hz, 1H), 5.04 (d, $J = 20.8$ Hz, 1H), 4.34 (s, 1H), 3.57 – 3.17 (m, 9H), 3.17 – 2.95 (m, 2H), 1.49 (dd, $J = 13.1, 7.5$ Hz, 4H), 1.41 (s, 9H), 1.36 – 1.15 (m, 44H), 0.88 (t, $J = 6.8$ Hz, 6H); ESI-MS m/z $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{51}\text{H}_{86}\text{N}_2\text{O}_5$, 830; found, 830.

Example 36: (2S)-3-([1,1'-Biphenyl]-4-yl)-2-amino-N-(2,3-bis(tetradecyloxy)propyl)propanamide hydrochloride.



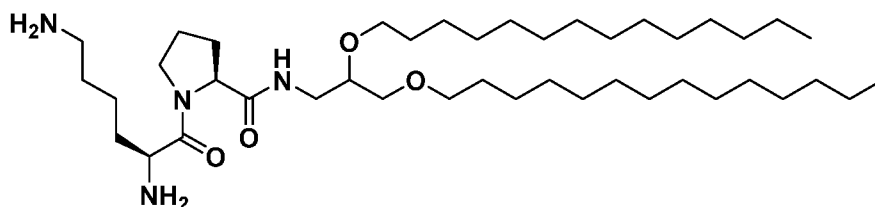
[0197] The title compound was prepared from tert-butyl ((2S)-3-([1,1'-biphenyl]-4-yl)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxopropan-2-yl)carbamate (162 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, DMSO-*d*₆) δ 8.41 (dd, $J = 13.0, 6.5$ Hz, 1H), 8.26 (s, 3H), 7.64 (t, $J = 7.0$ Hz, 4H), 7.45 (t, $J = 7.6$ Hz, 2H), 7.35 (dd, $J = 11.2, 7.7$ Hz, 3H), 4.05 (s, 1H), 3.67 (m, 1H), 3.58 – 3.15 (m, 7H), 3.15 – 2.84 (m, 3H), 1.56 – 1.32 (m, 4H), 1.21 (d, $J = 8.9$ Hz, 44H), 0.85 (t, $J = 6.8$ Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{46}\text{H}_{78}\text{N}_2\text{O}_3$, 708; found, 708.

Example 37: Di-tert-butyl ((5S)-6-((2S)-2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)pyrrolidin-1-yl)-6-oxohexane-1,5-diyl)dicarbamate.



[0198] The title compound was prepared from Boc-L-Lys-(Boc)-L-Pro-OH (222 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described in Example 33 to give a gummy solid (220 mg, 48% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 6.74-6.64 (t, J = 5.6 Hz, 1H), 5.38 – 5.24 (m, 1H), 4.92 (s, 1H), 4.55 – 4.37 (m, 2H), 3.77 – 3.61 (m, 1H), 3.61 – 3.19 (m, 10H), 3.10 (d, J = 8.4 Hz, 2H), 2.34 – 2.17 (m, 1H), 2.12 (m, 1H), 2.00 – 1.87 (m, 2H), 1.80 – 1.64 (m, 1H), 1.55 (tdd, J = 12.7, 9.4, 5.5 Hz, 6H), 1.43 (d, J = 1.5 Hz, 18H), 1.25 (s, 48H), 0.88 (t, J = 6.9 Hz, 6H); ESI-MS m/z $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{52}\text{H}_{100}\text{N}_4\text{O}_8$, 932; found, 932.

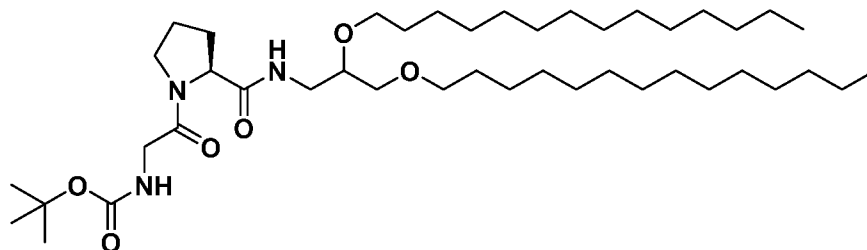
Example 38: (2S)-1-(L-Lysyl)-N-(2,3-bis(tetradecyloxy)propyl)pyrrolidine-2-carboxamide dihydrochloride.



[0199] The title compound was prepared from di-tert-butyl ((5S)-6-((2S)-2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)pyrrolidin-1-yl)-6-oxohexane-1,5-diyl)dicarbamate (182 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 8.33 (s, 3H), 7.93 (s, 3H), 4.74 (s, 1H), 4.45 (s, 1H), 4.00 – 3.31 (m, 10H), 3.04 (d, J = 51.0 Hz, 2H), 2.47 (s, 2H), 1.93 (q, J = 51.8, 39.5 Hz, 4H), 1.61 – 1.45 (m,

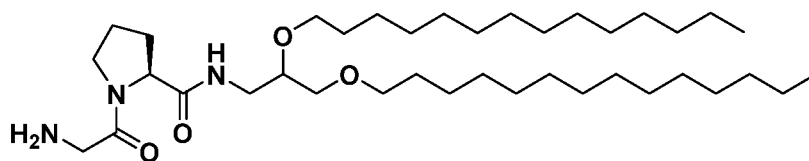
4H), 1.25 (s, 48H), 0.88 (t, $J = 6.8$ Hz, 6H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{42}H_{84}N_4O_4$, 710; found, 710.

Example 39: tert-Butyl (2-((2S)-2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate.



[0200] The title compound was prepared from Boc-Gly-L-Pro-OH (136 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described in Example 33 to give a white solid (185 mg, 50% yield). ^1H NMR (500 MHz, Chloroform- d) δ 6.87 (dt, $J = 16.5, 5.3$ Hz, 1H), 5.40 (s, 1H), 4.51 (d, $J = 8.1$ Hz, 1H), 4.08 – 3.80 (m, 2H), 3.79 – 3.12 (m, 11H), 2.34 (ddt, $J = 12.5, 5.8, 2.9$ Hz, 1H), 2.18 – 2.06 (m, 1H), 2.00 (ddt, $J = 12.6, 6.8, 3.6$ Hz, 1H), 1.90 (dddd, $J = 17.7, 12.9, 8.0, 2.3$ Hz, 1H), 1.65 (s, 1H), 1.55 (td, $J = 7.2, 3.8$ Hz, 4H), 1.45 (s, 9H), 1.25 (s, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[M+Na]^+$ calc'd for $C_{43}H_{83}N_3O_6$, 761; found, 761.

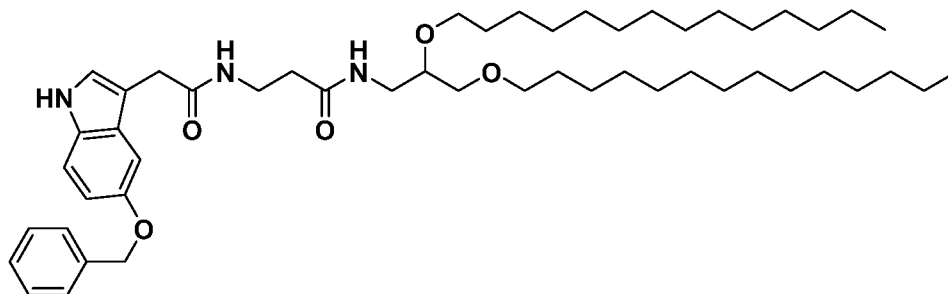
Example 40: (2S)-N-(2,3-Bis(tetradecyloxy)propyl)-1-glycylpyrrolidine-2-carboxamide hydrochloride.



[0201] The title compound was prepared from tert-butyl (2-((2S)-2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (148 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, Chloroform- d) δ 8.01 (d, $J = 193.1$ Hz, 3H), 4.57 (s, 1H), 4.01 (s, 1H), 3.83 – 3.04 (m, 11H),

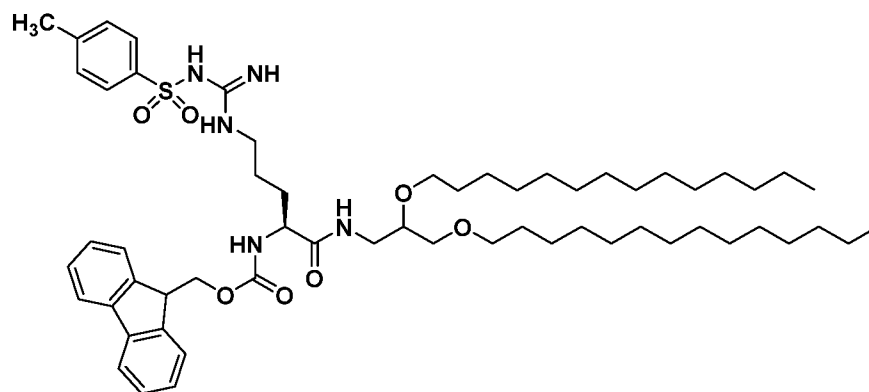
2.52 (s, 1H), 2.35 – 1.76 (m, 3H), 1.53 (s, 4H), 1.25 (s, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{38}H_{75}N_3O_4$, 639; found, 639.

Example 41: 3-(2-(5-(Benzyloxy)-1H-indol-3-yl)acetamido)-N-(2,3-bis(tetradecyloxy)propyl)propanamide.



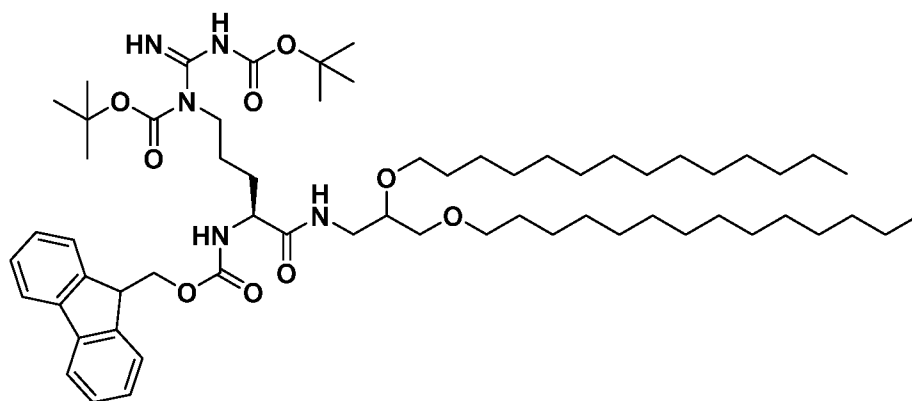
[0202] The title compound was prepared from 2-(5-(benzyloxy)-1H-indol-3-yl)acetic acid (80 mg, 0.283 mmol) and 3-amino-N-(2,3-bis(tetradecyloxy)propyl)propanamide hydrochloride (167 mg, 0.283 mmol) as described in Example 33 to give a brown solid (192 mg, 83% yield). ^1H NMR (499 MHz, Chloroform- d) δ 8.26 (d, $J = 2.3$ Hz, 1H), 7.47 (d, $J = 7.1$ Hz, 2H), 7.38 (t, $J = 7.6$ Hz, 2H), 7.33 – 7.27 (m, 1H), 7.12 (d, $J = 2.3$ Hz, 1H), 7.05 (d, $J = 2.4$ Hz, 1H), 6.94 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.53 (s, 1H), 6.24 (s, 1H), 6.11 (s, 1H), 5.09 (s, 2H), 3.77 – 3.61 (m, 2H), 3.48 – 3.31 (m, 9H), 3.16 (qd, $J = 7.4, 4.4$ Hz, 3H), 2.33 (dd, $J = 7.0, 5.1$ Hz, 2H), 1.53 (q, $J = 7.3$ Hz, 4H), 1.25 (s, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[M+Na]^+$ calc'd for $C_{51}H_{83}N_3O_5$, 841; found, 841.

Example 42: (9H-Fluoren-9-yl)methyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxo-5-(3-tosylguanidino)pentan-2-yl)carbamate.



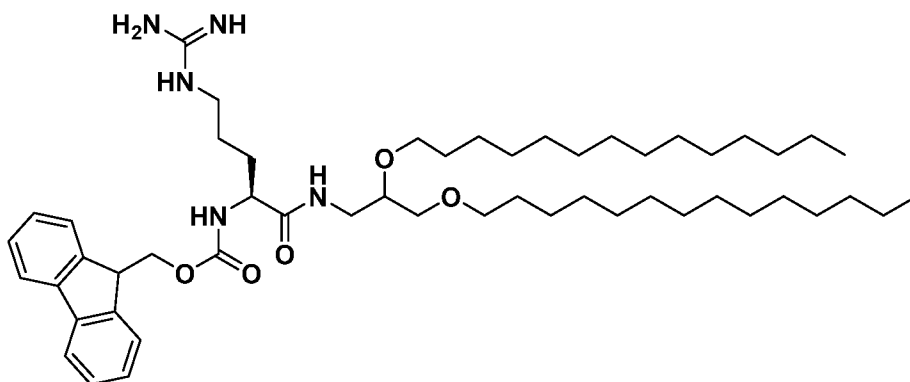
[0203] The title compound was prepared from N^α-Fmoc-L-Arg-N^W-Tos-OH (275 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described in Example 33 to give a gummy solid (182 mg, 36% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.75 (dd, *J* = 7.8, 4.5 Hz, 4H), 7.57 (dd, *J* = 7.5, 3.4 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.26 (m, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.76 (s, 1H), 6.44 (s, 2H), 5.82 (s, 1H), 4.47 – 4.26 (m, 2H), 4.16 (dd, *J* = 15.3, 8.3 Hz, 1H), 3.73 – 3.15 (m, 7H), 3.00 (d, *J* = 9.6 Hz, 3H), 2.35 (s, 3H), 2.04 (m, 2H), 1.68 – 1.41 (m, 4H), 1.36 – 1.10 (m, 46H), 0.88 (td, *J* = 7.0, 1.6 Hz, 6H); ESI-MS *m/z* [M+Na]⁺ calc'd for C₅₉H₉₃N₅O₇S, 1039; found, 1039.

Example 43: (9H-Fluoren-9-yl)methyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxo-5-(1,3-bis-(tert-butyloxy)guanidino)pentan-2-yl)carbamate.



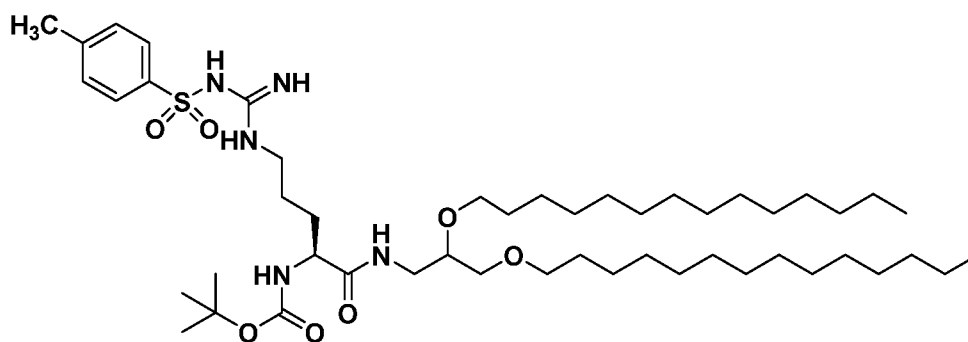
[0204] Prepared from N^α-Fmoc-L-Arg-(Boc)₂-OH (298 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described in Example 33 to give a gummy solid (105 mg, 20% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 10.72 (s, 1H), 7.76 (dd, *J* = 7.6, 4.5 Hz, 2H), 7.70 – 7.54 (m, 2H), 7.46 – 7.36 (m, 2H), 7.31 (dd, *J* = 8.3, 6.6 Hz, 2H), 6.59 (s, 1H), 6.08 – 5.85 (m, 1H), 5.63 (s, 1H), 4.62 – 4.18 (m, 5H), 3.89 – 3.18 (m, 8H), 3.00 (s, 2H), 2.54 (s, 1H), 2.04 – 1.84 (m, 1H), 1.78 – 1.56 (m, 4H), 1.51 (d, *J* = 8.9 Hz, 18H), 1.35 – 1.07 (m, 44H), 0.88 (td, *J* = 7.0, 1.4 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₆₂H₁₀₃N₅O₉, 1063; found, 1063.

Example 44: (9H-Fluoren-9-yl)methyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-5-guanidino-1-oxopentan-2-yl)carbamate dihydrochloride.



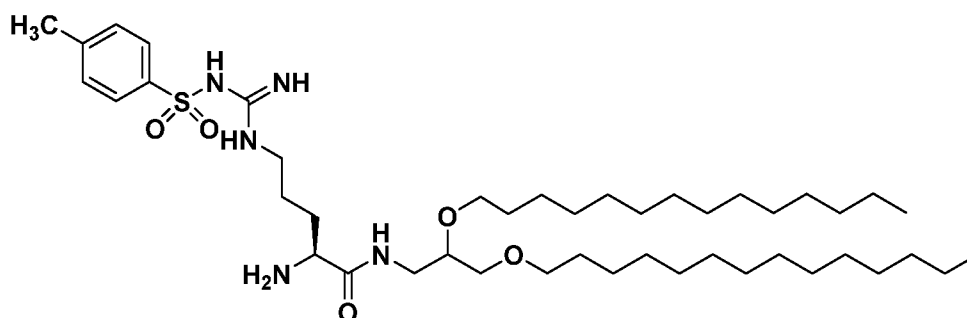
[0205] The title compound was prepared from Example 43 (53 mg, 0.05 mmol) as described in Example 1 to give a gummy solid (100% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.83 – 7.67 (m, 2H), 7.61 (s, 2H), 7.44 – 7.32 (m, 2H), 7.29 (d, *J* = 7.3 Hz, 2H), 4.33 (d, *J* = 19.7 Hz, 3H), 4.21 (dt, *J* = 17.1, 8.5 Hz, 1H), 3.90 – 3.15 (m, 11H), 2.13 – 1.64 (m, 2H), 1.57 – 1.39 (m, 6H), 1.25 (s, 44H), 0.87 (t, *J* = 6.8 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₅₂H₈₇N₅O₅, 963; found, 963.

Example 45: tert-Butyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxo-5-(3-tosylguanidino)pentan-2-yl)carbamate.



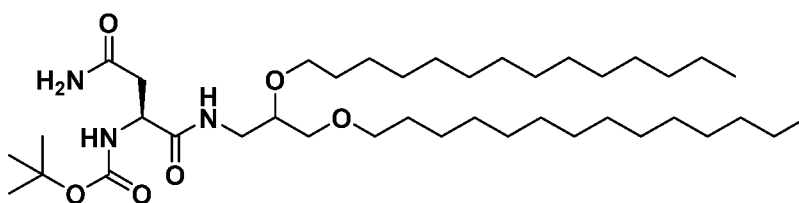
[0206] The title compound was prepared from N^α-Boc-L-Arg-(N^W-Tos)-OH (214 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give a gummy liquid (310 mg, 69% yield). ¹H NMR (499 MHz, Chloroform-*d*) δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.76 (s, 1H), 6.40 (s, 2H), 5.32 (d, *J* = 30.0 Hz, 1H), 4.11 (q, *J* = 8.1, 7.6 Hz, 1H), 3.72 – 3.14 (m, 9H), 3.00 (d, *J* = 8.1 Hz, 2H), 2.38 (s, 3H), 1.98 (s, 2H), 1.54 (qd, *J* = 13.5, 7.6, 6.7 Hz, 6H), 1.41 (s, 9H), 1.24 (s, 44H), 0.87 (t, *J* = 6.8 Hz, 6H); ESI-MS *m/z* [M+Na]⁺ calc'd for C₄₉H₉₁N₅O₇S, 917; found, 917.

Example 46: (2S)-2-Amino-N-(2,3-bis(tetradecyloxy)propyl)-5-(3-tosylguanidino)pentanamide hydrochloride.



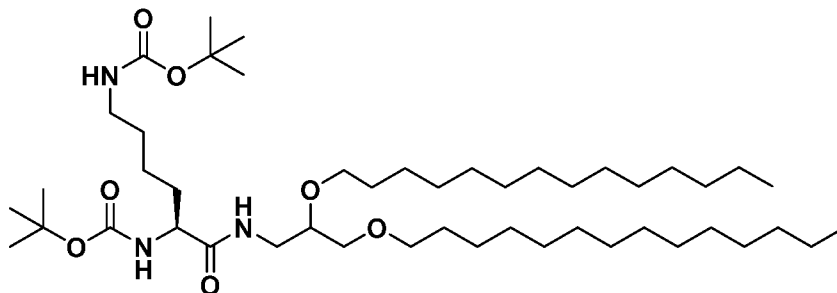
[0207] The title compound was prepared from Example 45 (179 mg, 0.2 mmol) as described for Example 1 to give a light pink solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 8.26 (d, $J = 52.4$ Hz, 3H), 8.03 (s, 1H), 7.88 (d, $J = 7.8$ Hz, 2H), 7.64 (s, 1H), 7.35 (d, $J = 7.9$ Hz, 2H), 4.29 (s, 1H), 3.86 – 3.19 (m, 11H), 2.42 (s, 3H), 2.06 (s, 2H), 1.88 (s, 2H), 1.51 (d, $J = 8.6$ Hz, 4H), 1.24 (dd, $J = 7.9, 4.8$ Hz, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{44}\text{H}_{83}\text{N}_5\text{O}_5\text{S}$, 795; found, 795.

Example 47: tert-Butyl ((2S)-4-amino-1-((2,3-bis(tetradecyloxy)propyl)amino)-1,4-dioxobutan-2-yl)carbamate.



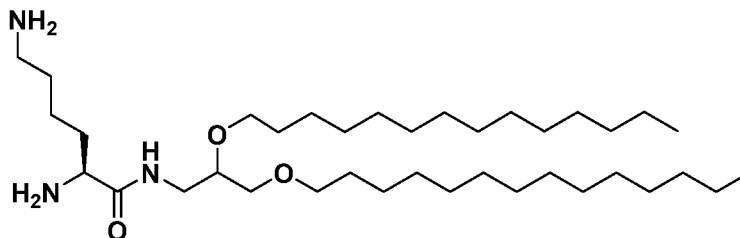
[0208] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and Boc-L-Asp-OSu (165 mg, 0.5 mmol) as described for Example 1 to give a white solid (200 mg, 57% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 3.61 (dt, $J = 9.3, 6.6$ Hz, 1H), 3.54 – 3.26 (m, 9H), 2.98 – 2.64 (m, 2H), 1.73 – 1.49 (m, 7H), 1.44 (s, 9H), 1.25 (s, 44H), 0.88 (t, $J = 6.9$ Hz, 6H).

Example 48: Di-tert-butyl ((5S)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexane-1,5-diyl)dicarbamate.



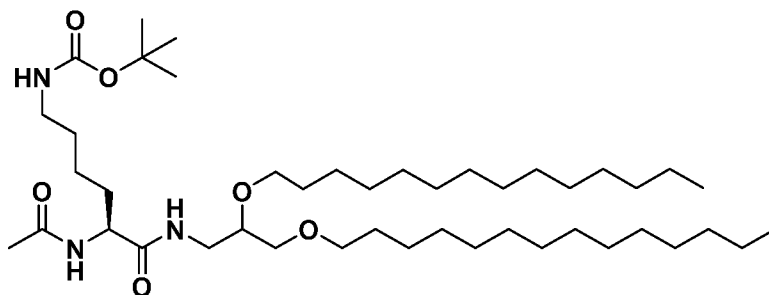
[0209] The title compound was prepared from 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) and Boc-L-Lys(Boc)-OSu (222 mg, 0.5 mmol) as described for Example 1 to give a white solid (180 mg, 44% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 6.38 (s, 1H), 5.08 (s, 1H), 4.58 (s, 1H), 4.03 (s, 1H), 3.68 – 3.19 (m, 9H), 3.10 (d, $J = 7.4$ Hz, 2H), 1.83 (dq, $J = 13.6, 7.3$ Hz, 1H), 1.65 – 1.46 (m, 7H), 1.44 (s, 18H), 1.37 (q, $J = 7.7$ Hz, 2H), 1.26 (s, 46H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{47}\text{H}_{93}\text{N}_3\text{O}_7$, 835; found, 835.

Example 49: (2S)-2,6-Diamino-N-(2,3-bis(tetradecyloxy)propyl)hexanamide dihydrochloride.



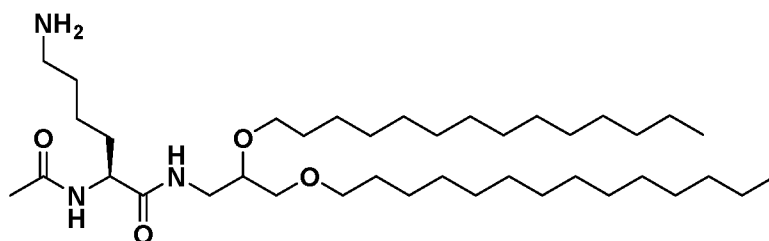
[0210] The title compound was prepared from Example 48 (162 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 8.26 (s, 3H), 8.01 (s, 3H), 4.41 (s, 1H), 3.83 – 3.24 (m, 10H), 3.15 (s, 2H), 2.55 (s, 2H), 2.05 (s, 1H), 1.98 – 1.64 (m, 3H), 1.54 (s, 4H), 1.26 (s, 44H), 0.88 (t, $J = 6.8$ Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{37}\text{H}_{77}\text{N}_3\text{O}_3$, 613; found, 613.

Example 50: tert-Butyl ((5S)-5-acetamido-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexyl)carbamate.



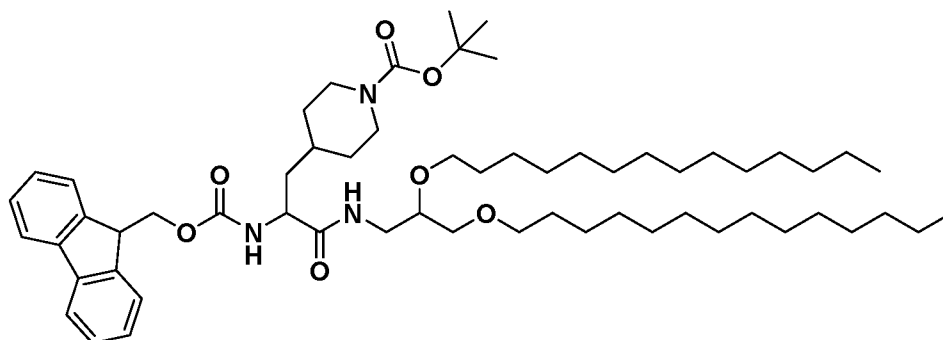
[0211] The title compound was prepared from N^α-acetyl-N^ε-Boc-L-Lysine (144 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as an off-white solid (152 mg, 40% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 6.34 (d, *J* = 16.1 Hz, 1H), 6.26 (s, 1H), 4.60 (s, 1H), 4.35 (dt, *J* = 8.2, 6.2 Hz, 1H), 3.65 – 3.19 (m, 9H), 3.09 (d, *J* = 7.4 Hz, 2H), 2.01 (s, 3H), 1.90 – 1.71 (m, 1H), 1.63 (dt, *J* = 15.1, 7.5 Hz, 1H), 1.51 (m, 6H), 1.44 (s, 9H), 1.25 (s, 46H), 0.88 (t, *J* = 6.9 Hz, 6H); ESI-MS *m/z* [M+Na]⁺ calc'd for C₄₄H₈₇N₃O₆, 777; found, 777.

Example 51: (2S)-2-Acetamido-6-amino-N-(2,3-bis(tetradecyloxy)propyl)hexanamide hydrochloride.



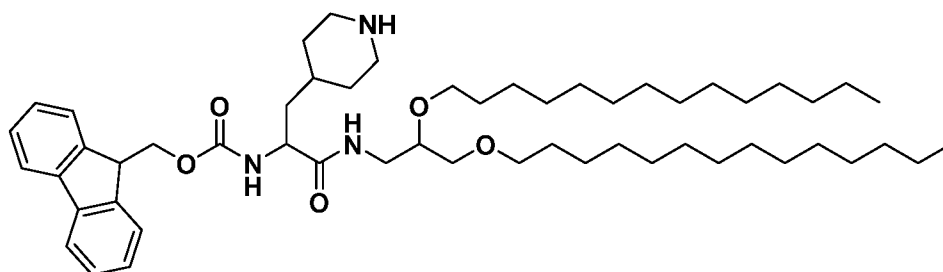
[0212] The title compound was prepared from Example 50 (151 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.26 (s, 3H), 7.96 (s, 1H), 4.57 (s, 1H), 3.70 – 3.24 (m, 10H), 3.09 (d, *J* = 11.8 Hz, 2H), 2.23 (d, *J* = 41.2 Hz, 3H), 1.97 – 1.71 (m, 5H), 1.54 (t, *J* = 7.1 Hz, 5H), 1.25 (s, 44H), 0.88 (t, *J* = 6.8 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₃₉H₇₉N₃O₄, 655; found, 655.

Example 52: tert-Butyl 4-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-((2,3-bis(tetradecyloxy)propyl)amino)-3-oxopropyl)piperidine-1-carboxylate.



[0213] The title compound was prepared from N^α-Fmoc-β-(1-Boc-piperidin-4-yl)-DL-alanine (247 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as a gummy solid (130 mg, 27% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.40 (td, *J* = 7.5, 2.0 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 6.31 (d, *J* = 17.7 Hz, 1H), 5.24 (d, *J* = 8.4 Hz, 1H), 4.56 – 4.30 (m, 2H), 4.26 – 3.95 (m, 4H), 3.71 – 3.15 (m, 9H), 2.66 (d, *J* = 12.3 Hz, 2H), 1.74 (s, 1H), 1.66 – 1.50 (m, 7H), 1.45 (s, 9H), 1.25 (d, *J* = 4.6 Hz, 45H), 1.12 (dd, *J* = 33.9, 12.7 Hz, 2H), 0.88 (t, *J* = 6.8 Hz, 6H); ESI-MS *m/z* [M+Na]⁺ calc'd for C₅₉H₉₇N₃O₇, 983; found, 983.

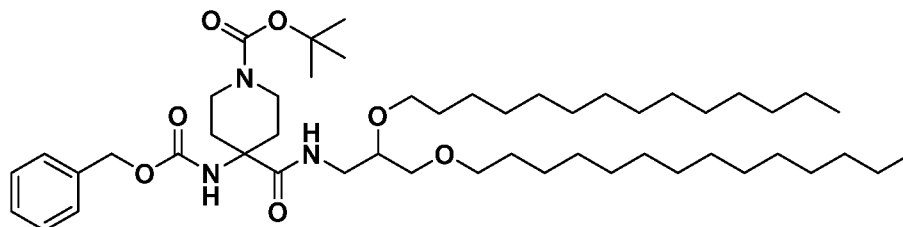
Example 53: (9H-Fluoren-9-yl)methyl (1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxo-3-(piperidin-4-yl)propan-2-yl)carbamate hydrochloride.



[0214] The title compound was prepared from Example 52 (96 mg, 0.1 mmol) as described for Example 1 to give a brown solid (100% yield). ¹H NMR (499 MHz, Chloroform-*d*) δ 9.43 (s, 1H), 9.13 (s, 1H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.34 – 7.28 (m, 2H), 6.80 (s, 1H), 5.64 (s, 1H), 4.55 – 4.29 (m, 2H), 4.20 (q, *J* = 10.1, 6.8 Hz, 2H), 3.58 – 3.13 (m, 13H), 2.83 (s, 2H), 2.14 – 1.59 (m, 2H), 1.57 – 1.42 (m, 5H), 1.35 – 1.13

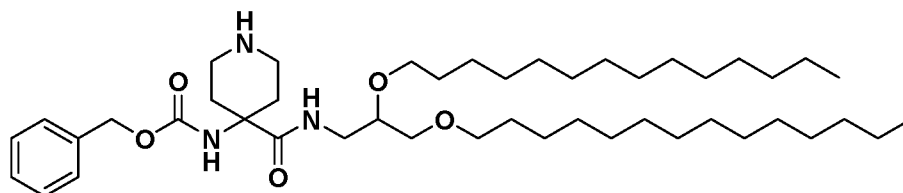
(m, 46H), 0.87 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{54}H_{89}N_3O_5$, 861; found, 861.

Example 54: tert-Butyl 4-(((benzyloxy)carbonyl)amino)-4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)piperidine-1-carboxylate.



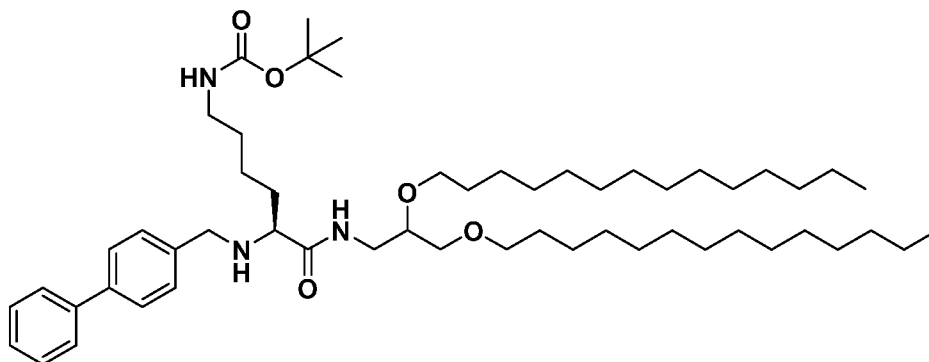
[0215] The title compound was prepared from Cbz-Pip(Boc)-OH (189 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as a gummy solid (160 mg, 38% yield). ^1H NMR (500 MHz, Chloroform- d) δ 7.34 (q, $J = 7.3, 6.8$ Hz, 5H), 6.88 (s, 1H), 5.08 (s, 2H), 4.88 (s, 1H), 3.83 (d, $J = 13.5$ Hz, 2H), 3.61 – 3.20 (m, 9H), 3.06 (ddd, $J = 14.0, 10.6, 3.1$ Hz, 2H), 2.17 – 1.83 (m, 4H), 1.64 – 1.45 (m, 4H), 1.45 (s, 9H), 1.35 – 1.13 (m, 44H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[M+Na]^+$ calc'd for $C_{50}H_{89}N_3O_7$, 867; found, 867.

Example 55: Benzyl (4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)piperidin-4-yl)carbamate hydrochloride.



[0216] The title compound was prepared from Example 54 (85 mg, 0.1 mmol) as described for Example 1 to give a tan solid (100% yield). ^1H NMR (499 MHz, Chloroform- d) δ 9.40 (s, 1H), 9.23 (d, $J = 59.5$ Hz, 1H), 7.41 – 7.28 (m, 5H), 6.99 (d, $J = 17.6$ Hz, 1H), 6.00 (s, 1H), 5.07 (d, $J = 2.1$ Hz, 2H), 3.58 – 3.11 (m, 11H), 2.47 (d, $J = 13.5$ Hz, 2H), 2.33 – 1.90 (m, 4H), 1.52 (m, 4H), 1.25 (d, $J = 4.7$ Hz, 44H), 0.88 (t, $J = 6.8$ Hz, 6H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{45}H_{81}N_3O_5$, 745; found, 745.

Example 56: tert-Butyl ((5S)-5-((1,1'-biphenyl)-4-ylmethyl)amino)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexyl)carbamate.



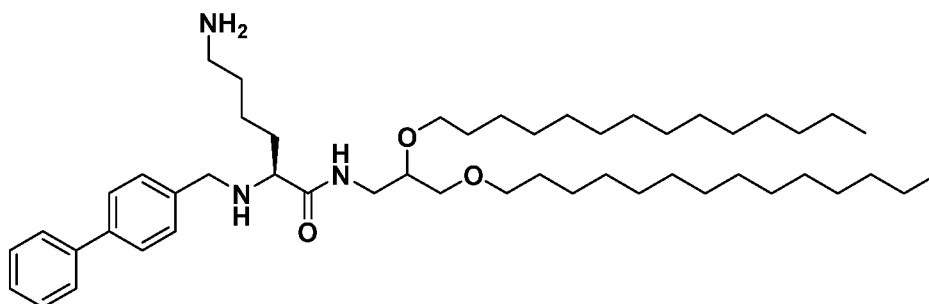
[0217] Step 1: Methyl N2-([1,1'-biphenyl]-4-ylmethyl)-N6-(tert-butoxycarbonyl)-L-lysinate. A mixture of [1,1'-biphenyl]-4-carbaldehyde (546 mg, 3.0 mmol) and methyl N6-(tert-butoxycarbonyl)-L-lysinate hydrochloride (890 mg, 3.0 mmol) in THF (50 mL) was treated with NaBH(OAc)₃ (763 mg, 3.6 mmol) and the reaction mixture was stirred at rt overnight. The reaction mixture was treated with satd. aq. K₂CO₃ (25 mL) and stirred for another 30 min. The resulting layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, evaporated, and purified using silica gel column chromatography (hexane-EtOAc (0-100%)) to give the title compound as a colorless liquid (520 mg). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.70 – 7.48 (m, 4H), 7.48 – 7.30 (m, 5H), 4.51 (s, 1H), 3.85 (d, *J* = 13.0 Hz, 1H), 3.73 (s, 3H), 3.67 (d, *J* = 13.0 Hz, 1H), 3.29 (t, *J* = 6.6 Hz, 1H), 3.10 (t, *J* = 6.5 Hz, 2H), 1.67 (m, 2H), 1.54 – 1.35 (m, 13H). ESI-MS *m/z* [M+H]⁺ calc'd for C₂₅H₃₄N₂O₄, 427; found, 427.

[0218] Step 2: N2-([1,1'-Biphenyl]-4-ylmethyl)-N6-(tert-butoxycarbonyl)-L-lysine. To a solution of methyl N2-([1,1'-biphenyl]-4-ylmethyl)-N6-(tert-butoxycarbonyl)-L-lysinate (427 mg, 1.0 mmol) in 1:1 THF-MeOH (6 mL) was added a solution of LiOH (96 mg, 4.0 mmol) in water (3.0 mL). After stirring at rt for 4 h, the mixture was neutralized by the addition of satd. aq. KHSO₄ (10 mL). A precipitate formed, which was collected by vacuum filtration, dried, and used in next step without further purification. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.62 (dd, *J* = 25.5, 7.8 Hz, 4H), 7.52 – 7.28 (m, 5H), 6.73 (s, 1H), 3.80 (d, *J* = 13.6 Hz, 1H), 3.62 (d, *J* = 14.0

Hz, 1H), 2.87 (d, $J = 6.6$ Hz, 2H), 2.79 (s, 1H), 1.47 (m, 2H), 1.36 (s, 13H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{24}H_{32}N_2O_4$, 413; found, 413.

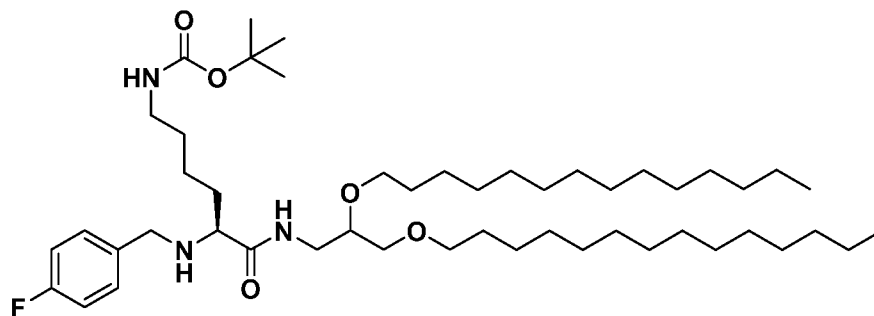
[0219] Step 3. The title compound was prepared from N2-([1,1'-biphenyl]-4-ylmethyl)-N6-(tert-butoxycarbonyl)-L-lysine (206 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as a gummy solid (285 mg, 65% yield). ^1H NMR (500 MHz, Chloroform- d) δ 7.66 – 7.52 (m, 4H), 7.51 – 7.30 (m, 6H), 4.67 (s, 1H), 3.98 (s, 2H), 3.74 – 3.21 (m, 8H), 3.06 (ddt, $J = 20.2, 13.2, 6.3$ Hz, 2H), 1.83 (d, $J = 52.7$ Hz, 2H), 1.63 – 1.40 (m, 6H), 1.35 (s, 9H), 1.30 – 1.13 (m, 46H), 0.88 (t, $J = 6.9$ Hz, 6H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{55}H_{95}N_3O_5$, 879; found, 879.

Example 57: (2S)-2-((([1,1'-Biphenyl]-4-ylmethyl)amino)-6-amino-N-(2,3-bis(tetradecyloxy)propyl)hexanamide dihydrochloride.



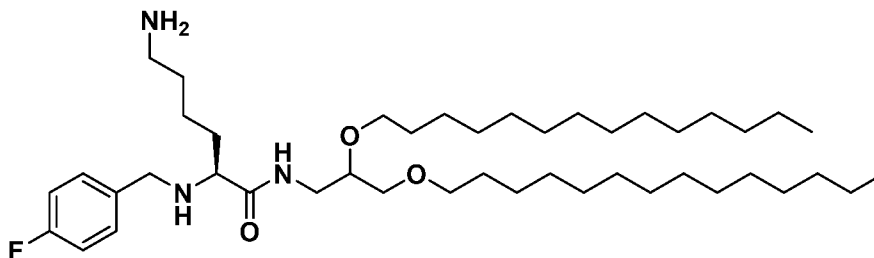
[0220] The title compound was prepared from Example 56 (176 mg, 0.2 mmol) as described for Example 1 to give a tan solid (100% yield). ^1H NMR (500 MHz, Chloroform- d) δ 9.81 (s, 1H), 8.36 (s, 1H), 7.95 (s, 3H), 7.67 – 7.26 (m, 9H), 4.33 (s, 2H), 4.09 (m, 1H), 3.74 – 3.16 (m, 9H), 3.13 – 2.89 (m, 2H), 2.08 (s, 2H), 1.81 (s, 2H), 1.63 – 1.39 (m, 6H), 1.38 – 1.01 (m, 44H), 0.87 (t, $J = 6.8$ Hz, 6H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{50}H_{87}N_3O_3$, 779; found, 779.

Example 58: tert-Butyl ((5S)-6-((2,3-bis(tetradecyloxy)propyl)amino)-5-((4-fluorobenzyl)amino)-6-oxohexyl)carbamate.



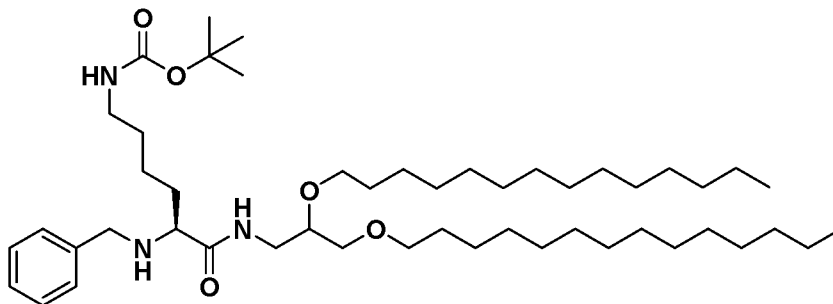
[0221] The title compound was prepared from N⁶-(tert-butoxycarbonyl)-N²-(4-fluorobenzyl)-L-lysine (176 mg, 0.5 mmol) (synthesized as described in Example 56) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described in Example 33 to give the title compound as a gummy solid (225 mg, 55% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.40 (dd, *J* = 8.2, 5.2 Hz, 2H), 7.21 (s, 1H), 7.05 (t, *J* = 8.6 Hz, 2H), 4.69 (s, 1H), 4.03 – 3.81 (m, 2H), 3.75 – 3.20 (m, 10H), 3.06 (m, 2H), 1.84 (m, 2H), 1.62 – 1.48 (m, 4H), 1.48 – 1.41 (m, 2H), 1.37 (s, 9H), 1.25 (d, *J* = 5.1 Hz, 46H), 0.88 (t, *J* = 6.8 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₄₉H₉₀FN₃O₅, 821; found, 821.

Example 59: (2S)-6-Amino-N-(2,3-bis(tetradecyloxy)propyl)-2-((4-fluorobenzyl)amino)hexanamide dihydrochloride.



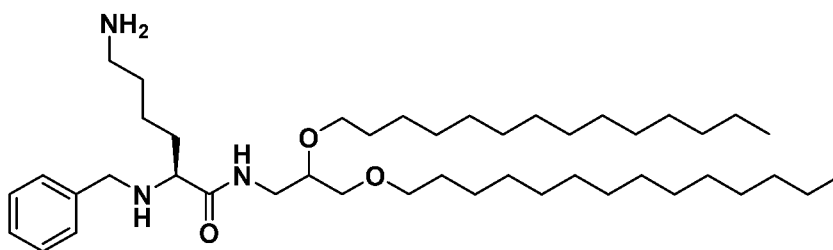
[0222] The title compound was prepared from Example 58 (164 mg, 0.2 mmol) as described for Example 1 to give a tan solid (100% yield). ¹H NMR (499 MHz, Chloroform-*d*) δ 9.82 (s, 1H), 8.79 (s, 1H), 8.07 (s, 3H), 7.56 (s, 2H), 7.04 (t, *J* = 8.4 Hz, 2H), 4.24 – 3.74 (m, 5H), 3.71 – 3.14 (m, 9H), 2.97 (s, 2H), 2.22 – 1.92 (m, 2H), 1.78 (s, 2H), 1.62 – 1.41 (m, 6H), 1.40 – 1.08 (m, 44H), 0.88 (t, *J* = 6.9 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₄₄H₈₂FN₃O₃, 721; found, 721.

Example 60: tert-Butyl ((5S)-5-(benzylamino)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexyl)carbamate.



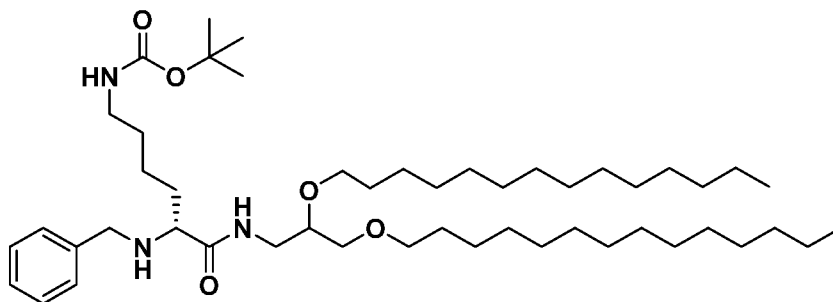
[0223] The title compound was prepared from N²-benzyl-N⁶-(tert-butoxycarbonyl)-L-lysine (168 mg, 0.5 mmol) (synthesized by following the same procedure as in Example 56) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described in Example 33 to give the title compound as a gummy solid (168 mg, 42% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.51 – 7.27 (m, 6H), 4.67 (s, 1H), 3.93 (s, 2H), 3.77 – 3.20 (m, 9H), 3.05 (qd, *J* = 14.0, 6.6 Hz, 2H), 1.81 (m, 2H), 1.54 (dt, *J* = 14.4, 7.4 Hz, 4H), 1.48 – 1.41 (m, 2H), 1.37 (s, 9H), 1.25 (br s, 46H), 0.88 (t, *J* = 6.9 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₄₉H₉₁N₃O₅, 803; found, 803.

Example 61: (2S)-6-Amino-2-(benzylamino)-N-(2,3-bis(tetradecyloxy)propyl)hexanamide dihydrochloride.



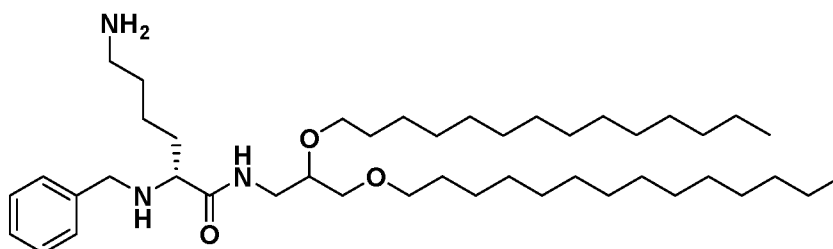
[0224] The title compound was prepared from Example 60 (160 mg, 0.2 mmol) as described for Example 1 to give a tan solid (100% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 9.80 (s, 1H), 8.69 (s, 1H), 8.35 (s, 1H), 7.95 (s, 3H), 7.53 (d, *J* = 5.7 Hz, 2H), 7.32 (d, *J* = 6.8 Hz, 3H), 4.05 (s, 3H), 3.67 – 3.03 (m, 9H), 3.03 – 2.86 (m, 2H), 2.02 (d, *J* = 36.0 Hz, 2H), 1.77 (s, 2H), 1.52 (p, *J* = 7.0 Hz, 6H), 1.35 – 1.08 (m, 44H), 0.88 (t, *J* = 6.8 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₄₄H₈₃N₃O₃, 703; found, 703.

Example 62: tert-Butyl ((5R)-5-(benzylamino)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexyl)carbamate.



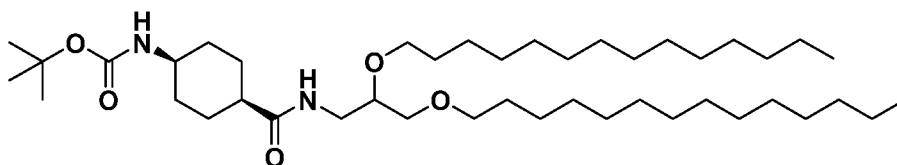
[0225] The title compound was prepared from N²-benzyl-N⁶-(tert-butoxycarbonyl)-D-lysine (168 mg, 0.5 mmol) (synthesized as in Example 56) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described in Example 33 to give the title compound as a gummy solid (185 mg, 46% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.58 – 7.30 (m, 5H), 7.21 (s, 1H), 4.71 (s, 1H), 4.09 – 3.86 (m, 2H), 3.79 – 3.23 (m, 10H), 3.16 – 2.97 (m, 2H), 2.04 – 1.67 (m, 2H), 1.54 (ddd, *J* = 14.0, 9.2, 5.2 Hz, 4H), 1.44 (t, *J* = 6.5 Hz, 2H), 1.35 (s, 9H), 1.25 (d, *J* = 5.3 Hz, 46H), 0.88 (t, *J* = 6.9 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₄₉H₉₁N₃O₅, 803; found, 803.

Example 63: ((2R)-6-Amino-2-(benzylamino)-N-(2,3-bis(tetradecyloxy)propyl)hexanamide dihydrochloride.



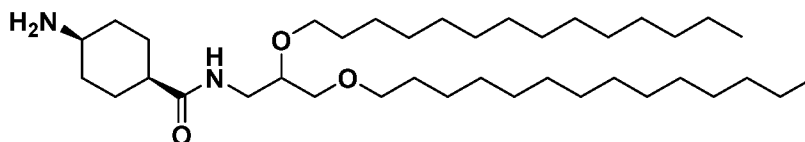
[0226] The title compound was prepared from Example 62 (160 mg, 0.2 mmol) as described for Example 1 to give an off-white solid \ (100% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 9.75 (s, 1H), 8.61 (s, 1H), 7.96 (m, 3H), 7.50 (d, *J* = 34.3 Hz, 2H), 7.34 (s, 3H), 3.91 – 3.20 (m, 3H), 3.19 – 2.88 (m, 11H), 2.37 – 1.69 (m, 4H), 1.54 (s, 6H), 1.41 – 1.05 (m, 44H), 0.88 (t, *J* = 6.8 Hz, 6H); ESI-MS *m/z* [M+H]⁺ calc'd for C₄₄H₈₃N₃O₃, 703; found, 703.

Example 64: tert-Butyl ((*cis*)-4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)cyclohexyl)carbamate.



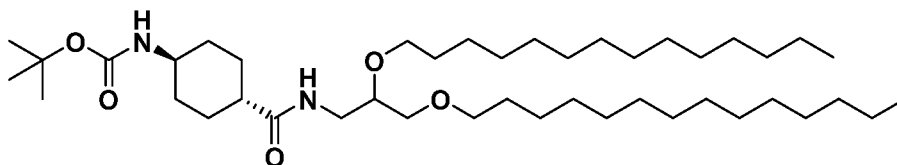
[0227] The title compound was prepared from (*cis*)-4-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid (122 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described in Example 33 to give a white solid (220 mg, 62% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 6.00 (t, J = 5.6 Hz, 1H), 4.70 (s, 1H), 3.71 (d, J = 20.6 Hz, 1H), 3.63 – 3.36 (m, 8H), 3.29 (dt, J = 13.6, 5.2 Hz, 1H), 2.16 (dt, J = 9.0, 4.5 Hz, 1H), 1.80 – 1.49 (m, 12H), 1.44 (s, 9H), 1.25 (s, 44H), 0.88 (t, J = 6.9 Hz, 6H); ESI-MS m/z $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{43}\text{H}_{84}\text{N}_2\text{O}_5$, 732; found, 732.

Example 65: (*cis*)-4-Amino-N-(2,3-bis(tetradecyloxy)propyl)cyclohexane-1-carboxamide hydrochloride.



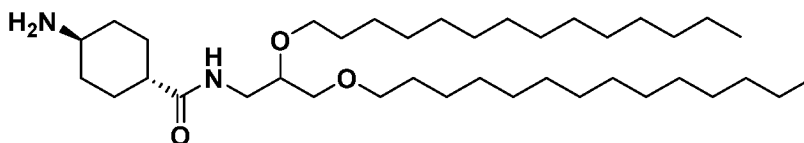
[0228] The title compound was prepared from tert-butyl ((*cis*)-4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)cyclohexyl)carbamate (142 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (499 MHz, Chloroform-*d*) δ 8.43 (s, 3H), 6.60 (s, 1H), 3.69 – 3.35 (m, 9H), 3.29 (s, 1H), 2.39 – 1.87 (m, 5H), 1.78 (d, J = 21.5 Hz, 4H), 1.54 (q, J = 6.9 Hz, 4H), 1.25 (s, 44H), 0.88 (t, J = 6.9 Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{38}\text{H}_{76}\text{N}_2\text{O}_3$, 610; found, 610.

Example 66: tert-Butyl ((*trans*)-4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)cyclohexyl)carbamate.



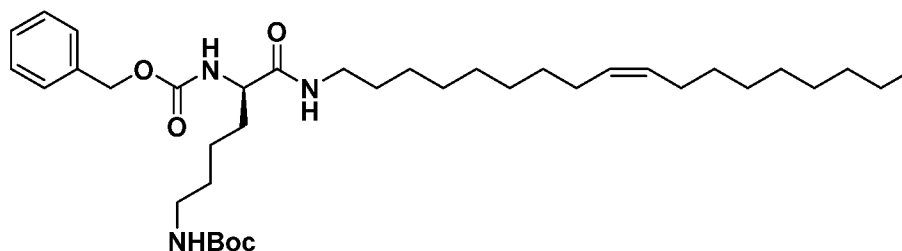
[0229] The title compound was prepared from (*trans*)-4-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid (122 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described in Example 33 to give a white solid (190 mg, 54% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 5.95 (t, J = 5.4 Hz, 1H), 4.35 (s, 1H), 3.65 – 3.33 (m, 9H), 3.28 (dt, J = 13.4, 5.2 Hz, 1H), 2.14 – 1.84 (m, 5H), 1.62 – 1.48 (m, 6H), 1.44 (s, 9H), 1.26 (s, 44H), 1.10 (qd, J = 12.8, 3.5 Hz, 2H), 0.88 (t, J = 6.9 Hz, 6H); ESI-MS m/z $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{43}\text{H}_{84}\text{N}_2\text{O}_5$, 732; found, 732.

Example 67: (*trans*)-4-Amino-N-(2,3-bis(tetradecyloxy)propyl)cyclohexane-1-carboxamide hydrochloride.



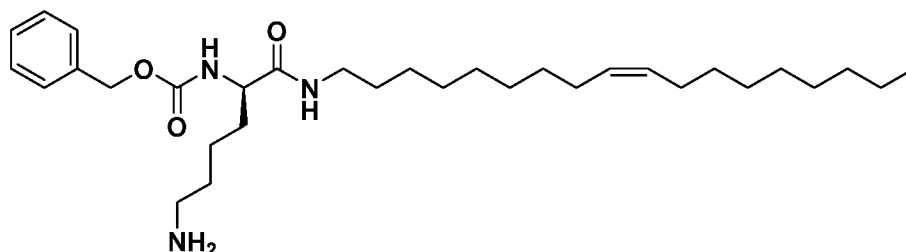
[0230] The title compound was prepared from Example 66 (142 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 8.38 (s, 3H), 5.97 (s, 1H), 3.64 – 3.02 (m, 11H), 2.18 (d, J = 85.5 Hz, 5H), 1.55 (s, 7H), 1.26 (s, 45H), 0.88 (t, J = 6.8 Hz, 6H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{38}\text{H}_{76}\text{N}_2\text{O}_3$, 610; found, 610.

Example 68: Benzyl tert-butyl (6-(octadec-9-en-1-ylamino)-6-oxohexane-1,5-diyl)(*R,Z*)-dicarbamate.



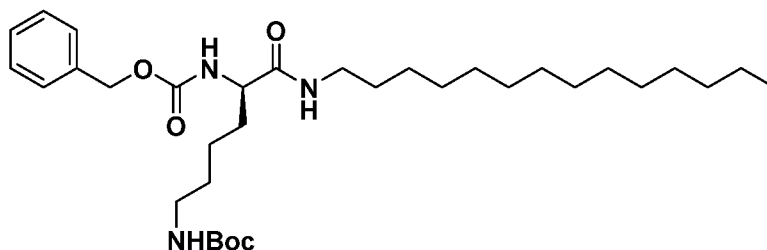
[0231] The title compound was prepared from oleylamine (70%) (191 mg, 0.5 mmol) and N^α-Z-N^ε-Boc-D-Lys-OSu (237 mg, 0.5 mmol) as described for Example 1 to give a white solid (225 mg, 71% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.45 – 7.29 (m, 5H), 6.05 (s, 1H), 5.43 (s, 1H), 5.40 – 5.28 (m, 2H), 5.10 (d, *J* = 2.4 Hz, 2H), 4.57 (s, 1H), 4.07 (q, *J* = 7.3 Hz, 1H), 3.22 (q, *J* = 6.8 Hz, 2H), 3.09 (d, *J* = 6.8 Hz, 2H), 2.10 – 1.89 (m, 4H), 1.85 (dtd, *J* = 13.5, 7.9, 5.3 Hz, 1H), 1.64 (q, *J* = 7.8 Hz, 2H), 1.57 – 1.47 (m, 4H), 1.42 (s, 9H), 1.34 – 1.10 (m, 26H), 0.88 (t, *J* = 6.8 Hz, 3H); ESI-MS *m/z* [M+Na]⁺ calc'd for C₃₇H₆₃N₃O₅, 653; found, 653.

Example 69: Benzyl (R,Z)-(6-amino-1-(octadec-9-en-1-ylamino)-1-oxohexan-2-yl)carbamate hydrochloride.



[0232] The title compound was prepared from Example 68 (126 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.12 (s, 3H), 7.75 (s, 1H), 7.30 (m, 5H), 6.35 (s, 1H), 5.43 – 5.22 (m, 2H), 5.06 (s, 2H), 4.31 (s, 1H), 3.89 – 3.44 (m, 2H), 3.19 (s, 2H), 2.97 (s, 2H), 2.11 – 1.87 (m, 2H), 1.75 (d, *J* = 44.9 Hz, 4H), 1.48 (s, 4H), 1.26 (q, *J* = 9.6, 8.4 Hz, 24H), 0.88 (t, *J* = 6.8 Hz, 3H); ESI-MS *m/z* [M+H]⁺ calc'd for C₃₂H₅₅N₃O₃, 531; found, 531.

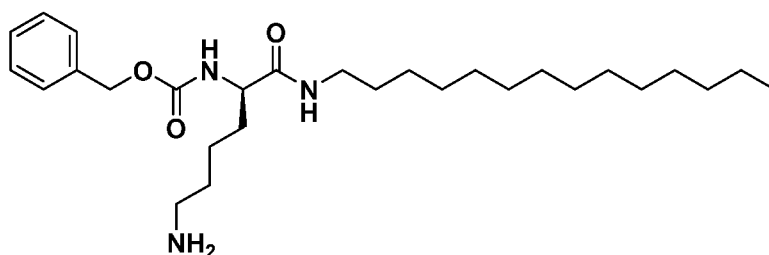
Example 70: Benzyl tert-butyl (6-oxo-6-(tetradecylamino)hexane-1,5-diyl)(R)-dicarbamate.



[0233] The title compound was prepared from tetradecylamine (112 mg, 0.5 mmol) and N^α-Z-N^ε-Boc-D-Lys-OSu (237 mg, 0.5 mmol) as described for Example 1 to give a white solid (248

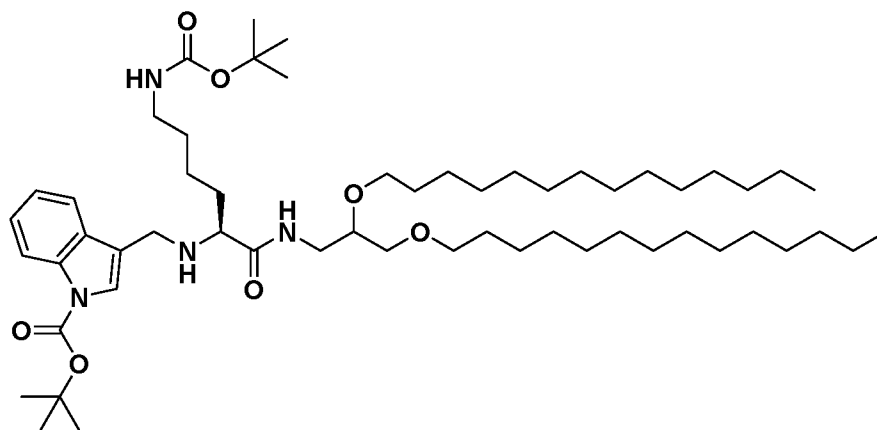
mg, 86% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.45 – 7.29 (m, 5H), 6.04 (s, 1H), 5.43 (s, 1H), 5.10 (d, $J = 2.4$ Hz, 2H), 4.57 (s, 1H), 4.10 (dd, $J = 23.2, 7.1$ Hz, 1H), 3.22 (q, $J = 6.8$ Hz, 2H), 3.09 (d, $J = 6.8$ Hz, 2H), 1.85 (dtd, $J = 13.5, 7.9, 5.3$ Hz, 1H), 1.71 – 1.55 (m, 1H), 1.54 – 1.45 (m, 2H), 1.42 (s, 9H), 1.37 (q, $J = 7.6$ Hz, 2H), 1.25 (s, 24H), 0.88 (t, $J = 6.9$ Hz, 3H); ESI-MS m/z $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{33}\text{H}_{57}\text{N}_3\text{O}_5$, 599; found, 599.

Example 71: Benzyl (R)-(6-amino-1-oxo-1-(tetradecylamino)hexan-2-yl)carbamate hydrochloride.



[0234] The title compound was prepared from Example 70 (115 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 8.24 (s, 3H), 7.40 – 7.29 (m, 6H), 6.02 (d, $J = 8.1$ Hz, 1H), 5.05 (s, 2H), 4.28 (s, 1H), 3.19 (d, $J = 11.6$ Hz, 2H), 2.98 (s, 2H), 2.09 – 1.58 (m, 4H), 1.48 (s, 2H), 1.36 – 1.16 (m, 24H), 0.88 (t, $J = 6.9$ Hz, 3H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{28}\text{H}_{49}\text{N}_3\text{O}_3$, 477; found, 477.

Example 72: tert-butyl 3-((((10S)-2,2-dimethyl-4,11-dioxo-14-(tetradecyloxy)-3,16-dioxo-5,12-diazatriacontan-10-yl)amino)methyl)-1H-indole-1-carboxylate

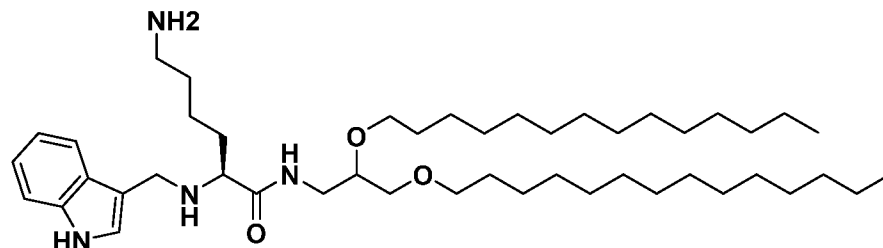


[0235] Step 1: tert-butyl (S)-3-(((6-((tert-butoxycarbonyl)amino)-1-methoxy-1-oxohexan-2-yl)amino)methyl)-1H-indole-1-carboxylate: A mixture of tert-butyl 3-formyl-1H-indole-1-carboxylate (736 mg, 3.0 mmol) and methyl N⁶-(tert-butoxycarbonyl)-L-lysinate hydrochloride (890 mg, 3.0 mmol) in THF (50 mL) was treated with NaBH(OAc)₃ (763 mg, 3.6 mmol) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was treated with satd. aq. K₂CO₃ (25 mL) and stirred for another 30 min. The resulting layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layer washed with brine, dried over sodium sulfate, evaporated and purified using silica gel column chromatography (hexane-EtOAc (0-100%)) to give the title compound as a colorless liquid (1325 mg). ESI-MS m/z [M+H]⁺ calc'd for C₂₆H₃₉N₃O₆, 490; found, 490.

[0236] Step 2: N⁶-(tert-butoxycarbonyl)-N²-((1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl)-L-lysine. To a solution of methyl N²-([1,1'-biphenyl]-4-ylmethyl)-N⁶-(tert-butoxycarbonyl)-L-lysinate (1225 mg, 2.5 mmol) in 1:1 THF-MeOH (15 mL) was added a solution of LiOH (180 mg, 7.5 mmol) in water (8.0 mL). After stirring at room temperature for 4 h, the mixture was neutralized by the addition of saturated aq. KHSO₄ (20 mL). A precipitate formed, which was separated by vacuum filtration, and extracted the aqueous layer with EtOAc (2 x 50 mL) and evaporated. Then purified on a silica gel column using dichloromethane-methanol (0-10%) as eluent to get the desired product (680 mg). ESI-MS m/z [M+H]⁺ calc'd for C₂₅H₃₇N₃O₆, 476; found, 476.

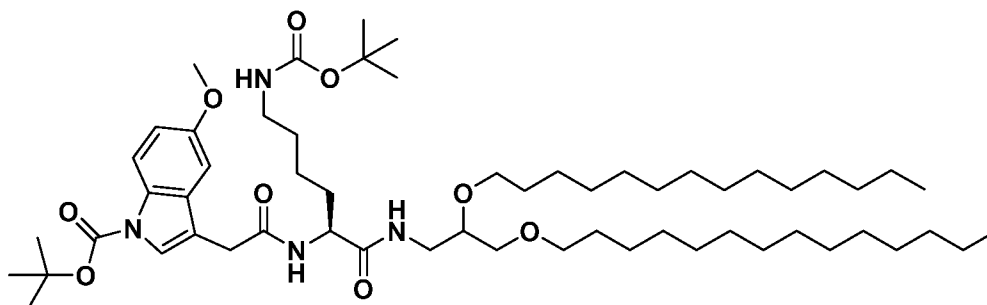
[0237] Step 3. The title compound was prepared from N⁶-(tert-butoxycarbonyl)-N²-((1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl)-L-lysine (238 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as a gummy solid (235 mg, 50% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.18 (d, *J* = 8.3 Hz, 1H), 7.82 (s, 1H), 7.67 (t, *J* = 6.4 Hz, 1H), 7.32 (dt, *J* = 30.8, 7.6 Hz, 2H), 7.08 (d, *J* = 35.6 Hz, 1H), 5.92 (s, 1H), 4.72 (s, 1H), 4.25 (m, 2H), 3.79 – 3.20 (m, 12H), 3.17 – 2.90 (m, 2H), 1.92 – 1.80 (m, 1H), 1.53 (m, 6H), 1.47 – 1.36 (m, 2H), 1.33 – 1.04 (m, 66H), 0.87 (d, *J* = 7.0 Hz, 6H).; ESI-MS m/z [M+H]⁺ calc'd for C₅₆H₁₀₀N₄O₇, 942; found, 942.

Example 73 : (2S)-2-(((1H-indol-3-yl)methyl)amino)-6-amino-N-(2,3-bis(tetradecyloxy)propyl)hexanamide dihydrochloride



[0238] The title compound was prepared from Example 72 (188 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 9.40 (s, 1H), 8.46 (br s, 2H) 8.32 – 7.35 (m, 3H), 7.07 (d, $J = 20.4$ Hz, 1H), 5.99 (s, 1H), 5.05 – 3.95 (m, 2H), 3.95 – 3.14 (m, 6H), 2.86 (m, 2H), 1.77 – 1.33 (m, 6H), 1.40 – 1.02 (m, 48H), 0.88 (td, $J = 6.8, 4.3$ Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{46}\text{H}_{84}\text{N}_4\text{O}_3$, 742; found, 742.

Example 74: tert-butyl 3-(2-(((10S)-2,2-dimethyl-4,11-dioxo-14-(tetradecyloxy)-3,16-dioxo-5,12-diazatriacontan-10-yl)amino)-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate



[0239] Step 1. methyl N^6 -(tert-butoxycarbonyl)- N^2 -(2-(5-methoxy-1H-indol-3-yl)acetyl)-L-lysinate.

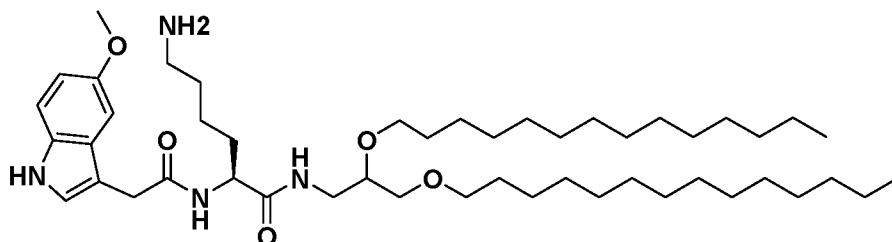
[0240] The title compound was prepared from 2-(5-methoxy-1H-indol-3-yl)acetic acid (616 mg, 3.0 mmol) and methyl N^6 -(tert-butoxycarbonyl)-L-lysinate hydrochloride (890 mg, 3.0 mmol) as described for Example 33 to give the title compound as a gummy solid (680 mg, 51% yield). ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{23}\text{H}_{33}\text{N}_3\text{O}_6$, 448; found, 448.

[0241] Step 2. tert-butyl (S)-3-(2-((6-((tert-butoxycarbonyl)amino)-1-methoxy-1-oxohexan-2-yl)amino)-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate: Methyl N⁶-(tert-butoxycarbonyl)-N²-(2-(5-methoxy-1H-indol-3-yl)acetyl)-L-lysinate (1119 mg, 2.5 mmol) dissolved in dichloromethane (20 mL) and added di-tert-butyl dicarbonate (818 mg, 3.75 mmol), N,N-dimethylaminopyridine (DMAP) (55 mg, 0.25 mmol) to the mixture and continued the reaction at room temperature for two hours. After confirming the product formation by TLC, evaporated volatiles from the reaction mixture and purified on silica gel column chromatography using hexane through hexane-EtOAc (0-100%) as eluent. Pure product fractions combined and evaporated to give the desired product as a gummy liquid (1342 mg, 98% yield). ESI-MS m/z [M+H]⁺ calc'd for C₂₈H₄₁N₃O₈, 548; found, 548.

[0242] Step 3. N⁶-(tert-butoxycarbonyl)-N²-(2-(1-(tert-butoxycarbonyl)-5-methoxy-1H-indol-3-yl)acetyl)-L-lysine: The title compound was prepared from above obtained tert-butyl (S)-3-(2-((6-((tert-butoxycarbonyl)amino)-1-methoxy-1-oxohexan-2-yl)amino)-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate (1370 mg, 2.5 mmol) and LiOH (180 mg, 7.5 mmol) by following the procedure described in step 2 of Example 72 to give the title compound as a gummy solid (850 mg, 64% yield). ESI-MS m/z [M+H]⁺ calc'd for C₂₇H₃₉N₃O₈, 534; found, 534.

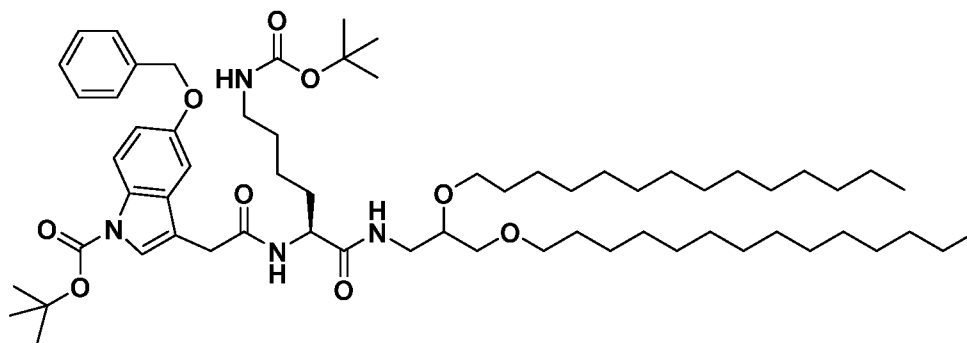
[0243] Step 4. The title compound was prepared from N⁶-(tert-butoxycarbonyl)-N²-(2-(1-(tert-butoxycarbonyl)-5-methoxy-1H-indol-3-yl)acetyl)-L-lysine (267 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as a white solid (232 mg, 46% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.02 (s, 1H), 7.64 – 7.46 (m, 1H), 7.05 – 6.85 (m, 2H), 6.27 (d, *J* = 18.3 Hz, 1H), 5.93 (s, 1H), 4.57 (s, 1H), 4.36 (q, *J* = 7.0 Hz, 1H), 3.83 (s, 3H), 3.71 – 3.34 (m, 10H), 3.29 (dt, *J* = 12.5, 5.1 Hz, 2H), 2.97 (d, *J* = 21.8 Hz, 2H), 1.66 (s, 9H), 1.55 (h, *J* = 7.9, 7.4 Hz, 9H), 1.43 (s, 9H), 1.26 (br s, 44H), 0.88 (t, *J* = 6.8 Hz, 6H).; ESI-MS m/z [M+H]⁺ calc'd for C₅₈H₁₀₂N₄O₉, 1000; found, 1000.

Example 75: (2S)-6-amino-N-(2,3-bis(tetradecyloxy)propyl)-2-(2-(5-methoxy-1H-indol-3-yl)acetamido)hexanamide hydrochloride



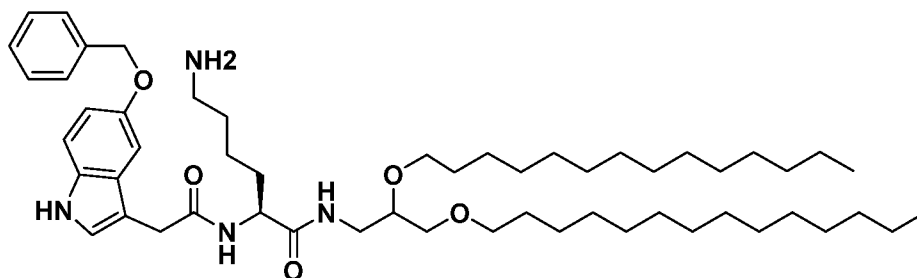
[0244] The title compound was prepared from Example 74 (200 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.98 (s, 4H), 7.51 (m, 1H), 7.15 – 6.95 (m, 1H), 6.95 – 6.68 (m, 1H), 6.00 (s, 1H), 4.51 (s, 1H), 3.95 – 3.62 (m, 5H), 3.60 – 3.11 (m, 12H), 1.81 – 1.43 (m, 10H), 1.25 (br s, 44H), 0.88 (td, J = 6.9, 2.9 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{48}\text{H}_{86}\text{N}_4\text{O}_5$, 800; found, 800.

Example 76: tert-butyl 5-(benzyloxy)-3-(2-(((10S)-2,2-dimethyl-4,11-dioxo-14-(tetradecyloxy)-3,16-dioxo-5,12-diazatriacontan-10-yl)amino)-2-oxoethyl)-1H-indole-1-carboxylate



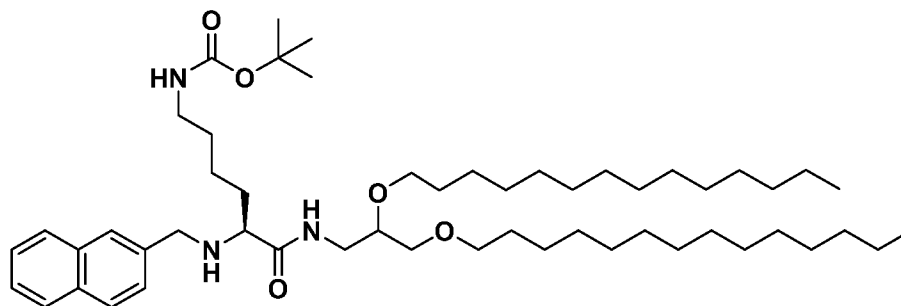
[0245] The title compound was prepared from N^2 -(2-(5-(benzyloxy)-1-(tert-butoxycarbonyl)-1H-indol-3-yl)acetyl)- N^6 -(tert-butoxycarbonyl)-L-lysine (synthesized as in Example 74) (305 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as a white solid (310 mg, 58% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 8.03 (s, 1H), 7.53 (s, 1H), 7.46 (d, J = 7.6 Hz, 2H), 7.38 (dd, J = 8.5, 6.6 Hz, 2H), 7.31 (dd, J = 8.6, 6.1 Hz, 1H), 7.13 – 6.90 (m, 2H), 6.27 (d, J = 14.2 Hz, 2H), 5.09 (s, 2H), 4.51 (s, 1H), 4.35 (q, J = 7.0 Hz, 1H), 3.60 – 3.09 (m, 9H), 2.96 (s, 2H), 1.67 (s, 9H), 1.53 (tq, J = 13.8, 7.3 Hz, 6H), 1.42 (s, 9H), 1.26 (br s, 48H), 0.88 (t, J = 6.8 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{64}\text{H}_{106}\text{N}_4\text{O}_9$, 1076; found, 1076.

Example 77: (2S)-6-amino-2-(2-(5-(benzyloxy)-1H-indol-3-yl)acetamido)-N-(2,3-bis(tetradecyloxy)propyl)hexanamide hydrochloride



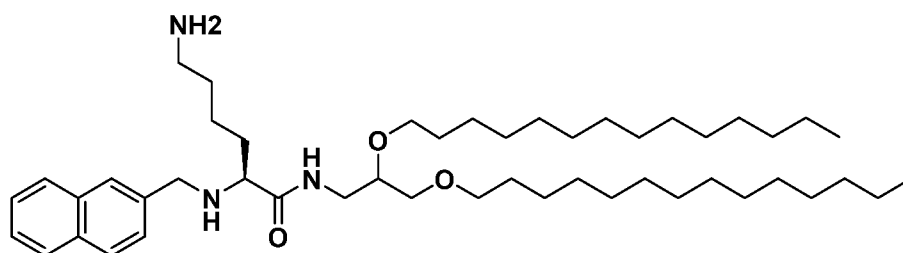
[0246] The title compound was prepared from Example 76 (215 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 8.03 (m, 3H), 7.83 – 7.51 (m, 1H), 7.49 – 6.73 (m, 11H), 5.06 (d, J = 15.3 Hz, 2H), 4.48 (s, 1H), 3.88 – 3.58 (m, 3H), 3.58 – 3.09 (m, 8H), 2.81 (m, 2H), 1.61 – 1.38 (m, 6H), 1.26 (br s, 48H), 0.88 (t, J = 6.6 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{54}\text{H}_{90}\text{N}_4\text{O}_5$, 876; found, 876.

Example 78: tert-butyl ((5S)-6-((2,3-bis(tetradecyloxy)propyl)amino)-5-((naphthalen-2-ylmethyl)amino)-6-oxohexyl)carbamate



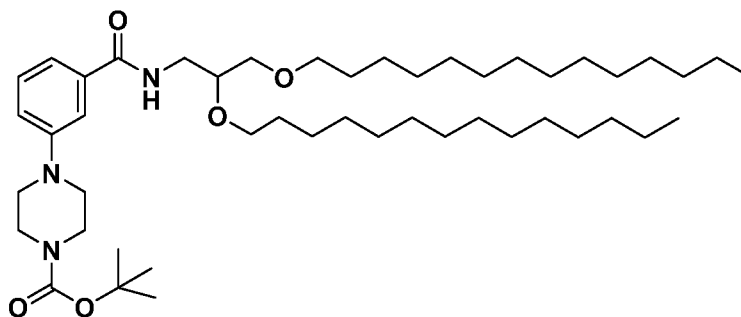
[0247] The title compound was prepared from N^6 -(tert-butoxycarbonyl)- N^2 -(naphthalen-2-ylmethyl)-L-lysine (synthesized as in Example 56) (194 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as off-white solid (315 mg, 74% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 8.05 – 7.73 (m, 4H), 7.58 – 7.45 (m, 3H), 7.23 (s, 1H), 4.67 (s, 1H), 4.32 – 3.99 (m, 2H), 3.74 (m, 1H), 3.65 – 3.21 (m, 8H), 3.19 – 2.89 (m, 2H), 1.87 (br s, 2H), 1.53 (dq, J = 11.8, 6.5, 6.0 Hz, 4H), 1.47 – 1.04 (m, 57H), 0.88 (t, J = 6.9 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{53}\text{H}_{93}\text{N}_3\text{O}_5$, 853; found, 853.

Example 79: (2S)-6-amino-N-(2,3-bis(tetradecyloxy)propyl)-2-((naphthalen-2-ylmethyl)amino)hexanamide dihydrochloride

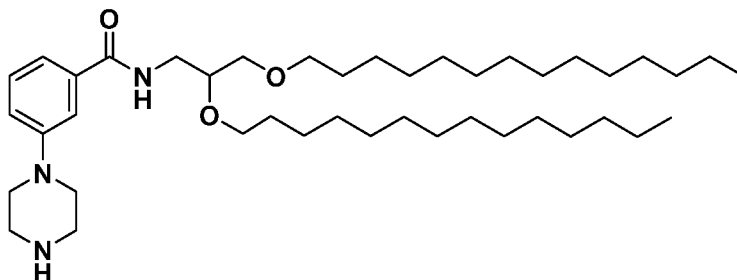


[0248] The title compound was prepared from Example 78 (171 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ^1H NMR (499 MHz, Chloroform-*d*) δ 9.58 (s, 1H), 8.60 (s, 1H), 7.94 (s, 1H), 7.69 (m, 6H), 7.35 (s, 2H), 4.45 – 3.88 (m, 3H), 3.42 (s, 10H), 2.89 (s, 1H), 2.20 – 1.83 (m, 2H), 1.84 – 1.59 (m, 2H), 1.49 (s, 6H), 1.37 – 1.02 (br s, 44H), 0.88 (t, J = 6.9 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{48}\text{H}_{85}\text{N}_3\text{O}_3$, 753; found, 753.

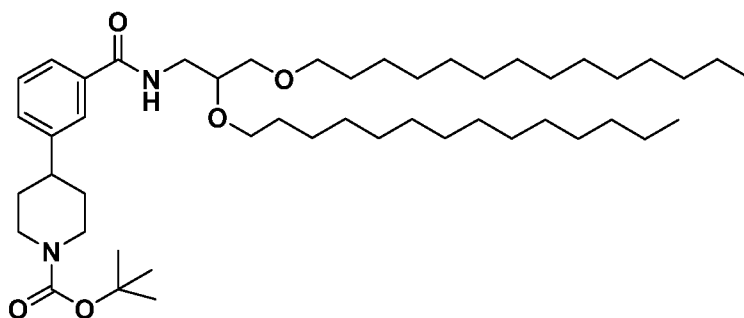
Example 80: tert-butyl 4-(3-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperazine-1-carboxylate



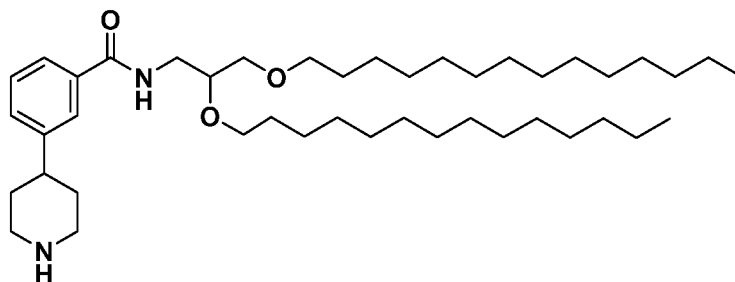
[0249] The title compound was prepared from 3-(4-(tert-butoxycarbonyl)piperazin-1-yl)benzoic acid (153 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as white solid (285 mg, 74% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.46 (d, J = 2.6 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 6.69 (t, J = 5.3 Hz, 1H), 3.74 (dt, J = 13.5, 5.4 Hz, 1H), 3.67 – 3.34 (m, 12H), 3.21 (t, J = 5.2 Hz, 4H), 1.57 (m, 4H), 1.49 (s, 9H), 1.41 – 1.11 (m, 44H), 0.88 (t, J = 6.9 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{47}\text{H}_{85}\text{N}_3\text{O}_5$, 773; found, 773.

Example 81: N-(2,3-bis(tetradecyloxy)propyl)-3-(piperazin-1-yl)benzamide hydrochloride

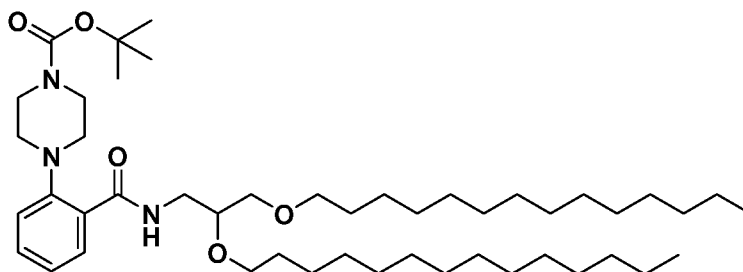
[0250] The title compound was prepared from Example 80 (155 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 10.09 (s, 2H), 8.15 (s, 1H), 8.03 – 7.38 (m, 2H), 3.92 – 3.00 (m, 16H), 1.56 (s, 4H), 1.25 (br s, 44H), 0.88 (t, J = 6.8 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{42}\text{H}_{77}\text{N}_3\text{O}_3$, 673; found, 673.

Example 82: tert-butyl 4-(3-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate

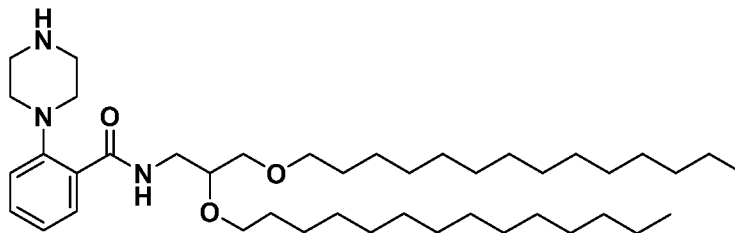
[0251] The title compound was prepared from 3-(1-(tert-butoxycarbonyl)piperidin-4-yl)benzoic acid (153 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as white solid (280 mg, 73% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.67 (d, J = 1.9 Hz, 1H), 7.53 (dt, J = 7.2, 1.8 Hz, 1H), 7.41 – 7.29 (m, 2H), 6.69 (t, J = 5.4 Hz, 1H), 4.26 (d, J = 13.5 Hz, 2H), 3.75 (dt, J = 13.7, 5.4 Hz, 1H), 3.66 – 3.26 (m, 8H), 2.92 – 2.59 (m, 3H), 1.83 (d, J = 12.7 Hz, 2H), 1.66 (td, J = 12.6, 4.3 Hz, 2H), 1.57 (m, 4H), 1.49 (s, 9H), 1.40 – 1.06 (m, 48H), 0.88 (t, J = 6.9 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{48}\text{H}_{86}\text{N}_2\text{O}_5$, 772; found, 772.

Example 83: N-(2,3-bis(tetradecyloxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride

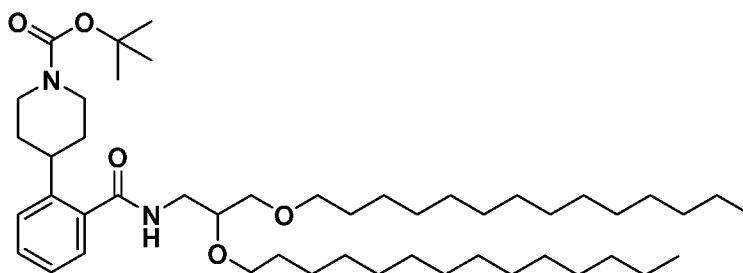
[0252] The title compound was prepared from Example 82 (154 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 9.73 (br d, Hz, 2H), 7.72 (s, 1H), 7.54 (d, $J = 7.0$ Hz, 1H), 7.39 (d, $J = 8.3$ Hz, 2H), 6.74 (s, 1H), 3.98 – 3.30 (m, 11H), 3.04 (s, 2H), 2.85 (s, 1H), 2.26 (s, 2H), 2.07 (d, $J = 12.9$ Hz, 2H), 1.76 (s, 4H), 1.57 (m, 4H), 1.26 (br s, 46H), 0.88 (t, $J = 6.9$ Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{43}\text{H}_{78}\text{N}_2\text{O}_3$, 672; found, 672.

Example 84: tert-butyl 4-(2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperazine-1-carboxylate

[0253] The title compound was prepared from 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)benzoic acid (153 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as colorless liquid (325 mg, 84% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 9.58 (s, 1H), 8.15 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.42 (td, $J = 7.7, 1.8$ Hz, 1H), 7.23 (t, $J = 7.5$ Hz, 1H), 7.16 (d, $J = 8.0$ Hz, 1H), 4.12 (q, $J = 7.1$ Hz, 1H), 3.88 – 3.31 (m, 12H), 2.94 (t, $J = 5.2$ Hz, 4H), 1.55 (m, 4H), 1.49 (s, 9H), 1.35 – 1.09 (m, 44H), 0.88 (t, $J = 6.8$ Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{47}\text{H}_{85}\text{N}_3\text{O}_5$, 773; found, 773.

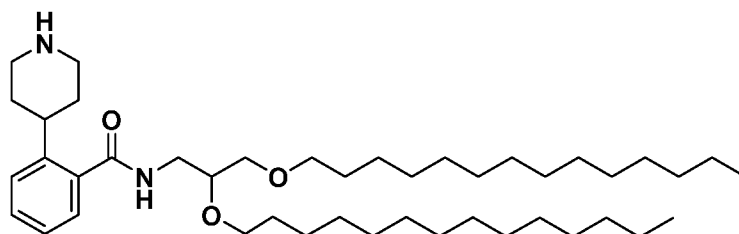
Example 85: N-(2,3-bis(tetradecyloxy)propyl)-2-(piperazin-1-yl)benzamide hydrochloride

[0254] The title compound was prepared from Example 84 (155 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 10.41 (s, 2H), 7.96 (d, $J = 7.7$ Hz, 1H), 7.56 (dd, $J = 19.1, 11.8$ Hz, 2H), 7.38 (t, $J = 7.4$ Hz, 1H), 3.97 – 3.23 (m, 21H), 1.55 (m, 4H), 1.36 – 1.07 (m, 44H), 0.88 (t, $J = 6.9$ Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{42}\text{H}_{77}\text{N}_3\text{O}_3$, 673; found, 673.

Example 86: tert-butyl 4-(2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate

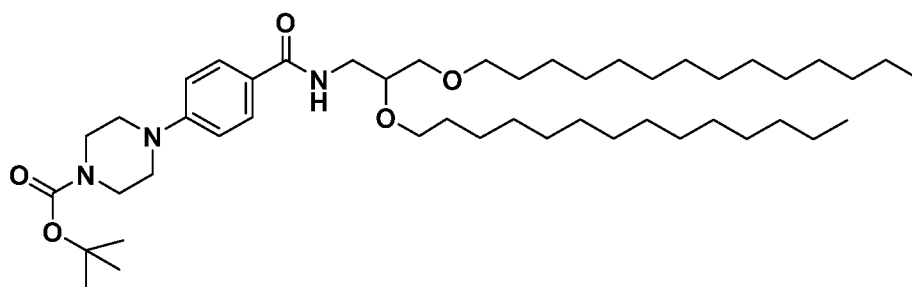
[0255] The title compound was prepared from 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)benzoic acid (153 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as white solid (315 mg, 81% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.38 (td, $J = 7.6, 1.4$ Hz, 1H), 7.34 – 7.28 (m, 2H), 7.21 (t, $J = 7.3$ Hz, 1H), 6.31 (t, $J = 5.6$ Hz, 1H), 4.39 – 4.13 (m, 2H), 3.77 (ddd, $J = 13.7, 6.3, 4.6$ Hz, 1H), 3.68 – 3.36 (m, 8H), 3.17 (tt, $J = 12.1, 3.5$ Hz, 1H), 2.80 (td, $J = 13.0, 2.6$ Hz, 2H), 1.83 (dd, $J = 13.3, 3.3$ Hz, 2H), 1.70 – 1.51 (m, 6H), 1.48 (s, 9H), 1.26 (br s, 44H), 0.88 (t, $J = 6.9$ Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{48}\text{H}_{86}\text{N}_2\text{O}_5$, 772; found, 772.

Example 87: N-(2,3-bis(tetradecyloxy)propyl)-2-(piperidin-4-yl)benzamide hydrochloride



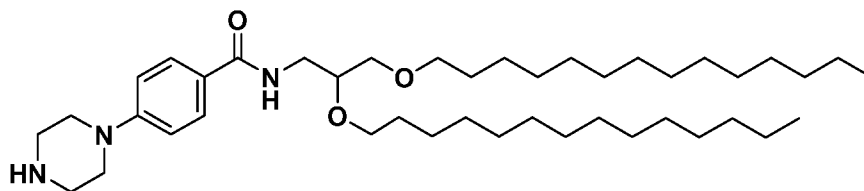
[0256] The title compound was prepared from Example 86 (154 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 9.63 (br d, 2H), 7.52 – 7.40 (m, 2H), 7.36 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 7.5 Hz, 1H), 6.42 (t, J = 5.5 Hz, 1H), 3.88 – 3.21 (m, 11H), 3.01 (m, 2H), 2.33 – 2.14 (m, 2H), 2.16 – 1.98 (m, 2H), 1.55 (m, 4H), 1.25 (br s, 44H), 0.88 (t, J = 6.8 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{43}\text{H}_{78}\text{N}_2\text{O}_3$, 672; found, 672.

Example 88: tert-butyl 4-(4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperazine-1-carboxylate



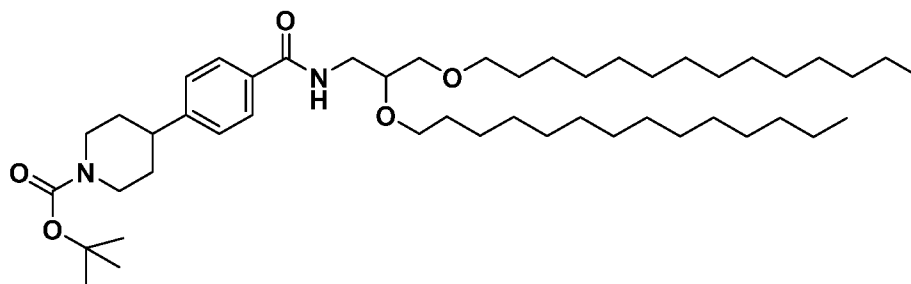
[0257] The title compound was prepared from 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)benzoic acid (153 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as light pink solid (310 mg, 80% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.81 – 7.57 (m, 2H), 6.93 (d, J = 8.5 Hz, 2H), 6.61 (t, J = 5.5 Hz, 1H), 3.73 (dt, J = 13.7, 5.4 Hz, 1H), 3.65 – 3.36 (m, 12H), 3.25 (t, J = 5.2 Hz, 4H), 1.57 (m, 4H), 1.49 (s, 9H), 1.38 – 1.14 (m, 44H), 0.88 (t, J = 6.9 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{47}\text{H}_{85}\text{N}_3\text{O}_5$, 773; found, 773.

Example 89: N-(2,3-bis(tetradecyloxy)propyl)-4-(piperazin-1-yl)benzamide hydrochloride



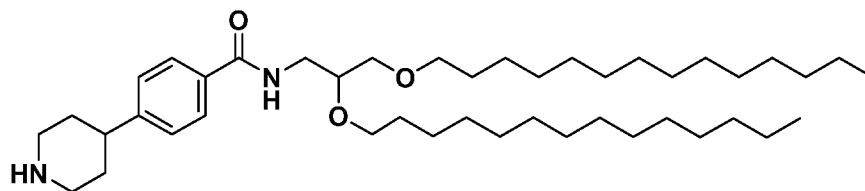
[0258] The title compound was prepared from Example 88 (155 mg, 0.2 mmol) as described for Example 1 to give a tan solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 10.08 (s, 2H), 7.79 (s, 2H), 6.86 (s, 1H), 4.04 – 3.21 (m, 11H), 2.52 (s, 6H), 1.56 (q, J = 6.9 Hz, 4H), 1.25 (br s, 44H), 0.88 (t, J = 6.9 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{42}\text{H}_{77}\text{N}_3\text{O}_3$, 673; found, 673.

Example 90: tert-butyl 4-(4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate



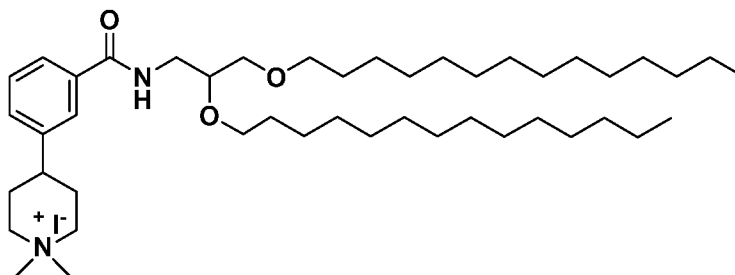
[0259] The title compound was prepared from 4-(1-(tert-butoxycarbonyl)piperidin-4-yl)benzoic acid (153 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as white solid (325 mg, 84% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.71 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 6.71 (t, J = 5.5 Hz, 1H), 4.25 (d, J = 13.1 Hz, 2H), 3.75 (dt, J = 13.7, 5.4 Hz, 1H), 3.67 – 3.29 (m, 8H), 2.80 (t, J = 12.9 Hz, 2H), 2.69 (t, J = 12.1, 3.6 Hz, 1H), 1.90 – 1.74 (m, 2H), 1.70 – 1.52 (m, 6H), 1.48 (s, 9H), 1.41 – 1.16 (m, 44H), 0.88 (t, J = 6.8 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{48}\text{H}_{86}\text{N}_2\text{O}_5$, 772; found, 772.

Example 91: N-(2,3-bis(tetradecyloxy)propyl)-4-(piperidin-4-yl)benzamide hydrochloride

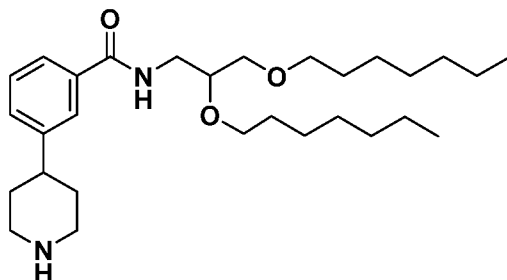


[0260] The title compound was prepared from Example 90 (154 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 9.73 (br d, 2H), 7.73 (d, $J = 7.5$ Hz, 2H), 7.30 (d, $J = 7.7$ Hz, 2H), 6.72 (t, $J = 5.4$ Hz, 1H), 3.97 – 3.29 (m, 11H), 3.03 (s, 2H), 2.83 (s, 1H), 2.25 (s, 2H), 2.06 (d, $J = 13.1$ Hz, 2H), 1.70 (s, 4H), 1.56 (m, 4H), 1.37 – 1.10 (m, 44H), 0.87 (t, $J = 6.8$ Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{43}\text{H}_{78}\text{N}_2\text{O}_3$, 672; found, 672.

Example 92: 4-(3-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)-1,1-dimethylpiperidin-1-ium iodide



[0261] Title compound prepared from Example 83 (336 mg, 0.5 mmol) that suspended in DMF (3.0 mL) and added K_2CO_3 (207 mg, 1.5 mmol) and methyl iodide (62 μL , 1.0 mmol) to the mixture. Then heated at 60°C for 2 hours. After completion (monitored by TLC-5% MeOH-dichloromethane), evaporated volatiles and extracted using chloroform (2 x 25 mL) in water. Resulting organic layer dried over sodium sulfate and evaporated. Then dried completely on lyophilized to remove residual DMF to give the desired product as white solid (295 mg, 71% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.87 (d, $J = 1.9$ Hz, 1H), 7.57 (dt, $J = 7.6, 1.5$ Hz, 1H), 7.45 – 7.33 (m, 2H), 7.08 (s, 1H), 4.15 – 3.91 (m, 2H), 3.83 (d, $J = 12.6$ Hz, 2H), 3.71 – 3.51 (m, 9H), 3.48 – 3.33 (m, 5H), 3.22 (m, 1H), 2.24 (q, $J = 13.2$ Hz, 2H), 2.13 (d, $J = 14.8$ Hz, 2H), 1.98 (s, 3H), 1.56 (h, $J = 6.8, 6.0$ Hz, 4H), 1.43 – 1.12 (m, 47H), 0.87 (t, $J = 6.9$ Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{45}\text{H}_{83}\text{N}_2\text{O}_3$, 701; found, 701.

Example 93: N-(2,3-bis(heptyloxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride

[0262] Step 1: tert-butyl (2,3-bis(heptyloxy)propyl)carbamate : Aqueous NaOH (50 %, 15 mL) and Bu₄NI (2.76 g, 7.5 mmol) were added at room temperature to a stirred solution of *t*-Butyl (2,3-dihydroxypropyl) carbamate (3 g, 15 mmol) and 1-Bromoheptane (7.5 ml, 45 mmol) in toluene (30 mL). After vigorous stirring for 6 h at 50-60°C, the reaction mixture was allowed to obtain ambient temperature, ethyl acetate and water were added. The organic phase was washed with brine and dried (Na₂SO₄). The residue was purified by column chromatography using 10-20% Ethyl acetate in Hexane to get the desired product (3.0 g, 52%). ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₄₅NO₄, 388; found, 388.

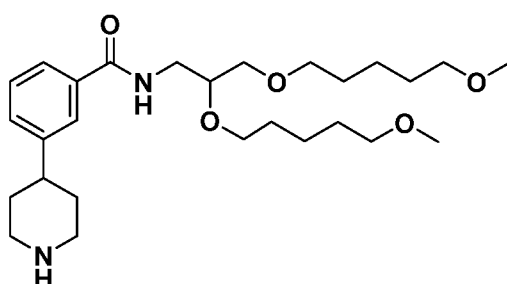
[0263] Step 2: 2,3-bis(heptyloxy)propan-1-amine hydrochloride : Product obtained in above step 1 was dissolved in methanol (10 mL) and methanolic HCl (20 mL) was added and stirred at room temperature for 3 hours. Then solvent was evaporated to dryness to get the desired product (100% yield). ESI-MS *m/z* [M+H]⁺ calc'd for C₁₇H₃₇NO₂, 288; found, 288.

[0264] Step 3: tert-butyl 4-(3-((2,3-bis(heptyloxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate:

[0265] 3-(1-(*t*-butoxycarbonyl) piperidin-4-yl) benzoic acid (500 mg, 1.637 mmol) was dissolved in dichloromethane (5.0 mL). 2,3-bis(heptyloxy)propan-1-amine.HCl (478 mg, 1.637 mmol) and HBTU (620 mg, 1.637 mmol) were added and the reaction mixture was stirred for 10 min. DIPEA (0.84 ml, 6.548 mmol) was added and stirred for 3 hours at room temperature. The solvent was removed and purified by silica gel column chromatography using 15% ethyl acetate in hexane to obtain the desired product (550 mg, 58% yield). ESI-MS *m/z* [M+H]⁺ calc'd for C₃₄H₅₈N₂O₅, 575; found, 575.

[0266] Step 4: Compound obtained in step 3 (230 mg, 4.0 mmol) was dissolved in methanol (3.0 mL) and methanolic HCl (10 mL) was added and stirred at room temperature for 3 h and the solvent was evaporated to dryness under reduced pressure to get the desired product (100% yield). ^1H NMR (300 MHz, DMSO- d_6) δ ppm: 9.3-9.2 (br s, 1H), 9.0 (br s, 1H), 8.6-8.4 (s, 1H), 7.8-7.3 (m, 4H), 3.6-3.2 (m, 11H), 3.1-2.8 (m, 3H), 2.0-1.8 (m, 4H), 1.6-1.3 (m, 4H), 1.3-1.0 (m, 16 H), 0.87 (m, 6H). ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{29}\text{H}_{50}\text{N}_2\text{O}_3$, 475; found, 475.

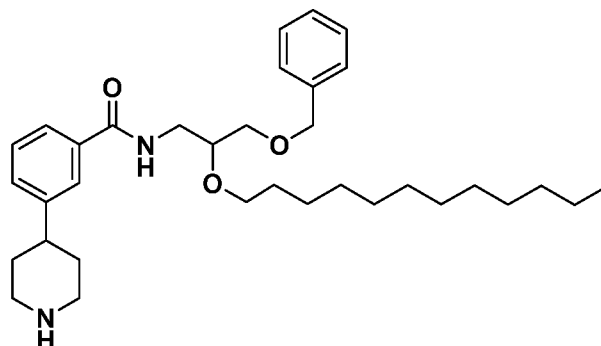
Example 94 : N-(2,3-bis((5-methoxypentyl)oxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride



[0267] Step 1: tert-butyl 4-(3-((2,3-bis((5-methoxypentyl)oxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate : 3-(1-(t-butoxycarbonyl) piperidin-4-yl) benzoic acid (500 mg, 1.637 mmol) was dissolved in dichloromethane (5.0 mL). Then 2,3-bis (5-methoxypentyl)oxy) propan-1-amine.HCl (476 mg, 1.637 mmol) (prepared following the procedure in Example 93) and HBTU (620 mg, 1.637 mmol) were added and the reaction mixture was stirred for 10 min. DIPEA (0.84 ml, 6.548 mmol) was added and stirred for 3h at room temperature. The solvent was removed and purified by silica gel column chromatography using 25% ethyl acetate in hexane to obtain the desired product (500 mg, 53 % yield). ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{32}\text{H}_{54}\text{N}_2\text{O}_7$, 579; found, 579.

[0268] Step 2: Compound obtained in step 1 (232 mg, 4.0 mmol) was dissolved in methanol (3.0 mL) and methanolic HCl (10 mL) was added and stirred at room temperature for 3 h and the solvent was evaporated to dryness under reduced pressure to get the desired product (100% yield). ^1H NMR (300 MHz, DMSO- d_6) δ ppm: 9.3 (br s, 1H), 9.2-9.0 (br s, 1H), 8.6-8.4 (s, 1H), 7.8-7.3 (m, 4H), 3.6-3.3 (m, 13H), 3.2 (m, 8H), 3.1-2.8 (m, 3H), 2.0-1.8 (m, 4H), 1.6-1.3 (m, 8H), 1.3-1.2 (m, 4H). ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{27}\text{H}_{46}\text{N}_2\text{O}_5$, 479; found, 479.

Example 95 : N-(3-(benzyloxy)-2-(dodecyloxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride



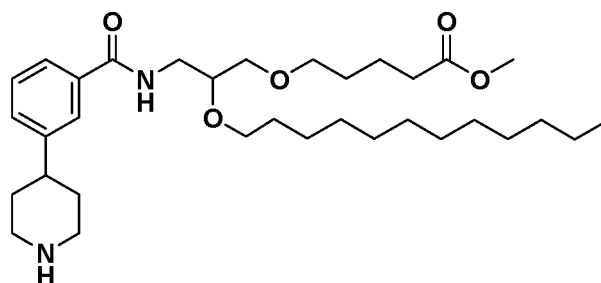
[0269] Step 1: tert-butyl 3-(benzyloxy)-2-(dodecyloxy)propylcarbamate : To a stirred mixture of *tert*-butyl-3(benzyloxy)2-hydroxypropylcarbamate (3.0 g, 16 mmol) and 1-bromododecane (7.98 g, 48 mmol) in toluene (15 mL) were added 50% aq. NaOH solution (9.0 mL) and Bu₄NI (2.95 g, 8 mmol) and the resulting mixture was heated to 50-60 °C and maintained on vigorous stirring for 6 hours at the same temperature. After completion the mixture was cooled to ambient temperature and performed work up with ethyl acetate and water. The organic phase was concentrated and purified by silica gel column chromatography eluting with 5-20% ethyl acetate in hexane to get desired as a brown liquid (3.0 g, 63% yield). ESI-MS m/z [M+H]⁺ calc'd for C₂₇H₄₇NO₄, 450; found, 450.

[0270] Step 2: 3-(benzyloxy)-2-(dodecyloxy)propan-1-amine hydrochloride : To a stirred solution of compound obtained in step 1 (3 g) in methanol (5 mL) was added methanolic. HCl (10 mL) and stirring was continued for 1h at room temperature. After completion the mixture was concentrated to obtain the desired product as a colorless liquid (100% yield). ESI-MS m/z [M+H]⁺ calc'd for C₂₂H₃₉NO₂, 350; found, 350.

[0271] Step 3: tert-butyl 4-(3-((3-(benzyloxy)-2-(dodecyloxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate : The title compound was prepared from 3-(1-(*t*-butoxycarbonyl) piperidin-4-yl) benzoic acid (1.76 g, 5.76 mmol) and 3-(benzyloxy)-2-(dodecyloxy)propan-1-amine hydrochloride (2.0 g, 5.76 mmol) as described for Example 93 to give the title compound as colorless liquid (2.1 g, 57% yield). ESI-MS m/z [M+H]⁺ calc'd for C₃₉H₆₀N₂O₅, 637; found, 637.

[0272] Step 4: The title compound was prepared from above obtained step 3 product (64 mg, 0.1 mmol) as described for Example 1 to give an off-white solid (100% yield).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{34}H_{52}N_2O_3$, 537; found, 537.

Example 96 : methyl 5-(2-(dodecyloxy)-3-(3-(piperidin-4-yl)benzamido)propoxy)pentanoate hydrochloride

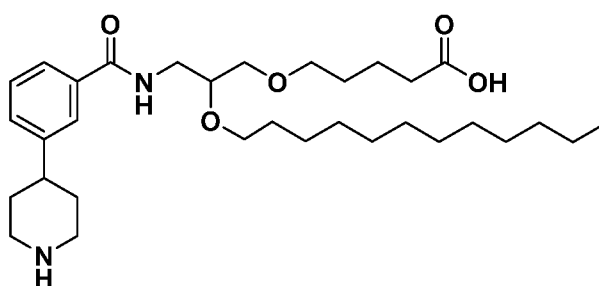


[0273] Step 1: tert-butyl 4-(3-((2-(dodecyloxy)-3-hydroxypropyl)carbamoyl)phenyl)piperidine-1-carboxylate : To a stirred solution of tert-butyl 4-(3-((3-(benzyloxy)-2-(dodecyloxy)propyl) carbamoyl)phenyl) piperidine-1-carboxylate (2.0 g, 3.14 mmol) in methanol (20 mL) was added 10% Pd/C (200 mg) portion wise under nitrogen and then the reaction mixture was stirred under pressure of hydrogen (10-15 psi) for 18 hours. After completion the mixture was filtered through celite pad and concentrated to obtain crude product as a colorless liquid, which was used directly in the next step. ESI-MS m/z $[M+H]^+$ calc'd for $C_{32}H_{54}N_2O_5$, 547; found, 547.

[0274] Step 2: tert-butyl 4-(3-((2-(dodecyloxy)-3-((5-methoxy-5-oxopentyl)oxy)propyl)carbamoyl) phenyl)piperidine-1-carboxylate : To a stirred mixture of tert-butyl 4-(3-(2-(dodecyloxy)-3-hydroxypropylcarbamoyl)phenyl)piperidine-1-carboxylate (1.2 g, 2.19 mmol) and methyl 5-bromopentanoate (1.37 g, 6.59 mmol) in Toluene (10 mL) were added 50% aq. NaOH solution (4.0 mL) and Bu_4NI (400 mg, 0.001 mol) and the resulting reaction mixture was heated to 50-60 °C and maintained on vigorous stirring for one hour at same temperature. After completion the reaction mixture was cooled to ambient temperature and performed work up with ethyl acetate and water. The organic phase was concentrated and purified by silica gel column chromatography with 5-30% ethyl acetate in hexane to get desired product as a colorless liquid. ESI-MS m/z $[M+H]^+$ calc'd for $C_{38}H_{64}N_2O_7$, 661; found, 661.

[0275] Step 3: The title compound was prepared from above obtained step 2 product (264 mg, 0.4 mmol) as described for Example 1 to give a colorless gummy solid (100% yield). ^1H NMR (300 MHz, DMSO- d_6): δ 8.62-8.41 (s, 1H), 7.74-7.65 (s, 2H), 7.45-7.31 (m, 2H), 3.66 (s, 3H), 3.63-3.31 (m, 10H), 2.96-2.71 (m, 4H), 2.31-2.19 (m, 2H), 2.03-1.83 (m, 5H), 1.58-1.32 (m, 7H), 1.31-1.24 (m, 18H), 0.85-0.83 (t, J = 5.7 Hz, 3H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{33}\text{H}_{56}\text{N}_2\text{O}_5$, 561; found, 561.

Example 97 : 5-(2-(dodecyloxy)-3-(3-(piperidin-4-yl)benzamido)propoxy)pentanoic acid hydrochloride

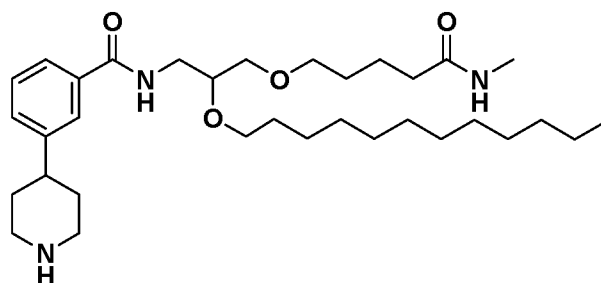


[0276] Step 1: 5-(3-(3-(1-(tert-butoxycarbonyl)piperidin-4-yl)benzamido)-2-(dodecyloxy)propoxy) pentanoic acid: To a stirred solution of tert-butyl 4-(3-((2-(dodecyloxy)-3-((5-methoxy-5-oxopentyl)oxy)propyl)carbamoyl) phenyl)piperidine-1-carboxylate (1.15 g) in methanol (5 mL) was added 2M LiOH.H₂O solution (10 mL) slowly at room temperature under inert atmosphere and stirring was continued for 18 hours. The reaction mixture was concentrated to dryness. The crude was diluted with water and washed with isopropyl ether. The resulting aqueous phase was acidified to P^H 2 using 2N HCl and extracted with ethyl acetate. The collected organic layer was concentrated and purified by silica gel column chromatography gradient elution with 5-10% Methanol in dichloromethane to provide desired product as a colorless liquid (900 mg, 82%). ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{37}\text{H}_{62}\text{N}_2\text{O}_7$, 647; found, 647.

[0277] Step 2: To a stirred solution of above obtained step 1 product (500 mg) in dichloromethane (4 mL) was added 4N HCl in 1,4-Dioxane (10 mL) slowly and continued to stir for 30 min at room temperature. The resultant reaction mixture was concentrated to furnish the desired product as an off white solid (100% yield). ^1H NMR (300 MHz, DMSO - d_6): δ 12.0 (s, 1H), 8.5 (br s, 1H), 8.62-8.51 (m, 2H), 7.71 (s, 2H), 7.43-7.36 (m, 2H), 3.58-3.45 (m, 11H),

3.16-2.91 (m, 3H), 2.31-2.19 (m, 2H), 1.91-1.82 (m, 4H), 1.51-1.62 (m, 6H), 1.22-1.03 (m, 18H), 0.85-0.83 (t, $J=5.7$ Hz, 3H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{32}H_{54}N_2O_5$, 547; found, 547.

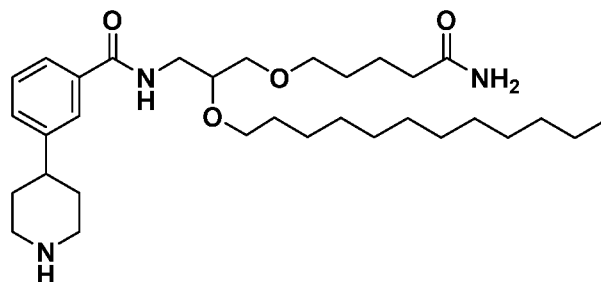
Example 98 : N-(2-(dodecyloxy)-3-((5-(methylamino)-5-oxopentyl)oxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride



[0278] Step 1: tert-butyl 4-(3-(2-(dodecyloxy)-3-(5-(methylamino)-oxopentyl)oxy)propylcarbamoyl) phenyl)piperidine-1-carboxylate: To a stirred solution of 5-(3-(3-(1-(tert-butoxycarbonyl) piperidin-4-yl)benzamido)-2-(dodecyloxy)propoxy) pentanoic acid (250 mg, 0.38 mmol) in DMF (5 mL) were added DIPEA (0.656 mL, 3.8 mmol) and HBTU (230 mg, 0.608 mmol) and stirred for 30 min at room temperature. Then $MeNH_2 \cdot HCl$ (60 mg, 0.874 mmol) was added to the reaction mixture and stirring was continued for 18 hours at room temperature. Reaction mixture was diluted with ethyl acetate and washed with sat. $NaHCO_3$ solution, sat. NH_4Cl solution, water and brine solution. The collected organic phase was dried, concentrated and purified by basic silica gel column chromatography gradient elution with 5% Methanol in dichloromethane to isolate desired pure product as a yellow liquid (220 mg, 88%).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{38}H_{65}N_3O_6$, 661; found, 661.

[0279] Step 2: To a stirred solution of above step 1 product (220 mg) in dichloromethane (2 mL) was added HCl in 1,4-Dioxane (5 mL) and continued to stir for 30 min at room temperature. The resultant reaction mixture was concentrated to furnish the desired product as viscous oil (100% yield). ^1H NMR (300 MHz, $DMSO-d_6$): δ 8.91 (br s, 1H), 8.67 (br s, 1H), 8.54 (s, 1H), 7.67 (s, 2H), 7.37-7.35 (m, 2H), 3.58-3.41 (m, 11H), 3.16-2.91 (m, 3H), 2.92-2.71 (m, 3H), 2.31-2.19 (m, 2H), 1.91-1.82 (m, 4H) 1.61-1.32 (m, 6H), 1.22-1.03 (m, 18H), 0.85-0.83 (t, $J=5.7$ Hz, 3H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{33}H_{57}N_3O_4$, 561; found, 561.

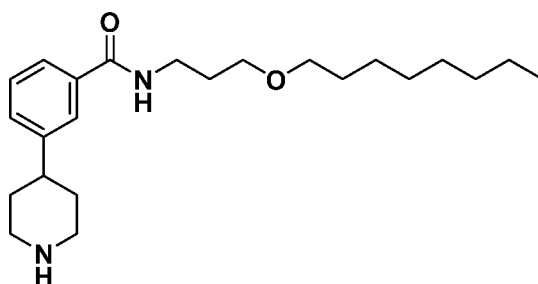
Example 99 : N-(3-((5-amino-5-oxopentyl)oxy)-2-(dodecyloxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride



[0280] Step 1: tert-butyl 4-(3-((3-((5-amino-5-oxopentyl)oxy)-2-(dodecyloxy)propyl)carbamoyl) phenyl)piperidine-1-carboxylate: The title compound was prepared from 5-(3-(3-(1-(tert-butoxycarbonyl) piperidin-4-yl)benzamido)-2-(dodecyloxy)propoxy) pentanoic acid (250 mg, 0.38mmol) and NH_4Cl (46.75 mg, 0.874 mmol) as described for Example 98 to give the desired product as yellow liquid (220 mg, 88%). ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{37}\text{H}_{63}\text{N}_3\text{O}_6$, 647; found, 647.

[0281] Step 2: To a stirred solution of above step 1 product (220 mg) in dichloromethane (2 mL) was added HCl in 1,4-Dioxane (5 mL) and continued to stir for 30 min at room temperature. The resultant reaction mixture was concentrated to furnish the desired product as viscous oil (100% yield). ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 8.91 (br s, 1H), 8.67 (br s, 1H), 8.54 (s, 1H), 7.67 (s, 2H), 7.37-7.35 (m, 2H), 7.13 (s, 1H), 6.85 (s, 1H), 3.75-3.41 (m, 11H), 3.16-2.91 (m, 3H), 2.31-2.19 (m, 2H), 1.91-1.82 (m, 4H), 1.62-1.45 (m, 6H), 1.22-1.03 (m, 19H), 0.85-0.83 (t, $J=5.8$ Hz, 3H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{32}\text{H}_{55}\text{N}_3\text{O}_4$, 547; found, 547.

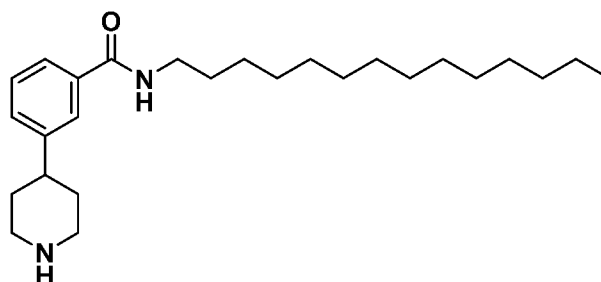
Example 100 : N-(3-(octyloxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride



[0282] Step1: tert-butyl 4-(3-((3-(octyloxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate: The title compound was prepared from 3-(1-(tert-butoxycarbonyl)piperidin-4-yl)benzoic acid (153 mg, 0.5 mmol) and 3-(octyloxy)propan-1-amine (112 mg, 0.5 mmol) as described for Example 33 to give the title compound as colorless gummy liquid (226 mg, 95% yield). ESI-MS m/z $[M+H]^+$ calc'd for $C_{28}H_{46}N_2O_4$, 475; found, 475.

[0283] Step 2: The title compound was prepared from above step 1 product (95 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, Chloroform- d) δ 9.67 (br d, 2H), 7.55 (d, J = 6.9 Hz, 1H), 7.45 – 7.32 (m, 3H), 7.14 (s, 1H), 3.83 – 3.50 (m, 6H), 3.44 (t, J = 6.6 Hz, 2H), 3.10 (d, J = 49.3 Hz, 2H), 2.85 (s, 1H), 2.26 (s, 2H), 2.13 – 1.97 (m, 2H), 1.85 (m, 4H), 1.57 (q, J = 6.9 Hz, 2H), 1.34 – 1.15 (m, 8H), 0.95 – 0.70 (m, 3H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{23}H_{38}N_2O_2$, 375; found, 375.

Example 101: 3-(piperidin-4-yl)-N-tetradecylbenzamide hydrochloride

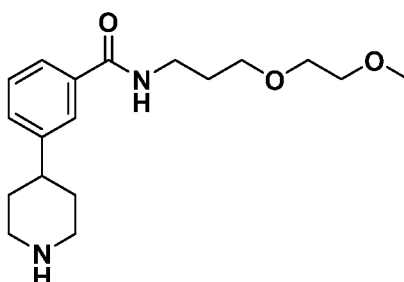


[0284] Step1: tert-butyl 4-(3-(tetradecylcarbamoyl)phenyl)piperidine-1-carboxylate: The title compound was prepared from 3-(1-(tert-butoxycarbonyl)piperidin-4-yl)benzoic acid (153 mg, 0.5 mmol) and tetradecan-1-amine (107 mg, 0.5 mmol) as described for Example 33 to give the title compound as gummy white solid (210 mg, 84% yield). ESI-MS m/z $[M+H]^+$ calc'd for $C_{31}H_{52}N_2O_3$, 501; found, 501.

[0285] Step 2: The title compound was prepared from above step 1 product (100 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, Chloroform- d) δ 9.69 (br d, 2H), 7.67 (s, 1H), 7.61 (t, J = 4.3 Hz, 1H), 7.39 (d, J = 4.6 Hz, 2H), 6.24 (s, 1H), 3.65 (d, J = 10.8 Hz, 2H), 3.43 (q, J = 9.3, 8.2 Hz, 2H), 3.04 (s, 2H), 2.85 (s, 1H), 2.26 (d, J = 12.8 Hz, 2H), 2.07 (d, J = 13.2 Hz, 2H), 1.80 (s, 2H), 1.70 – 1.53 (m, 2H), 1.44 –

1.11 (m, 20H), 0.88 (t, $J = 6.9$ Hz, 3H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{26}H_{44}N_2O$, 401; found, 401.

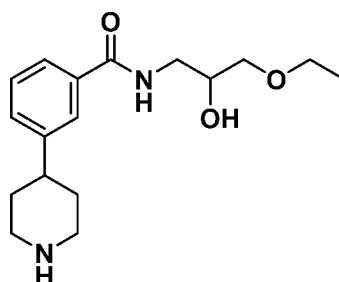
Example 102 : N-(3-(2-methoxyethoxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride



[0286] Step1: tert-butyl 4-(3-((3-(2-methoxyethoxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate: The title compound was prepared from 3-(1-(tert-butoxycarbonyl)piperidin-4-yl)benzoic acid (153 mg, 0.5 mmol) and 3-(2-methoxyethoxy)propan-1-amine (67 mg, 0.5 mmol) as described for Example 33 to give the title compound as colorless liquid (158 mg, 75% yield). ESI-MS m/z $[M+H]^+$ calc'd for $C_{23}H_{36}N_2O_5$, 421; found, 421.

[0287] Step 2: The title compound was prepared from above step 1 product (84 mg, 0.2 mmol) as described for Example 1 to give a colorless liquid (100% yield). ^1H NMR (500 MHz, Chloroform- d) δ 9.44 (s, 1H), 9.17 (s, 1H), 7.71 (m, 2H), 7.61 (d, $J = 6.9$ Hz, 1H), 7.37 (d, $J = 7.7$ Hz, 2H), 3.94 – 3.42 (m, 10H), 3.29 (s, 3H), 3.08 (d, $J = 16.1$ Hz, 2H), 2.87 (s, 1H), 2.22 (t, $J = 8.5$ Hz, 2H), 2.06 (q, $J = 13.8, 11.3$ Hz, 2H), 1.92 (d, $J = 5.7$ Hz, 2H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{18}H_{28}N_2O_3$, 321; found, 321.

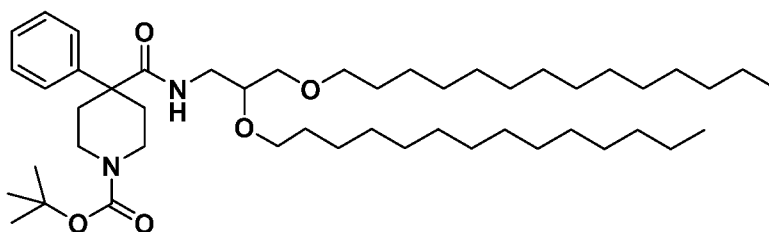
Example 103: N-(3-ethoxy-2-hydroxypropyl)-3-(piperidin-4-yl)benzamide hydrochloride



[0288] Step1: tert-butyl 4-(3-((3-ethoxy-2-hydroxypropyl)carbamoyl)phenyl)piperidine-1-carboxylate: The title compound was prepared from 3-(1-(tert-butoxycarbonyl)piperidin-4-yl)benzoic acid (153 mg, 0.5 mmol) and 1-amino-3-ethoxypropan-2-ol (60 mg, 0.5 mmol) as described for Example 33 to give the title compound as colorless liquid (165 mg, 75% yield). ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{34}N_2O_5$, 407; found, 407.

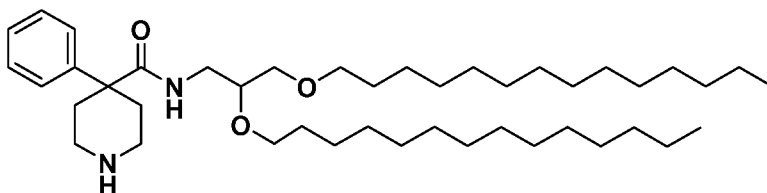
[0289] Step 2: The title compound was prepared from above step 1 product (81 mg, 0.2 mmol) as described for Example 1 to give a colorless liquid (100% yield). ^1H NMR (500 MHz, Chloroform- d) δ 9.69 (s, 1H), 9.37 (s, 1H), 7.77 (s, 1H), 7.68 (d, J = 6.5 Hz, 1H), 7.39 (d, J = 6.4 Hz, 2H), 7.07 (m, 1H), 4.03 (s, 1H), 3.42-3.80 (m, 10H), 2.69 (m, 1H), 2.55 (s, 29H), 2.36 – 2.17 (m, 2H), 2.15 – 1.97 (m, 2H), 1.21 (t, J = 7.0 Hz, 3H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{17}H_{26}N_2O_3$, 307; found, 307.

Example 104: tert-butyl 4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)-4-phenylpiperidine-1-carboxylate



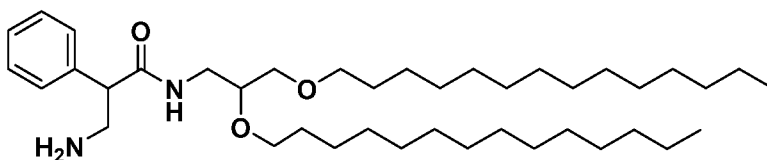
[0290] The title compound was prepared from 1-(tert-butoxycarbonyl)-4-phenylpiperidine-4-carboxylic acid (153 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as colorless liquid (315 mg, 81% yield). ^1H NMR (500 MHz, Chloroform- d) δ 7.35 (d, J = 4.3 Hz, 3H), 7.29 – 7.22 (m, 2H), 5.74 (t, J = 5.5 Hz, 1H), 3.60 (t, J = 8.5 Hz, 2H), 3.55 – 3.02 (m, 11H), 2.47 – 2.25 (m, 2H), 2.02 (m, 2H), 1.48 (s, 2H), 1.45 (s, 9H), 1.42 – 1.35 (m, 2H), 1.27 (d, J = 4.3 Hz, 44H), 0.89 (t, J = 6.9 Hz, 6H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{48}H_{86}N_2O_5$, 772; found, 772.

Example 105: N-(2,3-bis(tetradecyloxy)propyl)-4-phenylpiperidine-4-carboxamide hydrochloride



[0291] The title compound was prepared from Example 103 (154 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 9.62 (s, 2H), 7.52 – 7.27 (m, 5H), 5.77 (d, J = 5.5 Hz, 1H), 3.87 – 3.60 (m, 1H), 3.51 (d, J = 13.0 Hz, 2H), 3.42 (m, 7H), 2.55 (s, 2H), 2.39 (s, 2H), 1.66 (s, 4H), 1.55 – 1.08 (m, 44H), 0.88 (t, J = 6.8 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{43}\text{H}_{78}\text{N}_2\text{O}_3$, 672; found, 672.

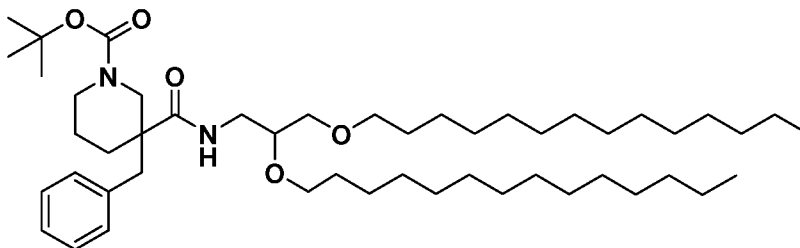
Example 106: 3-amino-N-(2,3-bis(tetradecyloxy)propyl)-2-phenylpropanamide hydrochloride



[0292] Step1: tert-butyl (3-((2,3-bis(tetradecyloxy)propyl)amino)-3-oxo-2-phenylpropyl)carbamate: The title compound was prepared from 3-((tert-butoxycarbonyl)amino)-2-phenylpropanoic acid (133 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as colorless liquid (310 mg, 85% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.27 (m, 5H), 5.83 (t, J = 5.8 Hz, 1H), 5.17 (s, 1H), 3.83 – 2.99 (m, 12H), 1.70 – 1.45 (m, 4H), 1.42 (s, 9H), 1.27 (br s, 44H), 0.89 (t, J = 6.8 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{45}\text{H}_{82}\text{N}_2\text{O}_5$, 732; found, 732.

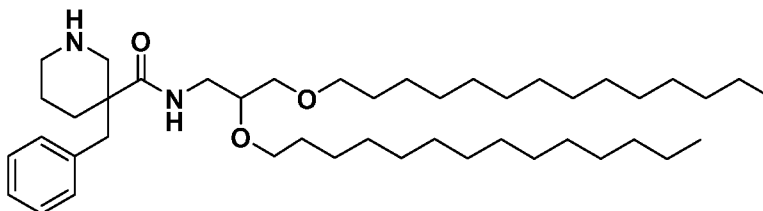
[0293] Step 2: The title compound was prepared from above step 1 product (146 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 8.71 (s, 3H), 7.35 (q, J = 10.5, 8.7 Hz, 3H), 7.26 (s, 2H), 5.96 (d, J = 26.3 Hz, 1H), 4.18 (s, 1H), 3.63 – 3.03 (m, 9H), 1.71 (s, 2H), 1.40 (dd, J = 14.3, 7.1 Hz, 4H), 1.26 (br s, 44H), 0.88 (t, J = 6.8 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{40}\text{H}_{74}\text{N}_2\text{O}_3$, 632; found, 632.

Example 107: tert-butyl 3-benzyl-3-((2,3-bis(tetradecyloxy)propyl)carbamoyl)piperidine-1-carboxylate



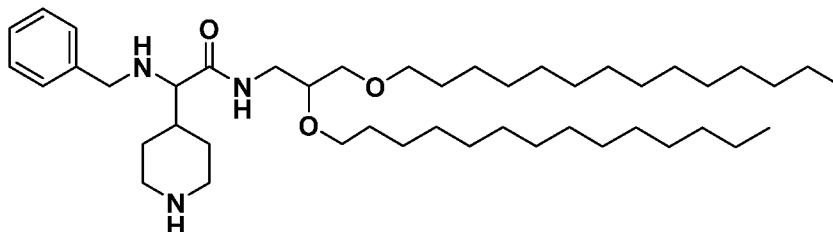
[0294] The title compound was prepared 3-benzyl-1-(tert-butoxycarbonyl)piperidine-3-carboxylic acid (170 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as colorless liquid (273 mg, 70% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.25 – 7.16 (m, 3H), 7.14 – 7.06 (m, 2H), 4.03 (m, 1H), 3.65 – 3.21 (m, 6H), 3.19 – 2.73 (m, 4H), 2.62 (m, 2H), 1.73 – 1.47 (m, 4H), 1.43 (s, 9H), 1.26 (s, 44H), 0.88 (t, J = 6.9 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{49}\text{H}_{88}\text{N}_2\text{O}_5$, 786; found, 786.

Example 108: 3-benzyl-N-(2,3-bis(tetradecyloxy)propyl)piperidine-3-carboxamide hydrochloride



[0295] The title compound was prepared from Example 107 (157 mg, 0.2 mmol) as described for Example 1 to give a white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 11.69 (s, 1H), 7.32 – 7.27 (m, 4H), 7.09 (t, J = 9.2 Hz, 2H), 6.65 (d, J = 19.4 Hz, 1H), 3.94 – 3.22 (m, 12H), 2.98 (t, J = 13.0 Hz, 1H), 2.77 (d, J = 13.9 Hz, 2H), 1.94 (m, 3H), 1.69 (m, 2H), 1.58 – 1.46 (m, 4H), 1.42 – 1.14 (m, 44H), 0.88 (t, J = 6.9 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{44}\text{H}_{80}\text{N}_2\text{O}_3$, 686; found, 686.

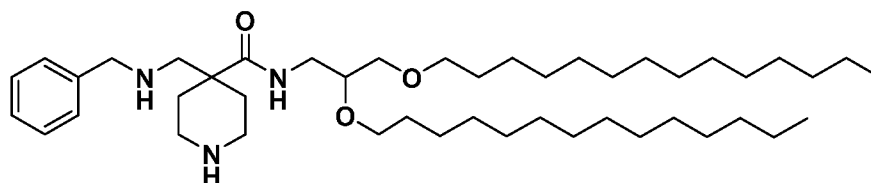
Example 109: 2-(benzylamino)-N-(2,3-bis(tetradecyloxy)propyl)-2-(piperidin-4-yl)acetamide hydrochloride



[0296] Step1: tert-butyl 4-(1-(benzylamino)-2-((2,3-bis(tetradecyloxy)propyl)amino)-2-oxoethyl) piperidine-1-carboxylate: The title compound was prepared from 2-(benzylamino)-2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid (174 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5 mmol) as described for Example 33 to give the title compound as light yellow liquid (262 mg, 64% yield). ESI-MS m/z $[M+H]^+$ calc'd for $C_{50}H_{91}N_3O_5$, 815; found, 815.

[0297] Step 2: The title compound was prepared from above step 1 product (163 mg, 0.2 mmol) as described for Example 1 to give a light yellow solid (100% yield). ^1H NMR (500 MHz, Chloroform- d) δ 9.96 (d, $J = 72.6$ Hz, 1H), 8.95 (d, $J = 94.9$ Hz, 3H), 8.37 (s, 1H), 7.60 (s, 2H), 7.32 (s, 3H), 4.16 (s, 3H), 3.76 – 3.27 (m, 12H), 3.03 (d, $J = 75.6$ Hz, 5H), 2.51 (s, 1H), 2.27 (s, 1H), 1.90 (s, 2H), 1.52 (s, 4H), 1.24 (t, $J = 10.2$ Hz, 44H), 0.88 (t, $J = 6.9$ Hz, 6H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{45}H_{83}N_3O_3$, 715; found, 715.

Example 110: 4-((benzylamino)methyl)-N-(2,3-bis(tetradecyloxy)propyl)piperidine-4-carboxamide hydrochloride

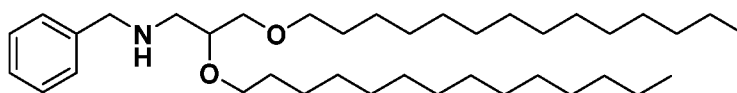


[0298] Step1: tert-butyl 4-((benzylamino)methyl)-4-((2,3-bis(tetradecyloxy)propyl)carbamoyl) piperidine-1-carboxylate: The title compound was prepared from 4-((benzylamino)methyl)-1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (174 mg, 0.5 mmol) and 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (260 mg, 0.5

mmol) as described for Example 33 to give the title compound as yellow liquid (215 mg, 53% yield). ESI-MS m/z $[M+H]^+$ calc'd for $C_{50}H_{91}N_3O_5$, 815; found, 815.

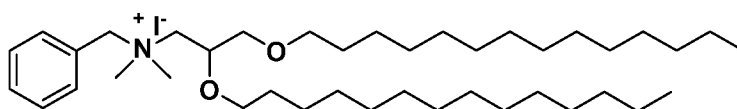
[0299] Step 2: The title compound was prepared from above step 1 product (163 mg, 0.2 mmol) as described for Example 1 to give a yellow solid (100% yield). ^1H NMR (500 MHz, Chloroform- d) δ 9.82 – 8.66 (m, 4H), 7.62 (m, 2H), 7.36 (m, 3H), 6.03 (s, 1H), 4.32 (m, 2H), 3.98 – 2.77 (m, 14H), 2.57 – 2.04 (m, 4H), 1.54 (m, 4H), 1.25 (br s, 44H), 0.88 (td, $J = 7.0, 2.0$ Hz, 6H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{45}H_{83}N_3O_3$, 715; found, 715.

Example 111: N-benzyl-2,3-bis(tetradecyloxy)propan-1-amine



[0300] In a 50 mL round bottom flask, 2,3-bis(tetradecyloxy)propan-1-amine hydrochloride (520 mg, 1.0 mmol) and benzaldehyde (127 mg, 1.2 mmol) were dissolved in THF (15 mL), then added $NaBH(OAc)_3$ (414, 2.0 mmol) portion wise to the reaction mixture and continued stirring overnight at room temperature. Then neutralized with sat. $NaHCO_3$ solution and extracted into ethyl acetate (2 x 50 mL). Combined organic phase washed with brine and dried over sodium sulfate and evaporated. Then, purified on silica gel column chromatography using dichloromethane-MeOH (0-10%) as eluent. Pure product fractions combined evaporated to give the desired product as colorless liquid (225 mg, 39% yield). ^1H NMR (500 MHz, Chloroform- d) δ 7.51 – 7.28 (m, 7H), 3.62 (ddd, $J = 11.2, 8.1, 5.4$ Hz, 2H), 3.54 – 3.32 (m, 6H), 2.77 (qd, $J = 12.2, 5.7$ Hz, 2H), 1.55 (m, 4H), 1.38 – 1.20 (m, 44H), 0.88 (t, $J = 6.9$ Hz, 6H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{38}H_{71}NO_2$, 575; found, 575.

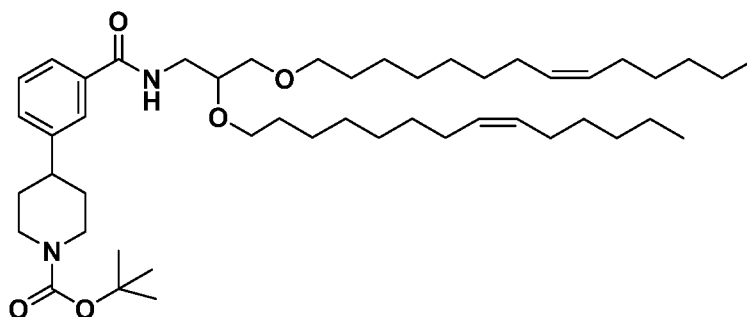
Example 112: N-benzyl-N,N-dimethyl-2,3-bis(tetradecyloxy)propan-1-aminium iodide



[0301] The title compound was prepared from Example 110 (175 mg, 0.305 mmol) as described for Example 92 to give a light yellow solid (178 mg, 80%). ^1H NMR (500 MHz, Chloroform- d) δ 7.68 (dd, $J = 7.0, 1.8$ Hz, 2H), 7.59 – 7.37 (m, 3H), 5.19 – 4.86 (m, 2H), 4.19

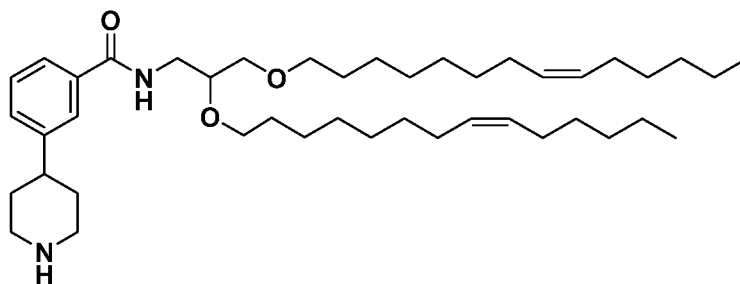
(dq, $J = 10.0, 3.3, 2.8$ Hz, 1H), 4.01 (dd, $J = 13.8, 2.2$ Hz, 1H), 3.80 – 3.45 (m, 5H), 3.43 – 3.26 (m, 8H), 1.74 – 1.47 (m, 4H), 1.25 (br s, 44H), 0.88 (t, $J = 6.8$ Hz, 6H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{40}H_{76}INO_2$, 731; found, 731.

Example 113: tert-butyl 4-(3-(((2,3-bis(((Z)-tetradec-8-en-1-yl)oxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate



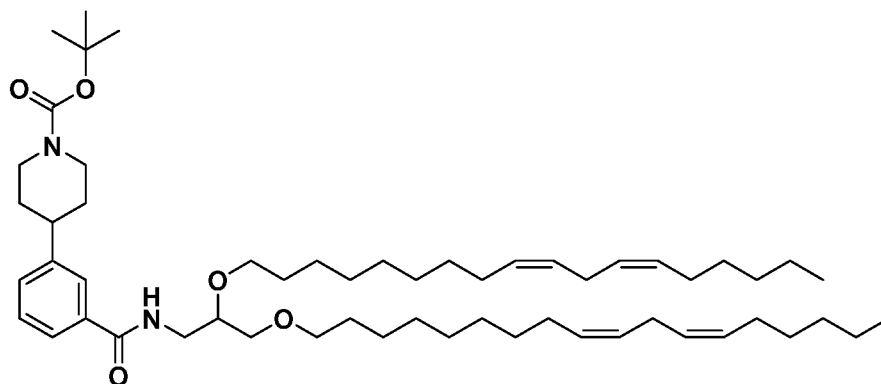
[0302] To a stirred mixture of *tert*-butyl 4-(3-(2,3-dihydroxypropylcarbamoyl)phenyl)piperidine-1-carboxylate (500 mg, 1.322m mol) and olelyl bromide (2.2 g, 7.936 m mol) in toluene (15 mL) were added 50% aq. NaOH solution (4.0 mL) and Bu_4NI (2.95 g, 0.661 m mol) and the resulting reaction mixture was heated to 50-60 °C and maintained on vigorous stirring for 6 hours at same temperature. The completion of reaction was monitored by TLC. The reaction mixture was work up with ethyl acetate (2X 20 ml) and water (10 ml) at room temperature. The combined organic phases were concentrated and purified by silica-gel column chromatography gradient elution with 5-20% ethyl acetate in hexane to obtain pure desired product as a colorless gel (450 mg, 54%). ESI-MS m/z $[M+H]^+$ calc'd for $C_{48}H_{82}N_2O_5$, 768; found, 768.

Example 114: N-(2,3-bis(((Z)-tetradec-8-en-1-yl)oxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride



[0303] To a stirred solution of Example 113 (550 mg) in methanol (5 ml) was added Methanolic HCl (10 mL) and stirring was continued for 1h at room temperature. The completion of reaction monitored by TLC, the mixture was concentrated and the obtained crude product was purified by Preparative HPLC to furnish desired target product (N-(2,3-bis(((Z)-tetradec-8-enyloxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride as colorless sticky solid (230 mg, 48%). ¹H NMR (300 MHz, DMSO-d₆): δ 7.70 (d, *J*=5.7 Hz, 2H), 7.43-7.35 (m, 2H), 5.36-5.26 (m, 4H), 3.56-3.26 (m, 16H), 3.01-2.89 (m, 3H), 1.97-1.93 (m, 12H), 1.44-1.41 (m, 5H), 1.41-1.2 (m, 23H), 0.845 (t, *J*= 6.0, 7.2 Hz, 6H).; ESI-MS *m/z* [M+H]⁺ calc'd for C₄₃H₇₄N₂O₃, 668; found, 668.

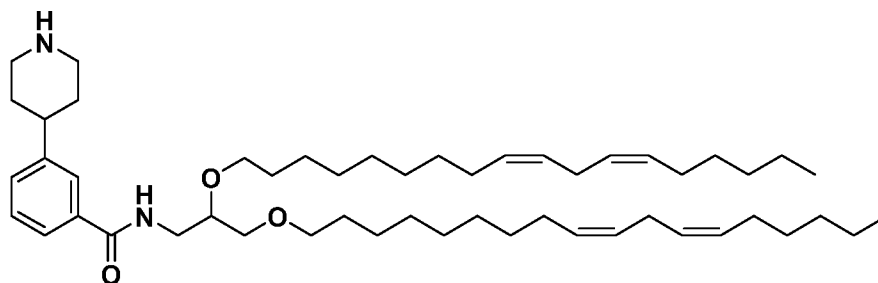
Example 115: tert-butyl 4-(3-(((2,3-bis(((9Z,12Z)-octadeca-9,12-dien-1-yl)oxy)propyl)carbamoyl phenyl)piperidine-1-carboxylate



[0304] The title compound was prepared from 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)benzoic acid (153 mg, 0.5 mmol) and 2,3-bis(((9Z,12Z)-octadeca-9,12-dien-1-yl)oxy)propan-1-amine hydrochloride (313 mg, 0.5 mmol) (prepared as in Example 1 using lenoleyl bromide) as described for Example 33 to give the title compound as colorless oil (325 mg, 74% yield). ¹H NMR (499 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 1.9 Hz, 1H), 7.53 (dt, *J* = 7.1, 1.8 Hz, 1H), 7.42 –

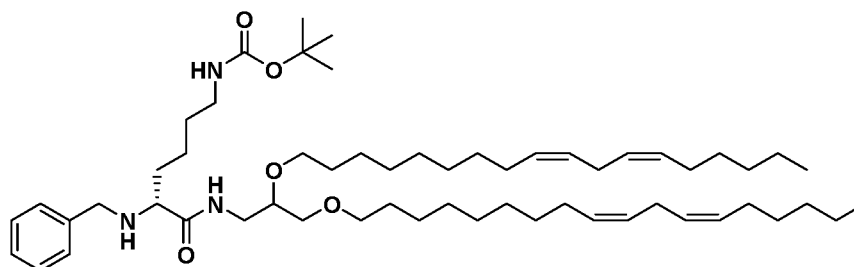
7.29 (m, 2H), 6.72 (t, $J = 5.5$ Hz, 1H), 5.63 – 5.05 (m, 8H), 4.25 (s, 2H), 3.83 – 3.33 (m, 10H), 2.88 – 2.56 (m, 7H), 2.20 – 1.93 (m, 9H), 1.92 – 1.73 (m, 2H), 1.72 – 1.51 (m, 6H), 1.48 (s, 9H), 1.40 – 1.17 (m, 26H), 0.89 (t, $J = 6.8$ Hz, 6H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{56}H_{94}N_2O_5$, 876; found, 876.

Example 116: N-(2,3-bis(((9Z,12Z)-octadeca-9,12-dien-1-yl)oxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride



[0305] The title compound was prepared from Example 115 (175 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ^1H NMR (500 MHz, Chloroform- d) δ 9.69 (br d, 2H), 7.73 (s, 1H), 7.54 (d, $J = 7.0$ Hz, 1H), 7.39 (d, $J = 8.2$ Hz, 2H), 6.77 (d, $J = 6.0$ Hz, 1H), 5.55 – 5.13 (m, 8H), 3.90 – 3.30 (m, 9H), 3.04 (s, 2H), 2.77 (t, $J = 6.7$ Hz, 6H), 2.26 (s, 2H), 2.15 – 1.92 (m, 10H), 1.77 (s, 4H), 1.56 (q, $J = 7.2$ Hz, 4H), 1.44 – 1.12 (m, 28H), 0.88 (t, $J = 6.7$ Hz, 6H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{51}H_{86}N_2O_3$, 776; found, 776.

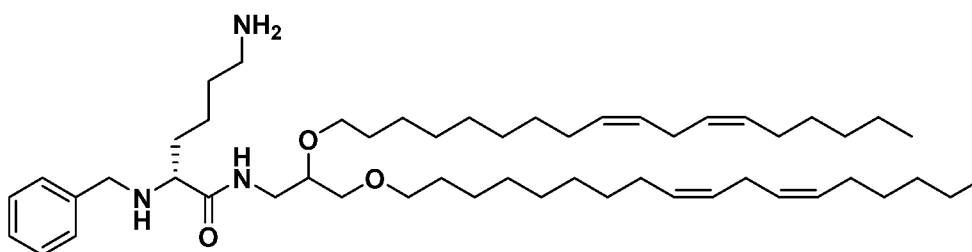
Example 117: tert-butyl ((5R)-5-(benzylamino)-6-((2,3-bis(((9Z,12Z)-octadeca-9,12-dien-1-yl)oxy)propyl)amino)-6-oxohexyl)carbamate



[0306] The title compound was prepared from N2-benzyl-N6-(tert-butoxycarbonyl)-D-lysine (168 mg, 0.5 mmol) and 2,3-bis(((9Z,12Z)-octadeca-9,12-dien-1-yl)oxy)propan-1-amine

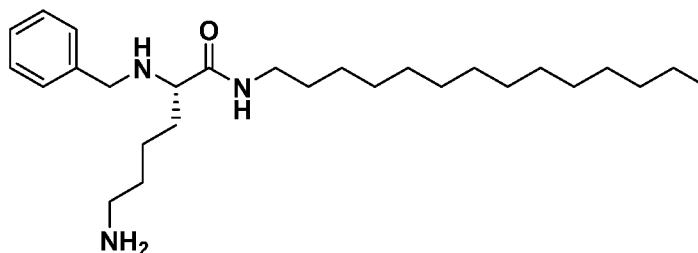
hydrochloride (313 mg, 0.5 mmol) as described for Example 33 to give the title compound as colorless oil (410 mg, 90% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.45 (d, J = 5.6 Hz, 2H), 7.43 – 7.32 (m, 3H), 7.13 – 6.92 (m, 1H), 5.48 – 5.20 (m, 8H), 4.82 (s, 1H), 4.24 (d, J = 12.9 Hz, 1H), 4.16 – 3.99 (m, 3H), 3.84 – 3.69 (m, 1H), 3.69 – 3.27 (m, 7H), 3.18 – 2.94 (m, 3H), 2.79 (s, 6H), 2.13 – 1.80 (m, 8H), 1.66 – 1.41 (m, 5H), 1.40 – 1.16 (m, 44H), 0.89 (t, J = 6.8 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{57}\text{H}_{99}\text{N}_3\text{O}_5$, 907; found, 907.

Example 118: (2R)-6-amino-2-(benzylamino)-N-(2,3-bis(((9Z,12Z)-octadeca-9,12-dien-1-yl)oxy)propyl)hexanamide dihydrochloride



[0307] The title compound was prepared from Example 117 (181 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 9.65 (s, 1H), 8.51 (s, 1H), 7.76 (s, 3H), 7.52 (s, 2H), 7.33 (s, 3H), 5.34 (m, 8H), 4.19 (m, 8H), 3.49 (m, 9H), 2.90 (m, 2H), 2.76 (dt, J = 6.6, 4.3 Hz, 4H), 2.04 (q, J = 8.0, 7.6 Hz, 8H), 1.77 (s, 1H), 1.53 (s, 5H), 1.30 (br s, 32H), 0.88 (t, J = 6.7 Hz, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{52}\text{H}_{91}\text{N}_3\text{O}_3$, 807; found, 807.

Example 119: (S)-6-amino-2-(benzylamino)-N-tetradecylhexanamide dihydrochloride

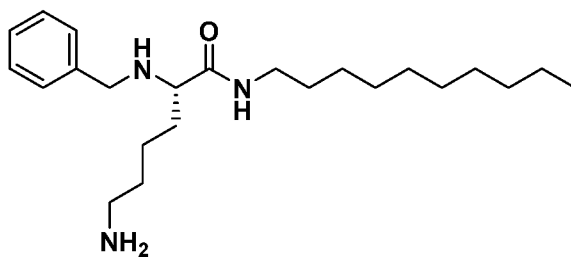


[0308] Step 1: tert-butyl (S)-(5-(benzylamino)-6-oxo-6-(tetradecylamino)hexyl)carbamate:
The title compound was prepared from N^2 -benzyl- N^6 -(tert-butoxycarbonyl)-L-lysine (168 mg, 0.5 mmol) and tetradecan-1-amine (107 mg, 0.5 mmol) as described for Example 33 to give the

title compound as gummy solid (155 mg, 58% yield). ESI-MS m/z $[M+H]^+$ calc'd for $C_{32}H_{57}N_3O_3$, 532; found, 532.

[0309] Step 2: The title compound was prepared from above obtained step 1 product (106 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 9.19 (s, 1H), 8.30 (s, 1H), 7.78 (s, 1H), 7.40 (m, 5H), 4.19 (s, 1H), 4.00 (s, 2H), 3.36 – 3.10 (m, 1H), 3.07 – 2.80 (m, 3H), 1.97 (s, 2H), 1.70 (m, 2H), 1.46 (s, 3H), 1.25 (d, J = 8.6 Hz, 26H), 0.88 (td, J = 6.9, 3.5 Hz, 3H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{27}H_{49}N_3O$, 432; found, 432.

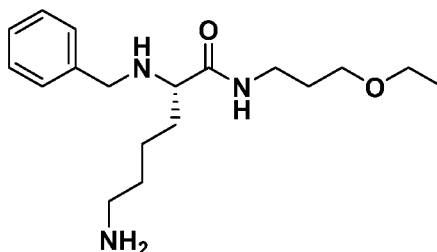
Example 120: (S)-6-amino-2-(benzylamino)-N-decylhexanamide dihydrochloride



[0310] Step 1: tert-butyl (S)-(5-(benzylamino)-6-(decylamino)-6-oxohexyl)carbamate: The title compound was prepared from N^2 -benzyl- N^6 -(tert-butoxycarbonyl)-L-lysine (168 mg, 0.5 mmol) and decyl-1-amine (79 mg, 0.5 mmol) as described for Example 33 to give the title compound as semi solid (158 mg, 66% yield). ESI-MS m/z $[M+H]^+$ calc'd for $C_{28}H_{49}N_3O_3$, 476; found, 476.

[0311] Step 2: The title compound was prepared from above obtained step 1 product (97 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 9.30 (s, 1H), 8.39 (s, 1H), 7.42 (m, 7H), 4.10 (m, 3H), 3.52 – 2.63 (m, 4H), 1.88 (m, 5H), 1.47 (s, 4H), 1.26 (br s, 14H), 0.87 (t, J = 6.9 Hz, 3H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{23}H_{41}N_3O$, 376; found, 376.

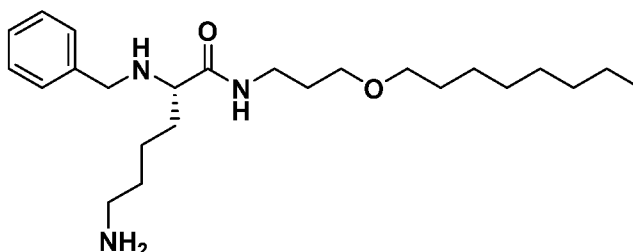
Example 121: (S)-6-amino-2-(benzylamino)-N-(3-ethoxypropyl)hexanamide dihydrochloride



[0312] Step 1: tert-butyl (S)-((5-(benzylamino)-6-((3-ethoxypropyl)amino)-6-oxohexyl)carbamate: The title compound was prepared from N²-benzyl-N⁶-(tert-butoxycarbonyl)-L-lysine (168 mg, 0.5 mmol) and 3-ethoxypropan-1-amine (52 mg, 0.5 mmol) as described for Example 33 to give the title compound as semi solid (153 mg, 73% yield). ESI-MS m/z [M+H]⁺ calc'd for C₂₃H₃₉N₃O₄, 422; found, 422.

[0313] Step 2: The title compound was prepared from above obtained step 1 product (84 mg, 0.2 mmol) as described for Example 1 to give a gummy solid (100% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.86 – 7.31 (m, 8H), 3.68 – 3.54 (m, 3H), 3.50 (m, 3H), 3.25 (s, 5H), 2.04 (m, 2H), 1.81 (m, 2H), 1.52-1.00 (m, 7H).; ESI-MS m/z [M+H]⁺ calc'd for C₁₈H₃₁N₃O₂, 322; found, 322.

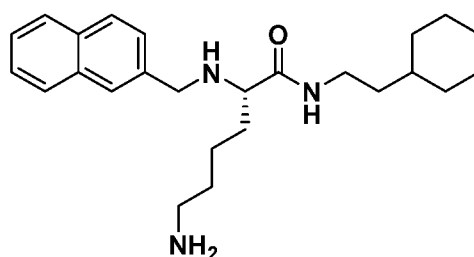
Example 122: (S)-6-amino-2-(benzylamino)-N-(3-(octyloxy)propyl)hexanamide dihydrochloride



[0314] Step 1: tert-butyl (S)-((5-(benzylamino)-6-((3-(octyloxy)propyl)amino)-6-oxohexyl)carbamate: The title compound was prepared from N²-benzyl-N⁶-(tert-butoxycarbonyl)-L-lysine (168 mg, 0.5 mmol) and 3 3-(octyloxy)propan-1-amine (112 mg, 0.5 mmol) as described for Example 33 to give the title compound as semi solid (172 mg, 68% yield). ESI-MS m/z [M+H]⁺ calc'd for C₂₉H₅₁N₃O₄, 506; found, 506.

[0315] Step 2: The title compound was prepared from above obtained step 1 product (101 mg, 0.2 mmol) as described for Example 1 to give a gummy solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 9.34 (s, 1H), 8.42 (s, 1H), 7.42 (m, 7H), 4.10 (m, 3H), 3.40 (s, 5H), 2.97 (m, 3H), 2.04 (m, 2H), 1.75 (s, 3H), 1.52 (s, 3H), 1.33 – 1.10 (m, 12H), 0.87 (t, $J = 6.7$ Hz, 3H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{43}\text{N}_3\text{O}_2$, 406; found, 406.

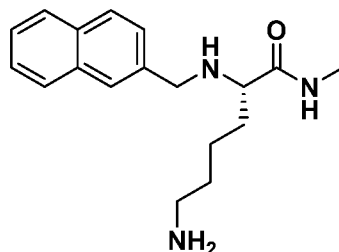
Example 123: (S)-6-amino-N-(2-cyclohexylethyl)-2-((naphthalen-2-ylmethyl)amino)hexanamide dihydrochloride



[0316] Step 1: tert-butyl (S)-(6-((2-cyclohexylethyl)amino)-5-((naphthalen-2-ylmethyl)amino)-6-oxohexyl)carbamate: The title compound was prepared from N6-(tert-butoxycarbonyl)-N2-(naphthalen-2-ylmethyl)-L-lysine (193 mg, 0.5 mmol) and 2-cyclohexylethan-1-amine (82 mg, 0.5 mmol) as described for Example 33 to give the title compound as semi solid (182 mg, 73% yield). ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{30}\text{H}_{45}\text{N}_3\text{O}_3$, 496; found, 496.

[0317] Step 2: The title compound was prepared from above obtained step 1 product (100 mg, 0.2 mmol) as described for Example 1 to give an off-white solid (100% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 9.53 (s, 1H), 8.52 (s, 1H), 7.62 (m, 10H), 4.09 (m, 5H), 2.93 (m, 2H), 2.21 – 0.51 (m, 19H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{25}\text{H}_{37}\text{N}_3\text{O}$, 396; found, 396.

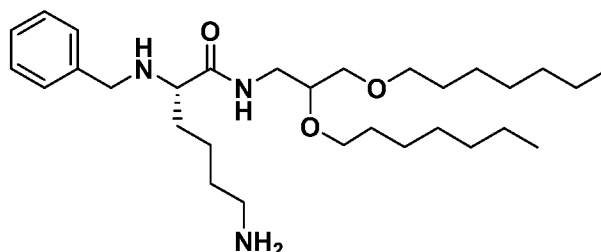
Example 124: (S)-6-amino-N-methyl-2-((naphthalen-2-ylmethyl)amino)hexanamide dihydrochloride



[0318] Step 1: tert-butyl (S)-6-((2-cyclohexylethyl)amino)-5-((naphthalen-2-ylmethyl)amino)-6-oxohexylcarbamate: The title compound was prepared from N⁶-(tert-butoxycarbonyl)-N²-(naphthalen-2-ylmethyl)-L-lysine (193 mg, 0.5 mmol) and methylamine hydrochloride (34 mg, 0.5 mmol) as described for Example 33 to give the title compound as semi solid (156 mg, 78% yield). ESI-MS m/z $[M+H]^+$ calc'd for $C_{23}H_{33}N_3O_3$, 400; found, 400.

[0319] Step 2: The title compound was prepared from above obtained step 1 product (80 mg, 0.2 mmol) as described for Example 1 to give an off-white gummy solid (100% yield). ^1H NMR (500 MHz, $DMSO-d_6$) δ 9.85 (s, 1H), 9.35 (s, 1H), 8.63 (q, $J = 4.7$ Hz, 1H), 8.14 – 7.80 (m, 7H), 7.79 – 7.39 (m, 3H), 4.22 (q, $J = 13.1$ Hz, 2H), 3.88 – 3.36 (m, 1H), 2.79 – 2.70 (m, 2H), 2.50 (s, 3H), 2.10 – 1.06 (m, 6H).; ESI-MS m/z $[M+H]^+$ calc'd for $C_{18}H_{25}N_3O$, 300; found, 300.

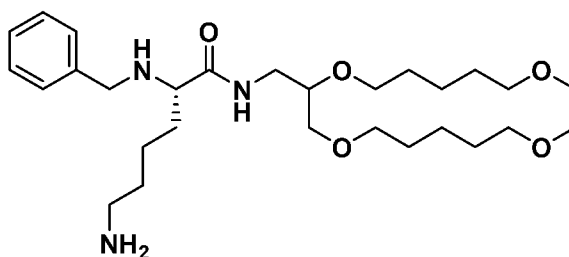
Example 125: (2S)-6-amino-2-(benzylamino)-N-(2,3-bis(heptyloxy)propyl)hexanamide dihydrochloride



[0320] Step 1: tert-butyl ((5S)-5-(benzylamino)-6-((2,3-bis(heptyloxy)propyl)amino)-6-oxohexyl) carbamate: The title compound was prepared from N²-benzyl-N⁶-(tert-butoxycarbonyl)-L-lysine (400 mg, 1.19 mmol) and 2,3-bis(heptyloxy)propan-1-amine (347 mg, 1.19 mmol) as described for Step 3 of Example 93 to give the title compound as semi solid (370 mg, 51% yield). ESI-MS m/z $[M+H]^+$ calc'd for $C_{35}H_{63}N_3O_5$, 606; found, 606.

[0321] Step 2: The above compound was dissolved in methanol (2 mL) and methanolic HCl (10 mL) was added and stirred at room temperature for 3 hours and the solvent was concentrated to dryness under vacuum gave title compound (100% yield). ^1H NMR (300 MHz, DMSO- d_6) δ ppm: 10.0 (br s, 1H), 9.4-9.2 (br s, 1H), 8.8-8.6 (s, 1H), 8.0 (s, 3H), 7.6-7.3 (m, 5H), 4.0 (s, 2H), 3.8-3.6 (s, 1H), 3.6-3.2 (m, 10H), 3.2 (m, 1H), 2.8-2.6 (m, 2H), 2.0-1.7 (m, 2H), 1.6-1.4 (m, 4H), 1.4-1.0 (m, 18H), 0.8 (m, 6H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{30}\text{H}_{55}\text{N}_3\text{O}_3$, 506; found, 506.

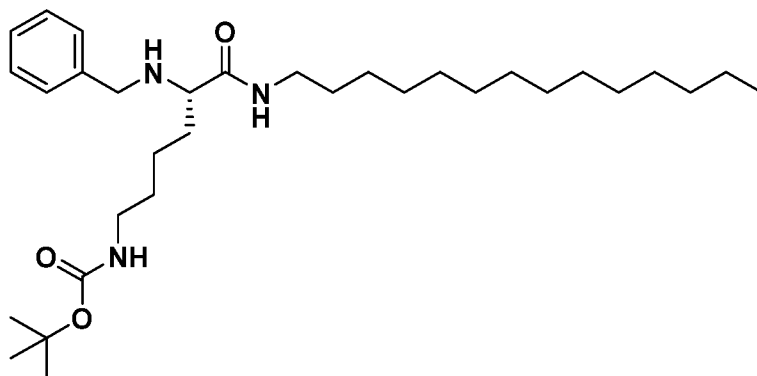
Example 126: (2S)-6-amino-2-(benzylamino)-N-(2,3-bis((5-methoxypentyl)oxy)propyl)hexanamide dihydrochloride



[0322] Step 1: tert-butyl ((5S)-5-(benzylamino)-6-((2,3-bis((5-methoxypentyl)oxy)propyl)amino)-6-oxohexyl)carbamate: The title compound was prepared from N^2 -benzyl- N^6 -(tert-butoxycarbonyl)-L-lysine (400 mg, 1.19 mmol) and 2,3-bis (5-methoxypentyl)oxy) propan-1-amine.HCl (476 mg, 1.637 mmol) as described for Step 3 of Example 93 to give the title compound as semi solid (400 mg, 55% yield). ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{33}\text{H}_{59}\text{N}_3\text{O}_7$, 610; found, 610.

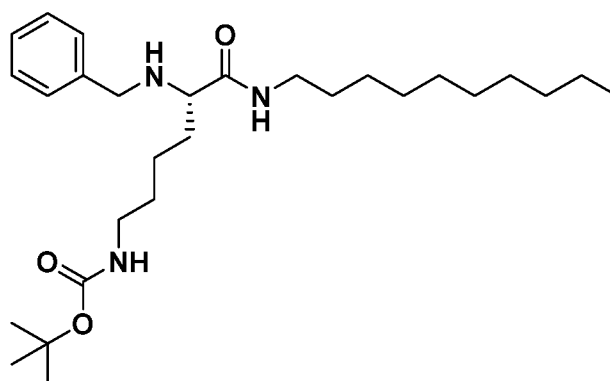
[0323] Step 2: The above compound was dissolved in methanol (2 mL) and methanolic HCl (10 mL) was added and stirred at room temperature for 3h and the solvent was concentrated to dryness under vacuum gave title compound (100% yield). ^1H NMR (300 MHz, DMSO- d_6) δ ppm: 10.0-9.8 (br s, 1H), 9.3 (br s, 1H), 8.7 (s, 1H), 8.0 (s, 3H), 7.6-7.3 (m, 5H), 4.0 (s, 2H), 3.8-3.7 (s, 1H), 3.6-3.3 (m, 11H), 3.0 (s, 6H), 2.8-2.6 (m, 2H), 2.0-1.7 (m, 2H), 1.6-1.3 (m, 18H).; ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{28}\text{H}_{51}\text{N}_3\text{O}_5$, 510; found, 510.

Example 127: tert-butyl (S)-(5-(benzylamino)-6-oxo-6-(tetradecylamino)hexyl)carbamate



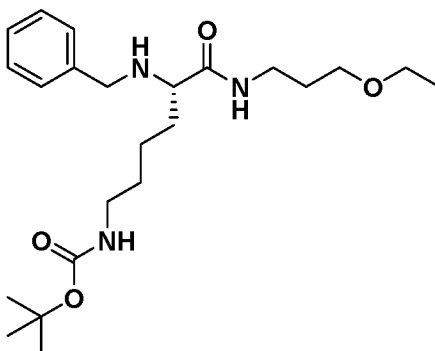
[0324] The title compound was prepared from N²-benzyl-N⁶-(tert-butoxycarbonyl)-L-lysine (168 mg, 0.5 mmol) and tetradecan-1-amine (107 mg, 0.5 mmol) as described for Example 33 to give the title compound as gummy solid (155 mg, 58% yield). ESI-MS m/z [M+H]⁺ calc'd for C₃₂H₅₇N₃O₃, 532; found, 532.

Example 128: tert-butyl (S)-5-(benzylamino)-6-(decylamino)-6-oxohexylcarbamate



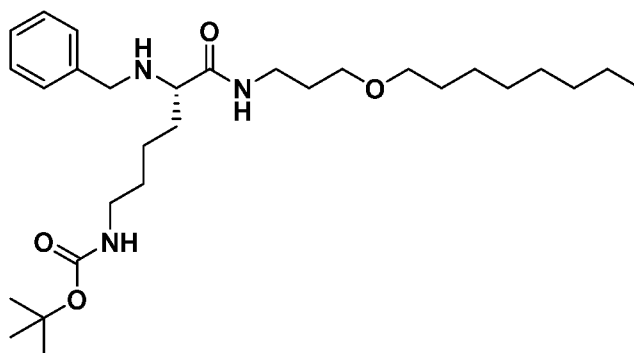
[0325] The title compound was prepared from N²-benzyl-N⁶-(tert-butoxycarbonyl)-L-lysine (168 mg, 0.5 mmol) and decyl-1-amine (79 mg, 0.5 mmol) as described for Example 33 to give the title compound as semi solid (158 mg, 66% yield). ESI-MS m/z [M+H]⁺ calc'd for C₂₈H₄₉N₃O₃, 476; found, 476.

Example 129: tert-butyl (S)-5-(benzylamino)-6-((3-ethoxypropyl)amino)-6-oxohexylcarbamate



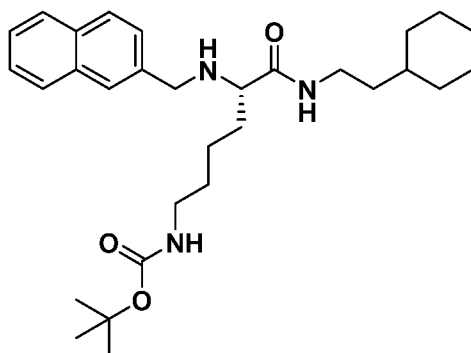
[0326] The title compound was prepared from N²-benzyl-N⁶-(tert-butoxycarbonyl)-L-lysine (168 mg, 0.5 mmol) and 3-ethoxypropan-1-amine (52 mg, 0.5 mmol) as described for Example 33 to give the title compound as semi solid (153 mg, 73% yield). ESI-MS m/z [M+H]⁺ calc'd for C₂₃H₃₉N₃O₄, 422; found, 422.

Example 130: tert-butyl (S)-5-(benzylamino)-6-((3-(octyloxy)propyl)amino)-6-oxohexyl)carbamate



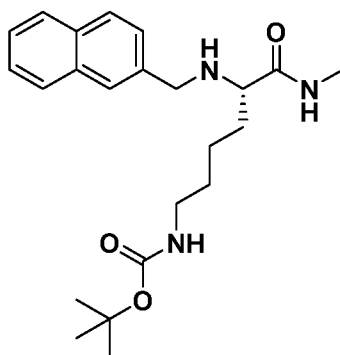
[0327] The title compound was prepared from N²-benzyl-N⁶-(tert-butoxycarbonyl)-L-lysine (168 mg, 0.5 mmol) and 3 3-(octyloxy)propan-1-amine (112 mg, 0.5 mmol) as described for Example 33 to give the title compound as semi solid (172 mg, 68% yield). ESI-MS m/z [M+H]⁺ calc'd for C₂₉H₅₁N₃O₄, 506; found, 506.

Example 131: tert-butyl (S)-6-((2-cyclohexylethyl)amino)-5-((naphthalen-2-ylmethyl)amino)-6-oxohexyl)carbamate



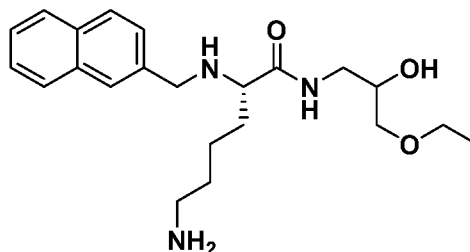
[0328] The title compound was prepared from N6-(tert-butoxycarbonyl)-N2-(naphthalen-2-ylmethyl)-L-lysine (193 mg, 0.5 mmol) and 2-cyclohexylethan-1-amine (82 mg, 0.5 mmol) as described for Example 33 to give the title compound as semi solid (182 mg, 73% yield). ESI-MS m/z $[M+H]^+$ calc'd for $C_{30}H_{45}N_3O_3$, 496; found, 496.

Example 132: tert-butyl (S)-6-((2-cyclohexylethyl)amino)-5-((naphthalen-2-ylmethyl)amino)-6-oxohexyl)carbamate



[0329] The title compound was prepared from N6-(tert-butoxycarbonyl)-N2-(naphthalen-2-ylmethyl)-L-lysine (193 mg, 0.5 mmol) and methylamine hydrochloride (34 mg, 0.5 mmol) as described for Example 33 to give the title compound as semi solid (156 mg, 78% yield). ESI-MS m/z $[M+H]^+$ calc'd for $C_{23}H_{33}N_3O_3$, 400; found, 400.

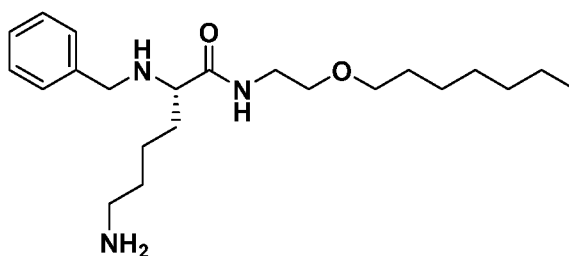
Example 133: (2S)-6-amino-N-(3-ethoxy-2-hydroxypropyl)-2-((naphthalen-2-ylmethyl)amino)hexanamide dihydrochloride



[0330] Step 1: tert-butyl ((5S)-6-(((3-ethoxy-2-hydroxypropyl)amino)-5-((naphthalen-2-ylmethyl)amino)-6-oxohexyl)carbamate: The title compound was prepared from N⁶-(tert-butoxycarbonyl)-N²-(naphthalen-2-ylmethyl)-L-lysine (synthesized as in Example 56) (194 mg, 0.5 mmol) and 1-amino-3-ethoxypropan-2-ol (60 mg, 0.5 mmol) as described for Example 33 to give the title compound as yellow liquid (173 mg, 71% yield). ESI-MS m/z $[M+H]^+$ calc'd for C₂₇H₄₁N₃O₅, 488; found, 488.

[0331] Step 2: The title compound was prepared from above obtained step 1 product (98 mg, 0.2 mmol) as described for step 2 of Example 1 to give a yellow solid (100% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.76 (s, 1H), 9.34 (s, 1H), 8.63 (s, 1H), 8.12 – 7.78 (m, 8H), 7.76 – 7.38 (m, 3H), 4.21 (s, 2H), 4.05 – 3.62 (m, 3H), 3.53 – 3.22 (m, 6H), 3.09 (td, J = 13.8, 7.1 Hz, 1H), 2.04 – 1.68 (m, 2H), 1.56 (q, J = 7.7 Hz, 2H), 1.35 (s, 2H), 1.12 (dd, J = 7.4, 6.5 Hz, 3H).; ESI-MS m/z $[M+H]^+$ calc'd for C₂₂H₃₃N₃O₃, 388; found, 388.

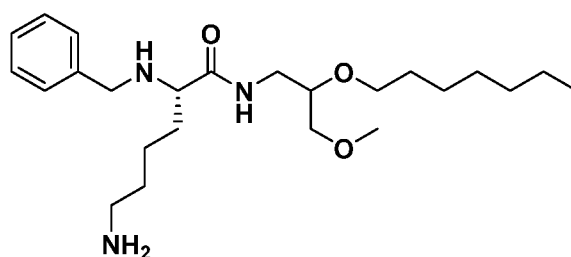
Example 134: (S)-6-amino-2-(benzylamino)-N-(2-(heptyloxy)ethyl)hexanamide dihydrochloride



[0332] Step 1: tert-butyl (S)-(5-(benzylamino)-6-((2-(heptyloxy)ethyl)amino)-6-oxohexyl)carbamate: Title compound was prepared from (S)-2-(benzylamino)-6-(tert-butoxycarbonylamino)hexanoic acid (400 mg, 1.19 mmol) and 2-(heptyloxy) ethanamine (189 mg, 1.19 mmol) as described for Step 3 of Example 93 to give the title compound as semi solid (380 mg, 67% yield). ESI-MS m/z $[M+H]^+$ calc'd for C₂₇H₄₇N₃O₄, 478; found, 478.

[0333] Step 2: The above compound was dissolved in methanol (2 mL) and methanolic HCl (10 mL) was added and stirred at room temperature for 3h and the solvent was evaporated to dryness gave title compound (100% yield). ¹H NMR (300 MHz, DMSO-d₆) δ 10.0 (br s, 1H), 9.3 (br s, 1H), 8.8 (s, 1H), 8.1 (s, 2H), 7.6-7.3 (m, 5H), 4.0 (s, 2H), 3.7 (s, 1H), 3.5-3.2 (m, 6H), 2.8-2.6 (m, 2H), 1.9-1.4 (m, 8H), 1.4-1.0 (m, 8H), 0.9-0.7 (m, 3H).; ESI-MS m/z [M+H]⁺ calc'd for C₂₂H₃₉N₃O₂, 378; found, 378.

Example 135: (2S)-6-amino-2-(benzylamino)-N-(2-(heptyloxy)-3-methoxypropyl)hexanamide dihydrochloride

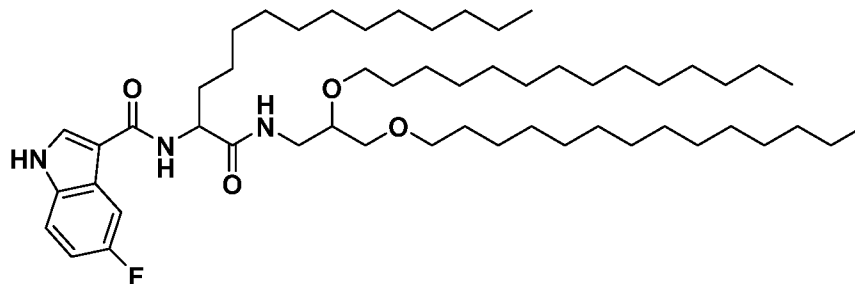


[0334] Step 1: tert-butyl ((5S)-5-(benzylamino)-6-((2-(heptyloxy)-3-methoxypropyl)amino)-6-oxohexyl)carbamate: Title compound was prepared from (S)-2-(benzylamino)-6-(tert-butoxycarbonylamino)hexanoic acid (400 mg, 1.19 mmol) and 2-(heptyloxy)3-methoxypropan-1-amine hydrochloride (241 mg, 1.19 mmol) as described for Step 3 of Example 93 to give the title compound as semi solid (350 mg, 56% yield). ESI-MS m/z [M+H]⁺ calc'd for C₂₉H₅₁N₃O₅, 522; found, 522.

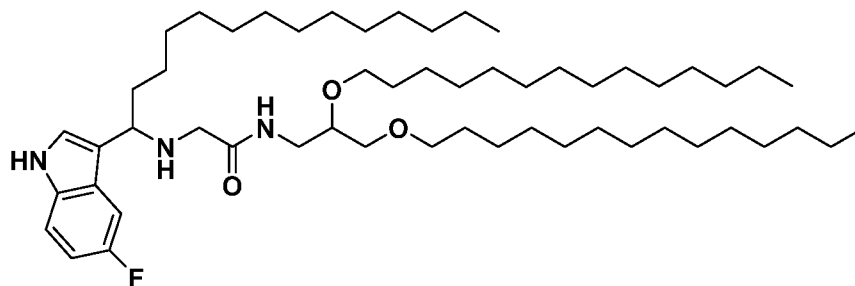
[0335] Step 2: The above compound was dissolved in methanol (2 mL) and methanolic HCl (10 mL) was added and stirred at room temperature for 3h and the solvent was evaporated to dryness gave title compound (100% yield). ¹H NMR (300 MHz, DMSO-d₆) δ 9.7 (br s, 1H), 9.3 (br s, 1H), 8.7 (s, 1H), 8.0-7.8 (s, 2H), 7.6-7.3 (m, 5H), 4.0 (s, 2H), 3.8-3.6 (s, 1H), 3.5-3.2 (m, 8H), 2.8-2.6 (m, 3H), 2.9-2.7 (m, 2H), 1.6-1.4 (m, 4H), 1.4-1.1 (m, 12H), 0.9-0.7 (m, 3H).; ESI-MS m/z [M+H]⁺ calc'd for C₂₄H₄₃N₃O₃, 422; found, 422.

[0336] The following compounds may be prepared using methods analogous to those described herein.

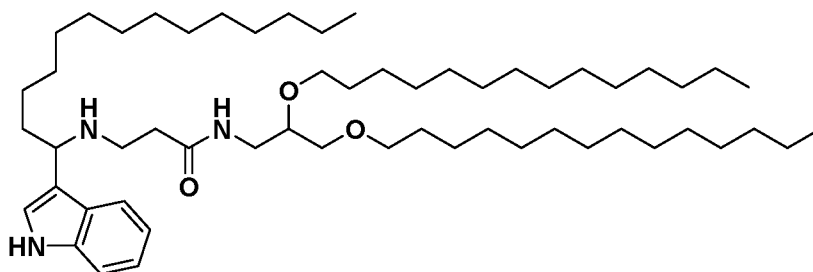
Example 136: N-(1-((2,3-Bis(tetradecyloxy)propyl)amino)-1-oxotetradecan-2-yl)-5-fluoro-1H-indole-3-carboxamide.



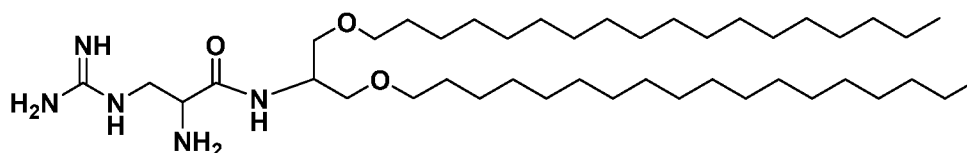
Example 137: N-(2,3-Bis(tetradecyloxy)propyl)-2-((1-(5-fluoro-1H-indol-3-yl)tetradecyl)amino)acetamide.



Example 138: 3-((1-(1H-Indol-3-yl)tetradecyl)amino)-N-(2,3-bis(tetradecyloxy)propyl)propanamide.

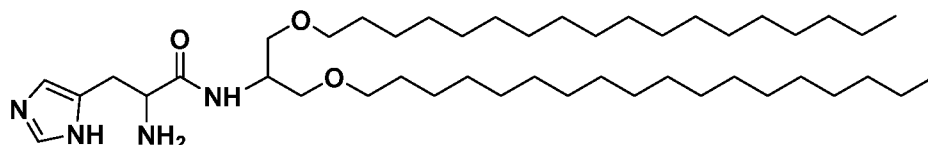


Example 139: 2-Amino-N-(1,3-bis(octadecyloxy)propan-2-yl)-3-guanidinopropanamide.

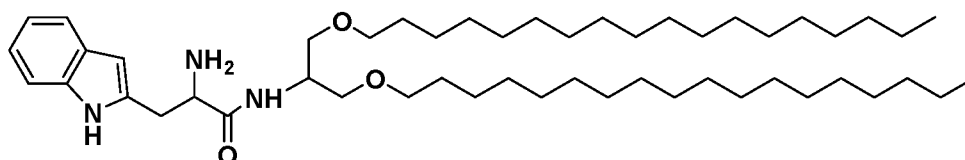


[0337] The title compound may be prepared from 1,3-bis(octadecyloxy)propan-2-amine using methods analogous to those described herein.

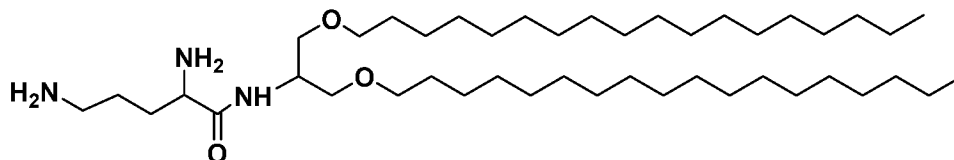
Example 140: 2-Amino-N-(1,3-bis(octadecyloxy)propan-2-yl)-3-(1H-imidazol-5-yl)propanamide.



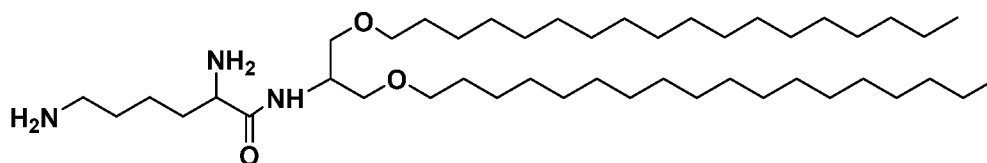
Example 141: 2-Amino-N-(1,3-bis(octadecyloxy)propan-2-yl)-3-(1H-indol-2-yl)propanamide.



Example 142: 2,5-Diamino-N-(1,3-bis(octadecyloxy)propan-2-yl)pentanamide.



Example 143: 2,6-Diamino-N-(1,3-bis(octadecyloxy)propan-2-yl)hexanamide.



Biological Example 1: Preparation of liposomal formations.

[0338] Eight milligrams of Example 13 was dissolved in 1 mL of chloroform. The resulting colorless clear solution was evaporated using a Bueche rotovap apparatus under reduced pressure at 40 °C.

[0339] To the resulting uniform nearly-clear coating on the glass walls was added 1 mL of 1X PBS buffer at pH 7.3. The vial was vortexed for 3 min, resulting in a turbid suspension of the liposome. The vial was then immersed in a sonication bath for 3 min, followed by probe sonication at 5 second intervals repeatedly five times. The translucent solution was then extruded through a 100 nm membrane filter repeatedly 10 times, and the nearly clear solution was stored at 4 °C. Differential light scattering of this solution using a Wyatt (dynapro) apparatus showed the average particle size to be 120 nm with a dispersion factor of 0.15.

[0340] This procedure can be used to create liposomal formulations with mixtures of other nonactive lipids such as those sold commercially (Avantis polar lipids).

Biological Example 2: In vitro Assay

[0341] Synthetic diacylated lipoprotein (Pam2CSK4, TLR2/6 agonist) and synthetic triacylated lipoprotein (Pam3CSK4, TLR1/2 agonist) were obtained from InvivoGen and were dissolved in endotoxin-free water to a concentration 1 mg/mL, vortexed until complete solubilization, and stored in aliquots at -20 °C. TNF α was obtained from Thermo Fisher Scientific and was used as a counter-screen for specificity to TLR signaling. It was dissolved in endotoxin-free water to a concentration 0.2 mg/mL, and stored in aliquots at -20°C. Prior to addition to cells, an aliquot of the dissolved ligand was vortexed shortly and then was diluted in medium to 25 ng/mL Pam2CSK4, 1000 ng/mL Pam3CSK4 or TNF α . The final top concentration used to determine the agonist EC₅₀ for each assay run was 5 ng/mL (Pam2CSK4) or 200 ng/mL (Pam3CSK4 or TNF α).

[0342] Test compounds were solubilized fresh to 3 - 10 mM stocks in 50% DMSO/50% EtOH and sonicated for 5-10 minutes in a water bath sonicator. Serial dilutions were prepared in 50% DMSO/50% EtOH, and then diluted in medium. The final concentration of DMSO used in the assay was 0.5%, and the final concentration of EtOH was 0.5%.

[0343] HEK-Blue hTLR2 reporter cells (InvivoGen) are HEK-293 cells stably expressing both the human TLR2 gene and a secreted embryonic alkaline phosphatase (SEAP) reporter construct downstream of NF κ B promoter sites. HEK-Blue hTLR2 reporters were cultured according to manufacturer's protocol using Dulbecco's Modified Eagle Medium (DMEM;

Gibco) containing 1X GlutaMax (Gibco), 10% heat-inactivated Fetal Bovine Serum (Gibco), Pen-Strep (50 U/mL penicillin, 50 µg/mL streptomycin, Gibco), 100 µg/mL Normocin (InvivoGen), and the selective antibiotic, 1x HEK-Blue Selection (InvivoGen). Quanti-Blue reagent (InvivoGen) for detection and quantification of secreted alkaline phosphatase was dissolved in 100 mL of endotoxin-free water, warmed to 37 °C for 30 minutes and then filtered using a 0.2 µm membrane.

HEK-Blue hTLR2 antagonism assay

[0344] On day 1, 50 µL of each test compound dilution in duplicates or a vehicle control was added to each well of a 96-well plate followed by addition of 150 µL of HEK-Blue hTLR2 cell suspension (1×10^5 cells/well) and incubated at 37 °C/5% CO₂ for 2 h. Next, 50 µL of an approximate EC₅₀ concentration of each agonist (Pam2CSK4, Pam3CSK4, or TNFα) was added to the wells containing test compounds or the vehicle control. The plates were then incubated at 37 °C/5% CO₂ for 18 h. For each assay run, non-treated HEK-Blue hTLR2 cells were treated with serial dilutions of agonists to determine EC₅₀ values for the respective run.

[0345] On day 2, secreted alkaline phosphatase (SEAP) activity was detected in cell culture supernatants. In brief, 20 µL was collected from each well and transferred to a 96-well plate. Next, 200 µL of Quanti-Blue detection reagent was added to each well. Plates were incubated at room temperature for 15 min and SEAP activity was assessed by spectrophotometer OD reading at 655 nm. Table 7 shows the activities of the compounds against Pam2CSK4, Pam3CSK4, and TNFα. The activities of the compounds against Pam2CSK4 and Pam3CSK4 are presented as IC₅₀ values for the response from cells treated with agonists with the background signal subtracted. The compound of Example 93 displayed an IC₅₀ of 10 µM against TNFα. The activities of all other compounds against TNFα are shown in Table 7 and are denoted as (+) for IC₅₀ values ≤ 30 µM and (-) for IC₅₀ values > 30 µM.

Table 7:

Example	IC ₅₀ (µM) with Pam2CSK4	IC ₅₀ (µM) with Pam3CSK4	TNFα activity
1	>30	>30	(-)
2	>30	>30	(-)
3	>30	>30	(-)

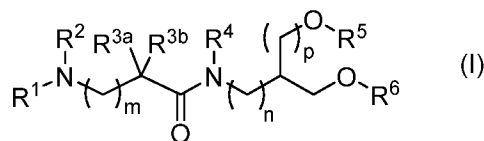
4	>30	19.3	(-)
5	>30	>30	(-)
6	>30	9.2	(-)
7	>30	>30	(-)
8	>30	>30	(-)
9	>30	>30	(-)
10	>30	1.6	(-)
11	>30	>30	(-)
12	>30	>30	(-)
13	>30	>30	(-)
14	>30	>30	(-)
15	>30	>30	(-)
16	>30	>30	(-)
17	>30	14.3	(-)
18	>30	>30	(-)
19	>30	>30	(-)
20	>30	12.6	(-)
21	>30	>30	(-)
22	>30	6.2	(-)
23	>30	>30	(-)
24	>30	>30	(-)
25	>30	>30	(-)
26	>30	11.4	(-)
27	>30	>30	(-)
28	>30	26.3	(-)
29	>30	>30	(-)
30	13.3	15.3	(-)
31	>30	>30	(-)
32	>30	2.3	(-)
33	>30	>30	(-)
34	>30	>30	(-)
35	>30	>30	(-)
36	>30	>30	(-)
37	>30	>30	(-)
38	18	11.2	(-)
39	>30	>30	(-)
40	19.6	4.9	(-)
41	>30	>30	(-)
42	>30	>30	(-)
43	>30	>30	(-)
44	>30	18	(-)
45	>30	>30	(-)
46	>30	11	(+)

47	>30	12	(-)
48	>30	>30	(-)
49	>30	4.5	(-)
50	>30	>30	(-)
51	17	7.1	(-)
52	>30	>30	(-)
53	16.7	1.8	(-)
54	>30	>30	(-)
55	>30	2.6	(-)
56	>30	>30	(-)
57	27.9	2.8	(-)
58	>30	>30	(-)
59	>30	2.9	(-)
60	>30	>30	(-)
61	>30	0.2	(-)
62	>30	>30	(-)
63	>30	0.3	(-)
64	>30	>30	(-)
65	>30	3.4	(-)
66	>30	>30	(-)
67	>30	3.7	(-)
68	>30	>30	(-)
69	14.3	12.4	(+)
70	>30	>30	(-)
71	8.4	7.4	(+)
72	>30	>30	(-)
73	>30	0.9	(-)
74	>30	>30	(-)
75	>30	2.5	(-)
77	>30	2.1	(+)
78	>30	>30	(-)
79	>30	2.9	(-)
80	>30	>30	(-)
81	>30	6.6	(-)
82	>30	>30	(-)
83	>30	0.2	(-)
85	>30	3.6	(-)
86	>30	>30	(-)
87	>30	7.7	(-)
88	>30	>30	(-)
89	>30	12.5	(-)
90	>30	>30	(-)
91	>30	5.5	(-)

92	22.2	3.9	(-)
93	12.0	10.0	(+)
94	>30	>30	(-)
95	11.8	13.0	(+)
96	14.3	21.0	(+)
97	>30	>30	(-)
98	11.0	13.1	(+)
99	13.0	13.0	(+)
100	11.8	11.9	(+)
101	10.2	10.9	(+)
102	>30	>30	(-)
103	>30	>30	(-)
104	>30	>30	(-)
105	>30	2.8	(-)
106	>30	3.9	(+)
107	>30	>30	(-)
108	9.1	1.8	(+)
109)	>30	2.1	(-)
110	>30	30	(-)
111	>30	>30	(-)
112	>30	10.1	(-)
114	16.9	18.5	(+)
115	>30	>30	(-)
116	16.1	3.3	(+)
117	>30	>30	(-)
118	10.7	2.8	(-)
119	11.3	14.1	(+)
120	10.9	15.0	(+)
121	>30	>30	(-)
122	13.4	15.9	(+)
123	10.9	11.7	(+)
124	>30	>30	(-)
125	4.9	7.0	(+)
126	>30	>30	(-)
127	20.1	25.3	(+)
128	29.1	>30	(+)
129	>30	>30	(-)
130	>30	>30	(-)
131	>30	>30	(-)
132	>30	>30	(-)
133	>30	>30	(-)
134	13.7	22.6	(+)
135	>30	>30	(+)

Claims

1. A compound of Formula (I):



wherein

R^1 is H, $-\text{CO}_2\text{-C}_{1-8}\text{alkyl}$, $-\text{CO}_2\text{-CHR}^a\text{-aryl}$, $-\text{CO}_2\text{-CHR}^a\text{-heteroaryl}$, $-\text{C(O)-C}_{1-4}\text{alkyl}$, $-\text{C(O)aryl}$, $-\text{C(O)-heteroaryl}$, $-\text{C(O)-CHR}^b\text{-NR}^c\text{R}^d$, $-\text{C(O)-CHR}^a\text{-heteroaryl}$, $-\text{CHR}^a\text{-aryl}$, $-\text{CHR}^a\text{-heteroaryl}$, $-\text{SO}_2\text{-C}_{1-4}\text{alkyl}$, $-\text{SO}_2\text{-aryl}$, or $-\text{SO}_2\text{-heteroaryl}$;

wherein R^a is H or $\text{C}_{1-15}\text{alkyl}$;

R^b is H or $-\text{C}_{1-5}\text{alkyl-NR}^e\text{R}^f$;

where R^e is H or $\text{C}_{1-4}\text{alkyl}$ and R^f is H, $\text{C}_{1-4}\text{alkyl}$, or $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$;

R^c is H or $\text{C}_{1-4}\text{alkyl}$ and R^d is H, $\text{C}_{1-4}\text{alkyl}$, or $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$; and

each aryl or heteroaryl is optionally substituted with halo, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{fluoroalkyl}$, $-\text{OH}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{OC}_{1-4}\text{fluoroalkyl}$, $-\text{CN}$, phenyl, $-\text{OC}_{1-4}\text{alkyl-aryl}$, or $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$;

R^2 is H or $\text{C}_{1-4}\text{alkyl}$;

R^{3a} is H, $-\text{C}_{6-14}\text{alkyl}$, $-\text{CHR}^g\text{-aryl}$, $-\text{CHR}^g\text{-heteroaryl}$, $-\text{CHR}^g\text{-heterocycloalkyl}$, $-\text{C}_{1-4}\text{alkyl-NR}^h\text{R}^i$, $-\text{C}_{1-4}\text{alkyl-CO}_2\text{C}_{1-4}\text{alkyl}$, $-\text{C}_{1-4}\text{alkyl-CO}_2\text{H}$, or $-\text{C}_{1-4}\text{alkyl-CONR}^j\text{R}^k$;

R^g is H or $\text{C}_{1-4}\text{alkyl}$;

R^h is H, $\text{C}_{1-4}\text{alkyl}$, or $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$;

R^i is H, $\text{C}_{1-4}\text{alkyl}$, or $-\text{C(=NH)-NHR}^m$;

wherein R^m is H, $-\text{SO}_2\text{aryl}$, or $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$;

R^j is H or $\text{C}_{1-4}\text{alkyl}$; and

R^k is H or $\text{C}_{1-4}\text{alkyl}$;

and wherein each aryl, heteroaryl, and heterocycloalkyl is optionally substituted with $-\text{OH}$,

$\text{C}_{1-4}\text{alkyl}$, $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$, phenyl, or benzyloxy;

or R^2 and R^{3a} taken together with the atoms to which they are attached form $\text{C}_{2-4}\text{alkylene}$;

R^{3b} is H; or R^{3a} and R^{3b} taken together with the carbon to which they are attached form a 4- to 7-membered heterocycloalkyl, optionally substituted with $\text{C}_{1-4}\text{alkyl}$ or $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$;

R⁴ is H or C₁₋₄alkyl;

R⁵ is C₈₋₁₆alkyl or C₈₋₁₆alkenyl;

R⁶ is C₈₋₁₆alkyl or C₈₋₁₆alkenyl;

m is 0 or 1;

n is 0 or 1; and

p is 0 or 1;

wherein at least one of n and p is 1;

or a pharmaceutically acceptable salt thereof;

provided that the compound is not a compound of Table 1x, or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is H, -CO₂-C₁₋₈alkyl, -CO₂-CHR^a-aryl, -CO₂-CHR^a-heteroaryl, -C(O)-C₁₋₄alkyl, -C(O)aryl, -C(O)-heteroaryl, -C(O)-CHR^b-NR^cR^d, -C(O)-CHR^a-heteroaryl, -CHR^a-aryl, -CHR^a-heteroaryl, -SO₂-C₁₋₄alkyl, -SO₂-aryl, or -SO₂-heteroaryl; or is H; or is -CO₂-C₁₋₈alkyl; or is -CO₂-CHR^a-aryl or -CO₂-CHR^a-heteroaryl; or is -C(O)-C₁₋₄alkyl, -C(O)aryl, or -C(O)-heteroaryl; or is -C(O)-CHR^b-NR^cR^d; or is -C(O)-CHR^a-heteroaryl; or is -CHR^a-aryl or -CHR^a-heteroaryl; or is -SO₂-C₁₋₄alkyl, -SO₂-aryl, or -SO₂-heteroaryl.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is H, -CO₂-CHR^a-aryl, -CO₂-CHR^a-heteroaryl, -C(O)-C₁₋₄alkyl, -C(O)aryl, -C(O)-heteroaryl, -C(O)-CHR^a-heteroaryl, -CHR^a-aryl, -CHR^a-heteroaryl, -SO₂-C₁₋₄alkyl, -SO₂-aryl, or -SO₂-heteroaryl.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein the R¹ aryl is phenyl; or the R¹ aryl is fluorenyl; or the R¹ heteroaryl is a bicyclic heteroaryl; or the R¹ heteroaryl is indolyl, benzofuranyl, benzothiophenyl, benzoxazolyl, or benzothiazolyl; or the R¹ heteroaryl is indolyl.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein the R¹ aryl or heteroaryl is unsubstituted; or the R¹ aryl or heteroaryl is substituted with

one or more substituents independently selected from the group consisting of halo, C₁₋₄alkyl, C₁₋₄fluoroalkyl, -OH, -OC₁₋₄alkyl, -OC₁₋₄fluoroalkyl, -CN, phenyl, and -OC₁₋₄alkyl-aryl; or the R¹ aryl or heteroaryl is substituted with methyl, fluoro, phenyl, benzyloxy, or tert-butyloxycarbonyl.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R¹ is -CO₂-CH₂-fluorenyl, acetyl, or carbobenzyloxy; or R¹ is tert-butyloxycarbonyl; or R¹ is substituted or unsubstituted benzyl; or R¹ is benzyl substituted with halo or phenyl.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^a is H; or R^a is C₁₋₁₅alkyl; or R^a is C₁₀₋₁₅alkyl.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R^b is H; or R^b is -C₁₋₅alkyl-NR^eR^f.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^e is H; or R^e is C₁₋₄alkyl.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^f is H; or R^f is C₁₋₄alkyl; or R^f is -CO₂C₁₋₄alkyl.

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^c is H; or R^c is C₁₋₄alkyl.

12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^d is H; or R^d is C₁₋₄alkyl; or R^d is -CO₂C₁₋₄alkyl.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R² is H; or R² is C₁₋₄alkyl.

14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are both hydrogen.

15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is H; or R^{3a} is $-C_{6-14}$ alkyl; or R^{3a} is $-CHR^g$ -aryl, $-CHR^g$ -heteroaryl, or $-CHR^g$ -heterocycloalkyl; or R^{3a} is $-C_{1-4}$ alkyl- NR^hR^i ; or R^{3a} is $-C_{1-4}$ alkyl- CO_2C_{1-4} alkyl, $-C_{1-4}$ alkyl- CO_2H , or $-C_{1-4}$ alkyl- $CONR^jR^k$. In some embodiments, R^{3a} is substituted or unsubstituted $-CH_2$ -phenyl; or R^{3a} is $-CH_2$ -phenyl substituted with benzyloxy, hydroxyl, or phenyl; or R^{3a} is $-CH_2$ -imidazolyl, optionally substituted with tert-butoxycarbonyl; or R^{3a} is $-CH_2$ -indolyl; or R^{3a} is $-CH_2$ -piperidine, optionally substituted with tert-butoxycarbonyl; or R^{3a} is butylamine, optionally substituted with tert-butoxycarbonyl; or R^{3a} is propylamine, optionally substituted with guanidynyl, wherein the guanidynyl is optionally substituted; or R^{3a} is carboxyethyl, optionally substituted with tert-butyl; or R^{3a} is carboxymethyl, optionally substituted with tert-butyl.

16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein the R^{3a} aryl is phenyl; or the R^{3a} heteroaryl is pyrrolyl, imidazolyl, indolyl, or benzimidazolyl; or the R^{3a} heteroaryl is pyrrolyl or indolyl; or the R^{3a} heterocycloalkyl is a monocyclic heterocycloalkyl; or the R^{3a} heterocycloalkyl is pyrrolidinyl or piperazinyl; or the R^{3a} aryl, heteroaryl, and heterocycloalkyl are unsubstituted; or the R^{3a} aryl, heteroaryl, and heterocycloalkyl are substituted with $-OH$, C_{1-4} alkyl, or $-CO_2C_{1-4}$ alkyl; or the R^{3a} aryl and heteroaryl are optionally substituted with phenyl or benzyloxy.

17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^g is H; or R^g is C_{1-4} alkyl.

18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein R^h is H; or R^h is C_{1-4} alkyl; or R^h is $-CO_2C_{1-4}$ alkyl.

19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein R^i is H; or R^i is C_{1-4} alkyl; or R^i is $-C(=NH)-NHR^m$.

20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^m is H; or R^m is $-\text{SO}_2\text{phenyl}$; or R^m is $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$.
21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein R^j is H; or R^j is $\text{C}_{1-4}\text{alkyl}$.
22. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein R^k is H; or R^k is $\text{C}_{1-4}\text{alkyl}$.
23. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^{3a} taken together form $\text{C}_{2-4}\text{alkylene}$; or R^2 and R^{3a} taken together form $\text{C}_3\text{alkylene}$.
24. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein R^{3b} is H; or R^{3a} and R^{3b} taken together with the carbon to which they are attached form a 4- to 7-membered heterocycloalkyl, optionally substituted with $\text{C}_{1-4}\text{alkyl}$ or $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$.
25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{3b} are both hydrogen.
26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein R^4 is H; or R^4 is $\text{C}_{1-4}\text{alkyl}$.
27. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, wherein R^5 and R^6 are each independently $\text{C}_{8-16}\text{alkyl}$ or $\text{C}_{8-16}\text{alkenyl}$; or R^5 and R^6 are each independently $\text{C}_{8-16}\text{alkyl}$; or R^5 and R^6 are the same; or R^5 and R^6 are different; or R^5 and R^6 are unbranched hydrocarbons; or R^5 and R^6 are each $\text{C}_{14}\text{alkyl}$.

28. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein R^5 and R^6 are each independently C_{13-16} alkyl or C_{13-16} alkenyl.
29. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein R^5 and R^6 are each independently C_{8-11} alkyl, C_{13-16} alkyl, C_{8-11} alkenyl, or C_{13-16} alkenyl.
30. The compound of claim 29, wherein R^1 is H, $-\text{CO}_2\text{-C}_{1-8}$ alkyl, $-\text{CO}_2\text{-CHR}^a\text{-heteroaryl}$, $-\text{C(O)-C}_{1-4}$ alkyl, $-\text{C(O)aryl}$, $-\text{C(O)-heteroaryl}$, $-\text{C(O)-CHR}^b\text{-NR}^c\text{R}^d$, $-\text{C(O)-CHR}^a\text{-heteroaryl}$, $-\text{CHR}^a\text{-aryl}$, $-\text{CHR}^a\text{-heteroaryl}$, $-\text{SO}_2\text{-C}_{1-4}$ alkyl, $-\text{SO}_2\text{-aryl}$, or $-\text{SO}_2\text{-heteroaryl}$.
31. The compound of claim 29 or 30, wherein R^{3a} is H, $-\text{C}_{6-14}$ alkyl, $-\text{CHR}^g\text{-aryl}$, $-\text{CHR}^g\text{-heterocycloalkyl}$, $-\text{C}_{1-4}$ alkyl- $\text{CO}_2\text{C}_{1-4}$ alkyl, $-\text{C}_{1-4}$ alkyl- CO_2H , or $-\text{C}_{1-4}$ alkyl- CONR^jR^k ;
32. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein R^5 and R^6 are each independently C_{14} alkyl or C_{14} alkenyl.
33. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt thereof, wherein m is 0; or m is 1.
34. The compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, wherein n is 0; or n is 1.
35. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt thereof, wherein p is 0; or p is 1.
36. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, wherein n is 1 and p is 0; or n is 0 and p is 1.
37. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-\text{CO}_2\text{-C}_{1-8}$ alkyl or $-\text{C(O)-CHR}^b\text{-NR}^c\text{R}^d$, and R^{3a} is $-\text{C}_{6-14}$ alkyl, $-\text{CHR}^g\text{-aryl}$, $-\text{CHR}^g\text{-heteroaryl}$, -

CHR^g-heterocycloalkyl, -C₁₋₄alkyl-NR^hRⁱ, -C₁₋₄alkyl-CO₂C₁₋₄alkyl, -C₁₋₄alkyl-CO₂H, or -C₁₋₄alkyl-CONR^jR^k.

38. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is -CO₂-C₁₋₈alkyl and m is 1.

39. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is -CO₂-C₁₋₈alkyl and R² is C₁₋₄alkyl.

40. A compound selected from the group consisting of:

tert-Butyl ((2S)-3-(4-(benzyloxy)phenyl)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxopropan-2-yl)carbamate;

(2S)-2-Amino-3-(4-(benzyloxy)phenyl)-N-(2,3-bis(tetradecyloxy)propyl)propanamide;

tert-Butyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate;

(2S)-2-Amino-N-(2,3-bis(tetradecyloxy)propyl)-3-(1H-indol-3-yl)propanamide;

tert-Butyl (2S)-2-((2,3-bis(tetradecyloxy)propyl)carbamoyl) pyrrolidine-1-carboxylate;

(2S)-N-(2,3-Bis(tetradecyloxy)propyl)pyrrolidine-2-carboxamide;

tert-Butyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate;

(2S)-2-Amino-N-(2,3-bis(tetradecyloxy)propyl)-3-(4-hydroxyphenyl)propanamide;

(9H-Fluoren-9-yl)methyl tert-butyl ((5S)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexane-1,5-diyl)dicarbamate;

(9H-Fluoren-9-yl)methyl ((2S)-6-amino-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxohexan-2-yl)carbamate;

(9H-Fluoren-9-yl)methyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate;

tert-Butyl ((2R)-1-((2,3-bis(tetradecyloxy)propyl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate;

(2R)-2-Amino-N-(2,3-bis(tetradecyloxy)propyl)-3-(1H-indol-3-yl)propanamide;

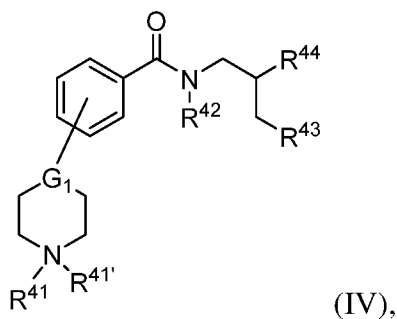
tert-Butyl (4S)-5-((2,3-bis(tetradecyloxy)propyl)amino)-4-((tert-butoxycarbonyl)amino)-5-oxopentanoate;
(4S)-4-Amino-5-((2,3-bis(tetradecyloxy)propyl)amino)-5-oxopentanoic acid;
tert-Butyl (2R)-2-((2,3-bis(tetradecyloxy)propyl)carbonyl)pyrrolidine-1-carboxylate;
(2R)-N-(2,3-Bis(tetradecyloxy)propyl)pyrrolidine-2-carboxamide;
N-(2,3-Bis(tetradecyloxy)propyl)-2-((4-methylphenyl)sulfonamido)acetamide;
tert-Butyl 4-((2S)-3-((2,3-bis(tetradecyloxy)propyl)amino)-2-((tert-butoxycarbonyl)amino)-3-oxopropyl)-1H-imidazole-1-carboxylate;
(2S)-2-Amino-N-(2,3-bis(tetradecyloxy)propyl)-3-(1H-imidazol-4-yl)propanamide;
tert-Butyl (3-((2,3-bis(tetradecyloxy)propyl)amino)-3-oxopropyl) carbamate;
3-Amino-N-(2,3-bis(tetradecyloxy)propyl)propanamide;
tert-Butyl (3S)-4-((2,3-bis(tetradecyloxy)propyl)amino)-3-((tert-butoxycarbonyl)amino)-4-oxobutanoate;
(3S)-3-Amino-4-((2,3-bis(tetradecyloxy)propyl)amino)-4-oxobutanoic acid;
tert-Butyl (2-((2,3-bis(tetradecyloxy)propyl)amino)-2-oxoethyl) (methyl)carbamate;
N-(2,3-bis(tetradecyloxy)propyl)-2-(methylamino)acetamide;
tert-Butyl (3S)-3-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-((2,3-bis(tetradecyloxy)propyl)amino)-4-oxobutanoate;
(3S)-3-(((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-4-((2,3-bis(tetradecyloxy)propyl)amino)-4-oxobutanoic acid;
tert-Butyl (4S)-4-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-((2,3-bis(tetradecyloxy)propyl)amino)-5-oxopentanoate;
(4S)-4-(((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-5-((2,3-bis(tetradecyloxy)propyl)amino)-5-oxopentanoic acid;
Benzyl tert-butyl ((5R)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexane-1,5-diyl)dicarbamate;
Benzyl ((2R)-6-amino-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxohexan-2-yl)carbamate;
tert-Butyl ((2R)-3-([1,1'-biphenyl]-4-yl)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxopropan-2-yl)carbamate;

(2R)-3-([1,1'-Biphenyl]-4-yl)-2-amino-N-(2,3-bis(tetradecyloxy)propyl)propanamide;
tert-Butyl ((2S)-3-([1,1'-biphenyl]-4-yl)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxopropan-2-yl)carbamate;
(2S)-3-([1,1'-Biphenyl]-4-yl)-2-amino-N-(2,3-bis(tetradecyloxy)propyl)propanamide;
Di-tert-butyl ((5S)-6-((2S)-2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)pyrrolidin-1-yl)-6-oxohexane-1,5-diyl)dicarbamate;
(2S)-1-(L-Lysyl)-N-(2,3-bis(tetradecyloxy)propyl)pyrrolidine-2-carboxamide;
tert-Butyl (2-((2S)-2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate;
(2S)-N-(2,3-Bis(tetradecyloxy)propyl)-1-glycylpyrrolidine-2-carboxamide;
3-(2-(5-(Benzyloxy)-1H-indol-3-yl)acetamido)-N-(2,3-bis(tetradecyloxy)propyl)propanamide;
(9H-Fluoren-9-yl)methyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxo-5-(3-tosylguanidino)pentan-2-yl)carbamate;
(9H-Fluoren-9-yl)methyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxo-5-(1,3-bis-(tert-butyloxy)guanidino)pentan-2-yl)carbamate;
(9H-Fluoren-9-yl)methyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-5-guanidino-1-oxopentan-2-yl)carbamate;
tert-Butyl ((2S)-1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxo-5-(3-tosylguanidino)pentan-2-yl)carbamate;
(2S)-2-Amino-N-(2,3-bis(tetradecyloxy)propyl)-5-(3-tosylguanidino)pentanamide;
tert-Butyl ((2S)-4-amino-1-((2,3-bis(tetradecyloxy)propyl)amino)-1,4-dioxobutan-2-yl)carbamate;
Di-tert-butyl ((5S)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexane-1,5-diyl)dicarbamate;
(2S)-2,6-Diamino-N-(2,3-bis(tetradecyloxy)propyl)hexanamide;
tert-Butyl ((5S)-5-acetamido-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexyl)carbamate;
(2S)-2-Acetamido-6-amino-N-(2,3-bis(tetradecyloxy)propyl)hexanamide;
tert-Butyl 4-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-((2,3-

bis(tetradecyloxy)propyl)amino)-3-oxopropyl)piperidine-1-carboxylate;
 (9H-Fluoren-9-yl)methyl (1-((2,3-bis(tetradecyloxy)propyl)amino)-1-oxo-3-(piperidin-4-yl)propan-2-yl)carbamate hydrochloride;
 tert-Butyl 4-(((benzyloxy)carbonyl)amino)-4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)piperidine-1-carboxylate;
 Benzyl (4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)piperidin-4-yl)carbamate;
 tert-Butyl ((5S)-5-([1,1'-biphenyl]-4-ylmethyl)amino)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexyl)carbamate;
 (2S)-2-([1,1'-Biphenyl]-4-ylmethyl)amino)-6-amino-N-(2,3-bis(tetradecyloxy)propyl)hexanamide;
 tert-Butyl ((5S)-6-((2,3-bis(tetradecyloxy)propyl)amino)-5-((4-fluorobenzyl)amino)-6-oxohexyl)carbamate;
 (2S)-6-Amino-N-(2,3-bis(tetradecyloxy)propyl)-2-((4-fluorobenzyl)amino)hexanamide;
 tert-Butyl ((5S)-5-(benzylamino)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexyl)carbamate;
 (2S)-6-Amino-2-(benzylamino)-N-(2,3-bis(tetradecyloxy)propyl)hexanamide;
 tert-Butyl ((5R)-5-(benzylamino)-6-((2,3-bis(tetradecyloxy)propyl)amino)-6-oxohexyl)carbamate;
 ((2R)-6-Amino-2-(benzylamino)-N-(2,3-bis(tetradecyloxy)propyl)hexanamide;
 tert-butyl 3-((((10S)-2,2-dimethyl-4,11-dioxo-14-(tetradecyloxy)-3,16-dioxo-5,12-diazatriacontan-10-yl)amino)methyl)-1H-indole-1-carboxylate;
 (2S)-2-(((1H-indol-3-yl)methyl)amino)-6-amino-N-(2,3-bis(tetradecyloxy)propyl)hexanamide dihydrochloride;
 tert-butyl 3-(2-((((10S)-2,2-dimethyl-4,11-dioxo-14-(tetradecyloxy)-3,16-dioxo-5,12-diazatriacontan-10-yl)amino)-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate;
 (2S)-6-amino-N-(2,3-bis(tetradecyloxy)propyl)-2-(2-(5-methoxy-1H-indol-3-yl)acetamido)hexanamide hydrochloride;
 tert-butyl 5-(benzyloxy)-3-(2-((((10S)-2,2-dimethyl-4,11-dioxo-14-(tetradecyloxy)-3,16-dioxo-5,12-diazatriacontan-10-yl)amino)-2-oxoethyl)-1H-indole-1-carboxylate;
 (2S)-6-amino-2-(2-(5-(benzyloxy)-1H-indol-3-yl)acetamido)-N-(2,3-

bis(tetradecyloxy)propyl)hexanamide hydrochloride;
 tert-butyl ((5S)-6-((2,3-bis(tetradecyloxy)propyl)amino)-5-((naphthalen-2-ylmethyl)amino)-6-oxohexyl)carbamate;
 (2S)-6-amino-N-(2,3-bis(tetradecyloxy)propyl)-2-((naphthalen-2-ylmethyl)amino)hexanamide dihydrochloride;
 N-(1-((2,3-Bis(tetradecyloxy)propyl)amino)-1-oxotetradecan-2-yl)-5-fluoro-1H-indole-3-carboxamide;
 N-(2,3-Bis(tetradecyloxy)propyl)-2-((1-(5-fluoro-1H-indol-3-yl)tetradecyl)amino)acetamide;
 3-((1-(1H-Indol-3-yl)tetradecyl)amino)-N-(2,3-bis(tetradecyloxy) propyl)propanamide;
 2-Amino-N-(1,3-bis(octadecyloxy)propan-2-yl)-3-guanidinopropanamide;
 2-Amino-N-(1,3-bis(octadecyloxy)propan-2-yl)-3-(1H-imidazol-5-yl)propanamide;
 2-Amino-N-(1,3-bis(octadecyloxy)propan-2-yl)-3-(1H-indol-2-yl)propanamide;
 2,5-Diamino-N-(1,3-bis(octadecyloxy)propan-2-yl)pentanamide; and
 2,6-Diamino-N-(1,3-bis(octadecyloxy)propan-2-yl)hexanamide,
 and pharmaceutically acceptable salts thereof.

41. A compound of Formula (IV):



wherein

G^1 is N or CH;

R^{41} is H, C_{1-4} alkyl, or $-CO_2C_{1-4}$ alkyl;

$R^{41'}$ is absent, H, or C_{1-4} alkyl; wherein when $R^{41'}$ is H or C_{1-4} alkyl, the nitrogen attached to $R^{41'}$ has a positive charge;

R^{42} is H or C_{1-4} alkyl;

R^{43} is $-OC_{1-18}alkyl$, $-OC_{1-18}alkenyl$, $-C_{1-18}alkyl$, or $-C_{1-18}alkenyl$, each optionally substituted with $-OH$, $-OC_{1-4}alkyl$, $-C(O)OH$, $-C(O)OC_{1-4}alkyl$, $-C(O)NHR^{4b}$, or aryl; and R^{44} is $-OC_{4-18}alkyl$ or $-OC_{4-18}alkenyl$, each optionally substituted with $-OH$, $-OC_{1-4}alkyl$, $-C(O)OC_{1-4}alkyl$, $-C(O)NHR^{4c}$, or aryl; wherein R^{4b} and R^{4c} are each independently H or $C_{1-4}alkyl$; or a pharmaceutically acceptable salt thereof.

42. The compound of claim 41, or a pharmaceutically acceptable salt thereof, wherein G^1 is N.

43. The compound of claim 41, or a pharmaceutically acceptable salt thereof, wherein G^1 is CH.

44. The compound of any one of claims 41-43, or a pharmaceutically acceptable salt thereof, wherein R^{41} is H, methyl, or tert-butyloxycarbonyl.

45. The compound of any one of claims 41-44, or a pharmaceutically acceptable salt thereof, wherein $R^{41'}$ is absent.

46. The compound of any one of claims 41-45, or a pharmaceutically acceptable salt thereof, wherein R^{42} is H.

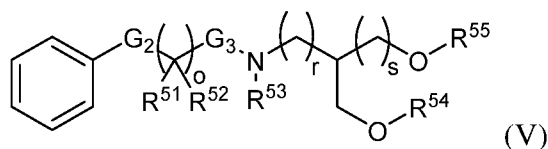
47. The compound of any one of claims 41-46, or a pharmaceutically acceptable salt thereof, wherein R^{43} is $OC_{1-18}alkyl$, $-OC_{1-18}alkenyl$, $-C_{1-18}alkyl$, or $-C_{1-18}alkenyl$, wherein the alkyl or alkenyl is optionally substituted with $-OH$ or $-OC_{1-4}alkyl$.

48. The compound of any one of claims 41-47, or a pharmaceutically acceptable salt thereof, wherein R^{44} is $OC_{4-18}alkyl$ or $-OC_{4-18}alkenyl$, wherein the alkyl or alkenyl is optionally substituted with $-OH$, $-OC_{1-4}alkyl$, $-C(O)OC_{1-4}alkyl$, $-C(O)NH_2$, $-C(O)NHC_{1-4}alkyl$, or phenyl.

49. A compound selected from the group consisting of
tert-butyl 4-(3-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperazine-1-carboxylate;
N-(2,3-bis(tetradecyloxy)propyl)-3-(piperazin-1-yl)benzamide hydrochloride;
tert-butyl 4-(3-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate;
N-(2,3-bis(tetradecyloxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride;
tert-butyl 4-(2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperazine-1-carboxylate;
N-(2,3-bis(tetradecyloxy)propyl)-2-(piperazin-1-yl)benzamide hydrochloride;
tert-butyl 4-(2-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate;
N-(2,3-bis(tetradecyloxy)propyl)-2-(piperidin-4-yl)benzamide hydrochloride;
tert-butyl 4-(4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperazine-1-carboxylate;
N-(2,3-bis(tetradecyloxy)propyl)-4-(piperazin-1-yl)benzamide hydrochloride;
tert-butyl 4-(4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)piperidine-1-carboxylate;
N-(2,3-bis(tetradecyloxy)propyl)-4-(piperidin-4-yl)benzamide hydrochloride;
4-(3-((2,3-bis(tetradecyloxy)propyl)carbamoyl)phenyl)-1,1-dimethylpiperidin-1-ium iodide;
N-(2,3-bis(heptyloxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride;
N-(2,3-bis((5-methoxypentyl)oxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride;
N-(3-(benzyloxy)-2-(dodecyloxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride;
methyl 5-(2-(dodecyloxy)-3-(3-(piperidin-4-yl)benzamido)propoxy)pentanoate hydrochloride;
5-(2-(dodecyloxy)-3-(3-(piperidin-4-yl)benzamido)propoxy)pentanoic acid hydrochloride;
N-(2-(dodecyloxy)-3-((5-(methylamino)-5-oxopentyl)oxy)propyl)-3-(piperidin-4-yl)benzamide
hydrochloride;
N-(3-((5-amino-5-oxopentyl)oxy)-2-(dodecyloxy)propyl)-3-(piperidin-4-yl)benzamide
hydrochloride;
N-(3-(octyloxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride;
3-(piperidin-4-yl)-N-tetradecylbenzamide hydrochloride;
N-(3-(2-methoxyethoxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride;
N-(3-ethoxy-2-hydroxypropyl)-3-(piperidin-4-yl)benzamide hydrochloride;
tert-butyl 4-(3-((2,3-bis(((Z)-tetradec-8-en-1-yl)oxy)propyl)carbamoyl)phenyl) piperidine-1-
carboxylate;
N-(2,3-bis(((Z)-tetradec-8-en-1-yl)oxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride;

tert-butyl 4-(3-((2,3-bis(((9Z,12Z)-octadeca-9,12-dien-1-yl)oxy)propyl) carbamoyl phenyl)piperidine-1-carboxylate; and
 N-(2,3-bis(((9Z,12Z)-octadeca-9,12-dien-1-yl)oxy)propyl)-3-(piperidin-4-yl)benzamide hydrochloride,
 or pharmaceutically acceptable salts thereof.

50. A compound of Formula (V):



wherein

G₂ is a bond, -CH₂-, -CH₂NH-, or -CH₂NHCH₂-;

G₃ is -C(O)- or -CH₂-;

R⁵¹ is H, C₁₋₄alkyl, -CO₂C₁₋₄alkyl, heterocycle, or -C₁₋₄alkyl-NR^{5a}R^{5b}; where R^{5a} is H or C₁₋₄alkyl and R^{5b} is H, C₁₋₄alkyl, or -CO₂C₁₋₄alkyl; and

R⁵² is H or C₁₋₄alkyl;

or R⁵¹ and R⁵², together with the carbon to which they are attached, form a heterocycloalkyl optionally substituted with -CO₂C₁₋₄alkyl;

R⁵³ is H or C₁₋₄alkyl;

o is 0 or 1;

r is 0 or 1;

s is 0 or 1;

R⁵⁴ is C₈₋₁₈alkyl or C₈₋₁₈alkenyl; and

R⁵⁵ is C₈₋₁₈alkyl or C₈₋₁₈alkenyl;

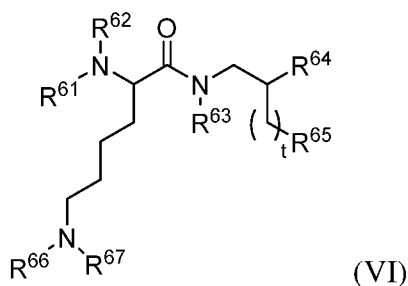
or a pharmaceutically acceptable salt thereof.

51. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein G₂ is a bond.

52. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein G₂ is -CH₂-.
53. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein G₂ is -CH₂NH- or -CH₂NHCH₂-.
54. The compound of any one of claims 50-53, or a pharmaceutically acceptable salt thereof, wherein G₃ is -C(O)-.
55. The compound of any one of claims 50-53, or a pharmaceutically acceptable salt thereof, wherein G₃ is -CH₂-.
56. The compound of any one of claims 50-55, or a pharmaceutically acceptable salt thereof, wherein R⁵¹ is H or -C₁₋₄alkyl-NR^{5a}R^{5b}; where R^{5a} is H or C₁₋₄alkyl and R^{5b} is H, C₁₋₄alkyl, or -CO₂C₁₋₄alkyl.
57. The compound of any one of claims 50-56, or a pharmaceutically acceptable salt thereof, wherein R⁵² is H.
58. The compound of any one of claims 50-55, or a pharmaceutically acceptable salt thereof, wherein R⁵¹ and R⁵², together with the carbon to which they are attached, form a heterocycloalkyl; wherein the heterocycloalkyl is optionally substituted with tert-butyloxycarbonyl.
59. The compound of any one of claims 50-55, or a pharmaceutically acceptable salt thereof, wherein R⁵¹ and R⁵², together with the carbon to which they are attached, form a piperidinyl, optionally substituted with -CO₂C₁₋₄alkyl.
60. A compound selected from the group consisting of
tert-butyl 4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)-4-phenylpiperidine-1-carboxylate;

N-(2,3-bis(tetradecyloxy)propyl)-4-phenylpiperidine-4-carboxamide hydrochloride;
 3-amino-N-(2,3-bis(tetradecyloxy)propyl)-2-phenylpropanamide hydrochloride;
 tert-butyl 3-benzyl-3-((2,3-bis(tetradecyloxy)propyl)carbamoyl)piperidine-1-carboxylate;
 3-benzyl-N-(2,3-bis(tetradecyloxy)propyl)piperidine-3-carboxamide hydrochloride;
 2-(benzylamino)-N-(2,3-bis(tetradecyloxy)propyl)-2-(piperidin-4-yl)acetamide hydrochloride;
 4-((benzylamino)methyl)-N-(2,3-bis(tetradecyloxy)propyl)piperidine-4-carboxamide hydrochloride;
 N-benzyl-2,3-bis(tetradecyloxy)propan-1-amine; and
 N-benzyl-N,N-dimethyl-2,3-bis(tetradecyloxy)propan-1-aminium iodide,
 or pharmaceutically acceptable salts thereof.

61. A compound of Formula (VI):



wherein

R^{61} is H, $-\text{CO}_2\text{-C}_{1-8}\text{alkyl}$, $-\text{CO}_2\text{-CHR}^{6a}\text{-aryl}$, $-\text{CO}_2\text{-CHR}^{6a}\text{-heteroaryl}$, $-\text{C(O)-C}_{1-4}\text{alkyl}$, $-\text{C(O)aryl}$, $-\text{C(O)-heteroaryl}$, $-\text{C(O)-CHR}^{6b}\text{-NR}^{6c}\text{R}^{6d}$, $-\text{C(O)-CHR}^{6a}\text{-heteroaryl}$, $-\text{CHR}^{6a}\text{-aryl}$, $-\text{CHR}^{6a}\text{-heteroaryl}$, $-\text{SO}_2\text{-C}_{1-4}\text{alkyl}$, $-\text{SO}_2\text{-aryl}$, or $-\text{SO}_2\text{-heteroaryl}$;

where R^{6a} is H or $\text{C}_{1-15}\text{alkyl}$;

R^{6b} is H or $-\text{C}_{1-5}\text{alkyl-NR}^{6e}\text{R}^{6f}$;

R^{6c} is H or $\text{C}_{1-4}\text{alkyl}$;

R^{6d} is H, $\text{C}_{1-4}\text{alkyl}$, or $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$;

R^{6e} is H or $\text{C}_{1-4}\text{alkyl}$;

R^{6f} is H, $\text{C}_{1-4}\text{alkyl}$, or $-\text{CO}_2\text{C}_{1-4}\text{alkyl}$; and

each aryl or heteroaryl is optionally substituted with halo, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{fluoroalkyl}$, $-\text{OH}$, $-\text{OC}_{1-4}\text{alkyl}$, $-\text{OC}_{1-4}\text{fluoroalkyl}$, $-\text{CN}$, phenyl, or $-\text{OC}_{1-4}\text{alkyl-aryl}$;

R^{62} is H or $\text{C}_{1-4}\text{alkyl}$;

R⁶⁶ is H, C₁₋₄alkyl, or -CO₂C₁₋₄alkyl;

R⁶⁷ is H, C₁₋₄alkyl, or -C(=NH)-NHR^{6m};

where R^{6m} is H, -SO₂aryl, or -CO₂C₁₋₄alkyl;

R⁶³ is H or C₁₋₄alkyl;

R⁶⁴ is H or -OH,

or R⁶⁴ is -C₁₋₁₈alkyl, -C₁₋₁₈alkenyl, -OC₁₋₁₈alkyl, or -OC₁₋₁₈alkenyl, each of which is optionally substituted with -OH or -OC₁₋₄alkyl;

R⁶⁵ is H or -C₄₋₈cycloalkyl,

or R⁶⁵ is -C₁₋₁₈alkyl, -C₁₋₁₈alkenyl, -OC₁₋₁₂alkyl, or -OC₁₋₁₂alkenyl, each of which is optionally substituted with -OH or -OC₁₋₄alkyl; and

t is 0 or 1;

or a pharmaceutically acceptable salt thereof.

62. The compound of claim 61, or a pharmaceutically acceptable salt thereof, wherein R⁶¹ is -CH₂-phenyl or -CH₂-naphthyl.

63. The compound of claim 61 or claim 62, or a pharmaceutically acceptable salt thereof, wherein R⁶² is H.

64. The compound of any one of claims 61-63, or a pharmaceutically acceptable salt thereof, wherein R⁶⁶ is H or -CO₂C₁₋₄alkyl

65. The compound of any one of claims 61-64, or a pharmaceutically acceptable salt thereof, wherein R⁶⁶ and R⁶⁷ are both H.

66. The compound of any one of claims 61-65, or a pharmaceutically acceptable salt thereof, wherein R⁶³ is H or methyl.

67. The compound of any one of claims 61-66, or a pharmaceutically acceptable salt thereof, wherein R⁶⁴ is H or -OH.

68. The compound of any one of claims 61-66, or a pharmaceutically acceptable salt thereof, wherein R⁶⁴ is -C₁₋₁₈alkyl, -C₁₋₁₈alkenyl, -OC₁₋₁₈alkyl, or -OC₁₋₁₈alkenyl, each optionally substituted with -OH or -OC₁₋₄alkyl;

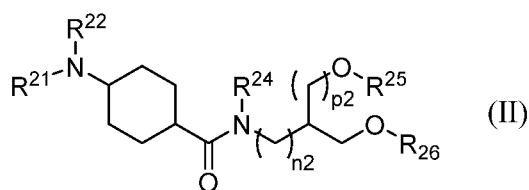
69. The compound of any one of claims 61-68, or a pharmaceutically acceptable salt thereof, wherein R⁶⁵ is H or -C₄₋₈cycloalkyl.

70. The compound of any one of claims 61-68, or a pharmaceutically acceptable salt thereof, wherein R⁶⁵ is -C₁₋₁₈alkyl, -C₁₋₁₈alkenyl, -OC₁₋₁₈alkyl, or -OC₁₋₁₈alkenyl, each optionally substituted with -OH or -OC₁₋₄alkyl.

71. A compound selected from the group consisting of
 tert-butyl ((5R)-5-(benzylamino)-6-((2,3-bis(((9Z,12Z)-octadeca-9,12-dien-1-yl)oxy)propyl)amino)-6-oxohexyl)carbamate;
 (2R)-6-amino-2-(benzylamino)-N-(2,3-bis(((9Z,12Z)-octadeca-9,12-dien-1-yl)oxy)propyl)hexanamide dihydrochloride;
 (S)-6-amino-2-(benzylamino)-N-tetradecylhexanamide dihydrochloride;
 (S)-6-amino-2-(benzylamino)-N-decylhexanamide dihydrochloride;
 (S)-6-amino-2-(benzylamino)-N-(3-ethoxypropyl)hexanamide dihydrochloride;
 (S)-6-amino-2-(benzylamino)-N-(3-(octyloxy)propyl)hexanamide dihydrochloride;
 (S)-6-amino-N-(2-cyclohexylethyl)-2-((naphthalen-2-ylmethyl)amino)hexanamide dihydrochloride;
 (S)-6-amino-N-methyl-2-((naphthalen-2-ylmethyl)amino)hexanamide dihydrochloride;
 (2S)-6-amino-2-(benzylamino)-N-(2,3-bis(heptyloxy)propyl)hexanamide dihydrochloride;
 (2S)-6-amino-2-(benzylamino)-N-(2,3-bis((5-methoxypentyl)oxy)propyl) hexanamide dihydrochloride;
 tert-butyl (S)-(5-(benzylamino)-6-oxo-6-(tetradecylamino)hexyl)carbamate;
 tert-butyl (S)-(5-(benzylamino)-6-(decylamino)-6-oxohexyl)carbamate;
 tert-butyl (S)-(5-(benzylamino)-6-((3-ethoxypropyl)amino)-6-oxohexyl)carbamate;

tert-butyl (S)-(5-(benzylamino)-6-((3-(octyloxy)propyl)amino)-6-oxohexyl)carbamate;
 tert-butyl (S)-(6-((2-cyclohexylethyl)amino)-5-((naphthalen-2-ylmethyl)amino)-6-oxohexyl)carbamate;
 tert-butyl (S)-(6-((2-cyclohexylethyl)amino)-5-((naphthalen-2-ylmethyl)amino)-6-oxohexyl)carbamate;
 (2S)-6-amino-N-(3-ethoxy-2-hydroxypropyl)-2-((naphthalen-2-ylmethyl)amino) hexanamide dihydrochloride;
 (S)-6-amino-2-(benzylamino)-N-(2-(heptyloxy)ethyl)hexanamide dihydrochloride; and
 (2S)-6-amino-2-(benzylamino)-N-(2-(heptyloxy)-3-methoxypropyl)hexanamide dihydrochloride,
 or pharmaceutically acceptable salts thereof.

72. A compound of Formula (II):



wherein

R^{21} is H, C_{1-4} alkyl, or $-CO_2C_{1-4}$ alkyl;

R^{22} is H or C_{1-4} alkyl;

R^{24} is H or C_{1-4} alkyl;

R^{25} is C_{8-16} alkyl or C_{8-16} alkenyl;

R^{26} is C_{8-16} alkyl or C_{8-16} alkenyl;

n_2 is 0 or 1; and

p_2 is 0 or 1;

wherein at least one of n_2 and p_2 is 1;

or a pharmaceutically acceptable salt thereof.

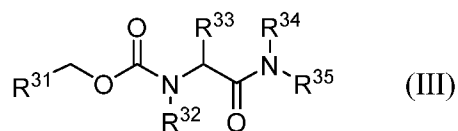
73. A compound selected from the group consisting of:

tert-Butyl ((*cis*)-4-((2,3-bis(tetradecyloxy)propyl) carbamoyl)cyclohexyl)carbamate;

(*cis*)-4-Amino-N-(2,3-bis(tetradecyloxy)propyl)cyclohexane-1-carboxamide;

tert-Butyl ((*trans*)-4-((2,3-bis(tetradecyloxy)propyl)carbamoyl)cyclohexyl)carbamate;
 and
 (*trans*)-4-Amino-N-(2,3-bis(tetradecyloxy)propyl)cyclohexane-1-carboxamide;
 and pharmaceutically acceptable salts thereof.

74. A compound of Formula (III):



wherein

R^{31} is phenyl or monocyclic heteroaryl;

R^{32} is H or C_{1-4} alkyl;

R^{33} is C_{1-4} alkyl- NR^xR^y ;

where R^x is H, C_{1-4} alkyl, or $-\text{CO}_2\text{-C}_{1-4}$ alkyl; and

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

R^{34} is H or C_{1-4} alkyl; and

R^{35} is C_{14-18} alkyl or C_{14-18} alkenyl;

or a pharmaceutically acceptable salt thereof.

75. A compound selected from the group consisting of:

Benzyl tert-butyl (6-(octadec-9-en-1-ylamino)-6-oxohexane-1,5-diyl)(*R,Z*)-dicarbamate;

Benzyl (*R,Z*)-(6-amino-1-(octadec-9-en-1-ylamino)-1-oxohexan-2-yl)carbamate;

Benzyl tert-butyl (6-oxo-6-(tetradecylamino)hexane-1,5-diyl)(*R*)-dicarbamate; and

Benzyl (*R*)-(6-amino-1-oxo-1-(tetradecylamino)hexan-2-yl)carbamate;

and pharmaceutically acceptable salts thereof.

76. A pharmaceutical composition comprising at least one compound according to any one of claims 1-75, or a pharmaceutically acceptable salt thereof, optionally further comprising a pharmaceutically acceptable excipient.

77. A method of treating a disease or condition associated with TLR2 heterodimerization, comprising administering to a subject in need of such treatment an effective amount of at least one compound according to any one of claims 1-75, or a pharmaceutically acceptable salt thereof.

78. The method of claim 77, wherein the disease or condition is selected from the group consisting of: Alzheimer's disease, Parkinson's disease, fronto-temporal dementia, dementia with Lewy bodies (Lewy body disease), Parkinson's disease with dementia, multiple system atrophy, amyotrophic lateral sclerosis, Huntington's disease, inflammatory diseases, asthma, chronic obstructive pulmonary disease (COPD), chronic peptic ulcers, tuberculosis, rheumatoid arthritis, chronic sinusitis, hepatitis, hepatitis B, hepatitis C, gout, lupus, pleurisy, eczema, gastritis, psoriasis, psoriatic arthritis, vasculitis, laryngitis, allergic reactions, multiple sclerosis, Crohn's disease, traumatic brain injury, CIDP (chronic inflammatory demyelinating polyneuropathy), atopic dermatitis, acne vulgaris, rosacea, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, corneal wounds, corneal disorders, Stargardt disease (Juvenile macular degeneration), age-related macular degeneration, sepsis, diabetic wounds, herpes simplex virus, and anti-fungal, anti-bacterial, antiviral and antitumor diseases or conditions.

79. A method of interfering with the heterodimerization of TLR2 in a cell, or modulating, preventing, slowing, reversing, or inhibiting TLR2 heterodimerization in a cell, comprising contacting the cell with an effective amount of at least one compound according to any one of claims 1-75, or a salt thereof, and/or with at least one pharmaceutical composition according to claim 76, wherein the contacting is *in vitro*, *ex vivo*, or *in vivo*.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/44984

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/66; C07F 9/02 (2017.01)

CPC - A61K 31/661; C07F 9/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2005/0175682 A1 (HEYES, J et al.) 11 August 2005; figure 1; paragraphs [0017], [0076]	1-3
Y	US 2015/0337009 A1 (UNIVERSITY OF KANSAS) 26 November 2015; paragraphs [0009]-[0011], [0016]	1-3
A	US 2011/0130349 A1 (CHOW, J et al.) 02 June 2011; entire document	1-3

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

18 September 2017 (18.09.2017)

Date of mailing of the international search report

22 NOV 2017

Name and mailing address of the ISA/

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/44984

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 5-36, 45-48, 56-59, 64-70, 76-79
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-Please See Within the Next Supplemental Box-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/44984

----Continued from Box No. III Observations where unity of invention is lacking ----

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid. Groups I+, Claims 1-4, 37-44, 49-55, 60-63, 71-75 (in-part); compound of Formula (I), wherein wherein R1 is -H; R2 is H; R3a is H; R3b is H; R4 is H; R5 is C8-16alkyl; R6 is C8-16alkyl; m is 1; n is 1; and p is 1; wherein at least one of n and p is 1; provided that the compound is not a compound of Table 1x (first exemplary compound structure).

The compound, compositions and methods will be searched to the extent the compound encompasses a compound of Formula (I), wherein wherein R1 is -H; R2 is H; R3a is H; R3b is H; R4 is H; R5 is C8-16alkyl; R6 is C8-16alkyl; m is 1; n is 1; and p is 1; wherein at least one of n and p is 1; provided that the compound is not a compound of Table 1x (first exemplary compound structure). Applicant is invited to elect additional compound(s), with fully specified structure (e.g. no optional or variable atoms or substituents) for each, to be searched. Additional compound(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 2 (in-part), and 3 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound of Formula (I), wherein wherein R1 is -H; R2 is H; R3a is H; R3b is H; R4 is H; R5 is C8-16alkyl; R6 is C8-16alkyl; m is 1; n is 1; and p is 1; wherein at least one of n and p is 1; provided that the compound is not a compound of Table 1x (first exemplary compound structure). Applicants must specify the claims that encompass any additionally elected compound structure(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a compound of Formula (I), wherein wherein R1 is -CO₂-C1-8alkyl; R2 is H; R3a is H; R3b is H; R4 is H; R5 is C8-16alkyl; R6 is C8-16alkyl; m is 1; n is 1; and p is 1; wherein at least one of n and p is 1; provided that the compound is not a compound of Table 1x (first exemplary elected compound structure).

Groups I+ share the technical features including: a compound of Formula (I), wherein wherein R1 is -H; R2 is H; R3a is H; R3b is H; R4 is H; R5 is C8-16alkyl; R6 is C8-16alkyl; m is 1; n is 1; and p is 1; wherein at least one of n and p is 1; provided that the compound is not a compound of Table 1x.

However, these shared technical features are previously disclosed by US 2005/0175682 A1 to Heyes, et al. (hereinafter 'Heyes') in view of US 2015/0337009 A1 (UNIVERSITY OF KANSAS) (hereinafter 'Kansas').

Heyes discloses a compound of Formula (I): as shown (conjugate of the formula PEG-A-DMA; figure 1; paragraphs [0017], [0076]), wherein R3a is H; R3b is H; R4 is H; R5 is C8-16alkyl; R6 is C8-16alkyl; m is 1; n is 1; and p is 1; wherein at least one of n and p is 1; provided that the compound is not a compound of Table 1x (conjugate of the formula PEG-A-DMA (R3a, R3b, and R4 are H, R5 and R6 are C14alkyl, m is 1, n is 1 and p is 1, wherein compound is not a compound in Table 1x); figure 1; paragraphs [0017], [0076]), but Heyes does not disclose wherein the compound comprises the terminal moiety -NR1R2 wherein R1 is H and R2 is H. However, Kansas discloses wherein the compound comprises the terminal moiety -NR1R2 wherein R1 is H and R2 is H (compound formula I wherein L is -CO-NH- and R1 is C1-50alkyl substituted by NH2 (terminal -NR1R2 moiety wherein R1 and R2 are H); paragraphs [0009]-[0011], [0016]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound, as previously disclosed by Heyes, in order to have provided wherein the compound comprises the terminal moiety -NR1R2 wherein R1 is H and R2 is H, as previously disclosed by Kansas, for providing conjugated lipopeptide compounds that can be formulated as vaccine adjuvants to treat infectious diseases (Kansas; abstract; Heyes; paragraphs [0025], [0178], [0220]).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Heyes and Kansas references, unity of invention is lacking.